Practical GynecologicOncology

4st Edition

2005

Lippincott Williams & Wilkins

Philadelphia

530 Walnut Street, Philadelphia, PA 19106 USA LWW.com

0-7817-5059-8

Printed in the USA

Library of Congress Cataloging-in-Publication Data

Practical gynecologic oncology / [edited by] Jonathan S. Berek, Neville F. Hacker ; illustrations by Timothy C. Hengst.—4th ed.

p. ; cm.

Includes bibliographical references and index.

ISBN 0-7817-5059-8 (HC)

1. Generative organs, Female—Cancer. I. Berek, Jonathan S. II. Hacker, Neville F.

[DNLM: 1. Genital Neoplasms, Female WP 145 P895 2004]

RC280.G5P73 2004

616.99′465—dc22

2004056723

10 9 8 7 6 5 4 3 2 1

Editors

Jonathan S. Berek MD, MMSc

Professor and Chair
College of Applied Anatomy; Executive Vice Chair, Department of Obstetrics and Gynecology; Chief, Division of Gynecologic Oncology and Gynecology Service; Director, UCLA Women's Reproductive Cancer Program, David Geffen School of Medicine at UCLA, UCLA Center for the Health Sciences, Los Angeles, California

Neville F. Hacker MD

Associate Professor
Department of Obstetrics and Gynaecology, University of New South Wales, Kensington, New South Wales, Australia; Director, Gynaecological Cancer Centre, Royal Hospital for Women, Randwick, New South Wales, Australia

Secondary Editors

Timothy C. Hengst CMI, FAMI
Illustrations

Ruth Weinberg

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Senior Marketing Manager

Doug Smock

Creative Director

Compositor: Compset, Inc.

Printer: Quebecor World-Kingsport

Contributing Authors

Barbara L. Andersen PhD

Professor
Department of Psychology, Ohio State University; Director, Behavioral Measurement Shared Resource, Ohio State University Comprehensive Cancer Center, Columbus, Ohio

Walter F. Baile MD

Professor of Psychiatry
Chief, Psychiatry Section, Department of Neuro-Oncology, MD Anderson Cancer Center, University of Texas, Houston, Texas

Andrew Berchuck MD

Professor
Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Duke University Medical Center, Durham, North Carolina

Ross S. Berkowitz MD

William H. Baker Professor of Gynecology
Department of Obstetrics and Gynecology, Harvard Medical School; Co-Director, New England Trophoblastic Disease Center, Division of Gynecologic Oncology, Brigham and Women's Hospital, Boston, Massachusetts

Robert Buckman MD, PhD

Professor and Medical Oncologist
Department of Medicine, University of Toronto, Toronto-Sunnybrook Regional Cancer Centre, Toronto, Ontario, Canada

Michael J. Campion MB, BS

Director of Preinvasive Disease
Department of Gynaecological Cancer Centre, Royal Hospital for Women, Paddington, New South Wales, Australia

Kristen M. Carpenter MA

Graduate Research Assistant
Department of Psychology, Ohio State University, Columbus, Ohio

Susan S. Chang MD

Director, Breast Program
Department of Surgery, St. Luke's Hospital and Health Network, Bethlehem, Pennsylvania

Daniel W. Cramer MD, ScD

Professor of Obstetrics, Gynecology, and Reproductive Biology
Department of Obstetrics and Gynecology, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts

Patricia J. Eifel MD

Professor
Department of Radiation Oncology, M.D. Anderson Cancer Center, University of Texas, Houston, Texas

Armando E. Giuliano MD

Professor
Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, California; Chief, Department of Surgical Oncology, John Wayne Cancer Institute, Santa Monica, California

Donald P. Goldstein MD

Professor
Department of Obstetrics and Gynecology, Harvard Medical School; Director, New England Trophoblastic Disease Center, Division of Gynecologic Oncology, Brigham and Women's Hospital, Boston, Massachusetts

Philip I. Haigh MD, MSc

Surgical Oncologist
Department of Surgery, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California

Kenneth D. Hatch MD

Professor and Chairman
Department of Obstetrics and Gynecology, University of Arizona, Tucson, Arizona

David Heber MD, PhD

Professor
Department of Medicine, David Geffen School of Medicine at UCLA; Chief, Division of Clinical Nutrition, UCLA Center for the Health Sciences, Los Angeles, California

Olga B. Ioffe MD

Associate Professor
Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland

Ian J. Jacobs MD

Professor
Head Institute of Cancer, Bart's and The London, Queen Mary's School of Medicine & Dentistry, London, United Kingdom

Roger M. Lee MD

Clinical Instructor
Department of Internal Medicine, David Geffen School of Medicine at UCLA, Santa Monica/UCLA Medical Center, Santa Monica, California

J. Norelle Lickiss MD

Professor
Department of Medicine, University of Sydney; Senior Staff Specialist, Sydney Institute of Palliative Medicine, Royal Prince Alfred Hospital, Royal Hospital for Women, Sydney, Australia

Maurie Markman MD

Professor of Medicine; Vice President for Clinical Research

MD Anderson Cancer Center, University of Texas, Houston, Texas

Otoniel Martínez-Maza PhD

Professor
Department of Obstetrics and Gynecology, Department of Microbiology, Immunology, and Molecular Genetics, David Geffen School of Medicine at UCLA, Los Angeles, California

G. Larry Maxwell MD
Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, Bethesda, Maryland

Usha Menon MD

Senior Lecturer/Consultant
Gynaecology Oncology Unit, Institute of Cancer, Bart's and The London, Queen Mary's School of Medicine & Dentistry, London, United Kingdom

Jennifer A. M. Philip MB, BS

Lecturer
Department of Medicine, Monash University; Director, Department of Palliative Care Service, The Alfred Hospital, Prahran, Victoria, Australia

Steven G. Silverberg MD

Professor
Department of Pathology, University of Maryland School of Medicine, University of Maryland Medical Center, Baltimore, MD

Aylin Simsir MD

Assistant Professor
Department of Pathology, University of Maryland School of Medicine; Director, Anatomic Pathology, University of Maryland Medical Center, Baltimore, Maryland

Samuel A. Skootsky MD

Professor
Department of Medicine, David Geffen School of Medicine at UCLA, UCLA Center for the Health Sciences, Los Angeles, California

M. Iain Smith MD

Associate Professor
Department of Medicine, David Geffen School of Medicine at UCLA, UCLA Center for the Health Sciences, Los Angeles, California

Dedication

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

Foreword to the First Edition

Close to the beginning of this century, William Osler observed, “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 work “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 subspeciality 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 the 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 opposites shores of the Pacific Ocean.

Sherman M. Mellinkoff M.D.

Dean Emeritus; Professor of Medicine
University of California, Los Angeles, School of Medicine, Los Angeles, California

Preface

In many countries over the past three decades, 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 Fourth Edition of *Practical Gynecologic Oncology* incorporates the most recent information while preserving the basic format and style of the previous editions. The book is divided into four sections: general principles, disease sites, medical and surgical topics, and quality of life. All chapters have been thoroughly revised and updated. The recent literature has been critically reviewed and the most important references have been included in our bibliography. 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 pre-invasive 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...."

This book would not have been possible without the important input from our co-authors, 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 Kairis, Richard Rothschild, and Steve Martin. At UCLA, we wish to acknowledge the wonderful generosity of our benefactors, especially Nicole Kidman and the UCLA Women's Reproductive Cancer Program. At the Royal Hospital for Women, we would like to thank Helen McGilligan for her assistance with the manuscript, and we would like to acknowledge the support of our Gynaecological Oncology (GO) Committee, especially Steven Eckowitz, our Chairman, and Jenny Mansell-Black our Fund Raising Co-ordinator. At both institutions, the enduring support of our benefactors has been critical to our gynecologic oncology research and clinical programs.

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

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

Jonathan S. Berek

Neville F. Hacker

Contents

Section I General Principles

1

Biology and Genetics

G. Larry Maxwell

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 often plays a role in allowing mutations to accumulate. **Cancers also are characterized by the ability to invade surrounding tissues, stimulate the development of new blood vessels, and metastasize.** The initial sections of this chapter outline what is known regarding the basic molecular mechanisms involved in the development and evolution of the malignant phenotype. The molecular alterations that characterize gynecologic cancers are outlined in the latter sections.

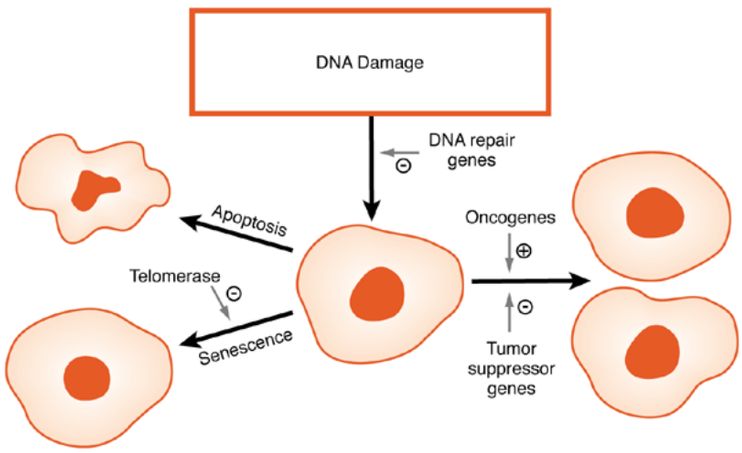

Figure 1.1 Role of proliferation, apoptosis, senescence, and DNA damage in cancer development.

- Regulation of Proliferation
- Origins of Genetic Damage
- Invasion and Metastasis
- Gynecologic Malignancies

Regulation of Proliferation

Part of "1 - Biology and Genetics "

The rate of proliferation is a major determinant of the number of cells in a population. To prevent excessive proliferation, DNA synthesis and cellular division are tightly regulated. When proliferation is appropriate, inhibitory mechanisms are turned off, and growth stimulatory signals are generated. The final common pathway for cell division involves distinct molecular switches that control cell cycle progression from G_1 to the S phase of DNA synthesis. These include the Rb and E2F proteins and their various regulatory cyclins, cyclin-dependent kinases (cdks) and cdk inhibitors. Likewise, the events that facilitate progression from G2 to mitosis and cell division are regulated by other cyclins and cdks (Fig. 1.2).

Figure 1.2 Regulation of cell cycle arrest in G1 by cyclin dependent kinase (cdk) inhibitors. Left: cell cycle arrest. Right: cell cycle progression.

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 is not strikingly different than that seen in some normal cells. Increased proliferation is only one of several factors that contributes to cancerous growth.

Cell Death (Apoptosis)

Cells are capable of activating a suicide pathway of programmed cell death referred to as apoptosis (1). Apoptosis is an active energy-dependent process that involves cleavage of the 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 are complex and have been partially elucidated (Fig. 1.3). Regulation of apoptosis is dependent on a balance between stimuli such as growth factors that enhance survival and those that favor death. **Apoptosis can be triggered by withdrawal of survival factors or by DNA-damaging agents such as chemotherapy and radiation. Extracellular ligands of the tumor necrosis factor family** (e.g., TNF-α TNF-β, Fas ligand and TRAIL) that interact with cell surface death receptors **also can trigger apoptosis** via a somewhat different cascade of events.

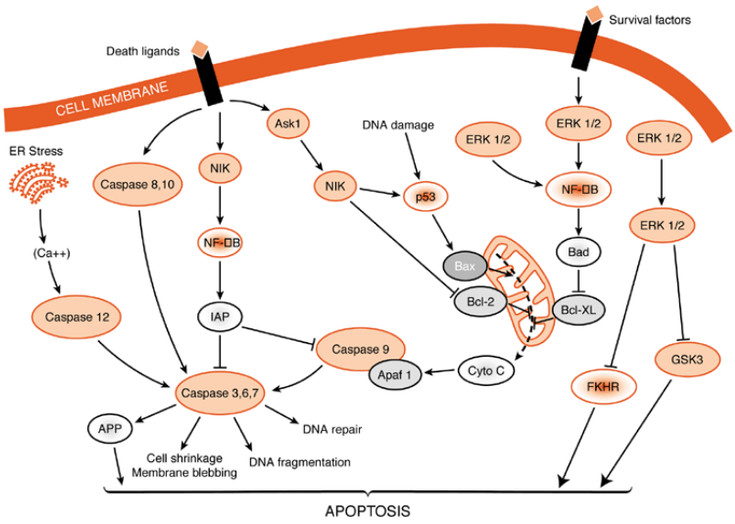

Figure 1.3 Apoptosis pathways. Cyto C = cytochrome C, ER = endoplasmic reticulum.

Many of the intracellular events involved in apopotosis have been elucidated. The *bcl-2* gene was first identified at a translocation breakpoint in B-cell lymphomas and expression of this gene inhibits apoptosis. The *bcl-*X_L gene also inhibits apoptosis, whereas others, such as *bax* and *bcl-*X_S, have pro-apoptotic activity. Proteins that reside in the mitochondrial membrane play a critical role in regulation of apoptosis. Apoptosis results when mitochondrial membrane permeability increases, leading to the release of cytochrome C and Apaf-1, which form a complex with caspase-9 that is referred to as the apoptosome. This effects activation of a series of other caspases, which are proteases that act to fragment DNA and breakdown cellular proteins. **Direct activation of caspase-8 is a key event in induction of apoptosis in response to extracellular death ligands. Regardless of the initiating signals, the process of apoptosis is completed by phagocytosis of the dying cell.**

Apoptosis pathways play a critical role both in cancer prevention and treatment. First, because the size of a cell population is normally static, growth of a neoplasm theoretically could result from either increased proliferation or decreased apoptosis. In addition to counterbalancing proliferation, apoptosis serves an important role in preventing malignant transformation by eliminating cells that have undergone mutations. **Following exposure of cells to mutagenic stimuli, the cell cycle is arrested so that DNA damage may be repaired. If DNA repair is not sufficient, the *p53* gene stimulates apoptosis to insure that cells with significant damage do not survive** (Fig. 1.3). This serves as an anticancer surveillance mechanism by which mutated cells are eliminated before they become fully transformed.
Many chemopreventives, such as retinoids and selective estrogen response modulators (SERMs), have been shown to increase apoptosis. **The apoptotic pathway also plays an integral role in mediating the cytotoxic effects of chemotherapeutic drugs. The efficacy of these agents is attributable to the development of DNA damage that triggers apoptosis, but the threshold for apoptosis is elevated in some cancers, leading to resistance**. A number of approaches are being explored that would enhance the apoptotic effect of chemotherapy, including the use of proapoptotic death ligands such as TRAIL (2 ,3 ,4).

Cellular Senescence

Normal cells are only capable of undergoing division a finite number of times before becoming senescent. **Cellular senescence is due to shortening of repetitive DNA sequences (TTAGGG) called telomeres that cap the ends of each chromosome** (5 ,6). **Telomeres are thought to be involved in chromosomal stabilization and in prevention of recombination during mitosis**. At birth, chromosomes have long telomeric sequences (150,000 bases) that become progressively shorter by 50 to 200 bases each time a cell divides. Telomeric shortening is the molecular clock that triggers senescence (Fig. 1.1). **Malignant cells avoid senescence by turning on expression of telomerase to prevent telomere shortening.** 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 it might be a useful marker for early diagnosis of cancer. **Telomerase activity is detectable in a high fraction of many cancers, including ovarian** (7 ,8 ,9), **cervical** (10 ,11 ,12), **and endometrial** (13). Although telomerase expression is elevated in cancers, some normal cells also maintain significant expression. **Endometrium is one of the adult tissues in which telomerase expression is most common** (14). Perhaps this relates to the need for a large number of lifetime cell divisions because of rapid growth and repetitive shedding during the reproductive years. Finally, therapeutic approaches to inhibiting telomerase are under development that focus on reversing the immortalized state of cancer cells to make them susceptible once again to normal replicative senescence (5 ,15).

Origins of Genetic Damage

Part of "1 - Biology and Genetics "
Human cancers arise because of a series of genetic alterations that lead to disruption of cellular behavior (16 **). Genetic damage may be inherited or occur as a result of exposure to exogenous carcinogens or via endogenous mutagenic processes within the cell** (Table 1.1). The incidence of most cancers increases with aging, because the longer one 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 to fully transform a cell.

Table 1.1 Origins of Genetic Damage in Human Cancers

Type of Genetic Damage	*Examples*
Hereditary	
High penetrance genes	*BRCA1, BRCA2, MLH1, MSH2*
Low penetrance genes	*APC I1307K* in colorectal cancer
Exogenous Carcinogens	
Ultraviolet radiation	*p53* and other genes in skin cancer
Tobacco	K-*ras* and *p53* in lung cancer
Endogenous DNA Damage	
Cytosine methylation and deamination	*p53* in ovarian and other cancers
Hydrolysis	Various genes
Spontaneous errors in DNA synthesis	Various genes
Oxidative stress/with free radical damage	Various genes

Although most cancers arise sporadically because of acquired genetic damage, inherited mutations in cancer susceptibility genes are responsible for some cases. Families

that carry these mutations exhibit a striking 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 recently have been identified. The most common forms of hereditary cancer predispose to breast/ovarian, colon/endometrial, and melanoma (Table 1.2). Examples of rarer hereditary cancer syndromes are also outlined in Table 1.2 .

Table 1.2 Cancer: Types in which Hereditary Syndromes are Common

Syndrome	*Genes*	*Predominant Cancers*
Common Hereditary Cancer Syndromes		
Hereditary breast/ovarian cancer	*BRCA1, BRCA2*	Breast, ovary
Hereditary nonpolyposis colorectal cancer (HNPCC)	*MSH2, MLH1, PMS1, PMS2, MSH6*	Colon, endometrium, other gastrointestinal tract, ovary
Familial melanoma	*CMM1, CMM2, CDK4, CDKN2 (p16)*	Melanoma
Rare Hereditary Cancer Syndromes		
Familial adenomatous polyposis	*APC*	Colonic polyps and cancers
Li-Fraumeni syndrome	*p53*	Sarcomas, leukemias, breast, brain, and others
Wilm's tumor	*WT1*	Kidney
von Hippel-Lindau	*VHL*	Kidney and others
Neurofibromatosis	*NF1, NF2*	Neurofibromas
Retinoblastoma	*Rb*	Retinoblastoma, sarcomas
Multiple-endocrine neoplasia 1	*MEN1*	Thyroid, adrenal, pancreas, pituitary, parathyroid
Multiple-endocrine neoplasia 2	*ret*[a]	Thyroid, adrenal, parathyroid
Hereditary papillary renal cancer	*met*[a]	Papillary kidney

[a]Oncogenes.

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, paradoxically, cancer susceptibility genes are characterized by a limited repertoire of cancer types. In addition, 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 develop testicular

cancer. In addition, **the penetrance of these cancer susceptibility genes is incomplete, as all individuals who inherit a mutation do not develop cancer.** The emergence of cancers in carriers is dependent on the occurrence of additional genetic alterations.

Finally, **it is thought that genetic polymorphisms may exist that confer slightly increased cancer risks.** These polymorphisms may be fairly common, but because of their low penetrance do not cause striking familial aggregations of cancer. Rather, they play a role in the development of cancers that presently would be characterized as sporadic. For example, 6% of Ashkenazi Jewish individuals carry the rare allele of the I1307K polymorphism in the adenomatous polyposis coli (*APC)* gene, which increases the risk of colorectal cancer by about 50% to 75% (17).

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, endometrial, ovarian), a strong association with specific carcinogens does not exist. It is thought that the genetic alterations responsible for these cancers may arise because of endogenous mutagenic processes such as oxidative stress with free radical generation and methylation, deamination, and hydrolysis of DNA. **In addition, spontaneous errors in DNA synthesis may occur during the process of DNA replication associated with normal proliferation**. Although DNA synthesis occurs with a high level of fidelity, it is estimated that errors occur about once every million base pairs. Several families of DNA repair genes exist, but some types of mutations more readily evade detection and repair. In addition, the efficiency of these DNA repair systems may vary between individuals because of inheritance of allelic variants with less activity.

Oncogenes

Alterations in genes that stimulate cellular growth (oncogenes) can cause malignant transformation. Oncogenes can be activated via 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 latter mechanism frequently occurs in leukemias and lymphomas, but not 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 via amplification, mutation, or translocation. On this basis, a large number of genes have been classified as oncogenes. Studies in human cancers have suggested that the actual spectrum of genes altered in the development of human cancers may be more limited. 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 will be summarized and particular attention will be paid to those that are altered in gynecologic cancers.

Peptide Growth Factors and Their Receptors

Peptide growth factors in the extracellular space can stimulate a cascade of molecular events that leads to proliferation by binding to cell membrane receptors (Fig. 1.4). Growth factors are involved in normal cellular processes such as development, stromal-epithelial communication, tissue regeneration, and wound healing. Unlike hormones, which are secreted into the bloodstream to act in 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. In addition, growth factors produced in the local environment by other cell types can act in a paracrine fashion to stimulate growth of tumor cells. Although peptide growth factors provide a growth stimulatory signal, there is little evidence to suggest that overproduction of growth factors is a precipitating event in the development of most cancers. **Peptide growth factors likely serve as necessary cofactors rather than as the driving force behind malignant transformation.**

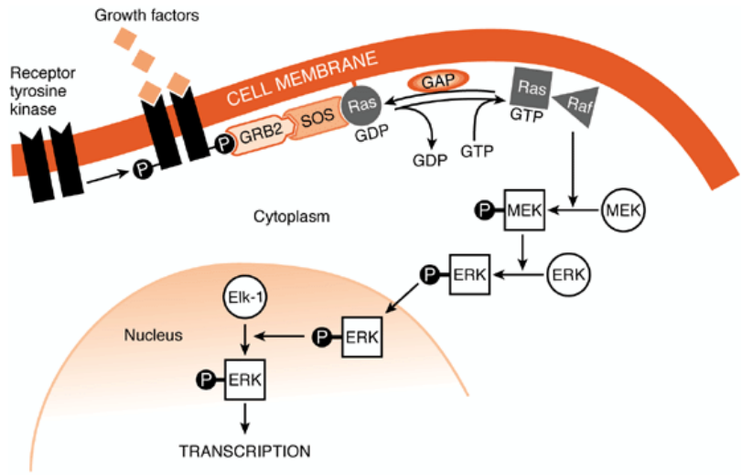

Figure 1.4 Mitogenic signal transduction pathways.

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 dimerization and conformational shifts in the receptor and activation of the inner tyrosine kinase domain. The kinase phosphorylates tyrosine residues on both the growth factor receptor (*autophosphorylation*) and targets in the cell's interior, leading to activation of secondary signals. **Growth of some cancers may be driven by overexpression of receptor tyrosine kinases.** Therapeutic strategies that target receptor tyrosine kinases have been an active area of investigation. ***Herceptin* is a monoclonal antibody that blocks the HER-2/*neu***, and it has been approved for treatment of breast cancers that overexpress this tyrosine kinase receptor (18 ,19). ***Erbitux* is a monoclonal antibody that targets the epidermal growth factor receptor (EGFR)**, whereas ***Iressa* is a direct inhibitor of the EGFR tyrosine kinase** (20 ,21). ***Gleevec* antagonizes the activity of the BCR-ABL, c-kit, and platelet-derived growth factor (PDGF) receptor tyrosine kinases** and has proven effective in treatment of chronic myelogenous leukemias and gastrointestinal stromal tumors.

Extranuclear Signal Transduction

Following interaction of peptide growth factors and their receptors, 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 kinases (22). 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 (ATP) to tyrosine residues of target proteins. This includes the extracellular-regulated kinase (ERK) and the mitogen-activated protein (MAP) kinase pathways. 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** (23). **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.**

***G proteins* represent another class of molecules involved in transmission of growth stimulatory signals in toward the nucleus.** They are located on the inner aspect of the cellular membrane and have intrinsic GTPase activity that catalyzes the exchange of GTP (guanine triphosphate) for GDP (guanine diphosphate). In their active GTP-bound form, G proteins turn on kinases that are involved in relaying the mitogenic signal. Conversely, hydrolysis of GTP to GDP, which is stimulated by GTPase activating proteins (GAPs), leads to inactivation of G proteins. **The *ras* family of G proteins are involved in transmission of mitogenic signals generated by receptor tyrosine kinases, such as the epidermal growth factor receptor**. *Ras* genes are among the most frequently mutated oncogenes in human cancers (e.g., gastrointestinal and endometrial cancers). Mutations in r*as* genes usually involve codons 12, 13, or 61, which produce constitutively active forms. **Therapeutic approaches to interfering with *ras* signaling are being developed, including farnesyltransferase inhibitors that block attachment of *ras* to the inner cell membrane, antisense oligonucleotides, and RNA interference** (24).

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 cellular 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 cellular 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* family has most often been implicated in the development of human cancers** (25). Ultimately, nuclear transfection factors regulate proliferation by affecting the regulatory pathways described above that control cell cycle progression. Recently it has been found that **many of the nuclear regulatory genes, such as *myc*, that control proliferation also impact the threshold for apoptosis**. Thus, there is overlap in the molecular pathways that regulate the opposing processes of proliferation and apoptosis.

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 segment of the chromosome where the gene resides. There is also evidence that some tumor suppressor genes may be inactivated as a result of methylation of the promoter region of the gene (26). The promoter is an area proximal to the coding sequence that regulates whether the gene is transcribed from DNA into messenger RNA. When the promoter is methylated, it is resistant to activation, and the gene is essentially silenced despite remaining structurally intact. **This two-hit paradigm is relevant to both hereditary cancer syndromes, in which one mutation is inherited and the second acquired, and sporadic cancers, in which both hits are acquired**. Tumor suppressor gene products are found throughout

the cell, reflecting their diverse functions. **With the recognition that inactivation of tumor suppressor genes is a defining feature of cancers, gene therapy strategies have been developed that aim to deliver functional copies of these lost genes to cancer cells in an attempt to restore normal regulation of proliferation and apoptosis** (27).

Nuclear Tumor Suppressor Genes

The retinoblastoma gene (*Rb*) was the first tumor-suppressor gene discovered (28). It was found in the context of a rare hereditary cancer syndrome, as have many other tumor suppressor genes (Table 1.2). The *Rb* gene plays a key role in the regulation of cell cycle progression (Fig. 1.2). 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. G_1 arrest is maintained by cyclin-dependent kinase (cdk) inhibitors, such as *p16, p21*, and *p27*, that prevent phosphorylation of Rb (29). When Rb is phosphorylated by cyclin/cdk complexes, E2F is released and stimulates entry into the DNA synthesis phase of the cell cycle. Other cyclins and cyclin-dependent kinases are involved in 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.** By maintaining G_1 arrest, the cdk inhibitors p16, p21, p27, and others act as tumor suppressor genes. Loss of p16 tumor suppressor function as a result of genomic deletion or promoter methylation occurs in some cancers, including familial melanomas. Likewise, loss of p21 and p27 has been noted in some cancers.

Mutation of the *p53* tumor suppressor gene is the most frequent genetic event described thus far in human cancers (Fig. 1.5) (30 ,31 ,32). The p53 gene encodes a

393 amino acid protein that plays a central role in the regulation of both proliferation and apoptosis. 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. The *MDM2* gene product degrades p53 protein when appropriate, whereas ^{p14AFR} down-regulates *MDM2* when up-regulation of p53 is needed to initiate cell cycle arrest. **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** (33 ,34). 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.

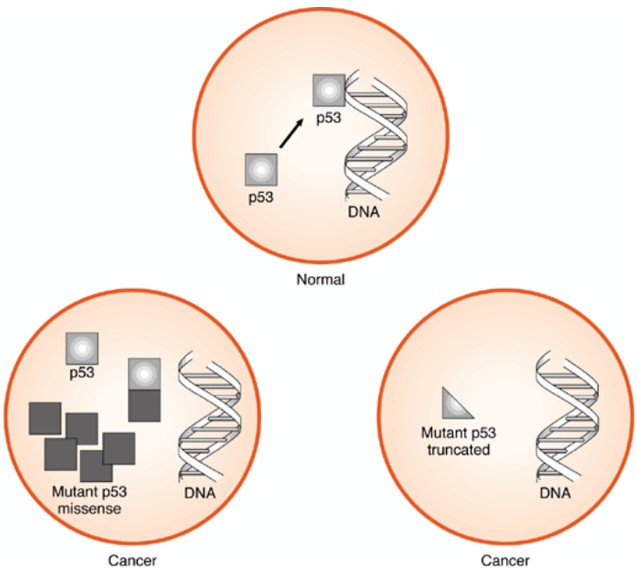

Figure 1.5 Inactivation of the p53 tumor suppressor gene by "dominant negative" missense mutation or by truncation mutation and deletion.

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. Whereas normal cells have low levels of p53 protein because it is rapidly degraded, missense mutations encode protein products that are resistant to degradation. The resultant overaccumulation of mutant p53 protein in the nucleus can be detected immunohistochemically. A smaller fraction of cancers have mutations in the p53 gene that encode truncated protein products. 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 many tumor suppressor genes, including *p53*, *Rb*, and *p16*, encode nuclear proteins, some extranuclear tumor suppressors have been identified. Theoretically, any protein that normally is involved in inhibition of proliferation has the potential to 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. Analysis of deletions on chromosome 10q23 in human cancers led to the discovery of the *PTEN* **gene** (35). **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**. The *APC* gene encodes a cytoplasmic protein involved in the wnt signaling pathway that regulates both cellular proliferation and adhesion. Inactivation of *APC* leads to malignant transformation. Inherited mutations in this gene are responsible for familial adenomatous polyposis syndrome.

The transforming growth factor-beta (TGF-ß) family of peptide growth factors inhibit proliferation of normal epithelial cells and serve as a tumor suppressive pathway (36). It is thought that TGF-ß causes G_1 arrest by inducing expression of cyclin-dependent kinase inhibitors such as *p27*. Three closely related forms of TGF-ß have been discovered that are encoded by separate genes (*TGF-ß1*, *TGF-ß2*, *TGF-ß3*). TGF-ß 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-ß. Active TGF-ß interacts with type I and type II cell surface TGF-ß receptors and initiates serine/threonine kinase activity. Prominent intracellular targets include a class of molecules called Smads that translocate to the nucleus and act as transcriptional regulators. Although mutations in the TGF-ß receptors and Smads have been reported in some cancers, this does not appear to be a feature of gynecologic cancers.

Invasion and Metastasis

Part of "1 - Biology and Genetics "

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** (37). Many of the molecular events involved in invasion and metastasis have recently been elucidated and are described below (Fig. 1.6).

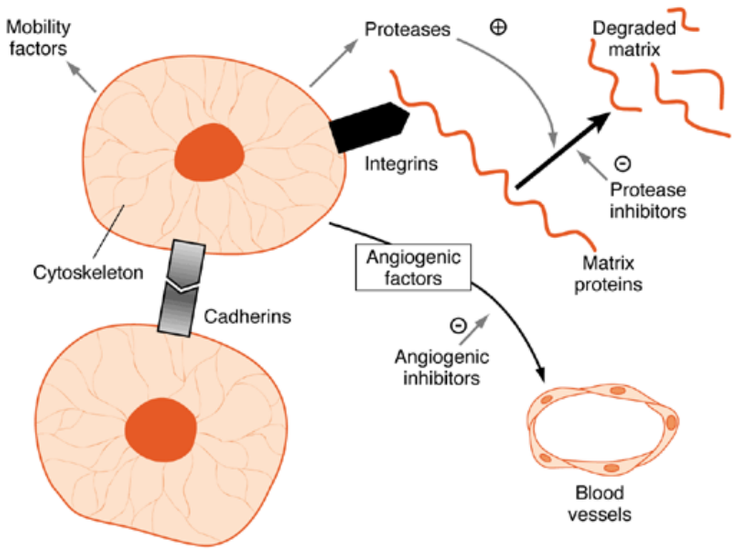

Figure 1.6 Molecular pathways involved in invasion and metastasis.

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** (38 ,39). Approximately 15 ß subunits and 9 α 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 (40). **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 (41), but cadherin expression may also be down-regulated in the

absence of mutations. The cytoplasmic tails of cadherins exist as a macromolecular complex with ß-catenin, which is involved in the wnt signaling pathways that regulate both adhesion and growth (42). Regulation of ß-catenin activity also is dependent on the adenomatous polyposis coli *(APC)* gene product and others in the wnt pathway (Fig. 1.7). Mutations in the *APC* gene that abrogate its ability to inhibit ß-catenin activity are common in both the hereditary adenomatous polyposis coli syndrome and sporadic colon cancers (43). Likewise, mutations in the ß-*catenin* gene that result in constitutively activated molecules also have been observed in some cancers, including endometrial cancers (44).

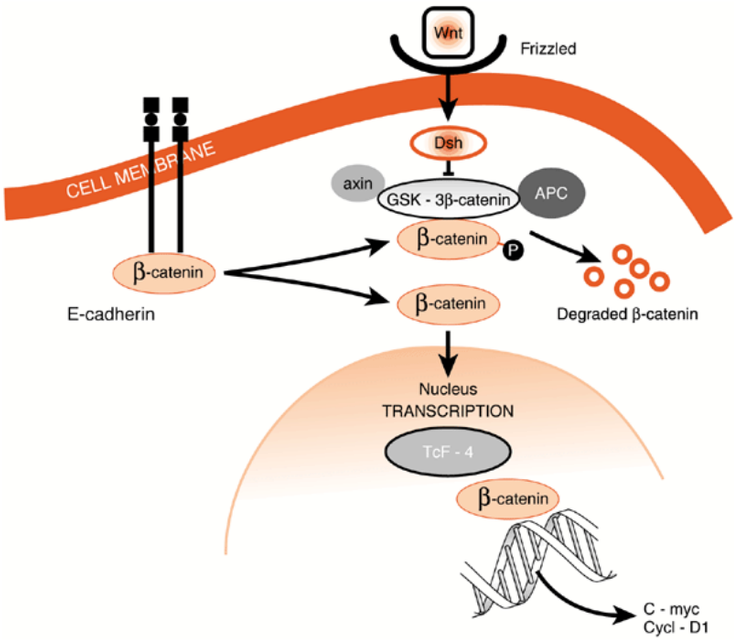

Figure 1.7 wnt signaling pathway. (ß = ß-catenin)

Invasion

Lysis of the basement membrane and matrix proteins such as collagen, laminin, and fibronectin is required for tumor cell invasion and migration (45 ,46 ,47). Breakdown of the extracellular matrix is mediated by a family of matrix metalloproteinases (MMPs) that are characterized by a zinc atom at their active site (48). 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 tissue inhibitors of metalloproteinases (TIMPs). **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, cervix, and ovarian cancer cell lines (49). Preclinical trials using the TIMPs *batimastat* and *marimastat* to inhibit tumor cellular invasion have been promising (50).

In addition to degradation of the extracellular matrix, cancer cell motility is an important component of the invasive process (45 ,46). 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 via their interaction with cell surface integrins.

Angiogenesis

The growth of cancer cells is dependent on diffusion of nutrients from the surrounding stroma. Expansion of a solid tumor beyond 1 mm^3 in volume requires neovascularization (51). **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 (52 ,53). Tumor angiogenesis requires proliferation and migration of endothelial cells and is stimulated by several cytokines, including the fibroblast growth factor family, angiogenin, angiopoietin, and vascular endothelial growth factor (VEGF). These proangiogenic factors are produced by both cancer cells and by other types of cells in the local environment. A number of naturally occurring inhibitors of angiogenesis, including angiostatin and thrombospondin, also have been described.
The development of antiangiogenesis approaches to cancer therapy have generated considerable excitement (54). Promising results have been noted using anti-VEGF approaches in intraperitoneal ovarian cancer mouse models (55). Currently, the clinical utility of monoclonal antibodies that block the VEGF receptor (*Avastin*) and other approaches—such as administration of antiangiogenic compounds—are being tested in clinical trials. 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

Part of "1 - Biology and Genetics "
Gynecologic cancers vary with respect to grade, histology, stage, response to treatment, and survival. **This clinical heterogeneity is attributable to differences in underlying molecular pathogenesis.** Some cancers arise in a setting of inherited mutations in cancer susceptibility genes, but most occur sporadically in the absence of a strong hereditary predisposition. The spectrum of genes that are mutated varies between cancer types. There also is significant variation with respect to the spectrum of genetic changes within a given type of cancer. **Cancers with a similar microscopic appearance may differ greatly at the molecular level.** In some instances, molecular features may be predictive of clinical phenotypes, such as stage, histologic type, and survival. As a more complete understanding of the clinical implications of various genetic alterations in gynecologic cancers is gained, **the molecular profile may prove valuable in predicting clinical behavior and response to treatment**.

Endometrial Cancer

Epidemiologic and clinical studies of endometrial cancer have suggested that there are two distinct types of endometrial cancer (56). **"Type I" cases are associated with unopposed estrogen stimulation and often develop in a background of endometrial hyperplasia.** Type I lesions are characterized by well-differentiated, endometrioid histology, early stage, and favorable outcome. **In contrast, "type II" cancers are poorly differentiated and/or nonendometrioid and are more virulent.** They often present at an advanced stage, and survival is relatively poor. In practice, not all cancers can be neatly characterized as either pure type I or II lesions, and endometrial cancers can also be viewed as a continuous spectrum with respect to etiology and clinical behavior. However, **as the genetic events involved in the development of endometrial cancer have been elucidated, it has been found that specific alterations often, but not always, are seen primarily in either type I or II cases** (Table 1.3).

Table 1.3 Genetic Alterations in Endometrial Adenocarcinomas

	Class	*Mechanism*	*Approximate Frequency*	*Type I/II**
Hereditary				
MSH2, *MLH1*, *PMS1*, *PMS2*, *MSH6*	DNA repair	Mutation	5%	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%	I/II
ß-*catenin*	Transcription factor	Mutation	10%	I
c-*myc*	Transcription factor	Amplification/overexpression	20%–30%	?
Tumor Suppressor Genes				
p53	Transcription factor	Mutation/overexpression	20%	II
PTEN	Phosphatase	Mutation/deletion	40%	I
MLH1	Mismatch repair	Promoter methylation	10%–20%	I
CDC2	Cell cycle	Mutation/deletion	15%	II

*Type I, well-differentiated, endometrioid, estrogen-associated cancers; Type II, poorly differentiated, nonendometrioid cancers.

Similar to other human cancers, endometrial cancers are believed to result from a series of genetic alterations. **About 5% of endometrial cancers occur in women with a strong hereditary predisposition that is due to germline mutations in DNA repair genes in the context of hereditary nonpolyposis colon cancer (HNPCC) syndrome.** A central unresolved issue in the understanding of endometrial carcinogenesis is the role of unopposed estrogenic stimulation. It has long been thought 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 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” that both promote carcinogenesis by stimulating proliferation and act as initiating agents by virtue of their carcinogenic metabolites.

Hereditary Endometrial Cancer

HNPCC typically manifests as familial clustering of early-onset colon cancer (57 ,58). There is also an increased incidence of several other types of cancers - most notably endometrial cancer in women. The risk of ovarian, stomach and biliary tract cancers also is somewhat increased. **The identification of the DNA mismatch repair genes responsible for HNPCC has facilitated the development of genetic testing** (59). Most HNPCC cases are due to alterations in *MSH2* and *MLH1*. *MSH6* mutations also are associated with an increased incidence of endometrial cancer (60). *PMS1* and *PMS2* have been implicated in a small number of these cancers as well. Loss of mismatch repair leads to a “mutator phenotype” in which there is accumulation of genetic mutations throughout the genome, particularly in repetitive DNA sequences called microsatellites. Examples of microsatellite sequences include mono (AAAA), di (CACACACA), and tri (CAGCAGCAGCAG) nucleotide repeats. **The propensity to accumulate mutations in microsatellite sequences is referred to as microsatellite instability** (MSI). Some microsatellite sequences are in noncoding areas of the genome, whereas others are within genes. It is thought that accumulation of mutations in microsatellite sequences of tumor suppressor genes may accelerate the process of malignant transformation.

The Amsterdam and Bethesda criteria have been developed to provide clinical guidelines for the diagnosis of HNPCC based on the spectrum of cancers noted in a family. These criteria are inexact, and genetic testing should be considered in all families suspected of

having HNPCC based on family history (58 ,61). Involvement of genetic counselors is often useful in facilitating this process. Analysis of cancers for MSI has been proposed as a genetic screening test for HNPCC. Among families with germline mutations in mismatch repair genes, MSI is seen in greater than 90% of colon cancers and about 75% of endometrial cancers (62 ,63). However, MSI is found in 20% to 25% of endometrial cancers (64) and 15% to 20% of colorectal cancers overall (65), and most of these cases are attributable to silencing of the *MLH1* gene as a result of promoter methylation (66 ,67). Presently, **mutational analysis of the responsible genes remains the gold standard for diagnosis of HNPCC** (59). Mutational analysis typically involves analysis of only *MSH2* and *MLH1*, which may overlook mutations in the other mismatch repair genes. About half of the families in which there is a strong suspicion of HNPCC will be found to have a germline *MLH1* or *MSH2* mutation (68).

Endometrial cancer is the most common extracolonic malignancy in women with HNPCC. **The risk of a woman developing endometrial cancer has ranged from 20% to 60%** in various reports (69 ,70 ,71), and in some studies this exceeds the risk of colon cancer. In addition, **the risk of ovarian cancer is increased to about 5% to 12%. The most striking clinical feature of HNPCC-related cancers is early onset**, typically at least 10 years earlier than sporadic cases. The average age of women with sporadic endometrial cancers is in the early 60s, whereas cancers that arise in association with HNPCC are often diagnosed before menopause (average age in the 40s) (69 ,72 ,73).

The clinical features of HNPCC associated endometrial cancers are similar to those of most sporadic cases (well differentiated, endometrioid, early stage), and survival is about 90% (72 ,74). **The mean age at onset of ovarian cancer in HNPCC families is in the early 40s, and the clinical features of these cancers generally are more favorable than sporadic cases** (75). They usually are early stage and well or moderately differentiated, and about 20% occur in the setting of synchronous endometrial cancers. However, analysis of groups of patients with synchronous cancers of the ovary and endometrium has revealed that few of these exhibit MSI and most probably are not attributable to HNPCC syndrome (76).

The optimal strategy for prevention of HNPCC associated mortality is unclear. Screening and surgical prophylaxis are both employed for colonic and extracolonic malignancies. Surveillance and prophylactic surgery should be considered early (between ages 25 and 35), generally 10 years before the earliest onset of cancer in other relatives who had an HNPCC related malignancy (73 ,77 ,78) (see Chapter 11).

Sporadic Endometrial Cancer

Cytogenetic studies have described gross chromosomal alterations in endometrial cancers, including changes in the number of copies of specific chromosomes (79). More recently, comparative genomic hybridization studies (CGH) have demonstrated areas of chromosomal loss and gain in both endometrial cancers and atypical hyperplasias (80 ,81). The most common sites of chromosomal gain are 1q, 8q, 10p, and 10q (82 ,83 ,84). Chromosomal losses also are frequently observed, both using CGH and in loss of heterozygosity studies (85).

A correlation has been noted between higher numbers of chromosomal alterations on CGH and more virulent clinical features (86). The overall number of chromosomal alterations detected using CGH is lower in endometrial cancers relative to other cancer types. Ploidy analysis simply measures total nuclear DNA content. **About 80% of endometrial cancers have a normal diploid DNA content as measured by ploidy analysis**. Aneuploidy occurs in 20% and is associated with advanced stage, poor grade, nonendometrioid histology, and poor survival (87). The frequency of aneuploidy (20%) is relatively low in endometrial cancers relative to ovarian cancers (80%). One might speculate that endometrial cancers more often present at an early stage than ovarian cancers

because they usually have a lower level of genetic aberrations, as opposed to the conventional wisdom that attributes the favorable outcome of endometrial cancers to earlier diagnosis.

Finally, patterns of genetic expression have been described using microarrays that distinguish between normal and malignant and between various histologic types (85 ,88). Different types of microarrays have been employed by various groups, and study results often cannot be compared directly. Thus far, predictive patterns defined in initial microarray studies have not been entirely reproducible from one lab to the next, but this approach has the potential to dramatically increase our understanding of the molecular pathogenesis of endometrial cancer and to enhance prediction of clinical phenotypes.

Tumor Suppressor Genes

Inactivation of the *p53* tumor suppressor gene is among the most frequent genetic events in endometrial cancers (30). Overexpression of mutant p53 protein occurs in about 20% of endometrial adenocarcinomas and is associated with several known prognostic factors including advanced stage, poor grade, and nonendometrioid histology (87 ,89). **Overexpression occurs in about 10% of stage I/II and 40% of stage III/IV cancers** (89). Numerous studies have confirmed the strong association between p53 overexpression, poor prognostic factors, and decreased survival (90 ,91 ,92 ,93 ,94 ,95 ,96). In some of these studies, p53 overexpression has been associated with worse survival even after controlling for stage (97 ,98). This suggests that loss of *p53* tumor suppressor function confers a particularly virulent phenotype. Although little is known regarding molecular alterations in uterine sarcomas, **overexpression of mutant *p53* occurs in a majority of mixed mesodermal sarcomas of the uterus (74%) and in some leiomyosarcomas** (99 ,100).

Endometrial cancers that overexpress p53 protein usually harbor missense mutations in exons 5 through 8 of the gene that result in amino acid substitutions in the protein (89 ,101 ,102 ,103 ,104). These mutations lead to loss of DNA binding activity. **Because *p53* mutations rarely, if ever, occur in endometrial hyperplasias** (101 ,105), **this likely represents a 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 “type II” endometrial cancer that does not transition through a phase of hyperplasia and is associated with rapid spread of disease. In a study of papillary serous carcinoma and its putative precursor (endometrial intraepithelial carcinoma), p53 overexpression was observed in 90% and 78% of cases, respectively (106).

Mutations in the *PTEN* tumor suppressor gene on chromosome 10q occur in about 30% to 50% of endometrial cancers (107 ,108 ,109), **and this represents the most frequent genetic alteration described thus far in these cancers**. Deletion of the second copy of the gene is also a frequent event, which results in complete loss of *PTEN* function. Most of these mutations are deletions, insertions, and nonsense mutations that lead to truncated protein products, whereas only about 15% are missense mutations that change a single amino acid in the critical phosphatase domain. **The *PTEN* gene encodes a phosphatase that opposes the activity of cellular kinases**. For example, it has been shown that loss of *PTEN* in endometrial cancers is associated with increased activity of the PI3 kinase with resultant phosphorylation of its downstream substrate Akt (110).

Mutations in the *PTEN* gene are associated with endometrioid histology, early stage, and favorable clinical behavior (111). Well-differentiated, noninvasive cases have the highest frequency of mutations. 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 “Type I” endometrial cancers (112). One group also has reported that loss of *PTEN* may occur in normal-appearing endometrial glands, and it is

proposed that this may represent the earliest event in endometrial carcinogenesis (113 ,114).

Synchronous endometrioid cancers are sometimes encountered in the endometrium and ovary that are indistinguishable microscopically. In some of these cases, identical *PTEN* mutations have been identified, suggesting that the ovarian tumor represents a metastasis from the endometrium (115). In other cases, the *PTEN* mutation seen in the endometrial cancer was not found in the ovarian tumor, suggesting that these represent two distinct primary cancers. ***PTEN* mutations also have been observed in about 20% of endometrioid ovarian cancers that arise in the absence of endometrial cancers** (116).

Inherited mutations in DNA mismatch repair genes are responsible for the HNPCC syndrome. Cancers that arise in these individuals are characterized by mutations in multiple microsatellite repeat sequences throughout the genome. This microsatellite instability also has been seen in about 20% of sporadic endometrial cancers (117 ,118). **Endometrial cancers that exhibit microsatellite instability tend to be type I cancers**. Because microsatellite instability has been noted in some sporadic endometrial cancers in women who do not carry germline DNA repair gene mutations (117), several groups have attempted to identify acquired somatic mutations in these genes. **DNA repair gene mutations have been identified in only a minority of endometrial cancers with microsatellite instability** (64 ,119). Loss of mismatch repair in these cases appears to be most often due to silencing of the *MLH1* gene by way of promoter methylation (66 ,67). **Methylation of the *MLH1* promoter also has been noted in endometrial hyperplasias (**118 ,120 **) and normal endometrium adjacent to cancers, suggesting that this is an early event in the development of some of these cancers** (121). It is thought that global changes in methylation that result in decreased expression of a number of tumor suppressor and DNA repair genes may be a characteristic of some endometrial cancers, particularly type I cases (26 ,122). Loss of DNA mismatch repair may accelerate the process of malignant transformation by facilitating accumulation of mutations in microsatellite sequences present in genes involved in malignant transformation.

Finally, **mutations in the *CDC4* gene, which is involved in regulating cyclin E expression during cell cycle progression, have been noted in 16% of endometrial cancers** (123). Mutations were accompanied by loss of the wild-type allele and were more common in cancers with poor prognostic factors, such as high grade and lymph node metastases. It is postulated that *CDC4* may act as a tumor suppressor by restraining the activity of cyclin E in promoting progression from G_1 to S phase.

Oncogenes

Alterations in some oncogenes have been demonstrated in endometrial cancers, but this occurs less frequently than inactivation of tumor suppressor genes (Table 1.3). **Increased expression of the HER-2/*neu* receptor tyrosine kinase has been noted in 10% to 15% of endometrial cancers** (94 ,124 ,125 ,126 ,127) and is associated with advanced stage and poor outcome. In a study of HER-2/*neu* expression in 247 endometrial cancers (125), expression was scored as high in 15% of cases, moderate in 58%, and absent in 27%; disease-free survival was 56%, 83%, and 95% in these groups, respectively. Among stage I cases, 13% had high expression of HER-2/*neu*, and progression-free survival 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. Papillary serous endometrial cancers most frequently overexpress HER-2/*neu***, and it has been suggested that this might represent an appealing therapeutic target (128). The levels of HER-2/*neu* overexpression in endometrial cancers are much less striking than in breast cancers, however, and thus far there is no evidence that Herceptin (anti HER-2/*neu* antibody) is of therapeutic benefit in endometrial cancer.

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** (129 ,130). 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 (131). 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 (132).

The *ras* oncogenes undergo point mutations in codons 12, 13, or 61 that result in constitutively activated molecules in many types of cancers. Initially, these codons of the K-*ras*, H-*ras*, and N-*ras* genes were examined in 11 immortalized endometrial cancer cell lines (133). Mutations in codon 12 of K-*ras* were seen in four cell lines, whereas three had mutations in codon 61 of H-*ras*. **Subsequent studies of primary endometrial adenocarcinomas have confirmed that codon 12 of K-*ras* is mutated in about 10% of American cases and 20% of Japanese cases** (101 ,134 ,135 ,136 ,137 ,138 ,139 ,140). These mutations occur more often, but not exclusively, in type I endometrial cancers. K-*ras* mutations also have been identified in some endometrial hyperplasias (135 ,140 ,141), which suggests that **this may be a relatively early event in the development of some type I cancers.**

E-cadherin is a transmembrane glycoprotein involved in cell–cell adhesion, and decreased expression in cancer cells is associated with increased invasiveness and metastatic potential (Fig. 1.7). E-cadherin mutations occur only rarely in endometrial cancers (41), but cadherin expression may also be down-regulated in the absence of mutations (40 ,142). The cytoplasmic tail of E-cadherin exists as a macromolecular complex with the ß-*catenin* and *APC* gene products, which link it to the cytoskeleton. It appears that a critical function of the *APC* tumor suppressor gene is to regulate phosphorylation of serine and threonine residues (codons 33, 37, 41, 45) in exon 3 of ß-*catenin*, which results in degradation of ß-catenin. Mutational inactivation of *APC* allows accumulation of ß-catenin, which translocates to the nucleus and acts as a transcription factor to induce expression of cyclin D1 and perhaps other genes involved in cell cycle progression (40). Germline *APC* mutations are responsible for the adenomatous polyposis coli syndrome, and somatic mutations are common in sporadic colon cancers; but *APC* mutations have not been described in endometrial cancers (43 ,143). The *APC* gene may be inactivated in some endometrial cancers because of promoter methylation (144). In addition, it has been shown that missense mutations in exon 3 of ß-*catenin* lead to the same end result—namely, abrogation of the ability of *APC* to induce ß-catenin degradation—which results in abnormal transcriptional activity. In view of this, the ß-*catenin* gene is considered an oncogene (145). ***ß-catenin* mutations have been observed in several types of cancers, including hepatocellular, prostate, and endometrial cancers. Mutation of *ß-catenin* occurs in about 10% to 15% of endometrial cancers**, but abnormal accumulation of ß-catenin protein occurs in about one-third of cases, suggesting that mechanisms other than mutation might be involved in some cases (44 ,143).

Among 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. C-*myc* is expressed in normal endometrium (146) with higher expression in the proliferative phase. **Several studies have suggested that *myc* may be amplified in a fraction of endometrial cancers** (127 ,147 ,148).

Ovarian Cancer

About 10% of ovarian cancers arise in women who carry germline mutations in cancer susceptibility genes, predominantly *BRCA1* or *BRCA2* (Fig. 1.8). The vast majority of ovarian cancers are sporadic and arise because of accumulation of genetic damage.

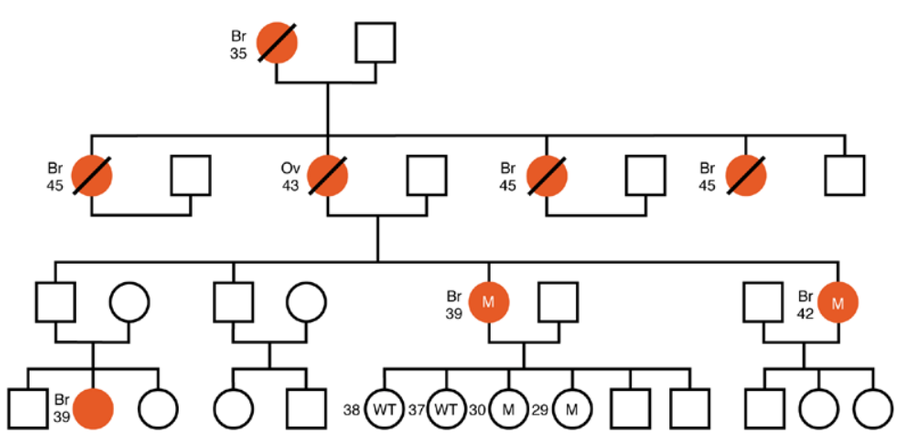

Figure 1.8 Familial Ovarian cancer pedigree with *BRCA1* mutation. The age of family members and type of cancers are noted. **Solid circles** represent individuals affected with cancer, and **slashes** denote those who have died of cancer. Individuals denoted *M* have the 5382 insert C mutation in *BRCA1*, whereas those denoted WT have normal *BRCA1*.

The causes of acquired genetic alterations in the ovarian epithelium remain uncertain, but exogenous carcinogens, with the possible exception of talc, have not been strongly implicated. Some mutations may arise spontaneously because of increased epithelial proliferation required to repair ovulatory defects. Oxidative stress and free radical formation that are due to inflammation and repair at the ovulatory site may also contribute to accumulation of DNA damage. **Regardless of the mechanisms involved, reproductive events that decrease lifetime ovulatory cycles** (e.g., pregnancy and birth control pills) **are protective against ovarian cancer** (149) (see Chapter 11).

The protective effect of these factors is greater in magnitude than one would predict based on the extent that ovulation is interrupted, however. **Five years of oral contraceptive use provides a 50% risk reduction** while only decreasing total years of ovulation by less than 20% (see Chapter 11). 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 (150). The action of other reproductive hormones such as estrogens, androgens, and gonadotropins also may contribute to the development of ovarian cancers.

Epithelial ovarian cancers are heterogeneous with respect to behavior (borderline vs. invasive) **and histologic type** (serous, mucinous, endometrioid, clear cell). Although the strongest epidemiologic risk factors (e.g., parity) affect risk of all disease subsets, differences have been observed with respect to etiology and molecular alterations. For example, although it is thought that serous ovarian cancers arise from epithelial cells on the surface of the ovary or in underlying inclusion cysts, **many endometrioid and clear cell cancers likely develop in deposits of endometriosis.** Likewise, differences in the pattern of genetic alterations have been noted between serous and endometrioid/clear cell ovarian cancers. As our understanding of the molecular pathogenesis of ovarian cancer continues to mature, it is likely that the various disease subsets will increasingly be thought of as distinct entities that are defined by characteristic patterns of molecular signatures. **Elucidation of the molecular basis for the clinical heterogeneity of ovarian**

cancer has the potential to facilitate improvements in diagnosis, treatment, and prevention in the future.

Hereditary Ovarian Cancer

The *BRCA1* gene was identified on chromosome 17q in 1994 and *BRCA2* was identified on chromosome 13q in 1995. Inherited mutations in these two breast/ovarian cancer susceptibility genes are responsible for about 6% and 3% of ovarian cancers, respectively (151). Inherited mutations in the DNA mismatch repair genes involved in HNPCC that are described in the section on hereditary endometrial cancer are responsible for about 1% of ovarian cancer cases. **The vast majority of *BRCA*-associated ovarian cancers are papillary serous** (152 ,153 ,154), **as are most peritoneal and fallopian tube cancers and some uterine cancers.** Although there are conflicting reports regarding whether *BRCA* mutations increase the risk of serous cancers of the uterus (155 ,156), the evidence to support inclusion of serous fallopian tube cancers in this syndrome is stronger (157 ,158). In two studies, *BRCA* mutations were found in 28% (159) and 17% (160) of women with fallopian tube cancer. Likewise, **germline *BRCA* mutations have been reported in about one-third of patients with primary peritoneal cancer** (160 ,161).

The finding that *BRCA1* and *BRCA2* complex with Rad51 and other proteins involved in repair of double-stranded DNA breaks suggests a role for these genes in this process (162 ,163). *BRCA1* and *2* have been classified as tumor suppressor genes, because the nonmutated copy is invariably deleted in breast and ovarian cancers that arise in women who inherit a mutant gene. In some studies, survival of *BRCA* carriers with ovarian cancer was better than that of sporadic cases that were matched for age, stage, and other prognostic factors (164). Not all subsequent studies have confirmed this favorable prognosis (165), but none of the studies performed to date is large enough to be definitive (see Chapter 11).

***BRCA1* and *2* both are associated with 60% to 90% lifetime risks of breast cancer, and this begins to manifest before age 30** (see Chapter 11 **for complete discussion of clinical issues)**. ***BRCA2* also increases the risk of breast cancer in men. The most recent estimates of the lifetime risk of ovarian cancer range from 20% to 56% in *BRCA1* carriers and 10% to 20% in *BRCA2* carriers, but this increased risk is not manifest until about age 40** (166 ,167 ,168 ,169 ,170).

It is unclear why only a fraction of women who carry *BRCA1* mutations develop ovarian cancer. It has been postulated that incomplete penetrance may be due to the effect of modifying genes or to genetic-environmental interactions (e.g., birth control pill use) (171). In some series, mutations in the carboxy terminus of *BRCA1* have been associated with a higher frequency of breast cancer relative to ovarian cancer (172). Conversely, mutations in the proximal amino end of the gene resulted in a higher likelihood of developing ovarian cancer. Likewise, some studies have suggested that ovarian cancer may occur more often in families with truncation mutations in exon 11 of *BRCA2* (173 ,174). Further studies are needed to examine whether a genotypic-phenotypic correlation exists.

BRCA1 and *2* mutations are rare and are carried by fewer than 1 in 500 individuals in most populations, but there are some notable exceptions (175). Founder mutations that presumably arose thousands of years ago in a single ancestor have been identified in some ethnic groups. **The most common founder mutations described thus far are the *BRCA1* 185delAG and *BRCA2* 6174delT mutations, which occur in about 1.0% and 1.4% of Ashkenazi Jews, respectively** (176 ,177 ,178). The high frequency of these mutations implies that they likely arose about 100 generations ago. A third less common founder mutation (*BRCA1* 5382insC) also has been noted in the Ashkenazi population. Because about 1 in 40 Ashkenazi individuals carries a *BRCA* founder mutation and testing for this panel of specific mutations is much less expensive, the threshold for genetic testing is much lower in this population.

Because mutations in *BRCA1* and *2* in the general population occur throughout the entire coding sequence, **the most reliable method of detecting mutations is complete genetic sequencing.** The effort and cost involved in sequencing these large genes are relatively high, however, and presently it remains impractical to perform mutational analysis in low-risk individuals. **The probability of finding a *BRCA1* or *2* mutation in a woman older than age 50 who is the only individual 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% (174 ,179). **When a specific mutation is identified in an affected individual, others in the family can be tested much more rapidly and inexpensively for that specific mutation.** Most deleterious *BRCA* mutations encode truncated protein products, but missense mutations that alter a single amino acid have been found to segregate with breast and/or ovarian cancer in some families (180).

In a significant fraction of high-risk families, *BRCA* testing reveals sequence variants of uncertain significance or no detectable alterations. and these results represent a counseling dilemma (181 ,182 ,183 ,184). Failure to identify a *BRCA1* or *2* 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 (185 ,186 ,187).

Peritoneal papillary serous carcinoma, indistinguishable histologically or macroscopically from ovarian cancer, has been described in rare instances following prophylactic oophorectomy (188 ,189 ,190). These reports preceded the identification of *BRCA1* and *2*, however, and it is unclear what fraction of these women were mutation carriers. The origin of primary peritoneal cancers after prophylactic bilateral salpingo-oophorectomy (BSO) is uncertain, and case reports have been published in which retrospective examination of the ovaries has revealed occult ovarian cancers that were not recognized by the pathologist (191). Thus, **some cancers thought to originate in the peritoneal cavity may actually represent recurrences of occult ovarian cancer**.

Some reports have noted an increased frequency of abnormalities in the ovarian epithelium (invaginations, inclusion cysts, stratification, and papillations) in *BRCA* carriers (192), but other studies have not confirmed the presence of a consistent pattern of premalignant histologic features (193 ,194). **Careful examination of prophylactic salpingo-oophorectomy specimens has led to the identification of occult cancers in as many as 12% of women in some series** (195 ,196). This adds support to the theory that primary peritoneal cancers that occur years after BSO may represent recurrences of ovarian cancer. Malignant cells also have been found in pelvic peritoneal washings from women undergoing prophylactic BSO (3/35 cases), and in some of these cases, a primary cancer in the ovary has not been identified (197). **Early-stage fallopian tube cancers also have been found in *BRCA1* carriers undergoing prophylactic BSO** (198). In one study, two women with occult fallopian tube cancer also had positive pelvic peritoneal cytology and received adjuvant chemotherapy (198). In view of these data, it seems reasonable to **recommend that cytologic washings of the pelvis be obtained routinely in concert with prophylactic BSO**. Finally, the pathologist must be informed of the indication for prophylactic BSO, and **multiple sections of the fallopian tubes and ovaries should be examined** to exclude the presence of occult carcinoma.

Sporadic Ovarian Cancer

Global Genomic Changes

Invasive epithelial ovarian carcinoma generally is a monoclonal disease that develops as a clonal expansion of a single transformed cell in the ovary (199). There is evidence that some serous borderline tumors (126), as well as cancers that arise in the peritoneum of patients with *BRCA1* mutations, may be polyclonal, however (200). Most

ovarian cancers are characterized by a high degree of genetic damage that is manifest at the genomic and molecular levels. Gains and losses of various segments of the genome have been demonstrated using comparative genomic hybridization (CGH) (201). Likewise, loss of heterozygosity (LOH), indicative of deletion of specific genetic loci, also has been demonstrated to occur at a high frequency on many chromosomal arms (202). It is unclear whether the wide range of genetic alterations in ovarian cancers reflects the need to alter several genes in the process of malignant transformation or is the result of generalized genomic instability.

Both CGH and LOH studies have shown that advanced-stage, poorly differentiated cancers have a higher number of genetic changes than early-stage, low-grade cases (203 ,204 ,205). This finding could be interpreted as reflective of the fact that the number of genetic changes accumulates with progression from an early to an advanced cancer. Alternatively, advanced-stage cancers may be intrinsically more virulent even in their early stages by virtue of their specific mutations and/or increased genomic instability. If this latter theory is correct, early- and advanced-stage ovarian cancers could be thought of as different diseases rather than as steps in a progressive pathway. This could have significant implications for the early diagnosis, treatment, and prevention of ovarian cancer.

It is estimated that the human genome contains about 30,000 genes. Recently, microarray chips that contain sequences complementary to thousands of genes have been created that allow global assessment of the level of expression of each gene. Expression arrays have proven useful in predicting clinical phenotypes in several types of solid tumors. Several groups have applied expression array technology to the analysis of ovarian cancers. Many of these studies have compared genetic expression between normal ovarian epithelial cells and ovarian cancers. **Numerous genes have been identified that appear to be up- or down-regulated in the process of malignant transformation** (206 ,207 ,208). In addition, microarrays have demonstrated patterns of genetic expression that distinguish between histologic types (209) and between early- and advanced-stage cases (208 ,210).

Tumor Suppressor Genes

Alteration of the *p53* tumor suppressor gene is the most frequent genetic event described thus far in ovarian cancers (Table 1.4) (211 ,212 ,213 ,214 ,215 ,216 ,217 ,218). The frequency of overexpression of mutant *p53* is significantly higher in advanced-stage (40% to 60%) relative to early-stage cases (10% to 20%). The histologic distribution of early- and advanced-stage cases varies significantly, however, and may in part account for the differences in p53 mutation rate. **The frequency of *p53* mutations is highest in serous and endometrioid ovarian cancers.** Mutations in p53 are a less prominent feature of clear cell cases (219 ,220).

Table 1.4 Genetic Alterations in Epithelial Ovarian Cancers

	Class	*Mechanism*	*Approximate Frequency*	*Comments*
Hereditary				
BRCA1	Double-stranded DNA repair	Mutation/deletion	6%	Breast/ovarian syndrome
BRCA2	Double-stranded DNA repair	Mutation/deletion	3%	Breast/ovarian syndrome
MSH2/MLH1	DNA mismatch repair	Mutation/deletion	1%	HNPCC syndrome
Sporadic Oncogenes				
HER-2/*neu*	Tyrosine kinase	Amplification/overexpression	5%–10%	Gene amplification rare
K-*ras*	G protein	Mutation	5%	Common in serous borderline
AKT2	Serine/threonine	Amplification	5%–10%	
PIK3CA	Tyrosine kinase	Amplification	5%–10%	
c-*myc*	Transcription factor	Amplification/overexpression	20%–30%	
Tumor Suppressor Genes				
p53	Transcription factor	Mutation/deletion methylation	50%–70%	Most common in invasive cancers
p16	cdk inhibitor	Deletion, promoter	15%	
p21, p27	cdk inhibitor	Promoter methylation	10%–40%	
BRCA1	Double-stranded DNA repair	Promoter methylation	10%	

The higher frequency of *p53* alteration in advanced-stage cases may indicate that this is a “late event” in ovarian carcinogenesis. Alternatively, it is possible that loss of p53 confers an aggressive phenotype associated with more rapid progression. There is a suggestion that overexpression of mutant p53 protein may be associated with slightly worse survival in advanced stage ovarian cancers (211 ,213 ,214 ,215 ,217 ,218 ,221 ,222). Finally, although there is a high concordance between *p53* missense mutations in exons 5 through 8 and protein overexpression, about 20% of advanced ovarian cancers contain mutations that result in truncated protein products, which usually are not overexpressed (212 ,222). Some of these mutations may lie outside of exons 5–8. **Overall, about 70% of advanced ovarian cancers have either missense or truncation mutations in the *p53* gene**. Most *p53* missense mutations are transitions rather than transversions (223 ,224), which suggests that these mutations occur spontaneously, rather than as a result of exogenous carcinogens.

Several studies have examined the correlation between chemosensitivity and *p53* mutation in ovarian cancers *in vitro* (225 ,226 ,227 ,228 ,229 ,230). 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 just one of a multitude of factors that determines chemosensitivity.

Overexpression of p53 is rare in stage I serous borderline tumors, but occurs in as many as 20% of advanced-stage borderline cases (231 ,232). In a study of advanced serous borderline tumors, p53 overexpression was associated with a sixfold higher risk of death (232). In some cases, invasive serous cancers may arise following an earlier diagnosis of borderline tumor. The *p53* mutational status was not concordant between the original borderline tumor and the subsequent invasive cancer (233). This suggests that the invasive cancer either arises independently or as a clonal outgrowth within the original tumor.

Although mutations in the *Rb* tumor suppressor gene are not a common feature of ovarian cancers, recent evidence suggests that inactivation of *Rb* greatly enhances tumor formation in ovarian cells with *p53* mutations (234). In a mouse model in which these genes were inactivated in the ovarian epithelium, few cancers developed in response to loss of either *p53* or *Rb* alone. When both genes were inactivated, epithelial ovarian cancers with serous features developed in almost all cases. Given that *Rb* mutations are rare in ovarian cancers, it is possible that inactivation of one of a number of genes in the *Rb* pathway can initiate transformation cooperatively with *p53*. Inactivation of *Rb* itself may not be requisite.

This mouse model of ovarian cancer has the potential to add greatly to our understanding of epithelial ovarian carcinogenesis. A notable feature of this model is the development of dysplastic premalignant epithelium. Although ovarian dysplasia has long been thought to represent the precursor of serous ovarian cancers (235) and is an appealing target for early detection and prevention (236), the inaccessibility of the ovaries has presented a significant obstacle to studying its natural history. The ability to track the development of preinvasive and invasive lesions in this new mouse model presents the

opportunity to develop chemopreventive approaches in a setting that appears similar to human ovarian carcinogenesis.

The cyclin-dependent kinase (cdk) inhibitors act as tumor suppressors by virtue of their inhibition of cell cycle progression from G_1 to S phase. Expression of several cdk inhibitors appears to be decreased in some ovarian cancers. ***p16* undergoes homozygous deletions in about 15% of ovarian cancers** (237). There is evidence to suggest that *p16* (238) and some other tumor suppressor genes such as *BRCA1* (239 ,240 ,241) may be inactivated via transcriptional silencing that is due to promoter methylation rather than mutation and/or deletion. Likewise, **decreased expression of the p21 cdk inhibitor has been noted in a significant fraction of ovarian cancers** despite the absence of inactivating mutations (242 ,243). **Loss of the p27 cdk inhibitor also may occur and correlates with poor survival** (244 ,245 ,246 ,247).

Normal ovarian epithelial cells are inhibited by the growth inhibitory peptide TGF-ß, whereas most immortalized ovarian cancer cell lines are unresponsive (248 ,249). The effect of TGF-ß on primary ovarian cancer cells obtained directly from patients is less straightforward. **Thus far, it has not been convincingly demonstrated that derangement of the TGF-ß pathway plays a role in the development of ovarian cancers** (249 ,250 ,251).

Oncogenes

Ovarian cancers produce and/or are capable of responding to various peptide growth factors. For example, **epidermal growth factor (EGF)** (252) **and transforming growth factor-alpha (TGF-α)** (253) **are produced by some ovarian cancers** that also express the receptor that binds these peptides (EGF receptor) (254 ,255). **Some cancers produce insulinlike growth factor-1 (IGF-1), IGF-1 binding protein, and express type 1 IGF receptor** (256). **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 (248 ,257 ,258). In addition, **ovarian cancers produce basic fibroblast growth factor (FGF) and its receptor**, and basic FGF acts as a mitogen in some ovarian cancers (259). **Ovarian cancers produce macrophage-colony stimulating factor (M-CSF)**, and serum levels of M-CSF are elevated in some patients (260). Because the M-CSF receptor (*fms*) is expressed by many ovarian cancers, this could comprise an autocrine growth stimulatory pathway in some cancers (261). Ascites of patients with ovarian cancer also contain phospholipid factors, such as LPA, that stimulate proliferation and invasiveness of ovarian cancer cells (262). The edg-2 G-protein coupled receptors act as functional receptors for LPA. The finding that neutralization of LPA activity decreases growth and increases apoptosis of ovarian cancers suggests that manipulation of this pathway may be therapeutically beneficial (263).

Normal ovarian epithelial cells produce and are responsive to many of the same peptide growth factors as malignant ovarian epithelial cells (255 ,264 ,265 ,266). Thus, it remains unclear whether alterations in expression of growth factors are critical early events involved in the development of ovarian cancers. It is possible that growth factors may primarily act as “necessary but not sufficient” cofactors that support growth and metastasis following malignant transformation.

The HER-2/*neu* tyrosine kinase is a member of a family of related transmembrane receptors that includes the EGF receptor (267). **Expression of HER-2/*neu* is increased in a fraction of ovarian cancers**, and overexpression has been associated with poor survival in some (268 ,269), but not all (270 ,271), studies. Unlike breast cancers, ovarian cancers that exhibit HER-2/*neu* overexpression rarely have high-level gene amplification. **Monoclonal antibodies that interact with HER-2/*neu* can decrease growth of breast and ovarian cancer cell lines that overexpress this receptor** (272 ,273). Although

anti–HER-2/*neu* antibody therapy (Herceptin) is active against breast cancer (274), a study performed by the Gynecologic Oncology Group found only 11% of ovarian cancers exhibited significant HER-2/*neu* overexpression (275). The response rate to single-agent Herceptin therapy was disappointingly low (7.3%).

Mutations in the *ras* genes are rare in invasive serous ovarian cancers (136 ,276 ,277 ,278 ,279). Although K-*ras* mutations have been noted in about 50% of mucinous ovarian cancers and some clear cell cases, these tumors compose only a small fraction of epithelial ovarian cancers. **In contrast, K-*ras* mutations are common in borderline serous ovarian tumors**, occurring in 20% to 50% of cases (280 ,281). This is supportive of the hypothesis that the molecular pathology of borderline tumors differs from that of invasive ovarian cancers.

Cytoplasmic kinases relay mitogenic signals from receptor tyrosine kinases and G proteins on the cell membrane toward the nucleus. The region of chromosome 3p26 that includes the phosphatidylinositol 3-kinase (*PIK3CA*) has been shown to be amplified in some ovarian cancer cell lines using comparative genomic hybridization (282). In addition, the *AKT2* serine/threonine kinase also has been shown to be amplified and overexpressed in some ovarian cancers (283). *PIK3CA* and *AKT2* kinase activity is opposed by the *PTEN* phosphatase. *PTEN* mutations may be uncommon in ovarian cancers because amplification of *PIK3CA* or *AKT2* in some cases abrogates the need for loss of this tumor suppressor.

***Β-catenin* mutations are present in about 30% of endometrioid ovarian cancers** (284), but not other histologic types. This provides further evidence of the molecular heterogeneity of the various histologic types of ovarian cancer. In some endometrioid ovarian cancers with abnormal nuclear accumulation of β-catenin that lacked mutations, the *APC, AXIN1*, or *AXIN2* genes that regulate β-catenin activity were found to be mutated (284). This suggests that alterations in the wnt signaling pathway maybe a feature of endometrioid ovarian cancers.

Increased activity of nuclear transcription factors also may enhance malignant transformation. Amplification of the c-*myc* oncogene has been reported to occur in about 30% of ovarian cancers (285 ,286 ,287 ,288 ,289 ,290). Despite these reports of gene amplification, evidence of c-*myc* protein overexpression has been less convincing. Some ovarian cancers have been reported to have increased expression of cyclin E, which is involved in cell cycle progression (291 ,292).

Cervical Cancer

Molecular and epidemiologic studies have demonstrated that sexually transmitted human papillomavirus (HPV) infections play a role in almost all cervical dysplasias and cancers (293 ,294 ,295 ,296) (see Chapter 8). HPV infection also is involved in the development of some dysplasias and cancers of the vagina and vulva. The peak incidence of HPV infection is in the 20s and 30s, and the incidence of cervical cancer increase from the 20s to a plateau between ages 40 and 50. Although HPV plays a major role in the development of most cervical cancers, only a small minority of women who are infected develop invasive cervical cancer. This suggests that other genetic and/or environmental factors also are involved in cervical carcinogenesis. For example, **individuals who are immunosuppressed, either because of human immunodeficiency virus (HIV) infection** (297) **or immunosuppressive drugs, are more likely to develop dysplasia and invasive cervical cancer following HPV infection.**

Cervical screening programs in developed nations have dramatically reduced both the incidence of invasive cervical cancer and disease-related mortality in the twentieth century. The recent report that an HPV 16 vaccine was highly effective in preventing HPV infection and dysplasia provides exciting evidence of the potential utility of this approach in the future (298).

Human Papillomavirus Infection

There are more than 80 HPV subtypes, but not all infect the lower genital tract. HPV 16 and 18 are the most common types associated with cervical cancer and are found in more than 80% of cases (see Chapter 8). Types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 should be considered high-risk types, and types 26, 53, and 66 should be considered probably carcinogenic (296). Low-risk types that may cause dysplasias or condyloma in the lower genital tract, but rarely cause cancers, are types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81.

The HPV DNA sequence consists of 7,800 nucleotides divided into “early” and “late” open reading frames (ORFs). “Early” ORFs are within the first 4,200 nucleotides of the genome and encode proteins (E1–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.

Examination of the biological 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. 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 epidermal growth factor receptors or platelet factor growth receptors. **The E6 and E7 oncoproteins are the main transforming genes of oncogenic strains of HPV** (Fig. 1.9) (299). 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 (CKII) 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 CKII mutation, implying a role for this binding site in the development of HPV-mediated neoplasias.

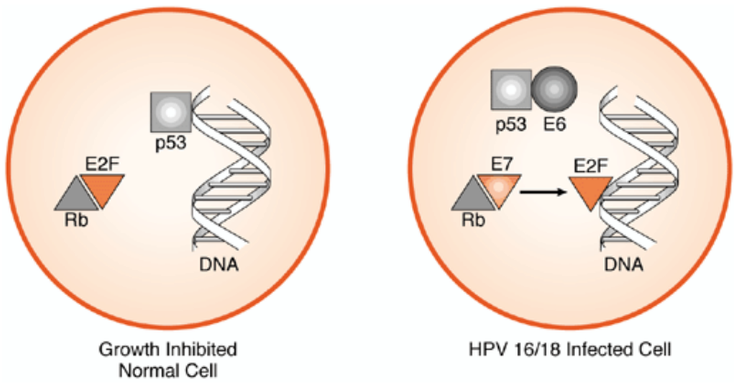

Figure 1.9 Neutralization of p53 and Rb by HPV 16/18 in cervical cancer.

The E6 proteins of oncogenic HPV subtypes bind to and inactivate the p53 tumor suppressor gene product (300 ,301). 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.

HPV negative cervical cancers are uncommon, but have been reported to exhibit overexpression of mutant p53 protein (302). This suggests that inactivation of the *p53* tumor suppressor gene either by HPV E6 or by mutation is a requisite event in cervical carcinogenesis.

Genomic Changes

Comparative genomic hybridization techniques have been used to identify chromosomal loci that are either increased or decreased in copy number in cervical cancers. **A strikingly consistent finding of various studies is the high frequency of gains on chromosome 3q in both squamous cell cancers (**303 ,304 ,305 ,306 ,307 ,308 **) and adenocarcinomas** (309). Other chromosomes that exhibit frequent gains include 1q and 11q. The most common areas of chromosomal loss include chromosomes 3p and 2q. For the most part, with the exception of the *FHIT* gene on chromosome 3p, it has not been proven that these genomic gains and losses result in the recruitment of specific oncogenes and tumor suppressor genes in the process of malignant transformation. It is conceivable that these chromosomal alterations may be frequent sequelae of infection with oncogenic HPVs while playing no significant role in the pathogenesis of cervical cancers. Abnormalities seen in invasive cancers using comparative genomic hybridization also have been identified in high-grade dysplasias, however, suggesting that these are early events in cervical carcinogenesis (304 ,307 ,310).

Oncogenes and Tumor Suppressor Genes

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 (302 ,311 ,312 ,313 ,314). **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 cervix cancers (315). 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. In some studies, amplification correlated with poor prognosis in early-stage cases (316). Further studies are needed to clarify the role of *ras* genes, c-*myc*, and other oncogenes in cervical carcinogenesis.

The fragile histidine triad (*FHIT*) gene localized within human chromosomal band 3p14.2 **is frequently deleted in many different cancers, including cervical cancer** (317 ,318 ,319).

Decreased expression of this putative tumor suppressor gene is an early event in some cervical cancers (319 ,320). In one study, FHIT protein expression was markedly reduced or absent in 71% of invasive cancers, 52% of HSILs associated with invasive cancer, and 21% of HSILs without associated invasive cancer (319). In addition, reduced expression is associated with poor prognosis in advanced cervical cancers (321).

As is the case in endometrial and ovarian cancers, it is thought that gene silencing that is due to promoter hypermethylation also may play a role in cervical carcinogenesis (322 ,323). In this regard, the *RASSF1A* gene is located on chromosome 3p21.3 in an area that is frequently a site of deletions in cervical cancer. This gene is thought to be involved in *ras*-mediated signal transduction pathways. Although mutations in *RASSF1A* do not occur in cervical cancers, inactivation of the gene as a result of promoter methylation occurs in a fraction of cases, particularly adenocarcinomas (324 ,325).

Molecular analyses can readily be performed using cell pellets obtained from liquid based Pap smears. This promises to facilitate future investigation of the role of promoter methylation and other alterations in the molecular pathogenesis of cervical cancer (326).

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 generally 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 about 1%, women who have had two molar pregnancies have about a 25% risk of developing another mole. Although this suggests a hereditary defect that affects gametogenesis, this remains speculative. Thus far **there is no convincing 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
Ian J. Jacobs

One of the established strategies for combating cancer in the twenty-first century is screening the asymptomatic population for premalignant conditions and early-stage disease. **These screening strategies are based on criteria laid down by the WHO** (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 ,4).

Table 2.1 World Health Organization Criteria for a Screening Program

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, Jungner G.** *WHO Principles and practise of screening for disease.* Geneva: World Health Organization, 1968:66–67.

Ovarian cancer is the other gynecological 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 increase long-term survival. In a randomized controlled trial of ovarian cancer screening using a screening strategy incorporating sequential CA125 and transvaginal ultrasound, median survival was significantly increased in women with ovarian cancer in the screened group (72.9 months) when compared with the control group (41.8 months) (6).

Mass screening for endometrial cancer is unlikely to be of benefit as women present in early stages with symptomatic disease. However, screening of “high-risk” populations is recommended (7). Vaginal and vulval cancers are too rare to justify screening, although it is important to raise the awareness of these conditions among the elderly population.

Screening of cancers is based on detection of tumor markers. The term *tumor marker* **is ill-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; cytological, 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. As the study of the human “proteome” gains momentum, evidence is

rapidly accumulating to show that global nondirected screening strategies can produce novel tumor markers to complement those previously identified by candidate gene or antibody-based approaches. 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 it 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 form the bulk of serum markers in clinical use.** Most of them were initially thought to be highly tumor specific but subsequently found to be produced in normal physiological states as well as in benign and other malignant diseases. The most useful among those described are the macromolecular tumor antigens, which are either enzymes, hormones, receptors, growth factors, biological response modifiers, or glycoconjugates (8).

Evaluation of exfoliated cells has been in use for many decades. In gynecology, the cervical screening program is based on nucleocytoplasmic changes detected on microscopy of Papanicolaou stained cells obtained from cervical sampling. These changes do not entirely fulfill the criteria for true tumor markers as their presence usually denotes an underlying premalignant condition—cervical intraepithelial neoplasia rather than frank malignancy. **There are now an increasing number of sophisticated molecular techniques available for examining exfoliated cells for key events associated with the carcinogenesis, including presence of "high risk" human papillomavirus (HPV) DNA, telomerase activity, and K-ras mutation.**

Cancers possess some morphological 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 as it has minimal side effects and provides detailed tumor morphology, which can be quantified using a variety of scoring systems. **Detailed characterization of**

morphology 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 decreased resistance in the thin walled new vessels in ovarian and endometrial cancers. Colposcopy exploits the same phenomenon in an entirely different manner: 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 is used to define the population—in the United Kingdom, currently the screening guidelines are being revised to limit screening to women between the ages of 25 and 64 years. Risk groups for sporadic ovarian cancer are defined by postmenopausal status and age (≥50) and for hereditary ovarian malignancy by family history criteria and presence of *BRCA1* or *BRCA2* mutations. Increased risk based on family history is also the basis of defining a target population for endometrial cancer screening (7).

- Ovarian and Fallopian Tube Cancer
- Endometrial Cancers
- Cervical Cancer

Ovarian and Fallopian Tube Cancer

Part of "2 - Tumor Markers and Screening "

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 (5). Biochemical, morphological, vascular, and cytological tumor markers have all been explored with varying success. There is as yet only preliminary evidence that ovarian cancer screening can reduce mortality (6). **Until a mortality impact has been reported, women in the general population should not be screened outside the context of research trials.**

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 coelomic epithelium. In the adult, it is found in tissue derived from coelomic epithelium (mesothelial cells of the pleura, pericardium, and peritoneum) and müllerian 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 (9). More recently, expression has been identified outside the female genital tract in epithelial cells of the lung, breast, conjunctiva, and glandular epithelium of the prostate gland (10).

CA125 was initially detected using a murine monoclonal antibody OC125 raised in response to immunologic challenge with an ovarian cancer cell line (11). Subsequently at least 26 other antibodies have been described (12). It is now known that **the CA125 antigen carries two major antigenic domains classified as A, the domain binding monoclonal antibody OC125, and B, a domain binding monoclonal antibody M11** (12). 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. Molecular analysis of the CA125 antigen has identified a mucin-type glycoprotein that is highly glycosylated with the protein moiety rich in serine, threonine, and proline (13).

A serum CA125 of 35U/mL, initially measured using the homologous assay and representing 1% of healthy female blood donors, is usually accepted as the upper limit of normal (14). This cutoff value is fully retained by the CA125 II assay (15), which is now

preferred because of reduced interassay variation (16). **An upper limit of normal of 35U/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; 20U/mL and 26U/mL have been suggested** (17 ,18).

Interest in CA125 as a screening test was initiated by the fact that approximately 83% of patients with epithelial ovarian cancer had CA125 levels ≥35U/mL (14 ,19). Elevated levels were found in 50% of patients with stage I disease and more than 90% of women with more advanced stages (20). In addition, **CA125 can be elevated in the preclinical asymptomatic phase of the disease, as raised levels were found in 25% of 59 stored serum samples collected 5 years before the diagnosis of ovarian cancer** (21). In a prospective ovarian cancer screening study of Swedish women, a specificity of 97% and positive predictive value (PPV) of 4.6% was achieved using CA125 (≥30U/mL) in 4,290 volunteers aged 50 years and older (22). **The low specificity and PPV 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, benign ovarian cysts, tuboovarian abscess, hyperstimulation syndrome, ectopic pregnancy, and physiological conditions [pregnancy and menstruation]** (23 ,24). In postmenopausal women, an elevated CA125 in the absence of ovarian cancer has been found to be a risk factor for death from other malignant disease (23 ,25). These findings have implications when screening asymptomatic postmenopausal women.

Improving Sensitivity and Specificity of Ovarian Cancer Screening

Pelvic Ultrasound as a Second-Line Test

Specificity of screening with CA125 was initially improved by the addition of pelvic ultrasound as a second-line test to assess ovarian volume and morphology. Using multimodal screening incorporating sequential CA125 measurements and pelvic ultrasound, a specificity of 99.9% and PPV of 26.8% (approximately four operations for each cancer) for detection of ovarian and fallopian tube cancer was achieved in 22,000 postmenopausal women (26 ,27). With the accumulation of data, ovarian morphology has been used to refine algorithms for the interpretation of ultrasound in postmenopausal women with elevated CA125 levels (28 ,29).

Risk of Ovarian Cancer Algorithm

Developing a more sophisticated approach to replace absolute cutoff levels for interpretation of CA125 levels has made further improvements to the strategy. Detailed analysis of more than 50,000 serum CA125 levels involving 22,000 volunteers followed up for a median of 8.6 years in the study by Jacobs et al. (6 ,26) revealed that **elevated CA125 levels in women without ovarian cancer were static or decreased with time, whereas levels associated with malignancy tended to rise. This finding has been incorporated into a computerized algorithm that uses an individual's age-specific incidence of ovarian cancer and CA125 profile to estimate her risk of ovarian cancer (ROC)** (30 ,31). The closer the CA125 profile to the CA125 behavior of known cases of ovarian cancer, the greater the ROC. The final result is presented as the individual's estimated risk of having ovarian cancer so that a ROC of 2% implies a risk of 1 in 50. **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. At the same time, specificity is improved, as women with static but elevated levels are now classified as low risk.** For a target specificity of 98%, the ROC calculation achieved a sensitivity of 86% for preclinical detection of ovarian cancer (31).

This approach forms part of the multimodal screening strategy in the recently completed pilot randomized controlled trial of ovarian cancer screening at St. Bartholomew's Hospital, London (32), and is part of the ongoing U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) (http://www.ukctocs.org.uk/) (Figure 2.1). The ROC algorithm is also being evaluated prospectively in a pilot ovarian cancer screening trial in “high-risk” women under the auspices of the Cancer Genetics Network in the United States.

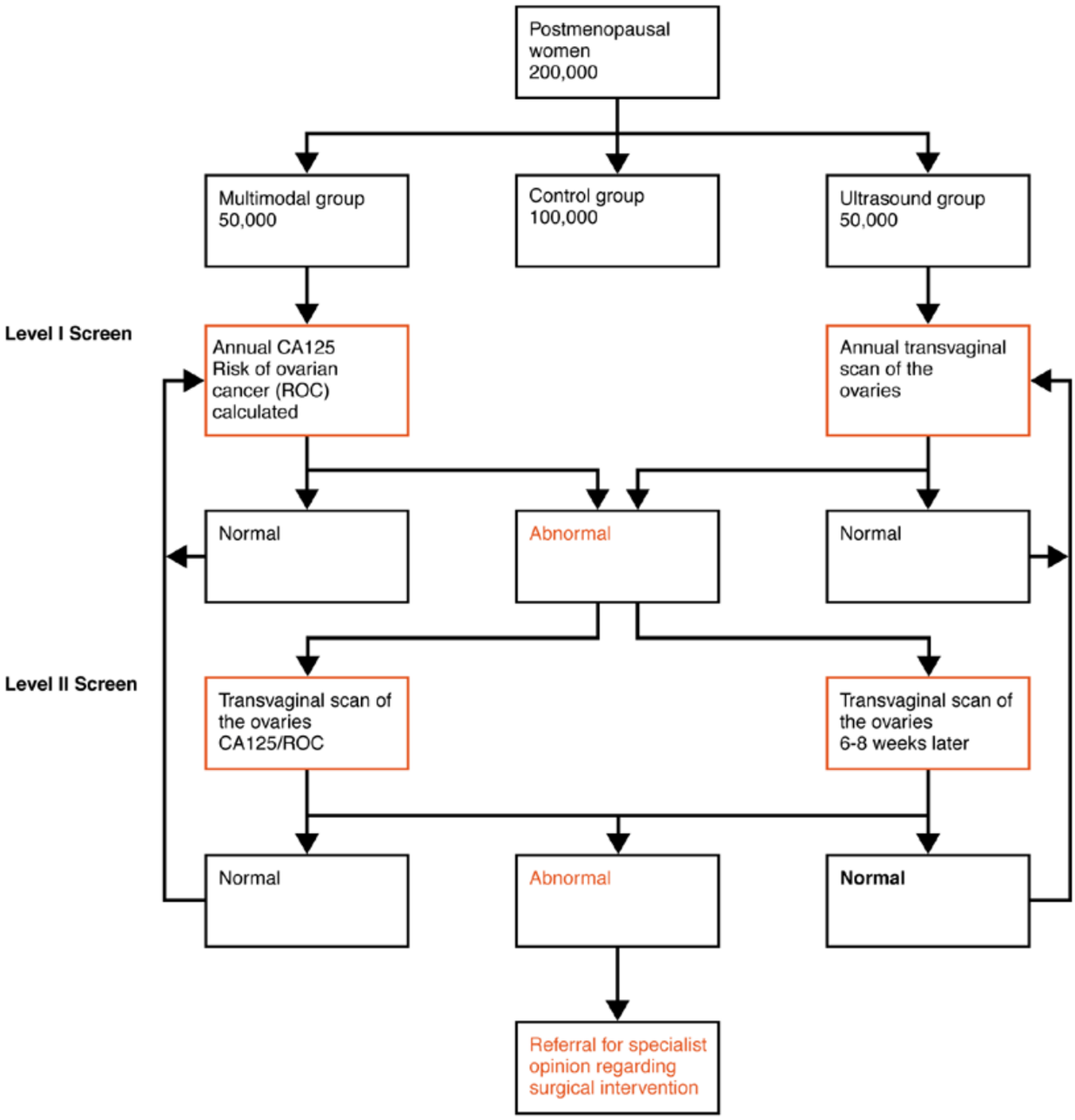

Figure 2.1 The United Kingdom Collaborative Trial of Ovarian Cancer Screening (http://www.ukctocs.org.uk/**).** After a normal risk of ovarian cancer (ROC) (<1 in 2,000), a repeat CA125 level is done in 1 year: after an intermediate ROC (>1 in 2,000 to <1 in 500), a repeat CA125 level is done in 6 weeks; and after an elevated ROC (>1 in 500), a transvaginal ultrasound and CA125 level are done in 6 to 8 weeks. The primary outcome is mortality from ovarian or fallopian tube cancer. Follow-up is by postal questionnaire and the U.K. National Office of Statistics. Women in the screened arm undergo six screens, and each woman is in the trial for 7 years.

New Tumor Markers

Certain tumors (e.g., mucinous and borderline carcinomas) are less likely to be associated with elevated CA125 levels than invasive serous cancers (20). In the past 5 years, significant progress has been made in developing novel tumor markers for early detection of ovarian cancer (Table 2.2). Most of these studies have used samples from women with clinically diagnosed ovarian cancer (i.e., in the differential diagnosis of ovarian cancer)

as opposed to asymptomatic women with preclinical disease (i.e., early detection of ovarian cancer).

Table 2.2 Tumor Markers That May Be Useful in Screening for Ovarian Carcinoma

Tumor Marker	*Description*
CA72-4 or TAG 72	**Cancer antigen 72 or tumor-associated glycoprotein 72 is a glycoprotein surface antigen found in colon, gastric, and ovarian cancer. It is more frequently elevated in mucinous tumors.** There are conflicting reports regarding additional sensitivity for detection of ovarian cancer when combined with CA125 compared with CA125 alone (33,34,35,36).
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 controls (37). Elevated levels have been found in ovarian cancer patients with normal levels of CA125 (37). Whereas CA 125 alone was elevated in 67% of 46 patients with stage I ovarian cancer, CA125 or M-CSF was elevated in 91% (38).
OVX1	**Monoclonal antibody OVX1 recognizes an antigenic determinant present in ovarian and breast cancer cells** (39). A combination of OVX1, M-CSF, and CA125 can detect a greater fraction of patients with stage 1 ovarian cancer than CA125 alone, but this is accompanied by an additive effect on false positives (38,40). However, the OVX1 radioimmunoassay is highly dependent on sample handling (41).
LPA	**Lysophosphatidic acid is a bioactive phospholipid with mitogenic and growth factor–like activities that stimulates the proliferation of cancer cells.** Plasma LPA may represent a potential biomarker for ovarian and other gynecologic cancers. Elevated plasma LPA levels were detected in 9 of 10 patients with stage I ovarian cancer and all 24 patients with stage II–IV ovarian cancer. In comparison, only 28 of 47 had elevated CA125 levels, including 2 of 9 patients with stage I disease. LPA levels were also elevated in patients with other gynecologic cancers (42).
Prostasin	**Prostasin is a serine protease normally secreted by the prostate gland.** It was identified as a biomarker following identification of overexpression of the gene using microarray technology on RNA pooled from ovarian cancer and normal human ovarian surface epithelial cell lines. The combination of CA125 and prostasin in 37 patients with nonmucinous ovarian cancer and 100 control subjects resulted in a sensitivity of 92% (95% CI = 78.1% to 98.3%) and a specificity of 94% (95% CI = 87.4% to 97.7%) for detection of ovarian cancer (43).
Osteopontin	**Osteopontin is another biomarker that has been identified by exploiting gene expression profiling techniques.** Plasma levels of osteopontin were significantly higher in 51 patients with epithelial ovarian cancer compared with 107 healthy controls, 46 patients with benign ovarian disease, and 47 patients with other gynecologic cancers (44).
Inhibin	**Serum inhibin is an ovarian product that decreases to nondetectable levels after menopause.** However, certain ovarian cancers (mucinous carcinomas and sex cord stromal tumors, such as granulosa cell tumors) continue to produce inhibin, which provides a basis for a serum diagnostic test. Available data show that inhibin assays that detect all inhibin forms, i.e., assays that detect the alpha subunit both as the free form and as an alphabeta subunit dimer, provide the highest sensitivity/specificity characteristics as an ovarian cancer diagnostic test (45).
Kallikrein	**The human kallikrein gene family currently consists of 15 members, including prostate-specific antigen (hK3).** Preliminary reports indicate that two kallikreins (hK6 and hK10) may be useful serum biomarkers for diagnosis of ovarian cancer (46,47,48).

Among others undergoing preliminary evaluation are the 110kD component of the extracellular growth factor receptor (p110EGFR) (49,50), creatinine kinase B (51), and mesothelin protein (52).

In the new era of proteomics, there has been a great deal of interest in identifying global patterns of serum proteins and peptides that relate to cancer risk. A wide range of techniques is now available for protein identification and characterization in which high sensitivity and specificity are combined with high throughput.

Surface-enhanced laser desorption ionization time-of-flight (SELDI-TOF) analysis and matrix-associated laser desorption ionization time-of-flight (MALDI-TOF) technology have the potential to identify patterns or changes in thousands of small proteins (<20 kd). When combined with matrices that selectively absorb certain serum proteins, these approaches can globally analyze almost all small proteins in complex solutions, such as serum or plasma (53 ,54). A combination of mass spectra generated by these new technologies and artificial-intelligence–based informatic algorithms have been used to discover small sets of key protein values that discriminate normal from ovarian cancer patients.

A preliminary study reported that when using SELDI-TOF to analyze the proteomic spectra patterns generated from 50 women with and 50 women without ovarian cancer, the algorithm identified a cluster pattern that, in the training set, completely segregated cancer from noncancer. The discriminatory pattern correctly identified all 50 ovarian cancer cases in the masked set, including all 18 stage I cases. Of the 66 cases of nonmalignant disease, 63 were recognized as not cancer. This result yielded a sensitivity of 100% (95% confidence interval 93 to 100), specificity of 95% (87 ,88 ,89 ,90 ,91 ,92 ,93 ,94 ,95 ,96 ,97 ,98 ,99), and PPV of 94% (55). Although the limitations of this study design and its analysis have been discussed in some detail in the literature (56 ,57 ,58 ,59), the implications of such proteomic spectrum analysis for the identification of novel tumor markers is huge.

It is likely that in the future, the early detection of ovarian cancer (and other cancers) will involve high throughput proteomic profiling, either alone or in combination with markers already in use.

Use of Marker Panels

Use of multiple markers may increase the sensitivity for early detection of ovarian cancer. However, increased sensitivity is usually associated with decreased specificity. A panel of eight different markers (CA125, M-CSF, OVX1, LASA, CA15-3, CA72-4, CA19-9, CA54/61) improved the sensitivity for discriminating malignant from benign pelvic masses (60). Using the same data set, a subset of four markers analyzed using an artificial neural network demonstrated improved sensitivity over CA125 alone (87.5% versus 68.4%) while maintaining comparable specificity (61). In addition, greater specificity using multiple markers might be attained if serial values were employed as in the case of CA125. Preliminary data on a panel of five serum tumor markers (CA125, HER-2/neu, urinary gonadotropin peptide, lipid-associated sialic acid, and Dianon marker 70/K) obtained during 6 years of follow-up of 1,257 healthy women at high risk of ovarian cancer suggest that individual-specific screening rules may be developed with the potential to improve early detection of ovarian cancer (62).

Morphological Markers

Real-time ultrasonic 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 mL to 20 mL, depending on menopausal status (63). The transvaginal route is preferred because of the more detailed images obtained. Persistence of abnormalities on repeat scanning 4 to 6 weeks following initial detection helps reduce false-positive rates (64). The lack of physiological changes in ovarian volume in postmenopausal women further decreases the number of false positives in this group compared with premenopausal women. However, even in older women, there is a high prevalence of benign ovarian lesions. In an ultrasonic and histopathological autopsy study of 52 consecutive postmenopausal women who died from causes other than gynecological or intraperitoneal cancer, 56% were found to have a benign adnexal lesion ≤50 mm diameter (65).
Ultrasonography used in this manner can therefore lead to the detection of many benign ovarian tumors, which results in unnecessary surgery in healthy, asymptomatic women. As data regarding outcome accumulates with long-term follow-up of the participants of the early screening trials, it has been possible to further define the risk of ovarian cancer associated with various ultrasonic findings.

The use of complex ovarian morphology to interpret pelvic ultrasound increases the sensitivity and PPV in multimodal screening (29). Similarly, follow-up of participants in an ultrasound-based screening trial has established that **unilocular ovarian cysts <10 cm in diameter are found in 18% of asymptomatic postmenopausal women older than 50 years and are associated with an extremely low risk of malignancy.** In contrast, complex ovarian cysts with wall abnormalities or solid areas are associated with a significant risk for malignancy (64 ,66).

To decrease the number of false positives, many screening protocols use a weighted scoring system or morphological index based on ovarian volume, outline, presence of papillary projections, and cyst complexity (i.e., number of locules, wall structure, thickness of septae, and echogenecity of fluid). There is no standardized index as yet, with systems varying on the number and type of variables evaluated (67 ,68 ,69 ,70 ,71 ,72). Others use subjective assessment of the gray-scale images. Based on gross anatomic changes at the time of surgery, papillary projections have the highest and simple cysts and septal thickness the lowest correlation with a diagnosis of ovarian malignancy (73).

In the ultrasound-based European Randomised Controlled Trial of Ovarian Cancer Screening, which recruited about 15,000 postmenopausal women, multicystic and multilocular cysts in addition to unilocular cysts were managed conservatively if the morphology remained unchanged (74). This parallels the move in clinical practice of conservative management of adnexal cysts judged to be benign at transvaginal ultrasound examination when they are incidentally detected in postmenopausal women (75). Follow-up data on such women will be important in determining optimal strategies for operative intervention in screening.
Various second-line tests have been explored to reduce the false-positive rate and facilitate discrimination between benign and malignant ovarian lesions. These include CA125 levels (76), multiple serum tumor markers, computerized tomography, magnetic resonance imaging (77), and newer modalities, such as three-dimensional ultrasound and three-dimensional power Doppler (78 ,79). Self-teaching computer models, such as neural networks that may increase the reproducibility of results, are being investigated in order to address the problem of the subjectivity of ultrasound (80 ,81 ,82).

Vascular Markers

Neovascularization is an obligate early event in tumor growth and neoplasia (83). Fast-growing tumors contain many new vessels that have less smooth muscle in their walls and therefore provide less resistance to blood flow when compared with vessels within benign ovarian tumors. **Color flow Doppler imaging uses these altered 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 (84 ,85), as well as a second-line test following an abnormal ultrasound (86 ,87) in both general and high-risk population screening.
The initial promise of Doppler to differentiate between malignant and benign ovarian masses and

therefore improve the specificity of ultrasound (84 ,85) **has not been confirmed** (88 ,89 ,90).

While it has been demonstrated that the mean pulsatility index (PI) of vessels supplying ovarian cancers is lower than that of vessels supplying benign ovarian tumors, the overlap in vascular resistance between these two groups prevents reliable separation of malignant from benign disease. The optimal parameters and cutoff levels of PI (<1.0), resistance index (<0.4 or 0.6), or peak flow velocity with the highest predictive value for malignancy have been difficult to define.

It was reported that lack of blood flow in an ovarian tumor, as detected by color Doppler, may preclude cancer (90). This was not substantiated in data from the Kentucky screening trial, in which 6% of ovarian tumors without blood flow were malignant (89). Even when Doppler examinations were simplified and limited to the expression of internal color flow, gray-scale sonography was a more sensitive indicator of malignancy than Doppler sonography (91).

Key issues with regard to Doppler examination as a possible second-line study for ultrasound-based ovarian cancer screening protocols are whether the examination should focus on quantitative or qualitative differences in blood flow within complex masses, and the difficulties with interobserver variation and standardization. The consensus of opinion is that Doppler evaluation of ovarian masses will not significantly improve the sensitivity and PPV of gray-scale sonography as applied to screening strategies. However, further analysis of this technology is warranted. The UKCTOCS trial is collecting Doppler data on abnormal adnexal masses detected on ultrasonic screening, although this is not being used in the screening algorithm (http://www.ukctocs.org.uk/). Recently, some studies have shown that three-dimensional power Doppler examinations may be more accurate than two-dimensional Doppler examinations (92 ,93), although this is also controversial (94).

Target Populations

There are two distinct populations who are at increased risk for ovarian cancer.

General Population

The majority of ovarian cancers are sporadic and occur in the general population. **More than 90% of sporadic cancers occur in women older than 50 years**, therefore screening studies in the general population usually target this group. Among the host of factors that increase the risk in the general population, those in use for determining risk in trials are menopausal status, years of oral contraceptive use, and parity. Groups are also investigating the role of single nucleotide polymorphisms in low-penetrance genes. In the future, it may be possible to identify women with increased susceptibility for sporadic ovarian cancer by virtue of their genetic profile.

High-Risk Population

Hereditary syndromes account for approximately 5% to 10% of ovarian cancers. First-degree female relatives of affected members from ovarian, breast and ovarian, or hereditary nonpolyposis colon cancer (HNPCC) families have a lifetime risk of developing ovarian cancer of greater than 10%. Much of this risk is due to mutations arising in the *BRCA1* and *BRCA2* genes. An analysis of 22 studies indicates that the average cumulative risks by age 70 years for ovarian cancer is 39% (18% to 54%) in *BRCA1*-mutation carriers and 11% (2.4% to 19%) in *BRCA2* mutation carriers (95).

In women with strong evidence of a hereditary predisposition, screening from the age of 35 is frequently advocated, although the efficacy of such surveillance has not yet been established (96). Screening premenopausal women can be problematic, as this

Table 2.3 Prospective Ovarian Cancer Screening Studies in Women with a Family History of Ovarian or Breast Cancer or a Personal History of Breast Cancer

Study	*Population*	*Screening Protocol*	*No. Screened (Premenopausal %)*	*No. Referred for Diagnostic Tests[A] (%)*	*No. of Invasive EOC Detected (Borderline Tumors)*	*Cancers in screen-negative women*
Bourne et al.	Aged >17 (mean 47)	TVS then CDI	1,502 (60)	62 (3.8)	4 (3) 2 stage I	2—PP (2–8 mo)

1994 (97)		F/H of Ov cancer			4—EOC (24-44 mo)	
Weiner et al. 1993 (98)	P/H Br cancer	TVS and CDI	600	12 (3)	3 1 stage I	Not stated
Muto et al. 1993 (99)	Aged >25 F/H of Ov cancer	TVS and CA125	384 (85.4)	15 (3.9)	0	Not stated
Schwartz et al. 1995 (100)	Aged >30 F/H of Ov cancer	TVS and CDI and CA125	247	1 (0.4)	0	Not stated
Belinson et al. 1995 (101)	Aged >23 (mean 43) F/H of Ov cancer	TVS and CDI and CA125	137	2 (1.5)	1	Not stated
Menkiszak et al. 1998 (102)	Aged >20 F/H of Br/Ov cancer	TVS and CA125 (6 monthly)	124	Not available	1 (3)	Not available
Karlan et al. 1993 (103)	Aged >35 F/H of Ov,	TVS and CDI and	597[b] (75)	10 (1.7) Not stated	0 (1) 1 EOC,	Not stated 4 PP
Karlan et al. 1999 (104)	Br, Endo, Colon cancer P/H Br cancer	CA125 6 monthly until 1995, then annually	1,261		3 PP (2) 1 stage I	(5, 6, 15, 16 mo)
Dorum et al. 1996 (105)	Aged >25 (mean 43)	TVS and CA125	180[b] 803	16 (8.9) Not stated	4 (3)[b] 16 (4)	2[c] Not stated
Dorum et al. 1999 (106)	Strict criteria for F/H of Br/Ov cancer					
Scheuer et al. 2002 (107)	Aged >35 BRCA1/BRCA2 mutation carriers	TVS and CA125 (6 monthly)	62	22 (35.5) 10 had surgery	5 4 EOC, 1 PP 3 stage I	0[d]

P/H, personal history; F/H, family history; Ov. ovarian; Br, breast; Endo, endometrial; EOC. epithelial ovarian cancer; PP, primary peritoneal cancer; TVS, transvaginal ultrasound; CDI, color Doppler imaging.

[a]Following positive secondary screens.

[b]Not included in total as there are more recent updates on the trial.

[c]Further 13 women underwent oophorectomy for breast cancer; two had ovarian cancer not detected by TVS.

[d]Two women who opted for oophorectomy with normal scans and CA125 had stage I ovarian cancer.

population has a variety of both physiological (e.g., menstrual cycle variations) and benign (e.g., endometriosis, ovarian cysts) conditions that can give rise to false-positive abnormalities on ultrasound and CA125. Hence criteria for interpretation of the screening tests need to be different from those developed for postmenopausal women in the general population.

To date, nine prospective studies have reported on screening for familial ovarian cancer (Table 2.3). More than 5,000 women have been screened, and 33 primary invasive epithelial ovarian and peritoneal cancers have been detected using mainly ultrasonography and CA125 levels as first-line tests. Criteria for interpreting the test results vary, and screening protocols are not always clearly reported. Only three of the studies have reported interval cancers, which presented between 2 and 24 months following the last screen (97 ,104 ,106). Multifocal peritoneal serous papillary carcinoma may be a phenotypic variant of familial ovarian cancer, and screening strategies using ultrasonography and CA 125 testing are not reliable in detecting this disease (104 ,108). **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. The other option for these women is risk-reducing salpingo-oophorectomy after completion of their families (109 ,110).

Current Ovarian Cancer Screening Trials

Two distinct screening strategies have emerged, one based on ultrasonography and the other based on measurement of the serum tumor marker CA125 with ultrasonography as the secondary test (multimodal screening) (111 ,112 ,113 ,114 ,115 ,116 ,117 ,118 ,119 ,120). Overall, the data from large prospective studies of screening for ovarian cancer in the general population (Table 2.4) suggest that sequential multimodal screening has superior specificity and PPV compared with strategies based on transvaginal ultrasound alone. However, ultrasonography as a first-line test may offer greater sensitivity for early-stage disease.

Table 2.4 Prospective Ovarian Cancer Screening Studies in the General Population

Study	*Main Features*	*Screening Strategy*	*No. Screened*	*No. of Invasive Epithelial Ovarian Cancers Detected*[a]	*No. of Positive Screens*	*No. of Operations/Cancer Detected*
CA125 alone						
Einhorn et al. 1992 (22)	Age ≥40 years	Serum CA125	5,550	6 2 stage I	175[b]	29[b]
Multimodal approach—CA125 (level 1 screen), then USS (level 2 screen)						
Menon et al. 2003 (32)	Age ≥50 years Postmenopausal	Serum CA125 ROCA, TVS if ROC↑	13,582	3 (1) 2 stage I	16	3
Jacobs et al. 1993 (27), **1996** (26)	Age ≥45 years (median 56) Postmenopausal	Serum CA125 TAS, if CA125↑	22,000	11 4 stage I	41	3.7
Jacobs et al. 1999 (6)	Age ≥45 years (median 56) Postmenopausal	RCT Serum CA125 TAS/TVS, if CA125↑	10,958 3 annual screens	6 3 stage I	29	4.8
Grover et al. 1995 (111)	Age ≥40 years (median 51) or with family history (3%)	Serum CA125 TAS/TVS, if CA125↑	2,550	1 0 stage I	16	16
Adonakis et al. 1996 (112)	Age ≥45 years (mean 58)	Serum CA125 TVS, if CA125↑	2,000	1(1) 1 stage I	15	15
USS only approach—USS (level 1 screen), then repeat USS (level II screen)						
De Priest et al. 1997 (113) **van Nagell et al. 2000** (114)	Age ≥50 years and postmenopausal or ≥30 with family history	TVS Annual screens Mean 4 screens/woman	14,469	11 (6) 5 stage I	180	16.3

Sato et al. 2000 (77)	Part of general screening program	TVS TVS + markers at level 2	51,550	22 17 stage I	324	14.7
Hayashi et al. 1999 (115)	Age ≥50 years	TVS	23,451	3 (3)	258	[c]
Tabor et al. 1994 (116)	Aged 46–65 years	TVS	435	0	9	—
Campbell et al. 1989 (117)	Age ≥45 years (mean 53) or with family history (4%)	TAS 3 screens at 18 monthly intervals	5,479	2 (3) 2 stage I	326	163
Millo et al. 1989 (118)	Age ≥45 years or postmenopausal (mean 54)	USS (mode not specified)	500	0	11	—
Goswamy et al. 1983 (119)	Age 39–78 Postmenopausal	TAS	1,084	1 1 stage I		
USS and CDI (level 1 screen)						
Kurjak et al. 1995 (120)	Aged 40–71 years (mean 45)	TVS and CDI	5,013	4 4 stage I	38	9.5
Vuento et al. 1995 (85)	Aged 56–61 years (mean 59)	TVS and CDI	1,364	(1)	5	—
USS (level 1) and other test (level II screen)						
Parkes et al. 1994 (87)	Aged 50–64 years	TVS then CDI if TVS positive	2,953	1 1 stage I	15[d]	15
Holbert et al. 1994 (76)	Postmenopausal Aged 30–89 years	TVS then CA125 if TVS positive	478	1 1 stage I	33[e]	33

RCT, randomized controlled trial; TAS, transabdominal ultrasound; TVS, transvaginal ultrasound; USS, ultrasound; CDI, color Doppler imaging.
[a]Primary invasive epithelial ovarian cancers. The borderline/granulosa tumors detected are shown in parenthesis.
[b]Not all of these women underwent surgical investigation as the study design involved intensive surveillance rather than surgical intervention.
[c]Only 95 women consented to surgery, and there are no follow-up details on the remaining.
[d]86 women had abnormal USS before CDI.
[e]Only 11 of these women underwent surgery.

Trials in the General Population

Randomized controlled trials are now under way in the general population to assess the impact of screening on ovarian cancer mortality (121 ,122). The UKCTOCS has recruited 110,000 postmenopausal women from 13 centers in the United Kingdom (Figure 2.1); 200,000 women in all will be randomized to either control, screening with ultrasonography, or multimodal screening. Apart from ovarian cancer mortality, the study also addresses the issues of target population, compliance, health economics, and physical and psychological morbidity of screening. Results are expected in 10 years (http://www.ukctocs.org.uk/).

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is enrolling women aged 55 to 74 at 10 screening centers in the United States with balanced randomization to intervention and control arms (Figure 2.2). For ovarian cancer, women are screened using both CA125 and transvaginal ultrasonography for 3 years and CA125 titers alone for a further 2 years. Follow-up will continue for at least 13 years from randomization to assess health status and cause of death (121).

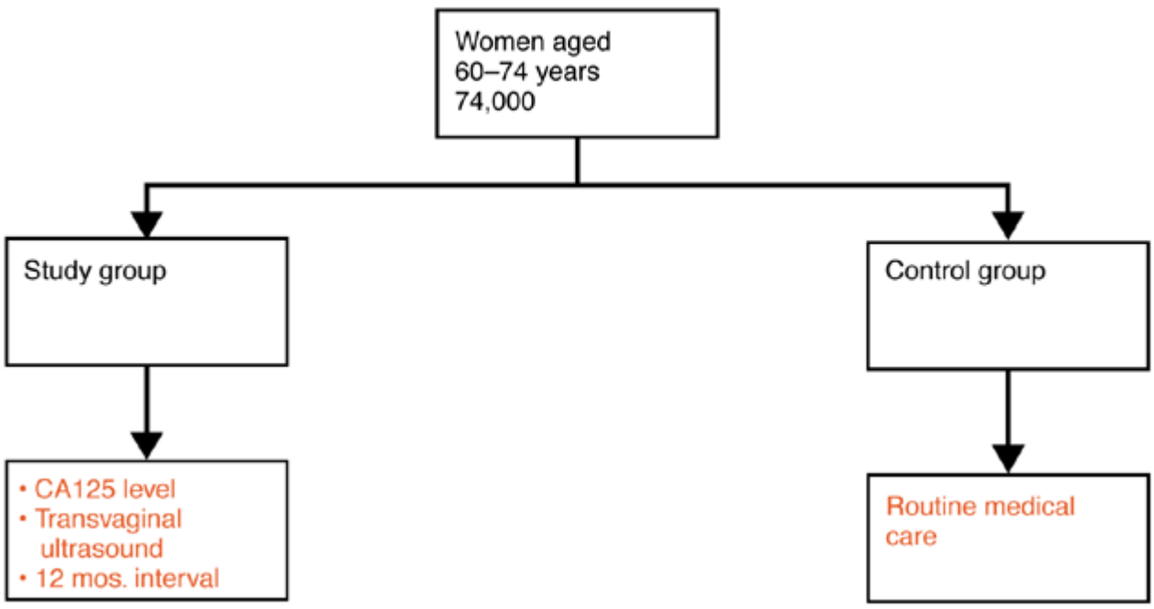

Figure 2.2 The National Institutes of Health Prostrate, Lung, Colorectal and Ovarian cancer screening study (NIH-PLCO) (121). Ovarian screening is part of the study, and the primary outcome measure is mortality from ovarian cancer. The follow-up is 13 years.

Trials in a High-Risk Population

In order to develop an optimal screening strategy in the high-risk population, a multicenter National Familial Ovarian Cancer Screening Study (UK-FOCSS) has started recruiting “high-risk” women in the United Kingdom. This is a prospective study based on annual screening with CA125 titers and transvaginal ultrasonography. The trial design includes collection and storage of serial serum samples every 4 months for retrospective analysis of CA125 and other markers (122). A similar trial is under way in the United States under the auspices of the Cancer Genetics Network of the National Cancer Institute with the scope for metaanalysis in the future. In the U.S. trial, screening is based on 3-monthly serum CA125 levels, which are interpreted using the ROC algorithm. Women with elevated ROC values are triaged to ultrasonography. More than 2,000 high-risk women have been recruited onto this study to date with the scope for metaanalysis in the future.

Endometrial Cancers

The prevalence of endometrial cancer in asymptomatic women is low and the overall prognosis is good as women present in early stages with abnormal bleeding. Most endometrial cancers (77%) are diagnosed at an early, favorable stage. The consensus is that screening for endometrial cancer is not warranted for women who have no identifiable risk factors (7 ,123 ,124 ,125 ,126). The only trial to support mass screening for endometrial cancer is from Tohoku University, Japan. The study reported that early stage (88.1% vs. 65.3%), low grade (74.7% vs. 61.0%), and 5-year survival (94% vs. 84.3%) were significantly more frequent in 126 cases of endometrial cancer detected by mass screening using endometrial smears compared with the 1,069 cases diagnosed clinically during the period 1987 to 1997 (127). However, even in women at increased risk as a result of unopposed use of estrogen, *tamoxifen* therapy, nulliparity, infertility or anovulation, obesity, diabetes, or hypertension, the American Cancer Society Working Group does not, based on an extensive literature review, recommend screening for endometrial cancer. As is the case with average-risk women, individuals at increased risk who develop endometrial cancer tend to present with symptoms at an early, favorable stage.

Screening is only recommended in women with or at high risk for HNPCC (7). The population defined at high risk for endometrial cancer includes women known to carry HNPCC—associated mutations of DNA mismatch repair genes, women who have a substantial likelihood of being a mutation carrier (i.e., a mutation is known to be present in the family), and women from families with an autosomal-dominant predisposition to colon cancer in the absence of genetic testing results. **These women have a cumulative incidence of endometrial carcinoma of 20% by age 70, compared with 3% in the general population** (128).

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 best age to begin screening women with the HNPCC risk factor is not known. Most authorities recommend annual screening from the age of 35. This is based on expert opinion in the absence of scientific evidence. Women in this high-risk group should be counseled about the risks and symptoms of endometrial cancer, and the potential benefits, risks, and limitations of endometrial cancer screening. **Women who are no longer considering childbearing and who are undergoing surgery for colorectal cancer should be offered the option of having a prophylactic hysterectomy. Prophylactic oophorectomy to reduce the risk of ovarian cancer should also be offered.**

Morphological Markers

The most commonly used tumor marker is endometrial thickness measured using transvaginal ultrasound. It is 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 >4.0 mm has a sensitivity for detection of endometrial cancer of 98% and a negative predictive value of 99% (129). This cutoff effectively excludes endometrial atrophy, but it fails to differentiate between hyperplasia and carcinoma (130).

As a tumor marker in asymptomatic postmenopausal women, the same poor PPV but high negative predictive value for the detection of serious endometrial disease persists (131). Screening studies using conventional and color Doppler ultrasonography in apparently healthy postmenopausal women have established that endometrial carcinomas can be detected at a preclinical stage (84 ,132 ,133) and that transvaginal ultrasonography is more sensitive than blind endometrial biopsy (134). However, in the absence of symptoms,

repeat sampling is not warranted in patients with a thickened endometrium and negative findings at initial biopsy (135).
Endometrial fluid accumulation is detected in 12% of asymptomatic elderly postmenopausal women and is rarely a sign of malignancy (136). Newer techniques under investigation include three-dimensional ultrasonography for the measurement of endometrial volume (137) and sonohysterography (138).

In asymptomatic women on long-term *tamoxifen*, **abnormal ultrasonographic findings are common in the absence of underlying endometrial pathology.** The apparent increase in thickness observed on ultrasound is probably due to *tamoxifen*-induced changes of endometrial stroma and myometrium (139 ,140). 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 (141 ,142). Sonohysterography has been proposed as a useful tool for the surveillance of the endometrium in these asymptomatic patients, but a recent study has shown no benefit (143). Recently, 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 (144).

Cytological Markers

Although the Papanicolaou stained cervical 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. **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** (145). 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 of carcinoma had endometrial carcinoma (145). A similar PPV of 64% for the 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 1982–87 (146). In a more recent series, 13.5% of women with endometrial cells of some type on Pap smears had endometrial carcinoma (147). The presence of glandular abnormalities and high-grade squamous intraepithelial lesions on smear is also associated with an increased risk of endometrial carcinoma (147 ,148 ,149 ,150). The sensitivity of cervical cytology performed within 2 years of the diagnosis of endometrial malignancy is 28% (146).

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. While 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 diagnosed to have a positive result on first-line ultrasonic screening (151). **The American Cancer Society guidelines are that “high risk women” should be screened annually with endometrial biopsy.** Diagnostic outpatient hysteroscopy, another modality increasingly used in evaluating symptomatic patients, is neither as sensitive nor as acceptable as transvaginal ultrasonography in screening asymptomatic women (152).

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. (153) found that six of seven cervical

smears taken immediately before surgery for endometrial cancer contained identical K-ras mutations 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 diagnosis of endometrial carcinoma had K-ras mutations, despite having normal cytological appearances. **Although K-ras mutations are only found in 10% to 30% of tumors, the model indicates the possibility of using mutations in oncogenes and tumor suppressor genes as molecular markers to detect endometrial carcinoma from cervical smears.** Other markers that may be suitable include microsatellite instability present in 15% of endometrial carcinomas, p53 mutations in 20%, and PTEN/ MMACI gene mutation in 34% (154 ,155). Some of these are late events in endometrial carcinogenesis and may not be suitable for screening. 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 compensating for the progressive loss of telomeric DNA that normally accompanies cell division. **There is now increasing evidence that telomerase expression is preferentially expressed in most malignant tissues, including endometrial carcinoma** (156). It is expressed by normal cycling endometrium (157 ,158) but activity is absent or weak in postmenopausal atrophic endometrium (157 ,159 ,160), raising the possibility of its use as a marker for endometrial hyperplasia and carcinoma in postmenopausal women (161 ,162).

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. While 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

Part of "2 - Tumor Markers and Screening "

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 cytological markers on a Pap smear with colposcopy as a second-line test. Although Pap smear screening remains the best available method of reducing the incidence and mortality of invasive cervical cancer (163), it is now clear that cytological screening alone will not eradicate the disease. An audit of smear histories in women younger than 70 years with cervical cancer revealed that 49% occurred despite adequate cytological screening and follow-up in the 5 years before diagnosis (164). **Numerous strategies, such as neural network-based automated slide reading systems and thin layer slide preparations, are being investigated in order to decrease the false-negative rate of cervical cytology.** Immunostaining with antibodies against DNA regulation proteins Cdc6 and Mcm5 have been described to improve the detection efficiency for dyskaryotic cells in Pap smears (165).

Human Papillomavirus

There is a well established causal link between HPV and all grades of cervical intraepithelial neoplasia (CIN) and invasive cervical cancer (166). The association is type specific with HPV types 6, 11, 42, 43, and 44 associated with low-grade cervical intraepithelial lesions (CIN I) and HPV types 16, 18, 31, 33, 35, 45, 51, 52, 56, and 58 associated with high-grade cervical intraepithelial lesions (CIN II/III) and cervical carcinoma (167). 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 atypical squamous cells

of unknown significance and low-grade squamous intraepithelial lesions, as well as in primary screening. Although **most studies have shown that the detection rate of CIN 2-3 is improved by HPV testing** (168 ,169 ,170 ,171 ,172) and **a negative HPV test result virtually excludes risk of underlying high-grade disease unlike a negative cytologic result** (169 ,173), other trials have failed to establish a definite advantage over cytological screening, mainly due to the lower specificity and increased false-positive rates (174 ,175 ,176 ,177 ,178). One of the recent trials has suggested that a potential approach to improving detection rates of high-grade lesions without increasing the rate of referral for colposcopy would be to manage HPV-positive women with normal or borderline cytology (about 6% of screened women) by repeat testing after 12 months (179).

Screening with HPV plus cytology tests may save additional years of life at reasonable costs compared with cytology testing alone (180 ,181). Although most of the recent trials have reported use of the Hybrid Capture II test, the technology for HPV detection is still evolving, with optimization of type spectrum, sensitivity, specificity, and ease of use continuing to be developed. The value of HPV typing may be further increased by subtyping, as some variants of HPV 16 confer a 6.5-fold increase in risk of CIN 2-3 compared with other HPV 16 variants (182). Data are awaited regarding these factors, as well as a clear cost-benefit analysis from several ongoing large trials. Until such data are available, caution in clinical implementation of HPV testing is warranted.

Telomerase

Telomerase expression may be a marker of premalignant and malignant squamous cell lesions of the cervix. Telomerase activity, using the telomere repeat amplification protocol (TRAP), was detected in 100% of squamous cell carcinomas, 62% to 96% of CIN 2-3 lesions, 33% to 56% of CIN 1 lesions, and only 0% to 18% of normal cervical tissues (162 ,183 ,184). Assessment of cytological 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 (185 ,186 ,187 ,188). Interest in the role of telomerase in cervical screening was further stimulated by the finding that five cases of CIN with no cytological abnormality had telomerase activity (189). However, other studies have found telomerase assay of cervical cytological samples to have poor (4.5% to 25%) sensitivity for detection of CIN 2-3 (183 ,188). Poor correlation was reported between telomerase activity in paired cervical cytological samples and frozen sections (188), and the use of the telomerase activity assay in cervical samples, unlike HPV 16 typing, did not improve the detection of high-grade CIN (189). In addition, telomerase activity was detected in 46% to 56% of benign cervical lesions (162 ,190). The detection of hTRT mRNA, using reverse transcription–PCR analysis of exfoliated cells, may also be useful in cervical screening (191).

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3

Immunology and Biologic Therapy

Otoniel Martínez-Maza
Jonathan S. Berek

Cancer is caused by the accumulation of successive molecular lesions that result in an altered cellular phenotype that is 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. In addition to these molecular changes, ineffective host antitumor immune responses may play a role in the development of cancer. 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 of immune-based biologic therapies for gynecologic cancers.

Components of the Immune System Involved in Antitumor Responses

Part of "3 - Immunology and Biologic Therapy "

Various types of human immune responses can target tumor cells. Immune responses can be 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).

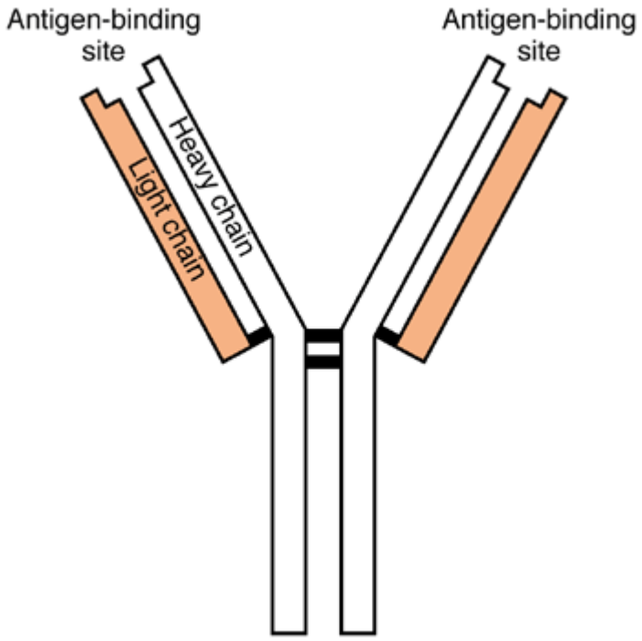

Figure 3.1 The basic immunoglobulin structure. The unit consists of two identical light chains and two identical heavy chains linked together by disulfide bonds.

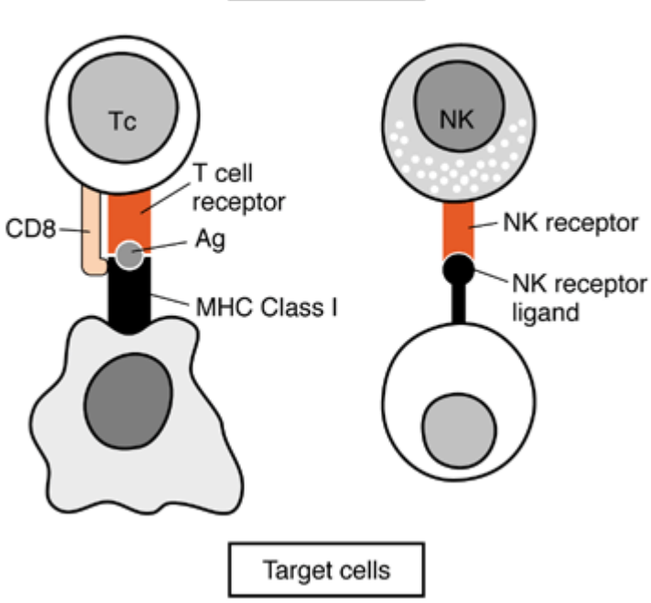

Figure 3.2 Cell-mediated cytotoxicity: two different types of cell-mediated cytotoxicity.1: Cytotoxic T cells (Tc) bind their target while recognizing antigen (Ag) and major histocompatibility complex (MHC) determinants. **2:** Natural killer (NK) cells recognize determinants expressed on target cells, including neoplastic cells.

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 various effector functions, such as antibody production, cytokine secretion, or the stimulation and expansion of cytotoxic T cells (CTL) (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.**

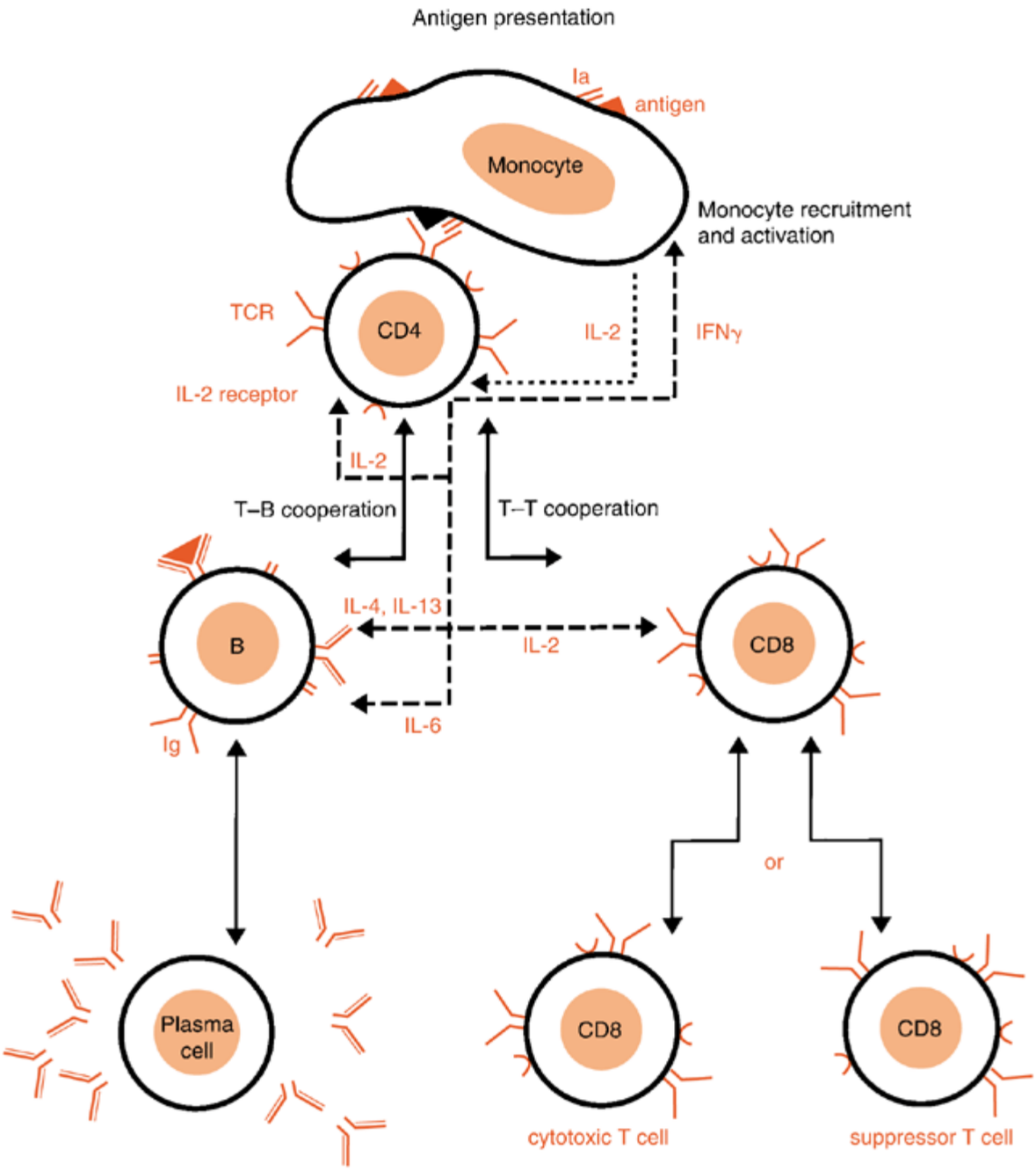

Figure 3.3 Scope of cell-mediated immunity: cellular communication in the immune response through interleukins. IFNγ, gamma interferon; TCR, T-cell receptor; IL, interleukin; Ig, immunoglobulin.

Another way of categorizing immune responses is as adaptive or innate responses. **Adaptive immunity is the response of antigen-specific cells to molecules that are seen**

as “foreign” by the immune system, including the evolution of immunologic memory; **innate responses are of non-antigen-specific mechanisms, which are characterized by rapid responses, and which do not increase with repeated exposure to a given antigen** (1). Both innate and adaptive immune responses can exert potent antitumor activity. 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 (Fig. 3.2).

Innate immune responses form the initial immune responses to invading pathogens and contribute directly to the generation of subsequent adaptive responses. For example, phagocytosis of microbes by monocytes and macrophages, which is an innate form of immunity, contributes to adaptive, antigen-specific T-cell responses, as these cells serve as antigen-presenting cells in the stimulation of helper T cells (Fig. 3.3).

Although many effective antitumor immune responses have been described, **it is not clear 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 is associated with a γ-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, especially those associated with oncogenic viruses. **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 (Fig. 3.2) (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. 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 (Fig. 3.2). 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.

Recent studies have identified a subset of T cells that inhibit autoreactive cells, perhaps acting to prevent autoimmune responses (7). This subset of T cells has been called **regulatory T cells**, T_{reg} cells, or TR1 cells.

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 (Fig. 3.3). Pre-B cells originate from progenitor stem cells after the rearrangement of immunoglobulin genes from their germ cell configuration to the configuration that can encode 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, an anti-HER-2 monoclonal antibody (Herceptin, Genentech, South San Francisco, CA) has been tested in several clinical trials and found to be an effective adjuvant therapy for HER-2 positive breast and ovarian cancer patients (8). **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 some 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 the development of “humanized” murine monoclonal antibodies (genetically engineered monoclonal antibodies composed of human constant regions with specific antigen-reactive murine variable regions), 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, IL-10, and TNF, which are 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-γ (IFN-γ). 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.

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, as a whole, share little structural or amino acid homology. Cytokine molecular families include the hematopoietins (IL-2, IL-4, IL-6, IFNs, and related cytokines), the TNF family (*TNF*-α, lymphotoxin, and related molecules), chemokines (IL-8 and related cytokines), and the IL-1 family (IL-1α, IL-1β, IL-1RA).

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

Cytokine	*Sources*	*Principal Cellular Targets*	*Biologic Effects*
Type 1			
IL-2	T cells (TH1)	T Cells B cells NK cells	Activation, induction of growth Activation and Ab production Activation, induction of growth
IFN-γ	T cells (TH1) NK cells	Monocytes/macrophages NK cells T cells B cells	Activation Activation Activation Enhances Ig isotype switching
IL-12	Monocytes/macrophages	NK cells, T Cells	Induction of TH1 cells
Type 2			
IL-4	T cells (TH2) Mast cells	B Cells T cells	Activation, growth, switch to IgE, increased major histocompatibility complex class II expression Growth
IL-10	T cells (TH2) Monocytes/macrophages	T Cells (TH1) Monocytes/macrophages B cells	Cytokine synthesis inhibition Inhibition of ag presentation and monokine production Activation
Proinflammatory			
IL-1	Monocytes/macrophages B cells Tumor cells	T Cells, B cells Neurons (hypothalamus) Endothelial cells	Co-stimulator Pyrogen Activation
IL-6	Monocytes/macrophages T cells B cells Fibroblasts Various cancer cells	B cells Hepatocytes Stem cells T cells Tumor cells	Differentiation, enhanced Ab production and isotype switching Induction of acute-phase response Growth and differentiation Co-stimulator Autocrine/paracrine growth and viability-enhancing factor
IL-8	Monocytes/macrophages Fibroblasts	Neutrophils	Chemotaxis
TNF-α	Monocytes/macrophages T cells Some tumor cells	Monocytes/macrophages T cells, B cells Neurons (hypothalamus) Endothelial cells Muscle and fat cells Tumor cells	Stimulates monokine production Co-stimulator Pyrogen Activation, inflammation Catabolism/cachexia Autocrine/paracrine growth factor
IFN-α, β	Leukocytes	Most cells NK cells	Antiviral, antiproliferative Activation
Differentiation-inducing			
IL-3	T cells	Hematopoietic stem cells	Growth and differentiation
IL-7	Bone marrow stromal cells	Pre-B cells, T cells	Proliferation

Ab, antibody; Ag, antigen; IFN, interferon; Ig, immunoglobulin; IL, interleukin; NK, natural killer; TH, helper T; TNF, tumor necrosis factor.

There are three types of IFNs: *IFN-α*, *IFN-β*, and *IFN-γ*. 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-γ, 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.

Cytokines are produced by various types of cells and play critical roles not only in immune responses, but also 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 subsets 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 (9 ,10 ,11). **TH1 clones produce IL-2 and IFN-γ**, **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-γ 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*-α) by activated monocytes (9 ,11). Conversely, TH1 cytokines, such as IL-2 and IFN-γ, can downregulate TH2 responses.

Recent work has identified CD4-positive T cells that participate in the maintenance of immunologic self-tolerance by actively suppressing the activation and expansion of self-reactive lymphocytes. These cells are called regulatory T cells, or T_{reg} cells. T_{reg} are characterized by the expression of CD25 (the IL-2 receptor α-chain) (12 ,13). **T_{reg} activity is thought to be important in preventing the development of autoimmune diseases.** Removal of T_{reg} also may enhance immune responses against infectious agents or cancer. While much remains to be learned about the role of T_{reg} activity in antitumor immunity, it is clear that such cells may play a role in modulating host responses to cancer.

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.

Potential Roles of Cytokines 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:

- **The enhancement of host cytokine production** induced nonspecifically by exposure to biologic response modifiers
- **Direct treatment with recombinant cytokines**
- **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
- **Gene therapy-based approaches**, in which tumor cells are transduced with a cytokine gene, the expression of which will presumably enhance antitumor immune responses
- **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. **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 types of human tumor cells, can act as an autocrine growth factor for various human cancers (14 ,15 ,16 ,17).

It has been proposed that epithelial ovarian cancer may be a cytokine-propelled disease (18 ,19 ,20 ,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*-α, and IL-6 (24 ,25 ,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 are 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 (14), **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-1α, IL-1ß, IL-6, *TNF*-α, 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). In other work, it was seen that IL-6 enhanced the resistance of ovarian cancer cells to apoptosis induced by cytotoxic drugs (33). Also, IL-6 expression was seen to be elevated in drug-resistant ovarian cancer cells (34). In our own work, the pretreatment of the ovarian cancer cells with IL-6 resulted in decreased sensitivity to *cisplatin*-induced cytotoxicity (35). Together, these results suggest that this cytokine can promote enhanced viability, and resistance to cytotoxic drugs, in ovarian cancer cells. Interestingly, serum levels of IL-6 were seen to correlate with disease-free survival time, as well as with International Federation of Gynecology and Obstetrics (FIGO) stage, in ovarian cancer patients (36).

It has been suggested that the growth of ovarian cancer might be enhanced by a local deficiency of antitumor immune effector mechanisms (37). Therefore, the local production of immune-inhibitory cytokines, such as IL-6 or IL-10, could contribute to tumor growth in the peritoneal environment. Therefore, IL-6 may enhance ovarian cancer cell growth indirectly, by inhibiting T-cell activation, as it has been seen that elevated serum levels of IL-6 and other cytokines were correlated with decreased immune cell activation (38). 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 (39) could result in a peritoneal environment characterized by immune unresponsiveness and the promotion of tumor growth. Consistent with this notion, it was reported in a recent study that monocytes produce the IL-10 seen in ovarian cancer ascites, and that such IL-10–producing monocytes inhibit T-cell activation (40). This is consistent with our own results, which indicate that ovarian cancer cells do not produce IL-10 (unpublished observations).

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 (41). 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

Part of "3 - Immunology and Biologic Therapy "

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 (42 ,43). Also, many patients with

advanced disease are significantly immunocompromised (44), suggesting a role for immune-enhancing therapeutic approaches. Dysplastic cervical epithelial cells infected with HPV, an oncogenic virus, also present an attractive target for immune enhancement-based therapeutic strategies, including the development of prophylactic and therapeutic vaccines for HPV. Advances in molecular biology, biotechnology, immunology, and cytokine biology have resulted in the availability of many new, promising immunotherapeutic approaches for gynecologic cancers (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 Chapters 2 and 11). Monoclonal antibodies also have been used for radioimmunodetection (45 ,46) and are being used for treatment. 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).

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 (IP), have been used in patients with advanced chemotherapy-resistant ovarian cancer (45 ,46 ,47 ,48 ,49 ,50). This approach has the potential to reduce exposure of the monoclonal antibody to normal body tissue antigens. Phase I therapeutic trials, using IP administration of ^{131} *I-labeled OC125 monoclonal antibody*, led to the conclusion that such treatment could be administered safely (47 ,48). In a phase I study, such patients were treated IP with a murine monoclonal antibody targeted to TAG-72, an antigen expressed in epithelial ovarian carcinomas, and labeled with ^{177}Lu (50). 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 (IV) (49). Another approach has been to link monoclonal antibodies to toxins, such as ricin A or *Pseudomonas* exotoxin (51), or detoxified *Salmonella* endotoxin (52).

Anti-HER2 Monoclonal Antibody-Based Therapy

Monoclonal antibody–based therapeutic strategies also can target the biologic function of cell surface signaling molecules (43). 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 (53). **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** (54). 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 (55), and to block DNA repair after *cisplatin* administration to human breast and ovarian cancer cells (56), confirming the value of *anti-HER-2/neu* monoclonal antibodies in the immunotherapy of HER-2/*neu*-expressing gynecologic cancers.

Anti-HER-2 monoclonal antibodies, specifically, the humanized monoclonal antibody Herceptin (Genentech, South San Francisco, CA), **have been tested in several clinical trials and found to be an effective adjuvant therapy for HER-2 positive breast and ovarian cancer patients** (7 ,57). This monoclonal antibody has established itself as an active agent, in conjunction with *paclitaxel* chemotherapy, in relapsed breast cancer patients who express the HER2/*neu* protein product.
The Gynecologic Oncology Group (GOG) has conducted phase I/II trials of Herceptin in ovarian cancer (58 ,59). Among patients with recurrent ovarian cancer, the rate of HER2/*neu*

overexpression was less than 12% (i.e., lower than expected). In a trial of 41 patients, the overall response rate appears to be less than 10% (GOG data, Society of Gynecologic Oncologists, 2000). The drug is undergoing testing in combination with platinum- and taxane-based chemotherapy to determine its activity in that setting. Clearly, not all patients respond to Herceptin therapy, and many patients who respond initially develop resistance within a year of treatment. This has led some workers to suggest that vaccination strategies that generate T-cell responses to HER-2 be developed (57).

Anti-CA125 Monoclonal Antibody-Based Therapy

A recent innovative approach to immunologic cancer therapy involves administration of monoclonal antibodies that target tumor-specific antigens circulating in the bloodstream, in addition to antigens on tumor cells themselves (60). Oregovomab (B43.13) is a murine monoclonal antibody to CA125, the overexpression of which is seen in more than 90% of patients with late-stage ovarian cancer. This monoclonal antibody binds to circulating CA125, resulting in the formation of immune complexes (antibody:antigen complexes) that are recognized as foreign, because these complexes include foreign (murine) antibody. These immune complexes are believed to be taken up by antigen-presenting cells, allowing the processing of the autologous CA125 antigen, leading to induction of CA125-specific antibodies, helper T cells, and cytolytic T cells. The antigen processing of the autologous antigen + xenotypic antibody complex is altered, relative to the processing of either component alone, and cellular and humoral immune responses directed to the tumor antigen have been demonstrated, following treatment.
The possible therapeutic value of this anti-CA125 monoclonal antibody was discovered serendipitously in a diagnostic study of B43.13 as a tumor-imaging agent: use of ^{99m}Tc-radiolabeled B43.13 for the immunoscintigraphic detection of recurrent ovarian cancer was seen to result in unexpectedly long survival times for many patients (60 ,61). This observation led to efforts to corroborate and extend these findings, by assessing the therapeutic efficacy of nonradiolabeled B43.13 in a series of prospective studies in patients with ovarian cancer. In addition to this, research characterizing the immune-altering properties of the B43.13–CA125 complexes continues to refine the understanding of the immunobiological mechanisms involved in this therapeutic approach (62 ,63 ,64 ,65 ,66). For instance, B43.13 has been seen to modify antigen processing of CA125 by dendritic cells *in vitro* (67 ,68 ,69).

B43.13 has been studied as consolidation following front-line surgery and chemotherapy, with the aim of providing immune stimulation at a time when patient disease burden is minimal (70 ,71 ,72 ,73). Berek et al. recently reported on the initial results of their placebo-controlled, multicenter study of patients with stage III/IV disease and no evaluable disease following front-line treatment (62). For the population as a whole, a significant difference was not seen between B43.13 treatment and placebo. However, in the patient subpopulation defined by more successful responses to front-line surgery and chemotherapy, the progression-free survival was 24.0 months for B43.13-treated subjects vs. 10.8 months for placebo (P=0.029).
Bookman et al. explored B43.13 treatment in a randomized, double-blind, placebo-controlled study of 55 patients with no clinical or radiographic evidence of disease but with elevated CA125 levels (>35 U/mL) following front-line therapy (70). Patients relapsed rapidly in this clinical population, limiting the value of the study, because treatment was discontinued on clinical relapse. However, in a subpopulation of patients who had time to mount an immune response and had small-diameter residual disease, a trend similar to that observed in the study by Ehlen et al. (69) was noted, with a 6-month progression-free survival of 75% for the B43.13 treated group and 35% for the placebo group.

A study that enrolled 20 patients with recurrent ovarian cancer assessed the clinical and immunologic effects of this immunotherapy, before and concurrent with salvage

chemotherapy (71). B43.13 treatment induced CA125-specific T-cell immunity in seven of 18 patients. Subsequent chemotherapy did not abrogate the induced immune responses: T-cell responses to autologous tumor increased in three patients and remained stable in the other two patients, who were treated with combined chemoimmunotherapy (72). Subjects who demonstrated T-cell responses to CA125 and/or autologous tumor showed a highly significant benefit in time to progression and in survival, compared with nonresponders ($P<0.01$). Another study was a long-term follow-up of patients who underwent imaging with radiolabeled B43.13 monoclonal antibody (69). B43.13 exposure was associated with prolonged survival times, which were correlated with induction of humoral responses (73.74). Together, these findings suggest that treatment with the B43.13 monoclonal antibody may induce host antitumor immune responses.

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), or modifications of these agents (75 ,76 ,77 ,78 ,79 ,80 ,81 ,82 ,83 ,84 ,85 ,86 ,87 ,88 ,89). Exposure to *C. parvum* results in the nonspecific enhancement of host immune responses, including the induction of an acute inflammatory response (77). In early animal studies, *C. parvum* was shown to be active in inducing antitumor responses (78 ,79). Biologic response modifier therapy for ovarian cancer, including treatment with *C. parvum* and BCG, was examined in several studies (80 ,81 ,82 ,83 ,84 ,85 ,86 ,87). However, IP treatment with *C. parvum* induced a profound local reaction, including peritoneal fibrosis, and its toxicity precluded more widespread testing.

Malignancies that tend predominantly to grow in the peritoneal cavity, such as residual ovarian cancer, have been treated in many experimental trials with IP drugs, most frequently with cytotoxic chemotherapy (84 ,85). IP 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 (43 ,51 ,86 ,89). 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 ,75 ,79 ,81 ,90 ,91).

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-y,TNF-a*, and *IL-2*.

Interferons

IFN-α and IFN-γ have been shown to be active against ovarian cancer both *in vitro* and *in vivo* (92 ,93 ,94 ,95). IFN-α, which is capable of augmenting the cytotoxicity of autologous peripheral blood mononuclear cells to human ovarian carcinoma cells (96), is well tolerated locally, but has significant systemic side effects, making it an attractive candidate for intraperitoneal immunotherapy. The earliest clinical trials of IFN-α administered intraperitoneally were conducted in women with persistent ovarian cancer at second-look laparotomy (97 ,98 ,99). Intraperitoneal IFN-α can augment NK cytotoxicity but this was not invariably associated with clinical response. The dominant mechanism responsible for killing tumor cells in the peritoneal cavity may involve the direct effect of IFN on cancer cells, rather than the enhancement of antitumor immune responsiveness (100). In several confirmatory second-line trials in women with minimal residual disease, the surgically documented response rates to IFN-α were 30% to 50% (101). Adverse effects, such as lethargy, fatigue, and flulike symptoms, are common with the administration of the interferons.

Interferon-α also has antitumor effects *in vitro* as well as clear immune-enhancing effects *in vivo* in humans (102). The biologic effects of this cytokine have led to the examination of IFN-α therapy in gynecologic malignancies. Treatment of cervical cancer cells *in vitro* with IFN-α 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 (103).

In a cooperative European trial, patients with residual ovarian cancer after initial *cisplatin*-based chemotherapy were treated IP with recombinant human *IFN*-α; approximately one third of evaluable patients achieved a complete response (104). In a more recent French study, recombinant human *IFN*-α was evaluated as second-line treatment in patients with persistent ovarian cancer at second-look laparotomy (105). One hundred and eight patients were studied, and 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 IP *IFN*-α as adjuvant treatment in ovarian cancer.

In a randomized phase III trial, Windbichler and colleagues (106) demonstrated that the use of subcutaneous *IFN*-γ in women receiving first-line platinum-based chemotherapy in ovarian cancer was well tolerated. A higher proportion of the *IFN*-γ-treated patients developed fever and flulike syndrome. However, there was no appreciable increase in gastrointestinal, neurological, or hematological toxicity. Importantly, a higher response rate and longer disease progression-free survival was seen in women receiving *IFN*-γ plus chemotherapy when compared with women treated with chemotherapy alone. No statistically significant improvement in overall survival was observed. The addition of *IFN*-γ to current treatment regimens needs to be explored to determine whether it would also have a similar advantage when combined with those agents.

Although the mechanisms of action of *IFN*-γ in patients with ovarian cancer are unknown, it has been speculated that this cytokine may inhibit the expression of dysregulated oncogenes (e.g., HER-2/*neu*), improving the response of *cisplatin*-resistant cells. Evidence for this is mixed (107 ,108 ,109). Cytokine administration IP appears to be necessary to augment local cytotoxic effector cells, but in the randomized trial by Windbichler et al. systemic administration conferred the survival benefit. This could be attributed to the stimulatory effects of *IFN*-γ on cells of the immune system, including NK cells and macrophages, thereby enhancing responsiveness to chemotherapy. Interferons, including *IFN*-γ, have been shown to have not only an antiproliferative effect, but also antiangiogenic effects. Therefore, the combination of agents, such as *IFN*-γ, thalidomide, or anti-VEGF, with cytotoxic therapy presents a new opportunity for the development of innovative pharmacologic agents in solid tumors.

Tumor Necrosis Factor-a

In various preclinical studies, *TNF*-α displayed significant antineoplastic activity against a variety of malignant cell lines (110). However, **in phase I trials of *TNF*-α delivered systemically, there was limited clinical activity with considerable systemic toxicity**, especially fevers, rigors, and hypotension (111 ,112 ,113 ,114). As with other cytokines and biologic response modifiers, it had been hoped that IP TNF would produce an increased antitumor response with lower systemic side effects. In a phase I trial, IP administration of recombinant human *TNF*-α was shown to be safe and to have a marked pharmacokinetic advantage over systemic administration (115).

In another study, IP recombinant human TNF was used to control malignant ascites (116). 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 ascites. On the basis of this report, **further studies are indicated of IP 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* (116 ,117).

Interleukin-2

Interleukin-2 also has been used for systemic experimental immunotherapy. In an early study, recombinant human IL-2 administered IV 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, i.e., lymphokine-activated killer (LAK) cells, and augmented NK cytotoxicity (118). The IP administration of IL-2 also has been the subject of some studies (83 ,88). The major rationale for developing the IP route of administration is the observation that IL-2 activity against malignant tumors *in vitro* is enhanced with increasing drug concentrations (118 ,119). In a phase I trial, administration of IL-2 IP resulted in a 100-fold increase in peritoneal cavity exposure compared with systemic administration (91). In a phase I to II study of IP IL-2 in refractory ovarian cancer, 2 of 13 patients had a complete response (119). Systemic toxicities were mild and included fever, fatigue, myalgias, diarrhea, emesis, and abdominal pain.

Although few ongoing clinical trials are focused on IL-2 based therapies, experimental work with this cytokine is ongoing, especially in combination with other forms of treatment. For instance, a recently published study examined the effect of administration of low-dose IL-2 (2×10^5 IU/m^2/day) plus G-CSF and EPO after autologous peripheral stem cell transplantation in patient with breast and ovarian cancer (120). Hematopoietic recovery and posttransplantation clinical courses were comparable in G-CSF plus EPO without IL-2 and in G-CSF + EPO plus IL-2-treated patients, without significant side effects attributable to IL-2 administration. A significantly higher polymorphonuclear cell count was observed posttransplant in the G-CSF + EPO–treated patients who also received IL-2. However, addition of IL-2 treatment did not result in any significant acceleration in the kinetics of recovery of lymphocyte subsets or in NK activity.

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 (121). 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 and the identification of the region of *paclitaxel* responsible for the induction of IL-8 (122 ,123). 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 (124 ,125 ,126 ,127 ,128 ,129 ,130). Adoptive immunotherapy, involving the infusion of autologous *ex vivo*–activated immune effector

cells, has been shown to produce tumor regression in various animal and human tumors (124). Exposure of peripheral blood mononuclear cells to IL-2 leads to the generation of lymphokine-activated killer (LAK cells) that are cytotoxic for a variety of tumor cells. Experimental treatment of human subjects with LAK cells and IL-2 has yielded some responses (42 ,87 ,124 ,138). *Tumor-infiltrating lymphocyte* (TIL) immunotherapy, with or without added IL-2, also has been examined in ovarian cancer (129 ,130 ,133). In a phase I trial, recombinant IL-2 and LAK cells were administered IP after systemic administration of IL-2, with partial clinical responses observed in several patients (91 ,132). 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. **Given that the overall response rate to LAK treatment is low, that this type of adoptive immunotherapy can result in high morbidity, and that it is impractical in most medical settings, adoptive immunotherapy may not be a practical option for the treatment of ovarian cancer** (98).

Dendritic Cell Therapy

Cancers may develop or grow because the immune system is not given a strong enough signal to become activated to destroy the tumor cells. In some cases, cancers are able to down-regulate immune responses, as cytokines or other molecules produced by tumor can inhibit antitumor immune responses. It may be possible to counter this lack of antitumor immune responsiveness by enhancing antigen-presenting cell activity. **Dendritic cells (DC) are highly effective antigen-presenting cells, and play a central role in the induction of both CD4 and CD8 T-cell responses.** DC can be pulsed with tumor antigen peptides or bioengineered to express tumor antigens, allowing them to be used in experimental therapies that aim to enhance antitumor immunity. Exposure of T cells to DC pulsed with ovarian cancer–derived antigen preparations resulted in the generation of cytolytic effector T cells that could kill autologous tumor cells *in vitro* (134 ,135 ,136). In a recent phase I clinical trial, Hernando and co-workers (137) showed that patients with advanced gynecological malignancies could be effectively vaccinated with DC pulsed with a nontumor test antigen, keyhole limpet hemocyanin (KLH), and autologous tumor antigens; lymphoproliferative responses to KLH and to tumor lysate stimulation were noted. The treatment was safe, well tolerated, immunologically active, and generally devoid of significant adverse effects.

There are two major challenges that need to be overcome for the successful development of effective DC-based therapies for ovarian cancer: the identification of tumor-specific antigens and the induction of therapeutically effective immune responses to these antigens (138). The recent identification of a group of serine proteases that may be novel ovarian tumor-associated antigens may offer the opportunity to expand the potential of DC-based immunotherapy (139). As novel ovarian cancer-associated antigens are identified, and the techniques of DC activation and antigen expression are better developed, DC-based immunotherapy may provide a therapeutic alternative for the treatment of these cancers.

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. **This has led to the development of prophylactic and/or therapeutic vaccines to HPV, as well as treatment approaches based on the enhancement of host immune function** (140 ,141 ,142 ,143). In fact, an HPV vaccine has been shown to have an exceptional level of

efficacy in a recent clinical trial: An HPV-16 viruslike-particle vaccine was seen to result in 100% efficacy in the reduction of the incidence of persistent HPV-16 infection (143). All cases of HPV-16–related cervical intraepithelial neoplasia seen in this study occurred among the placebo recipients. Therefore, administration of this HPV-16 vaccine clearly reduced the incidence of both HPV-16 infection and HPV-16–related cervical intraepithelial neoplasia. These findings suggest that immunization of HPV-negative women with similar vaccines, especially polyvalent vaccines providing immunity to several oncogenic HPV subtypes, will markedly reduce the incidence of cervical cancer in the future, especially in developing countries, where clinical screening for cervical dysplasia is not widely available.

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 therapeutic interventions at the molecular level (144 ,145 ,146). 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 (147 ,148 ,149 ,150).

One natural target for gene therapy is p53, which is mutated in many ovarian cancers. Initial preclinical and clinical results were promising (151 ,152) and led to the initiation of a trial in which replication-deficient adenoviral vectors carrying wild-type p53 were given intraperitoneally in combination with standard chemotherapy to patients with ovarian cancers with p53 mutations (153). **No significant therapeutic benefit was seen**, and given the multiple genetic changes that result in cancer, repair of single genes, such as p53, may not be an appropriate strategy (153). Therefore, significant problems exist, including limitations in the ability to deliver therapeutic genes at a sufficiently high level, and with specificity, into tumor cells.

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4

Chemotherapy

Maurie Markman

- General Principles
- Biologic Factors Influencing Treatment
- Pharmacologic Factors Influencing Treatment
- Principles of Combination Chemotherapy
- Antineoplastic Drugs

General Principles

Part of "4 - Chemotherapy "

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.

Table 4.1 Issues To Be Considered before Using Antineoplastic Drugs

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)

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 or tumor marker so that response can be assessed.**
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 indicated, the patient should be referred to a properly equipped facility.

Tumors can be grouped into four categories by their likelihood of chemotherapeutic response:

- **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.
- **In the second group (e.g., epithelial ovarian cancer), chemotherapy improves survival but does not restore a normal life expectancy in the majority of patients.** Individuals with these tumors usually benefit from chemotherapy, and it should be offered unless there are exceptional circumstances.
- **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.**
- **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

Part of "4 - Chemotherapy "

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.

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, expanding, and renewing.

- 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.
- 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.
- 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.

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

- A 1-mm mass will have undergone approximately 20 tumor doublings.
- A 5-mm mass (a size that might be first visualized on a radiograph) will have undergone 27 doublings.
- 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).

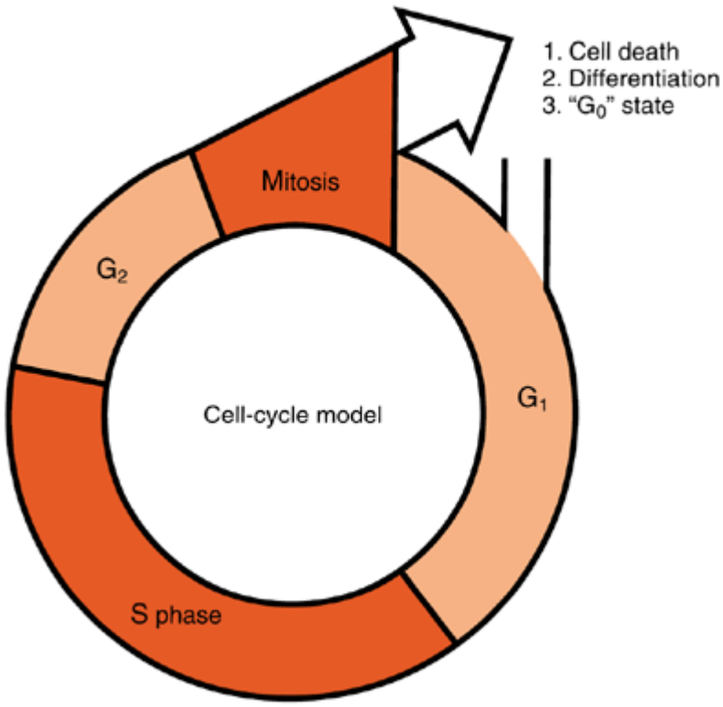

Figure 4.1 The cell cycle. After cell division, a cell can either (1) die, (2) differentiate, or (3) enter resting (G_0) phase. Cells in the latter two phases can reenter the cycle at G_1.

- **M phase (mitotic phase)** of the cell cycle is the phase of cell division.
- **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.
- **S phase (DNA synthetic phase)** is the period in which new DNA replication occurs.
- **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.
- **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. 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:

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

Cell Cycle–Specific Versus Cell Cycle–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).

Table 4.2 Cell Cycle-Specificity of Chemotherapeutic Agents

Classification	*Examples*
Cell cycle-specific, proliferation-dependentn	*Hydroxyurea, cytosine arabinoside*
Cell cycle-specific, less proliferation-dependent	*5-Fluorouracil, methotrexate*
Cell cycle-nonspecific, proliferation-dependent	*Cyclophosphamide, actinomycinD, carboplatin, cisplatin*
Cell cycle-nonspecific, less proliferation-dependent	*Paclitaxel, topotecan*

Cell Cycle Nonspecific

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

Cell Cycle Specific

At the other end of the spectrum, cell cycle–specific agents, such as hydroxyurea, depend on the proliferative activity and on the phase of the cell cycle for their action. The agents kill in only one phase 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 against 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).

Table 4.3 Site of Action in the Cell Cycle

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

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 (1). 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.

Theories for Overcoming Drug Resistance

It has been suggested that spontaneous mutation to phenotypic drug resistance occurs in rapidly growing malignant tumors: the somatic mutation theory (2). **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:

- Tumors are curable with chemotherapy if no permanently resistant cell lines are present and if chemotherapy is begun before resistant cells develop.
- If only one antineoplastic agent is used, the probability of cure diminishes rapidly with the development of a single resistant line.
- 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.
- 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.

An alternative hypothesis, developed by Norton and Simon, focuses on the Gompertzian growth rates exhibited by malignant tumors (3 ,4). This mathematical model suggests that the efficacy of treatment of tumors exhibiting sensitivity to particular chemotherapeutic agents will be enhanced if single agents, or combination regimens, are delivered at their optimal dose levels in a "dose-dense" manner, rather than as alternating regimens.
The fundamental difference between the Norton-Simon and Goldie-Coldman models is that in the former approach, the individual drugs are given in sequence at their optimal levels to produce a cytotoxic effect, whereas in the later strategy, which focuses on the rapid administration of as many active agents as possible, dose levels of individual drugs will frequently need to be modified due to overlapping toxic effects (e.g., bone marrow suppression). Active research is ongoing to test both concepts in clinical trials in the management of gynecologic malignancies.

Pleiotropic 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.

Dose Intensity

Full doses of chemotherapy are necessary to obtain optimal clinical results. 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.**
Most of the data on the clinical impact of dose intensity have 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* in patients with advanced ovarian cancer failed to demonstrate improved duration of remission or survival, although the

dose-intense regimen was only double the relative dose intensity of the standard regimen (6). Several additional randomized trials have confirmed the results of the GOG trial (7 ,8 ,9), although at least one well-designed trial has suggested some benefit associated with dose intensity in ovarian cancer (10). 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 being explored to increase the intensity of drug regimens 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 have also been studied** and offer the advantage of not requiring marrow harvest under general anesthesia. More recent studies have attempted 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), or who are previously untreated with chemotherapy (11 ,12 ,13).

Attempts have been 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 (14). A role for this bone marrow stimulatory agent in the routine treatment of ovarian cancer remains to be defined.

Principles of Combination Chemotherapy

Part of "4 - Chemotherapy "

Pharmacologic Factors Influencing Treatment

Part of "4 - Chemotherapy "

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 (15).

$$\text{Drug effect} = \text{Drug concentration} \times \text{Duration of exposure} = C \times T$$

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, or intramuscularly. **Over the past decade, considerable attention has been given to the** regional administration of chemotherapeutic agents, particularly in ovarian cancer (**16 ,17 ,18**). The intraperitoneal approach is based on the concept that the peritoneal clearance of the agent is slower

than its plasma clearance and, as a result, an increased concentration of the drug in the 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 1000-fold, depending on the molecular weight, charge, and lipid solubility of the particular drug. Clinical trials in ovarian cancer have been performed with *cisplatin, carboplatin, paclitaxel*, and drug combinations (16). A number of reports have noted that approximately 30% of patients with ovarian cancer who have small volume residual disease after initial systemic platinum-based chemotherapy can achieve a surgically defined complete response following second-line treatment with intraperitoneal *cisplatin*.

Several randomized trials have now revealed that the intraperitoneal administration of *cisplatin* as primary therapy of small volume advanced ovarian cancer (largest tumor nodule within the peritoneal cavity ≤1 cm in maximal diameter) **results in an improvement in both the time to subsequent disease progression and overall survival**, compared with intravenous delivery of this agent (17 ,18). It is anticipated that ongoing research with intraperitoneal therapy will define a standard role for this method of drug delivery in the management of ovarian cancer.

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*), 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. Types of drug interaction of potential importance include those listed in Table 4.4 .

Table 4.4 Drug Interactions in Cancer Chemotherapy

Effect	*Caused by*	*Interaction*	*Resulting in*	*Bioavailable Drug*
↓**Renal function/excretion**	Nephrotoxic antibiotics	*Methotrexate; cisplatin*	↓Excretion	↑
↓**Hepatic metabolism/biliary excretion**	*Vincristine*	*Doxorubicin*	↓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**	*Phenobarbitol*	*Cyclophosphamide*	↑Metabolism	↑
	Methotrexate	*5-Fluorouracil*	↑Activation	↓
	5-Fluorouracil	*Methotrexate*	↓Metabolism	

Important drug interactions with antineoplastic drugs include:

- The alkylating agents are highly reactive compounds and may produce direct chemical or physical inactivation when multiple drugs are mixed.
- 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.
- 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.*
- 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.*
- The nephrotoxic antibiotics frequently alter *methotrexate* excretion and may increase the renal toxicity of *cisplatin.*

Combination chemotherapy has become the standard approach to management of many adult solid tumors, including breast cancer and female pelvic malignancies. 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:

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

Table 4.5 Mechanisms of Resistance to Anticancer Drugs

Mechanism	*Example Drug*
Insufficient activation of drug	*Intraperitoneal cyclophosphamide, 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*
Rapid DNA repair of a drug-related lesion	*Alkylating agents, cisplatin, carboplatin*
Gene amplification	*Methotrexate*
Altered enzyme expression	*Topotecan*

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.

Table 4.6 Important Factors in the Design of Drug Combinations

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.

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

A partial remission has been variously defined as a 30% to 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.

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

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

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 (Table 4.8). Dose adjustments are based on glomerular filtration rate (GFR) or creatinine clearance and the target serum concentration multiplied by the *area under curve (AUC)* or platelet nadir for the drugs” antitumor activity (19). The formula is:

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

Table 4.8 Carboplatin Dosing

Area Under the Curve (AUC) Method: Calvert Formula

Dose (mg) = target AUC (mg/mL × min) × [CrCl (mL/min) + 25]

CrCl = creatinine clearance

Guidelines

Untreated adults target AUC for *carboplatin* alone	= 5–27
Previously treated adults target AUC for *carboplatin* alone	= 4–25
Target AUC for *carboplatin* in combination	= 5

Platelet Nadir Method: Egorin Formula

Untreated patients

$$\text{Dose (mg/M}^2) = 0.091 \times (\text{CrCl/BSA}) \times (\text{PreRx Plt} - \text{Desired nadir Plt/PreRx Plt} \times 100) + 86$$

Previously treated patients

$$\text{Dose (mg/M}^2) = 0.091 \times (\text{CrCl/BSA}) \times [(\text{PreRx Plt} - \text{Desired nadir Plt/PreRx Plt} \times 100) - 17] + 86$$

M^2 = meters squared; BSA = body surface area;
PreRx Plt = pretreatment platelet count

Creatinine Clearance (CrCl)

Based on a timed urine collection

$$\frac{\text{Urine Creatinine}}{\text{Serum Creatinine}} \times \frac{\text{Urine Volume}}{\text{Time}}$$

Based on age, weight and serum creatinine

Method of Cockcroft and Gault

$$\text{CrCl men} = \frac{(140 - \text{Age}) \times (\text{Lean Body Weight})}{(\text{Serum Creatinine}) \times 72}$$

$$\text{CrCl women} = \text{CrCl men} \times 0.85$$

Method of Jeliffe

$$\frac{\text{CrCl}}{1.73} = \frac{100}{\text{Serum Creatinine}} - 2$$

CrCl = mL/min; Time = duration of collection in minutes; Age = years; Weight = kg; Urine Volume = mL; Urine creatinine = mg/dL; Serum creatinine = mg/dL

Modified from **Calvert AH, Newell DR, Gumbrell**, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989;7:1748–1756; and **Egorin MJ, Van Echo DA, Olman EA**, et al. Prospective validation of a pharmacologically based dosing scheme for the cis-diamminedichloroplatinum (II) analogue diamminecyclobutanedicarboxylatoplatinum. *Cancer Res* 1985;45:6502–6506; and modified and reproduced with permission from **Rubin SC**. *Chemotherapy of gynecologic cancers: Society of Gynecologic Oncologists handbook*, 2nd ed. Philadelphia: Lippincott Williams and Wilkins, 2004.

The desired target AUC is 4 to 5 mg/mL for previously treated patients and 5 to 7 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.

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.

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 exposure to 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. **The importance of quickly initiating broad-spectrum antibiotics in the presence of fever in a neutropenic patient, even in the absence of localizing signs of infection, cannot be overemphasized.** 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.

Whenever possible, before the initiation of antibiotics in a febrile granulocytopenic patient, cultures of possible sites of infection (e.g., blood, urine, sputum, recent surgical wound, indwelling intravenous delivery device) should be obtained. In addition, a detailed physical examination (including the throat, perianal region, and skin) should be performed looking for a specific site of infection, which may influence the choice of antibiotic therapy (e.g., catheter infection).

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 10,000 to 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:

- If the patient manifests active bleeding
- If the patient has active peptic ulcer disease
- 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)* can be considered for use in patients with, or anticipated to develop, severe thrombocytopenia.** The drug is administered subcutaneously beginning 6 to 24 hours after chemotherapy (50 µ/kg once daily) and continued until the platelet count exceeds 50,000/mm^3.

It is important to remember that treatment with this agent 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. Mild oral candidiasis (thrush) responds to several oral agents. More intensive therapy will be required for esophageal or severe oral candidiasis or herpes simplex infections (e.g., *amphotericin B, acyclovir*). 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, as does cytotoxic chemotherapy that can interfere with the integrity of the bowel wall. This condition is more common in patients receiving intensive chemotherapy (e.g, patients with leukemia), but can be observed with treatment of solid tumors (e.g., gynecological malignancies). The most common organism associated with this extremely serious condition is *Pseudomonas aeruginosa*. 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. The performance of an abdominal/pelvic computed tomography scan or ultrasound will be helpful in the evaluation of this constellation of signs and symptoms. Treatment includes the administration of broad-spectrum antibiotics with specific activity against aerobic gram-negative rods and anaerobes. Nasogastric decompression, intravenous fluids, and bowel rest can also be quite helpful. In the neutropenic patient, recovery of normal blood counts is essential for improvement of the condition. Surgical intervention may be required.

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 débridement 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, docetaxel*, 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 a variety of methods have generally been ineffective.

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*, 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:

- *Cisplatin*, which produces renal tubular toxicity associated with azotemia and magnesium wasting
- *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.
- *Nitrosoureas*, which cause a chronic interstitial nephritis with chronic renal failure
- *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* to prevent bladder toxicity by inactivating the toxic metabolite *(acrolein)*. Persistent hemorrhagic cystitis that does not respond to conservative management may be treated with ε-*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*, which may be 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 sclerodermalike reaction. The same reactions have been reported with *procarbazine, etoposide*, and *teniposide*.

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. A similar incidence of hypersensitivity reactions is observed with *docetaxel*, a closely related antineoplastic agent to *paclitaxel*.

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. Prolonged use of *etoposide* has also been associated with the development of leukemia.**

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:

- Extensive radiation therapy plus combination chemotherapy
- Prolonged alkylating agent therapy (>1 year)
- 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 (26 ,27 ,28).

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:

- The documentation of hyponatremia
- The presence of a urine that is hypertonic to plasma
- The exclusion of hypothyroidism or adrenal insufficiency

Hyperuricemia

Hyperuricemia may be a complication of effective cancer chemotherapy in certain tumors, particularly hematologic malignancies in which 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*.

Antineoplastic Drugs

Part of "4 - Chemotherapy "

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 *cyclophosphamide, melphalan, thiotepa, chlorambucil, busulfan*, and *ifosfamide*.
In addition to the more common alkylating agents, several antineoplastic agents of different types are usually classified as alkylatinglike agents, although their precise mechanism of action is less well understood and is probably not exclusively alkylation. These include the *nitrosoureas, DTIC (dacarbazine)*, and the platinum analogs *cisplatin* and *carboplatin*.
The characteristics of the commonly used alkylating agents are listed in Table 4.9 and the alkylating-like agents are listed in Table 4.10 .

Table 4.9 Alkylating Agents Used for Gynecologic Cancer

Drug	*Route of Administration*	*Common Treatment Schedules*	*Common Toxicities*	*Diseases Treated*
***Cyclophosphamide* (Cytoxan)**	Oral, IV	1.5–3.0 mg/kg/day orally 10–50 mg/kg IV every 1–4 weeks 600–1,000 mg/m^2 every 3–4 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), mucosal ulceration (rare), second malignancies	Ovarian, breast cancer
***Triethylenethiophosphoramide* (TSPA, Thiotepa)**	IV	IV.: 0.8 mg/ks every 4–6 weeks	Myelosuppression, nausea and vomiting, headaches, fever (rare)	Ovarian, breast cancer; intracavitary for malignant effusions
	Intracavitary	Intracavitary: 45–60 mg		
***Ifosphamide* (Ifex)**	IV	1.0 or 1.2 g/m^2/day × 5 days With mesna: 200 mg/m^2 immediately before and 4 and 8 h after ifosphamide	Myelosuppression, bladder toxicity, central nervous system dysfunction, renal toxicity	Cervical, ovarian cancer

IV, intravenous.

Table 4.10 Alkylating-like Agents Used for Gynecologic Cancer

Drug	*Route of Administration*	*Common Treatment Schedules*	*Common Toxicities*	*Diseases Treated*
***Cis-dichlorodiamino-Platinum* (cisplatin)**	IV	10–20 mg/m^2/day × 5 every 3 weeks 50–75 mg/m^2 every 1–3 weeks	Nephrotoxicity, tinnitus and hearing loss, nausea or and vomiting, myelosuppression, peripheral neuropathy	Ovarian and germ cell carcinomas, cervical and endometrial cancer
Carboplatin	IV	300–400 mg/m^2 × 6 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 carcinomas endometrial cancer
***Dacarbazine* (DTIC)**	IV	2–4.5 mg/kg/day × 10 days every 4 weeks	Myelosuppression, nausea and vomiting, flulike syndrome, hepatotoxicity	Uterine sarcomas, soft tissue sarcomas

IV, intravenous; AUC, area under “concentration versus time” curve.

Antitumor Antibiotics

The antitumor antibiotics are antineoplastic drugs that, in general, have been isolated as natural products from fungi found in the soil. 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, liposomal doxorubicin*, and *daunorubicin*, as well as *actinomycin D, bleomycin, mitomycin C*, 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 4.11 .

Table 4.11 Antitumor Antibiotics Used for Gynecologic Cancer

Drug	*Route of Administration*	*Common Treatment Schedules*	*Common Toxicities*	*Disease Treated*
Actinomycin D **(dactinomycin, Cosmegen)**	IV	0.3–0.5 mg/m^2 IV × 5 days every 3–4 weeks	Nausea and vomiting, skin necrosis, mucosal ulceration, myelosuppression	Germ cell ovarian tumors, choriocarcinoma, soft tissue sarcoma
Bleomycin **(Blenoxane)**	IV, SC, IM, IP	10–20 units/m^2 1–2 times/week to total dose of 400 units; for effusions: 60–120 units	Fever, dermatologic reactions, pulmonary toxicity, anaphylactic reactions	Cervical, germ cell ovarian tumors, malignant effusions
Mitomycin-C **(Mutamycin)**	IV	10–20 mg/m^2 every 6–8 weeks	Myelosuppression, local vesicant, nausea and vomiting, mucosal ulcerations, nephrotoxicity	Breast, cervical, ovarian cancer
Doxorubicin **(Adriamycin)**	IV	60–90 mg/m^2 every 3 weeks or 20–35 mg/m^2 every day × 3 every 3 weeks	Myelosuppression, alopecia, cardiotoxicity, local vesicant, nausea and vomiting, mucosal ulcerations	Ovarian, breast, endometrial cancer
Mithramycin **(Mithracin)**	IV	20–50 mg/kg/day every 4–6 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)**	IV	40–50 mg/m^2 every 4 weeks	Palmar-plantar erythrodysesthesia, myelosuppression, stomatitis	Ovarian and endometrial cancers

IV, intravenous; SC, subcutaneous; IM, intramuscular; IP, intraperitoneal.

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:

- The folate antagonist, *methotrexate*, which inhibits the enzyme dihydrofolate reductase

- The purine antagonists, *6-mercaptopurine* and *6-thioguanine*
- The pyrimidine antagonists, *5-fluorouracil (5-FU)* and *cytosine arabinoside*
- The ribonucleotide reductase inhibitor, *hydroxyurea*
- The nucleoside analog, *gemcitabine*

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 4.12 .

Table 4.12 Antimetabolites Used for Gynecologic Cancer

Drug	*Route of Administration*	*Common Treatment Schedules*	*Common Toxicities*	*Disease Treated*
***5-Fluorouracil* (fluorouracil, 5-FU)**	IV	10–15 mg/kg/week	Myelosuppression, nausea and vomiting, anorexia, alopecia	Breast, ovarian cancer
***Methotrexate* (MTX, amethopterin)**	PO, IV, intrathecal	Oral: 15–40 mg/day × 5 days; IV: 240 mg/m^2 with leucovorin rescue; intrathecal: 12–15 mg/m^2/week	Mucosal ulceration, myelosuppression, hepatotoxicity, allergic pneumonitis; with intrathecal: meningeal irritation	Choriocarcinoma; breast, ovarian cancer
***Hydroxyurea* (Hydrea)**	PO, IV	1–2 g/m^2/day for 2–6 weeks	Myelosuppression, nausea and vomiting, anorexia	Cervical cancer
***Gemcitabine* (Gemzar)**	IV	800–1000 mg/m^2/week × 3 weeks, followed by 1 week rest, then repeated	Myelosuppression, fever	Ovarian, breast cancer

IV, intravenous; PO, oral.

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 4.13). 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 4.13 Plant Alkaloids

Drug	*Route of Administration*	*Common Treatment Schedules*	*Common Toxicities*	*Disease Treated*
***Vincristine* (Oncovin)**	IV	0.01–0.03 mg/kg/week	Neurotoxicity, alopecia, myelosuppression, cranial nerve palsies, gastrointestinal	Ovarian germ cell, sarcomas, cervical cancer
***Vinblastine* (Velban)**	IV	5–6 mg/m^2 every 1–2 weeks	Myelosuppression, alopecia, nausea and vomiting, neurotoxicity	Ovarian germ cell, choriocarcinoma
***Epipodophyllotoxin* (etoposide, VP-16)**	IV	300–600 mg/m^2 divided over 3–4 days every 3–4 weeks	Myelosuppression, alopecia, hypotension	Ovarian germ cell, choriocarcinoma
	PO	50 mg/m^2/day × 21 days, then 1 week rest, then repeat		Ovarian cancer
***Paclitaxel* (Taxol)**	IV	135–250 mg/m^2 as a 3-to 24-hour infusion every 3 weeks	Myelosuppression, alopecia, allergic reactions, cardiac arrhythmias	Ovarian, breast cancer
***Vinorelbine* (Navelbine)**	IV	20–25 mg/m^2 weekly	Myelosuppression, constipation, peripheral neuropathy	Ovarian, breast cancer
***Docetaxel* (Taxotere)**	IV	60–100 mg/m^2 every 3–4 weeks	Myelosuppression, alopecia, hypersensitivity reactions, peripheral edema	Breast, ovarian cancer

IV, intravenous; PO, oral.

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 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* has been used in the treatment of cervical carcinoma.

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 (29). 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.

A second taxane, *docetaxel*, is also active in cancers of the ovary, endometrium, and breast (29). The dose-limiting toxicity of *docetaxel* is bone marrow suppression, principally neutropenia. Hypersensitivity reactions are also observed.

Topoisomerase-1 Inhibitors

This class of antineoplastic agents exerts its cytotoxic effect through inhibition of the enzyme topoisomerase-1 (Table 4.14) (26). 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 4.14 Topoisomerase-1 Inhibitors

Drug	*Route of Administration*	*Common Treatment Schedules*	*Common Toxicities*	*Disease Treated*
***Topetecan* (Hycamtin)**	Intravenous	1.25–1.5 mg/m^2/day × 5 days, every 3–4 weeks	Myelosuppression	Ovarian cancer
***Irinotecan* (Camptosar)**	Intravenous	250–300 mg/m^2 every 3–4 weeks or 125 mg/m^2/wk × 4, followed by 2 week rest	Myelosuppression, diarrhea	Cervix and ovarian cancers

Topotecan, the first topoisomerase-1 inhibitor approved for clinical use in the United States, is active in platinum-refractory ovarian cancer and cervix cancer. The major toxicity of the agent is bone marrow suppression (30). The drug is usually administered on a 5-day schedule, but more convenient weekly dosing regimens are currently undergoing investigation, as is an oral form of the drug.

Irinotecan, a second topoisomerase-1 inhibitor, has revealed activity in both cancers of the ovary and cervix (30). The major side effects of the agent are bone marrow suppression and diarrhea.

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* (Table 4.15).

Table 4.15 Miscellaneous Agent

Drug	*Route of Administration*	*Common Treatment Schedules*	*Common Toxicities*	*Disease Treated*
Hexamethylmelamine (also altretamine) (Hexalen)	Oral	120 mg/m^2/day × 14 days every 4 weeks	Nausea and vomiting, myelosuppression, neurotoxicity, skin rashes	Ovarian, breast cancer

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 treatment of patients with gynecologic malignancies. For women with cervical cancer, radiation therapy is the primary treatment for patients with advanced disease (1 ,2), yields cure rates equal to those seen after radical surgery for patients with early tumors (3 ,4), and reduces the risk of local recurrence after surgery for patients with high-risk features (5 ,6). For women with endometrial cancer, radiation therapy reduces the risk of local recurrence after hysterectomy for patients with high-risk features (7) and is potentially curative primary treatment for patients with inoperable cancers (8 ,9). In selected women with ovarian cancer, postoperative, adjuvant, whole-abdominal radiation therapy improves long-term survival (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 ,15).

Computer technology and information systems have transformed many aspects of radiation practice in the past two decades, making possible computed tomography (CT)–based 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. **In 1999 and 2000, the results of randomized clinical trials 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** (16 ,17 ,18). These results have led to one of the most significant changes in the standard treatment of gynecologic cancers in decades.

In this chapter, the basic principles of radiation therapy, radiation biology, and radiation physics are reviewed, and an overview of the indications for and techniques of radiation therapy in the treatment of gynecologic malignancies is presented.

- Radiation Biology
- Physical Principles
- Radiation Techniques
- Clinical Uses of Radiation

Radiation Biology

Part of "5 - Radiation Therapy "

Radiation Damage and Repair

Cellular Effects of Ionizing Radiation

Cell death can be 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 within 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 (mitotic cell death).** In some cases, a damaged cell may undergo a limited number of divisions before it dies, having lost the ability to reproduce indefinitely.
Apoptosis (programmed cell death) may also play an important role in radiation-induced cell death (19). In contrast with the more typical mitotic cell death described above, 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. Currently, 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 mammalian cell populations *in vitro* **are typically expressed graphically as dose-response or "cell survival" curves** (20). The surviving fraction of cells is plotted (on an exponential scale) against the dose of radiation (on a linear scale). Experimental data using single doses of sparsely ionizing radiation (e.g., x-rays, gamma (γ)-rays, electrons, or protons) typically produce cell survival curves with two components (Fig. 5.1): a shoulder region and an exponential region.

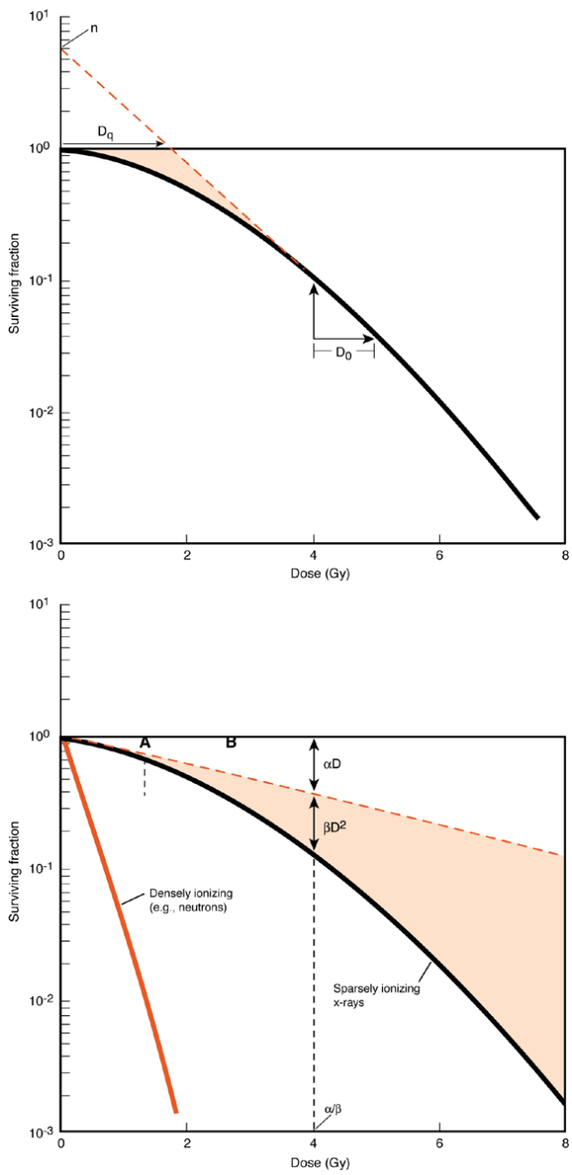

Figure 5.1 Parameters commonly used to characterize the relationship between radiation dose and cell survival in mammalian culture. In the multitarget, or N-D_0, model **(A)**, N is the extrapolation number, N and D_q measure the width of the shoulder, and D_0 represents the slope of the final exponential portion of the survival curve. The multitarget model provides an accurate description of experimental data in the exponential portion of the survival curve. The linear-quadratic model **(B)** more accurately describes the shape of the initial shoulder portion of the curve. Because the shoulder has more influence on fractionated radiation therapy, the linear-quadratic model is more often used to predict the results of fractionated clinical radiation therapy. (Modified, with permission, from **Hall EJ.** *Radiobiology for the radiologist*, 5th ed. Philadelphia: JB Lippincott, Williams & Wilkins 2000.)

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

- The multitarget model (also referred to as the N-D_0 model)
- The linear-quadratic model (also referred to as the α/ß model)

The *multitarget model* (Fig. 5.1A) is described by the expression $\log_e N = 5\ D_q/D_0$, 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 classical target theory, which holds 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 (21). 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. 5.1B).

The linear-quadratic model describes the dose-response relationship according to the equation $S = e^{-\alpha+\beta D_2}$ where S is the surviving fraction, D is the dose of radiation, and

α and β are constants (Fig. 5.1B). This model presupposes two components to cell death: one that is proportional to the dose (αD) and one that is proportional to the square of the dose (βD^2). The dose at which the linear and quadratic components are equal is α/β (Fig. 5.1A). 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 cell 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 with a response to radiation characterized by a relatively broad shoulder, reflecting the cells' greater ability to accumulate and repair sublethal damage during the interfraction interval (Fig. 5.2B). Many normal tissues and some poorly responsive tumors exhibit this type of fractionation response *in vivo* and *in vitro*. In contrast, most tumors and some acutely responding normal tissues (i.e., bone marrow and intestinal crypt cells) have a dose-response curve with a relatively narrow shoulder, indicating relatively little fractionation effect. **The difference between the *fractionation sensitivity* of tumors and normal tissues is an important determinant of the *therapeutic ratio* (the difference between tumor control and normal tissue complications) of fractionated radiation.**

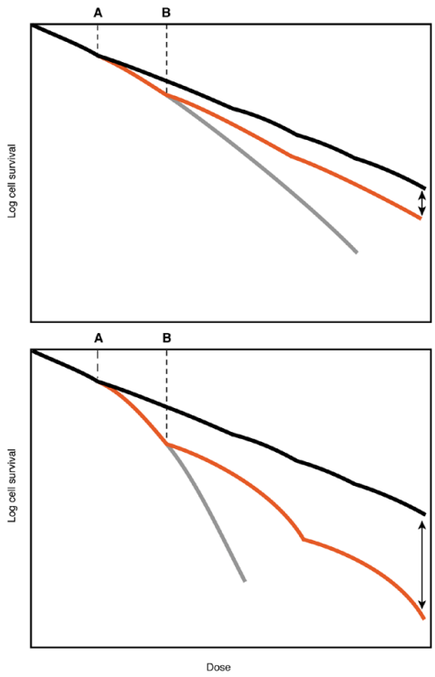

Figure 5.2 Relationship between radiation dose and surviving fraction of cells treated *in vitro* with radiation delivered in a single dose or in fractions. For most tumors and acutely responding normal tissues, the cellular response to single doses of radiation is described by a curve with a relatively shallow initial shoulder *(A)*. Cellular survival curves for late-responding normal tissues *(B)* have a more pronounced shoulder, suggesting that these cells have a greater capacity to accumulate and repair sublethal radiation injury. 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. 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.)

Dose-Rate Effect

So far, this discussion of cell survival curves and fractionation has referred toradiation given in acute exposures, i.e., 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 opportunity to repair sublethal injury during the exposure. This is called the *dose-rate effect***. 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 cells than for tumor cells. This differential effect implies a favorable therapeutic ratio that is exploited with LDR intracavitary and interstitial brachytherapy.**

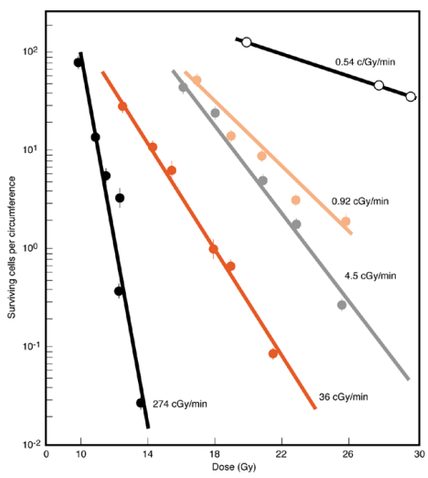

Figure 5.3 Response of mouse jejunal crypt cells to different dose rates of γ rays. The mice were subjected to total body irradiation, and the proportion of surviving crypt cells was determined by counting regenerating microcolonies in the crypts 3.5 days after irradiation. There was a dramatic difference in cell killing because of repair of sublethal injury at low dose rates. In this system, the lowest dose rate (0.54 cGy per 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 Rs

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

- Repair
- RepopulationRepair
- RedistributionRepair
- ReoxygenationRepair

Repair

As previously discussed, **because fractionated irradiation permits greater recovery of sublethal injury during treatment, a higher total dose of radiation is required to achieve a given biological 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 same level of cell death 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 (skin, mucosal surfaces, etc.) 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 (22 ,23). 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** (24 ,25).

Redistribution

Studies of synchronized cell populations have shown significant changes in the radiosensitivity of cells passing through different phases of the cell cycle (26). **Cells are usually most sensitive to radiation in the late G_2 phase and during mitosis and are most resistant in the mid- to late S and early G_1 phases.** When asynchronous dividing cells receive a fractionated dose of radiation, the first fraction 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** (Fig. 5.4).

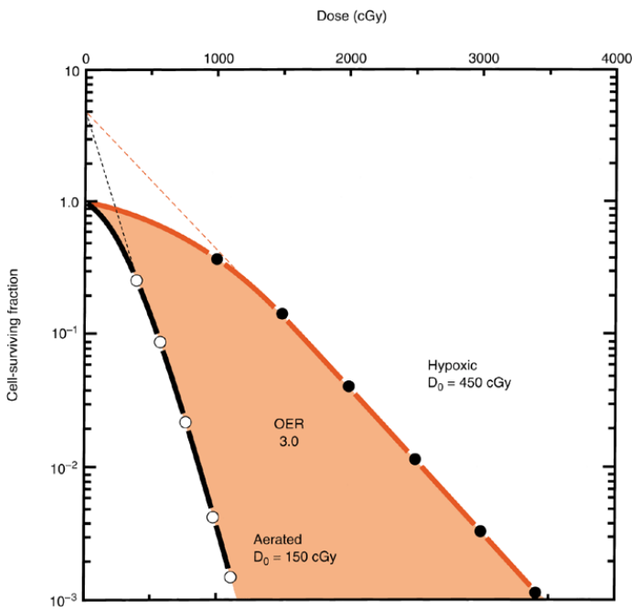

Figure 5.4 Survival curves for mammalian cells irradiated under aerated and hypoxic conditions. The dose required to produce a given level of damage is approximately three times greater under hypoxic/anoxic than under fully oxygenated conditions. The ratio of doses is the oxygen enhancement ratio (OER). Sometimes the shoulder also is reduced under hypoxic conditions. (Modified, with permission, from **Hall EJ.** *Radiobiology for the radiologist*, 5th ed. Philadelphia: JB Lippincott, Williams & Wilkins 2000.)

Most normal tissues are fully oxygenated, but 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 (27). 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 (28 ,29 ,30 ,31 ,32). These include:

- **Hyperbaric oxygen or carbogen breathing**
- **Red cell transfusion or growth factors**
- **Pharmacologic agents** (e.g., misonidazole) that act as hypoxic cell sensitizers
- **High-linear-energy-transfer radiation**

None of these approaches have clearly demonstrated an improvement in outcome; however, most of the studies have been severely compromised by technical or logistical problems.

Numerous retrospective studies have found correlations between the minimum hemoglobin during treatment and outcome, but all have been compromised by possible confounding risk factors (33 ,34 ,35). Even with multivariate analysis, investigators cannot

rule out the possibility that patients whose hemoglobin levels fell despite transfusion also had tumors that were more aggressive or less responsive to treatment. Studies of intratumoral oxygen tension also suggest that hypoxic tumors tend to have a poor prognosis; however, this correlation appears to be present even in surgically treated patients and may in part reflect a tendency for biologically aggressive tumors to be hypoxic (36).

An early randomized study of transfusion in anemic patients with locally advanced cervical cancer (37) hinted at improved local control when oxygen carrying capacity was increased. However, the findings of this small study have not yet been confirmed in a larger prospective trial, and the results remain inconclusive. One group of investigators (38) has even suggested that allogeneic transfusion may be harmful, although their results conflict with those of most other studies. Nevertheless, 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), and most clinicians recommend that the hemoglobin level at least be maintained above 10 g/dL during radiation therapy (39).

Linear-Energy Transfer and Relative Biological Effectiveness

Photons and high-energy electrons produce sparsely ionizing radiation, whereas larger atomic particles (e.g., neutrons and alpha particles) produce much more densely ionizing radiation. The rate of deposition of energy along the path of the beam is referred to as its linear-energy transfer (40). The biological effects of densely ionizing (high linear-energy transfer) radiation beams differ in several important ways from those of more sparsely ionizing radiation. **With high-linear-energy-transfer radiation beams**:

- **There is little or no repairable injury** and therefore no shoulder on the tumor cell survival curve.
- **The magnitude of cell death from a given dose is greater**, increasing the terminal slope of the survival curve.
- **The oxygen enhancement ratio is diminished**.

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

In practice, few facilities exist for the production of high-linear-energy-transfer 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 (20). Supraphysiological 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° 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. Biologists and clinicians have been trying to find ways to exploit this effect for many years but have been hampered by technological limitations on the ability to selectively heat deep-seated tumors (41). Recent results of a small trial from Amsterdam (42) suggested that survival was improved when hyperthermia was used with radiation in patients with locally advanced cervical cancer. The patients in this study received relatively low doses of radiation and did not receive concurrent chemotherapy but the findings suggest that the approach may still deserve further study.

Interactions between Radiation and Drugs

Drugs and radiation interact in a number of ways to modify cellular responses. Steel and Peckham (43) categorized these interactions into four groups: spatial cooperation (independent action), additivity, supraadditivity, 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 (i.e., the brain) may be treated with radiation to prevent recurrence. Alternatively, a drug may be used to destroy microscopic distant disease while radiation is used to sterilize 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 (the amount 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 be only additive or even subadditive.

Treatment Strategies

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. In this situation, the therapeutic ratio is improved.

There is no clinical evidence that sequential chemotherapy and radiation are more effective that radiation alone (44). However, **a number of prospective randomized studies have now been reported that demonstrate a clear supraadditive effect when chemotherapy and radiation are given concurrently to patients with locoregionally advanced cervical cancer** (17 ,18 ,45 ,46 ,47). The most successful treatments in all of these studies include concurrent *cisplatin*, while several include 5-*fluorouracil*, a drug that has been demonstrated to be an effective radiation sensitizer in other tumor systems. Other randomized trials have demonstrated benefit from concurrent administration of *mitomycin C* (48) or *epirubicin* (49) with radiation. A number of groups have also reported using concurrent chemoradiotherapy in patients with advanced vulvar cancer, usually with *cisplatin, fluorouracil*, or *mitomycin C* (50 ,51 ,52 ,53), 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 only be considered an effective cancer treatment if there is a differential biological 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 (54 ,55). 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 may achieve tumor control without causing 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, maximizing the probability of complication-free tumor control.

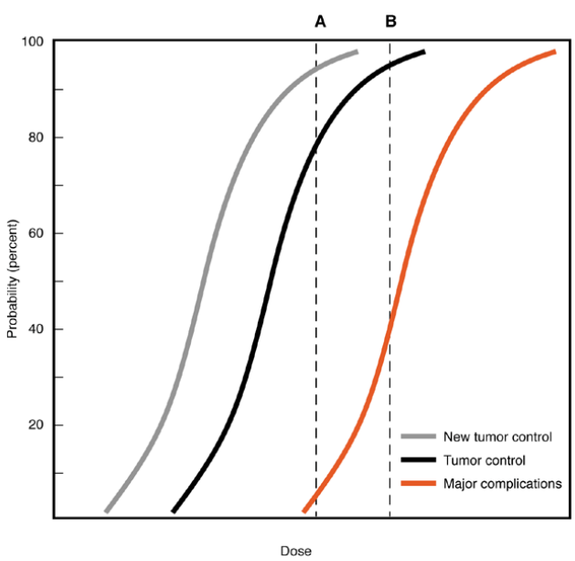

Figure 5.5 Theoretical sigmoid dose-response curves for tumor control and severe complications. The therapeutic ratio is related to the distance between the two curves. Dose A controls tumor in 80% of cases with a 5% incidence of complications. Dose B yields a 10% to 15% increase in the tumor control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

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**. In some normal tissues, cell death may occur through the mechanism of apoptosis. Although apoptosis is not the primary mechanism of damage in most normal tissue injury, it is important in the response of lymphocytes, salivary gland cells, and a small proportion of intestinal crypt cells (19).

Acute Reactions

Acute reactions to pelvic irradiation, such as diarrhea, are usually associated with mucosal denudation, which in turn stimulates an increase in cell proliferation (56). 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 is 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**:

- **Damage to vascular stroma** that causes an epithelial proliferation with decreased blood supply and subsequent fibrosis (57)
- **Damage to slowly or infrequently proliferating parenchymal stem cells** that eventually results in loss of tissue or organ function (56)

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, for a given dose of radiation administered over a given period, the risk of late effects will be greater with larger 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 (58 ,59 ,60) (Fig. 5.2).

The likelihood of developing serious late effects from radiation depends on many factors, including (but not limited to) the dose of radiation, radiation dose per fraction, volume of tissue irradiated, radiation dose rate, patient characteristics, other treatments (such as surgery or chemotherapy), and the end point being measured. Some tissues, such as the liver, kidney, and lung, consist of functional subunits that are arranged more or less in parallel; these tissues can tolerate a high dose of radiation given to a small portion of the organ without serious late effects but tend to be relatively sensitive to moderate whole-organ doses. Other organs, such as bowel or ureter, are organized in a serial fashion—delivery of a damaging dose to even a small portion of the organ can cause total organ failure. For all of the reasons discussed previously, normal tissue tolerances cannot be described in terms of simple dose limits. However, some generalizations about the tolerance of individual tissues can be made (doses refer to external radiation given in daily fractions of 1.8 to 2 Gy or with low dose-rate brachytherapy).

Uterus

The uterus and cervix are typically described as resistant to radiation; however, what is really meant by this is that the uterus can be treated to very high doses (more than 100 Gy in some cases) without the patient developing serious complications in adjacent critical structures (e.g., bowel and bladder). The uterus probably cannot sustain pregnancy after such doses. Even moderate doses of 40 to 50 Gy probably cause enough smooth muscle atrophy to prohibit successful term pregnancy, but this has rarely been tested. Women who were treated to the pelvis during the perimenarchal period have become pregnant after having received 20 to 30 Gy or more to the uterus but tend to have spontaneous second trimester abortions, probably due to underdevelopment of the uterus. Patches of endometrium frequently continue to function after doses of 50 Gy or more.

Ovary

The radiation dose required to cause ovarian failure is highly dependent on the patient's age. Perimenarchal girls may continue to menstruate and can even become pregnant after receiving up to 30 Gy to the ovaries; however, they usually experience premature menopause 10 to 20 years later. Most adult women have ovarian failure after 20 Gy; as little as 5 to 10 Gy can induce menopause in older premenopausal women.

Vagina

Tolerance depends on the region (upper, mid-, lower, anterior, posterior, or lateral) and length of vagina treated as well as radiation dose, fraction size, dose rate, hormonal support, and other factors. **Small portions of the surface of the lateral apical vagina can be treated to a very high dose (≥140 Gy) without causing major complications in adjacent structures.** However, these high doses do cause atrophy and shortening of the apical vagina. The tolerance is much less if treatment includes more than the surface of the apical vagina or if the dose includes the anterior, posterior, or distal vagina. Even moderate doses (40 to 50 Gy) may decrease elasticity of the vagina although it is sometimes difficult to distinguish the direct effects of radiation from those of tumor, altered hormonal environment, aging, and other factors.

Small Intestine

The risk of side effects is highly dependent on the dose and volume of radiation and on the patient's history. **In the absence of complicating factors, the entire small intestine can tolerate doses of up to 30 Gy without major late effects**. Smaller volumes can tolerate 45 to 50 Gy with a low risk of complications; the risk of chronic diarrhea and bowel obstruction increases rapidly with doses greater than 60 Gy and approaches 100% if a significant volume of small bowel receives 70 Gy or more. The risk of bowel obstruction is significantly increased in patients who have had major transperitoneal surgery, pelvic infection, or a history of heavy smoking (61).

Rectum

In most cases, the entire rectum can tolerate 45 to 50 Gy with a low risk of major sequelae. Small portions of the anterior rectal wall can tolerate doses of at least 70 to 75 Gy. However, the risk of serious late effects (severe bleeding, obstruction, fistula) increases steeply as the volume of rectum treated to high dose is increased.

Bladder

The entire bladder can be treated to 45 to 50 Gy with a very low rate of serious morbidity. This dose may have subtle effects on bladder contractility, particularly in patients who have also undergone radical hysterectomy. **Small portions of the bladder tolerate doses of 80 Gy or more with a low risk of major morbidity (severe bleeding, contracture, fistula).** However, the dose-response relationship is poorly defined in this range because it is difficult to accurately determine the maximum dose given to the bladder during intracavitary treatments.

Ureters

Surgically undisturbed ureters appear to tolerate 85 to 90 Gy of combined external beam and low-dose-rate intracavitary treatment with a low risk of stricture.

Kidneys

Most patients can tolerate up to 18 to 22 Gy to both kidneys with very little risk of long-term damage. Higher doses cause permanent damage to renal parenchyma. If the patient has normal renal function, 50% or more of the renal parenchyma can be treated to a high dose without causing renal failure; however, renal hypertension may occur if an entire kidney is obliterated with radiation. Underlying renal disease or concurrent use of chemotherapy can decrease renal tolerance.

Liver

In most cases, the liver can tolerate up to 30 Gy (at 1.5 Gy per fraction) to the entire organ, although this dose will cause transient elevation of alkaline phosphatase levels and can cause dysfunction in a small proportion of patients. Higher doses cause serious damage to liver parenchyma but can be tolerated if delivered to a portion of the liver only. Tolerance is highly dependent on underlying hepatic function and can be markedly decreased with concurrent delivery of some chemotherapeutic agents and during periods of hepatocyte regeneration (for example, after partial hepatectomy).

Spinal Cord and Nerves

Transverse myelitis and paralysis can occur in a small proportion of patients who receive doses as low as 50 Gy to the spinal cord, and the risk increases rapidly as the dose approaches 60 Gy at 2 Gy per fraction. However, **peripheral nerves, including the cauda equina**, are rarely effected after 50 Gy and **usually tolerate doses up to 60 Gy without serious sequelae.**

Bone

As little as 10 to 15 Gy of radiation causes transient depletion of bone marrow elements. **With doses of more than 30 to 40 Gy, permanent damage is done to supporting elements, and bone marrow within the irradiated area will not repopulate normally**. This can be seen as fatty replacement of the marrow cavity on MRI. The risk of fracture after radiation depends on the bone irradiated, volume of bone in the high-dose region, bone density, coexistent steroid use, and other factors. Symptomatic fracture is rare after treatment with 40 to 45 Gy of pelvic radiation. However, routine MRI sometimes detects small, usually asymptomatic insufficiency fractures of the pelvis after this dose (62). Hip fracture may be seen after doses as low as 40 Gy to the entire femoral head and neck, and the risk probably increases rapidly as the dose approaches 60 Gy.

Treatment Strategies

A variety of altered fractionation schemes have been devised to exploit the different sensitivities of tumor and normal tissues to fractionation and the possible effects of tumor cell repopulation. These include **hyperfractionation**, in which the dose per fraction is reduced, the number of fractions and total dose are increased, and the overall treatment time is relatively unchanged, and **accelerated fractionation**, in which the dose per fraction is unchanged, the overall treatment duration is less, and the dose is unchanged or decreased.

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. Hyperfractionation schemes may have an advantage if the increased dose delivered per day does not cause unacceptable acute effects and if patients are willing to accept the added inconvenience of two or three treatments daily.

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 (60). 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 schedules are usually avoided when treatment is likely to cure the patient because the α/ß 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 α/ß, may be a rare exception to this pattern. 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:

- Preoperative irradiation
- Diagnostic surgery (surgical staging) followed by definitive irradiation
- Intraoperative irradiation
- Surgical resection followed by postoperative irradiation
- Combinations of these approaches

Preoperative Irradiation

Preoperative irradiation 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—for example, the urethra or anus in a patient with locally advanced vulvar cancer.

Preoperative irradiation has largely been abandoned in favor of postoperative irradiation, which can be planned when information from the surgical specimen is available, and this avoids unnecessarily treating patients with very-early-stage disease. Preoperative irradiation is still sometimes used to treat patients with stage II endometrial cancer that grossly involves the cervix and is also 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, doses given when surgical resection is anticipated are usually lower than doses given when a tumor is treated definitively with radiation. **The greatest risk of preoperative radiation therapy is that if the tumor remains unresectable, the effectiveness of additional irradiation will be markedly decreased by the long interval between treatments.**

Intraoperative Irradiation

In some cases, intraoperative irradiation 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. **Removal of normal tissues from the treatment field is an important physical advantage of intraoperative external-beam techniques** that must counterbalance the biological disadvantage to any normal tissues remaining in the field when an entire dose is delivered in a single large fraction.

Postoperative Irradiation

Postoperative irradiation has been demonstrated to improve locoregional control and even survival in several settings important to gynecologic oncologists. **In vulvar cancer**, postoperative pelvic and groin irradiation reduces the risk of groin recurrence and improves the survival rate of patients with multiple positive inguinal nodes (14). **In endometrial cancer**, postoperative pelvic irradiation reduces the incidence of pelvic recurrences in patients with high-risk stage I disease (7 ,63 ,64). **In cervical cancer**, postoperative pelvic irradiation reduces pelvic recurrences in patients with lymph node involvement and in those with high-risk features in the cervical specimen (5 ,6).

Combination Approaches

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 therapy, combined treatment should usually be limited to situations in which 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 (65).

Physical Principles

Part of "5 - Radiation Therapy "

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 gamma (γ) rays, negatively charged beta (ß) rays (electrons), positively charged alpha (α) particles (helium ions), and 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 via 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 γ-rays are both composed of photons and differ only in that x-rays are produced by extranuclear forces and γ-rays are produced by intranuclear forces.

Interactions of Radiation with Matter

X-rays and γ-rays

Photons interact with matter by means of three distinct mechanisms: the photoelectric effect, Compton scatter, and pair production.

The photoelectric effect is most important at energies used for diagnostic purposes. However, this type of absorption also occurs with 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 effect is responsible for the increased absorption of bone that provides contrast between bone and soft tissue with diagnostic x-ray beams of 250 kV or less, but the increased bone absorption, high skin dose, and poor penetration make these beams unsuitable for most modern therapeutic applications. Superficial kilovoltage radiation beams, delivered using a transvaginal cone, are occasionally used for patients with large bleeding exophytic tumors to achieve hemostasis before definitive treatment (66).

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.

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 therapy 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 MV or greater make them particularly useful for pelvic treatment.

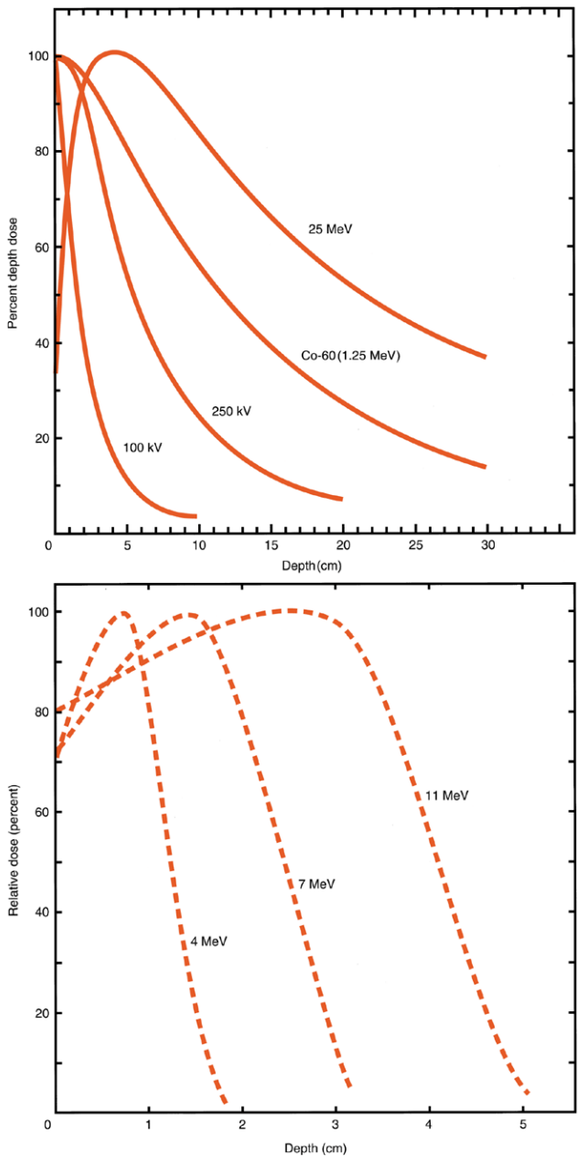

Figure 5.6 *Top:* **Depth dose curves for selected x-ray and γ-ray beams**. As the energy increases, the depth of maximum dose (D_{max} or D_{100}) increases. For kilovoltage beams, the dose is maximum at the skin surface. With appositionally directed megavoltage beams (e.g., ^{60}Co or 25-MeV photon 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.

Pair production absorption is related to Z^2. In soft tissue, this type of absorption only begins to dominate at photon energies of more than approximately 30 MeV, so pair production is of limited importance to current radiation therapy planning.

Electrons and Other Particles

Several types of particle beams are used in radiation therapy: electron beams, proton beams, and neutron beams.

Electron *s* are very light particles. When they 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 fall-off in dose occurs can be estimated by dividing the electron energy by 3.

Protons are positively charged particles that are much heavier than electrons. Protons scatter minimally as they interact with matter, depositing increasing amounts of energy as they slow down, and then stopping 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 are neutral particles that tend to deposit most of their energy in a single intranuclear event. For this reason, there is little or no recoverable injury, and there is no shoulder on the cell survival curve. The falloff of a neutron dose is similar to that of a photon beam of 4 to 6 MV, but the high relative biological effectiveness of these densely ionizing beams has been of interest to clinical investigators. However, **clinical studies of neutron treatments in cervical cancer patients were plagued by high complication rates** (67), 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 radians (rads), where 1 rad = 1 cGy and 1 Gy = 100 rad.

The rate of decay of a sample of radioactive material (such as radium or cesium) is referred to as the activity of the sample and is measured in curies (Ci), where 1 Ci = 3.7×10^{10} disintegrations per second and 1 mCi = 10^{-3} Ci.

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 (68). 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

Part of "5 - Radiation Therapy "

Radiation therapy is delivered in three ways:

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

Teletherapy

Several terms are commonly used to describe the dose distributions produced by external-beam irradiation of tissues.

Percentage depth dose is the change in dose with depth along the central axis of a radiation beam (Fig. 5.6).

D_{max} is the maximum dose delivered to the treated tissue. With a single appositional photon beam, the D_{max} is located at a distance below the tissue surface that increases with the energy of the photon beam (Fig. 5.6).

Source to skin distance is the distance between the source of x-rays (e.g., a cobalt source or the target in a linear accelerator) and the skin surface.

Isocenter is a point within the patient that remains a fixed distance from the radiation source as the treatment source (gantry) is rotated around the patient (Fig. 5.7).

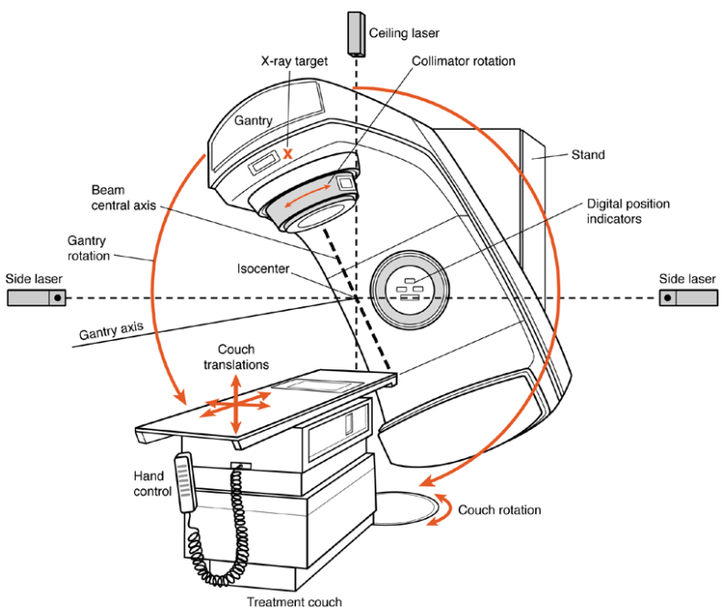

Figure 5.7 Diagram of a therapeutic linear accelerator. Patients are positioned on the treatment couch with a system of lasers that are aligned precisely with the center of the radiation beam. Collimators in the treatment head that is located on a rotating gantry define the size and rotation of the radiation field. The treatment couch can also be rotated around 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, Inc., 1993.)

Source to axis distance is the distance from the source of x-rays to the isocenter.

Isodose curve is a line or surface that connects points of equal radiation dose (Fig. 5.8).

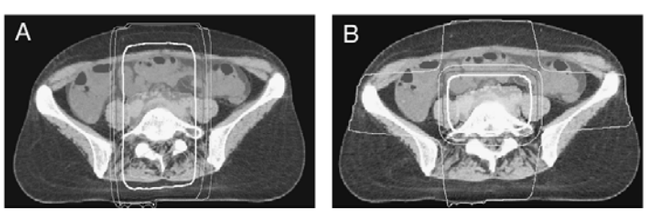

Figure 5.8 Isodose distribution for external-beam irradiation of the pelvis using an 18-MV beam. A: a pair of parallel opposed anterior and posterior fields; **B:** anterior, posterior, and two lateral fields (four-field box technique). The heavy white isodose line represents the region of tissue treated to ≥45 Gy.

Many factors influence the dose distribution in tissue from a single external beam of photons. These include:

- **The energy of the beam** (determined by its voltage). Higher-energy photon beams are more penetrating than lower-energy beams. In other words, the dose of radiation delivered to deep tissues relative to more superficial tissues is greater with higher-energy beams. Higher-energy beams also have a larger *buildup region* than lower-energy beams; this results in a relative sparing of the skin surface, facilitating irradiation of deep tissues (Fig. 5.6).
- **The distance from the source to the patient.** As the source to skin distance increases, the percentage depth dose increases.
- **The size of the radiation field.** The percentage depth dose increases with increasing field size because of the increasing contribution of internal scatter to the radiation dose. This effect is greatest with relatively low-energy radiation beams.
- **The patient's contour and the angle of the beam's incidence.**
- **The density of tissues in the target volume** (particularly air vs. soft tissue).
- **A variety of beam-shaping devices placed between the radiation source and the patient** that alter the shape or distribution of the radiation dose.

Modern linear accelerators permit many variations in these factors (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.

Most radiation therapy treatment plans combine two or more beams to create a dose distribution designed to accomplish three aims: (i) **to maximize the dose of radiation delivered to the target**; (ii) **to 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; and (iii) **to minimize the dose delivered to uninvolved tissues**, taking into account the different tolerances of various normal tissues.

The 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., anterior-posterior and posterior-anterior) 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. The simplest form of conformal therapy uses fairly conventional beam arrangements but exploits modern CT-based treatment planning techniques to more accurately define the target volume and to design blocks that conform closely to that volume. CT reconstructions permit more accurate shaping of fields that enter the patient from oblique angles. **Multileaf collimators** have computer-controlled leaves that can form irregularly shaped fields, replacing hand-loaded beam-shaping devices. Because the therapist no longer needs to enter the room to replace blocks on each field, it is possible to treat patients with more fields and more complex beam arrangements in a treatment visit of acceptable duration.

More recently, attention has been focused on intensity-modulated radiation therapy (IMRT) (Fig. 5.9). This approach uses complex computer algorithms to optimize delivery of radiation from multiple beam angles. The physician must carefully contour target volumes and all critical normal tissue structures on each slice of a CT scan that has been obtained in the treatment position. The minimum and maximum acceptable doses of radiation to be delivered to each area are specified. Recursive partitioning techniques are used to design an optimized plan, which usually includes multiple irregularly shaped fields from each of several (usually 6 to 9) beam angles. The leaves of multileaf collimators enter the field or retract dynamically to deliver the desired amount of radiation to tissues within the target. Very tightly conforming radiation distributions can be obtained with this approach. However, the time required to plan treatments is lengthened, as is the duration of daily treatments; quality assurance is also very demanding for this type of treatment because the fields are less readily visualized than static radiation fields.

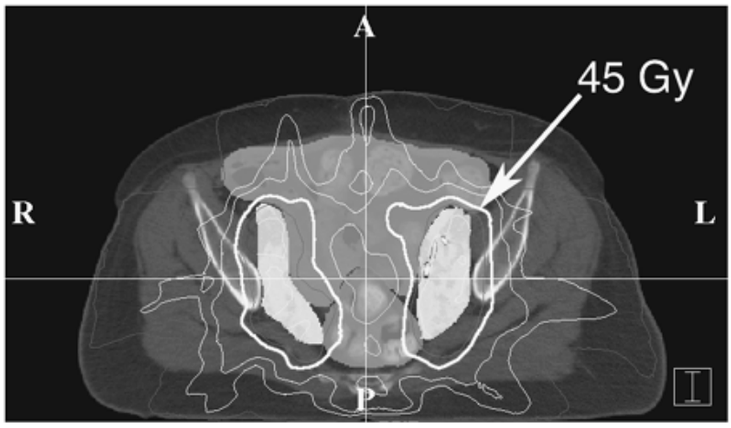

Figure 5.9 Dose distribution obtained using intensity modulated radiation therapy (IMRT) to treat the pelvic lymph nodes after hysterectomy. In this case, each of eight fields were modulated to obtain a distribution that covered the iliac and presacral lymph nodes while sparing bowel in the central pelvis from high dose. A somewhat larger volume receives low-dose radiation than with standard techniques, and the very tight dose distribution requires an accurate understanding of anatomy, tissues at risk, and internal organ motion.

Theoretically, the aforementioned teletherapy approaches should improve the therapeutic ratio by making it possible to deliver higher doses to tumor with greater sparing of normal tissues in many different clinical situations. However, because the dose of radiation falls off very rapidly outside the designated target volume, these plans require a high degree of confidence in the distribution of disease and meticulous patient immobilization.

Brachytherapy

Intracavitary Treatment

Any treatment that involves placement of radioactive sources within 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 (69 ,70). One applicator that is commonly used to treat intact carcinomas of the cervix is the Fletcher-Suit-Delclos system (Fig. 5.10). Other applicator systems, such as the Delclos dome cylinder, have been designed specifically for treatment of the vaginal apex after hysterectomy (71).

Table 5.1 Isotopes Used in Gynecologic Oncology

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_{avg}	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	1,620 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.

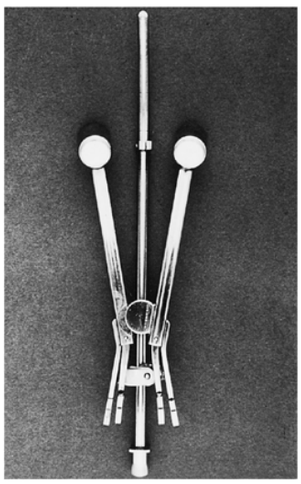

Figure 5.10 Intrauterine tandem and vaginal colpostats used for intracavitary irradiation in cervical cancer.

Figure 5.11 illustrates a typical pear-shaped isodose distribution produced by a line of intrauterine sources and Fletcher-Suit-Delclos vaginal colpostats loaded with ^{137}Cs. 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 (i.e., the cervix and paracervical tissues) without excessive treatment of 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.

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 anterior-posterior and lateral x-rays of the pelvis. Recent use

of remote afterloading devices automatically retract sources from the applicator to a lead-lined safe when someone enters the patient's room, further reducing the radiation exposure to visitors and medical personnel.

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 above, differentially sparing late-responding normal tissues as compared with acutely responding tissues and tumor cells. The dose of intracavitary therapy needed to radically treat cervical cancer is usually delivered in 72 to 96 hours during one or two hospital admissions. Although some investigators have tried to reduce the duration of these treatments by doubling the dose rate (from 40 cGy per hour to 80 cGy per hour), the limited clinical data evaluating this approach suggest that doubling the dose rate results in a less favorable therapeutic ratio (72).

With the advent of computer-controlled remote afterloading 20 to 30 years ago, 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 past 10 years, particularly for intracavitary gynecologic applications. However, many clinicians have been reluctant to change to HDR therapy because of the theoretical radiobiological disadvantages of large-fraction radiation and the absence of well-controlled randomized clinical trials comparing HDR and LDR regimens (73).

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 five fractions of 5.5 to 6 Gy each to point A after 45 Gy to the pelvis, although there is wide variation in the number of fractions (2 to 13) and the dose per fraction (3 to 9 Gy) (74 ,75). 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 seen with 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 when converting 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 (76 ,77).

HDR intracavitary therapy is the primary form of brachytherapy used to treat cervical cancer in several Asian and European countries. In the United States, the proportion of patients treated with HDR intracavitary therapy has gradually increased to about 20%. For patients with relatively favorable normal tissue and tumor anatomy treated with 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 (73 ,76 ,78 ,79).

Interstitial Implants

Interstitial brachytherapy refers to the placement of radioactive sources within tissues. Various sources of radiation, such as ^{192}Ir, ^{198}Au, and ^{125}I, may be obtained as radioactive wires or seeds. ^{192}Ir may be obtained as separate sources that are usually distributed at regular intervals (usually 1 cm) in Teflon tubes or as wires with activity specified in terms of the mCi per cm. Sources may be positioned in the tumor or tumor bed in a variety of ways:

- **Permanent seed implants (usually ^{125}I or ^{198}Au)** can be inserted using a specialized seed inserter. These implants are sometimes used to treat pelvic or aortic lymph nodes, particularly in the case of nodal recurrence after radiation.
- **Temporary Teflon catheter implants** can be intraoperatively placed and subsequently loaded with radioactive sources (usually ^{192}Ir). These are sometimes used to treat tumor beds (80).
- **Temporary transperineal interstitial needle implants** can be placed with guidance using a Lucite template with regularly spaced holes and a central obturator that can hold a tandem or additional needles. Needles are afterloaded, usually with ^{192}Ir. These implants are used to treat vaginal and some cervical tumors. In some cases, guidance by laparoscopy or laparotomy may facilitate needle placement, particularly during implantion of apical vaginal lesions (81 ,82 ,83).
- **Temporary 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 for treating urethral and vaginal tumors (Fig. 5.12) (84).

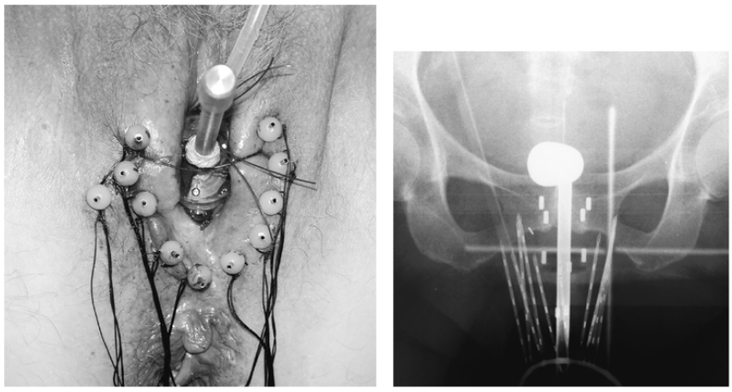

Figure 5.12 Interstitial implant for a stage II distal vaginal cancer. Needles are individually inserted transperineally; a finger is placed in the vagina while the needles are inserted to monitor the position of each needle relative to the tumor and mucosal surface. ***Left*** A Lucite cylinder in the vagina displaces uninvolved vagina from the needles. ***Right*** Postoperative radiographs show placement of the needles and can be used for dose calculations and treatment planning.

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 (85 ,86) (Fig. 5.13). The ability to place sources in the lateral parametrium with this technique suggests a theoretical advantage over intracavitary treatment for patients with pelvic wall involvement. Some investigators have claimed high local control rates with this approach (85 ,86). 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. The risk of major complications also may be greater than that with external-beam and intracavitary treatment (82 ,83). With greater clinical experience and CT- or MRI-guided dosimetry, these results may be improved.

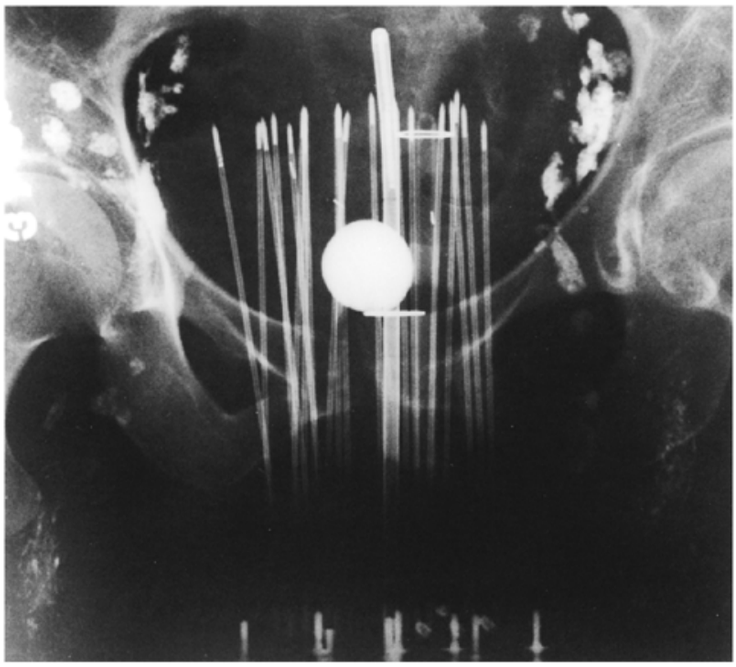

Figure 5.13 Interstitial implant for an advanced cervical cancer. (Reproduced with permission from Dr. Mark Schray, Division of Radiation Oncology, Mayo Clinic).

The radiation oncology community remains polarized as to the appropriateness of interstitial therapy for patients with intact cervical carcinomas, and as yet no randomized trials have been conducted to compare the therapeutic ratio of conventional intracavitary irradiation with that of interstitial treatment. Interstitial implants may also be used in a variety of other gynecologic applications, including vaginal cancer, vaginal recurrence of cervical or endometrial cancer, and urethral cancer.

Intraperitoneal Radioisotopes

Intraperitoneal radioisotopes have been used to treat epithelial ovarian cancer in an effort to address the transperitoneal spread of the disease (87). Radioactive chromic phosphate (^{32}P) has largely replaced colloidal gold (^{198}Au) for peritoneal treatment. The longer

half-life (14.3 days), pure ß decay, and higher mean energy (0.698 MeV) of ^{32}P yield 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 within the peritoneal cavity. **In practice, isotope is seldom distributed uniformly to the peritoneal and omental surfaces** (88). 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 (89). 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 (90).

Clinical Uses of Radiation

Part of "5 - Radiation Therapy "

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 (69). 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, most importantly 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 locoregional 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 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 anterior-posterior and posterior-anterior pelvic fields are as follows:

- **Inferior**—at the midpubis or 3 to 4 cm below the most distal disease in the cervix or vagina (usually demonstrated using a radioopaque vaginal marker).
- **Superio**r—at the L4–L5 interface so that the common iliac nodes are encompassed. For patients with very small tumors that are at less risk for extensive nodal spread, the upper border may be placed at the L5–S1 interface.
- **Latera**l—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 beams (anterior, posterior, and right and left lateral) rather than an opposed pair of anterior and posterior beams** (Fig. 5.8) **can sometimes reduce the volume of tissue irradiated to 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 (91 ,92). 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. However, when the pelvis is treated after hysterectomy, four or more fields usually produce a more favorable dose distribution than two opposed fields.

For most patients with locally advanced disease, an initial course of treatment is given with external-beam irradiation. Four to five weeks (40 to 45 Gy) of external 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. Because the number of brachytherapy treatments is greater when HDR treatments are given, practitioners who use this approach often begin brachytherapy before external-beam therapy has been completed if the initial tumor response has been adequate. The balance between external-beam and intracavitary therapy may vary somewhat according to the tumor extent (69). However, several studies have suggested that intracavitary therapy is critically important to successful treatment, even for patients with very bulky stage IIIB tumors (1 ,93).

Patients with International Federation of Gynecology and Obstetrics (FIGO) stage IA disease can often be treated with intracavitary irradiation alone. Most patients

with stage IB1 disease have a sufficiently high risk of metastasis to the pelvic lymph nodes to justify at least a moderate dose (e.g., 39.6 Gy) of pelvic radiation to sterilize possible microscopic regional disease.
For patients with carcinoma of the cervix who have vaginal hemorrhage, hemostasis can usually be achieved with vaginal packing, application of Monsel's solution, and rapid initiation of external-beam irradiation. For patients with excessive bleeding, transvaginal irradiation (if available) or several days of accelerated pelvic radiation therapy (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 (94). A number of methods have been used to prescribe and specify the doses delivered with intracavitary therapy. Most radiation oncologists specify treatment using some variation of the Manchester system, which is identified with the use of two primary reference points (Fig. 5.11):

- **Point A—a point 2 cm lateral and 2 cm superior to the external cervical os in the plane of the implant**
- **Point B—a point 3 cm lateral to point A**

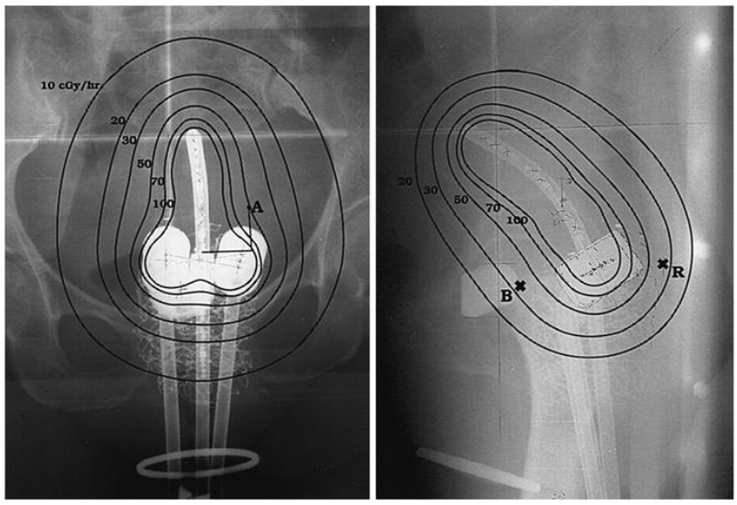

Figure 5.11 Posterior-anterior and lateral views of a Fletcher-Suit-Delclos applicator system loaded with ^{137}Cs sources for treatment of invasive cervical cancer. Units on the isodose contours are cGy per hour. Point A*(A)*, point B*(B)*, and bladder*(B)* and rectal*(R)* reference points are indicated on the figure. (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: J.B Lippincott Co., 2001:1526–1556.)

Although the cGy doses from intracavitary and external radiation therapy may not be biologically equivalent (particularly with HDR therapy), these doses are frequently summed to determine the total doses to points A and B. **The total dose to point A (from external-beam and LDR intracavitary therapy) believed to be adequate to achieve central disease control is usually between 75 Gy (for stage IB disease) 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**.

Prescription and treatment planning cannot be limited to specification of these reference points. Other factors that should be considered include the following:

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

A number of methods and reference doses 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 (95 ,96). For this reason, it is important to qualitatively examine each intracavitary system rather than to depend solely on normal-tissue reference points.

Some centers also document the total “milligram-Radium-equivalent hours” (mgRaEq-hr) 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-hr 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-hr (from intracavitary radiation therapy given at 40 to 60 cGy/hr) should not exceed 6,000 to 6,500. An alternative measure is the **reference air kerma**, defined as the total dose delivered at 1 meter from the center of the activity and measured in $\mu Gy \cdot m^2$; this unit serves the same purpose but can more easily be used with isotopes other than radium or cesium.

Results of Treatment

Radiation therapy is extremely effective in the treatment of stage IB1 cervical cancer, producing central and pelvic disease control rates of greater than 98% and greater than 95%, respectively, and disease-specific survival rates of approximately 90% (4 ,97). **Pelvic control rates decrease as tumor size and FIGO stage increase**, although large single-institution 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 treated with radiation alone (e.g., before routine use of concurrent chemotherapy) (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.

Recent 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 (17 ,18 ,45 ,46 ,47). Several of the regimens tested in these studies also included *fluorouracil*. This drug is known to be a potent radiation sensitizer, particularly effective in the treatment of gastrointestinal malignancies, but its contribution to chemoradiation in patients with carcinoma of the cervix is still uncertain. Recent randomized trials suggest that other drugs, including *mitomycin C* (48 ,98) and *epirubicin* (49), may improve outcome when they are given concurrently with radiation to patients with locally advanced cervical cancer.

Adjuvant Pelvic Radiation Therapy after Radical Hysterectomy

For patients with stage IB and IIA cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy, lymph node involvement is probably the strongest predictor of local recurrence and death—patients with nodal involvement have survival rates only about 50% to 60% those of patients with negative nodes (99 ,100 ,101). **Parametrial involvement and involvement of surgical margins also predict a high rate of pelvic recurrence and are considered to be indications for postoperative irradiation.** In 2000, the Southwest Oncology Group published results of a study comparing postoperative radiation with combined chemoradiation in patients who had positive lymph nodes, parametrium, or surgical margins; the study demonstrated a 50% reduction in the risk of recurrence when *cisplatin* and *fluorouracil* were added to pelvic irradiation (46).

For patients with negative nodes but high-risk features in the primary tumor (i.e., tumor size <4 cm, deep stromal invasion, or vascular space involvement), postoperative radiation has also been demonstrated to produce a significant reduction in the risk of recurrence (6). This is discussed further in Chapter 9 .

The price of adjuvant pelvic radiation is a somewhat greater risk of major complications than with surgery alone or radiation alone (6 ,102). For this reason, a National Cancer Institute Consensus Conference (65) 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 who have an isolated pelvic recurrence after radical hysterectomy can sometimes be treated successfully 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. These patients have 5-year survival rates as high as 60% to 70% (103). The prognosis is much poorer for patients whose tumors involve the pelvic wall or nodes; few groups report better than a 20% 5-year survival rate for these patients when they are treated with radiation alone. Some groups have reported encouraging results with combined radiation and concurrent chemotherapy (104). It probably is also reasonable to extrapolate from recent randomized trials that demonstrate improved survival with concurrent chemoradiation for locally advanced cervical cancer to justify a similar approach in patients 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 (105). Patient factors such as a history of pelvic infection, heavy smoking, previous abdominal surgery, and diabetes mellitus may increase the risk of complications (61 ,106). The positioning of the intracavitary system also may influence the risk of complications. Late effects may be seen in the bladder (hematuria, fibrosis and contraction, or fistulas) and in the rectosigmoid or terminal ileum (bleeding, stricture, obstruction, or perforation). 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 (107 ,108). Unfortunately, our understanding of the factors influencing sexual dysfunction in patients treated for cervical cancer is still incomplete. Although late effects may occur many years after treatment, most gastrointestinal complications occur within 30 months of radiation therapy (108).

In the United States, late complications of radiation treatment (occurring more than 90 days after treatment) are usually scored according to the RTOG/EORTC Late Radiation Morbidity Scheme which is part of the National Cancer Institute system for reporting of adverse events (Table 5.2). However, it is important to recognize that with today's multimodality treatments, several factors may contribute to adverse events. In Europe, many groups use the Franco-Italian Glossary, a scoring system that incorporates early and late surgical and radiation-related side effects (109).

Table 5.2 RTOG/EORTC Late Radiation Morbidity Scoring Schemea

Adverse Event[b]	Grade				
	0	1	2	3	4
Bladder	No change from baseline	Slight epithelial Atrophy/minor telangiectasia (microscopic hematuria)	Moderate frequency/generalized telangiectasia/intermittent macroscopic hematuria	Severe frequency and dysuria/severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (<150 mL)	Necrosis/contracted bladder (capacity <100 mL), severe hemorrhagic cystitis, fistula
Bone	No change from baseline	Asymptomatic; reduced bone density	Moderate pain or tenderness; irregular bone sclerosis	Severe pain or tenderness; dense bone sclerosis	Necrosis/spontaneous fracture
Joint	No change from baseline	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement	Severe joint stiffness; pain with severe limitation of movement	Necrosis/complete fixation
Kidney	No change from baseline	Transient albuminuria; no hypertension; mild impairment of renal function; urea 25–35 mg %; creatinine 1.5–2.0 mg %; creatinine clearance >75%	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea >36–60 mg %; creatinine clearance >50%–74%	Severe albuminuria; severe hypertension; persistent anemia (<10 g %); severe renal failure; urea >60 mg %; creatinine clearance <50%	Malignant hypertension; uremic coma/urea >100 mg %
Liver	No change from baseline	Mild lassitude; nausea; dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling hepatic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis/hepatic coma or encephalopathy
Vagina	No change from baseline	Partial stenosis or shortening but less than complete occlusion	Complete occlusion Telangiectasis with frequent bleeding	Radionecrotic ulcer	Fistula to bladder, bowel, or peritoneal cavity
Small/large	No change from baseline	Mild diarrhea; mild cramping; bowel movement 5x daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement >5x daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/perforation fistula
Spinal cord	No change from baseline	Mild Lhermitte's syndrome	Severe Lhermitte's syndrome	Objective neurologic findings at or below cord level treatment	Mono-, para-quadriplegia
Subcutaneous tissue	No change from baseline	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture >10% linear measurement	Necrosis

RTOG, Radiation Therapy Oncology Group; EORTC, European Organization for Research and Treatment of Cancer.

[a]Used for adverse events occurring more than 90 days after radiation therapy.

[b]Includes sites most pertinent to treatment of gynecological malignancies.

Palliation

Because cervical cancers are usually responsive to radiation, the latter plays an important role in the palliation of metastatic disease. **Short courses of palliative radiation, such as 2,000 cGy in five fractions or 3,000 cGy in 10 fractions, usually will alleviate symptoms related to bony metastases or paraaortic nodal disease**. Such treatment 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 . **Indications for radiation therapy in the treatment of endometrial cancer are as follows:**

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

In the past, disease confined to the uterus often was routinely treated with preoperative intracavitary radiation therapy. 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 (110). Preoperative irradiation reduces the risk of vaginal apex recurrence but has never been proven to improve survival, although no randomized studies have been done (111 ,112). 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 (111 ,113 ,114).

Most patients with stage I endometrial cancer have minimally invasive grade 1–2 tumors that rarely recur after hysterectomy alone and usually need no additional treatment. 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 or cervical stromal involvement) (115 ,116). This treatment reduces the risk of pelvic recurrence but has never been proven to improve survival. The Gynecologic Oncology Group 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 (64). In another randomized trial, Creutzberg et al. (63) reported that postoperative radiation therapy reduced the risk of pelvic recurrence but had no significant impact on survival. Unfortunately, both of these trials included a large number of patients who had relatively favorable findings (grade 1 disease or less than 50% invasion); neither trial included a sufficient number of patients who had grade 3 tumors or deep myometrial invasion to rule out clinically important differences in these subgroups.

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. Whole-abdominal irradiation appears to be valuable treatment for some patients with minimal residual disease after hysterectomy (117 ,118).

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 (119 ,120).

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 (121 ,122 ,123 ,124). Because many of the patients in these series had 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 (122 ,123 ,124 ,125 ,126) are summarized in Table 5.3 . The survival rates are very similar in the five 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 was confined to the pelvis—a situation in which a relatively high dose of radiation can be given.

Table 5.3 Evidence of Long-Term Control of Stage II and III Ovarian Cancer with Macroscopic Residual Disease Using Abdominopelvic Radiation Therapy

		Size of Residual Disease	
Center	***End Point***	***<2 cm***	***≥2 cm***
Princess Margaret Hospital (125)	(n) 10-year RFS	(91) 38%	(91) 6%
Stanford (123)	(n) 15-year RFS	(42) 50%	(54) 14%
Salt Lake City (122)	(n) 10-year RFS	(12) 62%	(10) 0%
Walter Reed Hospital (124)	(n) 10-year OS	(24) 42%	(20) 10%
Yale (126)	(n) ~6-year OS	(27) 41%	

RFS, relapse-free survival rate; OS, overall survival rate; n, number of patients

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, and spinal cord) limit the dose of radiation that can be given to the whole abdomen to about 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.**

Technique

Two techniques have been used to treat the whole abdomen:

- The **moving-strip** technique: A 10-cm-high field (usually ^{60}Co) is moved by 2.5-cm increments so that each "strip" receives 8 or 10 fractions, usually of 2.25 Gy each (127 ,128). This approach was developed when available equipment could not treat very large volumes in one field.
- The **open-field** technique: The whole abdomen receives 1 to 1.5 Gy each day with a single pair of anterior-posterior and posterior-anterior fields (Fig. 5.14).

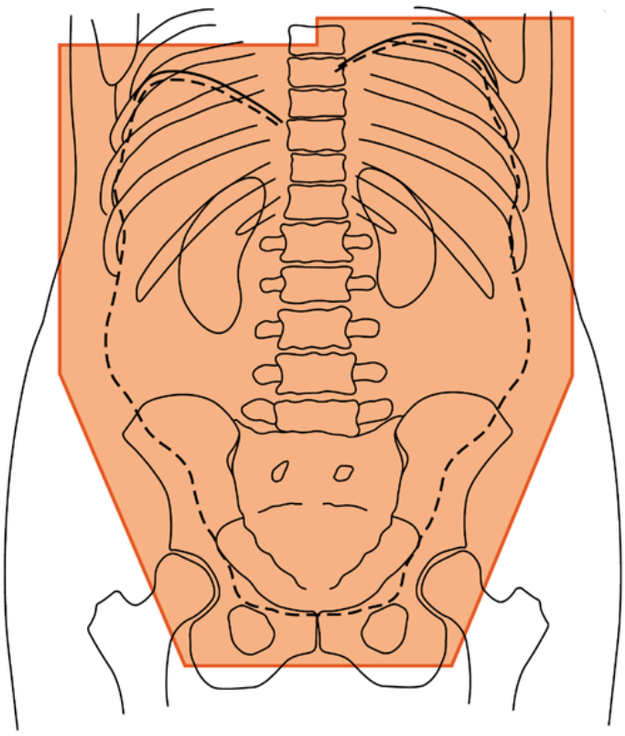

Figure 5.14 Treatment portals for carcinoma of the ovary or for uterine papillary serous carcinoma. The field must encompass the entire peritoneal cavity. Shielding is usually added to limit the dose to the kidneys to less than 18 to 20 Gy. The liver dose is usually limited to 25 Gy.

These two techniques have been compared in randomized trials that demonstrated no significant difference in survival (128 ,129). In the Princess Margaret Hospital Study (128), 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. 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 (123). 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 side effects of abdominopelvic irradiation include nausea, anorexia, general fatigue, and diarrhea in most patients (125). These symptoms are usually fairly well controlled with appropriate medications. About 10% of patients develop significant myelotoxicity (platelet count <100,000 or neutrophil count <1,500). 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 about 15% of patients, and as many as 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) (130).

A patient's suitability for postoperative abdominopelvic irradiation 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 (131 ,132). Abdominopelvic irradiation should be considered as primary treatment only for patients with stage I–III disease who have no macroscopic disease in the upper abdomen and minimal (<2 cm) residual disease in the pelvis (125 ,126 ,130 , 131 ,133 ,134).

The high response rates but frequent relapses observed after treatment of ovarian cancer with chemotherapy have encouraged many investigators to add whole-abdominal irradiation either as a salvage treatment for incomplete responses or as part of an up-front multimodality program. Fuks and coworkers (135) summarized the rationale for this sequential, multimodality approach to advanced ovarian cancer. 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 irradiation compared with historical controls treated with radiation alone (136). However, three randomized studies have compared chemotherapy alone with multimodality treatment (137 ,138 ,139) 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 (121 ,140 ,141).

Vulvar Cancer

The role of radiation therapy in the treatment of vulvar cancer has increased dramatically during the past 20 years. 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, **the possible benefits of radiation therapy in the treatment of vulvar cancer** include: (i) reduced regional recurrence and improved survival in patients with **inguinal node metastases** (14); (ii) reduced risk of vulvar recurrence in patients with **positive surgical margins**, **multiple local recurrences**, or other high-risk features (142 ,143); and (iii) **avoidance of exenterative surgery in patients whose disease involves the anus or urethra** (144). Radiation therapy may also be an alternative to inguinal lymphadenectomy in selected patients with clinically negative groins (15 ,145).

Several reports have emphasized the critical importance of careful radiation therapy technique (15 ,145 ,146). 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 only be accomplished with detailed CT-based treatment planning. Treatments that employ 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 about 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. 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., continuous-infusion *fluorouracil* or *cisplatin*) to improve control rates has been explored in a number of uncontrolled studies (50 ,51 ,52 ,147 ,148 ,149 ,150). 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* species is particularly frequent during treatment. **Late complications may include lymphedema, particularly after radical groin 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.

Vaginal Cancer

Although small apical vaginal lesions can sometimes be resected, the intimate relationship of the vagina to the bladder and rectum usually makes it impossible to perform curative surgical resection without sacrificing those organs. **For this reason, most patients who have invasive vaginal cancers are treated with radiation therapy, which achieves cure rates that are, stage for stage, similar to those achieved for patients with cervical cancer** (12 ,151). Treatment usually consists of a combination of external-beam irradiation and brachytherapy. Interstitial or intracavitary techniques may be used, depending on the size and site of the primary lesion and its response to external-beam therapy (Fig. 5.12). Because the dose gradient from intracavitary therapy is very steep, interstitial techniques are usually used to treat tumors that are more than 3 to 5 mm thick. Tumors that are very advanced, diffuse, or fixed may be boosted to a high dose using conformal external-beam therapy. The vaginal apex can move 2 to 3 cm with bladder filling and emptying; this internal organ motion should be carefully considered during treatment planning.

Concurrent chemoradiation may have a role in treatment of vaginal cancers, although there are no large trials in this group of patients. Many clinicians believe that similarities in histology and behavior justify the use of regimens that have been proven beneficial for cervical cancer to treat locally advanced vaginal cancers. Also, because vaginal cancer is very rare and the radiation therapy techniques are specialized, these patients may benefit from referral to centers with relatively large gynecologic radiation oncology practices.

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6
Pathology

Olga B. Ioffe

Aylin Simsir

Steven G. Silverberg

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

Part of "6 - Pathology "

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 tumor viruses. They belong to the Papovaviridae family, together with simian virus 40 (SV 40) and polyoma virus. To date, more than 100 types of HPV have been identified. Genital HPV types fall into two major categories based on oncogenic risk (2 ,3) (Table 6.1). **Low-risk HPV types, mostly HPV 6 and 11, are associated with condylomas and occasionally with low-grade squamous intraepithelial lesions (SILs) [cervical intraepithelial neoplasia (CIN) 1, mild dysplasia]. High-risk HPV types, mostly HPV 16 and 18, are found**

in more than 90% of high-grade squamous intraepithelial lesions [CIN 2 and 3, moderate and severe dysplasia and carcinoma *in situ* **(CIS)] and invasive squamous cell carcinomas.** Low-grade SILs are very heterogeneous with regard to HPV types. Twenty-nine percent to 83% of low-grade lesions are associated with high-risk HPVs (3 ,4).

Table 6.1 Classification of Human Papillomaviruses by Oncogenic Risk

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, 55, 56, 59, 66, 68

The physical state of HPV DNA differs in SIL and invasive carcinoma of the cervix (5). **In condylomas and low-grade squamous lesions, the viral genome is maintained as extrachromosomal circular episomes. In some high-grade SILs and in most carcinomas, the high-risk HPV genome is integrated into the host chromosomal DNA.** 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 3p, 4p, 4q, 11q) and protooncogene (c-*myc* and c-Ha-*ras*) inactivation.

Human papillomavirus infections of the cervix may take the form of flat condyloma (Fig. 6.1), **condyloma acuminatum** (Fig. 6.2), **or cervical neoplasia**. These lesions most commonly affect women of reproductive age and often are asymptomatic.

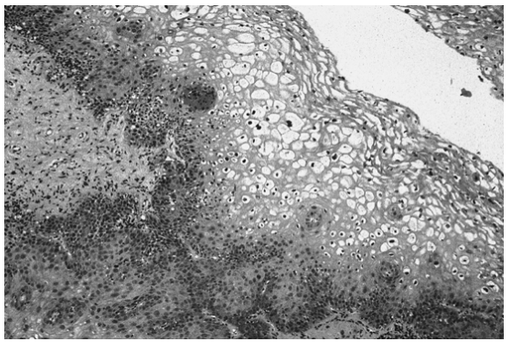

Figure 6.1 Flat condyloma without dysplasia. Koilocytes (perinuclear halo, binucleation, and nuclear hyperchromasia) are seen in the upper portion of squamous epithelium.

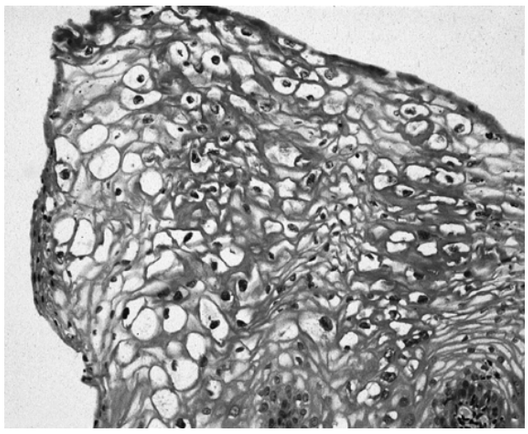

Figure 6.2 Condyloma acuminatum. Squamous epithelium with spikelike projections and koilocytosis (perinuclear halo, nuclear enlargement, and hyperchromasia).

Squamous Lesions of the Cervix

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 (halos), 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.**

Squamous Intraepithelial Lesions

The terminology used for squamous intraepithelial lesions (SIL) has evolved over time. Dysplasia (mild, moderate, severe) and CIS were the earliest terms used. Later, it was suggested that cervical intraepithelial neoplasia (CIN) be used. More recently, the Bethesda system for reporting cervicovaginal cytologic diagnoses proposed the term SIL (6). Laboratories use these terms interchangeably for reporting cervical biopsies. Table 6.2 provides the comparative usage of these terms.

Table 6.2 Comparative Terminology for Reporting Cervical Biopsy Diagnoses

Low-Grade SIL	Mild dysplasia
	CIN 1
	Condyloma
High-Grade SIL	Moderate/severe dysplasia
	CIN 2, 3
	Carcinoma *in situ*

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

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, SILs 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. Low-risk HPV types are predominantly seen in low-grade SIL (LSIL). The high-risk HPV types are predominantly seen in high-grade SIL (HSIL). By nuclear ploidy analysis, LSILs display

diploid/polypoid patterns, whereas HSILs display aneuploid patterns (7). **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).

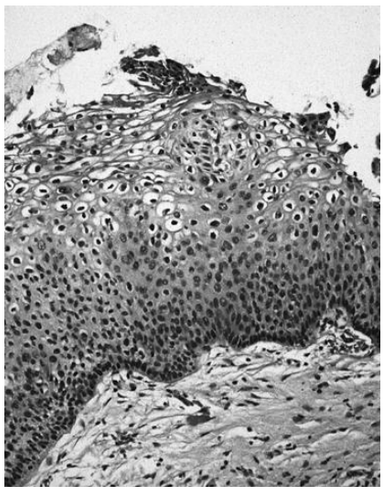

Figure 6.3 Mild squamous dysplasia and condyloma. The dysplastic changes are confined to the lower third of the epithelium, and the upper portion shows koilocytosis (condyloma).

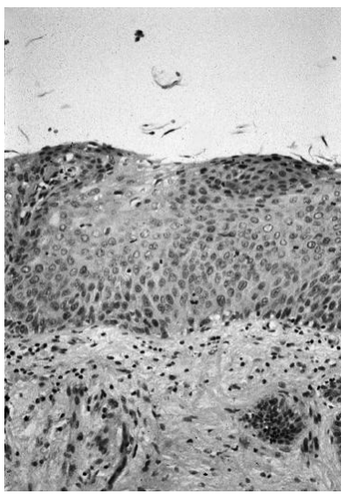

Figure 6.4 Moderate squamous dysplasia. The dysplastic cells show loss of polarity and increased mitotic activity. These changes involve the lower two-thirds of the epithelium.

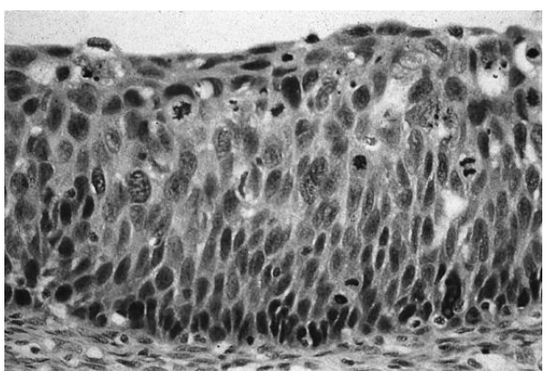

Figure 6.5 Severe squamous dysplasia. There is an almost full-thickness involvement of the squamous epithelium by dysplastic cells. Note that mitotic figures extend close to the surface of the epithelium.

It is difficult to predict the course and the outcome of HPV infection and SIL in a particular woman. In general, low-grade lesions are more likely to regress, and high-grade lesions are more likely to persist or progress. The cumulative data Ostor calculated based on his review of the literature since 1950 showed that 60% of CIN 1 lesions regress, 30% persist, 11% progress to CIS, and 1% progress to invasive carcinoma (8). For CIN 2, these rates were 40%, 40%, 20%, and 5%, respectively. **The likelihood of regression in CIN 3 is 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, as many as 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 (9). **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 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).

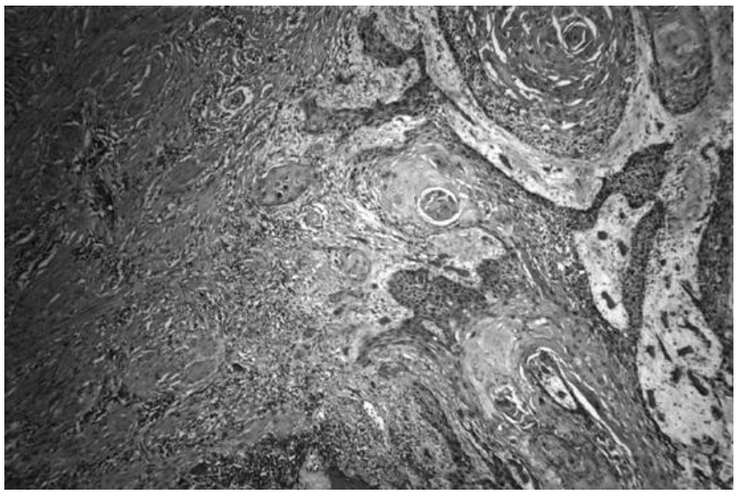

Figure 6.6 Invasive well-differentiated keratinizing squamous cell carcinoma. Note infiltrating irregular nests of squamous cells with keratin pearl formation.

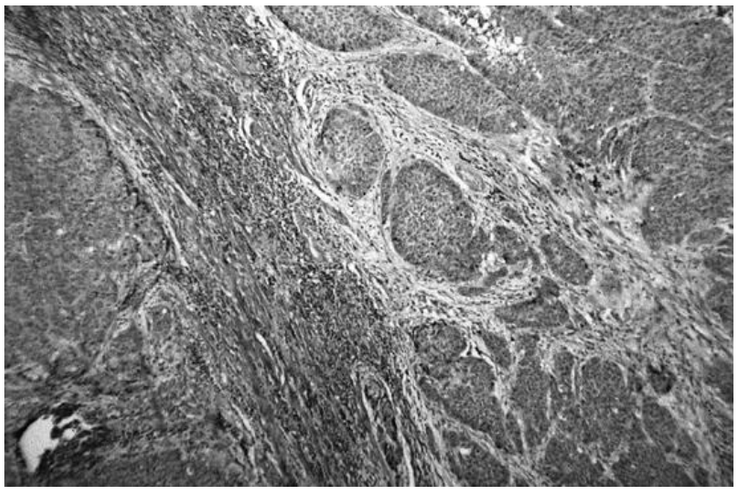

Figure 6.7 Invasive moderately differentiated nonkeratinizing squamous cell carcinoma. Invasive squamous nests do not show evidence of keratin formation and are surrounded by desmoplastic stroma.

Histologic Grading

The histologic grading of squamous cell carcinoma is based on the modification of the original Broders system (9). 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 most significant histopathologic parameters predictive of clinical outcome in early-stage cervical cancer are the tumor size, depth of invasion, and presence or absence of vascular space involvement (10).

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 cytologic 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 (11). **In both circumstances, the maximum horizontal tumor spread should be less than 7 mm.** The diagnosis of microinvasion 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 (9): For tumors with stromal invasion up to 1 mm, the incidence of pelvic lymph node metastasis is 0.2%, with no recurrences; for tumors with stromal invasion up to 3 mm, the incidence of pelvic lymph node metastasis is 0.7% and the recurrence rate is 0.3%; for tumors showing 3.1 to 5.0 mm of stromal invasion, the pelvic lymph node metastasis and recurrence rates are 4.3% and 1.4%, respectively.

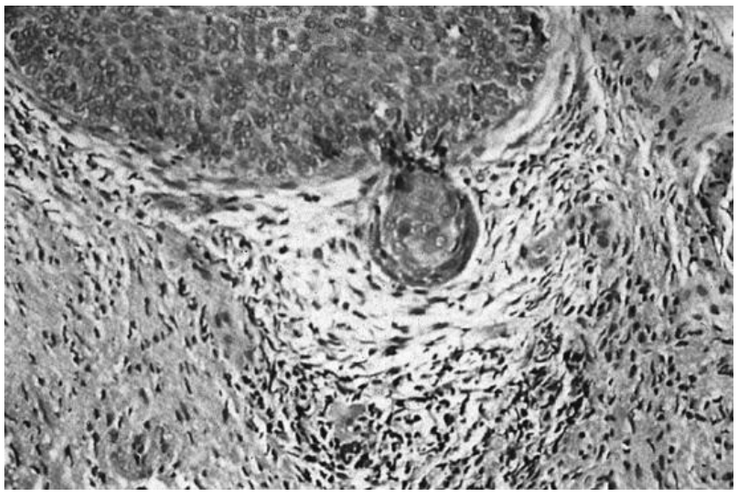

Figure 6.8 Microinvasive squamous cell carcinoma. An irregular protrusion from the overlying dysplastic epithelium is accompanied by a desmoplastic stromal response.

Lymphovascular Space Involvement

The clinical significance of lymphovascular space involvement remains controversial (12). Some studies have shown no relationship between lymphovascular involvement and lymph node metastasis in tumors showing less than 5 mm stromal invasion, whereas others have identified lymphovascular involvement as an adverse prognostic indicator.

Variants of Squamous Cell Carcinomam

Verrucous Carcinoma

This is a rare type of very well-differentiated squamous cell carcinoma (13) 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 wide local excision.

Papillary Squamous (Transitional) Cell Carcinoma

This is a rare variant of squamous cell carcinoma with similar clinical behavior (14 ,15). 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.

Warty (Condylomatous) Carcinoma

Warty carcinoma is a recently described rare type of squamous cell carcinoma (1). It is identical to the warty carcinoma occurring in the vulva. It superficially resembles a condyloma, but invasion occurs at the deep margin

similar to conventional type squamous cell carcinoma. Based on several cases described, **its behavior tends to be less aggressive** than conventional well-differentiated squamous cell carcinoma.

Lymphoepithelioma-Like Carcinoma

This lesion is composed of syncytiallike 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 (16). 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 (17). The differential diagnosis includes a lymphoproliferative disorder; this problem can be resolved by the application of immunohistochemistry for epithelial and lymphoid markers.

Glandular Lesions of the Cervix

Endocervical Glandular Dysplasia

Although endocervical adenocarcinoma *in situ* (AIS) is generally accepted as a precursor of invasive endocervical adenocarcinoma, endocervical glandular dysplasia (EGD) as a precursor of AIS is a highly controversial concept (18 ,19 ,20). EGD is defined as a preneoplastic lesion showing some of the cytologic and architectural atypia of AIS but to a lesser degree. **The presence of high-risk HPV in EGD, the younger age of patients with EGD compared with AIS, and the presence of EGD in some cases adjacent to AIS and invasive adenocarcinoma suggest that EGD and AIS represent a continuous spectrum.** However, these findings have not been widely replicated, and thus conclusive evidence for such progression is lacking. The morphologic criteria and outcome of EGD, particularly at the mild end of the spectrum, are not well defined. Some pathologists believe atypical glandular proliferations less than AIS should not be diagnosed at all.

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 (18). AIS is associated with squamous dysplasia/carcinoma in more than 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. Recent studies have shown that AIS treated by conization only is associated with a high rate of recurrence or residual disease if the excision margins are positive (21 ,22). With negative margins, recurrence rate is as low as 6%.

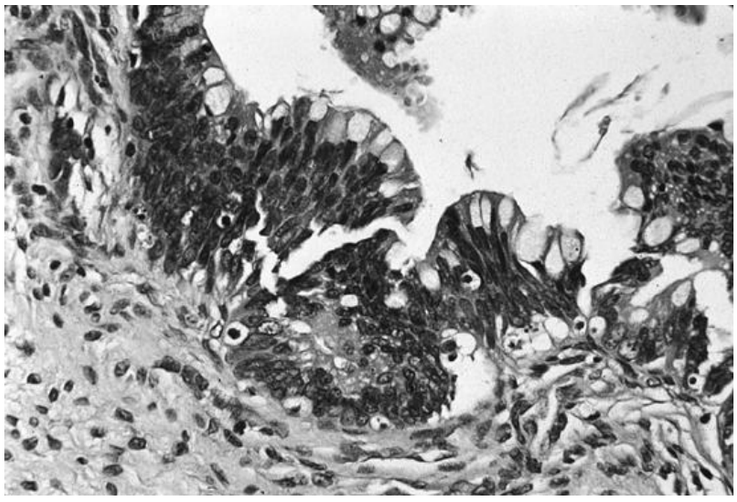

Figure 6.9 Adenocarcinoma *in situ*, intestinal type. The endocervical glands are lined by dysplastic cells that show stratification, nuclear enlargement, and hyperchromasia. Note the goblet cells.

Invasive Adenocarcinoma

The absolute and relative incidences of cervical adenocarcinoma have been increasing, particularly in women younger than 35 years of age (18). 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 are 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 can be graded histologically as well, 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. The prognosis is closely related to the degree of differentiation, tumor size, stage, and pelvic lymph node status (23).

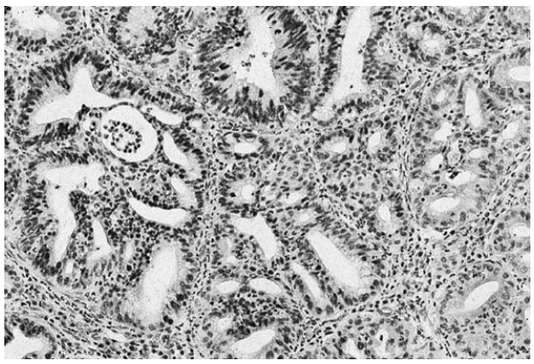

Figure 6.10 Invasive adenocarcinoma. Infiltrating glands show extensive cribriforming.

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. 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.

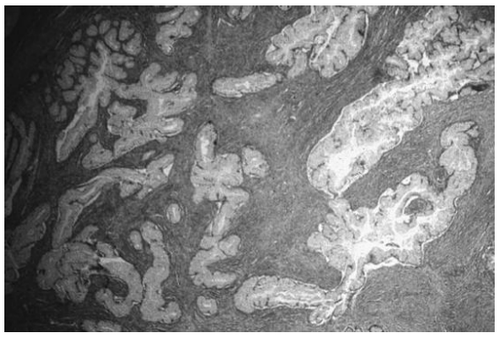

Figure 6.11 Minimal deviation adenocarcinoma. Deeply infiltrating, irregular glands are lined by benign-appearing endocervical epithelium.

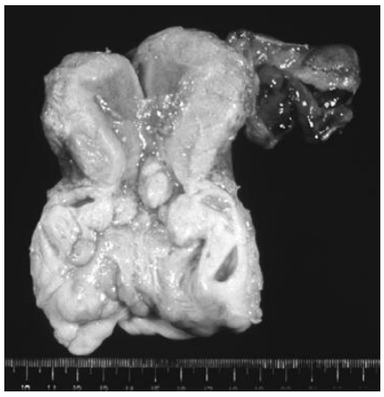

Figure 6.12 Minimal deviation adenocarcinoma. This hysterectomy specimen shows an enlarged (“barrel-shaped”) cervix with wall thickening and polypoid projections.

Villoglandular Adenocarcinoma

Villoglandular adenocarcinoma tends to occur in young women, sometimes in pregnancy, and is associated with an excellent prognosis (24). 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 large number of papillae gives this tumor an exophytic friable appearance.

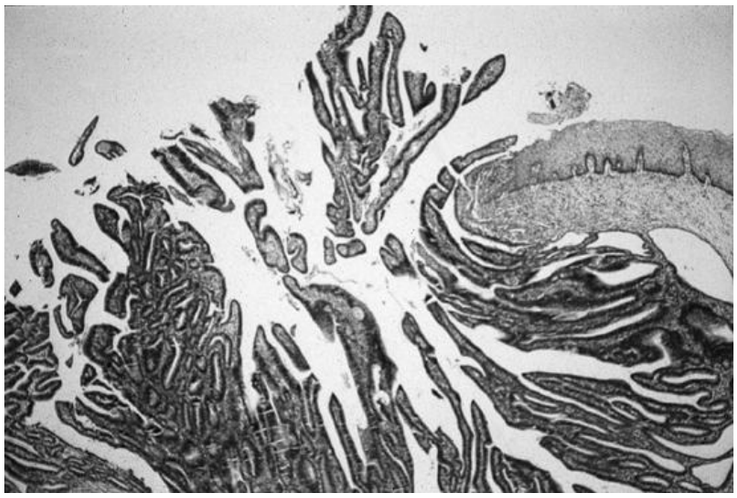

Figure 6.13 Invasive adenocarcinoma, villoglandular type. Thin, slender villous projections with exophytic and invasive growth patterns are lined by well-differentiated glandular epithelium.

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 (12). 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.

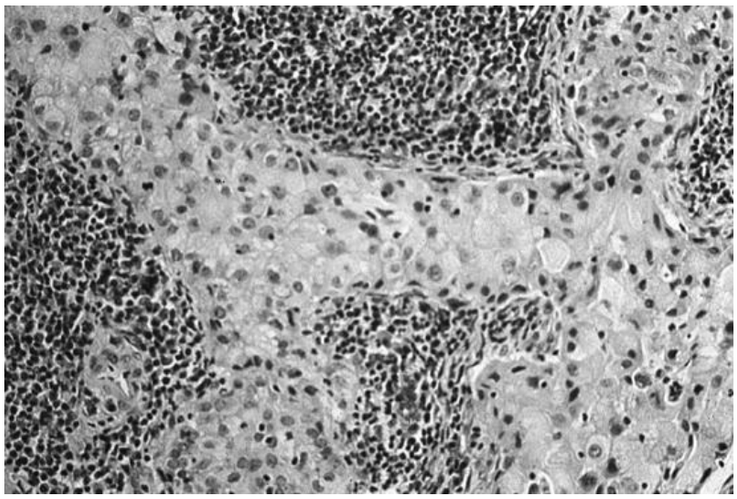

Figure 6.14 Glassy cell carcinoma. This lesion is characterized by sheets of malignant cells with abundant cytoplasm. Note the prominent inflammatory infiltrate.

Adenoid Basal Carcinoma

Adenoid basal carcinoma is a distinct neoplasm affecting women in their fourth to eighth decades (25). 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.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is an aggressive neoplasm with a high incidence of local recurrence and distant metastasis (12). 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 (26). 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 (26). 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 (26). 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.**

Leiomyosarcoma

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

Other Tumors

Malignant Melanoma

Most malignant melanomas of the cervix are metastatic rather than primary. Primary cervical melanoma is rare (27). Its macroscopic appearance is similar to that of melanomas occurring at other sites. The prognosis is poor. It is usually diagnosed at an advanced stage and is not amenable to curative therapy.

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 (26). 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 (26). 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 Papanicalaou 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 test 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 2001 Bethesda system for reporting cervical/vaginal cytologic diagnoses, summarizes the diagnostic criteria used in the 2001 Bethesda system, and focuses on the more recent advances in cervicovaginal cytology.

The Bethesda System

Currently, more than 90% of laboratories in the United States use the Bethesda system for reporting cervicovaginal cytology (28). 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 and standardized communication of Pap test diagnoses to overcome the confusion created by the inconsistent use of different grading and classification systems among laboratories and clinicians. A second NCI meeting in 1991 modified the Bethesda system based on its impact, advantages, and disadvantages 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 (6). In the past 10 years, numerous advances have been made in the field of cervicovaginal cytology, including liquid-based cytology, HPV testing, and a better understanding of the Bethesda 1991 diagnostic categories. In 2001, the 1991 Bethesda system was revised to reflect these new developments (Table 6.3) (28).

Table 6.3 Comparison of the Papanicolaou and the Bethesda Classification

The Old Papanicolaou Classification					
I	II	II	II/III	II/III/IV	V
↓	↓	↓	↓	↓	↓
WNL	**BCC**	**Rx/Rp changes**	**ASC**	**LSIL, HSIL**	**Malignancy**
The New Bethesda System					

WNL, within normal limits; BCC, benign cellular changes; Rx/Rp changes, reactive/reparative changes; ASC, atypical squamous cells; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; malignancy, carcinoma.

The major changes in the Bethesda 2001 in comparison to Bethesda 1991 are summarized as follows:

- **Specimen adequacy:** “Satisfactory but limited by” category is eliminated. This term was considered confusing to many clinicians and often resulted in unnecessary repeat testing.
- **General categorization:** The previous categories “within normal limits,” “benign cellular changes,” and “reactive cellular changes” are combined under a single heading, “negative for intraepithelial lesion or malignancy,” to facilitate triage of reports by clinical staff.
- **Epithelial cell abnormalities:**
  - **Atypical squamous cells (ASC):** The ASC category is now subclassified into two groups: ASC—of undetermined significance (**ASC-US**) and ASC—cannot rule out high-grade SIL (**ASC-H**). Studies have shown that women with an ASC-H Pap result represent a higher risk group for

harboring a CIN 2–3 lesion (24% to 94%) in comparison to ASC-US (5% to 20%). “ASC- favor reactive” category is eliminated.

- **Atypical glandular cells (AGC):** The term “atypical glandular cells of undetermined significance (AGUS)” is replaced with AGC to avoid confusion with ASC-US. “AGC- favor reactive” is no longer used because it led to a false sense of security. **Most studies have shown that AGC is associated with high-grade squamous or glandular lesions in 10% to 39% of cases. Endocervical adenocarcinoma *in situ* (AIS) is now a separate category** based on well-documented and reproducible morphologic criteria that allows its recognition on Pap test.

- **“Other” category:** “Other” is added as a separate category to indicate an increased risk for a significant lesion despite the absence of morphologic abnormalities in the cells, such as presence of endometrial cells in women older than 40 years of age. **Endometrial cells are reported in women older than 40 years of age regardless of the last menstrual period** because hormonal status is often unclear to the laboratory. In the 1991 Bethesda System, endometrial cells were reported only for postmenopausal women. Identification of endometrial cells on a Pap test may be indicative of endometrial pathology.

In the current Bethesda system, the format of the cervical/vaginal cytology report consists of five parts:

- **A statement of the adequacy of the specimen**

  Satisfactory for evaluation (note presence/absence of endocervical/transformation zone component)

  Unsatisfactory for evaluation… (specify reason)

- **An optional general categorization of the diagnosis**

  Negative for intraepithelial lesion or malignancy

  Epithelial cell abnormality

  Other

- **Interpretation/result**

  Negative for intraepithelial lesion or malignancy

  Organisms (*Trichomans vaginalis*, etc.)

  Other nonneoplastic findings (reactive change, glandular cells in a postmenopausal woman, atrophy)

  Epithelial cell abnormality

  Squamous cell

  ASC-US

  ASC-H

  LSIL

  HSIL

  Squamous cell carcinoma

  Glandular cell

  AGC (specify endocervical, endometrial, or not otherwise specified)

  AGC, favor neoplastic (specify endocervical or not otherwise specified)

  Endocervical adenocarcinoma *in situ* (AIS)

  Adenocarcinoma

  Other

  Endometrial cells in a woman > 40 years of age

- **Automated review and ancillary testing (such as HPV testing)**
- **Educational notes and suggestions (optional)**

Specimen Adequacy

Inclusion of a statement of adequacy is one of the most important contributions of the Bethesda system. **Most false-negative Pap smears occur as a result of inadequate or**

poor sampling. In the Bethesda system, four factors are evaluated for specimen adequacy:

- **Correct patient and specimen identification**
- **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.
- **Technical interpretability:** Delayed fixation of the cells for conventional Pap smears and obscuring blood and inflammation may render the smear uninterpretable.
- **Cellularity:** Minimal cellularity is based on the specimen type. Eight thousand to 12,000 well visualized squamous cells are required for conventional smears and 5,000 for liquid-based preparations. There should be 10 well-preserved endocervical or metaplastic squamous cells for an adequate representation of the transformation zone. The presence or absence of the transformation zone is noted separately on a Pap report, but it does not affect specimen adequacy by itself.

Squamous Epithelial Abnormalities

Squamous epithelial abnormalities range from benign reactive cellular changes associated with benign processes such as infections and atrophic vaginitis to atypical squamous cells of undetermined significance (ASC-US), LSIL, HSIL, and squamous cell carcinoma (Table 6.4 , Fig. 6.15 , Fig. 6.16 , Fig. 6.17 , Fig. 6.18).

Table 6.4 Cytologic Features in Squamous Cell Abnormalities in Papanicolaou Smears

Cytology	*Reactive*	*ASC-US*	*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 (koilocytes)	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

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

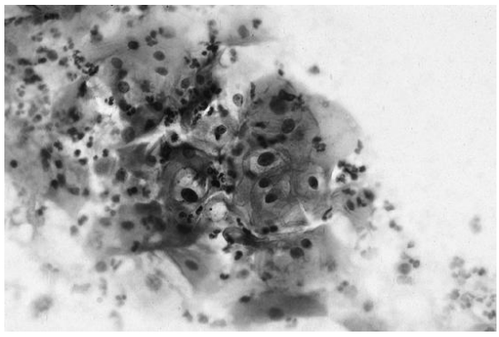

Figure 6.15 Atypical squamous cells of undetermined significance (ASC-US). This Pap smear shows superficial-type squamous cells with mild nuclear enlargement and hyperchromasia. These features are suggestive but not diagnostic of a low-grade squamous intraepithelial lesion.

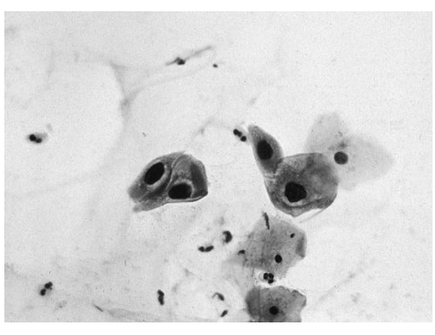

Figure 6.16 Low-grade squamous intraepithelial lesion (Pap smear). These lesions show mildly dysplastic squamous cells with nuclear enlargement, hyperchromasia, and irregular nuclear contours that are more pronounced than in Figure 6.15.

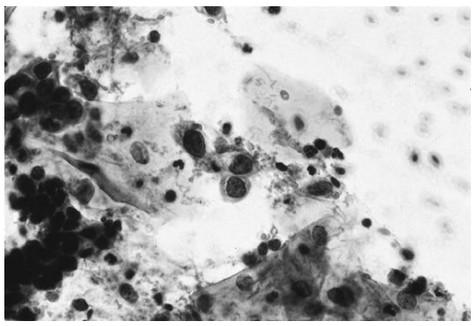

Figure 6.17 High-grade squamous intraepithelial lesion (Pap smear). The dysplastic cells seen in the center show a high nuclear-to-cytoplasmic ratio.

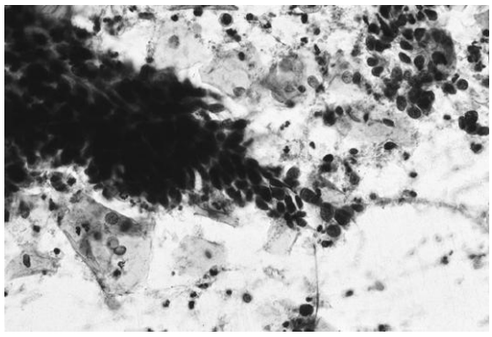

Figure 6.18 High-grade squamous intraepithelial lesion (Pap smear). A cluster of overlapping, markedly dysplastic cells forms a sheet. Note single, severely dysplastic cells.

Atypical Squamous Cells

The term ASC 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). The atypia seen may be due to an exuberant but benign change or a potentially serious lesion. **Follow-up biopsies of up to one-third of patients with ASC reveal SIL. Approximately 30% of these are high grade and 70% low grade.** The 2001 Bethesda system subdivides ASC into two categories: “ASC–of undetermined significance (ASC-US)” and “ASC–cannot rule out high grade SIL (ASC-H).” ASC-US refers to cellular abnormalities suggestive of LSIL. ASC-H refers to cellular abnormalities suggestive of HSIL but not sufficient to warrant an unequivocal HSIL diagnosis.

The rationale in separating ASC-H from ASC-US is based on studies that showed a higher incidence of biopsy-confirmed CIN 2 and 3 after an ASC-H Pap test (28 ,29). Overall, **ASC-H represents 5% to 10% of ASC cases**. A downside of this category is that **ASC-H has poor interobserver agreement**, even among expert pathologists. This is reflected in the wide range of percentages varying from 24% to 94% reported for women who have biopsy-proven high-grade lesions on follow-up.

Squamous Intraepithelial Lesions

Cytomorphologic abnormalities seen in SIL constitute a spectrum. **LSIL encompasses condyloma and CIN 1 (mild dysplasia), and HSIL encompasses CIN 2 and 3 (moderate/severe dysplasia and CIS)**. 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, adenocarcinomas of the endocervix and endometrium, and, rarely, metastatic lesions from genital (ovary) or extragenital (e.g., breast carcinoma) sites.

Atypical Glandular Cells

The term AGC refers to cells displaying nuclear atypia that exceed obvious reactive or reparative changes but lack unequivocal features of *in situ* or invasive adenocarcinoma (28). The diagnosis of AGC is further qualified whenever possible to indicate whether the cells are thought to be of endocervical or endometrial origin, and whether a neoplastic process is favored. However, because the AGC category includes a broad morphologic spectrum ranging from atypical reactive/reparative processes to adenocarcinoma, this distinction is not straightforward. Criteria for subclassifying AGC are not well established and suffer from poor interobserver agreement (30). In addition, it may be very difficult to differentiate SIL with endocervical gland involvement from a true glandular neoplasia. **In general, most AGC cases are high-grade SILs rather than glandular lesions on follow-up.**

Adenocarcinoma In Situ

AIS was initially reported as “AGC, probably neoplastic” in the 1991 Bethesda system. Since then, studies have shown that endocervical AIS has distinctive and reproducible morphologic features that allow its recognition as a separate entity on Pap test (Fig. 6.19). However, there is considerable cytologic overlap between AIS and invasive adenocarcinoma. Criteria indicating invasion, such as macronucleoli and tumor diathesis, may be absent in invasive adenocarcinoma. Therefore, this distinction ideally requires histologic evaluation.

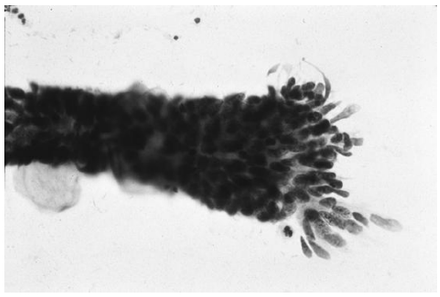

Figure 6.19 Adenocarcinoma *in situ* (Pap smear). This lesion is characterized by a cluster of columnar cells with nuclear enlargement and hyperchromasia. Note the “feathering” effect at the edges.

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).

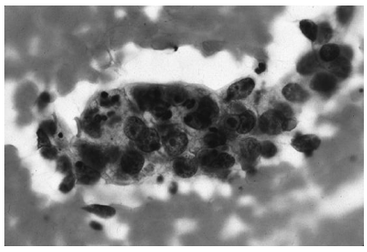

Figure 6.20 Invasive endocervical adenocarcinoma (Pap smear). This lesion shows a three-dimensional cluster of glandular cells with nuclear atypia and very prominent nucleoli in a bloody background.

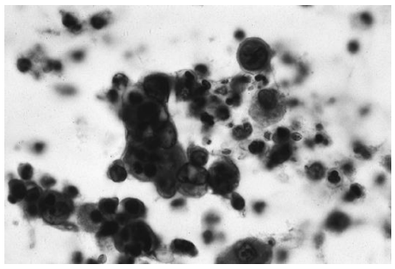

Figure 6.21 Endometrial adenocarcinoma (Pap smear). The malignant cells are smaller than in Figure 6.20, with less prominent nucleoli. No feathering or columnar morphology is seen.

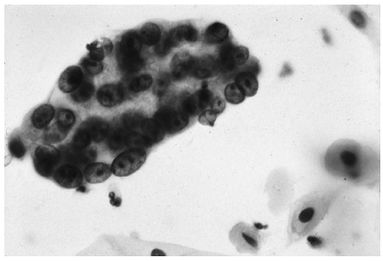

Figure 6.22 Ovarian adenocarcinoma cells seen in a Pap smear. Note the clean background.

New Technologies

Liquid-Based Technology

Liquid-based technology, also known as thinlayer, aims to reduce false negativity by optimizing the collection and preparation of cells. Two devices are available to prepare cells collected in a liquid medium: the **Thin Prep processor** (Cytyc Corporation, Boxborough, MA) and the **Surepath Prep Stain Processor** (Tripath Imaging, Burlington, NC). In the Thin Prep 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 Tripath system, the underlying concept is similar and therefore is not discussed separately in this chapter.

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

- **With the thinlayer technique, mucus, blood, and inflammatory cells are removed by the fixative and the filter**, providing a “clean background”

without loss of tumor diathesis. Studies have shown a higher detection rate of LSIL and HSIL.

- **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.**
- It is suggested that collection of cells into a fixative solution provides **immediate fixation and better cellular detail.**
- **HPV testing can be done directly on the residual specimen in the vial** if ASC is detected by the Pap test, i.e., "reflex HPV testing."

Several disadvantages are inherent in the thinlayer 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 thinlayer, 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

The Thin Prep Imaging System (Imager) (Cytyc Corporation, Boxborough, MA) and the **Focal Point (AutoPap 300 system)** (Tripath Imaging, Inc., Burlington, NC) are both approved by the Food and Drug Administration (FDA) for primary screening. Both systems are automated devices designed to screen thinlayer slides using computer imaging technology. Several studies have shown better sensitivity and accuracy for FocalPoint compared with manual screening in detection of abnormal cells (31 ,32). Future clinical trials will define the role of automated techniques in clinical practice based on the cost/benefit ratio.

Human Papillomavirus Testing

Almost all cervical carcinomas and most CIN 2 and 3 lesions 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 (29). In addition, **low-grade lesions have a higher rate of progression 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 hybrid capture system (HC II) is currently the only FDA-approved commercially available method.** HC II 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 13 most common high-risk HPV types.

HC II is not as sensitive as PCR and requires 5,000 viral copies per nucleus for detection. **Polymerase chain reaction (PCR) is currently not commercially available**. PCR requires very little viral DNA (10 copies) 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 and has the ability to type for specific HPV. PCR is very sensitive, simple, and rapid; however, sample

contamination is a problem that can cause false-positive results. ***In situ*** **hybridization is commercially available**, and it has the advantage of combining morphology with cellular localization of the virus, **but it is yet to be validated in large trials.** It requires 10 to 50 viral copies per nucleus for detection.

Clinical Application of Human Papillomavirus Testing

There is no role for HPV testing as a screening tool. Especially in young women, HPV infection is very common and is a marker of sexual activity rather than cervical cancer risk. HPV testing alone leads to many unnecessary colposcopic examinations. In one study, 26% of women were HPV positive when they entered college, and another 43% became HPV positive over the next 3 years (33). Many had high-risk HPV types. **Most infections were transient in that 92% were negative for HPV within 24 months**. Persistent infection with HPV occurs in only 10% of infected individuals who are then at risk for developing high-grade SIL (34).

Five percent (5%) to 17% of women with ASCUS have a high-grade lesion on biopsy (29). HPV testing is most useful in this group of women to determine which subset is at risk for harboring or developing a high-grade lesion (3).

Vagina

Part of "6 - Pathology "

Tumorlike Lesions

Vaginal Polyp

A vaginal polyp is a benign fibroepithelial lesion, most common in women older than 20 years of age (35). 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 of 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.

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 (36 ,37). 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. 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 cervical or vulvar intraepithelial neoplasia.

Squamous Cell Carcinoma

Primary squamous cell carcinoma of the vagina is rare, accounting for 2% of all female genital tract malignancies (36 , 37 , 38). 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-year disease-free interval is necessary to rule out recurrent disease before diagnosing a new vaginal primary.

Vaginal squamous cell carcinoma is more common in women older than 60 years of age. 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) Carcinoma

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

Most cases of adenosis regress. However, because of the risk of development of clear cell carcinoma, these patients should be monitored. 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 observed even more carefully.

Adenocarcinoma

Clear Cell Adenocarcinoma

Clear cell adenocarcinoma (1 ,36) 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.

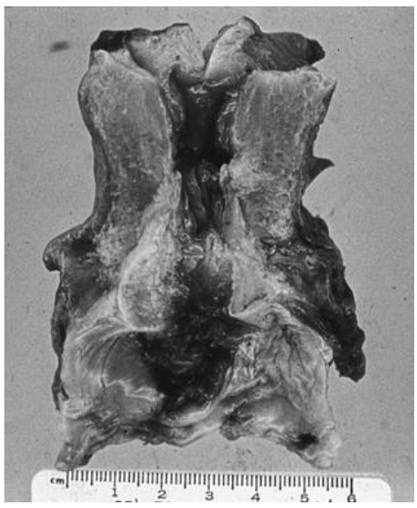

Figure 6.23 Clear cell adenocarcinoma of the vagina. This is a hemorrhagic, friable tumor in the posterior wall of the vagina.

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 (39). 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 grapelike 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.

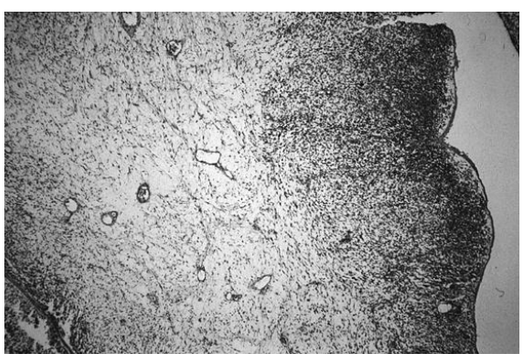

Figure 6.24 Embryonal rhabdomyosarcoma. A hypercellular cambium layer lies beneath the surface epithelium and deep myxoid stroma.

Leiomyosarcoma

Leiomyosarcoma is the most common vaginal soft tissue malignancy in adults (40). It occurs in a wide age range, from 25 to 86 years of age. Leiomyosarcoma 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 10 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 (41). 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 (42).

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 (43).

Vulva

Part of "6 - Pathology "

Squamous Lesions

Condyloma Acuminatum

Condyloma acuminatum similar to that in the cervix occurs in the vulva as well as the vagina.

Squamous Intraepithelial Lesions

Squamous intraepithelial lesions of the vulva have been designated VIN (vulvar intraepithelial neoplasia), similar to the terminology used for the cervix (44). 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:

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

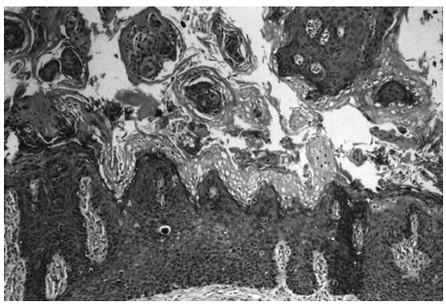

Figure 6.25 Warty vulvar intraepithelial neoplasia. This lesion is characterized by a condylomatous-appearing squamous epithelium with full-thickness epithelial atypia.

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

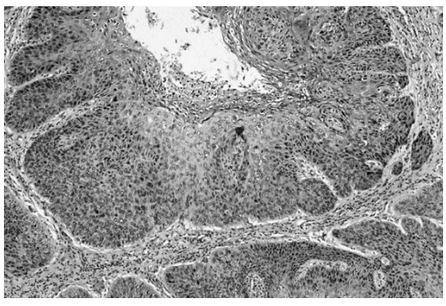

Figure 6.26 Basaloid vulvar intraepithelial neoplasia. The neoplastic squamous lining shows a flat surface. The proliferating atypical cells are small and show peripheral palisading.

- **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)

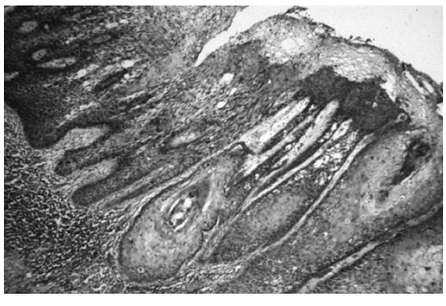

Figure 6.27 Differentiated vulvar intraepithelial neoplasia. The squamous epithelium is thickened and shows irregular, fingerlike projections into the underlying stroma. The atypia is more pronounced in the basal layers. The neoplastic epithelial cells are strikingly eosinophilic compared with the basaloid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

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 LSILs are HPV 6 and 11 related, and HSILs 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 (45). **It is suggested that vulvar squamous cell carcinoma occurs in two different patient populations.**

- The first group is **young women with a history of cigarette smoking, VIN, and HPV infection**.
- 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. 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.

The International Federation of Gynecology and Obstetrics (FIGO) 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 (46). The depth of invasion is measured from the epidermal–dermal junction of the adjacent normal dermal papilla to the deepest point of invasion (Fig. 6.28).

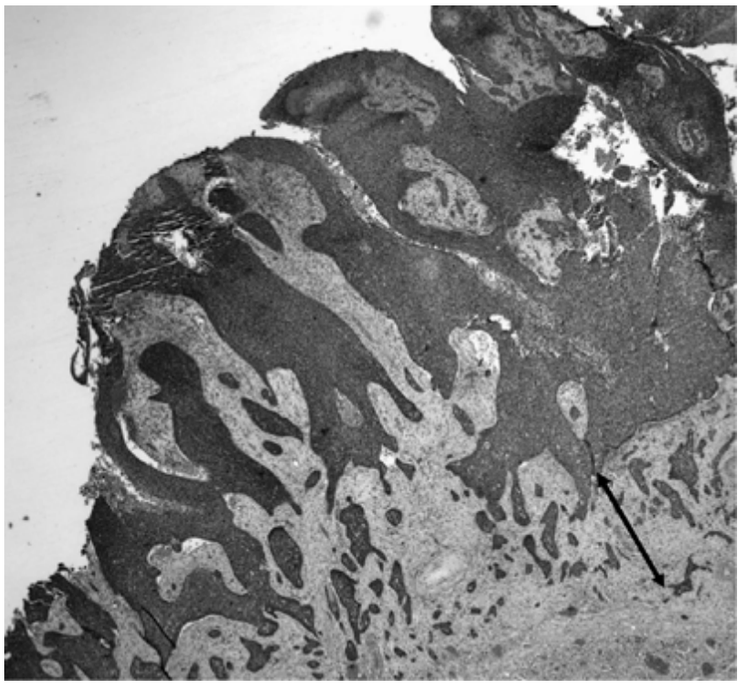

Figure 6.28 Microinvasive squamous cell carcinoma of the vulva. Vulvar intraepithelial neoplasia grade 3 (VIN3) involving the full thickness of the overlying epithelium; at the base of the lesion, there are irregular infiltrating nests of superficially invasive (1 mm in depth measured from the basement membrane to the deepest point of invasion, *arrow*) squamous cell carcinoma.

The prognosis of vulvar squamous cell carcinoma depends on the tumor depth, size, vascular invasion, and node involvement. There are differences of 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** (47). 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.

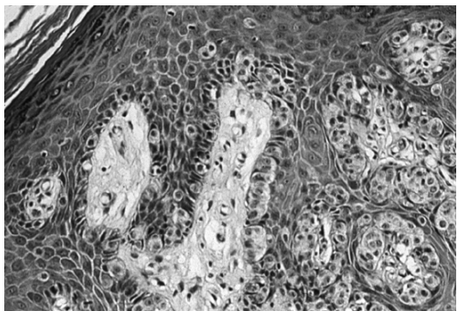

Figure 6.29 Paget's disease of the vulva. This lesion shows intraepidermal proliferation of malignant cells with abundant, pale cytoplasm and prominent nucleoli, arranged singly and in clusters.

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 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 (48). 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 is present. The spindle and stellate cells in the stroma are myofibroblasts and fibroblasts.

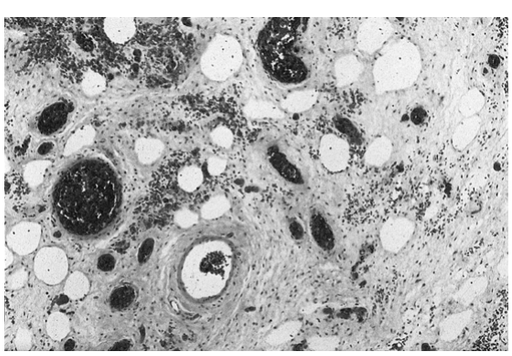

Figure 6.30 Aggressive angiomyxoma. Dilated vessels are seen in a loose stroma that contains spindle cells.

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 (49). Most patients are older than 50 years of age. 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.

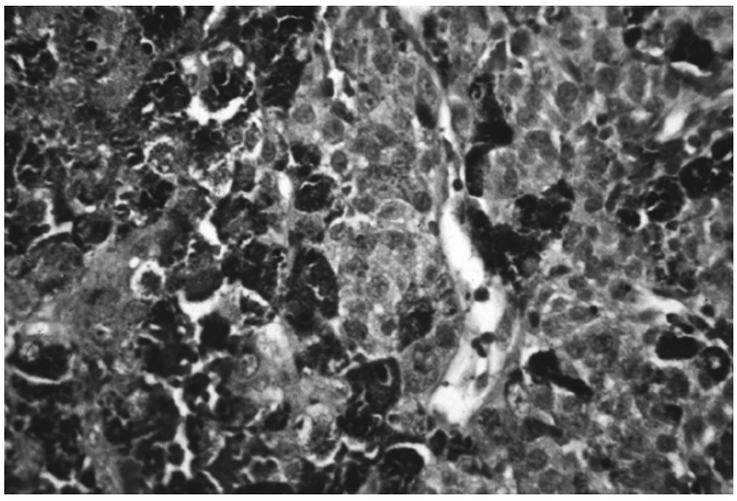

Figure 6.31 Vulvar melanoma. This lesion is characterized by a proliferation of epithelioid cells with eosinophilic cytoplasm and prominent nucleoli characteristic of melanoma. Note the abundant pigment (melanin).

Histologic staging of malignant melanoma provides useful prognostic information. Both the level of invasion (**Clark's levels**) and the tumor thickness (**Breslow's thickness**) should be measured. The prognosis is poor and does not seem to be altered by surgical techniques.

Metastatic Tumors

Metastatic tumors to the vulva are rare (50). They present as single or multiple intradermal or subcutaneous nodules, masses, and less commonly as pain and ulcerations. In approximately half of the cases, the primary tumor is of gynecologic origin (most commonly cervix). Common nongynecologic sites include urethra, kidney, breast, and lung. About 10% originate from unknown primaries.

Uterine Corpus

Part of "6 - Pathology "

Endometrium: Normal Histology and Cycling Changes

The normal endometrium is divided into three layers:

- **Superficial layer (compacta**), consisting of surface epithelium and immediately underlying gland necks
- **Middle layer (spongiosa, or functionalis)**, occupying most of the thickness of the endometrium and most responsive to hormonal effects
- **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).

Table 6.5 Endometrial Morphology during the Menstrual Cycle

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
Midsecretory	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 “balls”

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 Endometriumm

- **Atrophy** (prepubertal, postmenopausal): A cystic atrophic pattern (dilated glands with an attenuated lining in a dense stroma) may be confused with simple hyperplasia.
- **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.

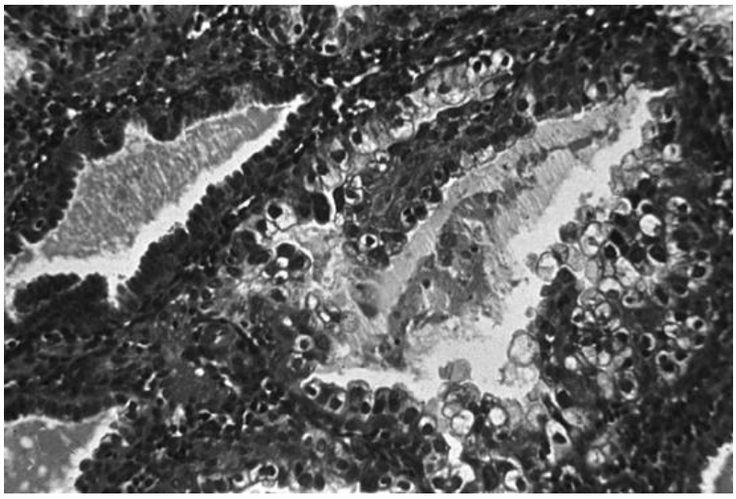

Figure 6.32 Arias-Stella reaction of the endometrium. The glandular lining shows enlarged hobnail cells with clear cytoplasm and “smudged” nuclei.

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 and Fig. 6.34) (51 , 52 , 53 , 54).

Table 6.6 Features of Endometrial Hyperplasias

	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 so 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[a]	Slight (<5%)	5%–15%	≥30%

[a] See references 51,52,53,54.

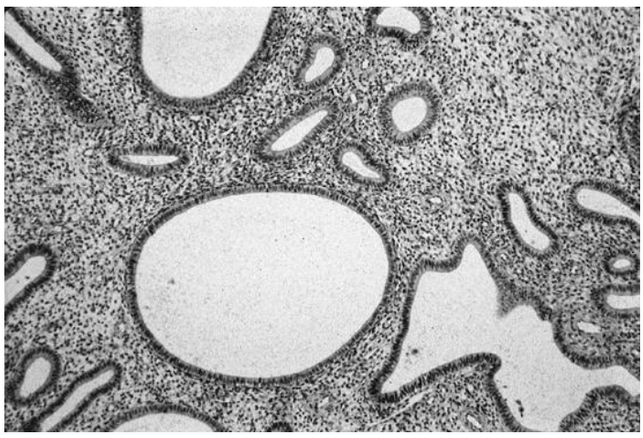

Figure 6.33 Simple endometrial hyperplasia without atypia. An increased number of round glands is seen, some of which are cystically dilated. There is no cytologic atypia.

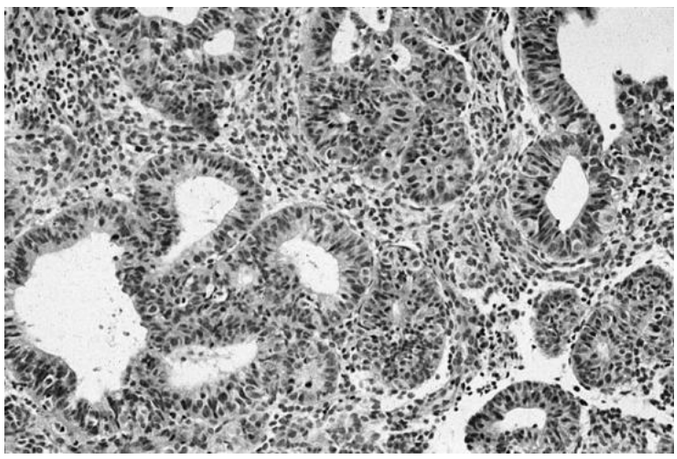

Figure 6.34 Atypical complex hyperplasia. Crowded, irregular glands show little intervening stroma. The glands show rounded, pleomorphic nuclei with prominent nucleoli.

Differential Diagnosis

- **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.
- **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 (55). Other criteria listed by Kurman and associates (55) 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. 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% (56) of hysterectomies performed immediately after the diagnosis of atypical hyperplasia.

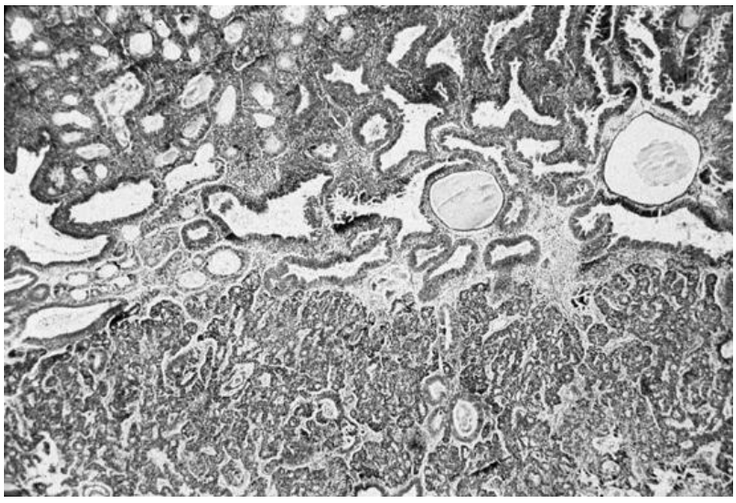

Figure 6.35 Well-differentiated endometrioid adenocarcinoma arising in atypical complex hyperplasia. The upper portion of the figure shows complex hyperplasia with closely packed glands with cytologic atypia. In the bottom portion, the glands become confluent, with no intervening stroma, and represent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

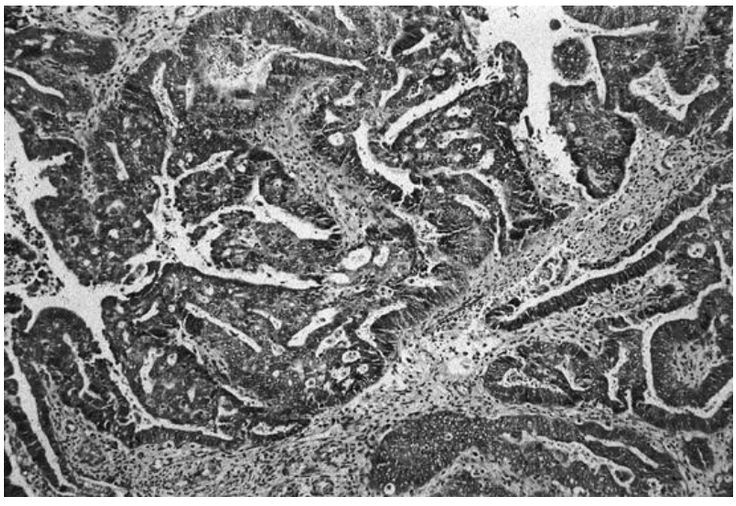

Figure 6.36 Well-differentiated endometrioid adenocarcinoma. Glandular nests with extensive cribriforming are surrounded by desmoplastic, loose stroma.

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 (57). Furthermore, this relationship is stressed in Ferenczy's classification, which regards atypical hyperplasia as endometrial intraepithelial neoplasia (EIN). **Recently, the concept of EIN has been corroborated by molecular studies and has been gaining increased popularity** (58 ,59). The EIN lesions are

composed of complex atypical hyperplasia and minimal FIGO grade 1 endometrioid adenocarcinoma.

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 presence of squamous differentiation does not affect the prognosis (60). Importantly, the squamous areas (benign or malignant) are excluded from histologic grading.

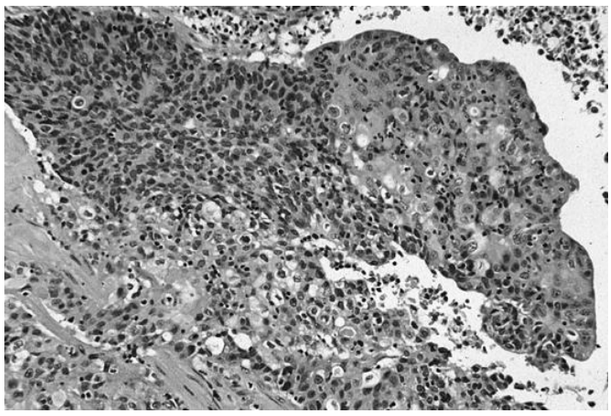

Figure 6.37 Endometrioid adenocarcinoma with squamous differentiation (adenoacanthoma). A solid area of benign-appearing squamous cells is seen in the right half of the field.

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.

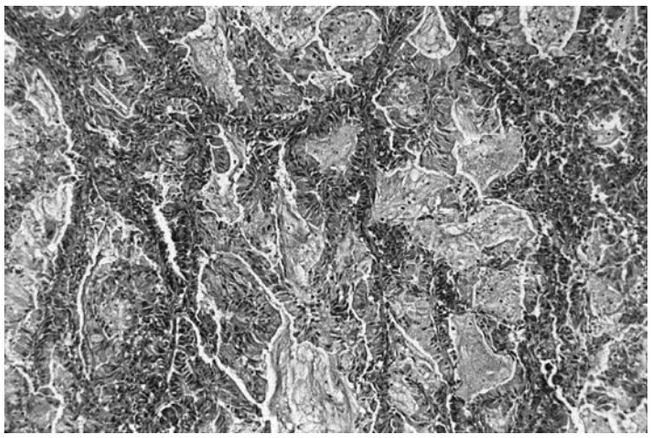

Figure 6.38 Mucinous adenocarcinoma. Confluent and cribriform glands are lined by mucinous epithelium.

Serous Carcinoma

This tumor makes up 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). **Even when serous carcinoma is confined to a polyp, recurrence occurs in up to 60% of cases** (Fig 6.39) (61). 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.**

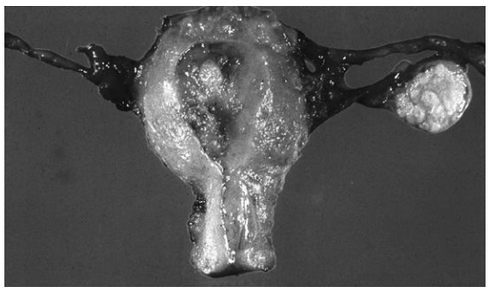

Figure 6.39 Serous carcinoma of the endometrium. The tumor is a polypoid mass arising in an atrophic uterus. Extensive myometrial lymphatic spread and involvement of the ovary were seen. (See Color Figure 6.39).

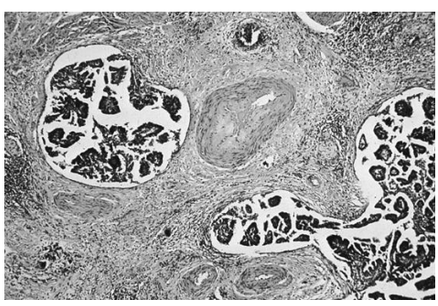

Figure 6.40 Serous carcinoma of the endometrium. This tumor shows extensive lymphatic space invasion deep in the uterine wall.

Endometrial Intraepithelial Carcinoma

This lesion is characterized by replacement of benign (often atrophic) endometrial epithelium by highly malignant cells resembling serous carcinoma (62). 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 hobnaillike and grow in tubular or papillary arrangements (Fig. 6.41).

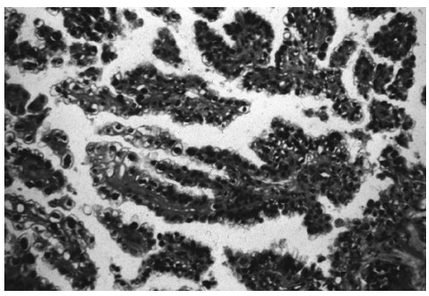

Figure 6.41 Clear cell carcinoma of the endometrium. Papillary fronds are lined by anaplastic hobnail cells with clear cytoplasm.

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.

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 compose 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).

- **FIGO grade 1–the tumor exhibits good gland formation and has 5% or less of solid growth pattern.**
- **FIGO grade 2–the solid growth pattern occupies between 6% and 50% of the tumor.**
- **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.

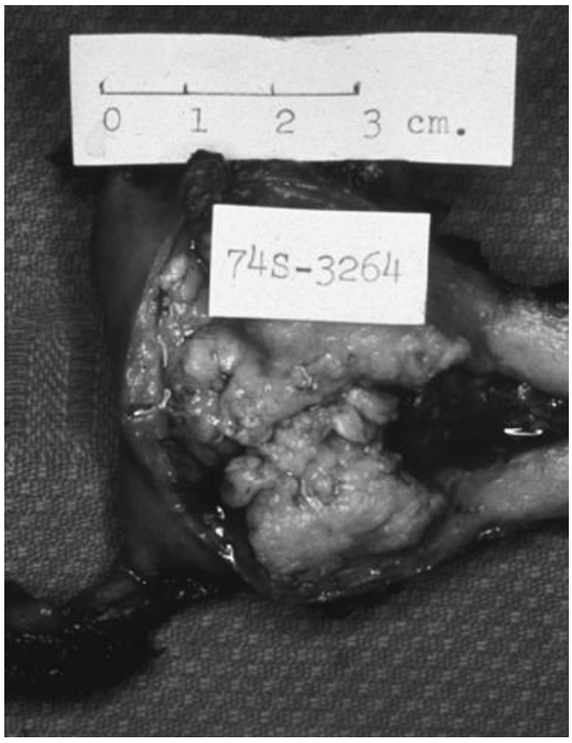

Figure 6.42 Endometrial adenocarcinoma. This is a polypoid exophytic tumor with myoinvasion into the outer third of the myometrium. (See Color Figure 6.42).

Endometrial Stromal Tumors

Endometrial stromal tumors include the benign stromal nodule, low-grade endometrial stromal sarcomas, and the undifferentiated uterine sarcomas. They compose approximately 10% of uterine mesenchymal tumors.

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, in which 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.

Low-Grade Endometrial 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 wormlike 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.

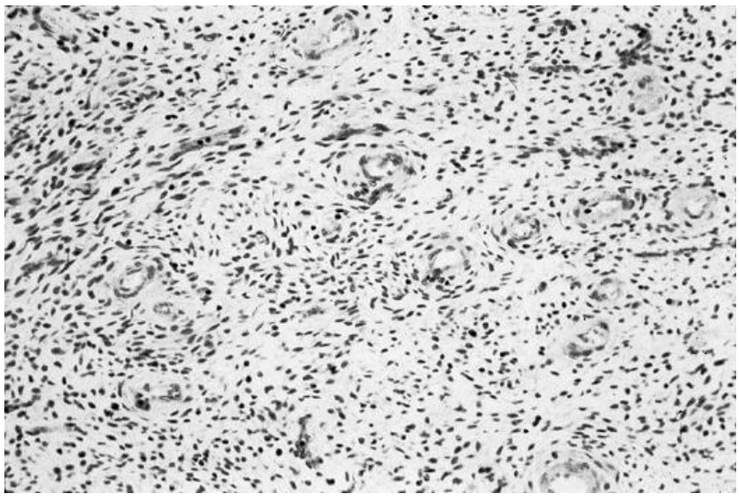

Figure 6.43 Endometrial stromal sarcoma, low grade. The tumor resembles benign endometrial stroma of proliferative phase, with small bland cells and prominent small vessels.

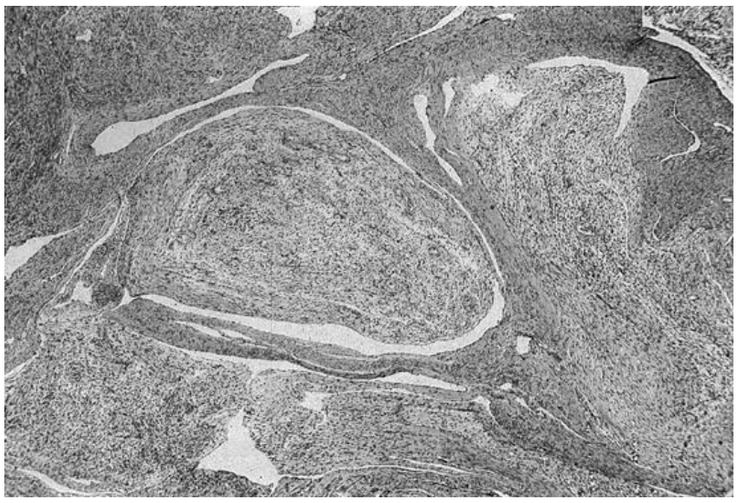

Figure 6.44 Endometrial stromal sarcoma, low grade. This tumor shows deep myometrial invasion.

Undifferentiated Uterine Sarcoma

Undifferentiated uterine sarcoma refers to 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 .

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

	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

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 3 to 4 per 10 high-power fields; Fig. 6.46). The stroma may distend the epithelium, producing compressed, narrow glands and leaflike 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.

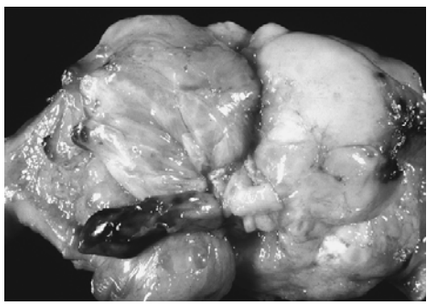

Figure 6.45 Adenosarcoma. Multiple polypoid masses arise in the endometrium. (See Color Figure 6.45).

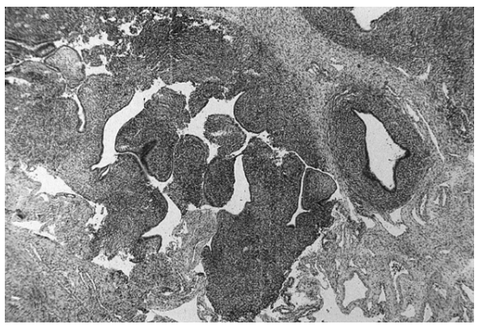

Figure 6.46 Adenosarcoma. Benign endometrial glands are surrounded by cuffs of hypercellular, mitotically active endometrial stroma.

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** (63). 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.

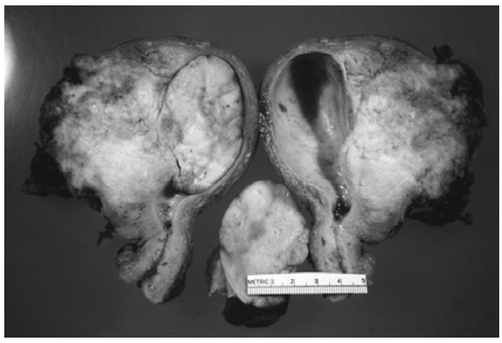

Figure 6.47 Carcinosarcoma. This hysterectomy specimen shows a large, partially necrotic polypoid mass filling the endometrial cavity and extensively invading the uterine wall. (See Color Figure 6.47).

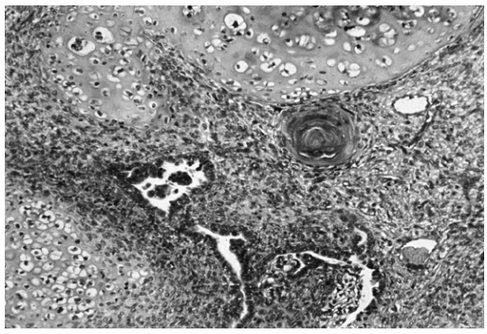

Figure 6.48 Carcinosarcoma. In this lesion, malignant glands lie within sarcomatous stroma, both of homologous and heterologous (malignant cartilage) types.

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 5 mitotic figures per 10 high-power fields). **Mitotically active leiomyoma** is a cytologically benign tumor with

higher-than-usual mitotic activity; these occur in premenopausal women (64). 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 5 mitotic figures per 10 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 (65).

Leiomyosarcoma

Leiomyosarcoma constitutes 1.3% of uterine malignancies. 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).

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

	Leiomyoma	*Leiomyosarcoma*
Number	Usually multiple	More often single
Size	Variable	Large (usually >10 cm)
Gross 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

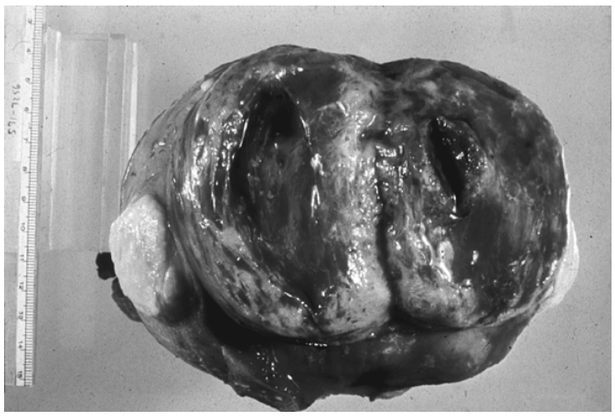

Figure 6.49 Leiomyoma and leiomyosarcoma. The small nodule on the left is well circumscribed, with the bulging, white, firm and whorled cut surface, typical of leiomyoma. The large, soft, hemorrhagic, and fleshy mass represents a leiomyosarcoma. (See Color Figure 6.49).

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).

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

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 leiomyomas.
[b]Other combinations of features also may result in a diagnosis of STUMP.

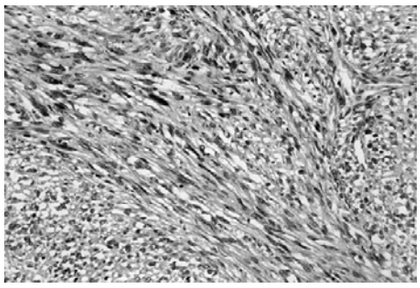

Figure 6.50 Uterine leiomyosarcoma. This is a pleomorphic, cellular, and mitotically active spindle cell tumor; elsewhere there was tumor cell necrosis.

Smooth Muscle Tumors of Uncertain Malignant Potential (STUMP)

Smooth muscle tumors of uncertain malignant potential do not meet the necessary diagnostic criteria for leiomyosarcoma, but exhibit some features that make prediction of behavior difficult. The algorithm for the differential diagnosis of uterine smooth muscle tumors (66) 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 cordlike 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.

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

Part of "6 - Pathology "

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. 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.*

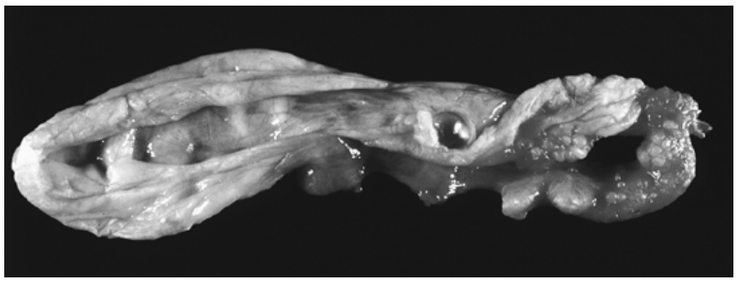

Figure 6.51 Serous cystadenoma of the ovary. This unilocular cyst has a smooth lining, microscopically resembling the fallopian tube epithelium. (See Color Figure 6.51).

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 cuboidal 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.

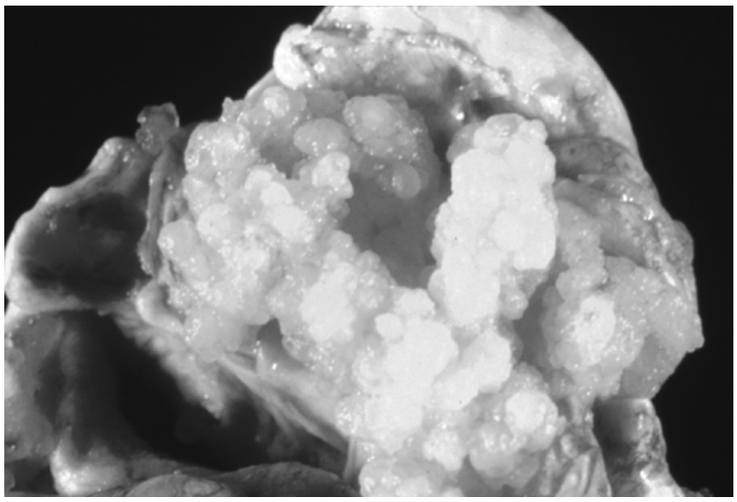

Figure 6.52 Ovarian serous tumor of low malignant potential. Abundant papillary projections involve the ovarian surface in this case. (See Color Figure 6.52).

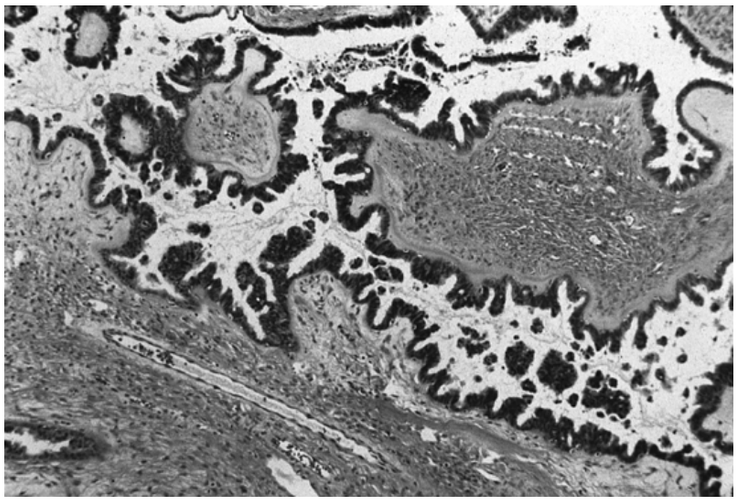

Figure 6.53 Ovarian serous tumor of low malignant potential. Papillae are lined by stratified epithelium with extensive tufting and budding. No stromal invasion seen.

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; the tumor has to contain a focus of micropapillary component measuring 5 mm or more to be classified as micropapillary (67). It appears that their poorer prognosis is related strictly to invasive extraovarian disease (68).

Microinvasion

This is defined by the presence of single epithelial cells or papillary clusters in the stroma of the tumor, which do not elicit stromal reaction. Usually the cells in the invasive foci have more abundant eosinophilic cytoplasm and may or may not exhibit more atypia. **None of the invasive foci should measure more than 10mm². The presence of microinvasion does not adversely affect the prognosis** (69 ,70).

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* (71). 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**, especially in stage III disease, whereas the presence of noninvasive implants (desmoplastic or nondesmoplastic) does not (72).

Up to 10% of patients have lymph node involvement, but the clinical significance of this finding is uncertain (73).

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 slitlike 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.**

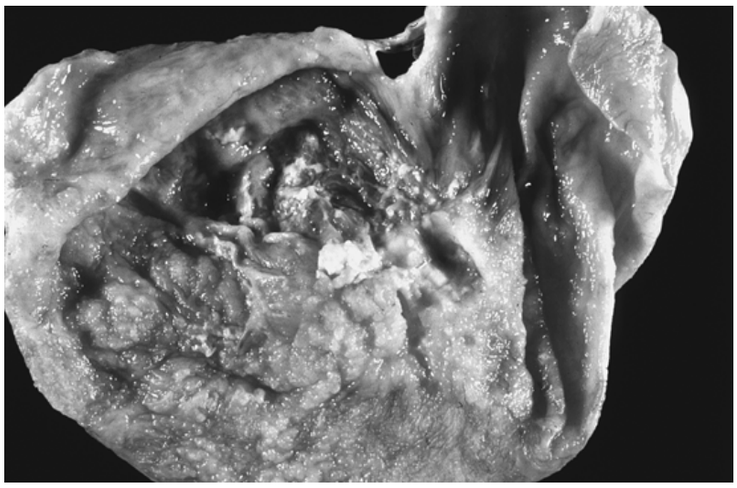

Figure 6.54 Serous carcinoma of the ovary. This partially cystic tumor exhibits papillary and solid areas. (See Color Figure 6.54).

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 (74).

Mucinous Tumors

Mucinous tumors compose 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. (See Color Figure 6.55).

Benign Mucinous Tumors

Benign mucinous tumors are most common in the third to fifth decades. Bilaterality is very uncommon (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 (75). Microinvasion (<5 mm focus of stromal invasion or of confluent glandular pattern) does not adversely affect the prognosis (76). **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.

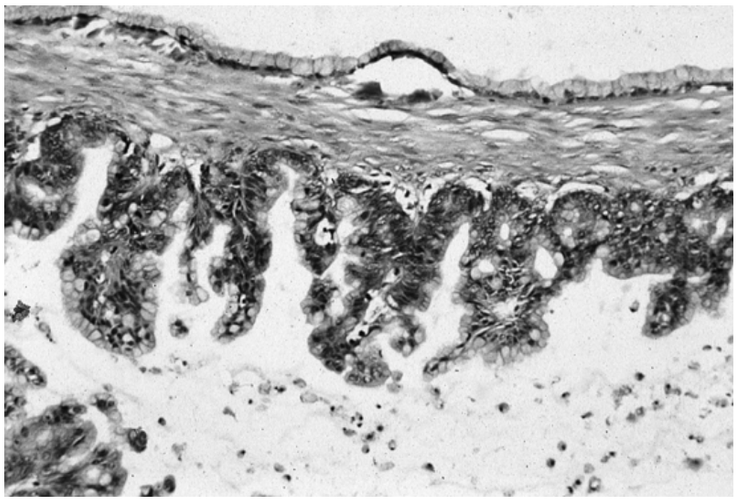

Figure 6.56 Mucinous tumor of low malignant potential, intestinal type. The mucinous tumor shows a benign component (*top*) with a single layer of goblet cells, and areas with borderline features (*bottom*) exhibiting papillary projections with stratification and atypia. No stromal invasion is seen.

Mucinous borderline tumors are subdivided into intestinal and endocervical types. These two types have several differences in presentation and clinical implications (75 ,77) (Table 6.10).

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

	Mucinous Borderline Tumor of Endocervical Type	*Mucinous Borderline Tumor of Intestinal Type*
Average age (yr)	33	45
Bilateral (%)	35	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—5%; with pseudomyxoma peritonei, 50% 5-yr survival

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 (78). **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.**

n these cases, the ovarian tumors are metastatic from the appendix (79 ,80). **Thus, an intraoperative diagnosis of a mucinous intestinal borderline tumor should always prompt an appendectomy.** Recently, it has been proposed to subclassify the epithelial component of pseudomyxoma peritonei into **disseminated peritoneal adenomucinosis** (bland, benign-appearing strips of mucin-producing epithelium) and **peritoneal mucinous carcinomatosis** (adenocarcinomalike, cytologically malignant glandular elements); these have been shown to significantly differ in prognosis (80). 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 (81).

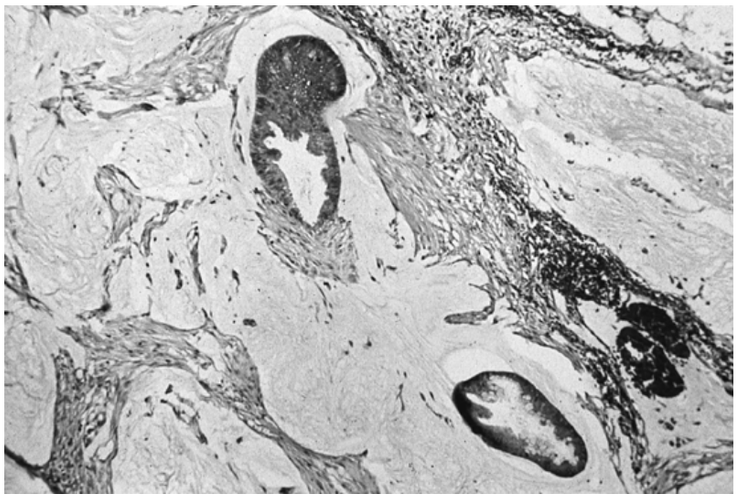

Figure 6.57 Pseudomyxoma peritonei. The tumor involving the pelvis shows pools of mucin with floating nests of stratified mucinous epithelium (mucinous borderline tumor, intestinal type).

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, and in fact is much more likely than an ovarian primary, because such metastases 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

Benign endometrioid tumors represent less than 1% of all benign ovarian tumors, about 2% to 3% of ovarian borderline tumors, and 25% of carcinomas. All endometrioid tumors are more common in postmenopausal women. Endometriosis can often be seen either in the same ovary or elsewhere. Endometrial hyperplasia can be observed in

endometriosis (82), as well as focal cytologic and architectural atypia, so-called **atypical endometriosis**; the premalignant potential of these lesions has been suggested (83).

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. It should be remembered that metastases from colonic primary adenocarcinoma most often have an endometrioid appearance in the ovaries (78); therefore, such metastases should be ruled out in all cases of bilateral endometrioid adenocarcinomas.

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% (84).

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 (85), favoring the independent primary hypothesis. Criteria for this distinction are presented in Table 6.11 .

Table 6.11 Endometrioid Carcinoma with Ovarian and Uterine Involvement

	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.

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 compose 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 (urotheliallike) 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** (86). 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 (87). However, this has not been confirmed by other studies (88).

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 (89).

Undifferentiated Carcinoma

According to the World Health Organization 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 the 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 representing both cell types can arise in the ovary. Although most tumors in this category consist of cells of ovarian origin **(granulosa and theca 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

	Age	*Clinical*	*Bilaterality*	*Gross*	*Behavior*
Granulosa cell tumor, adult type	15–80 yr, average, 52 yr	Hyperestrogenism	>90% Unilateral	Small to very large; gray, solid-cystic	Low-grade malignancy
Granulosa cell tumor, juvenile type	Less than 20 yr	Sexual precocity	98% Unilateral	Solid and cystic with hemorrhage	Low-grade malignancy
Thecoma	Perimenopausal, postmenopausal	Hyperestrogenism	Unilateral	Golden-yellow	Benign
Fibroma	Postmenopausal	Meigs' syndrome	8% Bilateral	3 cm or more; solid, firm	Benign
Sclerosing stromal tumor	Second to third decades	Rarely functional	Unilateral	Partly cystic, gray-white	Benign
Sertoli-Leydig cell tumor	20–40 yr	Most commonly—virilization	Unilateral	5–20 cm, solid, lobulated, yellow	Good (well differentiated); Guarded (intermediate and poorly differentiated); Poor (retiform)
SCST with annular tubules (with Peutz-Jeghers syndrome)	27 yr (mean)	Estrogenic or nonfunctioning	Bilateral	Multiple, small	Benign
SCST with annular tubules (without Peutz-Jeghers syndrome)	34 yr (mean)	Estrogenic or nonfunctioning	Unilateral	Single, large	Malignant (low grade)
Gynandroblastoma	Young adults	Androgenic or estrogenic	Unilateral		Benign

SCST, sex cord-stromal cell tumor.

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. They 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**: more than one-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 coexistent, are macrofollicular, 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 a **granulosa-theca cell tumor**.

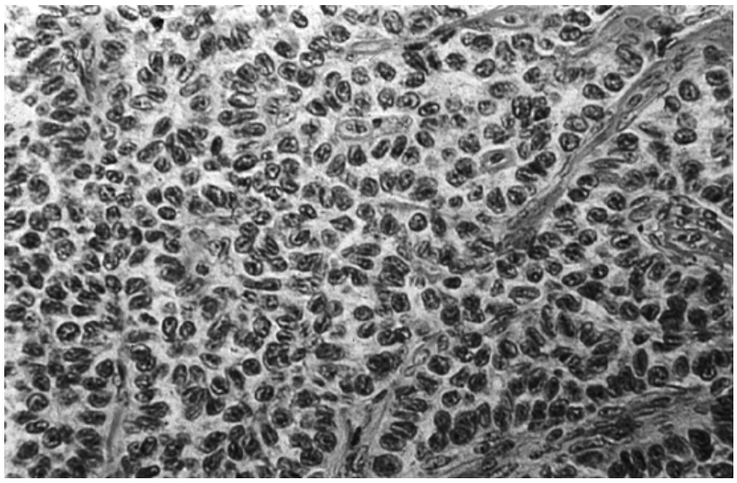

Figure 6.58 Granulosa cell tumor, adult type. This lesion is characterized by a microfollicular growth pattern with Call-Exner bodies; nuclei show the classical longitudinal groove (“coffee bean”).

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. (See Color Figure 6.59).

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 10 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–Leydig 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 (90). Sertoli–stromal tumors are almost always unilateral.

Well-differentiated Sertoli-Leydig cell tumors are composed of hollow tubules lined by mature Sertoli cells. They recapitulate 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.

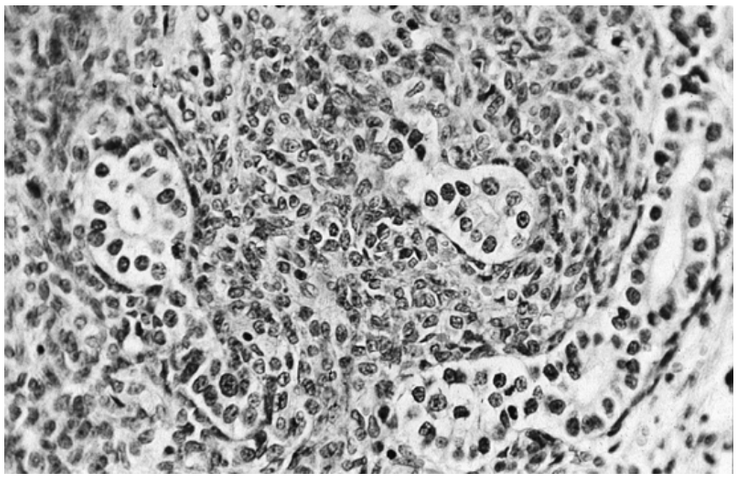

Figure 6.60 Sertoli-Leydig cell tumor of intermediate differentiation. Hollow tubules lined by Sertoli cells lie in a densely cellular stroma.

Poorly differentiated (sarcomatoid) Sertoli-Leydig cell tumors represent a diffuse, sarcomalike 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 Sertoli-Leydig cell tumors and are usually seen in teenagers (91). 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 (92). 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 compose 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 (93).

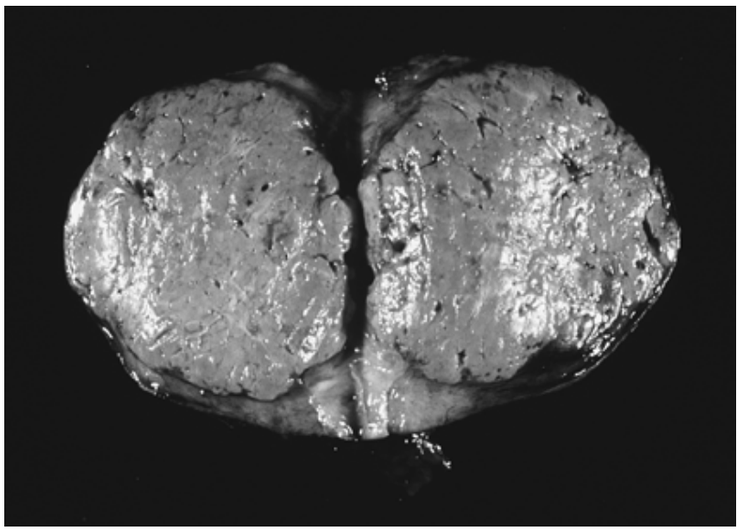

Figure 6.61 Steroid cell tumor, not otherwise specified. This tumor is a solid, golden-yellow mass. (See Color Figure 6.61).

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.**

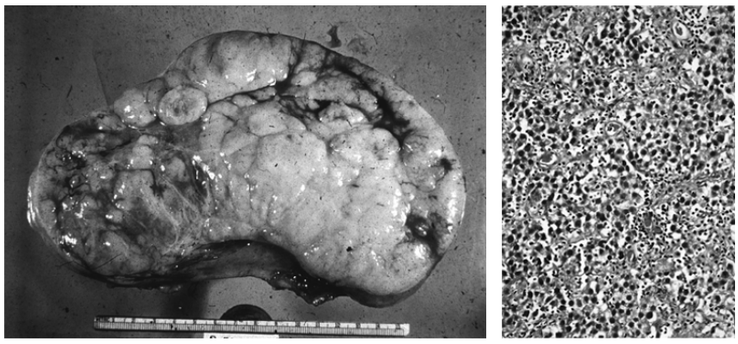

Figure 6.62 Dysgerminoma. *Left:* This solid tumor has a gray, fleshy, and lobulated cut surface. *Right:* The histologic appearance showing solid nests of tumor cells with clear cytoplasm and prominent cell borders. Note an admixture of small mature lymphocytes. (See Color Figure 6.62).

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 (81). 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 α-fetoprotein immunostain are commonly seen.

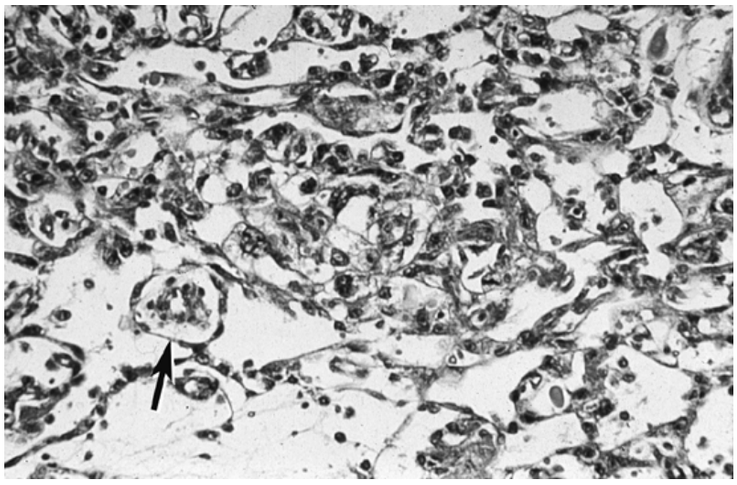

Figure 6.63 Yolk sac tumor. Microcystic spaces are lined by highly pleomorphic cells. A Schiller-Duval body (glomeruloid structure) is seen on the left *(arrow)*.

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. α-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 (94). Most tumors occur in children and young women, and hCG secretion is responsible for the clinical presentation. Both syncytiotrophoblast and cytotrophoblast must be present to make 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, composing more than 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).

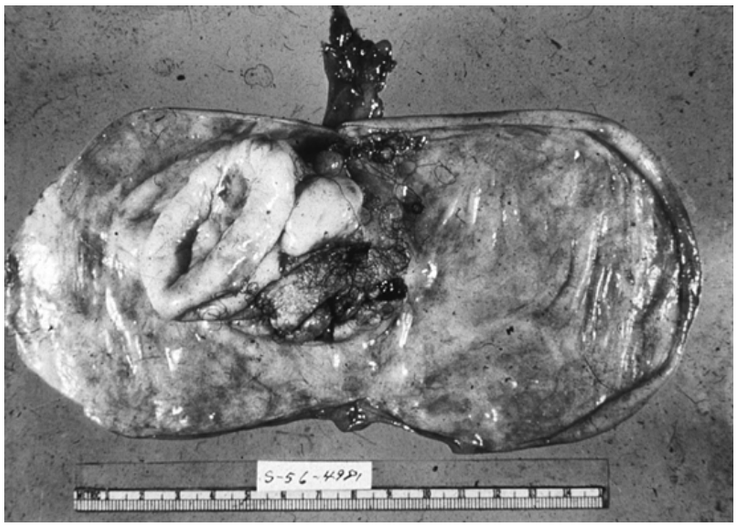

Figure 6.64 Mature teratoma. This cystic neoplasm contains hair and sebaceous material. The solid white area represents mature cartilage. (See Color Figure 6.64).

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, making up 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 (95) defines **grade 1 tumors** as having immature elements limited to no more than 1 low-power field in any one slide. In **grade 2 tumors**, the areas occupied by immature elements should not exceed 3 low-power fields, and **grade 3 tumors** show immature elements in more than 3 low-power fields. Grade 2 and 3 tumors are regarded as high-grade immature teratomas. 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 (96). The prognosis is ominous, and no therapeutic regimen has proven effective.

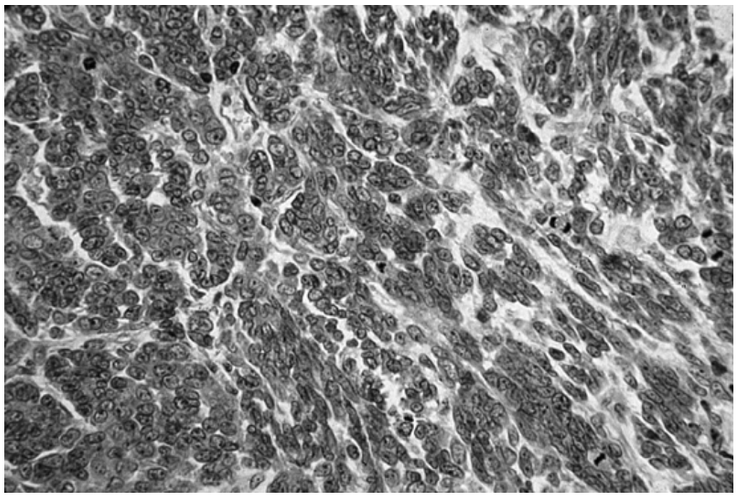

Figure 6.65 Small cell carcinoma with hypercalcemia. This lesion shows sheets of immature small cells with high mitotic rate.

Tumors Metastatic to the Ovary

Metastatic tumors compose 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.

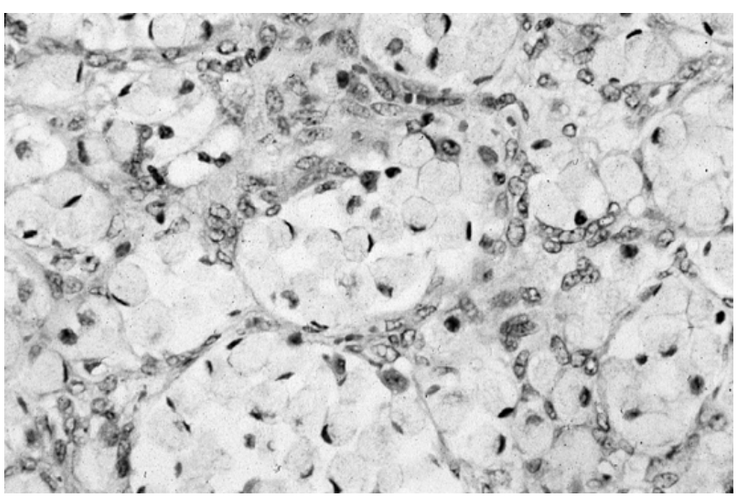

Figure 6.66 Krukenberg tumor. This metastatic gastric carcinoma shows diffuse infiltration of the ovarian stroma by signet ring cells. Both ovaries were diffusely enlarged.

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 (97).

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 (81).

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.

Tumorlike Lesions

A follicular cyst is lined by granulosa and theca cells and results from anovulation. These cysts are thus more common in menarchal and perimenopausal patients. Follicular cysts may cause pain or may even rupture; they may also cause symptoms secondary to autonomous estrogen production by the cyst lining. Grossly, follicular cysts are unilocular, have a smooth lining, and rarely exceed 8 cm in diameter.

A 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 follicular cysts. Grossly, the ovaries are rounded, with multiple small cysts beneath a thickened fibrotic cortex (Fig. 6.67).

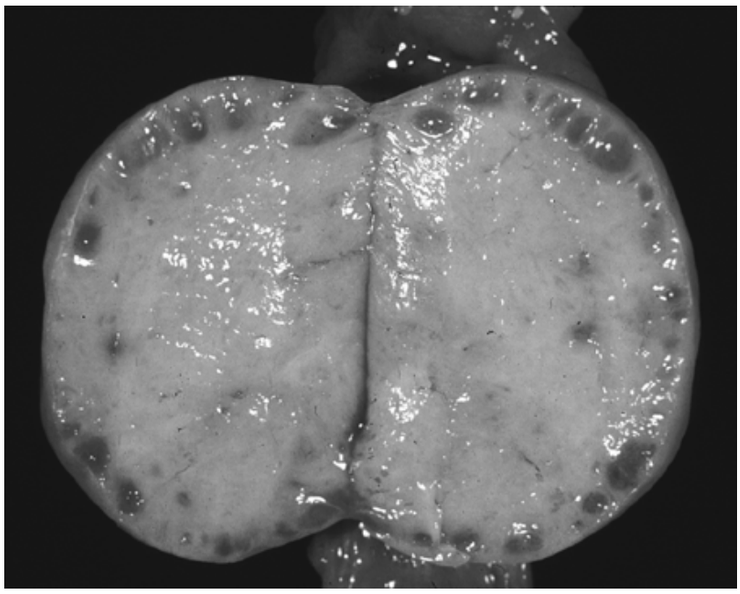

Figure 6.67 Polycystic ovarian disease. Both ovaries are enlarged and contain multiple subcortical follicle cysts.

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 hyperplasiais 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 tumorlike 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 consists of single or multiple, red-brown nodules of luteinized cells producing ovarian enlargement during pregnancy or the puerperium. The 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.

Theca Lutein Cysts (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 (theca lutein cysts) (Fig. 6.68).

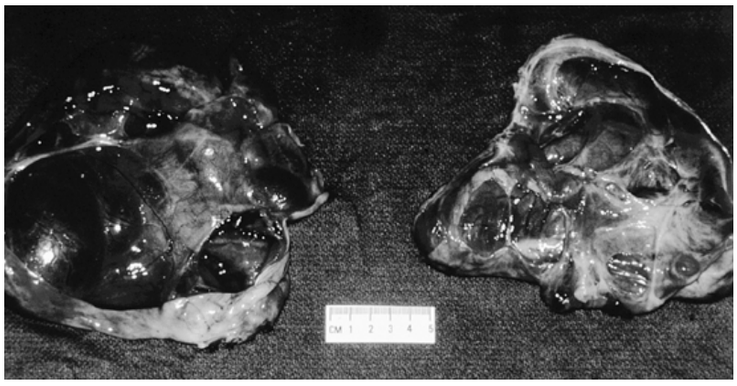

Figure 6.68 Theca lutein cysts (Hyperreactio luteinalis). Both ovaries are enlarged and contain multiple, tense, thin-walled cysts. (See Color Figure 6.68).

Solitary Luteinized Follicular Cyst of Pregnancy and the Puerperium

This consists of a large unilateral cyst lined by luteinized cells with bizarre nuclei.

Fallopian Tube Tumors

Part of "6 - Pathology "

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 glandlike 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 (98) and produce a fusiform swelling of the fallopian tube that may simulate hydrosalpinx. A papillary, friable tumor is discovered on opening the tube. 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

Part of "6 - Pathology "

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; 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 (99). 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 (100). Fluorescent *in situ* hybridization is another technique that has the advantage of examining the DNA content in tissue sections (101).

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, grapelike 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).

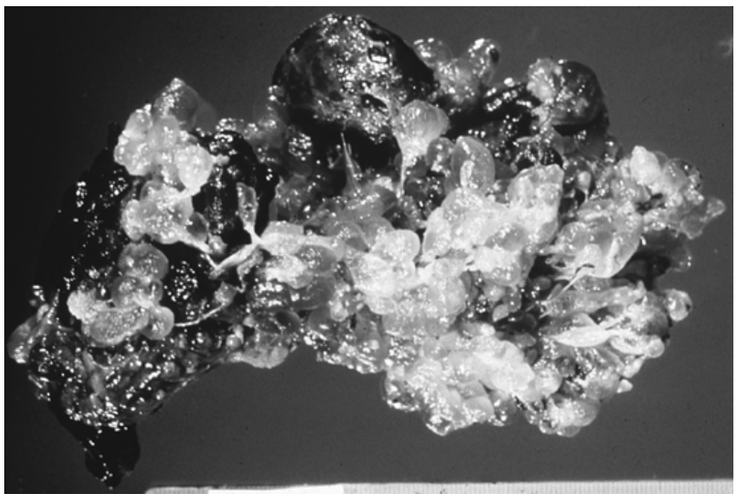

Figure 6.69 Complete hydatidiform mole. This lesion comprises placental tissue with multiple, grapelike, thin-walled vesicles. No embryo is present. (Figure courtesy of C. C. Sun, MD, University of Maryland Medical Center, Baltimore, Maryland.)(See Color Figure 6.69).

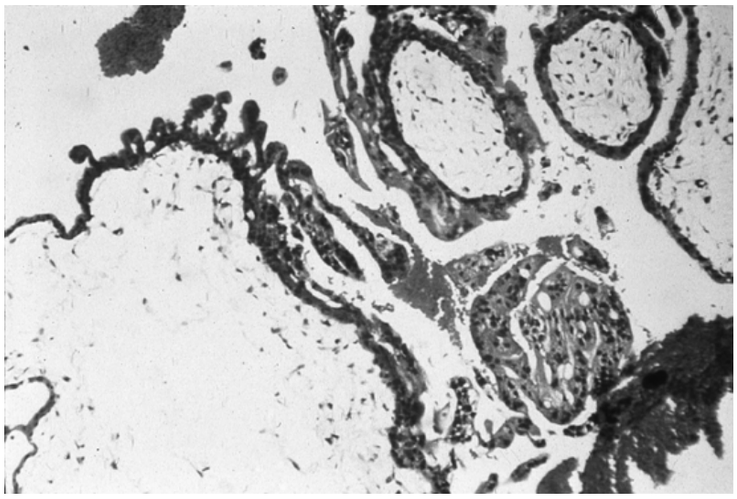

Figure 6.70 Complete hydatidiform mole. This lesion is characterized by markedly swollen chorionic villi with cistern formation and prominent circumferential trophoblast hyperplasia. (Figure courtesy of C. C. Sun, MD, University of Maryland Medical Center, Baltimore, Maryland.)

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).

Table 6.13 Features of Complete and Partial Hydatidiform Moles

	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	30%	5%
Risk of choriocarcinoma	3%–4%	Virtually none

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 the distinction between an invasive mole and choriocarcinoma cannot be made without**

pathologic examination, 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% develop choriocarcinoma (102).

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).

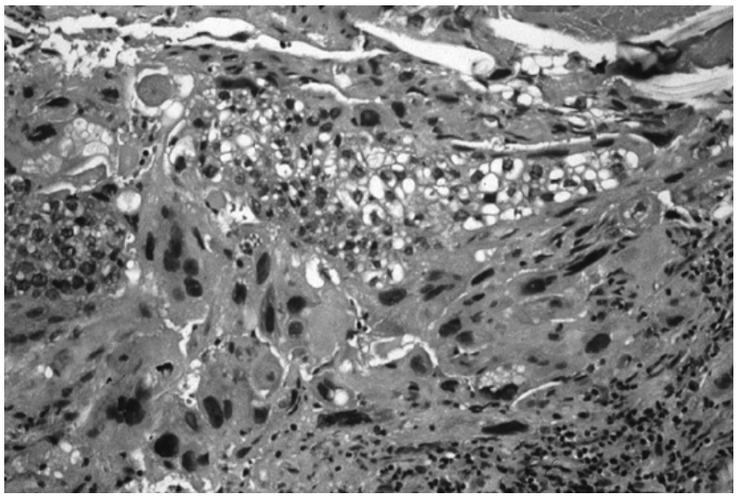

Figure 6.71 Choriocarcinoma. Large bizarre cells that represent syncytiotrophoblast are admixed with smaller uniform cells (cytotrophoblast).

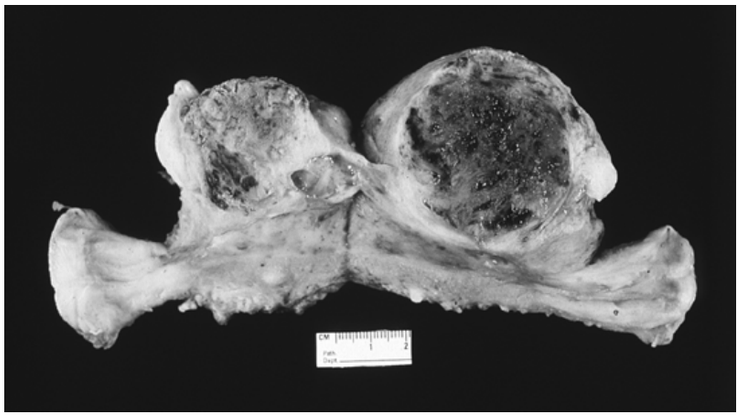

Figure 6.72 Choriocarcinoma. A hysterectomy specimen (rarely seen today) with hemorrhagic and necrotic tumor within the uterine wall. (See Color Figure 6.72).

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.

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 trophoblas—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 reliable histopathologic features that help predict the behavior of this tumor.

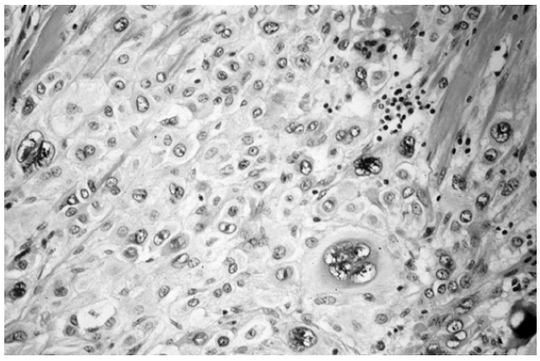

Figure 6.73 Placental site trophoblastic tumor. Large pleomorphic cells (intermediate trophoblast) diffusely infiltrate the myometrium.

Table 6.14 Features of Choriocarcinoma and Placental Site Trophoblastic Tumor

	Choriocarcinoma	*Placental Site Trophoblastic Tumor*
Clinical	Persistent gestational trophoblastic disease after hydatidiform mole	Missed abortion
Types of trophoblast	Syncytiotrophoblast and cytotrophoblast	Intermediate trophoblast
Behavior	Highly malignant chemoresponsive	Unpredictable—benign, persistent, or highly aggressive; poor response to chemotherapy

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7

Epidemiology and Biostatistics

Daniel W. Cramer

The disciplines of epidemiology and biostatistics apply to gynecologic oncology in defining cancer occurrence and survival, identifying risk factors, and implementing strategies for treatment or prevention. Principles of epidemiology and biostatistics are also essential to the practice of evidence-based medicine (1). 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 (2 ,3).

- Descriptive Statistics
- Etiologic Studies
- Statistical Inference and Validity
- Cancer Risk and Prevention

Descriptive Statistics

Part of "7 - Epidemiology and Biostatistics "

Cancer is described in populations by statistics related to its occurrence and survival after it. Descriptive statistics about cancer in the United States can be obtained from the National Cancer Institute through its Web site: http://www.seer.cancer.gov/; descriptive statistics about cancer in the world can be obtained from the International Agency for Research on Cancer through its Web site: http://www-dep.iarc.fr/globocan/globocan.html.

Incidence

The incidence rate (IR) is defined as the number of new cases of disease in a population within a specified time period.

$$\mathbf{IR = New\ cases/Person\text{-}time}$$

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, country or 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 region.

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 malignant gynecologic cancers in the United States based on all women in the Surveillance, Epidemiology, and End Results Survey (SEER) area for 1996 to 2000 (4) are shown in Figures 7.1 and 7.2 .

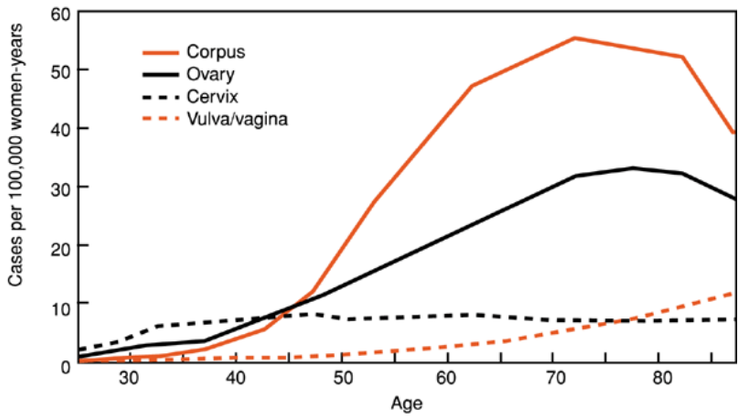

Figure 7.1 Age-specific incidence curves for the gynecologic cancers in women in the United States, 1996 to 2000 (4).

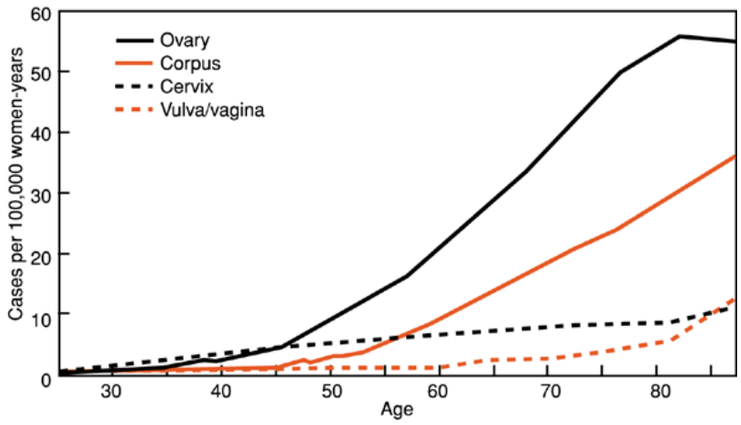

Figure 7.2 Age-specific mortality curves for the gynecologic cancers in women in the United States, 1996 to 2000 (4).

Invasive cervical cancer shows a 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 100 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 20 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. *In situ* cervical cancers are no longer being tabulated by the SEER registries. The vast majority of these cases are seen between ages 20 and 50, with a peak occurrence of about 200 cases per 100,000 women per year at ages 25 to 29.

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:

$$CIR = {}_{I}\Sigma IR_i(\Delta T_i)$$

where IR_i is the age-specific rate for the "i" age stratum and ΔT_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 corpus than cervical or ovarian cancer, but a higher risk of dying from ovarian cancer than cervical or endometrial cancer combined.

Table 7.1 Lifetime Risk of Acquiring or Dying from Gynecologic Cancers in White and Black U.S. Women (4)

	Risk of Acquiring			*Risk of Dying*		
	All	***White***	***Black***	***All***	***White***	***Black***
Cervix	0.8%	0.8%	1.0%	0.3%	0.2%	0.5%
Corpus	2.6%	2.8%	1.7%	0.5%	0.5%	0.7%
Ovary	1.7%	1.8%	1.1%	1.0%	1.1%	0.7%

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:

$$AAI = \frac{\Sigma IR_i(W_i)}{\Sigma W_i}$$

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 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 .

Table 7.2 Age-Adjusted Incidence Ratea for the Gynecologic Cancers in Comparison with Other Major Cancers in Women

Region	*Breast*	*Colon*	*Lung*	*Stomach*	*Cervix*	*Corpus*	*Ovary*
World	35.7	14.4	11.0	10.4	16.1	6.4	6.5
Northern Africa	28.3	5.2	2.8	3.3	16.8	2.2	3.2
Southern Africa	31.8	8.7	7.3	3.7	30.3	4.6	3.9
Eastern Africa	20.2	4.9	2.1	6.7	44.3	3.4	9.0
Western Africa	24.8	3.8	0.4	3.9	20.3	1.6	3.1
Northern America	90.1	30.6	33.6	3.7	7.9	15.5	10.7
Central America	36.2	9.1	8.4	11.7	40.3	15.8	7.0
South America	45.1	14.2	8.3	11.7	30.9	14.3	7.3
Eastern Asia	18.1	12.5	15.0	19.6	6.4	2.4	3.7
Southeast Asia	25.6	10.0	9.1	4.8	18.3	4.3	7.1
Western Asia	27.9	8.3	4.8	6.1	4.8	4.9	5.9
Northern Europe	73.2	25.2	18.9	6.1	9.8	11.1	12.6
Eastern Europe	49.4	21.5	8.8	14.5	16.8	10.7	10.3
Western Europe	78.2	29.4	10.7	7.0	10.4	10.9	11.1
Southern Europe	56.2	22.0	8.0	9.7	10.2	13.8	8.7
Australia-New Zealand	82.7	36.7	18.2	5.0	7.7	10.8	9.6
Micronesia	37.5	9.9	18.6	5.2	12.3	12.1	5.6
Polynesia	55.2	13.7	14.2	9.2	29.0	15.3	8.4

[a]Age-adjusted to the world standard in cases per 100,000.
Data from IARC Web site: http://www-dep.iarc.fr/globocan/globocan.html.

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. To say that survival is exponential means that the rate of death is constant over time, which can 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 have died, and the probability of survival at 1, 2, and 5 years.

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. Relative survival rates for U.S. women diagnosed in 1995 are shown in Figure 7.3 for the major gynecologic cancers and reveal that survival is best after cancer of the corpus, worst after cancer of the ovary, and intermediate after cancer of the cervix. Five-year relative survival rates are shown in Table 7.3 by type and stage of gynecologic cancer for U.S. women.

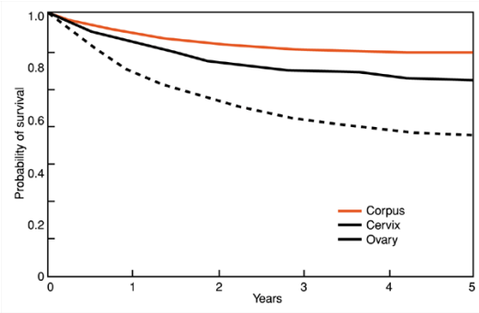

Figure 7.3 Relative survival rates for invasive cancers of the cervix, corpus, and ovaries for women diagnosed in the United States in 1995 (4).

Table 7.3 Stage at Diagnosis for the Gynecologic Cancers a and 5-Year Survival Rates for U.S. Women (4)

	Stage Distribution at Diagnosis (%)			*5-Year Survival Rate (%)*		
	All	***White***	***Black***	***All***	***White***	***Black***
Cervix						
All stages				71.3	72.9	61.0
Localized	54	56	47	92.2	92.6	87.2
Regional	32	30	35	50.9	51.8	41.4
Distant	8	7	8	16.5	17.5	11.6
Corpus						
All stages				84.4	86.3	60.0
Localized	73	74	53	96.2	97.0	83.5
Regional	15	14	22	64.7	67.3	42.5
Distant	8	8	17	26.0	28.0	13.4
Ovary						
All stages				53.0	52.4	51.5
Localized	29	29	28	94.7	94.8	92.5
Regional	6	6	8	72.0	71.3	72.0
Distant	59	60	56	30.7	30.8	26.3

[a]Data from 1992 to 1999. Information insufficient to stage 7% of cervical, 4% of corpus, and 6% of ovarian cases. **Reis LAG, Eisner MP, Kosany CL, Hankey BF, Miller BA, Clegg L, et al., eds.** *SEER Cancer Statistics Review, 1975-2000*. Bethesda, MD: National Cancer Institute, 2000.

Stage at presentation and 5-year 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, especially for cancer of the cervix and corpus.

Etiologic Studies

Part of "7 - Epidemiology and Biostatistics "

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, ethnicity, and geography, etiologic studies describe the relationship between cancer occurrence and survival and personal factors, such as diet or reproductive history. This relationship is often described by the epidemiologic parameters, 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. Absence of association is indicated by a RR of 1 (null value); a number greater than 1 may indicate that exposure increases the risk of disease and a number less than 1 that exposure decreases 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. The null value is 0; a number greater than 0 may indicate that exposure increases the risk of disease and a number less than 0 that exposure decreases the risk.

Case-Control Study

In a 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).

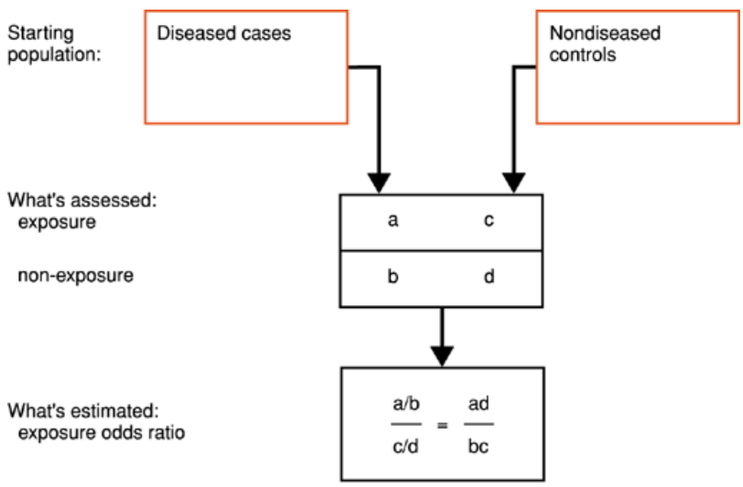

Figure 7.4 Case-control study design.

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:

$$\text{Population attributable risk} = \frac{(RR - 1) \times \text{Proportion of controls exposed}}{RR}$$

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 monitored 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 studied 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).

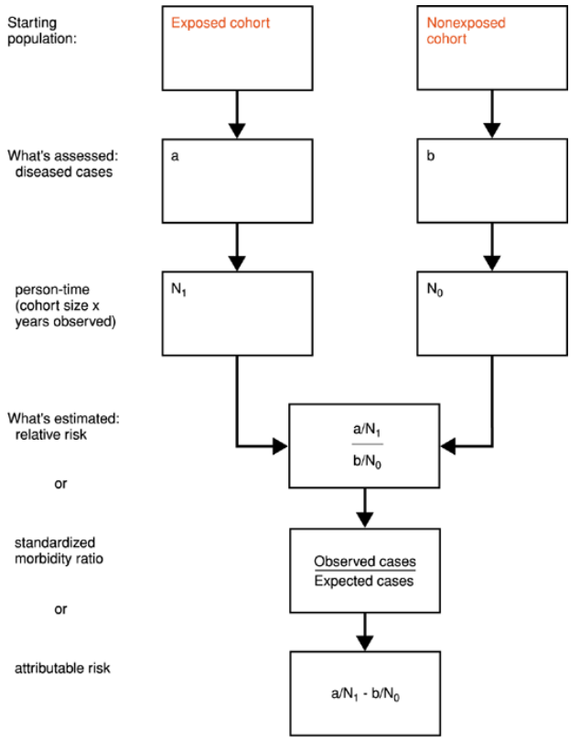

Figure 7.5 Cohort study design.

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

Part of "7 - Epidemiology and Biostatistics "

Clinicians should understand issues affecting statistical significance and validity to evaluate studies claiming that some exposure causes cancer, a new therapy is superior to standard treatment, or a screening test can improve mortality.

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:

- Observations are made and summarized by some statistical parameter such as a mean, a proportion, a relative risk, and so forth.
- A research question is stated in terms of a null hypothesis claiming no difference between the observed parameter and some theoretical value.
- A statistical test is chosen based on the study design and nature of the parameters being studied.
- The test statistic is calculated and its associated *p* value is read from the appropriate statistical table.
- A *p* value less than the traditional 5% leads to the decision to reject the null hypothesis, whereas a value greater than 5% leads to the decision not to reject the null hypothesis. Errors are possible with either decision.
- 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. **Precision** refers to a characteristic of a parameter falling into a narrow confidence interval, a desirable feature of large studies.

Type I and II Erros

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. 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.

Power

Power is 1 minus the beta error and reflects the ability of a study to detect an actual effect. More precisely, power is the ability of a test statistic to detect differences of a specified size in test parameters. In planning a clinical trial, an investigator often calculates the power 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 or samples.

Validity

Validity has two components: internal validity and external validity. **Internal 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. The external validity of a study refers to the ability to generalize the results observed in one study population to another**. Although there is controversy about what characteristics of a study make for generalizability, it is clear that external validity is only an issue for those studies that possess internal validity, which is the main focus of this discussion.

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 or an exposed or nonexposed cohort member, then the observation bias would be nondifferential and would cause the relative risk to be biased toward the null value, 1. Alternatively, if misclassification was more likely to occur for case than control subjects or for exposed than nonexposed cohort members, then a falsely elevated (or decreased) 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, and whenever possible, exposure or disease confirmed from medical records. 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 or blinded to key hypotheses. **In a clinical trial, observation bias may be minimized by double blindness**, when neither the subject nor investigator knows which specific treatment the subject is receiving.

Selection Bias

Selection bias is an error that is 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 newly 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, ethnicity, 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 analytic 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, confounding is avoided by randomization; that is, subjects are allocated to treatment groups by chance such that prejudices of the investigator or preferences

by the subject do not influence allocation of treatment. The initial table in a clinical trial usually shows how the treatment groups compared with respect to age, ethnicity, or other important variables to demonstrate whether randomization indeed balanced key variables. Similar tables are helpful in case–control and cohort studies.

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, especially those in which different study methods have been used, provide evidence for a causal association. However, the possibility that a systematic bias affected all the studies should also be considered. 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 there are statistical differences among the results of different studies. The meta-analysis has become an important component of evidenced-based medical reviews. 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 (5).

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 (5).

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:

- Administration of unopposed estrogen may cause endometrial hyperplasia (6).
- Endometrial cancer may develop in women with excessive endogenous estrogen from granulosa tumors (7).
- Endometrial cancer may develop in women with decreased degradation of estrogen secondary to liver failure (8).
- Women who are obese have excessive peripheral conversion of androstenedione to estrone and are at increased risk of endometrial cancer (9 ,10).
- 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 also 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

Part of "7 - Epidemiology and Biostatistics "

In this section, risk factors for the gynecologic cancers are discussed, along with the application of this information to cancer prevention. Table 7.4 summarizes major epidemiologic risk factors for cervical, endometrial, and ovarian cancer.

Table 7.4 Risk Factors for Gynecologic Cancers

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 and tubal ligation
Childbirth	Increasing risk with increasing parity	Decreasing risk with increasing parity	Decreasing risk with increasing parity
Age at menopause	No clear association	Late menopause increase 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
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; acetaminophen may decrease risk

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 that increase the opportunity for genital infection and include intercourse with multiple sexual partners or with “high-risk” men (11). Early age at first intercourse may also be important because adolescence is a period of heightened squamous metaplasia, and intercourse at this time may increase the likelihood of atypical transformation (12). 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. Many sexually transmitted pathogens have, at one time or another, been linked to cervical cancer in epidemiologic

studies. Although there remains the possibility of synergy between infections, certain subtypes of the human papillomavirus (HPV) have emerged as the most likely infectious agents (13). **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** (14). Male circumcision would appear to decrease the risk of male HPV infection and cervical cancer in their partners (15). Finally, HPV vaccines offer another exciting approach to true primary prevention of this important cancer worldwide (16).

There may also be risk factors of a nonsexual nature that may induce atypical transformation or, more likely, act synergistically with HPV infection. Douching with coal tar substances, as was a practice earlier in the twentieth 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 increased risk for 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). In third world countries, chronic exposure to wood smoke may increase the risk for cervical cancer in HPV-infected women (20).

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** (21). **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 with women who have never had a Pap test** (22). 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** (23), **and a link to adenocarcinomas of the cervix has also been postulated** (24). Butterworth et al. attributed the potential harmful effects of oral contraceptives on the cervix to folate deficiency and recommended supplementation (25). More recent studies found that high homocysteine levels may correlate with risk for invasive cervical cancer, again suggesting the importance of folates and vitamins B_{12} or B_6 (26). Finally, **progression of CIN is likely to be greater in immunosuppressed women**, such as those with human immunodeficiency virus infection (27), or after kidney transplantation (28).

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 (7). More commonly, obesity leads to increased production through the peripheral conversion of androstenedione (9). 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 (29). Leanness and regular exercise lower estrogen levels and protect against endometrial cancer (30). Smoking also lowers estrogen and protects against endometrial cancer, but obviously cannot be encouraged as a preventive measure (31). Endometrial cancer as a consequence of decreased degradation of estrogen is illustrated by case reports of the disease in women with cirrhosis of the liver (8).

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 (5). *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 clinical trial data (32). Alternatively, menopausal estrogen taken with a progestin has not been shown to increase risk (33), and past use of combination birth control pills has been reported to decrease the risk of endometrial cancer (34). 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 (35).

Fitting with key roles for estrogen and progesterone in this disease, risk for endometrial cancer may be modified by genetic polymorphisms of the progesterone receptor (36) and estrogen receptor alpha (37). It is less clear how the DNA mismatch repair genes that are associated with increased risk for colorectal and endometrial cancers would operate through the “estrogen excess” model (38). Although the majority of risk factors for endometrial cancer are nicely explained by estrogen excess, the observation that even inert intrauterine devices (IUDs) may decrease risk suggests that immune factors related to the low-grade inflammation that occurs with IUDs may also play a role (39).

Ovarian Cancer

Ovarian cancer has been associated with a number of diverse findings with a variety of theories offered to explain them. **Consistently observed risk factors for ovarian cancer include a protective effect of pregnancy, breastfeeding, and 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** (40). 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 (41). Classic animal models for ovarian cancer involved disruption of ovarian–pituitary feedback either by prematurely destroying oocytes using radiation or chemical toxins (42 ,43) or by transplanting the animal's ovary to its spleen, leading to enhanced metabolism of ovarian hormones before they could exert feedback inhibition (44). 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 (45 ,46). More recently, it has been shown that gonadal stromal tumors invariably developed in mice with a targeted deletion of the gene for the gonadotropin down-regulator, α-inhibin, (47) unless the mice were also incapable of secreting gonadotropins (48). 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 incidence rises sharply between ages 45 and 54 years and remains 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 (49) duplicates the modifying effects of exogenous estrogen in the animal models. 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 (50 ,51).

Parmley and Woodruff proposed that epithelial ovarian cancers might be ovarian mesotheliomas that arise from transformation of the surface lining of the ovary exposed

to pelvic contaminants (52). One such contaminant might be talc used in genital hygiene, which has fairly consistently been identified as a risk factor (53). 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 (54). Indeed, prior endometriosis is a risk factor for ovarian cancer (55), especially the endometrioid and clear cell types (56). **The pelvic contamination theory might also explain why tubal ligation decreases the risk of ovarian cancer** (57). More recently introduced theories have suggested roles for androgens, progesterone, and inflammation, and offer alternate but not necessarily competing explanations for ovarian cancer risk factors (58 ,59).

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 (60). **Specific genetic factors include mutations of the *BRCA1* and *BRCA2* as well as the DNA mismatch genes** (61). Although a genetic factor is more likely to be found in families in which 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 (62) and up to 40% among women with a Jewish ethnic background (63).

Other Gynecologic Neoplasms

Other than clear cell adenocarcinomas of the vagina associated with maternal use of diethylstilbestrol (64), 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 (65 ,66 ,68). Thus, **risk factors known to exist for cervical neoplasms may be pertinent for vulvar and vaginal neoplasms, including HPV infection and smoking** (69 ,70). This is discussed in Chapter 13 . Further study of dietary factors, especially folates and 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 (71). Clearly, **the risk of having a molar pregnancy increases with maternal age** (72 ,73), but it is less certain whether adolescents are also at increased risk (74). 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. (75) 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 (76 ,77 ,78). In addition, regions where molar pregnancy is common have a high incidence of night blindness (79).

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:

- **For cervical cancer**, avoidance of tobacco, use of barrier methods of contraception, and a diet high in folates, the B vitamins and ß-carotene may be beneficial. HPV vaccines may soon be available and should be initially targeted for populations at highest risk for cervical cancer.
- **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.
- **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 undergo prophylactic salpingo-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 (80). 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 .

Table 7.5 Measures of Validity for a Screening Procedure

	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[a]***	
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	$\frac{a}{a+b}$ or	$\frac{SN(P)}{[SN(P)+(1-SP)(1-P)]}$

[a]Where SN = Sensitivity, SP = specificity, and P = Prevalence of Disease

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 defined as the proportion of true positives out of all those who screened positives. The alternate formula shown in Table 7.5

reveals that predictive value 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 7.5).

Screening Strategies

Cervical cytology represents one of the most effective screening tests for cancer ever developed; controversies relate to how to make it more efficient. Recent guidelines suggested by the American Cancer Society (81) are that the interval between screenings may be safely lengthened to 3 years in women who have had at least three consecutive negative screens and are at otherwise low risk (e.g., no history of immunosuppression). Similar guidelines were proposed by the American College of Obstetricians and Gynecologists in 2000, although the less frequent intervals were to be at the discretion of the physician (82). A recent analysis of the potential effects of extending screening intervals concluded that an average excess risk of three cases of cervical cancer per 100,000 women screened would result (83). However, to avert one additional case of cancer by screening women annually for 3 years would necessitate approximately 280,000 additional Papanicolaou tests and 15,000 colposcopic examinations. Additional discussion of this complicated issue, including the role of HPV testing in cervical cancer screening, is presented in Chapter 8 .

Screening for endometrial cancer in asymptomatic women in the general population is not justified, but endometrial biopsies or assessment of the endometrial stripe by transvaginal ultrasound may be appropriate for perimenopausal or postmenopausal women at risk for endometrial cancer, including those who are obese, are exposed to unopposed estrogen, use *tamoxifen*, or who come from families with both colon and endometrial cancer. **Based on expert opinion only, women at high risk for ovarian cancer by virtue of a *BRCA1* or *2* mutation are recommended to have annual or semiannual screening with transvaginal ultrasound and CA125 measurements** (84). A large trial is under way in the United Kingdom to determine whether use of annual CA125 measurements with secondary ultrasonic screening would be effective at reducing ovarian cancer mortality in postmenopausal women at normal risk (85).

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Section II Disease Sites

8

Preinvasive Disease

Michael J. Campion

- Cervix
- Vagina
- Vulva and Perianal Area
- Multicentric Lower Genital Tract Neoplasia

Cervix

Part of "8 - Preinvasive Disease "

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 ,4 ,5). This difference largely reflects the impact of mass screening using cervical cytologic methods (6).

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 (7 ,8 ,9). 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 (10). The term “carcinoma *in situ*” was later introduced to describe cancerous changes confined to the epithelium (11).

The Dysplasia Terminology

Although referred to earlier by Papanicolaou and Traut (12), Reagan and Hamonic in 1956 (13) described cytologic differences between “carcinoma *in situ*” and a group of “less anaplastic” lesions, for which they introduced the term **dysplasia** (14). 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 (15 ,16 ,17 ,18).

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 (17 ,18 ,19 ,20).

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 (20). 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** (21) **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 (22 ,23 ,24 ,25 ,26 ,27 ,28).

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 (29 ,30 ,31 ,32 ,33 ,34), have led recently to further reclassification of the terminology for reporting cytologic abnormalities consistent with preinvasive disease (35 ,36 ,37 ,38 ,39 ,40). **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 (41). Separating CIN 2 from CIN 3 is again often nonreproducible and achieves no useful clinical purpose. In reality, **the two critical questions in the assessment of the cervical epithelium are: (a) do the changes represent a cancer precursor, and (b) is the lesion invasive cancer?**

The biologic heterogeneity of low-grade lesions (HPV infection alone/CIN 1) is well recognized. Recent data from the United States National Cancer Institute ASC-US/LSIL Triage Study (ALTS trial) indicate considerable heterogeneity in the biologic and clinical behavior of CIN 2 lesions (42). **CIN 3 is clearly established as a *bona fide* cancer precursor, but there still exists uncertainty in relation to the progressive potential of less severe dysplastic lesions.** The clinical dilemma remains the inability to reliably predict those lesions less severe than CIN 3 that are at greatest risk of progression to cancer and those that are likely to regress. New molecular markers hold promise in this regard (43 ,44). These issues are discussed in more detail later in this chapter.

Understanding the Cervical Transformation Zone

Embryogenesis

The cervix and vagina are derived from the müllerian ducts and are initially lined by a single-layer of müllerian-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.

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 (45). 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 (46). The position of the original squamocolumnar junction determines the extent of cervical squamous metaplasia (46 ,47). **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. 8.1).

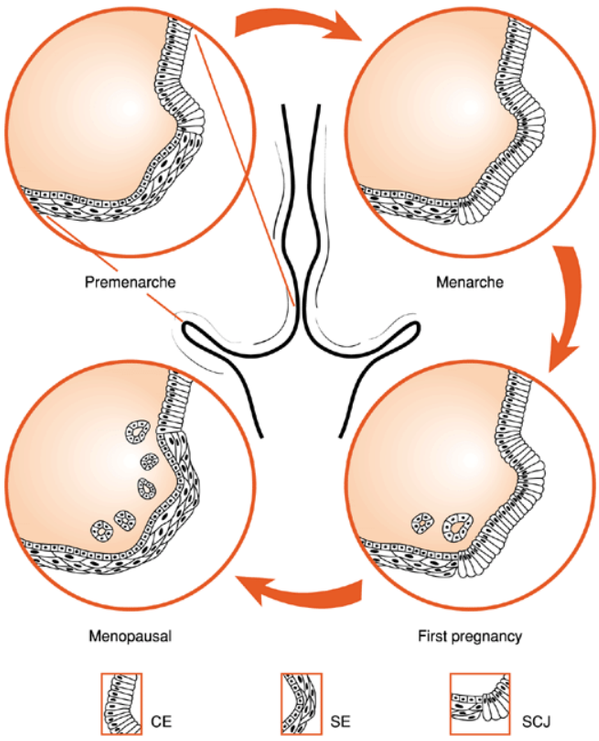

Figure 8.1 Location of squamocolumnar junction at various times in a woman's life. *CE*, columnar epithelium; *SE*, squamous epithelium; *SCJ*, squamocolumnar junction.

New Squamocolumnar Junction

The volume of the cervix alters throughout a woman's life in response to hormonal stimulation (45 ,46). 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 (46). **This eversion of columnar epithelium onto the ectocervix is called an ectropion. An ectropion is often mistakenly referred to as an erosion**.

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 (46). Everted endocervical columnar epithelium is exposed in

the postpubertal years to the 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 (46 ,47). **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, and 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. As the transformation zone matures, the original squamocolumnar junction becomes impossible to delineate. Only the presence of Nabothian follicles and gland openings hint 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. 8.2). **Squamous metaplasia is a permanent process but is not continuous. It occurs in "spurts," with greatest activity during puberty and the first pregnancy.**

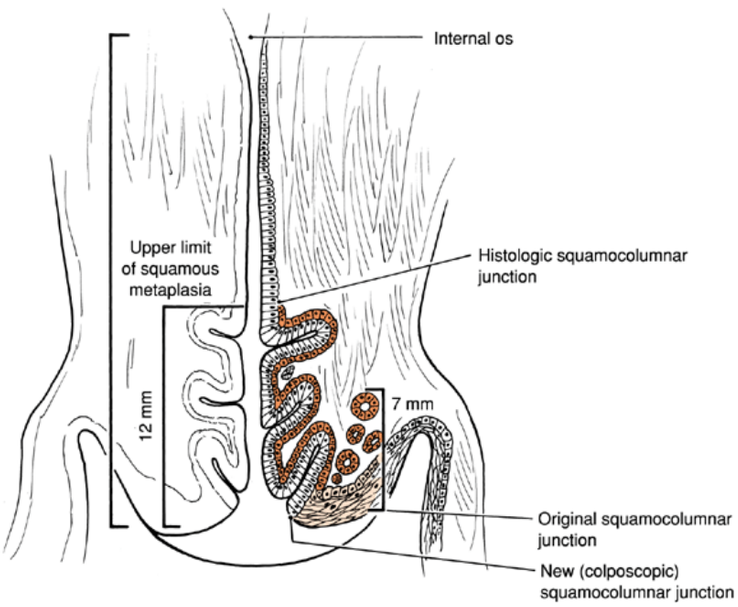

Figure 8.2 The anatomy of the transformation zone.

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 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. 8.3).

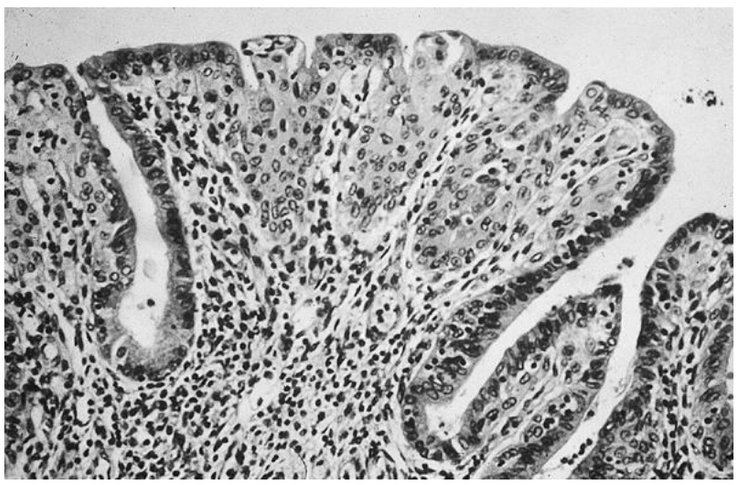

Figure 8.3 Histology of immature squamous metaplasia (chronic cervicitis).

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, and **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. 8.4). 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.

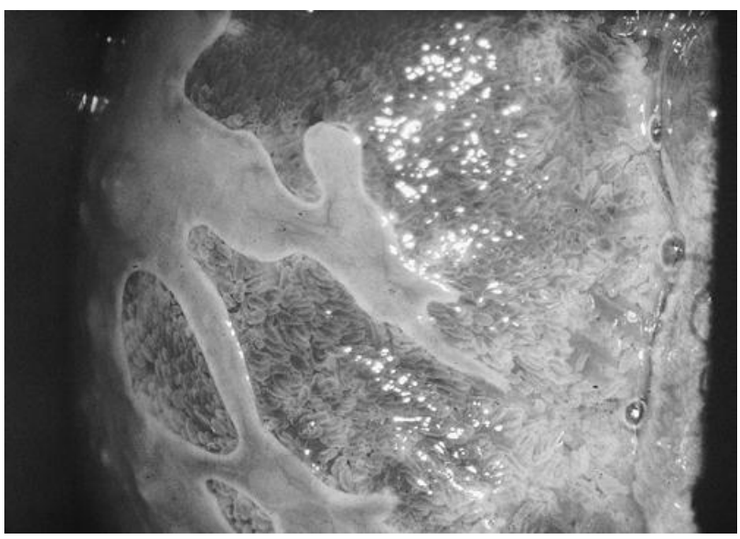

Figure 8.4 Colposcopy of immature squamous metaplasia.

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 (46). **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 (48 ,49 ,50 ,51). 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 (50). Potential carcinogens in the vaginal environment at times of active metaplasia can deviate early metaplastic transformation along a neoplastic pathway. 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 (52). **Extensive molecular biologic and epidemiologic research confirms certain HPV types to be carcinogenic in humans** (53 ,54 ,55 ,56 ,57 ,58 ,59 ,60 ,61). **The magnitude of the association between HPV and cervical cancer is higher than the association between smoking and lung cancer.**

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 (61). **More than 70 types of HPV have been fully sequenced** (62 ,63 ,64). 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 (65). 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 (Fig. 8.5) (66 ,67 ,68). 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 well-differentiated keratinocytes (69).

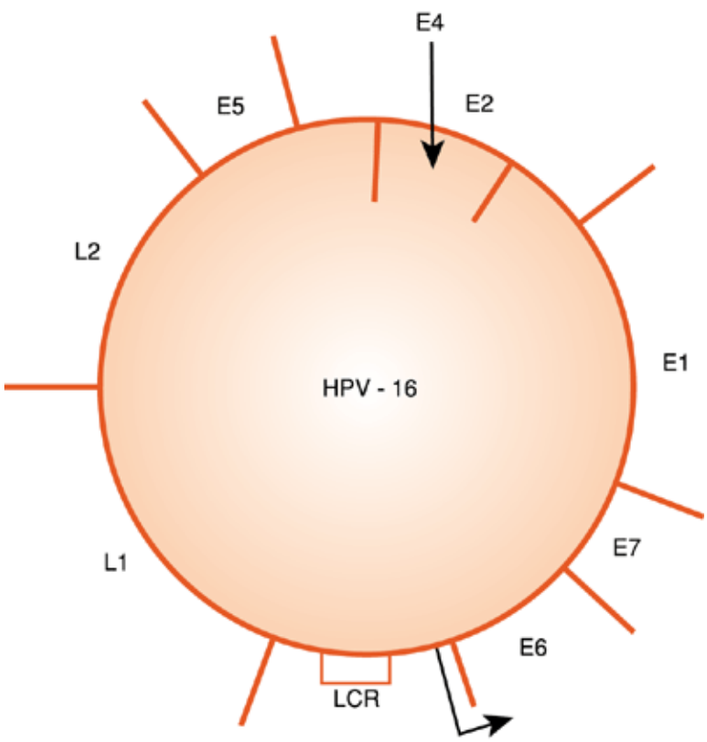

Figure 8.5 Schematic representation of the human papillomavirus genome.

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 (59 ,70). Both E6 and E7 proteins can immortalize primary keratinocytes from cervical epithelium and can influence transcription from viral and cellular promoters (59 ,71). 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** (72 ,73). This induces degradation of p53, removing the p53-dependent control of the host cell cycle (74 ,75 ,76 ,78). E6 also increases telomerase activity in keratinocytes through increased transcription of the telomerase catalytic subunit gene (TERT) through induction of c-Myc (79).

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 (80 ,81). 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.

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 (82). 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 (61). This results in increased levels of E6 and E7 expression, correlating with increased immortalization activity (61 ,83 ,84 ,85).

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. 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 (HPVs 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) (86 ,87 ,88 ,89).

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 alone in low-grade cervical lesions (exophytic condylomata acuminata, subclinical HPV infection, and CIN 1). 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 (90 ,91) and more than 30% of adenocarcinomas (92). It is present in more than 80% of high-grade cervical, vaginal, vulvar, perianal, and penile preinvasive lesions. It is detected in more than 25% of low-grade cervical lesions, 40% of subclinical vulvar HPV infections, and 10% of genital condylomata acuminata, particularly the recalcitrant lesions (86 ,87 ,88 ,89). **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 (93 ,94). Although this remains a controversial issue (95), epidemiologic and molecular data support the hypothesis (96 ,97). **HPV 18 DNA is detected 2.6 times more frequently in invasive cervical cancers occurring within 1 year of a negative smear** (94). 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 (98).

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 more than 60% of sexually active women younger than 35 years of age exposed (99). Recent prospective data demonstrate 2-year cumulative incidence for first time genital HPV infection for young women to be 32%. Incidences are similar for virgins and nonvirgins from the time of acquisition of a new

partner. Smoking, oral contraceptive use, and report of a new male sexual partner are predictive of incident infection. Male condom usage is not protective. Infection in virgins is rare, but any nonpenetrative sexual contact is associated with an increased risk. Basal cells of the cervical epithelium are inoculated with the virus at sites of microtrauma.

Exposure to specific high-risk HPV types, in the presence of cofactor activity, may deviate the metaplastic process along a neoplastic pathway (84 ,85 ,100). 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 (87 ,88 ,89).

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 (101). Viral burden appears to have an independent effect on CIN incidence as a surrogate for HPV persistence but does not independently predict future risk of CIN 3 or cancer. **Only persistent HPV infection of the cervical epithelium appears to trigger neoplastic progression** (101 ,102). The reported progressive potential of low-grade lesions 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 (,19 ,20 ,103 ,104 ,105 ,106).

CIN 3 lesions are a homologous population of aneuploid lesions, mostly associated with oncogenic HPVs, and are genuine cancer precursors (104). Recent data indicate a greater degree of heterogeneity in CIN 2 lesions than has been generally appreciated (42). The progressive potential of these lesions is established but no reliable marker for increased risk of progression is clinically available. As such, CIN 2 remains combined with CIN 3 as a high-grade lesion and is managed accordingly. 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. 8.6). HPV is necessary for tumor induction, tumor 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.

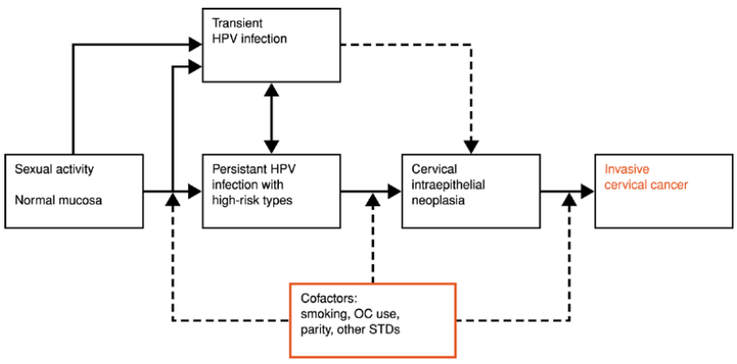

Figure 8.6 "Seed, soil, and nutrient" model for cervical carcinogenesis.

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.

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 (107).

Cigarette Smoking **Cigarette smoking has been demonstrated to be a risk factor for cervical and vulvar carcinoma** (108 ,109 ,110 ,111 ,112 ,113 ,114 ,115 ,116 ,117 ,118 ,119 ,120 ,121 ,122 ,123). An increased risk of developing a high-grade squamous intraepithelial lesion (HSIL) has been demonstrated among high-risk HPV positive women who smoke or who are passive smokers. 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 (113 ,114).

Cigarette smoking influences epithelial immunity by decreasing the numbers of antigen-presenting Langerhans cells in the genital epithelium (120 ,121). Cervical HPV infection and CIN are associated with diminished numbers of intraepithelial Langerhans cells. Such local immunologic depletion could favor viral persistence, contributing to malignant transformation. Cigarette smoke concentrates have been demonstrated *in vitro* to transform HPV-16–immortalized endocervical cells (122), although no increased risk of adenocarcinoma has been identified in association with use of tobacco products. The increased risk associated with passive smoking is as strong as that observed in association with personal cigarette smoking (118 ,119). 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 (110 ,124 ,125). An increased incidence of other sexually transmitted diseases has been reported in association with genital HPV infection and cervical neoplasia (126). **Disruption of epithelial integrity and reparative metaplasia associated with acute cervicitis that is 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 (127 ,128 ,129 ,130 ,131).

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 (132 ,133).

CIN and cervical cancer are more frequently found in women with increased parity (134) and in women on oral contraceptives independent of sexual activity (110 ,135 ,136 ,137).

Epidemiologic studies show an increased risk of CIN in long-term oral contraceptive pill (OCP) users, rising to twofold for 5 or more years of OCP use. OCP-induced folate deficiency with reduced metabolism of mutagens is a proposed mechanism for increased risk (135 ,136 ,137 ,138). There has been no demonstrable clinical value to ceasing oral contraceptives in the management of HPV-associated disease. Protective benefits of barrier contraception remain unclear (139).

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** (140). The risk of CIN and cervical cancer is increased in human immunodeficiency virus (HIV)–infected women, and failure rates of treatment for preinvasive lesions are increased (141 ,142 ,143). 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 (140).

Dietary Factors **Dietary deficiencies of Vitamin A or beta-carotene may increase the risk of CIN and cervical cancer.** Higher dietary consumption of vitamins A, C, and E as well as beta-carotene and increased circulating levels of certain micronutrients may be protective against cervical neoplasia (144 ,145 ,146 ,147 ,148). Higher levels of dietary vitamin A and carotenoids, reflected in higher dietary vegetable intake and increased circulating levels of cis-lycopene, are associated in a greater than 50% reduction in persistence of high-risk HPV DNA (148). **Persistence of high-risk HPV DNA is the major marker of risk for development of cervical neoplasia** (102 ,149 ,150).

Human Papillomavirus Vaccines

Most invasive cervical cancers and CIN lesions are attributable to high-risk HPV infection (91 ,151). A prophylactic or therapeutic vaccine against HPV has the potential to have a substantial impact on HPV infection and rates of CIN and cervical cancer (152).

Considerable research effort has been expended in this endeavor over the past two decades. Polynucleotide and recombinant viral vaccines show therapeutic and prophylactic efficacy in animal models (153). Such vaccines are candidate immunotherapies, particularly for established low-grade, benign genital HPV infection (154 ,155). Vaccines have been designed to elicit cytotoxic T lymphocytes specific for the HPV oncoproteins E6 and E7 (156 ,157).

HPV 16 L1 VLP Vaccine Trial

A recent phase III double-blind, multicenter, randomized clinical trial of an HPV 16 L1 viruslike-particle vaccine demonstrated high levels of immunogenicity, safety, and efficacy (158). The immunogenicity of HPV involves presentation of the major capsid protein L1 to the immune system. Empty viral capsids, termed *viruslike particles (VLP)*, are synthesized using microbial or cellular expression systems. L1 VLP vaccines induce strong cell-mediated as well as humoral immune responses (159 ,160 ,161 ,162).

Administration of an HPV 16 L1 VLP vaccine to 2,392 young women produced reductions in the incidence of both HPV 16 infection and HPV 16–related CIN. The vaccine was well tolerated with no serious adverse effects. **The vaccine demonstrated 100% efficacy with all new cases of HPV 16 infection and HPV 16 related CIN occurring among placebo recipients. Cross-protection to other HPV types was either minimal or absent** (158). Although HPV 16 is the most common HPV type associated with high-grade CIN and cervical cancer, vaccines that prevent infection with a broad spectrum of HPV types (multivalent vaccines) would be preferable (163).

The development of an effective HPV vaccine could provide a powerful strategy for the control of cervical cancer. However, the policies surrounding a vaccine directed against a sexually transmitted disease and aimed at prevention of a related disease in

women alone, possibly years later, will be extremely challenging (163 ,164). For example, a vaccination program for men and women with a vaccine that is 75% effective and provides a mean of 10 years of immunity, achieving 90% population coverage, would lead to a 44% decrease in the endemic prevalence in women of the HPV the vaccine is directed against. A female-only vaccination strategy would only lead to a 30% decrease in HPV prevalence (163).

Vaccination against a single high-risk HPV type or a subset of high-risk HPV types will not have the same long-term protective effect as destruction or excision of the transformation zone among women with established CIN lesions. The reduction in incidence of high-grade CIN and invasive cancer would be less, as some of the HPV-associated lesions, which are prevented by type-specific HPV vaccination, will be replaced by lesions caused by other HPV types (165 ,166). Recent studies also suggest that elimination of some HPV infections by vaccination (e.g., HPV types 6 or 11) may increase the oncogenic potential of break-through infections with high-risk types (e.g., HPV 16) (163 ,164). Vaccines are unlikely to eliminate cervical cancer. They may eliminate the need for treatment and follow-up of a substantial number of CIN lesions and may safely reduce the frequency of screening interventions.

Screening for Cervical Neoplasia

Incidence and mortality rates for cervical cancer in the United States have steadily decreased since the 1950s (167). 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 (167 ,168 ,169 ,170 ,171 ,172). **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 (173). **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. There has been an increasing incidence of cervical cancer in young women in many Western countries since the 1970s in spite of dramatic increases in diagnosis and treatment of preinvasive cervical disease (174 ,175 ,176 ,177).

Test Performance Characteristics of Conventional 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. **Pap smear screening decreases the incidence and mortality of cervical cancer**, but the accuracy of the Pap smear was never tested in a prospective, double-blinded study. Only relatively recently has the accuracy of the Pap smear been questioned (177), although it has long been apparent that it has a definite false-negative rate for invasive cancer and its precursors (178 ,179 ,180 ,181 ,182 ,183 ,184 ,185 ,186 ,187 ,188 ,189 ,190).

Sensitivity of Cervical Cytologic Screening

Sensitivity levels reported by experts under research conditions are not reproducible 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) (177 ,191 ,192 ,193). 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, many women in whom invasive cancer develops have never been screened but up to 50% have been screened yet still develop cancer (182 ,183 ,185 ,187 ,188 ,189 ,190). This occurs more frequently among younger women with invasive cancer and reflects the inherent suboptimal sensitivity of conventional cytologic screening (Fig. 8.7).

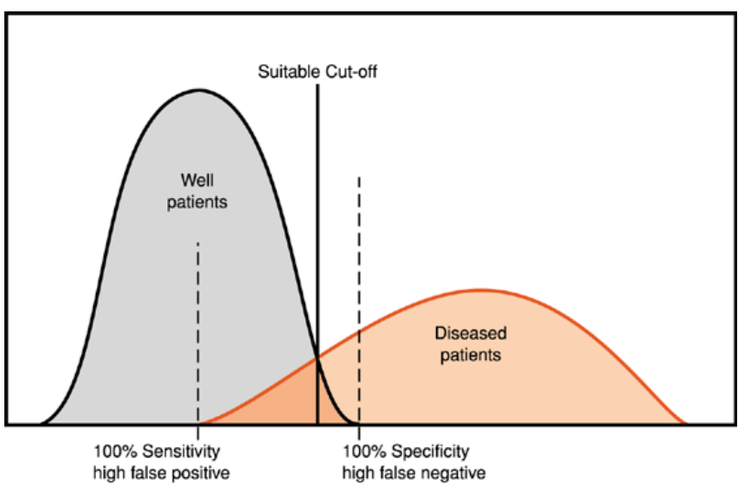

Figure 8.7 Sensitivity and specificity of screening test as reciprocal ratios.

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%) (184 ,185). **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. **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

One-third of false-negative smear reporting is attributable to laboratory error (177 ,184 ,192). 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 low-grade lesions. 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 high-grade lesions and cancer (193 ,194 ,195 ,196 ,197).

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 high-grade lesions 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 (177). 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** (198). Clinicians must be extremely cautious in dismissing an unexplained high-grade cytologic report. The specificity of cytologic screening has been eroded by cytologic overcall of low-grade disease (194 ,195 ,196 ,197). **Colposcopic assessment of women with low-grade cytologic abnormalities reveals no disease in as many as 30% of cases** (195).

Liquid-Based, Thin-Layer Cervical Cytology

A metaanalysis 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 (193). A large U.S. study recently concluded that estimates of the sensitivity of the conventional smear were biased in most studies (195). **Based on the least biased studies, they concluded the sensitivity of conventional cytology was 51%, much lower than generally believed.**

Sampling and preparation errors are responsible for more than 70% of false-negative Pap smears (182 ,183 ,196). The manual procedure of applying the cells to the glass slide is impossible to standardize. Up to 80% of cervical cells are discarded with collection devices used in taking conventional smears (197 ,198). **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** where there may be insufficient permeation of the fixative.

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 (182 ,183 ,199). 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.

Liquid-Based Cytology Techniques

The most widely researched of the liquid-based cytology (LBC) techniques is the ***ThinPrep* method** [Cytyc Corporation, Boxborough, MA; approved by the Food and Drug Administration (FDA) in May 1996] (200). **The slide preparation technique is automated.** Slide evaluation is usually performed by cytotechnicians/cytologists, but **automated image analysis technology also may be used** (Fig. 8.8). Another LBC technique, ***SurePath*** [TripPath Imaging, Burlington, NC; approved by FDA in May 2003], is available for gynecologic use. Fewer data are available on the clinical effectiveness of *SurePath* LBC. A recent Dutch analysis suggests further evaluation of *Surepath* LBC is necessary (201), whereas the United Kingdom evaluation of both technologies concluded that there was insufficient evidence to recommend one LBC product over another (202).

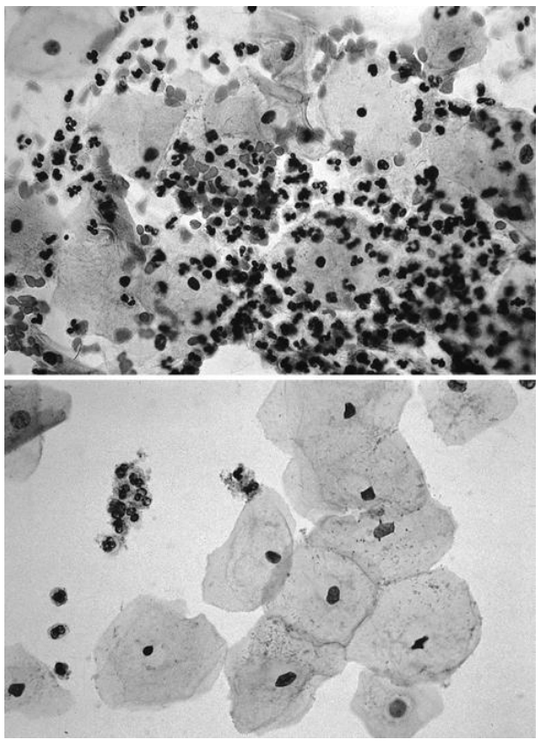

Figure 8.8 Comparison of (top) **standard Papanicolaou smear with** (bottom) **monolayer preparation.**

Studies assessing the *ThinPrep* method include both split-sample studies (203 ,204 ,205 ,206), in which 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 (207 ,208 ,209 ,210), in which 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 100%. The same studies show a significant decrease in "unsatisfactory" 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.

In the United States, there has been rapid adoption of LBC for cervical screening over the past 5 years (211). More than 60% of all cervical smears currently taken in the United States are taken into solution. Recent technological improvements in automation of processing and assessing LBC specimens are likely to increase this utilization. **The ability to test LBC specimens for HPV DNA and other sexually transmitted organisms further enhances the clinical appeal of this technology**.

The challenging questions asked by screening programs around the world are (a) Is LBC more sensitive and specific than conventional cytology? and (b) Is implementation of LBC cost-effective? Screening programs rely on analyses that adopt a population-based model as opposed to limited laboratory and clinical studies of specific clinical populations. The results of these analyses have been as varied as the screening programs (212 ,213 ,214 ,215 ,216 ,217).

Liquid-Based Cytology: Clinical Efficacy and Cost Effectiveness

A 1999 analysis conducted for the U.S. Agency for Health Care Policy and Research (AHCPR) assessed the efficiency and cost-effectiveness of new cervical cytologic screening technologies based on a metaanalysis of published research (195). **This study reported that the *ThinPrep* 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 indicated an improved sensitivity for LBC as opposed to conventional cytology but found no precise estimates for the effect on specificity, particularly with reported increased detection of atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesions (LSIL). It reported there was insufficient evidence to make recommendations for adopting LBC and suggested further study.

Following an extensive literature review and assessment, **the American Cancer Society reported in 2002 that LBC (ThinPrep) was more sensitive but possibly less specific than conventional cytology for the detection of HSIL** (218). The revised guidelines of the ACS recommended liquid-based cytology as an alternative to conventional smears with screening to be performed every 2 years. The U.S. Preventive Services Task Force, reporting in 2003 on cervical cancer screening, concluded there was insufficient evidence to make a recommendation to adopt LBC (217).

The recent United Kingdom experience has lent strong support to the claim that LBC offers improved clinical performance in cervical screening. The 2001 Scottish Cervical Screening Programme pilot study reported that use of LBC increased detection of HSIL and significantly reduced unsatisfactory smear rates when compared with the

conventional smear (216). **LBC was subsequently introduced into the Scottish Cervical Screening Programme.** Similar findings were reported in England after interim clinical assessment of the pilot conducted by the U.K. National Screening Program (214). **This led the National Institute for Clinical Excellence, U.K. (NICE) in 2003 to recommend LBC be used as the primary cervical cancer screening tool in England and Wales.**

The U.K. experience, coupled with the results of recent metaanalyses of LBC performance compared with conventional cytology, argues strongly in favor of improved clinical effectiveness of LBC (219). **Cost-effectiveness will be influenced by a number of additional variables**, such as availability and implementation of automated screening devices, increased screening intervals with increased screening sensitivity, reduction in unsatisfactory smear rates, colposcopic referral guidelines, introduction of HPV DNA testing in older age groups to further increase safe screening intervals, use of reflex HPV DNA testing for triage of equivocal LBC results, and use of LBC specimens for broader testing for other sexually transmitted diseases.

The 2001 Bethesda System

The Bethesda System for reporting cervical/vaginal cytological diagnoses was originally developed in 1988 at a United States National Cancer Institute (Bethesda, MD) workshop (34). The workshop was convened to address the current “diagnostic chaos” in cervical cytology and to develop a uniform system of terminology that would provide clear guidance for clinical management. Of paramount importance was the need to communicate the cytologic findings to clinicians in unambiguous terms that were clinically relevant. It was also intended to facilitate peer review and quality assurance in both laboratories and clinical practice.

The recommendations of the 1988 workshop rapidly gained widespread acceptance in laboratory practice in the United States and beyond. In 1991, a second NCI-sponsored workshop reviewed and modified the Bethesda System on the basis of laboratory and clinical experience (36) (Fig. 8.9).

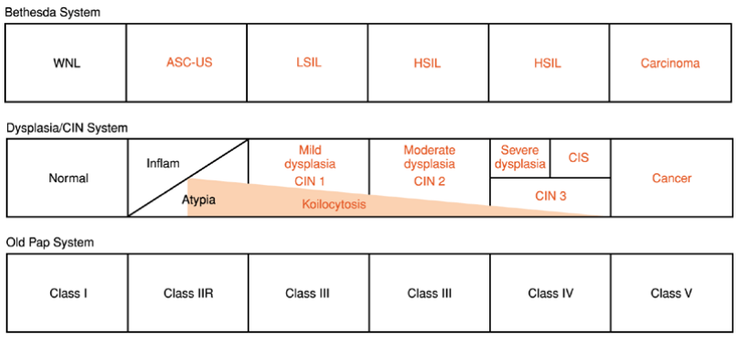

Figure 8.9 Comparison of the terminology for cervical preinvasive squamous disease. Top: The Bethesda System; **(middle)** the dysplasia/cervical intraepithelial neoplasia classification; **(bottom)** the old Papanicolaou classification.

A cervical-vaginal smear report using the revised 1991 Bethesda system had three components: (a) a description of smear adequacy; (b) a general categorization (i.e., “within normal limits” or “not within normal limits”); and (c) description of cytologic abnormality, specifying whether squamous or glandular. Abnormal morphology that may represent pre-invasive squamous disease falls into three descriptive categories: ASC-US, LSIL, and HSIL.

With the increased utilization of new cervical cancer screening technologies and in response to recent research findings, in 2001, the NCI sponsored a further multidisciplinary workshop to reevaluate and update the Bethesda System (38 ,39 ,40) (Table 8.1). The most clinically relevant changes are described below.

Table 8.1 The 2001 Bethesda System for Reporting Cervical Cytologic Diagnoses

Specimen Adequacy

Satisfactory for evaluation
Presence or absence of endocervical or transformation zone components or other quality indicators such as partially obscuring blood or inflammation
Unsatisfactory for evaluation (specify reason)
Specimen rejected or not processed (specify reason)
Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormalities (specify reason)

General Categorization (optional)

Negative for intraepithelial lesion or malignancy
Epithelial cell abnormality
Other

Interpretation/Result

Negative for intraepithelial lesion or malignancy
- Organisms
  - *Trichomonas vaginalis*
  - Fungal organisms morphologically consistent with Candida species
  - Shift in flora suggestive of bacterial vaginosis
  - Bacteria morphologically consistent with Actinomyces species
  - Cellular changes consistent with herpes simplex virus
- Other non-neoplastic findings (optional to report)
  - Reactive cellular changes associated with:
    - Inflammation (includes typical repair)
    - Radiation
    - Intraruterine contraceptive device
  - Glandular cells status posthysterectomy
  - Atrophy

Epithelial cell abnormalities
- **Squamous cell**
  - Atypical squamous cells (ASC)
    - ASC of undetermined significance (ASC-US)
    - ASC, cannot exclude high-grade squamous intraepithelial lesion (ASC-H)
  - Low-grade squamous intraepithelial lesion (LSIL)
    - Encompassing: human papillomavirus, mild dysplasia, and cervical intraepithelial neoplasia (CIN) 1
  - High-grade squamous intraepithelial lesion (HSIL)
    - Encompassing: moderate and severe dysplasia, carcinoma in situ, CIN 2, and CIN 3
  - Squamous cell carcinoma
- **Glandular cell**
  - Atypical glandular cells (AGC)
    - Specify endocervical, endometrial, or glandular cells not otherwise specified
  - Atypical glandular cells, favor neoplastic
    - Specify endocervical or not otherwise specified
  - Endocervical adenocarcinoma *in situ* (AIS)
  - Adenocarcinoma

Other (list not comprehensive)
- Endometrial cells in a woman 40 years or older

Automated review and ancillary testing (include if appropriate)
Educational notes and suggestions (optional)

Adapted with permission from **Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al.** The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA* 2002; 287;2116.

Specimen Adequacy

The 2001 Bethesda System maintains the "satisfactory for evaluation" and "unsatisfactory for evaluation" categories but eliminates the "satisfactory but limited by" category. This term was often used in the reporting of smears that lacked endocervical or squamous metaplastic cells. It is recommended that the presence or absence of a transformation zone component, defined as at least 10 well-preserved endocervical or squamous metaplastic cells, should be reported to improve overall specimen quality and to encourage efforts to optimize sample collection.

If the specimen shows a high-grade precursor lesion or cancer, it is not necessary to report the presence or absence of the transformation zone component. If the transformation zone component is absent, the laboratory may make a comment about the significance of the transformation zone component or the effect of hormonal changes, such as atrophy, in causing difficulty in determining its presence.

Minimal squamous cellularity requirements for the specimen to qualify as "satisfactory" were changed from an assessment of slide coverage with squamous cells to a numerical assessment of cellularity. Conventional smears should contain an estimated 8,000 to 12,000 well-preserved, well-visualized squamous cells, and LBC preparations should contain 5,000. Simple mechanisms were provided for rapid assessment of cellularity in conventional smears using comparison charts. In LBC specimens, a random subsample of cells is distributed over a circumscribed area facilitating accurate estimation of cellularity.

Criteria for specimen inadequacy that is due to obscuring factors, such as blood and inflammation, are unchanged and apply to conventional and liquid-based specimens. Specimens with more than 75% of cells obscured are "unsatisfactory." The specimen is considered "partially obscured" when 50% to 75% of epithelial cells cannot be visualized.

General Categorization

The previous categories of "within normal limits" and "benign cellular changes" are combined into the single, negative category reported as "negative for intraepithelial lesion or malignancy." Reactive and other nonneoplastic changes are more clearly identified as "negative."

Interpretation/Result

In the 2001 Bethesda System, the term *diagnosis* is replaced by *interpretation* or *result*. This conveys the importance of correlating cytologic findings with clinical, colposcopic, and other laboratory results to derive a definitive diagnosis.

Epithelial Cell Abnormalities

Atypical Squamous Cells

In a deliberate attempt to reduce confusion and unnecessary colposcopic referrals associated with the previous Papanicolaou class II or “atypical” category, the 1988 Bethesda system introduced a purposely restricted “atypical squamous cells of undetermined significance” (ASCUS) category. The ASCUS category designated “cellular abnormalities” that were more marked than those attributable to reactive changes but quantitatively or qualitatively fell short of a definitive diagnosis of “squamous intraepithelial lesion (SIL).” Pathologists were encouraged to qualify ASCUS with respect to whether a reactive process or SIL was favored. In practice, pathologists reported a significant proportion of smears as “ASCUS, not otherwise specified.”

When the 1988 Bethesda System was introduced, the focus of screening in the United States was to identify all SIL, including low-grade lesions (LSIL). The progressive potential of some low-grade lesions had been recently defined, as had the association between SIL lesions and oncogenic HPV types associated with cervical cancer (103 ,104 ,105 ,106). All grades of SIL were perceived as closely linked cancer precursors requiring colposcopy and treatment. **More recent research has better defined the heterogeneity of LSIL with many lesions representing a self-limited HPV infection**, particularly in younger women (220 ,221 ,222 ,223). This has led to more conservative management of LSIL and a current emphasis on detection and treatment of high-grade disease, particularly CIN 3 (221).

The 2001 Bethesda System introduced fundamental changes in the reporting of equivocal results. **“Atypical squamous cells” are qualified as “of undetermined significance” (ASC-US) or “cannot exclude HSIL” (ASC-H)**. ASC is no longer a diagnosis of exclusion. All ASC smear reports are considered suggestive of possible underlying CIN. The category of “ASC-US, favor reactive” is eliminated. It is anticipated that this should serve to decrease ASC-US reporting rates. The frequency of ASC smear reporting is often viewed as a crude indicator of quality assurance within laboratories. With recent attempts to standardize diagnostic criteria, **the rate of ASC reporting should be 3% to 5%** (224 ,225). **Reporting rates above this reflect overcall of benign reactive, inflammatory, and reparative changes**, often in response to medicolegal pressure and resulting in unnecessary colposcopic referrals. **The ASC-H category should compose 5% to 10% of ASC cases** and reflects a mixture of HSIL and mimics. The detection of histologically confirmed CIN 2 or 3 with an ASC-H report is intermediate between ASC-US and HSIL (226 ,227).

Squamous Intraepithelial Lesions

The two-tiered terminology, LSIL and HSIL, for reporting noninvasive squamous cervical lesions, introduced in the 1988 Bethesda System, remains unchanged. This reflects the substantial epidemiologic, clinical, and molecular evidence that **LSIL is a heterogeneous group of lesions, many being transient HPV infection, whereas HSIL is often associated with viral persistence and an increased risk of progression**. Recent research further supports basic tenets of the 1988 Bethesda System, specifically (228 ,229):

- The diagnostic breakpoint between LSIL and HSIL is reproducible and clinically meaningful.
- Subdividing HSIL into CIN 2 and 3 (moderate and severe dysplasia) is not very reproducible.
- HPV cytopathic effect is not reliably differentiated from CIN 1 (mild dysplasia).

Low-Grade Squamous Intraepithelial Lesion

The 2001 Bethesda system continues the combination of cytopathic effects of HPV infection in the absence of CIN with cytologic abnormalities suggestive of CIN 1 into the category of LSIL. The inclusion of HPV infection alone with CIN 1 in the LSIL category

has been the subject of significant criticism. However, 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 (227 ,228 ,229 ,230).

Atypical Glandular Cells

The 2001 Bethesda System significantly revised the classification of glandular abnormalities. **The term "atypical glandular cells of undetermined significance (AGUS)" has been eliminated.** Glandular cell abnormalities are classified as "atypical endocervical, endometrial or glandular cells." **A smear report of atypical glandular cells (AGC) is associated with high-grade lesions, either squamous or glandular, in 10% to 39% of cases** (231 ,232). Based on the clearly documented predictive value and reproducibility of cytological criteria for the reporting of adenocarcinoma *in situ* (AIS) (233), **"endocervical adenocarcinoma *in situ*" is now a separate category**. A significant percentage of women with smears reported as AIS will have invasive cancer on histological assessment. A morphological spectrum of endocervical glandular lesions that are precursors to AIS is not clearly identified. **The intermediate category of "atypical endocervical cells, favor neoplastic" is used when cells show some features of, but are not sufficient to reach an interpretation of AIS.**

ASCUS-LSIL Triage Study (The ALTS Trial)

In the United States, more than 55 million Papanicolaou tests are performed annually. Five percent are reported as ASC-US and 2% as LSIL. More than 3 million women each year receive an ASC-US or LSIL diagnosis. The resultant management cost is estimated to be several billion dollars. The clinical dilemma is the need to identify the small number of women with CIN 3 and invasive cancer weighed against the high prevalence of ASC-US and LSIL reporting. Effective colposcopic triage strategies are needed to identify the minority of women with clinically significant disease while avoiding excessive intervention for others.

The ASC-US/LSIL Triage Study (ALTS) (41 ,42 ,222 ,234 ,235 ,236 ,237) was a multicenter, randomized trial comparing the sensitivity and specificity of the following management strategies to detect CIN 3 among women referred with ASC-US and LSIL smear reports: (a) **immediate colposcopy** (considered to be the reference standard), (b) **triage to colposcopy based on enrollment HPV DNA testing results** from Hybrid Capture 2 (HC 2) and thin-layer LBC results with a colposcopy referral threshold of HSIL, or (c) **conservative management with triage based on repeat cytology results alone** at a referral threshold of HSIL (42). The trial had a majority of young women with a mean age of 29 years and included 2-year follow-up with exit colposcopy. Loop electrosurgical excision procedure (LEEP) was offered to women with histologic diagnoses of CIN 2 or CIN 3 at any visit or persistent CIN 1 at exit. This trial represents the single most costly clinical trial yet completed by the National Cancer Institute in the prevention and management of cervical neoplasia.

ALTS Trial: ASCUS Results

There were 3,488 women recruited with a community-based referral smear report of ASC-US. ASC-US interpretation was not highly reproducible, with only 32.4% of women having repeat ASC-US reported on enrollment LBC (42). **The overall percentage of CIN 23 in the ASC-US study population was 15.4%**. The 2-year cumulative diagnosis of CIN 3 was 8% to 9% in all study arms. **A single enrollment HPV DNA test identified 92% of women ultimately diagnosed with CIN 3 with 53% of women with an ASC-US smear report being referred for colposcopy**. Only 1.4% of women who were HPV negative at enrollment were ultimately found to have CIN 3 over 2 years. Serial cytology with a repeat ASC-US result as threshold for referral required two visits to achieve similar sensitivity (95%) and would have referred 67% of women to colposcopy. **HPV triage is at least as sensitive as immediate colposcopy for detecting CIN 3 but refers about half as many women to colposcopy**. Repeat cytology is sensitive at an ASC-US referral threshold, but requires two follow-up visits and more colposcopic examinations than HPV triage.

The ALTS trial demonstrates that testing for cancer-associated HPV-DNA is a viable option in the management of women with ASC-US. The American Society for Colposcopy and Cervical Pathology (ASCCP) 2001 Consensus Management Guidelines state that reflex HPV testing is the preferred triage for an ASC-US smear result when LBC methods are used (238).

The 2001 Bethesda System did not specifically endorse HPV DNA testing. Various reporting formats for such ancillary testing were discussed. Simultaneous reporting of the cytology and HPV DNA testing results is recommended but not always feasible. Probabilistic and interpretive reporting models were reviewed (239). Simple result reporting with or without educational comments and management recommendations is probabilistic reporting (238). The laboratory may include a statement as to the likelihood of associated HSIL or above given a specific HPV DNA result. **With interpretive reporting, the actual cytologic result may be altered based on the HPV DNA testing.** An HPV-negative ASC-US is revised to a negative result, and an HPV-positive ASC-US result is revised to a LSIL report.

ALTS Trial: LSIL Results

There were 1,572 women recruited with a community-based referral smear report of LSIL (235). A cytologic interpretation of LSIL was more reproducible and was associated with a 25% risk of CIN 2–3 within 2 years. There were five invasive cancers and one case of adenocarcinoma *in situ* detected. No intermediate triage strategy significantly decreased the need for colposcopic referral. **Most (more than 85%) LSIL cases are oncogenic HPV DNA positive, and the use of HPV DNA testing for the initial triage of LSIL is discouraged**.

Repeat cytology with an HSIL threshold for referral for colposcopy required only 19% of women to be referred for colposcopy but detected only 48% of cumulative CIN 3 cases. This strategy is not sufficiently sensitive for the timely detection of CIN 3. If the referral threshold was decreased to a single ASCUS result or above on repeat cytology, more than 80% of women were referred, achieving 90% sensitivity in detection of CIN 3. **Three sequential cytologic examinations with a referral threshold of LSIL demonstrated acceptable sensitivity (93%) and referral rate (69%). High patient retention is critical to this strategy, requiring a commitment from patient and provider to obtain quality cervical samples every 6 months**. Two-thirds of women would still be eventually referred for colposcopy.

If compliance can be achieved, cytologic follow-up of LSIL might be considered in selected populations such as adolescents who are at high risk of HPV infection and abnormal smear results but at low risk of cancer. Loss to follow-up of patients remains a major concern. **The ALTS data suggest that there is currently no efficient triage for LSIL. In general, the level of risk of CIN 2–3 warrants colposcopic evaluation.**

In both the ASCUS and LSIL study groups, the cumulative 2-year detection rates of CIN 3 did not vary significantly by study arm. However, in both study groups, the cumulative detection of CIN 2 was significantly reduced among women who were followed by 6-monthly conventional cytology compared with those referred for immediate colposcopy. This implies significant regression of missed prevalent cases of CIN 2 over the 2 years. **CIN 2 may represent a heterogeneous group of lesions, only some of which are incipient CIN 3**. CIN 2 lesions are currently treated. To avoid possible overtreatment, **it would be useful to determine those lesions likely to regress, possibly through identification of biomarkers of cancer risk among CIN 2 cases.**

ALTS Trial: Performance of Colposcopy

The strategy of immediate colposcopy was included as an arm in the ALTS study as the reference standard of optimal sensitivity and safety. **Of significant concern was the finding that immediate colposcopy in response to either an ASC-US or LSIL smear report was only 56% sensitive for the cumulative CIN 3 detected during the trial** (236).

Some of the CIN 3 lesions may have developed after enrollment to be appropriately detected at follow-up visits. Review of CIN 3 cases suggested that many represented prevalent cases missed at initial colposcopic examination. Some of the CIN 3 lesions were detected in LEEP specimens at exit from the study.

Prospective follow-up of CIN 3 lesions is not ethically justifiable. If the goal of cervical screening is the timely detection of CIN 3, **the ALTS trial suggests that colposcopically directed biopsy is not a gold standard of absolute sensitivity**.

ALTS Trial: Risk of CIN 2–3

The 2-year cumulative risk of CIN 2–3 was virtually the same for women with LSIL and HPV-positive ASC-US (27.6% and 26.7%, respectively) (237). Women with HPV-positive ASC-US were more likely to have negative colposcopy or negative histology on reporting of colposcopically directed biopsies. Both LSIL and HPV-positive ASC-US had an 18% risk of detection of CIN 2–3 at initial colposcopically directed biopsy, which underlies the need for identical initial colposcopic management as indicated in the 2001 ASCCP Management Consensus Guidelines.

Women with documented CIN 1 are most commonly managed expectantly by intermittent colposcopy and repeat cytology. Women with negative findings at colposcopy and biopsy tend to be followed by cytology alone. Women with CIN 1 detected at initial colposcopic workup are presumed to be at higher risk of subsequent CIN 2–3 than women who have no pathology confirmed, but **the 2-year follow-up of women in the ALTS study revealed no difference in the subsequent risk of CIN 2–3 between women with no disease documented at initial colposcopy and women with documented CIN 1.** This reinforces the need for follow-up of the majority of women (82%) with LSIL or HPV-positive ASC-US smear reports and who have CIN 1 or less diagnosed from the initial colposcopic assessment.

The ALTS longitudinal data were reviewed to determine the most efficient follow-up strategy for detection of prevalent high-grade disease in women referred with LSIL or HPV-positive ASC-US and who had CIN 1 or less at initial colposcopy. **An HPV DNA test at 12 months was the single test with the highest sensitivity and lowest referral to repeat colposcopy**. HPV DNA testing at the 6-month follow-up examination was equally sensitive, but referred 13% more patients for repeat colposcopy (62.4% vs. 55.0%). Addition of cytology to the HPV test only marginally increased sensitivity but significantly increased referral. Three repeat cytologic tests at a threshold of ASC-US and without HPV testing achieved marginally higher sensitivity but referred a much higher percentage of women for colposcopy and required multiple office visits.

ALTS Trial: Cost-Effectiveness Model

A recent comprehensive cost-effectiveness analysis of alternative strategies based on the ALTS trial was conducted (240). A policy of ignoring equivocal smear results significantly reduced the effectiveness of cervical cancer screening and was not considered a viable alternative. The three management strategies of repeat cytology, immediate colposcopy, and oncogenic HPV DNA testing produce extremely small differences in cancer incidence reduction, although repeat cytology was less effective than both alternative strategies under all model conditions. Costs associated with each management strategy differed substantially. **Reflex HPV DNA testing was always less costly than repeat cytology, as it eliminates the need for repeat clinical examination to obtain a further cervical specimen and reduces the number of colposcopic examinations by 40% to 60%.** Referral of all women with ASC-US smears for colposcopy was always more costly than repeat cytology or HPV DNA testing.

ALTS Trial: Implications for Screening

The model then assessed the most efficient screening options by considering alternative strategies to manage equivocal smear results while simultaneously varying screening frequencies and types of cytological tests (240). **Triennial screening using liquid-based cytology with reflex HPV DNA testing for ASC-US smear results appeared the most cost-effective model.**

In part because of these findings and citing lack of direct evidence that annual screening leads to better outcomes than wider interval screening, the U.S. Preventive Services Task Force recently recommended that screening for cervical cancer be performed "at least every three years" rather than every year (241). **Recent guidelines issued by the American Cancer Society suggested 3-yearly interval screening for women 30 years of age and older who have had negative results on three or more consecutive cervical smears** (218). A combined cytologic and HPV DNA test was also recommended by the American Cancer Society as a reasonable alternative to cytologic testing alone for women 30 years of age or older, with an explicit recommendation that the testing not be performed more often than every 3 years.

A recent analysis of data from the National Breast and Cervical Cancer Early Detection Program administered by the Centers for Disease Control and Prevention (CDC) concluded that "women 30 to 64 years of age with three or more previous negative smears who are screened three yearly after the last negative test rather than annually have an excess risk of cancer of no more than 3 in 100,000" (242). This is similar to the annual 1 to 4 in 100,000 risk of breast cancer among men 45 to 64 years of age. Swedish investigators recently reported an annual incidence of squamous cervical cancer of 0.8 per 100,000 women with at least one previous negative test (243).

In part because of these findings, **the CDC program recently changed its screening policy, in line with the other national organizations, increasing the interval between screening to 3 years after three consecutive negative tests.** More than 80% of women in the United States have undergone cervical screening in the past 3 years.

Human Papillomavirus Testing in Primary Screening

Recent large HPV DNA screening studies, employing both cross-sectional and longitudinal study designs, provide compelling evidence supporting the adjunctive use of HPV DNA testing in routine screening in women older than 30 years and for younger women in certain settings (244 ,245 ,246 ,247 ,248 ,249 ,250 ,251 ,252 ,253 ,254). These studies demonstrate that **HPV DNA testing using clinically available detection tools can identify almost all patients with CIN 3, high-grade glandular neoplasia, and invasive cancer**. Addition of LBC to HPV DNA testing increases sensitivity by 5%. **Combination HPV DNA testing and LBC has 90% to 100% sensitivity for CIN 3 and invasive cancer. The negative predictive value of such combined testing is above 99% in all studies and approaches 100% in most.**

A negative HPV DNA test virtually excludes any risk of underlying disease even in the presence of a reported cytologic abnormality. In response to this collective experience, **HPV DNA testing was approved as a primary screening tool in conjunction with cytology in women aged more than 30 years by the FDA on March 31, 2003.**

Although the high sensitivity and the high negative predictive value are obvious advantages of the HPV test, **its use as a primary screening tool is potentially hampered by low specificity and risk of overtreatment of HPV DNA–positive women** (255). Specificity and positive predictive value is further decreased when HPV DNA testing is combined with LBC, reflecting the inverse relationship between sensitivity and specificity in screening methodology.

HPV DNA testing identifies many transient HPV infections not associated with high-grade CIN, particularly in younger women. This is the main contributing factor to

reduced specificity. **Women who are HPV DNA positive but who have a normal cervical smear or have no clinical evidence of HPV-related disease are at greatest risk of developing cervical neoplasia prospectively** (256 ,257). Such women should not be viewed as having "false-positive" tests but require close follow-up and repeat testing. For HPV testing to be cost-effective in primary screening, an efficient policy is required for the management of women who test positive for high-risk HPV-DNA but who have negative or equivocal cytologic reporting (258). This strategy would use HPV DNA testing alone as primary screening and cytology would be used to triage HPV DNA–positive women.

The HART Study

The recently reported HART (HPV in Addition to Routine Testing) study from the United Kingdom investigated this approach. Recruited for this study were 11,085 women attending 161 U.K. family practices for routine cervical screening (254). **This study confirmed HPV DNA testing to be a more sensitive primary screening technique than conventional (not liquid-based) cytology for detecting high-grade CIN (97.1% vs. 76.6%)**. High-risk HPV DNA detection combined with conventional cytology had 100% sensitivity for high-grade CIN lesions and above. HPV DNA testing was significantly less specific than conventional cytology (93.3% vs. 95.8%) and had a positive predictive value of 12.8%, less than that of an equivocal or worse conventional smear (15.8%). **The high rate of positive HPV DNA testing in women with no significant histologic abnormality appears to be an impediment to use of HPV DNA testing in primary screening.**

The authors estimated that referral rates for colposcopy would be reduced if (a) women with equivocal (and possibly with LSIL) smear reports but who were HPV DNA negative were returned to routine screening, (b) HPV DNA–positive women with negative or equivocal smears were retested at 12 months, and (c) the screening interval was extended to 5 years.

These issues would all require significant reeducation efforts for women and health-care providers. This study does not address cost, patient acceptability of HPV DNA testing, nor compliance with follow-up recommendations in broader screening settings. The screening algorithm for women younger than 30 years must be developed. A large trial comparing LBC with reflex HPV DNA testing for equivocal results with primary screening by HPV DNA testing with cytologic triage of HPV DNA–positive women is identified as a priority.

Based on currently available data, the combination of HPV DNA testing with LBC significantly increases screening sensitivity. Women with "double-negative" results can be screened safely at longer intervals, offsetting the increased cost of the initial screen (259). **The duration of low-risk after a negative HPV DNA test is unknown**. Patients identified as being at increased risk on the basis of a positive HPV DNA test but who do not have identifiable disease would be monitored more closely.

There is no consensus regarding the appropriate age for cessation of screening. Lifetime screening continues to save lives but the benefits for regularly screened women beyond age 65 years are minimal. The probability of a false-positive cervical smear result is much greater than a true-positive result after age 65 years. **The high negative predictive value of HPV DNA testing could be used as an additional means of safely exiting women from routine screening beyond a certain age** (260). The wider use of HPV DNA testing in the primary screening setting will inevitably hinge on the acceptability of testing for a sexually transmitted virus to the target population and the provision of HPV DNA testing at low cost (261).

HPV testing may have an important role in primary cervical screening in developing countries (262 ,263 ,264). 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 are all advantages in developing countries.

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.

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, 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 Workup

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.

A complete medical history and general examination should be obtained. A history of previous premalignant cervical disease or cervical treatment should be determined. A history of endogenous or exogenous immune suppression is relevant. A social history of smoking or other “recreational” drug use should be obtained.

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).

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, adnexae, 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. 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.

- **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**.
- **A 3% to 5% acetic acid solution is then liberally applied to the cervix using soaked swabs or a spray technique. 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.
- **Lugol's iodine (one-quarter strength) application to the cervix (if the patient is not allergic to iodine) is called a 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, but 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. 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 exclude an occult cancer in the canal (265). 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 (266).

Routine performance of endocervical curettage is controversial. **When the entire new squamocolumnar junction can be visualized**, **it is reasonable to omit the routine endocervical curettage**. A negative endocervical curettage from a patient with an abnormal high-grade cytology 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 (267).

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. **Photodocumentation can be extremely valuable**. A system for recording patient information, laboratory results, management plan, and 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 (268). The colposcopic signs of the abnormal transformation zone are described in Table 8.2 .

Table 8.2 Colposcopic Signs of the Abnormal Transformation Zone

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

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.

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 (269 ,270 ,271 ,272).

Routine determination of a colposcopic diagnosis permits quality-control measures to be implemented in colposcopy (273 ,274). In colposcopic quality control programs, the colposcopist is required to achieve at least an 80% accuracy rate in colposcopic–histologic correlation or receive remedial training in colposcopic assessment of cervical lesions (275).

In current colposcopic experience, the Reid Colposcopic Index represents the most reproducible and clinically valid means of standardizing the evaluation of cervical lesions (271 ,272) (Table 8.3).

Table 8.3 Scoring System for Deriving the Colposcopic Index

	Score		
Colposcopic Sign	***Zero Points***	***One Point***	***Two Points***
Margin	Exophytic condylomas; areas showing a micropapillary contour	Lesions with a regular (circular or semicircular) shape, showing smooth, straight edges	Rolled, peeling edges
	Lesions with distinct edges		Any internal demarcation between areas of differingcolposcopic appearance
	Feathered, scalloped edges		
	Lesions with an angular, jagged shape		
	“Satellite” areas and acetowhitening distal to the original squamocolumnar junction		
Color	Shiny, snow-white color	Intermediate shade (shiny, but gray-white)	Dull reflectance with oyster-white color
	Areas of faint (semitransparent) whitening		
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 (by first three criteria)	Partial iodine staining (mottled pattern)	Mustard-yellow staining of a significant lesion (an acetowhite area scoring 3 or more points by 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.

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** are (a) **the margin of the lesion**, (b) **the color of the acetowhitening**, (c) **the type of vascular pattern**, and (d) **the iodine staining reaction.**

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 . The total score is then 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 low-grade lesions (HPV infection/CIN 1**; Fig. 8.10). **Scores of 6 to 8 usually denote high-grade lesions** (CIN 2 to 3; Fig. 8.11). Scores of 3 to 5 represent an area of overlap between low-grade and high-grade lesions.

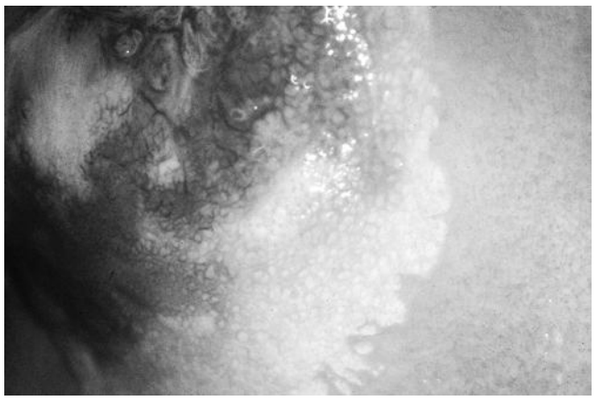

Figure 8.10 Colposcopy of low-grade cervical lesions showing acetowhite epithelium with fine abnormal vascular pattern.

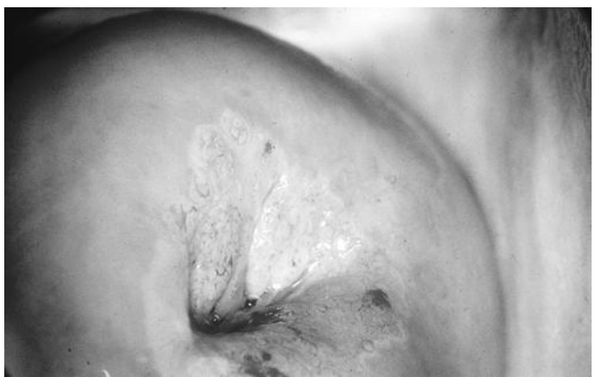

Figure 8.11 Colposcopy of high-grade cervical lesion showing dense acetowhite epithelium and coarse abnormal vascular pattern.

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.

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 oncologic 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 knowledge of warning signs. Colposcopic warning signs are shown in Table 8.4 .

Table 8.4 Colposcopic Warning Signs of Invasive Cancer

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.

Other warning signs for invasive cancer include:

- **Any cytologic evidence of possible squamous carcinoma, adenocarcinoma, or AIS or recurrent high-grade cytologic findings in a patient previously treated for CIN 3**
- **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**
- **High-grade cytologic abnormality in a postmenopausal or previously irradiated woman**

ASCCP 2001 Consensus Guidelines

The American Society for Colposcopy and Cervical Pathology (ASCCP) 2001 Consensus Guidelines were developed to assist in the management of women with cytological abnormalities (238) and in the management of cervical cancer precursors (276). The guidelines were developed in part in response to the 2001 Bethesda System.

The guidelines reflect improved understanding of the pathogenesis and natural history of cervical HPV infection and cervical cancer precursors, and the results of the NCI's randomized trial of management modalities for ASCUS and LSIL (ALTS trial) (42 ,234 ,235 ,236 ,237).

The ASCCP guidelines are presented in Figure 8.12A ,Figure 8.12B ,Figure 8.12C ,Figure 8.12D ,Figure 8.12E ,Figure 8.12F ,Figure 8.12G ,Figure 8.12H .

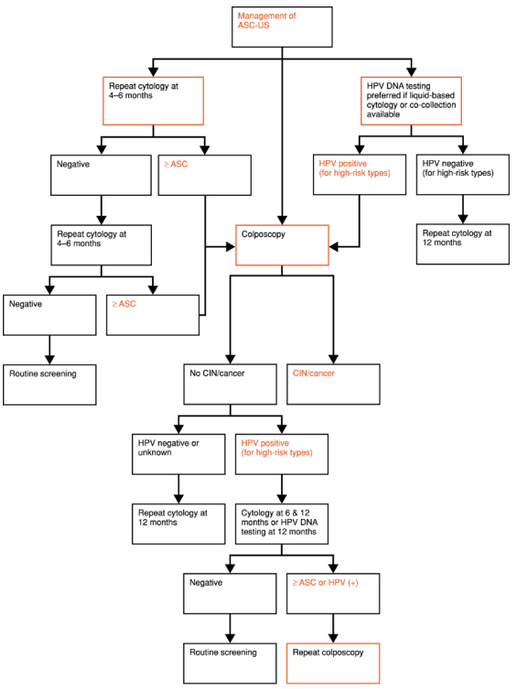

Figure 8.12 A-H: The Management of Abnormal Pap Smear: Recommendations of the American Society for Colposcopy and Cervical Pathology. (Redrawn with permission from the American Society for Colposcopy and Cervical Pathology) **A: Management of women with atypical squamous cells of unknown significance (ASC-US).**

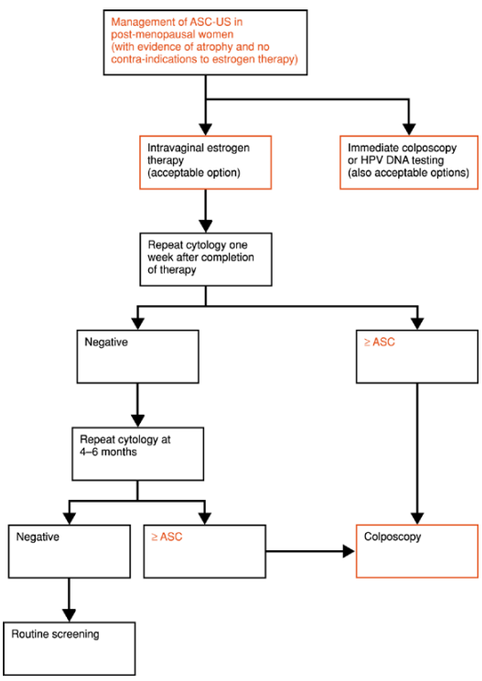

Figure 8.12 B: Management of women with atypical squamous cells of unknown significance (ASC-US) in special circumstances.

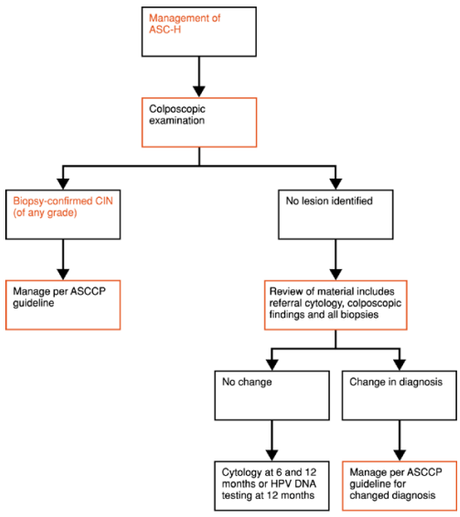

Figure 8.12 C: Management of women with atypical squamous cells: cannot exclude high-grade squamous intraepithelial lesions (ASC-H).

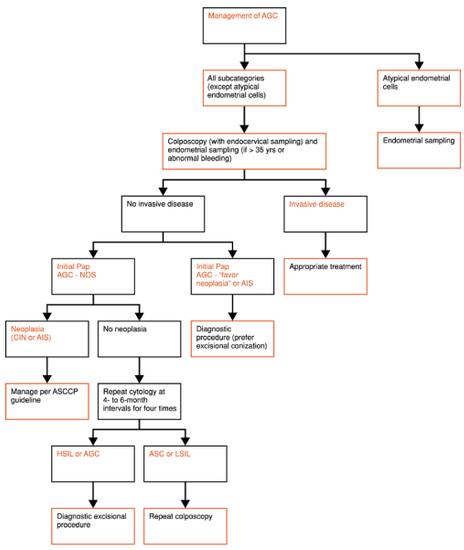

Figure 8.12 D: Management of women with atypical glandular cells (AGC).

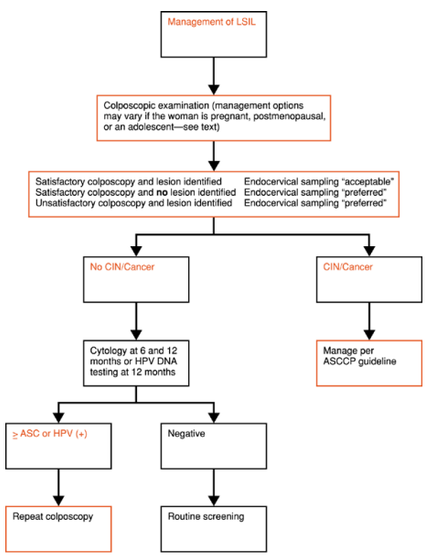

Figure 8.12 E: Management of women with low-grade squamous intraepithelial lesions (LSIL).

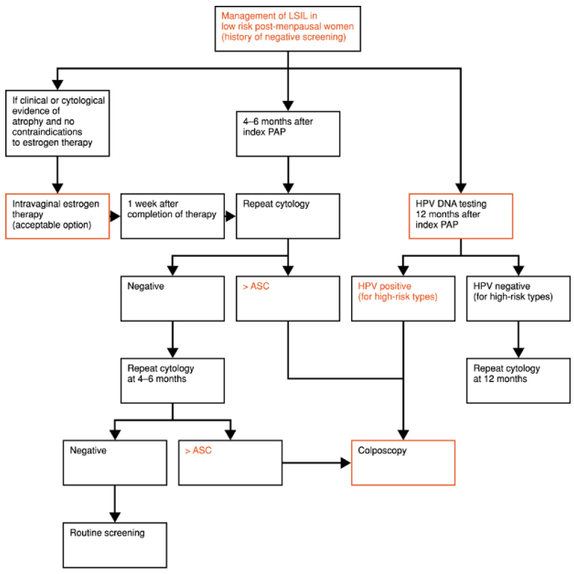

Figure 8.12 F: Management of women with low-grade squamous intraepithelial lesions (LSIL) in special circumstances: postmenopausal women.

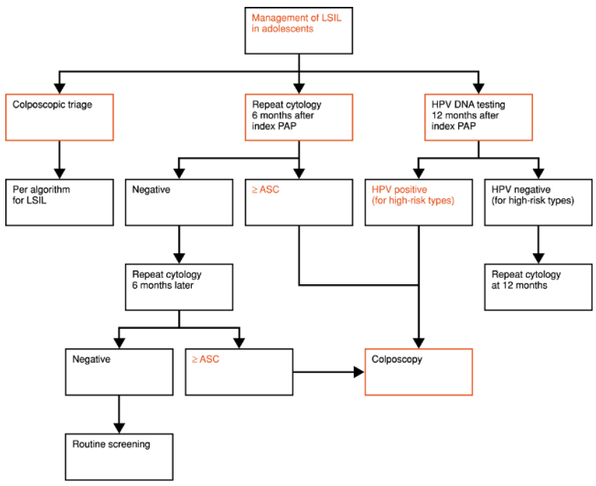

Figure 8.12 G: Management of women with low-grade squamous intraepithelial lesions (LSIL) in special circumstances: adolescents.

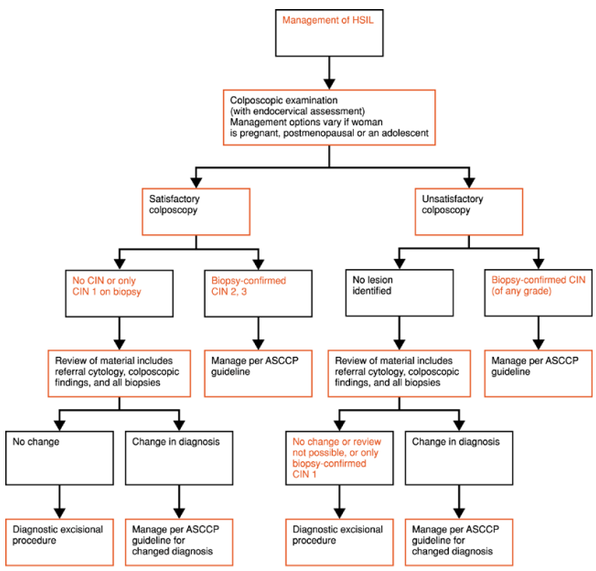

Figure 8.12 H: Management of women with high-grade squamous intraepithelial lesions (HSIL).

Treatment of Cervical Intraepithelial Neoplasia

In 1965, Anderson (277) 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 (278) 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 (279) 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 (280), **electrocoagulation diathermy** (281), **and the carbon dioxide laser** (282). 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.

Table 8.5 Triage Rules for Ablative Therapy for Cervical Intraepithelial Neoplasia

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 1 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

In the 1990s, loop electrosurgical excision procedures (LEEP) gained in popularity because of concerns regarding the occurrence of invasive cervical cancer in patients who had undergone ablative treatment (283). Invasive cancer has been reported after each of the ablative modalities (284). **When cancer occurred after ablative therapy, it occurred within 12 months in 66% of cases and within 2 years in 90%.** This suggested 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 (285 ,286 ,287).

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 artefact and orientation difficulties.

Treatment Modalities

The treatment modalities for preinvasive cervical disease are ablative procedures and include cryosurgery, electrocoagulation diathermy, and CO_2 laser; and excisional procedures, including LEEP, cervical (excisional) conization, CO_2 laser excision, and hysterectomy. A recent (2003) Cochrane Database of Systematic reviews examined surgical treatment modalities for cervical intraepithelial neoplasia (288). The evidence from 28 randomized controlled trials suggested that **there is no overwhelmingly**

superior technique for eradicating CIN. Cryotherapy is an effective treatment of LSIL but not HSIL.

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 by cryonecrosis of the lesion, including the entire transformation zone. 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 tips are the 19-mm and 25-mm minicone. 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 overlapping 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.

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:

- **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.**
- **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.**

- **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.
- **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.
- **The probe is defrosted completely and then disengaged from the cervix.**

A freeze—thaw—freeze technique is commonly used. This technique was reported by Creasman et al. (289) to reduce the failure rate from 29% to 7%, although others claimed similar results from a single freeze (290 ,291). 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 débridement 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. **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 increases the failure rate from 9% to 27%. 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 (292). This may in part reflect the increased size of HGLs, which more frequently occupy two or more quadrants of the cervix (293). (Table 8.6).

Table 8.6 Comparison of Therapeutic Modalities for Cervical Intraepithelial Neoplasia

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 benefit; ++, medium benefit; +++, high benefit.

Loop Electrosurgical Excision Procedures

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-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 (294).

Prendiville et al. (295 ,296) 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 technique for electrosurgical loop excision is as follows:

- **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 sidewall.
- **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.
- **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.
- **A grounding pad is attached to the patient's thigh, with care taken to ensure proper adherence.**
- **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.**
- **Suction is attached to the speculum.**
- **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. **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 (Fig 8.13). 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.

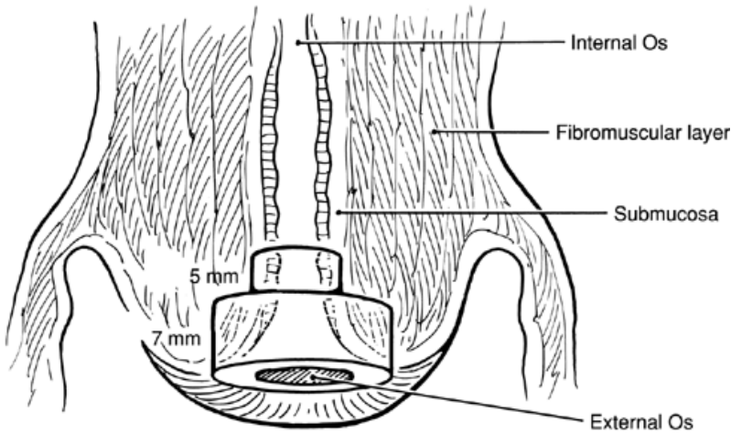

Figure 8.13 “Cowboy-hat” configuration for LEEP.

- **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.

- **An endocervical curettage, sampling, or "cowboy hat" biopsy should be performed if one has not been previously performed.**
- **Monsel's solution is applied to the cervix to maintain hemostasis.**

Complications are minimal, comparing favorably with those associated with CO_2 laser procedures (295 ,296 ,297 ,298 ,299 ,300). **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 (298 ,299 ,300 ,301) and with "cold-knife" conization (302 ,303), **often in excess of 95%**.

Electrosurgical loop excision offers several advantages over CO_2 laser ablation (288). 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% (304 ,305 ,306 ,307).

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 ,220).

Sequelae of Conservative Treatment Procedures

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. Rarely, sutures may be required to secure hemostasis with **secondary bleeding.** The patient should refrain from tampon use, douching, and vaginal intercourse for 3-4 to 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. **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.

Excisional Cervical Conization

Excisional conization performed with a scalpel, sometimes referred to as a "cold-knife conization," was traditionally the standard response to cytologic abnormalities (308) and remains an important therapeutic option in the management of CIN. It is both diagnostic and therapeutic. The geometry of the conization should adapt to the size and shape of the lesion as well as the geometry of the cervix (Fig 8.14). The procedure is performed in the following manner:

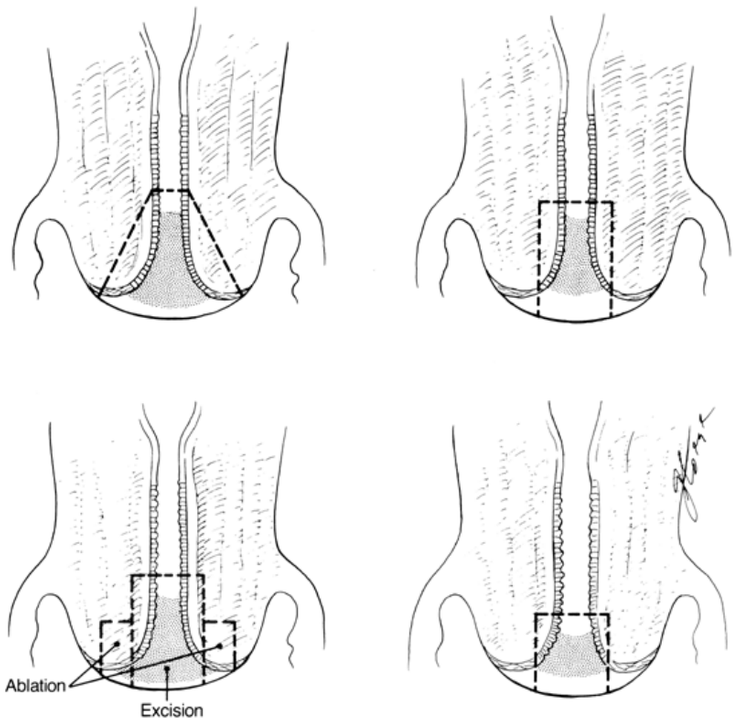

Figure 8.14 Tissue excised for cervical conization procedures depending on the extent of disease and the anatomy and shape of the cervix.

- **Careful colposcopic examination is performed** to delineate the lateral margins of the lesion and transformation zone. Lugol's iodine solution aids in this determination.
- **Lateral sutures are placed** on the side of the cervix at the 3 and 9 o'clock positions to provide traction and hemostasis.
- **The cervix may be infiltrated with a vasospastic agent** to decrease intraoperative bleeding.
- **The endocervical canal is sounded** to guide the direction and depth of the excision.
- **The specimen is excised using a no. 11 scalpel blade**, preferably with a cylinder-shaped geometry.
- **The excised specimen is tagged at the 12 o'clock position** using suture to allow for proper orientation by the pathologist.

- **A fractional curettage (or biopsy) 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.
- **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 may be used if bleeding persists.

Cervical conization achieves cure rates for high-grade CIN in excess of 95%. **The risk of cervical stenosis and cervical incompetence is higher** for cervical conization performed with a scalpel than for CO_2 laser and electrosurgical excisional conization. This in part reflects the fact that cervical conization performed with a scalpel has been traditionally used for the most severe lesions, when invasive cancer has not been excluded or when colposcopy has been unsatisfactory, often with significant disease extension to within the endocervical canal (309).

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.

Before any hysterectomy, colposcopic assessment is important. 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 (310). 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 (311) 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. She should be screened by vaginal vault smears on an annual basis thereafter.

Cervical Adenocarcinoma In Situ

The reported incidence of cervical glandular neoplasia has increased (312 ,313 ,314 ,315 ,316). Adenocarcinoma is diagnosed with increased frequency in younger women, with up to 30% of cases occurring in women younger than 35 years of age (312 ,313 ,314 ,315 ,316).

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 (317).

Clinical Presentation

Adenocarcinoma *in situ* is usually diagnosed after an abnormal Pap test result. 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 2001 Bethesda system includes a category for atypical glandular cells (AGC). **Patients with AGC smear reports have a 30% to 50% risk of having high-grade cervical disease** and are at much higher risk of significant disease than those with ASC smear reports (319 ,320 ,321). An AGC smear report is an indication for referral for colposcopy and careful endocervical assessment.

The underlying lesion is most frequently high-grade squamous 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 (319 ,320 ,321).

The colposcopic features of AIS and early adenocarcinoma are widely seen as nonspecific. 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. 8.15). 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**.

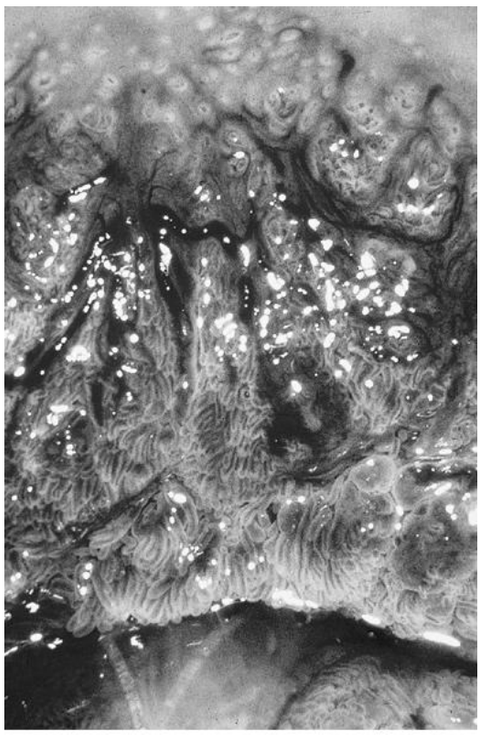

Figure 8.15 Colposcopy of adenocarcinoma *in situ* lesion showing prominent atypical vessels.

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 and be performed with a cold knife to avoid thermal injury to the specimen. 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, more than 80% of patients have negative cytologic and colposcopic follow-up beyond 12 months from treatment (322 ,323 ,324 ,325).

Younger women may be managed by excisional conization alone if margins of excision are clear, although residual squamous and glandular preinvasive disease has been reported in as many as 33% of such patients (326 ,327). 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, more than 50% of patients have residual disease at hysterectomy (326). 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 should be seriously considered in the younger patient, if fertility is not desired, because of the continued risk of residual and recurrent disease.

Vagina

Part of "8 - Preinvasive Disease "

Classification of Vaginal Intraepithelial Neoplasia

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.

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, suggests the malignant potential of VAIN is low, but progression to invasive cancer does occur (328).

High-grade VAIN lesions usually occur in association with high-grade CIN lesions, which extend onto the vaginal fornices in approximately 3% of cases. Alternately, primary foci of high-grade VAIN do occur (329 ,330). **VAIN 2–3 involves the upper third of the vagina in more than 70% of cases** and less commonly the lower third, with the middle 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 (331).

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 the time of colposcopy. In addition, certain specific indications require careful vaginal colposcopy (Table 8.7).

Table 8.7 Indications for Vaginal Colposcopy

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.

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. 8.16 , Fig. 8.17). 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. **Occasionally, recalcitrant condylomatous lesions of the vagina reveal a high-grade dysplastic morphology.**

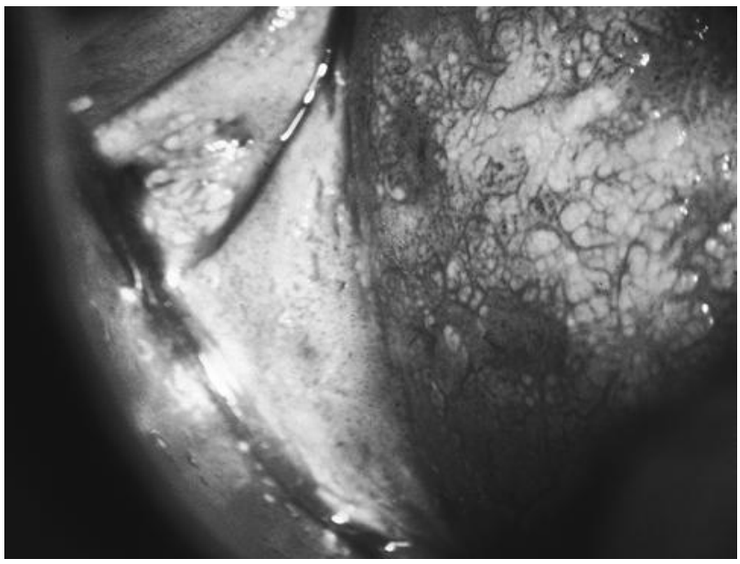

Figure 8.16 Colposcopic appearance of high-grade vaginal intraepithelial neoplasia with acetic acid.

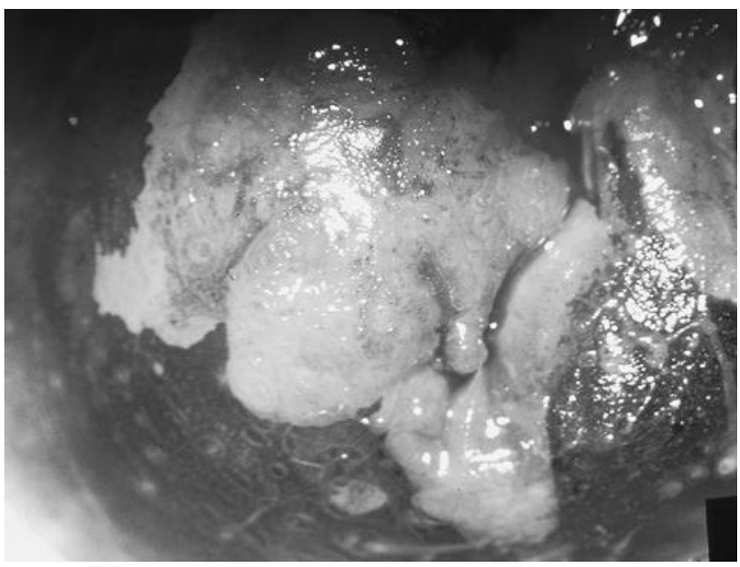

Figure 8.17 Colposcopy of high-grade vaginal intraepithelial neoplasia with iodine.

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**.

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 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.

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 regarded as the treatment of choice for most VAIN cases** (332 ,333). 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 (334).

Topical *5-fluorouracil (5-FU)* **cream can also be used with good effect for carefully selected patients** (335 ,336). *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 an appropriate beam geometry (see vulvar section) 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 only 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. (337) reported results of vaginal vault laser surgery for VAIN 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. (338) reported 32 patients who underwent upper vaginectomy for VAIN 3. Occult invasive cancer was found in nine 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. **This very difficult problem is increasingly viewed as an indication for excision.**

Vulva and Perianal Area

Part of "8 - Preinvasive Disease "

Since approximately 1970, there has been a marked increase in the incidence of high-grade preinvasive vulvar disease and a decrease in the modal age of diagnosis. There has not been an associated increase in the incidence of invasive vulvar cancer, presumably because the preinvasive disease is actively treated.

Classification

Preinvasive neoplasia of the vulva has been recognized for more than 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** (339). This confusion was compounded by the use of similar terms to describe a group of nonneoplastic vulvar diseases to which Jeffcoate (340) in 1966 assigned the term **chronic vulvar dystrophy**. In 1989, the International Society for the Study of Vulvar Disease (341) agreed on a new classification of vulvar epithelial disorders (Table 8.8).

Table 8.8 Classification of Epithelial Vulvar Disorders

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 I (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* 1989;8:83.

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 2–3**/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. When mild squamous atypia is seen, usually limited to the lower epidermis, the lesion is more likely to be nonneoplastic reactive atypia. If a genuine VIN 1 lesion exists, it is almost always associated with high-grade VIN, either in the same lesion or in other coexisting lesions.

Although more than 95% of cervical malignancies are HPV-associated cancers, **HPV DNA is detected only in approximately 50% of vulvar cancers** (342). Many of the HPV-negative cancers, particularly in older women, are associated with lichen sclerosus (343 ,344 ,345 ,346 ,347 ,348).

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) (349 ,350 ,351). **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** (352 ,353 ,354). 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 (355 ,356 ,357). There is a strong association between VIN 3 and sexually transmitted disease, with rates varying from 20% to 60%.

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 lichen sclerosis and without a prior history of VIN 3 or coexisting histologic evidence of VIN 3 (344 ,345 ,346 ,347).

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

More than 30% of women with VIN 3 experience vulvar symptomatology. The most common symptoms are pruritus, burning, pain, and dysuria (357). Vulvar symptoms are often exacerbated by voiding. Patients may present reporting 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 (357 ,358 ,359). Opportunistic inspection of the vulva, particularly at the time of colposcopy for abnormal cervical cytology, is recommended.

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. 8.18 , Fig. 8.19). 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 more than 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.

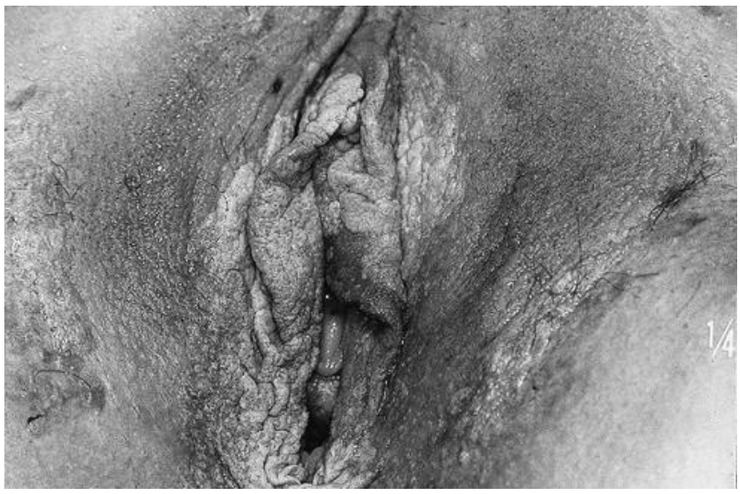

Figure 8.18 Clinical appearance of vulvar intraepithelial neoplasia showing hyperkeratotic papular lesions.

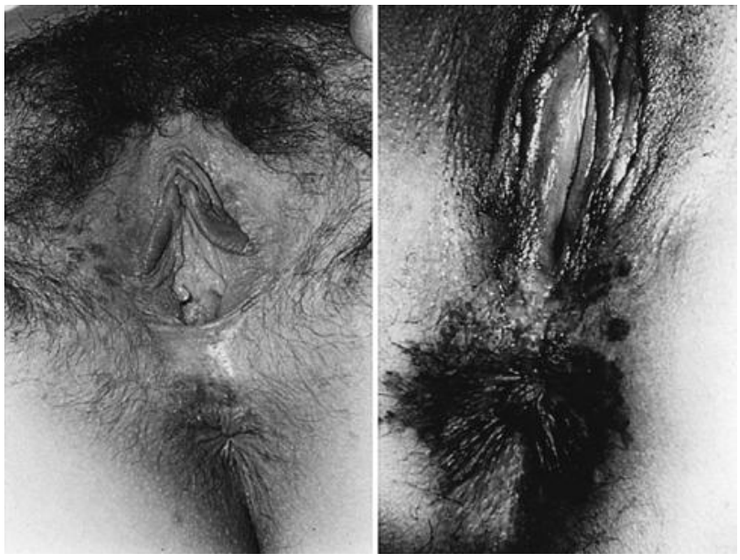

Figure 8.19 *Left:* **A multifocal VIN 3 lesion with multiple small hyperpigmented lesions on the labia major.** *Right:* **VIN 3 with more confluent hyperpigmented areas on the posterior fourchette with extensive perianal involvement.**

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. 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**. Condylomatous lesions exhibiting a severely dysplastic morphology on biopsy frequently harbor high-risk HPV types, with HPV 16 and 18 detected in more than 70% of such lesions (360).

Diagnosis

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 **represent a definite warning sign of invasive cancer**, and the lesion must be excised. Colposcopic warning signs of vulvar cancer occur late in the neoplastic process, limiting the sensitivity of colposcopy for the identification of early invasive cancer. Histologic evidence of VIN 3 may be seen outside colposcopically identified margins of disease, particularly laterally in the hair-bearing areas.

Diagnosis ultimately depends on liberal use of directed biopsy. This is particularly the case if ablative treatment is being considered, either alone or in combination with excisional procedures. **Biopsies 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 (357 ,358 ,359).

Few studies have examined the natural history of untreated VIN. Jones and Rowan (361) reported in 1994 on the 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.

A more recent review from the same authors studied women who experienced spontaneous regression of CIN 2–3 (362). These women had a median age of 19 years, an initial presentation through a sexual health clinic, and a previous history of condylomata acuminata. Most had multifocal, pigmented lesions. Median time to regression was 9.5 months.

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”** (363). 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. Many treatment modalities have been used and, historically, vulvar carcinoma *in situ* was managed by simple vulvectomy (364). 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 “castrationlike” self-image.

Since the 1970s, there has been a trend toward more conservative therapy, initially using excisional approaches and more recently, ablative modalities (357 ,358 ,365).

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. Women undergoing excisional treatment for VIN 3 are reported to have a 15% to 23% incidence of unsuspected invasive squamous cell carcinoma on histology of the excised specimens (357 ,358 ,359 ,366 ,367).

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. **As long as all macroscopic disease has been removed, reexcision is not justified for positive margins of excision**. Most recurrences occur within 3 years of treatment, although late recurrence and progression to cancer can occur. Development of symptoms should prompt urgent review.

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 superficial (skinning) vulvectomy with a split-thickness skin graft. **"Skinning" vulvectomy was introduced** by Rutledge and Sinclair (368) **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 or laser ablated. The epithelium regenerates without loss of sensation.

DiSaia (369) 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 more than 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 (370 ,371 ,372 ,373 ,374). The morbidity associated with ablation of large areas of VIN 3 has been found to be unacceptable in some studies. The initial 2 weeks following more extensive laser ablative procedures will be associated with significant pain, particularly with micturition. The use of appropriate laser technology and settings, advanced surgical expertise with careful control of depth of ablation, and appropriate postoperative care will mitigate much of the potential morbidity. The preservation of anatomy and function is a substantial benefit, particularly for younger women.

Physical Principles Governing Vulvar Laser Surgery

- **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.
- **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.
- **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.
- **Choice of appropriate power density:** CO_2 laser ablation requires power densities in the range of 800 to 1,400 W/cm^2.
- **Choice of appropriate beam geometry:** 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 clinical importance of the concept of beam geometry is that the crater shape mirrors the intensity profile of the incident energy (Fig. 8.20). 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 or for excisional procedures. If the incident laser beam is flattened completely, it will simply coagulate a broad zone of tissue at the impact site but will not have sufficient power to vaporize tissue. The wide, flattened spot size produces the ***Z-beam geometry***. 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.

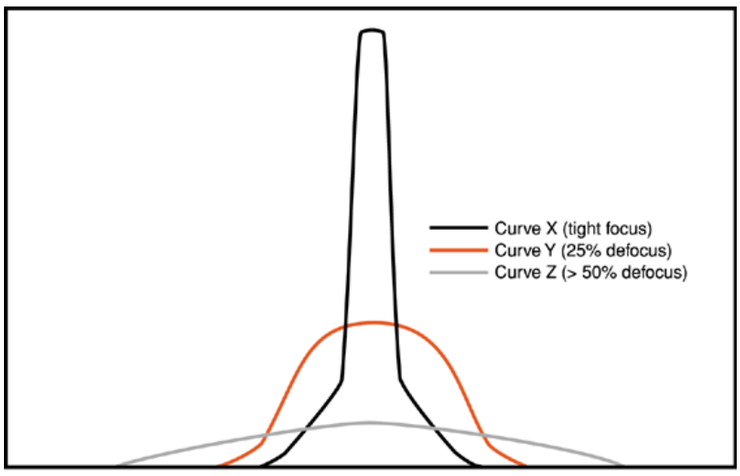

Figure 8.20 Diagrammatic representation of CO_2 laser beam geometry.

- For ablative treatment of VIN, 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 is hemispherical. This permits controlled tissue vaporization with minimal lateral heat conduction. 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.
- **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

- **Choice of appropriate beam delivery system:** 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 angle of impact of the laser is controlled by traction on the skin. A handheld mirror may occasionally be required to reflect the beam to difficult-to-access sites.
- **Minimization of thermal injury:** 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.
- **Accurate delineation of treatment margins:** The laser is used under colposcopic control. The possible extension of high-grade VIN beyond areas that are colposcopically evident indicates the need for treatment margins of several spot sizes. The laser can be used initially to circumscribe the distribution of the lesions before the acetic acid reaction fades.
- **Accurate depth control:** 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. (371 ,372).

First surgical plane

Destruction to the first surgical plane removes the surface epithelium to the level of the basement membrane. The laser beam 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 because of 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 midreticular 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).

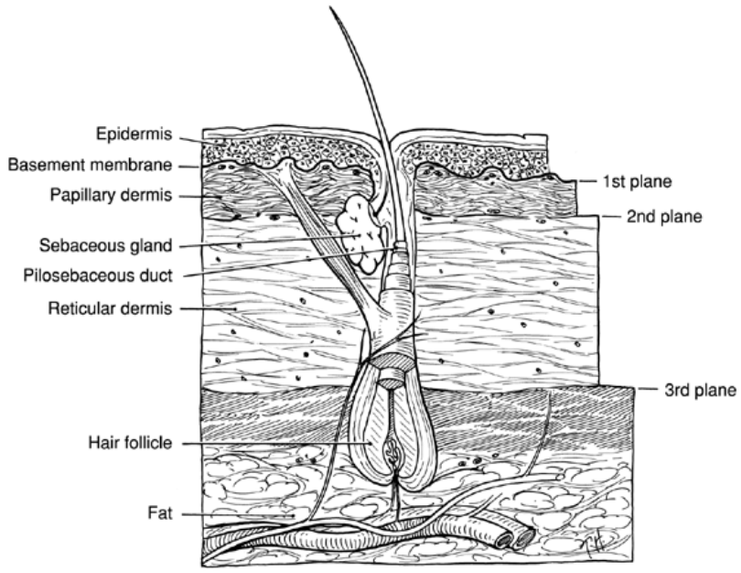

Figure 8.21 Diagrammatic representation of three surgical planes.

The skin appendages are involved with the VIN process in more than 50% of cases (372). 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. Beyond 3 mm, 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 midreticular dermis.

Fourth surgical plane

Destruction of the reticular dermis creates a thermal injury extending to the subcutaneous tissues and must be avoided.

6. 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 on completion of the procedure diminishes pain in the immediate postoperative period.

Narcotic analgesia is usually required in the immediate postoperative period or, alternatively, prolonged epidural 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 have available appropriate oral narcotic analgesics to provide relief after discharge from hospital.

Long-Term Follow-up

Regardless of treatment modality, **recurrence of VIN is common**. Lifelong vigilance is an important component of the management of high-grade VIN.

Immune Response Modifiers: Imiquimod

The discovery that VIN 2–3 lesions, particularly multifocal lesions in younger women, are strongly HPV associated, argues for the possible efficacy of immune response modifiers in treatment of high-grade VIN (375 ,376).

Imiquimod (Aldara) is an imidazoquinoline, a novel synthetic compound that is a topical immune response stimulator, enhancing both the innate and acquired immune pathways, particularly T helper cell type 1–mediated immune response, resulting in antiviral, antitumor, and immunoregulatory activities (376 ,377). Imiquimod causes cytokine induction in the skin which up-regulates the host immune system to recognize the presence of a viral infection or tumor, theoretically leading to eradication of the lesion. It also stimulates activation, maturation, and migration of Langerhans cells, the major antigen-presenting cells of the skin, which are depleted by HPV infection (376 ,377).

A patient-applied topical 5% *imiquimod* cream is clinically efficacious and safe in the management of condylomata acuminata (378 ,379 ,380). It was licensed in 1997 for the treatment of anogenital condylomata acuminata and is recommended for this application in sexually transmitted disease guidelines from the U.S. Centers for Disease Control and Prevention, as well as guidelines from Europe, Latin America, and Australia.

The beneficial effects, patient acceptability, and low morbidity of *imiquimod* in the treatment of genital condylomata acuminata led to its recent evaluation in the treatment of VIN 2–3. Case reports demonstrated efficacy against VIN 2–3, including in an immune-suppressed lung transplant patient (381). Pilot studies, applying *imiquimod* one to three times a week at night, indicate a 30% complete response rate and 60% partial response after 6 to 30 weeks of treatment (382 ,383). In contrast to surgical treatment, *imiquimod* focuses on the cause of many VIN cases and preserves the anatomy and function of the vulva. Exclusion of invasive cancer is an extremely important aspect of pretreatment assessment.

No treatment modality is ideal for every woman. Treatment should be individualized according to age, distribution, severity, associated disease, and previous treatment.

Multicentric Lower Genital Tract Neoplasia

Part of "8 - Preinvasive Disease "

The concept of multicentricity of lower genital tract neoplasia is well established (384). Multiple primary preinvasive or invasive lesions can occur synchronously or metachronously in this region.

High-grade *perianal intraepithelial neoplasia (PAIN)* **occurs in more than 30% of patients with VIN 3 or multicentric squamous neoplasia** (384). 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 (385), although its incidence has increased significantly in homosexual men (386 ,387). Viral analysis confirms a strong association with HPV 16 (388).

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 posteriorly to the anus and onto 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** after exclusion of invasive cancer.

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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, 10,520 new cases were anticipated in 2004, with 3,900 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).

In recent years, molecular biology has firmly established a causal relationship between persistent infection with high-risk human papillomavirus (HPV) genotypes and cervical cancer. In a study of almost 1,000 cases of cervical cancer worldwide, the prevalence of HPV infection was 99.7% (3).

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. Hence, appropriate screening programs are an important public health issue. **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, and 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.

Knowledge that cervical cancer is causally related to a viral infection has raised hopes that it may be preventable by vaccination. A recent trial of a monovalent HPV genotype 16 vaccine provided evidence that those vaccinated could be protected against incident and persistent HPV 16 infection and HPV 16–related cervical intraepithelial neoplasia (4). Current clinical trials are evaluating multivalent vaccines (HPV types 6, 11, 16, and 18).

- Diagnosis
- Staging
- Patterns of Spread
- Treatment
- Nonsquamous Histologic Types
- Special Problems
- Recurrent Cervical Cancer

Diagnosis

Part of "9 - Cervical Cancer "

Early diagnosis of cervical cancer can be extremely challenging because of three factors:

- **The frequently asymptomatic nature of early-stage disease**
- **The origin of some tumors from within the endocervical canal or beneath the epithelium of the ectocervix**, making visualization on speculum examination impossible
- **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. (5) 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** (6).

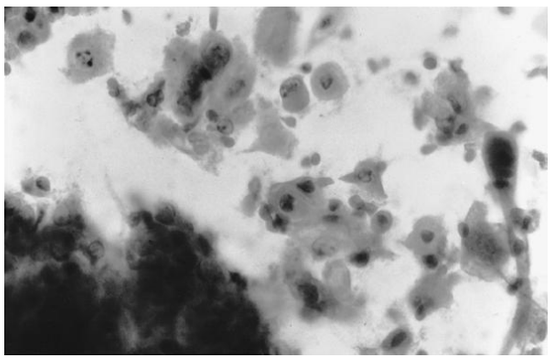

Figure 9.1 Pap smear of cervical squamous cell carcinoma. Malignant squamous cells, singly and in groups, show nuclear pleomorphism. A “tadpole” cell is present on the right. (Original magnification 165X.)

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 (7). 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 (7).

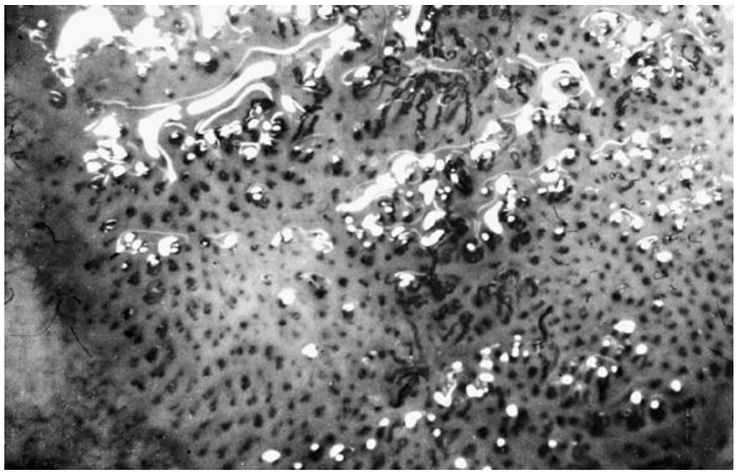

Figure 9.2 Colposcopic appearance of microinvasive cervical cancer. Note the severe vericose vascular abnormality with course punctation and transitional forms to atypical vessels.

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.

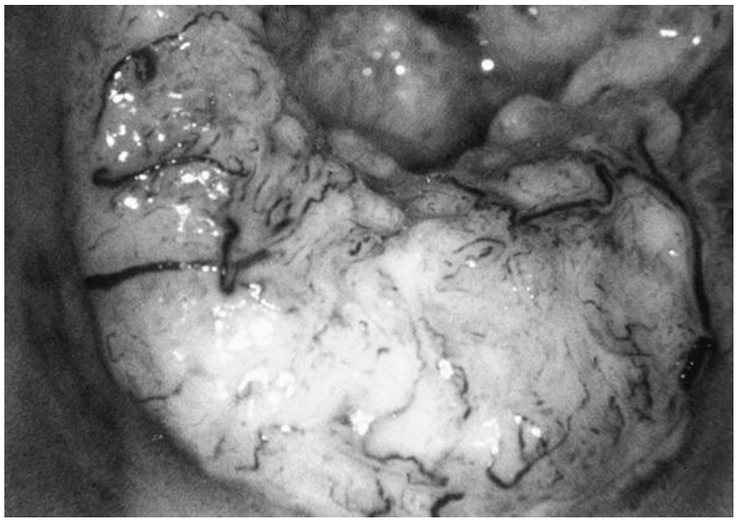

Figure 9.3 Colposcopic appearance of invasive cervical cancer. Note the surface irregularity, yellow degenerate epithelium and dilated atypical vessels.

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 (tumor, nodes, metastasis) classification is shown in Table 9.2 .

Table 9.1 Carcinoma of the Cervix Uteri: FIGO Nomenclature (Montreal, 1994)

Stage 0	Carcinoma *in situ*, cervical intraepithelial neoplasia 3 (CIN 3).
Stage 1	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).
IA	Invasive carcinoma that can be diagnosed only by microscopy. All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0 mm and a horizontal extension of ≤7.0 mm. Depth of invasion should not exceed 5.0 mm from the base of the epithelium of the original tissue—superficial or glandular. The involvement of vascular spaces—venous or lymphatic—should not change the stage allotment.
IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm.
IA2	Measured stromal invasion of >3.0 mm and ≤5.0 mm with an extension of ≤7.0 mm.
IB	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA.
IB1	Clinically visible lesions ≤4 cm.
IB2	Clinically visible lesions >4 cm.
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina.
IIA	No obvious parametrial involvement.
IIB	Obvious parametrial involvement.
Stage III	The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower one-third of the vagina. All cases with hydronephrosis or a nonfunctioning kidney are included, unless they are known to be due to another cause.
IIIA	Tumor involves lower one-third of the vagina, with no extension to the pelvic wall.
IIIB	Extension to the pelvic wall or hydronephrosis or nonfunctioning kidney.
Stage IV	The carcinoma extends beyond the true pelvis or involves (biopsy-proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV.
IVA	Spread of the growth to adjacent organs.
IVB	Spread to distant organs.

FIGO, International Federation of Gynecology and Obstetrics.

The following “Rules for Classification” are reproduced from the 24th volume of the *Annual Report on the Results of Treatment in Gynaecological Cancer* (8).

Clinical-Diagnostic Staging

Staging of cervical cancer is based on clinical evaluation; therefore, careful clinical examination should be performed in all cases, preferably by an experienced examiner and under anesthesia. The clinical staging must not be changed because of subsequent findings. When there is doubt as to which stage a particular cancer should be allocated, the earlier stage is mandatory. The following examinations are permitted: palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and x-ray examination of the lungs and skeleton. Suspected bladder or rectal involvement should be confirmed by biopsy and histologic evidence. Conization or amputation of the cervix is regarded as a clinical examination. Invasive cancers so identified are to be included in the reports. Findings of optional examinations, e.g., lymphangiography, arteriography, venography, laparoscopy, ultrasound, computed tomographic scan, and magnetic resonance imaging are of value for planning therapy but, because these are not generally available and the interpretation of results is variable, the findings of such studies should not be the basis for changing the clinical staging. Fine-needle aspiration of scan-detected suspicious lymph nodes may be helpful in treatment planning.

Postsurgical Treatment-Pathologic Staging

In cases treated by surgical procedures, the pathologist's findings in the removed tissues can be the basis for extremely accurate statements on the extent of disease. The findings should not be allowed to change the clinical staging, but should be recorded in the manner described for the pathologic staging of disease. The TNM nomenclature is appropriate for this purpose. Infrequently it happens that hysterectomy is carried out in the presence of unsuspected extensive invasive cervical carcinoma. Such cases cannot be clinically staged or included in therapeutic statistics, but it is desirable that they be reported separately.

As in all gynecological cancers, staging is determined at the time of the primary diagnosis and cannot be altered, even at recurrence.

Only if the rules for clinical staging are strictly observed will it be possible to compare results among clinics and by differing modes of therapy.

Table 9.2 Carcinoma of the Cervix Uteri: Stage Grouping

	UICC		
***FIGO* Stage**	***T***	***N***	***M***
0	Tis	N_0	M_0
IA1	T_{1a1}	N_0	M_0
IA2	T_{1a2}	N_0	M_0
IB1	T_{1b1}	N_0	M_0
IB2	T_{1b2}	N_0	M_0
IIA	T_{2a}	N_0	M_0
IIB	T_{2b}	N_0	M_0
IIIA	T_{3b}	N_0	M_0
IIIB	T_1 T_2 T_{3a} T_{3b}	N_1 N_1 N_1 any N	M_0 M_0 M_0 M_0
IVA	T_4	any N	M_0
IVB	any T	any N	M_1

FIGO, International Federation of Gynecology and Obstetrics; UICC, International Union Against Cancer; T, tumor; N, nodes; M, metastasis.

Clinical Staging

Clinical staging is often inaccurate in defining the extent of disease. The Gynecologic Oncology Group (GOG) (9), 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. **Most patients were 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 were the parametrium, peritoneum, and omentum. Up to 14% of patients may also be downstaged (10), 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 imaging 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 (11). In a review of the literature, Hacker and Berek (12) 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 (12) 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 (13 ,14).

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 and less time consuming, and avoiding exposure to radiation (15).

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** (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). **The ability of MRI to more accurately determine tumor diameter and parametrial infiltration, particularly in patients with bulky cervical tumors, makes it a useful adjunct to clinical evaluation in treatment planning** (18). **MRI is also appropriate for the evaluation of pregnant patients because it poses no risk to the fetus.**

A metaanalysis comparing the utility of lymphangiogram, CT, and MRI for the detection of pelvic and paraaortic lymph node metastases in patients with cervical cancer concluded that the three imaging modalities performed comparably (19).

Positron Emission Tomography

This imaging technique has been available in some centers since the mid-1990s. It depends on metabolic, rather than anatomic, alteration for the detection of disease. Positron emission tomography (PET) uses 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 (FDG), can be used to detect sites of malignancy by identifying sites of increased glycolysis. **The PET scan has the potential more accurately to delineate the extent of disease, particularly in lymph nodes that are not enlarged** and in distant sites that are undetectable by conventional imaging studies.

Rose et al. (20) 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%. In a study aimed at determining whether PET scanning could obviate the need for surgical staging, Narayan et al. reported a sensitivity of 83%, specificity of 92%, positive predictive value of 91%, and negative predictive value of 85% for 24 patients evaluable for pelvic nodal status (21). However, PET detected only 4 of 7 (57%) cases of positive paraaortic nodes. All histologically confirmed nodes not visualized on PET were < 1 cm in diameter.

Grigsby et al. retrospectively compared the results of CT lymph node staging with whole-body FDG–PET in 101 consecutive patients with cervical cancer who were referred for primary radiation therapy (22). CT demonstrated abnormally enlarged pelvic lymph nodes in 20 patients (20%) and paraaortic lymph nodes in 7 (7%). PET demonstrated abnormal FDG uptake in pelvic nodes in 67 patients (67%), in paraaortic nodes in 21 patients (21%), and in supraclavicular nodes in 8 patients (8%). For the 94 patients with negative paraaortic nodes on CT scan, the 2-year progression-free survival was 64% in PET-negative patients and 18% in PET-positive patients ($p < 0.0001$) (Fig. 9.4). **A multivariate analysis demonstrated that the most significant factor for progression-free survival was the presence of positive paraaortic lymph nodes as detected by PET imaging** ($p = 0.025$).

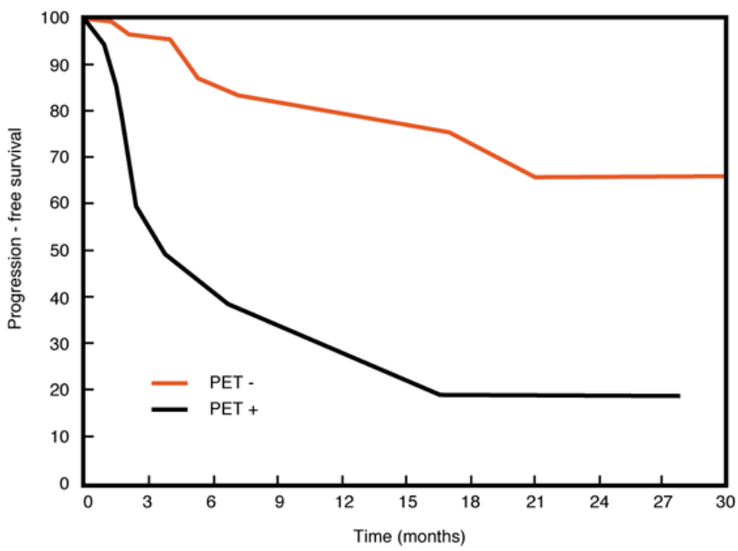

Figure 9.4 Survival curves for patients with a negative CT scan in relation to PET scan status of the paraaortic lymph nodes. (Reproduced with permission from **Grigsby PW, Siegel BA, Dehdashti F**. Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. *J Clin Oncol* 2001;19: 3745–3749.)

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% (23 ,24). **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 (25). 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 (26). 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 (26). 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 (9), the operative mortality was 0.3% (one case), intraoperative injuries to the vein or ureter occurred in four cases (1.6%), and a postoperative urinary fistula or bowel obstruction occurred in seven patients (2.9%).

Laparoscopic Staging

In the 1990s, some investigators have proposed laparoscopic staging (27). This is discussed in Chapter 20 .

In spite of the theoretical advantages of surgical staging, the benefits in terms of patient outcomes remain unproven. Lai et al., from Taipei, conducted a randomized trial to compare clinical with surgical staging for patients with locally advanced cervical cancer (28). Patients in the surgical arm were randomly allocated to either a laparoscopic or an extraperitoneal approach. Although paraaortic nodal metastases were documented in 25% of patients in the surgical arm, patient accrual was terminated after 61 patients were entered because interim analysis showed a significantly worse outcome in terms of progression-free survival ($p = 0.003$) and overall survival ($p = 0.024$) for patients in the surgical arm.

Patterns of Spread

Part of "9 - Cervical Cancer "

Cervical cancer spreads by the following means:

- **Direct invasion** into the cervical stroma, corpus, vagina, and parametrium
- **Lymphatic permeation and metastasis**
- **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.

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 (29), 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 (30). 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 .

Table 9.3 Incidence of Pelvic Lymph Node Metastases in Stage IB Cervical Cancer

Author	*Patients*	*Positive Nodes*	%
Zander et al., 1981 (31)	860	163	18.9
Fuller et al., 1982 (32)	280	42	15.0
Timmer et al., 1984 (33)	119	18	15.1
Inoue and Okamura, 1984 (34)	362	47	13.0
Creasman et al., 1986 (35)	258	36	14.0
Finan et al., 1986 (36)	229	49	21.4
Artman et al., 1987 (37)	153	13	8.5
Monaghan et al., 1990 (38)	494	102	20.6
Samlal et al., 1997 (39)	271	53	19.6
Total	**3,026**	**523**	**17.3**

The concept of sentinel node identification for cervical cancer was first introduced by Dargent in 2000 (49). Using a combination of patent blue dye and radiolabeled colloid injected into the cervix preoperatively, several authors have subsequently confirmed the ability to identify sentinel nodes in 70% to 100% of patients (50 , 51 , 52). Sentinel nodes have usually been located in the hypogastric, external iliac, or obturator nodal groups, but have also been reported in the common iliac and paraaortic region. In one patient, a sentinel node was found in the left groin (53).

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 (54) 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 (55). 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 (56).

Table 9.4 Incidence of Paraaortic Lymph Node Metastases in Stages II and III Cervical Cancer

	Stage II			*Stage III*		
Author	*Explored*	*Positive*	%	*Explored*	*Positive*	%
Nelson et al., 1977 (25)	63	9	14.3	39	15	38.5
Delgado et al., 1977 (40)	18	8	44.4	13	5	38.5
Piver and Barlow, 1977 (41)	46	6	13.0	49	18	36.7
Sudarsanam et al., 1978 (42)	43	7	16.3	19	3	15.8
Buchsbaum, 1979 (43)	19	1	5.3	104	34	32.7
Hughes et al., 1980 (44)	80	14	17.5	96	23	24.0
Ballon et al., (45)	48	9	18.8	24	4	16.7
Welander et al., 1981 (46)	63	13	20.6	38	10	26.3
Berman et al., 1984 (47)	265	43	16.2	180	45	25.0
Potish et al., 1985 (48)	47	5	10.6	11	4	36.4
La Polla et al., 1986 (10)	47	6	12.8	38	14	36.8
Total	**739**	**121**	**16.4**	**611**	**175**	**28.6**

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 (57).

Treatment

Part of "9 - Cervical Cancer "

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 (58) 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 (59 , 60 , 61).

In 1985, FIGO included measurements in the definition of stage IA disease for the first time (62). 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, in which there was minimal 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 still failed to define the border between stage IA1 and IA2 lesions.

A more precise definition of microinvasive carcinoma was adopted by FIGO in 1995. 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 and 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: Squamous Carcinoma

Although stromal invasion can be seen in small punch biopsies, a definitive diagnosis of microinvasion can be made only in conization (or hysterectomy) specimens (63). The conization specimen must be thoroughly sampled, not only to make the correct diagnosis, but also to be certain about the margins.

In an extensive review of the literature, Ostor (64) 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%). No horizontal limitation was placed on these lesions, so they do not strictly fit the current FIGO definition of stage IA1 disease, and most of the cases were treated without lymph node dissection. Elliott et al. reported 476 tumors fitting the 1995 FIGO definition of stage IA disease (65). There were 418 (88%) squamous and 58 (12%) glandular tumors. Of 180 patients undergoing lymphadenectomy, the incidence of positive nodes in patients with stage IA1 disease was 0.8% (1 of 121 cases).

Roman et al. (66) 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 (64) reporting an incidence of 15% from a literature review. Elliott et al. (65) reported lymph vascular space invasion in 8.5% of tumors invading 1 mm or less, 19% between 1.1 and 2 mm, 29% between 2.1 and 3 mm, and 53% between 3.1 and 5 mm. 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. 9.5 .

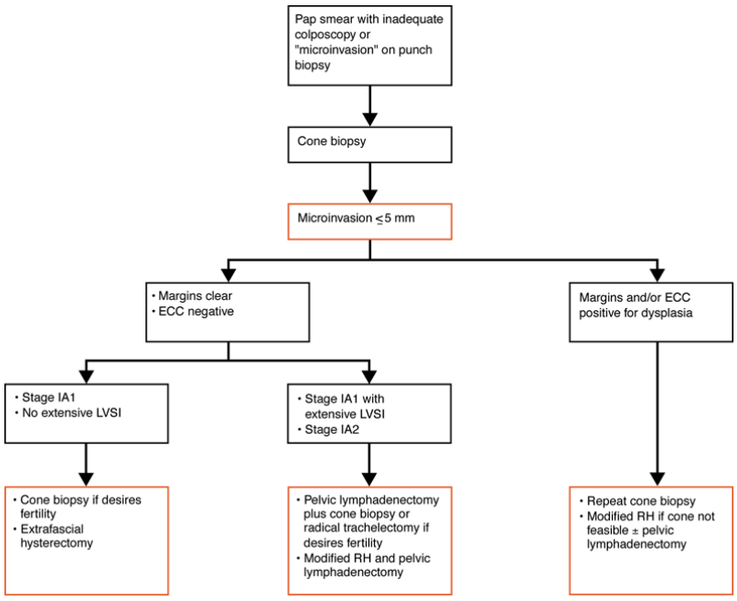

Figure 9.5 Algorithm for the management of patients with an abnormal Pap smear and inadequate colposcopy or with microinvasive squamous cervical carcinoma on punch biopsy. ECC, endocervical curettage; LVSI, lymph vascular space invasion; RH, radical hysterectomy.

Stage IA2: Squamous 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., 1995 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 (67), 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. (68) 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 7.1%, although it varied from 0% to 13.8% (Table 9.5). The incidence of invasive recurrence was 3.6%, and 2.9% of patients died of their disease. Most patients were treated by radical hysterectomy and pelvic lymph node dissection.

Table 9.5 Incidence of Lymph Node Metastases with Stromal Invasion of 3 to 5 mm—Horizontal Dimension Not Stated

Author	*No.*	*Nodal Metastases*	*Invasive* Recurrences	*Dead of Disease*
Van Nagell et al., 1983 (69)	32	3 (9.4%)	3	2
Hasumi et al., 1980 (70)	29	4 (13.8%)	NS	NS
Simon et al., 1986 (61)	26	1 (3.8%)	0	0
Maiman et al., 1988 (71)	30	4 (13.3%)	0	0
Buckley et al., 1996 (72)	94	7 (7.4%)	5	4
Creasman et al., 1998 (73)	51	0 (0.0%)	0	0
Takeshima et al., 1999 (74)	73	5 (9.6%)	3	3
Total	**335**	**24 (7.1%)**	**11 (3.6%)**	**9 (2.9%)**

NS, not stated.

Takeshima et al. (74) **reported that of 73 patients with depth of invasion between 3 and 5 mm, the incidence of lymph node metastasis was 3.4% for tumors with a horizontal spread of 7 mm or less and 9.1% for those with greater than 7 mm spread.** Elliott et al. also reported positive nodes in 3.4 % of patients (2 of 59) with stage IA2 cervical cancer (65).

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. In a medically unfit patient, intracavitary radiation may be used.**

Many patients with early cervical cancer are young, and preservation of fertility is a major concern. Consequently, surgical approaches that remove the primary lesion and regional lymph nodes, while conserving the corpus for future childbearing, have been explored.

Cone biopsy and extraperitoneal lymphadenectomy have been used in the past, but in 1994, Dargent et al. pioneered the use of **radical trachelectomy and laparoscopic pelvic lymphadenectomy** (75). A nonabsorbable cervical cerclage is usually placed around the uterine isthmus at the time of the trachelectomy. Several other groups have subsequently confirmed that the operation is feasible in experienced hands, that cure rates are high, and that subsequent pregnancies can be carried to viability in many cases (76 , 77 , 78 , 79). Covens et al. reported an actuarial conception rate at 12 months of 37% following radical trachelectomy on 30 patients with stage IA–early IB disease (78).

Radical abdominal trachelectomy was first reported by Smith et al. in 1997 (80). One advantage of this approach is that the anatomy is more familiar to most gynecologic oncologists. Although the procedure has not yet gained wide acceptance, successful pregnancy outcomes have been reported (81).

A critical issue for trachelectomy by either route is the extent of tumor extension up the endocervical canal. An adequate endocervical surgical margin is mandatory if local recurrence is to be avoided, so some type of preoperative imaging is desirable. **Magnetic resonance imaging appears to be highly sensitive and specific for the determination of tumor extension beyond the internal os** (82).

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 (83 ,84) or from the base of the surface epithelium (85). Width and volume of tumor involvement have varied considerably, and only recently have reports looked specifically at microinvasion as now defined by the FIGO staging.

Most cases arise adjacent to the transformation zone, although Teshima et al. (86) reported that 3 of 30 cases (10%) arose outside the transformation zone. Adenocarcinoma *in situ* may extend up the entire endocervical canal, and invasion may occur at any point (86). Lee and Flynn (87), in a study of 40 cases of adenocarcinoma invasive to 5 mm or less, reported that in 78% of the cases, the midpoint of the invasive focus was in the region of the transformation zone. The endometrioid variant was particularly likely to arise higher in the canal.

Whereas squamous lesions are usually unifocal, glandular lesions are sometimes multifocal. Ostor et al. (84) 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. More than one focus of invasive disease was present in 4 of 40 cases (10%) reported by Lee and Flynn (87).

Positive lymph nodes have rarely been reported in FIGO stage IA1 lesions, although Elliott et al. reported a solitary nodal metastasis in a patient with <1 mm stromal invasion (65). Berek et al. (83), 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. (85) 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. (84) involved a patient whose tumor invaded to a depth of 3.2 mm but was 21 mm in length (i.e., stage IB1).

The Surveillance, Epidemiology and End Results (SEER) database was used to identify 131 cases of stage IA1 and 170 cases of stage IA2 adenocarcinoma of the cervix treated between 1988 and 1997 (88). There was no histologic review, and patients were treated in a variety of ways, from cone biopsy to radical hysterectomy and pelvic lymphadenectomy. Simple hysterectomy alone was used for 118 patients (39.2%). **With a mean follow-up of 46.5 months, the censored survival was 99.2% for patients with stage IA1 disease and 98.2% for stage IA2.**

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. (89) reported that ECC was positive before cervical conization in only 43% of patients with glandular lesions. Loop excision procedures obscure depth of invasion and margins and are not acceptable either for diagnosis or therapy (90).

Stage IB1 and Early Stage IIA Cervical 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 (91). 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 “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 (92). 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** (93).

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 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. Samlal et al. (94) 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 (95 ,96). 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. (97) 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 (98). 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. (97) described removal of the upper one-third of the vagina, but this is rarely necessary unless vaginal intraepithelial neoplasia (VAIN) 3 is extensive. 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 (99). 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. (97) 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 ureteric fistula is increased with this procedure, which Piver et al. (97) 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 removed 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 (Figs. 9.6 , 9.7).

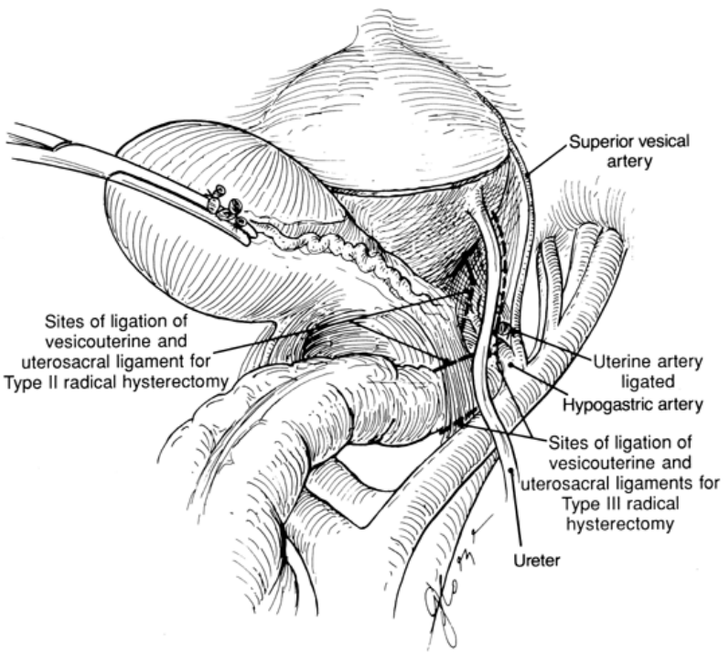

Figure 9.6 Radical hysterectomy. Uterine artery is ligated, ureter is dissected, and sites for division of the vesicouterine and uterosacral ligaments are shown.

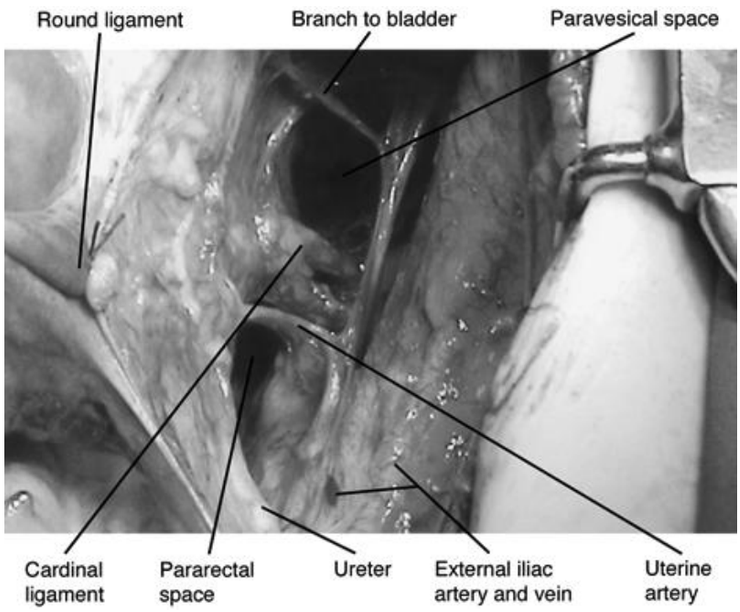

Figure 9.7 Paravesicle and pararectal spaces.

The **paravesicle space** (Fig. 9.7) is bordered by:

- The obliterated umbilical artery (a continuation of the superior vesicle artery) running along the bladder medially
- The obturator internus muscle laterally
- The cardinal ligament posteriorly
- The pubic symphysis anteriorly

The **pararectal space** is bordered by:

- The rectum medially
- The hypogastric artery laterally
- The cardinal ligament anteriorly
- 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 (Fig. 9.8), 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.

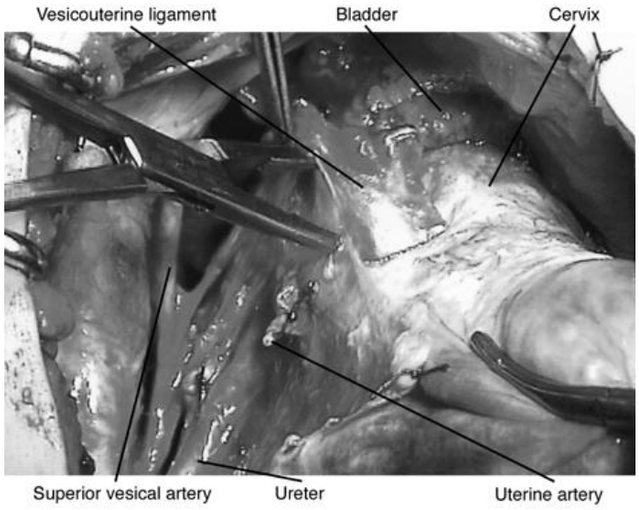

Figure 9.8 Piecemeal dissection of anterior vesicouterine ligament.

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. 9.9).

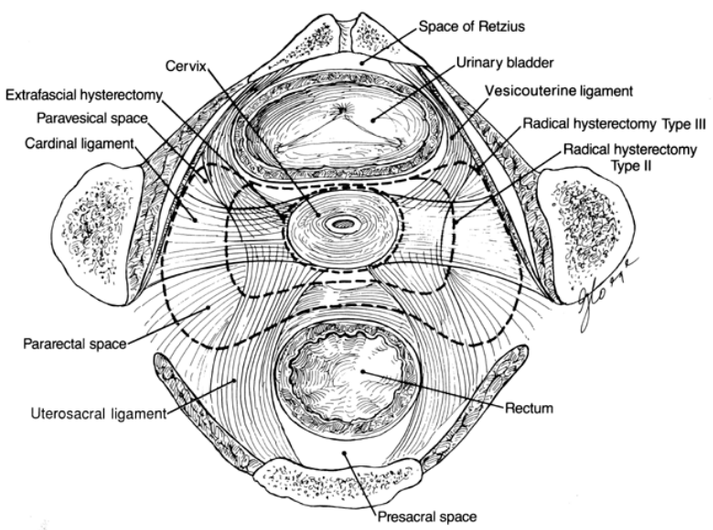

Figure 9.9 The pelvic ligaments and spaces.

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 and uterosacral ligaments.

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. 9.10). Using sharp dissection with Metzenbaum scissors, all fatty tissue is stripped off the vessels from the mid-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 30% of patients and is easily torn if not identified. It enters the distal external iliac vein inferiorly.

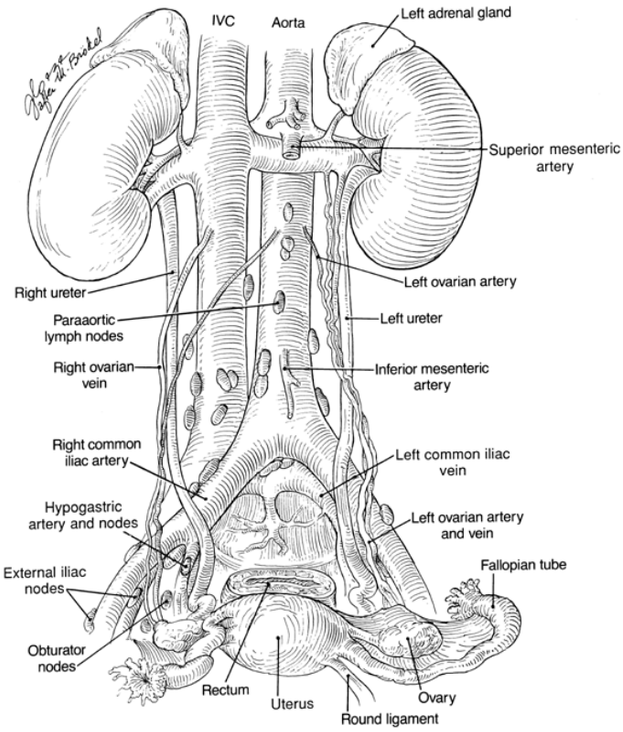

Figure 9.10 The pelvic and paraaortic lymph nodes and their relationship to the major retroperitoneal vessels.

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 (100). 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 (101) and 1,500 mL (102). 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 significant 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.

Table 9.6 Postoperative Complications of Radical Hysterectomy

Complication	*Powell et al. (1981) (103) N = 135 (%)*	*Samlal et al. (1996) (102) N = 271 (%)*	*Sivanesaratnam et al. (1993) (104) N = 397 (%)*	*Total (%)*
Early				
Urinary tract infection	10 (7.4)	NS	36 (9.1)	46/532 (8.6)
Venous thrombosis	6 (4.4)	6 (2.2)	9 (2.3)	21/803 (2.6)
Pulmonary embolism	4 (3.0)	1 (0.4)	2 (0.5)	7/803 (0.9)
Ureterovaginal fistula	0 (0.0)	5 (1.8)	1 (0.3)	6/803 (0.8)
Vesicovaginal fistula	2 (1.5)	2 (0.7)	2 (0.5)	6/803 (0.8)
Fever[a]	16 (11.9)	10 (3.7)	2 (0.5)	28/803 (3.4)
Lymphocyst	2 (1.5)	8 (3.0)	3 (0.8)	13/803 (1.6)
Ileus	3 (2.2)	9 (3.3)	NS	12/406 (1.5)
Burst abdomen	0 (0.0)	1 (0.4)	1 (0.2)	2/803 (0.3)
Ureteral obstruction	2 (1.5)	1 (0.4)	0 (0.0)	3/803 (0.4)
Late				
Prolonged bladder dysfunction	4 (3.0)	14 (5.2)	3 (0.8)	21/803 (2.6)
Lymphedema	NS	20 (7.4)	4 (1.0)	24/668 (3.6)
Sexual dysfunction	NS	6 (2.2)	NS	6/271 (2.2)

[a]Pelvic abscess, pelvic cellulitis, atelectasis, wound infection, psoas abscess.

NS, not stated.

Late Complications

Bladder Dysfunction

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. Covens et al. (105) 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 eight surgeons concerned varied from 0% to 44%. Samlal et al. (102) 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 and bowel dysfunction are inevitable in the immediate postoperative period, and suprapubic or urethral catheter drainage and laxatives are

desirable for at least the first week. If cystometry is performed to evaluate bladder dysfunction, two abnormal patterns are found (106). 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.

Sexual Dysfunction

A large Swedish study of sexuality in cervical cancer survivors reported sexual dysfunction in 55% of patients treated by radical hysterectomy alone (107). Problems included insufficient lubrication, reduced genital swelling at arousal, reduced vaginal length and elasticity, and dyspareunia. The addition of preoperative brachytherapy and/or external beam radiation yielded no excess risk of sexual dysfunction.

This is in marked contrast to our own experience at the Royal Hospital for Women where Grumann et al., in a more detailed study of a much smaller group of patients, reported that radical hysterectomy was not associated with major sexual sequelae (108).

The differences between the two groups may be explained by the radicality of the surgery. We do not take more than 1.5 cm of normal vagina at radical hysterectomy, so reports of vaginal shortness are very unusual.

In order to avoid bowel, bladder and sexual dysfunction, a nerve-sparing radical hysterectomy, similar to procedures performed in Japan (109 ,110), **has been proposed by European surgeons** (111 ,112). From the superior hypogastric plexus located over the sacral promontory, two hypogastric nerves containing sympathetic fibers run into the small pelvis beneath the ureter and are responsible for such functions as bladder compliance, urinary continence, and small muscle contractions at orgasm (113 ,114). The hypogastric nerves fuse with parasympathetic fibers of the pelvic splanchnic nerves, coming from sacral roots 2.3 and 4, to form the inferior hypogastric plexus, which is situated in the dorsal part of the parametrium and the dorsal vesicouterine ligament. The parasympathetic fibers are responsible for vaginal lubrication and genital swelling during sexual arousal, detrusor contractility, and various rectal functions.

Performance of the nerve-sparing operation, as described by Trimbos et al. (111), involves three basic steps: (a) the hypogastric nerve is identified and preserved as it runs in a loose sheath beneath the ureter and lateral to the uterosacral ligament, (b) the inferior hypogastric plexus is lateralized and avoided during parametrial dissection, and (c) the most distal part of the inferior hypogastric plexus is preserved during the dissection of the posterior part of the vesicouterine ligament.

Nerve sparing occurs inevitably with a more conservative type of radical hysterectomy. A prospective, randomized study of type II versus type III radical hysterectomy for stage IB–IIA cervical cancer was reported by Landoni et al. (115). There was no significant difference in recurrence rate (24% type II vs. 26% type III) or the number of patients dead of disease (18% type II vs. 20% type III) for the two procedures, but urologic morbidity was significantly reduced with the less radical operation (13% vs. 28%).

Lymphedema

Lymphedema as a late complication of pelvic lymphadenectomy is underreported in the medical literature. In a study of 233 patients having pelvic lymphadenectomy in our center, 47 (20.2%) developed lymphedema (116). The onset of the swelling was within 3 months in 53%, within 6 months in 71%, and within 12 months in 84% of patients. The addition of pelvic radiation postoperatively increases the risk of lymphedema.

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

There is a strong correlation between tumor size and outcome for patients with stage IB cervical cancer (117). Bulky tumors require aggressive radiotherapy, and complication rates are high. Perez et al. (118), 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. (119) 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.

Presently, chemoradiation is usually given, in line with reports for advanced cervical cancer (120).

Radiation and Extrafascial Hysterectomy

In 1969, Durrance et al. (121) 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 following primary pelvic radiation. The GOG recently reported the results of a trial of 256 eligible patients with tumors ≥4 cm diameter who were randomized between radiation alone (N = 124) and attenuated radiation followed by extrafascial hysterectomy (N = 132) (122). Twenty-five percent of patients had tumors ≥7 cm diameter. There was a lower incidence of local relapse in the hysterectomy group (27% vs. 14% at 5 years), although outcomes were not statistically different. Their conclusions were somewhat ambiguous: “Overall, there was no clinically important benefit with the use of extrafascial hysterectomy. However, there is good evidence to suggest that patients with 4, 5, and 6 cm tumors may have benefited from extrafascial hysterectomy.”

Radiation, Extrafascial Hysterectomy, and Chemotherapy

A 1999 GOG study (123) 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% vs. 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.

Neoadjuvant Chemotherapy

In 1993, Sardi et al. (124) 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.

A recent metaanalysis was reported using updated individual patient data from five randomized controlled trials conducted worldwide between 1988 and 1999 that compared neoadjuvant chemotherapy plus surgery with radiotherapy alone (125). There were 872 patients in the metaanalysis and 368 deaths. **The overall results showed a highly significant benefit for the neoadjuvant chemotherapy and surgery arm, with a 36% reduction in the risk of death and an absolute improvement in survival of 15% at 5 years.**

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. 9.11). 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. 9.12 . **Older patients tolerate radical surgery remarkably well, although approximately 10% of patients older than 70 years of age have a medical contraindication to surgery** (93). 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 (126).

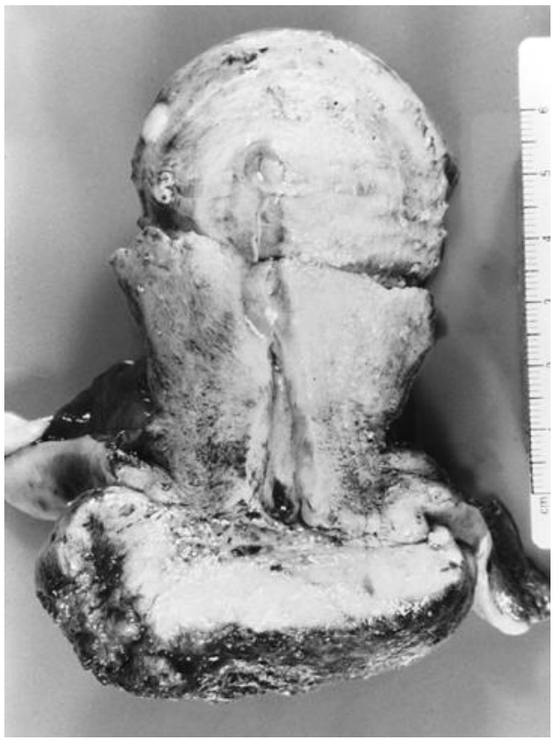

Figure 9.11 Radical hysterectomy specimen from a patient with an exophytic stage IB2 cervical cancer.

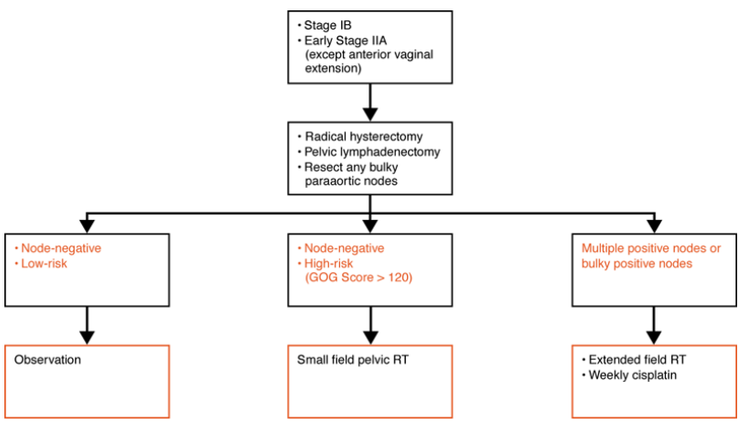

Figure 9.12 Algorithm for the management of stages IB and early IIA carcinoma of the cervix. RT, radiation therapy; GOG, Gynecologic Oncology Group.

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 (127). **Second, it allows resection of bulky positive lymph nodes**, thereby improving the prognosis significantly (128 ,129). **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 (130).

In a retrospective study comparing radical hysterectomy for stage IB1 versus IB2 disease, Finan et al. (36) 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 (44).

In addition, **approximately half of the 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** (128 ,129).

In the report by Finan et al. (36), 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.

Although the optimal management of patients with stage IB2 disease awaits further randomized, prospective studies, our experience, and that of others (130 , 131 , 132 , 133 , 134), suggests that good survival rates with tolerably low morbidity can be achieved with a primary surgical approach, giving tailored postoperative radiation in the majority of cases.

In the only randomized, prospective study looking at radical surgery versus primary radiation for stage IB to IIA cervical cancer, Landoni et al. (91) 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 Stages IB to IIA

The major prognostic factors for patients having radical hysterectomy and pelvic lymphadenectomy for stages IB to IIA cervical cancer are as follows:

- Status of the lymph nodes
- Size of the primary tumor
- Depth of stromal invasion
- Presence or absence of lymph-vascular space invasion
- Presence or absence of parametrial extension
- Histologic cell type
- Status of the 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 a single positive node below the common iliac bifurcation have a prognosis similar to that of patients with negative nodes (142 ,145). Patients with positive paraaortic nodes treated with extended-field radiation have a 5-year survival rate of approximately 50% (129 ,146).

Table 9.7 Survival after Radical Hysterectomy for Stages IB and IIA Cervical Cancer

		5-Year Survival Rate (%)		
Author	*No.*	*Negative Nodes*	*Positive Nodes*	*Overall*
Langley et al., 1980 (135)	204	94	65	87
Benedet et al., 1980 (136)	202	81	66	73
Kenter et al., 1989 (137)	213	94	65	87
Lee et al., 1989 (138)	954	88	73	86
Monaghan et al., 1990 (139)	498	91	51	83
Ayhan et al., 1991 (140)	278	91	63	84
Averette et al., 1993 (141)	978	96	64	90
Samlal et al., 1997 (39)	271	95	76	90
Kim et al., 2000 (142)	366	95	78	88

Table 9.8 Five-Year Survival Rate (%) versus Number of Positive Pelvic Nodes in Stage IB Cervical Carcinoma

		No. of Positive Nodes		
Author	*Patients*	*1*	*1-3*	*>4*
Noguchi et al., 1987 (143)	177	—	54	43
Lee et al., 1989 (138)	954	62	—	44
Inoue and Morita, 1990 (144)	484	91	—	50

Tumor Size, Depth of Stromal Invasion, Lymph-Vascular Space Invasion

In 1989, the GOG (147) 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:

- **The clinical size of the tumor**
- **The presence or absence of lymph-vascular space invasion**
- **The 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. 9.13). It can be seen that the likelihood of recurrence for a patient with a GOG score greater than 120 is 40% at 3 years.

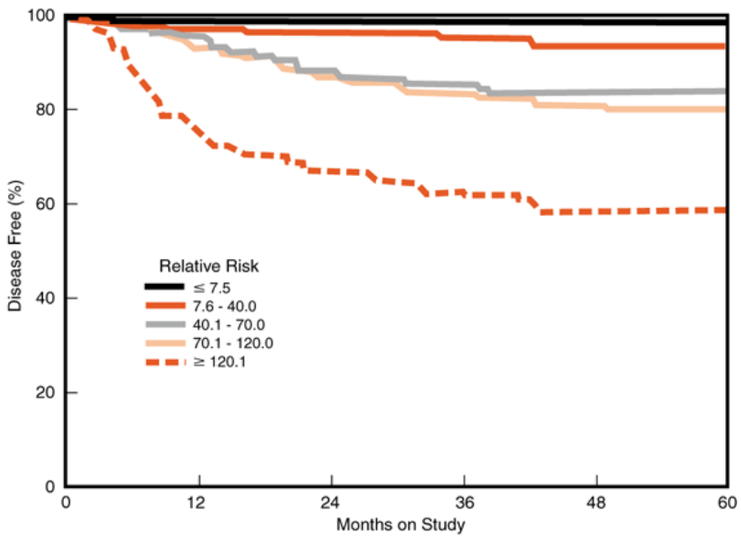

Figure 9.13 Disease-free survival for patients with cervical cancer after radical hysterectomy and bilateral pelvic lymphadenectomy. (From **Delgado G, Bundy B, Zaino R, Sevin B-U, Creasman WT, Major F**. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous 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. (148) 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. (149) 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 (150) 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.

Histologic Cell Type

Small cell carcinoma of the cervix is uncommon but has an unequivocally poor prognosis (151).

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** (142 ,152 ,153), but Shingleton et al. (154) 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 (155 ,156), whereas others report no difference from squamous lesions with respect to metastatic potential or outcome (157). Farley et al. investigated 185 women with pure adenocarcinomas (AC) and 88 women with adenosquamous carcinomas (ASC) (158). They reported no difference in survival for patients with FIGO stage I disease (AC, 89%; ASC 86%; p = 0.64) but a significantly decreased median and overall survival for adenosquamous carcinoma in patients with advanced disease (FIGO stage II–IV).

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 (141). 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 (159). 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 (160 ,161). It has also been suggested that HPV 18–containing tumors may progress to invasion without a prolonged preinvasive phase (162).

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 (163).

Postoperative Radiation

Adjuvant pelvic radiation following radical hysterectomy should be given in two circumstances: (a) patients with positive nodes, positive parametria, or positive surgical margins, and (b) patients with negative nodes but high-risk features in the primary tumor.

Patients with Positive Nodes, Positive Parametria, or Positive Surgical Margins

The Southwest Oncology Group (164) **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 four 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.

Patients with Negative Nodes but High-Risk Features in the Primary Tumor

Although patients with negative nodes 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 (165 ,166).

The GOG conducted 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 (167). 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 ≥4 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 versus 79% for observation at 2 years.** Severe (GOG grade 3–4) gastrointestinal or urologic toxicity occurred in 6.2% of patients receiving radiation versus 1.4% of controls.

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. 9.14). **The small field decreases the amount of small and large bowel that is irradiated** (168).

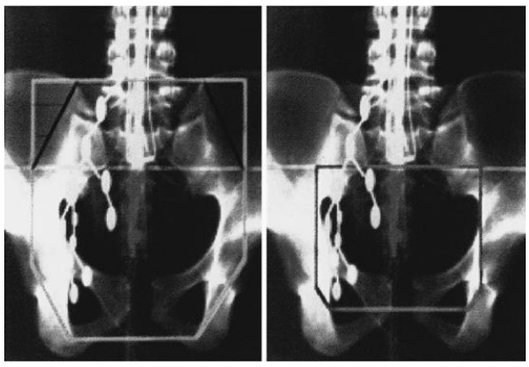

Figure 9.14 Comparison between (A) **standard field and** (B) **small field for pelvic radiation.**

Table 9.9 Anteroposterior and Lateral Portals for Standard- and Small-Field Pelvic Radiation Used for Patients from the Royal Hospital for Women, Sydney

	Standard Field	*Small Field*
Anteroposterior		
Superior	L4-5 junction	S1-2 junction
Inferior	Inferior obturator foramen	Midobturator 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

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 ($p = 0.005$) (168). No major morbidity occurred, but minor morbidity was recorded in four patients: lymphedema in three, and mild rectal incontinence in one.

A recent Japanese study compared adjuvant small field pelvic radiation for 42 patients with high-risk, node-negative stage I or II cervical cancer **with whole pelvic radiation** for 42 patients with node-positive disease (169). **The 5-year pelvic control rate was 93% in the small pelvic field cohort and 90% in the whole pelvic field group.** They concluded that small pelvic field radiation appeared to be adequate for high-risk node-negative patients.

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 disease, 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.**

Strategies that have been investigated include:

- **Hyperfractionation** of the radiation
- **Neoadjuvant chemotherapy before radiation**
- **Use of hypoxic cell radiation sensitizers**
- **Concurrent use of radiation and chemotherapy** (chemoradiation)

Hyperfractionated radiation has not been adequately studied for cervical cancer (170), and trials of neoadjuvant chemotherapy followed by radiation have generally been disappointing. A recent metaanalysis from the United Kingdom looked at updated individual patient data from 18 randomized controlled trials conducted worldwide between 1982 and 1995 (171). There was a high level of statistical heterogeneity, although trials using a higher dose intensity of *cisplatin* and shorter cycle length appeared to increase survival, whereas a lower dose intensity and longer cycle length appeared to reduce survival.

Hydroxyurea **is the best-studied radiation sensitizer** (172 ,173) **but it has been shown to be inferior to *cisplatin*-based chemoradiation** (120).

Concurrent Chemotherapy and Radiation

Three large randomized prospective trials, all reported in 1999, have established chemoradiation as the treatment of choice for patients with advanced cervical cancer.

The GOG reported the 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 (120). Chemotherapy regimens were as follows:

- **Regimen I: Weekly *cisplatin 40 mg/m²/week for 6 weeks***
- **Regimen II: *Hydroxyurea orally 2 mg/m² twice weekly for 6 weeks***, *5-FU* 1,000 mg/m²/day as a 96-hour infusion on days 1 and 29, *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.

The Radiation Therapy Oncology Group (RTOG) randomized 403 patients with advanced cervical cancer confined to the pelvis between pelvic and paraaortic radiation, and pelvic radiation with concurrent *cisplatin* and *5-fluorouracil* (174). With a median follow-up of 43 months, the actuarial survival at 5 years was 73% among patients having chemoradiation and 58% among those having radiation alone (*p* = 0.004). Disease-free 5-year survivals were 67% in the chemoradiation arm and 40% in the radiation alone arm, respectively (*p* <0.001). The rates of distal metastases and locoregional recurrences were significantly higher among patients treated with radiation alone.

The GOG–SWOG groups randomized 388 patients with FIGO stages IIB, III, or IVA disease and negative paraaortic nodes at retroperitoneal paraaortic lymph node sampling between standard pelvic radiation with *hydroxyurea* and standard pelvic radiation with *5-fluorouracil* and *cisplatin* (175). Both progression-free (*p* = 0.03) and overall survival (*p* = 0.02) were significantly better for patients randomized to receive *5 FU-cisplatin*.

The optimal regimen for the chemotherapy is yet to be defined, but single-agent *cisplatin* at a dose of 40mg/m² given weekly during external beam therapy is widely used.

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 (127).

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.**

Table 9.10 Sites of Recurrence in Patients with Cervical Cancer Having Extended-Field Radiation for Positive Paraaortic Nodes

Author	*Patients*	*Distinct Metastases*	*Pelvic Recurrence*
Nelson et al., 1977 (25)	23	12 (52%)	NS
Piver et al., 1981 (176)	31	14 (45%)	NS
Welander et al., 1981 (46)	31	17 (55%)	12 (38%)
Tewfik et al., 1982 (177)	23	10 (44%)	5 (22%)
Berman et al., 1984 (47)	90	32 (36%)	25 (28%)
Rubin et al., 1984 (146)	14	5 (36%)	2 (14%)
La Polla et al., 1986 (10)	13	8 (62%)	7 (54%)
Vigliotti et al., 1992 (178)	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 9.11 Survival after Extended-Field Radiation

Author	*Patients*	*Five-Year Survival Rate (%)*
Buchsbaum, 1979 (43)	21	23.0
Hughes et al., 1980 (44)	22	29.0
Ballon et al., 1981 (45)	18	23.0
Piver et al., 1981 (176)	31	9.6
Welander et al., 1981 (46)	31	25.8
Rubin et al., 1984 (146)	14[a]	57.1
Potish et al., 1985 (48)	17	40.0
La Polla et al., 1986 (10)	16	30.0
Vigliotti et al., 1992 (178)	43	28.0
Total	**213**	**27.2**

[a]All patients had stage IB or IIA disease.
Modified from **Hacker NF.** Clinical and operative staging of cervical cancer. *Baillieres Clin Obstet Gynaecol* 1988;2:747–759, with permission.

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 (179).

The RTOG in the United States conducted a randomized trial of prophylactic paraaortic radiation (4,500 cGy) in 330 patients with stages IB/IIA (>4 cm) or IIB

cervical cancer (180). Patients with lymphangiographic or surgical evidence of paraaortic nodal involvement were excluded. **Significantly better 5-year survival rates (66% vs. 55%) were demonstrated 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.

The GOG conducted a trial of extended field chemoradiation for patients with biopsy-proven paraaortic lymph node metastases (181). The radiation dose to the paraaortic area was 4,500 cGy, and the chemotherapeutic regime was *5-fluorouracil* 1,000 mg/m^2/day for 96 hours and *cisplatin* 50 mg/m^2 in weeks 1 and 5. There were 86 evaluable patients with stage IB–IVA disease, and the 3-year overall and progression-free survivals were 39% and 34%, respectively. Severe acute toxicity was mainly gastrointestinal (18.6%) and hematologic (15%), and the major late morbidity was gastrointestinal (14% actuarial risk at 4 years). **This trial demonstrated the feasibility of extended field chemoradiation and confirmed that not all patients with paraaortic nodal metastases have systemic disease.**

For patients without proven paraaortic nodal disease, the most recent RTOG study demonstrated that pelvic radiation plus concurrent chemotherapy was superior to prophylactic extended field radiation without chemotherapy (174).

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. 9.15 . 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 or (b) pelvic or paraaortic lymph nodes at least 2 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** (128 ,129). Patients with bulky positive nodes that have been resected from the pelvic or paraaortic area are given extended-field radiation with weekly *cisplatin* 40 mg/m^2, and all other patients are given pelvic chemoradiation. Recently, we have been obtaining a PET scan if the CT scan is negative. If the PET scan shows positive paraaortic nodes, extended-field chemoradiation is given.

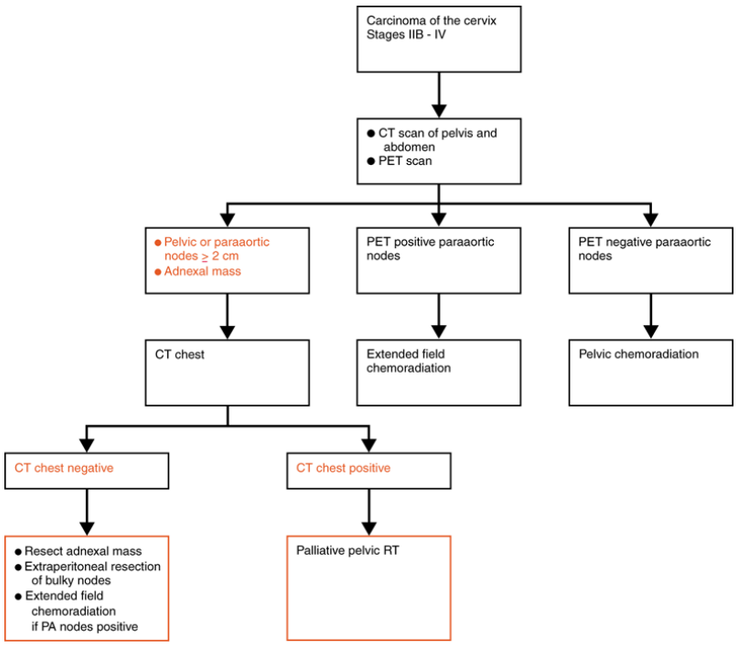

Figure 9.15 Algorithm for the management of patients with advanced cervical cancer. RT, radiation therapy.

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. Differences due to case mix, age group, type of tumor and other factors may be responsible for variations or differences between centers.

Table 9.12 Carcinoma of the Cervix Uteri: Patients treated in 1993 to 1995: Survival by FIGO Stage (N = 11,620)

		Overall Survival Rates (%)				
Stage	*Patients*	*1 yr*	*2 yr*	*3 yr*	*4 yr*	*5 yr*
Stage IA1	787	98.3	96.6	95.7	95.2	94.6
Stage IA2	313	97.7	94.9	94.5	93.7	92.6
Stage IB1	2,470	96.1	90.5	85.8	83.2	80.7
Stage IB2	440	96.0	90.8	86.3	84.0	79.8
Stage IIA	993	96.3	88.8	82.9	78.5	76.0
Stage IIB	2,775	95.0	86.1	79.7	76.0	73.3
Stage IIIA	131	85.5	66.5	55.7	52.9	50.5
Stage IIIB	2,271	79.9	63.6	54.9	49.4	46.4
Stage IVA	258	63.9	45.5	38.5	30.7	29.6
Stage IVB	196	48.6	32.2	30.8	27.3	22.0

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** 2001;6:5–44, with permission.

Post-treatment 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.

After the immediate postradiation surveillance or postoperative checkup, patients are usually seen every 3 months until 2 years, every 6 months until 5 years, and annually thereafter. The role of routine follow-up has been questioned, because most recurrences are detected at self-referral because of symptoms (182). Nevertheless, follow-up also allows psychosocial support for the patient as well as data collection, and in a Dutch study, 32% of all cases of recurrence were diagnosed at routine follow-up (182). The mean disease-free interval was 18 months.

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. (183) 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. **Whole-body FDG PET appears to be a sensitive and specific tool for the detection of recurrent cervical cancer in patients who have clinical findings suspicious for recurrence** (184).

Nonsquamous Histologic Types

Part of "9 - Cervical Cancer "

Adenocarcinoma

Adenocarcinomas presently represent 20% to 25% of cervical cancers in the industrialized countries. In the United States, the age-adjusted incidence rates for adenocarcinoma have increased by 29.1% over the past 24 years, and the proportion of adenocarcinomas relative to squamous carcinomas has increased by 95.2% (185). Most of this relative increase is related to a decreasing incidence of squamous carcinomas secondary to screening programs, but **oral contraceptive use has been implicated in the absolute increase in adenocarcinomas in women younger than 35 years of age** (186). In England, the substantial increase in adenocarcinomas in recent years has been largely attributed to a birth-cohort effect, presumably associated with greater exposure to human papillomavirus after the sexual revolution of the 1960s (187). **A Canadian study reported HPV in 70% of cases (53 of 77), with HPV 16 the predominant type** (188). There was no correlation between HPV status and outcome.

Adenocarcinomas are generally regarded as being more radioresistant than squamous carcinomas. **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 (91). 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 levels are of prognostic significance for adenocarcinomas (189). The 5-year survival rate for stage IB adenocarcinomas was 52.4% when CA125 levels were elevated, versus 95.6% when normal levels were present ($p < 0.01$). Similarly, 42% of patients with elevated serum CA125 levels had lymph node metastases, versus 4% when normal levels were found ($p = 0.012$).

Although the prognostic significance of adenocarcinoma is somewhat controversial, the presence of lymph node metastases seems to portend a much worse prognosis for patients with adenocarcinomas than squamous carcinomas (102 ,185 ,190).

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 series of surgically staged IB cases, Helm et al. (191) 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.

Gallup et al. reported 127 patients with stage IB carcinoma of the cervix (192). The survival for women with adenosquamous carcinoma was 27%, compared with 91% for those with squamous carcinoma and 83% for those with adenocarcinoma. Fu et al. attributed the poor prognosis of adenosquamous carcinoma to the high frequency of vascular space invasion (50%), persistence of tumor following preoperative radiotherapy (86%), and metastasis to distant sites (25%) (193).

Glassy Cell Carcinoma

In 1956, Glucksman and Cherry (194) 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 (195) suggested that **poorly differentiated large cell, nonkeratinizing squamous carcinomas have a similar histologic appearance.** Subsequently, Tamimi et al. (196) 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.**

A contemporary series of 22 patients from the University of Washington suggests a better prognosis than previously reported (197). The overall survival for the series was 73%, with the overall survival for patients having stage I disease being 86% (12 of 14). Pelvic relapse was associated with lymph vascular space invasion, deep stromal invasion, and large tumor size.

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** (198) **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 Hurt (199) 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 (200).

These tumors represent approximately 1% of adenocarcinomas of the cervix and occur mainly in the fifth and sixth decades (201). **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 (202). **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 (202). 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 (203).

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is sometimes also referred to as a **cylindroma**, a term first used by Billroth (204) 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 occurs in Bartholin's gland, the endometrium, and the cervix** (205). 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 (206), whereas adenocarcinoma has a less frequent association.

These tumors usually occur in postmenopausal black women of high parity (205 ,207). Most present with postmenopausal bleeding, but some may be suspected by the presence of small "undifferentiated" cells on a routine Pap smear (205). Approximately half the cases are stage I at presentation, but **overall survival is poor.** Prempree et al. (207), 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* (208).

Adenoid Basal Carcinoma

This is a rare tumor with an excellent prognosis. Most adenoid basal carcinomas have coexistent *in situ* or invasive squamous carcinoma, and 50% have coexistent *in situ* or invasive adenocarcinoma (209). The disease is almost invariably confined to the cervix, and in a review of 26 cases reported in the literature, only one died of disease (with lung

metastases) (210). Invasion is usually superficial, and extrafascial or radical hysterectomy without lymphadenectomy is a reasonable treatment option.

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 eighteenth week of pregnancy to *diethylstilbestrol* and related nonsteroidal estrogens (211). The tumor occurs in two distinct age groups: those younger than 24 years and those older than 45 years (212). 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.** 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** (212 ,213).

Villoglandular Papillary Adenocarcinoma

This uncommon lesion tends to occur in younger women and to have a more favorable prognosis. Young and Scully (214) 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. (215), 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. (216) revealed lymph vascular invasion in two patients, both of whom had pelvic lymph node metastasis. One of the two recurred at 30 months and died at 46 months.

Because of their generally excellent prognosis and young age at presentation, conservative management may be justified in selected patients who want to retain fertility (215).

Small Cell Carcinoma

Small cell cancers are a rare, heterogeneous group of tumors, representing 0.5% to 5% of all invasive cervical cancers (217). In a thorough evaluation of 2,201 invasive cervical cancers at the University of Kentucky Medical Center, Van Nagell et al. (151) 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 or APUD cells (**a**mine **p**recursor **u**ptake and **d**ecarboxylation) in the cervix (217). 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 then have elevated levels of 5-hydroxy-indoleacetic acid in the urine.**

An epidemiological study using population-based data reported to the Surveillance Epidemiology and End Results (SEER) program in the United States compared 239 cases of endocrine tumors of the cervix with 18,458 squamous cell carcinomas (218). Mean age at diagnosis was 49 years for the endocrine tumors versus 52 years for the squamous carcinomas ($p < 0.01$). Endocrine tumors were more likely to present at a later FIGO stage

(p <0.01) and to have lymph node involvement at diagnosis (57% vs. 18%, p <0.01). At all stages of disease, survival was worse for the women with endocrine tumors.

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 (219). 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.

The group in Buenos Aires (220) reported 20 patients with neuroendocrine cervical carcinoma. Patients with stages IA2 (one) or IB1 (four) were treated by radical hysterectomy and pelvic lymphadenectomy with or without adjuvant chemotherapy, and all patients survived. Thirteen patients with stages IB2 to IVA disease received neoadjuvant chemotherapy with the quick *VBP* scheme (*vincristine* 1 mg/m^2/day on day 1; *bleomycin* 25 mg/m^2/day on days 1 to 3; and *cisplatin* 50 mg/m^2/day on day 1, for 3 courses with 10-day intervals). Treatment was completed by 5,000 cGy whole pelvic adjuvant radiation. Response to neoadjuvant chemotherapy was greater than 50% in 9 of 13 patients (69.4%), and complete response occurred in 2 of 13 patients (15.3%). When residual tumor was less than 2 cm after neoadjuvant chemotherapy, the overall survival was 58%, compared with 21% when it was greater than 2 cm (p <0.05). For patients with negative nodes, the overall survival was 72%, compared with 11% for those with positive nodes (p <0.01).

Sarcoma

A literature review by Rotmensch et al. (221) 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. The authors concluded that more rigid criteria for diagnosis were needed to allow evaluation of the various therapies.

Table 9.13 Classification of Cervical Sarcomas

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;38:456–460, with permission.

Sarcoma Botryoides

In 1988, Daya and Scully (222) 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 (222) 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 (223). 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 (224).

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 (225).

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 (226) reported that only 15 of 25 cases (55%) referred for consultation were correctly diagnosed by the referring pathologist. Komaki et al. (227) 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.**

Perrin et al. (228) 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 the 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** (228). 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

This slow-growing, locally aggressive, papillomatous lesion was first reported in the cervix in 1972 (229).

In a literature review in 1988, Crowther et al. (230) 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, 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. (230), 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. 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 of the 34 cases (62%), with 82% of relapses occurring within 8 months.

Schwade et al. (231) reported anaplastic transformation and rapid clinical deterioration following radiation therapy 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.

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. (232) in 1989 and Santosa et al. (233) 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 (232).

Metastatic Carcinoma

Metastasis of malignant epithelial tumors to the uterine cervix is a rare occurrence. Lemoine and Hall (234) 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

Part of "9 - Cervical Cancer "

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 (235), whereas others have included cases diagnosed within the first 12 months postpartum (236). 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 (235). In a literature review that included cases diagnosed up to 12 months postpartum, Hacker et al. (237) 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 Figure 9.16 .

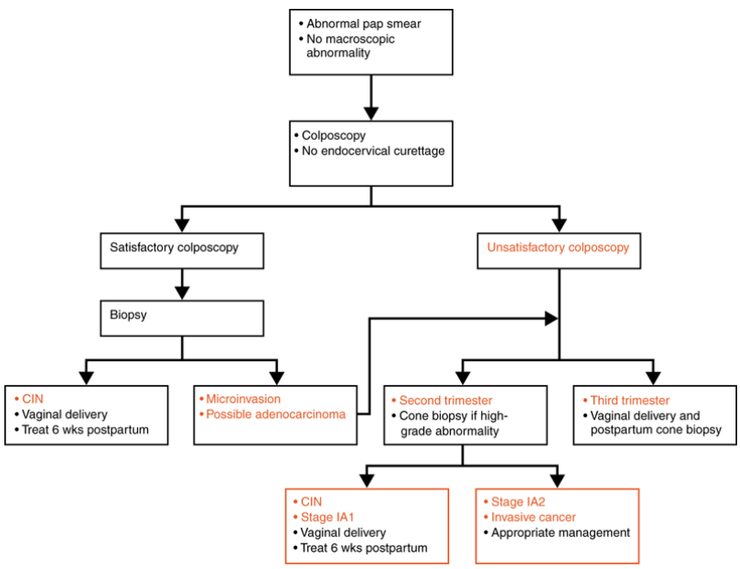

Figure 9.16 Algorithm for the management of an abnormal Pap smear in pregnancy. Consideration may be given to colposcopic observation without biopsy for low-grade lesions during pregnancy because of the risk of hemorrhage. CIN, cervical intraepithelial neoplasia.

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. (237) 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, which 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** (238).

Management

A suggested algorithm for the management of cervical cancer in pregnancy is shown in Figure 9.17 . **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.

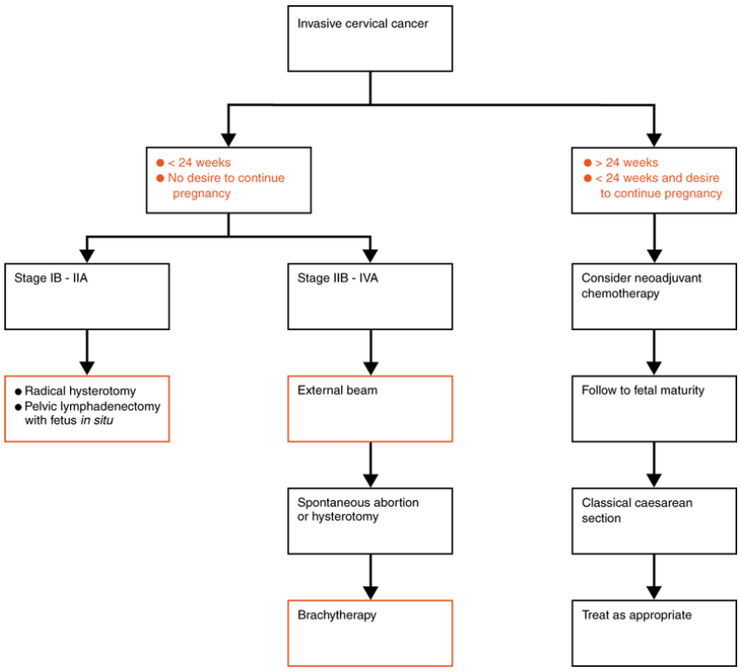

Figure 9.17 Algorithm for the management of invasive cervical cancer in pregnancy.

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 28 weeks, the recommendation should be to await fetal viability.**

The dilemma arises for patients diagnosed between 20 and 28 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 (235 ,239), 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** (240). 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 (237).

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 and await spontaneous abortion. 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. (237) 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** (241 ,242).

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 abdominal 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 adherent 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 (243).

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 perform radical surgery, as long as a chest radiograph and pelvic and abdominal CT scan show no evidence of metastatic disease, and there are no high-risk features in the hysterectomy specimen (i.e., positive surgical margins, tumor deeply infiltrating, or prominent vascular space invasion). In the presence of high-risk features, we prefer primary pelvic radiation.

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. (244) from the Mayo Clinic reported 27 patients undergoing reoperation. Ureterovaginal fistulas developed in 2 of the 27 cases (7%), but the 5-year absolute survival rate was 82%.

Hopkins et al. (245) 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.

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.**

Coexistent adnexal masses must be explored and a histologic diagnosis obtained. A laparoscopic approach may be appropriate if the risk of malignancy is low. 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.

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 (246), 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 Andersen (247) 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

Part of "9 - 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. With pelvic recurrence after primary surgery, radiation therapy is the treatment of first choice (248). Using radiation with concurrent chemotherapy (*5-fluorouracil* with or without *mitomycin C*), Thomas et al. reported 8 of 17 patients (47%) alive and disease free 21 to 58 months after therapy. The recurrent disease was present in the pelvis alone or pelvis and paraaortic nodes, and seven of the eight survivors had a component of pelvic sidewall disease (249).

Pulmonary metastases following primary radical hysterectomy have been reported in 6.4% of patients (24 of 377) with negative pelvic nodes and 11.3% of patients (16 of 142) with positive pelvic nodes (250). When the lung was the only site of recurrence, a 5-year survival of 46% was achieved by surgical resection followed by chemotherapy in 12 patients who initially had negative pelvic nodes and who now had one to three pulmonary metastases. Surgery was performed in the presence of bilateral metastases.

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.

Rutledge et al. (251) 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.

An Italian study of 34 patients reported an actuarial 5-year survival of 49% for the whole group, with major complications in 44% of cases and a fistula rate of 15 % (252). Patients with FIGO stage IB–IIA disease at primary diagnosis, no clinical parametrial involvement, and small (≤4 cm) tumor diameter at the time of recurrence had a survival of 65% (11 of 17).

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.

Chemotherapy

For recurrent or metastatic disease, the role of chemotherapy is merely palliative to relieve symptoms and prolong life. Complete responses are unusual and generally limited to patients with lung metastases.

Response rates for single agents are shown in Table 9.14 . ***Cisplatin* is the single most active agent for squamous cell carcinoma, and its preferred schedule of administration is 50 to 100 mg/m² every 3 weeks, intravenously** (253). Doses of *cisplatin* greater than 50 mg/m² have not been shown to improve response duration, progression- free interval, or survival (254 ,255). 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.

Table 9.14 Single Conventional Agent Chemotherapy in Cervical Carcinoma

Drugs	*Patients (Response/Treated)*	*Response (%)*
Alkylating agents		
Cyclophosphamide	36/271	13
Chlorambucil	11/44	25
Melphalan	4/20	20
Lomustine (CCNU)	3/63	5
Semustine (Methyl-CCNU)	7/94	7
Antimetabolites		
5-Fluorouracil	36/270	13
Methotrexate	12/73	16
6-Mercaptopurine	1/18	6
Hydroxyurea	0/27	0
Antibiotics		
Doxorubicin	32/172	19
Bleomycin	19/176	11
Mitomycin C	5/23	22
Porfiromycin	17/78	22
Plant alkaloids		
Vincristine	10/58	17
Vinblastine	2/20	10
Miscellaneous		
Cisplatin	238/968	25
Carboplatin	50/250	20
Ifosfamide	34/93	37
Hexamethylmelamine	11/50	22
Dacarbazine (DTIC)	3/12	25
Paclitaxel	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;3:129, with permission.

The GOG reported data on *cisplatin* and *paclitaxel* as first-line therapy for advanced and recurrent squamous cell carcinoma (255). Of 41 evaluable patients, 5 (12.2%) had a complete response and 14 (34.1%) had a partial response, for an **overall response rate of 46.3%.** The median progression-free interval was 5.4+ months (range of 0.3 to 22+ months), with a median survival of 10.0+ months (range 0.9 to 22.2 months). Response rates were higher in patients with disease in nonirradiated sites (70% vs. 23%; *p* = 0.008).

Fiorica et al. reported a phase II trial of ***cisplatin* and *topotecan*** as first-line therapy for patients with persistent or recurrent squamous and nonsquamous cervical cancer (256). There were 32 evaluable patients, and **the overall response rate was 28%** (9 of 32), with 3 complete responses (9%). Response rates were the same in irradiated and nonirradiated tissues. Median duration of response was 5 months (range 2 to 15+ months), and the median survival was 10 months.

The combination of ***cisplatin* with *ifosfamide* and *paclitaxel*** for the treatment of patients with metastatic and recurrent cervical cancer was reported in a phase II study of the Hellenic Cooperative Oncology Group (257). **The overall response rate was 46%** (26 of 57 patients), with a complete response rate of 19%. Median progression free interval was 8.3 months and median survival 18.6 months, respectively. Better responses were seen in patients with an excellent performance status, disease outside the irradiated field, and nonsquamous tumors.

The GOG confirmed the effectiveness of ***cisplatin* and *topotecan in a phase III study of 356 patients with stage IV, recurrent, or persistent cervical cancer*** (258). ***Patients were randomized to one of three treatment arms: single agent*** *cisplatin* 50 mg/m^2 every 3 weeks (n = 146), *topotecan* 0.75 mg/m^2 on days 1–3 plus *cisplatin* 50 mg/m^2 on day 1 every 3 weeks (n = 147), or *methotrexate* plus *vinblastine* plus *doxorubican* plus *cisplatin (MVAC)* every 4 weeks (n = 63). The *MVAC* arm was closed prematurely because of excessive toxicity. Nearly 80% of patients had received radiotherapy, and almost 60% had received *cisplatin*-based chemotherapy before randomization. **Response rates were achieved in 39 of 147 patients (27%) on the combination**, compared with 19 of 146 (13%) treated with single-agent *cisplatin* (*p* = 0.004). There were 14 complete responses with the combination (10%) compared with 4 (3%) with the single agent. Median progression-free survival for the combination was 4.6 months versus 2.9 months (*p* = 0.014), and median overall survival for the combination was 9.4 months versus 6.5 months (*p* = 0.017). The authors concluded that *topotecan* and *cisplatin* should now be considered the standard of care for patients with advanced or recurrent cervical cancer. Quality of life scores were similar in the two arms of the study.

In a phase II study of ***topotecan* and *paclitaxel*** for recurrent, persistent, or metastatic cervical cancer, a New York group reported **7 responses (54%) among 13 evaluable patients** (1 complete, 6 patients) (259). Progression-free and overall survivals were 3.8 and 8.6 months, respectively.

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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 2004, 40,320 new cases and 7,090 deaths were anticipated (1). It is predominantly a disease of affluent, obese, postmenopausal women of low parity. **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** (2).

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 (3).

Since the mid-1980s, careful surgical staging has more accurately defined patterns of spread and has allowed more individualization of treatment.

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 (3). The impact of these factors differs in various populations, and in northern Italy, established risk factors account for

only approximately 50% of the cases (4). Endometrial cancer may occasionally develop following radiation treatment for cervical cancer, in which case there is a preponderance of high-risk histological subtypes and consequently a poor prognosis (5).

Screening of Asymptomatic Women

Part of "10 - Uterine Cancer "

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 .

Table 10.1 Patients for Whom Screening for Endometrial Cancer Is Justified

1. Postmenopausal women on exogenous estrogens without progestins
2. Women from families with hereditary nonpolyposis colorectal cancer syndrome
3. Premenopausal women with anovulatory cycles, such as those with polycystic ovarian disease

Only approximately 50% of women with endometrial cancer have malignant cells on a Papanicolaou (Pap) smear (6). 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 (7).

The appearance of normal-appearing endometrial cells in cervical smears taken in the second half of the menstrual cycle or in postmenopausal women is controversial. Montz reported endometrial histology from 93 asymptomatic postmenopausal women receiving hormone replacement therapy with normal endometrial cells on a Pap smear. Eighteen patients (19%) had abnormalities identified, including seven endometrial polyps, seven cases of simple hyperplasia (one with atypia), three cases of complex hyperplasia (one with atypia), and one endometrial carcinoma (8). By contrast, workers at the University of Miami reported that the prevalence of normal endometrial cells in the Pap smears of women with endometrial carcinoma or hyperplasia did not differ significantly from that in women without these conditions (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).

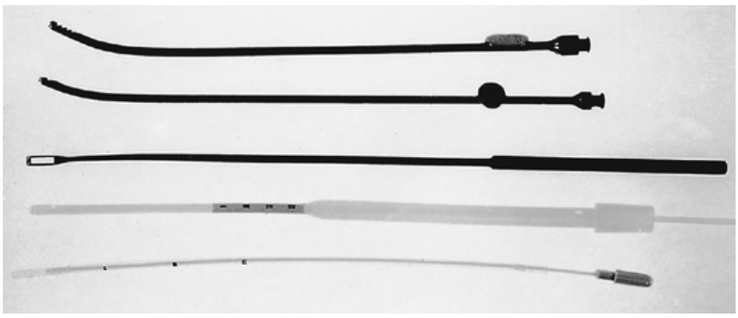

Figure 10.1 Devices used for sampling endometrium. From top to bottom: Serrated Novak, Novak, Kevorkian, Explora (Mylex), and Pipelle (Unimar).

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).

A meta-analysis reported that the Pipelle was the best device, with detection rates for endometrial cancer in postmenopausal and premenopausal women of 99.6% and 91%, respectively (13). The sensitivity for the detection of endometrial hyperplasia was 81%. The specificity for all devices was >98%.

In the 1990s, transvaginal ultrasonography, with or without color flow imaging, was investigated as a screening technique. Mean thickness of the endometrial strip was measured as 3.4 ± 1.2 mm in women with atrophic endometrium, 9.7 ± 2.5 mm in women with hyperplasia, and 18.2 ± 6.2 mm in women with endometrial cancer (14). 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). **A recent metaanalysis reported that 4% of endometrial cancers would be missed using transvaginal ultrasonography for the investigation of postmenopausal bleeding, with a false-positive rate as high as 50%** (16).

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). Routine ultrasonic surveillance of asymptomatic women on *tamoxifen* is not useful because of its low specificity and positive predictive value. Canadian workers studied 304 women on *tamoxifen* as therapy for breast cancer. Even using an endometrial thickness cutoff of 9 mm, the positive predictive value for the detection of endometrial cancer was only 1.4% (19).

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

Part of "10 - Uterine Cancer "

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.

Table 10.2 Patients in Whom a Diagnosis of Endometrial Cancer Should Be Excluded

1. All patients with postmenopausal bleeding
2. Postmenopausal women with a pyometra
3. Asymptomatic postmenopausal women with endometrial cells on a Papanicolaou smear, particularly if they are atypical
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 10.3 Etiology of Postmenopausal Bleeding

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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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 (20). 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 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 (21). There has been speculation that fluid hysteroscopy may facilitate the abdominal dissemenation of malignant cells, but there is no evidence that it has any impact on the disease-free survival (22 ,23).

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 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.

Table 10.4 Routine Preoperative Investigations for Early-Stage Endometrial Carcinoma

Full blood count
Serum creatinine and electrolytes
Liver function tests
Blood sugar
Urinalysis
Chest radiograph

Nonroutine tests are sometimes indicated, particularly for more advanced cases. **Cystoscopy** and **sigmoidoscopy** are necessary only if bladder or rectal involvement is suspected clinically. A colonoscopy 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 tomographic (CT) scan** may be helpful to determine the extent of metastatic disease in the following circumstances:

- Abnormal liver function test results
- Clinical hepatomegaly
- Palpable upper abdominal mass
- Palpable extrauterine pelvic disease
- Clinical ascites

However, it has limited usefulness in determining the depth of myometrial invasion or the presence of nodal disease (24 ,25). **Magnetic resonance imaging (MRI)** was evaluated as a tool for preoperative staging in a National Cancer Institute cooperative study (26). 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**.

Elevated CA 125 levels have been demonstrated to correlate with advanced stage of disease and positive lymph node status (27).

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.

Table 10.5 1971 FIGO Clinical Staging for Endometrial Carcinoma

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.

Several studies in the literature demonstrated significant understaging when patients were subjected to adequate surgical evaluation (28 ,29 ,30 ,31 ,32). Therefore, in 1988, the Cancer Committee of FIGO introduced a **surgical staging** system (Table 10.6).

Table 10.6 1988 FIGO Surgical Staging for Endometrial Carcinoma

Stage IA G123	Tumor limited to endometrium
Stage IB G123	Invasion to less than one-half the myometrium
Stage IC G123	Invasion to more than one-half the myometrium
Stage IIA G123	Endocervical glandular involvement only
Stage IIB G123	Cervical stromal invasion
Stage IIIA G123	Tumor invades serosa and/or adnexa, and/or positive peritoneal cytology
Stage IIIB G123	Vaginal metastases
Stage IIIC G123	Metastases to pelvic and/or paraaortic lymph nodes
Stage IVA G123	Tumor invasion of bladder and/or bowel mucosa
Stage IVB G123	Distant metastases including intraabdominal 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% to 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.	Notable 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 appreciated 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 should be noted.
3.	Ideally, width of the myometrium should be measured along with the width of tumor invasion.

FIGO, International Federation of Gynecology and Obstetrics.
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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:

- Many patients with endometrial carcinoma are treated in the community, where the necessary surgical skills may not be available to perform a lymphadenectomy.
- Many patients are obese and medically unwell, and not suitable for extensive nodal resections.
- 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/or paraaortic nodes, complete pelvic and/or paraaortic lymphadenectomy, or resection of any enlarged nodes only).

The distribution of endometrial carcinoma by surgical stage at initial presentation is shown in Table 10.7 .

Table 10.7 Carcinoma of the Endometrium: Distribution by Surgical Stage for Patients Treated in 1993 to 1995

Stage	*No.*	*Percent*
I	3,996	70.2
II	709	12.5
III	758	13.3
IV	231	4.0
Total	**5,694**	**100.0**

Reproduced from **Creasman W, Odicino F, Maisonneuve P, Benedet J, Shepherd J, Sideri M, et al.** Carcinoma of the corpus uteri: annual report on the results of treatment in gynecological cancer. *J Epidemiol Biostat* 2001;6:45–86, with permission.

Spread Patterns

Endometrial carcinoma spreads by the following routes:

- Direct extension to adjacent structures
- Transtubal passage of exfoliated cells
- Lymphatic dissemination
- 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 (33 ,34).

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 (35).

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 (36), 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 (37).

Hematogenous Spread

Hematogenous spread most commonly results in lung metastases, but liver, brain, bone, and other sites are involved less commonly.

Prognostic Variables

Part of "10 - Uterine Cancer "

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.

Table 10.8 Prognostic Variables in Endometrial Cancer Other than FIGO Stage

Age
Histologic type
Histologic grade
Nuclear grade
Myometrial invasion
Vascular space invasion
Tumor size
Peritoneal cytology
Hormone receptor status
DNA ploidy and other biological markers
Type of therapy (surgery vs. radiation)

FIGO, International Federation of Gynecology and Obstetrics.

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) (38). 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. Japanese workers have

reported menopausal status to be an independent prognostic variable for early endometrial cancer, but not for patients with advanced disease (39).

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 (40). 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.**

Zaino et al. (41) 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.** (41) **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 or lymph node metastasis (42 ,43 ,44 ,45). They disseminate widely, with a particular predilection for recurrence in the upper abdomen (46 ,47).

Sherman et al. (44) studied 13 pure uterine papillary serous carcinomas (UPSCs), 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. (44) 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. (48) 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 (44). **Vascular space invasion is more common in these lesions** (49). In a review of 181 patients with clear cell endometrial carcinoma treated between 1970 and 1992, Abeler et al. (50) 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 (51).

Squamous cell carcinomas of the endometrium are rare. In a review of the literature, Abeler and Kjorstad (52) 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 washings, local vault recurrence, and hematogenous spread** (45).

The GOG reported the surgical pathologic features of 621 patients with stage I endometrial carcinoma (32). The frequency of positive pelvic and paraaortic nodal metastases in relation to histologic grade and depth of myometrial invasion is shown in Tables 10.9 and 10.10 . When grade 1 carcinomas were confined to the inner third of the myometrium, the incidence of positive pelvic nodes was less than 3%, whereas when grade 3 lesions involved the outer third, the incidence of positive pelvic nodes was 34%. For aortic nodes, the corresponding figures were less than 1% and 23%, respectively.

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)	3/96 (3%)	7/131 (5%)	5/54 (9%)
Middle third (*N* = 115)	0/22 (0%)	6/69 (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, Homesley HD, Graham JE, Heller PB.** 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

	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, Homesley HD, Graham JE, Heller PB.** Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. *Cancer* 1987;60:2035–2041, with permission.

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 (53).

Table 10.11 Clinical Stage I Endometrial Carcinoma: Distant Metastases Versus Histologic Grade and Myometrial Invasiona

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

[a]Gynecologic Oncology Group data.

Reproduced from **DiSaia PJ, Creasman WT, Boronow RC, Blessing JA.** Risk factors and recurrent patterns in stage I endometrial cancer. *Am J Obstet Gynecol* 1985;151:1009–1015, with permission.

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 (54 ,55 ,56). Aalders et al. (54) 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. 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 (55).

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. (57) 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 (58), 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 (38).

Peritoneal Cytologic Results

The significance of a positive peritoneal cytologic result is controversial (59). 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** (32 ,59 ,60 ,61 ,62 ,63 ,64 ,65).

Table 10.12 Incidence of Positive Peritoneal Cytology in Clinical Stage I Endometrial Carcinoma

Author	*Cases*	*Positive Cytology*	*Percent*
Creasman et al., 1981 (60)	167	26	15.6
Creasman et al., 1987 (32)	621	76	12.2
Harouny et al., 1988 (61)	276	47	17.0
Hirai et al., 1989 (62)	173	25	14.4
Lurain et al., 1989 (63)	157	30	19.1
Takeshima et al., 2001 (64)	534	119	22.3
Total	**1,928**	**323**	**16.6**

The GOG study reported by Morrow et al. (66) 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, compared with 64 of 611 patients (10.5%) with negative washings. 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** (38).

Kadar et al. (65) studied 269 patients with clinical stage I and stage II endometrial cancer and 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.

In a review of the literature concerning patients with clinical stage I endometrial cancer, Milosevic et al. (67) 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 were 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.

Takeshima et al. (64) **studied 534 patients with endometrial cancer to assess the prognostic significance of positive peritoneal washings.** They concluded that they were not an independent negative prognostic indicator, but rather potentiated other prognostic indicators. **They felt that patients with positive peritoneal cytology in the absence of other adverse prognostic factors did not need upstaging.**

These same workers placed a tube in the abdomen to allow peritoneal irrigation in 50 patients with early-stage endometrial cancer and positive peritoneal smears detected at surgery (68). Washings were obtained via the tube 7 and 14 days postoperatively. Persistence of positive peritoneal cytology was observed in only 5 of 50 patients (10%), and four of these patients had adnexal metastases completely resected. They concluded that malignant cells found in the peritoneal cavity generally have a low malignant potential

and that only malignant cells from special cases, such as patients with adnexal metastases, may be capable of independent growth.

Hormone Receptor Status

In general, mean estrogen receptor (ER) and progesterone receptor (PR) levels are inversely proportional to histologic grade (69 ,70 ,71 ,72). 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** (69 ,70 ,71 ,73). Liao et al. (70) 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 (74).

Nuclear Grade

Nuclear grade is a significant prognostic indicator (74). Christopherson et al. (75) 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 (76).

Tumor Size

In an analysis of 142 patients with clinical stage I endometrial carcinoma, Schink et al. (77) 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 .

Table 10.13 Incidence of Lymph Node Metastasis in Endometrial Cancer by Tumor Size and Depth of Myometrial Invasion

	Tumor Size		
	≤2 cm	>2 cm	
Depth of Invasion	**Diameter (%)**	**Diameter (%)**	**Entire Surface (%)**
None	0/17 (0)	0/8 (0)	0/0 (0)
<1/2	0/27 (0)	5/41 (12)	2/9 (22)
≥1/2	2/9 (22)	6/23 (26)	4/8 (50)

Reproduced from **Schink JC, Lurain JR, Wallemark CB, Chmiel JS.** Tumor size in endometrial cancer: a prognostic factor for lymph node metastasis. *Obstet Gynecol* 1987;70:216–219, with permission.

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 (58 ,78 ,79). **The GOG estimated the relative risk to be 4.1 for disease-related death for patients with aneuploid tumors** (80). Mutations of the *p53* tumor suppressor gene and overexpression of the protooncogene HER-2/*neu* have been shown to have some prognostic significance (81), as has increasing expression of matrix metalloproteinases (MMPs) (82), nuclear

Bcl-2 expression (83), and Ki-67 expression (84). The clinical implications of these biologic markers are not yet clear.

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 (85 ,86 ,87). This appears to be related to the inability of radiation therapy effectively to eliminate disease in the myometrium (86 ,87). Grigsby et al. (86) 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 .

Table 10.14 Clinical Stage II Carcinoma of the Endometrium: Comparison of Treatment Methods

	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, Galakatos AE.** Stage II carcinoma of the endometrium: results of therapy and prognostic factors. *Int J Radiat Oncol Biol Phys* 1985; 11:1915–1921, with permission.

Endometrial Hyperplasia

Part of "10 - Uterine Cancer "

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 (88 ,89 ,90).
Since the mid-1980s, this continuum concept has been challenged. Independent studies by Kurman et al. (91) and Ferenczy et al. (92) have suggested that:

Endometrial hyperplasia and endometrial neoplasia are two biologically different diseases.

The only important distinguishing feature is the presence or absence of cytologic atypia.

Ferenczy et al. (92) 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. (91) 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 (93) 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%). The World Health Organization (WHO) classification of endometrial hyperplasia is shown in Table 10.15 .

Table 10.15 World Health Organization Classification of Endometrial Hyperplasia

Hyperplasia
Simple
Complex (adenomatous)
Atypical hyperplasia
Simple
Complex (atypical adenomatous)

Reproduced from **Scully RE, Bonfiglio TA, Kurman RJ, Silverberg SG, Wilkinson EJ.** Uterine corpus. In: *Histological typing of female genital tract tumors.* New York: Springer-Verlag, 1994:13–31.

Although the studies of Kurman and Ferenczy are important, they represent research work carried out by leading gynecological pathologists, examining a large number of cases over a relatively short period of time. In the everyday practice of pathology, the problem of differentiating the four subtypes of hyperplasia is encountered only sporadically, and diagnostic reproducibility is very unsatisfactory (94). **The data suggest that most women with endometrial hyperplasia respond to progestin therapy. Patients who do not respond are at a significantly increased risk of 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 Figure 10.2 .

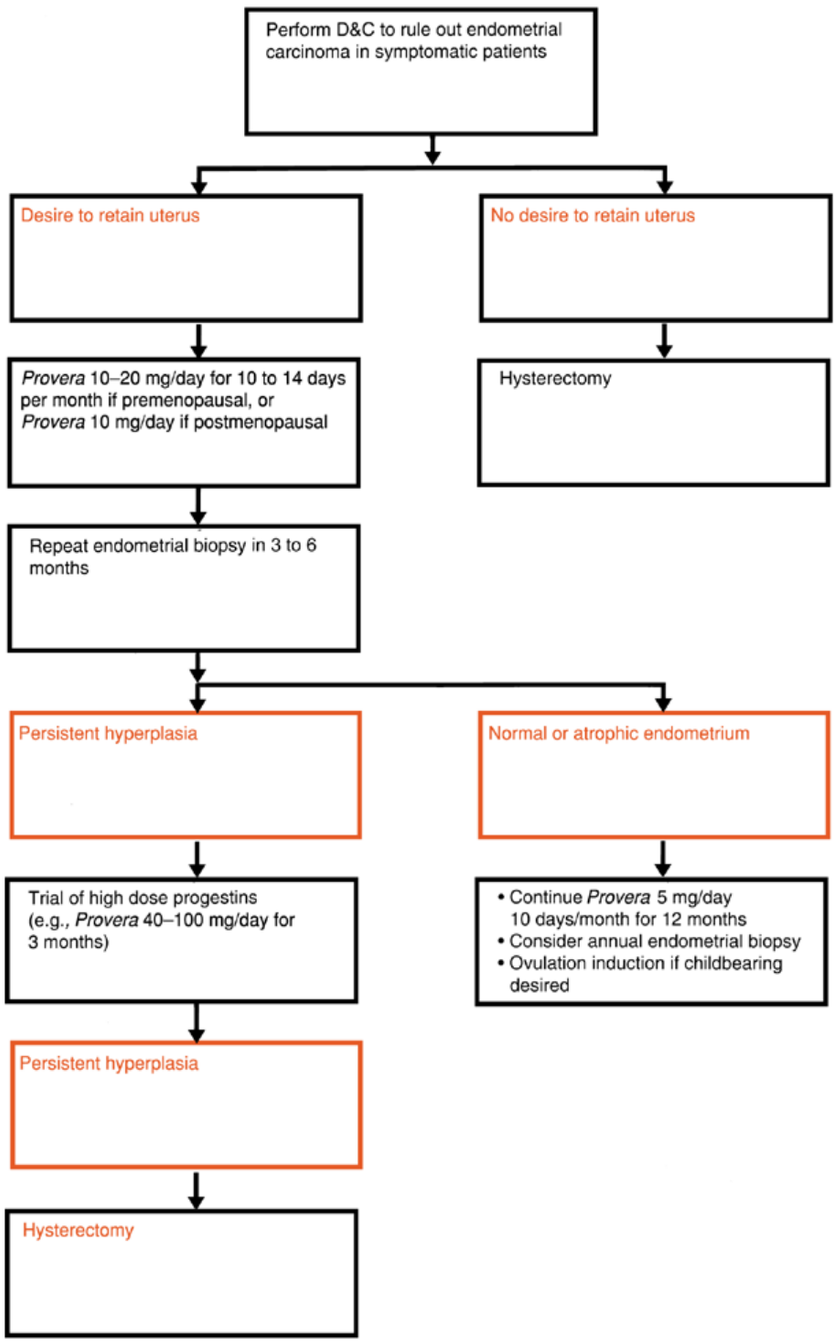

Figure 10.2 Management of endometrial hyperplasia.

Patients in whom endometrial carcinoma develops with concomitant hyperplasia are more likely to be younger, to have better-differentiated tumors of lower surgical stage, and to have a better 5-year survival rate. However, the presence of endometrial hyperplasia does not appear to be an independent prognostic factor in multivariate analysis (95).

Treatment of Endometrial Cancer

Part of "10 - Uterine 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, but both the GOG study (96) and the PORTEC trial (97) of surgery versus surgery plus adjuvant pelvic radiation for patients with intermediate to high-risk stage I endometrial cancer showed an improved disease-free survival rate for the radiation-treated group. Neither trial showed an improvement in the overall survival rate. 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.

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 (33 ,98). **False-positive rates of 40% to 50% have been reported for endocervical curettage** (98 ,99 ,100).

A false-negative endocervical curettage may also occur, so 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 .

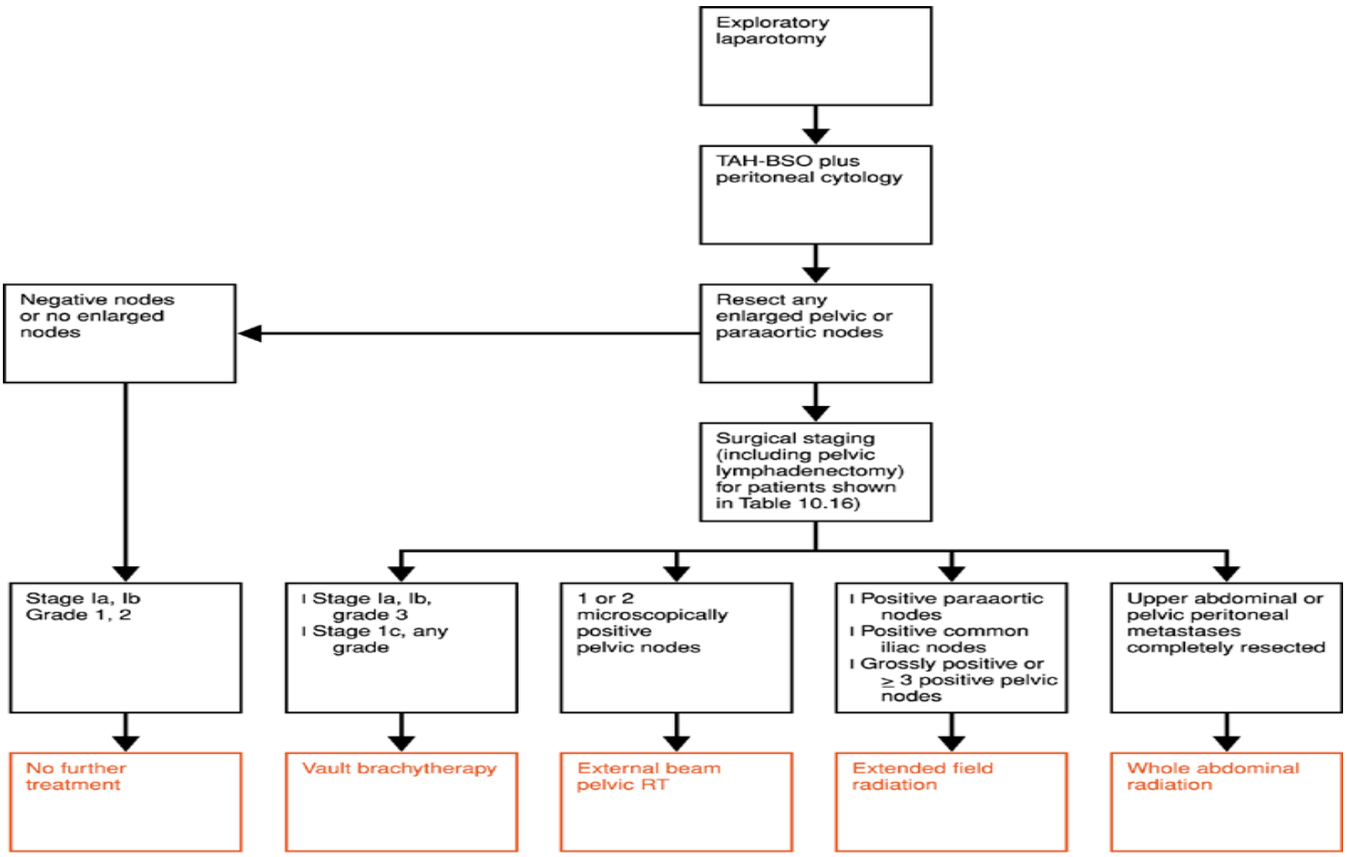

Figure 10.3 Management of patients with stage I and occult stage II endometrial carcinoma. TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy.

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 (101). Surgical staging, including lymphadenectomy, should be performed in those patients listed in Table 10.16 . The use of laparoscopically assisted vaginal hysterectomy is addressed in Chapter 20 .

Table 10.16 Endometrial Carcinoma Stages I and Occult II: Patients Requiring Surgical Staging

1.	Patients with grade 3 lesions
2.	Patients with grade 2 tumors >2 cm in diameter
3.	Patients with clear cell or papillary serous carcinomas
4.	Patients with greater than 50% of myometrial invasion
5.	Patients with cervical extension

Operative Technique

The laparotomy is best performed through a lower midline abdominal incision, particularly in the obese patient, 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 (102). **An alternative to this approach is to use a transverse, muscle-dividing incision (e.g., the Maylard or Cherney)**, as discussed in Chapter 19 .

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 biopsied.

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. With the retroperitoneum 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. 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.

The decision to undertake surgical staging is usually based on the histopathology from the uterine curettings, the gross findings on opening the uterus on the operating table, and possibly a frozen section of the resected uterus.

A relatively poor correlation has been reported between the grade of cancer on curettings or biopsy and the final grade in the resected uterus, presumably due to a sampling error in the diagnostic procedure. The poorest correlation is for grade 1 tumors, where 20% to 40% may be upgraded after evaluation of the hysterectomy specimen (103 ,104).

Our practice is to open the specimen on the operating table to determine the need for surgical staging in patients with grade 1 or 2 tumors (Figs. 10.4 and 10.5). All patients with grade 3 tumors (Fig. 10.6), serous papillary, or clear cell carcinoms are surgically staged.

Figure 10.4 A small fundal grade 1 endometrial carcinoma. This patient does not require surgical staging.

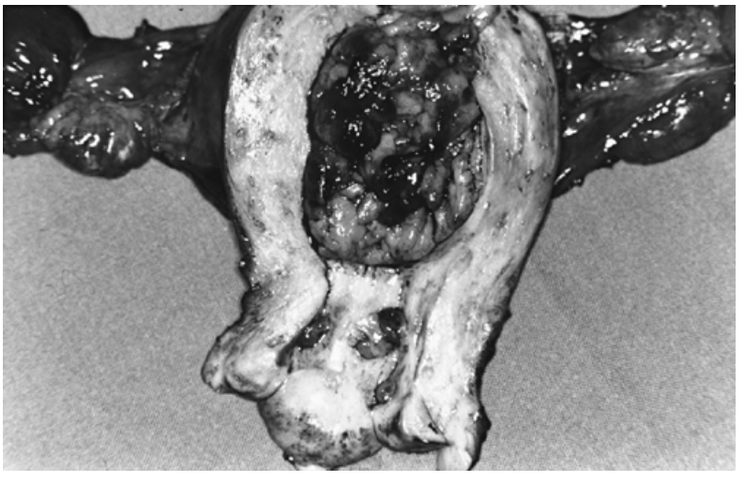

Figure 10.5 A grade 2 endometrial carcinoma occupying most of the corpus. A patient such as this should undergo surgical staging.

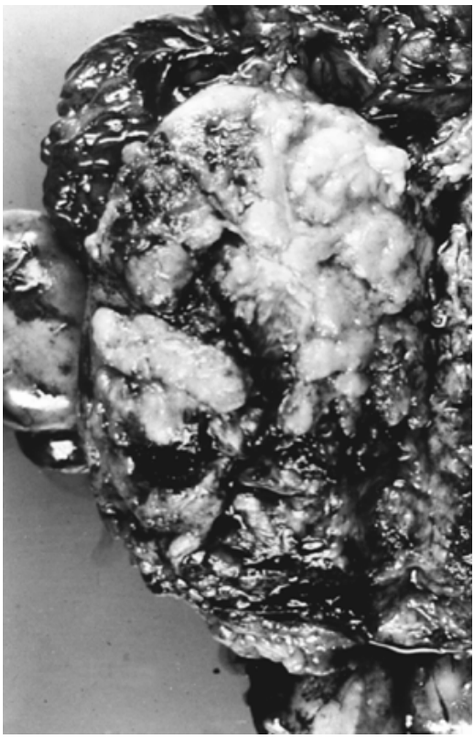

Figure 10.6 A patient with a grade 3 endometrial carcinoma invading the myometrium almost to the serosa and with extension to the upper endocervical canal.

For grade 1 tumors, gross examination fairly accurately predicts depth of myometrial invasion. In an analysis of 113 patients with surgical stage I endometrial carcinoma, Goff and Rice (105) 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%), but only 4 of 13 grade 3 lesions (30.8%). Franchi et al. also concluded that gross inspection of the opened uterus was a reliable and inexpensive approach after evaluating 403 endometrial cancers, and noting an accurate prediction of depth of invasion in 344 cases (85.3%) (106).

Tumor diameter should also be taken into account when determining the need for surgical staging, and we use this particularly for grade 2 lesions. Schink et al. (77) 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.

If doubt exists regarding the need for surgical staging, intraoperative frozen section can be obtained, but this is inaccurate in distinguishing superficial from deep myometrial invasion in 5% to 10% of cases (105 ,107). If the final histopathology is worse than was anticipated intraoperatively, the prognosis will not be impaired if external beam pelvic radiation is given on the basis of traditional indications, as long as any enlarged pelvic or paraaortic nodes have been resected as part of the standard management for all patients.

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 10.16 , and this is our current approach. Sampling will only lead to inaccurate information (108). The dissection should include 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.

It is not our current approach to perform full paraaortic lymphadenectomy on patients with endometrial carcinoma. The GOG data (66) would suggest that **patients with positive paraaortic nodes are likely to have:**

- **Grossly positive pelvic nodes**
- **Grossly positive adnexae, or**
- **Grade 2 or 3 lesions with outer-third myometrial invasion**

In addition to the lymphadenectomy, **an omental biopsy is also performed as part of the surgical staging**, because occult omental metastases may occur, particularly in patients with grade 3 tumors or deeply invasive lesions (109). A few authorities recommend lymphadenectomy for all patients with endometrial cancer (110 ,111), pointing to the very

small risk of lymph node metastases in patients with grade 1, superficially invasive tumors, and the low acute morbidity associated with the procedure. However, the **real morbidity associated with pelvic lymphadenectomy is lower limb lymphedema, which occurs in 20% of patients in our experience** (112). Lymphedema is a lifelong affliction, which is often complicated by recurrent episodes of cellulites. To avoid progressive deterioration of the condition, regular massage and use of surgical stockings are essential, and both become progressively more burdensome, particularly for elderly patients. In our opinion, primary prevention of lymphedema by selective use of pelvic lymphadenectomy is highly desirable.

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. (113) 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 (114), and this approach is clearly preferable to treatment of these patients with radiation alone. Laparoscopically assisted vaginal hysterectomy is increasingly being used for the management of endometrial cancer, and use of the laparoscope facilitates removal of the adnexae and the pelvic lymph nodes.

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 (115). 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 among 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** (116 ,117 ,118 ,119 ,120 ,121).

Adjuvant Radiation

With increasing emphasis on appropriate surgical staging, a significant number of patients are found to have such good-prognosis tumors that radiation can be safely eliminated. For those patients who require adjuvant radiation, the therapy can be better tailored to the needs of the individual patient. The proper role of adjuvant radiation for endometrial cancer awaits further randomized trials, but with our present state of knowledge, the options for postoperative management are as follows:

- Observation
- Vault brachytherapy
- External pelvic irradiation
- Extended-field irradiation
- Whole abdominal irradiation
- 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% (122). Elliot et al. (123) 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 (124). With follow-up of 68 to 92 months, the disease-free survival rate was 93% (596 of 641). Fanning and colleagues (125) 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 (124 ,126).

Vaginal Brachytherapy

Vaginal brachytherapy significantly reduces the incidence of vault recurrence. With high dose-rate therapy, treatment can be accomplished as an outpatient, and the morbidity is low. When performed on patients who have negative lymph nodes after surgical staging, it is a cost-effective method of treatment (127).

Mohan et al. (116) 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 (117). 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.

Workers at Roswell Park reported 23 patients with stage I disease and either grade 3 histology or greater than 50% myometrial invasion who were treated with surgical staging followed by vaginal brachytherapy. With a median follow-up of 25 months, there were no recurrences (120).

The exact place of vaginal brachytherapy must await randomized, controlled trials, but the available evidence would support vault brachytherapy without teletherapy for patients with negative nodes after at least a complete pelvic lymphadenectomy.

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 level.

The GOG reported results of a randomized study of adjuvant pelvic radiation after complete surgical staging for patients with intermediate-risk endometrial carcinoma (96). 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.

A European randomized trial (the PORTEC Study) of surgery and postoperative external pelvic radiation (46 Gy) **versus surgery alone for patients with stage I endometrial cancer was published in 2000** (97). Eligible patients were those with stage IC, grade 1; stage IB or IC, grade 2; or stage IB, grade 3 disease. Patients with serous papillary or clear cell carcinoma were also eligible. Surgery consisted of total abdominal hysterectomy and bilateral salpingo-oophorectomy, without lymphadenectomy. A total of 715 patients from 19 radiation oncology centers were randomized.

Actuarial 5-year overall survival rates were similar in the two groups: 81% (radiotherapy) and 85% (controls) (p = 0.31). Endometrial cancer-related death rates were 9% in the radiotherapy group and 6% in the control group (p = 0.37). Treatment-related complications occurred in 25% of the radiotherapy patients and in 6% of the controls (p = 0.0001). Grade 3–4 complications were seen in eight patients, of which seven were in the radiotherapy group (2%). **Two-year survival after vaginal recurrence was 79%, in contrast to 21% after pelvic recurrence or distant metastases.** Survival after relapse was significantly better (p = 0.02) for patients in the control group. After multivariate analysis, investigators concluded that postoperative radiotherapy was not indicated in patients with stage I endometrial cancer younger than 60 years and in patients with grade 2 tumors with superficial invasion.

External irradiation appears to be as effective as vaginal brachytherapy 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 (128). Weiss and colleagues treated 61 women with stage IC endometrial cancer with postoperative pelvic radiation without vaginal brachytherapy. No patient developed a vaginal recurrence (129).

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 (130). Workers in Oklahoma reported that paraaortic lymph node metastases were associated with an increasing number of pelvic lymph node metastases and with bilateral pelvic nodal involvement (131). A Mayo Clinic report indicated that paraaortic nodal involvement was particularly associated with cervical involvement or positive obturator lymph nodes (132).

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 (133). Limited information is available on the outcome of 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 (134). **Our current indications for extended-field radiation are patients with:**

- **Biopsy-proven paraaortic nodal metastasis**
- **Positive common iliac nodes**
- **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. (134) 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. (135) treated 27 patients with open-field external-beam abdominal irradiation. Nine patients had positive peritoneal cytologic findings only. Patients with spread to the adnexae, 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 adnexae. Similar results have been reported with the moving-strip technique (136).

Martinez and colleagues recently reported 10-year survival data on a nonrandomized, prospective trial of whole abdominal radiation with a pelvic boost in patients with stage I–III endometrial cancer who were considered at high risk for intraabdominopelvic recurrence (137). There were 132 patients treated between 1981 and 2001, including 89 (68%) with stage III disease and 58 (45%) with serous papillary or clear cell histology. The 5- and 10-year cause-specific survival for patients with serous papillary/clear cell tumors was 80% and 74%, respectively. Chronic grade 3/4 gastrointestinal toxicity was seen in 14% of patients, and 2% developed grade 3 renal toxicity.

Our current indications for whole abdominal radiation are:

- **Patients with endometrioid carcinomas and omental, adnexal, or peritoneal metastases that have been completely excised**
- **Patients with serous papillary or clear cell carcinomas with positive peritoneal washings**

Intraperitoneal ^{32}P

Investigators at Duke University have reported favorable results with intraperitoneal ^{32}P for patients with malignant peritoneal cytologic findings (138). 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 (138). Other problems associated with ^{32}P include the uneven distribution of fluid commonly present and the potential for bowel injury from “hot spots.”

After reviewing the literature, Milosevic et al. (67) 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 (139 ,140). 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) (141). 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 (142). Patients received *MPA* (*medroxyprogesterone acetate*) 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 more likely to have endometrial cancer, whereas the younger woman with a bulky cervix and a normal corpus is more likely to have cervical cancer.

The lack of randomized, prospective studies precludes dogmatic statements about the optimal mode of therapy, but modern management favors primary surgery, with adjuvant radiation tailored to the surgical findings.

A large retrospective Italian study reported on 203 patients who underwent primary surgery for stage II endometrial cancer (143). Simple hysterectomy was performed in 135 patients (66%) and radical hysterectomy in 68 (34%). Adjuvant radiation was given to 66 of 111 patients (59%) with stage IIA disease and to 67 of 92 patients (73%) with stage IIB. Survival rates were 79% in the simple hysterectomy group and 94% in the radical hysterectomy group at 5 years, and 74% and 94% at 10 years, respectively (p <0.05). Although adjuvant radiation reduced locoregional recurrence, there was no significant difference in survival.

Surveillance, Epidemology and End Results (SEER) data were used in the United States to determine whether primary treatment with simple or radical hysterectomy, with or without adjuvant radiation, altered disease-related survival for patients with FIGO stage II endometrial cancer (144). Cases diagnosed between 1988 and 1994 were analyzed, and included 555 patients (60%) undergoing simple hysterectomy and 377 patients (40%) undergoing radical hysterectomy. The 5-year cumulative survival rates for patients who received surgery alone was 84.4% with simple hysterectomy and 93% with radical hysterectomy (p <0.05). There was no significant survival difference for adjuvant radiation versus no radiation in either arm. **They concluded that radical hysterectomy was associated with better survival when compared with simple hysterectomy for FIGO stage II corpus adenocarcinoma.**

Following a study of 82 patients with stage II endometrial cancer, workers at the Mayo Clinic also concluded that radical hysterectomy and pelvic lymphadenectomy gave excellent results in patients with negative nodes, with no benefit from the addition of adjuvant radiation (145).

Our current approach to patients with stage II endometrial carcinoma is to perform primary surgery and surgical staging, provided the patient is medically fit. The surgery is as follows:

- Modified (type II) radical hysterectomy
- Bilateral salpingo-oophorectomy
- Peritoneal washings for cytologic study
- Pelvic lymphadenectomy to the aortic bifurcation
- Resection of grossly enlarged paraaortic nodes
- Omental biopsy
- Biopsy of any suspicious peritoneal nodules

Postoperatively, adjuvant radiation is individualized. If lymph nodes are negative, no adjuvant radiation is given. Patients with one (possibly two) nodal micrometastases in the pelvis receive external pelvic radiation, whereas those with multiple positive pelvic nodes or grossly positive pelvic nodes are given extended-field external-beam therapy. Patients with completely resected upper abdominal disease receive whole-abdomen radiation.

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 (36). 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. (146) 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. (147) 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 clinical 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, with or without vaginal brachytherapy.

Surgical eradication of all macroscopic tumor is of major prognostic importance for all patients with clinical stage III disease (146). 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 for cytological examination, paraaortic lymph node sampling, and biopsy of the omentum.

Genest et al. (148) reported that the site of first recurrence was limited to the abdominal cavity in 79% (23 of 29) of their patients in whom treatment failed, suggesting a role for whole-abdominal radiation in stage III endometrial cancer, particularly in patients with positive peritoneal washings or demonstrable micrometastases to the upper abdomen. However, Mackillop and Pringle (36) 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.

Surgical FIGO Stage IIIB

The only study specifically of patients with surgical FIGO stage IIIB endometrial cancer was reported by Nicklin and Petersen in 2000 (149). Isolated vaginal metastases are very uncommon, and only 14 patients (0.7%) could be identified out of 1,940 patients with endometrial cancer treated at the Queensland Centre for Gynaecological Cancer from January 1982 to December 1996. None of the 14 patients in the study had pelvic or paraaortic lymph node dissection, so many may have been upstaged to IIIC had this been done. **Survival was similar to patients with stage IIIC disease**, and the authors concluded that a case could be made to abolish this substage and include these patients with those currently classified as having stage IIIC disease.

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. (150) from the Norwegian Radium Hospital, the lung was the main site of extrapelvic spread, with 36% of patients having lung metastases. **Treatment of stage IV disease must be individualized but usually involves a combination of surgery, radiation therapy, and/or chemotherapy**

There may be a role for cytoreductive surgery, although data are limited to small, retrospective studies. The largest series, from workers in Baltimore, reported results from 65 patients with stage IVB endometrial cancer. Optimal cytoreduction, defined as residual tumor ≤1 cm diameter, was accomplished in 36 patients (55.4%), whereas 29 patients (44.6%) underwent suboptimal resection (151). Median survival was 34 months in the optimal group compared with 11 months in the suboptimal group <0.0001). Patients with no macroscopic residual disease had a median survival of 40.6 months.

In making a decision to undertake primary surgery in a patient with advanced endometrial cancer, both the location and the extent of metastatic disease must be taken in account. In the study by Goff and colleagues, factors that influenced a decision not to undertake cytoreductive surgery included the presence of lung metastases, bladder invasion, clinical involvement of the pelvic sidewall, bone metastases, and liver metastases (152).

A major objective of therapy should be to try to achieve local disease control in the pelvis and to palliate bleeding, discharge, pain, and fistula formation. 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 the appropriate investigation of any abnormal vaginal bleeding preoperatively and by routinely opening the excised uterus in the operating room, so that the adnexae 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:

- A chest radiograph and a CT scan of the pelvis and abdomen
- A serum CA125 measurement

If there is any suggestion of metastatic disease on the chest radiograph, this should be investigated primarily. If the CA125 level 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:

- 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).
- All other lesions: further laparotomy with removal of adnexae, surgical staging, and appropriate postoperative radiation.

Synchronous Primary Tumors in the Endometrium and Ovary

This is an uncommon but well-recognized occurrence. In at least half of the cases, both endometrial and ovarian tumors are of the endometrioid type, and distinguishing between primary and metastatic lesions may be difficult.

Israeli workers reported that 62% of cases with simultaneous tumors of the endometrium and ovary could be differentiated from metastatic tumors by distinct immunohistochemical expression of ER and PR ($p = 0.0006$), and 32% could be differentiated by distinct immunostaining for bcl-2 ($p = 0.03$) (153).

The Gynecologic Oncology Group reported 74 cases, 23 (31%) of whom had microscopic spread of tumor in the pelvis or abdomen (154). Sixty-four (86%) patients had endometrioid tumors in both sites, and endometriosis was found in the ovary in 23 patients (31%). Patients with tumor confined to the uterus and ovary had a 10% probability of recurrence within 5 years, compared with a 27% probability for those with metastatic disease ($p = 0.006$). Similarly, patients with no more than grade I disease at either site had an 8% probability of recurrence within 5 years, compared with a 22 % probability for those with a higher grade in either the ovary or the endometrium ($p = 0.05$).

Treatment should be determined on the premise that each represents a primary lesion, and many require surgery only, without adjuvant chemotherapy or radiation (155).

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 (156), although Zuckerman et al. (157) 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** (158 ,159 ,160). Gotlieb and colleagues reported a complete response in all 13 patients treated, within a mean period of 3.5 months. Six patients (46%) recurred 19 to 358 months later, four of whom responded to a second course of progestins (159). Taiwanese workers reported complete remission in eight of nine patients (89%) using a combination of *megestrol acetate* and *tamoxifen* (160).

One patient failed to respond but achieved complete remission after a change from *tamoxifen* to *gonadotropin-releasing hormone analog (GnRHa).* Four (50%) of the responders later developed recurrent endometrial cancer.

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 younger patients (17.7%) had secondary ovarian involvement (161). **Therefore, adequate imaging of the ovaries is important before any decision is made regarding conservative management.**

In view of the high incidence of recurrent disease in the endometrium, it is reasonable to recommend hysterectomy once childbearing has been completed to avoid the need for ongoing hormonal manipulation and surveillance with transvaginal ultrasonography. Given the significant incidence of ovarian involvement (161) and the efficacy of modern hormone replacement therapy, there seems little justification for ovarian preservation, 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 (162) 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. (163) reviewed the literature and found 17 reported cases since 1927, to which they added five 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 were 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 these cases were considered to be synchronous endometrioid carcinomas of the endometrium and ovary.

Most patients underwent total abdominal hysterectomy, and prognosis has been excellent. 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, 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 24), approximately 24% of patients treated for endometrial cancer die within 5 years (Table 10.17). **Serum CA125 levels are usually elevated in patients with recurrent disease, particularly if the recurrence is intraperitoneal** (164). Pastner et al. (165) 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.

Table 10.17 Carcinoma of the Corpus Uteri in Patients Treated in 1993 to 1995: Survival Rates by FIGO Surgical Stage (N =5,694)

		Overall Survival (%)		
Strata	*Patients*	*1 yr*	*3 yr*	*5 yr*
IA	975	98.1	92.4	88.9
IB	2,035	98.1	93.5	90.0
IC	986	95.9	88.0	80.7
IIA	342	94.8	83.1	79.9
IIB	367	95.4	81.1	72.3
IIIA	457	88.4	71.0	63.4
IIIB	101	76.8	48.0	38.8
IIIC	200	86.5	63.4	51.1
IVA	57	50.5	27.9	19.9
IVB	174	48.0	21.8	17.2

Modified from **Creasman W, Odicino F, Maisonneuve P, Benedet J, Shepherd J, Sideri M, et al.** Carcinoma of the corpus uteri: annual report on the results of treatment in gynecological cancer. *J Epidemiol Biostat* 2001;6:45–86, with permission.

The large series of 379 patients with recurrent disease reported by Aalders et al. (166) 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.

Isolated vaginal metastases are the most amenable to therapy with curative intent. 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 (124). Similarly, in the PORTEC trial (97), the 2-year survival after vaginal recurrence was 79%, and was significantly better in the group that did not receive pelvic radiation.

Phillips et al. (167) 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 an isolated vaginal recurrence, 39 tumors (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 pelvic radiation plus some type of brachytherapy may be appropriate. **For bulky lesions (≥4 cm diameter), surgical resection before radiation may improve local control. Laparotomy has the advantage of allowing a thorough exploration of the pelvis and abdomen to exclude other metastatic foci.**

Hormone Therapy

Progestational agents have been used successfully as treatment for patients with advanced or recurrent endometrial cancer. Although parenteral administration has been used, oral administration is equally effective (168 ,169).

The Gynecologic Oncology Group randomized 299 patients with advanced or recurrent endometrial cancer to receive either 200 mg per day or 1,000 mg per day of oral *medroxyprogesterone acetate (MPA)* (170). Among 145 patients receiving the low-dose regimen,

there were 25 complete (17%) and 11 partial (8%) responses, for an overall response rate of 25%. For the 154 patients receiving the high-dose regimen, there were 14 complete (9%) and 10 partial (6%) responses, for an overall response rate of 15%. Median survival durations were 11.1 months and 7.0 months, respectively, for the low-dose and high-dose regimens.

The GOG concluded that 200 mg per day of *MPA* **was a reasonable initial approach to the treatment of advanced or recurrent endometrial cancer**, particularly for patients whose tumors were well differentiated or progesterone receptor (PR)-positive. Patients with poorly differentiated or PR-negative tumors had only an 8% to 9% response rate (170).

If an objective response is obtained, the progestogen should be continued indefinitely. Some responses may be sustained for several years. Side effects from progestins are usually minor and include weight gain, edema, thrombophlebitis, headache, and occasionally hypertension.

The nonsteroidal antiestrogen *tamoxifen* **has also been used to treat patients with recurrent endometrial cancer**. It is a first-generation selective estrogen response modulator (SERM) and 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 (171 ,172). *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. (173) reported a pooled response rate of 22% for single-agent *tamoxifen.*

The third-generation SERM *arzoxifene* has been evaluated in 29 patients with advanced or recurrent endometrial cancer (174). The drug was administered orally in a dose of 20 mg per day, and toxicity was minimal. There were nine responses (31%) and a median duration of response of 13.9 months, the longest reported in a phase II trial of this patient population. *Arzoxifene* **warrants further evaluation for patients with advanced and recurrent endometrial cancer.**

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 (175). 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% (176), 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** (177).

The GOG has reported *paclitaxel* **to have a 35% response rate in previously untreated women** (178) and a 27% response rate in previously treated patients. In the latter group, the median duration of response was 4.2 months, and the median overall survival was 10.3 months (179). *Topotectan* was also studied as a second-line agent by the GOG, but the response rate was only 9% (180).

Recently, the GOG reported the results of a randomized, phase III trial of whole abdominal radiation versus *doxorubicin–cisplatin* **in advanced endometrial cancer** (181).

To be eligible, the maximum size of residual disease had to be ≤ 2 cm diameter, and there were 388 evaluable patients. **There was a significantly better progression-free and overall survival in the chemotherapy arm**, but approximately 55% of all patients recurred.

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 (182). However, Rodriguez et al. (183) 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).

Our experience at the Royal Hospital for Women would justify further study of platinum-based chemotherapy in patients with serous endometrial carcinomas (184). All six patients with stages I or II disease given adjuvant platinum-based chemotherapy were tumor-free with a mean follow-up of 31.6 months (range 12 to 68 months), and 4 of 12 (33%) with stage III–IV disease remained tumor-free with a mean follow-up of 22.5 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 quality of life issues are important.** Although it has been frequently stated that estrogen replacement therapy is contraindicated in patients who have had endometrial cancer, Creasman et al. (185) 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 patients daily conjugated estrogens *(Premarin)* 0.625 mg.

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* (186). Results for 1993 through 1995 are shown in Tables 10.17 and 10.18 . 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.**

Table 10.18 Carcinoma of the Corpus Uteri in Patients Treated in 1993 to 1995: Survival Rates for Surgical Stages I and II by Histologic Grade

	Overall 5-Year Survival Rates (%)			
	Stage I		*Stage II*	
Grade	*No.*	*Percent*	*No.*	*Percent*
1	1,735	92.0	233	85.7
2	1,207	86.9	265	76.3
3	448	74.0	120	58.1

Modified from **Creasman W, Odocino F, Maisonneuve P, Benedet J, Shepherd J, Sideri M, et al.** Carcinoma of the corpus uteri: annual report on the results of treatment in gynecological cancer. *J Epidemiol Biostat* 2001;6:45–86, with permission.

Survival in relation to grade and depth of myometrial invasion for stage I disease is shown in Table 10.19 . The poor prognosis associated with papillary serous and clear cell carcinoma has been discussed earlier (see Table 10.20).

Table 10.19 Carcinoma of the Corpus Uteri in Patients Treated in 1993 to 1995: Survival Rates in Stage I by Surgical Stage and Grade of Differentiation (N = 3,390)

		Overall Survival Rates (%)		
Strata	*Patients*	*1 yr*	*3 yr*	*5 yr*
IA G1	520	98.2	94.5	92.8
IB G1	618	97.7	92.4	89.8
IC G1	342	97.3	92.6	88.7
IA G2	216	99.1	94.5	89.7
IB G2	873	98.7	95.9	92.8
IC G2	373	97.0	90.0	80.8
IA G3	71	97.2	78.3	68.6
IB G3	210	96.6	89.3	84.2
IC G3	167	90.5	74.8	62.9

Modified from **Creasman W, Odicino F, Maisonneuve P, Benedet J, Shepherd J, Sideri M, et al.** Carcinoma of the corpus uteri: annual report on the results of treatment in gynecological cancer. *J Epidemiol Biostat* 2001;6:45–86, with permission.

Table 10.20 Carcinoma of the Corpus Uteri in Patients Treated in 1993 to 1995: Survival Rates by Histologic Type (N = 5,914)

Histologic Type	*No.*	*Five-Year Survival Rate (%)*
Endometrioid	4,661	79.7
Adenosquamous	415	79.1
Mucinous	67	72.9
Clear cell	140	63.2
Papillary serous	305	54.3

Modified from **Creasman W, Odicino F, Maisonneuve P, Benedet J, Shepherd J, Sideri M, et al.** Carcinoma of the corpus uteri: annual report on the results of treatment in gynecological cancer. *J Epidemiol Biostat* 2001;6:45–86, with permission.

Uterine Sarcomas

Part of "10 - Uterine Cancer "

Uterine sarcomas are rare mesodermal tumors that account for approximately 3% of uterine cancers (187). 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 (188). Zelmanowicz et al. (189) reported that endometrial carcinomas and malignant mixed müllerian tumors have a similar risk factor profile, which is compatible with the hypothesis that the pathogenesis of these two tumors is similar.

Criteria for the histopathological classification of sarcomas has been changing, and such lesions should be reviewed by an expert gynecologic pathologist. **Much less emphasis is placed on mitotic counts than was previously the case.**

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:

- **Pure**, in which only malignant mesodermal elements are present (e.g., leiomyosarcoma, endometrial stromal sarcomas)
- **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.

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.

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) (190). **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 (191). 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 (192). 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 (193). 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 are divided into two major categories: **benign endometrial stromal nodules** and **endometrial stromal sarcomas**. The division of endometrial stromal sarcomas into low-grade and high-grade categories has fallen out of favor, and **the term endometrial stromal sarcoma is now considered best restricted to neoplasms that were formally referred to as "low-grade" endometrial stromal sarcomas** (194). High-grade tumors without recognizable evidence of a definite endometrial stromal phenotype are now termed endometrial sarcomas (195). Mitotic counts are no longer used to differentiate

high-grade from low-grade lesions. **Endometrial stromal sarcomas constitute 15% to 25% of uterine sarcomas** (187).

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. Abnormal vaginal bleeding is the most common presenting symptom, and abdominal pain and uterine enlargement may occur (195 ,196 ,197). **Although they may be intramural, most endometrial stromal sarcomas involve the endometrium, and uterine curettage usually leads to diagnosis.**

Endometrial stromal sarcomas have infiltrating margins and demonstrate venous and lymphatic invasion. Although their behavior is relatively indolent, late recurrences and distant metastases may occur (182 ,195 ,196). **The most frequent sites of recurrence for patients with stage I disease are the pelvis and abdomen** (198). Prolonged survival and even cure are not uncommon after surgical resection of recurrent or metastatic lesions.

Endometrial sarcomas behave aggressively compared with endometrial stromal sarcomas. In the original series reported by Evans, six of the seven patients died of disease between 10 and 34 months after diagnosis (195).

Mixed Mesodermal Tumors

Mixed mesodermal tumors usually occur in an older age group, most patients being postmenopausal (199). 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** (187). 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 (200). Lissoni et al. (201) 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 high-power field (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 of some uterine sarcomas, as performed for high-risk endometrial carcinomas, gives prognostic information and may allow some individualization of adjuvant radiation therapy. The Gynecologic Oncology Group reported a clinicopathologic study of 301 **mixed mesodermal tumors** in 1993 (202). Adnexal metastases were present in 12% of patients, lymph node metastases in 18%, and positive peritoneal washings in 21%. No omental biopsies were taken.

A Californian study of 62 patients with carcinosarcoma apparently confined to the uterus reported occult metastases in 38 patients (61%) (203). Adnexal metastases were present in 23% of patients, positive pelvic nodes in 31%, positive paraaortic nodes in 6%, omental involvement in 13%, and positive peritoneal washings in 29%.

For **leiomyosarcomas**, the GOG study of 59 patients reported positive lymph nodes in only 3.5% of patients, positive washings in only 5.3%, and adnexal involvement in only 3.4%. For 71 patients with leiomyosarcoma confined to the uterus and/or cervix, the Memorial Sloan-Kettering group reported ovarian metastases in two patients (2.8%) and lymph node metastases in none. Three of 37 patients (8.1%) had positive nodes, but all had gross extrauterine disease and clinically suspicious nodes. **Spread of leiomyosarcomas is mainly hematogenous, so surgical staging appears to be of less importance for these tumors**.

Radiation Therapy

Although the value of adjuvant radiation is controversial (204), most authors suggest that **it improves tumor control in the pelvis without influencing final outcome** (205 ,206). 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 (207). A retrospective review of 43 patients with mixed müllerian tumors from Vanderbilt University revealed a significant survival advantage for patients with surgical stage I or II disease treated with surgery plus pelvic irradiation (208). This report noted that 29% of patients with clinical stage I or II disease were upstaged at laparotomy.

Our experience at the Royal Hospital for Women suggests that very good survival rates can be obtained in patients with mixed mesodermal tumors if they are subjected to surgical staging, postoperative radiation based on the surgical findings, and adjuvant chemotherapy with *cisplatin* and *epirubicin* (209).

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** (199).

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 (210). 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 (211).

Ifosfamide **also has good activity against mixed mesodermal sarcomas**, the GOG demonstrating 9 responses among 28 patients (31.2%) (212). A small improvement in progression-free survival was noted with the addition of *cisplatin* to *ifosphamide* in a phase III GOG trial, but the added toxicity may not justify use of this combination (213). For leiomyosarcomas, the response rate for *ifosfamide* was 17.2% (6 of 35), and all responses were partial (214).

The GOG evaluated *paclitaxel* in 44 patients with carcinosarcoma of the uterus. Four patients (9.1%) had a complete response, and four (9.1%) had a partial response (215). For leiomyosarcomas, the GOG reported three complete responses to *paclitaxel* (9%), whereas eight patients (24%) had stable disease for at least two courses of therapy (216).

Gemcitabine demonstrates activity in patients with persistent or recurrent leiomyosarcomas, the GOG reporting one of 44 patients (2.3%) achieving a complete response and eight (18.2%) a partial response in a phase II trial (217).

Peters et al. (218) treated 11 patients with advanced or recurrent uterine stromal sarcomas or mixed mesodermal tumors with *cisplatin* 100 mg/m² and *doxorubicin* 40 to 60 mg/m² 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. For advanced leiomyosarcomas, the GOG demonstrated a complete response rate of 9% (3 of 35) and a partial response rate of 14% (5 of 35) for the combination of *mitomycin, doxorubicin*, and *cisplatin* (219).

Adjuvant Chemotherapy for Early Stage Disease

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 (220).

A recent study of 27 patients from the Massachusetts General Hospital reported that use of adjuvant chemotherapy after optimal surgery did not decrease the rate of recurrence for patients with leiomyosarcomas (221).

In a nonrandomized study, Peters et al. (218) 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 experience is similar to our own data from the Royal Hospital for Women (209) with *cisplatin* **and** *epirubicin, and suggests that this combination* **justifies further study, at least for mixed mesodermal tumors.**

Hormonal Therapy

Endometrial stromal sarcomas are responsive to hormonal therapy. Chu et al. suggested that estrogen replacement therapy may be detrimental for patients with low-grade endometrial stromal sarcomas, although retention of normally functioning ovaries did not seem to be of concern (222). Ten of 22 patients in their study recurred, and eight patients were treated with progestin therapy. Complete responses were seen in four patients (50%), and three others (38%) had stable disease.

Prognosis

The frankly malignant uterine sarcomas usually have a poor prognosis. Surgical stage is the most important prognostic variable, and with better surgical staging and tailored adjuvant radiation and chemotherapy, survival rates can probably be improved, at least for mixed mesodermal tumors.

In the Mayo study of 208 patients with leiomyosarcoma (200), the median disease-specific survival for 130 patients with stage I disease was 7.8 years, whereas it was 3.7 years for 13 patients with stage II disease, 2.3 years for 18 patients with stage III, and 1.3 years for 41 patients with stage IV. Thirty-three patients with a tumor ≤ 5 cm diameter had a median survival of more than 30 years, whereas 128 patients with tumors larger than 5 cm diameter had a median survival of 3.5 years. The significance of tumor size confirmed the findings from a large Nordic study (223). Adjuvant chemotherapy or radiation therapy did not seem to be of any benefit (200). **If the leiomyosarcoma arises in a benign fibroid, the prognosis is improved** (191).

For 301 mixed mesodermal tumors, the GOG reported a recurrence rate of 53% (homologous 44%; heterologous 63%) (213). Factors significantly related to progression-free interval by univariate analysis were adnexal spread, lymph node metastases, tumor size, vascular space invasion, depth of myometrial invasion, positive peritoneal washings, histologic grade, and cell type. **On multivariate analysis, the significant prognostic factors were adnexal spread, lymph node metastases, cell type and cell grade.**

Endometrial stromal nodules are benign but can usually only be distinguished from endometrial stromal sarcomas after hysterectomy. For younger women wishing to preserve fertility, a combination of diagnostic imaging and hysteroscopy may be useful in monitoring the growth of the lesion, and in occasional cases, local excision has been successful (224).

Endometrial stromal sarcomas are relatively indolent tumors with a tendency to very late recurrence, one-third to one-half of patients recurring up to 30 years after treatment (198 ,222).

Chang et al. (198) 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. 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.

Endometrial sarcomas are highly aggressive tumors with a very poor prognosis (195).

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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 their symptoms are nonspecific 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 25,500 new cases annually in the United States, and more than 16,000 women can be expected to succumb to their illness (1). Ovarian cancer is the fifth most common cancer in women in the United States, accounting for 4% of all female cancers and 31% of cancers of the female genital organs. Ovarian cancer is the fourth most common cause of death from malignancy in women. **A woman's risk at birth of having ovarian cancer sometime in her lifetime is nearly 1.5%, and of dying from ovarian cancer, almost 1%** (2).

Classification

Part of "11 - Epithelial Ovarian Cancer "

Approximately 90% of ovarian cancers are derived from tissues that come from the coelomic 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 histology 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 ,5 ,6). 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 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 progressive, proliferative disease in the peritoneal cavity, which can lead to intestinal obstruction and death (4 ,5 ,6).

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 "müllerian" 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 (7 ,8 ,9). 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

Part of "11 - Epithelial Ovarian Cancer "

The peak incidence of invasive epithelial ovarian cancer is 56 to 60 years (2 ,10). The age-specific incidence of ovarian epithelial cancer rises precipitously from 20 to 80 years of age and subsequently declines (11). The average patient age of those with borderline tumors is about 46 years (2 ,3). Eighty percent 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 the age of 40 years is approximately 1 in 10, but after that age it rises to 1 in 3** (2). Fewer than 1% of epithelial ovarian cancers occur before the age of 20 years, two-thirds of ovarian malignancies in such patients being germ cell tumors (2 ,11). **About 30% of ovarian neoplasms in postmenopausal women are malignant, whereas only about 7% of ovarian epithelial tumors in premenopausal patients are frankly malignant** (2).

Etiology

Ovarian cancer has been associated with low parity and infertility (12). Although there have been a variety of epidemiologic variables correlated with ovarian cancer, such as increased risk with talc use and galactose consumption and decreased risk with tubal ligation (see Chapter 7), none has been so strongly correlated as prior reproductive history and duration of the reproductive career (12 ,13). **Early menarche and late menopause increase the risk of ovarian cancer** (13). 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 germ-line mutations or otherwise lead to the oncogenic phenotype (see Chapter 1).

In a cohort study of more than 1.1 million Norwegian women, a positive association was found between body mass index (BMI), height, and risk of ovarian cancer, particularly

of the endometrioid type in women younger than 60 years (14). Women who had a very high BMI and were clinically obese in adolescence and childhood had a relative risk of 1.56 of developing ovarian cancer compared with women with a medium BMI.

There has been considerable controversy as to whether fertility-enhancing drugs increase the risk of ovarian cancer. In a metaanalysis of eight case-control studies of fertility drugs and ovarian cancer (15), there were 5,207 women with cancer compared with 7,705 controls. The relative risk (RR) of fertility drug exposure for ovarian cancer was 0.97, i.e., the use of the drugs was not associated with an increased risk. However, in the same cohort, **nulliparity** (compared with multiparity >4) **carried a RR of 2.42**, **and infertility** *per se* **for 5 years or longer** (compared with <1 year) **carried a RR of 2.7.** These results support the hypothesis that the higher risk in these women is related to infertility, independent of fertility drug use.

Prevention

As 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. **The oral contraceptive reduces the risk of epithelial ovarian cancer** (12). **Women who use the oral contraceptive for 5 or more years reduce their relative risk to 0.5, i.e., there is a 50% reduction in the likelihood of developing ovarian cancer**. Women who have had two children and have used the oral contraceptive for 5 or more years have a relative risk of ovarian cancer as low as 0.3, or a 70% reduction (16). **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 the oral contraceptive should be emphasized. This is also important for women with a strong family history of ovarian cancer.

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 disease. In a prospective, randomized, placebo-controlled trial conducted in Italy (17), women with unilateral breast cancer were given either 6 months of *fenretinide* orally or a placebo. An early analysis revealed no ovarian cancers in the treatment group, whereas six cases developed in the control group. With 5-year follow up of the same cohort of patients, there was no difference in the incidence or survival from ovarian cancer, suggesting that the agent is not protective (18). **A larger trial is under way in the United States in an attempt to evaluate this agent as a chemoprotective drug.**

The performance of a prophylactic oophorectomy will reduce, but not eliminate, the risk of ovarian cancer (8 ,9). 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.

Routine annual pelvic examinations are disappointing for the early detection of ovarian cancer (19). Screening with transabdominal and transvaginal ultrasonography has been encouraging (20 ,21 ,22), but specificity has been limited. However, recent advances in transvaginal ultrasonography (23 ,24 ,25 ,26) have allowed a very high (>95%) sensitivity for the detection of early-stage ovarian cancer, although this test alone might require as many as 10–15 laparotomies per ovarian cancer detected (27). Transvaginal color flow Doppler to assess the vascularity of the ovarian vessels has been shown to be a useful adjunct to ultrasonography (24 ,25 ,26), but it has not been shown to be useful in screening.

CA125 has been shown to contribute to the early diagnosis of epithelial ovarian cancer (27 ,28 ,29 ,30 ,31 ,32 ,33 ,34). CA125 has been cloned, and although the true function of the molecule is still unknown, the elucidation of the MUC16 gene and its control may enhance the understanding of this important marker in ovarian cancer (35 ,36 ,37). Regarding the sensitivity of the test, CA125 can detect 50% of patients with stage I disease and 60% with stage II (31). Data suggest that the specificity of CA125 is improved when the test is combined with transvaginal ultrasonography (28) or when the CA125 levels are followed over time (34 ,35 ,36 ,37 ,38 ,39 ,40 ,41). In this manner, the risk of ovarian cancer (ROC) algorithm might help to improve the efficacy of screening (41). A more complete discussion of tumor markers and screening is 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. Screening in women who have a familial risk may have a better yield, but additional study is necessary (38 ,39).

A new approach is the use of proteomic patterns to identify ovarian cancer using surface-enhanced laser desorption ionization time-of-flight (SELDI-TOF) technology (42). In a study using this technology, the sensitivity for predicting ovarian cancer was 100% with a specificity of 95% and a positive predictive value of 94%. The assay correctly identified all 18 women with stage I tumors. This technology is in the early phases of development and validation, and its efficacy has yet to be demonstrated in large population-based studies.

Another new approach is the measurement of plasma DNA levels and allelic imbalance by a technique known as digital single nucleotide polymorphism (SNP) analysis. In a study by Chang and colleagues (43), this analysis had a 87% (13 of 15) positive correlation in stages I and II, and a 95% (37 of 39) correlation in patients with stages III and IV disease.

Genetic Risk for Epithelial Ovarian Cancer

Ovarian cancers appear to arise from a single clone—i.e., they are monoclonal—and thus they are initiated from a single mutation (see Chapter 1) (44). Conversely, there is evidence that peritoneal carcinomas may have a multifocal origin (45).

Hereditary Ovarian Cancer

The risk of ovarian cancer is higher than that of the general population in women with certain family histories (46 ,47 ,48 ,49 ,50 ,51 ,52 ,53 ,54 ,55 ,56 ,57 ,58). **Most epithelial ovarian cancer is sporadic, with familial or hereditary patterns accounting for 5% to 10% of all malignancies** (47). Further discussion of germ-line mutations and their biology is presented in Chapter 1 .

BRCA1 and BRCA2

Most hereditary ovarian cancer is associated with mutations in the *BRCA1* gene that is located on chromosome 17 (46). **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 (55).

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) (56).

The mutations are passed via autosomal dominance, and thus, a full pedigree analysis, i.e., both maternal and paternal sides of the family, must be carefully evaluated (50). There are numerous distinct mutations that have been identified on each of these genes, and the mutations have different degrees of penetrance, which 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** (47 ,48 ,54). **In women with a** *BRCA1* **or** *BRCA2* **mutation, the risk of ovarian and breast cancer may be as high as 54% and 82%, respectively** (58).

Hereditary ovarian cancers generally occur in women about 10 years younger than those with nonhereditary tumors (47 ,58). As 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 their breast cancers at a very 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 (46 ,51).

Founder Effect

There is a higher carrier rate of *BRCA1* **and** *BRCA2* **mutations in women of Ashkenazi Jewish descent and in Islandic women** (52 ,53 ,55). 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 of at least one of these mutations for a patient of Ashkenazi Jewish descent is 1 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,” i.e., a higher rate of mutations that have occurred within 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.

- 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 will have an affected gene could be as high as 23% to 54% (48 ,58).
- 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 will have an affected gene also may be increased. The risk may be two- to tenfold higher than in those without a familial history of the disease (48).
- 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 occurred in a premenopausal relative, this could be significant, and a full pedigree analysis should be undertaken.

- Women with a primary history of breast cancer have twice the expected incidence of subsequent ovarian cancer (47).

Lynch II Syndrome (Hereditary Nonpolyposis Colorectal Cancer Syndrome, HNPCC Syndrome)

HNPCC 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 (56). 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 more accurately determine the risk.

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 been clearly established, and some guidelines for testing now exists** (50 ,57 ,58). The importance of genetic counseling cannot be overemphasized, as the decision is complex. The American Society of Clinical Oncologists has offered guidelines that emphasize careful evaluation by geneticists, careful maintenance of medical records, as well as a clear understanding in a genetic screening clinic of how to counsel and manage these patients. There remain concerns of how the information would 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 germ-line mutations in *BRCA1* or *BRCA2* appears to be comparable to that of sporadic tumors (49). **Women with breast cancer who carry these mutations, however, are at a greatly increased risk of ovarian cancer, as well as of a second breast cancer: the lifetime risk of ovarian cancer is 54% for women who have a** *BRCA1* **mutation and 23% for those with a** *BRCA2* **mutation, and for the two groups together, there is an 82% lifetime risk of breast cancer** (58)**.**

Although recommended by the National Institutes of Health (NIH) Consensus Conference on Ovarian Cancer (59)**, 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. (39) have shown that this approach can detect tumors about 10 times more often than in the general population, and thus they recommend screening for 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 of development of ovarian cancer in women who have a mutation in either *BRCA1* **or** *BRCA2* (60). In women who had taken the oral contraceptive pill for 5 or more years, the relative risk of ovarian cancer is 0.4, or a 60% reduction in the incidence of the disease. Another study, however, failed to confirm this finding (61). Tubal ligation may also decrease the risk of ovarian cancer in patients with *BRCA1* (but not *BRCA2*) mutations, but the protective effect is not nearly as strong as oophorectomy (62).

The value of prophylactic oophorectomy in these patients has been documented (63 ,64 ,65 ,66 ,67 ,68). Women at high risk for ovarian cancer who undergo prophylactic oophorectomy have a risk of harboring occult neoplasia: in one series of 98 such operations, 3 (3.1%) patients had a low-stage ovarian malignancy (64). **The protection against ovarian cancer is excellent: the performance of a prophylactic salpingo-oophorectomy reduced the risk of *BRCA*-related gynecologic cancer by 96%** (66). 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 the *BRCA1* and *BRCA2* genes. In these series, the subsequent development of peritoneal carcinoma was 0.8% and 1 %, respectively (64 ,65). **In addition, the risk of developing subsequent breast cancer was reduced by 50% to 80%** (64 ,65)**.**

The role of hysterectomy is more controversial. Although most studies show no increase in the rate of uterine and cervical tumors, there are some reports of an increase of papillary serous tumors of the endometrium (69). Women on *tamoxifen* are at higher risk for benign endometrial lesions (e.g., polyps) and endometrial cancer. Therefore, **it is reasonable to consider the performance of a prophylactic hysterectomy in conjunction with salpingo-oophorectomy**, and this decision should be individualized.

Grann and associates reported the application of Markov modeling, i.e., quality-adjusted survival estimate analysis, in a simulated cohort of 30-year-old women who tested positive for *BRCA1* or *BRCA2* mutations (70). Quality adjustment of survival estimates were obtained from a survey of women aged 33 to 50 years. The analysis predicted that such a woman could prolong her survival beyond that associated with surveillance alone by 1.8 years with *tamoxifen*, 2.6 years with prophylactic salpingo-oophorectomy, 4.6 years with both *tamoxifen* and prophylactic salpingo-oophorectomy, 3.5 years with prophylactic mastectomy, and 4.9 years with both prophylactic surgeries. Quality-adjusted survival was estimated to be prolonged by 2.8 years for *tamoxifen*, 4.4 years with prophylactic salpingo-oophorectomy, 6.3 years for *tamoxifen* and prophylactic salpingo-oophorectomy, 3.5 years with mastectomy, and 4.9 years with both operations.

The survival of women who have a *BRCA1* or *BRCA2* mutation and develop ovarian cancer is longer than that for those who do not have a mutation. In one study, the median survival for mutation carriers was 53.4 months compared with 37.8 months for those with sporadic ovarian cancer from the same institution (71).

Recommendations

Current recommendations for management of women with high-risk for ovarian cancers are summarized below (57 ,58 ,59 ,60 ,61 ,62 ,63 ,64 ,65 ,66 ,67 ,67 ,68 ,69 ,70):

- **Women who appear to be at high-risk for ovarian and or breast cancer should undergo genetic counseling and, if the risk appears to be substantial, may be offered genetic testing for *BRCA1* and *BRCA2*.**
- **Women who wish to preserve their reproductive capacity can undergo periodic screening by transvaginal ultrasonography every 6 months**, although the efficacy of this approach is not clearly established.
- **Oral contraceptives should be recommended** to young women before a planned family.
- **Women who do not wish to maintain their fertility or who have completed their family should be recommended to undergo prophylactic bilateral salpingo-oophorectomy**. The risk should be clearly documented, and preferably established by *BRCA1* and *BRCA2* testing, preoperatively. These women should be counseled that this operation does not offer absolute protection, because peritoneal carcinomas may occasionally occur (64 ,65). The concurrent performance of a prophylactic hysterectomy is acceptable, and the option should be discussed with these patients.

- In women who have a strong family history of breast or ovarian cancer, annual mammographic screening should be performed commencing at age 30 years.
- Women with a documented HNPCC syndrome should be treated as above, but in addition, they should undergo periodic screening mammography, colonoscopy, and endometrial biopsy (56).

Symptoms

The majority of women with epithelial ovarian cancer have vague and nonspecific symptoms (72 ,73 ,74 ,75 ,76). In early-stage disease, the patient may report 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 report irregular or heavy menses, whereas vaginal bleeding may occur in postmenopausal women. **In one survey of 1,725 women with ovarian cancer, 95% recalled symptoms before diagnosis, including 89% with stage I and II disease and 97% with stages III and IV disease** (74). **Some 70% had abdominal or gastrointestinal symptoms, 58% pain, 34% urinary symptoms, and 26% pelvic discomfort.**

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 reports 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 not palpable. Thus any palpable pelvic mass in these patients should be considered suspicious. This situation has been referred to as the postmenopausal palpable ovary syndrome (77). This concept has been challenged, as subsequent authors have reported that **only about 3% of palpable masses measuring less than 5 cm are malignant in postmenopausal women** (19).

Diagnosis

The diagnosis of an ovarian cancer requires an exploratory laparotomy. The preoperative evaluation of the patient with an adnexal mass is outlined in Figure 11.1 .

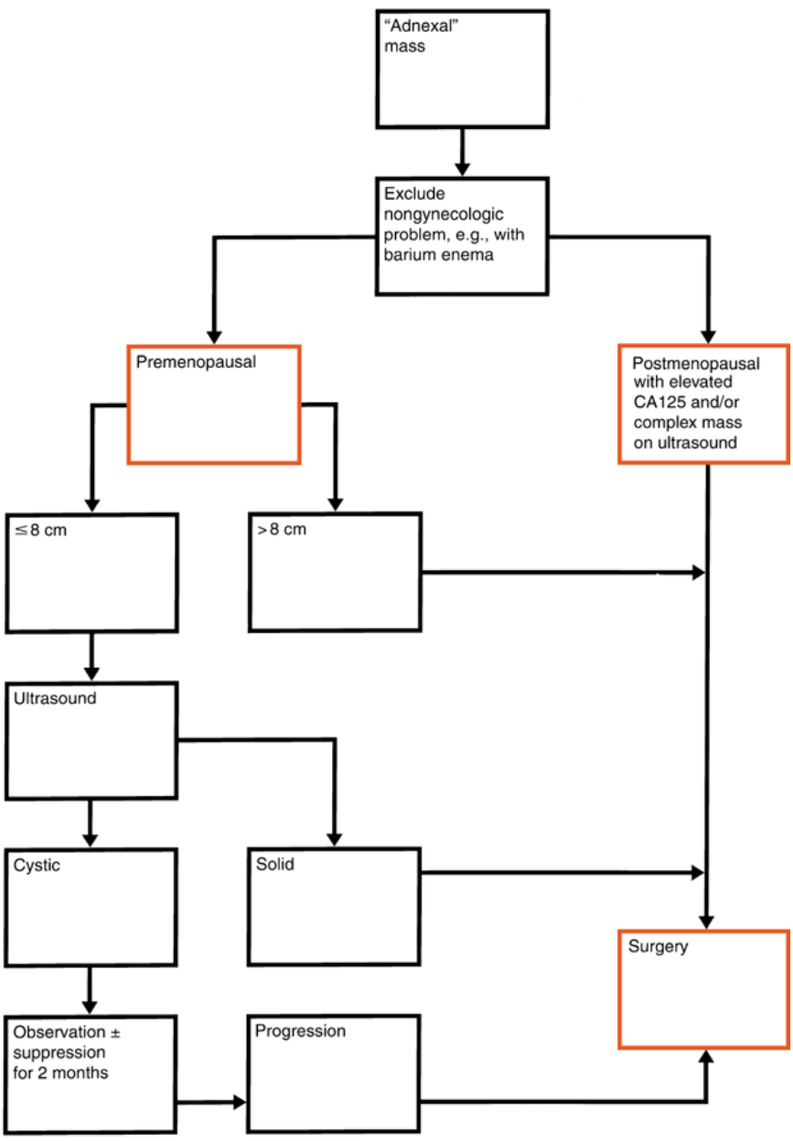

Figure 11.1 Preoperative evaluation of the patient with an adnexal mass.

Ultrasonographic signs of malignancy include an adnexal pelvic mass with areas of complexity, such as irregular borders, multiple echogenic patterns within the mass, and dense, multiple, irregular septae. Bilateral tumors are more likely to be malignant, although the individual characteristics of the lesions are of greater significance. **Transvaginal ultrasonography may have a somewhat better resolution than transabdominal ultrasonography for adnexal neoplasms** (20 ,21 ,22 ,23). Doppler color flow imaging may enhance the specificity of ultrasonography for demonstrating findings consistent with malignancy (24 ,25 ,26)

The size of the lesion is of importance. If a complex cystic mass is more than 8 to 10 cm in diameter, the probability is high that the lesion is neoplastic, unless the patient has been taking *clomiphene citrate* or other agents to induce ovulation (73). **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). Generally, an interval of no more than 2 months is allowed for observation. If the lesion is not neoplastic, it should remain stable or regress, as measured by pelvic examination and pelvic ultrasonography. If a mass increases in size or complexity, it must be presumed to be neoplastic and removed surgically.

In postmenopausal women with unilocular cysts measuring 8 to 10 cm or less and normal serial CA 125 levels, expectant management is acceptable, and this approach may decrease the number of surgical interventions (78 ,79 ,80).

Premenopausal patients whose lesions are clinically suspicious (i.e., large, predominantly solid, relatively fixed, or irregularly shaped) should undergo laparotomy, as should postmenopausal patients with complex adnexal masses of any size.

Before the planned exploration, the patient should undergo routine hematologic and biochemical assessments. A preoperative evaluation in a patient older than 40 years undergoing laparotomy should include a radiograph of the chest. An abdominal and pelvic computed tomographic (CT) or magnetic resonance imaging (MRI) scan is of no value in patients with a definite pelvic mass (81 ,82 ,83 ,84 ,85). Patients with ascites and no pelvic mass should have a CT or MRI scan to look particularly for liver or pancreatic tumors (82). The findings only rarely preclude laparotomy (85). If the hepatic enzymes are normal, the likelihood of liver disease is low. Liver-spleen scans, bone scans, 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 selected patients with symptoms and signs suspicious for colon cancer. This would include any patient who has evidence of frank or occult blood in the stool, or gives a recent history of diarrhea or constipation. An upper gastrointestinal series or gastroscopy is indicated if there are upper gastrointestinal symptoms such as nausea, vomiting, or hematemesis (86). Bilateral mammography is indicated if there is any breast mass, because occasionally breast cancer metastatic to the ovaries can simulate primary ovarian cancer.

A Pap smear should be performed, although its value in detecting ovarian cancer is very limited. Patients who have irregular menses or postmenopausal 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 (73). A pelvic kidney can simulate ovarian cancer.

Serum CA125 levels have been shown to be useful in distinguishing malignant from benign pelvic masses (87). 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.

Transcoelomic

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 (88 ,89 ,90 ,91). 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 (88).

Burghardt et al. performed systematic pelvic and paraaortic lymphadenectomy on 123 patients (90) and reported that 78% of patients with stage III disease have metastases to the pelvic lymph nodes. In another series (91), 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 about 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. (92) reported that **distant metastasis consistent with stage IV disease ultimately occurred in 38% of the patients whose disease was originally intraperitoneal**. Sites of hematogenous spread 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 in 2.4%, 2.3 months; central nervous system in 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 within the abdomen, and retroperitoneal lymph node involvement at the time of initial surgery.

Prognostic Factors

Part of "11 - Epithelial Ovarian Cancer "

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 (93 ,94 ,95 ,96 ,97 ,98). **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 (96 ,97).

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 (97 ,99). However, studies of the reproducibility of grading ovarian cancers have shown a high degree of intraobserver and interobserver variation (98). **Because there is significant heterogeneity of tumors and observational bias, the value of histologic grade as an independent prognostic factor has not been clearly established**. Baak et al. (99) 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 (100 ,101 ,102 ,103 ,104 ,105 ,106 ,107 ,108 ,109 ,110 ,111 ,112 ,113 ,114 ,115 ,116 ,117 ,118 ,119 ,120 ,121 ,122 ,123 ,124 ,125 ,126 ,127 ,128 ,129 ,130 ,131 ,132 ,133). Using flow cytometry, Friedlander et al. (101) showed that ovarian cancers were commonly aneuploid. Furthermore, they and others showed that there was a high correlation between FIGO stage and ploidy; i.e., low-stage cancers tend to be diploid and high-stage tumors tend to be aneuploid (100 ,101 ,102 ,103 ,104 ,105 ,106 ,107) (Figure 11.2). **Patients with diploid tumors have a significantly longer median survival than those with aneuploid tumors**: 5 years versus 1 year, respectively (102). Multivariate analyses have demonstrated that **ploidy is an independent prognostic variable** and one of the most significant predictors of survival (103). 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 (101).

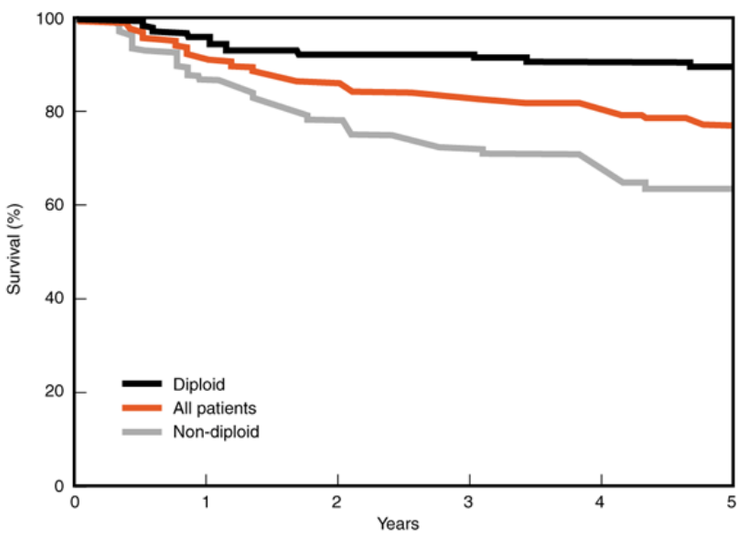

Figure 11.2 Survival of patients with stage I epithelial ovarian cancer based on ploidy evaluation. (From **Tropé C, Kaern J, Vergote I**. Adjuvant therapy for early-stage epithelial ovarian cancer. In: **Gershenson DM, McGuire WP**, eds. *Ovarian cancer: controversies in management*. New York: Churchill 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 (108 ,109 ,110 ,111 ,112 ,113 ,114 ,115 ,116 ,117 ,118 ,119 ,120 ,121 ,122 ,123 ,124). For example, Slamon et al. (110) reported that 30% of epithelial ovarian tumors expressed her-2/*neu* oncogene and that this group had a poorer prognosis, especially those patients with more than 5 copies of the gene. Berchuck et al. (111) 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 months versus 32.8 months). Others have not substantiated this finding (112), and a review of the literature by Leary et al. (113) 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 at this time.**

Additional prognostic variables include *p53, bcl-2*, k-*ras*, Ki67, interleukin 6, PTEN, lysophospholipids and platelet-derived growth factor (118 ,119 ,120 ,121 ,122 ,123 ,124 ,125 ,126 ,127 ,128 ,129). 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 (130 ,131 ,132 ,133). Multivariate analysis has found that clonogenic growth in a semisolid culture medium is a significant independent variable (132). The use of an “extreme drug resistance assay” has been suggested as a possible means of directing therapy by defining platinum-sensitive and resistant tumors *in vitro* (133). Further study will be needed to evaluate the clinical usefulness of these assays.

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 (134 ,135 ,136 ,137 ,138 ,139 ,140 ,141 ,142 ,143). Among patients with stage I disease, Dembo et al. (134) 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. confirmed these findings (135). A multivariate analysis of these and several other studies was perfomed by Vergote et al. (137), and they found that for early-stage disease, poor prognostic variables were the tumor grade, capsular penetrance, surfaces excrescences, and malignant ascites, but not iatrogenic rupture.

Initial Surgery for Ovarian Cancer

Part of "11 - Epithelial Ovarian Cancer "

Staging

Ovarian epithelial malignancies are staged according to the International Federation of Gynecology and Obstetrics (FIGO) system, and the staging system of 1987 is listed in Table 11.1 . The FIGO staging 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

Stage I	Growth limited to the ovaries.
Stage IA	Growth limited to one ovary; no ascites containing malignant cells. No tumor on the external surface; capsule intact.
Stage IB	Growth limited to both ovaries; no ascites containing malignant cells. No tumor on the external surfaces; capsules intact.
Stage IC[a]	Tumor either stage IA or IB but with tumor on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage II	Growth involving one or both ovaries with pelvic extension.
Stage IIA	Extension and/or metastases to the uterus and/or tubes.
Stage IIB	Extension to other pelvic tissues.
Stage IIC[a]	Tumor either stage IIA or IIB, but with tumor on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage III	Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals stage III. Tumor is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum.
Stage IIIA	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.
Stage IIIB	Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes negative.
Stage IIIC	Abdominal implants >2 cm in diameter and/or positive retroperitoneal or inguinal nodes.
Stage IV	Growth involving one or both ovaries with distant metastasis. If pleural effusion is present, there must be positive cytologic test results to allot a case to stage IV. Parenchymal liver metastasis equals stage IV.

FIGO, International Federation of Gynecology and Obstetrics.

These categories are based on findings at clinical examination or surgical exploration. The histologic characteristics are to be considered in the staging, as are results of cytologic testing as far as effusions are concerned. It is desirable that a biopsy be performed on suspect areas outside the pelvis.

[a]To evaluate the impact on prognosis of the different criteria for allotting cases to stage IC or IIC, it would be of value to know if rupture of the capsule was (a) spontaneous or (b) caused by the surgeon, and if the source of malignant cells detected was (a) peritoneal washings or (b) ascites.

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 for patients with apparent stage I epithelial ovarian cancer was only about 60% (144 ,145). 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 (145 ,146 ,147 ,148 ,149 ,150 ,151 ,152 ,153).

Technique for Surgical Staging

In patients whose preoperative evaluation suggests a probable ovarian 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:

- **Any free fluid, especially in the pelvic cul-de-sac, should be submitted for cytologic evaluation.**
- **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 from 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.
- **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 Treitz to the cecum should be inspected.
- **Any suspicious areas or adhesions on the peritoneal surfaces should be biopsied.** 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 biopsied.
- **The diaphragm should be sampled either by biopsy or by scraping with a tongue depressor and making a cytologic smear** (154). Biopsies of any irregularities on the surface of the diaphragm can be facilitated by use of the laparoscope and the associated biopsy instrument.
- **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.
- **The retroperitoneal spaces should be dissected and 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. If no metastases are present, a formal pelvic lymphadenectomy should be performed.

- **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 (155).

Results

Metastases in apparent stage I and II epithelial ovarian cancer are summarized in Table 11.2 . **As many as 3 in 10 patients whose tumor appears confined to the pelvis have occult metastatic disease in the upper abdomen or the retroperitoneal lymph nodes** (89 ,148 ,149 ,150 ,151 ,152 ,153 ,154 ,155).

Table 11.2 Site of Metastases in Patients with Apparent Stage I and II Ovarian Cancer

Ref.	Diaphragm	Aortic Lymph Nodes	Pelvic Nodes	Omentum	Positive Cytology
18		4/21 (19.0%)	2/21 (9.5%)		
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					7/36 (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%)	1/21 (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, 1987:112, with permission.

The importance of careful initial surgical staging is emphasized by the findings of a cooperative national study (145) 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; i.e., 16% of the patients with grade 1 lesions were upstaged, compared with 34% with grade 2 disease and 46% with grade 3 disease.

After a comprehensive staging laparotomy, only a minority of women will have local disease (FIGO stage I). Of the 25,000 to 26,000 women diagnosed yearly with epithelial ovarian cancer in the United States, approximately 3,000 to 4,000 have disease confined to the ovaries (156). The prognosis for these patients depends on the clinical–pathologic features, as outlined below. Because of this emphasis on the importance of surgical staging, the rate of lymph node sampling has increased in the United States, with a study showing that for women with stage I and II disease,

the percentage having lymph nodes sampled increased from 38% to 59% from 1991 to 1996 (157).

Early Stage Ovarian Cancer

The primary treatment for stage I epithelial ovarian cancer is surgical, i.e., a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and surgical staging (144 ,145 ,158). In certain circumstances, a unilateral oophorectomy may be permitted, as discussed below. Based on the prognostic variables outlined above (94 ,103 ,134 ,135 ,136 ,137 ,138 ,139 ,141 ,142 ,158), early-stage epithelial ovarian cancer can be subdivided into low-risk and high-risk disease (Table 11.3)

Table 11.3 Prognostic Variables in Early-Stage Epithelial Ovarian Cancer

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 excrescences	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

Borderline Tumors

The principal treatment of borderline ovarian tumors is surgical resection of the primary tumor (159 ,160 ,161 ,162 ,163 ,164 ,165 ,166 ,167). There are no prospective data to suggest that either adjuvant chemotherapy or radiation therapy improves survival (168 ,169 ,170). After a frozen section has determined that the histology is borderline, premenopausal patients who desire preservation of ovarian function may be managed with a “conservative” operation, i.e., a unilateral oophorectomy (160 ,161 ,163). In a study of patients who underwent unilateral ovarian cystectomy only for apparent stage I borderline serous tumors, Lim-Tan et al. (162) found that this conservative operation was also 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. 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, but the patient should be monitored with transvaginal ultrasonography.

Fertility Preservation in Early Stage Ovarian Cancer

In patients who have undergone a thorough staging laparotomy and in whom there is no evidence of spread beyond the ovary, the uterus and contralateral ovary can be retained in women who wish to preserve fertility. These women should be followed carefully with routine transvaginal ultrasonography and determination of serum CA125 levels. Generally, the other ovary and the uterus are removed at the completion of childbearing (see treatment section below).

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 Figure 11.3 .

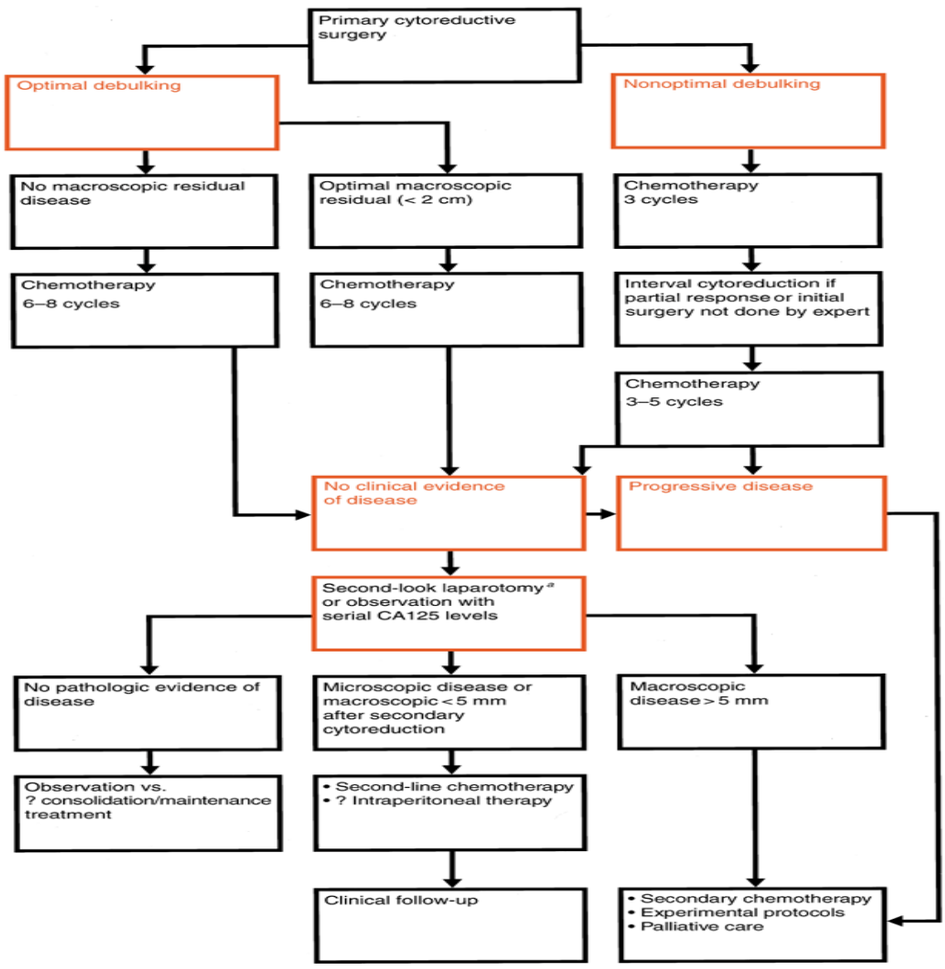

Figure 11.3 Treatment scheme for patients with advanced-stage ovarian cancer. [a]Under selected circumstances or clinical trials.)

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 laparotomy, or "second look," may be performed in certain circumstances. In patients with persistent disease at second-look laparotomy, second-line therapy may be recommended, as there are many options available.

Cytoreductive Surgery

Patients with advanced-stage epithelial ovarian cancer documented at initial exploratory laparotomy should undergo cytoreductive surgery (171 ,172 ,173 ,174 ,175 ,176 ,177 ,178 ,179 ,180 ,181 ,182). 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 will result in extirpation of all gross tumor, a situation that is associated with a reasonable chance of prolonged progression-free survival.

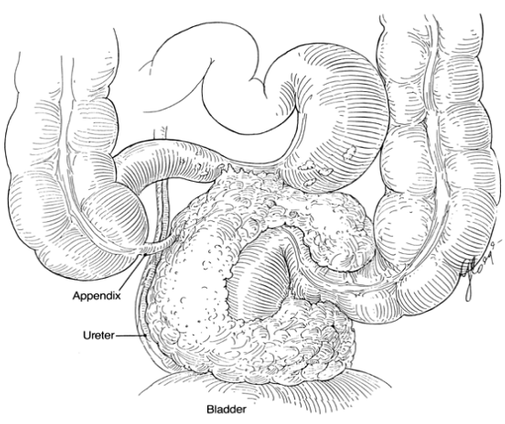

Figure 11.4 Extensive ovarian carcinoma involving the bladder, rectosigmoid, and ileocecal area. (From **Heintz APM, Berek JS**. Cytoreductive surgery for ovarian carcinoma. In: **Piver MS**, ed. *Ovarian malignancies.* Edinburgh: Churchill Livingstone, 1987:134, with permission.)

Theoretic Rationale

The rationale for cytoreductive surgery relates to three general theoretic considerations (180 ,182 ,181 ,182 ,183 ,184 ,185):

- **The physiologic benefits of tumor mass excision**
- **The improved tumor perfusion and increased growth fraction**, both of which increase the likelihood of response to chemotherapy or radiation therapy
- **The enhanced immunologic competence of the patient**

Physiologic Benefits

The removal of bulky tumor masses may reduce the volume of ascites present. Often, ascites will 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 Cellular Kinetics

A large, bulky tumor may contain areas that are poorly vascularized, and such areas will be 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, will be 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_o 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 (183) **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** (183 ,184). 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 the 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 lymphocytic activity** (185).

Goals of Cytoreductive Surgery

The principal goal of cytoreductive surgery is the 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 (171) initially proposed that all metastatic nodules should be reduced to ≤1.5 cm in maximum diameter and showed that survival was significantly longer in such patients.

Subsequently, Hacker and Berek (172 ,173 ,174 ,177 ,178 ,179 ,180) showed that patients whose largest residual lesions were ≤5 mm had a superior survival, and this was substantiated by Hoskins et al. presenting the data of the Gynecologic Oncology Group. (176). The median survival of patients in this category was 40 months, compared with 18 months for patients whose lesions were ≥1.5 cm and 6 months for patients with nodules >1.5 cm (Fig. 11.5). Clearly, **those patients whose disease has been completely resected have the best prognosis and approximately 60% of patients in this category will be free of disease at 5 years** (Fig. 11.6).

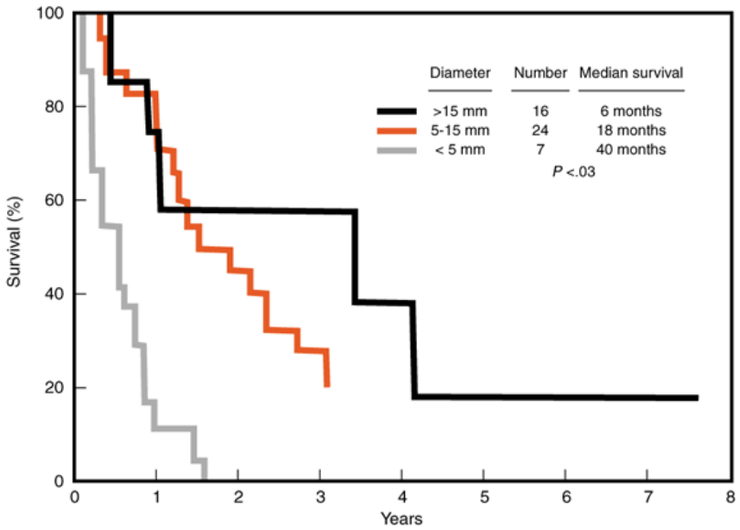

Figure 11.5 Survival versus diameter of largest residual disease. (From **Hacker NF, Berek JS, Lagasse LD, Nieberg RK, Elashoff RM.** Primary cytoreductive surgery for epithelial ovarian cancer. *Obstet Gynecol* 1983;61:413–420, with permission from the American College of Obstetricians and Gynecologists.)

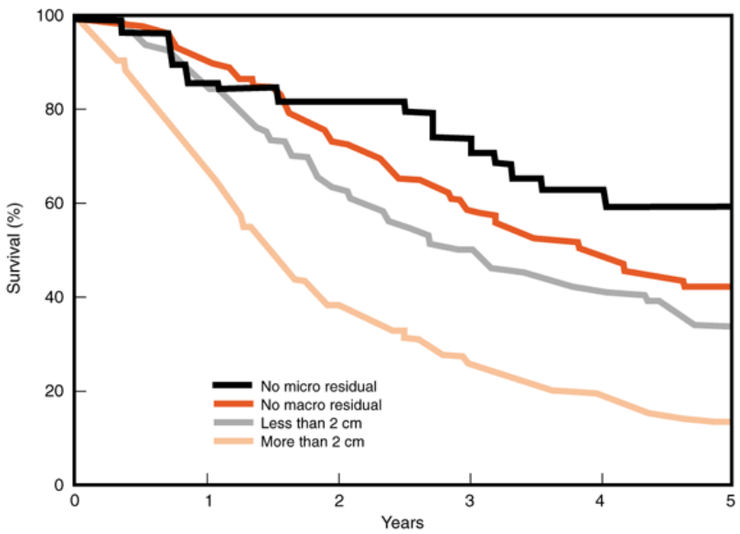

Figure 11.6 Survival of patients with stage IIIC epithelial ovarian cancer based on the maximum size of the residual tumor after exploratory laparotomy and tumor resection. (From **Heintz APM, Odicino F, Maisonneuve P, Beller U, Benedet JL, Creasman W, et al.** Carcinoma of the ovary. *25th annual report on the results of treatment in gynecologic cancer. Int J Gynecol Obstet* 2003;83:135–166.)

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 parenchyma of the liver, 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 (174 ,177). 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 <5 mm, may also worsen the survival (177 ,178 ,179 ,180).

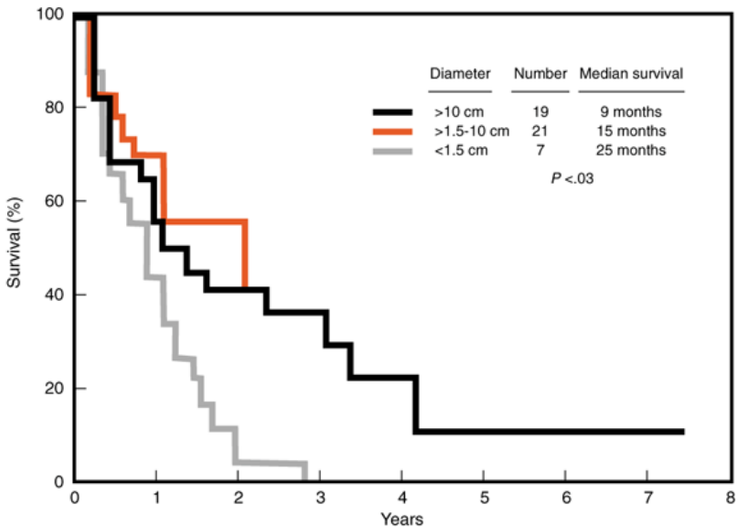

Figure 11.7 Survival versus diameter of largest metastatic disease before cytoreduction. (From **Hacker NF, Berek JS, Lagasse LD, Nieberg RK, Elashoff RM.** Primary cytoreductive surgery for epithelial ovarian cancer. *Obstet Gynecol* 1983;61:413–420, with permission from the American College of Obstetricians and Gynecologists.)

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 in order 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.

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 of removal of the pelvic tumor is to use the retroperitoneal approach (179 ,180). 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 within 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 paravesicle 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 in order 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 within 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 (186 ,187 ,188 ,189). 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** (Fig. 11.8) (186 ,187). 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 .

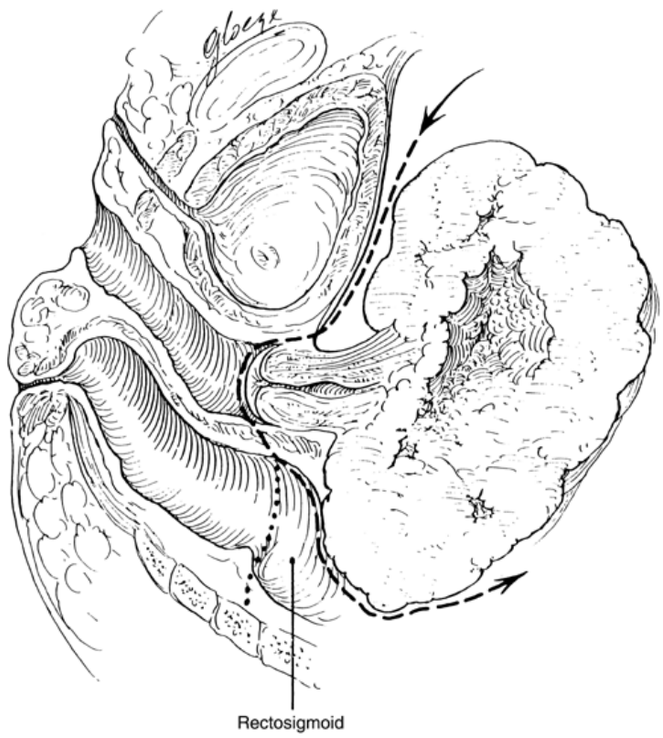

Figure 11.8 Resection of the pelvic tumor may include removal of the uterus, tubes, and ovaries, as well as portions of the lower intestinal tract. The *arrows* represent the plane of resection.

It is rarely necessary to resect portions of the lower urinary tract (188). 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).

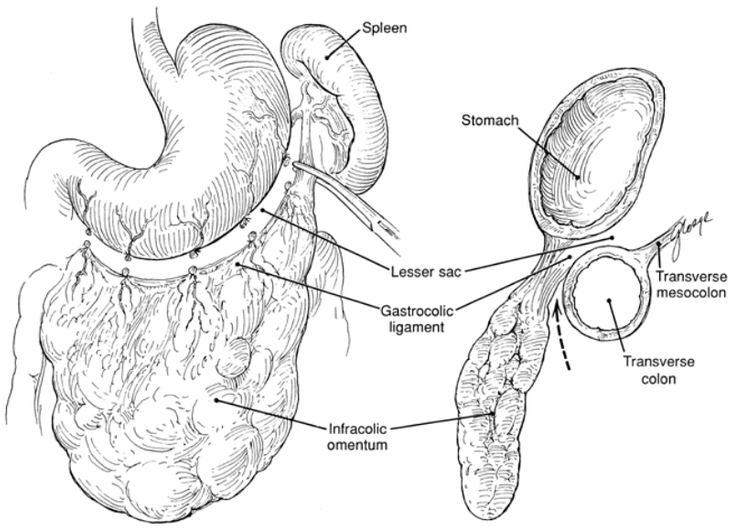

Figure 11.9 Separation of the omentum from stomach and transverse colon. (From **Heintz APM, Berek JS**. Cytoreductive surgery for ovarian carcinoma. In: **Piver MS**, ed. *Ovarian malignancies.* Edinburgh: Churchill Livingstone, 1987:134, with permission.)

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 will occasionally be necessary to perform splenectomy to remove all the omental disease** (189 ,190) (Fig. 11.10).

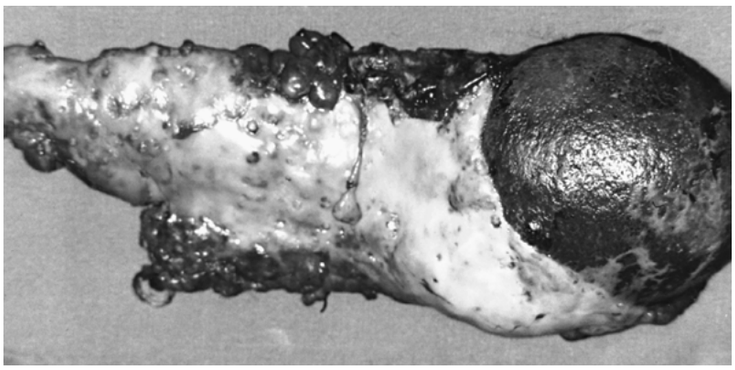

Figure 11.10 Omentum densely adherent to the spleen.

Intestinal Resection

The disease may involve focal areas of the small or large intestine, and resection should be performed if it would permit 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 (186 ,187 ,188 ,189).

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 will permit optimal cytoreduction. Resection of extensive disease from the surfaces of the diaphragm is generally neither practical nor feasible, although solitary metastases may be resected, the diaphragm sutured, and a chest tube placed if necessary for a few days (191). The use of the CUSA (Cavitron Ultrasonic Surgical Aspirator), the argon beam laser, and the loop electrosurgical devise may help facilitate resection of small tumor nodules, especially those on flat surfaces (192 ,193 ,194).

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 (178 ,180). Major morbidity is in the range of 5% and operative mortality in the range of 1% (173 ,178). Intestinal resection in these patients does not appear to increase the overall morbidity of the operation (178 ,180).

The performance of a pelvic and paraaortic lymphadenectomy in patients with stage IIIC–IV disease has been reported to prolong survival (91). In a nonrandomized trial, systematic pelvic and paraaortic lymphadenectomy performed in 60 optimally resected patients was associated with an improved survival (2-year survival = 59%) compared with a combination of historical and concurrent control patients (N = 45; 2-year survival = 16%) (p <0.01). 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 (196). Concern has been expressed that these operations are excessively morbid and that modern chemotherapies are sufficient. No randomized prospective study has ever 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.

In a meta-analysis of 81 studies of women who underwent cytoreductive surgery for advanced ovarian cancer, Bristow and colleagues documented that the extent of debulking correlated with incremental benefits in survival, i.e., the greater the percentage of tumor reduction, the longer the survival: each 10% increase in cytoreduction equaled a 5.5% increase in median survival (195). **Women whose cytoreduction was greater than 75% of their tumor burden had a median survival of 33.9 months compared with 22.7 months for women whose tumors were cytoreduced to less than 75%.** (p <0.001).

A prospective randomized study of "interval" cytoreductive surgery was carried out by the European Organization for the Research and Treatment of Cancer (EORTC). Interval surgery was performed after three cycles of platinum-combination chemotherapy in patient whose primary attempt at cytoreduction was suboptimal. Patients in the surgical arm of the study demonstrated a survival benefit when compared with those who did not undergo interval debulking (197). Most of these patients had not had an aggressive attempt to debulk their tumor at their initial surgery. The risk of mortality was reduced by more than 40% in the group that was randomized to the debulking arm of the study. 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** (198).

A prospective phase III study of interval cytoreductive surgery was conducted by the GOG (199), but the study design was different because the patients entered on the trial had already undergone a maximal attempt at tumor resection at their initial surgery. The randomized findings showed no difference between the group who had an additional attempt at debulking after three cycles of chemotherapy compared with those who did not. The median survival of the 216 women who underwent interval cytoreduction was 32 months compared with 33 months for the 209 women who did not undergo surgical cytoreduction.

There is evidence that the survival of women with advanced ovarian cancer is improved when the surgeon is specifically trained to perform cytoreductive surgery (200) and when there is centralization of care (201). Therefore, **whenever feasible, patients with advanced ovarian malignancy should be referred to a subspecialty unit for primary surgery, and every effort should be made to attain as complete a cytoreduction as possible.**

Treatment with Chemotherapy and Radiation

Part of "11 - Epithelial Ovarian Cancer "

Early-Stage Low-Risk Ovarian Cancer

Guthrie et al. (158) 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 and chemotherapy were unnecessary. Furthermore, the Gynecologic Oncology Group (GOG) carried out a prospective, randomized trial of observation versus *melphalan* for patients with Stage IA and IB, grade 1 and 2 disease. **Five-year survival for each group was 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 ,179). Some comparisons of these modalities have been made and are summarized below.

Chemotherapy

Chemotherapy for patients with early-stage high-risk epithelial ovarian cancer can be either single agent or multiagent (202 ,203 ,204 ,205 ,206 ,207 ,208). 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 (209 ,210). Furthermore, the risk of leukemia with alkylating agents and platinum make the administration of adjuvant therapy risky unless there is a significant benefit (203 ,204).

Because *cisplatin, carboplatin, cyclophosphamide*, and *paclitaxel* 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 (211 ,212 ,213 ,214 ,215 ,216 ,217 ,218 ,219). In a GOG trial of three cycles of *cisplatin* and *cyclophosphamide* versus intraperitoneal ^{32}P in patients with stage IB and IC disease, the progression-free survival of women receiving the platinum-based chemotherapy was 31% higher than those receiving the radiocolloid (Fig. 11.11a) (213). Similar results were also reported by a multicenter trial performed in Italy by the Gruppo Italiano Collaborativo Oncologica Ginecologica (GICOG) for progression-free survival (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 (219), although it is unclear if there is a survival benefit.

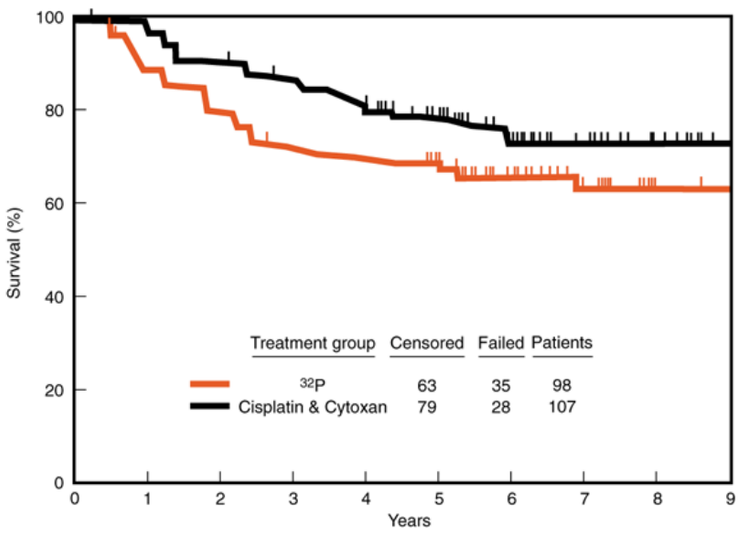

Figure 11.11 Progression-free survival of patients with stage I and II epithelial ovarian cancer treated with either *cisplatin* and *cyclophosphamide* ^{32}P in Gynecologic Oncology Group Protocol 95. The recurrence rate on the cisplatin regimen is 36% lower than the ^{32}P regimen (relative risk = 0.641). [From **Young RC, Brady MF, Nieberg RM, Long HJ, Mayer A, Lentz SS, et al.** Adjuvant treatment for ovarian cancer: a randomized phase III trial of intraperitoneal ^{32}P or intravenous cyclophosphamide and cisplatin: a Gynecologic Oncology Group study. *J Clin Oncol* 2003;21:4350–4355, with permission.]

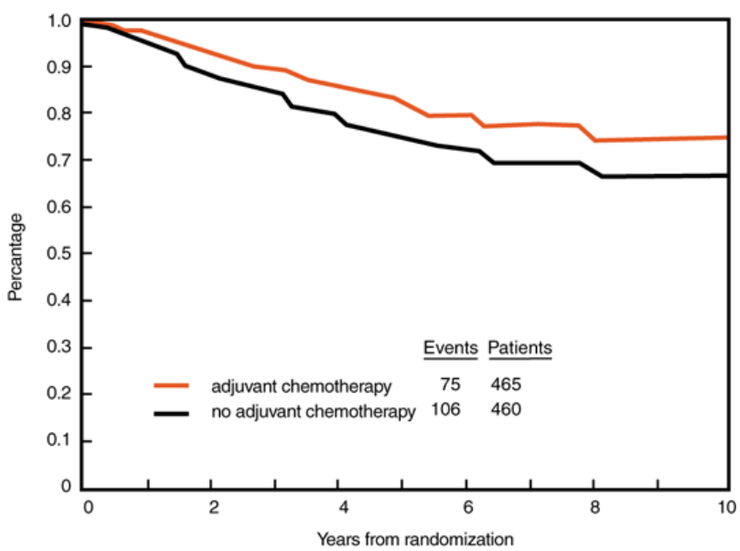

Figure 11.12 Overall survival in patients with early-stage ovarian carcinoma (The ICON1/ACTION Trials). Adjuvant *cisplatin*- or *carboplatin*-based single agent or combination chemotherapy (n = 465 patients) (red line) versus no adjuvant chemotherapy (n = 460 patients) (black line) until clinical progression. The hazard ratio is 0.67 (95% CI = 0.50 to 0.90, p = 0.008 using log-rank test) in favor of chemotherapy. Five-year survivals were 82% for the adjuvant chemotherapy group versus 74% for those who do not receive adjuvant chemotherapy (221). These data should be interpreted with caution, because most of the patients were not completely staged, and the benefit of treatment appears to be only in patients who did not have a complete staging laparotomy. (From **Trimbos JB, Parmar M, Guthrie D, Swart AM, Vergote I, Bolis G, et al.** International Collaborative Ovarian Neoplasm Trial 1 and Adjuvant Chemotherapy in Ovarian Neoplasm Trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst* 2003;95:105–112, with permission.)

Two large parallel randomized phase III clinical trials were recently reported on women with early-stage disease: the **International Collaborative Ovarian Neoplasm Trial 1 (ICON1)** and the **Adjuvant Chemotherapy Trial in Ovarian Neoplasia (ACTION)** (219 ,220).

In the ICON1 trial, 477 patients from 84 centers in Europe were entered. Patients of all stages were eligible for the trial if in the opinion of the investigator, it was unclear whether adjuvant therapy would be of benefit. Most patients were said to have stages I and IIA disease but optimal **surgical staging was not required**, so it is likely an unquantified number of these women had stage III disease. Adjuvant platinum-based chemotherapy was given to 241 patients, and no adjuvant chemotherapy was given to 236 patients. **The 5-year survival was 73% in the group who received adjuvant chemotherapy compared with 62% in the control group** (HR = 0.65, $p = 0.01$) (220).

In the ACTION trial, 440 patients from 40 European centers were randomized; 224 patients received adjuvant platinum-based chemotherapy, and 224 patients did not (219). Patients with stages I and IIA, grades 2 and 3 were eligible. Only **about one-third of the total group was optimally staged** (151 patients). In the observation arm, optimal staging was associated with a better survival [hazard ratio (HR) = 2.31, $p = 0.03$], and in the nonoptimally staged patients, adjuvant chemotherapy was associated with an

improvement in survival (HR = 1.78, *p* = 0.009). **In optimally staged patients, no benefit of adjuvant chemotherapy was seen.** Therefore, in the ACTION trial, the benefit from adjuvant chemotherapy was limited to the patients with nonoptimal staging, suggesting that patients might only benefit if they had a higher likelihood of occult microscopic dissemination.

When the data from the two trials were combined and analyzed (221), a total of 465 patients were randomized to receive platinum-based adjuvant chemotherapy and 460 to observation until disease progression. After a median follow-up of more than 4 years, the overall survival was 82% in the chemotherapy arm and 74% in the observation arm (HR = 0.67, *p* = 0.001). Recurrence-free survival was also better in the chemotherapy arm: 76% versus 65% (HR = 0.64, *p* = 0.001). The results of this analysis must be interpreted with caution, because most of the patients did not undergo thorough surgical staging, but **the findings suggest that platinum-based chemotherapy should be given to patients who have not been optimally staged**.

The current GOG trial includes patients with high-risk stage I and stage II disease, and offers three cycles of *carboplatin* and *paclitaxel* followed by a randomization to either observation versus 26 weeks of weekly low-dose (40 mg/m^2) *paclitaxel.* High-risk stage I is defined as stages IA or IB, grade 3, stage IC, or clear cell carcinomas.

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 (206 ,207 ,211 ,213 ,219 ,221).

Table 11.4 Randomized Trials in Stage I Epithelial Ovarian Cancer (Since 1995)

Study	*Patients (Author)*	*Stages*	*Treatment*	*Best Arm*
GOG 7601 (207)	81 (Young et al.)	Stage I low risk	Observation vs. *melphalan*	No difference
GOG 7602 (207)	141	Stage I high risk/II	^{32}P vs. *melphalan*	No difference
Italian Cooperative (214)	47 (Bolis et al.)	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
GOG 95 (213)	205 (Young et al.)	Stage I high risk/II	*Cisplatin* 75 mg/m^2/*cyclophosphamid* 750 mg/m^2 vs. ^{32}P	*Cisplatin/cyclophosphamide* 77% vs. 66% 5-yr survival
Scandinavian Cooperative (217)	134 (Tropé et al.)	Stage I high risk	*Carboplatin* AUC × vs. observation	No difference
ICON1 (220)	477	Most stage I and II, optimal staging not required	Platinum-based vs. observation	73% (chemotherapy) vs. 62% (observation) 5-yr survival
ACTION (219)	448 (Trimbos et al.)	Stage I high-risk, IIA, one-third staged	Platinum-based vs. observation	Improved survival in optimally staged patients only
ICON 1-ACTION (221)	925 (Trimbos et al.)	Combined analysis		82% (chemotherapy) vs. 72% (observation) 5-yr survival
GOG 172	331 Maturing	Stage I high risk/II	*Paclitaxel* 175 mg/m^2/*carboplatin* AUC 7.5 3 vs. 6 cycles	
GOG 175	Accruing	Stage I high risk/II	*Paclitaxel* 175 mg/m^2/*carboplatin* AUC 6 followed by observation vs. *paclitaxel* 40 mg/m^2 weekly × 26 weeks	

GOG, Gynecologic Oncology Group; AUC, area under the curve.

Radiation Therapy

There are two general approaches to the treatment of low-stage epithelial ovarian cancer with radiation: intraperitoneal radiocolloids or whole-abdominal radiation therapy. In one retrospective study of ^{32}P, the 5-year survival was 85% (206). In a series of patients with stage I disease treated with whole abdominal radiation (205), the 5-year relapse-free survival was 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 (207). 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 with *cisplatin* and 61% with ^{32}P ($p < 0.01$). Furthermore, as noted earlier, the GOG protocol that randomized *cisplatin* and *cyclophosphamide* versus ^{32}P showed that the platinum-based chemotherapy was superior (213). Therefore, **while ^{32}P produces results similar to single-agent** *melphalan*, **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 (202).

Recommendation for Adjuvant Treatment of Early-Stage Ovarian Cancer

Low-Risk Early-Stage Disease

No adjuvant chemotherapy is recommended for these patients.

High-Risk Early Stage Disease

- **Patients with high-risk stage I epithelial ovarian cancer should be given adjuvant chemotherapy. The type depends on the patient's overall health and status.**
- **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 frailer women.**

Advanced-Stage Ovarian Cancer

Chemotherapy

Systemic chemotherapy is the standard treatment for metastatic epithelial ovarian cancer (222 ,223 ,224 ,225 ,226 ,227 ,228 ,229 ,230 ,231 ,232 ,233 ,234 ,235 ,236 ,237 ,238 ,239 ,240 ,241 ,242 ,243 ,244 ,245 ,246). After the introduction of *cisplatin* in the latter half of the 1970s, platinum-based combination chemotherapy has become the most frequently used treatment regimen in the United States (230). *Paclitaxel* became available in the 1980s, and this drug was incorporated into the combination chemotherapy in the 1990s (222 ,223 ,224 ,225 ,226 ,227 ,228 ,229). Comparative trials of *paclitaxel*, *cisplatin*, and *carboplatin* are summarized below.

Cisplatin Combination Chemotherapy

Combination chemotherapy has been shown to be superior to single-agent therapy in most studies of initial chemotherapy in patients with advanced epithelial ovarian cancer (230 ,231 ,232 ,233 ,234 ,235 ,236 ,237 ,238 ,239 ,240 ,241 ,242 ,243). 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 (234). Concurrently, *cisplatin* was tested in a variety of different combinations and the platinum-containing regimens were superior (236). A metaanalysis compared outcomes for patients given *cisplatin*-containing combination chemotherapy, with those for patients not receiving *cisplatin* (233). The *cisplatin* group had a slight survival advantage from 2 to 5 years, but this difference disappeared by 8 years (Fig 11.13).

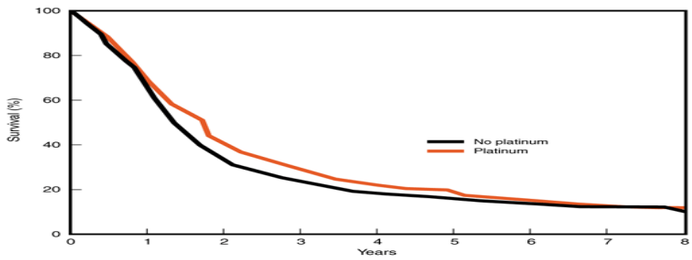

Figure 11.13 Survival of patients with advanced-stage ovarian cancer: a metaanalysis of multiple trials comparing *cisplatin*-containing combination chemotherapy with regimens without *cisplatin.* (From Advanced Ovarian Cancer Trialists Group. Chemotherapy in advanced ovarian cancer: an overview of randomized clinical trials. *BMJ* 1991;303:884, with permission.)

Most studies using the PC (*cisplatin* and *cyclophosphamide*) or PAC (*cisplatin, doxorubicin*, and *cyclophosphamide*) regimen have reported similar survival rates (237 ,238 ,239 ,240 ,241 ,242). The GOG's randomized prospective comparison of equitoxic doses of PAC versus PC showed no benefit to the inclusion of *doxorubicin* in the combination (238). Although a metaanalysis of the combined data from four trials showed a 7% survival advantage at 6 years for those patients treated with the *doxorubicin*-containing regimen (Fig. 11.14) (242), the survival curves converged at 8 years.

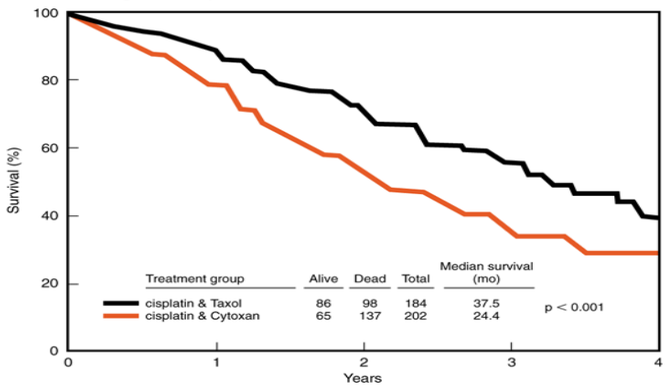

Figure 11.14 Survival of patients with suboptimal stage III and IV epithelial ovarian cancer treated with *paclitaxel* and *cisplatin* versus *cyclophosphamide* and *cisplatin*: a Gynecologic Oncology Group study (Protocol 111). (From **McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look 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.)

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 (230 ,231 ,232 ,246). These studies are listed in Table 11.5 .

Table 11.5 Randomized Trials Involving Platinum and Taxanes in Patients with Advanced-Stage Epithelial Ovarian Cancer

Group Protocol	*Ref.*	*Year*	*Author*	*Status*	*Drugs/Doses/(hrs)*[a]	*Best*
GOG 111	(230)	1996	McQuire et al.	Subopt	*Paclitaxel* 135 (3)/*cisplatin* 75 vs. *cyclophosphamide* 750/*cisplatin* 75	*Paclitaxel/cisplatin*
OV 10 EORTC/NOCOVA/NCIC	(231)	1998	Piccart et al.	Opt/subopt	*Paclitaxel* 175/*cisplatin* 75 vs. *cyclophosphamide* 750/*cisplatin* 75	*Paclitaxel/cisplatin*
GOG 132	(232)	2000	Muggia et al.	Subopt	*Cisplatin* 100 vs. *paclitaxel* 200 (24) vs. *cisplatin* 75/ *paclitaxel* 135 (24)	*Paclitaxel/cisplatin*
GOG 158	(246)	2003	Ozols et al.	Opt	*Carboplatin 7.5/paclitaxel 175 (3) vs. cisplatin* 75/*paclitaxel* 135 (24)	Paclitaxel/carboplatin
SCOT-ROC	(250)	1999	Vasey et al.	Opt/Subopt	*Docetaxel/cisplatin* vs. *paclitaxel/cisplatin*	*Docetaxel/carboplatin*
ICON3	(248)	2002	ICON3 Collaborators	Opt/subopt	*Carboplatin/paclitaxel* vs. *carboplatin* vs. *cisplatin/cyclophosphamide/doxorubicin*	*Carboplatin*
GOG 182/ICON5	(252)	2004	Completed, maturing	Opt/subopt	*Paclitaxel/carboplatin* × 8 vs. *paclitaxel/carboplatin/gemcitabine* × 8 vs. *paclitaxel/carboplatin/liposomal doxorubicin* × 8 vs. *carboplatin/topotecan* × 4 followed by *paclitaxel/carboplatin* × 4 vs. *carboplatin/gemcitabine* × 4 followed by *paclitaxel/carboplatin* × 4	

[a]*Carboplatin* doses in area under the curve; others in mg/m^2.

iv, intravenous; ip, intraperitoneal; AUC = area under the curve (Calvert formula); opt, optimal; subopt, suboptimal; GOG, Gynecologic Oncology Group; EORTC, European Organization for the Research and Treatment of Cancer; OV 10, Ovarian Protocol; NOCOVA, Nordic Ovarian Cancer Study Group; NCIC, National Cancer Institute of Canada; SCOT-ROC, Scottish Gynaecological Cancer Trials Group; ICON, International Collaborative Ovarian Neoplasm Group.

***Paclitaxel* was shown to be a very active agent in ovarian cancer** (222 ,223 ,224 ,225 ,226 ,227 ,228) The overall response rate of *paclitaxel* in phase II trials was 36% in previously treated patients (226), which is a higher rate than was seen for *cisplatin* when it was first tested.

Reporting the Gynecologic Oncology Group data (Protocol 111), McGuire et al. showed that the combination of *cisplatin* (75 mg/m²) and *paclitaxel* (135 mg/m²) was superior to *cisplatin* (75 mg/m²)and *cyclophosphamide* (600 mg/m²), each given for 6 cycles (230) (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 European Organization for the Research and Treatment of Cancer (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 (231). 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.**

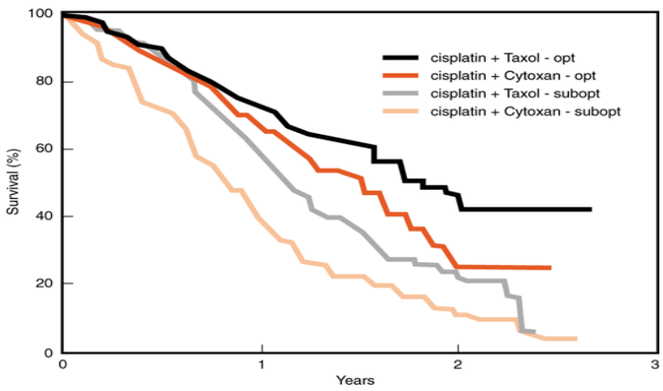

Figure 11.15 Survival of patients with stage III and IV epithelial ovarian cancer treated with *paclitaxel* and *cisplatin* or *cyclophosphamide* and *cisplatin:* results of a European cooperative group trials study. (a) Survival by treatment (b) Survival by treatment group (optimal vs. suboptimal). [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.]

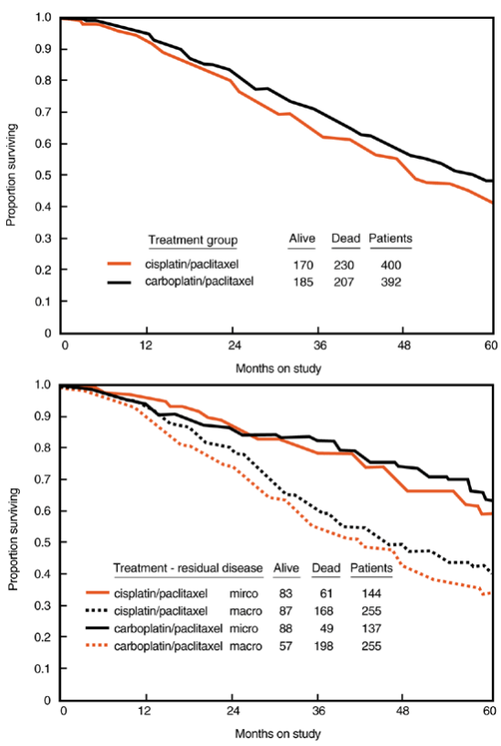

Figure 11.16 Survival of patients with stage III epithelial ovarian cancer treated with *carboplatin* and *paclitaxel* versus *cisplatin* and *paclitaxel:* a Gynecologic Oncology Group study (Protocol 158)

Top. Survival by treatment

Bottom. Survival by treatment group (microscopic vs. macroscopic)

[From **Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, et al.** Phase III trial of *carboplatin* and *paclitaxel* compared with *cisplatin* and *paclitaxel* in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 2003;21:3194–3200, with permission.]

A three-arm comparison of *paclitaxel* (T) versus *cisplatin* (P) versus PT in suboptimal stage III and IV patients (protocol 132) showed equivalency in the three groups, but crossover from one drug to the other was permitted (232). 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 analogue, *carboplatin*, was introduced and developed to have less toxicity than its parent compound, *cisplatin*. **Fewer gastrointestinal side**

effects, especially nausea and vomiting, are observed than with *cisplatin*, **and there is less nephrotoxicity, neurotoxicity, and ototoxicity** (243 ,244). *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 about 400 mg/m^2 *carboplatin* has been used in most phase II trials. **The precise dose of** *carboplatin* **is calculated by using the area under the curve (AUC) and the glomerular filtration rate (GFR) according to the Calvert formula** (245), as discussed in Chapter 4 . **The target AUC is 5 to 7 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 (245).

Carboplatin and Paclitaxel

Two randomized, prospective clinical studies have compared the combination of *paclitaxel* and *carboplatin* with *paclitaxel* and *cisplatin* (246 ,247) (Table 11.5). **In both studies, the efficacy and survivals were similar, but the toxicity was 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 (246). The progression-free survival of the *carboplatin*-containing arm was 20.7 months versus 19.4 months for the control arm. The overall survival was 57.4 months for the *carboplatin* arm versus 48.7 months for control arm. The relative risk (RR) of progression for the *carboplatin* plus *paclitaxel* group was 0.88, and the RR of death was 0.84. 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 (247), 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. The overall survival was 44.1 months for the *carboplatin*-containing arm versus 43.3 months for the control arm. **Thus, the preferred regimen in patients with advanced stage disease is the *paclitaxel* plus *carboplatin* combination**.

The International Collaborative Ovarian Neoplasm (ICON) 3 trial was a study of 2,074 women with all stages of ovarian cancer, including 20% who had stage I or II

disease (248 **).** *Carboplatin* **plus** *paclitaxel* **was compared with two non-***paclitaxel* **regimens**, *carboplatin* **(70%) or CAP (30%). The regimens were chosen before randomization and based on the clinical preference of the treating physician.** One-third of patients who received *carboplatin* or CAP subsequently received second-line *paclitaxel*, and this additional chemotherapy was often given before clinical progression. With a median follow-up of 51 months, the *carboplatin* plus *paclitaxel* and the control groups had a similar progression-free survival (0.93) and overall survival (0.98). **The median survival for the** *paclitaxel* **plus** *carboplatin* **and control groups was 36.1 and 35.4 months, respectively.** The median duration of progression-free survival was 17.3 and 16.1 months, respectively. **The researchers concluded that single agent** *carboplatin* **and CAP were as effective as** *paclitaxel* **and** *carboplatin* **for first-line chemotherapy.** Because *carboplatin* as a single agent had a lower toxicity than the other regimens and the median survival was similar in a prior trial that had compared *carboplatin* and CAP as first-line treatment (249), the researchers suggested that *carboplatin* alone was the preferred therapy. **However, the design of the study limits the validity of the results, because patients with FIGO stage I to IV disease were included, the extent of primary surgery was variable, and the study was not audited by an independent data monitoring committee. Also, the majority (85%) of patients who relapsed after single agent** *carboplatin* **subsequently received** *paclitaxel*. **Therefore, the study was not conclusive.**

Carboplatin and Docetaxel

Docetaxel **has a different toxicity profile from** *paclitaxel*. The SCOT-ROC (Scottish Gynaecological Cancer Trials Group) study randomly assigned 1,077 women with stage IC to IV epithelial ovarian cancer to *carboplatin* with either *paclitaxel* or *docetaxel* (250). **The efficacy of** *docetaxel* **appeared to be similar to** *paclitaxel*: the median progression-free survival was 15.1 months versus 15.4 months, and the *docetaxel* group had fewer neurologic effects, arthralgias, myalgias, and extremity weakness than the *paclitaxel* group. However, the *docetaxel* plus *carboplatin* regimen was associated with significantly more myelosuppression and its consequences, i.e., serious infections, and prolonged severe neutropenia. Therefore, additional study will be necessary to determine whether *docetaxel* should supplant *paclitaxel* in the primary treatment of epithelial ovarian cancer.

Five-Arm Trial

The ongoing intergroup, international trial (GOG 182/SWOG 182/ICON 5/ANZGOG) is comparing the standard combination of *carboplatin* and *paclitaxel* with these drugs in combination with *gemcitabine, topotecan*, or *liposomal doxorubicin* in sequential doublets or triplets (251 ,252).

A summary of these trials is presented in Table 11.5 .

Dose Intensification

Intravenous Chemotherapy

The issue of dose-intensification of *cisplatin* was examined in a prospective trial conducted by the GOG (253). In this study, 243 patients with suboptimal ovarian cancer were randomized to receive 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* (254). 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 (255). **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 (228 ,256).

Intraperitoneal Chemotherapy

A randomized, prospective trial in 546 evaluable patients of intraperitoneal *cisplatin* versus intravenous *cisplatin* (100 mg/m^2), each given with 750 mg/m^2 *cyclophosphamide*, was performed jointly by the Southwest Oncology Group (SWOG) and the GOG in patients with advanced ovarian cancer following optimal cytoreduction (residual nodules <2 cm diameter) (257). **The intraperitoneal *cisplatin* arm had a somewhat longer overall median survival than the intravenous arm, 49 versus 41 months** (p = 0.03). **In the patients with minimal residual disease (<0.5 cm maximum residual diameter), who would be expected to derive the most benefit, there was no difference between the two treatments, 51 versus 46 months** (p = 0.08). (Table 11.6)

Table 11.6 Intraperitoneal Chemotherapy

Group Protocol	*Ref.*	*Year*	*Author*	*Status*	*Drugs/Doses/(hrs)*	*Best Arm*
GOG 104	(257)	1996	Alberts et al.	Optimal	ip *cisplatin*/iv *cyclophosphamide vs.* iv *cisplatin*/iv *cyclophosphamide*	ip *cisplatin*/iv *cyclophosphamide*[a]
GOG 114	(258)	2001	Markman et al.	Optimal	iv *carboplatin* AUC = 9 ip *cisplatin* 100/iv *paclitaxel* 135 (24) vs. iv *cisplatin 75*/iv *paclitaxel* 135 (24)	ip *cisplatin*/iv *carboplatin*/iv *paclitaxel*[b]
GOG 172	(260)	Maturing	Armstrong et al.	Optimal	iv *paclitaxel* 135 (24)/ip *cisplatin* 100-day 2/ip *paclitaxel* 60-day 8 vs. iv *paclitaxel* 135 (24)/iv *cisplatin* 75	

[a]Median survival longer in ip arm, not in minimal residual (<0.5 mm) group.

[b]Progression-free survival longer in ip arm, no difference in overall survival.

AUC; area under the curve.

In a follow-up trial of 532 patients (GOG Protocol 114), the dose-intense arm was initiated by giving a moderately high dose of *carboplatin* (dose 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 (258). In the dose-intense arm, 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 months versus 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. A phase II trial of intravenous *paclitaxel* plus intraperitoneal *cisplatin* and *paclitaxel* was well tolerated and associated with a 2-year survival of 91% (259). **A randomized prospective GOG study is comparing intraperitoneal *cisplatin* and *paclitaxel* with intravenous *cisplatin* and *paclitaxel*** (260).

Based on these studies, the value of intraperitoneal chemotherapy in the primary treatment of optimally resected stage III ovarian cancer remains controversial.

Neoadjuvant Chemotherapy

Some authors have suggested that for patients with advanced disease, chemotherapy may be given before cytoreductive surgery. A series performed at Yale by Schwartz et al. (261)

suggested that the survival of patients treated with “neoadjuvant” chemotherapy was comparable to that of patients historically treated with primary cytoreductive surgery in the same institution. Neoadjuvant chemotherapy might be appropriate in selected patients who are at high risk for operative morbidity or mortality [e.g., those with significant cardiac disease (262 ,263), or those with large pleural effusions], but primary cytoreductive surgery should be considered the standard of care for most patients.

Chemotherapeutic Recommendations for Patients with Advanced Ovarian Cancer

For first-line chemotherapy of advanced epithelial ovarian cancer, we recommend (Table 11.7):

Table 11.7 Combination Chemotherapy for Advanced Epithelial Ovarian Cancer: Recommended Regimens

Drugs	*Dose*	*Administration (hr)*	*Interval*	*No. of Drugs Treatments*
Standard Regimens				
Paclitaxel	175 mg/m^2	3	Every 3 weeks	6–8 cycles
Carboplatin	AUC = 5–6			
Paclitaxel	135 mg/m^2	3	Every 3 weeks	6–8 cycles
Cisplatin	75 mg/m^2			
Alternative Drugs[a] (Can be given with platinum)				
Topotecan	1.0–1.25 mg/m^2		Daily × 3–5 days Every 3 weeks, or	
	4.0 mg/m^2		Weekly	
Gemcitabine	800–1000 mg/m^2		Every 3 weeks	
Doxorubicin, *liposomal*	40–50 mg/m^2		Every 4 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.

- **Combination chemotherapy with *carboplatin* and *paclitaxel* for six to eight cycles. The recommended doses and schedule are *carboplatin* (starting dose AUC = 5–6) and *paclitaxel* (175 mg/m^2) given over 3 hours every 3 weeks.**
- **In frail patients who may not tolerate the combination, single agent *carboplatin* (AUC = 5–6) can be given.**
- **In those who have a hypersensitivity to *paclitaxel*, an alternative drug can be substituted, e.g., *docetaxel, topotecan, gemcitabine*, or *liposomal doxorubicin.***
- **In patients who cannot tolerate intravenous chemotherapy, an oral agent can be substituted, e.g., *etoposide.***

Consolidation and Maintenance of Complete Clinical Response to First-Line Chemotherapy

Because as many as 80% of women with advanced-stage disease who completely respond to their first-line chemotherapy will ultimately relapse, several trials have been conducted that administer a drug to these patients immediately following their primary treatment in an effort to decrease the relapse rate.

Paclitaxel

In a study conducted by the GOG and SWOG, 277 women with advanced ovarian cancer who had a complete clinical response to first-line chemotherapy were randomized to receive 3 or 12 cycles of additional single-agent *paclitaxel* (175 or 135 mg/m^2 every 28 days) (264). Patients were excluded if they had developed grade 2 or 3 neurotoxicity during

their initial chemotherapy. Because of cumulative toxicity, the mean number of actual cycles of *paclitaxel* received by the group assigned to receive 12 cycles was 9. The treatment-related grade 2 to 3 neuropathy was more common with longer treatment, 24% versus 14% of patients, respectively. **The study was closed after a median follow-up of only 8.5 months, and an interim analysis showed a significant 7-month prolongation in median progression-free survival (28 versus 21 months) with 9 versus 3 months of consolidation** *paclitaxel*. **However, there was no difference in median overall survival.** The rate of disease progression increased significantly after maintenance therapy was discontinued, which suggested that long-term survival would not be likely to be improved. Furthermore, it is unlikely that a survival benefit will be seen with longer follow-up, because patients assigned to three cycles were given the option of receiving an additional nine courses of *paclitaxel* after the study was discontinued (265).

Topotecan

Four additional treatment courses of *topotecan* were administered to patients following six cycles of *carboplatin* and *paclitaxel* in two randomized trials, one conducted in Italy (266), and the other in Germany (267). In the larger trial conducted in Germany, 1,059 evaluable patients were randomly assigned to six cycles of *paclitaxel* (175 mg/m^2 over 3 hours) and *carboplatin* (AUC 5) with (537 patients) or without (522 patients) four additional cycles of *topotecan* (1.25 mg/m^2 IV days 1 to 5 every 3 weeks) (266). In the Italian trial, 273 women were randomly assigned to receive four additional cycles (137 patients) of *topotecan* at a dose of 1 mg/m^2 on days 1 to 5 every 3 weeks or no further chemotherapy (136 patients) (267). **Preliminary reports suggest no significant differences in either progression-free or overall survival in patients who received four to six cycles of consolidation** *topotecan.*

Cisplatin

In a randomized clinical trial of intraperitoneal cisplatin for consolidation versus observation, there was no difference in survival between the treatment arms (268).

Summary

The clinical benefit of consolidation and maintenance chemotherapy seems doubtful. Patients and their physicians may consider prolonged single agent *paclitaxel* **an option, but it should not be considered the standard of care at this time.**

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 infusions of *paclitaxel* (e.g., 3-hour) tend to reduce the likelihood of bone marrow depression when combining the drug with *carboplatin* (228). **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*; thus, patients do not require prehydration, and outpatient administration is more feasible. *Carboplatin* does tend to have significant bone marrow toxicity, and growth factors such as G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF) 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 (224 ,229). The use of growth factors is discussed more fully in Chapter 4 .

There are some data that suggest that *amifostine* can reduce *carboplatin*-induced neurotoxicity (269). In a phase III randomized trial of 187 women, the incidence of grade 3–4 neutropenia was lower in the arm with *amifostine* (31.3% versus 37.9%; P = 0.03), as was the incidence of severe mucositis (4.7% versus 15.4%, respectively; P <0.0001). *Amifostine* appears to be protective against neurotoxicity (grade 3–4 neurotoxicity 3.7% versus 7.2%; P = 0.02).

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 per hour for 2 to 4 hours until the urinary output is greater than 100 mL per 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 per hour for 6 hours, and it is discontinued if the patient is stable.

The principal toxicities of this regimen are renal, gastrointestinal, hematologic, and neurologic. The renal and neurologic toxicities generally 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, *ondancetron*, given as a 32-mg intravenous bolus, followed every 4 to 6 hours with 10 mg intravenously. Alternative regimens include (i) *diphenhydramine*, 25 mg orally, and *lorazepam*, 2 mg sublingually, both given 1 hour before the initiation of treatment, followed by *lorazepam*, 2 mg sublingually every 3 hours, or (ii) *metoclopramide*, 100 mg intravenously every 3 to 4 hours, and one dose of *dexamethasone*, 20 mg intravenously.

Radiation Therapy

An alternative to first-line combination chemotherapy for selected patients with metastatic ovarian cancer is the use of whole-abdominal radiation therapy. This approach is not used in the United States, but it has been standard treatment in some institutions in Canada for patients with no residual macroscopic tumor in the upper abdomen (205). It has been compared with oral *chlorambucil* and appears to be superior (205), but has not been tested against combination chemotherapy.

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 (270). No apparent benefit could be shown by adding whole-abdominal radiation after chemotherapy in patients with optimal disease.

Hormonal Therapy

There is no evidence that hormonal therapy alone is appropriate primary therapy for advanced ovarian cancer (271).

Immunotherapy

There is a great deal of interest in the use of biologic response modifiers in ovarian cancer, and in a trial of *gamma interferon* with *cisplatin* and *cyclophosphamide* chemotherapy, there appeared to be a benefit to the addition of the *interferon* (272). A trial of *carboplatin* and *paclitaxel* with or without *gamma interferon* is currently under way

Trials of monoclonal antibodies directed toward ovarian cancer-associated antigens are being conducted. Antibodies directed toward CA125 (*OvaRex*) (273 ,274 ,275) are being conducted.

Studies with monoclonal antibodies directed at HMFG (human milk fat globulin) tumor-associated antigens for consolidation have shown no survival benefit (276). *Herceptin*, an humanized 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. A trial of *herceptin* antibody in her-2/*neu* overexpressing ovarian cancers has been conducted by the GOG, and the response rate was low, i.e., 9.7% (277). The rationale for the use of these agents in ovarian cancer is discussed in Chapter 3 .

Treatment Assessment

Part of "11 - Epithelial Ovarian Cancer "

Many patients who undergo optimal cytoreductive surgery and subsequent chemotherapy for epithelial ovarian cancer will 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 has been the **"second-look" operation** (278 ,279 ,280 ,281 ,282 ,283 ,284 ,285 ,286). Far fewer such operations are now done than in the past because **it is unclear if the operation** *per se* **permits a change in therapy that affects overall survival**. Most often, patients have undergone a formal reassessment laparotomy, although the laparoscope has also been used in this circumstance (287 ,288 ,289).

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. **Positive CA125 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 (290), the positive predictive value was shown to be 100%; i.e., if the level of CA125 was >35 U/mL, disease was always detectable in patients at second-look laparotomy. The predictive value of a negative test was only 56%; i.e., if the level was <35 U/mL, disease was present in 44% of the patients. **A review of the literature suggests that an elevated CA125 level predicts persistent disease at second-look in 97% of the cases** (29).

Serum CA125 levels can be used during chemotherapy to follow those patients whose level was elevated at the initiation of treatment (29 ,290 ,292). The change in level generally correlates with response. Those patients with persistently elevated levels after three cycles of treatment most likely have resistant clones. **Rising levels on treatment almost invariably indicate treatment failure.** A retrospective study has determined that a doubling of the CA125 level from its nadir in those patients with a persistently elevated level accurately predicts disease progression (291).

Radiologic Assessment

In patients with stage I to III epithelial ovarian cancer, radiologic tests have generally been of limited value in determining the presence of subclinical disease. Ascites can be readily detected, but **even quite large omental metastases can be missed on CT scan** (82 ,293 ,294). If liver enzymes are abnormal, the liver can be evaluated with a CT scan or ultrasonography. CT scan–directed fine-needle aspiration (FNA) cytology will indicate tumor persistence if positive, but the false-negative rate of a CT scan is about 45% (293). **Positron-emission tomography (PET) alone or with CT imaging may help in the detection of relapse, although the relative value of adding PET has not been established.** There appears to be a higher false-positive rate with PET compared with CT (83 ,84 ,85). MRI can be used as an alternative to CT in patients with allergies to the contrast medium (85).

Second-Look Operations

A second-look operation is one performed on a patient who has no clinical evidence of disease after a prescribed course of chemotherapy in order to determine the response to therapy.

Second-Look Laparotomy

The technique for a second-look laparotomy is essentially identical to that for a 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 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.

About 30% of patients with no evidence of macroscopic disease will have microscopic metastases (278). Also, in many patients with microscopic disease, it will be detected in only the occasional biopsy or cytologic specimen. Therefore, a large number of specimens (20 ,21 ,22 ,23 ,24 ,25 ,26 ,27 ,28 ,29 ,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 (295 ,296 ,297 ,298 ,299 ,300 ,301 ,302 ,303 ,304), as well as permitting 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 correlates with subsequent outcome and survival (279 ,280 ,281 ,282 ,285 ,286). Patients who have no histologic evidence of disease have a significantly longer survival than those in whom microscopic or macroscopic disease is documented. **The operation should be performed selectively, e.g., in patients receiving therapy in a setting where second-line therapies are undergoing clinical trials.**

The likelihood that a patient will have a recurrence after a negative second-look laparotomy ranges from 30% to 60% at 5 years (282 ,283 ,284 ,285). The majority of recurrences after a negative second-look laparotomy are in patients with poorly differentiated cancers (285). Variables associated with the outcome of the second-look laparotomy are (i) initial stage, (ii) tumor grade, (iii) the size of the residual tumor and the size of the largest metastatic tumor before treatment, and (iv) the type of chemotherapy.

No single variable or combination of variables is sufficiently accurate to predict the histopathologic findings at second-look laparotomy (284). 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% (280 ,281 ,282). The majority of patients with low-stage 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 about 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** (278 ,285). The probability of a negative second-look is higher in those patients whose disease is microscopic or ≤5 mm at the start of therapy (278 ,281 ,282 ,285). **Patients with very extensive metastatic tumors have little likelihood of a negative second-look, regardless of the extent of tumor reduction.** 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 (230). In patients with optimally resected stage III disease treated with the platinum and *paclitaxel* regimen, the negative second-look rate is about 45% to 50% (246).

Second-Look Laparoscopy

The laparoscope in epithelial ovarian cancer patients 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. 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 (287 ,288 ,289). The development of newer techniques for retroperitoneal lymph node dissection has potentially increased the utility of the endoscopic approach to second-look.

Secondary Therapy

Part of "11 - Epithelial Ovarian Cancer "

Secondary Cytoreduction

Secondary cytoreduction maybe defined as an attempt at cytoreductive surgery at some stage following completion of first-line chemotherapy (295). Patients with progressive disease on chemotherapy are not suitable candidates for secondary cytoreduction, but patients who are clinically free of disease and undergo second-look laparotomy may benefit if all macroscopic residual disease can be resected (296). Patients with recurrent disease are occasionally candidates for surgical excision of their disease. **Tumor resection under these circumstances should be restricted to those who have a disease-free interval of at least 12, but preferably 24 months, or those in whom all macroscopic disease can be resected**, regardless of the disease free interval (297 ,299)**.**

Second-Line Chemotherapy

If disease persists at the time of second-look laparotomy, or if clinically progressive disease develops during primary therapy, patients usually have been switched to an alternative treatment, often a second-line agent. The response rates for second-line chemotherapies have been 15% to 35% for most drugs tested by the oral or intravenous route (305 ,306 ,307 ,308 ,309 ,310 ,311 ,312 ,313 ,314 ,315 ,316 ,317 ,318 ,319 ,320 ,321 ,322 ,323 ,324 ,325 ,326 ,327 ,328 ,329 ,330 ,331 ,332 ,333 ,334 ,335 ,336 ,337 ,338 ,339 ,340 ,341 , 342 ,343 ,344 ,345 ,346 ,347 ,348 ,349 ,350 ,351 ,352 ,353 ,354 ,355 ,356 ,357 ,358 ,359 ,360 ,361 ,362 ,363 ,364 ,365 ,366 ,367 ,368 ,369 ,370) (Table 11.7).

Platinum-Sensitive Disease

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 6 to 24 months or longer** (305 ,306 ,307 ,308 ,309) (Table 11.8).

Table 11.8 Second-Line Chemotherapy in Recurrent/Persistent Epithelial Ovarian Cancer

Drugs Used in Platinum- and Taxane-Sensitive Disease
Response Rates 20%–40%
Cisplatin
Carboplatin
Paclitaxel (Taxol)
Docetaxel (Taxotere)
Drugs Used in Platinum- and Taxane-Resistant and Refractory Disease
Response Rates 10%–25%
Topotecan (Hycamtin)
Etoposide (oral) (VP-16)
Liposomal doxorubicin (Doxil)
Gemcitabine (Gemzar)
Epirubicin
Hexamethylmelamine (Altretamine)
5-fluorouracil/leucovorin

There are studies that suggest that a platinum plus *paclitaxel* may be better in some patients for second-line therapy than platinum alone (310 ,311). In a study of 25 women who relapsed 6 months or longer after first-line *carboplatin* and *paclitaxel*, retreatment with the same combination had a response rate of 91% and a median progression-free survival of more than 9 months (311). Others suggest that single-agent therapy (*cisplatin* or *carboplatin*) should be considered the standard of care for platinum-sensitive disease (312 ,313). **In most studies, there is a lack of survival advantage and greater toxicity with multiagent compared with single-agent regimens**, although the combination of *carboplatin* and *paclitaxel* is well tolerated (314).

The use of combination platinum plus *paclitaxel* chemotherapy versus a single-agent platinum was tested in two multinational randomized phase III trials (315) and a randomized phase II study (316). In a report of the ICON4 (315) and AGO-OVAR-2.2 (316) trials, 802 women with platinum-sensitive ovarian cancer who relapsed after being

treatment-free for at least 6 to 12 months were randomized to platinum-based chemotherapy (72% *carboplatin* or *cisplatin* alone; 17% CAP; 4% *carboplatin* plus *cisplatin*; and 3% *cisplatin* plus *doxorubicin*) or *paclitaxel* plus platinum-based chemotherapy (80% *paclitaxel* plus *carboplatin*; 10% *paclitaxel* plus *cisplatin*; 5% *paclitaxel* plus both *carboplatin* and *cisplatin*; and 4% *paclitaxel* alone). The AGO-OVAR-2.2 trial did not accrue its planned number of patients. **In both trials, a significant proportion of the patients had not received** *paclitaxel as part of their initial chemotherapeutic regimen. Combining the trials for analysis, there was a significant survival advantage for the paclitaxel*-**containing therapy** (HR = 0.82) with a median follow up of 42 months. **The absolute 2-year survival advantage was 7% (57% vs. 50%), and there was a 5-month improvement in median survival (29 vs. 24 months).** Progression-free survival was better with the *paclitaxel* regimen (HR = 0.76); there was a 10% difference in 1-year progression-free survival (50% vs. 40%) and a 3-month prolongation in median progression-free survival (13 vs. 10 months). The toxicities were comparable, except there was a significantly higher incidence of neurologic toxicity and alopecia in the *paclitaxel* group, while myelosuppression was significantly greater with the non-*paclitaxel*-containing regimens. **These data support the slight advantage of a second-line regimen containing both** *paclitaxel* **and a platinum agent compared with platinum-based therapy alone in patients who have not received** *paclitaxel* **in their primary chemotherapeutic regimen.**

Platinum-Resistant and Refractory Disease

In *cisplatin*-**refractory patients, i.e., those progressing on treatment, response rates to second-line** *carboplatin* **are less than 10%** (309). **The management of women who are platinum resistant i.e., progressing within 6 months of completion of chemotherapy, requires the use of non-cross-resistant agents. Single-agent therapy is typically used, because combination regimens are associated with more toxicity without additional benefit. There are a variety of active drugs:** *paclitaxel, docetaxel, topotecan, liposomal doxorubicin, gemcitabine, oral etoposide*, **and** *tamoxifen* **are the most frequently used.** Other active agents include *vinorelbine, ifosfamide*, and *leucovorin-modulated 5-fluorouracil*.

Some researchers have used these drugs to prolong the “platinum-free interval,” hoping that their use will allow the tumor to become platinum sensitive during the interval use of non-cross-resistant agents. The rationale for this method is that the platinum-free interval is equivalent to the treatment-free interval, and before the availability of other active drugs, these two terms were synonymous. However, **there are no data to support the hypothesis that the interposition of another drug can produce an increased platinum sensitivity as a result of a longer interval since the last platinum treatment.**

Taxanes

Single-agent paclitaxel shows objective responses in 20% to 30% in phase II trials of women with platinum-resistant ovarian cancer (317 ,318 ,319 ,320 ,321 ,322 ,323). The main toxicities are asthenia and peripheral neuropathy. A dose of 135 to 175 mg/m^2 every 3 weeks, either as a 3-hour or 24-hour infusion, may be considered standard, because a randomized trial showed similar response rates for both regimes (318). Three-hour infusions produce more neurotoxicity but less myelosuppression. Higher doses of *paclitaxel* (250 mg/m^2 vs. 175 mg/m^2 per dose) using hematopoietic growth factor support can result in higher response rates, but with significantly more toxicity and no survival benefit (320).

Weekly *paclitaxel* is active, and the toxicity, especially myelosuppression, is less than with the every-3-weeks regimens. In a study of 53 women with platinum-resistant ovarian cancer, weekly *paclitaxel* (80 mg/m^2 over 1 hour) had an objective response of 25% in patients with measurable disease, and 27% of patients without measurable disease had a 75% decline in serum CA125 levels (320).

Docetaxel also has some activity in these patients (324 ,325 ,326). The GOG studied 60 women with platinum-resistant ovarian or primary peritoneal cancer (326). Although there was a 22% objective response rate, the median response duration was only 2.5 months, and therapy was complicated by severe neutropenia in three-quarters of patients.

Topotecan

Topotecan is an active second-line treatment for patients with platinum-sensitive and platinum-resistant disease (327 ,328 ,329 ,330 ,331 ,332 ,333 ,334 ,335 ,336 ,337 ,338 ,339 ,340 ,341 ,342). In a study of 139 women receiving *topotecan* 1.5 mg/m^2 daily for 5 days, response rates were 19% and 13% in patients with platinum-sensitive and platinum-resistant disease, respectively (327). **The predominant toxicity of *topotecan* is hematologic, especially neutropenia.** With the 5-day dosing schedule, approximately 70% to 80% of patients have severe neutropenia, and 25% have febrile neutropenia with or without infection (331 ,332). In some studies, regimens of 5 days produce better response rates than regimens of shorter duration (327 ,328 ,329 ,330 ,331 ,332 ,333 ,334 ,335 ,336 ,337), but in others, reducing the dose to 1.0 mg/m^2/day for 3 days is associated with similar response rates but lower toxicity (338 ,339). In a study of 31 patients, one-half of whom were platinum refractory (340), *topotecan* 2 mg/m^2/day for 3 days every 21 days had a 32% response rate. Continuous infusion *topotecan* (0.4 mg/m^2/day for 14–21 days) had a 27% to 35% objective response rates in platinum-refractory patients (333 ,334). **Weekly *topotecan* administered at a dose of 4 mg/m^2/week for 3 weeks with a week off every month produced a response rate similar to the 5-day regimen with considerably less toxicity; therefore, this is now considered the regimen of choice for this agent** (342).

Oral topotecan, not currently available in the United States, **results in similar response rates with less hematologic toxicity** (336). The intravenous and oral formulations of *topotecan* were compared in a randomized trial of 266 women as a third-line regimen after an initial platinum-based regimen (341). Compared with intravenous *topotecan* (1.5 mg/m^2 daily for 5 days every 3 weeks), oral *topotecan* (2.3 mg/m^2/day for 5 days

every 3 weeks) produced a similar response rate (13% vs. 20%), less severe myelosuppression, and only a slightly shorter median survival (51 vs. 58 weeks).

Liposomal Doxorubicin

Liposomal doxorubicin (*Doxil* in the United States and *Caelyx* in Europe) has activity in platinum- and taxane-refractory disease (343 ,344 ,345). **The predominant severe toxicity of *liposomal doxorubicin* is the hand-foot syndrome, also known as palmar-plantar erythrodysesthesia or acral erythema. This morbidity is observed in 20% of patients who receive 50 mg/m^2 every 4 weeks** (343). *Liposomal doxorubicin* tends to produce a low rate of both neurologic toxicity and alopecia. In a study of 89 patients with platinum-refractory disease, including 82 *paclitaxel*-resistant patients, *liposomal doxorubicin* (50 mg/m^2 every 3 weeks) produced a response in 17% (1 complete and 14 partial responses) (344). In another study, an objective response of 26% was reported, although there were no responses in women who progressed during first-line therapy (343).

There have been two randomized trials comparing *liposomal doxorubicin* with either *topotecan* or *paclitaxel*. In a study of 237 women who relapsed after receiving one platinum-containing regimen, 117 of whom (49.4%) had platinum-refractory disease (345), *liposomal doxorubicin* 50 mg/m^2 over 1 hour every 4 weeks was compared with *topotecan* 1.5 mg/m^2/day for 5 days every 3 weeks. **The two treatments had a similar overall response rate** (20% vs. 17%), **time to progression** (22 vs. 20 weeks), **and median overall survival** (66 vs. 56 weeks). The myelotoxicity was significantly lower in the *liposomal doxorubicin*-treated patients than with those receiving *topotecan*. In a second study comparing *liposomal doxorubicin* with single-agent *paclitaxel* in 214 platinum-treated patients who had not received prior taxanes (346), the overall response rates for *liposomal doxorubicin* and *paclitaxel* were 18% vs. 22%, respectively, and median survival durations were 46 and 56 weeks, respectively, and these were not significantly different.

Gemcitabine

Gemcitabine has been associated with response rates of 20% to 50%, with 15% to 30% in patients who are platinum resistant (349 ,350 ,351 ,352 ,353). **The principal toxicities are myelosuppression and gastrointestinal.** The drug has been used in doublet combinations with *cisplatin* or *carboplatin* with acceptable responses and toxicities, and in the triplet combination with *carboplatin* and *paclitaxel* (351).

Oral Etoposide

The most common toxicities with oral *etoposide* are myelosuppression and gastrointestinal: Grade 4 neutropenia is observed in about one-fourth of patients, and 10% to 15% have severe nausea and vomiting (354 ,355 ,356). Although an initial study of intravenous *etoposide* reported an objective response rate of only 8% among 24 patients (354), a subsequent study of oral *etoposide* given for a prolonged treatment (50 mg/m^2 daily for 21 days every 4 weeks) had a 27% response rate in 41 women with platinum-resistant disease, 3 of whom had durable complete responses (355). In 25 patients with platinum and taxane-resistant disease, 8 objective responses (32%) were reported. **Oral *etoposide* should be considered one of the principal drugs to be used in patients with *paclitaxel*- and platinum-resistant disease.**

Other Agents

Other active oral agents associated with response rates of 20% to 25% include *hexamethamelamine* (357 ,358) and *capecitabine* (359). Two other active agents, 5-fluorouracil with *leucovorin* (360) and *ifosphamide* with *mesna* (361), require the chemoprotective agent to ameliorate the toxicity of the cytotoxic agent.

Hormonal Therapy

Tamoxifen **has been associated with response rates of 15% to 20% in well-differentiated carcinomas of the ovary** (362 ,363 ,364 ,365 ,366). The gonadotropin-agonist *leuprolide acetate* (*Lupron*) has been shown to produce a response rate of 10% in one series (367). Trials combining *tamoxifen* and *leuprolide acetate*, and *tamoxifen* and combination chemotherapy are being conducted (368). Aromatase inhibitors, e.g., *letrozole, anastrozole*, and *exemestane*, which have been shown to have activity in metastatic breast cancer, are being studied in relapsed ovarian cancer (369). One of the principal advantages of this class of agents is the very low toxicity (370).

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 (371 ,372 ,373 ,374 ,375 ,376 ,377 ,378 ,379 ,380 ,381 ,382 ,383 ,384 ,385 ,386 ,387 ,388). 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-fluorouracil (5-FU), etoposide (VP-16)*, and *mitoxantrone*, have been used as single agents in patients with persistent epithelial ovarian cancer (371 ,372 ,373 ,374 ,375 ,376), 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 about 20% to 40% for carefully selected patients, and the complete response rate is about 10% to 20%. Although *cisplatin* is an effective drug, the response rates appear to be enhanced by combining it with *etoposide, 5-fluorouracil, cytosine arabinoside* or *thiotepa* (374 ,376 ,378 ,382). Although it has been suggested that this approach produces a significant subsequent improvement in survival (379), 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* (380 ,381 ,382) (see Chapter 3). It has been found to have some activity in patients with minimal residual disease (380 ,381 ,382 ,383 ,384 ,385 ,386 ,387). Because of recombinant DNA technology, the cytokines in particular are becoming increasingly available for clinical testing. Trials of intraperitoneal α-*interferon*, γ-*interferon, tumor necrosis factor*, and *interleukin 2* have been performed. **The response rate for the intraperitoneal cytokines, α-*interferon and* γ-*interferon*, is the same as that for the cytotoxic agents, i.e., about 28% to 50%** (380 ,381 ,382 ,385 ,387). The intraperitoneal administration of α-*interferon* 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* (380). This experience was replicated in a multiinstitutional trial in which the surgically documented complete response rate was 28% in platinum-sensitive patients (381).

The interferons have been combined with cytotoxic agents in an effort to increase the overall response rates. The combination of *cisplatin* and α-*interferon* produced a 50% complete response rate, which was greater than that produced by either single agent alone (382). The alternating use of the two agents produced a response rate similar to that seen with each of the single agents used separately (384). 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 (385).

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 peripheral stem cell protection is being tested in patients with advanced ovarian cancer (389 ,390 ,391). 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 (389).

A phase III randomized trial of 57 patients treated with high-dose chemotherapy (*cyclophosphamide* 6000 mg/M^2 and *carboplatin* 1600 mg/M^2) with peripheral blood stem cell support as consolidation vs. 53 patients treated with conventional dose maintenance (*cyclophosphamide* 600 mg/M^2 and *carboplatin* 300 mg/M^2) has been reported (391). Only 43 of the 57 (75%) women completed the high-dose therapy, while 48 of 53 (92%) completed the standard dose regimen. There was no statistically significant difference in progression-free and overall survival between the two groups of patients.

A prospective randomized clinical trial of a combination very high-dose chemotherapy supported with ABMT versus standard-dose chemotherapy with *paclitaxel* and *carboplatin* was initiated by the Gynecologic Oncology Group, but the trial was discontinued because of poor accrual.

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. **As many as 30% of patients treated with this approach develop intestinal obstruction**, which will necessitate potentially morbid exploratory surgery (392).

Intestinal Obstruction

Patients with epithelial ovarian cancer often develop intestinal obstruction, either at the time of initial diagnosis or, more frequently, in association with recurrent disease (393 ,394 ,395 ,396 ,397 ,398 ,399 ,400 ,401 ,402 ,403 ,404 ,405 ,406 ,407 ,408). **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 (393). 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., less than 2 months), surgical relief of the obstruction is not indicated (393 ,394 ,395 ,396 ,397 ,398). **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, and parenteral alimentation (399 ,400 ,401 ,402 ,403 ,404 ,405). In some patients, the obstruction may be alleviated by this conservative approach. A preoperative upper gastrointestinal series and a barium enema will define possible sites of obstruction.

If exploratory surgery is deemed appropriate, the type of operation to be performed will depend on (i) the site and (ii) 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 (405 ,406). 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. Intestinal bypass is generally less

morbid than resection, and in patients with progressive cancer, the survival time after these two operations is the same (402 ,403 ,404 ,405 ,406).

If multiple obstructions are present, resection of several segments of intestine is usually not indicated, and intestinal bypass and/or colostomy should be performed. A gastrostomy may occasionally be useful in this circumstance (406), and this can usually be placed percutaneously (407).

Surgery for bowel obstruction in patients with ovarian cancer carries an operative mortality of about 10% and a major complications rate of about 30% (394 ,395 ,396 ,397 ,398 ,399 ,400 ,401 ,402 ,403 ,404 ,405 ,406). The need for multiple reanastomoses and prior radiation therapy increase the morbidity, which consists primarily of sepsis and enterocutaneous fistulae. The median survival ranges from 3 to 12 months, although about 20% of such patients survive longer than 12 months (399).

Survival

Part of "11 - Epithelial Ovarian Cancer "

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 below (10 ,138 ,139 ,140 ,141 ,142 ,409):

Age

Including patients at all stages, patients younger than 50 years of age have a 5-year survival rate of about 40%, compared with about 15% for patients older than 50 years (10 ,138 ,139 ,143).

Stage

The 5-year survival rate for carefully staged patients with stage I disease is 76% to 93%, depending on the tumor grade (10 ,138). The 5-year survival for stage II disease is 60% to 74%, for stage IIIA 41%, for stage IIIB about 25%, for stage IIIC 23%, and for stage IV 11% (10 ,143). The proportion in each stage at the time of diagnosis is shown in Figure 11.17 , and the survival by substage is presented in Figure 11.18 .

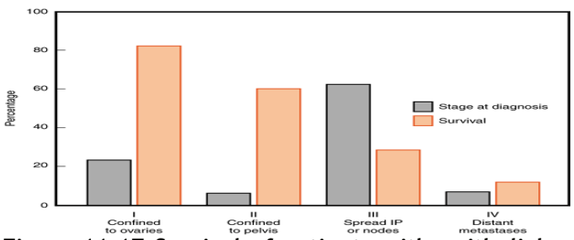

Figure 11.17 Survival of patients with epithelial ovarian cancer by stage. The percentage of patients diagnosed at a particular stage is shown next to the 5-year survival by stage. IP, intraperitoneal.

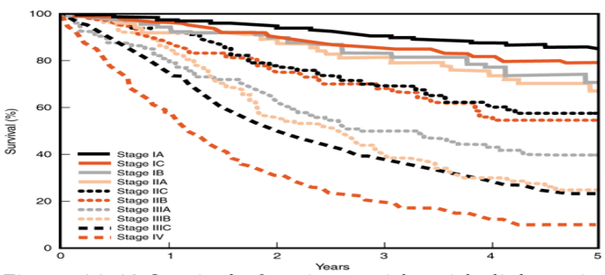

Figure 11.18 Survival of patients with epithelial ovarian cancer by substage. (From **Heintz APM, Odicino F, Maisonneuve P, Beller U, Benedet JL, Creasman W, et al.** Carcinoma of the ovary. *25th annual report on the results of treatment of gynecological cancer. Int J Gynecol Obstet* 2003;83:135-166.)

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 (1988-1994). In this cohort, the survival for stage I was 93%, for stage II 70%, for stage III 37%, and for stage IV 25% (409). **Compared with the interval 1983 to 1987, there was a statistically significant improvement in survival for stages I, III, and IV disease.**

Grade

Survival of patients with borderline tumors is excellent, with stage I lesions having a 98% 15-year survival (5 ,159 ,160 ,167). When all stages of borderline tumors are included, the 5-year survival rate is about 86% to 90% (5 ,10 ,159 ,160 ,167) (Fig. 11.19).

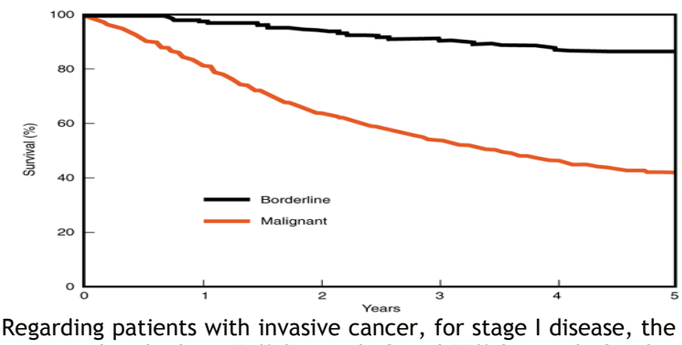

Figure 11.19 Survival of patients with borderline versus invasive epithelial ovarian cancer. (From **Heintz APM, Odicino F, Maisonneuve P, Beller U, Benedet JL, Creasman W, et al.** Carcinoma of the ovary. *25th annual report on the results of treatment of gynecological cancer. Int J Gynecol Obstet* 2003;83:135-166.)

Regarding patients with invasive cancer, for stage I disease, the 5-year survival rate for grade 1 epithelial ovarian cancer is about 91%, compared with about 74% for grade 2 and 75% for grade 3 (10 ,102) (Fig. 11.20). For stage II disease, the survivals are 69%, 60%, and 51%, respectively, for grades 1, 2, and 3 (10). Examining stage III-IV patients, the 5-year survivals for grades 1,2, and 3, respectively, are 38%, 25%, and 19% (10) (Fig. 11.21).

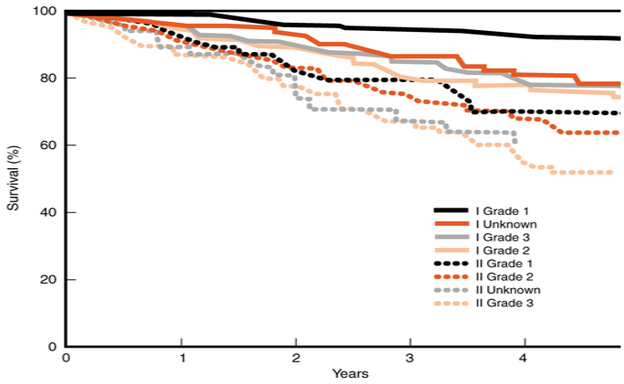

Figure 11.20 Survival of patients with FIGO stages I and II epithelial ovarian cancer by grade of the tumor. (From **Heintz APM, Odicino F, Maisonneuve P, Beller U, Benedet JL, Creasman W, et al.** Carcinoma of the ovary. *25th annual report on the results of treatment of gynecological cancer. Int J Gynecol Obstet* 2003;83:135–166.)

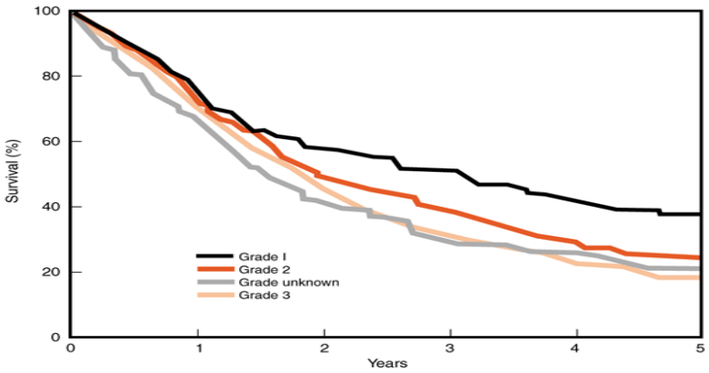

Figure 11.21 Survival of patients with FIGO stages III and IV epithelial ovarian cancer by grade of the tumor. (From **Heintz APM, Odicino F, Maisonneuve P, Beller U, Benedet JL, Creasman W, et al.** Carcinoma of the ovary. *25th annual report on the results of treatment of gynecological cancer. Int J Gynecol Obstet* 2003;83:135–166.)

Residual Disease

Patients with stage III disease with microscopic residual disease at the start of treatment have a 5-year survival rate of about 40% to 75%, compared with

about 30% to 40% for those with optimal disease and only 5% for those with nonoptimal disease (195) (Figure 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 about 35% for those with microscopic disease and about 5% for those with macroscopic disease (285 ,286).

Performance Status

Patients whose Karnofsky's index (KI) is low (<70) have a significantly shorter survival than those with a KI >70 (138 ,143).

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12

Nonepithelial Ovarian and Fallopian Tube Cancers

Jonathan S. Berek

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.

Non-epithelial malignancies of the ovary account for about 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 ,5).

- Germ Cell Malignancies
- Sex Cord–Stromal Tumors
- Uncommon Ovarian Cancers
- Metastatic Tumors
- Fallopian Tube Cancer

Germ Cell Malignancies

Part of "12 - Nonepithelial Ovarian and Fallopian Tube Cancers "

Germ cell tumors are derived from the primordial germ cells of the ovary. Their incidence is only about 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, the majority of 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 α-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 (PLAP) and lactate dehydrogenase (LDH)**

are produced by up to 95% of dysgerminomas, and serial measurements of LDH may be useful for monitoring the disease. α-1-antitrypsin (AAT) 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 (Fig. 12.1) (6).

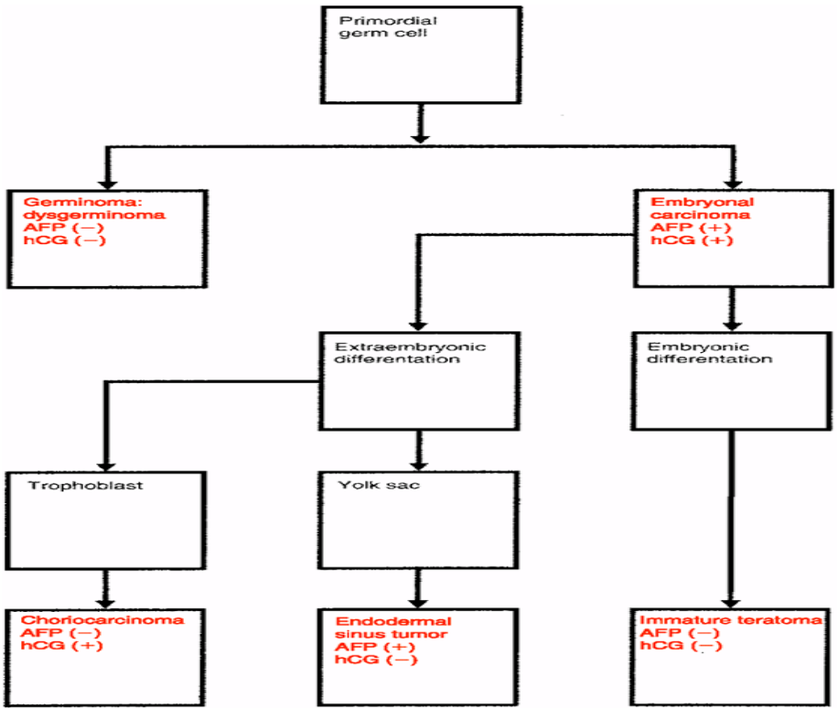

Figure 12.1 Relationship between examples of pure malignant germ cell tumors and their secreted marker substances.

Table 12.1 Histologic Typing of Ovarian Germ Cell Tumors

I. *Primitive germ cell tumors*
- Dysgerminoma
- Yolk sac tumor
- Embryonal carcinoma
- Polyembryoma
- Non-gestational choriocarcinoma
- Mixed germ cell tumor

II. *Biphasic or triphasic teratoma*
- Immature teratoma
- Mature teratoma
  - Solid
  - Cystic
    - Dermoid cyst
    - Fetiform teratoma (homunculus)

III. *Monodermal teratoma and somatic-type tumors associated with dermoid cysts*
- Thyroid tumor
  - Struma ovarii
    - Benign
    - Malignant
- Carcinoid
- Neuroectodermal tumor
- Carcinoma
- Melanocytic
- Sarcoma
- Sebaceous tumor
- Pituitary-type tumor
- Others

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, 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 about 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 will be 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.

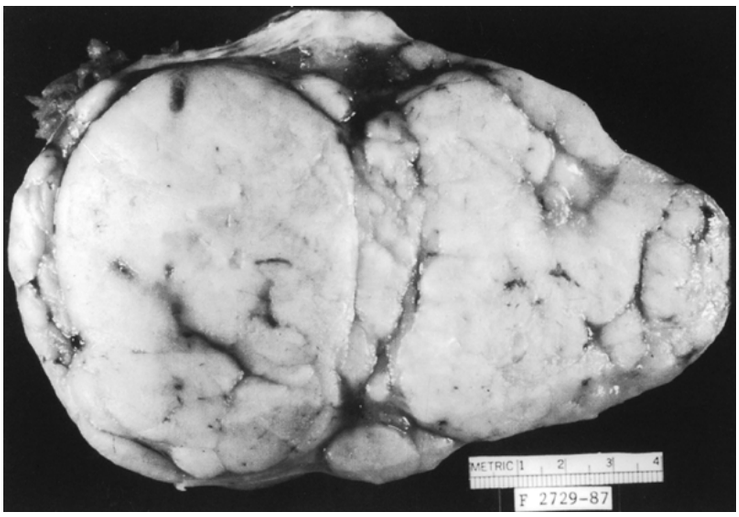

Figure 12.2 Dysgerminoma of the ovary. Note that the lesion is principally solid with some cystic areas.

Diagnosis

Adnexal masses measuring 2 cm or larger in premenarchal girls or complex masses 8 cm or larger in other premenopausal patients will 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 karyotype should be obtained preoperatively on all premenarchal girls because of the propensity of these tumors to arise in dysgenetic gonads** (3 ,7). A preoperative computed tomographic (CT) scan or magnetic resonance imaging (MRI) 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 observation or a trial of hormonal suppression for two cycles (8).

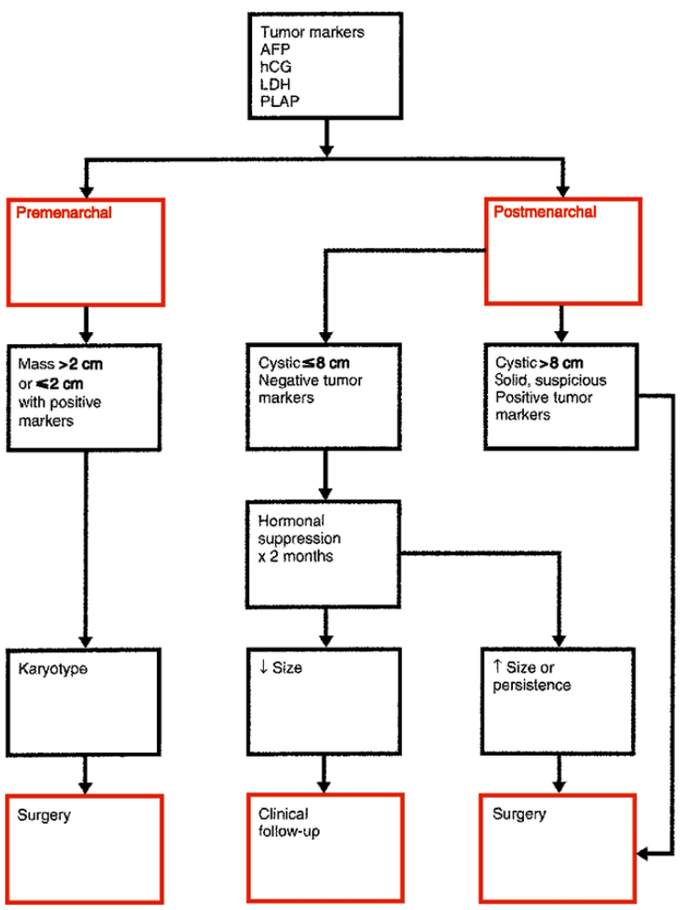

Figure 12.3 Evaluation of a pelvic mass in young female patients.

Dysgerminoma

The dysgerminoma is the most common malignant germ cell tumor, accounting for about 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 phenotypic females with 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).

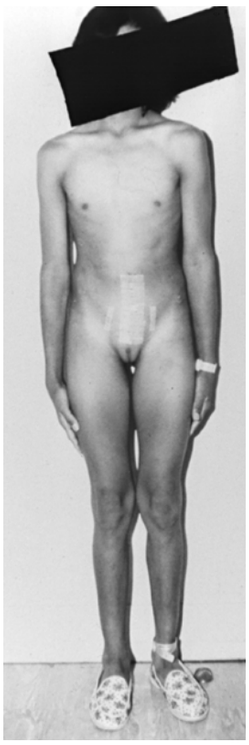

Figure 12.4 A 16-year-old girl with 46XY gonadal dysgenesis, showing lack of secondary sexual features, who developed dysgerminoma.

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% will develop into ovarian malignancies (9).

About 65% of dysgerminomas are stage I (i.e., confined to one or both ovaries) at diagnosis (1 ,3 ,10 ,11 ,12 ,13 ,14). **About 85% to 90% of stage I tumors are confined to one ovary; 10% to 15% are bilateral. Dysgerminoma is the only germ cell malignancy that has this significant rate of bilaterality, other germ cell tumors being rarely 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 via the lymphatics, particularly to the higher paraaortic nodes.

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, and 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 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 Figure 12.5 .

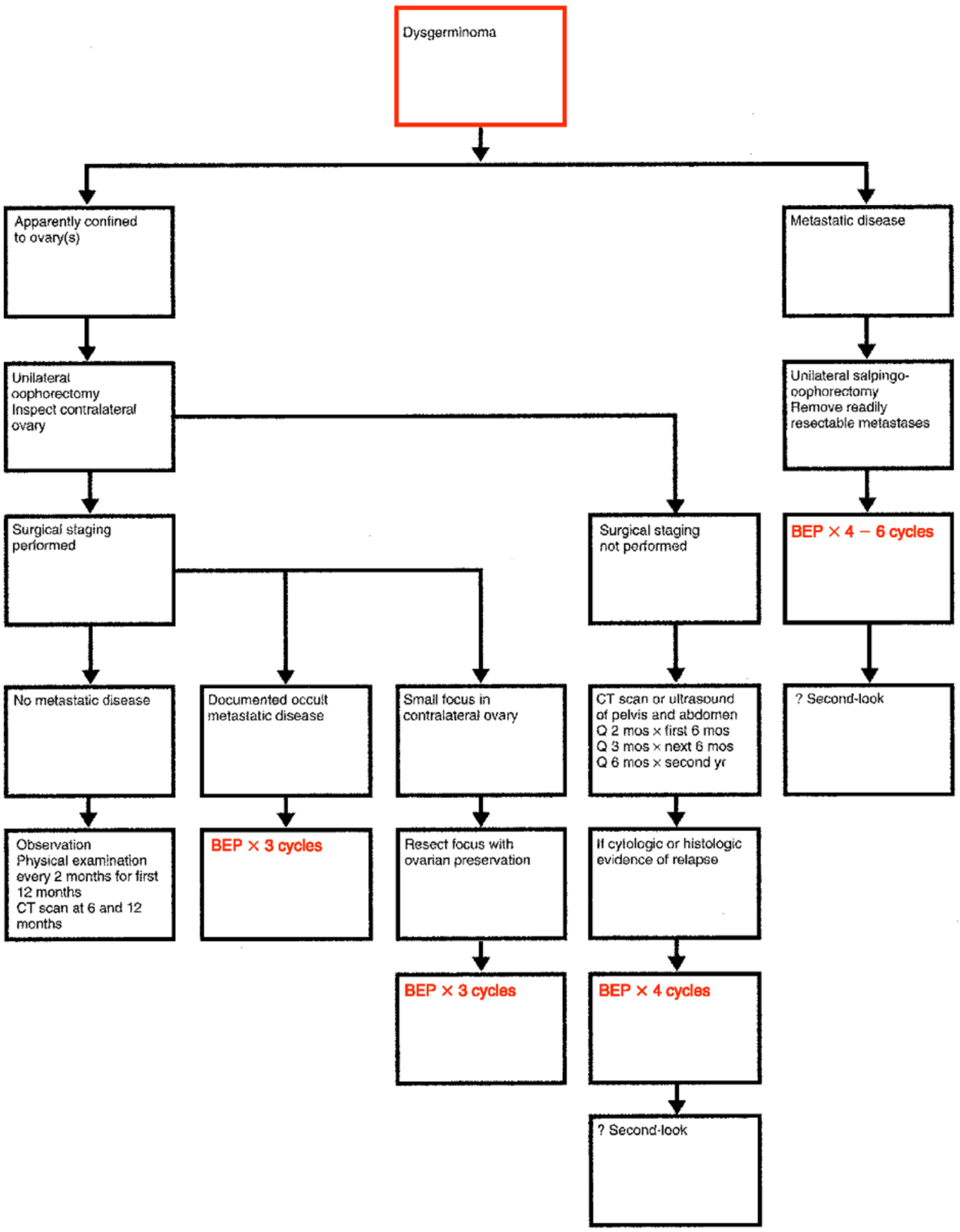

Figure 12.5 Management of dysgerminoma of the ovary.

BEP = *bleomycin, etoposide, cisplatin;* CT = computed tomogram

Surgery

The minimum operation for ovarian dysgerminoma is a unilateral oophorectomy (12 ,15). **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 contains a Y chromosome, both ovaries should be removed, although the uterus may be left *in situ* for possible future embryo transfer. Whereas 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 biopsied. Unilateral pelvic lymphadenectomy and at least careful palpation and *excisional* 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 careful inspection and palpation of the contralateral ovary and excisional biopsy of any suspicious lesion are desirable (12 ,13 ,14 ,15). If a small contralateral tumor is found, it may be possible to resect it and preserve some normal ovary.

Many patients with a dysgerminoma will have a tumor that is apparently confined to one ovary and will be referred after unilateral salpingo-oophorectomy without surgical staging. The options for such patients are (i) repeat laparotomy for surgical staging, (ii) regular pelvic and abdominal CT scans, or (iii) adjuvant chemotherapy. As these are rapidly growing tumors, our preference is to perform regular surveillance. Tumor markers (LDH, AFP, and β-hCG) should also be monitored in case occult mixed germ cell elements are present (Fig. 12.1).

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 {AQ1} radiation therapy, however, so radiation should rarely be used as first-line treatment (13 ,14).

Chemotherapy

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 (15 ,16 ,17 ,18 ,19 ,20 ,21 ,22 ,23 ,24 ,25). **The obvious advantage is the preservation of fertility** (15 ,26 ,27 ,28 ,29 ,30).

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*, **and** *cyclophosphamide***)** (15 ,16 ,17 ,18 ,19 ,20) (Table 12.2).

Table 12.2 Combination Chemotherapy for Germ Cell Tumors of the Ovary

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.

The Gynecologic Oncology Group (GOG) studied three cycles of EC: *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 (23). 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 (16 ,17). 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 (17). The VAC consolidation after BEP in patients with tumors other than dysgerminoma is still being investigated, but 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. A study at M.D. Anderson Hospital (20) used BEP in 14 patients with residual disease, and all patients were free of disease with long-term follow-up. In another series of 26 patients with pure ovarian dysgerminoma who received BEP chemotherapy, 54% of whom had stage IIIC or IV disease, 25 (96%) remained continuously disease-free following three to six cycles of therapy (26). **These results suggest that patients with advanced-stage, incompletely resected dysgerminoma have an excellent**

prognosis when treated with *cisplatin*-based combination chemotherapy (24 ,25 ,26 ,27 ,28 ,29 ,30). **The best regimen is four cycles of BEP based on the data from testes cancers** (31 ,32).

There appears to be no need to perform a second-look laparotomy in patients with dysgerminoma whose macroscopic disease has all been resected at the primary operation (33 ,34 ,35). 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

About 75% of recurrences occur within the first year after initial treatment (1 ,2 ,3 ,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 may be used (Table 12.3), and consideration should be given to the use of high-dose chemotherapy (e.g., with [EC] *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

POMB	
Day 1	*Vincristine* 1 mg/m^2 intravenously; *methotrexate* 300 mg/m^2 as a 12-h infusion
Day 2	*Bleomycin* 15 mg as a 24-h infusion: *folinic acid* rescue started at 24 h after the start of *methotrexate* in a dose of 15 mg every 12 h for 4 doses
Day 3	*Bleomycin* infusion 15 mg by 24-h infusion
Day 4	*Cisplatin* 120 mg/m^2 as a 12-h infusion, given together with hydration and 3-g *magnesium sulfate* supplementation
ACE	
Days 1–5	*Etoposide* (VP-16-213) 100 mg/m^2, days 1 to 5
Day 3, 4, 5	*Actinomycin D* 0.5 mg IV, days 3, 4, and 5
Day 5	*Cyclophosphamide* 500 mg/m^2 IV, day 5
OMB	
Day 1	*Vincristine* 1 mg/m^2 intravenously; *methotrexate* 300 mg/m^2 as a 12-h infusion
Day 2	*Bleomycin* 15 mg by 24-h infusion; *folinic acid* rescue started at 24 h after start of *methotrexate* in a dose of 15 mg every 12 h for 4 doses
Day 3	*Bleomycin* 15 mg by 24-h infusion

The sequence of treatment schedules is two courses of POMB followed by ACE. POMB is then alternated with ACE until patients are in biochemical remission as measured by human chorionic gonadotropin and α-fetoprotein, and placental alkaline phosphatase and lactate dehydrogenase. The usual number of courses of POMB is three to five. After biochemical remission, patients alternate ACE with OMB until remission has been maintained for approximately 12 weeks. The interval between courses of treatment is kept to the minimum (usually 9 to 11 days). If delays are caused by myelosuppression after courses of ACE, the first 2 days of etoposide are omitted from subsequent courses of ACE.

Reproduced from **Newlands ES, Southall PJ, Paradinas FJ, Holden L.** Management of ovarian germ cell tumors. In: **Williams CJ, Krikorian JG, Green MR, Ragavan D**, eds. *Textbook of uncommon cancer.* New York: John Wiley & Sons, 1988:37–53, with permission.

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 will depend on gestational age. Chemotherapy can be given in the second and third

trimesters in the same dosages as given for the no-pregnant patient without apparent detriment to the fetus (27).

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 combination chemotherapy (16 ,17 ,18 ,19 ,20 ,21 ,22 ,23 ,24 ,25 ,26 ,27 ,28 ,29 ,30).

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 women younger than 20 years of age and 30% of the deaths from ovarian cancer in this age group (1). About 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 (36).

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 below) (22). The risk is reported to be between 0.5% and 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 will contain calcifications similar to 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 pseudoprecocity (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 (2). 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).

It is unclear whether debulking of metastatic implants enhances the response to combination chemotherapy (37 ,38). Unlike epithelial lesions, immature teratomas are much more chemosensitive. Because cure ultimately depends on the ability to deliver chemotherapy promptly, any surgical resection that may be potentially morbid and therefore delay chemotherapy should be resisted.

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 (18 ,19 ,20 ,33 ,39 ,40 ,41 ,42 ,43 ,44 ,45 ,46 ,47 ,48 ,49 ,50 ,51). **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 (45 ,46 ,47). However, in a GOG study, the relapse-free survival rate in patients with incompletely resected disease was only 75% (47).

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 (22). 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 versus 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) (31). 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 4 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 (32). 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.**

The necessity of adjuvant chemotherapy for all patients with resected immature teratomas is uncertain. Several reports support the successful management of these patients with surgery alone (43 ,44 ,52). In the largest series, an intergroup study from the Pediatric Oncology Group and the Children's Cancer Group, 73 children with immature teratoma (44 of ovarian origin) underwent surgery followed by surveillance. With a median follow-up of 35 months, the overall 3-year event-free survival rates for all patients and those with ovarian teratomas were 93% and 100%, respectively. Thirteen of the 44 girls with an immature ovarian teratoma had microscopic foci of yolk sac tumor in the teratoma;

one developed recurrent disease and was successfully salvaged with *cisplatin*-based chemotherapy. Of note, 82% of the tumors were grade 1 or 2; however, 92% of those with foci of yolk sac tumor were grade 2 or 3.

Immature teratomas with malignant squamous elements appear to have a poorer prognosis than those tumors without these elements (22). The treatment in these patients is also with the BEP regimen.

Radiation

Radiation therapy is generally 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 ,33).

Second-Look Laparotomy

The need for a second-look operation has been questioned (34 ,35). 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 ,36). 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 (33 ,36 ,39).

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 (36). 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). However, mature glial elements can grow and mimic malignant disease, and may need to be resected to relieve pressure on surrounding structures.

Endodermal Sinus Tumor

Endodermal sinus tumors (ESTs) 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 tumors of the ovary.**

ESTs have a median age of 18 years (1 ,2 ,3 ,53 ,54). About 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 about 75% of patients, whereas an asymptomatic pelvic mass is documented in 10% of patients (3).

Most EST lesions secrete AFP, and rarely they may elaborate detectable AAT. 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 (53 ,54 ,55 ,56 ,57 ,58 ,59).

Treatment

Surgery

The treatment of the 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 ,57). 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 (2 ,4). 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 (59).

Chemotherapy

All patients with endodermal sinus tumors 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 about 25%. After the introduction of the VAC regimen, this rate improved to 60% to 70%, indicating the chemosensitivity of the majority of these tumors (46 ,47). Furthermore, with conservative surgery and adjuvant chemotherapy, fertility can be preserved as with other germ cell tumors.

VBP is a more effective regimen in the treatment of EST, particularly in the treatment of measurable or incompletely resected tumors (51). In the GOG series, only about 20% of patients with residual metastatic disease responded completely to the VAC regimen, whereas about 60% of those treated with VBP had a complete response (19). 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 (60) (Table 12.3). This protocol introduces seven drugs into the initial management, which is intended to minimize the chances of developing 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** (51 ,60). **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 (58 ,59). 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 (59). In patients whose AFP titers do not return to normal, persistent disease can be assumed and alternative chemotherapy (e.g., POMB-ACE) offered.

Rare Germ Cell Tumors of the Ovary

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) in two series (61). Older patients have been reported (62). 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 the EST. The primary lesions tend to be large, and about 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 (58).

The treatment of embryonal carcinomas is the same as for the EST (i.e., a unilateral oophorectomy followed by combination chemotherapy with BEP) (19 ,51 ,63).

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 (64). The majority of patients with this cancer are younger than 20 years. 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 about 50% of patients whose lesions appear before menarche (65).

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 (64) (see Chapter 15). Alternatively, the BEP regimen can be used. The prognosis for ovarian choriocarcinomas has been poor, with the majority of patients having metastases to organ parenchyma at the time of initial diagnosis.

Polyembryoma

Polyembryoma of the ovary is another extremely rare tumor, which 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. **Women with polyembryomas that are surgically staged and confined to one ovary may be followed with serial tumor markers and diagnostic imaging techniques to avoid cytotoxic chemotherapy. In patients who require chemotherapy, the BEP regimen is appropriate** (46).

Mixed Germ Cell Tumors

Mixed germ cell malignancies of the ovary contain two or more elements of the lesions described above. In one series (63), 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 of only 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 (63). In stage Ia lesions smaller than 10 cm, survival 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 compose the majority of the mixed lesions.

Late Effects of Treatment of Malignant Germ Cell Tumors of the Ovary

Although there are substantial data regarding late effects of *cisplatin*-based therapy in men with testicular cancer, sparse information is available for women with ovarian germ cell tumors. Among the adverse events from chemotherapy reported in men are renal and gonadal dysfunction, neurotoxicity, cardiovascular toxicity, and secondary malignancies.

Gonadal Function

An important cause of infertility in patients with ovarian germ cell tumors is unnecessary bilateral salpingo-oophorectomy and hysterectomy. **Although temporary ovarian dysfunction or failure is common with *platinum*-based chemotherapy, most women will resume normal ovarian function, and childbearing is usually preserved** (7 ,13 ,15 ,26 ,27 ,28 ,29 ,30). In one representative series of 47 patients treated with combination chemotherapy for germ cell malignancies, 91.5% resumed normal menstrual function, and there were 14 healthy live births and no birth defects (15). Factors such as older age at initiation of chemotherapy, greater cumulative drug dose, and longer duration of therapy all have an adverse effect on future gonadal function (27).

Secondary Malignancies

An important cause of late morbidity and mortality in patients receiving chemotherapy for germ cell tumors is the development of secondary tumors. *Etoposide* **in particular has been implicated in the development of treatment-related leukemias.**

The chance of developing treatment-related leukemia following *etoposide* is dose related. The incidence of leukemia is approximately 0.4% to 0.5% (representing a 30-fold increased likelihood) in patients receiving a cumulative etoposide dose of less than 2,000 mg/m^2 (66), compared with as much as 5% (representing a 336-fold increased likelihood) in those receiving more than 2,000 mg/m^2 (67). In a typical three- or four-cycle course of BEP, patients receive a cumulative *etoposide* dose of 1,500 or 2,000 mg/m^2, respectively.

Despite the risk of secondary leukemia, risk-benefit analyses have concluded that *etoposide*-containing chemotherapy regimens are beneficial in advanced germ cell tumors; one case of treatment-induced leukemia would be expected for every 20 additionally cured patients who receive BEP as compared with PVB. The risk-benefit balance for low risk disease, or for high-dose *etoposide* in the salvage setting, is less clear (67).

Sex Cord–Stromal Tumors

Sex cord–stromal tumors of the ovary account for about 5% to 8% of all ovarian malignancies (1 ,2 ,3 ,4 ,68 ,69 ,70 ,71). 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 .

Table 12.4 Sex Cord–Stromal Tumors

1. *Granulosa–stromal cell tumors*
- **A.** Granulosa cell tumor
- **B.** Tumors in thecoma–fibroma group
  - Thecoma
  - Fibroma
  - Unclassified

2. *Androblastromas; Sertoli-Leydig cell tumors*
- **A.** Well differentiated
  - Sertoli cell tumor
  - Sertoli-Leydig cell tumor
  - 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 RE, Scully RE**. Ovarian sex cord-stromal tumors: recent progress. *Int J Gynecol Pathol* 1980;1:153, with permission.

Granulosa-Stromal Cell Tumors

Granulosa-stromal cell tumors include granulosa cell tumors, thecomas, and fibromas. The granulosa cell tumor is a low-grade malignancy. Thecomas and fibromas are benign, but rarely may 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 (71 ,72 ,73 ,74). They are bilateral in only 2% of patients.

Of the rare prepubertal lesions, 75% are associated with sexual pseudoprecocity because of the estrogen secretion (72). 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 ,71 ,72 ,73). 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 about 10% of cases, and rarely a pleural effusion is present (71 ,72). 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 (70). 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).

Diagnosis

Inhibin is secreted by granulosa cell tumors and is a useful marker for the disease (75 ,76 ,77 ,78). Inhibin is an ovarian product which decreases to nondetectable levels after menopause. However, certain ovarian cancers (mucinous epithelial ovarian carcinomas and granulosa cell tumors) produce inhibin, which may predate clinical disease (79 ,80 ,81). An elevated serum inhibin level in a premenopausal woman presenting with amenorrhea and infertility is suggestive of a granulosa cell tumor.

Müllerian inhibitory substance (MIS), which is produced by granulosa cells, is emerging as a potential marker for these tumors (78). An elevated MIS level appears to have high specificity, but the test is not clinically available except for research purposes. An elevated estradiol level is not a sensitive marker of this disease (80).

The histological diagnosis can be facilitated by staining for markers of ovarian granulosa cell tumors (e.g., inhibin, CD99, and müllerian inhibiting substance) (75 ,76). Antibodies against inhibin appear to be the most useful, but they are not specific. In one report, positive staining for inhibin was present in 94% of granulosa cell tumors and in 10% to 20% of ovarian endometrioid tumors and metastatic carcinomas to the ovary (78). The latter demonstrated significantly weaker staining.

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 (71 ,72 ,73 ,74).

Surgery

Because granulosa cell tumors are bilateral in only about 2% of patients, a unilateral salpingo-oophorectomy is appropriate therapy for stage Ia tumors in children or in women of reproductive age (69). 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 biopsied. 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 (71).

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 (71). Radiation can induce clinical responses and occasional long-term remission in patients with persistent or recurrent granulosa cell tumors, particularly if the disease is surgically cytoreduced (81 ,82 ,83). In one review of 34 patients treated at one center for more than 40 years, 14 were treated with measurable disease (82). Three (21%) were alive without progression 10 to 21 years following treatment.

Chemotherapy

There is no evidence that adjuvant chemotherapy in patients with stage I disease will prevent recurrence.

Metastatic lesions and recurrences have been treated with a variety of different antineoplastic drugs. There has been no consistently effective regimen in these patients, although complete responses have been reported anecdotally in patients treated with the single agents, *cyclophosphamide* or *melphalan*, as well as the combinations, VAC (*vincristine, actinomycin, cyclophosphamide*), and PAC (*cisplatin, doxorubicin, cyclophosphamide*), or BEP (*bleomycin, etoposide*, and *cisplatin*) (84 ,85 ,86 ,87 ,88 ,89 ,90 ,91 ,92 ,93 ,94 ,95).

The rarity of these tumors has made it impossible to conduct well-designed randomized studies assessing the value of therapy for patients with stage II to IV disease. In retrospective series, postoperative chemotherapy has been associated with a prolonged progression-free interval in women with stage III/IV disease (87), but a survival benefit has not been shown (88). Despite the absence of data supporting a survival benefit, some experts recommend postoperative chemotherapy for women with completely resected stage II to IV disease because of the high risk of disease progression and the potential for long-term survival after platinum-based chemotherapy (81 ,89 ,90 ,91 ,92). Among the acceptable options are BEP (*bleomycin, etoposide*, and *cisplatin*), EP (*etoposide* and *cisplatin*), PAC (*cyclophosphamide, doxorubicin* and *cisplatin*), or *carboplatin or cisplatin* alone (81). **Although the data are inconclusive, we recommend four to six cycles of BEP in selected patients with stage III/IV disease.**

For patients with suboptimally cytoreduced disease, combinations of *bleomycin, etoposide*, **and** *cisplatin* **(BEP) have produced overall response rates of 58% to 83%** (89 ,94). In one study, 14 of 38 patients (37%) with advanced disease undergoing second-look laparotomy following four courses of BEP had negative findings (89). The median survival of those patients who had a complete clinical response was more than 2 years. *Doxorubicin* alone (86); EC (*carboplatin* and *etoposide*) (95); BVP (*cisplatin, vinblastine*, and *bleomycin*) (71); and PAC (*cyclophosphamide, doxorubicin*, and *cisplatin*) (84 ,96) are other chemotherapeutic regimens with reported antitumor effects. The value of *paclitaxel* is under active investigation (97).

Recurrent Disease

The median time to relapse is approximately 4 to 6 years after initial diagnosis (70 ,92 ,93). There is no standard approach to the management of relapsed disease. A common site of recurrence is the pelvis, although the upper abdomen may be involved as well. Further surgery can be effective if the tumor is localized, but diffuse intraabdominal disease is difficult to treat. Chemotherapy or radiation may be useful in selected patients.

The use of hormonal agents such as progestins or antiestrogens has been suggested, but there are no data to suggest effectiveness (81). Experimental data and small clinical series suggest that agents such as luteinizing hormone–releasing hormone agonists might have antitumor activity through the suppression of gonadotropin secretion (98 ,99 ,100 ,101), but other studies have failed to document activity (83 ,102).

Prognosis

The prognosis of granulosa cell tumor of the ovary depends on the surgical stage of disease at the time of diagnosis (70 ,72 ,81). Most granulosa cell tumors have an indolent growth pattern and are confined to one ovary; the cure rate for stage I disease is 75% to 92% (72 ,92). However, late recurrences are not uncommon (69 ,70 ,72). In one report of 37 women with stage I disease, survival rates at 5, 10, and 20 years were 94%, 82%,

and 62%, respectively. The survival rates for stages II to IV at 5 and 10 years were 55% and 34%, respectively (81).

In adult tumors, cellular atypia, mitotic rate, and the absence of Call-Exner bodies are the only significant pathologic predictors of early recurrence (91). Neither an abnormal tumor karyotype nor p53 overexpression appear to be prognostic (103). The DNA ploidy of the tumors has been correlated with survival. Holland and colleagues (85) 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 of 96%.

Juvenile Granulosa Cell Tumors

Juvenile granulosa cell tumors of the ovary are rare and make up less than 5% of ovarian tumors in childhood and adolescence (95). About 90% are diagnosed in stage I, and they have a favorable prognosis. The juvenile subtype behaves less aggressively than the adult type. Advanced stage tumors have been successfully treated with platinum-based combination chemotherapy, e.g., BEP (81).

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. These lesions 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 (104 ,105). 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) (105).

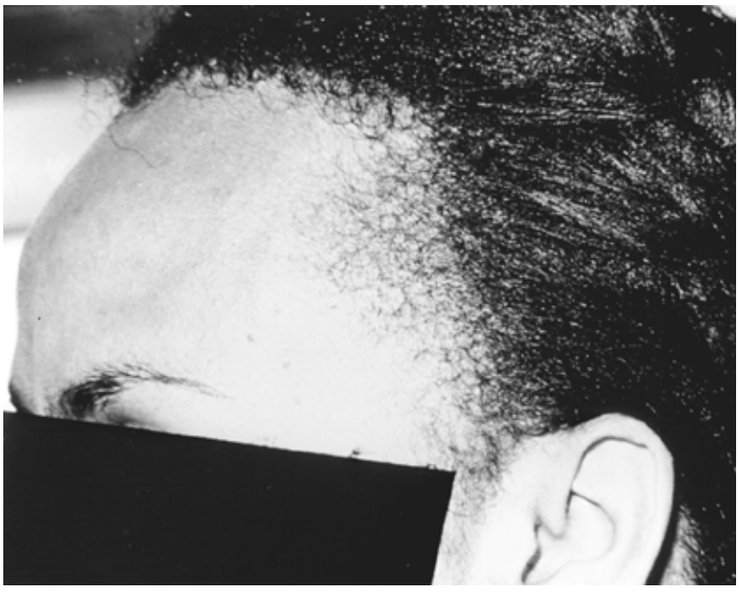

Figure 12.6 A young woman with a Sertoli-Leydig cell tumor demonstrating temporal baldness.

Treatment

Because these low-grade lesions are bilateral in less than 1% of cases, the usual treatment is unilateral salpingo-oophorectomy and evaluation of the contralateral ovary in patients who are in their reproductive years (105). In older patients, hysterectomy and bilateral salpingo-oophorectomy are appropriate.

There are limited data regarding the utility of chemotherapy in patients with persistent disease, but responses in patients with measurable disease have been reported with *cisplatin* in combination with *doxorubicin* and/or *ifosphamide* (105). Pelvic radiation can also be used for recurrent pelvic tumor, but with limited responses.

Prognosis

The 5-year survival rate is 70% to 90%, and recurrences thereafter are uncommon (1 ,2 ,105). Poorly differentiated lesions compose the majority of fatalities.

Uncommon Ovarian Cancers

Part of "12 - Nonepithelial Ovarian and Fallopian Tube 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.

The majority of these tumors have a benign or low-grade behavior, but about 20%, most of which are initially larger than 8 cm in diameter, develop metastatic lesions. Metastases are usually in the peritoneal cavity but rarely occur 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 (106 ,107 ,108 ,109 ,110 ,111 ,112). 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 the majority of patients have evidence of metastases.

Such patients should be treated by cytoreductive surgery and postoperative *platinum*-containing combination chemotherapy (111 ,112). 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) (113). The tumors are all bilateral. Approximately two-thirds of the tumors are accompanied by paraneoplastic hypercalcemia. This tumor accounts for one-half of all of the cases of hypercalcemia associated with ovarian tumors. About 50% of the tumors have spread beyond the ovaries at the time of diagnosis (1 ,2).

Management consists of surgery followed by *platinum*-based chemotherapy and 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 phosphonates.

The prognosis tends to be poor, with most patients dying within 2 years of diagnosis in spite of treatment.

Metastatic Tumors

Part of "12 - Nonepithelial Ovarian and Fallopian Tube Cancers "

About 5% to 6% of ovarian tumors are metastatic from other organs, most frequently from the female genital tract, the breast, or the gastrointestinal tract (114 ,115 ,116 ,117 ,118 ,119 ,120 ,121 ,122 ,123 ,124 ,125 ,126 ,127 ,128). The metastases may occur from direct extension of another pelvic neoplasm, by hematogenous spread, lymphatic spread, or transcoelomic 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 (129).

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 (114 ,115 ,116 ,117 ,118 ,119 ,120). Similarly, when ovaries are removed to palliate advanced breast cancer, about 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 (121 ,122). The primary tumor is most frequently 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 about 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. As many as 1% to 2% of women with intestinal carcinomas will develop metastases to the ovaries during the course of their disease (116 ,123 ,124). Before exploration for an adnexal tumor in a woman more than 40 years of age, a colonoscopy 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, and the histological distinction between the two can be difficult (123 ,124 ,125 ,126 ,127).

Lesions that arise in the appendix may be associated with ovarian metastasis and have frequently been confused with primary ovarian malignancies, especially when associated with pseudomyxoma peritonei (123 ,127) (see Chapters 6 and 11). Therefore, it is reasonable to consider the performance of prophylactic bilateral salpingo-oophorectomy at the time of surgery for women with colon cancer (128).

Melanoma

Rare cases of malignant melanoma metastatic to the ovaries have been reported (130). These must be distinguished from the rare case of a melanoma arising in an ovarian teratoma (131). 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 (132). Conversely, only about 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 (133). 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 (134 ,135 ,136). About 5% of patients with Hodgkin's disease will 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 such procedures if frozen section of a solid ovarian mass reveals a lymphoma. In general, most lymphomas no longer require extensive surgical staging, although enlarged lymph nodes should generally 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 (136).

Fallopian Tube Cancer

Part of "12 - Nonepithelial Ovarian and Fallopian Tube Cancers "

Carcinoma of the fallopian tube accounts for 0.3% of all cancers of the female genital tract (2 ,137 ,138 ,139 ,140 ,141 ,142 ,143). **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 (2). 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 histology. 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 ,137 ,138 ,139 ,140 ,141 ,142). **Women who have germ-line mutations in BRCA1 and BRCA2 are at substantially higher risk for developing fallopian tube carcinoma; therefore, prophylactic surgery in these women should include a complete removal of both tubes along with the ovaries** (144 ,145) (see Chapters 1 and 11).

Symptoms and Signs

The classic triad of symptoms and signs associated with fallopian tube cancer is (i) a prominent watery vaginal discharge, i.e., *hydrops tubae profluens*; (ii) pelvic pain; and (iii) a pelvic mass. However, this triad is noted in fewer than 15% of patients (2).

Either 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 ,138). 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 about 60% of patients, and ascites may be present if advanced disease exists. Patients with tubal carcinoma will have a negative dilatation and curettage (3 ,140 ,141 ,146), 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 transcoelomic exfoliation of cells that implant throughout the peritoneal cavity. In about 80% of the patients with advanced disease, metastases are confined to the peritoneal cavity at the time of diagnosis (139).

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 (139).

Staging

Fallopian tube cancer is staged according to the International Federation of Gynecology and Obstetrics (FIGO) (137). The staging is based on the surgical findings at laparotomy (Table 12.5). According to this system, about 37% of patients have stage I disease, 20% have stage II, 31% have stage III, and 10% have stage IV at the time of diagnosis (137). 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 (Based on Operative Findings Before Debulking and Pathologic Findings)

Stage 0	Carcinoma *in situ*[a] (limited to tubal mucosa).[b]
Stage I	Growth is limited to the fallopian tubes.
Stage IA	Growth is limited to one tube with extension into the submucosa[c] and/or muscularis but not penetrating the serosal surface; no ascites.
Stage IB	Growth is limited to both tubes with extension into the submucosa[c] and/or muscularis but not penetrating the serosal surface; no ascites.
Stage IC	Tumor either stage IA or IB but with tumor extension through or onto the tubal serosa; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage II	Growth involving one or both fallopian tubes with pelvic extension.
Stage IIA	Extension and/or metastasis to the uterus and/or ovaries.
Stage IIB	Extension to other pelvic tissues.
Stage IIC	Tumor either stage IIA or IIB but with tumor extension through or onto the tubal serosa; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage III	Tumor involves one or both fallopian tubes with peritoneal implants outside of the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equals stage III. Tumor appears limited to the true pelvis but with histologically proven malignant extension to the small bowel or omentum.
Stage IIIA	Tumor is grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.
Stage IIIB	Tumor involving one or both tubes with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Lymph nodes are negative.
Stage IIIC	Abdominal implants greater than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes.
Stage IV	Growth involving one or both fallopian tubes with distant metastases. If pleural effusion is present, there must be positive cytology to be stage IV. Parenchymal liver metastases equals stage IV.

FIGO, International Federation of Gynecology and Obstetrics.

[a]The staging system does not distinguish between microscopic foci or replacement of tubal epithelium by malignant epithelium and grossly evident masses in the tubal lumen that do not penetrate the wall beyond the epithelium. The former have not been reported to spread beyond the tube, whereas the latter can extend beyond the tube, recur, and be fatal.

[b]The "mucosa" presumably refers to the epithelium because involvement of the lamina propria component of the mucosa requires staging of the tumor as IA.

[c]Because the fallopian tube has no "submucosa," this designation presumably refers to the lamina propria.

Treatment

The treatment of this disease is identical to that of epithelial ovarian cancer (2 ,142 ,147 ,148). **Exploratory laparotomy is necessary to remove the primary tumor, to stage the disease, and to resect metastases. After surgery, the most frequently employed treatment is now 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

As with epithelial ovarian cancer, the most active agents are platinum and the taxanes. Recent experience with *cisplatin* in combination with *paclitaxel* indicates that complete responses can be obtained (2 ,148). **It appears justifiable, therefore, to employ the same protocols that are used for epithelial ovarian cancer in patients with epithelial tubal malignancies.**

A variety of other chemotherapeutic agents that are effective against ovarian cancer appear to be active in fallopian tube carcinomas as well. These agents include *docetaxel, etoposide, topotecan, gemcitabine* and *liposomally encapsulated doxorubicin* (149 ,150 ,151 ,152 ,153).

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 the majority of 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 (143). 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 (143). Intraperitoneal ^{32}P has also been used, but these data are limited. More recently, whole-abdominal 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 for patients with epithelial tubal carcinomas is 56% (137 ,142). 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 it is 36% for patients with stage III disease (137).

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, survival is generally poor, and most patients die of their disease within 2 years (110).

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13
Vulvar Cancer

Neville F. Hacker

Vulvar cancer is uncommon, representing approximately 4% of malignancies of the female genital tract. There were estimated to be 3,970 new cases of vulvar cancer diagnosed in the United States in 2004 and 850 deaths (1). 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 (2). The latter typically develops in women in their seventh or eighth decade of life, but the incidence of squamous cell vulvar carcinoma is increasing in women younger than the age of 40 years (3).

In the early part of the twentieth 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% (4 ,5). Basset (6), 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 (7), in the United States, and Way (8), 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:

- Individualization of treatment for all patients with invasive disease (9 ,10)
- Vulvar conservation for patients with unifocal tumors and an otherwise normal vulva (9 ,10 ,11 ,12 and 13)
- Omission of the groin dissection for patients with T_1 tumors and no more than 1 mm of stromal invasion (9 ,10)
- Elimination of routine pelvic lymphadenectomy (14 ,15 ,16 ,17 and 18)
- The use of separate groin incisions for the groin dissection to improve wound healing (19 ,20)

- Omission of the contralateral groin dissection in patients with lateral T_1 lesions and negative ipsilateral nodes (9 ,10 ,21)
- The use of preoperative radiation therapy to obviate the need for exenteration in patients with advanced disease (22 ,23)
- The use of postoperative radiation to decrease the incidence of groin recurrence in patients with multiple positive groin nodes (18)

Innovations that are currently being investigated include intraoperative lymphatic imaging and sentinel lymph node biopsy to obviate the need for complete groin dissection if the sentinel nodes are negative (24 ,25 ,26 and 27) and chemoradiation for advanced vulvar cancer (28 ,29 ,30 ,31 and 32).

This paradigm shift in the management philosophy of vulvar cancer has been well exemplified in retrospective reviews of the experience at the University of Miami (33) and the Mayo Clinic (34). Both centers reported a trend toward a more conservative approach, and both reported decreased postoperative morbidity, without compromised survival.

Etiology

Part of "13 - Vulvar Cancer "

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 (35). **VIN has traditionally been considered to have a low malignant potential**, with progression to invasive disease most likely in the elderly or immunosuppressed (36). **This concept has been challenged** by Jones et al. (37), 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.
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. (38) 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. (39) 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 (40). Hording et al. (41) 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 (41 ,42 ,43 and 44).

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 basaloid or warty 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.** If VIN is present, it is of the differentiated type.

Other diseases known to be occasionally associated with vulvar cancer include syphilis and nonluetic granulomatous venereal disease, particularly lymphogranuloma venereum and granuloma inguinale *(Donovanosis)*. Such diseases are not seen commonly in Western countries.

Noninvasive Disease

Part of "13 - Vulvar Cancer "

Nonneoplastic Epithelial Disorders

The most recent recommendation on classification of vulvar diseases from the International Society for the Study of Vulvar Disease (ISSVD) 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 (45).

Table 13.1 Classification of Vulvar Diseases

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* 1989;8:83, with permission.

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 (46) 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.

Carli and colleagues from the Vulvar Clinic at the University of Florence reported an association with lichen sclerosus in 32% of their cases of vulvar cancer that were not HPV related (47). They felt that the existence of accessory conditions necessary to promote the progression from lichen sclerosus to cancer remained to be established.

Vulvar Intraepithelial Neoplasia

The management of VIN is discussed in Chapter 8 .

Paget's Disease of the Vulva

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** (48). **When the anal mucosa is involved, there is usually an underlying rectal adenocarcinoma** (48 ,49 and 50).

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 (49). The more extensive lesions are usually raised and velvety in appearance and may weep persistently.

Treatment

Unlike squamous cell carcinoma *in situ*, in which the histologic extent of disease usually correlates reasonably with the macroscopic lesion, Paget's disease usually extends well beyond the gross lesion (51). This results in positive surgical margins and frequent local recurrence unless a wide local excision is performed. Surgical margins may be checked with frozen sections to ensure complete removal of the disease (50), although resection of the entire gross lesion will control symptoms and exclude invasive disease. **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 may require radical vulvectomy and at least an ipsilateral inguinofemoral lymphadenectomy.

The disease is characterized by local recurrences over many years (52 ,53). **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 (49). Investigators at the Norwegian Radium Hospital have demonstrated that nondiploid tumors have an increased risk of recurrence regardless of surgical radicality (54). In general, it is reasonable to treat recurrent lesions with surgical excision or laser therapy.

Invasive Vulvar Cancer

Part of "13 - 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** (55). These warty carcinomas may occur at any age after adolescence and are multifocal in approximately one-third of the cases (55). 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 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:

- **Direct extension**, to involve adjacent structures such as the vagina, urethra, and anus
- **Lymphatic embolization** to regional lymph nodes
- **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. 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** (56 ,57 ,58 and 59). In addition, Gordinier and colleagues recently reported groin recurrence in 9 of 104 patients (8.7%) treated by superficial inguinal lymphadenectomy at the M. D. Anderson Cancer Center (60). The median number of lymph nodes removed per groin was 7, and the median time to recurrence was 22 months.

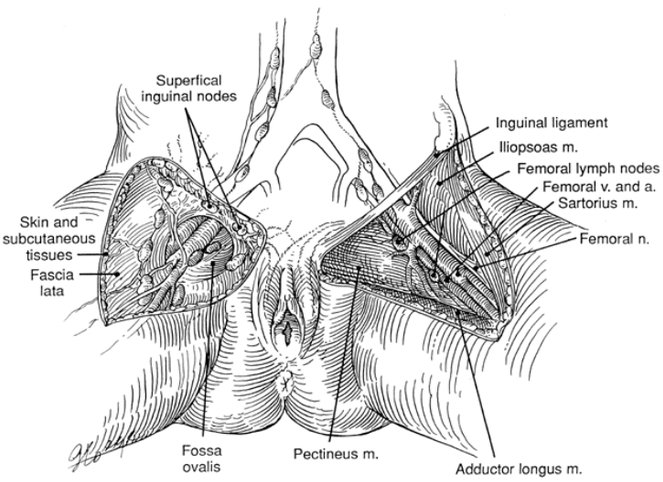

Figure 13.1 Inguinal-femoral lymph nodes. (Reproduced from **Hacker NF**. Vulvar cancer. In: **Hacker NF, Moore JG, Gambone JC**, eds. *Essentials of obstetrics and gynecology*, 4th ed. Philadelphia: Elsevier Saunders, 2004:472, with permission.)

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** (14 ,61 ,62).

Since 1970, the overall incidence of lymph node metastases is reported to be approximately 30% (Table 13.2). 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 .

Table 13.2 Incidence of Lymph Node Metastases in Operable Vulvar Cancer

Author	*No. of Cases*	*Positive Nodes*	*Percent*
Rutledge et al., 1970 (63)	110	40	36.4
Green et al., 1978 (64)	142	54	38.0
Krupp and Bohm, 1978 (65)	195	40	20.5
Benedet et al., 1979 (66)	120	34	28.3
Curry et al., 1980 (14)	191	57	29.8
Iversen et al., 1980 (67)	268	86	32.1
Hacker et al., 1983 (15)	113	31	27.4
Podratz et al., 1983 (68)	175	59	33.7
Monaghan and Hammond, 1984 (16)	134	37	27.6
Total	**1,448**	**438**	**30.2**

Table 13.3 Incidence of Lymph Node Metastases in Relation to Clinical Stage of Disease

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 **Green**, 1978 (64); **Iversen et al.**, 1980 (67); and **Hacker et al.**, 1983 (15).

Table 13.4 Nodal Status in T_1 Squamous Cell Carcinoma of the Vulva Versus Depth of Stromal Invasion

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 (57); **Magrina et al.**, 1979 (69); **Iversen et al.**, 1981 (9); **Wilkinson et al.**, 1982 (70); **Hoffman et al.**, 1983 (71); **Hacker et al.**, 1984 (10); **Boice et al.**, 1984 (72); **Ross and Ehrmann**, 1987 (73); **Rowley et al.**, 1988 (74); **Struyk et al.**, 1989 (75).

Metastases to pelvic nodes are uncommon, the overall reported frequency being approximately 9% (76). Pelvic nodal metastases are rare in the absence of clinically suspicious (N_2) groin nodes (15) and three or more positive groin nodes (14 ,15 ,67). **Approximately 20% of patients with positive groin nodes have positive pelvic nodes** (76).

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 (15).

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

FIGO Stage	*TNM*	*Clinical Findings*
Stage 0		Carcinoma *in situ* (e.g., VIN 3, noninvasive Paget's disease)
Stage I	$T_1N_0M_0$ $T_1N_1M_0$	Tumor confined to the vulva, 2 cm or less in largest diameter, and no suspect groin nodes
Stage II	$T_2N_0M_0$ $T_2N_1M_0$	Tumor confined to the vulva more than 2 cm in diameter, and no suspect groin nodes
Stage III	$T_3N_0M_0$ $T_3N_1M_0$ $T_3N_2M_0$ $T_1N_2M_0$ $T_2N_2M_0$	Tumor of any size with: 1. Adjacent spread to the urethra and/or the vagina, the perineum, and the anus, and/or 2. Clinically suspect lymph nodes in either groin
Stage IV	$T_xN_3M_0$ $T_4N_0M_0$ $T_4N_1M_0$ $T_4N_2M_0$ $T_xN_xM_{1a}$ $T_xN_xM_{1b}$	Tumor of any size: 1. Infiltrating the bladder mucosa, or the rectal mucosa, or both, including the upper part of the urethral mucosa, and/or 2. Fixed to the bone, and/or 3. Other distant metastases

TNM Classification

T:	**Primary Tumor**	**N:**	**Regional Lymph Nodes**
T_1	Tumor confined to the vulva, ≤2 cm in largest diameter	N_0	No nodes palpable
T_2	Tumor confined to the vulva, >2 cm in diameter	N_1	Nodes palpable in either groin, not enlarged, mobile (not clinically suspect for neoplasm)
T_3	Tumor of any size with adjacent spread to the urethra and/or vagina and/or perineum and/or anus	N_2	Nodes palpable in either or both groins, enlarged, firm and mobile (clinically suspect for neoplasm)
T_4	Tumor of any size infiltrating the bladder mucosa and/or the rectal mucosa, or including the upper part of the urethral mucosa and/or fixed to the bone	N_3	Fixed or ulcerated nodes
		M:	**Distant Metastases**
		M_0	No clinical metastases
		M_{1a}	Palpable deep pelvic lymph nodes
		M_{1b}	Other distant metastases

FIGO, International Federation of Gynecology and Obstetrics; VIN, Vulvar intraepithelial neoplasia; x, any T or N category.

Clinical evaluation of the groin lymph nodes is inaccurate in approximately 25% to 30% of the cases (8 ,16 ,77). 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** (78).

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.

Table 13.6 FIGO Staging for Vulvar Cancer (1994)

FIGO Stage	*TNM*	*Clinical/Pathologic Findings*
Stage 0	T_{is}	Carcinoma *in situ*, intraepithelial carcinoma
Stage I	$T_1N_0M_0$	Tumor ≤2 cm in greatest diameter, confined to the vulva or perineum; nodes are negative
IA	$T_{1a}N_0M_0$	As above with stromal invasion ≤1.0 mm[a]
IB	$T_{1b}N_0M_0$	As above with stromal invasion >1 mm
Stage II	$T_2N_0M_0$	Tumor confined to the vulva and/or perineum, >2 cm in greatest dimension, nodes are negative
Stage III	$T_3N_0M_0$ $T_3N_1M_0$ $T_1N_1M_0$ $T_2N_1M_0$	Tumor of any size with: 1. Adjacent spread to the lower urethra and/or the vagina and/or the anus 2. Unilateral regional lymph node metastasis
Stage IVA	$T_1N_2M_0$ $T_2N_2M_0$ $T_3N_2M_0$ T_4, any N, M_0	Tumor invades any of the following: Upper urethra, bladder mucosa, rectal mucosa, pelvic bone, or bilateral regional node metastasis
Stage IVB	Any T, any N, M_1	Any distant metastasis including pelvic lymph nodes

TNM Classification

T:	**Primary Tumor**	**N:**	**Regional Lymph Nodes**
T_x	Primary tumor cannot be assessed		Regional lymph nodes are the femoral and inguinal nodes
T_0	No evidence of primary tumor	N_x	Regional lymph nodes cannot be assessed
T_{is}	Carcinoma *in situ* (preinvasive carcinoma)	N_0	No lymph node metastasis
T_1	Tumor confined to the vulva and/or perineum 2 cm or less in greatest dimension	N_1	Unilateral regional lymph node metastasis
T_2	Tumor confined to the vulva and/or perineum more than 2 cm in greatest dimension	N_2	Bilateral regional lymph node metastasis
T_3	Tumor involves any of the following: lower urethra, vagina, anus	**M:**	**Distant Metastasis**
T_4	Tumor involves any of the following: bladder mucosa, rectal mucosa, upper urethra, pelvic bone	M_x	Presence of distant metastasis cannot be assessed
		M_0	No distant metastasis
		M_1	Distant metastasis (pelvic lymph node metastasis is M1)

FIGO, International Federation of Gynecology and Obstetrics.

[a]The depth of invasion is defined as the measurement of the tumor from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

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 (15 ,78), 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 (14 ,15 ,68 ,78). 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.

Treatment

After the pioneering work of Taussig (7) in the United States and Way (5 ,8) 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:

- **The disease is occurring in younger women, who are presenting with smaller tumors.** Jones et al. (79) 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). In the report of 21 cases of squamous vulvar cancer in women younger than 40 from the British Columbia Cancer Agency registry, 16 patients (76%) had stage I disease (3).

- **There has been concern about the postoperative morbidity and associated long-term hospitalization common with the *en bloc* radical dissection.**
- **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 (80). 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 (78): 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 (81). 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_1N_0 or N_1

The modern approach to the management of patients with T_1 carcinoma of the vulva should be individualized (9 ,10). 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:

- **The primary lesion**
- **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:

- **The condition of the remainder of the vulva**
- **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. (11) regarded psychosexual disturbance as the major long-term morbidity associated with the treatment of vulvar cancer. Andersen and Hacker (82) reported that, when compared with healthy adult women, sexual arousal was reduced to the eighth percentile and body image to the fourth percentile in women who had undergone vulvectomy.

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 (9 ,10 ,11 ,12 and 13 ,76). 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 primary lesion and should probably be regarded as second primary lesions.

Table 13.7 Incidence of Local Invasive Recurrence after Radical Local Excision and Radical Vulvectomy for T_1 Squamous Cell Carcinoma of the Vulva

	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 (57); **DiSaia et al.**, 1979 (11); **Iversen et al.**, 1981 (9); **Wilkinson et al.**, 1982 (70); **Chu et al.**, 1982 (83); **Hacker et al.**, 1984 (10); **Boice et al.**, 1984 (72); **Ross and Ehrmann**, 1987 (73); **Rowley et al.**, 1988 (74); **Berman et al.**, 1989 (84); **Struyk et al.**, 1989 (75).

Only in references 9, 10, and 70 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 unifocal lesions, only tumors ≤1 cm in diameter). Length of follow-up ranged from >12 months (78) to >63 months (76).

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 (85). 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 or lichen sclerosus, whereas VIN may require superficial local excision and primary closure or split thickness skin grafting.

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 (86).

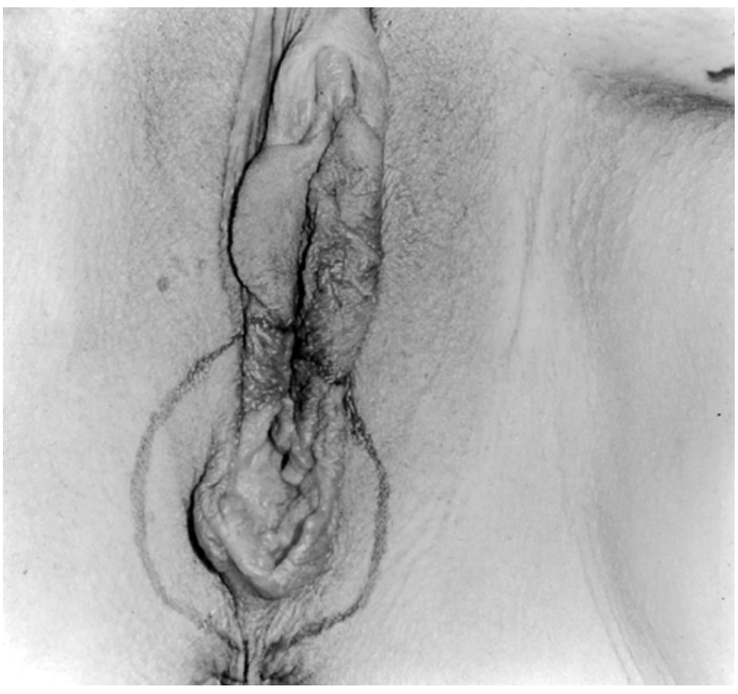

Figure 13.2 Small (T_1) vulvar carcinoma at the posterior fourchette.

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 Figure 13.2 .

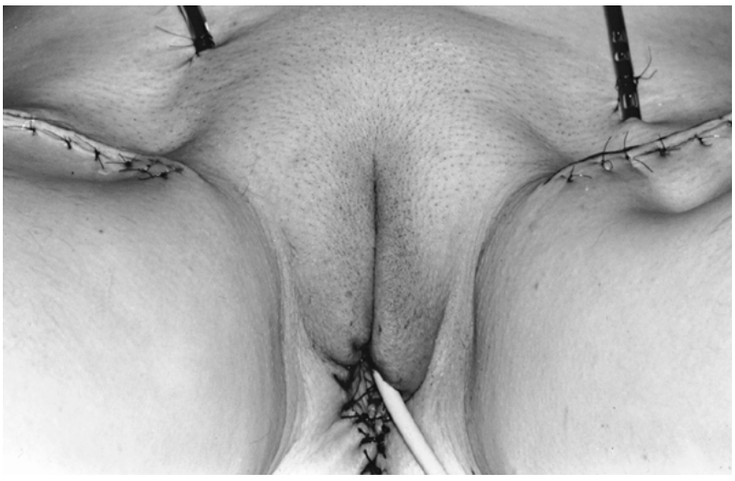

Figure 13.3 Satisfactory cosmetic result after radical local excision and bilateral groin dissection (for the small posterior vulvar carcinoma shown in Fig. 13.2**).**

Management of the Groin Lymph Nodes

Appropriate management of the regional lymph nodes is the single most important factor in decreasing the mortality from early vulvar cancer. With an increasing number of reports in the literature, two facts have become apparent:

- **The only patients without significant risk of lymph node metastases are those whose tumor invades the stroma to a depth no greater than 1 mm** (Table 13.4).
- **Patients in whom recurrent disease develops in an undissected groin have a very high mortality rate** (Table 13.8).

Table 13.8 Death from Recurrence in an Undissected Groin

Author	*Recurrence*	*Dead of Disease*
Rutledge et al., 1970 (63)	4	3
Magrina et al., 1979 (69)	4	3
Hoffman et al., 1983 (71)	4	4
Hacker et al., 1984 (10)	3	3
Monaghan and Hammond, 1984 (16)	4	4
Lingard et al., 1992 (88)	7	7
Total	**26**	**24 (92%)**

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 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 (89 ,90), the incidence is so low that it is of no practical significance.

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_1N_0 or N_1 tumors after a superficial (inguinal) dissection, even though the inguinal nodes were reported as negative (91). Whether all these recurrences were in the femoral nodes is unclear, but this large, 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 (93).

Table 13.9 Incidence of Positive Contralateral Nodes in Patients with Lateral T_1 Squamous Cell Vulvar Carcinomas and Negative Ipsilateral Nodes

Author	*Unilateral Lesions*	*Contralateral Nodes Positive*	*Percentage*
Wharton et al., 1974 (87)	25	0	0
Parker et al., 1975 (57)	41	0	0
Magrina et al., 1979 (69)	77	2	2.6
Iversen et al., 1981 (9)	112	0	0
Buscema et al., 1981 (92)	38	0	0
Hoffman et al., 1983 (71)[a]	70	0	0
Hacker et al., 1984 (10)	60	0	0
Struyk et al., 1989 (75)	53	0	0
Total	**476**	**2**	**0.4**

[a]Information not contained in reference but obtained from personal communication.

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. (94), **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 the injection of intradermal isosulfan blue dye around the primary vulvar lesion, either alone (24) or in combination with intradermal radioactive ^{99m}Tc-labeled sulfur colloid (25 ,26). After the injections, the node(s) is isolated in the groin by dissection and gamma counting.

In a review of the literature, Makar et al. reported successful identification of sentinel node(s) in 85 of 103 patients (82.5%) using the blue dye technique, and 128 of 128 patients (100%) using lymphoscintigraphy (27). **False-negative sentinel nodes have been reported** (95 ,96) **although the incidence appears to be low.** In the presence of palpably suspicious nodes, the incidence of false negatives is higher, presumably because metastatic disease obstructs flow to those nodes (97). **The incidence of false-negative sentinel nodes can be reduced by ultrastaging**, using either serial sectioning alone (98) or in combination with immunohistochemical staining for cytokeratin (99). Molpus et al. reported that 2 of 18 (11%) negative sentinel nodes had micrometastases (<0.2mm) upon serial sectioning and immunohistochemical staining (97).

Lymphatic mapping and sentinel node biopsy should be considered an experimental procedure at this time for patients with vulvar cancer. The European Organization for Research and Treatment of Cancer is presently carrying out an intergroup randomized study of sentinel node versus full inguinofemoral lymphadenectomy in patients with vulvar cancer (EORTC55001).

The key issue is really to determine the false-negative rate of the procedure, not just from the best centers, but in the hands of the average operator. The high mortality rate from recurrence in an undissected groin is vitally important to a patient undergoing this procedure, and proper informed consent will be crucial.

In this latter regard, a recent study by De Hulla et al. is important (100). They sent structured questionnaires both to patients who had been treated for vulvar cancer and to gynecologists. The response rate among patients was 91% (106 of 117), 40% of whom had experienced lower limb cellulitis and 49% of whom still experienced severe pain and/or lymphedema in the legs. Sixty percent of the patients preferred complete lymphadenectomy in preference to a 5% false-negative rate of the sentinel node procedure. Their preference was not related to age or the side effects they had experienced. The response among gynecologists was 80% (80 of 100), of whom 60% were willing to accept a 5% to 20% false-negative rate for the sentinel node procedure. The authors concluded that **although gynecologists may consider this a promising approach, the majority of vulvar cancer patients would not advise its introduction because they are not prepared to take any risk of missing a lymph node metastasis.** Exactly similar sentiments have been expressed about the sentinel node procedure by women with breast cancer (101).

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. (70). Tumor thickness is also commonly measured (69 ,102), and Fu (103) 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. Studies of bipedal lymphangiograms have demonstrated that **there are no lymph nodes adjacent to the anterior superior iliac spine** (104) (Fig. 13.4). On the basis of embryological and anatomical studies, Micheletti et al. have proposed that the superficial circumflex iliac vessels could represent the lateral surgical landmark (105). 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.**

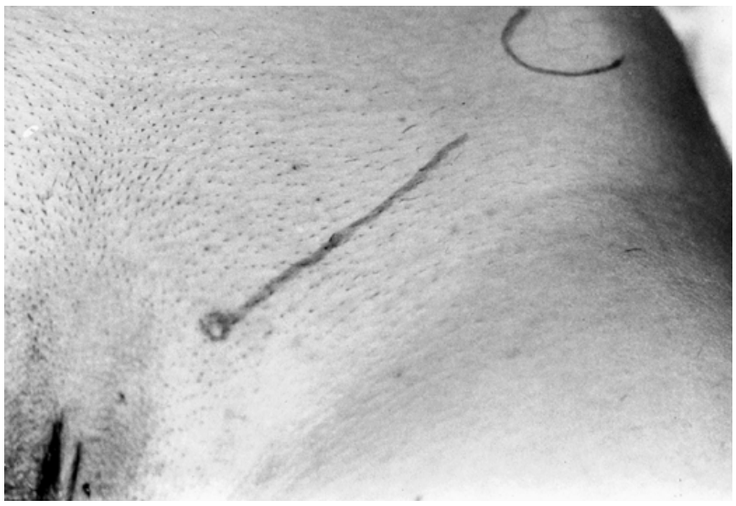

Figure 13.4 Skin incision for groin dissection through a separate incision. The incision is made along the medial four fifths of a line drawn between the anterior superior iliac spine and the pubic tubercle.

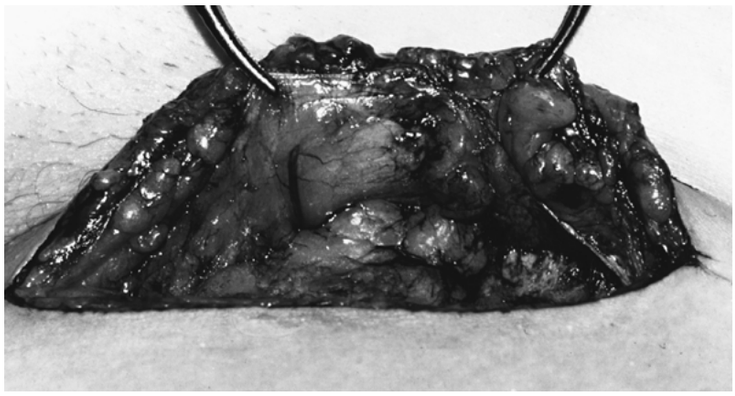

Figure 13.5 Camper's fascia kept on traction with forceps while the underlying node-bearing fatty tissue is dissected out of the femoral triangle. Note the preservation of the subcutaneous tissue above the superficial fascia. This ensures that skin necrosis will not occur.

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** (106). 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 dissection, a suction drain is placed in the groin and the wound is closed in two layers.

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 (15), 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 (18 ,107).

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:

- **The *en bloc* approach** through a trapezoid or butterfly incision (77) (Fig. 13.6)

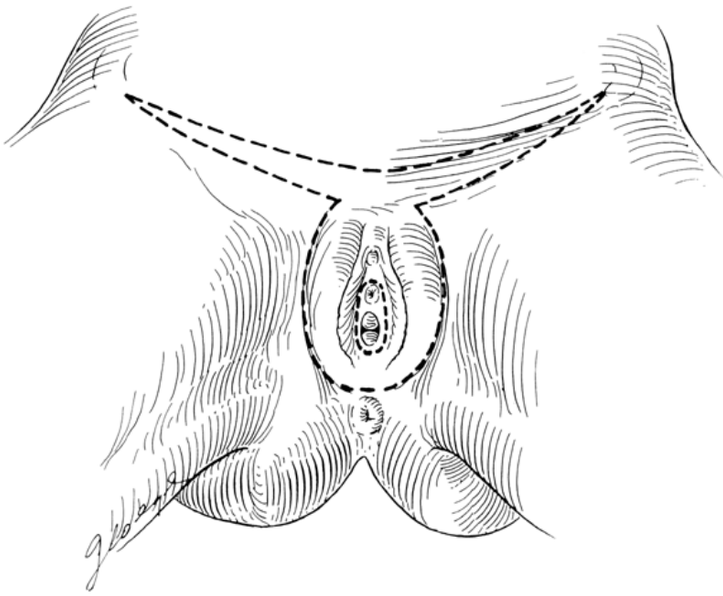

Figure 13.6 Incision used for *en bloc* radical vulvectomy and bilateral groin dissection.

- **The separate incision approach**, involving three separate incisions, one for the radical vulvectomy and one for each groin dissection (19 ,20) (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:

- **An area may be left open to granulate**, which it usually does over a period of 6 to 8 weeks (108). This is particularly useful around the urethra, where sutures can cause urethral deviation and misdirection of the urinary stream.
- **Full-thickness skin flaps may be devised** (109 ,110). An example is the rhomboid flap, which is best suited for covering large defects of the posterior vulva (111).
- **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 (112).
- **If extensive defects exist in the groin and vulva, the tensor fascia lata myocutaneous graft is applicable** (113).

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 (12 ,13 ,114), 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 (115) as long as surgical margins of at least 1 cm are obtained. Burke et al. (12) 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.

A study from Groningen, The Netherlands, compared 168 patients with T_1 and T_2 invasive squamous cell carcinomas treated by radical vulvectomy and *en bloc* groin dissection between 1982 and 1992, with 85 patients treated with radical local excision and groin dissection through separate incisions between 1993 and 1997 (116). Radical local excision and unilateral or bilateral groin dissection was associated with a small but significant increase in the overall recurrence rate compared with the *en bloc* approach. There was an increase in the number of groin and skin bridge recurrences, although the power of the study was

not sufficient to compromise the overall survival. In addition, there was an increased risk of local recurrence because of closer surgical margins. They suggested that surgical margins of 2 cm should be considered to minimize the incidence of local recurrence.

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.

In a review of the UCLA data in 1983, Hacker et al. (15) reported that **pelvic nodal metastases did not occur unless the patient had:**

- **Clinically suspicious (N_2) groin nodes, or**
- **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 (14), the Mayo Clinic (68), and the University of Michigan (17).

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 (18). 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. (117) 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 (118). Van der Velden et al. (119) 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:

- **Patients with one or possibly two micrometastases (≤ 5 mm diameter) should be observed.**
- **Patients with three or more micrometastases, one macrometastasis (≥10 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 1% to 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 2 to 3 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 7 to 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 (68). 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 (20). With débridement 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, lymphocysts in the femoral triangle, deep venous thrombosis, pulmonary embolism, myocardial infarction, hemorrhage, and, rarely, osteitis pubis.** Lymphocysts occur in about 40% of cases (120) 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. If large, they 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 and long walks immediately after discharge from hospital seem to increase the incidence of lymphocysts.

Late Complications

The major late complication is **chronic leg edema**, which has been reported in up to 69% of patients (68). In our experience at the Royal Hospital for Women, the incidence of lymphedema after groin dissection is 62% (121). In about 50% of patients, the onset of lymphedema occurs within 3 months, while about 85% experience the onset within 12 months (121). Lymphedema is significantly related to the occurrence of early complications (120). **Recurrent lymphangitis** or cellulitis of the leg occurs in approximately 10% of patients and usually responds to *erythromycin* tablets or *flucloxacillin.* **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 (82 ,122). 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 (123 ,124 and 125). 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 (22) **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. (23) 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 (Figs. 13.7 , 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 (23).

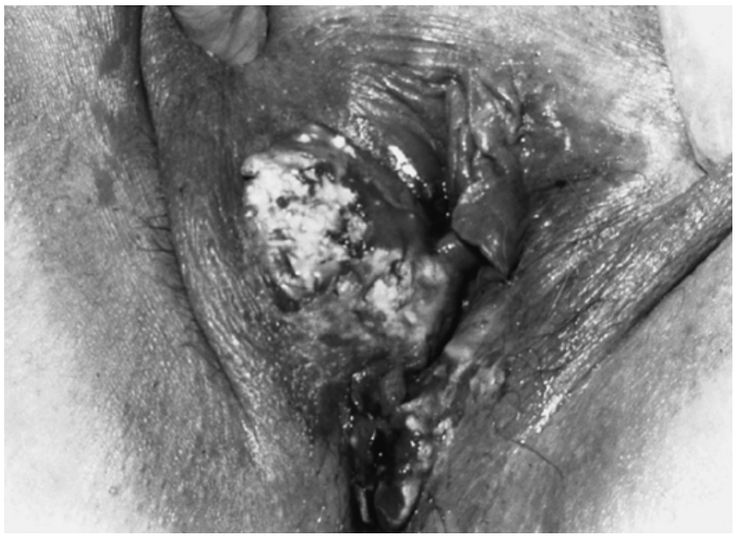

Figure 13.7 Advanced squamous cell carcinoma of the vulva involving the anal canal. A primary surgical approach would have necessitated radical vulvectomy, anoproctectomy, and permanent colostomy.

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. (126) 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.

This second report had three major refinements: (i) the use of external-beam therapy for all cases, with more selective use of brachytherapy; (ii) more conservative vulvar surgery; and (iii) resection of bulky N_2 and N_3 nodes without full groin dissection to minimize lymphedema.

In 1989, Thomas et al. (28) 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 (29). 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. A second similar Italian study of 58 patients reported a pathologic complete response rate of 31% in both the vulva and the groin (30).

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. (31) 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. (32) omitted groin dissection after preoperative 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.

Although the management of the groin nodes is controversial, 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 (18). 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:

- **A preoperative computed tomographic (CT) scan of the pelvis is obtained** to determine whether there are any enlarged pelvic nodes.
- **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.
- **Any enlarged pelvic nodes seen on CT scan are removed** by an extraperitoneal approach.
- **Full pelvic and groin irradiation is given as soon as the groin incisions are healed, which is usually approximately 2 weeks.**
- **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 .

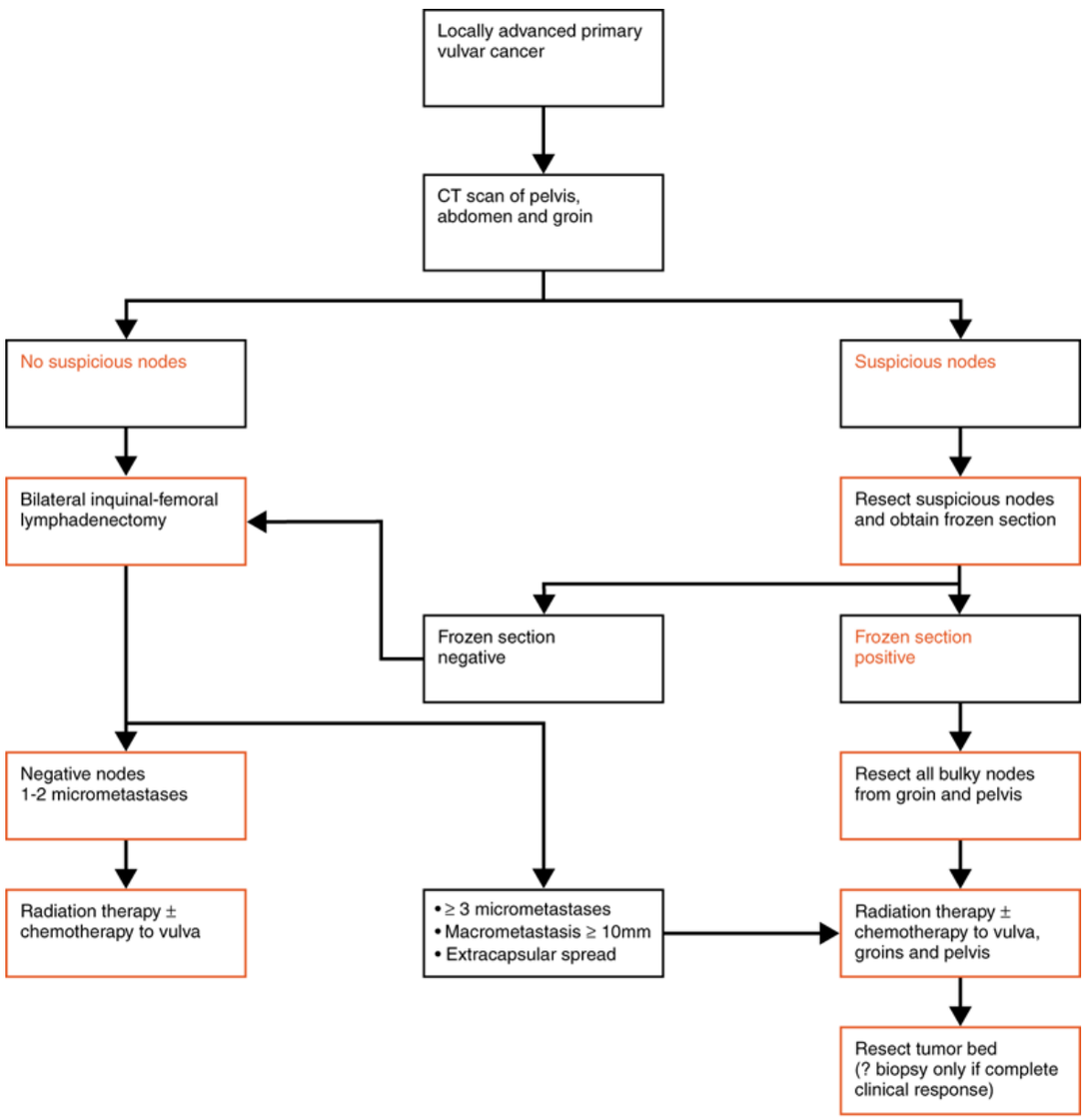

Figure 13.9 Algorithm for the management of patients with locally advanced vulvar cancer.

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:

- **Before surgery, in patients with advanced disease** who would otherwise require pelvic exenteration
- **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:

- **After surgery, to help prevent local recurrence** and improve survival **in patients with involved or close surgical margins** (<5 mm) (127 ,128 and 129)
- **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 (86)

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 (130). 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. (131) 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 18.5 cm, 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 (15). **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** (15 ,18). On multivariate analysis, margin status and depth of invasion are independent risk factors for local relapse (132).

Local vulvar recurrences **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 (20 ,133).

French workers have identified three patterns of local recurrence with very different prognoses: (i) primary tumor site recurrence (up to and including 2 cm from the vulvectomy scar), **(ii) recurrence at a distance from the primary tumor site**, and **(iii) skin bridge recurrence** (132). Their study included 215 patients, and the local relapse-free survival was 78.6% at 5 years. Patients with positive margins who did not receive radiotherapy and patients with greater than 1 mm stromal invasion who did not have a groin dissection were excluded from analysis.

Local recurrence at a site distant from the primary tumor (which could be considered a new primary lesion), **had a good prognosis**, 66.7% of patients surviving 3 years. **By contrast, survival after recurrence at the primary tumor site was poor**, only 15.4% of patients surviving 3 years. None of seven patients with a skin bridge recurrence was alive at 1 year.

Radiation therapy, particularly a combination of external-beam therapy plus interstitial needles, has also been used to treat vulvar recurrences. Hoffman et al. (134) reported on 10 patients treated in this manner, and 9 were still alive with a mean follow-up of 28 months. However, 6 of the 10 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 (127). 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 (127).

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).

Table 13.10 Five-Year Survival Rate Versus Stage for Patients Treated with Curative Intent

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 (63); **Boutselis**, 1972 (135); **Morley**, 1976 (77); **Japeze et al.**, 1977 (136); **Benedet et al.**, 1979 (66); **Hacker et al.**, 1983 (15); **Cavanagh et al.**, 1986 (137).

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 (63)	53	0	100.0
Morley, 1976 (77)	118	9	92.4
Green, 1978 (64)	63	3	95.2
Hacker et al., 1983 (15)	82	5	93.9
Podratz et al., 1983 (68)	115	12	90.0
Monaghan and Hammond, 1984 (16)	95	9	90.5
Cavanagh et al., 1986 (137)	96	16	83.3
Total	**622**	**54**	**91.3**

Table 13.12 Five-Year Survival Rate for Patients with Positive Lymph Nodes Treated with Curative Intent

Author	*No.*	*Dead of Disease*	*5-Year Survival (%)*
Rutledge et al., 1970 (63)	28	15	46.4
Morley, 1976 (77)	62	38	38.7
Green, 1978 (64)	46	18	60.9
Benedet et al., 1979 (66)	34	16	52.9
Curry et al., 1980 (14)	52	30	42.3
Hacker et al., 1983 (15)	31	10	67.7
Cavanagh et al., 1986 (137)	58	36	37.9
Total	**311**	**163**	**47.6**

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 (78).

The number of positive groin nodes is the single most important prognostic variable (15 ,17 ,18 ,68). Patients with one microscopically positive node have a good prognosis, regardless of the stage of disease (15 ,17), 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 (15), 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) (18). Extracapsular spread is a poor prognostic factor (117 ,118 and 119). **The survival rate for patients with positive pelvic nodes is approximately 11%** (76).

Workers at the Norwegian Radium Hospital evaluated DNA ploidy for its prognostic significance in 118 squamous cell carcinomas of the vulva (138). **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:**

- **Lymph node involvement** (p <0.0001)
- **Tumor ploidy** (p <0.0001)
- **Tumor size** (p <0.0039)

Dutch workers studied 75 patients aged 80 years or older, 57 (76%) of whom had standard treatment (139). When preoperatively available parameters of all patients were assessed in relation to survival in the total group, Eastern Cooperative Oncology Group (ECOG) performance status was the only independent prognostic variable. When all clinical and histopathological variables were assessed in the subgroup who had standard treatment, both **ECOG performance status and extracapsular lymph node involvement were independent prognostic variables for overall survival. Age was not a significant prognostic variable.**

Melanoma

Vulvar melanomas are rare, although they are the second most common vulvar malignancy. Most arise *de novo* (140), 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 biopsied, unless it is known to have been present and unchanged for some years.**

There are three basic histologic types: (i) the **superficial spreading melanoma**, which tends to remain relatively superficial early in its development; (ii) **the mucosal lentiginous melanoma**, a flat freckle, which may become quite extensive but also tends to remain superficial; and (iii) the **nodular melanoma**, which is a raised lesion that penetrates deeply and may metastasize widely. A recent Swedish study of 219 cases reported that the mucosal lentiginous melanoma was the most frequent type (57%) (141).

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 (142 ,143 and 144). The leveling system established by Clark et al. (145) for cutaneous melanomas is less readily applicable to vulvar lesions because of the different skin morphology. Chung et al. (142) 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 (146) 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 .

Table 13.13 Microstaging of Vulvar Melanomas

	Clark's Levels (145)	*Chung et al. (142)*	*Breslow (146)*
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

A newly revised American Joint Committee on Cancer (AJCC) Staging System for cutaneous melanomas came into effect in 2002 to reflect the new prognostic factors that have been found to be important in predicting survival (147). These factors include primary tumor thickness (replacing level of invasion), ulceration, number of metastatic lymph nodes, micrometastatic disease based on the sentinel lymph node biopsy technique or elective node dissection, the site(s) of distant metastatic disease, and serum lactate dehydrogenase (LDH) levels.

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** (142 ,143). 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 (148 ,149), **there is a trend toward more conservative resection for vulvar melanomas** (150 ,151 ,152 and 153). 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 (154).

Davidson et al. (151) 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. (152) 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 is controversial. **The Intergroup Surgical Melanoma Program conducted a prospective, multiinstitutional, randomized trial of elective lymph node dissection versus observation for intermediate thickness cutaneous melanomas** (1 to 4 mm) (155). 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 (156 ,157). 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. Podratz et al. (144) demonstrated a 10-year survival rate of 61% for lateral lesions, compared with 37% for medial lesions (p <0.027).

The author's current policy is to perform a radical local excision with 1–2 cm margins for the primary lesion. In the absence of clinically suspicious groin nodes that are proven positive on frozen section, at least an ipsilateral inguinofemoral lymphadenectomy is performed. The role of sentinel node biopsy deserves further study for vulvar melanomas.

***Interferon alpha-2b (IFN-a-2b)* is the first agent to show significant value as an adjuvant for melanoma in a randomized controlled trial** (158). The Eastern Cooperative Oncology Group entered 287 patients onto an adjuvant trial of high-dose *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%.

The results were confirmed in a larger intergroup trial that compared the efficacy of high-dose *interferon-a-2b* for 1 year with vaccination using GM2 conjugated to keyhole limpet hemocyanin (159). Eight hundred and eighty patients were randomized, and the trial was closed after interim analysis indicated inferiority of the vaccination compared with high-dose *interferon-a-2b*.

High-dose interferon regimens cause significant morbidity, but should be considered standard therapy for all high-risk melanoma patients expected to be able to tolerate the interferon (160). Immunotherapy for melanoma includes a number of different strategies with vaccines utilizing whole cell tumors, peptides, cytokine-mediated dendritic cells, DNA and RNA, and antibodies. Although initial clinical trials are promising, these approaches remain experimental (161).

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%** (140) **to 54%** (144). Patients with lesions invading to 1 mm or less have an excellent prognosis, but as depth of invasion increases, prognosis worsens. Chung et al. (142) 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 less than 100 mm^3 having an excellent prognosis (157). DNA ploidy and angioinvasion have been shown to be independent prognostic factors for disease-free survival (162).

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 (61 ,163).

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.** One case of small cell neuroendocrine cancer of the Bartholin gland has been reported (164).

Classification of a vulvar tumor as a Bartholin gland carcinoma has typically required that it fulfill **Honan's criteria**, which are:

- **The tumor is in the correct anatomic position**
- **The tumor is located deep in the labium majus**
- **The overlying skin is intact**
- **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.

Bartholin gland carcinomas are often misdiagnosed initially as a Bartholin cyst or abscess. A study from Tampa reported that 8 of 11 cases had initially been treated for an infectious process before referral (165). Hence, **delay of diagnosis is common, particularly in premenopausal patients.** Other differential diagnoses of any pararectovaginal neoplasm should include cloacogenic carcinoma and secondary neoplasm (163).

The **adenoid cystic variety** accounts for approximately 10% of Bartholin gland carcinomas. The largest series has been reported from the University of Michigan, where 11 cases were seen over a 58-year period (166). 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 (167).

Treatment

Although treatment has traditionally included radical vulvectomy and bilateral groin dissection, Copeland et al. (163) at the M. D. Anderson Hospital have reported good results with hemivulvectomy or radical local excision for the primary tumor (Fig. 13.11). 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's 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 chemoradiation is preferable to avoid exenterative surgery and permanent colostomy.

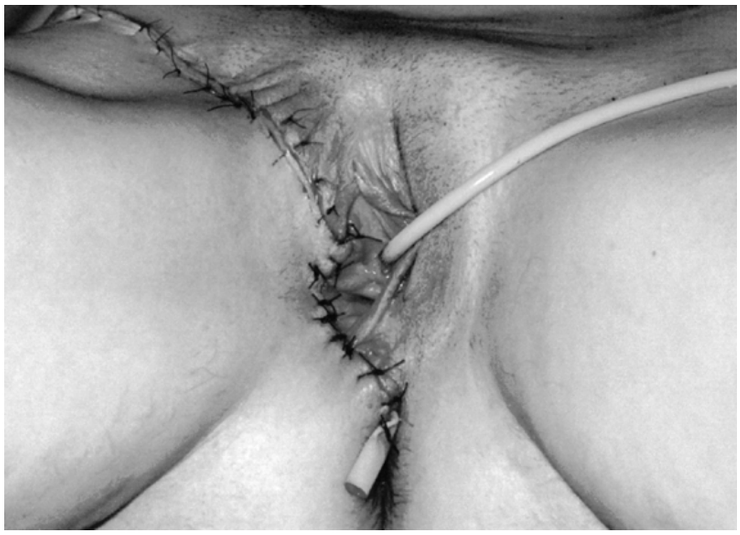

Figure 13.11 ***En bloc*** **resection of the right groin and right-posterior vulva for a Bartholin gland carcinoma.** Note the preservation of the clitoris and right anterior labium minus. (See Color Figure 13.11).

Radical local excision, with or without ipsilateral inguinal-femoral lymphadenectomy, 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 (168). The slowly progressive nature of these tumors is reflected in the disparity between progression-free interval and survival curves (169).

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** (103).

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. (170) 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 2% to 4% 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 (171).

Basal cell carcinomas usually affect postmenopausal white women, a Vancouver study reporting a mean age of 74 years (172). **They are locally aggressive, and radical local excision usually is adequate treatment.** They are moderately radiosensitive, so radiation may be useful in selected cases. **Metastasis to regional lymph nodes has been reported but is rare** (173 ,174 ,175 and 176), and there has been one reported case with hematogenous spread (176). The duration of symptoms prior to diagnosis is usually several years in patients with metastatic basal cell carcinomas (176). The local recurrence rate is 10-20% (176).

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** (175). **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 (176).

Verrucous Carcinoma

Verrucous carcinomas are most commonly found in the oral cavity, but may be found on any moist membrane composed of squamous epithelium (177). They are a distinct entity, with no association with human papillomavirus infection, and a peculiar distribution pattern of cytokeratins AE1 and AE3 on immunohistochemical staining (178).

Grossly, the tumors have a cauliflowerlike appearance, and the diameter of reported lesions ranges from 1 to 15 cm (179). **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 (103). 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 (180). **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 (181). If the nodes contain metastases, radical local excision and at least an ipsilateral inguinofemoral lymphadenectomy are indicated.

Radiation therapy is contraindicated because it may induce anaplastic transformation with subsequent regional and distant metastasis (182). Japaze et al. (181) 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** (103). A recent paper from Johns Hopkins reported seven cases of vulvar sarcoma among 453 patients with vulvar malignancies seen from 1977 to 1997, an incidence of 1.5% (183).

The primary treatment is wide surgical excision (184). Adjuvant radiation may be helpful for high-grade tumors and locally recurrent low-grade lesions (185). **The overall survival rate is approximately 70%**. There were no recurrences in the series from Johns Hopkins (183), with follow-up ranging from 60 to 172 months. Only one of their patients had groin dissection.

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 (186) 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 (186). **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. (187) 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 (188). 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. (189) 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 include the following.

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 (103). 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 (190). **Treatment is by surgical excision followed by chemotherapy and/or radiation**, and the overall 5-year survival rate is approximately 70% (190).

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 (103 ,191). 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 (192 ,193). 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 (194 ,195). **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 (103).

Secondary Vulvar Tumors

Eight percent of vulvar tumors are metastatic (103). **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 (196).

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14

Vaginal Cancer

Neville F. Hacker

Primary cancer of the vagina constitutes about 2% of malignant neoplasms of the female genital tract. More than 50% of patients are diagnosed in the seventh, eighth, and ninth decades, and squamous cell histology is the most common variant (1).

Until the late 1930s, vaginal cancer was in general considered to be incurable. Most patients have disease that has spread beyond the vagina at the time of diagnosis, but **with modern techniques for radiation therapy, cure rates of even advanced cases should now be comparable with those for cervical cancer** (2 ,3).

Fu (4) 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 (4). This apparent discrepancy 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 carcinoma of the vulva. **Endometrial carcinomas and choriocarcinomas commonly metastasize to the vagina, whereas tumors from the bladder or rectum may invade the vagina directly.**

Primary Vaginal Tumors

Part of "14 - Vaginal Cancer "

The histologic types of primary vaginal tumors are shown in Table 14.1 (5 ,6 ,7 ,8 ,9 ,10 ,11 ,12 ,13 ,14 ,15 ,16). Squamous cell carcinomas are the most common, although adenocarcinomas, melanomas, and sarcomas are also seen. Sarcomas occasionally follow radiation therapy for cervical cancer.

Table 14.1 Primary Vaginal Cancer: Reported Incidence of Histologic Types

Histologic Types	*Number*	*Percentage*
Squamous cell	740	81.5
Adenocarcinoma (including clear cell)	96	10.5
Sarcoma	27	3.0
Melanoma	29	3.2
Undifferentiated	8	0.9
Small cell	5	0.6
Lymphoma	2	0.2
Carcinoid	1	0.1
Total	**908**	**100.0**

Data compiled from **Perez et al.**, 1974 (5); **Pride and Buchler**, 1977 (6); **Ball and Berman**, 1982 (7); **Houghton and Iversen**, 1982 (8); **Benedet et al.**, 1983 (9); **Peters et al.**, 1985 (10); **Rubin et al.**, 1985 (11); **Sulak et al.**, 1988 (12); **Eddy et al.**, 1991 (13); **Ali et al.**, 1996 (14); **Tjalma et al.**, 2001 (15); and **Tewari et al.**, 2001 (16).

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 (3 ,5 ,8 ,11). Perez et al. (5) reported that 76% of patients were older than 50 years.

Etiology

Women who have been treated for a prior anogenital cancer, particularly of the cervix, have a high relative risk of developing vaginal cancer, although the absolute risk is low (17).

In a population-based study of 156 women with *in situ* or invasive vaginal cancer, Daling et al. determined that they had many of the same risk factors as patients with cervical cancer, including a strong relationship with human papilloma virus (HPV) infection (17). The presence of antibodies to HPV 16 was strongly related to the risk of vaginal cancer.

As many as 30% of patients with primary vaginal carcinoma have a history of *in situ* **or invasive cervical cancer treated at least 5 years earlier** (9 ,10 ,11). 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% (13). 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:

- **Occult residual disease**
- **New primary disease arising in an “at-risk” lower genital tract**
- **Radiation carcinogenicity**

In the first instance, extension of intraepithelial neoplasia from the cervix to the upper vagina was not appreciated and an adequate vaginal cuff was not taken because vaginal colposcopy was not performed before surgical management of the cervical tumor. Surgical margins of the upper vaginal resection usually show *in situ* neoplasia, 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 (6), and this may be particularly important in young patients who live long enough to develop a second neoplasm in the irradiated vagina (19).

The true malignant potential of vaginal intraepithelial neoplasia is unclear because once diagnosed, the condition is usually treated. Benedet and Saunders (18) 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. Rome and England reported 9 (6.8%) cases of early invasive vaginal cancer detected during the initial management of 132 cases of vaginal intraepithelial neoplasia (VAIN) (20). Chronic local irritation from long-term use of a pessary may also be of significance (4) (Fig. 14.1), although pessaries are used less commonly in modern gynecology.

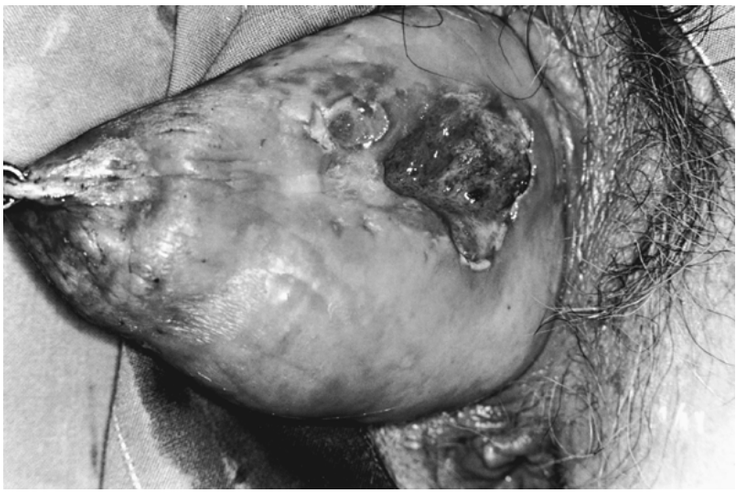

Figure 14.1 Squamous cell carcinoma of the vagina in a patient with a procidentia. The cancer was apparently related to long-term pessary use.

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 women, making routine screening of all patients inappropriate (21). However, **women with a history of cervical intraepithelial or invasive neoplasia are at increased risk and should be monitored carefully with Pap smears.**

As many as 59% of patients with vaginal cancer have had a prior hysterectomy (7). 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** (22).

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. 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 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 may need 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.** This is usually done with a cold knife, but Fanning et al. have reported the successful use of the loop electrosurgical procedure for partial upper vaginectomy in 15 patients (23). Inadvertent cystotomy may occur occasionally, and this requires immediate repair.

Hoffman et al. (24) 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 x-ray, and possible skeletal radiographs if the latter are indicated because of bone pain.

Table 14.2 Carcinoma of the Vagina: FIGO Nomenclature

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.

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 survivals within a given stage. The distribution by FIGO stage from 13 series is shown in Table 14.3 (2 ,3 ,7 ,8 ,9 ,10 ,11 ,13 ,14 ,15 ,16 ,25 ,26). Fewer than one-third of patients present with disease confined to the vagina.

Table 14.3 Primary Vaginal Carcinoma: Distribution by Stage of Disease

Stage	*Number*	*Percentage*
I	395	26.3
II	562	37.4
III	352	23.5
IV	192	12.8
Total	**1,501**	**100.0**

Data compiled from **Ball and Berman**, 1982 (7); **Houghton and Iversen**, 1982 (8); **Benedet et al.**, 1983 (9); **Peters et al.**, 1985 (10); **Rubin et al.**, 1985 (11); **Kucera et al.**, 1985 (25); **Eddy et al.**, 1991 (13); **Kirkbridge et al.**, 1995 (3); **Stock et al.**, 1995 (26); **Chyle et al.**, 1996 (2); **Ali et al.**, 1996 (14); **Tjalma et al.**, 2001 (15); and **Tewari et al.**, 2001 (16).

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. Positron emission tomography (PET) may also be increasingly used in the future to determine the extent of metastatic disease.

Peters et al. (27) 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. (28) 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:

- **Direct extension** to the pelvic soft tissues, pelvic bones, and adjacent organs (bladder and rectum).
- **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.
- **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. (11) 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 (29) 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. (26) 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. The possible role of magnetic resonance imaging (MRI) and PET scanning has not yet been defined.

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 (25). **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 (7 ,15 ,26 ,29). Surgery may be useful in the following circumstances:

- **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.
- **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.
- **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. (13) 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.
- **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 (2 ,3 ,5 ,16 ,25). Selected stage I and II lesions can be treated adequately with brachytherapy alone (2 ,3 ,30). 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 (2 ,31). 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 (16). Extended-field radiation has rarely been used for patients with vaginal cancer, but if positive paraaortic nodes are documented after either surgical staging, CT scanning and fine-needle aspiration cytologic evaluation, or PET scanning, 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 (3 ,32). However, in view of the problem with control of the central tumor, the concurrent use of *cisplatin*, and/or *5-fluorouracil (5-FU)* with radiation therapy, as is being done for cervical carcinoma, 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. 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 (2). **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.

Stryker reported vaginal morbidity in 9 of 15 patients (60%) undergoing external beam therapy plus intracavitary brachytherapy, and 3 of 10 patients (30%) undergoing external beam therapy plus interstitial brachytherapy. He suggested that when combining external beam therapy with brachytherapy, interstitial techniques were preferable (33).

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, at least every second night. There is inadequate documentation of the adequacy of vaginal function after either surgery or radiation therapy.

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 (3 ,8 ,9 ,11 ,13 ,16 ,25 ,34) (Table 14.4). Even for patients with stage I disease, the 5-year survival rate in combined series is only approximately 70%. In the 24th volume of the *Annual Report on the Results of Treatment in Gynecological Cancer*, the 5-year survival for 201 patients with vaginal cancer was as follows: stage I, 73.4%; stage II, 51.4%; stage III, 32.5%; stage IVA, 20.4%; stage IVB, 0% (1).

Table 14.4 Primary Vaginal Carcinoma: 5-Year Survival Rates

Stage	*No.*	*5-Year Survival*	*Percentage*
I	222	156	70.3
II	313	159	50.8
III	260	86	33.0
IV	139	24	45.5
Total	**934**	**425**	**45.5**

Data compiled from **Pride et al.**, 1979 (34); **Houghton and Iversen**, 1982 (8); **Benedet et al.**, 1983 (9); **Rubin et al.**, 1985 (11); **Kucera et al.**, 1985 (25); **Eddy et al.**, 1991 (13); **Kirkbridge et al.**, 1995 (3); and **Tewari et al.**, 2001 (16).

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. (2) 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. (3) 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 (35), so improved radiation therapy, which may include chemoradiation and/or increasing experience with interstitial techniques, may improve the results. Chyle et al. (2) reported that salvage after first relapse was uncommon, with a 5-year survival rate of only 12%.

Because of the rarity of the disease, patients with vaginal cancer should be referred centrally to a limited number of tertiary referral units so that increasing experience can be gained in their management.

Adenocarcinoma

Approximately 10% 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** (36). 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, and foci of endometriosis.

Vaginal adenosis is the sequestration of müllerian glandular epithelium into the vaginal mucosa during embryogenesis. It is thought to arise as a consequence of disrupted development and has been reported in non-DES-exposed women from infancy to old age (37). Intestinal metaplasia occasionally occurs in tissues of müllerian origin, and primary vaginal adenocarcinoma of intestinal type has been described (38). **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 (39) **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.** (40) **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 (41). 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 52 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 twenty-second 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. (42) 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 (43) 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 (44).

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. (45) 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, synechiae, diverticulae, 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 (46).

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, *DES*-related 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, the performance of radical hysterectomy, pelvic lymphadenectomy, vaginectomy, and replacement of the vagina with a split-thickness skin graft has 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 (47). 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 (48). If radiation alone is used, a pretreatment staging laparotomy to allow pelvic lymphadenectomy and ovarian transposition may facilitate an optimal functional outcome. Freezing of embryos with a view to a subsequent surrogate pregnancy may be considered if ovarian function is in jeopardy and the patient has a suitable partner.

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** (48). Survival for non–clear cell adenocarcinomas is significantly worse than for squamous cancers (2).

Small Cell Carcinoma

Primary small cell carcinoma of the vagina is extremely rare, but as many as 5% of such tumors arise in extrapulmonary sites. In the female genital tract, such tumors arise most commonly in the cervix, followed by the ovary, endometrium, vagina, and vulva (49). As with other primary sites, small cell carcinoma of the vagina has a proclivity for distant failure and a poor prognosis. Management should be with concurrent chemoradiation.

Verrucous Carcinoma

Verrucous carcinomas of the vagina are rare, but their clinical and pathologic features are similar to those of their vulvar counterparts (50). **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. (50), 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**, and Crowther et al. (50) reported recurrence in all four patients treated with primary radiation therapy.

Vaginal Melanoma

Malignant melanomas of the vagina are rare, with less than 250 reported cases (51). They presumably arise from melanocytes that are present in the vagina in 3% of normal women (52). The average age of the patients is 58 years, but vaginal melanomas have been reported from the third to the ninth decades of life (53). **Almost all cases occur in white women** (54).

Clinically, most patients present 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** (54 ,55). 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 (56)], Chung et al. (55) 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 (55).

Radical surgery has traditionally 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 have been treated with radical hysterectomy, subtotal vaginectomy, and pelvic lymphadenectomy, whereas small distal vaginal lesions have been treated by partial vaginectomy, total or partial vulvectomy, and bilateral inguinofemoral lymphadenectomy.

More recently, conservative operations (e.g., wide local excision) have been used, followed frequently by pelvic radiotherapy (51 ,54 ,57 ,58), and there appears to be no significant benefit in terms of survival or disease-free interval for radical versus conservative surgery. Postoperative radiation therapy is effective for prevention of local recurrence, and **high-dose fractions (>400 cGy) may be preferable to conventional or low-dose fractions** (59). 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. (57) 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. (54) and Buchanan et al. (57) 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 (57).

Adjuvant therapy with *interferon alfa-2b* **has been shown to improve relapse-free and overall survival in patients with high-risk cutaneous melanomas** (60), 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 (61) 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. A recent review of vaginal leiomyosarcomas revealed fewer than 70 cases reported in the English literature (62). The average age at presentation was 47 years, and the overall 5-year survival was 43%.

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 (63).

Embryonal Rhabdomyosarcoma

Embryonal rhabdomyosarcoma is a malignant tumor of the rhabdomyoblasts characterized by two structural variants, a solid form and a multicystic grapelike 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.** The Intergroup rhabdomyosarcoma studies have demonstrated a more favorable response to therapy and better prognosis for the vulvar and vaginal tumors, compared with those arising in the corpus or cervix (64).

The term *botryoides* comes from the Greek word *botrys*, which means "grapes," and, grossly, the tumor usually appears as a polypoid 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 (64 ,65). The usual chemotherapy has consisted of *vincristine*, *actinomycin D*, and *cyclophosphamide* (VAC), but *adriamycin* and *ifosphamide* have also been used. 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 (66). Permanent local control with drugs alone occurs in fewer than 15% of cases (67).

Endodermal Sinus Tumor (Yolk Sac Tumor)

These rare germ cell tumors are occasionally found in extragonadal sites such as the vagina. Leverger et al. (68) 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 α-fetoprotein levels. From 1977 to 1983, six of eight children were 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

Part of "14 - Vaginal Cancer "

Primary carcinoma of the female urethra is a rare malignancy, accounting for fewer than 0.1% of all female genital malignancies (69). 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 (69 ,70 ,71 ,72 ,73 ,74). Urethral carcinomas occasionally arise in a urethral diverticulum (72).

Table 14.5 Histology of Urethral Carcinomas

Type	*No.*	*Percentage*
Squamous cell	124	53.3
Adenocarcinoma	49	21.0
Transitional cell	44	18.9
Undifferentiated	8	3.4
Melanoma	5	2.2
Sarcoma	1	0.4
Non-Hodgkin's lymphoma	1	0.4
Unknown	1	0.4
Total	**233**	**100.0**

Data compiled from **Bracken et al**, 1976 (70); **Benson et al, 1982** (72); **Weghaupt et al.**, 1984 (69); **Prempree et al.**, 1984 (71); **Grigsby**, 1998 (73); and **Eng et al.**, 2003 (74).

There is no FIGO staging for the disease, and several staging classifications have been suggested (70 ,71 ,75 ,76). 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 workup.

Table 14.6 TNM Staging for Urethral Cancer

Stage	*TNM*		
Stage 0_a	T_a	N_0	M_0
Stage 0_{is}	T_{is}	N_0	M_0
Stage I	T_1	N_0	M_0
Stage II	T_2	N_0	M_0
Stage III	T_1	N_1	M_0
	T_2	N_1	M_0
	T_3	N_0	M_0
	T_3	N_1	M_0
Stage IV	T_4	N_0	M_0
	T_4	N_1	M_0
	Any T	N_2	M_0
	Any T	N_3	M_0
	Any T	Any N	M_1

TNM Classification			
T:	**Primary Tumor**	**M:**	**Distant Metastases**
T_a	Noninvasive papillary, polypoid, or verrucous carcinoma		
T_{is}	Carcinoma *in situ*	M_x	Presence of distant metastasis cannot be assessed
T_1	Tumor invades subepithelial connective tissue	M_0	No distant metastasis
T_2	Tumor invades the periurethral muscle	M_1	Distant metastasis
T_3	Tumor invades the anterior vagina or bladder neck	**Histopathologic Type**	
T_4	Tumor invades other adjacent organs	Cell types can be divided into transitional squamous, and glandular	
N:	**Regional Lymph Nodes**	**G:**	**Histopathologic Grade**
N_x	Regional lymph nodes cannot be assessed	G_x	Grade cannot be assessed
N_0	No regional lymph node metastasis	G_1	Well differentiated
N_1	Metastasis in a single lymph node, 2 cm or less in greatest dimension	G_2	Moderately differentiated
N_2	Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension	G_{3-4}	Poorly differentiated or undifferentiated
N_3	Metastasis in a lymph node more than 5 cm in greatest dimension		

The treatment of urethral cancer must be individualized (69) and multimodal (74 ,77). For small distal lesions, the distal half of the urethra can be excised without loss of urinary continence. **Bilateral inguinofemoral lymphadenectomy should be performed for all but the most superficial lesions involving the distal half of the urethra.** Interstitial radiation may be satisfactory for more proximal early lesions.

The majority of patients present with advanced disease, and surgery alone is suboptimal. **Radiation therapy is considered to be the treatment of choice, although it may cause complications such as urinary stricture, fistula, or total incontinence.** Surgery may be used in conjunction with radiation for advanced lesions (71). Anterior exenteration and high-dose^{192} iridium (^{192} Ir) intraoperative radiotherapy, followed several weeks later by external beam pelvic radiation, has been reported to give local control in four of six patients (67%), with a median follow-up of 21 months (range 12 to 47 months) (77). Four of the six patients were also treated with neoadjuvant or concomitant platinum-based chemotherapy. Klein et al. (78) 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. For medically inoperable patients, external beam therapy followed by high-dose–rate brachytherapy delivered with a remote afterloader, using a shielded vaginal applicator and modified urethral catheter, has been successfully used (79).

The main cause of treatment failure is local recurrence (77). Experience with chemoradiation is limited (74 ,80), but in view of the experience with other primary sites, this would seem to be an acceptable initial approach for locally advanced cases.

Prognosis

Bracken et al. (70) 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. Grigsby (73), 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.**

Malignant melanoma

This rare tumor accounts for 0.2% of all melanomas. Di Marco et al. reported the Mayo Clinic experience of 11 cases (mean age 68 years) treated from 1950 to 1999 (81). Most patients presented with hematuria or a urethral mass. Four patients were treated by radical surgery, including anterior exenteration in two patients. Two (50%) of the four patients undergoing radical surgery recurred at 4 and 34 months, respectively. The remaining seven patients underwent local excision with partial urethrectomy. This group experienced urethral recurrence in five of the seven patients (71%). No patient received any adjuvant therapy. The authors suggested that radical urethrectomy with bladder preservation and a continent catheterizable stoma may be a more appropriate option. The catheterizable stoma could be constructed using an appendicovesicostomy or an ileovesicostomy for urinary diversion.

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15
Gestational Trophoblastic Neoplasia

Ross S. Berkowitz
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 ,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
- Malignant Gestational Trophoblastic Neoplasia
- Chemotherapy
-

Hydatidiform Mole

Part of "15 - Gestational Trophoblastic Neoplasia "

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).

Table 15.1 Features of Complete and Partial Hydatidiform Moles

	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; 69XYY

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, 1993:425, with permission.

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):

- Chorionic villi of varying size with focal hydatidiform swelling and cavitation
- Marked villous scalloping
- Focal trophoblastic hyperplasia with or without atypia
- Prominent stromal trophoblastic inclusions
- 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. It is questionable whether nontriploid partial moles exist (9).

Clinical Features

The presenting symptoms and signs of patients with complete and partial molar pregnancy are presented in Table 15.2 (10 ,11).

Table 15.2 Presenting Symptoms and Signs in Patients with Complete and Partial Molar Pregnancy

Sign	*Complete Mole[a] N = 306 (%)*	*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. *Pathobiology Annual* 1981;11:391, and

[b]**Berkowitz RS, Goldstein DP, Bernstein MR**. Natural history of partial molar pregnancy. *Obstet Gynecol* 1985;66:677–681.

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) (12).

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 (12).

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. (13) 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 ß-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 ß-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. (14) 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 (12). 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 (15). **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 (16).

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 (17). 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 (17). 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. Furthermore, the histopathologic characteristics of complete mole are different in the first trimester (18). First trimester complete moles have less circumferential trophoblastic hyperplasia and smaller villi and their more subtle morphologic alterations may lead to misclassification as partial moles or nonmolar spontaneous abortions.

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** (19).

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%) (10). 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 only 2 patients.

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%** (11).

A review of 858 patients with complete hydatidiform mole (11) revealed that **two-fifths of the patients had** the following signs of marked trophoblastic proliferation at the time of presentation:

- **Human chorionic gonadotropin level greater than 100,000 mIU/mL**
- **Excessive uterine enlargement**
- **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%.

Table 15.3 Sequelae of Low- and High-Risk Complete Hydatidiform Moles

	No. of Patients (%)	
Outcome	*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.

Patients older than 40 years of age are also at increased risk of postmolar GTN. Tow (20) 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 (21). 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 continues to be useful in the detection of first trimester complete moles (22).

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 (23).

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:

- **Oxytocin infusion**—This is begun in the operating room before the induction of anesthesia.
- **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.
- **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.
- **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 evacuation of a complete mole is controversial (24). 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).

Table 15.4 Prophylactic Actinomycin D (Act-D) after Evacuation or Hysterectomy for Molar Pregnancy

	No. of Patients (%)	
Outcome	*Act-D*	*No Act-D*
Normal involution	237 (96.0)	698 (81.4)
Persistent GTN		
Nonmetastatic	10 (4.0)	126 (14.6)
Metastatic	0 (0)	34 (4.0)
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;26:208, with permission.

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. (25) and Limpongsanurak (26) performed prospective, randomized studies 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 (α and ß) attached to a carbohydrate moiety. There is considerable cross-reactivity between hCG and LH because they share indistinguishable α chains. Each of the ß chains of these four glycoprotein hormones is biochemically unique and confers biologic and immunologic specificity. The ß-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 ß-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 ß-hCG regression curve is presented in Figure 15.1 . When a patient with molar pregnancy achieves any nondetectable hCG level, the risk of developing tumor relapse appears very low (27).

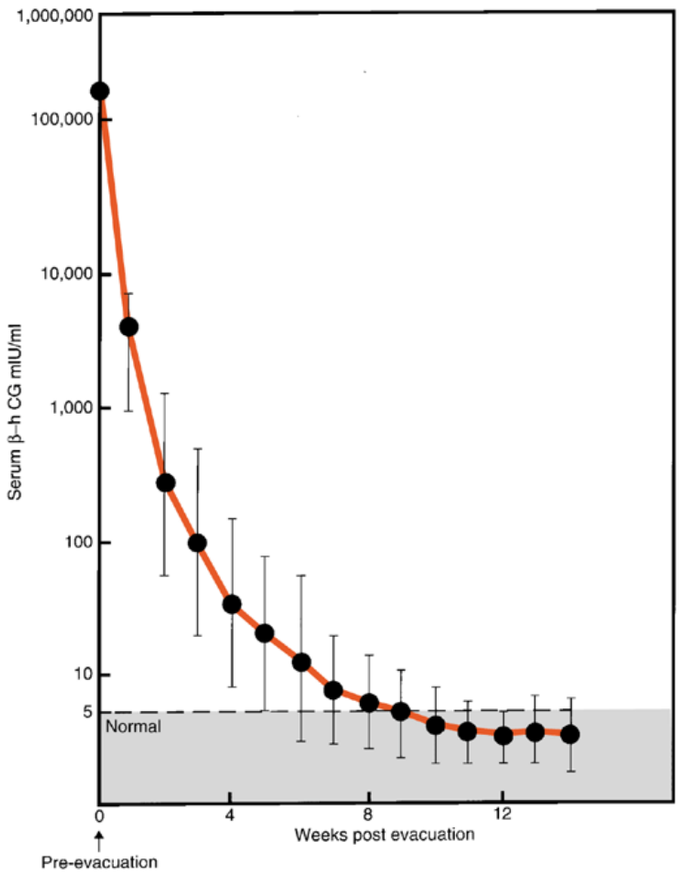

Figure 15.1 Normal regression curve of beta-subunit human chorionic gonadotropin (-hCG) after molar evacuation. (Reprinted from **Morrow CP, Kletzky OA, DiSaia PJ, Townsend DE, Mishell DR, Nakamura RM.** Clinical and laboratory correlates of molar pregnancy and trophoblastic disease. *Am J Obstet Gynecol* 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 (28). 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 (29 ,30). 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

Part of "15 - Gestational Trophoblastic Neoplasia "

Nonmetallic Disease

Locally invasive GTN develops in 15% of patients after evacuation of a complete mole and infrequently after other gestations (11). These patients usually present clinically with one or more of the following:

- Irregular vaginal bleeding
- Theca lutein cysts
- Uterine subinvolution or asymmetric enlargement
- 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 (31). 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. Intensive combination chemotherapy may achieve complete remission in patients with metastatic disease, particularly when the interval from the antecedent pregnancy is less than 4 years (32).

Metastatic Disease and Choriocarcinoma

Metastatic GTN occurs in 4% of patients after evacuation of a complete mole and is infrequent after other pregnancies (11). Metastasis is usually associated with choriocarcinoma, although the precise histology is usually not determined, because the diagnosis is based on rising hCG levels. Approximately one half of choriocarcinomas occur following a hydatidaform mole and one half after other pregnancies, including normal ones. Choriocarcinoma 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 .

Table 15.5 Relative Incidence of Common Metastatic Sites

Lungs	80%
Vagina	30%
Pelvis	20%
Brain	10%
Liver	10%
Bowel, kidney, spleen	<5%
Other	<5%
Undetermined[a]	<5%

[a]Persistent human chorionic gonadotropin titer after hysterectomy.
Reproduced from **Berkowitz RS, Goldstein DP**. Pathogenesis of gestational trophoblastic neoplasms. *Pathobiol Annual* 1981;11:391, with permission.

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:

- An alveolar or “snowstorm” pattern
- Discrete, rounded densities
- Pleural effusion
- 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

The current staging system for GTN combines both anatomic staging and a prognostic scoring system (Tables 15.6 , 15.7). It is hoped that this staging system will encourage the objective comparison of data among various centers.

Table 15.6 Staging of Gestational Trophoblastic Neoplasia

Stage I	Confined to uterine corpus
Stage II	Metastases to pelvis and vagina
Stage III	Metastases to lung
Stage IV	Distant metastases

Table 15.7 Scoring System Based on Prognostic Factors

	Scores			
	0	1	2	4
Age (yr)	<40	≥40	—	—
Antecedent pregnancy	Mole	Abortion	Term	
Interval months from index pregnancy	<4	4-<7	7-<13	≥13
Pretreatment serum hCG (IU/L)	$<10^3$	10^3-$<10^4$	10^4-$<10^5$	$\geq 10^5$
Largest tumor size (including uterus)		30 cm-<5 cm	≥5 cm	—
Site of metastases	Lung	Kidney/Spleen	Gastrointestinal/Liver	Brain
Number of metastases	—	1–4	5–8	>8
Previous failed chemotherapy	—	—	Single drug	2 or more drugs

Format for reporting to FIGO Annual Report: In order to stage and allot a risk factor score, a patient's diagnosis is allocated to a stage as represented by a Roman numeral I, II, III, and IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals e.g., stage II:4, stage IV:9. This stage and score will be alloted for each patient.

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, reliably predicts the potential for resistance to chemotherapy.

When the prognostic score is 7 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:

- A complete history and physical examination
- Measurement of the serum hCG value
- Hepatic, thyroid, and renal function tests
- Determination of baseline peripheral white blood cell and platelet counts

The metastatic workup should include:

- A chest radiograph
- An ultrasonogram or a computed tomographic (CT) scan of the abdomen and pelvis

- A CT or magnetic resonance imaging (MRI) scan of the head
- Measurement of cerebrospinal fluid (CSF) hCG level if any metastatic disease is present and the head CT scan is negative
- 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 (33). In the absence of lung or vaginal metastasis, the risk of cerebral and hepatic spread is exceedingly low.

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 (34). 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 (35).

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 (36). 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 (37).

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.

Table 15.8 Protocol for Treatment of Stage I Gestational Trophoblastic Neoplasia

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 wks, then monthly until normal for 12 mos
Contraception	12 consecutive mos 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.

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:

- To reduce the likelihood of disseminating viable tumor cells at surgery.
- To maintain a cytotoxic level of chemotherapy in the bloodstream and tissues in case viable tumor cells are disseminated at surgery.
- To treat any occult metastases that may already be present at the time of surgery. Occult pulmonary metastases may be detected by CT scan in about 40% of patients with presumed nonmetastatic disease (38).

Chemotherapy can be administered safely at the time of hysterectomy without increasing the risk of bleeding or sepsis. At the NETDC, 31 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 relatively resistant to chemotherapy, hysterectomy for nonmetastatic disease is most prudent.

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 489 patients with stage I GTN, and 446 (91.2%) achieved complete remission. The remaining 43 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:

- Weekly measurement of hCG levels until they are normal for 3 consecutive weeks
- Monthly hCG values until levels are normal for 12 consecutive months
- Effective contraception during the entire period 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 .

Table 15.9 Protocol for Treatment of Stages II and III Gestational Trophoblastic Neoplasia

Low risk[a]	
Initial	*MTX-FA*; if resistant, switch to *Act-D*
Resistant to both single agents	Combination chemotherapy
High risk[a]	
Initial	Combination chemotherapy
Resistant	Second-line combination chemotherapy
Follow-up hCG	Weekly until normal for 3 wks, then monthly until normal for 12 mos
Contraception	Until there have been 12 consecutive mos of normal hCG values

MTX, methotrexate; FA, folinic acid; Act-D, actinomycin D; hCG, human chorionic gonadotropin.

[a]Local resection optional.

Modified from **Goldstein DP, Berkowitz RS**, eds. *Gestational trophoblastic neoplasms: clinical principles of diagnosis and management*. Philadelphia: WB Saunders, 1982:1–301, with permission.

All 28 patients with stage II disease treated at the NETDC achieved remission. Single-agent chemotherapy induced complete remission in 16 (80.0%) of 20 low-risk patients. Four 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. Yingna et al. reported that 18 (35.3%) of 51 patients with vaginal metastases presented with vaginal hemorrhage (39). 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 153 patients with stage III disease managed at the NETDC, 152 (99%) attained complete remission. Gonadotropin remission was induced with single-agent chemotherapy in 85 of 104 (81.7%) 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 workup 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.

Table 15.10 Protocol for Treatment of Stage IV Gestational Trophoblastic Neoplasia

Initial	Combination chemotherapy
Brain	Whole-head irradiation (3,000 cGy) Craniotomy to manage complications
Liver	Resection to manage complications
Resistant[a]	Second-line combination chemotherapy Hepatic arterial infusion
Follow-up hCG	Weekly until normal for 3 wks, then monthly until normal for 24 mos
Contraception	Until there have been 24 consecutive mos of normal hCG values

hCG, human chorionic gonadotropin.

[a]Local resection optional.

Modified from **Goldstein DP, Berkowitz RS**, eds. *Gestational trophoblastic neoplasms: clinical principles of diagnosis and management*. Philadelphia: WB Saunders, 1982:1–301, with permission.

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, 15 of 19 patients (78.9%) 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 (40).

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 (41).

Follow-up

Patients with stage IV disease should be followed with:

- Weekly determination of hCG levels until they are normal for 3 consecutive weeks
- Monthly determination of hCG levels until they are normal for 24 consecutive months
- 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 Figure 15.2 .

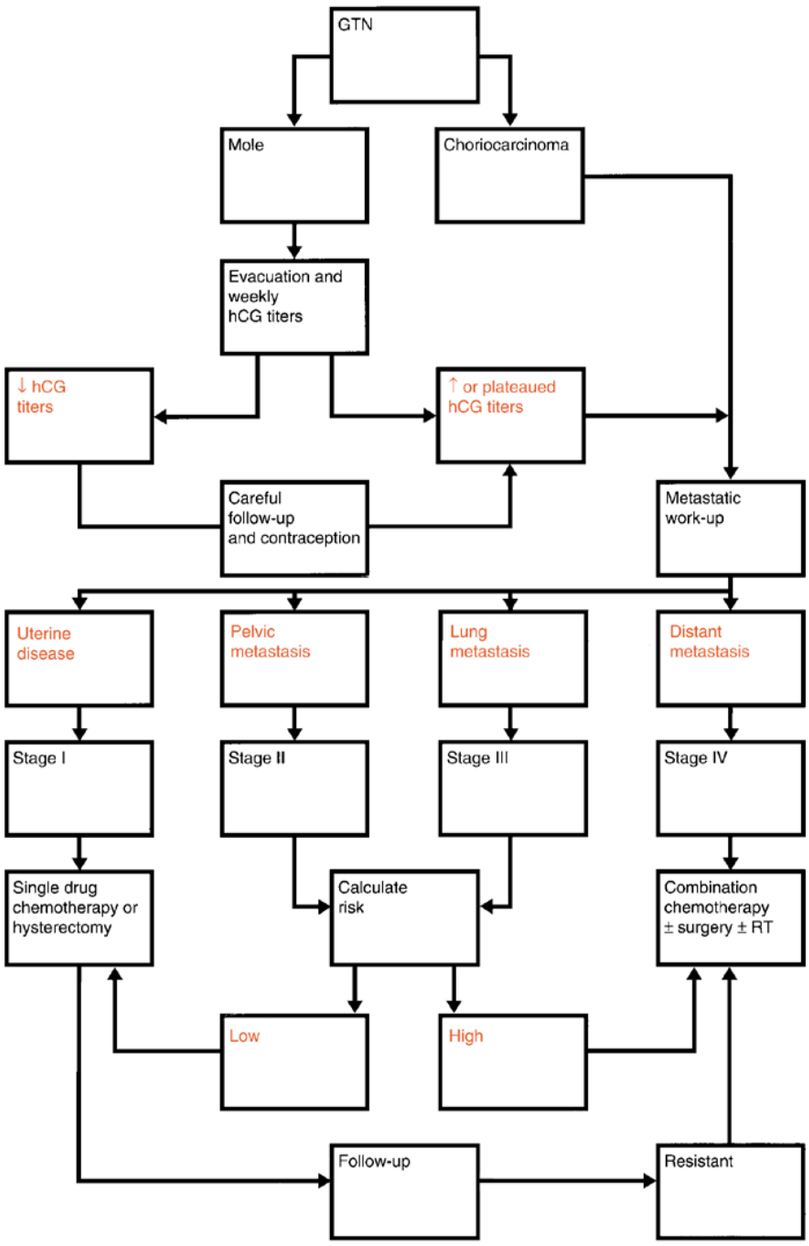

Figure 15.2 Management of gestational trophoblastic neoplasia. GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; RT, radiation therapy.

Many hCG assays have some cross-reactivity with luteinizing hormone. Following multiple courses of combination chemotherapy, ovarian steroidal function may be damaged, leading to rising luteinizing hormone levels. Patients who receive combination chemotherapy should therefore be placed on oral contraceptives to suppress luteinizing hormone levels and prevent problems with cross-reactivity.

Some patients may have a false-positive elevation in serum hCG values due to circulating heterophilic antibody (42). Patients with phantom choriocarcinoma or phantom hCG often have no progressive rise in their hCG levels and no clear antecedent pregnancy. The possibility of false-positive hCG levels should be evaluated by sending both urine and serum samples to a reference hCG laboratory.

Chemotherapy

Part of "15 - Gestational Trophoblastic Neoplasia "

Single-Agent Chemotherapy

Single-agent chemotherapy with either *actinomycin D (Act-D)* **or** *methotrexate (MTX)* **has achieved comparable and excellent remission rates in both nonmetastatic and low-risk metastatic GTN** (43). There are several protocols available for the treatment of patients with *Act-D* or *MTX* (Table 15.11).

Table 15.11 Single-Drug Treatment

I. *Actinomycin D treatment*
A. *5-Day actinomycin D* *Actinomycin D* 12 μg/kg IV 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/m^2 every 2 wk
II. Methotrexate treatment
A. 5-Day methotrexate *Methotrexate* 0.4 mg/kg IV or IM 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/m^2 IM weekly

CBC, complete blood count; IV, intravenous; IM, intramuscular.

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 and morbidity. 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 (44) 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 (45) (Table 15.12).

Table 15.12 Protocol for Therapy with *Methotrexate* and Folinic Acid "Rescue"

Day	*Time*	*Follow-up Tests and Therapy*
1	8 a.m.	CBC, platelet count, AST
	4 p.m.	*Methotrexate*, 1.0 mg/kg
2	4 p.m.	*Folinic acid*, 0.1 mg/kg
3	8 a.m.	CBC, platelet count, AST
	4 p.m.	*Methotrexate*, 1.0 mg/kg
4	4 p.m.	*Folinic acid*, 0.1 mg/kg
5	8 a.m.	CBC, platelet count, AST
	4 p.m.	*Methotrexate*, 1.0 mg/kg
6	4 p.m.	*Folinic acid*, 0.1 mg/kg
7	8 a.m.	CBC, platelet count, AST
	4 p.m.	*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, Bernstein MR**. Ten years' experience with methotrexate and folinic acid as primary therapy for gestational trophoblastic disease. **Gynecol Oncol** 1986;23:111, with permission.

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 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 (45). *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:

- Further chemotherapy is withheld as long as the hCG level is falling progressively.
- 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:

- If the hCG level plateaus for more than 3 consecutive weeks or begins to rise again
- 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 4 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)* (46). 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) (47 ,48 ,49).

EMA-CO

Etoposide was reported to induce complete remission in 56 (93%) of 60 patients with nonmetastatic and low-risk metastatic GTN (50). In 1984, Bagshawe (51) 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 (51). Bolis et al. (52) confirmed that primary EMA-CO induced complete remission in 76% of the patients with metastatic GTN and a high-risk score. Bower et al. updated the data from Charing Cross Hospital and reported that EMA-CO induced complete remission in 130 (86.1%) of 151 patients with high-risk metastatic GTN (53). Furthermore, Newlands et al. (41) reported remission using EMA-CO with intrathecal MTX in 30 (86%) of 35 patients with brain metastases.

Table 15.13 EMA-CO Regimen for Patients with Gestational Trophoblastic Neoplasia

Regimen	
Course 1 (EMA)	
Day 1	*VP-16 (etoposide)*, 100 mg/m^2, IV infusion in 200 mL of saline over 30 min *Actinomycin D*, 0.5 mg, IV push *Methotrexate*, 100 mg/m^2, IV push, followed by a 200 mg/m^2 IV infusion over 12 hr
Day 2	*VP-16 (etoposide)*, 100 mg/m^2, IV infusion in 200 mL of saline over 30 min *Actinomycin D*, 0.5 mg, IV push *Folinic acid*, 15 mg, IM or orally every 12 hr for 4 doses beginning 24 hr after start of *methotrexate*
Course 2 (CO)	
Day 8	*Vincristine*, 1.0 mg/m^2, IV push *Cyclophosphamide*, 600 mg/m^2, IV in saline

IV, intravenous; IM, intramuscular.

This regimen consists of two courses: (a) course 1 is given on days 1 and 2; (b) 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;29:813, with permission.

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 (54). 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 (55).

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 (56). **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 (57). From 1965 to 2001, patients who were treated at the NETDC for complete molar gestation had 1,278 subsequent pregnancies that resulted in 877 full-term live births (68.6%), 95 premature deliveries (7.4%), 11 ectopic pregnancies (0.9%), 7 stillbirths (0.5%), and 18 repeat molar pregnancies (1.4%). First- and second-trimester spontaneous abortions occurred in 229 pregnancies (17.9%). There were 41 therapeutic abortions (3.2%). Major and minor congenital malformations were detected in 40 infants (4.1%). Primary cesarean section was performed in 70 of 373 (18.8%) term or premature births from 1979 to 2001. **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 (57). **Approximately 1 in 100 patients has at least two molar gestations**. Some patients with repetitive molar pregnancy have molar pregnancy with different male partners (58). 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:

- A pelvic ultrasonogram during the first trimester to confirm normal gestational development
- 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 (57). Patients who were treated with chemotherapy at the NETDC from 1965 to 2001 reported 581 subsequent pregnancies that resulted in 393 term live births (67.6%), 35 premature deliveries (6.0%), 7 ectopic pregnancies (1.2%), 9 stillbirths (1.5%), and 8 repeat molar pregnancies (1.4%). First- and second-trimester spontaneous abortions occurred in 99 pregnancies (17.0%). There were 28 therapeutic abortions (4.8%). Major and minor congenital anomalies were detected in only 10 infants (2.0%). Primary cesarean section was performed in 68 (20.3%) of 335 subsequent term and premature births from 1979 to 2001. 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

Susan S. Chang

Philip I. Haigh

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

Part of "16 - Breast Disease "

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).

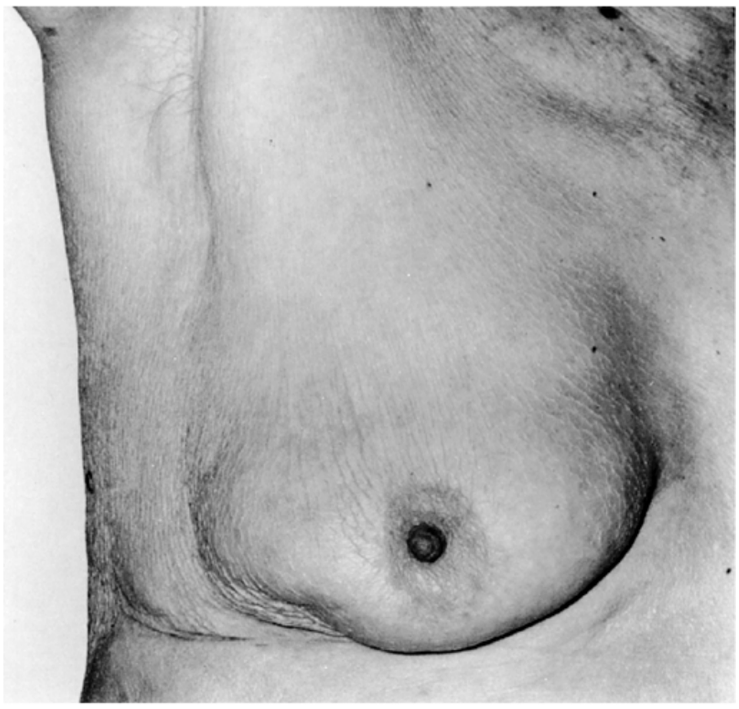

Figure 16.1 Retraction of the skin of the lower, outer quadrant seen only on raising the arm. A small carcinoma was palpable.

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.

Trials were conducted 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 more than 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 10 years from entry were similar. Thus, in the absence of mammography, BSE alone would be unlikely to reduce mortality from breast cancer.**

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:

- In all patients with a dominant mass, even if biopsy is planned, to exclude disease in the opposite breast
- In all patients with axillary or supraclavicular lymphadenopathy
- 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 midbreast, with a total skin dose of 0.2 to 0.3 cGy (4 ,5).

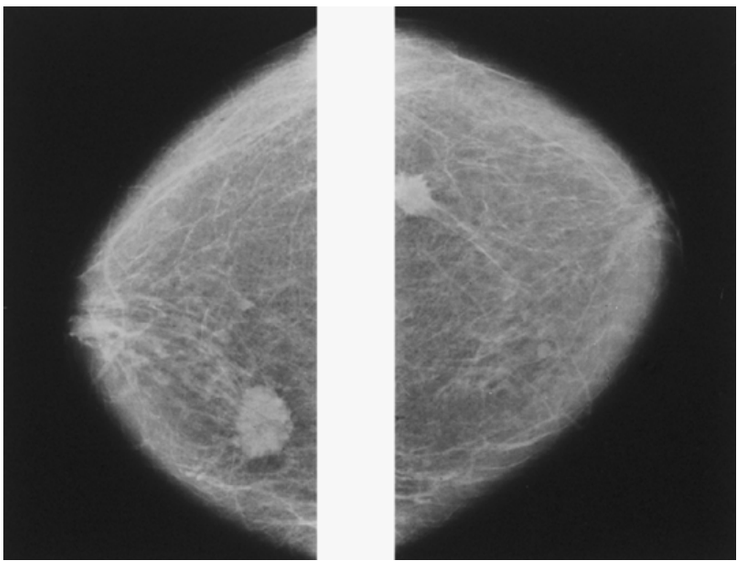

Figure 16.2 Bilateral film screen mammograms showing typical carcinoma in each breast, illustrating the importance of bilateral mammography in the workup of a clinically apparent mass.

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:

- A cluster of small calcifications
- A mass seen as an area of increased radiodensity
- An area of breast parenchymal distortion
- 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 one of the trials that was specifically designed to investigate screening in that age cohort. **An update at 13 years from entry into the CNBSS trial shows no impact on mortality from breast cancer in women who are in their fifth decade** (9). However, the study remains controversial. The Swedish Two-County Trial reported a 23% reduction in the breast cancer mortality among women 40 to 49 years of age with screening mammography **after 18 years of follow up** (10). When the eight randomized, controlled trials for women screened before 50 years of age were analyzed in a metaanalysis, the mortality rate for this group of women was found to be reduced significantly by 18% (11).

Table 16.1 Randomized Trials of Screening Mammography for Breast Cancer

Trials	*Age Range (yr)*	*Annual Clinical Breast Examination*	*Screening Interval (mo)*	*Age Category*	*No. Women Screened*	*No. Control Subjects*	*Percentage (%) Mortality Reduction*	*Range*
HIP	40–64	Yes	12	All women	30,131	30,565	23R	47R,11E
1969				<49 yr	14,432	14,701	23R	
Kopparberg	40–74	No	24	All women	38,562	18,478	32R	63R, 41E
1983				<49 yr	9,582	5,031	27R	
Ostergotland	40–74	No	24	All women	38,405	37,145	22E	48R, 99E
1983				<49 yr	10,262	10,573	2E	
Stockholm	40–64	No	28	All women	38,525	20,651	20R	47R, 105E
1985				<49 yr	14,375	7,103	4E	
Malmo	45–69	No	18–24	All women	20,695	20,783	29R	27R, 17E
1986				<49 yr	3,658	3,679	49R	
Canada 1 1987	40–49	Yes	12	All women	25,214	25,216	36E	16R, 121E
Canada 2 1987	50–59	Yes	12	All women	19,711	19,694	3R	38R, 52E
Edinburgh	45–64	Yes	24	All women	23,226	21,904	26R	54R, 51E
1988				<49 yr	5,913	5,810	22R	
Gothenburg	40–59	No	18	All women	20,724	28,809	1114R	63R, 97E
1988				<49 yr	10,600	12,800	4R	

E, excess; R, reduced.

From **Kopans D**. Updated results of the trials of screening mammography. *Surg Oncol Clin N Am* 1997;6:233–263, with permission from the Elsevier Saunders Company.

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 (12).

Digital Mammography

To improve mammography as a screening tool for breast cancer, full-field digital mammography (FFDM) has been introduced as a breast imaging modality. Digital mammography has the advantages of speed and higher contrast resolution, which should make it better for detecting densities and masses in dense tissue. Screen-film mammography (SFM) has the advantage in spatial resolution, which is better for detecting calcifications. However, in a prospective study involving 4,500 women comparing FFDM with SFM for cancer detection in a screening population, there was no difference in cancer detection rate between the two modalities. The study was limited by a small sample size and included only one of several federally approved digital mammography machines. Currently, a larger trial, known as Digital Mammography Imaging Screening Trial (DMIST) involving 49,500 female volunteers undergoing both conventional mammography and digital mammography, is under way to determine whether digital mammography is as good as or better than film mammography (13).

Ultrasonography

Both handheld 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 (14).

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.

Handheld or real-time ultrasonography is 95% to 100% accurate in differentiating solid masses from cysts (14). 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, handheld ultrasonography adds little to the evaluation. **The primary role of handheld 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 workup is necessary**. However, handheld 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, a strong suspicion of lobular carcinoma, scattered calcifications suggestive of extensive ductal carcinoma** *in situ* **(DCIS) or extensive** intraductal cancer, a bloody nipple discharge, silicone implants, or postlumpectomy scarring that makes evaluation by mammography difficult (15). In women who have an occult primary breast cancer presenting as axillary adenopathy, there is evidence that MRI can localize these lesions, therefore offering the potential for more accurate breast cancer staging and breast conserving surgery (16 ,17 ,18).

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 (19). 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

Part of "16 - Breast Disease "

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** (20).

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** (20).

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 (21). 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 (22). 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 (22 ,23). 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 (24), but the increased incidence in these patients may be a reflection of increased surveillance.

In a study by Dupont and Page (24) 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 reports a unilateral bloody or serous nipple discharge. **The most common etiology of bloody nipple discharge without an associated mass is an intraductal papilloma** (25). 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.

A new technique for evaluating bloody nipple discharge is fiberoptic ductoscopy, which allows direct visualization of the ductal system of the breast through a nipple orifice. For nipple discharge diagnosis, fiberoptic ductoscopy demonstrated 77% specificity, 88% sensitivity, 83% positive predictive value, and 82% negative predictive value. **Ductal lavage is another screening procedure in women with nipple discharge**. The ductal lavage involves irrigation of the duct with saline and retrieval of the saline, which is then processed for cytology. The cytologic analysis alone has a positive predictive value of 72% and the negative predictive value of 50%. When ductal lavage is combined with fiberoptic ductoscopy, the positive predictive value increases to 86% and the negative predictive value increases to 87% (26).

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 (27).

Fibroadenoma

Fibroadenomas are the most common benign tumors of the breast. They usually occur in young women and may occur in teenagers (24). 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 (24).

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. (28) 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** (29 ,30).

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 (31). 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 (32).

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 (32). 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 (33). **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** (34 ,35 ,36). 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 (32 ,35). 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

Part of "16 - Breast Disease "

Breast cancer accounts for approximately 31% of all new cancer cases in women and is second only to lung cancer as the leading cause of cancer deaths in women. In 2004 in the United States, an estimated 217,440 new cases of invasive breast cancer will be diagnosed in women, with approximately 40,580 deaths (37). **In the United States, the overall lifetime risk for development of breast cancer in women is one in eight** (38). 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** (39). 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 (40). 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 risk of developing breast cancer increases steadily with age. Before the age of 25 years, breast cancer is rare; this age group accounts for less 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 (41). Women between 40 and 50 years of age may have a lower mortality rate from the disease than older women (42).

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 (43). 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 (44). 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 developing 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** (45). 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 (46). **Mutations of the** *BRCA1* **gene carry a lifetime risk of up to 87% for the development of breast cancer and 44% for ovarian cancer** (47 ,48). 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 (49 ,50). **The** *BRCA2* **gene is often responsible for the early-onset breast cancer syndrome not associated with** *BRCA1* (45 ,51). 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 (52) (see Chapter 1).

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 (HNPCC) syndrome. 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 (53 ,54 ,55 ,56). The median age at menarche is lower for women with breast cancer than for those who never developed the disease (56). **The longer a woman's reproductive phase, the higher the risk for development of breast cancer** (54). 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 (55). **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 (55).

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** (57). 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. Women's Health Initiative investigators demonstrated the effect of hormone replacement therapy in four randomized trials, including more than 20,000 women followed up for 5 years. Overall, **women randomized to combined (estrogen plus progesterone) hormone replacement therapy compared with placebo had a significantly increased incidence of breast cancer, stroke, and pulmonary embolus. In the women who had undergone a prior hysterectomy and received estrogen-only therapy, there was no increase in the incidence of breast cancer** (58). The hormone replacement therapy significantly decreased the incidence of colorectal cancer and fractured femoral neck. There was no overall significant change in the incidence of endometrial cancer or coronary heart disease with the usage of hormone replacement therapy (58). Another recent study, the Million Women Study in United Kingdom (UK), also demonstrated the effect of hormone replacement therapy in breast cancer. This study recruited 1,084,110 UK women who were followed for cancer incidence and death. The study showed that the current use of hormone replacement therapy was associated with an increased risk of incident and fatal breast cancer (59). **This increase in risk of breast cancer from combined hormone replacement therapy must be balanced with the improved quality of life achieved in reducing postmenopausal symptoms.**

The decision to initiate combined hormone replacement therapy is influenced by the estimated risk of breast cancer and the variable mortality reduction when such factors as colorectal cancer or femoral fracture 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 (60). 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** (56). 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 (61). 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 (62 ,63). 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 (64). However, two large cohort studies have found little evidence that these vitamins have any role in influencing breast cancer risk (65 ,66).

Alcohol

Alcohol consumption may increase the risk of breast cancer (67). 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 (68). 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 (69 ,70).

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 Figures 16.3 and 16.4 .

Figure 16.3 Schematic evaluation of breast masses in premenopausal women.

1 complex mass—a cystic mass with a solid component that may be malignant.

2 complicated cyst—usually multiple simple cysts or cysts with septations.

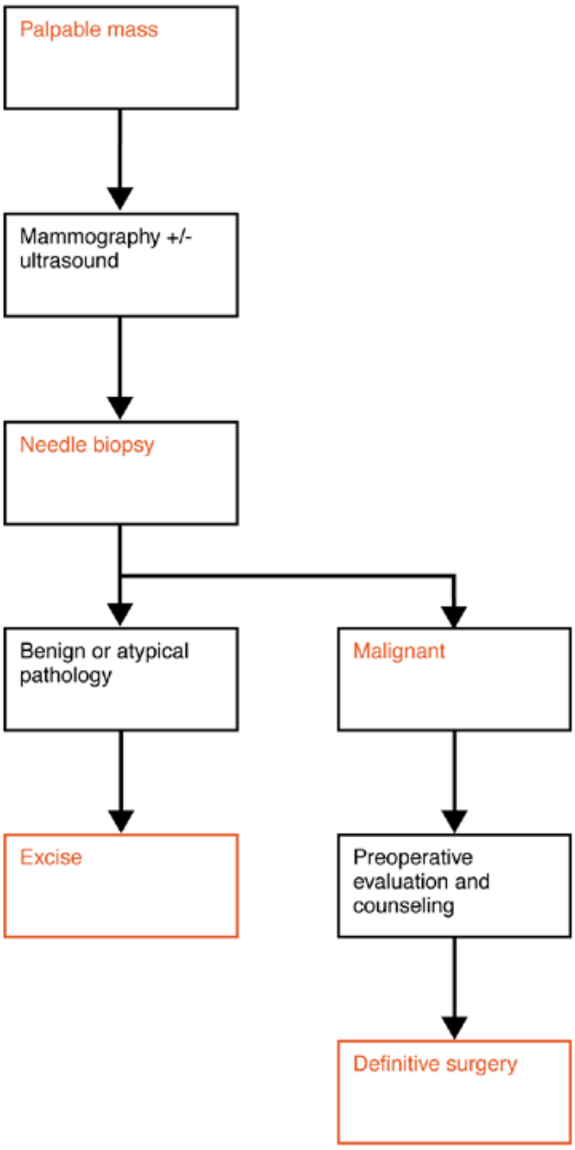

Figure 16.4 Schematic evaluation of breast masses in postmenopausal women.

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 (69). Conversely, 15% to 20% of lesions believed clinically to be benign are proven malignant by open biopsy (70). 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 (71).

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** (72). 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. Handheld 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 (72). 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:

- **Local anesthesia** is used to infiltrate the skin and subcutaneous tissue surrounding the palpable mass. Intravenous sedation often aids in easing anxiety.
- **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.
- Once the skin and underlying tissue are incised, **the mass can be gently grasped with Allis forceps** or with a stay suture and delivered into the operative field.
- **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.
- **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.

Pathology and Natural History

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.

Numerous histologic types of breast cancer can be identified microscopically (21 ,73). 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 (73). 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 (73).

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 (74) (Fig. 16.5). During this preclinical phase, tumor cells may be circulating throughout the body.

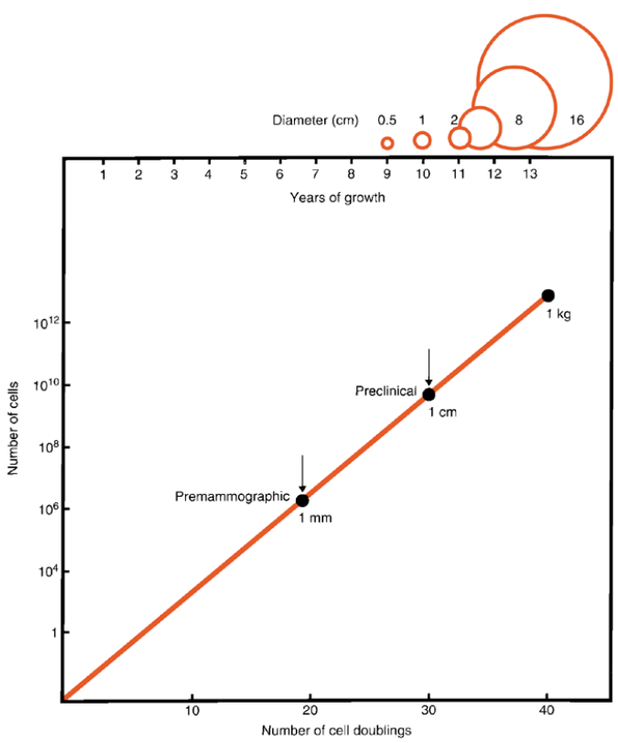

Figure 16.5 Growth rate of breast cancer, indicating long preclinical phase. (From **Gullino PM.** Natural history of breast cancer: progression from hyperplasia to neoplasia as predicted by angiogenesis. *Cancer* 1977;39:2699. Copyright 1977 American Cancer Society. Reprinted by permission of Wiley-Liss, 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 (75 ,76 ,77). 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 (76).

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 Tables 16.2 and 16.3 (78). This system has the advantage of being both a preoperative clinical staging system and a postoperative or pathologic staging system.

Table 16.2 TNM (Tumor-Nodes-Metastases) System for Staging of Breast Cancer

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
Tis	Carcinoma *in situ* Tis (DCIS) Ductal carcinoma *in situ* Tis (LCIS) Lobular carcinoma *in situ* Tis (Paget) Paget's disease of the nipple with no tumor
T_1	Tumor 2 cm or less in greatest dimension T_{1mic} Microinvasion 0.1 cm or less in greatest dimension T_{1a} Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension T_{1b} Tumor more than 0.5 cm but not more than 1 cm in greatest dimension T_{1c} Tumor more than 1 cm but not more than 2 cm in greatest dimension
T_2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T_3	Tumor more than 5 cm in greatest dimension
T_4	Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below T_{4a} Extension to chest wall, not including pectoralis muscle T_{4b} Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast T_{4c} Both (T_{4a} and T_{4b}) T_{4d} Inflammatory carcinoma (see section on Inflammatory Carcinoma)
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N_0	No regional lymph node metastasis
N_1	Metastasis in movable ipsilateral axillary lymph node(s)
N_2	Metastasis in ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent[a] ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis N_{2a} Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures N_{2b} Metastasis only in clinically apparent[a] ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
N_3	Metastasis in ipsilateral infraclavicular lymph node(s), or in clinically apparent[a] ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement N_{3a} Metastasis in ipsilateral infraclavicular lymph node(s) and axillary lymph node(s) N_{3b} Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s) N_{3c} Metastasis in ipsilateral supraclavicular lymph node(s)
Pathologic Classification (pN)	
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN_0	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells $pN_{0(i-)}$ No regional lymph node metastasis histologically, negative IHC $pN_{0(i+)}$ No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm $pN_{0(mol-)}$ No regional lymph node metastasis histologically, negative molecular findings (RT-PCR) $pN_{0(mol+)}$ No regional lymph node metastasis histologically, positive molecular findings (RT-PCR) pN_{1mi} Micrometastasis (>0.2 mm, none >2.0 mm)
pN_1	Metastasis in one to three axillary lymph nodes and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent pN_{1a} Metastasis in one to three axillary lymph nodes pN_{1b} Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent pN_{1c} Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
pN_2	Metastasis in four to nine axillary lymph nodes, or in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis pN_{2a} Metastasis in four to nine axillary lymph nodes (at least one tumor deposit >2.0 mm) pN_{2b} Metastasis in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN_3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes pN_{3a} Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit >2.0 mm), or metastasis to the infraclavicular lymph nodes pN_{3b} Metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent pN_{3c} Metastasis in ipsilateral supraclavicular lymph nodes
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M_0	No distant metastasis
M_1	Distant metastasis

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

IHC, immunohistochemistry; RT-PCR, reverse transcription—polymerase chain reaction.

[a]"clinically apparent" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

Table 16.3 TNM (Tumor-Nodes-Metastases) Stage Grouping of Breast Cancer

Stage 0	Tis	N_0	M_0
Stage I	T_1[a]	N_0	M_0
Stage IIA	T_0	N_1	M_0
	T_1[a]	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[a]	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	N_0	M_0
	T_4	N_1	M_0
	T_4	N_2	M_0
Stage IIIC	Any T	N_3	M_0
Stage IV	Any T	Any N	M_1

[a] T_1 includes $T_{1mic.}$

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*, 6th ed. New York: Springer-Verlag, 2002.

Preoperative Evaluation

The extent of preoperative workup varies with the initial stage of the disease (79). 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:

- Bilateral mammograms
- Chest radiograph
- Complete blood count
- 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 (80).

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 nineteenth century, surgical treatment of breast cancer was haphazard, and it varied from local excision alone to total mastectomy (81). 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 (82) (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.

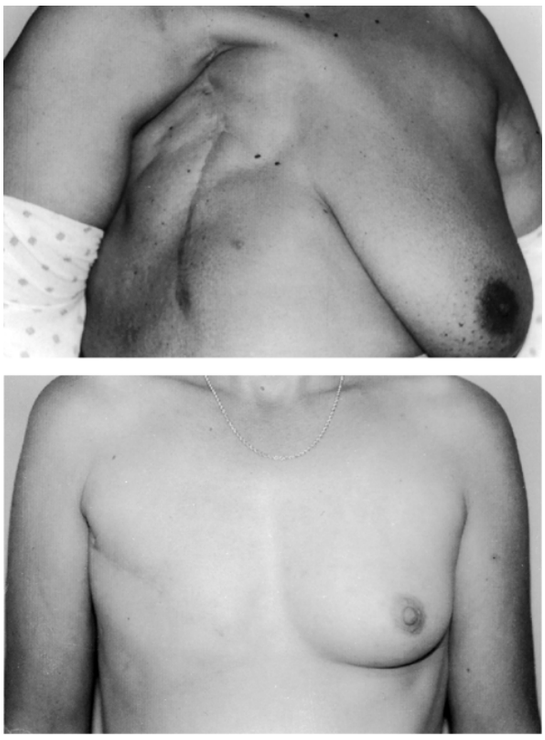

Figure 16.6 Defect after radical mastectomy (A), compared with modified radical mastectomy (B).

During the twentieth 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 (83). In addition, supraclavicular, mediastinal, and internal mammary lymph node dissections were performed, with high mortality rates (84).

Urban (85) 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 (86). 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) (87 ,88). 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 compared with radical mastectomy. 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 (89).

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.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) conducted a randomized trial comparing Halsted radical mastectomy with a less extensive surgery with or without radiation therapy. Patients with clinically negative axillary nodes were randomly assigned to Halsted mastectomy, total mastectomy, or total mastectomy with postoperative irradiation. Patients with clinically positive axillary nodes either underwent radical mastectomy or total mastectomy with postoperative irradiation. After 25-year follow-up, there was no significant difference among the three groups of women with negative nodes or between the two groups of women with positive nodes with respect to disease-free survival, relapse-free survival, distant-disease free survival, or overall survival (90). Thus, **radical mastectomy has no advantage over total mastectomy in local control or overall survival. Removal of lymph nodes also does not appear to affect survival.**

Breast-Conserving Surgery

Radiation therapy alone without excision of the tumor is associated with a high local failure rate (91 ,92 ,93 ,94). Veronesi et al. (95 ,96) 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 (96). After 20 years of follow-up, there have been no statistically significant differences between the two groups in contralateral breast cancer, distant metastases, second primary cancer, or overall survival (Table 16.4).

Table 16.4 Halsted Radical Mastectomy versus Breast-Conserving Surgery: Results of Twenty-Year Follow-Up

	Halsted (%)	*Quadrantectomy + RT (%)*
No. of patients	349	352
Contralateral-breast carcinoma	9.7	8.2
Distant metastases	23.8	23.3
Other primary cancers	8.6	8.8
Overall survival	43.6	44.3

RT, radiation therapy.

From **Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al.** Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;347:1227–1232.

The NSABP conducted a trial that extended these observations (97). 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 1,851 women were randomized among the three treatment arms, and the groups were comparable. **The lowest ipsilateral breast recurrence rate (14.3%) was seen among patients treated with segmental mastectomy and postoperative radiation therapy, whereas 39.2% of the patients undergoing segmental mastectomy without radiation therapy had a recurrence in the ipsilateral breast within 20 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. **After 20-year follow-up, 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 (98). The high local recurrence rate without radiation therapy makes limited surgery alone unacceptable except in unusual circumstances.

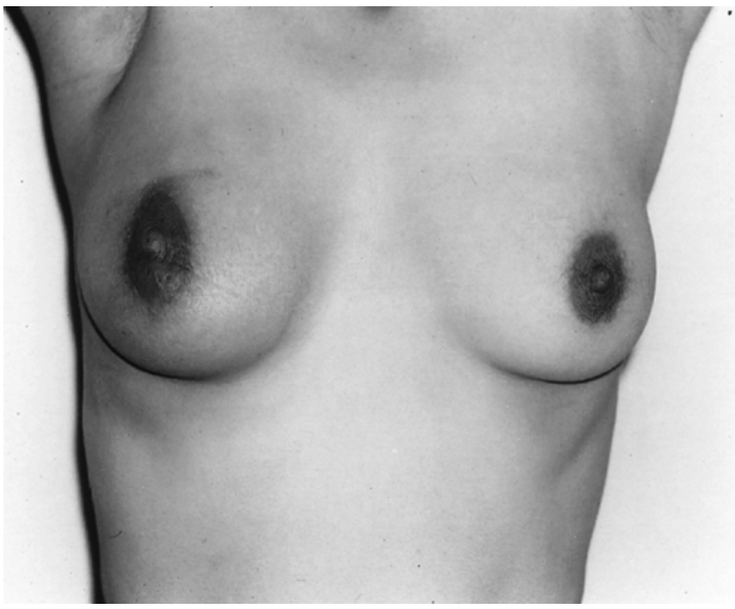

Figure 16.7 Appearance after lumpectomy, axillary dissection, and radiation therapy.

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 (99). 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 (100) 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** (40). **This has led some authorities to question the value of routine axillary dissection in patients with early invasive breast cancers** (40). 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 routine hematoxylin and eosin (H&E) staining or immunohistochemistry (IHC) to identify small foci of metastases. IHC may be performed when the H&E stained slides have suspicious cells that are equivocal. However, the IHC findings should not affect the choice of adjuvant therapy regimens.

It has been shown that if the sentinel node is free of tumor histopathologically, then the rest of the axillary nodes are free of tumor, thus abrogating the need for a complete lymph node dissection (101 ,102 ,103). The false-negative rate is low in experienced hands, and can be 0% with adherence to technical detail and proper patient selection (102). **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.** If the sentinel node is positive for metastatic disease, then the standard treatment is to undergo completion axillary dissection. There is currently an ongoing American clinical trial comparing completion axillary dissection with observation alone and an European clinical trial comparing axillary radiation with completion axillary dissection.

In 2001, a Consensus Conference on the role of Sentinel Lymph Node Biopsy in Carcinoma of the Breast was held in Philadelphia, Pennsylvania. At the consensus, the following issues were addressed: the best definition of the sentinel node; accuracy of sentinel lymph node biopsy (SLNB); techniques used to identify the sentinel node(s); learning the procedure and maintaining the skills over time; safety, contraindications, and complications of the procedure; handling of the specimen; the role of IHC; the role of SLNB in ductal carcinoma *in situ* (DCIS); and the role of SLNB in mastectomy (104). A controversy exists in the issue of SLNB in DCIS. The panel recommended SLNB in patients with DCIS with microinvasion. For patients with DCIS detected as a palpable mass or with extensive calcifications, SLNB may be of value. Although the DCIS is noninvasive in nature, the invasion may be overlooked with a needle biopsy because the area of disease is large.

The panel at the consensus conference endorsed the use of SLNB during mastectomy. The consensus recommendation was that **lymph node dissection should be limited to**

SLNB if the sentinel nodes were negative or there was a single micrometastasis. If the metastasis was greater than 2 mm in diameter or there was more than one positive node, additional axillary dissection should be undertaken despite the technical challenge. **Specific contraindications to SLNB include (a) the patient with a clinically positive axilla (N_1), (b) pregnant patients, and (c) patients with multicentric cancer.** Multifocal cancer is not a contraindication to SLNB if the total diameter of the primary tumor remains 3.0 cm or less. Prior axillary procedures are relative contraindications for SLNB (104).

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 (105). Most prospective, randomized and historical control studies show that radiation therapy, when combined with radical surgery, improves local control but does not improve survival (106 ,107 ,108 ,109).

A prospective, randomized trial by the NSABP examined the role of postoperative radiation therapy (110). 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 (111). 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 (112). **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.

Interest in intraoperative radiation therapy has emerged for localized breast cancer. The rationale for this partial breast radiation therapy is based on the finding that 85% of relapsed breast cancer is confined to the same quadrant of breast as the primary tumor. Clinical trials to evaluate the effectiveness of intraoperative radiation therapy are currently ongoing (113).

Adjuvant Systemic Therapy

The 10-year survival rate for women who have metastases in axillary nodes is only approximately 40% to 50%. The 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 (114). 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 metaanalyses of these trials on the effects of adjuvant chemotherapy, *tamoxifen*, and ovarian ablation on recurrences and mortality (115 ,116 ,117).

Adjuvant Radiation Therapy

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 (116). **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 metaanalysis 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 (118).

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 have been conducted and have suggested that taxanes are valuable components of adjuvant chemotherapy for patients with node-positive breast cancer, including those with estrogen receptor positivity and/or extensive lymph node involvement (119). **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** (120). Final results from this trial may make AC plus sequential *paclitaxel* the preferred adjuvant regimen.

Adjuvant Hormone Therapy

In 1998, the EBCTCG reported a metaanalysis of women who participated in any randomized trial of adjuvant *tamoxifen* versus no *tamoxifen* before 1990. Data were available on 37,000 women (117).

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**

significantat 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 (117).

For years, *tamoxifen* has been the gold standard of endocrine treatment for patients with breast cancer. **With the recent development of a third generation of aromatase inhibitors, such as** *anastrozole (Arimidex), letrozole (Femara),* **and** *exemestane (Aromasin),* **there is an alternative approach to management of postmenopausal patients with hormone-sensitive breast cancer**. Several ongoing clinical trials are under way comparing the effectiveness of these aromatase inhibitors with that of *tamoxifen*. The preliminary results of these trials indicate that these new drugs can achieve better treatment results with fewer side effects (121).

Two randomized trials have shown a survival benefit of *anastrozole* over *megestrol acetate* in women whose disease progressed while they were taking tamoxifen (122). In 1996, a randomized double-blind multicenter trial known as Arimidex, Tamoxifen, Alone or in Combination (ATAC) compared *tamoxifen* with Arimide*x* alone and in combination with *tamoxifen* as adjuvant endocrine therapy for postmenopausal patients with operable, invasive, early stage (stage I and II) breast cancer. **The preliminary results of the ATAC trial demonstrated** *Arimidex* **to be better tolerated and more effective in improving disease-free survival and reducing relapse rate than** *tamoxifen* **after median follow-up of 3 years** (123). However, this was at the expense of accelerated bone loss. Longer follow-up of this trial is warranted to determine the long-term safety of aromatase inhibitors.

The relative merits of *tamoxifen* combined with chemotherapy remain controversial. An important finding of the metaanalysis was that *tamoxifen*, **when added to chemotherapy, produced additional benefits over the same chemotherapy given alone, especially with 5 years of** *tamoxifen* (117). 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 (124). 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 (125 ,126 ,127).

In practice, oncologists are using systemic adjuvant therapy for most patients with early-stage breast cancer >1 cm, 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 (128). Table 16.5 summarizes these prognostic factors and their effect on recurrence.

Table 16.5 Prognostic Factors in Node-Negative Breast Cancers

Factor	*Increased Risk of Recurrence*
Size	Larger tumors
Histologic grade	High-grade tumors
DNA ploidy	Aneuploid tumors
Labeling index	High index (>3%)
S-phase fraction	High fraction (>5%)
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

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 (115). 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 10 extra lives saved.

The current recommendations for adjuvant chemotherapy and hormonal therapy in breast cancer can be summarized as follows (Table 16.6):

Table 16.6 Summary of Adjuvant Systemic Therapy for Women with Breast Cancer

Patient Age	*Estrogen-Receptor Status*	*Level of Risk*	*Adjuvant Systemic Therapy*[a]
<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

[a]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 **Hortobagyi GN.** Drug therapy: treatment of breast cancer. *N Engl J Med* 1998;339:974–984.

- **Premenopausal women who have ER-negative tumors should be treated with adjuvant chemotherapy.**
- **Premenopausal women with ER-positive tumors can be considered for hormonal therapy in addition to chemotherapy.**
- **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.**
- **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 ovarian ablative surgery, drugs that block hormonal receptor sites, or drugs that block synthesis of hormones (129 ,130). 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 with chemical ablation using the GnRH analog *goserelin* found similar response rates and overall survival in premenopausal patients with hormone receptor-positive metastatic breast cancer** (131).

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 (132). When *tamoxifen* becomes ineffective, a selective aromatase inhibitor should be used, such as *anastrozole (Arimidex)* or *letrozole (Femara).* These new aromatase inhibitors are highly selective and much less toxic than *aminoglutethimide*, an early, nonselective aromatase inhibitor.

Letrozole is another third-generation aromatase inhibitor that is being used in postmenopausal women with hormone-sensitive breast cancer. In a recent phase III clinical trial, *letrozole* has demonstrated superiority in overall response and clinical benefits

and lower toxicity compared with *tamoxifen* in women with advanced breast cancer. However, as with the ATAC trial, a longer follow-up is needed (121 ,133).

A third aromatase inhibitor undergoing a randomized phase II clinical trial by the European Organization for Research and Treatment of Cancer (EORTC) is *exemestane*. This agent is being compared with *tamoxifen* with respect to effectiveness and toxicity as first-line treatment for patients with metastatic breast cancer (121 ,134)

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 are treated with anti-HER-2/*neu* antibodies combined with *cisplatin*** (135). 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 (136 ,137). 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; 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** (138). 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%) (139).

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 (140). 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 (141). 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.

The NSABP-21 randomized clinical trial also helped in the treatment of women with small, localized, mammographically detected DCIS. The trial involved 1,804 women with DCIS who were randomly assigned to either lumpectomy, radiation, and *tamoxifen*, or lumpectomy, radiation, and placebo to determine the prevention of invasive and noninvasive ipsilateral breast recurrences, contralateral breast tumors, and metastatic disease. **The findings through 12 years of follow-up demonstrated that the addition of *tamoxifen* after lumpectomy and radiation significantly reduced the rate of all breast cancer events, particularly for invasive cancer** (142).

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 (143). 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 (144). 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 (145).

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 (146). 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 (147 ,148 ,149). 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 (150 ,151). 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:

- **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.
- **Localized tumors found in the third trimester of pregnancy must be managed on an individual basis**. Initially, tumors should be excised 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 the third trimester, with no obvious adverse effects to the fetus (152 ,153). Radiation therapy can be delayed until after delivery. If delivery is imminent, standard therapy can be performed immediately postpartum.
- **Should the breast cancer be diagnosed during lactation, lactation should be suppressed and the cancer treated definitively**.
- **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 (154). 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 (155).

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 (147 ,150 ,156). 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. Recently, Fisher et al. reported 15-year prognostic factors for invasive breast carcinoma from NSABP-06. In this study, 31 pathologic and 6 clinical features were evaluated. In the multivariate analysis, the presence of ipsilateral breast tumor recurrence, black race, intermediate or unfavorable histologic tumor type, positive nodal status, poor nuclear grade, blood vessel invasion, and patient age were found to be independently significant in predicting poor survival (157).

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 (158). 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 (159 ,160 ,161 ,162).

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 (163). 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 69 months of follow-up, women who received** *tamoxifen* **for 5 years had a 50% reduction in both noninvasive and invasive breast cancers compared with those women taking a placebo** (164). 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.

Due to the concern over the side effects of *tamoxifen*, **a second-generation selective estrogen receptor modulator**, *raloxifene*, **was introduced**. *Raloxifene*, which has been used for the prevention of osteoporosis in postmenopausal women, **exhibited antiestrogenic properties in the breast** and possibly in the endometrium, and estrogenic properties in the bone and on the lipid profile. This has led to an ongoing, multicenter, randomized, double-blind trial named Study of Tamoxifen and Raloxifene (STAR) NSABP P-2.

The STAR trial will compare the effectiveness of *raloxifene* with *tamoxifen* in postmenopausal women who are at increased risk for developing breast cancer. Study end points will include invasive and noninvasive breast cancer, cardiovascular disease, endometrial cancer, bone fractures, and thromboembolic events. Until the results of the trial are available, the use of *raloxifene* for chemoprevention in breast cancer is premature (165 ,166).

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Section III Medical and Surgical Topics

17

Preoperative Evaluation, Medical Management, and Critical Care

M. Iain Smith

Roger M. Lee

Samuel A. Skootsky

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
- Critical Care

Preoperative Evaluation

Part of "17 - Preoperative Evaluation, Medical Management, and Critical Care "

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 that occur 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.

Cardiovascular Risk Factors

Multiple studies have been published over the last 25 years assessing clinical risks for cardiac events during surgery (1 ,2 ,3 ,4 and 5). In addition, several reviews and clinical guidelines have been proposed to identify, evaluate, and manage patients at risk for cardiac events perioperatively (6 ,7 ,8 and 9).

The recently revised guidelines of the American College of Cardiology (ACC) and the American Heart Association offer a comprehensive approach to the assessment of cardiac risks for patients undergoing surgery (9). This approach represents a consensus view derived from a review of the literature to date and is periodically updated on the ACC Web site (http://www.acc.org/). The algorithm is as shown in Figure 17.1 . In order to use the algorithm, one needs to categorize patient risk factors into major, intermediate, and minor clinical predictors of increased perioperative cardiovascular risk (Table 17.1), assess the patients' functional capacity (Table 17.2), and assess the type of surgery that the patients will endure (Table 17.3).

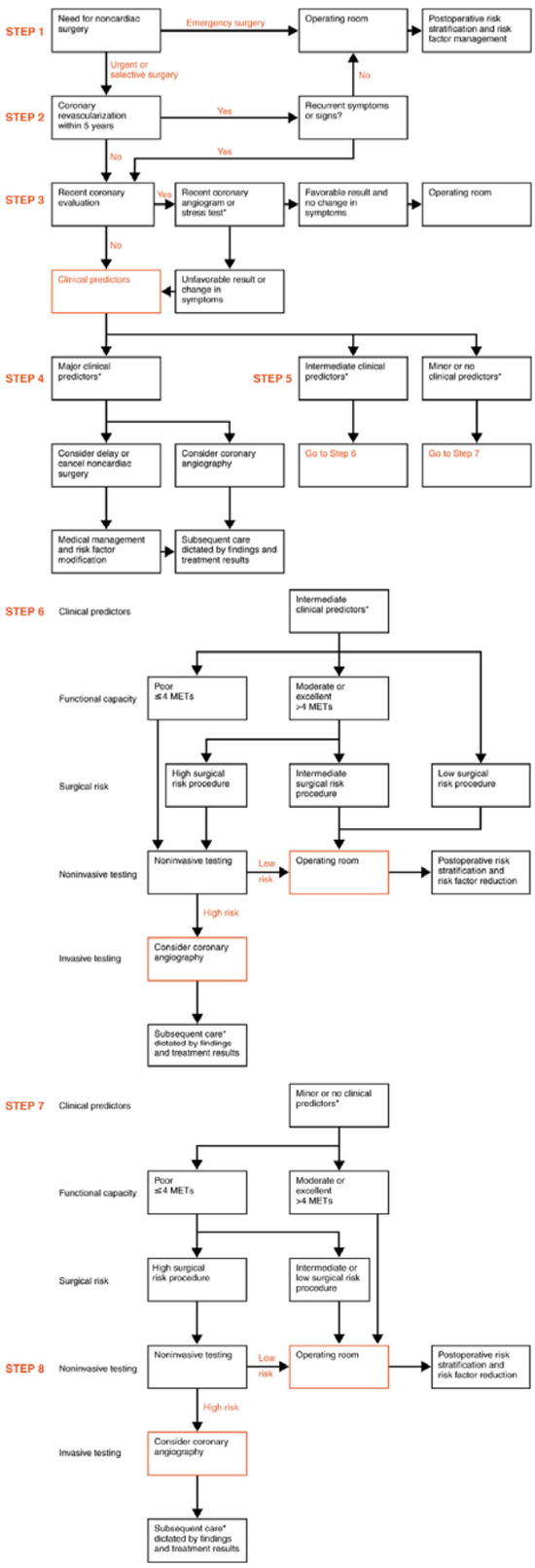

Figure 17.1 Stepwise approach to preoperative cardiac assessment. * refers to subsequent care, which may include cancellation or delay of surgery, coronary revascularization followed by noncardiac surgery, or intensified care. MET, metabolic equivalent (see Table 17.2) (Used with permission from **Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy, EA, Fleischmann KE, et al.** ACC/AHA Guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2002;105:1257.)

Table 17.1 Clinical Predictors of Increased Perioperative Cardiovascular Risk (Myocardial Infarction, Heart Failure, Death)

Major
Unstable coronary syndromes
Acute (<7 days) or recent (7–30 days) myocardial infarction with evidence of important ischemic risk by clinical symptoms or noninvasive study
Unstable or severe angina (Canadian class III or IV)
Decompensated heart failure
Significant arrhythmias
High-grade atrioventricular block
Symptomatic ventricular arrhythmias in the presence of underlying heart disease
Supraventricular arrhythmias with uncontrolled ventricular rate
Severe valvular disease
Intermediate
Mild angina pectoris (Canadian class I or II)
Previous myocardial infarction by history or pathological Q waves
Compensated or prior heart failure
Diabetes mellitus (particularly insulin-dependent)
Renal insufficiency
Minor
Advanced age
Abnormal electrocardiogram (left ventricular hypertrophy, left bundle-branch block, ST-T abnormalities)
Rhythm other than sinus (e.g., atrial fibrillation)
Low functional capacity (e.g., inability to climb one flight of stairs with a bag of groceries)
History of stroke
Uncontrolled systemic hypertension

Table 17.2 Estimated Energy Requirements for Various Activities

1–4 Metabolic Equivalents (METs)
Can you take care of yourself?
Eat, dress, or use the toilet?
Walk indoors around the house?
Walk a block or two on level ground at 2–3 mph (3.2–4.8 km/hr)?
Do light work around the house like dusting or washing dishes?
5–10 Metabolic Equivalents (METs)
Climb a flight of stairs or walk up a hill?
Walk on level ground at 4 mph (6.4 km/hr)?
Run a short distance?
Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?
Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?
>10 Metabolic Equivalents (METs)
Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?

MET, Metabolic Equivalent, which can be used as a measure of energy requirements and may be used in treadmill reports.

Adapted from the Duke Activities Status Index. **Hlatky MA, Doineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, et al.** *Am J Cardiol* 1989;64:651–654.

Table 17.3 Cardiac Risk Stratification for Noncardiac Surgical Procedures

High (Reported cardiac risk often greater than 5%)
Emergent major operations, particularly in the elderly
Aortic and other major vascular surgery
Peripheral vascular surgery
Anticipated prolonged surgical procedures associated with large fluid shifts and/or blood loss
Intermediate (Reported cardiac risk generally less than 5%)
Carotid endarterectomy
Head and neck surgery
Intraperitoneal and intrathoracic surgery
Orthopedic surgery
Prostate surgery
Low (Reported cardiac risk generally less than 1%)
Endoscopic procedures
Superficial procedure
Cataract surgery
Breast surgery

If emergent surgery is needed, the patient will proceed immediately to the operating room. For urgent or elective surgery, there is more time to assess a patient's cardiac risks. In general, patients who have low to intermediate clinical predictors with good functional capacity and who are to undergo low- to intermediate-risk surgical procedures can proceed with the planned surgery without additional cardiac testing. On the other hand, noninvasive testing is recommended for those patients with intermediate to major clinical predictors, with poor functional capacity, and who are to undergo high-risk surgical procedures. Dipyridamole-thallium imaging or dobutamine stress echocardiography can be considered for noninvasive testing in these patients (10 ,11). If noninvasive testing shows significant findings, subsequent care may include cancellation or delay of surgery, coronary revascularization followed by noncardiac surgery, or intensified care.

Myocardial Infraction

Even with the best preoperative assessment and preparation, postoperative myocardial infarction (MI) can still occur after surgery with general anesthesia. The risk factors for perioperative MI are related to the underlying risk of ischemic heart disease. Before the advent of more modern management of ischemic heart disease, the risk of a second MI after anesthesia and general surgery was considered too high during the first few months after a myocardial infarction (12). Current cardiologic practice, including revascularization, angioplasty, or very aggressive medical therapy with lipid-lowering agents and use of ß-blockers, makes this rule less useful. It is now commonly believed that with proper treatment, patients can undergo surgery 6 weeks after myocardial infarction if necessary. In addition, there is evidence that coronary artery bypass surgery lowers the risk substantially (13 ,14).

Postoperative MI can be painless. The risk of MI is throughout the first week, but the incidence is thought to peak on the third postoperative day. Hence, it is prudent to monitor high-risk patients with daily electrocardiograms (ECGs), beginning in the immediate postoperative period and continuing at least through postoperative day 3 (15). Serum troponin assays may be helpful for surveillance as well. Because the risk of perioperative MI is increased in patients who are subjected to intraoperative hypotension, measures must be taken to maintain high-risk patients in a normotensive state during surgery. **If intraoperative hypotension occurs, the patient should be considered at high risk of postoperative MI and monitored appropriately**.

Theoretically, ß-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, abrupt discontinuation of ß-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 (16). Patients tolerate general anesthesia in the presence of continued ß-blocker treatment. Furthermore, perioperative ß-blocker use reduces postoperative nonfatal myocardial infarction and mortality (17 ,18). If anything, use of ß-blockers in the perioperative period should be expanded.

The recommended target heart rate for effective ß-blockade is below 65 beats per minute, but not lower than 50 beats per minute. The ß-blockers should begin before surgery and

be continued throughout the hospitalization. If needed, ß-blockers can be started 1 month before surgery to titrate the heart rate and be continued after hospitalization if adequate postoperative medical follow up can be arranged (19).

Congestive Heart Failure

Patients with moderate or severe congestive heart failure should be treated before surgery with appropriate medications to optimize their cardiovascular status. **Preoperative placement of a pulmonary artery (Swan-Ganz) catheter has been advocated to allow cardiac function to be optimized and to aid in the intraoperative management of fluids and cardiac medications. Recent studies, however, have not shown clear benefit to these devices in managing high-risk surgical patients, and this procedure is generally no longer recommended** (20).

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 (21). 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.

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. Patients with implanted defibrillators typically have their devices turned off shortly before surgery and then turned back on shortly afterward.

Even newer pacemakers and defibrillators 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. Inappropriate discharges from the implanted defibrillator are avoided by having the device turned off during the time of surgery.

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, patients undergoing 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* (22).

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 (23). However, the presence of hypertension may be of consequence because such patients frequently demonstrate marked intraoperative blood pressure lability and postoperative hypertensive episodes. It is also generally agreed that severe hypertension (systolic pressure greater than 180 mm Hg, diastolic greater than 110 mm Hg) should be controlled with effective oral medications in the days to weeks before an elective operation.

The causes of perioperative hypertension are presented in Table 17.4 . Patients with both hypertensive and atherosclerotic heart disease may be at greater risk than those with uncomplicated hypertension alone. 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.

Table 17.4 Causes of Perioperative Hypertension

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

Hypertensive management begins with identification, followed by development of a plan for control. 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 (24). 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. 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. An exception to this would be the use of ß-blockers, which, because of their presumed benefit in decreasing cardiac events and concern about rebound hypertensive effects if they are stopped, should be continued in the postoperative setting. Patients whose only antihypertensive drugs are thiazide diuretics are best observed in the immediate postoperative period. In general, patients who need additional antihypertensive therapy in the immediate preoperative period should not be treated with diuretics because of the risk of associated hypovolemia and hypokalemia.

Pulmonary

One recent review found nearly 5% of all surgical patients developed significant postoperative pulmonary complications (25). Unlike cardiac risks, which have been carefully studied for several decades, pulmonary risk prediction and modification has not been investigated as thoroughly. Atelectasis, postoperative pneumonia, acute respiratory distress syndrome, and respiratory failure can all develop after abdominal and pelvic surgery.

Reduction in lung volumes, particularly functional residual volume, is the primary pathophysiology brought on by surgery and anesthesia. Clinicians should attempt to identify patients at increased risk for pulmonary complications from surgical procedures and reduce these risks whenever possible (Fig. 17.2).

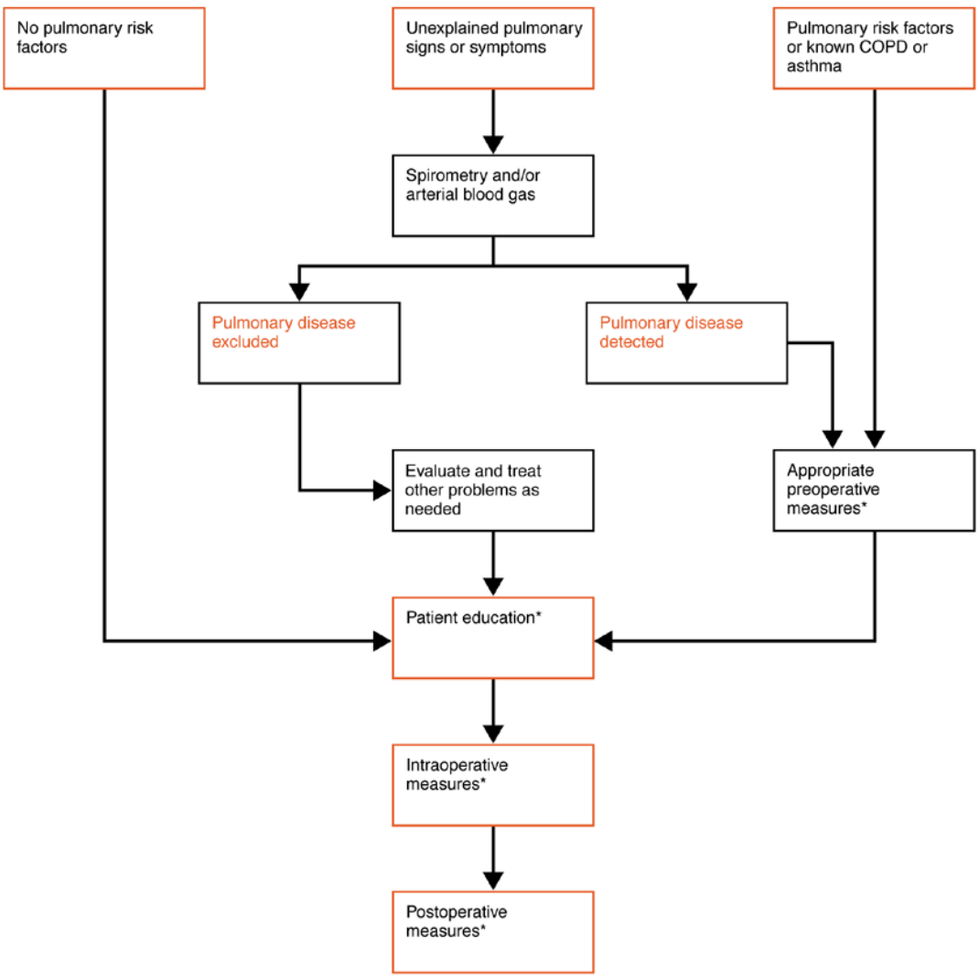

Figure 17.2 Pulmonary evaluation and postoperative care. COPD, chronic obstructive pulmonary disease; * refers to measures to reduce pulmonary complications (see Table 17.3).

Pulmonary Risk Factors

Pulmonary risk factors are typically grouped as "procedure related" or "patient related." Two recent analyses of large operative populations have identified preoperative predictors of postoperative pneumonia (26) and postoperative respiratory failure (27).

For **"procedure-related" risks**, these reviews confirm that **upper abdominal surgeries carry higher risks than lower abdominal procedures**. These increased risks are believed to be due to the higher likelihood of diaphragmatic dysfunction, or related postoperative pain and shallow inspiration. Both reviews also showed **general anesthesia**

increased pulmonary risks as compared with spinal or regional anesthesia. An older review also identified longer anesthesia time (>3 hours) as a predictor for increased postoperative pulmonary complications (28).

“Patient-related” risk factors that have been identified include (i) current smoking, (ii) advanced age, (iii) chronic obstructive pulmonary disease, and (iv) general health status. Current smoking, as well as lifetime amount of smoking, have been associated with more pulmonary complications. This may be related to mucous hypersecretion and ciliary dysfunction, and seems to be independent of the fixed airways disease that develops in some smokers [chronic obstructive pulmonary disease (COPD)] (29). A

recent review suggested that substantial risk seems to occur with ages in excess of 70 to 80 years (30).

COPD is a well-known risk factor for postoperative pulmonary complications and has been estimated to increase relative risk by three- to fourfold (29). There has been considerable debate about the routine use of spirometry to screen for this condition before nonthoracic surgery. Currently, the American College of Physicians (ACP) recommends spirometry only if the history and physical examination suggest an undefined lung condition (31). A history of prolonged cigarette smoking, dyspnea, chronic cough, sputum production, wheezing, or prolonged expiration and hyperinflation noted on examination would all be suggestive findings for COPD. Patients with these findings would typically receive pulmonary function testing with spirometry (and possibly a blood gas), whether an operation was intended or not.

Although COPD increases the risk for postoperative complications, it does not make these risks prohibitive. Even patients with severe COPD can tolerate abdominal surgery (32). When patients with COPD are identified before elective operations, every effort should be made to optimize their lung function and minimize any other perioperative risks.

Recent reviews have not identified asthmatic patients as having significant risks of serious postoperative complications when managed appropriately (33).

General health status, either measured by functional status, American Society of Anesthesiologists (ASA) risk class, or by markers of poor health such as weight loss, low serum albumin, or elevated blood urea nitrogen, has been shown to correlate with increased pulmonary complications (34).

Obesity is not necessarily associated with increased pulmonary risks, although many of its attendant comorbidities are known to increase perioperative risks. One known complication of severe obesity is obstructive sleep apnea. **Sleep apnea has been shown in at least one study of operative patients to increase serious postoperative pulmonary complications** (35). These patients are often prescribed positive pressure airway masks to assist their breathing at home during the night. This equipment should be available in the postoperative period to assist with apneic breathing episodes as well. Obese patients (as well as other patients with unusual upper airways anatomy) may present difficulties for intubation, and fiberoptic instruments may be needed in the operating room.

Pulmonary Risk Reduction

Physicians should attempt to reduce perioperative risks whenever possible (Table 17.5). Some identified risks (such as location of surgery, type of anesthesia, age, poor general health status, and fixed airway obstruction) can not be improved. **Smoking cessation**, however, **should be encouraged**. At least 4 weeks of smoking abstinence is needed to reduce smoking-related pulmonary risks (36). **Patients with airways obstruction (COPD and asthma) should be optimized to their baseline pulmonary status before surgery.** This may involve bronchodilator use, inhaled steroids, or possibly antibiotics and/or oral steroids. As an example, a 1-week course of preoperative oral steroids in severe asthmatics has been shown to be safe in reducing the risks of postoperative bronchospasm (37).

Table 17.5 Measures to Reduce Pulmonary Complications

Preoperative
Identification of patients at risk
Patient education to ensure optimal preoperative and postoperative compliance and performance
Cessation of smoking for at least 4 wks
Instruction in incentive spirometry
Bronchodilation (e.g., ß-adrenergic agonist by inhaler)
Inhaled or possibly oral steroids for asthmatics
Antibiotics for bronchitis
Control of secretions
Intraoperative
Avoidance of prolonged anesthesia (>3 hr)
Regional anesthesia if possible in higher-risk patients
Avoidance of aspiration
Maintenance of bronchodilation
Use of laparoscopic procedures when possible
Postoperative
Continuation of preoperative measures, especially encouragement of incentive spirometry
Early ambulation
Pain control
Attention to the effects of analgesia on respiration

Both COPD and asthmatic patients should continue their home medications during their postoperative course. Modern ambulatory therapy for asthma emphasizes the use of inhaled steroids as well as inhaled beta agonists. Exacerbations during the postoperative period can be treated with additional doses of inhaled bronchodilators, and intravenous steroids if necessary.

COPD management typically involves both inhaled beta agonists and anitcholinergics. Exacerbations can also be treated with additional doses of inhaled medications or

steroids. Noninvasive ventilation has been used successfully in postoperative patients with COPD exacerbations (38).

Because low lung volumes produced by anesthesia, operative site pain, and bowel distension all contribute to respiratory dysfunction in the postoperative period, clinicians have tried deep breathing exercises, intermittent positive pressure breathing (IPPB), and simple incentive spirometry to attempt lung expansion in the postoperative period. Although they all decrease the frequency of pulmonary problems, IPPB is associated with some side effects (39). **In recent years, clinicians have routinely prescribed incentive spirometry and deep breathing exercises postoperatively**, as these methods are low risk and inexpensive. Adequate pain control is also important to improve deep breathing and lung expansion after abdominal surgery.

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. 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 17.6 . 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.

Table 17.6 Complications of Diabetes

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

The management of diabetes begins with some understanding of the factors that influence perioperative glucose metabolism. 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 17.7). **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 *rosiglitazone (Avandia)* improves peripheral use of glucose by improving insulin sensitivity. This class of medication has a risk of fluid retention. It is generally not recommended for patients with NYHA class III or IV status. The use of thiazolidinediones around the perioperative period should be exercised with caution, especially in patients with cardiac disease and/or those who have received more intravenous fluids during the perioperative period.

Table 17.7 Characteristics of Oral Hypoglycemics

Agent	*Brand*	*Dose Range (mg)*	*Duration (hr)*	*Metabolism*
Sulfonylureas				
Tolbutamide	*Orinase*	500–3,000	6–12	Liver
Chlorpropamide	*Diabinese*	100–500	60	Liver/renal
Acetohexamide	*Dimelor*	250–1,500	12–24	Liver
Tolazamide	*Tolinase*	100–1,000	10–18	Liver
Glyburide	*DiaBeta*	2.5–30	10–30	Liver
Glipizide	*Glucotrol*	5.0–4.0	18–30	Liver
Glimepiride	*Amaryl*	1.0–8.0	8–12	Liver/renal
Biguanide				
Metformin	*Glucophage*	850–2,300	18	Renal
Glucosidase inhibitors				
Acarbose	*Precose*	25–30	2	Gastrointestinal
Miglitol	*Glyset*	75–300	2	Renal
Meglitinides				
Repaglinide	*Prandin*	0.5–16	1	Liver/renal
Nateglinide	*Starlix*	180–720	4	Liver/renal
Thiazolidinediones				
Rosiglitazone	*Avandia*	4.0–8.0	3–4	Liver
Pioglitazone	*Actos*	15–45	16–24	Liver/renal

Management

It is known that hyperglycemia impairs neutrophil functions, wound healing, and increases the risk of wound infection (40 ,41 ,42 ,43 ,44 and 45). In a recent study in critically ill patients, it was shown that tight glycemic control with blood glucose at or around 110 mg/dL

reduced blood stream infections, acute renal failure requiring dialysis, blood transfusion, length of mechanical ventilation and critical care, and in-hospital mortality. Mortality at 12 months was reduced as well in intensive *insulin* therapy patients (46). Thus, **the goal of management is to keep blood sugar at least below 200 mg/dL or as close to the normoglycemic range as possible.**

Details of the management of the diabetic patient who is taking an oral sulfonylurea hypoglycemic agent are presented in Table 17.8 . The same principles may be applied to *metformin* and the thiazolidinediones. Patients with very well-controlled diabetes who take sulfonylueas are at risk of hypoglycemia if an oral hypoglycemic agent is given while the caloric intake is reduced. This is not true of *metformin* or thiazolidinediones. **Metformin should not be used in the perioperative period.** In general, oral agents 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 whom 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.

Table 17.8 Details of Perioperative Diabetes Management for Well-Controlled Patients Taking Oral Hypoglycemics

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 hrs **3.** Measure early a.m. glucose (use sliding-scale insulin for glucose <200 mg/dL)
Intraoperative
4. Measure intraoperative glucose frequently (e.g., every 1 hr) and start insulin drip to keep blood glucose <200 mg/dL
Postoperative
5. Measure recovery room glucose (use sliding-scale insulin for glucose <200 mg/dL) **6.** Measure postoperative glucose every 6 hrs (use sliding-scale insulin to keep blood glucose <200 mg/dL) **7.** Return to previous regimen incrementally in a.m. if eating

The management of the diabetic patient who takes *insulin* is presented in Table 17.9 . **It is important to reduce the total daily dose of** *insulin* **because caloric intake on the day of surgery is reduced** (46) **(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.

Table 17.9 Details of Perioperative Insulin Management for Well-Controlled Patients Taking Insulin

Preoperative
1. Plan for surgery early in the day **2.** Measure early a.m. glucose (use sliding-scale insulin to keep glucose <200 mg/dL) **3.** Use one-third of NPH (or equivalent) insulin subcutaneously **4.** Start D5W at 100 mL/hr
Intraoperative
5. Measure intraoperative glucose frequently (e.g., every 2 hrs) and make adjustments
Postoperative
6. Measure recovery room glucose (use sliding-scale insulin to keep glucose <200 mg/dL) **7.** Measure postoperative glucose every 6 hrs (use sliding-scale insulin to keep glucose <200 mg/dL) **8.** Use regular insulin according to sliding scale as needed **9.** Use one-third of NPH 8–12 hrs 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

NPH, neutral protamine Hagedorn; D5W, dextrose in 5% water.

In critically ill patients or patients with uncontrolled diabetes, continuous *insulin* **infusion is a better strategy for glycemic control** (47 ,48). Continuous *insulin* infusion with glucose infusion maintains normal insulin sensitivity during the perioperative period and decreases blood cortisol, glucagons, fat oxidation, and free fatty acids when compared with controls (49). An *insulin* infusion can be started at 1 U per hour and the rate titrated by 0.5 U per hour increments to keep blood glucose levels below 200 mg/dL. Five percent dextrose infusion with or without potassium at a rate of 100 mL per hour should be given as well to avoid any hypoglycemia. Frequent blood glucose monitoring is prudent during therapy.

Thyroid Disorders

Hypothyroidism

Hypothyroidism is common and may go undetected in patients being prepared for surgery (50). 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 (51 ,52). 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 (53), 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 should not have adrenal suppression** (54). There is variability between patients in their response to suppression of the hypothalamic–pituitary–adrenal (HPA) axis by exogenous steroid. In a prospective cohort study, 75 patients were given short-term, high-dose glucocorticoid treatment of at least 25 mg *prednisone* daily for 5 to 30 days (55). Forty-five percent of the patients experienced HPA suppression. Of those patients, the majority recovered within 14 days. However, a couple of patients remained suppressed at 3 and 6 months.

In a retrospective study, 279 patients were taking *prednisone* or its equivalent steroid at doses of 5 to 30 mg per day for between 1 week and 15 years (56). Human corticotropin-releasing hormone (CRH) was used to assess HPA suppression. There was a trend toward an inverse correlation between dosage and duration of therapy and the plasma cortisol response to CRH. On the other hand, there were numerous patients taking high-dose steroids for more than 100 weeks who still had an intact HPA axis. Despite this variability, **suppression of the HPA axis should be anticipated in patients taking more than 30 mg of** *hydrocortisone*, **7.5 mg of** *prednisone*, **or 0.75 mg** *dexamethasone* **per day for more than 3 weeks** (57).

Corticosteroid supplementation for patients suspected of adrenal suppression will depend on the type of surgery performed. **Patients having minor surgeries should be able to take their usual dose of steroid on the day of surgery without additional supplementation**. Patients undergoing moderate surgical stress, such as hysterectomy, should take their usual steroid dose on the morning of the surgery and be supplemented with 50 mg intravenous *hydrocortisone* on call to surgery followed by a similar dose every

8 hours, quickly tapering over 24 to 48 hours. **Patients undergoing very major surgery, such as primary cytoreduction for advanced ovarian cancer, should take their usual steroid dose on the morning of surgery and be supplemented with 100 mg intravenous *hydrocortisone* on call to surgery, followed by a similar dose every 8 hours, tapering the dose by half each day over the next 24 to 48 hours**. The patients can resume their usual oral steroid dose when they are off intravenous *hydrocortisone* and are able to take medications by mouth (58 ,59).

There are some patients (e.g., those with diabetes) in whom it is important to avoid any 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. The procedure is to give 250 *m*g 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 *m*g/mL (55 ,60).

Thromboembolic Disease

Hospitalized patients, particularly those with multiple risk factors (Table 17.10) are at increased risk for thromboembolic disease. Gynecological surgery patients, especially cancer patients, are at high risk in the postoperative setting. It has been estimated that **in the highest-risk patients not treated prophylactically, the risk of developing a calf thrombosis may be as high as 80%, and the risk of pulmonary embolism as high as 5%** (61).

Table 17.10 Factors Related to Increased Risk of Thromboembolic Disease

Inherited disorders
Antithrombin III deficiency
Protein C deficiency
Protein S deficiency
Prothrombin G20210A mutation
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 >40 yr
Estrogen therapy
Sepsis
Bed rest
Trauma
Stroke
Polycythemia rubra vera
Inflammatory bowel disease
Obesity
Prior thromboembolism

Numerous studies have looked at mechanical devices like elastic stockings and intermittent pneumatic compression and have shown that they are protective against venous thrombosis (62 ,63 and 64). Similarly, low-dose subcutaneous *heparin* was shown to decrease venous thromboembolism (65 ,66). Clarke-Pearson et al. looked specifically at gynecologic oncology patients and initially compared the efficacy of low-dose subcutaneous

heparin with pneumatic compression devices. They showed that both had similar efficacy, but low-dose subcutaneous *heparin* was associated with increased bleeding risks (67). **Low-molecular-weight** ***heparin (LMWH)*** **has been shown in other general surgical patients to be at least as effective as low-dose** ***heparin*** **in preventing thrombosis, and perhaps superior** (68 ,69 and 70). In a follow-up study on gynecologic oncology patients, the Clarke-Pearson group compared *LMWH* with intermittent pneumatic compression devices and showed no increased in risk of bleeding (71). Several other studies, however, have shown that *LMWH* may have increased bleeding risks in postoperative patients (72 ,73). Some of these discrepancies may be due to various doses and types of *LMWH*.

Overall, mechanical devices or ***heparin*** **products are effective in preventing deep venous thrombosis**. One should weigh the risk of bleeding versus the risk of thrombosis in each postoperative patient. **In patients with the highest risk for thrombosis, combination therapy should be considered**. In a retrospective review of gynecological surgery patients treated with intermittent pneumatic devices alone, there was a 1.3% incidence of thromboembolism. Further analysis showed that **patients with a diagnosis of cancer, history of previous deep venous thrombosis, and age greater than 60 had the highest risks** (74). The addition of *heparin* to mechanical devices should be considered in patients such as these. A recent consensus conference summarized postoperative recommendations for thromboembolic prophylaxis in postoperative gynecology patients and is shown in Table 17.11 (61).

Table 17.11 The Sixth (2000) American College of Chest Physicians Guidelines for Antithrombotic Therapy for Prevention and Treatment of Thrombosis

Recommendations for Venous Thromboembolic Prophylaxis in Gynecologic Surgery	
1.	For gynecologic surgery patients undergoing brief procedures for benign disease, we recommend early mobilization alone (clear benefit from observational trials).
2.	We recommend that patients having major gynecologic surgery for benign disease, without additional risk factors, receive twice-daily low-dose unfractionated heparin (grade 1A). Alternatives include once-daily low-molecular-weight heparin (LMWH) or intermittent pneumatic compression devices, started just before surgery and continued for at least several days postoperatively (clear benefit from observational trials)
3.	For patients undergoing extensive surgery for malignancy, we recommend routine prophylaxis with three daily doses of low-dose unfractionated heparin (grade 1A). Alternative considerations include the combination of low-dose unfractionated heparin plus mechanical prophylaxis with elastic stockings or intermittent pneumatic compression devices, or higher doses of LMWH, because these options may provide additional protection (clear benefit from observational trials).

From **Geerts WH, Heit JA, Clagett GP, Pineo GF, Calwell CW, Anderson FA**. Prevention of venous thromboembolism. *Chest* 2001;119:132s–175s

Preoperative Testing

The question of how much preoperative laboratory testing is warranted has been the subject of considerable interest and debate (75 ,76). The data from many 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**. Certainly, in low-risk surgery for healthy patients, outcomes are no different whether preoperative tests are ordered or not (77 ,78). For gynecologic surgery in the cancer patient, however, few clinicians would advocate no preoperative testing. Tests that are performed should be focused on identifying the risks of surgery and anesthesia, and modifying them when possible.

A preoperative **ECG** should be obtained on all women over 50 years of age. A **chest x-ray** is often ordered before major surgery and can be useful in identifying perioperative risks (particularly in a cancer patient). Lung masses, pleural effusions, and other

parenchymal abnormalities may modify anesthetic technique or reveal treatable conditions to optimize the patient's preoperative condition. A **urinalysis** is typically obtained before gynecologic surgery because of the need for catheterization.

A baseline hematocrit and complete blood count should be obtained. Serum electrolytes and renal chemistries should be determined. Liver chemistries are also useful in cancer patients who may have received prior chemotherapy with associated toxicities or may be suffering the consequences of metastatic spread. An elevated creatinine has been identified as a predictor for cardiac problems during and after surgery (79). **A serum albumin may also be useful** to assess a patient's nutritional status and reserve. A large study of patients undergoing major noncardiac surgery showed low serum albumin to be the single strongest predictor of perioperative morbidity and mortality (80).

Blood glucose testing is an important part of perioperative management of the diabetic patient (see previous section, “Diabetes Mellitus ”). Other laboratory tests to consider as part of a focused preoperative screening should include a **TSH** (thyroid-stimulating hormone) on a patient being treated for hypothyroidism, and all elderly women (older than 70 years). **Drug levels should be obtained on patients receiving medications with narrow therapeutic windows, e.g.**, *digoxin* **or** *Dilantin*. In each case, the purpose of the test is to identify abnormalities that should be corrected before the intended operation.

Screening for Hemostatic Dafects

A good history and physical examination are often most helpful in screening patients for hemostatic defects before operations. Some of 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**. Patients should be questioned about nose bleeds, intestinal bleeding, and heavy menstrual bleeding. Large ecchymosis and mucosal bleeding on examination can be a cause for concern.

Like other laboratory tests, some have suggested that in otherwise healthy patients, screening for hemostatic defects may not be warranted (81). For cancer patients undergoing surgery for which bleeding is expected, some laboratory screening seems prudent. **A platelet count, INR (international normalized ratio), and PTT (partial thromboplastin time) are the most commonly ordered screening tests for this purpose**. A low platelet count can be caused by decreased production, sequestration into the spleen, or increased destruction. For platelet counts less than 100,000/cc, platelet transfusions may be necessary before the operation, depending on additional risks. Certain commonly prescribed drugs [such as aspirin and nonsteroidal antiinflammatory drugs (NSAIDs)] can inhibit platelet function and should be held for a week before the operation if possible. Renal dysfunction is another common cause of acquired platelet dysfunction.

Elevated INR and PTT values often reflect blood coagulation protein deficiencies (or inhibitors). Patients with elevated values may require plasma factor replacement before surgery to minimize their bleeding risks.

There are some patients with normal screening laboratory tests who nonetheless have suggestive histories and/or examinations for hemostatic defects. One possible culprit might be **Von Willebrand's disease—an inheritable coagulation defect in platelet function**. Identification and perioperative management of this and other more uncommon bleeding disorders may require further laboratory testing and the expertise of a hematologist.

Perioperative Antibiotics for Wound Infection Prophylaxis

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** (82). In addition, if bowel resection is anticipated, mechanical cleansing of the bowel on the day before surgery is prudent, with or without oral *neomycin* and *erythromycin* base.

Critical Care

Part of "17 - Preoperative Evaluation, Medical Management, and 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 ß-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.** Several controlled trials have now shown improved long-term morbidity and mortality with routine use of these agents after surgery (17 ,18). As more studies support this finding, **ß-blocker medications may become routine in perioperative care** (19). 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. Patients with pain and anxiety are best treated with appropriate analgesics and anxiolytics. When evaluating the hypertensive postoperative patient, 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. Intravenous drugs with short half-lives are chosen to allow safe titration** (**the vasodilator** *nitroprusside* **or the ß-blocker** *esmolol* **are two popular choices**), and the patient is changed over to longer-acting agents as their condition stabilizes (83).

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 (10). The last two decades have seen remarkable progress in the management of what are now called **acute coronary syndromes**: 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 (84). *Aspirin* **therapy** (85) **and ß-blockers** (86) **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 (87 ,88), 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 are 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 (89). 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 electrically 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** *amiodarone* **or** *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 ß-blockers (if left ventricular function is preserved)**, *diltiazem*, **or** *digoxin.* Once heart rate and blood pressure are controlled, many clinicians would attempt chemical or electrical conversion for a new case of atrial fibrillation (duration less than 48 hours). 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 with atrial fibrillation lasting longer than a few days, who have no contraindication, should be considered for anticoagulation, to decrease their risk of a cerebrovascular accident** (90).

Bradyarrhythmias often arise from excessive vagal stimulation. Nausea, bladder distention, pain, and endotracheal tube manipulation can all stimulate excessive 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 (91):

- **Hypovolemic shock**—secondary to fluid losses and decreased cardiac filling pressures (e.g., postoperative bleeding or intravascular fluid redistribution)
- **Distributive shock**—secondary to inappropriate "vasodilation" and venous pooling (e.g., sepsis syndrome, anaphylaxis, decreased vasomotor tone from spinal anesthesia, and adrenal insufficiency from steroid withdrawal)
- **Cardiogenic shock**—secondary to decreased myocardial contractility and function (e.g., acute myocardial infarct or ischemia and/or congestive heart failure)
- **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:

- **Hemorrhage (hypovolemic)**
- **Sepsis (distributive)**
- **Postoperative MI (cardiogenic)**
- **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. One of the most popular systems 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. The amount and duration of these temperature changes are then used to calculate cardiac output.

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 (92 ,93). A careful physical examination and consideration of the clinical situation often suggest the etiology of a patient's shock syndrome. Therapy should typically begin without invasive hemodynamic measurement. These instruments, however, are still frequently used in the ICU, particularly in patients with known or suspected myocardial dysfunction.

If a pulmonary artery catheter is placed, CO values can 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^3. Differences in body size are often adjusted for by "indexing" CO and therefore SVR

values **(cardiac index = CO divided by body surface index).** 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:

- **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 clear evidence that colloids have any benefits over crystalloids 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.”
- **Distributive shock** often **requires vasopressor management** with catecholamines active at the α 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 an allergic reaction is suspected.
- **Cardiogenic shock** is characterized by inadequate CO, such that **inotropic 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. This allows contractility to improve without excessive cardiac work, which might exacerbate myocardial ischemia.
- **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 Figure 17.3 , although critically ill patients may often develop mixed shock states.

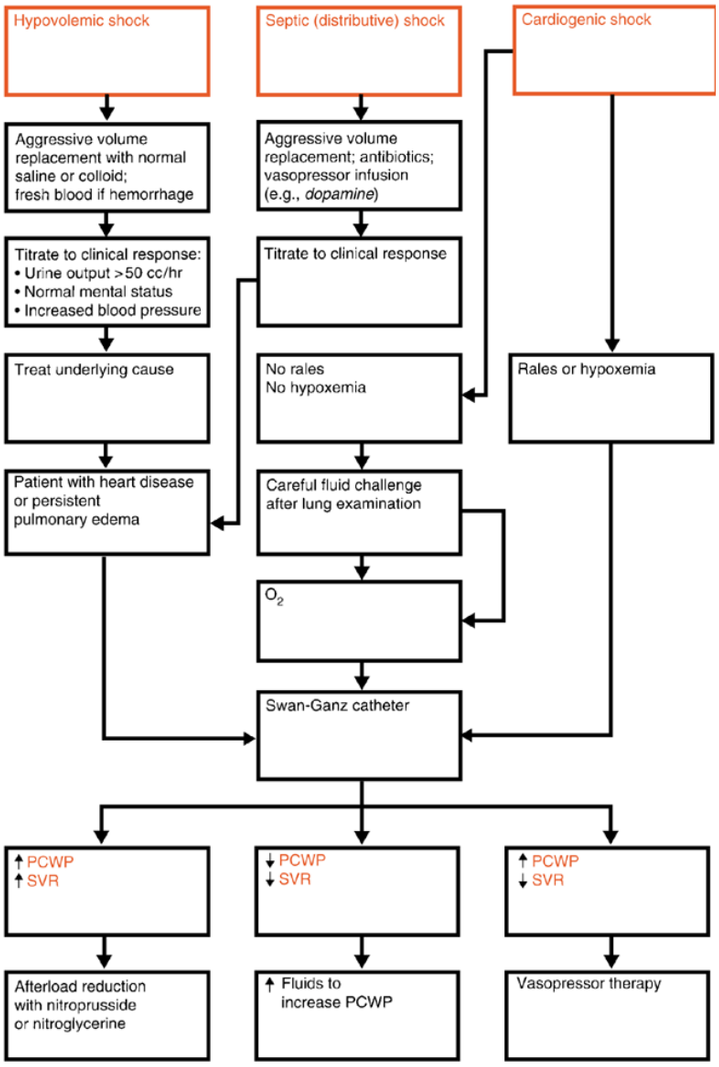

Figure 17.3 Management of hypotension. PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

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 entities, 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 commonly have abnormal mental status (agitation, somnolence, and disorientation), and physical findings may include tachycardia, hypertension, and occasionally cyanosis and sweating (Fig. 17.4).

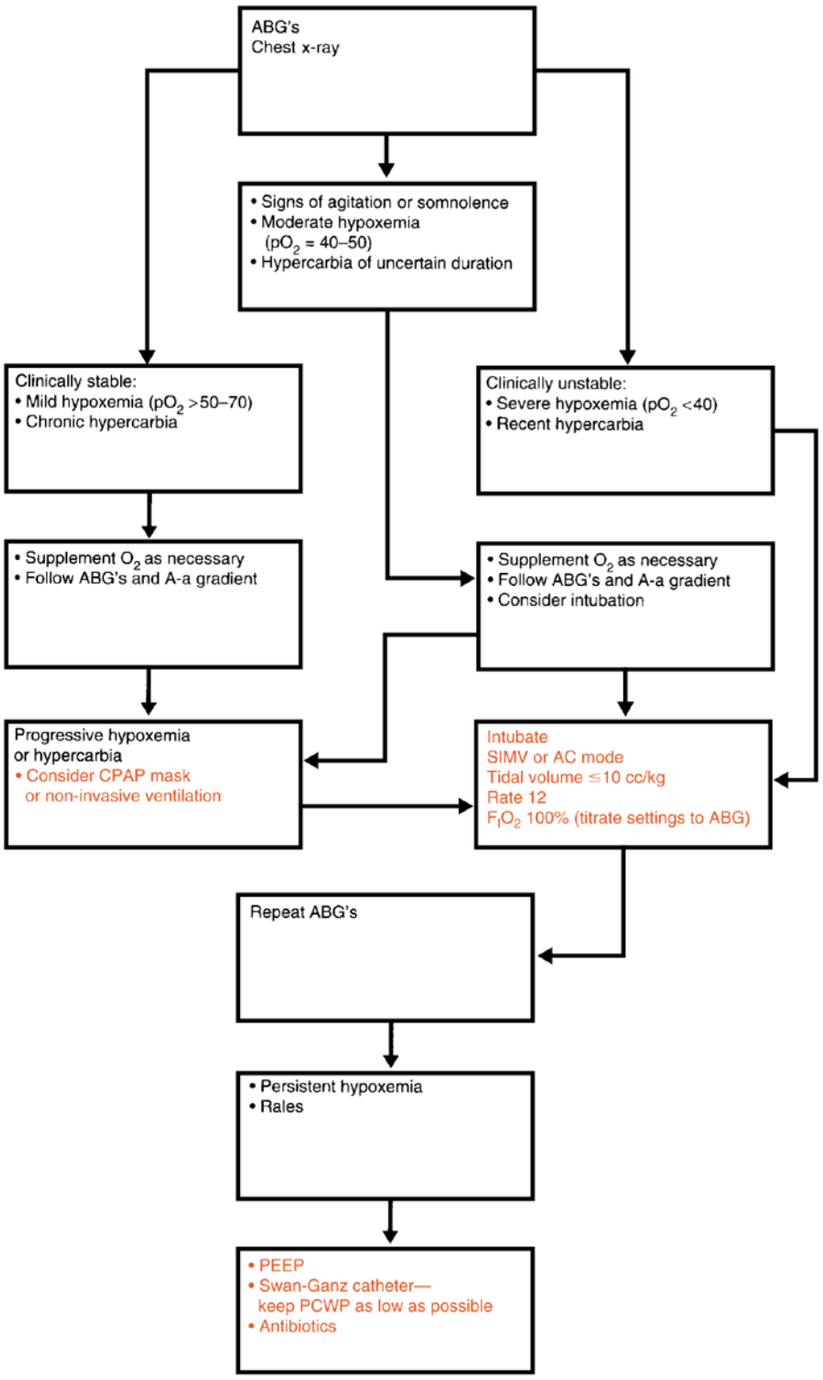

Figure 17.4 Management of respiratory failure. ABG, arterial blood gases; PCWP, pulmonary capillary wedge pressure; CPAP, continuous positive airway pressure; PEEP, positive end-expiratory pressure; SIMV, synchronized intermittent mandatory ventilation; AC, assist control; F_IO_2, fraction of inspired oxygen; A-a gradient, alveolar-arterial gradient.

Common causes of respiratory failure in the perioperative management of gynecologic cancer patients include:

- **Nervous system depression secondary to sedative or analgesic medications**
- **Bronchospasm**
- **Pneumonia**
- **Pulmonary edema**
- **Lymphangitic spread of cancer**
- **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 the bedside using the following alveolar gas equation:

$$\text{Alveolar } Po_2 = \text{Inspired } O_2 \text{ concentration} - \text{alveolar } CO_2 \text{ concentration}$$
$$\text{Alveolar } Po_2 = (Fio_2 \times [\text{barometric pressure} - \text{water vapor pressure}^*]) - ([Paco_2 \text{ arterial}] \times 1.25)$$

*713 mm Hg at sea level

Without oxygen supplementation at sea level, the inspired oxygen concentration is approximately 150 mm Hg. Normal $Paco_2$ 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 Po_2 - arterial Po_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 a dramatic improvement in oxygenation. On a mechanical ventilator, different manipulations can be made to increase airway 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:

- **Bronchodilators for bronchospasm**
- **Diuretics for excess lung edema**
- **Antibiotics for pneumonia**
- **Chest physiotherapy for atelectasis**
- **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 Pco_2 builds up in the alveoli, the arterial Pco_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 oncologic patient include the oversedated patient with an 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 an 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** (38).

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 Po_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" Pco_2 on blood gas measurement may lead to dangerous alkalemia in a patient with chronic lung disease who was in acid–base balance at a higher Pco_2. **The goal of 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 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 (94). Despite aggressive support, the mortality rate from this syndrome remains high (95).

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) (38). 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 of one ventilator setting versus another in terms of long-term outcome (96).

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 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** (97). 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 (or larger) tidal volumes with each breath if lung mechanics (or patient effort) changes. **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 (F_iO_2) to below 65%. Values above this for prolonged periods are believed to be damaging to lung parenchyma (98). 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 or changing patients to the prone position. Unfortunately, these interventions have not been shown in any prospective trials to improve long-term outcomes (96).

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 (99). **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. In one study, a rapid shallow breathing value less than 105 breaths/minute/L had a 90% positive predictive value for successful extubation (100).

Perhaps the most useful test 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 (101). 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** (102). **In the hospital setting, acute oliguria or renal failure is usually caused by hypovolemia, decreased cardiac output, postoperative kidney injury, or the use of nephrotoxic drugs** (103). **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 electrolytes and osmolality 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 (104). 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. **It was shown many years ago that one of the best urinary indices for distinguishing prerenal from other causes of oliguria is the fractional excretion of filtered sodium ($F_{ex}Na$)** (105). This can be calculated from sodium and creatinine concentrations as follows:

$$F_{ex}Na = \frac{\text{Urine sodium} \times \text{plasma creatinine}}{\text{Plasma sodium} \times \text{urine creatinine}} \times 100$$

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) are associated with levels greater than 2%. Causes of prerenal oliguria and acute renal failure include hypovolemia that is due to fluid losses or redistribution, cardiogenic shock, or renal vasculature abnormalities caused by stenosis, obstruction, or disruption of autoregulation—the latter 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 17.12 .

Table 17.12 Urinary Diagnostic Indicesa

	Prerenal Azotemia	*Acute Oliguric Renal Failure*	*Acute Nonoliguric Renal Failure*	*Acute Obstructive Uropathy*	*Acute Glomerulo-nephritis*
Urine osmolality, mOsm/kg H_2O	518 ± 35	369 ± 20	343 ± 17	393 ± 39	385 ± 61
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	16 ± 4	43 ± 7
Fractional excretion of filtered sodium	0.4 ± 0.1	7 ± 1.4	3 ± 0.5	6 ± 2	0.6 ± 0.2

[a]Values are expressed as mean ± standard error of the mean (SEM).

Reproduced and adapted from **Miller TR, Anderson RJ, Linas SC, Henrich WL, Berns AS, Gabow PA, et al**. Urinary diagnostic indices in acute renal failure: a prospective study. *Ann Intern Med* 1978;89:47, with permission.

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 acute tubular necrosis (ATN), although a small percentage of patients may have interstitial nephritis or a form of glomerulonephritis (102). 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 (106). Recent studies have suggested *acetylcysteine* may be useful in preventing radiocontrast dye–induced ATN as well (107). One cause of intrinsic renal failure that should be considered in any oncology patient being treated with chemotherapy is **tumor lysis syndrome. This condition is believed to be caused by the rapid destruction of large numbers of tumor cells and the sudden release of intracellular phosphate.** The syndrome is most commonly seen in lymphoma, but 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 the management of acute renal failure and will administer diuretics when volume status is restored. Whether this improves outcome is debatable, but, if successful, this strategy can make volume management easier (108).

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 useful for patients with decreasing mental status (uremic encephalopathy), bleeding (uremic platelet dysfunction), or pericarditis. Patients who are hemodynamically unstable might benefit from continuous renal replacement techniques (continuous venovenous hemodialysis or ultrafiltration) rather than intermittent therapy (109). An algorithm for managing oliguria and/or rising serum creatinine is shown in Figure 17.5 .

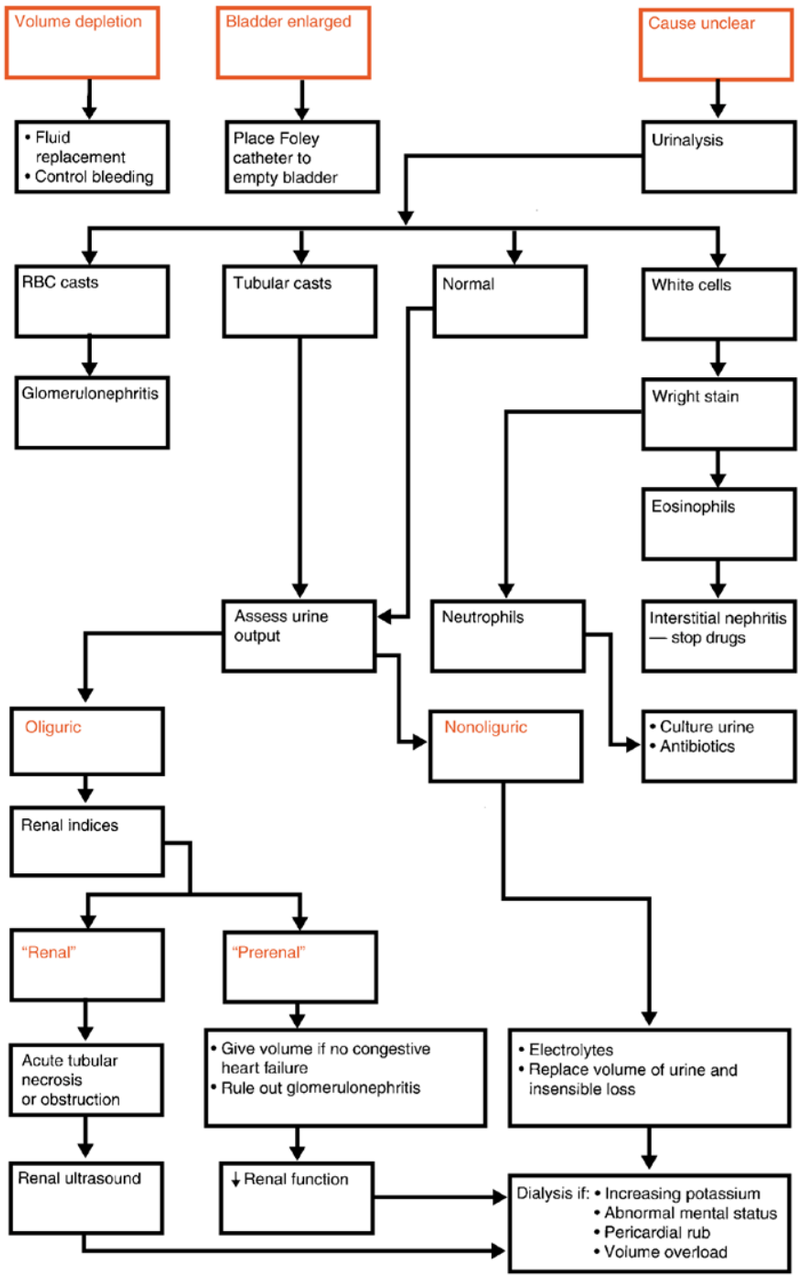

Figure 17.5 Management of a rising serum creatinine.

Acid-Base Didorders

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 (110 ,111).

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. This buffering system is reflected in serum bicarbonate levels and carbon dioxide tension (which is in equilibrium with serum carbonic acid). Changes in these measurements from baseline reflect changes in acid or base balance.

Changes in serum carbon dioxide tension (Pco_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, thereby creating compensatory changes in the Pco_2. By studying the serum pH and comparing changes in the serum Pco_2 to changes in the serum bicarbonate concentration, the clinician is often able to distinguish primary respiratory alkalemia and acidemia (as well as their duration) from secondary compensation (110 ,111). 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. **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 a primary metabolic acidosis is to measure serum electrolytes and calculate the anion gap**. A formula for the anion gap using serum electrolyte concentrations is:

$$\text{Anion gap} = (Na^+) - (Cl^- + HCO_3^-)$$

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 17.13 .

Table 17.13 Causes of Metabolic Acidosis

Elevated Anion Gap	*Normal Anion Gap*	*Normal–Hyperkalemic Acidosis*
Renal failure	Renal tubular acidosis	Early renal failure
Ketoacidosis	Diarrhea	Hydronephrosis
Lactic acidosis	Post-hypocapnic acidosis Carbonic anhydrase inhibitors Ureteral diversions	Addition of HCl Sulfur toxicity

The second step in evaluating a metabolic acidosis 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 Pco_2 and offsets the impact of the decreased bicarbonate on serum pH. The expected response to a primary metabolic acidosis can be estimated by the following equation (112):

$$\text{Expected } Pco_2 = 1.5\ (\text{measured } HCO_3^-) + 8\ (\text{range} \pm 2)$$

Patients who have metabolic acidosis and whose measured Pco_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 Pco_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 can be considered. **Bicarbonate therapy should be undertaken with caution, however, 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 (113), 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 the 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 17.14 lists the causes of metabolic alkalosis.

Table 17.14 Differential Diagnosis to Metabolic Alkalosis in Gynecologic Oncology Patients

A. Sodium chloride responsive (urinary chloride <10 mmol/L)

1. Gastrointestinal disorders
   Vomiting
   Gastric drainage
   Diarrhea
2. Diuretic therapy
3. Correction of chronic hypercapnia

B. Sodium chloride resistant (urinary chloride >15 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.

Maintenance Fluids

Management of water and electrolyte therapy is an important component in the care of surgical and oncologic 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 (111).

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 below), 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. Total body sodium content, in fact, is reflected in extracellular fluid volume. **Hyponatremia represents relative water excess.** Disorders of sodium excess or deficit are expressed as either extracellular volume overload or depletion. **Hyponatremic conditions are best grouped into three different categories:**

- **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.
- **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.
- **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 an infusion of normal saline. 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. 17.6 .

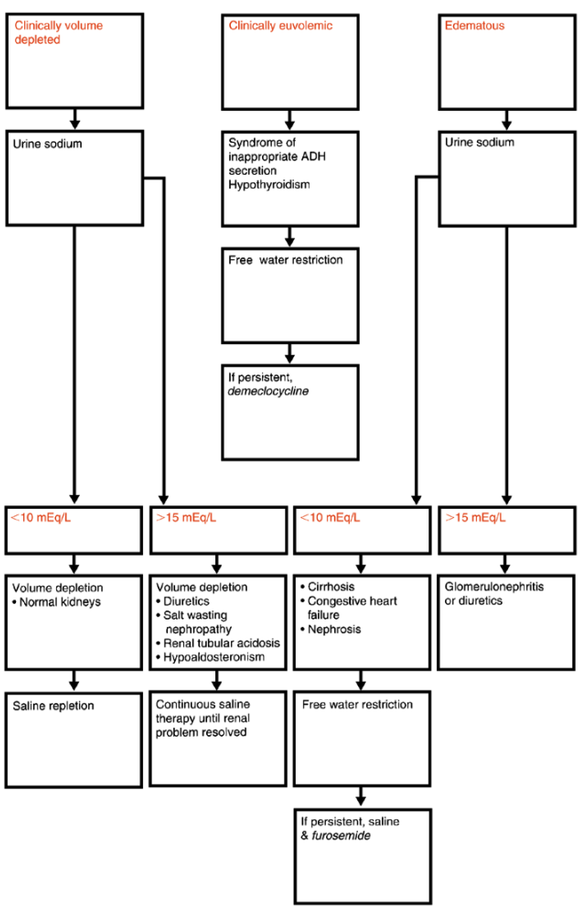

Figure 17.6 Evaluation of hyponatremia. ADH, antidiuretic hormone.

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 to adequately reabsorb water (concentrate urine), a condition termed **diabetes insipidus. Hypercalcemia affects the kidney's ability to concentrate. Hyperglycemia can also worsen water losses** by causing an osmotic diuresis. Treatment of hypernatremia is directed at providing adequate hypotonic fluids (often as “free water” or fluids with very minimal solute) and treating hypercalcemia and/or hyperglycemia. Rare patients may have disorders of antidiuretic hormone manufacture and secretion in 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 underestimated.

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 circumstances 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 equivalent dangers of hyperkalemia (discussed below).

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 the 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 oral or rectal potassium exchange resins and a loop diuretic such as** *furosemide.* **If there is associated renal failure, urgent 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. This 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 above), 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 (114). **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** (115). 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:

- **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.

- **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 study suggested that restricting red cell transfusion to patients with hemoglobin levels less than 7.0 g/dL (and who were not actively losing blood) did not worsen outcomes (116). Although controversial, a "restrictive" strategy of red cell transfusion may be at least as effective and possibly safer than a more liberal transfusion policy in some critically ill patients. Patients with unstable angina and risks for cardiac ischemia may require more liberal blood transfusion. More recent studies suggest that **patients with acute coronary syndromes do better with hemoglobin levels kept closer to 10.0 g/dL** (117).

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 signs or symptoms 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, and each 50-mL platelet "unit" from a whole blood fraction contains approximately 6×10^{10} platelets. Platelets may also be obtained by pheresis from a single donor, and each "unit" of single donor platelet pheresis is equivalent to 5 or 6 whole blood fraction units.

Platelet transfusions are indicated in patients with:

- **Platelet counts less than 50,000/mL^3 who show evidence of bleeding**
- **Platelet counts less than 10,000/mL^3 as prophylaxis against acute bleeding**

Each whole blood fraction unit of platelets should be expected to raise the recipient's 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. The two most commonly used fractions are fresh frozen plasma and cryoprecipitate.

Fresh Frozen Plasma

All the blood-clotting proteins 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. **Fresh frozen plasma may be used to rapidly reverse warfarin toxicity if bleeding is present.**

Plasma may also be used in reversing the coagulopathy associated with massive blood loss and red cell replacement by restoring the lost coagulation factors. It may require several “units” of fresh frozen plasma, however, to restore clotting factors to adequate levels. The half-life of transfused clotting factors is measured in hours, and bleeding risks can recur when these factors are consumed.

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. Cryoprecipitate units are smaller in volume than fresh frozen plasma and can be useful adjuncts in treating certain bleeding conditions such as DIC (see below).

Clotting Disorders

Massive Blood Transfusion

Pelvic surgeons may at times encounter unexpected and dramatic intraoperative bleeding. This may require large amounts of transfused blood, typically given as packed red blood cell (RBC) units. **“Massive transfusion” is typically defined as replacing the entire blood volume (5–6 L in a 70-kg patient) over a 24-hour period, or half the blood volume over a 3-hour period.** Such rapid blood transfusion can result in a **dilutional coagulopathy**, as these transfused units do not contain adequate amounts of blood proteins or platelets. **This can be worsened by the hypothermia and acidosis** brought on by hypovolemic shock.

The INR, activated PTT (aPTT), fibrinogen levels, and platelet counts should be followed closely in these cases. In general, INR and aPTT levels should be kept less than 1.5 times control values, fibrinogen maintained greater than 100 mg/dL, and platelet count supported to greater than 50,000. Such **“washout” coagulopathy has been shown in some studies to begin when greater than 10 units of packed red cells have been transfused** (118 ,119).

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. It occurs most commonly in critically ill patients with sepsis and/or liver disease. **In gynecologic oncology patients, it might also be associated with certain mucin-producing adenocarcinomas.**

In its acute form, DIC appears rapidly and is manifested by bleeding from multiple sites, including venipunctures, surgical wounds, gingiva, gastrointestinal tract, and skin. More rarely, DIC can take a chronic course over a period of months, with thrombotic complications more common than bleeding complications. This form is more typical for the syndrome associated with adenocarcinomas.

Direct evidence of DIC requires demonstration of intravascular fibrin deposition. The laboratory diagnosis of DIC depends on indirect evidence of coagulation activity. **The most common laboratory abnormalities in this disorder are decreased platelet count, elevated prothrombin time and PTT, elevated D-dimer (a breakdown product of fibrin), and decreased fibrinogen** (120).

The primary treatment of DIC is aimed at controlling the underlying cause. **Typical treatment would include empiric antibiotic therapy, treatment of other conditions adversely affecting coagulation**, and **replacement with appropriate hemostatic factors** in patients with active bleeding. **Some of the controversial options**, such as anticoagulation, factor replacement, *epsilon aminocaproic acid* with *heparin*, and antiplatelet drugs, might also be considered.

Risks of Disease Transmission from Blood Products

Blood products have become much safer with the development of better screening techniques. The risk of hepatitis B transmission has become almost negligible, and most units are safe from hepatitis C transmission as well. The risk of human immunodeficiency virus (HIV) transmission in the United States is estimated at 1:500,000 to 1:1,000,000 units (121). Cytomegalovirus can still be a problem, although seroconverters are typically asymptomatic. The use of pooled products, such as platelets and plasma, increases the risks because multiple donors are required. **Autologous blood donation may be considered for elective surgery in certain situations.**

Thromboembolic

Detection of 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 (122).

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 (123). 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 that the use of a serum marker for coagulation chemistry, **D-dimer concentration, might help rule out thromboembolic disease** (124). 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. **The reference standard for the diagnosis of pulmonary embolism remains direct angiography of the pulmonary arteries**, although this test is rarely performed. The diagnosis of pulmonary embolism is typically made by combining clinical probability with various forms of noninvasive testing (125).

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.** Traditionally this has been prescribed

as unfractionated heparin in a large initial intravenous bolus, followed by a 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. More recently, several trials have shown that **treatment with *low-molecular-weight heparin* is equal to, if not better than, treatment with standard *unfractionated heparin*** (126).

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 INR of 2.0 to 3.0.

The optimal duration of oral anticoagulation for deep venous thrombosis and/or pulmonary embolism remains controversial, but in general, these medications are continued for at least 6 months. Recent studies have suggested the risk of recurrent thrombosis persists indefinitely, regardless of the precipitant (127). Many clinicians now consider lengthy or even lifelong treatment with anticoagulation.

Thrombolytic therapy can be considered in cases of pulmonary embolism with hypotension (128). Many postoperative patients, however, are at high risk for bleeding from lytic therapy, and this treatment should be carefully considered. If patients have active bleeding, or a high risk of bleeding and can not be anticoagulated, a filter should be inserted into the inferior vena cava (IVC) to prevent recurrent pulmonary emboli. A percutaneously placed filter into the IVC can also be used for those patients who develop recurrent pulmonary emboli despite adequate anticoagulation.

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 (129). Clinicians should be particularly alert to possible central venous catheter infections because many oncologic patients require these devices for treatment. Central venous catheter infection rates range up to 5% depending on the type of catheter inserted (130).

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 in the febrile neutropenic patient (131 ,132 and 133). **For 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** (132). This approach is as effective as intravenous therapy and is therefore the preferred approach to the management of these patients (133). If intravenous antibiotics are considered necessary, a broad-spectrum semisynthetic *penicillin*, sometimes combined with an aminoglycoside and *vancomycin*, may be used. **If febrile neutropenia persists despite several days of broad-spectrum antibiotics, recent guidelines suggest the addition of antifungal agents** (131). 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 the use of *granulocyte colony-stimulating factor (G-CSF)* can shorten the duration of neutropenia. G-CSF is sometimes prescribed expectantly during courses of chemotherapy, although this usage remains controversial in many treatment regimens (134).

Fungemia

Fungemia is a life-threatening postoperative complication of surgery and severe medical illness. Typical patients at risk include those receiving multiple antibiotics and hyperalimentation. Central venous access lines and Foley catheters can provide entry sites for fungal organisms. Additional important risk factors are cancer, chemotherapy, corticosteroids, and hyperglycemia (135 ,136). **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. There are now several antifungal agents available to treat invasive disease (137). Patients with localized fungal infections should be aggressively treated with topical agents.

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18
Nutritional Therapy

David Heber

With advances in our understanding of the metabolic effects of cancer on the host, the impact of nutritional support on the outcome and quality of life of the gynecologic oncology patient has been widely recognized. **Early and appropriate nutritional intervention may improve the patient's ability to undergo definitive oncologic therapy, including surgery, radiation, or chemotherapy.** In order to be able to institute appropriate care early enough to make a difference, an understanding of the classification of malnutrition and its diagnosis is essential.

- Malnutrition
- Nutritional Support

Malnutrition

Part of "18 - Nutritional Therapy "

About 40% to 55% of adult hospitalized patients are malnourished or at risk for malnutrition, and 12% are severely malnourished (1 ,2 ,3). A study of 67 consecutively hospitalized gynecologic oncology patients (3) found a 54% prevalence of malnutrition (95% confidence interval, 41%-66%).

Risk Factors

Predisposing conditions frequently found in malnourished hospitalized patients include:

- **Heart failure**
- **Chronic obstructive pulmonary disease**
- **Infection**
- **Gastrointestinal (GI) disorders**
- **Psychiatric disorders**
- **Renal insufficiency**
- **Malignancy**

It is typical for undernourished patients to have more than one predisposing condition(4).

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.

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.

Normal Body Metabolism

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 degree 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).

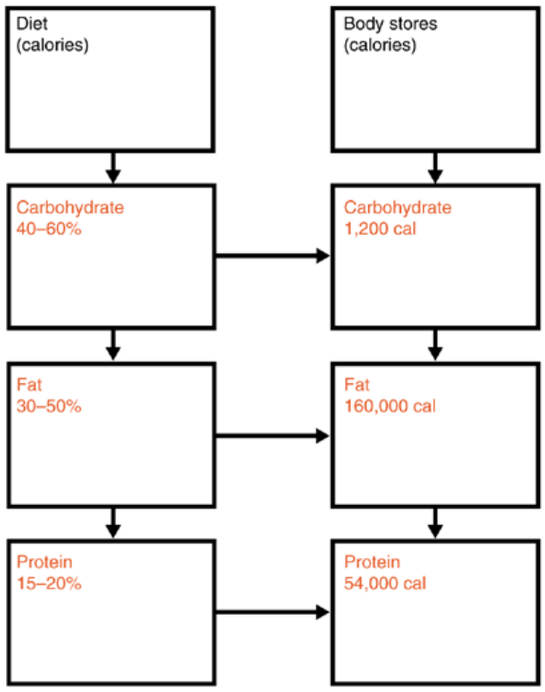

Figure 18.1 Body stores of energy versus dietary calories.

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.

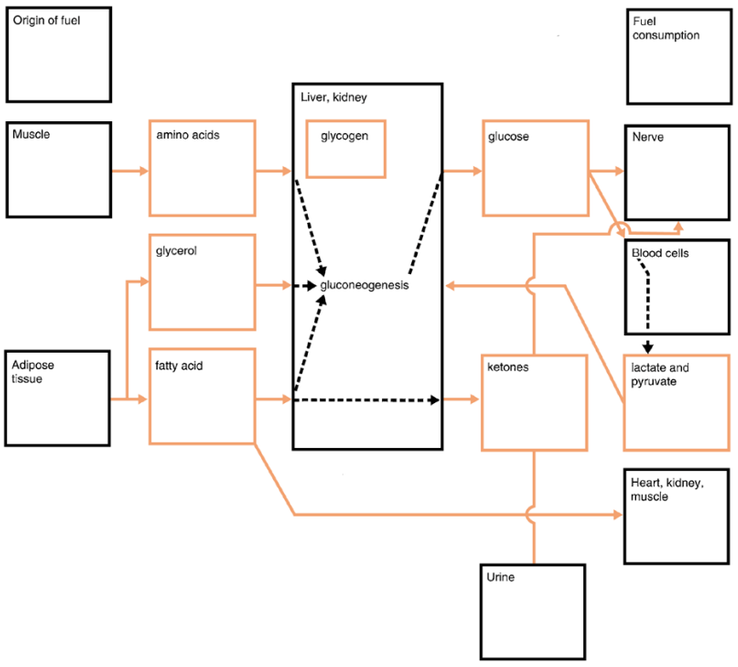

Figure 18.2 The metabolic adaptation to starvation.(Redrawn from **Cahill GF, Owen OE.** Some observations on carbohydrate metabolism in man. In: **Dickens F, Randle PJ, Whelan WJ, eds.** *Carbohydrate metabolism and its disorders.* New York: Academic Press, 1968:497, with permission.)

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:

$$\text{Ideal weight} = 100 \text{ lb for 5 ft} + 5 \text{ lb/inch} > 5 \text{ ft}$$

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.

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).

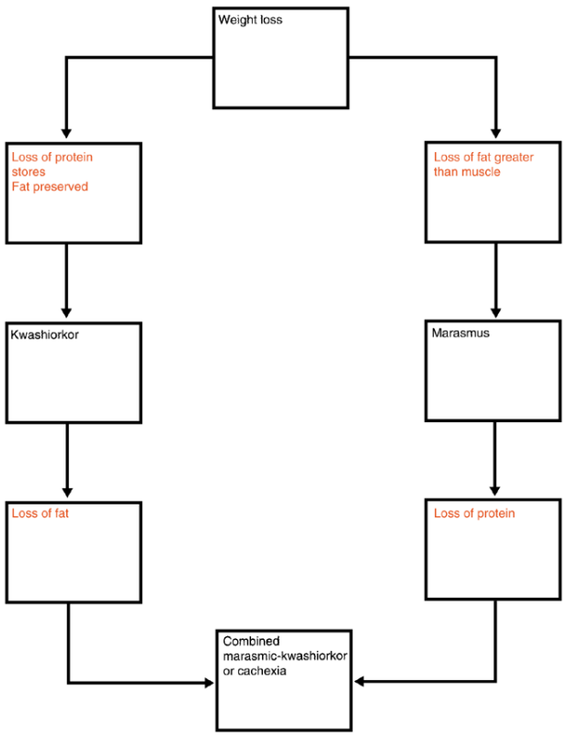

Figure 18.3 Classification of malnutrition.

***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:

- **Decrease in serum albumin** to less than 3.5 mg/dL
- **Decrease in absolute lymphocyte count** to less than 1,500/mm^3

- **Decrease in serum transferrin** to less than 150 mg/dL
- **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 c*ombined marasmic-kwashiorkor* or *mixed-form malnutrition of the adult*.

Infectious complications are more common in cachectic patients and often are fatal (8). 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 (9). 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 other-wise 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).

Table 18.1 Physical/Biochemical Markers of Malnutrition

	Marasmus	*Kwashiorkor*	*Cachexia*
Albumin	Normal	↓	↓
Transferrin	Normal	↓	↓
White blood cell count	Normal	↓	↓
Skin tests	Normal	Negative	Negative
Body weight	↓	Normal	↓
Body fat	↓	Normal	↓

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. 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 .

Table 18.2 Serum Half-Life of Circulating Proteins Decreased in Malnutrition

Protein	*Half-life*
Albumin	3–4 wk
Transferrin	1 wk
Thyroxine-binding prealbumin	2 days
Retinol-binding protein	10 hr

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:

- Depressed levels of complement components, including C3
- Reduced amounts of secretory immunoglobulin A in external body secretions
- Abnormal T-cell function
- Impairment of nonspecific defenses, including decreased epithelial integrity, decreased mucus production, and decreased ciliary motility

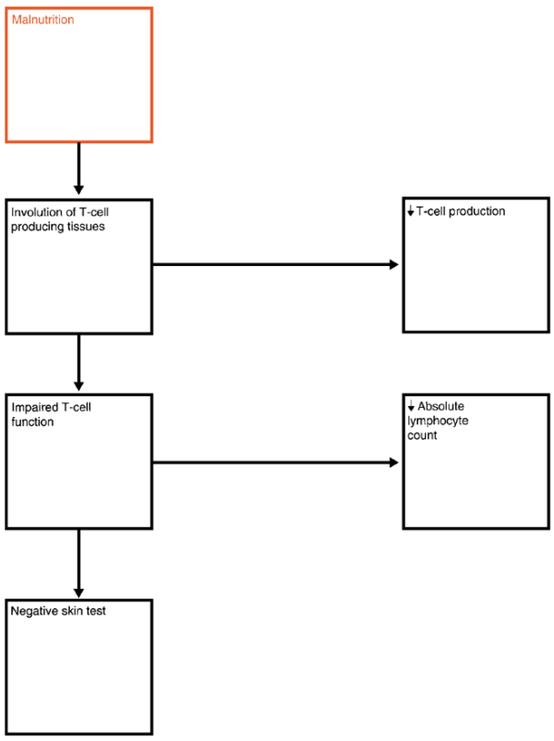

Figure 18.4 Immunologic alterations associated with malnutrition.

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:

- Processing of the antigen by macrophages resulting in the generation of both effector and memory T cells
- Recognition of antigen rechallenge resulting in blast transformation, cellular proliferation, and generation of lymphokine-producing effector cells
- 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:

- 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.
- 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.

Prognostic Nutritional Index The Prognostic Nutritional Index (PNI) combines anthropometric and laboratory tests to calculate a single index number. It is a linear predictive model of increased morbidity and mortality after surgical procedures, and uses serum albumin (A) in g/dL, triceps skin fold (TSF) in mm, serum transferrin (TFN) in mg/dL, and delayed hypersensitivity (DH) response (0–2), measured by leukocyte migration inhibition, transformation, and cytotoxicity tests. The formula is:

$$\mathbf{PNI\ \% = 158 - 16.6\ (A) - 0.78\ (TSF) - 0.2\ (TFN) - 5.8\ (DH)}$$

For example, a well-nourished patient with A = 4.8, TSF = 14, TFN = 250, and DH = 2 has a PNI of 158.0 - 152.2, or a 5.8% chance of complications. On the other hand, a malnourished patient with abnormal indexes (A = 2.8, TSF = 9, TFN = 180, and DH = 1) has a PNI of 158 - 95.3, or a 62.7% chance of complications. A PNI of < 40 is taken as well nourished, whereas a PNI of > 40 is taken as evidence of malnutrition. In one study of 76 gynecologic oncology patients, serum albumin could be substituted for PNI to detect malnutrition (3).

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. Many changes that occur in cancer patients are similar to those seen as a consequence of certain inflammatory diseases. In particular, **tumor necrosis factor (TNF), interleukins 1 and 6 (IL-1 and IL-6), and interferon-γ are possible etiologic agents of anorexia and cachexia** (15).

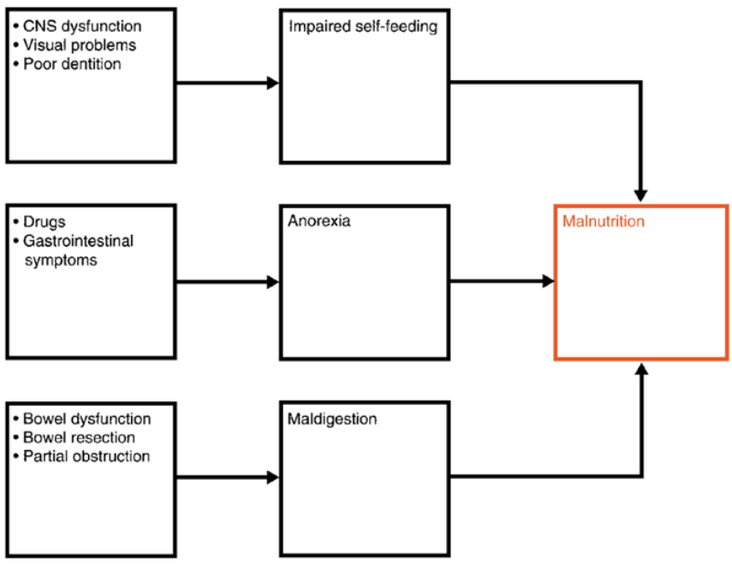

Figure 18.5 Impact of disease factors on nutrition.

Anorexia

Decreased appetite, or anorexia, is the major factor contributing to decreased intake in many disease processes. During tumor growth, anorexia and reduced food intake markedly contribute to the development of malnutrition. **Serotonin plays a key role in the control of appetite**, and there is evidence that administration of neutral amino acids can counteract anorexia mediated by increased tryptophan concentrations observed in cancer patients with anorexia (16).

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, diverticulae, 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 a disseminated intraabdominal malignancy such as ovarian cancer, anadynamic 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 (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 ,19). Specific metabolic disturbances and their consequences are presented in Table 18.3 .

Table 18.3 Metabolic Consequences of Cancer

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

Nutritional Support

Part of "18 - Nutritional Therapy "

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:

- The degree of prior malnutrition at the time of assessment
- 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:

- **If a patient is to be without nutrition for a period of 7 days, some form of nutritional support should be used.**
- **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.**

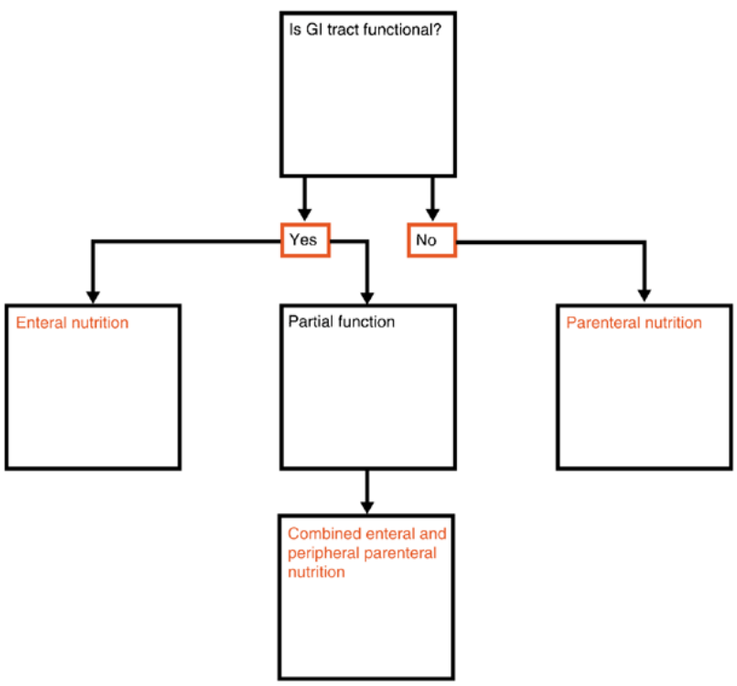

Figure 18.6 Parenteral versus enteral nutrition.

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:

- **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.
- **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.
- **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.
- **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.

TPN 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 per 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 metaanalysis 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 and organ metabolism, and the avoidance of overfeeding.** Metabolic costs of overfeeding include lipogenesis, gluconeogenesis, and thermogenesis. Excessive infusion rates and choice of the wrong mixture of macronutrients can be harmful in the critically ill patient (41).

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). **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:

- **Obese patients maintain their body weight when given only 25 kcal/kg actual body weight per day.**
- **Lean patients maintain their weight when given 35 kcal/kg/day.**
- 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:

$$\text{Nonprotein calories} = \frac{\text{Protein requirement} \times 150}{6.25}$$

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:

- 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.
- 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 g. Because protein = 4 kcal/g, the protein caloric need is 280 kcal.
- 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.
- 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.
- 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:

- 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).
- 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.
- The nonprotein caloric requirement thus equals approximately 1,785 kcal, which should include approximately 775 kcal fat and 1,010 kcal carbohydrate.
- 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.
- 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% × 2,000 kcal = 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 nutritional solutions are shown in Table 18.4 .

Table 18.4 Typical Parenteral Nutrition Solutions

Solution	*Na^+ (mEq/L)*	*K^+ (mEq/L)*	*Mg^{2+} (mEq/L)*	*Acetate (mEq/L)*	*Cl^- (mEq/L)*	*Protein (g/L)*	*Calories/L (D 20)[a]*
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	135	70	89	850
Travasol 3.5%	25	15	5	54	25	37	820

[a]If admixed with a solution of 20% dextrose.

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).

Table 18.5 Osmolarity and Caloric Content of Glucose and Lipids in Parenteral Nutritional Solutions

Glucose Concentration (wt/vol)	*Osmolarity (mOsm/L)*	*Calories (kcal/dL)*
5%	250	17
10%	500	34
20%	1,000	68
50%	2,500	170
Lipid Concentration (wt/vol)		
10%	280	110
20%	340	200

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 1 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).

Table 18.6 Guidelines for Daily Adult Parenteral Vitamin Supplementation

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
B_{12} (cobalamin)	5.0 mg
C (ascorbic acid)	100.0 mg
K	5.0 mg/wk[a]

[a] 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.

Major mineral requirements are listed inTable 18.7 . The daily requirement has a wide range that depends largely on the extent of GI and renal losses. In patients with an abnormally high excretion, the losses must be replaced aggressively.

Table 18.7 Range of Daily Requirements of Major Minerals and Electrolytes in Parenteral Solutions

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 mmol

Modified from**Alpers DH, Clouse RE, Stenson WF.** *Manual of nutritional therapeutics.* Boston: Little, Brown, 1983:238.

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.

Table 18.8 Suggested Daily Adult Intravenous Requirements of Essential Trace Elements and Associated Deficiency Syndromes

Trace Element	*Requirement*	*Deficiency Syndrome*
Iron	10–18 mg/day	Anemia
Copper[a]	30mg/kg/day	Rare hemolysis
Zinc[a]	15 mg/day	Blepharitis, conjunctivitis, growth retardation, dermatitis, diarrhea
Selenium[a]	50–200 mg/day	Cardiomyopathy
Chromium[a]	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[b]	200–500 µg/day	Muscle cramps

[a]Required in total parenteral nutrition solutions.

[b]Not absolutely required but included in most formulations.

Adapted from AMA Department of Foods and Nutrition. Guidelines for essential trace element preparations for parenteral use: a statement by an expert panel. *JAMA* 1979;241:2051–2054, with permission.

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

Jonathan S. Berek

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
- Incisions
- Intestinal Operations
- Urinary Tract Operations
- Reconstructive Operations

Central Lines

Part of "19 - Surgical Techniques "

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 ,2 ,3 ,4). The most frequently used veins are the subclavian and the jugular. **The brachial veins are used for peripherally inserted central catheters (PICC lines)** (5).

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 one most commonly employed 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.

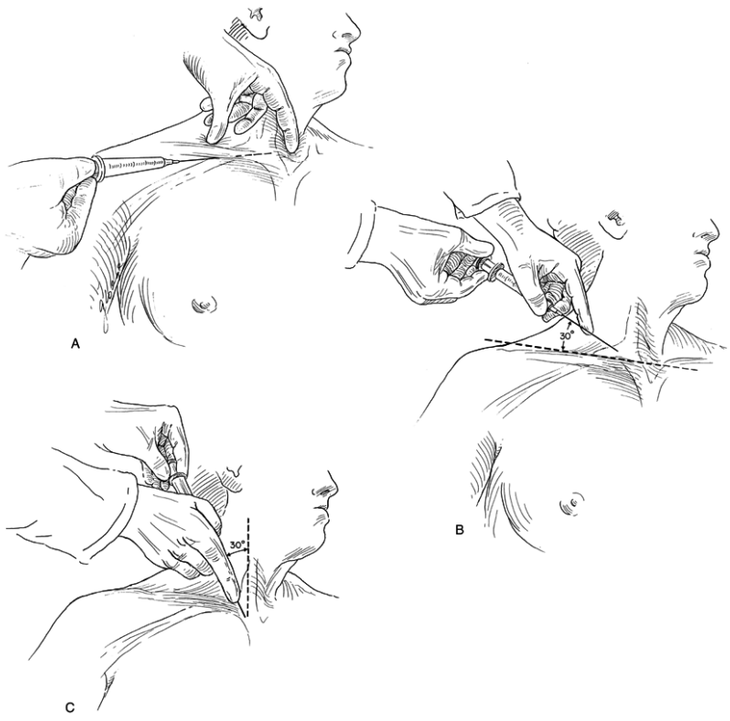

Figure 19.1 Central venous catheter insertion sites. The right subclavian and right internal jugular vein insertion sites are illustrated. The insertion sites for the subclavian venous catheter: **(A)** via the infraclavicular technique; **(B)** via the supraclavicular technique; **(C)** the site of insertion for the internal jugular vein. 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:

- The patient is placed in the supine position, with the foot of the bed elevated about 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 within the subclavian vein. The patient's head should be tilted away from the site of insertion so that the landmarks can be identified easily.
- After careful skin preparation with *povidone-iodine* solution, **the skin and subjacent tissues are anesthetized** by means of *lidocaine* without *epinephrine*.
- 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.
- 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.
- **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.
- **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.
- The syringe is pulled gently to apply suction as the needle is inserted. **The patient should exhale during insertion to avoid an air embolus.**
- 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.
- **While the needle is in place, the catheter should not be withdrawn** because the tip can be sheared off and embolize.
- **The end of the catheter is connected to an intravenous set**, and the catheter is sutured to the skin.
- **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, as this 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 about 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 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 about 1% to 2% (1 ,2 ,3 ,4). 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 about 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 with 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 midsternal notch. The angle of insertion is about 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 the use of the jugular veins, either the internal or external vein. **Jugular venous catheterization is frequently the method of choice when the catheter is inserted intraoperatively and the catheter 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 Figure 19.1C .

The technique for insertion is as follows:

- **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.
- The angle of insertion is about 20 to 30 degrees from the sagittal median of the patient, and the direction is toward the heart.
- As with subclavian catheterization, the use of a probe needle will help to localize the appropriate vessel.
- **The technique of catheter placement is the same as described above for the subclavian catheter.** However, the length of catheter that must be inserted is less, as the distance to the proper location in the superior vena cava is less.
- **The position of the line inserted intraoperatively 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 ,3).

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 employed 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.

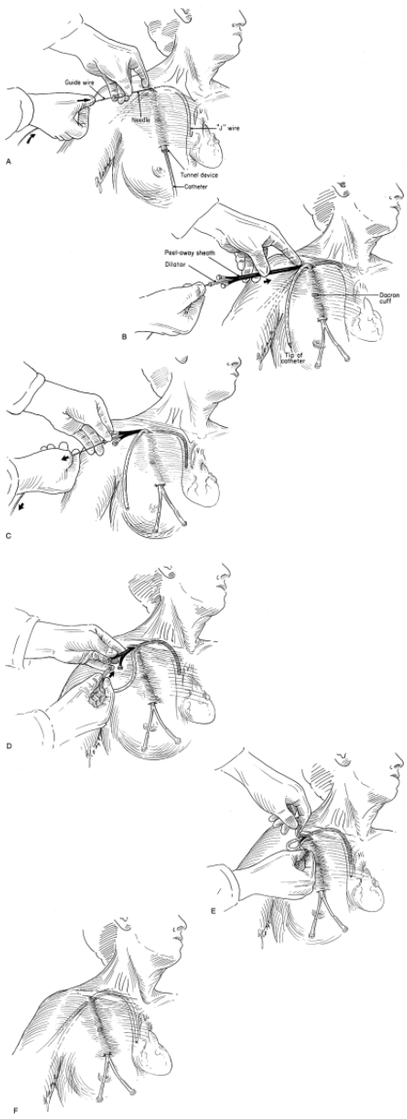

Figure 19.2 Semipermanent catheter insertion. The technique for insertion of the semipermanent (e.g., Hickman) catheter. **A:** A needle is inserted into the right subclavian vein, a guide wire is inserted through the needle, and the needle is withdrawn. **B:** The Cook introducer then is inserted over the guide wire. **C:** After the introducer with its outer sheath is in place in the right subclavian vein, the wire is withdrawn. **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 tunneled in the subcutaneous tissue under the skin of the right side of the chest, and the free end is exteriorized.

The technique is as follows:

- After the patient has been properly positioned and the anterior chest and clavicular areas prepared, **the subclavian vein is identified in the manner described above.**
- 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).
- 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).
- 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).
- After the semipermanent catheter has been inserted, **the outer sheath is peeled away**, leaving the catheter in place (Fig. 19.2E).
- **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 19.2F).
- **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, and is called the peripherally inserted central catheter or PICC line (5). 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. **The PICC line may be more desirable than a totally implantable line when short-term use is contemplated, e.g., 3 to 4 months.**

This approach is less durable than the centrally inserted catheters and somewhat more cumbersome because of the location of the insertion site. However, **its main advantage 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. Alternately, 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**. This dialysis catheter is designed to minimize the risk of infection, even though

it is left in place many months (6). 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.

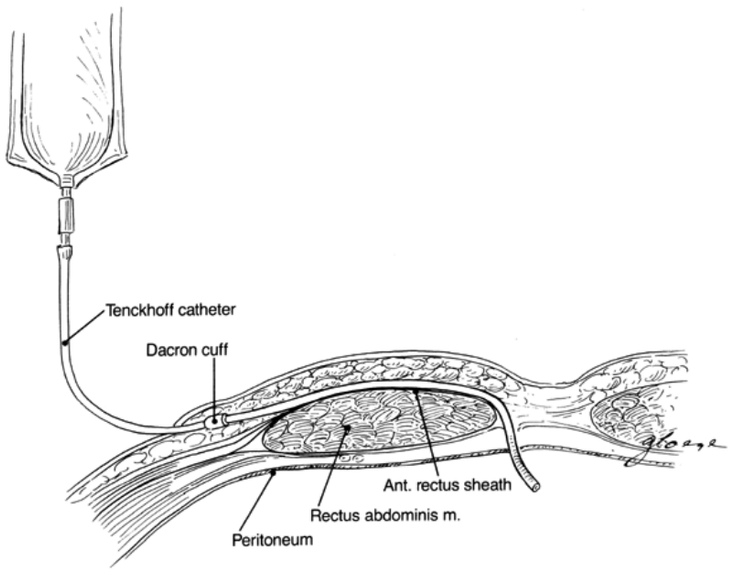

Figure 19.3 Tenckhoff peritoneal catheter. The placement of the Tenckhoff catheter into the peritoneal cavity is illustrated.

An alternative peritoneal access catheter is the Port-A-Cath, 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.

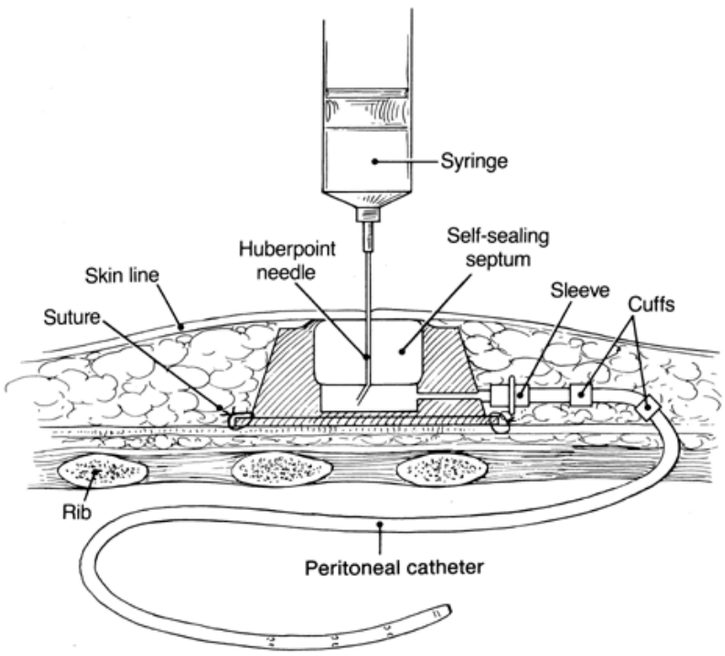

Figure 19.4 Port-a-Cath peritoneal catheter. The totally implantable peritoneal access catheter is tunneled through the subcutaneous tissues into the peritoneal cavity.

The most common problem associated with the 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; i.e., fluid will flow in but will not flow out. Minor infections can be treated with antibiotics, and low-grade peritonitis can be treated by the instillation of antibiotics directly via the catheter. **For persistent and severe infections, the peritoneal catheter may require removal.**

Incisions

Part of "19 - Surgical Techniques "

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 preoperatively. 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 for 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 when compared with all other incisions. The wound

disruption rate is about 0.1% to 0.65% (7 ,8 ,9 ,10 ,11 ,12), 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 (9). The majority of wound dehiscences are associated with wound infection or poor closure technique. **The occurrence of ventral hernia is associated with wound disruption secondary to infection and is more common in patients with malignancy** (12). The use of prosthetic meshes for herniorraphy can significantly reduce the rate of recurrence of hernia.

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 employed. **The advantage of this incision is that it is more cosmetic, is generally 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, i.e., 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 (7 ,8 ,9 ,10 ,11 ,12). 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** (7). 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 (13 ,14 ,15 ,16 ,17 ,18).

Internal Retention Suture

The Smead-Jones, or internal retention, technique uses interrupted sutures that are placed as illustrated in Figure 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 2.0 cm from the fascial edge and not more than 1 cm apart (7). **The disruption rate for midline incisions closed with this technique should be less than 0.2%**.

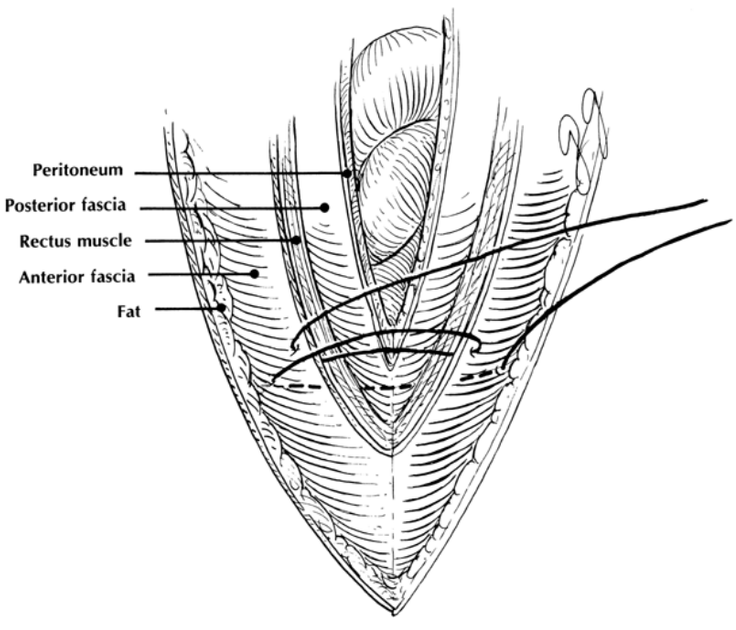

Figure 19.5 Internal retention abdominal closure. The "Smead Jones" far-far, near-near closure.

Suture Material

The choice of suture should be dictated by the circumstances (13 ,14 ,15 ,16 ,17 ,18). 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 monofilament polyglyconate suture (*Maxon*) or monofilament polydioxanone (*PDS*) (15). Braided, polyglycolic acid (*PGA*) 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 to 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 (18).

External Retention Suture

Retention sutures that are external 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, patients who have a major wound infection, and patients 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 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 cancer patients generally 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, e.g., 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

Part of "19 - Surgical Techniques "

Preoperative Intestinal Preparation

If bowel resection is planned or contemplated, a thorough mechanical and antibiotic “bowel preparation” should be undertaken preoperatively. **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 the cases** (16). 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 . There is controversy regarding the optimal “bowel prep,” as it is uncertain whether, in addition to the mechanical preparation, the antibiotic preparation is necessary (19). However, we prefer to use preoperative intravenous antibiotics along with a mechanical preparation. Before laparotomy for small intestinal obstruction caused by ovarian cancer, it is useful to insert a nasogastric (NG) tube for 24 to 48 hours preoperatively to avoid the possibility of vomiting and aspiration (20).

Table 19.1 Intestinal Preparation

Preoperative Day 2 Clear liquid diet
Preoperative Day 1 Clear liquid diet
Mechanical Prep
Fleet Phospho-Soda Saline Laxative (3 oz. bottle) (one bottle of laxative 1 p.m. and another at 7 p.m.) Fleet enemas until no solid stool in p.m. (Optional)
Antibiotic Prep (Optional)
Neomycin (oral), 1 g q 4 h for three doses (4, 8, 12 p.m.) *Erythromycin* (oral), 1 g q 4 h for three doses
Day of Surgery Fleet enemas until clear (Optional)

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 materials most commonly employed for this purpose are silk or PGA (*Vicryl* or *Dexon*). **The direction of closure should be perpendicular to the lumen of the bowel to minimize the potential for lumenal stricture** (Fig. 19.6).

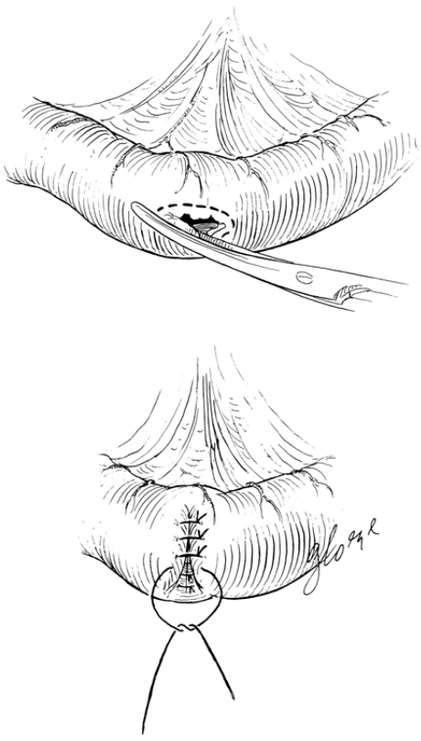

Figure 19.6 Closure of an intestinal enterotomy. A: The edges of the enterotomy are trimmed. **B:** The enterotomy is closed perpendicular to the lumen in two layers.

With small defects (i.e., <5–6 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 Witzel and the Stamm gastrostomies (20).

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 or PGA 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 or PGA. 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.

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 employed 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. A 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 employed 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 or PGA suture, 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.

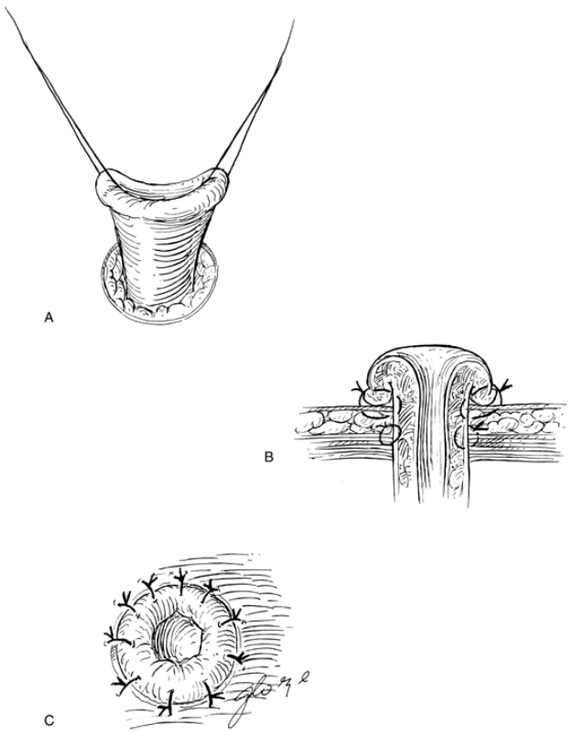

Figure 19.7 The formation of a colostomy. A: The end of the colon is brought through the abdominal wall. **B:** It is sutured to the fascia and skin. **C**: The "rosebud" stoma is formed.

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), a double-barrel 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**.

Major Intestinal Operations

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 (20 ,21 ,22 ,23 ,24 ,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, i.e., a segment of bowel created to improve low colonic continence (26 ,27 ,28 ,29 ,30 ,31 ,32 ,33 ,34 ,35 ,36 ,37). 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 PGA sutures (*Vicryl* or *Dexon*) (Fig. 19.8B). The clamps are removed, the devitalized ends are trimmed, and an inner continuous full-thickness layer of 3-0 silk or PGA suture 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 PGA sutures (Fig. 19.8D). The defect in the intestinal mesentery is repaired.

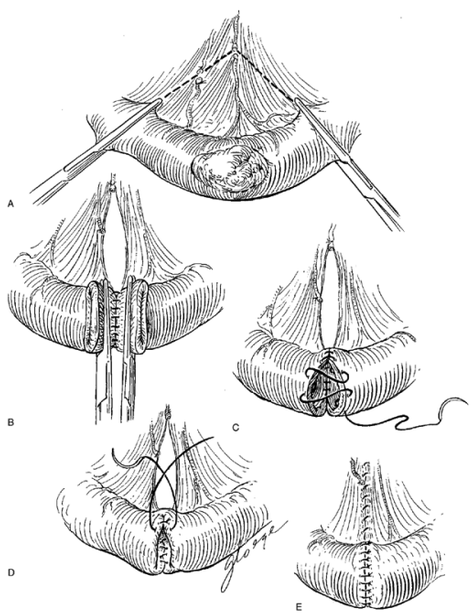

Figure 19.8 Hand-sewn end-to-end enteroenterostomy. A: The tumor and bowel are resected along with the mesentery. **B:** The posterior seromuscular layer is sutured. **C:** The Connell stitch is placed. **D:** The anterior seromuscular layer is placed. **E:** The completed anastomosis.

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 (24).

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, e.g., 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 PGA sutures is placed with interrupted Lembert sutures, and the lumina are created. An inner layer of continuous, full-thickness 3-0 PGA 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 PGA sutures.

Intestinal Staplers

The principal advantage of the gastrointestinal staplers is the speed with which they can be employed. There is no increase in the complication rate with the use of staplers as compared with hand-sewn anastomoses (20 ,21 ,22 ,23 ,24 ,25). 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. 19.9A–C).

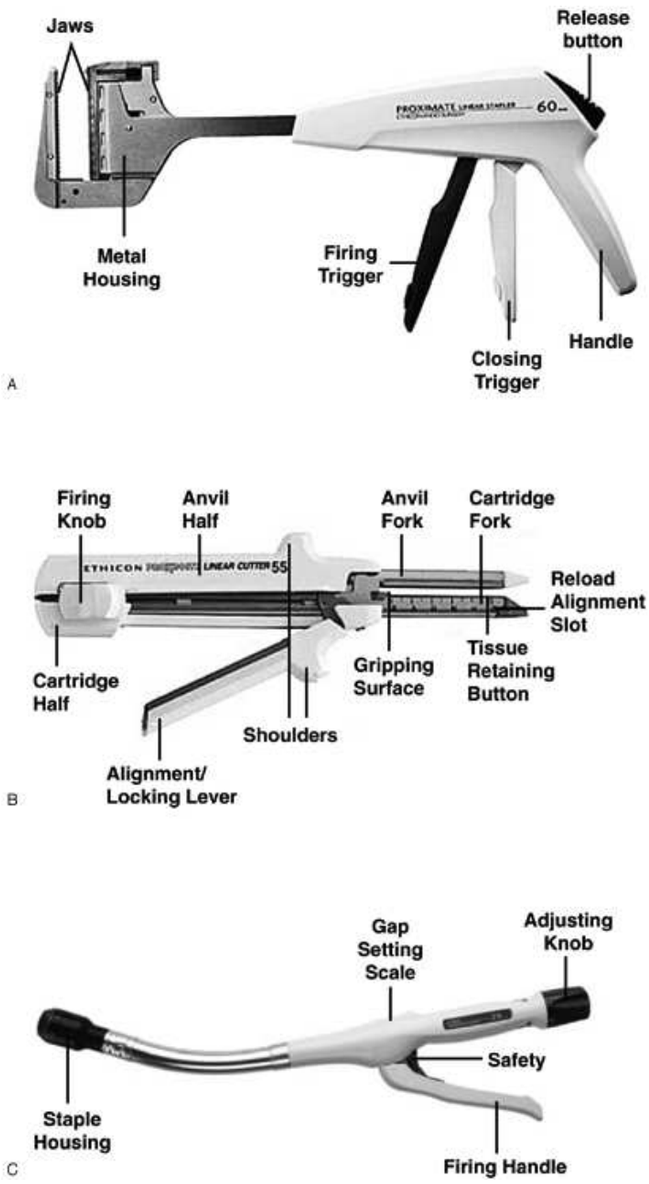

Figure 19.9 Stapling devices for intestinal anastomosis. The single-use staplers: **(A)** thoracoabdominal (TA); **(B)** gastrointestinal anastomosis (GIA); **(C)** end-to-end anastomosis (EEA).

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. A TA device is available with a flexible, rotating end, called a Roticulator-55, that can be adjusted for placement into narrow areas (e.g., the deep pelvis).

Gastrointestinal Anastomosis Stapler The gastrointestinal anastomosis (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 Figure 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.

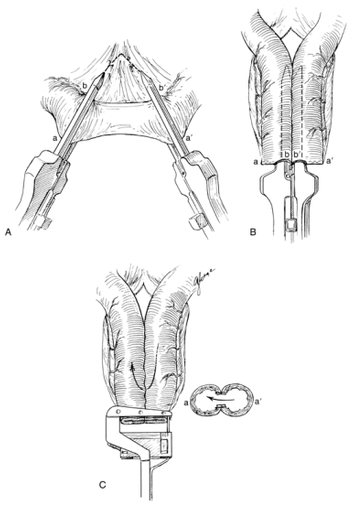

Figure 19.10 Functional end-to-end anastomosis using the stapling technique. A: The gastrointestinal anastomosis (GIA) stapler is used to resect the intestine. **B:** The segments of the transected intestine are placed side to side, and each antimesenteric corner is incised to create two holes into which 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 (20).

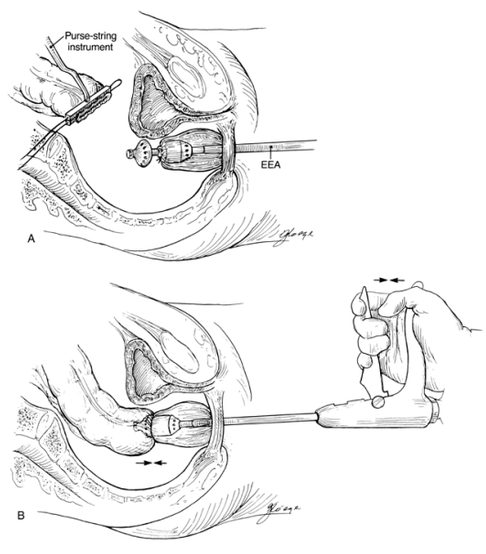

Figure 19.11 Low colonic end-to-end anastomosis using the end-to-end anastomosis (EEA) stapler. A: After resection of the rectosigmoid colon, the distal end of the descending colon is mobilized and a pursestring suture is placed by hand or with a special instrument (illustrated). A pursestring suture 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, which 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. 19.12A–D). **Studies comparing the colonic J-pouch with 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** (22 ,36). 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 about 5 centimeters in length (28).

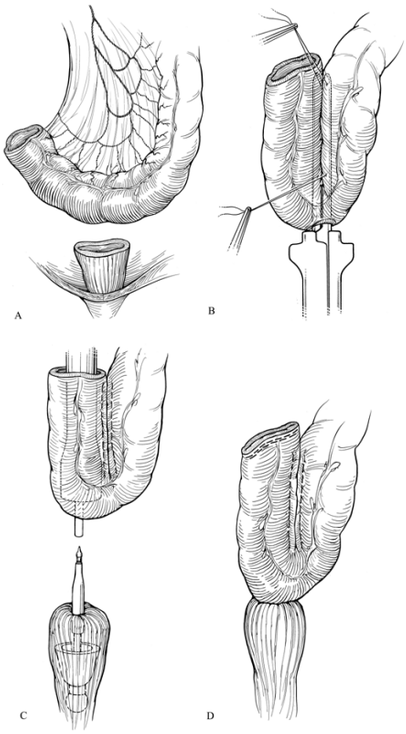

Figure 19.12 Low colonic end-to-side anastomosis (EEA) to create a J-pouch. A: The end-to-side anastomosis allows the mesocolon to be preserved and to cover the sacral hollow. **B:** The terminal end of the colon has the J-pouch created by stapling a loop side-to-side using a gastrointestinal anastomosis (GIA) stapler. **C:** The EEA devise is then inserted into the rectal stump and anastomosed 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 side to side with a GIA stapler (Figure 19.12A). The pouch is then anastomosed to the rectal stump using an end-to-side technique with an EEA stapler (Figure 19.12B) and by detaching the anvil, which is inserted in the proximal colon segment (Figure 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. Then the rod is inserted through or near the staple line. In the other segment of bowel, a pursestring suture is placed, and the free anvil is inserted within the lumen of the bowel within the pursestring suture (Figure 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 technique (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 about 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).

Low Colonic Coloplasty

A newer form of colorectal anastomosis is the coloplasty (see Chapter 21), which may have advantages over the colonic J-pouch for patients undergoing pelvic exenteration.

The principal advantage is that this technique may be easier to perform in a narrow pelvis, such as in those patients undergoing a pelvic exenteration and simultaneous creation of a neovagina. In a randomized study of the three techniques, patients undergoing the coloplasty and colonic J-pouch had significantly more favorable compliance, reservoir volume, and fewer bowel movements per day than those having a straight anastomosis (37).

The technique of coloplasty (Fig. 19.13) is illustrated. The lower part of the proximal colon is incised longitudinally and then reapproximated in the transverse direction (Fig. 19.13A). In this manner, a small, simple reservoir is created. The EEA stapler is used and then closed to create the anastomosis just as with the other techniques outlined above (Fig. 19.13B).

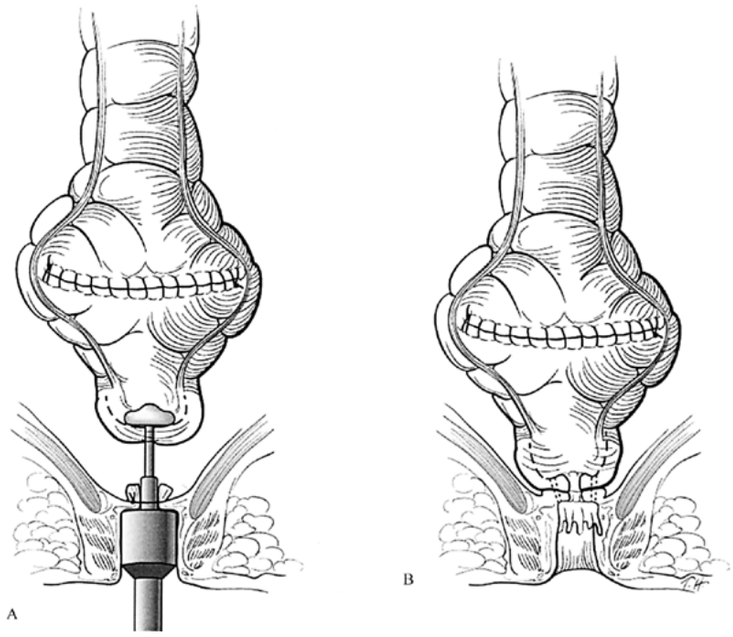

Figure 19.13 Low colonic coloplasty. A: The distal colon is incised in the longitudinal direction and resutured in the transverse direction to create a widening of the portion of the colon to be anastomosed to the rectum. **B:** The rectum is anastomosed to the distal colon using the end-to-end anastomosis (EEA).

Postoperative Care

After resection of the small bowel, a nasogastric tube is usually placed for about 24 to 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 or stool. Oral feeding can begin as patients develop an appetite, and **early feeding has been shown to be safe following both small and large bowel resection** (38 ,39 ,40). In patients who have undergone colonic resection and reanastomosis, enemas and cathartics should be avoided (37).

Intravenous fluids must be continued while the patient is receiving nil 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

Part of "19 - Surgical Techniques "

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 (41 ,42 ,43 ,44). Renal function and ureteric patency must be assessed preoperatively.

Cystoscopy

Cystoscopy should be performed as part of the staging for cervical and vaginal cancers unless the disease has been diagnosed early (41). 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. About 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 of the temporary disruption of bladder innervation that 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 (41). 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 18F 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:

- 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.
- The tip of the catheter is inserted into the bladder, and a seromuscular purse-string suture is placed around the defect with 3-0 PGA sutures.
- A second reinforcing layer consisting of either 2-0 absorbable braided PGA suture is placed in the bladder.
- With the Foley balloon distended, the catheter is pulled up so that the bladder is applied snugly to the anterior abdominal wall.
- The catheter can be attached to a urinary drainage bag, and it can also be attached 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** (42).

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 (41). 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 7F to 9F 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, as **this procedure has the risk of ureteral perforation.** When the stent does not pass readily, the 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 hyelonephrosis), **a computed tomography urogram should be performed if the serum creatinine value is less than 2.0 mg/dL**; 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 by either reanastomosis or reimplantation**.

Mild degrees of hydroureter are managed by bladder drainage alone in most patients, as these problems are usually temporary and resolve gradually as the 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 minimizing the collection of fluid in the retroperitoneal space by leaving the pelvic peritoneum open.

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 (41 ,42 ,43). 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 will stent 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 (42). 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 allow removal of 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 will have to 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 (44). Interrupted 4-0 absorbable PGA sutures are placed at close intervals in a circumferential fashion (Fig. 19.14). After several weeks, the absence of leakage can be established by means of intravenous pyelography, and the stent can be removed through a cystoscope.

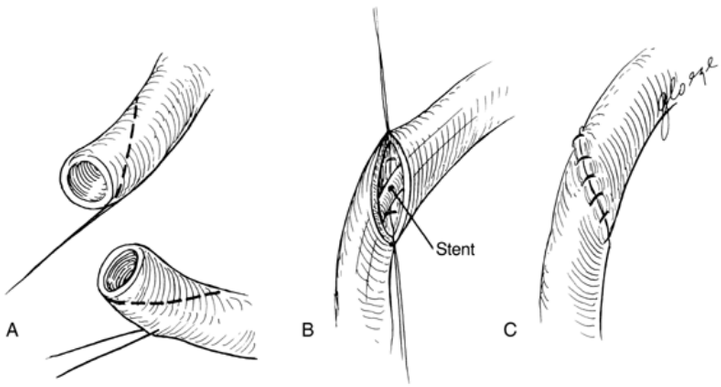

Figure 19.14 Ureteroureterostomy. A: The two ends of the ureters are cut diagonally. **B:** A ureteral stent is inserted into the proximal and distal ureter, and interrupted full-thickness sutures are placed. **C:** The completed anastomosis.

Ureteroneocystostomy

The reimplantation of the distal ureter into the bladder is known as the **Leadbetter procedure, or ureteroneocystostomy** (44). 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. Integral to successful ureteral reimplantation is the creation of a submucosal tunnel (Fig. 19.15). The tunnel minimizes the risk of vesicoureteral reflux and chronic, recurrent pyelonephritis (44).

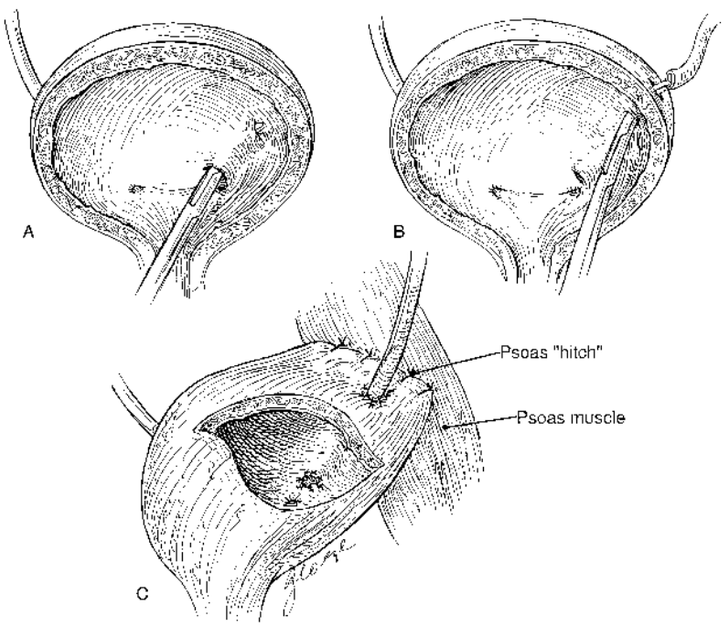

Figure 19.15 Ureteroneocystostomy. A: A submucosal tunnel is created. **B:** The ureter is brought into the bladder. **C:** The ureter is passed through the tunnel and sutured to the bladder serosa and mucosa. The serosa of the bladder is sutured to the psoas muscle to stabilize the anastomosis.

The technique is as follows:

- **The distal ureter is prepared by careful resection of any devitalized tissue** while the maximum length is preserved.
- **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.

- **A cystotomy is made, and a 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.
- **The ureter is gently pulled through the submucosal tunnel, and mucosa-to-mucosa stitches are placed with interrupted 4-0 PGA 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 PGA.
- **A suprapubic cystostomy is performed, and the cystotomy 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.

Transureter-oureterostomy

Another procedure that can be useful in the carefully selected patient is the transureteroureterostomy (TUU). When the distal ureter must be resected on one side, and the proximal ureter is too short to permit ureteroneocystostomy, it is possible to anastomose the distal

end of the resected ureter into the contralateral side (45). The distal end of the partially resected ureter is tunneled under the mesentery of the sigmoid colon and approximated, end to side, to the recipient ureter. A ureteral stent is used to protect the anastomosis and is left in place for at least 7 to 10 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 pelvic irradiation. The most common fistula is ureterovaginal.

Urinary Conduit

The most frequently employed techniques for urinary diversion are the creation of an **ileal conduit** (the **"Bricker procedure"**) (46), the creation of a **transverse colon conduit** (47), and the creation of a **"continent" urinary conduit** (e.g., the Koch, Miami, Indiana, or Mainz pouch) (48 ,49 ,50 ,51 ,52 ,53 ,54 ,55 ,56 ,57 ,58 ,59 ,60). 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.

The continent urinary conduit may be helpful for gynecologic oncology patients who require exenterative surgery. The first such conduit was the **continent ileal conduit (or "Koch pouch").** It requires a longer portion of the ileum (up to 100 cm), a longer operative time (4 to 6 hours), and greater technical skills for the creation of the continence mechanism. It is now rarely performed (48).

The **continent colon conduit** utilizes the intestine from the terminal ileum to the midportion of the transverse colon and has been popularized in Indiana, Miami, and Mainz. These pouches are technically somewhat easier to perform than the Koch pouch. The type of continent conduit created is generally determined by the training and preference of the surgeon (49 ,50 ,51 ,52 ,53 ,54 ,55 ,56 ,57).

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 about 30 to 40 cm proximal to the ileocecal junction. The conduit requires a segment of ileum measuring approximately 20 cm and its associated mesentery (46). After isolation of the segment, the ileum is reanastomosed (Fig. 19.16). 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 employed for the ureteric stent, as it is relatively atraumatic. The "butt" end of the conduit is sutured to the area of the sacral promontory.

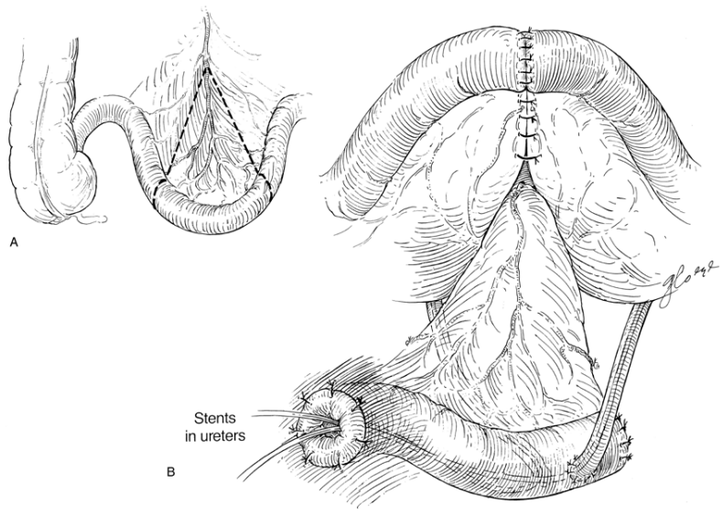

Figure 19.16 Ileal urinary conduit. A: A segment of nonirradiated ileum is used for the conduit. **B:** The ileum is reanastomosed, and the ureters are sewn into the "butt" end of the conduit. Note that ureters are stented individually.

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 about 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 continent Miami or Indiana pouch (49 ,50 ,51 ,52 ,53 ,54 ,55) involves resection of the intestine from the last 10 to 15 cm of ileum to the midportion of the transverse colon. The colon is opened along the antimesenteric border through the teniae coli (Fig. 19.17A). The ileum is used to create the continence mechanism (Fig. 19.17B). The ileal-cecal 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. 19.17C). 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. 19.17D).

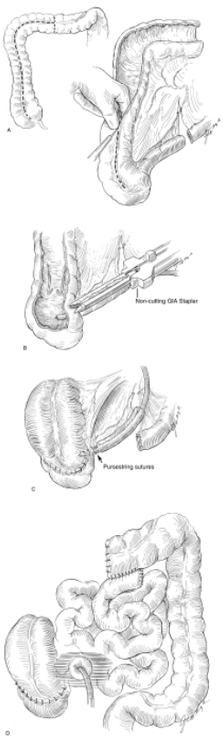

Figure 19.17 Colon continent urinary conduit: the "Miami" pouch. A: The segment of distal ileum and ascending and transverse colon is isolated, and the segment is opened on its antimesenteric border along the teniae coli. **B:** The ureters are reimplanted into the mesenteric side of the ascending colon, a continence mechanism is created with pursestring sutures near the ileal-cecal junction, and a non-cutting double staple line is performed with a gastrointestinal anastomosis (GIA) stapler. **C:** The conduit is closed with running sutures, and the ileal stoma is created. **D:** The intestines are reconstituted with an ileal-transverse colon anastomosis.

Skin Ureterostomy

In rare instances, a terminally ill patient undergoing exploratory surgery will have 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 (41).

Reconstructive Operations

Part of "19 - Surgical Techniques "

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 (see Chapter 21). 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 employed in the performance of these reconstructive operations and the techniques necessary to accomplish them (61).

Grafts

Grafts used for reconstructive operations in the pelvis are either **skin grafts**, which can be **full or partial (split) thickness** (61 ,62 ,63 ,64 ,65), 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 (66 ,67 ,68 ,69 ,70 ,71 ,72 ,73 ,74 ,75 ,76 ,77 ,78 ,79 ,80 ,81 ,82 ,83 ,84 ,85). 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 (61). 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 preoperatively 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 and the Padgett hand-driven dermatome. The surgeon should select the instrument with which he or she has the greatest facility, as an equally good graft can be harvested with either one.

The technique for obtaining the skin graft is as follows:

- 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.
- When using the dermatome, the surgeon must apply firm, steady pressure in order 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.
- 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.
- The harvested graft is kept moist in saline solution while the recipient site is being prepared.
- 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 (61 ,62 ,63 ,64 ,65 ,66 ,67). 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” (a “rhomboid flap”), or a myocutaneous graft, e.g., a rectus abdominis or gracilis.

Before harvesting a pedicle graft, the surgeon should carefully outline the incisions on the skin with a marker pen. During the 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 (62).

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 (62 ,63 ,64 ,65). 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. 19.18A). 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. 19.18B).

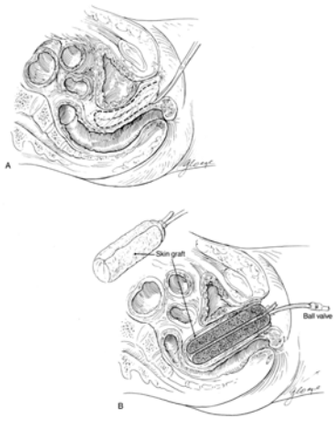

Figure 19.18 Creation of neovagina after radiation. A: The vaginal scar is resected in preparation for vaginal reconstruction with split-thickness skin grafts. **B:** A Heyer-Schulte vaginal stent has the skin graft placed around it, and this is inserted into the pelvic space to create a neovagina.

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 below. 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. 19.19A). 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 graft(s) are harvested, sewn over a vaginal stent, and inserted into the newly created pelvic space (Fig. 19.19B).

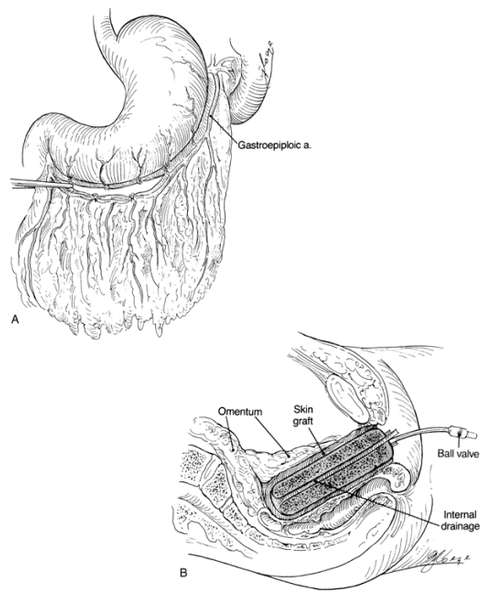

Figure 19.19 Mobilization of the omentum. A: This is accomplished by ligating and dividing the right gastroepiploic artery and the short gastric arteries along the greater curvature of the stomach. **B:** The omentum is used to create a “pocket” for the placement of a split-thickness skin graft.

Transpelvic Rectus Abdominis Myocutaneous Pedicle (TRAM Flaps) Grafts

A single rectus abdominis pedicle graft can be used to create a neovagina (66 ,67 ,68 ,69 ,70 ,71 ,72), or to repair a pelvic or perineal defect (70 ,71). This is our preferred technique for creation of a neovagina performed simultaneously with a pelvic exenteration (Fig. 19.20). The technique is relatively straightforward and has the advantage of a single pedicle harvested from the same site of 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 needed for the gracilis myocutaneous pedicle graft. The disadvantage is that the amount of tissue mobilized from the anterior abdominal 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.

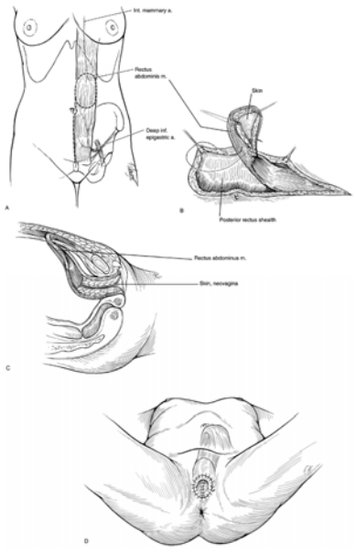

Figure 19.20 The transpelvic rectus abdominis myocutaneous (TRAM flap) pedicle graft. A: The location of the myocutaneous pedicle flap of the rectus abdominis muscle. **B:** The pedicle is harvested, and the tubular neovagina is created by suturing the full-thickness of the muscle, subcutaneous tissue, 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. **D:** The final result is a neovagina that also helps to protect the pelvic floor from intestinal adhesions.

The pedicle location is shown in Figure 19.19A . The oval-shaped pedicle should measure approximately 6 to 8 by 10 centimeters. The skin of the pedicle is incised, and the cephalad portion of the rectus abdominis muscle and attached myofascial tissues are transsected (Fig. 19.20B). 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. 19.20C). The pedicle graft is then sutured to the preserved vaginal introitus to complete the procedure (Fig. 19.20D).

Gracilis Myocutaneous Pedicle Grafts

Bilateral gracilis myocutaneous pedicle grafts can be used to construct a neovagina (61 ,62 ,76 ,77). In addition, the grafts provide excellent support for the pelvic viscera. The gracilis myocutaneous graft is harvested (Fig. 19.21A) from the inner aspect of the thigh.

A line is drawn from the pubic tubercle to the medial epicondyle, and this delineates the anterior margin of the graft. The graft should be about 5 cm wide and about 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. 19.21B). **The vascular pedicle is proximal, and it must be carefully identified and preserved**.

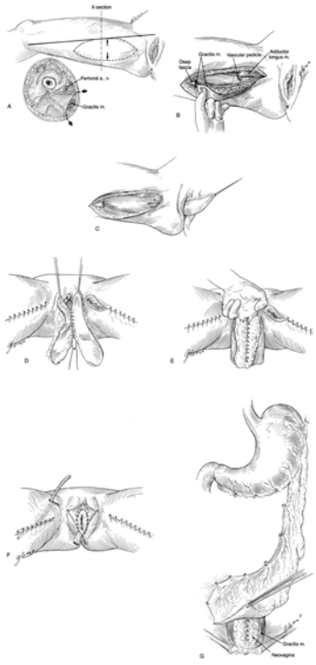

Figure 19.21 The gracilis myocutaneous pedicle graft. A: The pedicle graft is outlined on the inner thigh overlying the gracilis muscle. **B:** The myocutaneous pedicle graft is mobilized. **C:** The pedicle is brought under the skin bridge of the vulva. **D,E:** The two grafts are sutured together. **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, 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. 19.21C). The two grafts are sutured together to create a hollow neovagina (Fig. 19.21D, E). The entire neovagina is placed into the pelvis by posterior

and upward rotation and sutured to the introitus (Fig. 19.21F). 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. 19.21G).

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 (78 ,79). 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.

Colonic Segment

Some authors have preferred to use a segment of colon to create a neovagina (61 ,80). 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 (81 ,82 ,83 ,84 ,85 ,86). 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** (81). The technique (Fig. 19.22) involves the repositioning of a rhomboid flap of full-thickness skin and subcutaneous tissue. Use of these pedicle grafts will usually allow for the 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.

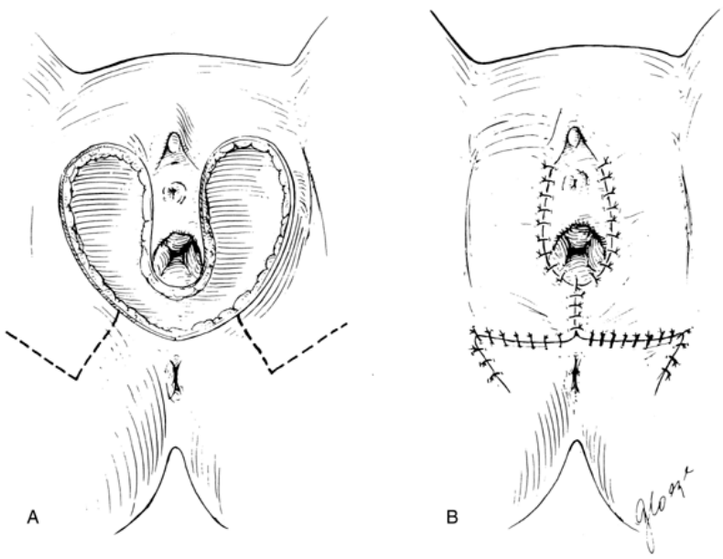

Figure 19.22 A: The "rhomboid flap" is used to close a posterior vulvar defect. **B:** The pedicle grafts are bilateral "Z-plasties" that are sutured together in the midline.

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 (82). 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. The length of the proposed flaps 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 about 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 in order 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 (84 ,85). This approach might be particularly useful for very large defects, such as for 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 above, there is occasionally a need to perform a vulvovaginoplasty, the so-called **William's procedure.** This procedure (86) 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 (87 ,88). All areas that can be directly peritonealized should be carefully covered with peritoneal pedicle grafts.

Synthetic grafts using **Marlex** 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** may be the best alternative (89 ,90).

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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 performing the procedures and the need to perform pelvic and/or paraaortic lymphadenectomy to stage several gynecologic malignancies.

Laparoscopic Pelvic and Paraaortic Lymphadenectomy

Part of "20 - Laparoscopy "

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 (2)

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. (3) 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**.

Querleu et al. (4) performed transperitoneal laparoscopic pelvic lymphadenectomy on 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 lymphadenectomy because of obesity. Paraaortic lymphadenectomy was 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 a radical hysterectomy 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 lymphadenectomy 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. All of the positive lymph nodes were identified and removed using the laparoscope. All complications were related to the hysterectomy and included transfusion in three patients and cellulitis in one patient. Laparoscopy added significantly to the combined operative time, which averaged 6 hours and 13 minutes. Querleu et al. (4), Childers et al. (5 , 6) and Fowler et al. (7) all used laparotomy to confirm

the accuracy of lymphadenectomy, and in each report, all positive lymph nodes were identified.

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 three**. The **operating time** for the six patients who underwent a bilateral paraaortic lymphadenectomy **ranged from 25 to 70 minutes**, and hospital stay for the 33 patients undergoing laparoscopic lymphadenectomy was 1.3 days. There was **one vena caval injury** that required transfusion and laparotomy, a complication rate comparable with that of open surgery.

In 1994, Querleu and LeBlanc (9) described a laparoscoic 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 average operative time of 111 minutes, postoperative stay of 2.8 days, and blood loss of less than 300 mL. None of the lymph nodes were 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, and 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 (15.5%), 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** (Fig. 20.1). **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.

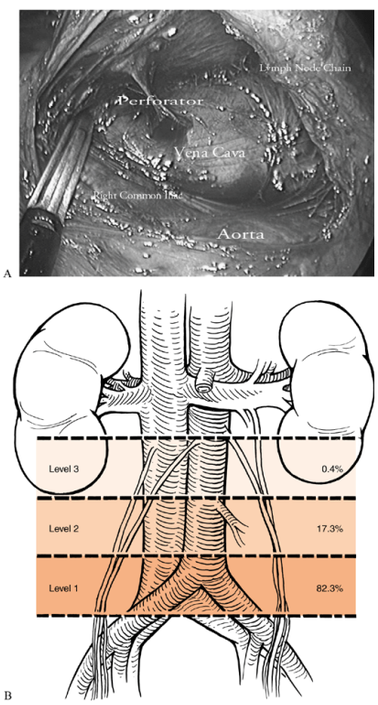

Figure 20.1 Perforators of the vena cava. A: **A vena cava perforator at the level of the bifurcation of the aorta**. B. **Diagram of the most common sites where perforators are encountered during the performance of a paraaortic lymphadenectomy**. The figure shows the anatomic distribution of 237 venous 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.)

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 .

Multiple recent studies continue to report the adequacy and safety of laparoscopic pelvic and paraaortic node dissections in gynecologic cancer (13 ,14 ,15 ,16).

These studies have demonstrated the ability of laparoscopic surgeons to perform pelvic and paraaortic lymphadenectomy. The American Medical Association Physicians Current Procedure Terminology (CPT 2004) lists a total of four laparoscopic lymph node dissection procedures, including total pelvic lymphadenectomy and paraaortic lymph node sampling. Now laparoscopic surgery has been used by many oncologic surgeons and has been applied to nearly every disease site in gynecologic oncology.

Indications for Laparoscopic Surgery

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 or laparoscopic total hysterectomy has been proposed as an alternative to laparotomy** (2 ,13 ,14 ,15 ,17 ,18 ,19).

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 they presented the first large series in 1993 (8). Laparoscopic staging was performed successfully in 93% of the patients, with obesity noted as a limiting factor. Two patients had complications related to the hysterectomy: 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. (17) 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 body mass index (BMI) (30.2 vs. 24.2).

The effect of surgical experience has been demonstrated by Melendez et al. (18). 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 patient.

More recent publications have continued to show a decrease in operative time, hospital stay, and total cost for laparoscopic treatment of endometrial cancer (16 ,20 ,21).

Women with endometrial cancer are often obese with BMI greater than 35 (22). This has been thought to be a limiting factor in using laparoscopy to stage and treat endometrial cancer. As surgical skills have grown, **laparoscopy has been used successfully in these women**. Holub et al. (23) have completed staging and hysterectomies successfully in 94.4% of 33 patients with BMIs of 30 to 40. Eltabbakh et al. (24) have completed staging in 88% of 42 women with BMIs of 28 to 60. In both studies, the benefits of shorter hospital stay with faster recovery were verified.

Long-term survival has been reported in five papers (Table 20.1). More than 480 patients have been studied for a median of 18 to 34 months. The recurrence rate ranges from 2.5% to 7%. When compared with historical laparotomy controls in these papers, there was no difference in survival.

Table 20.1 Recurrence Rates for Laparoscopic Surgery versus Laparotomy for Endometrial Cancer

	Laparoscopy			*Laparotomy*		
	n	*Months Followup*	*% Recurrence*	*n*	*Months Followup*	*% Recurrence*
Gemignani et al. 1999 (16)	59	18	6%	235	30	7%
Eltabbakh 2002 (25)	100	27	7%	86	48	10%
Malur et al. 2001 (26)	37	16	3%	33	16	3%
Holub et al. 2002 (21)	177	33	6%	44	45	7%
Hatch 2003 (27)	111	33	7%	55	33	14%

The concept of sentinel node removal has been studied in endometrial cancer in two pilot studies. Holub et al. (28) injected blue dye either into the subserosal myometrium (13 patients) or the cervix and subserosal myometrium (12 patients). Sentinel nodes were found most often in the cervico-subserosal myometrium group (83% vs. 61%). Garguilo et al. (29) used injection of both radioactive isotope and blue dye into the cervix and

subserosal myometrium in 11 patients. Seventeen sentinel nodes were identified and included all three of the positive nodes found after complete node dissection. Further studies are warranted in endometrial cancer.

Cervical Cancer

The use of laparoscopy in the treatment of cervical cancer was initially limited by the fact that there was no apparent advantage to laparoscopic lymphadenectomy because the standard operation for the primary cervical tumor was radical abdominal hysterectomy.

Dargent (30) **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 for 51 patients with negative pelvic lymph nodes was 95.5%. Querleu (31) 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 incision. Hatch et al. (32) 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. In two patients (5.4%), ureterovaginal fistulae developed that were treated by ureteral stents. These were removed 6 weeks later without further operative intervention.

Schneider and colleagues (33) reported 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. (34) 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 (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.

Recent studies have shown that the complication rates go down as the operator's experience increases (35 ,36). Long-term survival has been reported by Hertel et al. (37) for 200 patients, with a mean follow-up of 40 months. The projected 5-year survival was 83%. For the 100 patients who were stage I, lymphovascular space–negative and lymph node–negative, the survival was 98%.

Laparoscopic Radical 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. (38) and Canis et al. (39) have reported laparoscopic radical hysterectomy in separate case reports. Spirtos et al. (40) reported laparoscopic radical hysterectomy (type III) with aortic and pelvic lymphadenectomy in 78 patients. The average operative time was 205 minutes, length of hospitalization was 3.2 days, and blood loss was 225 mL; one transfusion was necessary. There were acceptable intraoperative and postoperative complications. With a minimum of 3 years follow-up, the disease-free survival was 95%.

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.

Laparoscopic staging of cervical cancer before treatment planning has been proposed (37 ,41 ,42). Vidaurreta et al. (41) staged 91 patients stages IIB, IIIA, IIIB, and IVA. Computed tomography (CT) was performed in 49 patients, with 38 read as normal and 11 as positive. Histologic evaluation revealed metastases in 18 of the 38 (47.4%) patients with negative scans, and no metastases were found in 5 of the 11 (45.5%) with positive scans. Hertel et al. (42) compared laparoscopic surgical staging with findings of magnetic resonance imaging (MRI) and CT scans in 101 patients, 91 of whom had CT scans, 67 of whom had an MRI scan, and 49 of whom had both. False-positive or false-negative results were found in 22% of patients. Ten patients had false-positive paraaortic nodal metastases.

Sentinel Nodes

The initial studies of sentinel node detection showed sensitivity, negative predictive value, and accuracy of 100% (43 ,44 ,45). Subsequent studies have used both blue dye and Technetium 99m detection methods with varying success (Table 20.2).

Table 20.2 Sentinel Node Detection for Patients with Cervical Cancer

Reference	*Number of Patients*	*Percent with Sentinel Nodes*	*Sensitivity*	*Negative Predictive Value*	*Detection Method*
Dargent et al. 2000 (43)	35	NS	85	100	Blue dye
Lantzsch et al. 2001 (44)	14	93	100	100	Technetium 99m
Malur et al. 2001 (45)	50	78	83	97	Blue dye
	50	100	100	100	Blue dye plus tech
Levenback et al. 2002 (46)	30	100	87.5	97	Tech plus blue dye
Buist et al. 2003 (47)	25	100	89	90	Tech plus blue dye
Lambaudie et al. 2003 (48)	12	100	66	90	Tech plus blue dye

NS, not stated.

Radical Vaginal Trachelectomy

In 1994, Dargent et al. (49) 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 attempted pregnancy, three had cesarean section at 36 weeks' gestation, and three had a spontaneous abortion.

The second report on radical vaginal trachelectomy was published in 1998 by Roy and Plante (50). 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.

A number of authors have now reported their experience with radical trachelectomy (Table 20.3). **The indications commonly used** are:

Table 20.3 Radical Trachelectomy for Fertility Preservation in Patients with Early-Stage Cervical Cancer

	Cases	*Follow-up (Months, Range)*	*Recurrences* (%)	*Pregnancies/Women Pregnant*	*Live Births*
Dargent 2001, 2002 (51,52)	68	34 (1–144)	1 (1.5%)	33/23	24
Shepherd et al. 2001 (53)	80/93[a]	30 (1–103)	7 (7.3%)	22/18	18
Plante 2003 (54)	82	76 (NS)	3 (3.6%)	47/29	27
Bernardini et al. 2003 (55)	26	23 (1–64)	0	14/8	9
Burnett et al. 2003 (56)	19	31 (22–44)	0	3/3	2
Schlaerth et al. 2003 (57)	10	47 (28–84)	0	4/4	2
Total	**298**	**40**	**11 (3.6%)**	**123/85**	**82 (67%)**

[a]Oncologic outcome based on 93 cases. Pregnancy outcome based on 80 cases.
NS, not significant.

- **Desire for future childbearing**
- **Stage IA1 disease with extensive lymph-vascular space invasion**
- **Stage IA2 disease**
- **Stage IB1 ≤ 2 cm diameter as long as there is no involvement of the upper endocervix on MRI or intraoperative frozen section**
- **No metastases to regional lymph nodes**

There have been no recurrences in the uterus. The risk factors for recurrence are lesion size greater than 2 cm, depth of invasion greater than 1 cm, and lymph-vascular space invasion (54).

Overall, 67% of 85 women having 123 pregnancies have delivered viable infants following radical trachelectomy (Table 20.3). The first trimester abortion rate was 17%, which is similar to the general population. **The second trimester rate was 12%—much higher than expected. Of the viable pregnancies, 10% to 15% were born between 24 and 28 weeks of gestation**. Therefore, the pregnancies should be managed by maternal fetal medicine specialists.

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 an adnexal mass is reported to be between 0.4% and 2.9% (58 ,59 ,60). Childers et al. (61) and Canis et al. (62) 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. (63) 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 (64) reported a stapling technique to perform an infracolic omentectomy on 13 patients. Possover (12) reported 13 patients staged for ovarian cancer, Pomel et al. (65) 10 patients, and Spirtos et al. (10) 4 patients. Thus, 62 patients have been reported in the literature who have been staged by laparoscopy, although no long-term follow-up is 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. Studies on laparotomy show that if the tumor is removed and proper treatment instituted, rupture does not affect the outcome (66 ,67 ,68), but 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 (69). 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% (70).

Improvement in laparoscopic equipment has encouraged investigators to perform the entire second-look procedure by laparoscopy. Childers et al. (63) 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 were similar to those obtained with second-look laparotomy.

Abu-Rustum et al. (71) 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 a negative second look were 14.8% for laparoscopy versus 14.3% for laparotomy. Clough et al. (72) reported 20 patients who had laparoscopy followed by laparotomy at the same surgery, with a positive predictive value for laparoscopy of 86% (12 of 14 patients).

The effects of the CO_2 pneumoperitoneum and laparoscopy on the long-term survival of women undergoing second-look operations has been reported by Abu-Rustum and associates (73). Over an 11-year period, there were 289 patients who had positive second-look

operations. There were 131 laparoscopies using CO_2, 139 laparotomies, and 19 laparoscopies converted to laparotomy. The groups were controlled for age, stage, histology, and grade and size of disease found at second look. The median survival for patients who had laparoscopy was 41.1 months and for laparotomy was 38.9 months ($p = 0.742$). Thus, the overall survival was independent of the surgical approach.

Complications

Part of "20 - Laparoscopy "

Complications of laparoscopy for malignant disease are higher than for benign disease (74). 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 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. (75) 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 et al. (76) reported a 0.17% rate of herniation among 3,560 laparoscopic operations.

Abdominal wall port-site implantations have been reported with nearly every tumor type, but are most common with ovarian cancer.

Technique

Part of "20 - Laparoscopy "

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:

- **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.

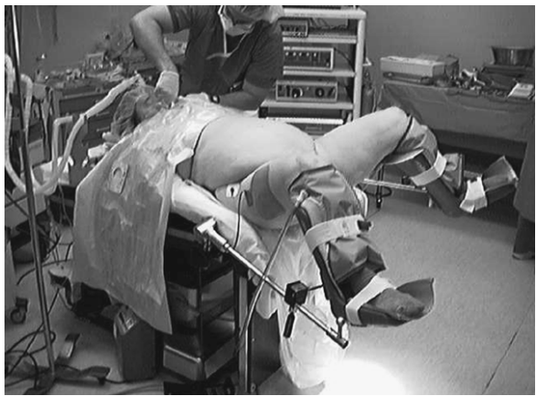

Figure 20.2 Patient position for laparoscopically assisted radical hysterectomy.

- **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.
- **Additional trocars are 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 (Fig. 20.2 , Fig. 20.3).

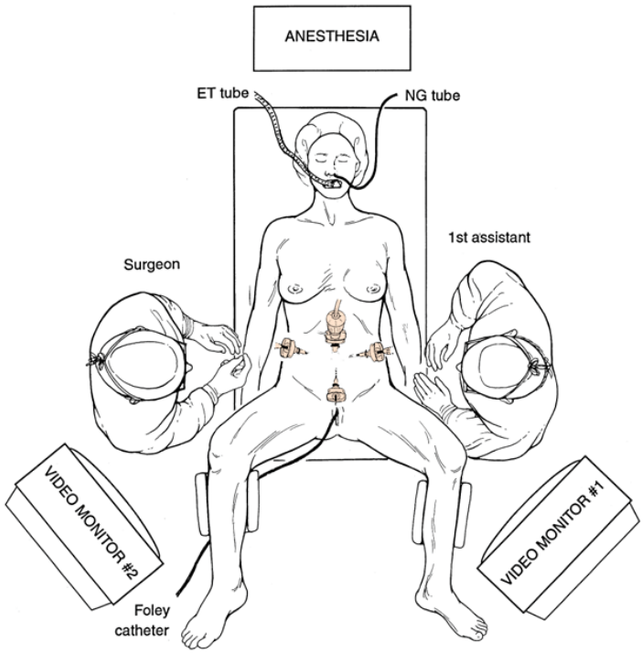

Figure 20.3 The position of the surgeons and placement of the trocars in the abdomen.

- **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.
- **The lymphadenectomy is 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.
- **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. Monopolar surgery, bipolar surgery, harmonic scalpel, 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).

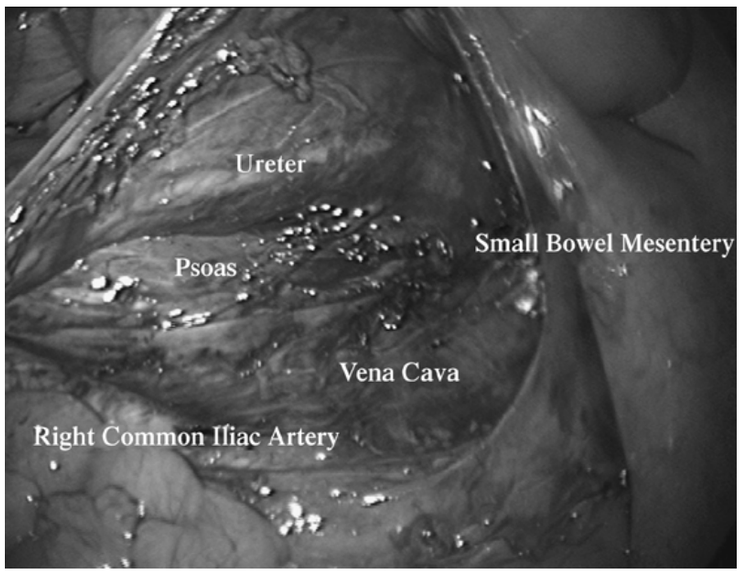

Figure 20.4 The right common iliac vessels and the vena cava after the removal of the right paraaortic lymph nodes.

- **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).

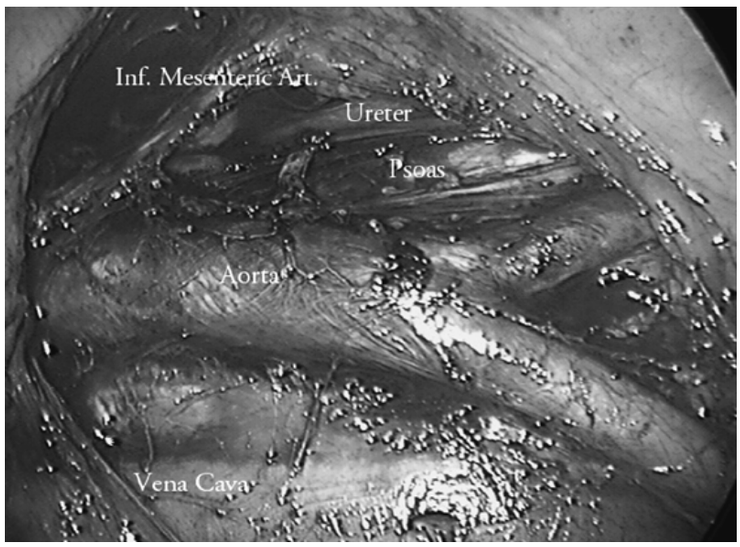

Figure 20.5 Completed bilateral common iliac and paraaortic lymphadenectomy.

- **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).

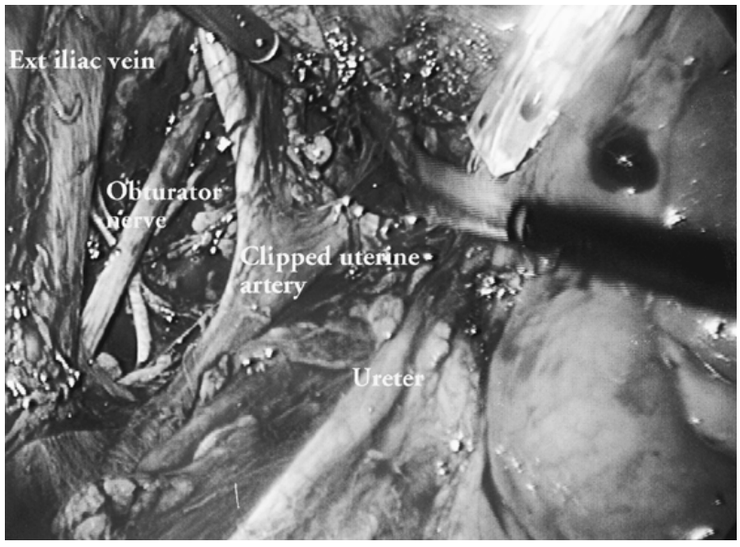

Figure 20.6 The left lateral pelvic space after a lymphadenectomy is completed and the uterine artery is clipped before a laparoscopically assisted radical vaginal hysterectomy.

- **The disease and clinical circumstances, 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.
- **All port sites 10 mm or larger should have the fascia and peritoneal layers closed to prevent herniation of bowel**. Several instruments are available to 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 site 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 in the peritoneal cavity. The CO_2 should be absorbed within hours, so any free air in the abdomen is highly suspicious.

Summary

Part of "20 - Laparoscopy "

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 the hands of experienced laparoscopic surgeons and with properly selected patients, laparoscopic surgery appears to result in shorter hospital stays, earlier return of function, and outcomes comparable with laparotomy. The results of prospective, randomized trials are awaited.

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21
Pelvic Exenteration

Kenneth D. Hatch

Jonathan S. Berek

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. His 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 .

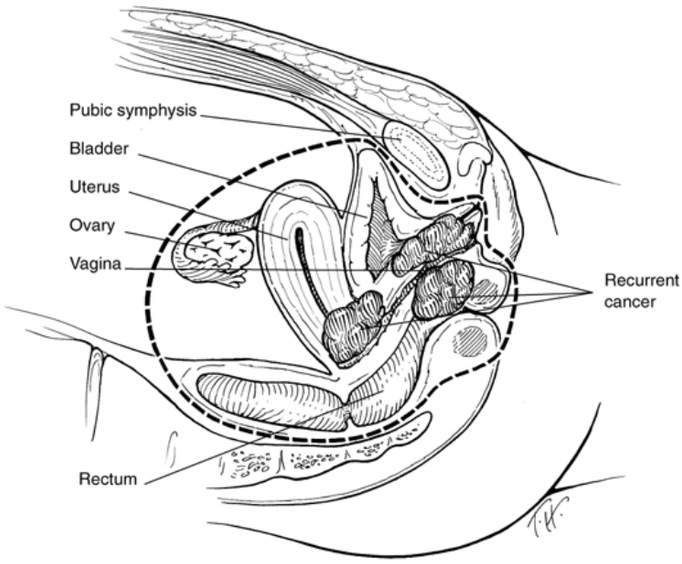

Figure 21.1 Total pelvic exenteration with perineal phase This operation includes removal of the bladder, uterus, vagina, anus, rectum, and sigmoid colon, as well as performance of a perineal phase, depending on the extent of the disease.

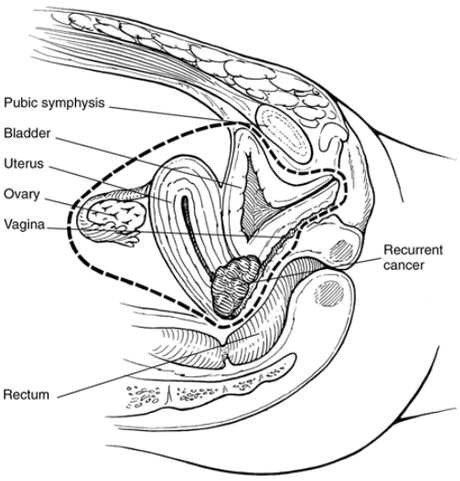

Figure 21.2 Anterior pelvic exenteration. This operation includes removal of the bladder, uterus, and varying amounts of the vagina, depending on the extent of disease.

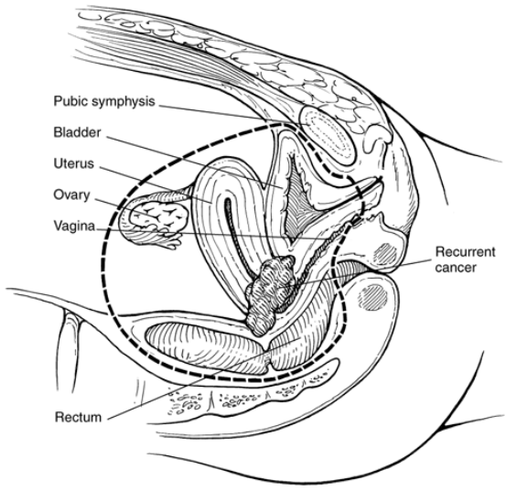

Figure 21.3 Supralevator total pelvic exenteration. This operation removes the uterus, vagina, and portions of the rectosigmoid colon with colonic reanastamosis.

- Indications

- Patient Selection
- Preoperative Patient Preparationm
- Operative Technique
- Low Rectal Anastomosis during Pelvic Exenteration
- Postoperative Care
- Complications
- Results
- Quality of Life

Indications

Part of "21 - Pelvic Exenteration "

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 uncommon.

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 lymphatic 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

Part of "21 - Pelvic Exenteration "

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 tomographic (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.**

The role of positron emission tomography (PET) is currently being investigated. Lai and colleagues in Taipei evaluated PET scan for the restaging of cervical carcinoma at the time of first recurrence. Forty patients had a PET scan, together with computed tomography and/or magnetic resonance imaging (10). Twenty two patients (55%) had their treatment modified due to the PET findings. PET was significantly superior to CT/MRI (sensitivity = 92% vs. 60%; p <0.0001) in identifying metastatic lesions. In addition, when compared with an earlier cohort of patients who did not undergo restaging with PET, there was a significantly better 2-year overall survival (72% vs. 36%; $p = 0.02$). In another series (11), the positive predictive value for left supraclavicular recurrence was 100%. Thus, **the PET scan may be an important addition to the preoperative investigation of a candidate for pelvic exenteration.**

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 the assessment of lymph nodes as well as the resectability of disease in the pelvis. In the hands of highly skilled laparoscopic surgeons, this may be an option (12).

The clinical triad of unilateral leg edema, sciatic pain, and ureteral obstruction is nearly always indicative of 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. (13) 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%), nodal metastasis in 45 (40%), parametrial fixation in 15 (13%), and hepatic or bowel involvement in 5 (4.5%).

Preoperative Patient Preparationm

Part of "21 - Pelvic Exenteration "

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 functioning will be permanently altered and that she may have one or two stomas. In addition, there is no guarantee of cure. The most difficult subject to broach is the possibility that she may have 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) should be started in advance of surgery.** Because these patients will not have significant oral caloric intake for a week or longer, postoperative TPN is commonly given.

Operative Technique

Part of "21 - Pelvic Exenteration "

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 against 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. **Multiple positive pelvic nodes, positive paraaortic 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 identified. Various sites for ligation of pubococcygeal muscle for total exenteration versus anterior exenteration are identified (Fig. 21.4).

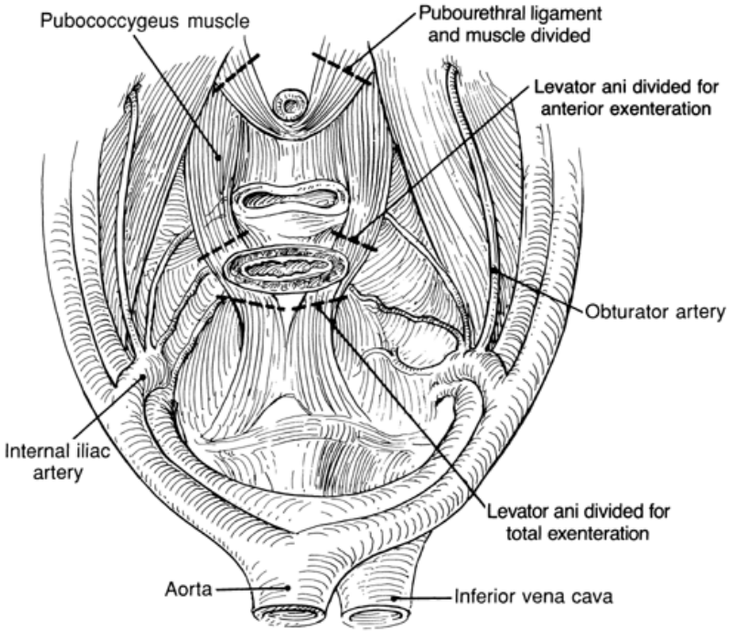

Figure 21.4 Cross-sectional diagram of pelvis showing lines of excision through the pubococcygeal muscle for anterior and total exenterations.

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 made under direct vision from below, insuring a surgical margin of at least 4 cm. The specimen is then ready to be removed. Hemostasis is provided by suture ligatures, and a pelvic pack is placed while the urinary diversion is performed. **The omentum is mobilized and brought down the left para-colic gutter into the pelvis.** It is used to cover the denuded area of the rectum and may 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 (14).

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 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-grafted 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 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

Part of "21 - 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 (15). **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 (16). These are most likely due to a better blood supply at the stapled anastomosis compared with a sutured anastomosis (17 ,18).

The anastomotic leak rate for low rectal anastomosis is reported to be less than 8% (19 ,20) 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** (21 ,22). Graffner et al. (22) 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. (23) 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 (24) reported 17 patients with a 12.4% anastomotic leak rate and a 12.4% stricture rate. Both groups advised using a diverting colostomy in the previously radiated patient. Hatch et al. (21) reported using a diverting colostomy 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. (21), **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.

Mirhashemi et al. (20) did a risk factor analysis of 77 patients at the University of Miami who had low rectal anastomosis after exenterative surgery. The indications for the surgery were recurrent cervical cancer (33), ovarian cancer (27), recurrent vaginal cancer (7), recurrent endometrial cancer (4), colon cancer (3) and endometriosis (3). **Previous radiation was the major factor in anastomotic leak rate, with 35% of the irradiated patients and 7.5% of the nonirradiated patients having a leak or a fistula. Protective colostomy did not make a difference**. Of the 40 patients who had total pelvic exenteration with low rectal anastomosis, 36 had received pelvic radiation therapy. A protective colostomy was used in 12 of these patients, and 6 developed fistulae. Of the 24 who did not have protective colostomies, 6 developed an anastomotic leak or fistulae. Only 1 of the 37 patients who had posterior exenteration and low rectal anastomosis had previous radiation therapy, and this patient had an anastomotic leak. Of the remaining 36 patients, 3 had an anastomotic leak. Protective colostomies were not used on any of these patients (20).

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 recto-anal reflex are significantly altered (25). **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 (26 ,27). When the anastomosis is above 12 cm, there is little alteration of function (28).

The colonic J-pouch has been popularized by colorectal surgeons to treat rectal cancer with low rectal resection. It has replaced colo-anal anastomosis because of its superior results. **Studies comparing colonic J-pouch with colo-anal 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** (29 ,30 ,31 ,32). Prospective, randomized trials have confirmed the observational studies (33 ,34) (Table 21.1).

Table 21.1 Randomized Comparison of Colonic J-Pouch versus Coloanal Anastamosis in 100 Patients

Factor	*Colo-anal* (n 5=52)	*J-Pouch* (n 5=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

Hallbook O, Pahlman L, Krog M, Wexner SD, Sjodahl R. Randomized comparison of straight and colonic J pouch anastomosis after low anterior resection. Ann Surg 1996;224:58–65, with permission (34).

The most significant drawback to the colonic J-pouch is the inability of some patients to empty the pouch. This is most likely because of the length of the staple line used to construct the pouch. Hida et al. (35) prospectively randomized patients to a 5-cm versus a 10-cm pouch and found the 5-cm pouch 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.

Table 21.2 Randomized Study of 5-cm J-Pouch versus 10-cm J-Pouch

	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, Okuno K, Ieda S, Machidera N, 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 (35).

Harris et al. have reported the long-term function of J-pouch anal anastomosis in 119 consecutive randomized patients with colorectal cancer from the Cleveland Clinic. Patients who had J-pouch versus colo-anal anastomosis had significantly better continence scores at 5 to 9 years after surgery and fewer nocturnal bowel movements (36).

A new procedure called a coloplasty has been developed at the Cleveland Clinic to improve on the poor bowel function after either a colo-anal anastomosis or a colonic J-pouch anastomosis (37) (see Chapter 19). In a randomized study of the three techniques, the coloplasty and colonic J-pouch patients had significantly more favorable compliance, reservoir volume, and fewer bowel movements per day than the straight anastomotic group. The advantage of the coloplasty was that it could be used in a narrow pelvis. This may apply to the female patient who is having vaginal reconstruction with myocutaneous graphs, where space for anastomosis is diminished (37).

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 blood supply.

Husain et al. reported the experience at Memorial Sloan-Kettering in 13 patients who had total pelvic exenteration and low rectal anastomosis with a continent urinary diversion. Of these, seven leaked early and two had fistulae later, for a 30% success rate. They recommend against low rectal anastomosis when a continent diversion is used (38).

The overall survival rate for patients with pelvic exenteration and low rectal anastomosis at the University of Alabama at Birmingham was 68%. This was superior to that of patients with anterior exenteration (53%) (39), although the difference was 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 total 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 was 38%.**

Postoperative Care

Part of "21 - Pelvic Exenteration "

Patients are best managed in an intensive care unit with an arterial line and central venous catheter. Central 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. Some advocate the use of the Swan-Ganz catheter (40). 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. The central catheter can also be used for 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

Part of "21 - Pelvic Exenteration "

Although the mortality rate is less than 5%, as many as 50% of patients may have a major complication (41 ,42 ,43). The most significant intraoperative complication is hemorrhage, with blood loss of 1,500 to 4,000 mL being typical (44 ,45). Postoperative hemorrhage is often handled by percutaneous embolization because reexploration carries a high morbidity. The length of surgery (4 to 8 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 central 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

A small bowel anastomotic leak or fistula is a serious complication, with a mortality rate of 20% to 50%. **The incidence of small bowel fistulae ranged from 10% to 32%** (41 ,42 ,43 ,44 ,45 ,46) **in patients who had an ileo-ileal anastomosis in previously irradiated bowel.** Small bowel fistulae 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 ileo-ileal anastomosis led to development of the transverse colon conduit (47). 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 fistulae 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 rehospitali zation in 14% of patients. The incidence of ureteral stricture has been decreased by the use of ureteral stents and is approximately 8% (48).

Results

Part of "21 - Pelvic Exenteration "

The 5-year survival rate has improved significantly over time (Table 21.3) (5 ,6 ,41 ,42 ,46 , 49 ,50 ,51 ,52). 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 (49). **The clinical factors that have been reported to affect survival most significantly are length of time from initial radiation therapy to exenteration** (50), **size of the central mass** (51 ,53), **and preoperative pelvic sidewall fixation determined by clinical examination** (52).

Table 21.3 Operative Mortality and 5-Year Survival Rates for Pelvic Exenteration

Author, Year	*N*	*Operative Mortality (%)*	*5-Year Survival (%)*
Brunschwig, 1965 (49)	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 (50)	143	6.3	50
Lawhead et al., 1989 (46)	65	9.2	23
Soper et al., 1989 (41)	69	7.2	40
Morley et al., 1989 (42)	100	2.0	61
Stanhope et al., 1990 (51)	133	6.7	41
Berek et al., 2003 (52)	75	4.0	54

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 (54) achieved the highest 5-year survival rate at 23%. In their analysis, they eliminated confounding high-risk factors, such as positive margins and metastasis to other peritoneal surfaces.

Table 21.4 Survival of Patients with Positive Nodes at Time of Exenteration for Postirradiation Recurrence

	Negative Nodes		*Positive Nodes*	
Author, Year	*N*	*5-Year Survival (%)*	*N*	*5-Year Survival (%)*
Barber and Jones, 1971 (53)	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 (54)	—	—	26	23
Rutledge and McGuffee, 1987 (55)	—	—	41	26.3
Hatch et al., 1988 (39)	54	52	7	14
Morley et al., 1989 (42)	87	70	13	0
Berek et al., 2003 (52)	59	61	8	0

[a]Thirty-nine patients with gross disease unresected and 10 with metastasis to ovaries.

[b]Includes positive inguinal nodes.

Rutledge et al. (5) in 1977 reported a 6.6% 5-year survival rate in 30 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 (55) reported a 26.3% survival rate in 41 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. (42) 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. (56) 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. (45) compared 63 patients aged 65 years or older with 363 patients younger than 65 years 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

Part of "21 - Pelvic Exenteration "

The quality of life after pelvic exenteration is significantly improved by organ reconstruction. Hawigorst-Knapstein et al. (57) 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. (58) 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, but sexual functioning will always be significantly impaired.

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Section IV Quality of Life

22
Communication Skills

Robert Buckman

Walter F. Baile

In gynecologic oncology, as in all branches of medicine, **the clinical encounter with the patient** (and often the family) **has four specific aims. The first is to gather information from the patient** (essential for determining the clinical diagnosis); **the second is to transmit information to the patient** (necessary to communicate the treatment plan); **the third is to build a relationship** (necessary to establish rapport and trust); and **the fourth is to support the patient and her family through the crisis of her illness**. When accomplished successfully, these aims will achieve the overarching goals of producing objective improvement in the patient's medical condition (“helping the patient get better”), if that is possible.

The last two aims take on particular significance because as a result of the increased survival rates of many cancers, the relationship with the oncologist and the clinical team now can extend over many years and encompass a progression of disease crises. The median survivals for women with advanced-stage ovarian cancer has increased substantially over the past several decades, and it is not uncommon today for patients to experience remission and recurrence four or five times during the course of their cancer (1). However, **each disease recurrence can be a crisis in which the patient receives bad news again and must endure the rigors of a new round of treatment, uncertainty about the outcome, and the threat of death**. In these instances, the application of supportive communication skills in the context of a long-standing relationship with the patient can reduce anxiety, facilitate patient coping, and assist in providing the patient with hope (2 ,3 ,4).

Regardless of whether medical improvement is possible, accomplishment of these goals can 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

Part of "22 - Communication Skills "

Good communication skills facilitate the clinician's ability to take an accurate clinical history and therefore to make a correct diagnosis and formulate 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, as well as her assessment (and feelings) about her management, her treatment, and her health-care team** (5). In fact, the literature suggests that patients are both likely to choose and to change physicians based on how they perceive their physician communicates and interacts with them (6).

An important and related issue is one of 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 Chaumeton (7) 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 are also important for ensuring informed consent, enlisting the family in the care of the patient, reducing the uncertainty associated with a new or recurrent illness, and increasing accrual to clinical trials (8 ,9).

Communication Skills as Learnable Techniques

Why Communication Skills Are So Difficult to Learn

Most oncologists have had little preparation in communicating with patients (8). Almost none have had any formal course work, and a fair number have learned by observing other clinicians (certainly no guarantee that anything useful will be learned!). Moreover, many clinical encounters, such as breaking bad news and making the transition to palliative care, are highly emotionally charged. The clinician is challenged not only to address the patient's feelings, but also his or her own, which can be characterized by the sense of helplessness and frustration in the face of incurable disease or self-doubt about having done everything possible for the patient (9). Sometimes these feelings may cause the doctor to offer false hope to the patient, avoid discussing issues important to the patient such as disease prognosis (10 ,11), or offer treatment when there is little or no chance of success.

Acquiring Communication Skills

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 (12 ,13 ,14 ,15).

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 (16), a booklet (17), and in illustrated form with videotaped scenarios using simulated patients in CD-ROM and video formats (18). Review of this video material can enhance the understanding of these communication techniques.

CLASS: A Protocol for Effective Communication

Part of "22 - Communication Skills "

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 oncologists (more than 85%) believe that dealing with emotions is the most difficult part of any clinical interview (19).

Trust and rapport are especially important to patients at times of illness crisis, and communication skills such as exemplified in the CLASS protocol are an important underpinning of establishing confidence and a working relationship with the patient and family.

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) and Connection (or building rapport), Listening skills, Acknowledgment of the patient's emotions, Strategy for clinical management, and Summary** (Table 22.1).

Table 22.1 The CLASS Protocol

C—Physical **context** or setting and **connection**
L—**Listening** skills
A—**Acknowledge** emotions and explore them
S—Management **strategy**
S—**Summary** and closure

C—Context (or Setting) and Connection (or Building Rapport)

The context of the interview means the physical context or setting, and connection means the steps that are necessary to begin building rapport or a relationship with the patient. Both of these steps are important because they encourage trust on the part of the patient and family, an essential ingredient of any collaborative endeavor. They are especially important in the first encounter, during which often the most lasting impressions

are formed. The essential components are listed in Table 22.2 . **The first component is to arrange the space optimally. The second is to get your own body language right. It is important to pay attention to eye contact, to whether touch is helpful, and to making introductions**.

Table 22.2 The Elements of Physical Context

Arrangement: 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. Introduce others.

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. Get any physical objects out of the way—e.g., 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 (20).

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** (20). 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, you 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 (21). 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 (22). **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. The “white coat syndrome” is a well-known phenomenon that describes how the medical setting induces anxiety in many patients (often even leading to blood pressure increases!), so that a friendly greeting may go a long way at putting the patient at ease. Also **remember to introduce others in the room** (e.g., medical students, nurse) that the patient may not know.

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. (23).] 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).

Table 22.3 Fundamental Listening Skills

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?” “How did that make you feel?”*)
2. Facilitating Pausing or silence when patient speaks. Try not to interrupt. Nodding, smiling saying *“mm hmm,” “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

Open-Ended 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 …” “How 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 (24). **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 it 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 second most important technique of all interviewing skills (after 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

Patients often have concerns about treatment or other issues related to their care. When not asked about them directly, they may hint or express them in nuances, protests, or questions that are not clear. Listed below are some examples of how important information may be indirectly communicated.

Statement: *"I don't know how my family can take any more of this."*

Patient means: *"I really feel guilty."*

Statement: *"I just couldn't stand another round of chemo."*

Patient means: *"I felt so awful when my hair fell out."*

Statement: *"Doctor, how long do you think I have to live?"*

Patient means: *"I wonder if I'll see my grandson graduate."*

Statement: *"What will the end be like?"*

Patient means: *"How much will I suffer?"*

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 or to amplify some aspect of the statement, now that the clinician has shown interest in the topic. The key to addressing questions is to use clarifying statements that get at the issue underlying the concern.

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).

Table 22.4 Acknowledgment of Emotions: The Empathic Response

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 felt awful," "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

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 consists of three mental steps:

- **Identifying the emotion that the patient is experiencing**.
- **Identifying the origin and root cause of that emotion**.
- **Responding in a way that tells the patient that you have made the connection between steps 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:

Table 22.5 Management Strategy

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 the 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).

- **Determine what you judge to be the optimal medical strategy.** In your mind (or out loud), define the ideal management plan.
- **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:

- **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 that she will follow. Check the patient's understanding by asking her to repeat back to you what you have told her (don't just ask if she understood … most of the time she will say yes, even if she hasn't).

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 **precis** 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.

Table 22.6 Summary and Closure

Ending of the interview has three main components: **A précis or summary of the main topics** you have discussed **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.) **A clear contract for the next contact**

SPIKES: A Variation of CLASS for Breaking Bad News

Part of "22 - Communication Skills "

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 (16 ,25 ,26).

Bad news can best be defined as “any news that seriously adversely affects the patient's view of her future” (27). 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).

Table 22.7 The SPIKES Protocol for Breaking Bad Newsa

S—Setting = Context, connection 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.

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?")*

Table 22.8 Patient's Perception of 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).

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 (28).

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 (29) study in 1961, when 95% of surgeons did not disclose to their patients a cancer diagnosis. Twenty years later, a study by Novack et al. (30) showed a dramatic reversal of this proportion. Regarding the proportion of patients who state they want to be informed, Jones's (31) 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% (32 ,33 ,34).

Table 22.9 Invitation from Patient to Give Information

Find out from the patient if she wants to know the details of the medical condition or treatment (e.g., *"Are you the sort of person who … ?"*).
Accept patient's right not to know (but offer to answer questions as patient wishes later).

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 shown in Table 22.10 .

Table 22.10 Knowledge: Giving Medical Facts

Bring the patient toward a comprehension of the medical situation, filling in any gaps.
Use language intelligible to the patient, and start at the level at which he or she finished.
Give information in small pieces.
Check the reception: Confirm that patient understands what you are saying after each significant piece of information.
Respond to the patient's reactions as they occur.

- **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 below).

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

Part of "22 - Communication Skills "

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

Part of "22 - Communication Skills "

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 (35). 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

Part of "22 - Communication Skills "

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 it 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

Part of "22 - Communication Skills "

The medical professional 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

Part of "22 - Communication Skills "

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. It is important to be mindful of the fact that if chosen poorly, words can be scalpels, but if chosen carefully, they can be perceived by the patient and family as a source of comfort and support.

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

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. If disease is likely to progress, it is important to clarify how and where the patient will be cared for when dependency increases, and the patient may need encouragement to address the personal issues involved in preparation for the close of life. **These matters should not be suddenly raised at time of crisis.** There is no dichotomy between care concerned with cure or control of cancer and care when disease is irreversibly progressive: All is concerned with enhancement of life (1 ,2)

Elements of care apart from anticancer strategies are sometimes grouped under the term *palliative care*. The concept of parallel care or "mixed management" is widely advocated for people with eventually fatal illnesses. The provision of palliative care concurrently with other aspects of care allows for input from particular members of the care team, depending on the problems presented. Recent reports highlight deficiencies associated with introducing palliation/symptom relief and death preparation only when anticancer treatment has failed (3 ,4). Palliative care involves appropriate palliative medicine—the scope of the whole subject is presented elsewhere (5 ,6).

The goals of palliative care should be to facilitate comfort, autonomy, dignity, and personal rehabilitation and development, especially in the face of an incurable illness and as the patient approaches death. Efforts must be directed at assisting her (and her family) to have realistic expectations and well-grounded hope in what will not fail, notably in the fidelity of her carers, and in recognition of her own unique value as a person, come what may. The concept of the patient as subject should be understood: The patient is a person with a unique personal inheritance and history, 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.

The final phase of life is as important as any other, possibly even more so, making it critical that all therapeutic maneuvers are carefully considered. There is no time to waste with careless prescribing. Through careful symptom relief, good communication, and a supportive relationship, the various members of the multidisciplinary team should 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 and desirable to maintain continuity of professional relationships**. The comprehensive care of a woman with gynecological cancer is always challenging, but even more so as life draws to a close (7).

Practical Aspects of Palliative Care

Part of "23 - Palliative Care and Pain Management "

The care of a woman with advanced gynecologic malignancy involves several components: assessment, delineation of therapeutic possibilities, implementation of treatment, evaluation of outcome, continuing review and reassessment, and prognostication. These are dimensions of a clinical partnership of high personal and social significance.

Assessment

It is essential to make a comprehensive assessment. This 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, establishing what supports she has previously found useful and will draw on in the future. It is also important to ascertain her current hierarchy of problems, for only the woman herself can determine that which is affecting her quality of life. **The narrative approach gives far more information than the use of checklists, as well as a richer appreciation of the woman as a person**. The telling of the story is often also therapeutic for the patient as she seeks to find meaning.

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
- **Clarification of her understanding of her illness and the treatment goals**
- **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** (The achievement of personal goals can do much to affirm a person's sense of self and autonomy, and can enhance her quality of life, even at a time of great disease burden.)

An adequate assessment may involve interaction not only with the patient but with family members and friends; however, the extent of this interaction is subject to the woman's wishes. Such wishes will vary between individuals and are not necessarily culturally determined. **Assessment may be best regarded as a continuous process**, with more formal assessment from time to time as the patient's situation changes.

Clinical Decision Making

On the basis of a comprehensive assessment, with or without further investigations, it is normally possible to delineate the therapeutic possibilities. Future discussions, including those at tumor board, should include the perspectives of palliative medicine.

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, transdermal, or subcutaneous techniques have not been adequately explored. It is inappropriate to schedule unnecessary clinic visits if telephone contact could clarify a problem.

Careful consideration of relevant antitumor measures is always mandatory, because control of the neoplastic process usually offers the best chance of alleviating symptoms. Factors that should be taken into account when considering further anticancer therapy include: (i) the stage of disease, (ii) the rate of disease progression, (iii) the likely natural history of the disease, (iv) the burden of investigation and treatment compared with potential gains for the patient, (v) the potential to prevent future symptoms, (vi) the potential for rehabilitation (physical, psychological, social, or spiritual), and (vii) the patient's priorities. If cost/benefit issues are considered, it is essential to avoid “flat of the curve” medicine. Good symptom relief is almost always a high benefit in relation to cost, whereas anticancer measures may vary in benefit. These matters justify reflection (Fig 23.1).

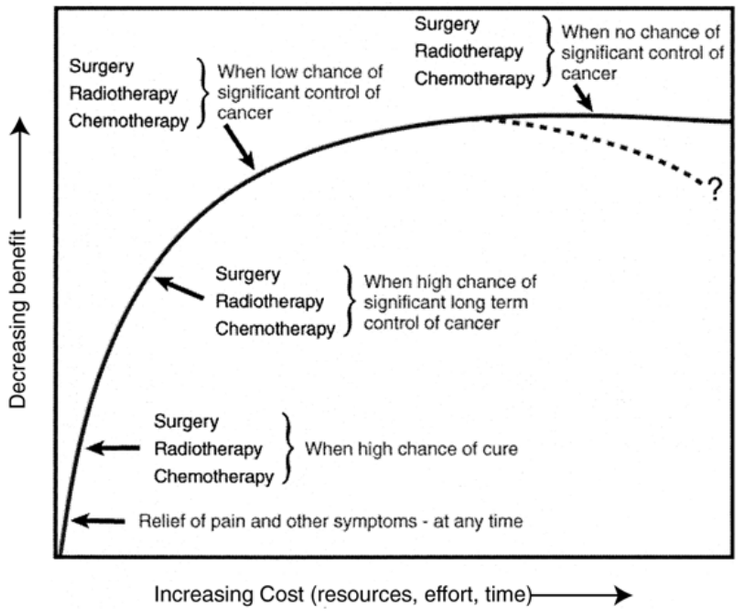

Figure 23.1 Factors to be taken into account when considering further anticancer therapy: benefit vs. cost.

Clinical decision making is always undertaken in a context of prevailing values and on the basis of facts. Ethical principles such as autonomy, beneficence, nonmaleficence and justice are greatly influenced by culture and social circumstances, as well as by individual factors. However, if clinical wisdom is brought to bear, an appropriate decision will emerge to a conscientious clinician (Fig 23.2).

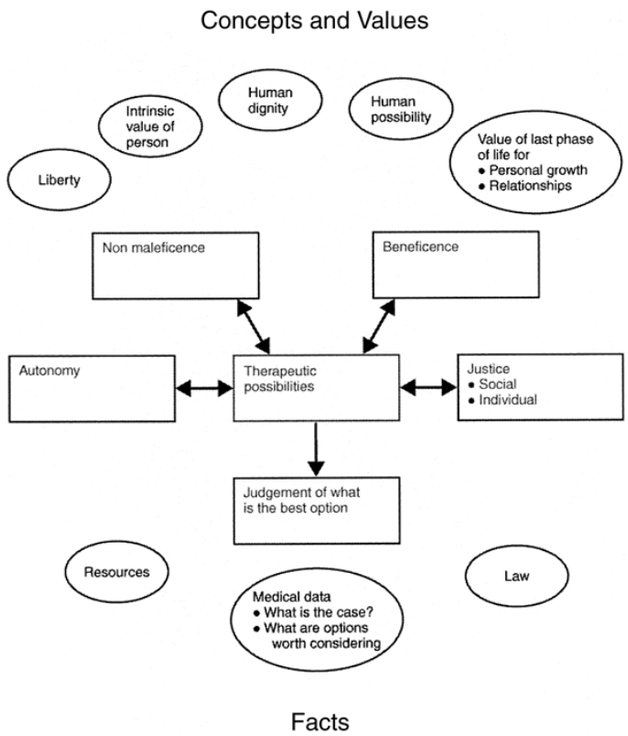

Figure 23.2 The context of clinical decision-making: ethics, social and individual factors, and judgement.

Decisions concerning treatment should usually 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 usually 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. **Whilst patient involvement is sought, 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." A decision not to pursue anticancer treatments, but to focus solely on symptomatic measures, does not indicate nihilism or inactivity. It may reflect authentic clinical wisdom with clear goals of comfort and dignity.

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 to avoid wasting time on ineffective interventions. Formal outcome measures based on subjective criteria, of which there are many examples (8 ,9 ,10), should ideally be introduced into routine clinical practice, with outcomes to be measured commensurate with the patient's priorities for comfort and for personal objectives.

Discussing Prognosis

Mention should 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 remains uncertain, and it is unhelpful and frequently inaccurate for a clinician to be too specific about the likely duration of survival (11). **In the face of a question concerning prognosis for patients with incurable disease, 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. 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 somewhat uncertain can be predicted precisely.

Symptoms and Their Relief

Part of "23 - Palliative Care and Pain Management "

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; reference works should be available (5 ,6).

Symptoms are subjective, and their presence and severity is not necessarily apparent to the observer. A patient in severe pain may show no signs of distress, yet she may admit upon careful questioning 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, and active listening in a supportive manner.

Symptoms vary in their significance for the patient. Certain symptoms (e.g., vaginal bleeding) may cause much emotional distress, whereas other symptoms that are more serious in their physiologic consequences (e.g., nausea secondary to renal failure) 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.

Symptoms may arise from the tumor itself, from the treatment, and/or from unrelated causes. Symptoms may precede signs or objective evidence (x-ray or scans) of disease spread. This is particularly true in the case of leg pain from lumbosacral plexus infiltration, which may herald recurrent cervical cancer. Magnetic resonance imaging or a computed tomographic scan may fail to 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.

There is now considerable literature concerning the understanding and therapy of major symptoms in cancer, and attention is given here to those seen more commonly, with emphasis on practical considerations. The management of some very difficult symptoms, such as perineal ulceration, will be enhanced if nurse specialists in palliative care are available (12).

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." Pain management of the 1990s has been based on a more adequate understanding of pain physiology and a better classification of pain mechanisms. Controversies relevant to gynecological practice remain, not least being the global inequity in access to pain relief for women with gynecological cancer (13).

Pain in gynecological cancer presents in many forms and may occur at any stage in the illness. **It may be caused by both the disease and its treatment**.

Many approaches to pain management have been published. Cancer pain assessment and treatment guidelines have been developed by the American Society of Clinical Oncology and other authorities (14 ,15 ,16). The following simple schema provides some guidelines in the face of the complexity of recent research and practice (Fig 23.3) (17).

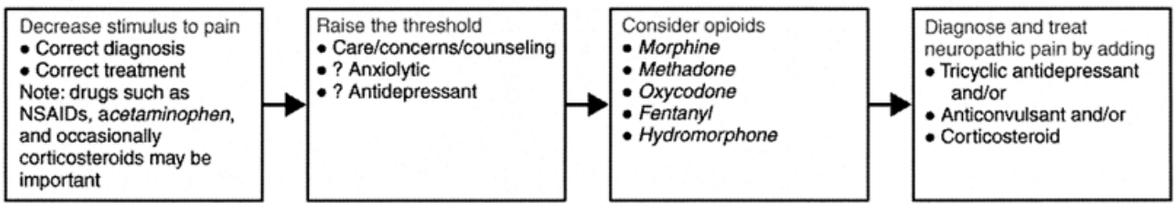

Figure 23.3 Schema for the approach to pain management.

Pain management may be considered to have four steps:

- **Reduce the noxious stimulus at the periphery**.
- **Raise the pain threshold**.
- **Consider and use appropriate doses of opioid drugs**.
- **Recognize neurogenic pain and treat it correctly**.

Such steps should be considered in order, but measures relating to all four steps may be instituted simultaneously if the clinical circumstances dictate.

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 is most commonly a result of 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 and may also interfere with the absorption of oral opioid drugs** (18).

The history should include the mode of onset, characteristics, distribution, aggravating factors, trends over time, and response to therapeutic endeavors thus far. The history, together with a clinical examination, provides 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, 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., non-steroidal anti-inflammatory 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 diathesis, renal impairment, or known idiosyncratic reactions to aspirin or related drugs. Where the use of NSAIDs is precluded, *acetaminophen* (*paracetamol*) is a useful alternative. Although its mechanism of action is yet to be fully elucidated, clinical utility suggests some peripheral action, although not a direct anti-inflammatory effect. Although *acetaminophen* is fairly well tolerated and safe, it should be used in reduced dosage in patients with extensive liver damage, especially in patients with alcoholic cirrhosis.

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, as well as gentle massage. Psoas spasm from a psoas abscess or direct tumor infiltration is not infrequent in gynecologic cancer (19). Psoas muscle infiltration should be suspected if there is pain in a lumbosacral distribution associated with difficulty achieving full extension of the hip. Relief can usually be achieved by careful adherence to the outlined principles, but spinal opioid might have a place in such patients, especially if pain is proving intractable. **Psoas muscle spasm will not be relieved by opioids alone**. *Acetaminophen* and/or NSAIDs, an oral opioid (such as *oxycodone*), and a laxative must be supplemented by a drug that is active against spasm in skeletal muscle, such as *diazepam*. Steroids may also be helpful. **Polypharmacy is absolutely justified to relieve pain in the malignant psoas syndrome. If the pain does not respond to these measures, specialist help must be sought** (20). No patient should die with intractable pain.

Experience at the Royal Hospital for Women in Sydney would suggest that **pain associated** with subacute and chronic radiation toxicity (e.g., vulvovaginal ulceration) may benefit from hyperbaric oxygen treatment.

Step Two: Raise the Pain Threshold

All persons should be considered to have a threshold above which they will be troubled by pain. This threshold may be influenced by many factors. **The threshold for pain may be raised by explanation, 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. Many complementary therapies, such as massage and meditation, assists in the relief of pain. **Threshold issues should not be treated with opioid drugs**.

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**.

Pain and suffering are related but distinct (21). Suffering has been described as a sense of impending personal disintegration (22). In common parlance, there may be a sense of being about to "go to pieces." Suffering may be triggered by symptoms out of control, perceived loss of dignity, loss of a sense of control or autonomy, fear for the future, and loss of a future. **Pain may be the main cause of suffering, or a manifestation (through threshold shifts) of suffering, with the language of suffering expressed through pain**. A conscientious clinical oncologist needs to be aware of distress in a patient and should seek to be a gentle comforter while seeking for ways to relieve distress—by understanding and alleviating the causes (such as pain) and seeking the help of colleagues (23). **It may be for others to contribute most to the spiritual care of women** with gynecological cancer—that dimension of care focused on profound existential issues that may or may not relate to religious matters. **But every doctor has the responsibility and privilege to be aware of such dimensions of care and to take time to be informed about current reflections on this area** (24).

Step Three: Precise and Appropriate Use of Opioid Drugs

There is abundant literature on opioid use, with a range of opioids available (25 ,26). 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 only partially responsive to opioids (27 ,28). **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**, but even in such circumstances, opioid drugs should be introduced and carefully calibrated to ensure that optimum benefit is achieved from this component of the analgesic regimen.

A variety of opioids is available, and the principles of choice need to be understood (26). **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 may be justified (29 ,30). ***Morphine*** **remains the preferred initial opioid of high potency** at a global level, but increasingly consideration is given to alternative high-potency opioids if available, such as *fentanyl, methadone, oxycodone*, and *hydromorphone*. It is crucial to stress the ethical implications of cost differentials: **no woman should be deprived of pain relief because expensive, unaffordable drugs have been prescribed if cheaper drugs would have given significant benefit.**

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. Doses of opioid drugs should be carefully titrated against response and side effects.

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. **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 very 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 more than 100 mg every 4 hours, but most patients need less than 50 mg every 4 hours.

Controlled-release *morphine* tablets are significantly more convenient for patients, with the proviso that for severe pain, or the less experienced prescriber, 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 fecal loading or impaction. Subcutaneous *morphine* is a better choice in such circumstances: immediate-release *morphine* may be worth a try, but at least in severe fecal loading, there is anecdotal evidence that absorption may be unreliable (18).

If parenteral *morphine* is essential, the subcutaneous route is appropriate, either with intermittent injections through an indwelling butterfly needle every 4 hours or with a continuous infusion through a battery-driven syringe driver. When a patient is constipated and pain is not well controlled with simple analgesics such as *acetaminophen* (*paracetamol*), 4-hourly *morphine* by the subcutaneous route is a useful maneuver to achieve pain relief and to calibrate the required *morphine* dose. Once her constipation is relieved, the subcutaneous 24-hourly dose may be easily converted to oral *morphine*. **The intramuscular route is rarely advantageous**. 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 necessary**.

Intravenous *morphine* infusions, although sometimes useful (for example in a patient with peripheral circulatory failure), may be occasionally associated with the development of tolerance, which may not always be overcome by the addition of further *morphine* (31). Cessation of the infusion and resumption of appropriate subcutaneous doses every 4 hours may be 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 may depend on the contribution of an active metabolite (*morphine 6-glucuronide*), which, like *morphine*, is a powerful mu receptor agonist. **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 four to eight or even twelve hours. The use of *morphine* in a patient on a dialysis program for renal failure is very complex, and specialist help is needed.

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 widely held fears:

- **The use of *morphine* with careful dose finding and monitoring does not, in the vast majority of patients, lead to addiction** (although physical dependence, a separate issue, occurs). However, specialist help is needed to use *morphine* appropriately in intravenous *heroin* users.
- **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 of 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 it will be ineffective 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.

Use of Alternative Opioids

Other potent opioids must be considered when: (i) pain persists despite careful drug calibration, **(ii) unacceptable side effects persist (e.g., cognitive impairment, nausea)** despite careful drug calibration, or **(iii) drowsiness or toxicity occurs** at levels of the drug required to control the pain.

In these circumstances, after reconsideration of the pain mechanism and the other analgesic steps, an alternative opioid should be considered. Availability varies from country to country, 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

	Dose (mg) Equianalgesic to Morphine 10 mg IM[a]				
Drug	***PO***	***IM***	***Half-Life (hr)***	***Duration (hr)***	***Comment***
Morphine	20–30[b]	10	2–3	2–4	Standard for comparison.
Morphine CR	20–30	10	2–3	8–12	Various formulations are not bioequivalent.
Morphine SR	20–30	10	2–3	24	
Oxycodone	20	—	2–3	3–4	
Oxycodone CR	20	—	2–3	8–12	
Hydromorphone	7.5	1.5	2–3	2–4	Potency may be greater; for example, IV *Hydromorphone*: IV *morphine* = 3:1 rather than 6.7:1 during prolonged use.
Methadone	20	10	12–190	4–12	Although 1:1 IV ratio with *morphine* was in single-dose study, there is a change with chronic dosing; large dose reduction (75%–90%) is needed when switching to methadone.
Oxymorphone	10 (rectal)	1	2–3	2–4	Available in rectal and injectable formulations.
Levorphanol	4	2	12–15	4–6	
Fentanyl	—	—	7–12	—	Can be administered as a continuous IV or SQ infusion; based on clinical experience, 100 µg/hr is roughly equianalgesic to IV *morphine* 4 mg/hr.
Fentanyl TTS	—	—	16–24	48–72	Based on clinical experience, 100 µg/hr is roughly equianalgesic to IV *morphine* 4 mg/hr; a ratio of oral *morphine*:transdermal *fentanyl* of 70:1 may also be used clinically.

IM, intramuscular; SQ, subcutaneous; IV, intravenous; CR, controlled release; PO, oral; SR, sustained release.

[a]Studies to determine equianalgesic doses of opioids have used *morphine* by the IM route. The IM and IV routes are considered to be equivalent. (Note: SQ route is increasingly used.)

[b]Although the PO:IM morphine ratio was 6:1 in a single-dose study, other observations indicate a ratio of 2–3:1 with repeated administration.

From **Derby S, Chin J, Portenoy RK.** Systemic opioid therapy for chronic cancer pain: practical guidelines for converting drugs and routes of administration. *CNS Drugs* 1998;9:99–109, with permission.

Oxycodone **(available as immediate-release tablets, suspension, slow-release preparations, and suppositories) is somewhat more potent (20% to 50%) than *morphine***: *Oxycodone* is being most often used in a dose of 5 mg 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 (32). *Oxycodone* may be more effective in neurogenic pain, so may be helpful to relieve leg pain in patients with recurrent cancer of the cervix.

Meperidine (***pethidine***) **is of very little value in palliative care**. It has poor oral bioavailability and a short half-life, requiring frequent administration, approximately every 2 hours. 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, particularly for those who appear to have pain that is more difficult to control**. Its long half-life is sometimes disadvantageous, particularly in the elderly, and its sedative action may outlast its analgesic activity. It has mechanisms of action that differ slightly from those of *morphine*, having both opioid receptor activity as well as activity on the N-methyl-D-aspartate (NMDA) receptor pathways (33). Therefore, *methadone* is occasionally useful when higher doses of other opioids are reached with only partial or inadequate response. Conversion from *morphine* to *methadone* may be difficult, with subsequent dose reduction frequently required. *Methadone* has a similar side-effect profile to *morphine*.

Like *morphine*, *hydromorphone* is a mu agonist but with far greater solubility. It can be administered orally, intravenously, and subcutaneously with a duration of action and half-life similar to *morphine*. Its high potency allows smaller volume injections (34).

Fentanyl **offers a transdermal route of administration, enabling continuous administration of a short-acting opioid** (35). 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 that 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, which can then be incorporated into the TTS *fentanyl* dose**.

TTS *fentanyl* is more expensive, but is an attractive option because of the convenience of the delivery system and the slightly less troublesome constipation compared with *morphine*. If rapid dose escalation occurs (without evidence of rapid tumor progression) a change to another opioid may be wise and less expensive.

The development of transmucosal *fentanyl citrate* provides an immediate-release *fentanyl* formulation for breakthrough pain that offers rapid onset of analgesia and similar or improved response compared with immediate release *morphine* (36). Expense may dictate that traditional preparations are still chosen.

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*, or transmucosal *fentanyl citrate*).

Side Effects of Opioids

Side effects can be avoided in large part by precise prescribing. Although there are some side effects that are almost invariable, such as constipation, individual variation in side-effect profile may be used to advantage by substituting an alternative opioid.

Constipation occurs in most patients, and prophylactic laxatives should be prescribed. A reasonable laxative prescription would be *senna* and *sodium docusate* tablets twice daily. Fecal impaction, much more likely if opioids are 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 some oral medications (18). TTS *fentanyl* is slightly less constipating than slow-release *morphine* (35).

Nausea and vomiting may occur in association with opioid therapy 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 anti-nauseants such as *metoclopramide*, 10 mg four times daily [oral/subcutaneous injection (SQ)], or *haloperidol*, 0.5 to 1.5 mg twice daily (oral/SQ), should be available if required. Regular prophylactic antiemetics should be prescribed for at least the first 48 hours if the patient is very anxious or if there is a history of *morphine*-induced nausea or vomiting. If vomiting persists, an alternative opioid should be substituted. All opioids may cause nausea, but there appears to be individual but unpredictable variability in response between the drugs. The evolving field of pharmacogenetics may in the future provide some ability to predict an individual's response.

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. Confusion or hallucinations indicate either excessive dosage or an idiosyncratic reaction. Hydration—either orally, subcutaneously, or intravenously—may assist in eliminating troublesome metabolites while dose reduction is undertaken. If the pain is not well controlled in the presence of drowsiness or confusion, 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 taking *morphine* because of its histaminogenic properties. It usually settles within 48 hours and can be managed with judicious use of *promethazine*. It is rarely reported for other opioids. Anticholinergic side effects of *morphine* are usually not troublesome.

Tolerance to opioids may be a significant clinical problem if the drug is not introduced and calibrated correctly. When opioids are 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 the analgesic. ***Ketamine*, a drug used traditionally in anesthesia, has been found to reverse opioid tolerance for some patients with pain** (37).

Step Four: Recognize Neuropathic Pain and Treat Correctly

Neuropathic pain is a term used to describe those pain syndromes in which the pathophysiology is related to aberrant somatosensory processes that originate with a lesion in the peripheral or central nervous system. Neuropathic pain frequently develops in gynecologic cancer, especially in advanced cancer of the cervix. It may be due to tumor infiltration (notably lumbar plexopathy) 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 neuropathic in origin, an opioid and a peripherally acting drug should usually be supplemented by tricyclic antidepressants, anticonvulsants, or corticosteroids (38). In general, medications should be started at low doses and gradually increased as tolerated, but treatment of severe neuropathic pain is a challenge (39).

Ketamine, a drug used in anesthesia, **has been found in lower doses to be useful in the management of very complex pain, both somatic and neuropathic in origin**. *Ketamine* acts as an antagonist to the N-methyl-D-aspartate (NMDA) receptor system, a system frequently activated in refractory pain states when high doses of opioids appear ineffective. Low doses of infusional subcutaneous *ketamine* can reduce opioid tolerance and improve analgesia (37). It should be used in consultation with palliative medicine or pain specialists because of side effects such as hallucinations. However, it has an emerging role in refractory pain states.

Regional blockade with local anesthetic and neurolytic techniques may be worthy of consideration if the area of pain is circumscribed and attributable to an accessible peripheral nerve. Spinal analgesia may benefit a carefully selected small group of patients. Anesthetic opinion should be considered for patients who continue to have pain despite an adequate trial of analgesia according to steps one to four, or for those who have very severe incident pain, that is, pain on particular activity, such as weight bearing. (40).

Special Considerations in Pain Management

The Patient with Renal Failure

NSAIDs should be avoided, as they will frequently worsen renal function, and the use of *morphine* will result in the accumulation of active, analgesic *morphine* metabolites. Therefore, **if prescribing *morphine*, a dose reduction may be necessary, and more**

importantly, the interval between doses should be extended. Use of an alternative opioid such as *fentanyl* or *oxycodone*, which are reported not to have active metabolites, may be preferable.

The Patient with Reduced Motility of the Gastrointestinal Tract

The patient who has a hypomotile gastrointestinal tract, most commonly seen in patients with disseminated ovarian cancer, may have not only impaired peristalsis, but also impaired absorption of oral medication.

Motility may be further impaired by drugs such as $5HT_3$ blockers (e.g., *ondansetron*), which, although very effective antinauseants for patients having chemotherapy, may induce constipation. Consideration should be given to delivering analgesics via an alternative route, such as transdermal *fentanyl* or, for the very ill, subcutaneously or rectally. Similarly, alternative routes of analgesic administration should be sought for the patient with established fecal loading.

The Patient with Cognitive Impairment

Special mention needs to be made of the cognitively impaired patient who develops pain. The patient may not state that she has pain, but if she does, she should be believed. **Facial expression may assist in diagnosis unless the pain is chronic** (41); **other clues may include restlessness and agitation**. The family should be questioned about any behavioral changes they have observed. The possibility of painful fecal loading should be considered.

An assessment should include knowledge of the cancer pathology and its usual resulting symptoms, and the presence of any physiological indicators, such as tachycardia. Ultimately, diagnosis may require a therapeutic trial of analgesia and observation of the response.

Difficult-to-Manage Postoperative Pain

Occasionally, the management of pain in the postoperative setting is difficult. Possible reasons could include the following:

- Inappropriate use of the patient-controlled analgesic (PCA) device. **Patients who are cognitively impaired (including those developing a delirium postoperatively), those who are anxious or depressed, the very frail, and those for whom the language of explanation is not their mother tongue may all struggle to use a PCA device effectively**,
- The patient may have been on **opioids before surgery**. This must be factored into the postoperative analgesic orders, with the additional analgesia for the surgery added to the baseline requirements.

Extreme Patient Anxiety

Extreme patient anxiety disturbs pain threshold levels. Explanation, support, counseling, and anxiolytics may be necessary.

Gastrointestinal Symptoms

Gastrointestinal symptoms are common in gynecological cancer both because of the cancer and because of various aspects of treatment (42).

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 (43), but the expense is considerable. **Corticosteroids** have also been shown to improve appetite and daily activity of patients with cancer, but this effect is short lived, usually with return to baseline responses by 28 days. Because patients must then undergo the problems of corticosteroid withdrawal, patient selection is critical.

Mouth Symptoms

Mouth symptoms, including xerostomia, pain, and altered taste, can be most distressing.

A dry mouth can result from many factors in the critically ill patient: oral candidiasis, previous radiation therapy, mouth breathing, nasal oxygen, 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.

Frank pain can occur from treatment-related mucositis and infected ulcers, so mouth care is crucial in very ill patients. **Oral candidiasis is often overlooked**. It 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).

Altered taste, a not uncommon symptom in patients with cancer, is hard to relieve. Once all of the above causes of mouth pathology have been excluded, a dietitian may be able to assist in food choice and encouragement.

Nausea and Vomiting

Nausea and vomiting are common in advanced gynecologic cancer, and each symptom requires precise diagnosis so that rational therapy may be applied, but mechanisms are complex (44). **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. 23.4 and Table 23.2). The search continues for better understanding and consequently, for better therapeutic approaches.

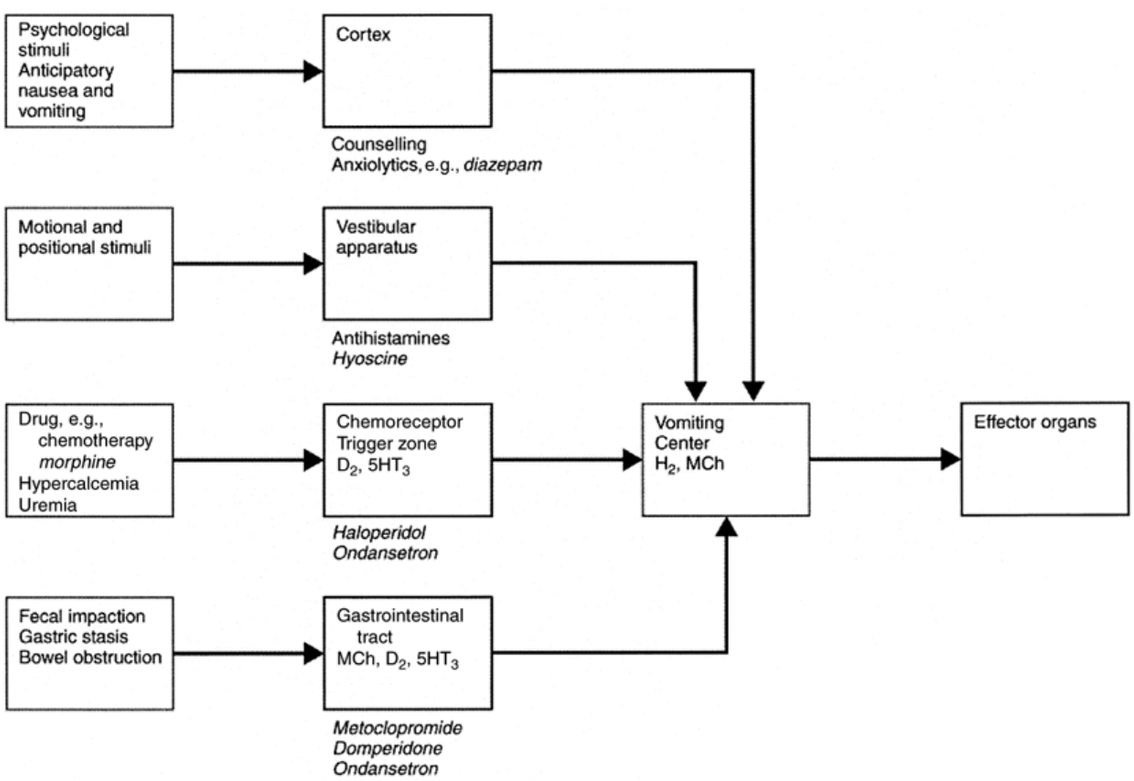

Figure 23.4 Factors that influence nausea and vomiting in the central nervous system and the gastrointestinal tract. Nausea, with or without vomiting, is mediated by the vomiting center.

D, dopaminergic; H, histaminic; MCh, muscarinic; $5HT_3$, hydroxytryptophan

Table 23.2 Emetic Stimuli, Sites of Action, and Antiemetics of Choice

Emetic Stimulus	*Site of Action*	*Class of Antiemetic*	*Antiemetic of Choice*
Emotional factors	Cerebral cortex	Benzodiazepines	*Lorazepam Diazepam*
Raised intracranial pressure	Vomiting center	Antihistamines	*Promethazine* or *cyclizine*
Meningeal metastasis		Corticosteroids	*Dexamethasone*
Motion and positional sickness	Vestibular nucleus	Antihistamines Anticholinergics	*Promethazine* or *cyclizine* *Hyoscine* or *scopolamine*
Drugs	Chemoreceptor trigger zone	Phenothiazine	*Levomepromazine*
Biochemical disorders		Butyrophenones	*Haloperidol*
Toxins		5-HT_3 antagonist	*Ondansetron*
Gastric distention		Antihistamines	*Promethazine* or *cyclizine*
Gastric irritation Intestinal obstruction Liver disease Constipation Abdominal cancer	Vomiting center	Anticholinergics	*Hyoscine*
Gastric stasis	Periphery	Orthobromides	*Domperidone, metoclopramide*

5-HT_3, 5-hydroxytryptamine (serotonin) group 3.
From **Lichter I.** Which antiemetic? *J Palliat Care* 1993;9:42–50, with permission.

Causal pathways 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 serotonergic receptors

Once the likely mechanism has been identified by means of a careful history, physical examination, and investigations if indicated, the appropriate antinauseant may be prescribed (Table 23.2 and Table 23.3). Recent work has cast doubt on the clarity of current ideas about mechanisms of nausea, but analysis continues to be useful in practice. It is especially valuable to differentiate gastric stasis from centrally induced nausea.

Table 23.3 Commonly Used Antinauseant Drugs

Drug	*Dose*	*Comment*
Metoclopramide	10–20 mg q 4 h (oral or subcutaneous)	Avoid if patient has bowel colic, or high gastrointestinal obstruction.
Haloperidol	1–3 mg bid or tid (oral) 0.5–2mg bid or tid	Lower doses required than when used as a sedative.
Prochlorperazine	5–25 mg bid or tid (oral or rectal)	May be useful if vomiting mechanism is unknown.
Meclozine	10–75 mg/day in divided doses (oral)	Antihistamine with doses that produce minimal sedation.
Cyclizine	25–100 mg/day in divided doses (oral, rectal, or subcutaneous)	Useful if patient has bowel obstruction.
Hyoscine	0.1–0.4 mg q 6–8 h (subcutaneous)	Central nervous system side effects can occur, particularly drowsiness and confusion.
Ondansetron	0.1 mg/kg q 8 h for three doses IV, 4–8 mg tid (oral)	Main use is for chemotherapy-related nausea. Constipation can be troublesome.

q 4 h, every four hours; IV, intravenous; bid, two times a day; tid, three times a day.
See text and manufacturers' information before prescribing; watch for side effects; review frequently; cease ineffective 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*) ***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. Similarly, *levomepromazine* (*methotrimeprazine*) is a phenothiazine with potent D_2- and α1-receptor antagonist and some $5HT_2$-receptor antagonist action. This means it is a broad-spectrum antiemetic, which is most commonly used as a second- or third-line drug when more specific drugs seem ineffective. It is significantly sedating, so is often reserved for patients in the final phase of their life (45).

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 or abdominal radiotherapy has become less of a problem for many patients with the introduction of serotonin antagonists, such as *ondansetron***. Such drugs may also be useful if nausea appears related to stimulation of the chemoreceptor trigger zone, but *haloperidol* is proving ineffective. The dose of a drug such as *ondansetron* should be kept to a minimum in patients with a tendency to constipation, because this is a serious side effect capable of interfering with analgesia.

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*, a $5HT_4$ agonist and $5HT_3$ antagonist, produces a prokinetic action, particularly on the upper gut. Although useful, particularly because it does not produce extrapyramidal side effects, *cisapride* has been largely withdrawn because of the occurrence of cardiac arrhythmias, thought to relate to its effect of prolonging the QT interval by an action on cardiac $5HT_4$ receptors (46).

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 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, psychosis, or severe emotional instability.

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, vomiting, spurious diarrhea, pain, and even confusion, especially in the elderly**. If unrecognized or untreated, it may result in inadequate absorption of oral medications including analgesics and even, rarely, perforation. Recent reviews highlight the diversity both of mechanisms leading to constipation and of classes of laxatives (Table 23.4) (47).

Table 23.4 Classification of Laxatives

I. Bulking or hydrophilic agents
- A. Dietary fiber
- B. *Psyllium (plantago)*
- C. *Polycarbophil*
- D. *Methylcellulose, carboxymethylcellulose*

II. Osmotic agents
- A. Poorly absorbed ions
  - *1. Magnesium sulfate (Epsom salt)*
  - *2. Magnesium hydroxide (milk of magnesia)*
  - *3. Magnesium citrate*
  - *4. Sodium phosphate*
  - *5. Sodium sulfate (Glauber's salt)*
  - *6. Potassium sodium tartrate (Rochelle salt)*
- B. Poorly absorbed disaccharides, sugar alcohols
  - *1. Lactulose*
  - *2. Sorbitol, mannitol*
- C. *Glycerin*
- D. *Polyethylene glycol*

III. Stimulant laxatives
- A. Surface-active agents
  - *1. Docusates (dioctyl sulfosuccinate)*
  - *2. Bile acids*
- B. Diphenylmethane derivatives
  - *1. Phenolphthalein*
  - *2. Bisacodyl*
  - *3. Sodium picosulfate*
- C. Ricinoleic acid (castor oil)
- D. Anthraquinones
  - *1. Senna*
  - *2. Cascara sagrada*

IV. Lubricating agent
- A. Mineral oil

V. Neuromuscular agents
- A. Cholinergic agonists
  - *1. Bethanechol*
  - *2. Neostigmine*
- B. $5\text{-}HT_4$ agonists
  - *1. Cisapride*
  - *2. Prucalopride*
  - *3. Tegaserod*
- C. Prostaglandin agonist
  - *1. Misoprostol*
- D. *Colchicine*
- E. Opiate antagonists
  - *1. Naloxone*
  - *2. Naltrexone*

Reproduced with permission from **Schiller LR.** The therapy of constipation (review article). *Aliment Pharmacol Ther* 2001;15:749–763.

Opioid-induced fecal impaction is usually avoidable, but if present, vigorous local treatment is required. This includes fecal softeners (e.g., *docusate-sodium*), large bowel stimulants (e.g., *senna*), stimulant suppositories, or careful enemas. Not infrequently osmotic laxatives (e.g., *lactulose*) may be helpful. Fecal impaction caused by a holdup at the sigmoid colon (with an empty, dilated rectum) sometimes requires high *docusate-sodium* enemas if oral laxatives fail to provide relief; suppositories may be ineffective.

Drugs other than opioids may also cause constipation. Most commonly implicated in this population would be $5HT_3$ antagonists (e.g., *ondansetron*) and tricyclic antidepressants. Constipation that is due to mechanical obstruction requires either surgical intervention or acceptance of the problem as an end-stage event.

Patients who have noted a reduction in the diameter of stools (so called “ribbon stools”) should avoid bulking laxatives, because any agent which increases the diameter of stools might precipitate a bowel obstruction.

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. Since the ground breaking work at St Christopher's Hospice, London (48), there have been several studies and reviews (49 ,50). The following represents a practical approach for the gynecologist.

Patients presenting with an acute bowel obstruction should initially be placed on nil by mouth and given intravenous fluids. If there is copious vomiting, nasogastric suction is helpful. If the obstruction is not relieved within 72–96 hours, a choice needs to be made between surgical intervention and medical management.

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. Occasionally, stents may be useful as a means of bypassing obstruction that is due to a defined tumor mass, but prolongation of life in such circumstances is a serious decision. In patients whose life expectancy is limited to 2 to 3 months, a nonoperative approach is usually preferable. Table 23.5 indicates some of the principles involved.

Table 23.5 Management of Gastrointestinal Obstruction in Patients with Gynecological Cancer

1. Is it an obstruction?

Clarify by:
- History
- Examination
- Investigation
  - Upright abdominal x-ray
  - Contrast studies
  - CT pelvis and abdomen

Clarify highest level of obstruction and likely mechanism.
Ensure relief of pain and nausea.
Treat conservatively initially with IV fluids and nasogastric suction.
If there is failure to resolve, and life expectancy ≥2 months, consider surgical exploration.

2. If surgery not an option:

Trial of steroids may be justified, e.g., 4–8 mg/day SQ for 3–5 days. Watch for emotional shift, worsening of infection (e.g., thrush), or instability of diabetes.
If clearly end stage, have clear goals.

If "high" obstruction:
- Decrease fluid intake (negative fluid balance).
- Decrease fluid production from and relax gastrointestinal tract with *hyoscine hydrobromide* 60–200 mg/day or *octreotide* (SQ).
- Continue to relieve discomfort with *morphine* (SQ) or rectal *proladone*.
- Continue to relieve nausea with *haloperidol*, e.g., 1.5–3 mg at bedtime.
- Perform exquisite mouth care.
- Do not check electrolytes.
- Consider venting gastrostomy.

If "low" obstruction:
- Be prepared to reconsider colostomy if disease is slowly progressive and more time is desired.
- If colostomy not an option:
  - Reduce abdominal discomfort with *morphine* (SQ).
  - Continue *hyoscine hydrobromide* (low dose) to relax gut as well as decrease fluid production; consider *octreotide*.
  - Could consider *metoclopramide* (SQ) to keep upper gastrointestinal tract empty (and reduce vomiting), especially if bowel sounds in upper abdomen are much reduced suggesting gastric stasis or if reflux is present. (Do not use *hyoscine hydrobromide* and *metoclopramide* together!)
  - Maintain a light diet if tolerated.
  - Keep in negative fluid balance.
  - Do not check electrolytes.

3. Recognize when the patient is actually dying.

Continue all of above measures until she dies (possibly with increased sedative/tranquilizer).
Anticipate sphincter relaxation (in high obstruction) at moment of death.

CT, computed tomography; IV, intravenous; SQ, subcutaneous.

One option for conservative management of obstruction at high or low levels is a trial of corticosteroids (e.g., *dexamethasone*, 4 to 8 mg parenterally daily for 3 to 5 days) (50). This presumably works by decreasing inflammatory edema, thereby improving luminal diameter. It may be repeated in the future. 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 high end-stage obstruction, when the aforementioned measures have failed to relieve the problem, **a conservative medical approach may be helpful. 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 opioid analgesics. Gastrokinetic antinauseants (e.g., *metoclopramide* or *domperidone*) are contraindicated.

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* (SQ) is often very helpful as an alternative to *haloperidol*. *Octreotide*, starting at a dose of 50 micrograms subcutaneously every 8 hours, can provide additional relief of symptoms by further reducing secretions and colic. Doses greater than 600 micrograms per day probably do not afford additional benefit. Tolerance to this medication may occur, and it is expensive.

Some patients prefer occasional bouts of vomiting to a continuous nasogastric tube. If the obstruction is very high, a percutaneous gastrostomy to allow venting 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 conservative medical approach to high 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.

Low bowel obstruction causes quite different symptoms, commencing with reduced then absent defecation, followed by severe abdominal distention, and later nausea and vomiting. If colostomy is not to be undertaken, the focus is on relief of discomfort with low-dose opioids. Subcutaneous *morphine* or transdermal *fentanyl* may be the drugs of choice. If nausea occurs, antinauseants are useful. *Metoclopramide* subcutaneously may help keep the stomach empty and may be combined with a centrally acting antinauseant (such as *haloperidol* or *cyclizine*). A very light diet may be tolerated if the patient wishes to try to eat.

Bowel Hypomotility

Hypomotility of the bowel can present with symptoms of bowel obstruction, vomiting, and constipation, but without the characteristic radiological signs. It is most frequently seen with disseminated ovarian cancer, where there is infiltration of the mesentery and presumed infiltration of the myenteric plexus, or where there is extensive paraaortic lymphadenopathy. It may be seen rarely in association with autoantibodies as a paraneoplastic phenomenon. **Abdominal radiographs are frequently normal or characterized by significant fecal loading**. Such patients, on closer questioning, will frequently describe a slowing of bowel movements over some weeks and will demonstrate a paucity of bowel sounds. Medication is aimed at increasing bowel peristalsis using infusional *metoclopramide*, 60 to 90 mg subcutaneously over 24 hours. Our own experience suggests corticosteroids (*dexamethasone* 4 to 8 mg daily) may also be useful for this group (50).

Hypomotility or dysmotility of the bowel sometimes follows apparently successful surgery for bowel obstruction. The condition may be temporary and related to the surgery, or it may be longer lasting and related to the underlying malignant infiltration. The difficulty facing the clinician is how best to support such patients postoperatively, particularly with respect to nutritional support. There is little literature to inform such a decision, and as always, it should be based on the patient's disease status, her performance status, the anticancer options still available, and her personal goals.

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.

Cases have been reported of the successful use of *octreotide* to reduce small bowel fistula drainage (51). 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, often in combination. Occasionally, resection of tumor or colostomy to bypass it as a palliative procedure may be justified. In severe cases, spinal local anesthetics or sacral nerve blocks may be necessary.

Many of the gastrointestinal symptoms (which are such a feature of gynecologic cancer) are disturbances of gastrointestinal motility. This subject is a focus of intense research, and the mechanisms involved are becoming more clear (52). The gynecologic oncologist needs to recognize the following:

- Gastrointestinal motility disturbances, such as a tendency to constipation and reduced bowel sounds, may be a feature of gynecologic cancer even before any use of opioid drugs.
- Drugs prone to constipate should be used with caution in such patients. For example, opioid drugs must always be accompanied by laxatives. The use of $5HT_3$ blockers as antinauseants in the postoperative period or as premedication for chemotherapy should be minimized if possible.

Ascites

Abdominal distention that is due to intractable ascites can be a major cause of distress. **Paracentesis, often unavoidable, needs to be minimized because of loss of protein, potential circulatory disturbances, and the potential for tumor implantation in the puncture site**. Diuretics, particularly *spironolactone*, 50 to 150 mg/day, if necessary coupled with a loop diuretic, may prove helpful initially. 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. Discomfort is usually controlled with a combination of a 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 that is 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, or the cause of dyspnea is not reversible, the careful use of *morphine* may improve the situation significantly, especially if the respiratory rate is increased. 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 with daily 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 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 goals are short term, for example, to prolong life for a few weeks (53).

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 by urinary 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 (54). **Compression bandages or support hosiery should not be applied to grossly edematous legs because venous circulation may be further compromised**.

Rarely, a patient who has serious nutritional deficiency (for example, associated with several weeks of nausea and anorexia) **may exhibit severe edema that is due to thiamine deficiency**. This is classically associated with an increase in jugular venous pressure and a bounding pulse. If recognized, improvement may be dramatic, occurring within 24–48 hours of giving thiamine.

Weakness

Weakness or fatigue can be profound when there is a large tumor burden, but there are many **reversible causes of this symptom** (55). **These include nutritional deficiencies,**

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, psychotic symptoms** (notably paranoia), **and exacerbation of bone 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, 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 (56).

Treatment of hypercalcemia depends on its severity. The following measures are necessary in moderate or severe cases:

- **Modest 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* 60 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*.

Improvement of symptoms with these measures can be expected within a few days, as calcium uptake in bone increases. When calcium is extremely high and intravenous bisphosphonate therapy is not causing a rapid reduction, subcutaneous *calcitonin* administration combined with bisphosphonate therapy may provide a more rapid reduction of calcium levels, but administration of *calcitonin* always warrants specialist assistance.

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 Patient Close to Death

Part of "23 - Palliative Care and Pain Management "

Good palliative care is concerned with the enrichment of life, even when facing the human task common to all, that of dying (57 ,58).

It is important to recognize that a woman is actually dying; this is an important diagnosis with clinical as well as social implications. What is medically possible at this stage, such as treatment of renal failure, septicemia, or hypercalcemia, may not necessarily be medically wise.

There are many indicators that a patient is actually dying, and these are well known to clinicians, although not necessarily to 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.

There are also psychological signs that a patient is dying. An experienced clinician may note 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**.

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. There are circumstances in which a patient should be able to sleep peacefully as she dies. **This is particularly the case if an agitated delirium is present** after treating any remediable factors such as fecal impaction, urinary retention, or unrelieved pain. Management in these instances depends on the predominant features: **If hallucinations are prominent, an antipsychotic may be most useful, whereas if agitation and distress are present, a benzodiazepine should be used**, either alone or in combination with an antipsychotic. Suitable benzodiazepines include *midazolam* (2–5 mg subcutaneously, intramuscularly, or intravenously stat and 10–50 mg over 24 hours by subcutaneous infusion if distress is protracted) or sublingual *lorazepam* (0.5–2.5 mg every 4–6 hours). Antipsychotics used commonly would include *haloperidol* (0.5–5 mg twice daily orally or subcutaneously), *risperidone* (0.5–1 mg twice daily orally), or *olanzapine* (2.5–10 mg daily orally or buccal wafer). *Chlorpromazine* (50–100 mg twice daily rectally) is an old drug that may still prove to be useful.

On rare occasions, distress and agitation may not be relieved with the combination of a benzodiazepine and an antipsychotic. In such circumstances, careful dosing of *phenobarbital* (50–100 mg twice daily orally or subcutaneously) **may allow calm in the final part of life. Large doses of opioids are not appropriate for sedation of the dying**. Ensuring that a patient sleeps most of the time during the last hours (or few days) of her life is not euthanasia.

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. **It is a crucial period of personal development and a time for clarifying, reconciling, healing and/or affirming personal relationships—always a complex task at the close 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. (58)

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** (59).

No patient should die in despair. Unrealistic expectations may increase, not relieve, suffering (60). 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 care of patients with incurable, progressive disease is concerned with enrichment of remaining life, with reduction of relievable distress, and with support for personal growth and development, even when facing the human task common to all, that of dying**.

Careful clinical decision-making is crucial not only to optimize control of the cancer at the time of diagnosis, but also to optimize the mode of death when curative options have failed. Decision making is complex (Fig 23.2), and the issues are profound. Cultural, legal, as well as personal issues influence the climate in which decisions are made, and the way traditional ethical principles are conceived. The exercise of wisdom is a profound challenge. **The question must be asked, in some very difficult circumstances, of what will this woman be allowed to die?**

What does this mean in practice? An example may illustrate.

Ureteric obstruction is common in recurrent cervical cancer. Stenting the ureters will usually correct renal function, but the patient may subsequently experience more distressing symptoms such as leg pain that is due to lumbar plexopathy or bone pain that is due to local infiltration. Hence, the consequences of stenting may be some short-term prolongation of survival at a cost of increased suffering at the end of life.

Similar issues arise with the application of bowel-stenting procedures in a patient with advanced cancer. Death may be postponed, but at a high cost.

Clearly, far more discussion is needed, especially in tertiary cancer centers, where treatment options are abundant: **ethical transparency, in accord with an adequate grasp of the human condition, is a challenge for the twenty-first century**.

A Final Note

Mention has been made of the suffering of patients. Nothing has been said of the distress of the caring multidisciplinary team—especially that of nurses. Mention should also be made of the often not articulated distress of doctors responsible for women living with, or dying with, distressing gynecological cancers. The sensitive clinician may take comfort from the words of a French oncologist:

Suffering is something like crossing a sea, traversing a mountain or a desert; it is an experience, painful indeed, in which the person will become more oneself and will discover oneself; it is an experience in which a person will experience evil, and yet, at the same

time, will be led to discover and express the deepest meaning of one's life. This is true also for the suffering of the doctor. (61)

However, the burden of distress remains with women with gynecologic cancer, especially in situations of oppression, poverty, and exploitation. Competent as well as compassionate palliative care may salvage dignity and meaning for the individual and serve as a catalyst for change in the depths of the global village. Few doctors have such an opportunity.

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24
Psychological Issues

Kristen M. Carpenter

Barbara L. Andersen

For most women, a diagnosis of gynecologic cancer is a crisis, followed by a period of extreme emotional distress that slowly dissipates with recovery. For others, cancer might become a chronic stressor, a way of life, either because the disease is disseminated and can be controlled only with radical treatments or because coping strategies are not adequate for this life experience. In any case, **management of patients with gynecologic malignancies must 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.

- Screening
- Diagnosis
- Intervention
- Cancer Treatment
- Recovery
- Intervention

Screening

Part of "24 - Psychological Issues "

Research suggests that **individuals become distressed during medical screening, long before a cancer diagnosis is suggested** (1). Reelick and colleagues (2) described negative reactions to abnormal Papanicolaou (Pap) test results in a sample of 350 women. **Common responses include tension and depression**. These reactions are pronounced in younger women and women who want to become pregnant, along with women worrying about test results at the time of screening. Lerman and colleagues (3) reported that women who receive abnormal Pap results have significantly elevated worry about cancer and disruptions in mood, daily activities, sexual interest, and sleep patterns compared with women with normal results. A similar study reported that women undergoing cervical cancer screening who received abnormal Pap results scored significantly higher on anxiety measures than did women who received normal results (4).

The relationship between increased psychological distress and nonadherence to screening and treatment recommendations is well documented in cancer patients [e.g., breast cancer (5 ,6)]. Specific to gynecologic cancer, **women with high levels of distress are less likely to comply with biopsy recommendations following an abnormal Pap result than women with low levels of distress** (3).

The issue of treatment nonadherence can be addressed through brief, low-cost interventions aimed at reducing distress. For example, Stewart and colleagues (7) prepared a brief psychoeducational brochure for women who had received abnormal Pap results and were referred for biopsy. Results demonstrated that women who received the brochure were significantly less distressed and significantly more likely to comply with treatment and follow-up 18 to 24 months later than women who had not received the materials. More than 75% of women who received the materials complied with treatment and follow-up compared with 46% of women not receiving the materials.

Diagnosis

Part of "24 - Psychological Issues "

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 during treatment (8). **The emotions and sources of distress may include:**

- **Depression** from life disruption and doubts concerning the future.
- **Anxiety** anticipating cancer treatment.
- **Confusion** from dealing with a complex medical environment.
- **Anger** from the loss of childbearing capacity and the opportunity to choose whether to have children.
- **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.

Since this early clinical work, several authors have reported specific emotional reactions to a diagnosis of gynecologic cancer and have found that psychological distress is common. In a prevalence study of psychiatric illness among patients with cancer, Derogatis et al. (9) 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 more recent review of studies using psychiatric criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (10), Thompson and Shear (11) reported that **as many as 23% of gynecologic cancer patients met diagnostic criteria for a major depressive disorder, much higher than the estimated incidence of 5% to 6% in the general population** (12 ,13). Reports of clinically significant depressive symptoms (14 ,15), anxiety symptoms (14), and worry, irritability, and frustration (15) are common. In general, depression is more common for those patients who have advanced disease, who are receiving palliative rather than curative treatment, and who are experiencing pain or other disturbing symptoms. Patients with a history of affective disorder or alcoholism are also at risk of depression (15 ,16 17).

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 (18). 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:

- Only women with cancer described themselves as significantly depressed.
- In contrast, high anxiety was reported by both groups with disease, whether benign or malignant.
- There were no differences in the level of anger between the groups.
- High levels of confusion were reported only by the patients with cancer.
- There were equivalent levels of fatigue among the disease groups.

Recurrence

Patients with recurrent cancer have even greater levels of distress than women receiving their initial diagnosis (19). This might result from higher levels of depression, hopelessness, and anger. Women with recurrent gynecologic cancer, compared with gynecologic cancer survivors who are disease-free, also report significantly higher levels of irritability and body image disruption and lower levels of general health and fitness (20). In contrast, the levels of anxiety and confusion are comparable with those reported by women receiving their initial diagnosis. Thus, the worries of a poorer prognosis, anger about treatment failure, and anticipatory concerns about beginning further treatment are evidenced.

Acute fear is also salient for women with recurrent gynecologic cancer. In a sample of patients with recurrent disease faced with the prospect of end-of-life decisions, Roberts and colleagues (21) found that 39% exhibited acute fears, the most common being fear of abandonment (32%) and fear of social isolation (17%). Taken together, these results suggest that difficult decisions associated with recurrence are made in a context of the emotional distress and physical debilitation.

Intervention

Part of "24 - Psychological Issues "

Severe emotional distress resulting from a cancer diagnosis and cancer treatment can be reduced with psychosocial interventions. Two studies, both using nonequivalent control group designs, have explored the effectiveness of brief psychological interventions for patients with gynecologic cancer.

Capone et al. (22) **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).

Houts et al. (23) **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 audiotaped description of the coping strategies at the pretreatment hospital visit. Two social workers were the peer counselors, although the patients were unaware that the counselors were cancer survivors. Thirty-two women (stage not specified) participated (14 intervention and 18 control). 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 moderate to severe problems with sexual functioning (18 ,24).

More recently, McQuellon and colleagues (25) developed a brief oncology clinic orientation program in the hope of reducing anxiety, distress, and uncertainty for newly diagnosed cancer patients. It lasted approximately 15 to 20 minutes and comprised a tour of the oncology clinic, a verbal description of the clinic's administrative procedures, a handout including important phone numbers and maps, and a brief question and answer session in which patients were encouraged to address all medical questions to the medical staff. One hundred fifty subjects who attended the clinic for their initial consultation were recruited. They were randomized into the treatment and assessment-only groups. When assessed 1 week after their initial visit, anxiety and mood disturbance decreased significantly for subjects who received the intervention, whereas distress increased for women in the assessment-only group.

These and other intervention studies involving patients with newly diagnosed cancer focus on the trauma of learning that one has a life-threatening illness (26 ,27 ,28). **Regarding psychological support, a crisis intervention or brief therapy model appears to be most appropriate. This provides an early assessment of the patient's emotional distress and other difficulties, a present-day focus on the immediate problems facing the patient, and limited therapeutic goals**. The therapist is active in making suggestions for coping and problem management. **Therapeutic components may include (i) 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, **(ii) information about the disease and treatment, (iii) behavioral coping strategies** e.g., role-playing difficult discussions with family or the medical staff, and **(iv) 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 also be useful.

The studies of women with cancer, specifically gynecologic or breast cancer, highlight the need for focused interventions for sexual functioning (24 ,29 ,30). Briefly, at least three components are essential: (i) **sexuality information** (e.g., male and female sexual anatomy, the sexual response cycle, sexual dysfunctions, and potential sources of difficulty after cancer treatment), (ii) **medical interventions** (e.g., hormonal therapy, reconstructive surgery), and (iii) **specific sexual therapeutic suggestions**.

Because psychological interventions may not alleviate all problems, such as loss of control and dependency on others, **pharmacologic agents may be useful**. Unfortunately, systematic research on their use and utility in cancer patients is sparse (31). The few available controlled trials have yielded promising results. For example, ***thioridazine*** **(75 mg daily) is superior to placebo in relieving the distress of patients with cancer**

experiencing anxiety or depression (32). 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 (33). More research is needed to determine which agents alleviate distress among specific groups of patients, but **available data suggest that the use of antidepressant medication in this population is increasing** (34 ,35).

Cancer Treatment

Part of "24 - Psychological Issues "

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 difficulties. These include (i) **problems understanding and remembering all that they have been told**, including simple information (e.g., what time they are to be admitted) or more complex information (e.g., the organs to be surgically removed and the nature of the side effects); (ii) **difficulty managing personal affairs** e.g., contacting one's insurance company or arranging for child care during recovery; and (iii) **difficulty with being a "patient"** and allowing others to care for one's needs.

Even for those with some previous knowledge, cancer treatment is 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 dysfunction). 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 women undergoing surgery for benign conditions (e.g., uterine fibroids). This research suggests 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 (36) 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 become distraught and have feelings of loss if their childbearing capability must be taken away from them to treat their cancer**. 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 has increased. 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 (37 ,38).

Intervention

Efforts to reduce distress from surgery or to facilitate recovery are typically informational. **Detailed descriptions of the procedure, sensations, or side effects and behavioral coping strategies (e.g., relaxation training or distraction exercises for pain management) have proved effective**. 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 (39 ,40). 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 (41).

External Radiation

External beam 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 is 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 (42). 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 routine, many patients report less emotional distress, but the side effects of fatigue, diarrhea, and anorexia begin. Side effects complicate living, requiring 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 flashes, 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 (43), as well as other patients with cancer (44), 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 slow. Nail et al. (45) 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 treatment. 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 (46). During intracavitary radiation, women report significant physical discomfort, even when there has been liberal analgesic medication (47). Gas pains, burning sensations, and lower backache are typical physical symptoms, 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 are reported to experience elevated levels of anxiety after their second application (48).

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** (44 ,47 ,48):

- **Those who exhibit relatively little emotional distress before treatment**
- **Those with a history of emotional problems**
- **Those with a disease causing chronic discomfort**
- **Those who are socially isolated**

Several strategies may be useful to address the anxiety-based concerns of the patient. General counseling focused on the patient's problems may be offered. For example, Forester et al. (49) 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; patients receiving intervention reported lower levels of emotional distress and less severe side effects.

Other interventions have focused primarily on provision of information. Topics 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 (50) 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. Alterations to the vaginal anatomy, including vaginal shortening and stenosis, begin during the course of radiation treatment (51). **Dyspareunia is the most frequent symptom**, 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 (24). 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 (52). Even with 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, because 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 to reinforce her understanding and to correct any 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** (53). This mix of emotions reflects the distress at having to undergo a difficult treatment, which many believe is only for “hopeless” cancers, and the fear that it will not control the disease. To allay patients' concerns, medical personnel usually provide descriptions of, and written materials about, the effects and side effects of treatment. In spite of this, as many as 10% of patients report uncertainty and lack of knowledge when beginning treatment (53). 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. Active coping and seeking social support are negatively correlated with anxiety and depression in gynecologic cancer patients receiving chemotherapy, whereas avoidance is positively correlated with both (54). In addition, women who attempt to control the side effects and fail become more distressed than those who report that they have coped successfully (53).

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 (55 ,56):

- **Age less than 50 years**
- **Lengthy infusion and higher doses of chemotherapy**
- **Severe posttreatment nausea or vomiting in the early cycles**
- **Extreme anxiety and/or depression**
- **Previous susceptibility to nausea and/or motion sickness**

Additionally, women with higher levels of state anxiety tend to be more susceptible to both anticipatory and posttreatment nausea and vomiting (57).

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 (58), 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** (56 ,59):

- **Hypnotic or biofeedback-assisted relaxation training**
- **Systematic desensitization**
- **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 (56). “Live” rather than audiotaped relaxation training instruction is more effective.

Recovery

Part of "24 - Psychological Issues "

Psychological

For decades, there has been the clinical impression that psychological and behavioral outcomes after cancer diagnosis and treatment were unsatisfactory (60 ,61 ,62). **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** (63 ,64). Longitudinal data also confirm this scenario for patients with gynecologic cancer. Emotions are within the normal range by 6 to 12 months posttreatment (65 ,66).

Lingering emotional distress from the trauma of diagnosis, treatment, and more generally, life threat, may occur for a small subset of patients with cancer (5% to 10%). 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 psychiatric diagnosis of posttraumatic stress disorder (10). Such distress occurs 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). Patients with a prior history of psychiatric treatment and/or traumatic stress may be at increased risk (67).

Some cancer survivors may need to cope with the expected but nevertheless troubling permanent sequelae of the disease or its treatment (e.g., infertility). This will demand new behaviors or emotions. Others may have to cope with losses such as a sexual relationship that no longer includes intercourse. Late side effects of cancer treatment, such as fatigue, pain, and constipation, are common in the first year posttreatment and can last up to 5 or more years posttreatment (68). Such changes in one's general health can have important consequences for psychological well-being (54).

Despite these possibilities, longitudinal data indicate that if the disease is controlled, the severe distress of diagnosis dissipates and emotions stabilize within 1 year of treatment. The first longitudinal studies conducted in the United Kingdom for patients

with breast cancer indicated that by 12 (69) and 24 months (70), 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 patients with breast cancer (71 ,72 ,73), gynecologic cancer (18 ,65 ,66), Hodgkin's disease and non-Hodgkin's lymphoma (74) have indicated no differences between the level of emotional distress of those with cancer and comparison subjects who either had benign disease or were 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**.

Sexuality

Increased national attention has been given to the sexual difficulties of patients with cancer (75) and to women with gynecologic cancer in particular (76). **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 resumption of sexual activity after treatment, all patients have indicated that these are important concerns that need to be addressed (37 ,38 ,77 ,78).

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, crossover experiment in women with surgically induced menopause (79). 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 (80). 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 (81).

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 (82) 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, ovarian, and vulvar cancer have been less well studied.

Cervical Cancer

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 (83).

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 sexual functioning 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 ,82). Many oncologists believe that radiation therapy is significantly more disruptive to sexual functioning than surgery, although one prospective study documented that surgery and radiation therapy produce comparable rates of disruption, with 30% to 40% of all patients experiencing significant sexual problems (84).

The most comprehensive descriptive study of sexual outcomes in women with gynecologic cancer comes from Andersen et al. (18 ,24). 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 related 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).

Table 24.1 Sexual Dysfunction Diagnoses According to Gynecologic Conditiona

	Sexual Dysfunction (% Affected)			
Group	***Desire***	***Excitement***	***Orgasm***	***Dyspareunia***
Cancer	32%	29%	29%	29%
Benign	13%	20%	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.

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 (38 ,85 ,86 ,87). 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 as a result of impaired 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 (88). 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** (89 ,90). 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 (91).

Andersen et al. (77) retrospectively studied sexual outcomes after vulvectomy versus wide local excision for patients with *in situ* vulvar disease. A pattern of sexual disruption was found. The patients 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 patients were not sexually active at follow-up. Greater sexual difficulties were experienced by those who underwent total vulvectomy.

Radical vulvectomy used to be the routine treatment for invasive vulvar cancer, but individualized treatment and less radical surgery have become the standard (92 ,93). **Radical vulvectomy causes substantial emotional and sexual disruption** (37). **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 (94 ,95).

Ovarian Cancer

Stewart et al. (96) retrospectively studied sexual and other quality-of-life outcomes in a sample of 200 women previously treated for ovarian cancer. **Fifty-seven percent reported that their cancer and its treatment had disrupted their sexual lives**. In fact, 75% rated their posttreatment sexual lives as adequate to poor, compared with 36% pretreatment. Sociodemographic and disease variables were related to sexual outcomes. Specifically, women treated with radiation therapy reported more severe/frequent symptoms, and younger women reported a greater sense of loss regarding their sexuality.

Wenzel and colleagues (97) conducted a similar retrospective investigation of 49 ovarian cancer survivors. Patients were assessed at least 5 years posttreatment, and rates of sexual difficulties remained high: 37% reported decreased libido, 28% decreased arousal, 13% difficulties with orgasm, and 20% difficulty engaging in intercourse as a result of treatment. Only 25% reported that they were sexually active at the time of follow-up, although 65% had access to a sexual partner. Thus, **the incidence of sexual difficulties among ovarian cancer survivors is comparable to that of women with other disease sites and appears to be long lasting**.

Intervention

Part of "24 - Psychological Issues "

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 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 intervention development is described.

Preparation

Physicians and nurses need to be familiar with 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 a plan for providing psychosexual assistance. For the individual patient, **preventive rather than rehabilitative efforts are desirable**. This should include the routine provision of sexual information to patients (97). Longitudinal data indicate that if sexual difficulties develop, most are evidenced in the early months of recovery (98); therefore, **information should be provided before and immediately after treatment as patients resume sexual activity**. With a preventive program in place, there will be fewer cases of severe sexual difficulties. Patients returning for follow-up need to be informed of the availability of referral resources for sexual problems.

Assessment

A brief sexual history should be obtained from all patients before treatment. **Obtaining a sexual assessment can achieve three goals:**

- **It identifies sexuality as an area of importance to the patient** with gynecologic cancer.
- **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.
- **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 determinant of the frequency of sexual activity for a woman is the presence of a healthy and interested sexual partner, not age per se** (99). 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 (100 ,101) or sexual arousal (102). The following areas can be briefly surveyed during a discussion with a patient:

- Marital status and availability of current sexual partner(s)
- Body image concerns
- Frequency of sexual activities (e.g., intercourse)
- Presence of female sexual dysfunction (e.g., lack of desire, orgasmic difficulties)
- Presence of sexual dysfunction in the partner (e.g., premature ejaculation, erectile difficulties, sexual difficulties secondary to medication usage)

Subsequent assessment should be more problem focused. Specific suggestions can be made based on the problem areas identified in the initial assessment. For patients with substantial sexual disruption or diagnosable sexual dysfunction, such as hypoactive desire disorder or sexual arousal disorder, referral to a trained professional is indicated (103).

Treatment

There have been few clinical (104 ,105) and empirical (22 ,106 ,107) reports of sexual intervention for female patients with cancer. Investigators have provided brief counseling to patients with gynecologic cancer on a variety of topics, such as causes of cancer, relaxation training, diet, exercise, and sexuality (22 ,108). Sexual function was significantly less disrupted among counseled patients than among control patients.

Provision of Information

Information per se is an important component of sexual therapy interventions (109). Gamel and colleagues (107) provide a review of the nature and timing of information that should be provided to gynecologic cancer patients. **At the time of diagnosis and treatment, patients should be well informed of the potential direct effects that the treatments might have on sexuality**, such as changed general health (e.g., chronic fatigue), structural changes to the genitals, hormonal changes, and interference with the physiologic components of the sexual response cycle. **During early recovery** (within 6 weeks of surgery), **the range of sexual behaviors possible after treatment should be outlined**, as should management of physical changes and complications of treatment. **During extended recovery, health-care professionals should discuss the long-lasting sexual complications and difficulties**. 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 (110) for a complete discussion]. For example, hormonal medication may be used for menopausal symptoms, a Fenton's operation may be necessary to treat introital stenosis after vulvectomy, and the regular use of a sterile lubricant may be necessary for patients undergoing radiation therapy. Despite these efforts, certain sexual activities may remain impossible. Vaginal stenosis may be impossible to correct, 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:

- **Determining what conditions for sexual activity are more or less appealing** and encouraging sexual activity under the most desirable circumstances

- **Increasing the frequency and variety of intimate activities** (not only sexual behaviors) that the woman might find pleasurable
- **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 masturbatory 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:**

- **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.
- **The activities are not strenuous**, which is helpful to the woman who is not fully recovered or who tires easily.
- **The activities do not focus on a particular area of the body**, and one objective is to find new, previously unexplored areas or methods of stimulation.
- **Touching 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 (111). 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** (112 ,113) **or individual sensate focus exercises** (114 ,115), **have proven 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 (116). This information helps her to decide when it might be most comfortable to resume intercourse.

Only one controlled intervention study has focused on sexuality in gynecologic cancer. Robinson et al. (116) evaluated the effectiveness of a psychoeducational group in improving sexual outcomes for women with early-stage cancer receiving both intracavitary and external beam radiotherapy. Thirty-two women who completed the study were randomized to the control (n = 14, 43.8%) or intervention (n = 18, 56.2%) group. Disease sites included the cervix (control, n = 10, 71.4%; intervention, n = 14, 77.8%) and endometrium (control, n = 4, 28.6%; intervention, n = 4, 23.2%). The control condition included a brief counseling session in which subjects received a booklet on sexuality and cancer and were directed to the appropriate sections to answer any questions. The intervention comprised two 90-minute group sessions with three components: information (extensive verbal and written instruction about sexuality and cancer), motivation (“sex can be pleasurable despite cancer treatment”), and behavioral skills (instruction on use of dilators, lubricants, and Kegel exercises). Subjects were assessed before randomization and every 3 months thereafter for 1 year. At baseline, intervention women had lower sexual functioning scores than controls, so sexual functioning was included as a covariate in all statistical analyses. Analyses revealed that **women receiving the intervention had significantly less fear about sex after treatment. They were also significantly more likely to follow recommendations for vaginal dilation than women in the control arm**; this was particularly true for younger women. Forty-four percent of women aged 41 and younger in the intervention complied with dilation recommendations, compared with 6% of controls.

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 innervations. 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 (117 ,118).

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 to enhance sexual arousal in healthy women (119) and sexually dysfunctional women (120) and as a treatment for dyspareunia (121). In gynecologic cancer, it might have some role, for example, in providing feedback during masturbatory 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. **Few controlled trials of these techniques have been conducted to date**; however, there are sufficient behaviorally oriented techniques available that preventive and rehabilitative efforts can begin.

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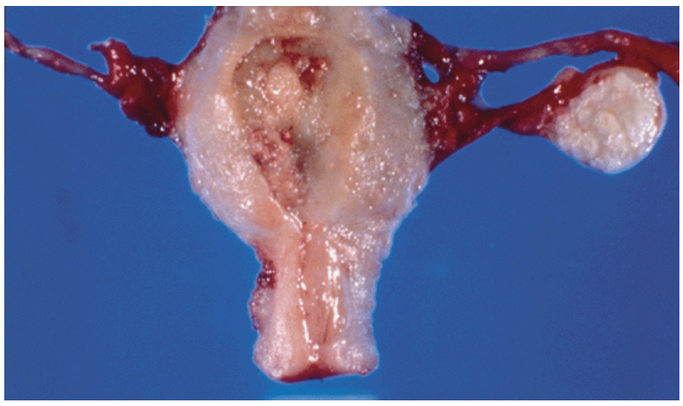
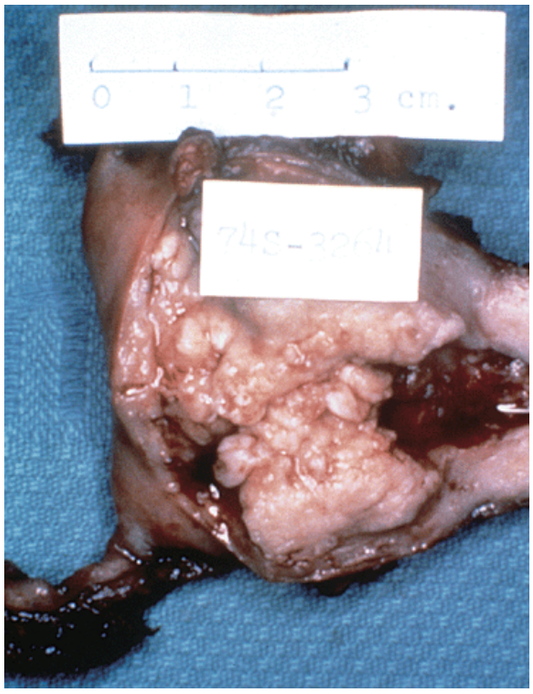
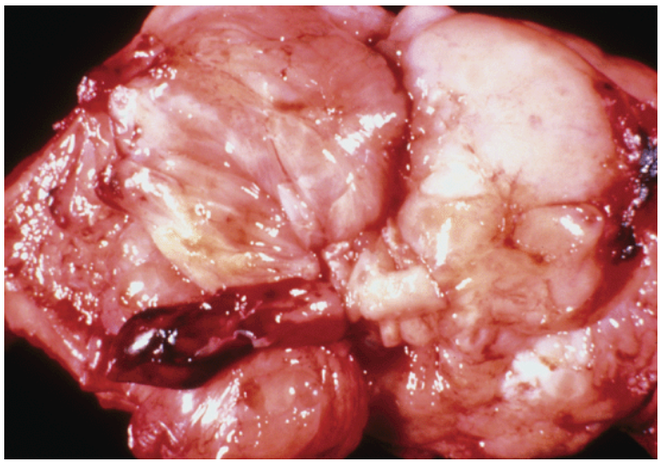
Color Plates



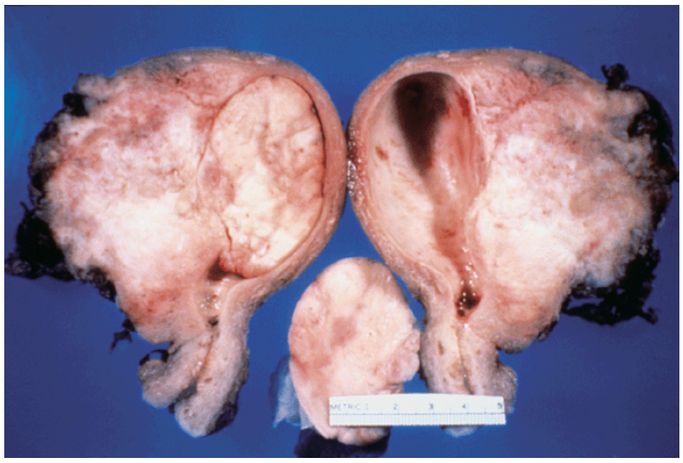
Color Figure 6.39 Serous carcinoma of the endometrium. The tumor is a polypoid mass arising in an atrophic uterus. Extensive myometrial lymphatic spread and involvement of the ovary were seen. (See **Figure 6.39**).



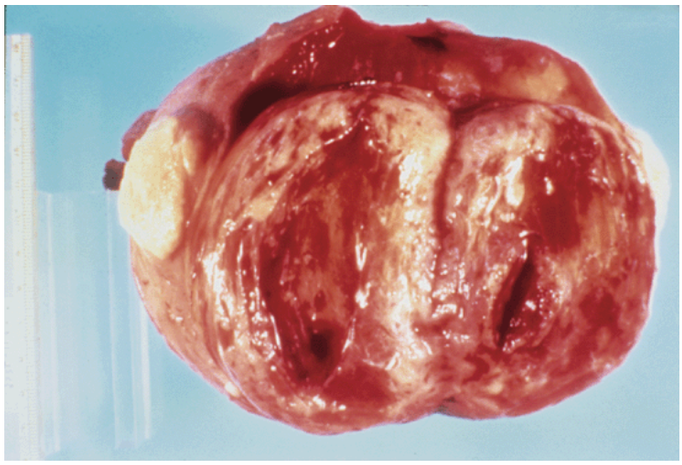
Color Figure 6.42 Endometrial adenocarcinoma. This is a polypoid exophytic tumor with myoinvasion into the outer third of the myometrium. (See **Figure 6.42**).



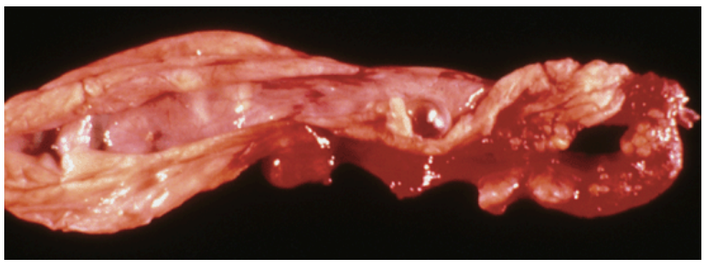
Color Figure 6.45 Adenosarcoma. Multiple polypoid masses arise in the endometrium. (See **Figure 6.45**).



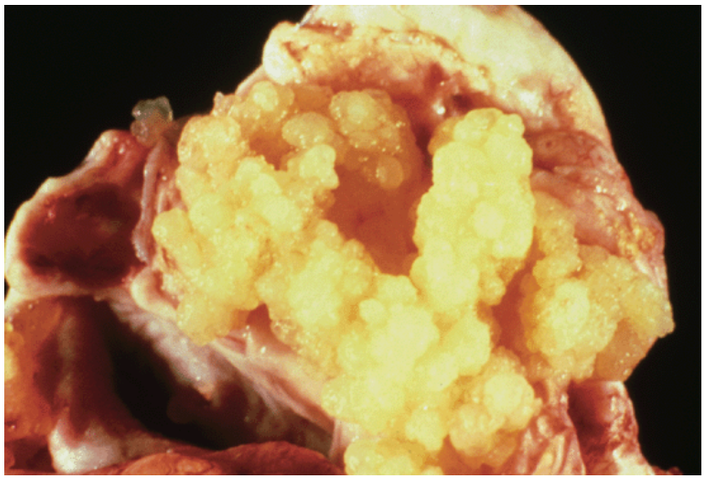
Color Figure 6.47 Carcinosarcoma. This hysterectomy specimen shows a large, partially necrotic polypoid mass filling the endometrial cavity and extensively invading the uterine wall. (See **Figure 6.47**).



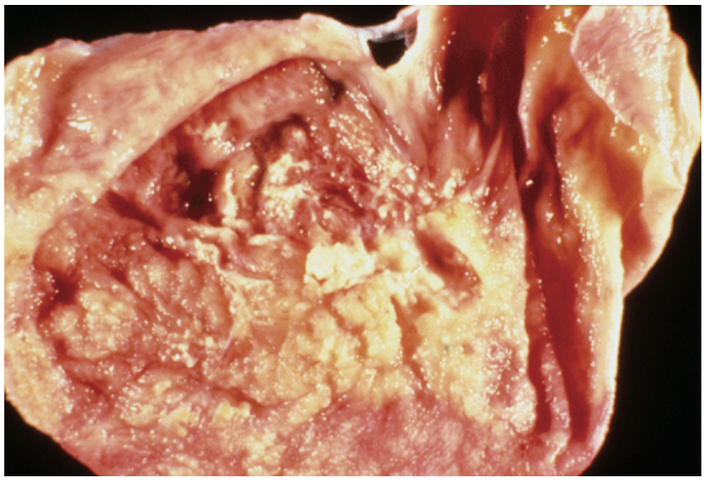
Color Figure 6.49 Leiomyoma and leiomyosarcoma. The small nodule on the left is well circumscribed, with the bulging, white, firm and whorled cut surface, typical of leiomyoma. The large, soft, hemorrhagic, and fleshy mass represents a leiomyosarcoma. (See **Figure 6.49**).



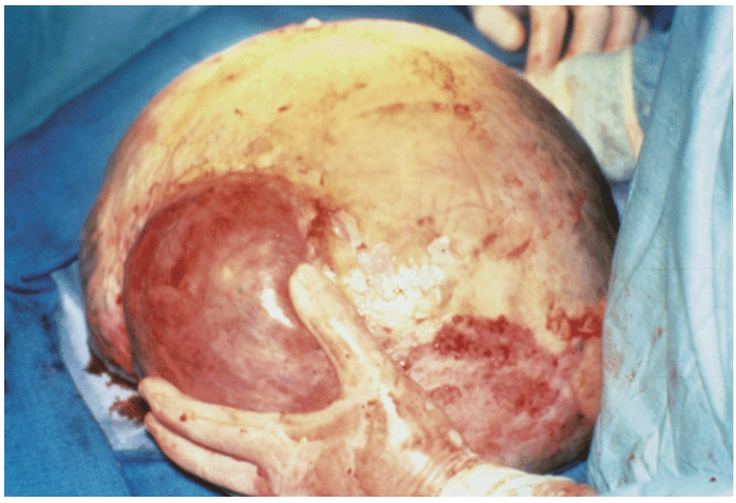
Color Figure 6.51 Serous cystadenoma of the ovary. This unilocular cyst has a smooth lining, microscopically resembling the fallopian tube epithelium. (See **Figure 6.51**).



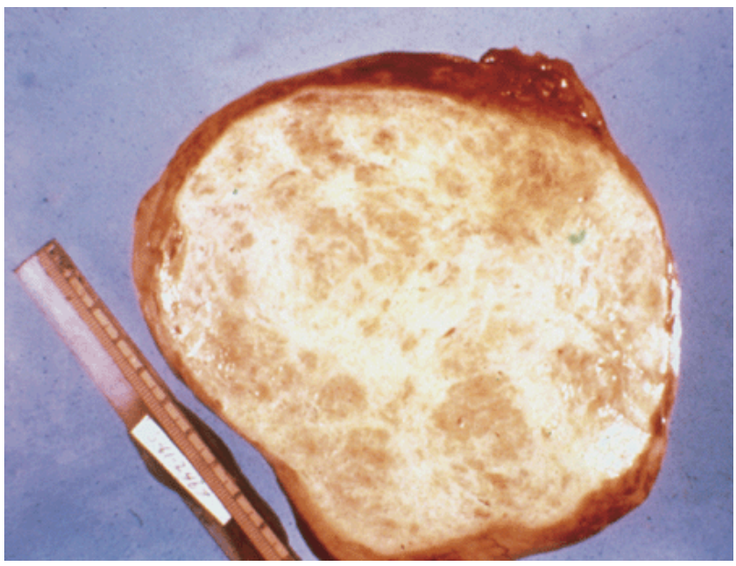
Color Figure 6.52 Ovarian serous tumor of low malignant potential. Abundant papillary projections involve the ovarian surface in this case. (See **Figure 6.52**).



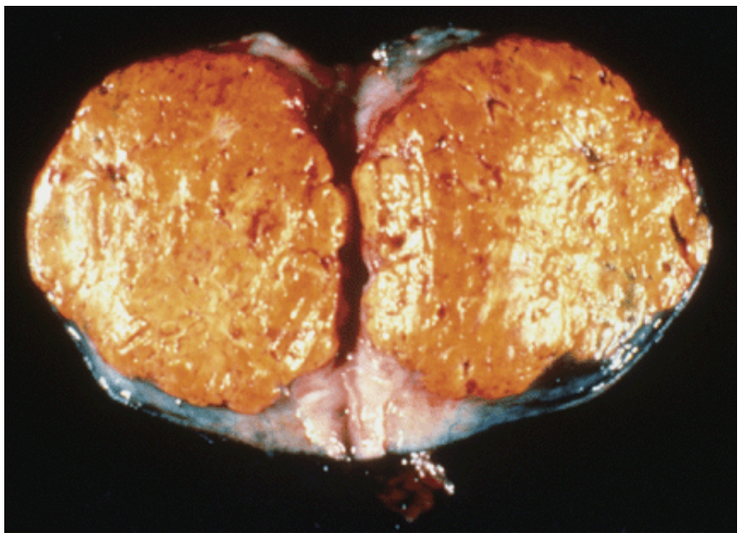
Color Figure 6.54 Serous carcinoma of the ovary. This partially cystic tumor exhibits papillary and solid areas. (See **Figure 6.54**).



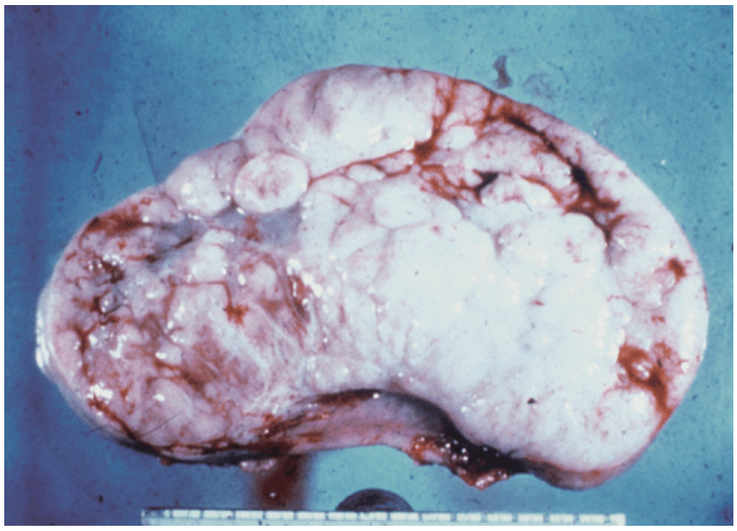
Color Figure 6.55 Mucinous intestinal tumor of low malignant potential. This unilateral cystic mass has attained a very large size. (See **Figure 6.55**).



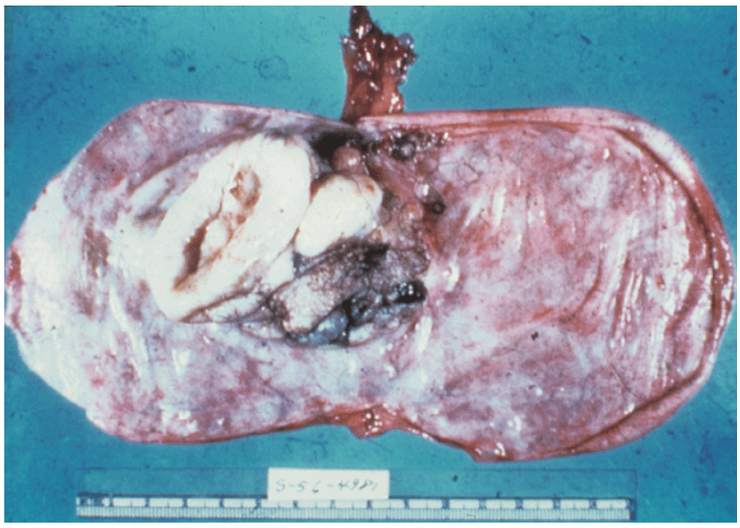
Color Figure 6.59 Ovarian fibroma. The ovary is enlarged, with a firm, white-gray cut surface. (See **Figure 6.59**).



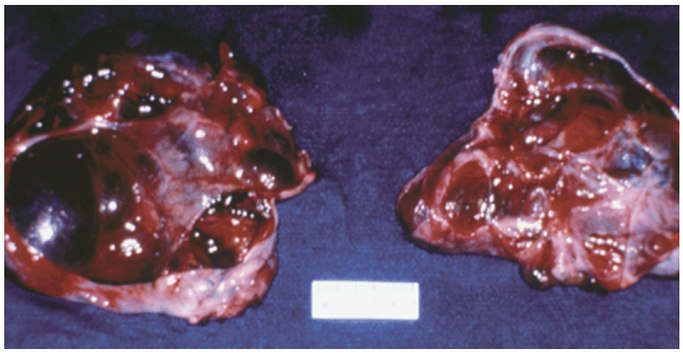
Color Figure 6.61 Steroid cell tumor, not otherwise specified. This tumor is a solid, golden-yellow mass. (See **Figure 6.61**).



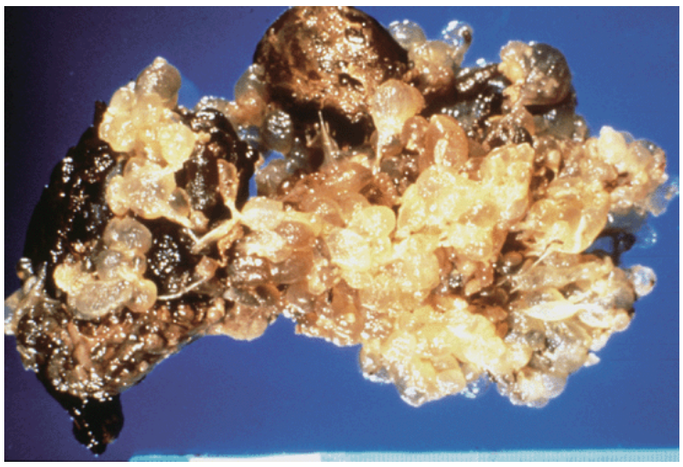
Color Figure 6.62 Dysgerminoma. This solid tumor has a gray, fleshy, and lobulated cut surface. (See **Figure 6.62** Left).



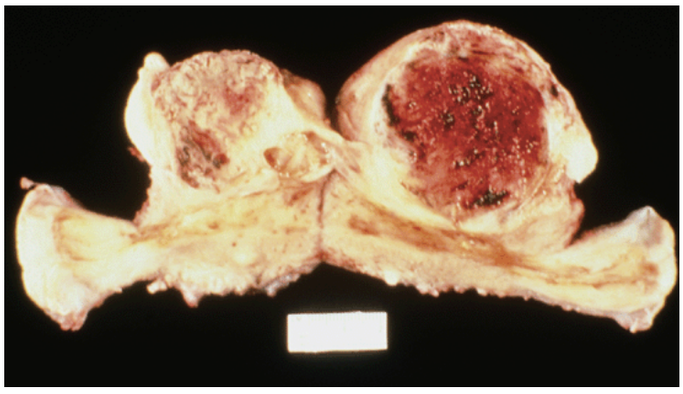
Color Figure 6.64 Mature teratoma. This cystic neoplasm contains hair and sebaceous material. The solid white area represents mature cartilage. (See **Figure 6.64**).



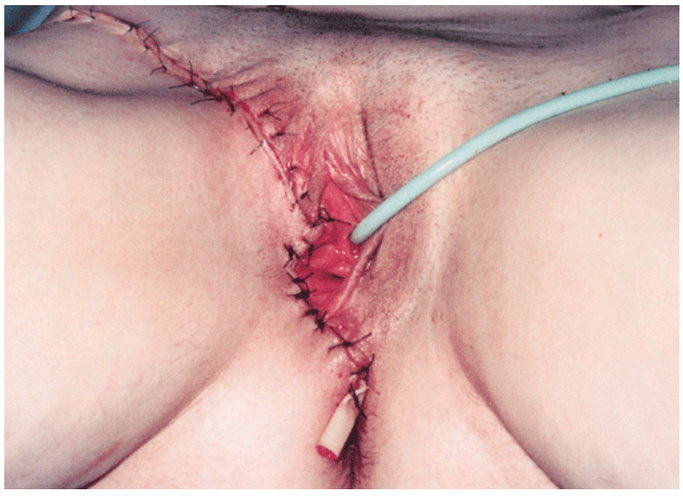
Color Figure 6.68 Theca lutein cysts (Hyperreactio luteinalis). Both ovaries are enlarged and contain multiple, tense, thin-walled cysts. (See **Figure 6.68**).



Color Figure 6.69 Complete hydatidiform mole. This lesion comprises placental tissue with multiple, grapelike, thin-walled vesicles. No embryo is present. (Figure courtesy of C. C. Sun, MD, University of Maryland Medical Center, Baltimore, Maryland.) (See **Figure 6.69**).



Color Figure 6.72 Choriocarcinoma. A hysterectomy specimen (rarely seen today) with hemorrhagic and necrotic tumor within the uterine wall. (See **Figure 6.72**).



Color Figure 13.11 En bloc resection of the right groin and right-posterior vulva for a Bartholin gland carcinoma. Note the preservation of the clitoris and right anterior labium minus. (See **Figure 13.11**).

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