BASIC AND CLINICAL ONCOLOGY

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Bruce D. Cheson, M.D.

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Integrated Cancer Management

Surgery, Medical Oncology, and Radiation Oncology

edited by

Michael H. Torosian
Fox Chase Cancer Center
Philadelphia, Pennsylvania

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To T.J.

For her love, kindness, compassion,
and her beautiful spirit

Series Introduction

The current volume, *Integrated Cancer Management: Surgery, Medical Oncology, and Radiation Oncology,* is Volume 20 in the Basic and Clinical Oncology series. Many of the advances in oncology have resulted from close interaction between the basic scientist and the clinical researcher. The current volume follows, expands on, and illustrates the success of this relationship as demonstrated by new and promising areas for scientific research.

As editor of the series, my goal has been to recruit volume editors who not only have established reputations based on their outstanding contributions to oncology, but also have an appreciation for the dynamic interface between the laboratory and the clinic. To date, the series has consisted of monographs on topics such as chronic lymphocytic leukemia, nucleoside analogs in cancer therapy, therapeutic applications of interleukin-2, retinoids in oncology, gene therapy of cancer, and principles of antineoplastic drug development and pharmacology. *Integrated Cancer Management* is certainly a most important addition to the series.

Volumes in progress include works on AIDS-related malignancies, secondary malignancies, chronic lymphoid leukemias, and controversies in gynecologic oncology. I anticipate that these volumes will provide a valuable contribution to the oncology literature.

Bruce D. Cheson, M.D.

Preface

Cancer is a devastating disease process with the potential to exert clinical effects at the local, regional, and systemic levels. Extensive physical, metabolic, nutritional, immunological, and psychological alterations occur in cancer patients that may adversely affect clinical outcome and functional recovery. Critical endpoints such as tumor remission rates, disease-free and overall survival, toxicity of antineoplastic therapy, surgical morbidity and mortality, and quality of life are influenced by these physiological and functional abnormalities. To achieve optimal outcome results, the cancer patient requires an integrated, multidisciplinary approach to treat local, regional, and distant disease. This fundamental concept in cancer therapy is explored throughout this book, *Integrated Cancer Management: Surgery, Medical Oncology, and Radiation Oncology.*

This book is a unique, state-of-the-art reference that emphasizes the clinical approach to the cancer patient—it is neither a treatise on cancer research nor a compendium of published literature. Effective integration of multidisciplinary management of cancer is the unifying theme throughout this text, and most chapters are coauthored by a surgeon, medical oncologist, and radiation oncologist with recognized clinical expertise in cancer therapy. Clear, concise, and pertinent summaries of oncological therapy are presented, with an emphasis on critical decision points in the management of cancer patients. Tumor biology is discussed in terms of clinical relevance as it impacts on the formation of a multidisciplinary treatment plan. Surgical treatment options are fully described along with insightful comparisons and critical distinctions among surgical alternatives based

on tumor stage and biology. Systemic treatment with chemotherapy, hormone therapy, and other agents is reviewed, with analysis of clinical prognostic factors, treatment indications, toxicity, and tumor response. Radiation therapy techniques, treatment planning, dose and duration of therapy, morbidity, and results are also critically reviewed.

My concept of the disease-management approach to cancer is the basis for the organization of this text. Treatment of breast, esophageal, gastric, small intestine, appendiceal, colorectal, and anal carcinomas is thoroughly reviewed. The clinical management of pancreatic and periampullary cancers, hepatic and biliary tumors, and endocrine tumors, which include carcinoids and pancreatic, adrenal, thyroid, and parathyroid tumors, is clearly summarized. Lymphomas, soft-tissue sarcomas, melanomas, lung and pleural tumors, mediastinal tumors, oncological emergencies, tumor vaccines, nutrition, and molecular biology are critically reviewed. The chapters of this book are organized according to clinical classification based on tumor biology, anatomy, pathophysiology, and prognostic factors relevant to making therapeutic decisions. For example, proximal gastric tumors are categorized with esophageal tumors but separate from mid and distal gastric tumors. This particular clinical classification is based on common treatment strategies designed for proximal gastric and esophageal tumors, in accordance with similarities in regional anatomy, local/regional recurrence, and metastatic potential; different diagnostic and treatment strategies exist for the management of patients with mid and distal gastric tumors. Similar clinical and biological considerations are used to classify pancreatic adenocarcinomas, with obstructing periampullary tumors, liver tumors with proximal biliary tumors, and pancreatic endocrine tumors in a separate category. Clinical relevance is the key determinant in the organization of this text and provides a rational framework for understanding cancer therapy based on clinical tumor biology.

Effective management of the cancer patient is complex and requires the coordinated and integrated efforts of the surgeon, medical oncologist, radiation oncologist, and many other physicians and health care providers. The aim of this text is to provide practicing clinicians with comprehensive management strategies for offering the highest quality of care to cancer patients. Great progress has been made in the treatment of cancer over the past 50 years. Current cancer therapy is summarized in this text by expert clinicians who will lead us into the next millennium when exciting discoveries in molecular biology and innovative technology are anticipated to treat, cure, and eventually prevent cancer.

Michael H. Torosian

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Contributors

Ross A. Abrams, M.D. Division of Radiation Oncology, The Johns Hopkins Oncology Center, Baltimore, Maryland

H. Richard Alexander, Jr., M.D. Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Jean-Pierre Ayoub, M.D. Department of Gastrointestinal Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

David L. Bartlett, M.D. Department of Surgery, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

David Berd, M.D. Division of Medical Oncology, Department of Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania

Michael Bouvet, M.D. Department of Surgery, The University of California at San Diego, San Diego, California

Thomas P. Bradley, M.D. Division of Hematology/Oncology, Department of Medicine, State University of New York, Health Science Center in Brooklyn, Brooklyn, New York

Douglas Brown, M.D. Department of Radiation Oncology, Allegheny General Hospital, Pittsburgh, Pennsylvania

Jamie Brown, M.D. University of Colorado Health Sciences Center and the Department of Veterans Affairs VA Medical Center, Denver, Colorado

Paul A. Bunn, Jr., M.D. University of Colorado Cancer Center, Denver, Colorado

Linda S. Callans, M.D. Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Alfred E. Chang, M.D. Department of Surgery, University of Michigan, Ann Arbor, Michigan

Michael A. Choti, M.D. Department of Surgery, The Johns Hopkins Medical Institutions, Baltimore, Maryland

Kathleen A. Cooney, M.D. Departments of Internal Medicine and Surgery, University of Michigan Medical School and School of Public Health, Ann Arbor, Michigan

Brian J. Czerniecki, M.D., Ph.D. Department of Surgery, University of Pennsylvania, Philadelphia, Pennsylvania

John L. Doppman, M.D. Department of Radiology, Warren G. Magnuson Clinical Center and National Institutes of Health, Bethesda, Maryland

Lee M. Ellis, M.D., F.A.C.S. Department of Surgical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

Mahmoud B. El-Tamer, M.D., F.A.C.S. State University of New York, Health Science Center in Brooklyn, Brooklyn, New York

Douglas Fein, M.D. Texas Oncology, PA, Austin, Texas

Antonio T. Fojo, M.D. Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Kevin R. Fox, M.D. Division of Hematology and Oncology, Department of Medicine, Hospital of the University of Pennsylvania and University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Douglas L. Fraker, M.D. Division of Surgical Oncology, Department of Surgery, University of Pennsylvania, Philadelphia, Pennsylvania

Brian Fuller, M.D. Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Eli Glatstein, M.D. Department of Radiation Oncology, University of Pennsylvania, Philadelphia, Pennsylvania

Arvin S. Glicksman, M.D., F.A.C.R. Department of Radiation Medicine, Brown University School of Medicine, Providence, Rhode Island

Richard M. Goldberg, M.D. Mayo Medical School and Mayo Clinic, Rochester, Minnesota

Stephen B. Gruber, M.D., Ph.D., M.P.H. Departments of Internal Medicine and Epidemiology, University of Michigan Medical School and School of Public Health, Ann Arbor, Michigan

Michael G. Haddock, M.D. Mayo Medical School and Mayo Clinic, Rochester, Minnesota

Alden H. Harken, M.D. Department of Surgery, University of Colorado, Denver, Colorado

Lawrence E. Harrison, M.D. Department of Surgery, University of Medicine and Dentistry, New Jersey Medical School, Newark, New Jersey

Brenda E. Haynes, M.D. Division of Hematology/Oncology, Delaware County Memorial Hospital, Drexel Hill, Pennsylvania

R. Alex Hsi, M.D. Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

Kelly K. Hunt, B.C.S., M.D. Department of Surgical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

Nora A. Janjan, M.D., F.A.C.P. Department of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

Lori Jardines, M.D. Medical College of Pennsylvania, Philadelphia, Pennsylvania

Robert T. Jensen, M.D. Digestive Diseases Branch, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

Timothy M. Johnson, M.D. Department of Dermatology, University of Michigan, Ann Arbor, Michigan

Dennie V. Jones, Jr., M.D. Oncology Section, Department of Medical Affairs, Genentech, Inc., South San Francisco, California

John Kairys, M.D. Department of Surgery, Thomas Jefferson University, Philadelphia, Pennsylvania

Larry R. Kaiser, M.D. Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Martin S. Karpeh, Jr., M.D. Gastric & Mixed Tumor Service and Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York

Michael L. Kochman, M.D., F.A.C.P. Division of Gastroenterology, Department of Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

Barry C. Lembersky, M.D. Department of Human Oncology, Allegheny General Hospital, Pittsburgh, Pennsylvania

Li Liu, M.D. Department of Medicine, Brown University School of Medicine and Roger Williams Medical Center, Providence, Rhode Island

Mitchell Machtay, M.D. Department of Radiation Oncology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Paul J. McMurrick, M.B.B.S., F.R.A.C.S. Division of Colon and Rectal Surgery, Mayo Clinic, Rochester, Minnesota

Sofia D. Merajver, M.D., Ph.D. Department of Internal Medicine, University of Michigan Medical School and School of Public Health, Ann Arbor, Michigan

Bruce D. Minsky, M.D. Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York

Halle C.F. Moore, M.D. Division of Hematology and Oncology, Department

of Medicine, Hospital of the University of Pennsylvania and University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Heidi Nelson, M.D. Division of Colon and Rectal Surgery, Mayo Clinic, Rochester, Minnesota

Hung Q. Nguyen, M.D. Division of Surgical Oncology, University of Pennsylvania, Philadelphia, Pennsylvania

Eileen M. O'Reilly, M.D. Solid Tumor Division, Gastrointestinal Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York

Seamus O'Reilly, M.D., Ph.D., M.R.C.P.I. Consultant Medical Oncologist, Waterford Regional Hospital, Waterford, Ireland

Floyd A. Osterman, Jr., M.D. Department of Radiology, Aventura Hospital and Medical Center, Aventura, Florida

Shreyaskumar R. Patel, M.D., F.A.C.P. Department of Melanoma-Sarcoma Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

Richard Pazdur, M.D. Department of Gastrointestinal Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

Peter W.T. Pisters, M.D., F.A.C.S. Department of Surgical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

Alan Pollack, M.D., Ph.D. Department of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

Rachel Rabinovitch, M.D. Department of Radiation Oncology, University of Colorado Health Sciences Center, Denver, Colorado

Mark S. Roh, M.D. Department of Surgery, Allegheny General Hospital, Pittsburgh, Pennsylvania

Ernest F. Rosato, M.D., F.A.C.S. Division of Gastrointestinal Surgery, Department of Surgery, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

Blair M. Rowitz, M.D. Anderson Area Medical Center, Anderson, South Carolina

Howard M. Sandler, M.D. Department of Radiation Oncology, University of Michigan Medical School, Ann Arbor, Michigan

Gary K. Schwartz, M.D. Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York

Alan Schulsinger, M.D. State University of New York, Health Science Center in Brooklyn, Brooklyn, New York

Jamie Siegel, M.D. Division of Hematology, Department of Medicine, Robert Wood Johnson Medical School, New Brunswick, New Jersey

Charles B. Simone, M.D. Simone Protective Cancer Institute, Lawrenceville, New Jersey

Sunil Singhal, M.D. Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland

Monica Skarulis, M.D. National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

David C. Smith, M.D. Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan

W. Roy Smythe, M.D. Department of Thoracic and Cardiovascular Surgery, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

Lawrence J. Solin, M.D. Department of Radiation Oncology, Hospital of the University of Pennsylvania and University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Ariel F. Soriano, M.D. Department of Medical Oncology, University of Colorado Cancer Center, Denver, Colorado

Michael H. Torosian, M.D., F.A.C.S. Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania

David J. Vaughn, M.D. Division of Hematology/Oncology, Department of

Medicine, University of Pennsylvania School of Medicine, University of Pennsylvania Cancer Center, Philadelphia, Pennsylvania

Harold J. Wanebo, M.D. Department of Surgery, Boston University School of Medicine, Boston, Massachusetts; and Department of Surgery, Roger Williams Medical Center, Providence, Rhode Island

Richard Whittington, M.D. Department of Radiation Oncology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

Noel N. Williams, M.D., F.R.C.S.I., F.R.C.S. Division of Gastrointestinal Surgery, Department of Surgery, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

1

Breast Cancer

Michael H. Torosian
Fox Chase Cancer Center, Philadelphia, Pennsylvania

Lawrence J. Solin, Halle C.F. Moore, and Kevin R. Fox
Hospital of the University of Pennsylvania and University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

INTRODUCTION

Breast cancer is the most common cancer in women. At present, the estimated incidence of breast cancer annually is 180,000–200,000 cases in the United States. Breast cancer is a very treatable and curable disease in most women and the key to effective treatment of this tumor, as with many solid tumors, is early detection and prompt institution of appropriate medical therapy.

The overall risk for women in America developing breast cancer is 1-in-8 (12.5%) during their lifetime. Risk factors for developing breast cancer include positive family history in a first-degree female relative (i.e., mother, sister, daughter), nulliparity or late childbirth, early menarche, late menopause, increasing age, greater number of breast biopsies, and a small subset of patients with fibrocystic breast disease. The majority of women with fibrocystic breast disease are not at increased risk of developing breast cancer. However, women with biopsies showing proliferative fibrocystic changes associated with cellular atypia or those with lobular carcinoma in situ have an increased risk of developing breast cancer. Other factors, such as family history, can modify the risk of breast cancer in women with atypical proliferative fibrocystic disease.

Hereditary breast cancer accounts for approximately 5% of breast cancers with the remaining 95% of breast cancer cases arising sporadically from noninherited etiologies. Genetic research has identified two genes, BR-CA1 and BR-CA2, which normally function as tumor suppressor genes to prevent the develop-

ment of breast and ovarian cancer. Women with mutations in either BR-CA1 or BR-CA2 exhibit defective tumor suppressor function and have an increased incidence of breast cancer during their lifetime. Typically, women with hereditary breast cancer are diagnosed 20 years earlier (average age = 45 years) than women with nonhereditary breast cancer. Although breast cancer is rare in men, BR-CA1 and BR-CA2 mutations can be inherited by children from either the maternal or paternal genome.

The relationship between the use of exogenous hormone therapy and breast cancer remains controversial. Most studies indicate that low-dose hormone replacement therapy plays a small, if any, role in the initiation of breast cancer. However, continued intake of exogenous hormones after the diagnosis of breast cancer can stimulate the growth of malignant cells possessing surface receptors for estrogen or progesterone. Breast cancer is the prototypical solid tumor responsive to all forms of antineoplastic therapy including surgery, radiation therapy, chemotherapy, and hormonal therapy. This chapter summarizes the state-of-the-art, integrated management of patients with breast cancer from a multidisciplinary perspective.

DIAGNOSIS

Histological examination of a tissue specimen is the gold standard for diagnosis of breast cancer. Tissue samples can be obtained by numerous techniques including fine-needle aspiration, needle biopsy, stereotactic core biopsy, stereotactic-directed mammotome, or open surgical biopsy. There is much individual and institutional variability in the relative use of these techniques. Clinical judgment based on preoperative physical examination, radiological imaging, and degree of suspicion of malignancy will determine the optimal technique of biopsy and subsequent cytopathological analysis.

Fine-needle aspiration is a commonly used technique to evaluate breast lesions; however, this technique may be overutilized. The false-negative rate of fine needle aspiration ranges from 5% to 20% depending on the technique of obtaining the specimen, the skill and experience of the cytopathologist, and the precise criteria used for defining malignancy. The author believes that fine-needle aspiration should be used only when: (1) the lesion is presumed to be cystic on physical examination or ultrasound and successful aspiration can avoid surgical biopsy or (2) a malignant diagnosis by cytological criteria will allow definitive treatment planning for subsequent breast-conserving surgery or mastectomy. If fine-needle aspiration is used only as an additional step in the management of solid breast masses in patients who subsequently undergo open biopsy, needle aspiration is neither cost-effective nor efficient medical care. Nevertheless, a benign cytological diagnosis in the presence of a dominant, solid breast mass requires further surgical intervention.

In general, excisional biopsy is preferred to incisional biopsy for both pal-

pable and nonpalpable lesions seen on mammography. Excisional biopsy permits complete histological evaluation of the lesion and allows hormone receptor analysis to be determined by conventional biochemical methods in all but the smallest lesions. However, exceptions to this rule exist and incisional biopsy has a role to play in patients with inflammatory breast cancer or locally advanced breast cancer. Incisional biopsy of such lesions can establish a histological diagnosis of malignancy and allows definitive treatment planning.

Surgical planning is required for placement of an optimal biopsy incision for several reasons. First, if excisional biopsy is planned, as is the case in most instances, the biopsy incision should permit adequate exposure to remove the entire lesion readily. If the lesion has a high suspicion of malignancy, a minimum of 1 cm margin of normally appearing breast tissue should be removed on all aspects of the lesion. If the lesion is felt to be benign, a more conservative approach is taken and the entire lesion is removed with a minimum of surrounding breast tissue. Second, cosmesis should always be considered when performing a breast biopsy. If the mass is centrally located in the breast, the optimal approach is a circumareolar incision on the areolar margin closest to the mass. For peripheral breast lesions, an arcuate incision is made in the direction of Langer's skin lines directly overlying the mass or in a more cosmetic position, depending on the exact location of the breast lesion. Arcuate incisions are made to minimize tension on the incision and thus reduce postoperative scarring. Only lesions located in the most medial and lateral portions of the breast should be removed through radial incisions for optimal cosmesis. Third, when excisional biopsy is performed for an obvious malignant lesion and a subsequent mastectomy is planned, this incision should be placed where it can readily be removed in the ellipse of skin excised at the mastectomy procedure.

Once the specimen has been removed, it is imperative to communicate with the pathologist regarding the need for frozen section and final pathological analysis. For example, conventional, biochemical determination of estrogen and progesterone receptor analysis requires that the breast specimen be sent to the pathology laboratory fresh and on ice. Fixing the specimen for permanent histological analysis will prevent this biochemical assay from being performed. Immunohistochemical assays for hormone receptors (ERICA analysis) agree with conventional hormone receptor analysis in at least 85–90% of cases. Immunohistochemical analysis of hormone receptors on tumor cells can be performed on fixed specimens and tumors with inadequate tissue for biochemical analysis. In fact, immunohistochemical methods for detecting hormone receptors on malignant cells have replaced standard biochemical techniques in many surgical pathology laboratories today.

In suspected cancers, marking the specimen with sutures for pathological orientation is critical if surgical margins are to be accurately assessed. When the side (i.e., left/right) of the biopsy is known, two marking sutures are required for precise pathological orientation. Our preference is to mark the superior margin

with a short suture (*s* = *s*hort and *s*uperior) and a long suture for the lateral margin (*l* = *l*ong and *l*ateral). Furthermore, the pathologist needs to be notified that histological evaluation of the resection margins is required. The specimen will be inked so that the true margins of resection can be determined. It is imperative that the surgeon does not bivalve the specimen prior to its arrival in the surgical pathology laboratory to avoid confusion in assessing the true margins of resection.

SURGERY

Most patients with breast cancer present with either a palpable breast mass or an abnormality seen on mammography. Approximately two-thirds of palpable breast cancers are detected on self-examination by patients. Therefore, findings of a mass, thickening, or change in breast texture detected by a woman who performs regular breast self-examinations warrants careful attention by the examining physician. Thorough breast examination by physicians should be performed during routine physical examinations, gynecological examinations, and in the presence of breast symptoms. A thorough examination consists of evaluation of the regional lymph nodes (cervical, supraclavicular, and axillary) as well as a thorough breast examination in both the sitting and lying positions. The physician's role is to detect the presence of a dominant lump compared to the background, fibroglandular breast tissue.

Mammography remains the best radiological screening technique for evaluating breast tissue. Current recommendations for mammography consist of annual mammography beginning at 40 years of age. Annual mammography beginning in the 30s can be performed for patients with a strong family history of breast cancer or other high-risk factors. In addition, patients with a palpable lump or with new symptoms may require mammography at an earlier age. Typically, screening mammography consists of two views of each breast including craniocaudad and mediolateral views. Occasionally, additional mammographic projections such as oblique views will be required to image the entire breast. Mammography should be performed at a radiology facility that is accredited by the American College of Radiology.

Approximately 60% of breast cancers can be identified on mammography. Breast carcinoma typically appears on mammograms as an irregular, spiculated area of increased density or a cluster of microcalcifications. Suspicious calcifications on mammography include tiny particles of calcification that are tightly clustered in a localized area of breast tissue. Calcifications in a linear or branching pattern are suspicious for ductal carcinoma in situ. In contrast, benign calcifications are large, coarse, and may be associated with a fibroadenoma, prior biopsy scar, or fibrocystic breast disease. Magnification spot mammograms can be used to provide high-detail imaging of areas of breast calcification. The number and pattern of calcifications as well as their stability as seen on prior mammograms

determine the level of suspicion of malignancy and whether or not breast biopsy is indicated.

The second most commonly used imaging modality of the breast is ultrasound. Ultrasound can be used to characterize palpable lumps or nonpalpable nodules seen on mammography. Ultrasound is not useful as a screening modality and, in fact, can be misleading as it magnifies the normal lobular elements of breast tissue. The most important feature of a nodule determined on ultrasound is whether the lesion is cystic (i.e., fluid containing) or solid. If a lesion is anechoic and demonstrates good through-transmission of ultrasound waves, definitive characterization of a simple cyst can be made. Typical clinical options for a simple cyst include needle aspiration or observation. Solid lesions can be further characterized as having an irregular or smooth border or representing a complex mass of partially cystic and solid components. Solid lesions should be biopsied by fine-needle aspiration, stereotactic core needle biopsy, or open surgical biopsy. The resolution of commonly used ultrasound techniques is best for lesions $\geq$1 cm; for lesions smaller than 1 cm, ultrasound evaluation is less precise.

Other imaging modalities are currently being developed. Digital mammography is promising for the future and has been an area of active clinical research for several years. Its major advantages over conventional mammography include superior image quality, improved efficiency for storage and retrieval of images, computerized evaluation of images with enhancement of lesions, and instantaneous transmission for remote reading by expert radiologists. Magnetic resonance imaging is an important diagnostic modality with excellent imaging resolution of the breast and will likely be used for specific subsets of patients in the future. In particular, magnetic resonance imaging has been useful for staging breast cancer patients and, in certain instances, finding additional foci of cancer that were previously undetected on examination or by conventional mammography. The discovery of multifocal disease by magnetic resonance imaging is critically important and may reduce the failure rate of breast conservation therapy by early recognition of multifocal cancer. Another group of patients likely to benefit from magnetic resonance imaging are young women with dense breast tissue in whom conventional mammography is less sensitive. Magnetic resonance imaging can also be used in women with breast implants to image mammary tissue adjacent to or near the implant and to assess the integrity of implants suspected of rupture. With current magnetic resonance techniques, breast imaging by this modality is too sensitive and too costly to advocate for screening purposes.

CLINICALLY RELEVANT CLASSIFICATIONS OF BREAST CANCER

For defining treatment options, breast cancer can be classified into the following biological categories: invasive/infiltrating carcinoma, ductal carcinoma in situ

(DCIS), microinvasive carcinoma, Paget's disease, inflammatory carcinoma, and lobular carcinoma in situ (LCIS). This clinically relevant classification is based on histopathology, clinical presentation, and, most importantly, prognostic and biological characteristics of different types of breast cancer. In the author's opinion, these clinical categories provide a practical classification of breast cancer from which important treatment decisions can be made. The histological subtype of invasive cancer plays a relatively small role in determining treatment decisions for breast cancer patients. The vast majority of invasive breast cancers arise from the terminal ducts and are designated as infiltrating ductal carcinomas. Favorable histological subtypes with a slightly better prognosis than infiltrating ductal carcinoma include tubular, colloid or mucinous, papillary, and medullary carcinomas. Only rarely does the identification of one of these favorable histological subtypes modify definitive surgical treatment of the primary tumor. Multicentricity and bilaterality are more common with lobular breast carcinomas. In general, critical treatment decisions are based on multiplicity or unifocality of disease, size of the primary tumor, presence or lack of regional lymph node involvement, and clinicopathological features of tumor aggressiveness (e.g., inflammatory carcinoma, histological/nuclear grade, hormone receptor status, percentage of S-phase tumor cells, and percentage of aneuploid tumor cells).

Invasive/Infiltrating Carcinoma

Invasive or infiltrating carcinomas represent the most common type of breast cancer and comprise approximately 75–80% of all breast cancers. The invasive or infiltrating characteristic signifies that these breast cancer cells have invaded through the lining of their structure of origin (e.g., terminal duct for infiltrating ductal carcinoma, breast lobule for infiltrating lobular carcinoma) into the surrounding breast tissue. This pathological characteristic is a critically important feature that confers upon the tumor cell the ability to penetrate surrounding lymphatic and vascular channels and subsequently to metastasize to regional lymph nodes or distant organs. Because of this ability to metastasize to regional or distant sites, preoperative metastatic evaluation typically consists of chest x-ray, bone scan, and blood tests including complete blood count and liver function tests. If liver function tests are elevated, abdominal computerized axial tomography (CAT) scan is performed to further evaluate the liver for possible metastases. Bone scans are extremely sensitive but not specific for skeletal metastases and, in the absence of symptoms, the probability of detecting bony metastasis in patients with early-stage breast cancer is extremely low. In fact, recent studies have challenged the routine use of bone scans in asymptomatic patients with early-stage (T1 and T2) breast cancers. Nevertheless, many physicians obtain bone scans routinely in all patients with invasive breast cancers.

In general, patients with invasive breast cancers have two options for treat-

ment of the primary tumor including breast conservation or modified radical mastectomy. The general principle is to treat the breast and ipsilateral axillary lymph nodes, the latter included because of the capacity of invasive tumor cells to metastasize to regional nodes and beyond. Breast conservation consists of lumpectomy, axillary dissection, and radiation therapy. A standard axillary lymph node dissection consists of removing the level I and II axillary nodes. To avoid injury to the axillary artery and brachial plexus, only lymph nodes inferior to the axillary vein are removed. The goal of axillary dissection is to remove at least 10 lymph nodes for accurate staging and prognostic information and to assist with postsurgical treatment planning. Level III axillary nodes should be removed only if they are obviously involved with cancer and all gross tumor can be resected by including their removal in the axillary dissection. The extent of axillary dissection is the same whether breast conservation or modified radical mastectomy has been selected for treating the primary tumor.

The ideal candidates for breast conservation therapy include patients with a unifocal tumor that can be removed with pathologically clear surgical margins such that cosmesis of the breast is preserved. At the time of lumpectomy, the tumor bed should be marked with surgical clips to facilitate future radiotherapy targeting. Contraindications to breast conservation include patients with multifocal cancer, diffuse involvement of the breast with carcinoma, or those in whom microscopically clear margins cannot be obtained with lumpectomy. The importance of pathologically clear margins cannot be overemphasized as numerous studies have demonstrated local recurrence rates of 20–50% in patients treated with breast conservation without obtaining clear margins of resection. Although there is no absolute size of the primary breast tumor for which breast conservation cannot be considered, local recurrence increases with increasing tumor size following breast conservation therapy. Nevertheless, tumor size relative to breast size is relevant as the primary motive for pursuing breast conservation therapy is to achieve effective therapeutic results with excellent cosmesis. Besides tumor size, additional relative contraindications to breast conservation include diffuse calcifications on mammography or extreme density of breast tissue rendering clinical and/or radiological follow-up after breast conservation therapy particularly difficult.

An alternative to breast conservation is modified radical mastectomy. Modified radical mastectomy consists of removing the breast tissue, nipple/areolar complex, and ipsilateral axillary lymph nodes. Skin-sparing incisions can be utilized to perform this surgical procedure with minimal removal of overlying skin, which is particularly important in cases of simultaneous breast reconstruction. Dissection proceeds in the plane between the subcutaneous tissue and breast tissue superiorly to the clavicle, medially to the sternum, inferiorly to the rectus abdominus muscle, and laterally to the latissimus dorsi muscle. Upon entry into the axilla, en bloc resection of level I and II lymph nodes inferior to the axillary

vein is typically performed. By restricting surgical dissection to axillary contents inferior to the axillary vein, limiting nodal removal to levels I and II, and avoiding transection of the pectoralis minor muscle, the incidence of lymphedema of the ipsilateral arm has been dramatically lower in recent years than previously reported. Owing to the indistinct plane between breast tissue and subcutaneous tissue, it is not possible to remove 100% of the mammary cells during mastectomy. However, the vast majority of mammary cells can be removed with careful attention to surgical dissection of the mastectomy flaps and adherence to the anatomical limits of breast tissue.

Reconstruction can be performed either simultaneously or delayed after mastectomy. Simultaneous breast reconstruction is discouraged when radiation therapy is indicated or has a high probability of being implemented after surgery. Radiation therapy administered after simultaneous breast reconstruction significantly impedes wound healing and may interfere with the ultimate cosmetic outcome of reconstruction. Breast reconstruction can be performed by numerous techniques including immediate implant insertion, placement of a tissue expander with subsequent conversion to a permanent implant, or autologous tissue reconstruction using the transverse rectus abdominus muscle (TRAM) or latissimus dorsi myocutaneous flaps. Major advantages for immediate implant or tissue expander insertion include a shorter operative time and reduced duration of postoperative recovery. In contrast, the major advantage of using autologous tissue reconstruction is avoiding the risk of prosthetic infection, which typically requires implant removal.

Radiation therapy is typically initiated 2–4 weeks after lumpectomy and axillary dissection. From a technical perspective, it is important to place radiopaque clips at the lumpectomy site to assist the radiation therapist in targeting radiotherapy for the tumor boost at this site. Finally, radiotherapy may also be indicated after mastectomy if microscopically positive margins are identified on permanent pathological examination, if there is extracapsular tumor extension in the axilla, or if more than three axillary lymph nodes are involved with carcinoma.

Ductal Carcinoma In Situ

Ductal carcinoma in situ (DCIS) by definition is a noninvasive carcinoma that originates and remains confined to the ductal system of the breast without penetrating the basement membrane into the surrounding stroma. The inability of these carcinoma in situ cells to penetrate the basement membrane has tremendous prognostic, biological, and treatment significance. As these cells are noninvasive, they are unable to penetrate lymphatic and vascular channels and, therefore, incapable of metastasis. DCIS is a disease locally confined to the breast and does not warrant regional or systemic staging.

Three treatment options exist for DCIS including lumpectomy with radiation therapy, lumpectomy without radiation therapy, and mastectomy. In contrast to the treatment of infiltrating breast carcinomas, treatment for DCIS is confined to the ipsilateral breast without removal of axillary lymph nodes. Standard breast conservation therapy consists of lumpectomy followed by radiation therapy to the entire breast. Lumpectomy without radiation therapy is currently being studied as a treatment option for patients with microscopic foci of DCIS. This treatment option should be considered experimental at this time, as the subset of DCIS patients adequately treated by lumpectomy alone remains to be defined. Mastectomy consists of ipsilateral total (or simple) mastectomy, which involves removal of the breast tissue and nipple/areolar complex. Since the axilla is not dissected with either approach, postoperative recovery is hastened and the incidence of lymphedema is rare compared to patients undergoing treatment for invasive carcinomas.

Much research has been conducted in recent years to classify different forms of ductal carcinoma in situ by histological subtype and biological behavior. The traditional classification of DCIS utilized architectural growth pattern and cytological characteristics but was limited in predicting clinical outcome. A clinically more relevant classification of DCIS separates comedo from all other noncomedo subtypes of DCIS. Comedo DCIS characteristically appears more aggressive under light microscopy and is clinically considered a high-grade in situ lesion. In contrast, noncomedo DCIS is considered intermediate or low grade in biological behavior and exhibits less aggressive pathological features. Comedo or high-grade DCIS typically exhibits central necrosis, aneuploidy, high proliferative rate, and increased microvessel density. Comedo or high-grade tumors are likely to be estrogen receptor negative, overexpress HER-2/Neu protein, and more commonly exhibit the p53 gene protein than noncomedo or low-grade DCIS. Perhaps the most critical difference is the finding of microinvasion, which is much more common in comedo compared to noncomedo subtypes. The identification of microinvasion is critically important and raises the possibility of spread outside the breast. Numerous classification systems have been proposed to stratify patients with DCIS into prognostic groups. Two-, three-, and four-tiered classification systems have been proposed based on presence or absence of necrosis, pattern of necrosis, nuclear grade, histological grade, and other histological features. DCIS is clearly a spectrum of disease states. Until a uniform classification for DCIS has been adopted, it is critical for clinicians to be familiar with the classification system used by pathologists in their institution.

An extremely important feature of DCIS is the propensity of these carcinoma cells to spread along the duct system. Although DCIS cells do not penetrate the basement membrane or extend into the surrounding breast stroma, significant linear extension of tumor cells can occur within duct lumens rendering adequate

lumpectomy difficult or impossible in certain cases. Thus, even though this form of carcinoma is noninvasive, extensive or diffuse involvement of the breast may render mastectomy a more appropriate treatment option than breast conservation.

Microinvasive Carcinoma

Microinvasive carcinoma is a relatively recent designation for patients with breast carcinoma characterized by biological and prognostic features midway between classic infiltrating carcinoma and DCIS. The term ''microinvasive carcinoma'' has been defined in various ways by different investigators in recently published reports. The definition of microinvasion has been used to classify tumors with less than 1 mm, up to 5 mm, and even up to 10 mm of infiltrating or invasive carcinoma. It is our opinion that microinvasive carcinomas should be defined as lesions with no more than 5 mm of invasive carcinoma with limits, perhaps, as low as 1–2 mm in size. Further clinical investigation is needed to correlate clinical outcome with size of invasive carcinoma to more precisely define this select group of patients.

In patients with a small region of invasive carcinoma, the incidence of regional metastases to axillary lymph nodes is $\leq$5% and prognosis is excellent. In the subgroup of patients with microinvasive carcinomas exhibiting poor pathological features (e.g., hormone receptor negative, aneuploid, high percentage of S phase, and increased microvessel density), the incidence of axillary lymph node metastasis may be as high as 10%.

Treatment of the primary tumor in patients with microinvasive carcinomas is similar to that for patients with infiltrating carcinomas—i.e., the two options of breast conservation or mastectomy exist for treatment of these patients. Adequate lumpectomy requires complete tumor excision with all margins free of disease. As the incidence of axillary lymph node metastasis is low in this group of patients, the role of axillary lymph node dissection has recently been challenged. Some authors have advocated observation of the axilla (i.e., without axillary dissection) for patients with microinvasive carcinoma. However, when the discovery of positive axillary lymph nodes will significantly alter systemic therapy or in the subgroup of high-risk patients, axillary dissection is indicated. For example, in patients $\leq$50 years of age, carcinomas with poor prognostic features, and tumors located in close proximity to the axilla, axillary dissection should be considered. If a lymph node dissection is to be performed in these patients, a reasonable alternative to the standard level I and II dissection performed for invasive carcinoma would be to perform a level I lymph node dissection only. This approach would allow for histological examination of the most lateral lymph nodes in the axilla with a very small risk of postoperative lymphedema. Alternatively, studies are currently underway to evaluate the role of sentinel lymph node biopsy in patients with breast carcinoma. The sentinel lymph node technique involves in-

jecting the site of the primary breast tumor with a blue dye, often used with a radioactive tracer, followed by axillary exploration to identify the first axillary lymph node to turn blue or become radioactive. This node is called the ''sentinel lymph node'' and is removed for histological examination. By preliminary reports, this technique appears to be a reliable method for detecting regional metastatic spread to the axilla and predicting the need for standard axillary dissection and subsequent systemic therapy.

Paget's Disease

Paget's disease is uncommon and represents approximately 1% of all breast carcinomas. Paget's disease typically presents with symptoms related to the nipple including erythema, persistent rash, ulceration, discharge, or retraction. Biopsy should be performed for such persistent symptoms and the classic pathological finding in Paget's disease is the Paget's cell within the nipple epidermis. The Paget's cell is characterized as a large, ovoid cell with abundant pale-staining cytoplasm with a large round or ovoid nucleus.

Controversy remains regarding the origin of the Paget's cell within the nipple epidermis. Two hypotheses have been proposed: (1) Paget's cells originate from in situ or noninvasive malignancies within the nipple epidermis or (2) Paget's cells migrate to the nipple surface from an underlying carcinoma. It is possible that neither of these theories explains all cases of Paget's disease but that Paget's disease may originate by either of these two mechanisms. The concept that Paget's disease can arise by either mechanism is plausible owing to the varied clinicopathological presentation of patients with this tumor. The majority of patients with Paget's disease present solely with noninvasive carcinoma confined to the nipple. Mammography is of limited value in these patients and serves to exclude a more advanced underlying malignancy or multifocal disease.

The standard treatment recommendation for patients with Paget's disease confined to the nipple has historically been total (or simple) mastectomy. Axillary lymph node metastasis does not occur in patients with pure Paget's disease confined to the nipple and axillary dissection is not indicated. Local excision including complete or partial resection of the nipple/areolar complex plus radiation has recently been reported in patients with Paget's disease. Limited outcome data exist regarding breast conservation therapy in patients with Paget's disease and clinical investigation of this approach is currently underway. Careful pathological evaluation of the specimen margins is imperative as tumor extension along the ducts can occur without being recognized clinically or by radiological imaging.

A less common presentation of Paget's disease includes patients with classic nipple symptoms and Paget's cells seen on biopsy but with an invasive, underlying breast carcinoma. Physical examination or mammography can be useful in detecting a mass, an area of increased density, or microcalcifications in the sub-

areolar region. Again, the standard treatment recommendation is to perform mastectomy as opposed to breast conservation in these patients. The decision regarding axillary lymph node dissection in these patients must be dictated by the histology of the associated breast carcinoma. If invasive or infiltrating carcinoma is identified, axillary lymph node dissection should be performed en bloc with the mastectomy. If the tumor is exclusively noninvasive, axillary lymph node dissection is not indicated.

Thus, Paget's disease consists of a heterogeneous group of patients when defined pathologically by finding Paget's cells within the nipple epidermis. Mastectomy with or without axillary lymph node dissection is the recommended treatment with the extent of surgery based on the most aggressive component of the tumor. Paget's disease should not be confused with a locally advanced, centrally located breast carcinoma that involves the nipple/areolar complex by direct tumor extension. These locally advanced breast carcinomas should be treated as standard, infiltrating breast carcinomas.

Inflammatory Carcinoma

Inflammatory breast carcinoma is a fast-growing, aggressive carcinoma that typically affects younger women. As its name implies, inflammatory breast carcinoma presents with clinical signs and symptoms of inflammation or infection such as: diffuse erythema, warmth and edema (peau d'orange) of the breast skin, and induration of the underlying breast tissue. Commonly, the breast is diffusely enlarged and only rarely is a dominant mass palpable on examination. These symptoms can evolve over the course of several weeks and many patients are initially diagnosed with mastitis—carcinoma is subsequently diagnosed when symptoms fail to resolve with antibiotics. Mammographic findings indicative of inflammatory carcinoma include a general increase in the density of the breast tissue and increased thickness of the skin and subcutaneous tissue characteristic of edema of the breast and its overlying tissue. Edema of the skin and subcutaneous tissue over the breast is caused by plugging of the dermal lymphatics with carcinoma cells, which is the classic pathological finding with inflammatory breast carcinoma.

Diagnosis is established by incisional surgical biopsy of the skin and underlying breast tissue. If a dominant mass is palpable in the breast, an ellipse of skin overlying this mass should be biopsied with a portion of the palpable mass. In the absence of a palpable mass, an ellipse of skin and subcutaneous tissue should be removed in an area exhibiting peau d'orange with a wedge of underlying breast tissue removed en bloc with the specimen. Due to the aggressive nature of this disease and presumed systemic spread at the time of diagnosis, initial therapy is chemotherapy. Both surgery and radiation therapy are also indicated in patients with inflammatory carcinoma after chemotherapy has been initiated. The timing

of surgery and radiation therapy is individualized and is primarily dependent upon clinical response to chemotherapy. Tumor response to chemotherapy is best monitored by resolution of the presenting symptoms including reduction of skin erythema, resolution of breast induration, and disappearance of peau d'orange. Multidisciplinary input from the medical oncologist, radiation therapist, and surgeon is essential to optimally integrate surgery and radiation therapy with chemotherapy to achieve the best therapeutic results for an individual patient.

Surgical therapy for patients with inflammatory carcinoma consists of total (or simple) mastectomy. Pathological evaluation of the mastectomy specimen is performed to correlate histological findings with preoperative, clinical response to chemotherapy and is critical for determining the need and duration of additional chemotherapy treatments. Axillary dissection is not performed in patients with inflammatory breast carcinoma as all of these patients receive systemic chemotherapy. In fact, axillary dissection is contraindicated in these patients as the surgical interruption of lymphatic channels may precipitate or accentuate upper extremity lymphedema. Lymphedema in patients with inflammatory carcinoma is not uncommon as obliteration of dermal, subcutaneous, and intramammary lymphatics can significantly impede lymphatic return from the ipsilateral upper extremity.

Lobular Carcinoma In Situ

Lobular carcinoma in situ (LCIS) is a misnomer. LCIS is not a true breast carcinoma but rather a tumor marker indicating an increased risk of developing breast carcinoma in the future. LCIS is also called lobular neoplasia by some pathologists and is characterized by acini that are distended and obliterated by round, regular cells that contain target-like mucinous cytoplasmic vacuoles. LCIS is an incidental microscopic finding seen pathologically in biopsy specimens indicated for clinical or mammographic abnormalities. The majority of patients with LCIS are premenopausal and up to 20% have a positive family history of breast cancer. The overall incidence of breast cancer occurring in patients with LCIS averages 30–35% over the course of their lifetime. Previously published series of patients with LCIS have reported a wide range of subsequent development of invasive and in situ carcinoma based on duration of follow-up. Presence or absence of family history of breast cancer, associated pathological findings, and additional risk factors can modify an individual's risk of developing breast cancer after the diagnosis of LCIS. The bilateral nature of LCIS was recognized in the 1950s–1960s with contralateral breast biopsies commonly demonstrating in situ carcinoma.

LCIS is an independent risk factor for the development of breast carcinoma. The development of invasive or in situ breast carcinoma is present equally in both breasts—regardless of the site of biopsy demonstrating LCIS. Therefore,

two vastly divergent options exist for treatment of patients with LCIS: (1) close observation or (2) prophylactic bilateral mastectomies. Close observation includes monthly breast self-examination, regular, careful physical examination, and mammography. Thorough breast evaluation by a physician should be performed at least every 4–6 months. Annual mammography should be instituted once the diagnosis of LCIS has been established. Aggressive surgical intervention is indicated to biopsy any change noticed on self-examination, physical examination, or mammography to detect developing carcinomas at the earliest stage. Alternatively, prophylactic surgical intervention can be performed to minimize the risk of subsequent development of breast carcinoma. Although total mastectomy cannot remove every mammary cell, the risk of developing breast cancer after an appropriate mastectomy should be small. Subcutaneous mastectomies are not adequate oncologic procedures as significant ductal tissue remains in the retroareolar and nipple regions and these procedures should not be performed for patients with LCIS. Bilateral total (or simple) mastectomies represent the only logical, surgical approach to the patient with LCIS owing to the bilateral risk for carcinoma that exists in these patients. Unilateral mastectomy, partial mastectomy, and subtotal mastectomy with preservation of the nipple/areolar complex are not indicated for patients with LCIS. A third intermediate treatment option is the use of tamoxifen as a chemopreventative agent in patients with LCIS. Results of the multi-institutional NSABP/NIH chemoprevention trial show a 49% reduction in the development of invasive breast cancer in women at high risk of developing this disease. However, several significant complications associated with this agent include endometrial cancer, deep venous thrombosis, and pulmonary embolism. A thorough risk assessment evaluation is recommended to determine if tamoxifen therapy is indicated in individual patients with the diagnosis of LCIS (see Clinical Research section of this chapter).

The decision to pursue close observation, tamoxifen chemoprevention, or bilateral prophylactic total mastectomies in patients with LCIS is difficult and should be thoroughly discussed with patients prior to making a definitive treatment decision. Treatment decisions for this condition should be made electively in a thoughtful and deliberate fashion. The physician should present all options as clearly as possible to the patient and elicit her input regarding the final treatment decision. Perhaps future research will uncover molecular biological markers able to distinguish the subset of patients with LCIS who eventually develop breast carcinoma from those who will remain cancer-free. At present, we recommend that the physician discuss treatment options with the patient in a deliberate manner so that an elective decision can be made that is best for that individual patient.

MALE BREAST CANCER

Breast cancer in men is relatively uncommon and represents 0.5–1.0% of newly diagnosed breast cancers. Male breast cancer typically presents as a palpable

lump in the breast. Less common presentations include nipple retraction or ulceration, nipple discharge, or pain. Mammography can be useful in distinguishing gynecomastia from carcinoma but the presence of a dominant mass on examination is an indication for breast biopsy. Once the diagnosis of carcinoma has been confirmed pathologically, metastatic evaluation includes chest x-ray, bone scan, complete blood count, and liver function tests. The pathology of breast cancer in men is similar to that for women with the majority of cases representing infiltrating ductal carcinomas.

Surgical treatment of male breast cancer has historically been mastectomy. Modified radical mastectomy with a level I and II lymph node dissection is recommended for patients with superficial, mobile breast carcinomas. In patients with carcinomas fixed to the chest wall, radical mastectomy is indicated. In instances of nonfixed tumors that are close to the chest wall, a portion of the pectoralis major muscle directly under the carcinoma can be removed en bloc with the mastectomy specimen to obtain a wider surgical margin of resection. Breast conservation therapy is not advocated for men with breast cancer as few, anecdotal reports exist regarding this treatment approach. Thus, mastectomy is the treatment of choice recommended for men who develop breast carcinoma.

RADIATION THERAPY

Introduction

Radiation treatment for breast cancer has long been employed in a number of different clinical circumstances. Recent emphasis has been on using radiation in combination with breast conservation surgery for early-stage invasive disease. Preoperative or postoperative radiation is combined with mastectomy for locally advanced disease or high-risk patients. Finally, palliative radiation is an important component of management for patients with metastatic disease.

Radiation Treatment for Early-Stage Disease

Breast conservation treatment is well established in the management of early-stage breast cancer. Breast conservation treatment is generally defined as breast conservation surgery (i.e., ''lumpectomy'' with or without axillary lymph node dissection) followed by definitive breast irradiation.

Breast conservation surgery includes complete gross excision of the primary tumor. The breast component of the surgery is called by various names (e.g., lumpectomy, excisional biopsy, partial mastectomy, quadrantectomy). There are some differences among the various breast surgeries; for example, quadrantectomy denotes removal of the entire quadrant of the tumor-bearing portion of the breast and removes more breast tissue than an excisional biopsy. Most commonly,

lumpectomy is defined by complete gross removal of the primary tumor with a small margin, generally 0.5 or 1 cm, of surrounding normal breast tissue.

Axillary lymph node dissection is used for the majority of breast conservation patients at present. There are some circumstances in which axillary dissection is not used. For example, older patients, patients with severe medical comorbid conditions who are not good candidates for general anesthesia, and patients with ductal carcinoma in situ (DCIS; intraductal carcinoma) are treated without an axillary lymph node dissection. When the axilla is dissected, generally a lower dissection of level I ± II is performed. A lower dissection gives axillary staging with a low false-negative rate (i.e., ''skip'' metastases to higher-level lymph nodes) and a lower risk of complications, particularly arm lymphedema, than a full axillary lymph node dissection.

Close communication between the surgeon and the radiation oncologist is important to optimize patient outcome in terms of maximizing survival, local control, and cosmetic outcome, while minimizing complications. Determining patient acceptability for breast conservation treatment is the joint responsibility of the surgeon and the radiation oncologist. Inasmuch as radiation is delivered after surgery, it is important for the radiation treatment to be delivered in a fashion appropriate for the surgical procedure performed and the pathology findings.

Patient Selection

A number of factors influence the selection of women for breast conservation treatment. These factors relate to the patient, the tumor, radiation treatment delivery, complications, and cosmesis. In selecting patients, particular attention must be paid to those factors that render the patient not acceptable for breast conservation treatment, so-called contraindications (Table 1). In general, the optimal patient for breast conservation treatment has: (1) a tumor that can be completely excised; (2) pathologically confirmed negative margins of resection; (3) little or no cosmetic deformity after excision; (4) the ability to undergo daily radiation treatments; and (5) no contraindication to breast conservation treatment.

Patient age has received much attention relative to patient selection. As a single factor, patient age should not represent a contraindication to breast conservation treatment.

Young patient age is associated with an increased risk of local recurrence after breast conservation treatment. The definition of young age differs among different investigators, but most often is defined as ≤30, ≤35, or ≤40 years. Breast tumors in younger patients behave in a more biologically aggressive fashion compared to breast tumors in older age groups. Younger patients treated with mastectomy generally have worse outcomes than similarly staged and treated older patients. Despite the increased risk of local recurrence, young age alone does not render the patient ineligible for breast conservation treatment.

Table 1 Contraindications to Breast Conservation Treatment

Tumor control
Multiple primary tumors (gross multicentric disease) on physical examination or mammography
Diffuse microcalcifications on mammography
Grossly positive margins of the tumor excision
Diffusely positive microscopic margins of the tumor excision
Radiation delivery
Pregnancy
Prior radiation treatment to the breast
Inability or refusal to undergo daily radiation treatments
High risk for complications
Collagen-vascular disease
High risk for poor cosmesis
Large tumor size relative to breast size
Large, pendulous breast
Subareolar primary

Source: Modified and reproduced with permission from Solin et al., 1997.

Conversely, older patient age is associated with a decreased risk of local recurrence after breast conservation treatment. The definition of older age also differs among different investigators, but most often is defined as ≥ 65, ≥ 70, ≥ 75, or ≥ 80 years. While tumors in older age patients behave less aggressively than tumors in younger patients, older patient age as an individual factor does not render the patient ineligible for breast conservation treatment.

For the surgery of the primary breast tumor, complete excision with a surrounding rim of normal tissue is optimal before definitive breast irradiation. Complete excision is associated with a lower risk of local failure in the treated breast than incomplete excision. Incisional biopsy or grossly incomplete excision is inadequate for breast conservation treatment, and must be followed by a re-excisional biopsy prior to radiation treatment.

Many different tumor characteristics have been evaluated in terms of patient outcome after breast conservation treatment. Tumor characteristics associated with a substantially increased risk of local recurrence in the treated breast are considered a contraindication to breast conservation treatment.

For the patient who has undergone an excisional biopsy, much attention has been given to the microscopic margins of resection. The definitions of negative margins, positive margins, or close margins vary among different institutions.

Most single institution studies use a minimum distance of 1 or 2 mm between all microscopic tumor and inked margins to classify margins as negative. Margins are also considered negative when no tumor is seen in a reexcisional biopsy specimen. Some investigators, including the National Surgical Adjuvant Breast Project, classify margins as negative when there is any distance between tumor and inked margins, and score margins as positive only when tumor cells are identified as transected by the inked margins. For the pathological classification of close or positive margins, infiltrating carcinoma and ductal carcinoma in situ (DCIS; intraductal carcinoma) are used; lobular carcinoma in situ (LCIS) is not considered in the assessment of margins.

The issue in classifying margins is to distinguish those patients at excess risk for local recurrence after breast conservation treatment and thereby prospectively identify those patients better served by mastectomy. Most studies have shown that patients with focally (i.e., one or two) close or positive margins can be treated without an excess risk of local recurrence, whereas patients with diffuse margin involvement should undergo mastectomy, not breast conservation treatment. While the distinction between focal and diffuse margin involvement is somewhat arbitrary, these guidelines serve as practical indicators of suitability for breast conservation treatment for the vast majority of patients. When the significance of margin involvement on microscopic pathological examination is uncertain, discussion and/or review of the specimen findings by the surgeon, pathologist, and radiation oncologist is warranted.

No clearly defined maximum primary tumor size has been defined for breast conservation treatment. Tumor size of up to 4 or 5 cm in diameter is acceptable in most patients for breast conservation treatment. Increasing tumor size does not correlate with an increasing risk of local recurrence. The risk of local recurrence is similar in most series for T1 and T2 lesions, provided negative margins are obtained. For larger tumors (i.e., large T2 lesions and even small T3 lesions), the limiting factor for selection for breast conservation treatment is the ability of the surgeon to excise the tumor with adequate margins, but with a satisfactory cosmetic outcome. Such a large tumor in a small breast may be better treated with a mastectomy, not breast conservation treatment, because of inadequate cosmetic outcome.

For invasive carcinomas, no primary tumor histology has consistently been reported to be associated with an increased risk of local recurrence after breast conservation treatment. Therefore, the histological subtype of the primary tumor does not determine acceptability for breast conservation treatment. After ductal carcinoma, lobular carcinoma is the second most common histology. Obtaining clear margins of resection for a lobular carcinoma can be difficult. However, when clear margins of resection are obtained, local control for lobular carcinomas is similar to that for ductal carcinomas. Adequate local control after breast conservation treatment has been reported for many uncommon histological subtypes, such as colloid carcinoma, medullary carcinoma, and tubular carcinoma. For rare

histological subtypes, such as adenoid cystic carcinoma and squamous cell carcinoma, too few cases have been reported to make firm conclusions.

For an infiltrating ductal carcinoma, the finding of associated ductal carcinoma in situ (DCIS; intraductal carcinoma) should be carefully assessed for amount and distribution. The presence versus absence of an extensive intraductal component (EIC) is one method for classifying the association of infiltrating and intraductal carcinoma. EIC-positive tumors have been defined as either: (1) intraductal carcinoma comprising 25% or more of the main tumor mass plus any intraductal carcinoma outside of the main tumor mass; or (2) intraductal carcinoma with microinvasion. The significance of an EIC-positive tumor is that careful attention needs to be paid to the margins of resection. An EIC-positive tumor can be treated with breast conservation treatment without an excessively high risk of local recurrence provided the margins of resection are negative. For the EIC-positive tumor with positive margins of resection, a reexcision must be performed to obtain negative margins prior to delivering definitive irradiation.

The location of the primary tumor within the breast does not influence the rate of local recurrence. Therefore, no location within the breast is a contraindication to breast conservation treatment. A subareolar primary tumor may require partial or complete nipple areolectomy for complete excision, with a subsequent cosmetic deformity. Notwithstanding this cosmetic consideration, the subareolar location is not associated with an increased risk of local recurrence relative to other locations within the breast. Because of the potential cosmetic deformity associated with excision, the subareolar primary tumor is sometimes considered a relative contraindication to breast conservation treatment (Table 1).

In a number of situations, radiation should not be administered (Table 1). For example, radiation treatment for early-stage Hodgkin's disease is associated with an increased risk of developing breast cancer. However, a history of prior radiation for Hodgkin's disease precludes definitive breast irradiation and mandates that the patient be treated with mastectomy. Pregnancy, while uncommonly associated with breast cancer, precludes radiation treatments because of the potential risk to the developing fetus. However, selected patients can undergo breast conservation treatment if the breast conservation surgery can be performed during the pregnancy and if the radiation is delayed until after delivery or termination of the pregnancy. Collagen-vascular disease is associated with an increased risk of serious soft tissue complications after breast irradiation and, therefore, is considered a contraindication to breast conservation treatment.

Radiology Studies

High-quality mammography is critical for assessing a patient's suitability for breast conservation treatment. The ipsilateral mammogram must be assessed for the size and extent of the primary tumor and the presence and extent of microcalcifications, if any. Gross multicentric disease (i.e., multiple tumors in more than

one quadrant of the breast) must be excluded. The contralateral breast must be imaged mammographically because of the low but real risk of bilateral breast cancer at presentation of approximately 1%.

For those lesions presenting with microcalcifications on mammography (with or without a mass), a postbiopsy, preradiation mammogram is required to exclude residual microcalcifications. Residual microcalcifications need to be excised before radiation treatments are delivered. When reexcision is performed for residual microcalcifications, approximately 86% of the reexcision specimens are positive for residual tumor. A small number of patients have been reported to have undergone radiation in the presence of known residual microcalcifications and have shown excessively high rates of local recurrence.

Mammography is currently the only imaging study that is the standard of care for evaluation of the breast for breast conservation treatment. Although ultrasound is used for the work-up of the abnormal mammogram, ultrasound does not play a role in determining acceptability for breast conservation treatment. Magnetic resonance imaging (MRI) of the breast is an experimental imaging modality that is currently under active investigation.

Technical Delivery of Radiation Treatment

Expert technical delivery of radiation treatment is important to optimize local control and cosmesis, and to minimize the risk of complications. For breast conservation patients, surgery will have been completed prior to the delivery of radiation therapy. Therefore, when designing the radiation treatment program, the radiation oncologist must consider the surgical procedures performed and the pathology findings. The target volumes for radiation treatment are listed in Table 2.

For daily radiation treatments, the patient must be positioned in a manner that is reproducible. To enhance daily reproducibility, the patient is placed in a custom cast on an angle board (Fig. 1).

Radiation to the whole breast is considered standard at present. Whole breast radiation is delivered using tangential fields (Fig. 2). The clinical marks used to set up the tangential fields are: (1) medially, at midline; (2) laterally, 2 cm beyond palpable breast tissue; (3) cephalad, at the inferior border of the head of the clavicle; and (4) caudad, 2 cm beyond palpable breast tissue. The radiographic borders of the tangential fields are: (1) anteriorly, a minimum of 1.5–2.0 cm of flash in air; (2) posteriorly, 1.5–3.5 cm of lung; (3) cephalad, at the inferior border of the head of the clavicle; and (4) caudad, 2 cm beyond breast tissue.

After the whole breast is irradiated, a boost is delivered to the primary tumor site. To facilitate the boost treatment, the surgeon should place surgical marking clips in the primary tumor site at the time of surgical excision. The boost

TABLE 2 Target Volumes for Definitive Irradiation

Target volume	Technique	Dose (Gy)[a]	Indication
Whole breast	Tangential fields	45–50[b]	All patients
Boost to the primary tumor site	Electrons or iridium implant	10–20[b]	All patients
Total dose[c]		60–66[b]	All patients
Axilla	Anterior axillary/supraclavicular field plus posterior axillary boost	45–50	Pathologically node positive axilla, no axillary staging, or inadequate axillary staging
Supraclavicular fossa	Anterior axillary/supraclavicular field	45–50	Pathologically node positive axilla, no axillary staging, or inadequate axillary staging
Internal mammary lymph nodes	Extended tangential fields or anterior (en face) field	45–50	Uncertain (possibly for inner quadrant lesions, central lesions, or node-positive axilla)

[a] Using standard fractions of 1.8–2.0 Gy/day, five fractions per week.
[b] When the margins of the primary tumor excision are pathologically confirmed as negative, an alternative radiation dose is 50 Gy to the whole breast without a boost to the primary tumor site.
[c] Sum of the dose to the whole breast plus the boost.
Source: Modified and reproduced with permission from Solin et al., 1997.

can be delivered either by an electron field (Fig. 3) or by an iridium implant. Electron boost treatment is currently more commonly used because it is performed on an outpatient basis, whereas an implant boost requires hospitalization. Most investigators have not found significant differences in local control or cosmesis between the two types of boost treatments. The electron boost field can be designed radiographically or through the use of computed tomography (CT) treatment planning systems. The total radiation dose is individualized for each patient based on the pathological margins of resection, the size of the tumor, whether or not a reexcision was performed, and whether or not residual tumor was found pathologically in the reexcision specimen.

In selected patients, radiation to one or more regional nodal areas may be indicated (Table 2). Regional lymph nodes that should be considered for treatment are the axillary, supraclavicular, and internal mammary lymph nodes. Because of their close anatomical proximity, the supraclavicular fossa and the apical

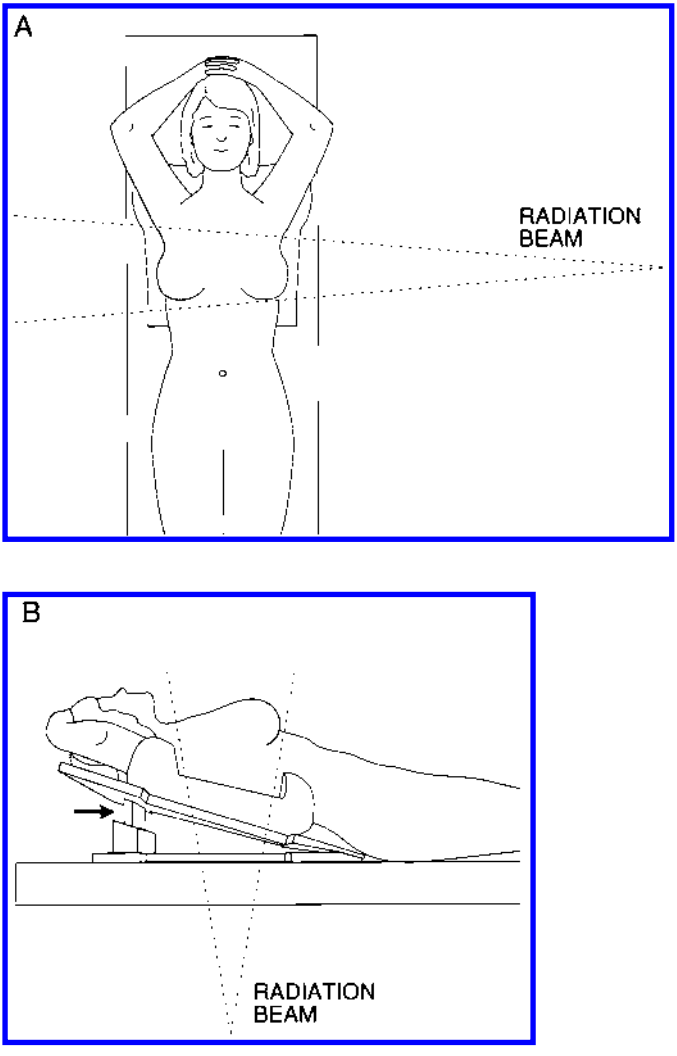

FIGURE 1 The patient in the standard treatment position. The patient lies in a customized cast which has been placed on top of the breast board. (A) Overhead view of the medial tangential field. (B) Lateral view of the lateral tangential field. A plastic insert (arrow) of variable height is used to adjust the angle of the breast board to the desired position to flatten the chest wall. (Reproduced with permission from Fowble et al., 1991.)

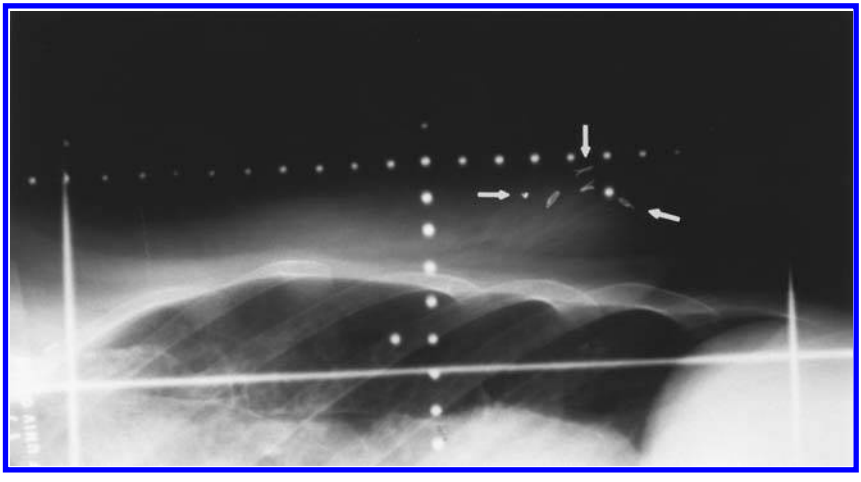

Figure 2 Simulator film of a lateral breast tangential field for a patient with a lower outer quadrant breast lesion. The surgeon has placed five marking clips (arrows) at the time of surgical resection. These surgical marking clips facilitate the radiographic identification of the primary tumor bed. (Reproduced with permission from Solin et al., 1985.)

axilla are included in a single field (Fig. 4). When the full axilla is treated, the lateral border of the radiation field is placed at the midhumeral head. When the supraclavicular fossa is treated without the full axilla, the lateral border of the field is placed at the medial border of the humeral head or at the coracoid process. Internal mammary lymph nodes, when treated, are included in the tangential fields by extending the medial entrance point 3 cm across the midline or are treated by a separate anterior (en face) field. If an anterior field is used, treatments should not be delivered using photons alone because of excessive dose to the heart and mediastinum; instead, either electrons or mixed photons and electrons should be used. Many authors have recommended the use of CT planning or lymphoscintigraphy to facilitate the treatment of internal mammary lymph nodes, as the location of these lymph nodes can vary significantly between patients.

Results

At least six prospective, randomized trials have compared breast conservation surgery plus radiation to mastectomy. These trials differ in a number of significant ways. First, the maximum tumor size was variable. Some of the trials were restricted to lesions 2 cm or less, some to 4 cm or less, and some to 5 cm or less.

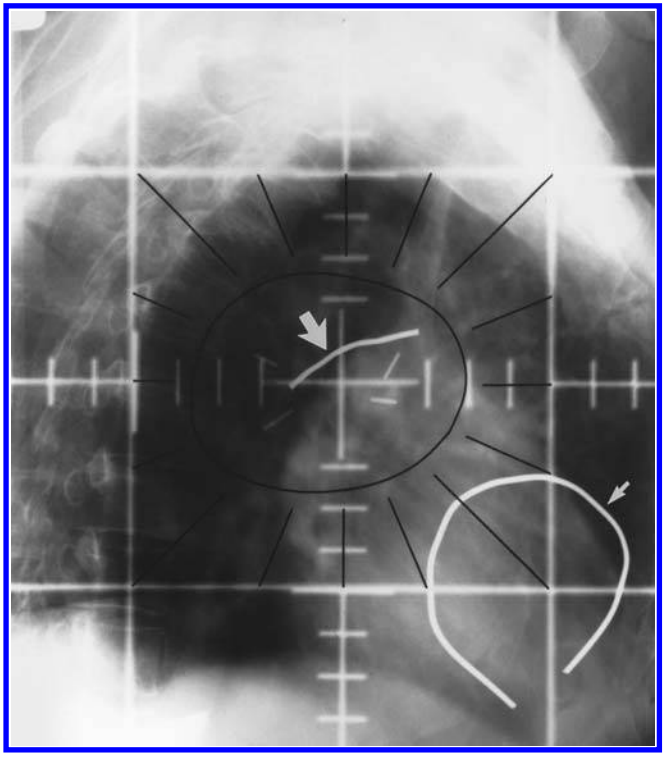

FIGURE 3 Simulator film of an electron boost field. A custom electron cutout is individually determined for each patient. A solder wire (large arrow) is placed on the surgical skin incision, and a second solder wire (small arrow) is placed to mark the edge of the areola. The surgical marking clips delineate the tumor bed. The surgical scar on the skin surface overlies the surgical marking clips. The external landmarks of the surgical skin incision and the areola are used clinically to verify the location of the electron boost field on the patient. (Reproduced with permission from Fowble et al., 1991.)

Second, the NSABP B-06 trial used a whole breast dose of 50 Gy without a boost to the primary tumor site, whereas all of the other randomized trials used a total radiation dose of 60 Gy or more including a boost to the primary tumor site. Third, the use of regional nodal radiation varied among the trials. Fourth, negative margins of the primary tumor resection were required in some, but not all, of the trials. Fifth, chemotherapy varied widely among the trials.

Notwithstanding these differences, the results of the randomized trials are remarkably consistent. These trials show equivalent survival rates for mastectomy

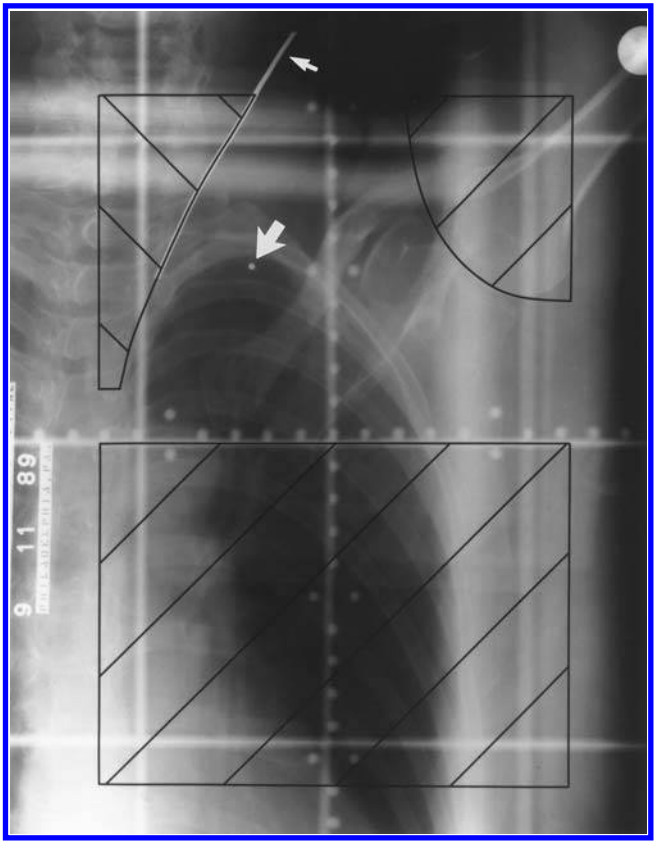

FIGURE 4 Simulator film of an anterior axillary/supraclavicular field. The field is treated to a depth of 3 cm. The depth is measured at the supraclavicular fossa, which is marked by a BB (large arrow). A solder wire (small arrow) is placed 1 cm medially to the medial border of the sternocleidomastoid muscle, and the area medial to this solder wire is blocked. (Reproduced with permission from Fowble et al., 1991.)

and breast conservation treatment. The equivalence in survival rates persists in multiple trials with 10 years or more of follow-up. Outcome after treatment is a function of known prognostic variables (e.g., pathological nodal status, tumor size), not of the method of treatment.

Those studies that have compared lumpectomy plus radiation to lumpectomy alone (without radiation) have shown that local recurrence in the breast is significantly reduced with the use of radiation. Further, the use of chemotherapy instead of radiation (i.e., lumpectomy plus chemotherapy vs. lumpectomy plus

radiation) in the NSABP B-06 trial showed that chemotherapy was not as effective as radiation in reducing local recurrence. However, chemotherapy did result in a small improvement in local control when radiation was given—i.e., local failure was slightly lower after lumpectomy plus radiation plus chemotherapy compared to lumpectomy plus radiation.

After lumpectomy plus radiation treatment, the rate of local recurrence in the treated breast is approximately 7% at 5 years, 15% at 10 years, and 20% at 15 years of follow-up. Over 90% of local failures can be treated with salvage mastectomy with curative intent. Prognosis after local recurrence is related to the histology of the local recurrence, the time to local recurrence, the ability to undergo salvage surgery, and the extent of disease. Because of the importance of salvage surgery after local failure, follow-up after initial treatment is important for early detection of local recurrence. A comprehensive follow-up program includes yearly bilateral mammography, monthly breast self-examination (BSE) by the patient, and periodic examination of the breasts by a physician, generally every 3–6 months for the first 5 years of follow-up and every 6–12 months thereafter.

Careful radiation technique with attention to integrating surgical and pathological findings is necessary to minimize the risk of complications. The incidence of arm edema is approximately 5–20%. Factors that increase the risk of arm edema include complete axillary lymph node dissection, nodal irradiation to the supraclavicular and axillary regions, and the use of chemotherapy. Symptoms of chest wall tenderness occur in approximately 10–20% of women after treatment. Other complications are uncommon or rare; the incidence of rib fracture, pneumonitis, brachial plexopathy, or pericarditis is 1% or less. The risk of pneumonitis correlates with the amount of lung treated as measured on the simulator films, and the amount of lung seen on the simulator films should be no more than 3.0–3.5 cm in greatest dimension.

RADIATION COMBINED WITH MASTECTOMY

Even though breast conservation treatment achieves survival rates equivalent to mastectomy for appropriately selected patients with early-stage disease, some fraction of patients will undergo mastectomy because of individual patient preference, contraindications to breast conservation treatment, or locally advanced disease. There is a long history of combining radiation with mastectomy with the goal of optimizing local-regional control.

For the patient who undergoes mastectomy, postoperative radiation is indicated when there is a high risk for local-regional failure. The goal of postoperative radiation treatment in this setting is to reduce the risk of local-regional failure. Whether postoperative radiation improves survival continues to be a matter of debate. Randomized studies have not consistently shown a survival benefit for

patients treated with postoperative radiation. However, a small improvement in survival has been suggested for some subsets of patients.

The indications for postoperative radiation are any one or more of the following: (1) T3 or T4 disease; (2) N2 or N3 disease; (3) four or more positive axillary lymph nodes; or (4) close or positive margins of resection. Each of these indications for postoperative radiation is associated with a 15–20% or greater risk of local-regional failure in the absence of postoperative radiation.

Most, if not all, of the patients treated with postoperative radiation would be considered for adjuvant systemic chemotherapy and/or hormonal therapy. However, the use of adjuvant systemic therapy should be considered in addition to, not instead of, postoperative radiation. Similarly, the use of high-dose chemotherapy with bone marrow or peripheral stem cell transplant should be considered in addition to postoperative radiation.

Patients with locally advanced (i.e., stage T3, T4, N2, and/or N3) or inflammatory breast cancer are treated with multimodality therapy consisting of chemotherapy, radiation therapy, and mastectomy. Although the sequencing of these treatment modalities varies among studies, some general principles have been determined. First, the best results are seen when all three treatment modalities are used. Second, chemotherapy is usually delivered first, followed by local-regional treatment (radiation then mastectomy or mastectomy then radiation), sometimes followed by further chemotherapy. Third, bone marrow or peripheral stem cell transplant is undergoing active clinical investigation because the results of multimodality treatment without transplant are poor.

PALLIATIVE RADIATION FOR METASTATIC DISEASE

Palliative radiation is an important modality for managing the patient with metastatic disease. Palliative radiation needs to be carefully integrated into an overall program of management, especially when chemotherapy is being delivered. Many of the common areas for metastatic spread of breast cancer are responsive to radiation for palliation. Brain metastases are generally managed with whole brain radiotherapy plus steroids. The selected favorable patient with a solitary metastatic brain lesion may benefit from surgical resection or stereotactic radiosurgery as a boost after whole brain radiotherapy. Bony lesions are often responsive to palliative radiation. Involvement of weight-bearing and/or long bones may require an orthopedic procedure for stabilization. Widespread bony disease may benefit from strontium with or without localized radiotherapy. Spinal cord compression should be managed with surgical decompression and/or radiation; steroids are also important for such patients. Intrathoracic lesions causing bronchial obstruction or superior vena cava syndrome may respond to palliative radiation, although stenting should be considered for bronchial obstruction. Palliative radiation may also be useful in managing less common situations on an individual

basis (e.g., painful liver metastases, skin metastases). It should be emphasized that the palliative program for each patient with metastatic disease must be individually designed; in many ways, the uniqueness of each palliative patient makes palliative treatment more difficult to design than definitive breast cancer treatment.

MEDICAL ONCOLOGY

Introduction

The staging system for breast cancer is relatively straightforward, as outlined in Table 3. At the time of initial evaluation, most patients with invasive breast cancer will have no evidence of spread beyond the breast and ipsilateral axillary lymph nodes. Despite adequate local therapy, however, many of these patients eventually develop metastatic disease. It is assumed that micrometastases occur early in the course of breast cancer and are frequently present at the time of diagnosis. The role of systemic therapy in breast cancer includes both the eradication of such occult disease and the control of macroscopic disease in patients who present with or subsequently develop true metastatic disease. The following discussion highlights some of the key principles in the medical management of breast cancer.

Early Breast Cancer

The goal of adjuvant systemic therapy is to improve survival by decreasing the risk of breast cancer recurrence through the use of chemotherapy, hormonal therapy, or both. Proper selection of patients for adjuvant therapy requires an assessment of the individual patient's risk for the future development of metastatic disease. While the relative benefits of adjuvant therapy are similar in patients at high and low risk for recurrence, the absolute survival benefit varies with the risk for recurrence. After it is determined who is at greater risk for relapse, those patients with minimal risk can be spared the toxicity of therapy. The most reliable prognostic indicators are nodal involvement, tumor size, hormone receptor levels, and histological grade of the tumor.

Selection of Patients for Systemic Therapy

The single most important predictor for disease related mortality in early-stage invasive breast cancer is the presence and degree of lymph node involvement. In an update of several National Surgical Adjuvant Breast and Bowel Project (NSABP) studies, the involvement of one to three axillary lymph nodes was associated with a significantly poorer disease-free survival than no lymph node involvement. The involvement of four or more axillary lymph nodes correlated with an even higher mortality, which increased with an increasing number of

TABLE 3 Staging of Breast Cancer (AJCC, 1992)

Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
Stage IIA	T0, N1, M0
	T1, N1, M0
	T2, N0, M0
Stage IIB	T2, N1, M0
	T3, N0, M0
Stage IIIA	T0, N2, M0
	T1, N2, M0
	T2, N2, M0
	T3, N1, M0
	T3, N2, M0
Stage IIIB	T4, any N, M0
	Any T, N3, M0
Stage IV	Any T, any N, M1

TNM definitions:
Tx Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor 2 cm or less in greatest dimension
T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3 Tumor more than 5 cm in greatest dimension
T4 Tumor of any size with direct extension to chest wall or skin, includes inflammatory carcinoma
Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis to movable ipsilateral axillary node(s)
N2 Metastasis to ipsilateral node(s) fixed to one another or to other structures
N3 Metastasis to internal mammary lymph nodes
Mx Presence of distant metastases cannot be assessed
M0 No distant metastases
M1 Distant metastases (includes metastasis to ipsilateral supraclavicular nodes)

positive nodes. Chemotherapy studies dating back as far as the 1970s have demonstrated a survival benefit with adjuvant treatment in node-positive patients, particularly in premenopausal patients.

With increasing frequency, adjuvant therapy has been incorporated into the treatment of patients with node-negative breast cancer. In node-negative patients, the risk of breast cancer recurrence is directly related to tumor size. Patients with tumors measuring less than 1 cm have less than a 10% risk of recurrence over a 10-year period and may not require systemic therapy. Patients with a tumor size greater than 1 cm, however, have a higher risk of recurrence and, in general, should be considered candidates for adjuvant systemic therapy.

For node-negative patients with breast cancers greater than 1 cm, additional factors are taken into account in determining the need for adjuvant therapy. Estrogen and progesterone receptor status is a well-established independent predictor of prognosis. Patients with estrogen-receptor (ER)-positive tumors have nearly a 10% increase in both disease-free and overall survival at 5 years compared with patients whose tumors are negative for estrogen receptors. The level of estrogen receptor positivity also correlates directly with outcome. Patients with nuclear grade 1 and 2 tumors have approximately a 15% survival advantage over those patients with nuclear grade 3 tumors. Hormone receptor negativity and high histological grade of the tumor suggest a greater need for more aggressive early treatment.

Results of Adjuvant Therapy and Choice of Regimen

Both hormonal therapy and chemotherapy have been shown to improve outcome in early-stage breast cancer. NSABP trial B-14 and the Scottish Tamoxifen Trial studied node-negative patients and found that women with hormone-receptor-positive tumors randomized to tamoxifen versus placebo achieved a significant benefit in 5-year disease-free as well as overall survival. The 1989 Intergroup Trial also demonstrated a significant survival benefit at 5 years in node-negative patients with either ER-negative tumors, or ER-positive tumors larger than 3 cm when randomized to receive CMFP (cyclophosphamide, methotrexate, and 5-fluorouracil plus prednisone) versus no therapy.

The majority of adjuvant therapy trials in breast cancer have been performed in the node-positive population. Many of these studies are included in the 1992 ''Overview Analysis'' of the Early Breast Cancer Trialists Collaborative Group (EBCTCG). In this meta-analysis, the primary data were obtained from patients in 133 randomized trials of systemic adjuvant therapy for breast cancer and included outcome results of 75,000 women taking part in trials evaluating the effect of tamoxifen, ovarian ablation, chemotherapy, and immunotherapy. To improve the statistical power of the study, the overview includes patients in both the test treatment group and the control group who may be receiving other adjuvant treatments or no additional therapy. This study design is valid but may underestimate the effect of the treatment being evaluated.

In the EBCTCG study, more than 30,000 women were analyzed in the tamoxifen overview. A significant reduction in mortality was observed in the group receiving up to 5 years of tamoxifen therapy. This benefit was sustained even at 10 years of follow-up. While an advantage was seen in all patient groups regardless of age, nodal status, and hormone receptor levels, the benefit was most pronounced in patients age 50 or older and in ER-positive patients.

In women under 50 years of age, the effect of ovarian ablation was evaluated in the overview analysis. Again, a significant survival advantage was seen

in patients receiving this treatment, with a greater effect in the node-positive group. The benefit persists for at least 15 years of follow-up.

The overview analysis also found a significant and durable survival advantage in patients receiving adjuvant chemotherapy. The CMF regimen or some variant was used in the majority of these trials, which included 11,000 women. Patients who received chemotherapy had a decreased mortality at 5 and 10 years of follow-up regardless of age or nodal involvement. The magnitude of the benefit of chemotherapy was greatest in patients less than 50 years old.

While the overview analysis clearly validates the use of adjuvant chemotherapy and hormonal therapy in early-stage breast cancer, the overview is unable to define the optimal type of such adjuvant treatment. One particularly important aspect of the 1992 Overview was the suggestion that the combination of both chemotherapy and tamoxifen was superior to tamoxifen alone, particularly in women over age 50. One study that supports a role for combination chemohormonal therapy is the NSABP trial B-16. This study randomized breast cancer patients, who were either age 50–59 with progesterone-receptor (PR)-positive tumors or age 60 or over with PR-positive or negative tumors, to receive either tamoxifen alone for 5 years or tamoxifen plus a 12-week course of doxorubicin (Adriamycin) containing chemotherapy. After 3 years of follow-up, an 84% disease-free survival was observed in patients receiving combination therapy compared with a 67% disease-free survival in patients receiving tamoxifen alone.

Two recent reports confirm the utility of combination chemohormonal therapy relative to tamoxifen alone in both node-positive and node-negative patients. One report from the Eastern Cooperative Oncology Group essentially confirms the NSABP study, suggesting an improvement in disease-free survival in postmenopausal, node-positive patients when doxorubicin-based therapy and tamoxifen together were used in comparison to tamoxifen alone. Another report from the NSABP compared non-doxorubicin-containing chemotherapy plus tamoxifen to tamoxifen alone in patients with node-negative, receptor-positive tumors (both pre- and postmenopausal), and demonstrated a modest improvement in disease-free survival in the patients receiving combined-modality therapy.

While CMF chemotherapy has been the most commonly used chemotherapy regimen for the adjuvant treatment of breast cancer, doxorubicin-based treatment is gaining increasing acceptance in this setting. The superior efficacy of doxorubicin-containing regimens in the treatment of metastatic breast cancer has led to their use as adjuvant therapy in all patient subsets. While subset analyses in several studies have suggested an advantage to doxorubicin-containing chemotherapy in patients at high risk for relapse by virtue of involvement of four or more axillary lymph nodes, no regimen has yet proven to be superior to CMF, especially in the node-negative patient. Doxorubicin-based adjuvant regimens should be considered adequate alternatives to CMF, and as discussed below, may

effect similar benefits while permitting shorter duration of therapy. The usual dosing schedules for common chemotherapy regimens used in the adjuvant setting are listed in Table 4.

The optimum duration of chemotherapy has been reasonably well defined. In studies from Milan, six monthly cycles of CMF are shown to be as effective as 12 months of CMF. This finding is supported by the EBCTCG overview, which found no benefit to long-term polychemotherapy relative to shorter (6 months) duration of therapy. According to the findings of the International Breast Cancer Study Group, however, three cycles of adjuvant CMF are not as effective as longer courses of treatment. Four cycles of cyclophosphamide and doxorubicin, on the other hand, has proven to be equivalent to six cycles of CMF in node-positive patients. The general recommendation for duration of adjuvant chemotherapy, therefore, is up to 6 months of CMF or at least 3 months of a doxorubicin-based regimen.

The optimal duration of tamoxifen treatment in the adjuvant setting is also addressed in the EBCTCG overview, which demonstrates a significant trend toward a greater effect with a longer duration of tamoxifen use. One recent study has clearly demonstrated that 5 years of adjuvant tamoxifen is superior to 2, while another study failed to demonstrate the superiority of 10 versus 5 years of tamoxifen therapy. Five years of therapy, therefore, remains the standard duration of treatment if tamoxifen is to be used.

General guidelines for the adjuvant treatment of early stage breast cancer are outlined in Table 5. These general recommendations do not emphasize the

Table 4 Common Chemotherapy Regimens Used in the Adjuvant Treatment of Breast Cancer

CMF (classic):	Cyclophosphamide 100 mg/m^2 PO days 1–14
	Methotrexate 40 mg/m^2 IV days 1 and 8
	Fluorouracil 600 mg/m^2 IV days 1 and 8
	Repeat every 28 days
''IV'' CMF:	Cyclophosphamide 600 mg/m^2 IV day 1
	Methotrexate 40 mg/m^2 IV day 1
	Fluorouracil 600 mg/m^2 IV day 1
	Repeat every 21 days
CAF:	Cyclophosphamide 100 mg/m^2 daily days 1–14
	Doxorubicin 30 mg/m^2 IV days 1 and 8
	Fluorouracil 500 mg/m^2 IV days 1 and 8
	Repeat every 28 days
AC:	Adriamycin 60 mg/m^2 IV day 1
	Cyclophosphamide 600 mg/mg IV day 1
	Repeat every 21 days

TABLE 5 Treatment Recommendations for Patients with Early-Stage Breast Cancer

Lymph node negative:	Tumor size < or = 1 cm		Observation
	ER+ Tumor size 1–2 cm Low histological nuclear grade		Tamoxifen
	Tumor size > or = 2 cm or Tumor size > or = 1 cm ER− High histological and nuclear grade		Chemotherapy ± tamoxifen
Lymph node positive:	ER−	premenopausal patient	Chemotherapy
		postmenopausal patient	Chemotherapy ± tamoxifen
	ER+	premenopausal patient	Chemotherapy ± tamoxifen
		postmenopausal patient	Tamoxifen ± chemotherapy (esp. ages 50–69)

need for individual discussion of risks and benefits of adjuvant treatment with each patient, and have become increasingly complicated by the emerging evidence that chemotherapy and hormone therapy in combination may be beneficial in most subsets of patients with ER- and/or PR-positive tumors. For patients who are at particularly high risk for relapse, more effective therapies are needed and consideration should be given to research protocols that include high-dose chemotherapy with autologous bone marrow or stem cell support (see discussion below).

Toxicities of Adjuvant Systemic Therapy

Chemotherapy

Nausea, vomiting, and malaise are common side effects of all of the adjuvant chemotherapy regimens used in breast cancer. Myelosuppresion and alopecia also occur frequently but are typically more severe with doxorubicin-based regimens than with CMF. Both types of therapy are associated with a high incidence of amenorrhea, which is age dependent in frequency with a greater than 95% incidence in women over age 40 as opposed to a less than 40% incidence in younger women if the CMF regimen is used. Weight gain is also common in patients receiving adjuvant chemotherapy for breast cancer and appears to be multifactorial in etiology.

An important, but infrequent, side effect of doxorubicin is anthracycline-associated myocardial toxicity. The incidence of this toxicity was previously re-

ported to be higher in patients who received radiation therapy to the left chest. However, with current techniques of administering radiation therapy, recent studies have shown no adverse cardiac effects from left chest wall irradiation. The frequency of clinical congestive heart failure is less than 2% in patients receiving a cumulative dose of up to 350 mg/m^2 of the drug.

Another important long-term toxicity of adjuvant chemotherapy is the potential for inducing second malignancies. Alkylating agents have been associated with an increased risk of acute leukemia within the first 10 years following therapy. When this risk has been assessed in patients receiving standard cyclophosphamide-containing adjuvant therapy for primary breast cancer, such patients do not appear to have a much higher risk of developing myelodysplasia or acute leukemia than the general population. However, as more patients are receiving combination treatment with an alkylating agent plus an anthracycline and with recent trends toward more dose intensive therapy, these findings may change.

Tamoxifen

Tamoxifen is well tolerated by most patients, but its side effects are not insignificant. Many patients develop menopausal symptoms such as hot flashes and atrophic vaginitis, which may be more pronounced in younger women. Treatment with tamoxifen is associated with an increased risk of thromboembolic phenomena, although this risk is quite small, affecting approximately 1% of patients. Recent evidence indicates that patients taking tamoxifen are at increased risk of developing cataracts or may experience accelerated progression of existing cataracts; however, the magnitude of this risk is unknown. Patients receiving tamoxifen also need to be aware of the increased risk of endometrial carcinoma associated with this drug. In a 1994 report from the NSABP, patients taking tamoxifen had an average annual hazard rate for developing endometrial cancer of 1.6/1000, which translates into a cumulative rate of 6.3/1000 over a 5-year period of therapy. While this is a concerning problem, it is important to keep in mind that the cumulative hazard for relapsing breast cancer was decreased by 104.3/1000 in patients receiving tamoxifen in this study.

Locally Advanced and Inflammatory Breast Cancer

Stage III breast cancer encompasses a diverse group of cancers including both operable and inoperable locally advanced breast cancer as well as inflammatory breast cancer. Combinations of surgery and radiation therapy have improved local control, but the overall survival of stage III breast cancer patients is poor when only local therapies are used. The majority of these patients will eventually die of metastatic disease, and the need for effective systemic therapy is compelling. Due to the infrequency of stage III presentation of breast cancer and the heterogeneity of this population, clinical studies in this disease are limited, and the literature is difficult to interpret.

Locally Advanced Breast Cancer

Cytoreductive chemotherapy has been administered to patients with locally advanced breast cancer prior to surgery or radiation in an attempt to improve operability of the disease. Several studies have demonstrated excellent response rates to such neoadjuvant therapy with good local control. A study at the M. D. Anderson Cancer Center evaluated the use of three cycles of neoadjuvant FAC (5-fluorouracil, Adriamycin, and cyclophosphamide), followed by modified radical mastectomy and/or radiation therapy, followed by additional chemotherapy. Five-year disease-free and overall survival in this study were significantly better than expected, based on historical experience. This study also demonstrated that the use of radiation therapy need not compromise the ability to give adequate doses of chemotherapy.

While multimodality treatment with chemotherapy, mastectomy, and irradiation is generally recommended for locally advanced, noninflammatory breast cancer, the sequencing of these treatments is not standardized. Often a flexible number of chemotherapy cycles is given to achieve an optimal response, followed by mastectomy and radiation therapy (the order of which may vary), frequently followed by additional cycles of chemotherapy. Hormonal therapy is also included in the treatment of selected patients, particularly when estrogen and/or progesterone receptors are positive.

Despite improvements in therapy for locally advanced breast cancer, many patients will eventually develop metastatic disease. Appropriate candidates should be considered for enrollment in clinical trials investigating new therapies, such as the use of high-dose chemotherapy with bone marrow or stem cell support, which have the potential to improve the prognosis of these patients.

Inflammatory Breast Cancer

Owing to its unique presentation and highly aggressive nature, inflammatory breast cancer is generally viewed as a separate category within stage III breast cancer. The diagnosis of inflammatory breast cancer can be made on the basis of clinical or pathological features including breast skin edema, breast enlargement, thickening of the breast, warmth, tenderness, and erythema of the breast, or the presence of dermal lymphatic invasion on histopathology. The prognosis for this disease remains poor, but survival has been significantly improved by advances in combined-modality treatment.

As a single modality, neither mastectomy, radiation, nor chemotherapy is adequate treatment for inflammatory breast cancer. Although approximately 20% of patients will have an apparent complete response to chemotherapy alone, a high prevalence of residual carcinoma is found in mastectomy specimens of such patients. The inadequacy of local therapy only, whether with mastectomy, radiotherapy, or both, is demonstrated by dismal 5-year survival rates ranging from

zero to 20% in patients receiving local treatment alone. Studies that have incorporated combined chemotherapy and locoregional treatment have achieved survival rates ranging from 25 to 75% at 4 or more years of follow-up, suggesting an advantage to this approach.

As with other selected patients with stage III breast cancer, high-dose chemotherapy with stem cell or bone marrow support is being offered with increasing frequency in the treatment of inflammatory breast cancer. Given the poor prognosis and a relative chemoresponsiveness of this disease, dose-intensive approaches are justified but are preferably done in the context of a clinical trial.

For patients not enrolled in clinical trials, nonmetastatic inflammatory breast cancer should be treated with initial cycles of doxorubicin-containing chemotherapy to maximum response. At that point, local therapy, usually consisting of both surgery and radiotherapy, is instituted. Chemotherapy, excluding doxorubicin, may be continued during radiation and should be resumed in full following completion of local therapy to complete 1 year of treatment. The role of tamoxifen has not been well studied, but it is often included in the treatment of patients with inflammatory breast cancer, particularly if ER-positive.

Metastatic Breast Cancer

Once metastatic breast cancer is diagnosed, the median survival is approximately 3 years, although up to 10% of patients may live more than 10 years with metastatic disease. Prognosis is determined by sites of disease, hormone receptor status, and the pace of the disease in the individual patient. Involvement of visceral sites such as liver, lung, and brain, ER negativity, and a short disease-free interval from the time of original diagnosis, all portend a poorer outcome. Treatment of metastatic disease may consist of surgery, radiation therapy, hormonal therapy, and/or chemotherapy. Surgery and radiation are often appropriate in patients with either a single site of disease or with a localized symptom-producing problem, but the majority of patients will require systemic therapy. Unfortunately, these therapies have a limited effect on survival and the goals of treatment are ultimately palliative with emphasis placed on avoidance of excessive toxicity and improvement in quality of life.

Hormonal Therapy for Metastatic Disease

In patients with hormone-receptor-positive tumors confined to the soft tissues and/or bone, and in patients with an indolent disease course, hormonal therapy should be strongly considered. Approximately two-thirds of patients with positive hormone receptors will have a clinical response to endocrine therapy with the likelihood of response correlating directly with the hormone receptor level. All of the hormonal manipulations used in the treatment of breast cancer have similar efficacy. Selection of treatment is based largely upon tolerability and ease of administration.

Oophorectomy is one option for hormonal treatment of premenopausal women with metastatic breast cancer. While this procedure may be performed effectively by either surgical or radioablative means, a more rapid response rate may be associated with the surgical approach. Medical oophorectomy with luteinizing hormone releasing hormone (LHRH) agonists should be considered as an alternative to surgical oophorectomy or radioablation. Patients under age 35 do not appear to respond as well to any form of oophorectomy compared to older patients.

Tamoxifen is a well-accepted alternative to oophorectomy in premenopausal patients and is considered standard first-line treatment in postmenopausal patients who are candidates for endocrine therapy. Tamoxifen is generally well tolerated and can be administered as a once-daily dose. The use of tamoxifen may be associated with a flare phenomenon resulting in increased bone pain and hypercalcemia in the first weeks of treatment. This self-limited reaction frequently predicts a response to treatment and is not an indication for discontinuing the drug. In the treatment of metastatic disease, tamoxifen is generally continued until there is evidence of disease progression.

Despite progression through first-line treatment, many patients who have previously responded to tamoxifen will maintain the ability to respond to alternative hormonal therapy. While progestational agents such as megestrol acetate (Megace) have been considered standard second-line therapy, the selective aromatase inhibitor anastrozole (Arimidex) may be better tolerated by some patients. A 1996 study from the M. D. Anderson Cancer Center demonstrated equal efficacy between megestrol acetate and a once-daily 1-mg dose of anastrozole. The side effect profiles of the two drugs differed in that megestrol acetate was associated with significantly more weight gain and peripheral edema.

Aminoglutethimide and androgens are also effective alternative endocrine therapies. The antiadrenal compound aminoglutethimide is generally reserved for second- or third-line treatment in patients without ovarian function. It is associated with a number of side effects including lethargy, dizziness, skin rash, and gastrointestinal effects. Hydrocortisone supplementation should be given with this drug. Androgens are generally reserved for patients refractory to other treatments owing to their masculinizing effects. Table 6 outlines the use of endocrine therapy for metastatic breast cancer.

Chemotherapy for Metastatic Disease

For patients who are not felt to be candidates for hormonal treatment, by virtue of rapid disease progression, visceral involvement, or hormone-receptor negativity, and for those who have failed hormonal therapy, chemotherapy is considered. In particular, patients with hepatic metastases may benefit from aggressive combination chemotherapy early in their course. While breast cancer is a relatively chemosensitive disease, it is important to remember that the toxicity of chemotherapy may be significantly greater than that of endocrine therapy.

Table 6 Hormonal Therapy for Metastatic Disease

Patient characteristics	
Disease-free interval >2 years from primary treatment	
Positive hormone receptors	
Absence of significant visceral disease	
Indolent disease progression	
Premenopausal patients	
First-line therapy:	Tamoxifen
	Oophorectomy (age > 35)
Second-line therapy:	Oophorectomy (if tamoxifen failure)
	Anastrozole
	Progestational agents
Third-line therapy:	Aminoglutethimide
	Androgens
Postmenopausal patients	
First-line therapy:	Tamoxifen
Second-line therapy:	Anastrozole
	Progestational agents
Third-line therapy:	Aminoglutethimide
	Androgens

The classic CMF regimen remains an effective treatment in metastatic breast cancer with over 50% of patients achieving a response that lasts a median of 6–12 months. In patients who have previously received CMF in the adjuvant setting, similar response rates are seen with reinstitution of this regimen assuming at least a 1-year interval has elapsed since the completion of adjuvant chemotherapy.

The doxorubicin-based regimen CAF (cyclophosphamide, Adriamycin, 5-fluorouracil) has demonstrated higher response rates and a longer duration of response when compared to CMF in randomized trials. The tradeoff for higher response rates is increased toxicity with a greater degree of myelosuppression and alopecia occurring in patients receiving doxorubicin. The choice of doxorubicin-containing chemotherapy, however, may be preferable in patients with rapidly progressive visceral disease. It is also an appropriate second-line choice in patients who have failed one or two prior non-doxorubicin-containing regimens as 30–50% of such patients will respond to single-agent doxorubicin.

For breast cancer patients who have become refractory to doxorubicin or have had a short disease-free interval following doxorubicin-based adjuvant therapy, paclitaxel (Taxol) has emerged as a highly effective agent. Response rates of at least 20–25% are seen with single-agent paclitaxel in patients who have previously received other treatments. Response rates of 50–60% are seen in pre-

viously untreated patients. The major toxicities of paclitaxel are myelosuppression, alopecia, and neuromuscular disturbances. A recent randomized trial by the Eastern Cooperative Oncology Group suggests that paclitaxel and doxorubicin are essentially equivalent when used as first-line, single-agent chemotherapy in patients with no prior exposure to doxorubicin. Recent reports of combination treatment with paclitaxel and doxorubicin have demonstrated variable response rates with metastatic breast cancer. A study from Milan reported a 94% overall response and a 41% complete response rate in patients who had not previously received chemotherapy for metastatic disease. Unfortunately, these patients also experienced significant toxicity including severe neutropenia, mucositis, as well as a 21% incidence of clinical congestive heart failure. Other studies have failed to confirm the same high response rates from combined paclitaxel and doxorubicin therapy, but suggest that excessive cardiotoxicity may be avoided by alterations in drug dose and scheduling.

The semisynthetic taxane docetaxel (Taxotere) has emerged as a highly effective chemotherapeutic agent in the treatment of metastatic breast cancer, with response rates that may be superior to both paclitaxel and doxorubicin in phase II trials. The actual superiority of docetaxel as a single agent awaits confirmation in ongoing randomized trials.

A battery of other drugs are commonly used in the treatment of metastatic breast cancer. Effective treatment regimens include older drugs such as mitomycin and vinblastine as well as newer agents such as navelbine and gemcitabine. Table 7 outlines an approach to the use of chemotherapy in metastatic breast cancer.

One recent advance in breast cancer therapy that deserves mention is use of the bisphosphonate pamidronate in patients with lytic bone metastases. A recent report by the Aredia Breast Cancer Study Group demonstrated that monthly infusions of 90 mg of pamidronate significantly reduced the incidence of skeletal complications in this group of patients, particularly those receiving chemotherapy, when compared to a placebo group. Pain scores were improved in patients receiving pamidronate relative to those receiving placebo. Pamidronate should, therefore, be administered as an adjunct to standard chemotherapy in breast cancer patients with lytic bone metastases.

Determining the duration for which to continue a chemotherapeutic regimen requires balancing the benefit obtained from the therapy with its tolerability in the individual patient. It is important to remember that responses to chemotherapy may be delayed, and a period of several months is often necessary before an objective response is ascertained. Intermittent short-term regimens of chemotherapy (3–6 months) have been compared to continuous administration until the time of disease progression. Survival has generally been found to be equivalent with the two approaches, but an advantage in both the disease-free interval and quality of life was found in patients receiving continuous chemotherapy. So,

TABLE 7 Chemotherapy Recommendations for Patients with Metastatic Breast Cancer

Patient characteristics	
Hormone receptor negative	
Disease-free interval <2 years following primary treatment	
Visceral disease (especially liver)	
Symptomatic disease requiring rapid response	
Failure to respond to hormone therapy for metastatic disease	
No prior adjuvant chemotherapy	
First-line treatment:	CMF
	CAF
	Single-agent doxorubicin
Prior adjuvant CMF	
Disease-free interval <1 year:	CAF
	Doxorubicin
Disease-free interval >1 year:	CMF
	CAF
	Doxorubicin
Prior adjuvant CAF or AC	
Disease-free interval <1 year:	Paclitaxel
	Docetaxel
	Vinorelbine
Disease-free interval >1 year:	CAF
	Doxorubicin (assuming dose limit not yet reached)
	Paclitaxel
	Docetaxel

while breaks from chemotherapy are reasonable for patients with a minimum of cancer-related symptoms, many patients will benefit from continuing treatment until the time of progression.

The use of high-dose chemotherapy with autologous bone marrow or peripheral stem cell support has a limited role in the treatment of metastatic breast cancer but is often considered in younger patients with chemotherapy-responsive disease.

Dose Intensity and "High-Dose" Chemotherapy

The rationale behind dose-intensive therapy is that resistance of cancer cells may be overcome with increasing drug doses. The 1994 Cancer and Leukemia Group B study evaluated the concept of dose intensity in breast cancer with a prospective randomized study of women with early-stage, nonmetastatic, node-positive disease who were assigned to three different dose levels of the CAF regimen. After 3 years of follow-up, patients who received intermediate to high total doses of

chemotherapy had a significant improvement in both disease-free and overall survival when compared to those on the lowest dose level. This study demonstrates the inadequacy of lower doses of chemotherapy as adjuvant treatment, but does not necessarily confirm that higher doses of therapy are better than standard doses. Confirmation of the hypothesis of dose intensity awaits studies of high-dose chemotherapy with autologous stem cell or bone marrow support.

The first studies of bone marrow transplantation in breast cancer were in patients with metastatic disease. High response rates were seen in patients who had been refractory to conventional chemotherapy, but such responses were not sustained. An occasional long-term remission was obtained when patients were transplanted as initial therapy for metastatic disease, but the median response duration has remained poor.

More recently, high-dose chemotherapy has been evaluated in patients who have previously demonstrated a response to conventional chemotherapy. Unfortunately, follow-up of these patients is short and a lack of prospective randomized trials limits the ability to judge whether this is a more effective treatment or whether extensive staging studies and response to initial treatment has selected out a more favorable group of patients. At this time, high-dose chemotherapy with stem cell or bone marrow support for metastatic breast cancer remains investigational.

Currently, autologous bone marrow and stem cell transplant after high-dose chemotherapy are being intensively studied in patients with primary breast cancer who are at exceptionally high risk for the development of metastatic disease. Such patients include those with a high degree of axillary lymph node involvement and patients with inflammatory breast cancer. Initial studies of bone marrow transplant in patients whose breast cancer involves 10 or more axillary lymph nodes have demonstrated a decreased risk of relapse relative to historical controls. Again, short follow-up and the lack of randomization hamper the ability to compare this dose-intensive approach to standard adjuvant therapy. Currently, two national cooperative group clinical trials in this country and additional trials in Europe are underway to help clarify the role of high-dose chemotherapy with stem cell or bone marrow support in patients with high-risk breast cancer.

CLINICAL AND BASIC RESEARCH

Clinical Research

Standard breast conservation therapy consists of lumpectomy plus radiation therapy for ductal carcinoma in situ and lumpectomy, axillary dissection, and radiation therapy for invasive breast carcinoma. Studies are currently underway to identify select subgroups of patients with ductal carcinoma in situ or early-stage invasive breast cancers who can be treated with surgery alone. Overall, radiation therapy substantially reduces the incidence of local recurrence but does not in-

crease survival. Current studies will attempt to define patients with small tumors and favorable pathological characteristics who can be treated with surgery alone in the future without an increased risk of local recurrence.

The role of axillary dissection in breast cancer patients is being critically analyzed. Axillary dissection provides important prognostic information in patients with invasive breast carcinomas and often modifies systemic hormone treatment or chemotherapy. The introduction of sentinel lymph node mapping and biopsy may avoid the risk of postoperative complications (most importantly lymphedema) in approximately two-thirds of patients with invasive breast cancer who have no metastatic disease in the axilla. It is well known that the incidence of negative axillary dissection increases in patients with smaller, less aggressive tumors. Patients with a histologically proven negative sentinel lymph node have only 1–2% chance of ''skip'' metastasis in a nonsentinel lymph node and may be spared axillary dissecton in the future. Those with a positive sentinel lymph node should undergo the standard level I and II lymph node dissection to provide prognostic information and, perhaps, to reduce locoregional recurrence.

Several new diagnostic tests are available to image the breast for screening high-risk patients and for staging patients with known breast cancer. The role of magnetic resonance imaging, PET scanning, and Sestimibi scanning is an area of active clinical investigation. The application of these tests appears particularly promising in young women in whom mammography is limited due to the increased density of fibrous breast tissue. Precise clinical indications for each of these radiological tests are currently being developed in clinical trials to supplement conventional breast imaging by mammography and ultrasound.

Hormone therapy in breast cancer patients is currently being reevaluated at multiple levels of clinical intervention. First, the role of surgical oophorectomy has recently gained popularity in some centers for two reasons. First, this procedure can now be performed with minimally invasive, laparoscopic surgery. Second, surgical oophorectomy may provide a more complete hormonal ablation than the use of oral antiestrogen agents. On the other end of the spectrum, hormone replacement therapy is currently being considered for breast cancer survivors who are judged to be at relatively low risk for recurrent disease. The rationale for considering hormone replacement therapy in these successfully treated patients is to prevent morbidity and mortality from arteriosclerotic heart disease and stroke, which become more prevalent than recurrent breast cancer as these patients age. Finally, results of the Breast Chemoprevention Trial sponsored by the National Cancer Institute and the NSABP indicate that tamoxifen can be used in high-risk women to prevent the development of breast cancer. Further studies are underway to compare the anticarcinogenic activity and adverse effects of tamoxifen, Raloxifene, and other hormonal agents in patients at high risk for breast cancer.

Bone marrow and stem cell transplantation are currently being evaluated

in clinical trials throughout the country. Autologous bone marrow and stem cell transplantation after high-dose chemotherapy is performed on protocol basis in patients at high risk for developing metastatic disease. Response rates and duration of response to this intense treatment regimen are now being analyzed.

Basic Research

Active investigation over the past decade has led to great insight into the development of breast cancer at the molecular biological level. Mutations of two tumor suppressor genes, BR-CA1 and BR-CA2, have a high degree of penetrance and significantly increase the risk of inherited breast cancer in affected individuals. Although the presence of mutation in either one of these genes was initially thought to confer an 85–90% chance of developing breast cancer, current estimates indicate that the actual rate of developing breast cancer may be half as high as originally predicted. Thus, additional factors not yet identified must significantly influence the expression of these mutated, tumor suppressor genes. There is an associated increased risk of ovarian cancer in patients carrying mutations of BR-CA1 and/or BR-CA2. The specific clinical population in whom bilateral prophylactic mastectomy and oophorectomy are indicated and the timing of this surgery are currently being established.

Other oncogenes undoubtedly play an important etiological and prognostic role in the growth and development of breast cancer. For example, the level of HER-2/Neu oncogene expression can be assayed in breast cancers and, in some studies, overexpression of this oncogene is associated with a poorer prognosis. Mutations of the p53 tumor suppressor gene have been associated with the development of many solid tumors and may play a significant role in the genetic etiology of breast cancer. Intense investigation at the molecular biological level will certainly lead to exciting advances of both therapeutic and prognostic significance for breast cancer patients in the future.

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Esophagus and Proximal Gastric Tumors

Noel N. Williams, David J. Vaughn, Richard Whittington, Michael L. Kochman, and Ernest F. Rosato
University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

INTRODUCTION

Malignant disease of the esophagus and the gastroesophageal junction remains a very difficult management problem for both patient and physician because the disease is advanced on presentation in a significant percentage of cases. It is for this reason that the care of these patients is undertaken in a multidisciplinary approach, with involvement of gastroenterologists, oncologists, and surgeons. The purpose of this chapter is to present a multidisciplinary approach to the management of patients with this difficult problem.

INCIDENCE, EPIDEMIOLOGY, AND ETIOLOGY

Worldwide, esophageal cancer is the third most common gastrointestinal cancer with more than 300,000 new cases being reported annually. In the United States, this disease affects 12,000 new patients annually, but unfortunately, the overall relative 5-year survival rate is only 12%, representing the 13th most common cause of cancer mortality in the country. From a demographic standpoint, esophageal cancer can be divided by its pathological types into squamous cell carcinoma and adenocarcinoma. The overall annual incidence for squamous cell carcinoma is 2.6 per 100,000 population, and for adenocarcinoma, the age-adjusted rate is 0.5 per 100,000. More recently, however, there appears to be a significant increase in the incidence of adenocarcinoma, with some series reporting that this pathological type now accounts for 60–80% of new cases of esophageal carcinoma being diagnosed in Western countries. There is a significant predilection

for men in both pathological groups with a 4:1 ratio for patients with squamous cell carcinoma, and a 9:1 ratio for patients with adenocarcinoma. In addition, incidence of squamous cell carcinoma is at least four times higher in black men than in white men, and there seem to be specific areas within the United States where there are higher incidences than others. When studied on an age basis, esophageal carcinoma is a disease of advancing age with the condition rarely being diagnosed before the age of 40 years. An adjacent area to be considered is the gastric cardia, a small, narrow portion of gastric mucosa that contains simple mucous glands somewhat like those found in the pylorus. A malignancy arising in this area is termed carcinoma of the gastric cardia and is grouped with adenocarcinoma and Barrett's carcinoma because they are often difficult to distinguish clinically and pathologically.

The etiology of the different pathological types of esophageal cancer varies significantly. In the case of squamous cell carcinoma there are specific predisposing factors. The most common etiological factors are alcohol and tobacco, which have been consistently implicated in epidemiological studies. In Western countries, including the United States, the amount of alcohol consumption appears to have an effect on the incidence of the disease with higher consumption rates being associated with an increased risk for developing esophageal cancer. In relation to tobacco, there is also a correlation between increased risk and the number of cigarettes smoked per day. It is claimed that men in Western countries who are well nourished and do not smoke or drink have no risk of developing squamous cell carcinoma. Carcinogens in the environment have also been associated with squamous cell carcinoma of the esophagus. *N*-nitrosamines, which are produced in the body from ingested nitrates and nitrites, are thought to be important etiological factors. Certain acquired diseases of the esophagus, including achalasia, chronic esophagitis, caustic injury, and human papillovirus, have been implicated in the development of squamous cell carcinoma.

In patients with achalasia, the risk is thought to be between 3 and 6% and the development of malignant change is thought to occur before age 40. In a Swedish study, patients with achalasia were noted to be at markedly increased risk of developing esophageal cancer. Patients with achalasia should therefore undergo corrective surgery, and if not, should be followed periodically with endoscopic examination. Caustic injury leading to esophageal cancer is well documented and usually occurs 30–40 years after the injury; it is therefore recommended that these patients should be followed closely throughout their life span.

The incidence of adenocarcinoma of the esophagus has increased significantly in the Western world over the past 30 years with some reports describing an incidence of 60–80%. The most important predisposing factor is Barrett's columnar-cell metaplasia, which is present in over 80% of patients with adenocarcinoma of the distal esophagus. This condition is characterized by replacement

of the normal squamous epithelium of the esophagus by metaplastic columnar epithelium containing goblet cells, developing as a complication of chronic gastroesophageal reflux disease. A number of prospective studies have found the incidence of adenocarcinoma in patients with Barrett's esophagus to be at least 50–100 times higher than in the general population. Recent studies suggest that areas of metaplasia can also occur in carcinoma of the cardia, but the etiology and epidemiology of these tumors appear to be different from those of adenocarcinoma of the esophagus. Carcinoma of the cardia is similar to gastric cancer in lymphatic extension in contrast to adenocarcinoma of the distal esophagus, which exhibits submucosal spread toward the proximal esophagus and extends through the lymphatic system toward the posterior mediastinum. In contradistinction to squamous cell carcinoma, alcohol and tobacco do not play an important role in the pathogenesis of adenocarcinoma. In addition, epidemiological studies investigating nutritional risk factors in adenocarcinoma have shown an increased risk with obesity and a decreased risk with the intake of raw fruits and vegetables. In relation to obesity, speculation exists as to an association with the recent epidemic increases in the incidence of adenocarcinoma of the esophagus.

The natural history of carcinoma of the esophagus does not vary with histological type. Patients most often present with dysphagia and weight loss and are often malnourished at the time of presentation. The long-term prognosis for esophageal carcinoma is universally poor with little difference in the distribution of regional and distant spread between adenocarcinoma and squamous cell carcinoma. However, surgical resection in the form of esophagogastrectomy remains the optimal palliative treatment for patients with cancer of the esophagus and gastric cardia without evidence of metastatic disease. The next section of this chapter will therefore deal with surgical aspects of esophageal cancer including the evaluation and staging of these patients and the different surgical approaches utilized. Subsequent to this, the role of radiation therapy and medical oncology in the treatment of esophageal cancer, as well as the palliation of this disease, will be addressed.

SURGERY: HISTORICAL PERSPECTIVE

Historically, surgical resection of the esophagus and gastric cardia remains the mainstay of treatment for patients with carcinoma of the esophagus and gastric cardia. A curative resection removes all detectable tumor. A palliative resection implies that detectable tumor has been left, while the primary tumor has been excised to restore swallowing function. Depending on the location of the tumor, a number of different surgical approaches can be utilized. These include the transthoracic or thoracoabdominal approach (utilizing a left thoracotomy), the Ivor-Lewis operation (combination of right chest and abdominal incisions), and

transhiatal esophagectomy (combination of separate abdominal and left cervical incisions).

Several individual reports of esophagectomy for the treatment of esophageal carcinoma were made in the early part of the twentieth century but it was not until the 1940s that this procedure became routine in the United States and the United Kingdom. The first reported case of resectional surgery for esophageal carcinoma was that of Torek in New York in 1913 where the esophagus was removed via the transthoracic approach. The first large series reported was that of Ohsawa, who reported over 100 cases of resection of the gastric cardia or the thoracic esophagus, with all the surgery being performed through a left thoracotomy. In the United States, Sweet employed routine resectional therapy for esophageal carcinoma at the Massachusetts General Hospital. He reported surgery on more than 300 patients with esophageal cancer during a 30-year period. Sweet advocated a left thoracotomy approach, in contrast to that of the Ivor-Lewis operation in the United Kingdom, which is a combined abdominal and right thoracotomy approach for surgical treatment of thoracic esophageal carcinoma. Orringer first described transhiatal or blunt esophagectomy in 1978. Thoracotomy was replaced by separate abdominal and cervical incisions, removing the entire esophagus and reconstituting gastrointestinal continuity by anastomosis of the stomach to the cervical esophagus.

PRETREATMENT DIAGNOSIS AND EVALUATION

Once the symptoms of esophageal carcinoma are presented to a physician, an intricate battery of investigations is undertaken to confirm the diagnosis and to evaluate the stage of disease prior to surgery. The single most important diagnostic test in esophageal cancer is endoscopy with biopsy and cytology to confirm the pathological nature of the lesion. Endoscopy is also the most important tool in the surveillance of patients with Barrett's esophagus.

Barrett's Esophagus

As previously mentioned, Barrett's esophagus is present when metaplastic specialized columnar epithelium lines the lower esophagus; this metaplastic columnar epithelium is now recognized as a premalignant condition. Barrett's esophagus is diagnosed endoscopically by the visualization of a reddish, salmon-pink, velvet-like mucosa. Accurate diagnosis requires endoscopy and biopsy with careful documentation of the landmarks of diaphragmatic pinchcock, top of gastric folds, lower esophageal sphincter zone, and the Z-line. Once this method is adhered to, hiatal hernia is much less likely to be missed and the misdiagnosis of hiatal hernia as Barrett's esophagus is less frequent. Once the diagnosis has been made and confirmed by biopsy, endoscopy plays the major role in the further

management of this condition, providing routine surveillance with biopsy to detect advancement to high-grade dysplasia. Routine screening of patients with established Barrett's esophagus is essential to detect high-grade dysplasia and early carcinoma, and provides the best hope for increasing the cure rate for this disease. The calculated incidence of the development of adenocarcinoma varies from 1 in 152 to 1 in 441 cases per patient-year, or a 30–125-fold increased risk. This has led to the proposal that high-grade dysplasia be used as a marker for detecting patients at high risk of developing adenocarcinoma and therefore recommending esophagectomy in this group of patients. Evidence now exists that not only is high-grade dysplasia a marker for carcinoma, but also 30–40% of patients with this complication of Barrett's esophagus already have invasive carcinoma. In contrast to high-grade dysplasia, which is equivalent to carcinoma in situ, low-grade dysplasia often remains stable, or in some instances regresses to Barrett's esophagus reflecting an inflammatory process.

When comparing patients with Barrett's esophagus who have regular endoscopic surveillance with those not under surveillance, studies have shown that the former group has a significantly improved postoperative survival as a result of earlier detection. The question is then posed as to how often to undertake endoscopic surveillance in this group of patients. Patients who have been labeled negative for any dysplasia on endoscopic biopsy should have surveillance on a yearly basis. When the diagnosis is that of low-grade dysplasia, medical acid suppressive therapy should be instituted and endoscopic biopsy should be repeated at 6-month intervals until there is regression to no dysplasia or progression to high-grade dysplasia and therefore surgical removal. If the initial biopsy indicates high-grade dysplasia, the biopsy should be reread by a second experienced pathologist to confirm the findings. If the diagnosis of high-grade dysplasia is confirmed, the question as to whether to proceed to surgery is then raised. Most authors would recommend esophagectomy if the patients are young, especially where there is difficulty in differentiating between high-grade dysplasia and early carcinoma. In patients who are at high risk or elderly with the potential for high mortality and morbidity, an argument can be made for endoscopic therapy such as photodynamic therapy. In summary, it is important to remember that whether cancer is present or not, high-grade dysplasia in itself carries a very high risk for developing cancer or being accompanied by carcinoma.

Staging

If a diagnosis of invasive carcinoma has been made, the next step in the evaluation of the patient is systematic staging of the disease to assess the extent of disease progression. A simple chest radiograph should be undertaken to rule out the possibility of distant metastasis to the lung before the localized area of disease is assessed. With the widespread use of endoscopy, upper gastrointestinal radiology

with barium has become less common in the diagnosis of esophageal cancer, but of significant benefit in assessing the exact location and size of the intraluminal component of the tumor. The next step in pretreatment evaluation is to assess the extraluminal extension of the malignant process. Prior to the introduction of endoscopic ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) of the chest were used to evaluate the local extension of the tumor. With these modalities, it is possible to demonstrate the entire esophagus with aid of oral and intravenous contrast (CT) and gadolinium (MRI) with the limiting factor being the ability to accurately stage lymph node involvement. The main strength of CT/MRI in these patients is the ability to demonstrate the surrounding structures (aorta and trachea) in the mediastinum in relation to local spread and also to extend the study into the abdomen to rule out the presence of liver metastasis. Overall, the sensitivity in this setting is 90% for assessing tracheal involvement and 90% for liver and lung metastases making these imaging modalities important in the staging process for esophageal carcinoma.

With the advent of endoscopic ultrasonography (EUS), it has become possible to image at close proximity the various morphological layers of the esophageal wall and also adjacent structures, thereby allowing for increased accuracy in staging the local tumor (T-stage). Though it is widely thought that EUS is superior to CT in the staging of esophageal carcinoma, this modality should not be used to replace CT but rather to complement its use in accurately staging the disease. Studies have demonstrated that while EUS assessment is superior for the T-stage and N-stage and limited for the M-stage of the disease, it nevertheless has an overall staging accuracy of 90%. In relation to vascular involvement, endosonography has also been shown to be more sensitive than CT scan in patients with esophageal cancer. EUS plays an important role in the determination of nodal status, where it is possible to determine not only the size of nodes, but also the shape, border characteristics, and central echogenicity. Another modality that is important in lesions of the upper third of the esophagus is bronchoscopy to rule out direct invasion of the trachea. In summary, the most effective and precise way to stage patients with esophageal carcinoma is to combine CT scanning or MRI, to rule out distant metastases, with endosonography to assess the depth of tumor penetration and the presence or absence of regional lymph nodes. The role of endosonography has been expanded even further with the introduction of ultrasound-guided, fine-needle aspiration of regional lymph nodes to correlate the images seen on EUS with the cytology of the nodes demonstrated. Pretreatment staging can be made provisionally using these investigative modalities but the more accurate posttreatment staging for prognosis can only be made following surgery. The TNM classification (Table 1) is the basis for staging (Table 2) and prognosis in patients with esophageal carcinoma.

Before proceeding to curative or palliative surgery for esophageal cancer,

Table 1 TNM Classification

T Primary tumor	
T_0	No evidence of primary tumor
T_{IS}	In situ carcinoma
T_1	Into, but not beyond, mucosa
T_2	Into, but not beyond, muscle
T_3	Into adventia
T_4	Adjacent structures
N Locoregional lymph nodes	
Cervical esophagus	Cervical, supraclavicular
Thoracic esophagus	Mediastinal, perigastric
N_0	No locoregional nodes
N_1	Positive locoregional nodes
M Distant metastases	
M_0	No distant metastases
M_1	Distant metastases
M_{LYN}	Celiac nodes or other than locoregional

it is necessary to evaluate the cardiopulmonary functional status of the patients as this will determine the ability of the patient to tolerate a major surgical procedure. Respiratory function should be assessed by forced expiratory volume during the first second and should be in excess of 2 L. In addition, if the patient is a tobacco smoker, he should discontinue smoking for at least 1 week prior to surgery. Cardiac assessment is also an important factor in this patient population and should be carried out by means of an electrocardiogram and noninvasive radionucleotide

Table 2 Staging by TNM Classification

Stage			
0	T(is)	N0	M0
I	T1	N0	M0
IIa	T2	N0	M0
	T3	N0	M0
IIb	T1	N1	M0
	T2	N1	M0
III	T3	N1	M0
	T4	N1	M0
IV	Any T	Any N	M1

scan for measurement of wall motion and ejection fraction. Any abnormalities detected should warrant a full assessment by a cardiologist prior to surgery.

SURGICAL APPROACHES TO ESOPHAGEAL CARCINOMA

Armed with all the relevant information as to the exact location, histological type, and stage of the tumor, the surgeon then decides which surgical approach is deemed appropriate for a particular patient. The question of multimodality treatment including radiotherapy and chemotherapy, and the timing of this treatment for patients with esophageal cancer, will be expanded upon in separate areas of this chapter and therefore will not be addressed here. From an anatomical standpoint, the esophagus is divided into the cervical portion and the intrathoracic portion, which is further divided into an upper, middle, and lower third. Anatomically, depending on where the primary tumor is located, a choice of surgical approach is chosen. For tumors arising in the upper and middle thirds of the esophagus, the transthoracic route is preferred through a right thoracotomy incision combined with an abdominal operation to mobilize the stomach or colon conduit. Tumors arising in the lower third and at the gastric cardia are usually approached by a left thoracotomy or by the transhiatal approach, but can also be dealt with via the combined right chest and abdomen approach. For descriptive purposes the surgical approaches will be discussed under the headings of transthoracic and transhiatal esophagectomy.

Left Thoracic Approach

Surgical resection for carcinoma located in the lower third of the esophagus and esophagogastric junction can be accomplished through various incisions. Exposure for esophagogastrectomy for these lesions is best obtained through a left transthoracic transdiaphragmatic approach and allows extension into the abdomen as a thoracoabdominal incision if warranted. Access to both the infra-aortic mediastinum and the upper half of the abdomen facilitates wide dissection of the tumor and potential tumor-bearing nodes in the mediastinum and upper abdomen. This exposure allows for dissection of the left gastric artery nodes and for possible resection of the nodes along the hepatic and splenic vessels. It facilitates careful dissection and preservation of the right gastroepiploic artery, which is the major blood supply to the gastric remnant. In addition, this approach allows flexibility for extended esophageal resection including a total esophagectomy with eventual cervical anastomosis. The left thorax is entered through the bed of the seventh rib and the diaphragm is opened circumferentially making sure to leave a 2-cm cuff of diaphragm to allow easy repair at the end of the procedure. Resectability is determined and the operation is begun in the upper half of the abdomen with

division of the short gastric vessels and mobilization of the entire greater curve of the stomach. With the stomach rotated upward and to the right, the lesser curvature dissection is begun along the superior border of the pancreas with exposure, suture ligature, and division of the coronary vein and the left gastric artery. All nodal tissue along both of these vessels is brought upward with the gastric specimen. After the stomach is returned to its normal position, the dissection is carried anteriorly through the peritoneum overlying the esophagus to completely free it from the diaphragmatic crus. The right gastric artery is divided at the incisura ensuring to include all the nodal tissue of the lesser curve of the stomach. Attention is then turned to performing a pyloroplasty by the Heinkeke-Mikulicz technique. A longitudinal incision is made and closed transversely in a single layer with 3/0 silk sutures. The percentage of the stomach to be resected is determined depending on the proximity of the lesion to the gastroesophageal junction, with an effort being made to preserve the fundus of the stomach to maximize the length of the gastric remnant. A stapling device is used to apply a staple line sequentially along the lesser curve of the stomach, creating a pouch approximately 5 cm in width.

Attention is then turned to the thoracic portion of the operation. A long incision is made in the pleura anterior to the aorta and posterior to the pericardial sac taking care to identify and preserve the phrenic nerve. The esophagus is then dissected up to the aortic arch and together with the paraesophageal nodal tissue it is removed en bloc. Once this is completed, the proximal esophagus is transected using a stapling device. It is optimal to transect the esophagus at least 5 cm above the tumor as any less than this figure doubles the rate of local recurrence at the anastomosis. The hiatus is then widened to allow passage and to prevent constriction of the gastric remnant as it passes into the thoracic cavity. The esophagogastrostomy can either be hand-sewn using a single layer or two-layer sutured anastomosis or performed using one firing of the Endo GIA-60 (US Surgical Corporation) stapling device. In the stapled anastomosis a portion of the staples in the middle of esophageal staple line is removed to allow passage of the Endo GIA, which on firing provides a long posterior anastomosis. The anterior wall is sutured with large seromuscular bites in the stomach and full-thickness bites in the esophagus. After completion of the anastomosis and placement of a feeding jejunostomy tube, the diaphragm is reattached with large nonabsorbable sutures and the chest closed in standard fashion.

The Ivor-Lewis Procedure

The Ivor-Lewis procedure can be utilized for lesions of the entire esophagus but preferentially facilitates a high intrathoracic esophagectomy and esophagogastrostomy. The right thoracic approach allows division of the azygos vein and

removes the aortic arch from the field of dissection, allowing esophagectomy to the level of the thoracic inlet. In this procedure the abdominal part of the operation is performed through an upper midline incision with mobilization of the stomach in a similar fashion to that in the previously described left thoracotomy esophagectomy. After complete mobilization of the stomach (as previously described), the esophageal hiatus is widened to ensure passage of the gastric tube into the chest. A jejunostomy feeding tube is then placed and the abdominal incision closed in standard fashion. The patient is then repositioned for right thoracotomy, which is carried out through the fourth or fifth intercostal space. The pleura is opened and the dissection begun taking care not to damage the thoracic duct. The azygous vein is divided and the proximal esophagus encircled at the site of proximal resection. The tumor and surrounding tissues are then dissected free and the stomach delivered into the thoracic cavity following which the lesser curve is transected using several firings of the GIA-60 stapling device. The esophagogastric anastomosis is then carried out as described earlier, utilizing either a suture or stapling technique. It is important to note that the thoracic duct runs anterior to the right side of the aorta and thus runs the risk of damage when tumors are locally adherent to surrounding structures. Because of the nature and complexity of the procedure, complications occur in 10–15% of cases.

Postoperative care is extremely important in esophageal surgery. All patients should have epidural catheters placed preoperatively for optimal postoperative pain control, therefore minimizing pulmonary complications. These patients are best managed in an intensive care setting in the immediate postoperative period, as many patients require postoperative ventilation. Specific complications, such as chylothorax due to thoracic duct injury, need to be recognized and rectified at an early stage. There is some controversy in the literature as to the benefit of early enteral feeding in the early postoperative period but as a rule we recommend commencing feeding via the feeding jejunostomy tube after 36–48 hr. A gastrograffin study is carried out at 5–6 days to ensure that there is no anastomotic leak. Once this has been demonstrated, the nasogastric tube is removed and the diet advanced prior to removal of the intercostal chest tubes. Patients who have an uncomplicated postoperative course are usually discharged within 10–12 days of surgery.

During the past 10 years there have been major advances in surgical therapy as a whole, which have translated into a higher resectability rate, an improved hospital mortality rate, and a markedly improved 5-year survival rate. Table 3 lists data extracted from a number of published reports from 1985 to 1993 for patients undergoing resection for either carcinoma of the esophagus or gastric cardia. As noted in the table, rates of operability varied between 46% and 82%, while resectability rates varied between 50% and 90% with a median overall hospital mortality of 16%. In addition, the complication rate ranged between 24% and 82% with a preponderance of pulmonary complications.

Table 3 Transthoracic Esophagogastrectomy for Carcinoma of the Esophagus: Results

Author	Country	# surgical cases	Resectibility (%)	Mortality (%)		5-yr survival (%)
				30-day	Hospital	
Bertelsen et al.	Denmark	298	63.4		24	14.8
Hennessey and O'Connell	Ireland	230	87	17.5	22	19.5
Galandiuk et al.	United States	168	50		7.1	15
Bluett et al.	United States	144	72	10		14
Wong	Hong Kong	284	81.7	6.9	18.5	24.4
King et al.	United States	100	NS	3		22.8
Lu et al.	China	1,306	78.5		4.9	20.9
Mathisen et al.	United States	104	NS	2.9		
Ellis	United States	310	88.7	2.2	4.4	20.8
Griffin et al.	England	202	NS		10.4	28
Page et al.	England	115	NS	8.7		22.1
Katlic et al.	United States	261	63.5		21.5	21.9
Lund et al.	Denmark	657	78	19		9
Law et al.	Hong Kong	500	81.6	4.8	16.5	15
Nakadi et al.	Belgium	187	89.8	5.9		34.2
Salama and Leong	England	133	73.6		10.2	17.3
Rahamin and Cham	England	298	NS	10	23	23

Transhiatal Esophagectomy

This approach may be utilized for carcinoma of any portion of the thoracic esophagus and is indicated for all types of esophageal cancer. However, transhiatal esophagectomy is most applicable for patients with dysplasia in Barrett's esophagus and who therefore do not need extensive mediastinal lymph node dissection. In patients who have large midesophageal lesions or who require mediastinal node dissection, this can be approached by adding either a right thoracotomy or thoracoscopy. The other advantages of this technique are, first, the avoidance of the potential morbidity of an intrathoracic anastomosis, and second, the avoidance of the higher operative risk factors. This operation consists of an abdominal and left cervical component, with the abdominal approach being similar to that of the Ivor-Lewis approach with mobilization and formulation of a gastric tube using the same technique described. Once this has been achieved, attention is turned to the diaphragmatic hiatus where retractors are placed to widen the opening and allow dissection of the lower esophagus and surrounding pleura and then carrying this dissection up as far as the carina. At this time an incision is made along the left sternocleidomastoid muscle down to the sternal notch. The muscle and the internal jugular vein and carotid artery are then retracted laterally and the cervical esophagus is encircled taking particular care to protect the recurrent laryngeal nerve from damage. Blunt finger dissection is initiated from above and carried to meet at the point of dissection from below in a simultaneous manner. To avoid injury to structures in the neck and superior mediastinum such as the membranous trachea and azygous vein, the dissection is kept in direct contact with the esophageal wall. Once the esophagus is freed from its mediastinal attachments, a Penrose drain or nasogastric tube is sutured to the transected lower end of the esophagus and the contents are then delivered into the neck and the esophagogastric anastomosis carried out in an end-to-side fashion. Postoperative care is as described in the other forms of esophagectomy.

With proper patient selection and good surgical technique, operative mortality with this procedure should be less than 5%. Orringer reported over 580 cases of transhiatal esophagectomy for a variety of benign and malignant conditions. Complications in this study included pneumothorax (74%), anastomotic leak (9%), and recurrent laryngeal nerve palsy (3%). Overall survival of patients with carcinoma was similar to that reported after the transthoracic approach.

One of the problems with esophageal carcinoma in the United States and many other Western countries is the fact that at presentation almost 80% of patients have stage III disease and hence the overall 5-year survival is between 10% and 15%. Improved survival for these patients therefore depends on adjuvant therapy, which includes radiation therapy and chemotherapy. The role of these two modalities in esophageal cancer, as well as methods of nonsurgical palliation, will be addressed in the remainder of this chapter.

CHEMOTHERAPY

Chemotherapy for Palliation of Advanced Disease

Patients with metastatic cancer of the esophagus have a poor prognosis. In addition, these patients may have significant symptoms related to their metastases. Commonly, the performance status of these patients is poor. The purpose of chemotherapy in this setting is to palliate symptoms.

Chemotherapy responses in this group of patients tend to be short term (on the order of only a few months) and most likely do not impact significantly on median survival. Multiple single agents have been documented to have modest antitumor activity in esophageal carcinoma. Bleomycin, 5-fluorouracil (5-FU), mitomycin-C, adriamycin, methotrexate, and the platinum analogs cisplatin and carboplatin have all been shown in phase II trials to have response rates in the 5–35% range. Many of these trials focused on squamous carcinomas of the esophagus. Two drugs have been developed more recently and appear promising. Venorelbine and paclitaxel both have been demonstrated to have activity in this disease.

The importance of identifying active single agents is ultimately to combine them into regimens that have potentially greater antitumor activity and more palliative benefit. In esophageal cancer, combination regimens have been tested predominantly in the squamous cell subtype, although more recent studies include patients with adenocarcinomas. Response rates for these combination regimens, most of which are cisplatin + bleomycin + methotrexate or cisplatin + 5-FU + Adriamycin or cisplatin plus infusional 5-FU, have resulted in response rates of 25–40%. The responses appear more durable than single-agent responses. However, median survival in patients with advanced disease receiving combination chemotherapy is approximately 6–8 months in most studies.

In summary, for the present, the ''standard'' treatment for patients with metastatic esophageal carcinoma is a cisplatin-based regimen. Given the palliative nature of this treatment and the potential for toxicity with resultant worsening of quality of life, selection of appropriate patients for this treatment is crucial. Factors such as specific symptoms, organ function, and performance status are utilized to determine who may benefit from treatment. Identification of novel agents with subsequent incorporation into combination regimens should hopefully result in improved outcomes for these patients. Patients should be encouraged to participate in clinical trials that further define the optimal systemic approach to this disease. Studies addressing the role of chemotherapy in the palliative disease setting need to include assessment of quality-of-life outcomes to document palliative benefits.

Neoadjuvant Chemotherapy

While development of chemotherapy in the advanced disease setting for patients with carcinoma of the esophagus is important, advances in systemic therapy may

be most effective when applied in the early- or minimal-disease setting. Specifically, in the early-disease setting, chemotherapy can be utilized in either the neoadjuvant (preoperative) or adjuvant (postoperative) setting. The potential advantage of the neoadjuvant or preoperative approach includes early treatment of micrometastases and downstaging of tumors. The disadvantages include delay in definitive local treatment, which may be important in patients with dysphagia or bleeding.

The initial trials of neoadjuvant chemotherapy focused on patients with localized squamous cell histology. These early trials performed in the late 1970s utilized preoperative cisplatin-based chemotherapy regimens. These trials resulted in tumor responses in 40–60% of treated patients, with an occasional pathological complete response documented. Based upon these early trials, two small randomized trials comparing cisplatin-based chemotherapy followed by surgery versus surgery alone for patients with localized squamous cell carcinomas showed no improvement in median survival with neoadjuvant chemotherapy.

Nonrandomized trials of neoadjuvant chemotherapy specifically for distal esophageal and gastroesophageal (GE) junction adenocarcinomas have also been reported. In one such study, 26 patients received treatment with two preoperative courses of intensive chemotherapy [etoposide, doxorubicin, and cisplatin (EA) with granulocyte-macrophage, colony-stimulating factor]. In this trial, 50% of patients achieved a major response to chemotherapy. Median survival of these patients was 12.5 months. No randomized trials of neoadjuvant chemotherapy specifically for patients with distal esophageal and GE junction adenocarcinomas have been reported.

The issue of the potential benefit of neoadjuvant chemotherapy in carcinoma of the esophagus has recently been examined in a large prospective trial. The recently completed Intergroup trial (INT-113) randomized patients with carcinoma of the esophagus to neoadjuvant cisplatin plus infusional 5-FU followed by surgery and then additional postoperative chemotherapy or to surgery alone. This trial included patients with squamous cell and adenocarcinoma histology; of the patients enrolled, 55% had adenocarcinomas. In a preliminary analysis of this trial, this neoadjuvant chemotherapy regimen did not appear to impact upon resection rate, relapse-free survival, or overall survival compared to surgery alone. Long-term follow-up of this trial with subgroup analysis should determine the potential role of neoadjuvant chemotherapy in this disease. Until randomized data shows benefit, the role of neoadjuvant chemotherapy should be considered experimental. Patients should be encouraged to participate in well-designed clinical trials.

ADJUVANT CHEMOTHERAPY AND RADIOTHERAPY

Chemotherapy and radiation therapy have four potential uses in the management of esophageal tumors. These treatments may be used preoperatively to facilitate

a complete resection or postoperatively to reduce the risk of local and systemic recurrence. They may also be used in lieu of surgery in some patients or be used for palliation of symptoms in patients with advanced disease. In planning treatment of these patients, it is important to distinguish among squamous carcinomas of the esophagus, adenocarcinomas of the esophagus and esophagogastric junction, and adenocarcinomas of the gastric cardia.

The dominant patterns of recurrence in patients with squamous carcinoma after curative resection without adjuvant therapy are mediastinal (12–67%), pulmonary parenchyma (26%), and liver (18%). Among patients with adenocarcinoma of the esophagus and GE junction, the most frequent sites of recurrence are mediastinal (62%), pleura (16%), pulmonary parenchyma (18%), and bone (16%). The dominant patterns of recurrence in patients with gastric adenocarcinoma are surgical bed and regional lymph node (68%), peritoneum (42%), and liver (20%). Local control of unresected squamous carcinomas is 40% while local control of unresected adenocarcinomas, even with maximally tolerated combinations of high-dose chemotherapy and radiation, is extremely poor ($<$10%). Unfortunately, most series reported to date have combined the adenocarcinomas of the esophagus and GE junction with squamous carcinomas of the esophagus or adenocarcinomas of the gastric cardia. This heterogeneous group of patients makes analysis of the reported literature extremely difficult.

The purpose of radiation is to control tumor in the region treated. Radiotherapy can be used as the only local therapy in patients with unresectable and metastatic tumors or as a preoperative or postoperative therapy to treat microscopic residual tumor in the mediastinum. The major challenge for the surgeon in resecting esophageal tumors is to obtain negative margins. This may not be feasible in some patients. The high risk of anastomotic recurrence following resection in most series has been attributed to the rich network of submucosal lymphatics that allow spread of the tumor proximally along the esophagus. The anatomy of the esophagus also predisposes patients to mediastinal recurrences because of the high frequency of transmural tumors and the lack of a serosa to limit local extension. In this respect, the esophagus more closely resembles the rectum than other structures of the alimentary canal. Esophageal resections also are limited by the adjacent structures, which limit the dissection, and poor visualization of the tumor bed, especially with the transhiatal and left thoracotomy approaches to resection. While the ability of radiation to control the mural and intraluminal tumor is inferior to surgery, it suggests that surgery and radiation may play complementary roles in treating these patients.

Chemotherapy has generally been associated with poor response rates in treating these patients, but most trials reported to date have treated only patients with metastatic or previously irradiated unresectable tumors. The rationale for using chemotherapy is fourfold: to provide systemic therapy to patients at high risk for micrometastatic tumor at diagnosis; to reduce the bulk of the tumor to

facilitate resection; to sensitize tumor to the effects of radiation; and, finally, to palliate symptoms in patients with metastatic disease.

Adjuvant Radiation

In the adjuvant setting among patients undergoing esophagectomy, the high risk of both local and systemic recurrence supports protocols investigating adjuvant therapy. Most trials reported thus far have used preoperative radiation followed by attempted surgery. Doses of 40–50 Gy are necessary to produce an objective response and to adequately control microscopic tumor. In other sites such as the head and neck, breast, and rectum, this dose has also been shown to reduce the risk of local-regional recurrence. Minsky found only three randomized trials that have used such a scheme and they showed no improvement when compared to surgery alone in the rate of resection or 5-year survival.

There is even less experience with adjuvant postoperative radiation in patients with esophageal cancer. There are only two randomized trials in patients with squamous carcinoma and one retrospective review in patients with adenocarcinoma. Fok reported the results in 130 patients treated with radiation after resection. Eighty percent of the patients had squamous carcinoma. Forty-six percent had had a complete resection, and 54% had minimal or microscopic residual tumor following resection. Radiation doses used were approximately 50 Gy. There was no difference in the survival of the two groups, although there was a reduced risk of local recurrence with adjuvant radiation after incomplete resection, 20% versus 46%, and the ultimate risk of severe esophageal obstruction was lower when adjuvant therapy was given, 7% versus 33%. A similar trial in patients with squamous carcinoma reported by Teniere showed some improvement in local control but no difference in survival. Finally, for patients with adenocarcinoma, Whittington reported the results in a nonrandomized series of patients treated at the University of Pennsylvania and found the risk of symptomatic local recurrence was reduced from 62% to 22% without any evidence of improved survival. A summary of the results of these studies is shown in Table 4.

Adjuvant Combined Radiation-Chemotherapy Regimens

Recently, there have been numerous studies investigating the potential of combined therapy with radiation, chemotherapy, and surgery. A number of pilot studies suggested that preoperative radiation with concomitant chemotherapy could produce an objective response in a substantial number of patients. These studies generally used a combination of 5-FU and cisplatin or mitomycin based on earlier reported results in head and neck tumors. There have been two large randomized

Table 4 Results of Adjuvant Radiation Therapy of Resected Carcinoma of the Esophagus

Author	Treatment	Number of patients	% pts. resected	Local recurrence	5-year survival
Preoperative therapy					
Minsky	Preop 40 Gy	475	≈88%	≈13%	≈32%
	Surgery only		≈83%	≈12%	≈24%
Postoperative therapy					
Teniere	Postop 45–55 Gy	119	N/A	≈20%	19%
	Surgery only	102	N/A	≈36%	19%
Fok	Postop 50 Gy	65	N/A	12%	10%
	Surgery only	65	N/A	26%	10%
Whittington	Postop 45–54 Gy	19	N/A	21%	12%
	Surgery only	50	N/A	62%	8%

trials to evaluate this regimen in patients with resectable squamous tumors. Bosset studied patients with squamous carcinoma treated with cisplatin and 37 Gy followed by surgery compared to surgery alone and found no improvement in survival. Nygaard found that radiation improved survival, but that adding cisplatin and bleomycin to the radiation did not further improve survival. Walsh studied patients with adenocarcinoma and used cisplatin with a 96-hr infusion of 5-FU and 40 Gy radiation and found a significant increase in 3-year survival. These results are shown in Table 5.

Table 5 Results of Adjuvant Combined Modality Radiation/Chemotherapy in Resected Carcinoma of the Esophagus

Author	Number of patients	Radiation therapy	Chemotherapy	Local recurrence	Survival
Bosset	257	37 Gy	DDP	Not reported	20 mo (med)
		None	None	Not reported	20 mo (med)
Nygaard	186	35 Gy	DDP/Blm	Not reported	17% (3 yr)
		35 Gy	None	Not reported	21% (3 yr)
		None	DDP/Blm	Not reported	3% (3 yr)
		None	None	Not reported	9% (3 yr)
Walsh	58	40 Gy	5-FU/DDP	Not reported	32% (3 yr)
	55	None	None	Not reported	6% (3 yr)

Radiation Therapy Without Surgery—corr. John 1-19

Early series treating patients who were medically inoperable or had unresectable tumors with radiation therapy alone have shown a high risk of local recurrence with a poor 5-year survival. This reflects both the limitations of radiation dose in the era before CT-based treatment planning and the selection of patients with smaller tumors and better performance status for surgery. Mantravadi found that 78% of the 142 patients treated with radiation alone had persistent or recurrent tumor in the esophagus at the time of death while Manard found a local recurrence rate of 73%. Mantravadi's series included 6% of patients with adenocarcinomas, and 20% of the patients were also treated with surgery or chemotherapy. Manard's series included only squamous carcinomas, but represents only those patients coming to autopsy. The University of Pennsylvania group has reported results of palliative high-dose radiation in patients treated with radiation alone for adenocarcinoma and found that the symptomatic local recurrence rate was 95%.

Chemosensitized Radiation Therapy

Because of these poor results with single modalities, several investigators, including Keane and Coia, began to treat patients with unresectable or marginally resectable tumors with a combination of 5-FU, mitomycin, and radiation therapy. They each treated a series of patients with conventional radiation doses and fields and added a concurrent course of chemotherapy with a 96-hr infusion of 5-FU (1 gm/m^2/day) and mitomycin-C. Keane reported a local control rate of 79% with continuous radiation to a dose of 50 Gy in 4 weeks with chemotherapy. Coia used a regimen of 50–60 Gy over 5.5–6.5 weeks with the same chemotherapy regimen and found that the local control rate was 66% and the overall survival was 34% at 5 years.

Based on these pilot studies, two large randomized trials were launched to compare this combined modality regimen to radiation alone. Herscovic has reported the results for the RTOG using 5-FU infusion and cisplatin with 50 Gy radiation. Eighty-four percent of these patients had squamous carcinomas. The regimen was well tolerated and the 2-year survival was significantly improved in patients treated with combined modality therapy (38% versus 10%); the risk of persistent or recurrent mediastinal tumor was reduced from 65% to 44%. The criticisms of this study are that the doses of radiation are lower than conventionally used to treat esophageal tumors and that the authors only reported first sites of recurrence; thus, the ultimate risk of mediastinal recurrence may be higher in both groups. Sischy has presented an abstract reporting the results of an ECOG trial randomizing patients to 60 Gy RT ± chemotherapy. The chemotherapy regimen consisted of two 96-hr 5-FU infusions (1 gm/m^2/day) during the first and fifth weeks of radiation with mitomycin. This study has been criticized because

the preliminary report does not list the number of patients with adenocarcinoma and there was an optional reevaluation after 40 Gy. At the time of reevaluation, patients could be sent for surgical resection or could continue radiation to a dose of 60–66 Gy. The patients treated with combined modality therapy had a better survival (14.9 months versus 9 months) but more patients in this arm were resected. This may represent a better response among patients receiving chemotherapy, which allowed more patients to go to surgery, or it may reflect an uneven distribution of patients with a cohort of patients assigned to combined therapy having better prognoses than those assigned to radiation alone. Because the patients were stratified for stage and performance status was similar in both groups, the latter situation seems unlikely. Because of the problems with the two studies, the current trial is randomizing patients between a dose of 50 versus 64.8 Gy with identical chemotherapy regimens of cisplatin plus infusion 5-FU during the first and fifth weeks of radiation. Patients in this study are stratified for histology, tumor size, and weight loss.

Adenocarcinomas appear to respond differently to chemosensitized radiation. Coia treated patients with mitomycin and 5-FU infusions with doses of radiation that varied from 50 to 60 Gy and found that the local recurrence-free survival was worse among patients with adenocarcinoma than squamous carcinoma (53% versus 80%). The survival was superior in patients treated to 60 Gy although these patients were selected because of their better performance status and less extensive tumors. Based on these and other observations, most authors currently recommend surgical resection with adjuvant therapy in patients with adenocarcinomas.

PALLIATION FOR ESOPHAGOGASTRIC CARCINOMA

The role for the palliative treatment of unresectable or recurrent tumors is rapidly expanding. Despite advances in the curative treatment of the disease, the overall 5-year survival remains less than 15%. In general, at presentation most of these tumors are advanced. Symptoms at initial presentation and at the time of recurrence include dysphagia, cough, and hypersalivation from obstruction. In addition, up to 12% of patients with squamous cell carcinoma of the esophagus may develop tracheoesophageal fistulae. The maintenance of esophageal luminal patency is a goal for the palliation of malnutrition, for the prevention of aspiration, and to allow the patient to obtain oral gratification.

The current standard of treatment in the United States usually limits endoscopic treatment to palliative procedures owing to the infrequent occurrence of an early lesion in a poor-operative-risk patient. The endoscopic palliation of gastrointestinal malignancies has dramatically improved over the past 20 years. Procedures involving tumor destruction, such as laser therapy, ethanol injection, drug injection, electrocoagulation, and advanced resection techniques, have been

successful for eradicating superficial cancers. These techniques are most easily sorted into two categories: the nonablative techniques and the ablative techniques (Table 6). Patients who are candidates for these techniques are those who have metastatic disease at presentation, recurrence of disease, or refuse primary curative therapy. The application of these techniques should take place in a multidisciplinary setting, where the desires and needs of the patient are placed foremost over the technical skills of individual physicians. For those who have recurrent disease, tissue documentation of recurrence is extremely important as radiation-induced and postoperative strictures may clinically simulate recurrent disease. Mucosal and submucosal biopsies can be relatively easily obtained with the development of larger-channel endoscopes and new techniques. New biopsy forceps are available that fit through the channel of the newly introduced 6-mm-channel endoscopes, potentially allowing for routine submucosal biopsy. Fine-needle aspiration (FNA) under endosonographic guidance has been used to biopsy submucosal lesions, extraluminal masses, and mediastinal lymph nodes. This technique, performed at specialized tertiary centers, involves identification of a mass or lymph node by endosonography and the passage of a specialized cytology needle through the working channel of the echoendoscope. This technique has proven

Table 6 Endoscopic Treatment Options for Palliation of Esophageal and Esophagogastric Tumors

Nonablative palliation
A. Dilation
Hydrostatic balloon dilators
Wire-guided polyvinyl dilators
Metal olives
Mercury-filled rubber bougies
B. Feeding tubes
Gastrostomy or jejunostomy
Endoscopic, radiological, surgical
Endoscopically placed/anchored duodenal tubes
Endoscopically placed/anchored jejunal feeding tubes
C. Endoprostheses
Rigid plastic stents
Expandable metal stents
Ablative palliation
A. Laser ablation
B. Chemonecrolysis
C. Bipolar electrocoagulation
D. Brachytherapy
E. Photodynamic therapy

useful for the documentation of mediastinal recurrence of disease and for sampling of celiac lymph nodes.

Nonablative Palliation: Dilation and Feeding Access

Dilation is a relatively safe, inexpensive, and easy procedure to perform that provides relief of dysphagia. Its major drawback is that its effect is frequently transitory requiring repeat dilation. Dilation may also be performed as a prelude to other procedures such as stent placement or laser treatment. A lumen diameter of greater than 12 mm has been shown to decrease dysphagia and repeated dilation to a diameter of 13–15 mm is often performed over multiple sessions. Ideally, the tumor should be traversed with an endoscope and a guidewire passed and left in place beyond the tumor. If the tumor cannot be traversed, a guidewire may be passed under fluoroscopic guidance and dilators may then be advanced. Owing to the development of other modalities, few patients or physicians choose repeated dilation as the singular palliation treatment of choice.

Gastrostomy and jejunostomy can be accomplished through surgery, radiological, or endoscopic techniques. There is scant data that overall outcome is improved with placement of a feeding tube. A meta-analysis was constructed to determine the efficacy and safety of each technique. It appears that no clear-cut clinical advantage exists for one method over another. Selection of approach for the placement of the feeding gastrostomy is largely the result of local expertise. The placement of a feeding tube is most easily accomplished at the time of another major surgical procedure, including the primary attempt at resection. Insertion of a percutaneous endoscopic gastrostomy (PEG) tube involves a standard upper endoscopic technique with conscious sedation. Endoscopy is performed and the gastric body or antrum is transilluminated and fully insufflated. An area on the anterior abdominal wall is transilluminated and the suitability of the site for a percutaneous tract is confirmed allowing for the selection of a safe site with the absence of intervening viscera (most often colon). Recently endoscopic ultrasound has been used as an adjunct to aid in the placement of endoscopically placed g-tubes when the transillumination and indentation are not optimal. The advantage of this technique is that it may be performed in formerly complicated situations, including patients with previous abdominal surgery, and in postpartial gastrectomy patients. Procedure-related deaths, typically defined as mortality within 30 days of the procedure, have been reported. High mortality rates within 30 days of the procedure may reflect consequences of the underlying disease and the overall poor status of the patients, rather than direct causation from the procedure. The vast majority of tubes are now designed in such a manner that they may be removed with firm traction and do not require a repeat surgical or endoscopic procedure. Replacement ‘‘button-type’’ devices are available, which the patients find to be quite comfortable and unobtrusive.

Indications for jejunal feeding tubes are multiple and include postoperative ileus and complications preventing rapid resumption of oral intake. The recent development of endoscopic jejunostomy using a technique similar to the placement of an endoscopic gastrostomy appears to be low-risk and beneficial in postgastrectomy patients. Jejunal feeding tubes can be placed under conscious sedation. The advantage of this technique is avoidance of the need for operative intervention and the inherent stability of the direct j-tube placement compared with a j-tube threaded through a g-tube.

Esophageal Endoprostheses

Malignant intrinsic obstructions or extrinsic compression may be relieved through the use of endoprostheses designed to restore both patency and function (Fig. 1). Over the past few years a dramatic improvement in the design of the endoprostheses has served to make their use more widely accepted and less dangerous to the patient, bringing palliative comfort to patients at lower risk. The indications for stent placement include the relief of dysphagia in patients with

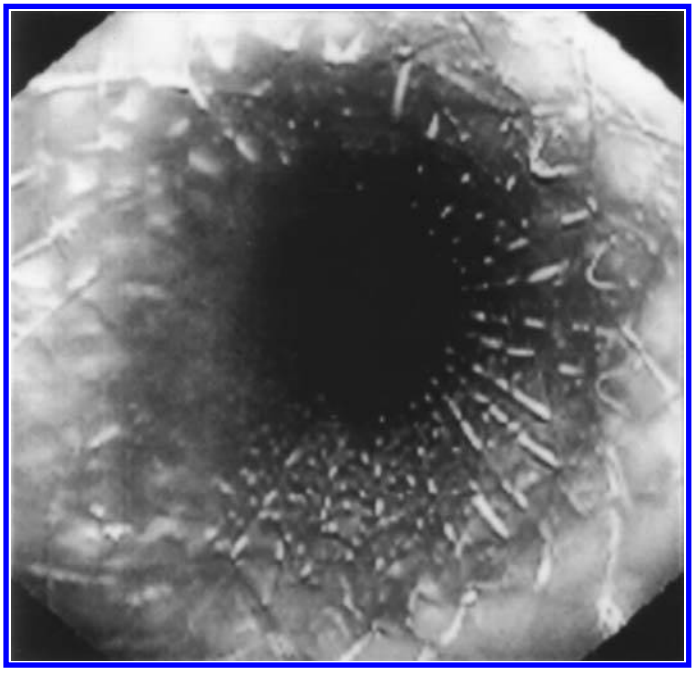

Figure 1 Endoscopic view of Schneider covered esophageal endoprosthesis at time of deployment demonstrating restoration of functional lumen.

Table 7 Relative Indications for Rigid Plastic and Expandable Metal Endoprostheses

Contraindications	Rigid	Expandable
Tumor within 2 cm of UES	—	—
Limited life expectancy (<4 weeks)	-	-
Lack of patient motivation	-	-
Obstruction preventing passage of a guidewire	—	—
Noncircumferential tumor	—	+
Necrotic tumor	—	+
Complex angled stricture	-	+

— = absolute contraindication.
- = relative contraindication.
+ = no contraindication.

unresectable or recurrent esophageal carcinoma and for the treatment of tracheoesophageal fistulae. A stent is the treatment of choice for fistulae resulting from either the malignancy or iatrogenically induced fistulae during treatment. Relative contraindications for endoprostheses include tumor growth that occludes the lumen and prevents passage of a guidewire and dilators, anticipated treatment with multimodality therapy (increased risk of complications), and lack of patient acceptance or compliance with dietary modifications.

A variety of rigid plastic and metal self-expandable stents are currently available and selection of the appropriate stent is dependent on several factors (Table 7). A rigid stent is a noncompressible tube usually made of materials such as silicone and reinforced by metal or nylon. The stents are available in various diameters and lengths. Repeated dilation is usually needed before placement of a rigid stent. These stents may also be used to occlude fistulae (Fig. 2); one design uses a collapsed sponge in a polymeric balloon that encircles the endoprosthesis. Once the stent is in place the sponge is allowed to expand to occlude the fistula track. Rigid stents may be deliberately removed or accidentally dislodged.

The newer self-expanding metal stents are technically much easier to insert and may be placed into a more stenotic lumen. There are several designs all of which have in common a folded, self-deploying mesh stent that expands when deployed within the stricture. Several advantages of these stents are their larger lumen (15–25 mm), ease of insertion, and decreased complication rate. Some expandable metal prostheses have a polymeric sheet that covers the metal mesh, which is intended to both treat the fistula and decrease tumor ingrowth. The disadvantages of metal stents are their high initial price (approximately 10 times the price of rigid prostheses) and the progressive reduction in luminal patency that may occur due to tumor ingrowth or inflammation in long-term survivors.

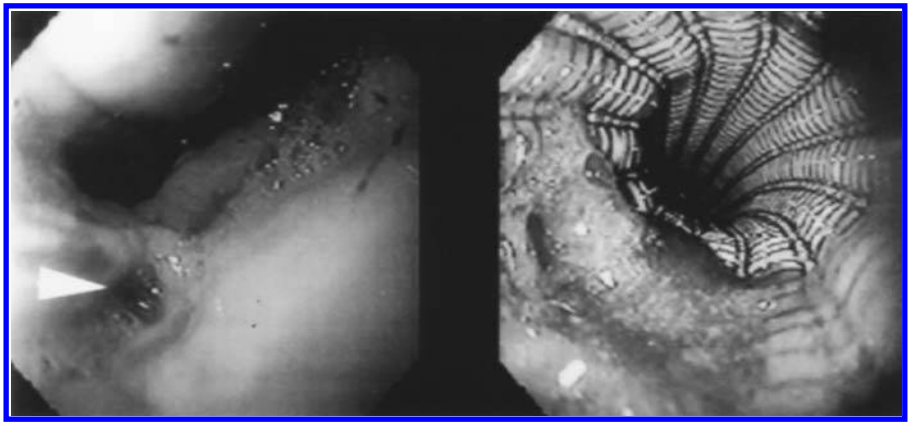

FIGURE 2 (Left) Endoscopic appearance of esophageal carcinoma with arrowhead demonstrating tracheoesophageal fistula. (Right) Endoscopic appearance of esophageal carcinoma with Microvasive-covered esophageal endoprosthesis in position functionally occluding fistula.

Clearance of obstructions with laser, electrocoagulation, or dilation may alter the structure of the stent; chemonecrolysis or photodynamic therapy (see below) may be preferable. Once these expandable stents have been deployed, they are essentially impossible to remove.

A study by Cusumano et al. of 445 consecutive patients with inoperable carcinoma of the esophagus and cardia referred for palliation reported that stent placement was successful in 409 patients (92%). Early resumption of semisolid oral feeding was possible in 80% of the discharged patients. The hospital mortality rate among patients who underwent intubation was 3.4% (14/409). The success rate and complication rate of stent placement is highly dependent upon the patient population and operator experience. Perforation is the most concerning complication of endoprosthesis placement, occurring in approximately 5–8% of cases in experienced hands. Several factors that may predispose to perforation include prior radiotherapy and surgery and sharp angulation of the tumor. Most perforations are recognized soon after they occur and the majority can be managed conservatively. Stent placement may seal off the perforation and prevent continued contamination. Migration of the prosthesis or tube dislocation occurs in more than 10% of rigid stents. Obstruction may be caused by a food impaction, tumor growth, or result from reflux-induced strictures. Pressure necrosis leading to fistula and hemorrhage due to erosion have been reported.

Knyrim reported the results of a randomized trial comparing an expandable metal stent (inner diameter 16 mm) with rigid plastic prostheses (inner diameter

12 mm). Twenty-one patients were randomized to each group. Dysphagia improved equally in both treatment arms, but complications were significantly reduced in the expandable stent group. The metal stent group had a lower 1-month mortality rate (14% vs. 29%) and a significantly shorter hospital stay.

Various complications have been reported with esophageal endoprosthesis placement, including esophageal perforation, aspiration, tracheal compression, and hemorrhage. Perforation of the esophagus is the most serious complication of esophageal endoprostheses, and occurs with a frequency of about 6–8% with the rigid endoprostheses. The rate of perforation may prove to be less than 5% with the newer expandable stents, though large series and follow-up are not available. Factors that appear to be associated with an increased risk of perforation include prior radiotherapy and sharp angulation. The stent itself may seal off the site of the perforation, and an additional endoprosthetic may seal off any communication. The management of mediastinitis in the setting of an endoprosthetic will vary significantly from patient to patient and is dependent upon local expertise. Aspiration may either occur during the placement of the endoprosthetic or subsequently due to reflux of gastric contents through a now patent esophagus. Patients should not lie supine or prone after stent placement, should be on a modified diet, and should be on lifelong gastric acid suppressive therapy. A persistent globus sensation may occur if the stent is placed within 2 cm of the upper esophageal sphincter. Mediastinal pain may occur with placement into a stenotic or fibrotic lesion. Stent migration and dislodgment may occur, though currently available expandable designs appear to have a small propensity to move.

Endoscopic Ablative Palliation

Palliation of gastrointestinal malignancies may also be achieved with tumor ablative techniques. These methods may be applied endoscopically and include thermal debulking techniques (bipolar cautery, monopolar cautery, laser), tissue destruction (alcohol, chemotherapeutic agents, photodynamic therapy), and radiotherapy (afterloading techniques, seed implantation). The use of any of these methods is dependent upon the local expertise and resources available, within the context of a multidisciplinary approach to the overall care of the patient.

Nd: YAG Laser

The most widely practiced and accepted procedure for debulking is thermal laser ablation. Nd: YAG laser treatment has been the mainstay of the clinically useful techniques. Studies have documented the ability of laser therapy to improve and often eliminate dysphagia and in selected patients shown to confer a survival advantage when compared with historical controls. Numerous difficulties, including perforation, may be encountered in its application, though careful patient selection may decrease these risks.

The most important indications for thermal laser ablation are relief of dysphagia and complete obstruction of the esophagus. The most widely used approach is the retrograde approach using a noncontact fiber. The endoscope is passed beyond the tumor and the tumor is progressively destroyed beginning from the distal margin. Other variations include the anterograde approach (tumor destruction from the most proximal aspect of the tumor, typically when the tumor is not passable) and using a contact fiber (fibers designed to be used directly on the tumor). The contact fiber is advantageous when there are anatomical constraints that prevent a clear endoscopic approach to the tumor or when large areas of tumor need to be treated tangentially. One session may be sufficient to achieve luminal patency, though optimal luminal patency may require two to four treatment sessions performed on alternating days. With this regime, luminal patency can be achieved in more than 90% of patients with functional success achieved in 70–85% of patients. Several factors have been identified that predict success with laser therapy (Table 8).

The most serious complication of endoscopic laser therapy is perforation. Perforation rates vary from 0 to 10%; however, many patients undergo dilation before laser therapy and some perforations may be due to the dilation and not the laser itself. Many studies have noted a low incidence of clinically significant bacteremia and sepsis. A new type of laser, which is being evaluated clinically, is the KTP (potassium-tetanyl-phosphate) laser. This laser has the advantage of a more limited depth of penetration with less scatter and may prove to decrease the risk of perforation. Bleeding may occur after laser therapy and usually is self-limited. Fistulae can occur within 6 weeks post–laser therapy. It is likely that these fistulae are a result of both laser-induced damage and the natural history of esophageal cancer. Transient worsening of dysphagia may occur post–laser therapy and is often due to transient tissue edema induced by the therapy. Benign pneumoperitoneum and pneumomediastinum may occur post–laser therapy and needs to be clinically differentiated from perforation.

Barr et al. reported a randomized trial comparing laser therapy only with

Table 8 Predictors of Successful Outcome for Treatment with Endoscopic Laser Therapy

	Favorable	Unfavorable
Tumor	Exophytic	Submucosal
Location	Distal 2/3	Cervical
Length	<5–6 cm	>8–10 cm
Performance status	Good	Poor
Response to first laser treatment	Symptomatic improvement	No symptom relief

laser followed by rigid endoprosthesis placement for the palliation of malignant dysphagia. It was concluded that both treatments were equally effective in relieving dysphagia and in maintaining quality of life. There was no procedure-related mortality in either group; however, the complication rate was significantly higher in the endoprosthesis group. Another study compared endoscopic stent *versus* laser and found that laser recanalization provided better functional results than intubation for short circumferential tumors (<4 cm), whereas stent placement at a single session appeared superior to repeated laser therapy for longer tumors.

A prospective nonrandomized trial by Loizou and colleagues enrolled 43 patients for treatment with Nd: YAG laser and 30 patients for treatment by rigid endoprosthesis. For patients with thoracic esophageal tumors the percentage of patients achieving short- and long-term relief of dysphagia was similar (laser: 95% and 77%; intubation: 100% and 86%, respectively). For tumors crossing the cardia, intubation was significantly better (laser: 59% and 50%; intubation: 100% and 92%, respectively). Long-term palliation was better in the laser group; however, more procedures and additional hospital days were required. The risk of perforation was 2% for laser treatment and 13% for rigid stent placement.

Chemical Necrolysis

Direct EtOH injection into tumor masses has been used with success to debulk lesions, to improve dysphagia, to salvage endoprostheses when overgrowth has occurred, and to maintain luminal patency. It is clearly the simplest and least expensive of the therapies, though scant data are available on overall safety and efficacy. Chemotherapeutic agents for intratumoral injection are in clinical trials and may prove to have long-lasting benefit. In preliminary studies, several groups have treated patients with unresectable esophageal carcinoma by injecting absolute alcohol directly into the tumor. The appeal of this approach is its low cost and the technical ease with which the procedure can be performed. No randomized trials have been published, though the preliminary studies reveal a success rate comparable to that seen with laser therapy. Randomized trials are necessary to demonstrate the efficacy and safety of this economically interesting approach.

Bipolar Electrocoagulation

The most commonly applied endoscopic treatment in the past was bipolar cautery, but this has fallen out of favor due to concerns over full-thickness injury, stricture formation, the need for a circumferential tumor, and difficulties inherent in the technical performance of the technique. The probe consists of a flexible shaft with embedded markers that can deliver bipolar electrical current. The probes are manufactured in various sizes allowing for treatment of various lumen diameters. After the tumor has been endoscopically assessed and measured, a guidewire is passed beyond the tumor. The probe is then passed over the guidewire under

fluoroscopic guidance and treated with either an anterograde or retrograde approach. Bipolar therapy has been shown to be as efficacious as laser therapy for the treatment of circumferential esophageal cancer. In one study by Jensen et al., functional improvement was achieved for both modalities in 86% of cases. A smaller study by Fleischer et al. found a reproducible rate of a 7–20% incidence of fistula formation and bleeding. It is postulated that these complications are often the result of coagulation and necrosis of normal tissue incidentally treated. When compared with laser therapy, potential advantages of bipolar treatment include lower costs, wider availability, and greater ability to treat tumors that are technically difficult to treat with laser therapy, including long tumors (>10 cm) and high cervical tumors. The inability of bipolar therapy to selectively treat tumor in noncircumferential lesions limits its utility as a primary therapy for establishing luminal patency.

Brachytherapy

Chemosensitized radiotherapy is discussed elsewhere in this chapter and is an excellent option for initial palliation in suitable candidates. Endoluminal radiotherapy may be directed and aided by endoscopic techniques including endoscopic ultrasound. Brachytherapy markers and delivery tubes may be placed endoscopically and location of the tumor precisely determined to allow for the precise delivery of intraluminal and external beam therapy. Brachytherapy is often performed with iridium 192 or cesium 137. A specialized applicator is available for precise dosimetry and may be precisely placed endoscopically with EUS guidance. A randomized trial compared brachytherapy with Nd: YAG laser and found that the overall results of palliation were similar; however, there were more minor complications in the brachytherapy group.

Photodynamic Therapy (PDT)

PDT is a new technique with numerous possible applications in the treatment and palliation of esophageal neoplasia. Its role is currently expanding and it is FDA approved for the palliation and restoration of luminal patency in esophageal cancer. Further bench and clinical research will most likely lead to better hematoporphyrin derivatives and to improved techniques. The basis for PDT is the ability of photosensitizing agents to produce fluorescence or cell-specific cytotoxicity after activation with photons by a low power laser. Fluorescence is used for the detection of neoplastic tissue and cytotoxicity for the destruction of tumors. PDT treatment involves the administration of exogenous photosensitizers, such as dihematoporphyrin ethers (DHE), which are then relatively preferentially localized to neoplastic tissue. Specific wavelength light is delivered by a laser fiber passed through the endoscope. The light activation of the compound creates highly reactive singlet oxygen. It is believed that the toxic radical reacts with cell membranes

and organelles to result in cell death. The depth of treatment varies with the wavelength of the light source and the specific photosensitizer, but affords a limited extent of injury by limiting tissue destruction to cells that preferentially accumulate the photosensitizer. Lightdale et al. reported a randomized trial involving 236 patients comparing PDT to Nd: YAG laser for the palliation of patients with malignant dysphagia. There was a tendency for PDT to be better among patients with long tumors (≥10 cm) and those with cervical esophageal lesions. Improvements in the dysphagia score both at 1 week and at 1 month were similar and complication rates were similar. The PDT group required fewer treatment sessions; however, photosensitivity reactions were reported in 20% of patients. A further study by Sibille et al. involved 123 patients, the majority of which had EUS stage T1 and T2 lesions who underwent PDT therapy. These patients were deemed inappropriate for surgical treatment. In the treatment group, the 5-year disease-specific survival rate was 74%. The authors concluded that for patients with small esophageal tumors, who pose a high surgical risk, PDT is an effective alternate therapy.

One of the major complications of PDT therapy is an iatrogenic porphyria with cutaneous photosensitivity that may cause erythema, cutaneous edema, or blistering of the skin when patients are exposed to sunlight. This typically occurs within 4–6 weeks of therapy. This occurs as a result of the specific photosensitizing agent that is generally used, which has a major absorption peak close to the peak of solar radiation (400–500 nm). Newer sensitizing agents are undergoing clinical trials for increased selectivity for malignant tissue and decreased skin photosensitivity.

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3

Mid and Distal Gastric Cancers

Lawrence E. Harrison
University of Medicine and Dentistry, New Jersey Medical School, Newark, New Jersey

Eileen M. O'Reilly, Bruce D. Minsky, Gary K. Schwartz, and Martin S. Karpeh, Jr.
Memorial Sloan-Kettering Cancer Center, New York, New York

INTRODUCTION

The stomach is the third most common site of cancer in the gastrointestinal tract. Despite a dramatic decrease in incidence, gastric cancer remains seventh in cancer-related deaths in the United States. Difficulties in treating gastric cancer arise from the fact that most patients present with advanced disease.

Epidemiology

In 1930, gastric cancer was the leading cause of cancer-related deaths in the United States. Over the last six decades, the incidence rates for gastric cancer have dropped dramatically. At present, there are approximately 22,400 new cases of gastric cancer per year in the United States. While there has been a decrease in the incidence of distal gastric cancers, there is epidemiological data suggesting a steady rise in the incidence of proximal adenocarcinoma of the stomach and gastroesophageal junction.

Gastric cancer rarely occurs before the fourth decade, but its incidence rises thereafter, peaking in the 60–70-year-old age group. Gastric cancer is twice as common in men as in women. In the United States, blacks, Hispanics, and Native Americans are 1.5–2.5 times more likely to have gastric cancer than whites.

Gastric cancer tends to be more prominent among populations of lower socioeconomic status, most likely reflecting dietary habits and environmental exposures. Low consumption of fruits and vegetables, high intake of salt, fat, and nitrates, and poorly preserved foods have been associated with an incidence of gastric cancer.

Pathology

Over 90% of all tumors of the stomach are adenocarcinomas. The remaining 10% comprise mostly non-Hodgkin's lymphomas or leiomyosarcomas. Gastric adenocarcinomas can be divided into two histological subtypes: intestinal type and diffuse type. The intestinal or so-called *epidemic* type, most commonly seen in lesser developed nations and the predominant histological subtype in high-risk populations, is on the decline in the United States. Intestinal lesions are often ulcerative, occur in the distal stomach more often than the diffuse type, and are preceded by a prolonged precancerous phase. The diffuse, or *endemic*, type presents at a younger age and appears to have a genetic component and to be less dependent on environmental factors. Diffuse lesions occur throughout the stomach, but especially in the cardia, and are associated with a worse prognosis. The decline in the incidence of gastric cancer is largely attributable to a decrease in the intestinal-type tumors, while the diffuse subtype is proportionally becoming more common in the United States.

Predisposing Factors

A host of environmental factors have been implicated as having the potential to increase the risk of developing gastric adenocarcinoma. A diet high in salt and nitrosamines, a lack of vitamin C and beta carotenes, and infection with *Helicobacter pylori* all appear to play some role in increasing risk. However, there is growing evidence to support the role of genetic factors as well in the pathogenesis of gastric cancer. Familial clustering has been documented and an increased risk of gastric cancer has been reported in patients with hereditary nonpolyposis colorectal cancers. Further support for a genetic influence comes from an elevated risk of gastric cancer in individuals with blood type A.

Chronic atrophic gastritis and intestinal metaplasia has repeatedly been recognized as a predisposing factor in the carcinogenesis of gastric cancer. Atrophic gastritis, the result of chronic inflammation, may progress to foci of intestinal metaplasia, dysplasia, and finally invasive carcinoma. A number of epidemiological studies have shown an association between chronic *H. pylori* infection and gastric cancer. However, the precise role of *H. pylori* in the carcinogenesis of gastric cancer is unclear and probably represents one of a number of cofactors responsible for gastric cancer. Importantly, the effect of treatment of *H. pylori* on the risk of gastric cancer is being studied. Pernicious anemia is also a risk

factor for gastric adenocarcinoma. An elevated risk of gastric carcinoid tumors have also been reported with pernicious anemia, most likely the result of prolonged acid suppression leading to hypergastrinemia. Patients who have had a prior gastric resection for benign disease are at increased risk for developing gastric cancer in the gastric remnant, but this risk does not begin to increase until after a period of 15–20 years (Table 1).

SURGERY

An algorithm for the diagnosis and treatment of gastric cancer is shown in Figure 1. The following discussion provides information and rationale for each of the steps along the treatment pathway. This section will concentrate on the surgical aspects of gastric cancer. The utility of chemotherapy and radiation therapy for gastric cancer will be discussed in subsequent sections.

Clinical Presentation

Most patients with gastric cancer present with symptoms regardless of stage. However, the insidious and transient nature of these symptoms often leads to procrastination in seeking medical evaluation. This late presentation is also exacerbated by the abundance of over-the-counter remedies for nonspecific abdominal complaints, which delay proper investigations. Unfortunately, there are no signs

Table 1 Risk Factors for Gastric Cancer

Epidemiologic factors
Geographic location
Gender
Race
Age
Precursor conditions
Pernicious anemia
Chronic atrophic gastritis
Intestinal metaplasia
Helicobacter pylori infection
Partial gastrectomy for benign disease
Genetic factors
Family history of gastric cancer
Blood type A
Hereditary nonpolyposis colon cancer syndrome
Environmental factors
Socioeconomic status
Diet
Cigarette smoking

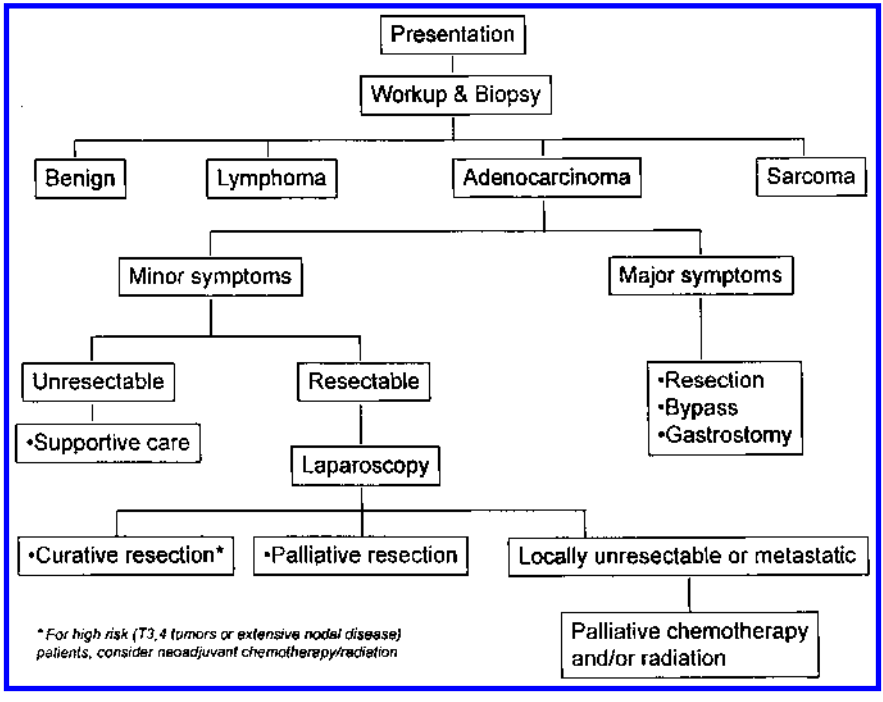

FIGURE 1 Algorithm for the workup, staging, and treatment of gastric adenocarcinoma.

or symptoms pathognomonic for gastric cancer. Consequently, the majority of patients with gastric cancer in the United States present with locally advanced or metastatic disease. The severity of symptoms is often related to the extent of the disease. Vague abdominal fullness and dyspepsia are earlier signs of gastric cancer. This often progresses to severe, steady abdominal pain, anorexia, and weight loss as the tumor progresses. In a large review of 18,365 patients with gastric cancer, abdominal pain and weight loss were the two most common presenting symptoms, reflecting the late stage of presentation. While vomiting is associated with distal lesions obstructing the pyloric channel, dysphagia is more commonly associated with proximal lesions. Hematemesis and melena occur in about 20% of cases, but acute upper gastrointestinal bleeding is rarely a presenting sign for gastric cancer. Similarly, gastric adenocarcinomas rarely present with perforation.

The physical findings of gastric cancer are also related to the extent of disease. Early gastric cancer infrequently presents with any obvious physical signs. As the tumor progresses, physical examination may reveal cachexia, abdominal mass or tenderness, ascites, or hepatomegaly. Supraclavicular lymph

nodes (Virchow's node) may be the first clue to the diagnosis of gastric cancer. Tumors spreading along the peritoneal surface may present with periumbilical lymphadenopathy (Sister Mary Joseph node). Adnexal mass on pelvic examination may be the manner of presentation for metastatic gastric cancer (Krukenberg's tumor). Rectal examination may demonstrate guaiac-positive stools or a mass in the cul-de-sac (Blumer's shelf).

Diagnostic Work-up

Unfortunately, nonspecific epigastric discomfort and vague feelings of indigestion are often interpreted as either of benign origin or nonorganic in nature and often delay the work-up of gastric cancer. Therefore, it is important to maintain a high index of suspicion for patients at risk for gastric cancer and to initiate a diagnostic work-up as soon as possible. After a complete history and physical examination, work-up should be tailored toward diagnosis, staging, and treatment of gastric cancer. Serum laboratory tests may demonstrate anemia and hypoproteinemia. Abnormal liver function tests may suggest the presence of metastatic disease. Although carcinoembryonic antigen (CEA) is elevated in a third of patients with gastric cancer at presentation, no single marker is specific for gastric cancer and none have been useful for early detection.

An upper gastrointestinal (UGI) series with barium is often the first diagnostic test to evaluate the vague symptoms related to upper gastrointestinal pathology. Radiographic evidence of a lack of distensibility of the gastric wall, enlarged gastric folds, and an obstructing mass are all highly suspicious and require further evaluation. While air contrast techniques allow better visualization of mucosal detail, false-negative rates can be high for small lesions, particularly in Western countries where the experience with early gastric cancers is low. In addition, differentiation of a benign ulcer from malignancy may be impossible. While an UGI series is a good first step in screening symptomatic low-risk individuals, there are data to support early endoscopic examination in symptomatic patients over the age of 55 if symptoms persist for more than 2 weeks.

While upper endoscopy is more invasive, it allows direct visualization and the ability to biopsy any abnormality. The accuracy and safety of upper endoscopy are well documented and it can be performed as an outpatient procedure with minimal sedation. Directed biopsy and cytological brushing of any suspicious mass, ulcer, or enlarged fold can easily be performed. Since diagnostic accuracy increases with the number of biopsies taken, a minimum of four biopsies for exophytic lesions and 12 for infiltrating tumors are recommended. While adenocarcinomas of the stomach are mucosally based, gastric lymphomas and leiomyosarcomas may be visualized as submucosal lesions and deeper biopsies may be indicated. Besides histological diagnosis, endoscopy also provides information

regarding site of the tumor, proximal and distal extension, distance from the gastroesophageal junction, and distensibility of the stomach and esophagus. Importantly, no endoscopic examination should be done without a biopsy.

Endoscopic ultrasonography (EUS) is a relatively new method of staging, which may complement staging information gained by computerized tomography (CT) scan. EUS is performed by placing a high-frequency (7.5–12 MHz) ultrasonic probe into the lumen of the stomach under direct endoscopic vision. The layers of the normal stomach (mucosa, submucosa, muscularis propria, and serosa) are easily visualized. EUS assessment of the primary tumor allows precise T staging. Importantly, EUS accurately predicts involvement of the muscularis propria by the primary tumor, thus separating early from late cancers. While not as precise in estimating tumor penetration, EUS can also estimate regional lymph nodal involvement with an accuracy up to 50–60%. EUS may impact treatment decisions since patients with locally advanced lesions (T3 or T4) by EUS have a low potential for cure after complete resection. These patients may be considered for neoadjuvant chemotherapy protocols (Fig. 2).

CT of the abdomen is an important staging modality for gastric cancer as it assesses tumor extent, nodal involvement, as well as the presence of metastatic disease. While not as accurate as EUS in determining depth of tumor invasion, the CT scan can accurately detect direct extension into spleen, liver, pancreas, or mesocolon. The CT scan can also identify regional lymph node involvement of the celiac, retrocrural, retroperitoneal, and porta hepatis regions. In addition, the CT scan demonstrates distant metastatic disease in the liver and omentum, as well as ascites and peritoneal carcinomatosis. However, even with high-quality dynamic CT scanning, approximately 25% of CT scan examinations underestimate the extent of disease compared with findings at laparotomy.

Staging/Prognosis

Gastric adenocarcinomas are staged using the TNM system (Table 2). The pathological stage of the tumor remains the most important factor for prognosis. The depth of tumor penetration as well as the presence or absence of metastases to regional lymph nodes or distant organs are the most important determinants of disease-free and overall survival. Beyond the TNM factors, numerous other factors appear to affect outcome. Tumor ploidy, differentiation, lymphovascular invasion, Lauren subtype (intestinal versus diffuse), gender, and p53 expression have all been studied as possible prognostic factors for gastric cancer but none consistently predict outcome independent of the TNM stage. Some authors have observed that tumor location does predict outcome independent of stage; as the tumor moves proximally, overall survival decreases (Fig. 3).

Recently, nomenclature regarding the completeness of resection has been proposed, as it strongly reflects prognosis. A curative gastric resection, which

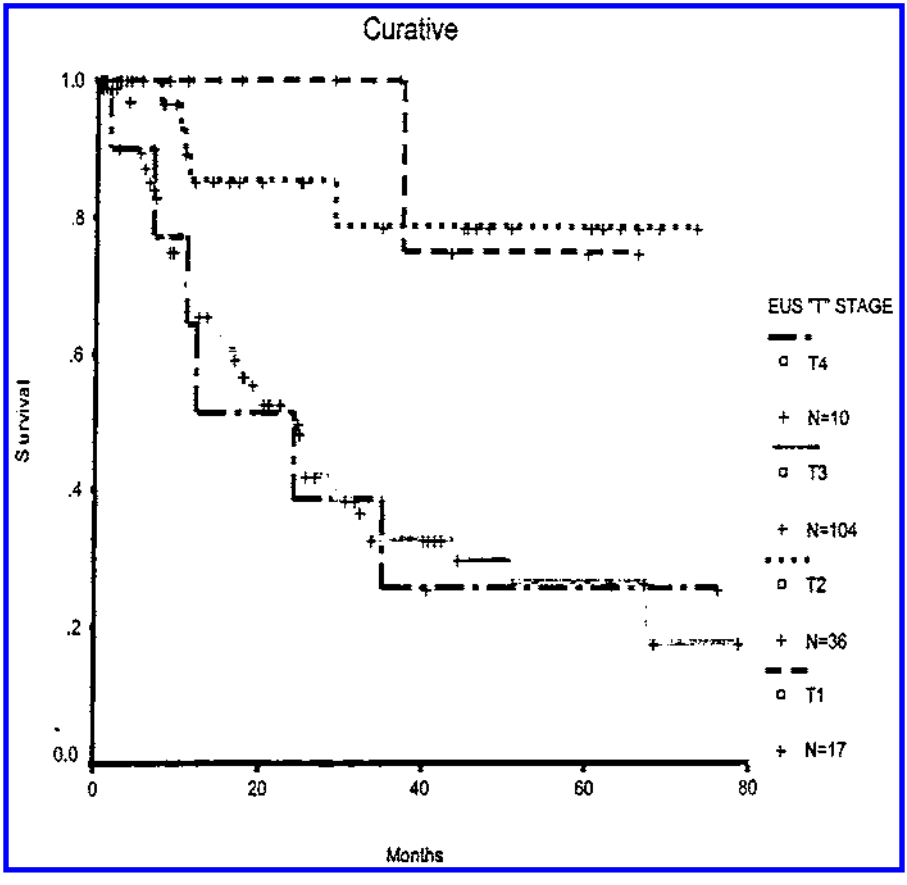

FIGURE 2 Survival by EUS T stage for 224 preoperatively staged patients. Patients with EUS T1 and T2 tumors made up the low-risk group and patients with EUS T3 or T4 were combined to form the high-risk group.

removes all gross tumor with microscopically negative margins, is designated an R0 resection. Resection of gross tumor with microscopic residual disease at the margins is called an R1 resection; leaving gross disease after resection is termed an R2 resection.

Treatment

After the patient has been evaluated and the diagnosis of gastric adenocarcinoma established, two additional factors are necessary to establish a treatment plan: (1) severity of symptoms and (2) extent of disease.

TABLE 2 TNM Classification of Gastric Carcinoma

		Primary tumor	
Tis	Carcinoma in situ		
T1	Invasion of lamina propria or submucosa		
T2	Invasion of muscularis propria		
T3	Invasion of serosa		
T4	Invasion into adjacent structures		
		Regional lymph nodes	
N0	No lymph node metastases		
N1	1–6 perigastric lymph node metastases		
N2	7–15 perigastric lymph node metastases		
N3	>15 perigastric lymph node metastases		
		Distant	
M0	No metastases		
M1	Metastases		
		Stage	
0	Tis	N0	M0
I	T1	N0,1	M0
	T2	N0	M0
II	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
III	T2	N2	M0
	T3	N1,2	M0
	T4	N0,1	M0
IV	T4	N2	M0
	any T	any N	M1

Major Symptoms

For gastric outlet obstruction or major bleeding from tumor, most patients should proceed directly to an exploratory laparotomy depending on their performance status. The extent of disease, per se, plays less of a role in the decision to operate. Intraoperative evaluation will dictate the procedure of choice. For gastric outlet obstruction, a gastric resection should be performed whenever possible, as it will provide the best palliation. In the presence of widely metastatic disease or in the rare case of a locally unresectable tumor, a gastrojejunostomy will offer palliation for the obstruction. A third option for patients with end-stage metastatic disease is placement of a gastrostomy tube to relieve symptoms. This may be placed at the time of exploration or later, endoscopically. For patients who present with an UGI bleed requiring blood transfusion, a gastric resection is the procedure of choice. Extent of resection is dependent on whether the surgeon feels it is for

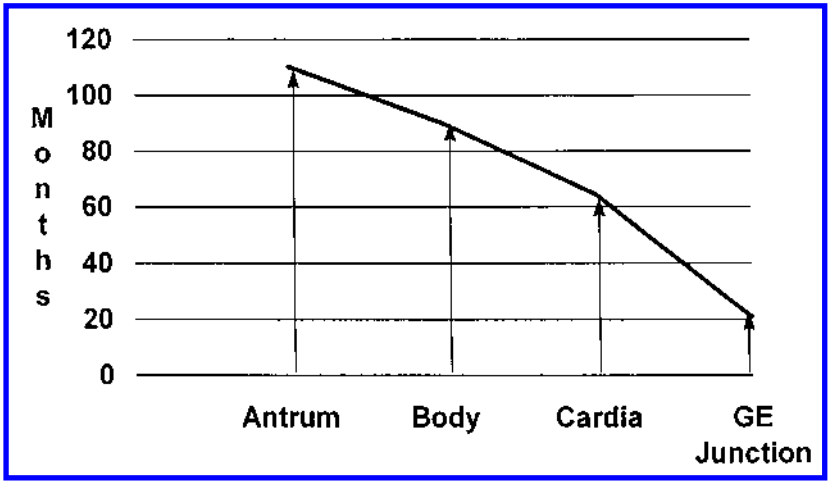

FIGURE 3 Independent of stage, survival is related to the primary site of the gastric carcinoma. Median survival decreases as the primary moves proximally.

curative or palliative intent. For patients with a technically unresectable tumor, external-beam radiation is an effective alternative to control bleeding. Endoscopic control of bleeding is often ineffective owing to the presence of friable tissue, which is diffuse rather than focal.

Minor Symptoms

A different approach should be undertaken for patients with minor symptoms of dyspepsia or minor bleeding. Once minor symptoms are established, the next step is to determine the extent of disease. For patients with metastatic disease (liver, lung, peritoneal surfaces, omentum) by physical examination or CT scan, palliative chemotherapy, radiation, or best supportive care should be offered. In this instance, gastric resection offers no chance of cure and palliation of minor symptoms can usually be adequately achieved medically. With modern combination chemotherapy a small proportion of these patients may respond and become eligible for complete resection.

Patients with resectable tumors as judged by CT scan should next be evaluated by laparoscopy. Preoperative staging using laparoscopy and laparoscopic ultrasound enables the identification of patients with occult M1 disease, thus avoiding an unnecessary noncurative operation. Laparoscopy is a useful modality for evaluating local, regional, and distant extent of disease. Laparoscopy has been shown to be more sensitive in detecting liver, peritoneal, and omental metastases compared to a quality CT scan examination of the abdomen and pelvis. The

addition of laparoscopic ultrasound has been useful for detecting hepatic metastases and defining the T stage of the primary tumor. Importantly, laparoscopic evaluation allows patients with minimal symptoms and advanced T stage (3,4) or extensive nodal disease (N2,3) to be considered for preoperative chemotherapy regimens without having to undergo the morbidity of an exploratory laparotomy. Very rarely, laparoscopy will detect a tumor that is locally unresectable, which was not appreciated on a good-quality CT scan. Patients with laparoscopic evidence of peritoneal or liver metastases with minimal or no symptoms should be considered for current-generation chemotherapy. Some of these patients will respond and be resected with a better chance for prolonged survival. Nonresponders should be treated as symptoms dictate. It has been our experience that unresected patients have a median survival of 6–8 months and almost uniformly die prior to developing symptoms severe enough to require surgical intervention from their primary tumor.

In the absence of peritoneal, hepatic, or omental metastases by laparoscopy, patients should proceed to gastric resection with curative intent. This includes surgical resection of the tumor with adjacent lymph nodes. The extent of gastric resection depends on the location and size of the primary tumor. For distal tumors in the antrum and body, a radical distal subtotal gastrectomy, resecting the greater and lesser omentum and regional lymph nodes, is the operation of choice. Reconstruction is most often done with a Billroth II gastrojejunostomy; a Billroth I gastroduodenostomy can be performed following resection of small early cancers of the distal stomach, as there is little documented difference in outcome or function. The issue of performing a more extended resection (total gastrectomy) for these lesions has been addressed by prospective studies and offers no improvement in survival. For proximal lesions in the cardia and fundus or large midbody tumors, a total gastrectomy or proximal gastrectomy with omentectomy can be performed with equal survival results provided a negative margin can be achieved.

For all advanced gastric cancers (T2 or greater), the proximal and distal margins should be 6 cm. For signet ring cell tumors and other diffusely growing tumors 8–10 cm will provide a safer clearance. Truly early gastric cancers (pT1) of the intestinal type can be adequately resected with a margin of 2 cm or more. Usually the limiting factor for margin length is proximal extent of resection. While local recurrence is increased with microscopically positive margins, the stage of tumor dictates its clinical significance. Microscopic disease at the resection margin is of more significance in patients with earlier-stage tumors, compared to those with more advanced disease; presumably the regional disease progresses before local recurrence is manifest clinically.

The extent of lymphadenectomy for gastric cancer has long been debated. Reports of excellent long-term survival have been reported from the East, where extended lymphadenectomy (D2 dissection) is performed routinely. Unfortu-

nately, Western results have not been as promising, with reports of high morbidity and mortality without obvious survival benefits. No doubt, extended lymphadenectomy improves the accuracy of staging. Whether it adds to long-term survival will be addressed in two large prospective trials from Europe designed around this question. We and others have shown that lymphadenectomy can be done safely, while providing the patient and clinician with important prognostic information. The benefit, if any, is probably not universal and may be limited to the large subset of patients with positive perigastric nodal metastases.

Related to the issue of lymphadenectomy is the question of performing a routine splenectomy with or without distal pancreatectomy to accomplish a more complete nodal dissection. Multiple studies demonstrate that routine pancreaticosplenectomy is not needed to perform a proper D2 lymphadenectomy and is rarely indicated, as it is associated with a higher incidence of postoperative complications without contributing a survival advantage. Adjacent organ resection is limited to a select subset of patients with suspected T4 primary tumors. Patients with T4 tumors in the absence of significant nodal or metastatic disease (T4 N0-1 M0) may benefit from adjacent organ resection to attain an R0 resection. It is difficult to be certain about the status of lymph nodes without a biopsy since associated adenopathy can be reactive. Frozen-section diagnosis of lymph nodes distant from the primary (N3 nodes) can help in deciding whether to proceed.

Surgical Results

In the United States, the survival rate for resectable gastric cancer is generally said to be poor, with an overall 5-year survival rate ranging from only 15 to 30%. In contrast, the Japanese report superior results, with 5-year survival rates approaching 50%. While distribution of tumor or patient-dependent prognostic factors between the East and West do not explain these differences in outcome, the Japanese assert that gastric resection with routine extended lymph node dissection (D2) contribute to their improved results. However, most believe that resected metastatic lymph nodes are *indicators* rather than *governors* of outcome for gastric adenocarcinoma. According to this philosophy, extended lymph node dissection merely improves the accuracy of tumor staging. With adequate staging, Western results of gastric resection for adenocarcinoma begin to approximate those seen in Japan (Table 3).

Survival in patients with gastric cancer is dependent on the stage of disease at the time of presentation. Over the last 50 years, there has been a worldwide trend for improved survival following curative resection for gastric adenocarcinoma. In Japan, this has been attributed to screening programs, which have increased the proportion of patients presenting with early-stage disease. The rationale for this trend in the United States and Europe is less clear, but recently the overall 5-year survival after curative resection for gastric adenocarcinoma in

TABLE 3 Five-Year Survival by Stage in Selected Populations

	Japan	United States[a]	United States[b]
Stage 1	91	50	84
Stage 2	72	29	61
Stage 3	44	13	29
Stage 4	9	3	25
Operative mortality (%)	1	7	3

[a] Results from a multi-institutional study where routine D2 lymphadenectomy was not employed.
[b] Results from a single institution where the majority of resections underwent D2 dissection.

many Western centers has exceeded 40%. Further progress in improving survival awaits further progress in physician willingness to refer symptomatic patients for endoscopy. Patients with late stages of disease at the time of presentation commonly report a past history of symptoms that were treated without resolution on further investigation. Although accounting for less than 10% of all gastric tumors in the United States, early gastric cancers are often associated with symptoms and when resected are associated with a 5-year survival rate of 90%. Two-thirds of patients traditionally present with stage III or IV disease, which is associated with 5-year survival rates of 20 and 5% respectively, we have seen a trend toward less invasive tumors at presentation perhaps reflecting a greater tendency to perform early endoscopy. Tumors limited to the muscularis propria are associated with a 60% survival at 5 years.

Historically, a pattern of recurrence after curative resection has been documented by autopsy studies, as well as by ''second-look'' operations. In those reports local-regional recurrence involving perigastric tissue and lymph nodes occur in approximately 40% of patients. Approximately 60% of patients recur systemically, most commonly in the peritoneum and liver. Metastatic disease outside of the abdomen occurs in 20–40% of patients, but is rarely the first site of recurrence.

As most patients present with advanced disease, the results of surgical palliation should be addressed. In treating patients with advanced gastric cancer, it is important to remember that one cannot provide palliation for a patient without symptoms. Palliation for symptoms should be considered carefully. While obstruction and bleeding can be alleviated with resection, nausea in the absence of obstruction will not be relieved by an operation. In the absence of widespread metastatic disease or ascites, palliative resection offers a better quality of life

with an acceptable morbidity and mortality. However, overall survival is not improved. For those patients with extensive disease and obstruction, bypass of the lesion can be performed. However, palliation after gastrojejunostomy is limited, often transient, with up to a 25% in-hospital mortality. Overall, operative palliation may have a role in selected cases, but the majority of patients will not be helped. Similarly, endoscopic palliation by percutaneous endoscopic gastrostomy/jejunostomy (PEG/PEJ) or laser ablation may also be useful in carefully selected patients.

CHEMOTHERAPY

Adjuvant Chemotherapy

Given the pattern of regional and systemic recurrence following the resection of advanced gastric cancer, it is evident that some form of adjuvant therapy is indicated to further improve the results of surgery. A variety of chemotherapeutic agents and regimens have been evaluated in the adjuvant setting over more than three decades. Some of the early studies showed promise using nitrosurea methyl-CCNU in combination with 5-fluorouracil. An initial prospective, randomized GITSG trial suggested an advantage to this adjuvant therapy; however, two follow-up trials, an Eastern Cooperative Oncology Group trial and a Veterans Administration Surgical Oncology Group trial, did not elicit either a disease-free or overall survival difference. A subsequent International Collaborative Cancer Study Group trial, using 5-fluorouracil, doxorubicin, and mitomycin C (FAM), also failed to demonstrate a disease-free or overall survival benefit at a median follow-up of 68 months. But an unplanned subgroup analysis suggested that patients with positive lymph nodes or deep primary tumors (T3/T4) did accrue a benefit from the adjuvant therapy ($p = 0.07$). Additional trials, including a SWOG study using the same regimen, all showed no benefit to using FAM as an adjuvant. The current overall conclusion is that FAM is ineffective as an adjuvant chemotherapeutic regimen.

Mitomycin alone and in combination has offered some promise over the past 30 years. One prospective, randomized Western trial of mitomycin C 20 mg/m^2 every 6 weeks for four treatments, in 70 patients with stage II and III gastric cancer, has provided encouraging results. The 5-year survival for the surgery-alone group was 26% and for the dual-modality arm was 41% ($p < 0.025$). A recent update continues to show a survival advantage for the patients who received adjuvant mitomycin. A second, larger Western trial using mitomycin C 10 mg/m^2 administered in the immediate postoperative period, monthly for 6 months, and oral UFT for 1 year versus observation, has, after a median follow-up of 3.3 years, shown no differences in disease-free or overall survival between the groups. Additionally, in most of the Japanese randomized trials using

mitomycin-based chemotherapy no clear benefit has emerged, although in the latter trials different timing and altered chemotherapeutic doses and schedules were utilized.

Meta-analyses of Adjuvant Chemotherapy Trials

A large meta-analysis published in 1993 reviewed data from 14 randomized trials involving 2096 patients, comparing surgery alone to surgery and postoperative adjuvant chemotherapy. The combined odds ratio was 0.88 (95% confidence interval, 0.78–1.08), suggesting that adjuvant chemotherapy did not increase the chance of survival compared to surgery alone. However, six of the trials used methyl-CCNU, a drug that has limited activity in gastric cancer and probably also has a small leukemogenic potential. In a late follow-up, two additional trials were included to recalculate the odds ratio. The amended value of the odds ratio was 0.82 (95% confidence interval, 0.68–0.98), which now showed a benefit to adjuvant chemotherapy. However, the author's conclusion was conservative, adjudicating that postoperative adjuvant chemotherapy was not a ''standard'' approach. A second meta-analysis of six random assignment trials from a single institution involving 1177 patients between 1959 and 1982, using mitomycin-based chemotherapy, also suggested a benefit to adjuvant chemotherapy. The combined odds ratio was 0.63 (95% CI 0.51–0.79). Various criticisms have been leveled at both these meta-analyses, including bias, incomplete data inclusion, lack of power, and the lack of surgical standards with which to judge the completeness of the resection, thus questioning the validity of the conclusions. The bottom line is that more positive trials are still needed before adjuvant chemotherapy can be added in the standard treatment of gastric cancer. More recently, reports of surgically staged unresectable gastric cancer patients being resected following dramatic responses to newer drug combinations like etoposide, doxorubicin, and cisplatin (EAP) and 5-FU, doxorubicin, and methotrexate (FAMTX) have garnered enthusiasm for taking a neoadjuvant approach to this disease.

Neoadjuvant Approaches

The concept of neoadjuvant chemotherapy is particularly attractive in gastric cancer because of the limited number of patients who can undergo curative surgery de novo, the well-defined failure patterns of this disease, and the propensity for early systemic spread. The putative benefits to neoadjuvant treatment include shrinkage of the primary tumor, sterilization of small-volume metastatic disease, and potentially reducing the extent of definitive surgery. On the obverse side, there is a risk of delaying local control and compromising the true initial pathological stage. Also, theoretically, drug-resistant clones of tumor cells may emerge during the induction chemotherapy phase.

EAP has been assessed in the preoperative setting, by Ajani and the group

Table 4 Intravenous Chemotherapy for Gastric Cancer

Combination	Drug	Dose (mg/m^2)	Schedule (days)
FAMTX	Fluorouracil	1500	Day 1
	Methotrexate	1500	Day 1
	Doxorubicin	30	Day 15
			Recycle day 29
FP	Cisplatin	75–100	Day 1
	Fluorouracil	1000	Day 1–5 cont. infusion
			Recycle day 29
ELF	Etoposide	120	Day 1–3
	Fluorouracil	500	Day 1–3
	Leucovorin	300	Day 1–3
			Recycle at 3–4 weeks
FAM	Fluorouracil	600	Day 1, 8, 29, 36
	Doxorubicin	30	Day 1, 29
	Mitomycin	10	Day 1
			Recycle at 8 weeks
EAP	Etoposide	125	Day 4–6
	Doxorubicin	20	Day 1, 7
	Cisplatin	40	Day 2, 8
			Recycle day 29

at M.D. Anderson. Patients received three cycles of chemotherapy before surgery. The trial design planned for two postoperative courses of treatment. Seventy-seven percent of patients underwent potentially curative surgery. The major toxicity was neutropenia and one death was recorded. The median survival duration was 15.5 months. A subsequent trial with etoposide, 5-fluorouracil, and cisplatin achieved similar results. Peritoneal carcinomatosis was identified as a major site of failure; hence postoperative intraperitoneal chemotherapy was added to future studies by some investigators. Leichman and colleagues, at the University of Southern California, have utilized this combined approach. A prolonged low-dose infusion of 5-fluorouracil, 200 mg/m^2/day over 3 weeks, with weekly intravenous folinic acid and monthly cisplatin 100 mg/m^2, was given preoperatively. Postoperatively intraperitoneal floxuridine with cisplatin was administered along with intravenous sodium thiosulfate. Eighty-seven percent of patients underwent surgical resection and 68% of patients received postoperative intraperitoneal therapy. The median survival was not reached at 17 months at the time of publication. Significant downstaging was noted at the time of pathological surgical assessment. Kelsen and colleagues, at Memorial Sloan-Kettering Cancer Center, administered three cycles of preoperative FAMTX (5-fluorouracil, methotrexate, doxorubicin), followed by surgery and then intraperitoneal 5-fluorouracil, cisplatin,

and concurrent intravenous 5-fluorouracil. Fifty-six patients, mostly with stage IIIA or IIIB tumors were enrolled. Eighty-nine percent underwent surgery for a resectability rate of 74%. Downstaging was noted in 51%. The major toxicity was neutropenia, with 60% requiring at least one hospitalization. The overall median duration of survival was 15.3 months and for the group with curative surgery was 31 months.

One of the reassuring facts that has emerged from these early neoadjuvant trials is that overall surgical morbidity and mortality appear not to be increased. Second, the theoretic concern that preoperative chemotherapy may render some patients inoperable by virtue of disease progression during the induction chemotherapy period does not appear to be borne out. The use of preoperative endoscopic and laparoscopic ultrasonographic techniques allows for proper patient selection. Laparoscopy helps to avoid entering patients with occult M1 disease and the sonographic techniques help to identify patients at highest risk for failure following resection alone (i.e., T3 tumors). Clearly, randomized clinical trials are needed to fully define the role of this encouraging approach but for the time being patients with advanced gastric cancers as evidenced by the presence of a T3 tumor are being encouraged to enter neoadjuvant protocols utilizing these newer drug combinations.

Intraperitoneal Chemotherapy

This is an attractive concept because of the direct administration of chemotherapy, in high-dose concentrations, to some of the major sites of expected tumor relapse. The gastric cancer strategy is modeled on colon cancer, where Sugarbaker et al. noted an alteration in the failure patterns, particularly a decline in peritoneal relapses with intraperitoneal 5-fluorouracil. In one phase II study by Atiq et al. patients with mostly stage IIIA and IIIB disease received IP cisplatin 25 mg/m^2 daily for 4 days and IP 5-fluorouracil 750 mg/m^2 every 4 weeks in addition to a continuous 5-fluorouracil intravenous infusion for 24 hr on day 1. Treatment was initiated within 4 weeks of surgery. A recent update of this trial reported a 40% disease-free survival at a median follow-up of 42 months. By historical comparisons, accepting the implicit criticisms of this approach, this treatment appears to impact favorably on the natural history of the disease. In the early part of this study, an unusual side effect of sclerosing capsulated peritonitis (SEP) was seen. This may have been attributable to administration of the cisplatin and 5-fluorouracil together in an alkaline environment, as when this was no longer performed, SEP was not noted.

Other IP trials have examined different drugs, e.g., mitomycin. Again, encouraging results have been reported. Using a charcoal–mitomycin C combination, given as a single dose in the immediate perioperative period, Hagiwara et al. noted a statistically significant survival difference in the treated group at 1.5,

3, and 5 years. The rationale for the combination is that the mitomycin is slowly released over a prolonged time period from the charcoal. Optimal effects have been achieved in the setting of small-volume microscopic disease.

Another innovative approach that has gained popularity in Eastern populations is the concept of continuous hyperthermic peritoneal perfusion (CHPP). This modality is used as an adjuvant post surgery or may be employed as a palliative treatment for malignant ascites. Mitomycin is a commonly utilized drug in this setting. Hamazoe et al. conducted a small randomized trial with CHPP of mitomycin C. Survival was unchanged, but peritoneal recurrences were reduced in the treated group (59% vs. 39%, $p = 0.08$). Yonemura et al. reported the results of their prospective randomized trial comparing surgical resection and intraoperative hyperthermic peritoneal lavage (IHPL) to resection alone in patients with advanced gastric cancer, they found a significant improvement in survival at 3 years (55% vs. 37%). In the West, CHPP remains an investigational option with no clearly apparent benefits over standard IP therapy.

RADIATION THERAPY

The rationale for radiation therapy in the adjuvant setting is based on the patterns of failure following potentially curative surgery. As seen with other gastrointestinal malignancies, the incidence of local/regional failure increases with increasing penetration of the tumor through the muscle wall and the presence of lymph node metastasis. Depending upon the method used for analysis, the incidence of local/regional failure as a component of failure following potentially curative surgery varies from 38% to 67%. The clinical method underestimates the extent and pattern of failure as it relies on physical examination, radiological studies, and in some patients, operative findings. In contrast, the reoperation method utilizing a planned 2nd-look operation at least every 6 months post operation picks up early asymptomatic recurrences. This method offers the most accurate appraisal of the anatomical distribution of failure but is no longer practical. The published patterns of failure data suggest that, even in the patients in whom a complete resection is performed, local/regional failure remains a significant problem.

Adjuvant Radiation Therapy

The seminal trial examining the role of postoperative combined-modality therapy in gastric cancer was reported by Moertel et al. in 1969 patients with advanced gastric cancers. Patients were randomized postoperatively to 40 Gy or 40 Gy plus 5-FU as a radiation sensitizer. There was a significant improvement in survival with the combination of radiation plus 5-FU. This improvement is consistent with the results obtained in other gastrointestinal malignancies such as esophagus, pancreas, rectal, and anal cancers in which the combination of radiation therapy plus concurrent 5-FU-based chemotherapy is superior to radiation therapy alone.

There are only two randomized trials of postoperative radiation therapy with or without chemotherapy following a ''curative'' resection. Virtually all of the other randomized as well as nonrandomized trials of postoperative radiation therapy or combined-modality therapy have included patients with residual disease.

In 1984, the results of a randomized trial from the Mayo Clinic of postoperative radiation (37.5 Gy) plus 5-FU versus surgery alone were reported. Although there was a significant improvement in survival in the patients who were in the postoperative combined-modality arm compared with the surgery-alone arm (23% vs. 4%), this improvement may have been due to the 10 patients who were randomized to receive the postoperative combined-modality therapy and refused. The 5-year survival of those 10 patients who refused the treatment was higher compared with the remaining 29 who were randomized to the treatment arm and accepted the treatment (30% vs. 20%). However, local/regional failure was decreased in the patients who actually received postoperative combined-modality therapy compared with those who were randomized to either surgery alone or refused the postoperative combined-modality treatment (39% vs. 54%). The second trial involves a subset analysis of a randomized trial by Dent et al. Limiting the analysis to the 30 patients with local/regional disease who underwent a potentially curative resection, they found that postoperative combined-modality therapy had a negative impact on 2-year survival compared with surgery alone. To date, the benefit of adjuvant radiation therapy remains an open question.

Given the moderate response rate seen with the combination of radiation-plus-5-FU-based chemotherapy in the advanced setting, a pilot study was performed by the Mayo Clinic/North Central Cancer Treatment Group. In this trial, patients with locally unresectable gastric cancer received 45 Gy plus concurrent 5-FU and Leucovorin. Based on this pilot study, a phase III Intergroup trial (INT 0116) has been activated. Eligibility includes patients with stages IB, II, IIIA, IIIB, and IV nonmetastatic adenocarcinoma of the stomach or gastroesophageal junction. Following an en bloc resection, patients are randomized to either observation alone or postoperative combined-modality therapy consisting of 45 Gy and four monthly cycles of 5-FU/Leucovorin. This Intergroup trial is one of the few in which adequate doses of 5-FU-based chemotherapy are delivered.

In summary, until the results of the Intergroup 0116 trial are available, the use of postoperative radiation therapy in the adjuvant setting remains investigational. In selected cases where adjuvant therapy is delivered, given the in vitro and in vivo evidence of 5-FU radiosensitization of radiation most investigators recommend the addition of 5-FU-based chemotherapy to radiation therapy.

Combined Systemic and Radiation Therapy

In reviewing the trials of combined-modality therapy it is clear that most have not used adequate doses of 5-FU-based chemotherapy. In general, patients have received 3–5 days of bolus 5-FU (350–500 mg/m^2 bolus) during the first and

sometimes the last 3 days of the radiation therapy. It must be emphasized that with this schedule, 5-FU is designed as a radiation sensitizer rather than as a systemic therapy. With regard to the dosing of radiation, in general, following a complete resection with negative margins, 45–50 Gy is recommended. Patients with residual disease require at least 55–65 Gy to achieve optimal responses, a dose that is beyond the tolerance of the stomach and small bowel.

In the study by Allum et al. from the British Stomach Cancer Group, an interim report revealed a significant decrease in local recurrence in patients who received postoperative radiation therapy compared with surgery alone (8% vs. 22%). In the final report with a 5-year minimum follow-up, there was no improvement in survival. It should be noted that in this trial, the chemotherapy was not delivered concurrently with the radiation therapy.

The Gastrointestinal Tumor Study Group (GITSG) performed two consecutive trials comparing combined-modality therapy versus radiation therapy alone in patients with locally unresectable gastric cancer. In the first GITSG study reported by Schein et al. almost 25% of patients who received the combined modality therapy either died or clinically deteriorated within the first 10 weeks of treatment. However, with further follow-up, there was a significant improvement in 4-year survival (18% vs. 6%) with combined-modality therapy compared with chemotherapy alone.

Due to the high incidence of early morbidity and mortality with this trial, the GITSG designed a replacement trial in which the combined-modality arm was modified. Modifications included the delivery of chemotherapy prior to receiving combined-modality therapy, the addition of Adriamycin, a rigorous review of surgical entry criteria, and radiation therapy delivered as continuous rather than split course. Patients were randomized to postoperative chemotherapy alone (5-FU/methyl-CCNU/Adriamycin) versus combined modality therapy. The incidence of grade 3+ toxicity varied from 52 to 59%. In contrast with the initial GITSG trial, combined-modality therapy in this modified GITSG trial did not improve survival.

In summary, the randomized data comparing postoperative combined-modality therapy versus surgery alone or postoperative chemotherapy in patients with locally unresectable disease are conflicting. The conflicting results may be explained, in part, by suboptimal doses of chemotherapy and radiation as well as the selection of poor prognostic patients who have unresectable disease.

Intraoperative Radiation Therapy

An alternative method of delivering radiation therapy is intraoperative radiation. The theoretical advantage of this approach is the ability to deliver a more intensive dose of radiation to the tumor bed while excluding the surrounding normal tissues from the high-dose field. The results of selected trials of electron beam intraoperative radiation (with or without external beam) are inconsistent.

In a limited randomized trial reported from the National Cancer Institute patients with grossly resected stage III or IV disease were randomized to receive either 20 Gy intraoperative radiation, or 50 Gy postoperative external-beam radiation. The mean time to local failure was significantly improved in patients who received intraoperative radiation (21 months vs. 8 months). In addition, the postoperative complication rate was lower (40% vs. 72%) and the median survival was higher (21 months vs. 10 months) in patients who received intraoperative radiation. None of these differences reached statistical significance.

In a phase II RTOG 8504 trial of intraoperative radiation with or without postoperative external-beam radiation 27 of the 43 patients who underwent surgery had local/regional disease and received a median of 13.75 Gy of intraoperative radiation. Postoperatively, 23 received an additional median of 45 Gy by external-beam radiation. No chemotherapy was delivered. Of the 27 patients, 27% had gross residual disease, 59% had stage III disease, 11% had stage IV disease. With a median follow-up of 19 months, the median survival was 19 months and the 2-year actuarial disease free survival was 27% and overall survival was 47%. The incidence of local failure, defined as failure within the intraoperative radiation field was 15% as the only site of failure and 37% as a component of failure. The results of patients with gross residual disease were not reported separately. Although significant postoperative complications developed in 15% of patients, only one developed an anastomotic leak.

In summary, the limited data suggest that intraoperative radiation may be beneficial in selected patients with gastric cancer. The optimal method by which to combine it with surgery and external-beam radiation has yet to be determined. At present, intraoperative radiation therapy in the treatment of gastric cancer remains investigational and should not be used outside of a protocol.

Palliative Radiation Therapy

Radiation therapy is an attractive and effective means of palliation. It provides symptomatic relief of symptoms such as bleeding, obstruction, and pain in approximately 50–75% of patients. Patients with favorable prognostic factors such as a high performance status, microscopic as compared with gross residual disease, and who received 5-FU-based chemotherapy tend to have a higher response rate. Overall, the median duration of palliation is 4–18 months. Borderline or nonoperative patients who present with obstruction or bleeding tumors are referred for radiation therapy.

SUMMARY

The survival of patients with gastric cancer will improve with earlier diagnosis and more effective adjuvant therapies. Earlier stages of gastric cancer can be detected and cured by resection if persistent symptoms (greater than 2 weeks)

are investigated in patients aged 55 or older. Patients with stages IA, IB, and II disease have a sufficiently long expected survival to avoid the need for entry into neoadjuvant or adjuvant treatment protocols at this time. However, patients with more advanced stages should be encouraged to enter active protocols as their prognosis remains very poor with surgery alone. Neoadjuvant approaches have placed a great deal of emphasis on preoperative staging. The accuracy of laparoscopy in detecting occult metastatic disease is currently unmatched by any other method of pretreatment staging. We now have the ability to select patients for definitive treatment without the need for laparotomy. Neoadjuvant chemotherapy with and without radiation has shown some promise and is being pursued further at several medical centers throughout the world including in the United States and Europe. It is unlikely that the treatment of gastric cancer will improve without the active participation of these and future protocols.

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4

Small Bowel Tumors

Michael Bouvet
The University of California at San Diego, San Diego, California

Nora A. Janjan and Lee M. Ellis
The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Dennie V. Jones, Jr.
Genentech, Inc., South San Francisco, California

INTRODUCTION

Incidence

Small bowel tumors are rare, which is surprising when one considers that the total length of the duodenum, jejunum, and ileum is much greater than that of the remaining gastrointestinal tract. One-third of small bowel tumors are benign and two-thirds are malignant. They comprise 1–3% of all gastrointestinal tumors and occur 36–60 times less frequently than malignancies of the colon. It was estimated that there will be an estimated 4900 new cases of cancer of the small intestine in the United States in 1997. These tumors occur most frequently in the sixth and seventh decades of life, with a slight male predominance. There are more than 1000 deaths annually in the United States from primary malignant small bowel tumors.

Predisposing Factors

Several hypotheses have been introduced to explain the low incidence of small bowel tumors. First, the transit time is more rapid in the small intestine than in the colon. Therefore, the effect of any carcinogen would be minimized. In addi-

tion, the proximal small bowel contains hydroxylases, which may detoxify carcinogens. There is also an alkaline environment in comparison to the relatively acid environment of the stomach and large bowel, where carcinoma is more prevalent. The relative lack of bacteria in the small bowel may provide protection by minimizing exposure to bacteria-produced potential carcinogens. Finally, the distal ileum contains increased numbers of immunoglobulin-secreting B cells as well as T lymphocytes, which may contribute to a local immune surveillance system.

Dietary fat intake has been correlated with the incidence of small bowel tumors in various countries around the world. Weekly or more frequent consumption of red meat and monthly or more frequent consumption of salt-cured smoked foods have been associated with a 2–3-fold increased risk of developing small bowel adenocarcinoma. Tobacco and alcohol use have not been correlated with an increased risk.

Epidemiological Considerations

Several groups of individuals are at increased risk of developing small bowel tumors. Duodenal and small intestinal neoplasms are associated with certain inherited disorders of the gastrointestinal tract including von Recklinghausen's disease (neurofibromatosis),familial adenomatous polyposis, Gardner's syndrome, and Peutz-Jeghers syndrome. Patients with chronic inflammation of the bowel, as in Crohn's disease, are at increased risk for small bowel adenocarcinoma. Patients with long-standing celiac sprue are more likely to develop both lymphoma and adenocarcinoma of the small bowel. Immunosuppressed patients are also at increased risk of developing small bowel neoplasia, especially lymphoma or Kaposi's sarcoma.

Presentation and Diagnosis

Although there are more than 35 different histological subtypes of small bowel tumors, some generalizations with regard to the presentation, workup, and diagnosis of these tumors can be made. Small bowel tumors can produce a variety of symptoms. More than 90% of patients with malignant small bowel tumors will develop symptoms prior to diagnosis, while fewer than half of patients with benign tumors will have symptoms. There is often a significant delay from the onset of symptoms to the time of diagnosis. Abdominal pain, nausea, vomiting, and distention may arise from bowel obstruction or intussusception. Gastrointestinal hemorrhage may occur secondary to an ulcerated lesion.

Physical examination findings are usually not helpful. The exceptions would be the occasional patient with carcinoid syndrome who presents with flushing and the patient with melanin spots on the buccal mucosa, as is seen in Peutz-Jeghers syndrome. A palpable mass is appreciated in less than 25% of patients with malignant small bowel tumors. Laboratory findings are usually non-

specific but may include mild anemia from chronic blood loss, an elevated 5-hydroxyindoleacetic acid (5-HIAA) level from a carcinoid, hyperbilirubinemia secondary to a periampullary lesion, or an elevated lactate dehydrogenase (LDH) level in the case of lymphoma.

Radiographic studies may be useful in the diagnosis of small bowel tumors. An abdominal x-ray series demonstrating obstruction in a patient who has not undergone prior laparotomy and does not have an incarcerated hernia should raise the suspicion of small bowel malignancy. An upper gastrointestinal tract barium study with small bowel follow-through or enteroclysis may help to define a point of obstruction or intussusception resulting from a small bowel tumor. A barium enema study with reflux into the terminal ileum may reveal a thickened, irregular lumen in case of lymphoma.

Computed tomography (CT) of the abdomen has been reported to detect small bowel tumors in 73–80% of patients. Several authors have described CT findings characteristic of small bowel tumors. Adenocarcinomas may appear as partially obstructing concentric narrowings in the proximal small bowel, most frequently seen with tumors more than 3 cm in diameter. Carcinoid tumors appear as homogeneous mesenteric masses and are often associated with characteristic stranding of the mesentery. Lymphoma is usually seen as thickened distal small

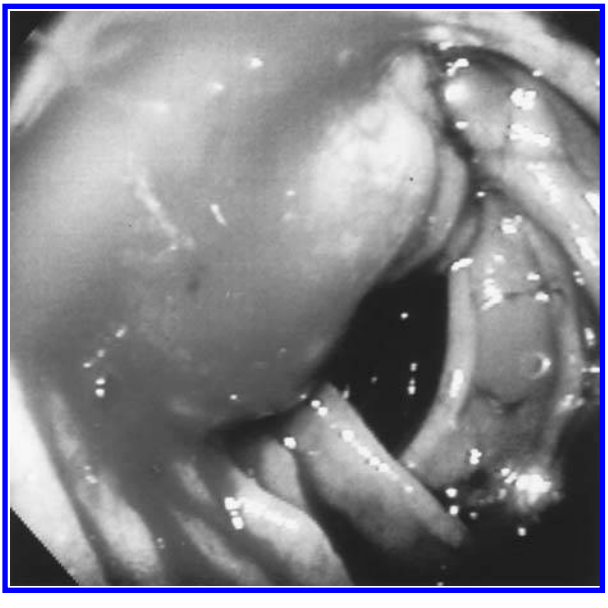


Figure 1 Submucosal leiomyoma of the proximal jejunum as seen on upper endoscopy.

bowel and is best detected when tumors are larger than 2 cm in diameter. Leiomyosarcomas are eccentric tumors of the middle or distal small bowel, with malignancy suggested by necrosis, ulceration, and size larger than 5 cm. Often these tumors will be associated with multiple intraperitoneal metastases. Lipomas are seen as a homogeneous, fat-density small bowel or mesenteric nodules.

Endoscopic evaluation of the small intestine is feasible. Three methods are used: push endoscopy, enteroscopy, and colonoscopy with intubation of the terminal ileum. Push endoscopy is the most commonly employed and involves the use of a long upper gastrointestinal tract endoscope or pediatric colonoscope to examine the small intestine beyond the ligament of Treitz. Push endoscopy has the advantages of using standard endoscopic techniques to directly advance the scope along the small intestinal lumen and standard endoscopic instruments to biopsy or snare abnormal areas (Fig. 1). Enteroscopy, a newer method, utilizes a 5-mm endoscope up to 9 ft in length with dual 1-mm-diameter internal channels. One channel is used to inflate a balloon along the side of the endoscope to permit peristalsis to carry the scope distally into the small intestine over time. The other channel is used to pass air into the small intestinal lumen during the examination but is too small to permit use of standard endoscopic instruments, precluding

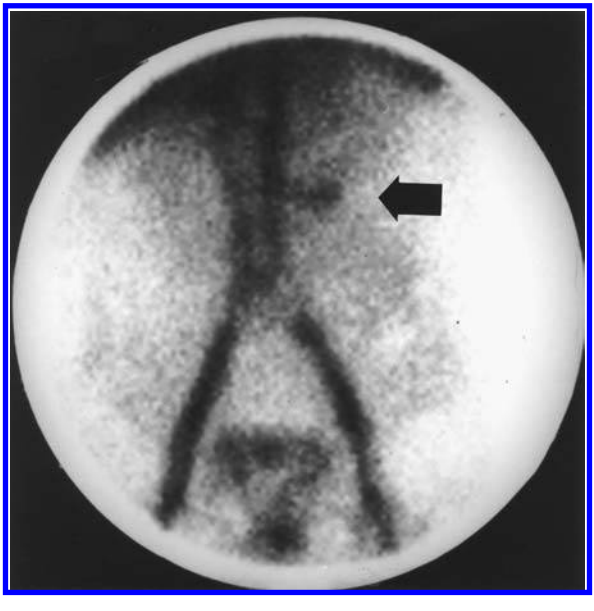


Figure 2 Technetium-99m-labeled red blood cell scan demonstrating bleeding in the proximal jejunum (arrow).

biopsy of small bowel tumors. Colonoscopy with intubation of the terminal ileum may allow diagnosis of distal small bowel lesions.

If a patient presents with bleeding believed to originate in the small intestine, a radiolabeled red blood cell scan may help to localize the lesion (Fig. 2). Angiography can also detect active bleeding from a small bowel tumor by extravasation of contrast material into the lumen of the small bowel.

SURGERY

General Remarks

Despite all the studies available to detect small bowel tumors, often the final diagnosis is not made until exploratory laparotomy. Surgical resection remains the primary mode of treatment for most small bowel tumors; however, there are several exceptions. Therefore, the surgical management of the most common small bowel tumors will be considered individually.

Malignant Tumors of the Small Intestine

Adenocarcinomas

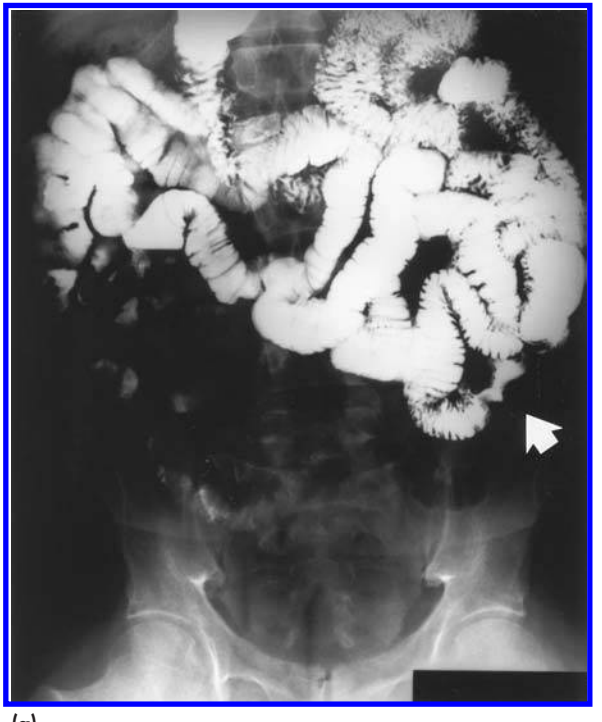
Adenocarcinomas comprise 44% of all small bowel malignancies (Table 1). These tumors are most common in the duodenum, but when they arise in association with Crohn's disease, adenocarcinomas tend to occur more often in the ileum. Signs and symptoms of obstruction are present in 50–75% of patients and of occult bleeding in 33–64% of patients. Although the diagnosis may be suspected on upper gastrointestinal tract barium study with small bowel follow-through or CT scan, histological confirmation is rarely made prior to laparotomy (Fig. 3). The primary tumor is staged according to its depth of penetration and involvement of adjacent structures or distant sites (Table 2).

Patients whose primary lesions arise in the first or second portions of the duodenum are usually treated with a pancreaticoduodenectomy, though there is no evidence of a superior outcome with this procedure compared to a segmental

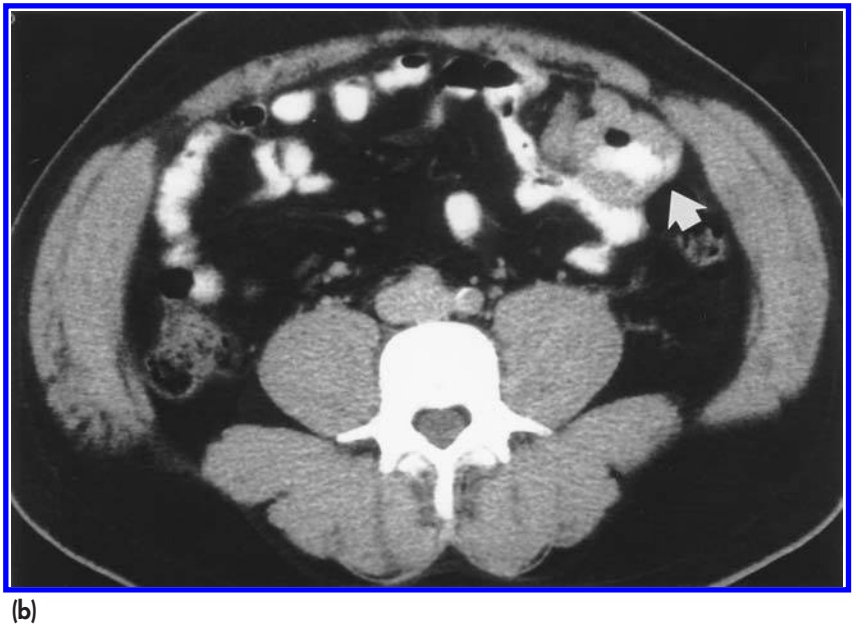
Table 1 Frequency Distribution of Malignant Tumors of the Small Bowel

Tumor type	Frequency (%)
Adenocarcinoma	44
Carcinoid	29
Lymphoma	15
Sarcoma	12

Source: Adapted from Coit, 1996.



(a)



(b)

FIGURE 3 (a) Upper gastrointestinal tract barium study with small bowel follow-through demonstrating proximal jejunal obstruction secondary to jejunal adenocarcinoma (arrow). (b) CT scan of a primary jejunal adenocarcinoma (arrow).

TABLE 2 American Joint Committee on Cancer TNM Staging System for Adenocarcinoma of the Small Bowel

Primary tumor (T)	
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through muscularis propria into the subserosa or into the nonperitonealized perimuscular tissue (mesentery or retroperitoneum) with extension 2 cm or less
T4	Tumor perforates the visceral peritoneum or directly invades other organs or structures (includes other loops of the small intestine, mesentery, or retroperitoneum more than 2 cm, and the abdominal wall by way of the serosa; for the duodenum includes only invasion of the pancreas)
Regional lymph nodes (N)	
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Staging	
Stage I	T1–2, N0, M0
Stage II	T3–4, N0, M0
Stage III	Any T, N1, M0
Stage IV	Any T, any N, M1

Source: Adapted from Beahrs et al., 1992.

resection in patients in whom a segmental resection is technically possible. A segmental resection is usually sufficient for patients with tumors arising from the third or fourth portions of the duodenum. Many patients with duodenal adenocarcinoma will have positive lymph nodes; therefore, curative resection should always include a regional lymphadenectomy. For patients with unresectable duodenal tumors who have biliary obstruction, endoscopic stent placement can provide palliation. If gastric outlet obstruction is present, gastrojejunostomy is appropriate treatment: surgical mortality is quite low (2.5%), as is morbidity, and long-term palliation may be achieved in some patients, with a mean postoperative survival duration approaching 8 months.

The prognosis of duodenal adenocarcinomas is determined by resectability, pathological status of the resection margins, histological grade, and presence or absence of lymph node involvement. The overall 5-year survival rate in most of the larger series is in the range of 20–35%. Patients with disease limited to the

mucosa and submucosa (stage I) have a 100% 5-year survival rate, while the 5-year survival rate for patients with tumor extension into the muscularis (stage II), through the serosa and/or to the regional lymph nodes (stage III), or to distant sites (stage IV) is 52%, 45%, and 0%, respectively. Patients with the good prognostic features of negative lymph nodes, negative surgical margins, well-differentiated or moderately differentiated histological grade, and primary lesions limited to the duodenum or ampulla have an actuarial 5-year survival rate of 80%; patients who lack these features have a 5-year survival rate of approximately 40%.

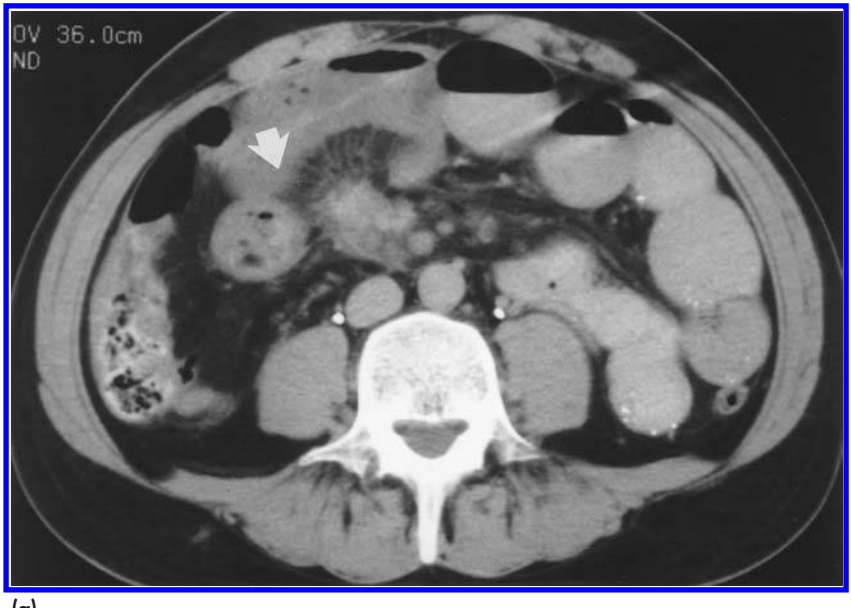
For adenocarcinomas in the jejunum or ileum, segmental bowel resection including lymphadenectomy is the treatment of choice. Most of these tumors are technically resectable, though lymph node metastases are common. As for more proximal lesions, the 5-year survival rate is 20–30%. Prognostic factors are similar to those for duodenal primary lesions: 5-year survival rates drop from 45–70% in patients with negative lymph nodes to 12–14% in patients with histologically involved lymph nodes.

Carcinoid Tumors

Carcinoid tumors represent 29% of all small bowel malignancies and are second only to adenocarcinoma in frequency. Carcinoid tumors are malignant neoplasms that arise from argentaffin cells. Eighty-five percent of carcinoid tumors occur in the gastrointestinal tract. After the appendix, the ileum is the second most common site of gastrointestinal carcinoids. Most carcinoid tumors are clinically silent and are discovered only during a laparotomy performed for other causes or at autopsy. Only 10% of patients with carcinoid tumors present with the carcinoid syndrome, which is usually associated with hepatic metastases. About 50% of patients will have elevated urinary levels of 5-HIAA.

Treatment of the primary lesion consists of wide resection of the tumor along with complete resection of the supporting mesentery (Fig. 4). Nodal metastases are unusual with tumors smaller than 1 cm in diameter but occur with 33–67% of tumors 1–3 cm and 75–90% of tumors larger than 3 cm. Since 30% of small bowel carcinoids are multiple and submucosal nodules may be present, a careful search of the remainder of the small bowel is mandatory. For those lesions that have metastasized, surgical debulking may still provide considerable palliation and prolonged symptomatic benefit. If hepatic metastases cannot be safely debulked, then patients may be treated with hepatic arterial embolization.

Carcinoids tend to be slow-growing and to metastasize late in their course, although patients with small bowel carcinoids tend to present with more advanced disease than do other carcinoid patients. Nevertheless, the prognosis for carcinoid tumors of the small intestine is considerably better than for adenocarcinomas arising from the same site. Five-year survival rates of 31–80% have been reported in some of the larger series. Prognostic features include tumor size, lymph node



(a)

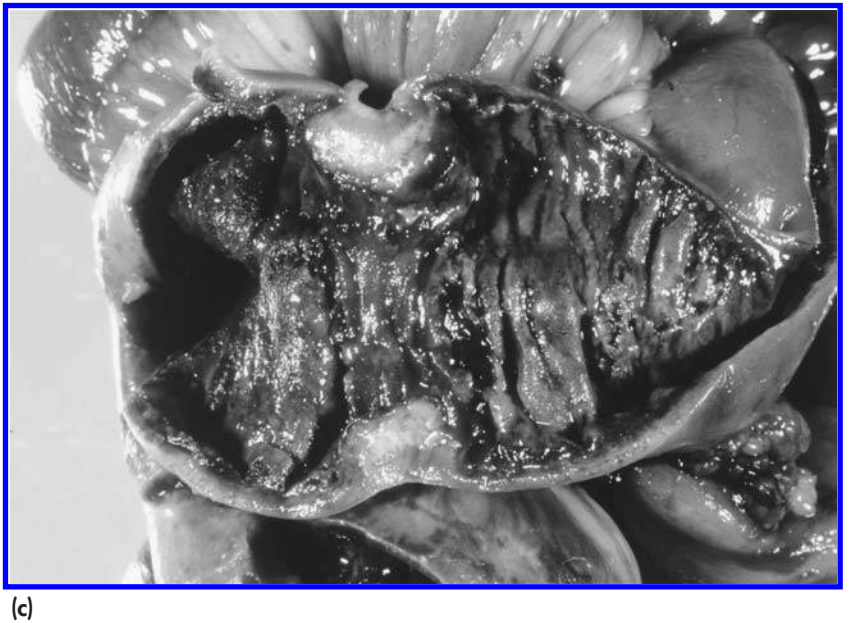
FIGURE 4 (a) CT scan of a small bowel obstruction secondary to carcinoid tumor (arrow) located in the terminal ileum. Note the stranding of the small bowel mesentery. (b and c) Resected specimen of ileal carcinoid tumor including associated small bowel mesentery.

status, patient gender, resectability, histological growth pattern, presence or absence of liver metastases, DNA ploidy status, and presence or absence of symptoms. Patients who undergo complete resection of localized disease have a 5-year survival rate of 75–94%; those with positive regional lymph nodes have a 5-year survival rate of 45–90%; and the 5-year survival rate of patients with liver metastases is 19–54%.

Primary Intestinal Lymphomas

Lymphoma of the small intestine may occur as primary lymphoma or, more commonly, as a gastrointestinal manifestation of systemic disease. In the West, primary gastrointestinal lymphomas account for only 5% of all lymphomas and 1–4% of all malignancies of the alimentary canal. Approximately one-half of Western gastrointestinal lymphomas originate in the stomach, slightly less in the small bowel, and a very few in the colon. Within the small bowel, the incidence of lymphoma increases at more distal sites, and the most frequent site is the ileum.

(b)



(c)

This incidence parallels the relative amount of lymphatic tissue in the wall of the small bowel at these locations.

Some authors have described primary gastrointestinal lymphomas as those in which involvement of the alimentary tract predominates or those with symptoms of gastrointestinal involvement upon presentation. More stringent guidelines include: (1) absence of palpable peripheral lymphadenopathy at the time of first clinical presentation; (2) no mediastinal adenopathy on chest x-ray; (3) a normal peripheral blood smear; (4) at laparotomy, involvement of only the esophagus, stomach, bowel, and/or regional lymph nodes (excluding retroperitoneal lymphadenopathy); and (5) no liver or spleen involvement except by direct spread of the disease from a contiguous focus.

Most small bowel lymphomas seen in Western countries are of B-cell lineage and of diffuse large cell type. In developing countries, particularly among people living in substandard hygienic conditions, a chronic lymphoproliferative disorder known as immunoproliferative small intestinal disease (IPSID) is quite common. A third type of small bowel lymphoma of note is enteropathy-associated T-cell lymphoma (EATCL). These primary gastrointestinal lymphomas represent a spectrum of distinct clinical entities with differing pathology and clinical behavior; thus, each will be considered separately.

Non-IPSID/Non-EATCL Primary Small Bowel Lymphomas. The most common presenting symptoms in primary small bowel lymphoma are abdominal pain and weight loss. More than 50% of patients will present with an abdominal mass, 20% with anemia, and 10% with intestinal perforation. The diagnosis of lymphoma can be made on the basis of a monoclonal lymphocytic infiltrate seen on endoscopic or percutaneous needle biopsy specimens, but surgical biopsy will frequently be necessary to determine the histological pattern of disease. A thorough workup should include a complete blood count with differential, measurement of serum LDH and alkaline phosphatase, hepatic and renal function studies, bone marrow biopsy, and chest radiography. An abdominal and pelvic CT scan should be done to assess extraintestinal involvement. Small bowel lymphomas are staged according to a modification of the Ann Arbor staging system (Table 3).

Surgery has been proven to be very valuable in the treatment of many primary non-IPSID, non-EATCL small bowel lymphomas, which by and large are focal in nature. Depending upon the size of the tumor and the bulk of the regional adenopathy, resection may be achieved in up to 80% of patients with a primary intestinal lesion. Evidence also suggests that surgical debulking prior to radiation therapy and/or chemotherapy, even in selected cases of stage III and IV disease, may increase survival. The increase in survival is due, at least in part, to the prevention of catastrophes during radiation therapy or chemotherapy; surgical resection of the tumor may prevent episodes of massive hemorrhage

TABLE 3 Ann Arbor Staging System for Non-Hodgkin's Intestinal Lymphoma

Stage I(E)[a]	Involvement of a single extralymphatic organ (i.e., intestine)
Stage II(E)	Involvement of a single extralymphatic organ (i.e., intestine) with involvement of one or more lymph node areas on one side of the diaphragm
Stage III(E)	Involvement of an extralymphatic organ (i.e., intestine) with involvement of lymph node areas on both sides of the diaphragm
Stage IV(E)	Diffuse or disseminated involvement of one or more extralymphatic organs

[a] (E) is used in Ann Arbor staging to denote extranodal involvement.
Source: Adapted from Beahrs et al., 1992.

and/or perforation (and thus avoid the need for emergency surgical intervention when the patient is leukopenic and thrombocytopenic). Furthermore, given that increased tumor bulk is an adverse prognostic variable, surgical debulking in and of itself appears to improve survival. In most cases, a multimodal approach is required, as attempts at curative resection alone have demonstrated less than optimal results, especially for aggressive types or diffuse lesions. While a staging laparotomy may be avoided by using other techniques during the initial evaluation of the patient, if the disease is found to be limited to the abdomen and/or to consist of a bulky mass, a laparotomy for resection should be attempted, with an aggressive approach taken to remove as much of the neoplasm as possible. If tumor is found in the resection margins, clips should be placed for future determination of radiation therapy portals. Should the lesion prove to be unresectable, its gross outline should be delineated with clips, and ample biopsies of all other suspicious lesions and of the liver should be taken.

Immunoproliferative Small Intestinal Disease. IPSID begins as a benign-appearing diffuse mucosal infiltration of plasma cells, and often it progresses to large cell immunoblastic lymphoma. IPSID has been reported predominantly in patients from the Mediterranean basin, with most of the cases being noted in Arabs and non-European Jews, Iranians, and South African blacks. Very few cases of IPSID have been reported from industrialized nations, and most of these have been in immigrants from regions where the disease is endemic. Although IPSID has been called ''Mediterranean lymphoma,'' the term has been discarded because the disease has been reported outside of this region, and because a lymphoma does not develop in all patients.

In contrast to other non-Hodgkin's lymphomas, which afflict patients irrespective of their socioeconomic status, IPSID effects mostly patients from lower socioeconomic strata. The peak incidence of IPSID is between the ages of 15

and 35 years; in contrast, non-IPSID lymphomas usually occur in the sixth decade of life.

The clinical picture in IPSID is distinct from that of other types of primary small bowel lymphoma. Most patients present with weight loss, anorexia, abdominal pain, and progressive diarrhea. The abdominal pain is often crampy and poorly localized. Severe anorexia may be reported and may be complicated by intermittent emesis. On physical examination, most patients are profoundly emaciated and are noted to have dependent edema and digital clubbing. Fever, abdominal masses, peripheral lymphadenopathy, hepatosplenomegaly, and ascites are uncommon until late in the course of the disease. *Giardia lamblia* is frequently isolated from the stool of patients with IPSID, but in some instances no infectious agent can be found.

Surgery plays little role in this disease other than in diagnosis and staging and in the treatment of rare abdominal catastrophes. As this disease involves virtually the entire small bowel, resection for cure is impossible. Some authors advocate resection of areas of bulky transmural disease prior to the initiation of chemotherapy to avoid a potential catastrophe, but such lesions are uncommon in IPSID.

Enteropathy-Associated T-Cell Lymphomas. The vast majority of gut-related lymphomas are of B-cell origin. Peripheral T-cell lymphomas, while frequently presenting in extranodal sites such as the skin (as in cutaneous T-cell lymphoma and the Sézary syndrome), rarely involve the gut at presentation. One exception to this is EATCL. First described in 1962, EATCL was initially termed ''malignant histiocytosis of the intestine''; however, the malignant cells have since been demonstrated to be of lymphocytic, not monocytic, lineage. EATCL most often develops in patients with previously diagnosed, long-standing celiac disease and/or dermatitis herpetiformis; EATCL may be diagnosed in 7–12% of such patients. As patients with celiac disease have a 50–100-fold greater-than-normal risk of developing lymphoma, some authors have suggested that celiac disease is a premalignant state. Occasional patients will present with EATCL and subsequently be noted to have mild or asymptomatic celiac disease.

EATCL is usually a high-grade lesion and, as such, progresses rapidly, with a poor clinical outcome. Most patients present with exacerbation of celiac disease, such as a worsening of the malabsorption syndrome and a loss of responsiveness to a gluten-restricted diet; nearly a quarter of patients will present with an intestinal perforation. The treatment of EATCL is difficult, at best. There is no evidence that a gluten-free diet will prevent the development of EATCL, and once a lymphoma has developed, patients often experience a worsening of what may already be a marginal nutritional status. Even though the Epstein-Barr virus may play a role in the etiology of a subset of EATCL, this relationship is not certain, and antiviral therapy of Epstein-Barr virus infections is ineffective at

present. Although the lymphoma tends to be localized in the jejunum, surgical resection for cure is precluded by the large area of gut involved and is reserved for emergency treatment of abdominal catastrophes.

Sarcomas

Sarcomas of the small intestine are unusual tumors comprising only 12% of all small bowel malignancies. Most are of smooth muscle origin (e.g., leiomyosarcoma, leiomyoblastoma). As with other small bowel tumors, patients can present with bleeding, obstruction, or perforation. The diagnosis is rarely made preoperatively. The outcome for patients with sarcoma of the small bowel is usually poor, with an overall survival rate of approximately 20% at 5 years. The prognosis depends on tumor size, histological grade, local invasiveness, and resectability.

The mainstay of treatment for leiomyosarcoma of the small bowel is complete en-bloc excision of the primary tumor along with any areas of direct extension (Fig. 5). Since lymphatic spread is uncommon, regional lymph nodes do not need to be included in the resection. Even in the face of extensive disease, local resection or bypass may offer considerable palliation. Isolated hepatic metastases may occasionally be amenable to resection or embolization, though this is very uncommon. Resection of isolated pulmonary disease results in a 5-year survival

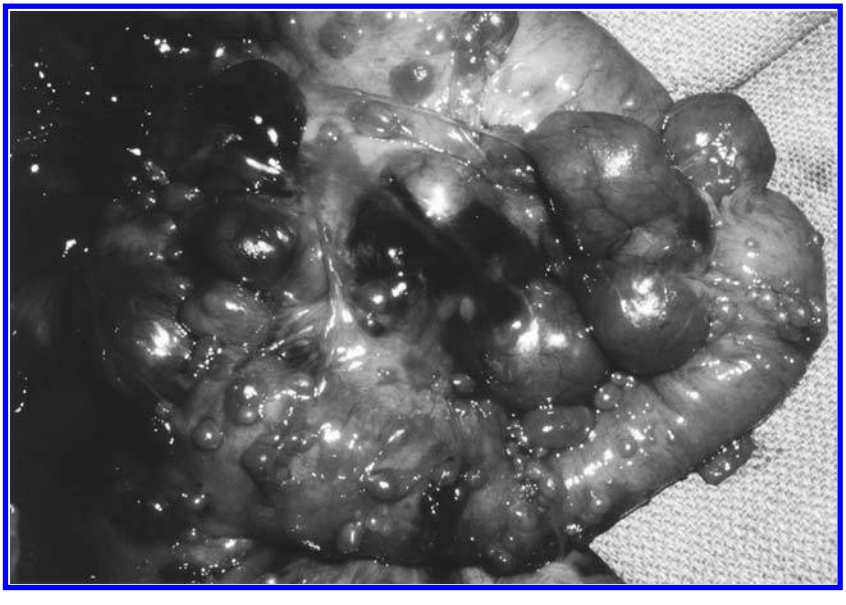


FIGURE 5 Resected specimen of leiomyosarcoma of the small bowel. Note the multiple intraperitoneal metastases.

rate of 20%. Following palliative resection, 25% of patients are alive at 5 years, and 6% at 10 years. In comparison, 50% and 35% of patients who undergo resection with curative intent are alive at 5 and 10 years, respectively.

Patients with small bowel leiomyosarcomas may present with multiple intraperitoneal metastases. In this case, surgical debulking may be helpful to palliate symptoms associated with abdominal distention due to tumor volume. Several investigators have attempted to treat this disease with intraperitoneal chemotherapy after surgery, but results of this approach have yet to be published.

Metastatic Disease

Metastasis to the small bowel may come by direct invasion or through the hematogenous, lymphatic, or transperitoneal routes. Metastases to the small bowel are seldom isolated. Obstruction and hemorrhage are frequent presenting symptoms. Surgical management includes resection, when possible, or palliative bypass. Surgical palliation is possible in approximately two-thirds of patients, even if obstruction is present at more than one level of the intestinal tract. Malignant melanoma is the most common extraperitoneal tumor that metastasizes to the small bowel (Fig. 6). Others include cancers of the lung (Fig. 7), breast, cervix, and kidney. Median survivals of between 4.5 and 8.5 months have been reported for patients who undergo small bowel resection for metastatic melanoma.

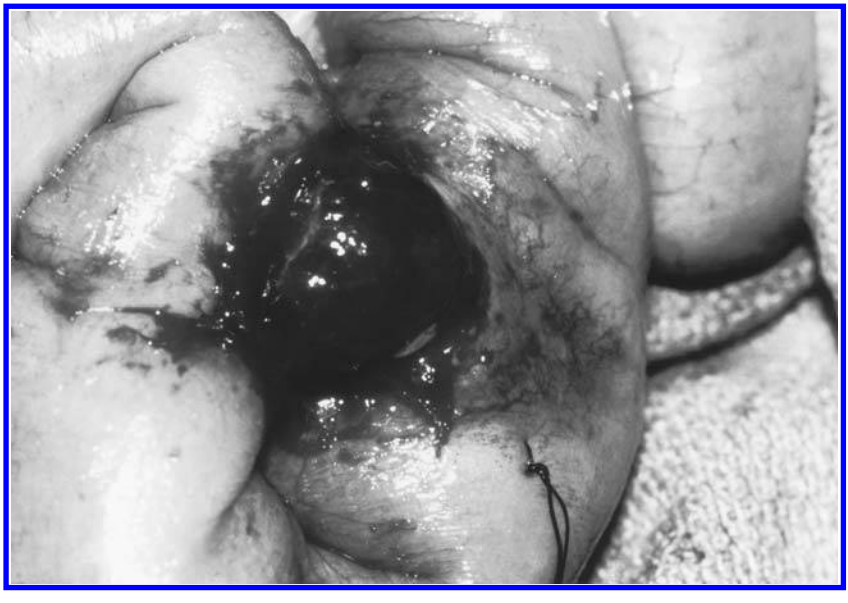


FIGURE 6 Intraoperative photograph of metastatic melanoma in the small bowel.

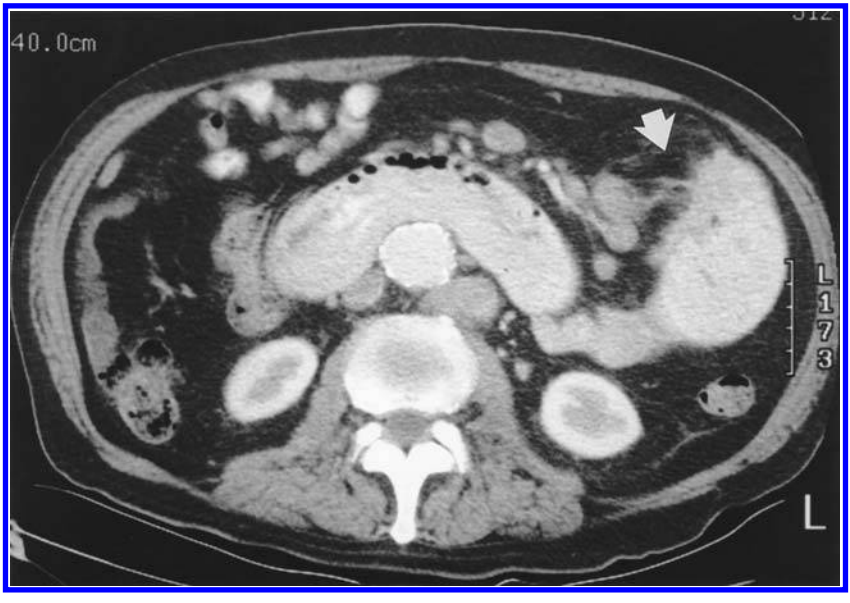


FIGURE 7 CT scan of metastatic lung carcinoma of the small bowel (arrow).

Benign Tumors of the Small Intestine

Leiomyomas

Leiomyomas of the small intestine account for 37% of all benign small bowel tumors (Table 4). Leiomyomas arise from smooth muscle cells and lack mitotic figures. These tumors may outgrow their blood supply and ulcerate, causing hem-

TABLE 4 Frequency Distribution of Benign Tumors of the Small Bowel

Tumor type	Frequency (%)
Leiomyoma	37
Adenoma	19
Lipoma	15
Hemangioma	10
Fibroma	6
Other	13

Source: Adapted from Coit, 1996.

orrhage. Obstruction is also common, and perforation has been reported. It can be difficult to distinguish between benign and malignant smooth muscle tumors, even with intraoperative frozen-section analysis. Owing to the difficulty of differentiating leiomyoma from leiomyosarcoma on frozen section examination, treatment should consist of segmental resection including adequate margins of normal tissue (Fig. 8). Extensive lymphadenectomy is not required since lymph node metastasis is unusual even for malignant leiomyosarcomas of the small bowel.

Adenomas

Adenomas of the small intestine can be divided into adenomatous polyps, villous adenomas, and Brunner's gland adenomas.

Adenomatous polyps are usually asymptomatic. They tend to be distributed in the proximal portion of the small bowel. They are frequently pedunculated and can be removed endoscopically if in the duodenum; otherwise, they should be removed by segmental resection. Of significance, cases of malignant degeneration have been reported.

Villous adenomas are often found in patients with familial adenomatous polyposis syndrome. These tumors are usually located in the duodenum and have a malignant potential that increases with the size of the lesion. Since their propensity for malignant degeneration averages 45%, lesions in the first and second

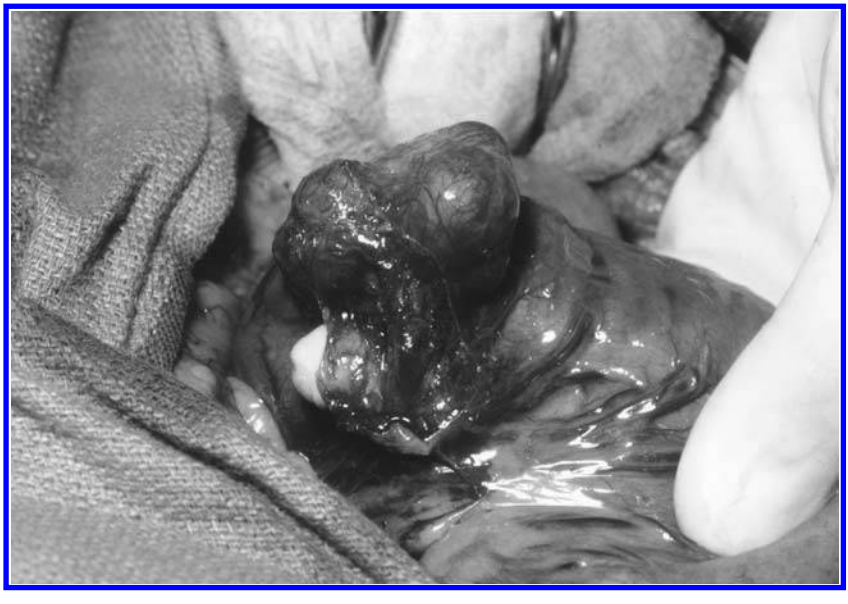


FIGURE 8 Intraoperative photograph of jejunal leiomyoma.

portion of the duodenum should be managed with pancreaticoduodenectomy. Lesions in the third and fourth portion of the duodenum can be managed with sleeve or wedge resection.

Brunner's gland tumors are extremely rare and arise in the proximal duodenum. The treatment of choice is endoscopic resection for pedunculated lesions or surgical resection for larger lesions.

Hamartomas

Hamartomas are small intestinal polyps that contain myoepithelial elements. Multiple hamartomas along with melanin pigmentation in the buccal mucosa, lips, and face is known as the Peutz-Jeghers syndrome, inherited as a single, dominant gene. Patients with hamartomas usually present in the second decade of life with bleeding and obstruction as a consequence of intussusception. The incidence of carcinoma is less than 3%. The treatment of these patients is conservative unless obstruction or uncontrollable bleeding occurs.

Other Benign Tumors

Less common benign tumors of the small bowel include lipomas, fibromas, and hemangiomas. Lipomas are usually asymptomatic and found at postmortem examination. Fibromas may be associated with neurofibromatosis. Hemangiomas can be found in individuals with Osler-Weber-Rendu disease.

RADIATION THERAPY

General Remarks

The role of adjuvant radiation therapy for small bowel tumors is largely undetermined owing to the rarity of these tumors and the wide range of clinical presentations. However, radiation therapy remains an important modality for palliation of small bowel tumors of all pathological types. Problems specific to radiation of the small bowel include mobility of the primary lesion and limited radiation tolerance of uninvolved tissues.

Adenocarcinomas

As for other tumors, radiation therapy can be used as an adjuvant to surgery or as primary palliative treatment of small bowel adenocarcinomas. Because of the sensitivity of the normal small bowel to radiation and the rarity of these tumors, the role of adjuvant radiation, administered either pre- or postoperatively, has not been clearly defined. Adjuvant radiation may improve local control following surgical resection that leaves microscopic residual disease, but overall survival

will likely not be affected because of the metastatic disease that develops at distant sites.

Adjuvant irradiation of small bowel tumors presents specific difficulties. Only the relatively nonmobile segments of the small bowel or fixed sites of tumor infiltration can be treated; this assures inclusion of the tumor in the treatment portal during delivery of daily radiation fractions. Furthermore, radiation toxicity is directly related to the total dose and the volume of tissue irradiated. For example, when preoperative radiation totaling 30 Gy in 10 fractions is administered for pancreatic cancers, the incidence of grade 3 toxicity is less than half that observed when 50.4 Gy in 28 fractions is given either pre- or postoperatively to the same treatment volume. Localized segments of the small bowel can tolerate doses of 45–50 Gy with conventional fractionation (1.8–2.0 Gy per fraction); however, tolerance to radiation is significantly less when large volumes of bowel are in the radiation field. Placement of a tube to administer supplemental enteral nutrition when high doses of radiation are prescribed significantly improves tolerance to radiation. The use of surgical clips to define areas, like the celiac region, found to be infiltrated by tumor and at high risk for microscopic residual disease is extremely important to help determine postoperative radiation portals and reduce radiation toxicity. Intraoperative radiation therapy permits administration of relatively high, localized doses of radiation that exclude uninvolved tissues and supplement the radiation given by external-beam therapy.

Palliative radiation can be of benefit in cases of unresectable or recurrent adenocarcinoma. Goals of palliative radiation include controlling blood loss, decreasing pain, and relieving obstructive symptoms. For these purposes, 30 Gy in 10 fractions is generally prescribed.

Sarcomas

Similar principles can be applied to radiation therapy for sarcomas of the small bowel. Adjuvant radiation may reduce the risk of local recurrence if negative surgical margins cannot be obtained because of tumor infiltration of adjacent structures. Effective palliation with tumor regression can be achieved with localized radiation.

Carcinoid Tumors

Information on indications for and principles of adjuvant radiation therapy for small bowel carcinoid tumors is lacking given the rarity of this clinical presentation. However, radiation has been shown to be of benefit in the palliation of unresectable disease.

Primary Intestinal Lymphomas

Unlike for lymphomas involving other sites of the gastrointestinal tract, the role of adjuvant radiation therapy for lymphoproliferative disorders of the small bowel is not well defined. Results have been equivocal. Phenotype, histological grade, disease stage, perforation, and surgical intervention are factors predictive of relapse, but the specific roles of adjuvant radiation therapy and chemotherapy at various stages of disease remain undetermined. Localized radiation combined with systemic therapy may be an option in early-stage disease with local infiltration of adjacent structures; however, such a recommendation awaits a clinical trial. Adjuvant chemotherapy has been advocated because of the extensive involvement within the abdomen and the risk for failure outside the abdomen seen with primary small bowel lymphomas. The doses of radiation used to treat intestinal lymphomas are low—usually 25–35 Gy at 1.5 Gy per fraction—because these tumors are highly radioresponsive and because the treated area is usually relatively large. Nevertheless, this dose of radiation and the volume of bone marrow treated are sufficient to affect bone marrow tolerance to chemotherapy. Whole abdominal irradiation has sometimes been used for small bowel lymphomas because of the mobility of the small bowel and the potential for disease extension within the abdomen.

Palliative radiation is highly effective in lymphoproliferative disease affecting the small bowel because of the low doses needed for this radioresponsive tumor. Symptom control is important in patients who present with advanced disease because even with unresectable disease, an overall 5-year survival rate of 25% has been reported.

Radiation Techniques

Radiation techniques are dependent on the tumor location and structures involved. The dose to adjacent critical structures, including the liver, kidneys, and uninvolved small bowel, must be considered. The radiation tolerance depends on the volume treated; if more than 50% of the liver, kidney, or small bowel volume is included in the field, the radiation dose must be limited to 25 Gy or less. This can be accomplished with beam angulation and weighting when localized radiation is used. For whole abdominal irradiation, thin blocks are placed over these structures to reduce the radiation dose administered with each fraction.

Complications

The toxic effects of radiation occur only within the area treated. Minimizing the volume of therapy can greatly reduce side effects. Side effects of radiation can occur either during treatment (acute) or months to years after completion of treat-

ment (late). However, the development or the severity of acute radiation reactions does not predict whether late effects will occur.

Rapidly proliferating tissues, like the mucosal surfaces, most commonly experience acute inflammatory effects. Acute effects of abdominal irradiation also include nausea, vomiting, and diarrhea. These effects are very predictable according to the treatment volume and dose administered.

Late radiation effects usually occur in tissues with limited proliferative capacity and are characterized by scar tissue formation. The late radiation effects associated with abdominal irradiation include radiation enteritis, bowel obstruction, radiation-induced pancreatitis, hepatitis, and nephropathy. These effects can usually be managed conservatively; however, surgical intervention may be required. Unlike with acute radiation effects, the time to development of late complications is extremely variable and unpredictable; late effects may be seen months or years after completion of therapy.

MEDICAL ONCOLOGY

General Remarks

Chemotherapy may be used in the treatment of disseminated small intestinal tumors or in the treatment of small bowel tumors that are not amenable to curative surgical resection. Specific chemotherapeutic regimens vary according to the pathological type of small bowel tumor; therefore, each type of tumor will be considered separately.

Adenocarcinomas

While it is clear that there are patients at risk who might benefit from adjuvant therapy, at present the routine utilization of adjuvant chemotherapy for adenocarcinomas of the small bowel cannot be supported. Data from retrospective studies indicate a possible role for adjuvant 5-fluorouracil-based chemotherapy; however, patients treated in such a manner should be enrolled in clinical trials. There are very few data on the use of palliative systemic chemotherapy, though physicians may justifiably offer a trial of 5-fluorouracil, with or without folinic acid, to these patients.

Carcinoid Tumors

Carcinoid tumors have the propensity to cause considerable morbidity by creating a syndrome of hormonal excess. Although the majority of carcinoids are hormonally inert, these neoplasms may produce excessive amounts of serotonin (from dietary tryptophan), prostaglandins, kinins (secondary to the release of kallikrein), and a variety of other hormones that may account for the carcinoid syn-

drome. The most common sign of the carcinoid syndrome is cutaneous flushing, which is often triggered by alcohol, catecholamines, or emotional stress and ranges in severity from a minor annoyance to profound vasodilation with near-syncope and hypotension. Diarrhea secondary to gastrointestinal hypermotility is also common; it is usually postprandial, though rarely of high volume, bulky, or foul-smelling. It may be associated with crampy pain, though other etiologies for such pain must be considered, including bowel obstruction due to tumor or mesenteric fibrosis. Patients also may develop bronchospasm, which may be mediated by histamine; bronchospasm is often associated with (though less common than) flushing. A late finding is right-sided valvular heart disease, although left-sided lesions may occasionally be noted. Fibrous deposits may lead to tricuspid insufficiency and/or pulmonary stenosis, though valve replacement is rarely necessary. Finally, if there is excessive shunting of dietary tryptophan from niacin to serotonin synthesis, patients may develop a triad of diarrhea, dermatitis, and dementia; however this is quite rare if patients can maintain a balanced diet. If diagnosed, this particular symptom complex can be treated with supplemental nicotinamide.

The management of carcinoid tumors consists of not only treating the bulk disease, in common with other solid malignancies, but also managing the complications of hormonal excess. The most active agent is the somatostatin analog octreotide acetate (SMS 201-995). Even though native somatostatin is effective in controlling many of the symptoms, its short half-life (less than 2 min) would necessitate a continuous infusion for this agent to be clinically useful. In contrast, octreotide may be administered subcutaneously every 8–12 hr, facilitating outpatient therapy. Octreotide is not only useful in managing the chronic problems of the carcinoid syndrome but also effective in the treatment of carcinoid crisis (volume-resistant hypotension), which may be precipitated by surgery or effective antitumor treatment. Octreotide is well tolerated, though long-term treatment may be associated with cholelithiasis, increased fecal fat excretion, fluid retention, nausea, and glucose intolerance. The median duration of symptomatic improvement with octreotide is 1 year. Other agents that have been used for symptomatic management include histamine H1 and H2 receptor antagonists, methoxamine, cyproheptadine, and diphenoxylate with atropine (Lomotil).

Because of their ability to affect the tumor biologically, both octreotide and αIFN have been evaluated as antineoplastic agents. In spite of its ability to improve the quality of life of many patients, octreotide has minimal tumoricidal activity, with response rates below 20%. However, octreotide may have a cytostatic effect on carcinoid tumors, and several studies have demonstrated disease stabilization in approximately half of treated patients; there is also a suggestion of a survival benefit. Likewise, αIFN can effect an objective response in about one-fifth of patients treated but appears to be cytostatic in the majority. As with octreotide, a potential survival benefit has been associated with αIFN therapy.

Carcinoid tumors tend to be resistant to most chemotherapeutic agents. Therefore, there are no standard regimens for the treatment of unresectable carcinoid tumors. Doxorubicin and 5-fluorouracil are considered to be the most active agents. As single agents, they produce response rates of approximately 10–25%; but complete responses are rare, and the median duration of response is usually less than 6 months. Combination chemotherapeutic regimens are somewhat more effective, with objective responses in 30–35% of patients; but response durations are less than 9 months. An anaplastic variant of carcinoid tumors may be more responsive to a combination of etoposide and cisplatin. Thus far, chemotherapy has demonstrated little impact upon patient survival. Therefore, because carcinoids are usually slowly progressive tumors and symptoms can be controlled with either octreotide or αIFN, chemotherapy is usually reserved until there is a loss of symptom suppression in the face of progressive disease.

Current directions of investigation include new somatostatin analogs, microencapsulated chemotherapeutic agents, and radiolabeled monoclonal somatostatin receptor antibodies, for the delivery of high doses of radiation directly to the tumor cells.

Primary Intestinal Lymphomas

Non-IPSID/Non-EATCL Primary Small Bowel Lymphomas

As may be surmised, the intensity and preferred modality of therapy for small bowel lymphomas are determined by the clinical stage of the disease. Patients with low tumor bulk (normal LDH and $beta_2$ microglobulin levels, tumor mass less than 10 cm in widest diameter, and only one anatomical site of involvement), low-grade tumor histology, no evidence of local or distant spread, and tumor penetration no deeper than the submucosa may be managed by conservative therapy, such as three or four courses of chemotherapy and local radiation therapy. However, most intestinal lesions will require resection, and the role of adjuvant chemotherapy or radiation therapy in this setting is unknown. If the disease cannot be controlled grossly by surgery, then radiation therapy will usually also fail, and chemotherapy is indicated.

The ideal chemotherapeutic regimen is the subject of intense debate, and the actual choice will likely be based on the experience of the medical team. Most evidence indicates that the most efficacious regimen will be an intensive anthracycline-based regimen, such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus bleomycin, MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin), or ProMACE-CytaBOM (prednisone, methotrexate, doxorubicine, cyclophosphamide, and etoposide; and cytarabine, bleomycin, vincristine, and methotrexate), which are utilized for nodal non-Hodgkin's lymphomas and other extranodal primary lesions.

Immunoproliferative Small Intestinal Disease

To date, there are no reports of large therapeutic trials for IPSID; however, a consensus has appeared among published reports. For the premalignant phase, most authors have utilized tetracycline, although metronidazole, with or without ampicillin, appears to be an effective alternative. Some patients may also require parenteral nutritional support. If a significant improvement has not been noted within 6 months or a complete clinical remission has not been achieved, an underlying lymphoma should be ruled out.

After the diagnosis of an IPSID lymphoma has been made, cytotoxic chemotherapy is warranted. Single-agent cytotoxic chemotherapy, such as with chlorambucil or cyclophosphamide, has been attempted with little success. In a randomized prospective study, combination chemotherapy with an anthracycline-based regimen, such as CHOP, produced a higher response rate (75%) than did C-MOPP (cyclophosphamide, mechlorethamine, vincristine, procarbazine, and prednisone) (50%) or whole abdominal radiation (63%). An alternative regimen that has demonstrated promising results consists of doxorubicin, teniposide (VM-26), cyclophosphamide, and prednisone (sometimes alternated with doxorubicin, bleomycin, and vinblastine). Some authors have noted that patients who received doxorubicin-based therapy experienced a significantly better outcome than those who received non-doxorubicin-based regimens.

Enteropathy-Associated T-Cell Lymphomas

Various combination chemotherapy regimens have been utilized for EATCL, and these tumors appear to be chemosensitive. However, responses are usually brief, and therapy is poorly tolerated owing to the malnourished state of most patients. To date, no carefully controlled study has been published that directly compares specific regimens in a population of patients with EATCL.

Sarcomas

Peritoneal and liver metastases are the most common causes of treatment failure in patients with small bowel sarcomas, and there is no evidence that adjuvant chemotherapy after complete resection diminishes this risk of relapse. Although patients with symptomatic metastatic disease can be treated with doxorubicin-based combination chemotherapy with response rates as high as 40%, a survival benefit has not been demonstrated.

CONCLUSIONS

Small bowel tumors are rare neoplasms that arise from a variety of cell types. They are often difficult to diagnose until laparotomy. The optimal treatment de-

pends on the histology and stage of the tumor and usually involves segmental bowel resection with or without lymphadenectomy. Although the role of adjuvant radiation therapy is not defined, radiation therapy remains an important modality for palliation of unresectable small bowel tumors. Chemotherapy may be used in the treatment of disseminated small intestinal tumors or in the treatment of small bowel tumors that are not amenable to curative surgical resection. The prognosis is excellent for benign small bowel tumors as well as some lymphomas and carcinoids. Survival rates are poor for patients with adenocarcinoma or sarcoma of the small bowel.

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5

Appendiceal Tumors

Mahmoud B. El-Tamer, Thomas P. Bradley, and Alan Schulsinger
State University of New York, Health Science Center in Brooklyn, Brooklyn, New York

INTRODUCTION

Tumors of the vermiform appendix represent less than 0.5% of all gastrointestinal malignancies and of all appendectomy pathology specimens. There are three distinct histological types: carcinoid, mucinous adenocarcinoma (or malignant mucocele), and colonic-type adenocarcinoma. Another variant of adenocarcinoma, termed adenocarcinoid, was recently added to this group. Their reported frequency and age at presentation are shown in Table 1. These histological variants have different clinical presentations, biological behavior, prognosis, and thus treatment. Appendiceal tumors are infrequently diagnosed preoperatively or during surgery. They usually present as an unexpected finding following an incidental appendectomy, or after an appendectomy for the clinical diagnosis of appendicitis. Hence, patients with appendiceal malignancies frequently require a second procedure for complete treatment. A synchronous or metachronous second malignancy is common in these patients (15–35%). More than 50% of the second malignancies are in the gastrointestinal tract, particularly the colon and rectum. Hence all patients with appendiceal tumors should be routinely evaluated and observed for a synchronous or metachronous second cancer.

The age-adjusted incidence for each histological type is 0.1 per 100,000 population. There is a higher percentage of carcinoid in women, probably as a result of the more frequent incidental appendectomies performed in this gender. The mean age of presentation of all appendiceal tumors is the fifth decade of life, but this varies with different histological types (Table 1). Few cases have been reported in the late teens. This chapter will cover mucinous cystadenocarcinoma and colonic-type adenocarcinoma of the appendix. Carcinoid of the appen-

Table 1 Histological Type, Frequency, and Median Age at Presentation of Malignant Tumors of the Appendix

Histological type	Frequency (%)	Median age (years)
Carcinoid	40.7	38
Mucinous adenocarcinoma	29.5	63
Colonic-type adenocarcinoma	28.9	65
Other	0.9	

dix will be covered in a different chapter. The etiologies of these entities are unclear, and are probably related to similar causative factors as in adenocarcinoma of the colon.

SURGICAL MANAGEMENT

Mucinous Cystadenocarcinoma

This entity is also known as malignant mucocele. The clinical presentation is usually subtle and nonspecific. The duration of symptoms is often prolonged. Abdominal distention, abdominal pain, abdominopelvic mass, inguinal hernia with mucin-containing sac, and appendicitis are frequent presentations. Preoperative evaluation includes a computerized axial tomogram (CT) and/or an ultrasound of the abdomen and pelvis. The CT scan may be completely normal or show either a mass with near-water density or ascites. The sonogram may show ascites or a right lower quadrant abdominal mass. Barium enema findings vary from nonvisualization of the appendix to a cecal mass, or an extrinsic compression of the cecum. Colonoscopy may demonstrate a mass in the cecum at the appendiceal orifice, but it is usually noncontributory. On abdominal exploration, 50% of patients have peritoneal spread with mucinous epithelium-lined cysts of various size and shape, containing a gelatinous and sticky substance. These cysts are adherent to the peritoneal surfaces of any organ and the omentum, hence the term ''pseudomyxoma peritonei.''

One must differentiate the benign form from the malignant variant as their treatments differ. Appendectomy is an adequate treatment of cystadenoma of the appendix, whereas the malignant variant (i.e., mucinous cystadenocarcinoma of the appendix) is more extensively treated. Rosai uses two criteria for malignancy: (1) invasion of malignant cells into the wall of the appendix, and (2) presence of epithelial cells in the peritoneal mucinous deposits, even if these cells are not atypical.

The disease seems to be localized to the peritoneal cavity. Visceral invasion of intra-abdominal organs or metastasis to lymph nodes draining the appendix is unusual, even with pseudomyxoma peritonei. The tumor is slow growing and spreads to other quadrants of the peritoneal cavity by shedding cells that will implant and grow (transcelomic), rather than through blood-borne or lymphatic metastasis. Most patients die as a result of locoregional disease rather than systemic metastasis. Hence, the philosophy behind managing this disease is concentrated on an aggressive locoregional multimodality treatment.

The surgical procedure for localized malignant mucocele of the appendix may be controversial and some authors advocate appendectomy alone as lymph node metastasis is infrequent. Patients who undergo a formal right hemicolectomy tend to do better when compared to those who had appendectomy alone (Fig. 1). This statistically significant difference in survival may be related to wider resection in the hemicolectomy group, or to patient selection bias. We advocate a formal right hemicolectomy for all patients with malignant mucocele, even if a second procedure is required. An aggressive surgical approach is also warranted in patients who present with pseudomyxoma peritonei. One should debulk all gross tumor in an attempt to render the abdomen free of disease, or to decrease the tumor load. It is advisable to resect the ovaries, particularly in postmenopausal females, as they may be concomitantly involved with cystadenocarcinoma in as high as 50% or more of the cases. The 5- and 10-year survival rate when the disease is localized to the appendix is 70% and 65%, respectively.

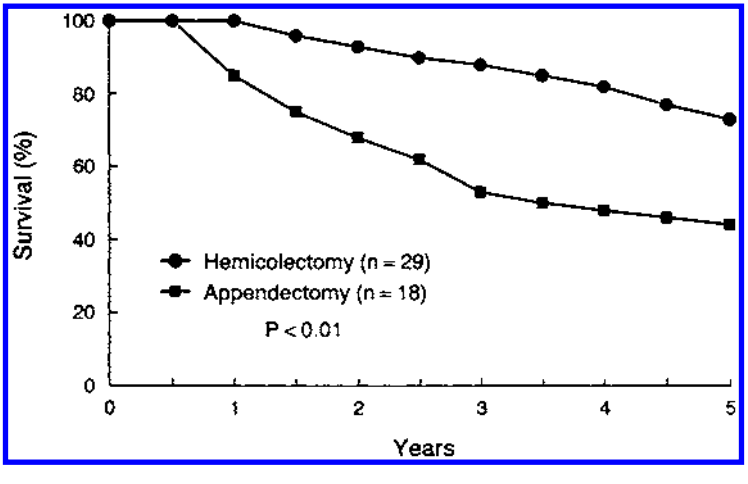

FIGURE 1 Actuarial survival of patients with malignant mucocele of the appendix based on hemicolectomy versus appendectomy. (From Nitecki et al., 1994, p. 54.)

With pseudomyxoma peritonei, the 5-year survival remains in the 50% range, if adequate cytoreduction is achieved.

Sugarbaker describes six defined peritonectomy procedures for pseudomyxoma peritonei: omentectomy and splenectomy, left upper quadrant peritonectomy, right subdiaphragmatic peritonectomy, subhepatic peritonectomy, lesser omentectomy with cholecystectomy, and pelvic peritonectomy. Each procedure is performed when the specified area is involved with disease. A single patient may undergo one or more peritonectomy procedures in one setting, depending on the extent of the disease. Some patients may require multiple debulking procedures if the disease recurs. Most of these procedures are performed with the ball tip electrocautery.

Omentectomy, Splenectomy, and Left Upper Quadrant Peritonectomy

Through a midline incision the omentum is detached from the colon. The peritoneal covering of the transverse mesocolon is elevated, exposing the pancreas. At the tail of the pancreas, the splenic artery and vein are ligated and cut, as well as the short gastrics. The spleen is resected from its bed. The omentum is detached from the stomach after ligation of the left and right gastroepiploic vessels. The peritoneum proper is stripped from the left upper quadrant. This is started at the left side of the abdominal wound, anteriorly. The peritoneum is freed from the posterior rectus sheath up to the diaphragm, exposing the adrenal and Gerota's fascia.

The right subdiaphragmatic peritonectomy is started from the right side of the abdominal incision. The peritoneum is elevated from the posterior rectus sheath up to the right diaphragm. The bare area of the liver is exposed. Frequently, a segment of diaphragm is resected with the peritoneum. The diaphragm is usually repaired primarily. Glisson's capsule is stripped from the liver into the subhepatic space to Morison's pouch. The right adrenal and Gerota's fascia are denuded of peritoneum. One must be careful at the level of the inferior vena cava and its branches to the caudate lobe.

Lesser Omentectomy and Cholecystectomy

The gallbladder is resected from the liver bed, after ligation of the cystic artery and duct. The porta hepatis is dissected, and the lesser omentum is resected. One must pay attention to the left gastric artery, as it is the sole blood supply to the stomach if the gastroepiploic arteries have been ligated. An antrectomy is performed with a gastrojejunostomy if the distal stomach is involved; otherwise a pyloroplasty is necessary for adequate emptying of the stomach, as the stomach may be denervated.

A pelvic peritonectomy is performed en bloc to clear the cul de sac. The peritoneum is elevated from the posterior rectus sheath anteriorly down to the

bladder. In women, the vaginal cuff is entered to perform a total abdominal hysterectomy and bilateral oophorectomy. The specimen is excised with the sigmoid colon from the rectosigmoid junction to the descending colon. A colorectal anastomosis is constructed to reestablish the continuity of the gastrointestinal tract. In men, the sigmoid colon is the only pelvic organ excised.

All quadrants of dissections are drained. A Tenckhoff catheter is left is the abdomen. Peritoneal dialysate fluid is instilled immediately postoperatively through the Tenckhoff catheter to limit intra-abdominal adhesions. This Tenckhoff catheter is utilized subsequently for the instillation of chemotherapy and may be utilized for radioactive colloid instillation.

It is unusual for a single patient to require all six peritonectomy procedures. Peritonectomy procedures are modified depending on the extent of organ involvement. If the spleen, gallbladder, and stomach are free of disease, they are spared. Resection of small bowel segments may be necessary. These peritonectomy procedures are lengthy and may be associated with major complications and organ dysfunction. Intraoperative bleeding could be a major risk, particularly when dissecting in the vicinity of the inferior vena cava. Postoperative small bowel adhesions and fistula formation are not infrequent. Leaks from the duodenal stump or anastomosis are issues of concern. These complications are more frequent in redo surgery.

Colonic-Type Adenocarcinoma

The appendix is lined by colonic epithelium, hence the similar potential for malignant transformation as in the colon. This entity is less frequent than cystadenocarcinoma. Most lesions arise in a preexisting adenoma that transforms into carcinoma and eventually obstructs the appendiceal lumen. The patients present with a clinical picture suggestive of appendicitis, frequently associated with perforation and a periappendiceal abscess. The diagnosis is made postoperatively in the majority of cases. Occasionally, some patients present with a right lower quadrant abdominal mass or intussusception. Preoperative evaluation, if performed, includes ultrasound or CT, which may show a mass in the area of the appendix. A barium enema will occasionally show nonfilling of the appendix. The lesion can occur in any part of the appendix, and has been reported to occur in inverted appendiceal stumps. The histological characteristics are essentially similar to those of adenocarcinoma of the colon.

The treatment of adenocarcinoma of the appendix follows the same principles as that of the colon. The main surgical procedure is a right hemicolectomy, including the lymph nodes draining that part of the intestine. When the lesion is confined to the mucosa, an appendectomy is usually sufficient. The more common clinical scenario is a patient, older than 50 years, who presents with signs and symptoms of appendicitis; an appendectomy is performed and the diagnosis of

adenocarcinoma of the appendix is made in the postoperative period. A right hemicolectomy should follow within a few weeks, even if the margins of resection are free of disease, provided the patient is medically fit for such a procedure. Patients with a ruptured appendix are at a high risk for local recurrence. One should attempt to resect all previous scar en bloc with the right hemicolectomy specimen. It may be advisable in certain cases to stent the right ureter to facilitate its identification during the right hemicolectomy. Applying hemoclips to the tumor bed is advisable to demarcate the area for possible postoperative radiation. We routinely remove the ovaries in postmenopausal women.

The muscular layer in the appendix is thinner than the colon, hence the more frequent presentation with subserosal infiltration or perforation of the serosa (T3 or T4 using American Joint Commission on Cancer Classification). The prognosis is similar stage for stage to adenocarcinoma of the colon. The crude 5-year survival is in the order of 50%, but it varies with the stage, grade, and surgical procedure. Patients with Dukes' stage A have almost a 100% 5-year survival, even when only an appendectomy is performed. The 5-year survival for Dukes' stage B, C, and D is 67%, 50%, and 6% respectively (Fig. 2). It is clear that patients who undergo a right hemicolectomy have a better survival when compared to those who have appendectomy alone (Fig. 3); 38% of patients are pathologically up-staged following right hemicolectomy.

Adenocarcinoid

In 1969, Gagne described three appendiceal tumors that displayed histological features of both adenocarcinoma and carcinoid. This variant is termed adenocarci-

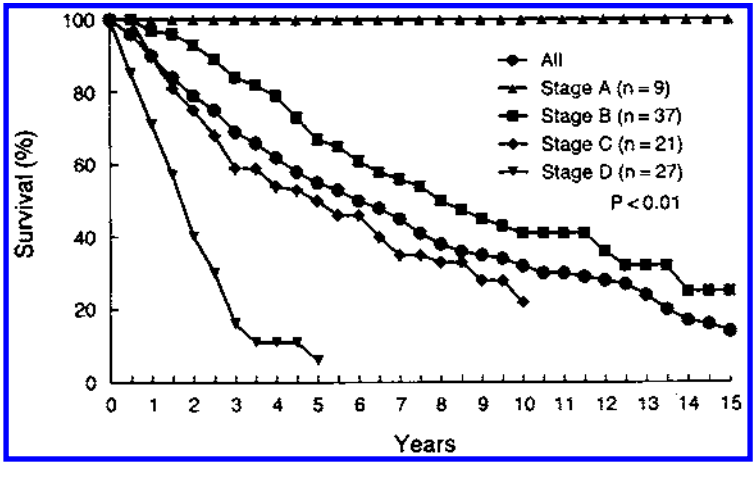

FIGURE 2 Actuarial survival of patients with adenocarcinoma of the appendix by Duke's staging (From Nitecki et al., 1994, p. 53.)

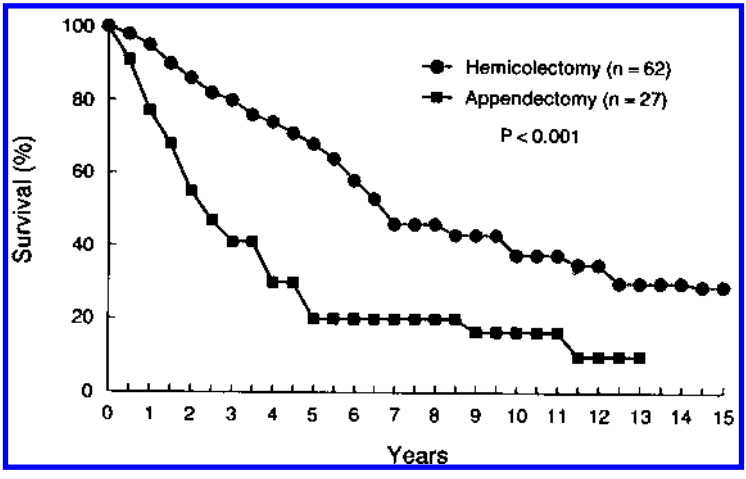

FIGURE 3 Actuarial survival of adenocarcinoma of the appendix patients by surgical procedures. (From Nitecki et al., 1994, p. 54.)

noid or goblet cell carcinoid. The cell of origin is unclear. The average age at presentation is 53 years, without any gender predilection. Patients most commonly present with a clinical picture of acute appendicitis, while others present with chronic abdominal pain, with or without a right lower quadrant mass. Occasionally the tumor is found following an incidental appendectomy. The tumor is smaller than 2.5 cm and is most frequently located at the tip, although some are located in the midportion or base of the appendix. Almost all diagnoses are made postoperatively. The extent of the surgical procedure required is a subject of controversy. Berardi recommends simple appendectomy for these tumors and reserves a right hemicolectomy for patients with one or more of the following criteria: (1) cellular undifferentiation; (2) increased mitotic activity; (3) involvement of the base of the appendix; (4) lymph nodes metastasis; (5) tumor diameter larger than 2 cm. Rutledge and Alexander advocate a right hemicolectomy for all patients, with oophorectomy in women. The prognosis of patients with goblet cell carcinoid is worse than for those with carcinoid of the appendix, but better than for those with adenocarcinoma of the appendix. The 5-year survival is approximately 75%.

Technical Considerations

If intraoperative radiation therapy (IORT) is available and its use indicated, the surgeon should mobilize adjacent normal structures such as the small bowel, ureter, and so forth out of the IORT field. Selection of cone size and shape as

well as radiation dose and energy of electrons selected is highly individualized, and is based on the characteristic features of the individual case.

The field arrangement for external-beam treatment will vary depending on the exact location of the tumor, but some general recommendations can be made. If surgical clips have been placed, a 2-cm margin around the clipped tumor bed should be sufficient for the initial 45 Gray (Gy) of treatment. If no clips are present to aid in tumor bed localization, larger margins may be necessary; this should be jointly determined by the operating surgeon and radiation oncologist. Small bowel contrast should be utilized to define the exact amount of small bowel in the radiation treatment field as seen on both anteroposterior and lateral radiographs. The patient is usually treated in the left lateral decubitus position, so that a maximal amount of small bowel will move out of the radiation treatment field and thus be spared. A total dose of 45 Gy in 1.8-Gy fractions should be delivered. If there is gross residual disease and normal tissue can be safely excluded, a 10–15-Gy boost should be delivered. The exact dose will vary according to the extent of residual disease and the ability of the radiation oncologist to exclude normal tissue.

MEDICAL ONCOLOGY

The role of the medical oncologist in the therapeutic approach to appendiceal carcinoma is poorly defined. Fluorouracil has been the mainstay of therapeutic interventions for tumors of the gastrointestinal tract for some time, and much has been learned about its limited efficacy. The use of bolus fluorouracil has been promoted for decades, and its antitumor effects are limited by its short primary half-life (6–20 min), owing to the high first-pass metabolism within the liver (80%). Use of this medication by continuous infusion has shown superior response rates in several reports. Studies of fluorouracil modulators have been performed, utilizing multiple agents in an attempt to improve upon the response rates of this agent alone.

Intraperitoneal administration of fluorouracil has been studied by several investigators. The drug concentration obtained can be as high as 300-fold the serum concentration, and owing to the lack of enzymes present for its metabolism, the effect may be present for a longer time. Experience with other agents in the intraperitoneal setting has been favorable in the treatment of other tumors.

Mucinous Cystadenocarcinoma of the Appendix

The approach to mucinous carcinoma is an unsettled area. As patients rarely succumb to distant metastasis in this tumor, the role of systemic chemotherapy is unclear. Several investigators have approached the treatment of pseudomyxoma peritonei with intraperitoneal chemotherapy, following the maximal surgical de-

bulking of the tumor. Most studies were performed in an uncontrolled setting. The use of intraperitoneal chemotherapy is based upon several potential advantages. These include the much higher attainable concentrations of drug at the site of tumor, as well as the lack of degradative enzymes that metabolize the medication.

Sugarbaker has published extensively regarding an aggressive approach to this tumor type, and his series encompasses the greatest experience in their management. The approach of Sugarbaker deserves further mention and analysis. At the time of surgical debulking, as described in the above section on the surgical approach, a Tenckhoff catheter is placed, and the abdomen in instilled with peritoneal dialysis fluid in the immediate postoperative setting. Early fluorouracil therapy is administered within peritoneal dialysis fluid over a 4–5-day period, and mitomycin C is similarly given. Studies have used several cycles of this regimen, and the data come from admittedly selected patients, without controls. Since this tumor is rare, and no one group has adequate numbers of patients to enroll in a randomized trial, information regarding the efficacy of this treatment approach must be extrapolated from phase II trials.

In 1995, Sugarbaker reported his phase II results of the aggressive cytoreduction technique followed by intraperitoneal chemotherapy for pseudomyxoma peritonei. This was a highly selected group of patients, and these techniques were utilized in only a small subset of patients with colorectal and appendiceal carcinoma. In these patients, the first dose of mitomycin C was given intraperitonealy, followed by intravenous use in subsequent cycles. Not surprisingly, those patients with grade I histology and negative lymph nodes had superior survival at an early analysis. Since the median survival of this low-grade malignancy is in excess of 5 years, any potential benefit of chemotherapy would not likely be seen at this early time interval. The inability of the grade I tumor to invade tissues and metastasize accounts for the long survival.

The intraperitoneal concentration of fluorouracil has also been reported in some studies, and the values were approximately 1500 μg/ml. This is more than sevenfold the concentration reported to be lethal to several in vitro cell lines established from colon carcinoma. It has been postulated that the mucinous material allows chemotherapy to diffuse along a gradient into the mass, or tumor cells. The retention of drug within the mucin may provide for prolonged exposure times, at high concentrations.

A paper from Memorial Sloan-Kettering reported a retrospective analysis of their experience with mucinous adenocarcinoma of appendiceal origin. Thirty-four cases were reviewed, spanning four decades. Ten patients received chemotherapy, and various regimens were used. In this small study, they concluded that there was no difference in survival of those patients who received surgery alone compared with those who received chemotherapy. They noted that four of seven patients alive at the time of this report had no evidence of disease (mean

follow-up, 6 years), and these patients did not receive chemotherapy, despite residual disease at the initial surgical debulking. This underscores the long survival and the poor documentation of any benefit of chemotherapy. The follow-up for these reports should represent patients who are followed for a significant duration of longer than 5 years, given the prolonged course of this disorder, with or without chemotherapy.

Adenocarcinoma of the Appendix

The approach to the patient with colonic-type adenocarcinoma should parallel the approach to colon cancer, with adjuvant therapy, consisting of fluorouracil and levamisole. Despite the absence of clinical data, the potential benefits exceed the risks, as the risk of systemic recurrence in appendiceal carcinoma of the colonic type is similar to that of colon cancer. It is not likely that firm data in support of this recommendation will be forthcoming. This is due to the low frequency of this disease, and the ethical concerns regarding the use of an untreated control arm, in view of the success of adjuvant treatment in colon carcinoma.

Treatment of Adenocarcinoid of the Appendix

In the case of adenocarcinoid, no clear recommendations have been published in the literature. This is a tumor of intermediate behavior, with a better prognosis than colonic-type cancer of the appendix and a worse prognosis than that of carcinoid. There are no data to support a recommendation of cytotoxic therapy; therefore, the approach to each case must be individualized. The presence of lymph node metastases portends a worse prognosis, but there is no published experience with the adjuvant regimens used in node-positive colon carcinoma. Randomized studies will be difficult to perform, owing to the rarity of this tumor. Local recurrence may be prevented by the use of radiation to the tumor bed, combined with fluorouracil as a radiosensitizer, and this approach seems reasonable at this time.

RADIATION ONCOLOGY

Mucinous Cystadenocarcinoma and Pseudomyxoma Peritonei

As previously mentioned, mucinous cystadenocarcinoma of the appendix is an aggressive locoregional disease. Systemic and lymph node metastases are infrequent. Based on these considerations, it follows that aggressive locoregional treatment is warranted. This approach must be tempered with the knowledge that most deaths are the result of small bowel obstruction or dysfunction, and thus any treatment modality that could compound these sequelae should be used with

caution. Appropriate adjuvant, postoperative, locoregional radiation therapies would include whole abdomen radiation (WAR) and intraperitoneal radioactive colloid instillation, such as radioactive phosphorous colloid (^{32}P).

We favor the use of postoperative intra-abdominal radioactive colloid instillation to WAR in patients with no gross residual disease, for the following reasons: (1) the deeper penetrating power of the external-beam radiation therapy (EBRTx) used in WAR would, in theory, seem to be unnecessary, as the deep lymphatic vessels and nodes are at minimal risk, (2) the less penetrating capabilities of radioactive colloid should be sufficient to treat the peritoneal surfaces where any residual cells are likely to be, and (3) WAR is associated with a higher complication rate, including bowel dysfunction and obstruction.

No controlled studies have established a curative advantage for any adjuvant postoperative therapy. Because of the minimal morbidity associated with use of intra-abdominal colloid therapy, one would intuitively guess that its use could be safely combined sequentially or concomitantly with intraperitoneal chemotherapy instillation. However, we have no experience with this combination, and thus this mode of therapy is a clinical research question that requires further investigation.

Patients with gross residual disease require management on an individualized basis. Treatment options include intraoperative radiation therapy (IORT), WAR, with localized EBRTx boost, or localized EBRTx alone, especially when the surgeon placed clips to demarcate the area of residual disease.

Technical Considerations for Radioactive Phosphorous Use

^{32}P is the radioactive form of phosphorous. It has a half-life of 14.2 days and emits only electrons (i.e., it is pure beta emitter). It can be combined with a colloid solution and delivered via intraperitoneal instillation. When administered in this fashion, a typical dose would range from 10 to 15 millicuries. Because it is a pure beta emitter, its effective range of penetration is very short, which makes shielding the patient from support personnel relatively easy. It is extremely well tolerated when delivered alone (i.e., without use of external-beam radiation). Given the limited penetrating power of ^{32}P, it should only be considered in the postoperative adjuvant setting in patient with mucinous cystadenocarcinoma who have no gross residual disease. In addition, there should be no intra-abdominal adhesions present, as this would possibly prevent the colloid from gaining access to potential sites of disease, and perhaps of greater concern, could allow the radioactive colloid to collect in a particularly sensitive region and overdose that region. For this reason, a technetium scan should be performed prior to ^{32}P use. A large volume of technetium colloid is instilled into the abdominal cavity, and a technetium scan is performed with the patient in various positions. The technetium should distribute evenly throughout the peritoneal cavity. After the techne-

tium colloid has been drained, the technetium scan should be repeated to make sure there are no remaining loculated collections of the technetium colloid.

Colonic-Type Adenocarcinoma

As previously noted, the majority of patients present with signs and symptoms of appendicitis. Thus, initially only an appendectomy is performed. This is inadequate tumor surgery in most patients. Hence, there is a significant risk of tumor contamination of the operative bed. Unless the operating surgeon is confident this is not the case, all such patients should be considered for postoperative radiation therapy to the tumor bed after right hemicolectomy. Patients with tumor adherent to adjacent structures, pathologically involved lymph nodes, and close or positive margins should also be considered for postoperative radiation therapy.

The major limitation to adjuvant radiation therapy is the tissue tolerance of the normal adjacent structures such as the ureter, small bowel, colon, and possibly the kidney, bladder, and rectum, depending on the extent of disease. The surgeon can minimize the risk to normal adjacent structures if he/she recognizes that adjuvant radiation therapy will be necessary. This is achieved by employing IORT, or by judiciously placing clips in the tumor bed so that the radiation oncologist will be able to better visualize the tumor bed in three dimensions; and thus exclude more normal tissue from the treatment volume. Clips should be placed at the lateral, medial, inferior, superior, anterior, and posterior boundaries of the local region considered to be at risk by the surgeon. Apart from exceptional circumstances, this will usually include the tumor bed alone, and not the draining lymphatics, as the surgeon can usually perform a satisfactory regional lymphadenectomy. However, if the tumor invades adjacent organs such as the bladder, the draining lymphatics of these organs should be treated with postoperative radiation therapy (i.e., with bladder involvement, the iliac lymph nodes should be treated).

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Colon Cancer

Harold J. Wanebo
Boston University School of Medicine, Boston, Massachusetts; and Roger Williams Medical Center, Providence, Rhode Island

Li Liu
Brown University School of Medicine and Roger Williams Medical Center, Providence, Rhode Island

Arvin S. Glicksman
Brown University School of Medicine, Providence, Rhode Island

SURGICAL RESECTION

The general principles of the surgical management of colon cancer are similar to those of other gastrointestinal cancers, with the focus on adequate removal of the primary tumor and its lymphatic drainage. The management of specific sites of the colon involves unique anatomical considerations, i.e., cecum versus transverse colon. Avoiding the pitfalls and complications unique to this surgery is integral to the management of specific problem areas of the disease.

The basic principles of resection are dictated by the site of the primary cancer. Cecal or ascending colon cancers require a full right hemicolectomy with removal of the mesentery served by the ileocolic, right colic, and midcolic vessels (Fig. 1). An extended right hemicolectomy is required for lesions closer to the hepatic flexure, and would include removal of the right and middle colic branches and the lymphatics in the mesentery serving the ascending colon and transverse colon to the splenic flexure. Splenic flexure lesions require removal of the ascending colon, the transverse colon, and the descending colon with the mesentery down to the junction with the sigmoid. This includes the vessels serving the ascending and transverse colon as described with additional dissection of the left

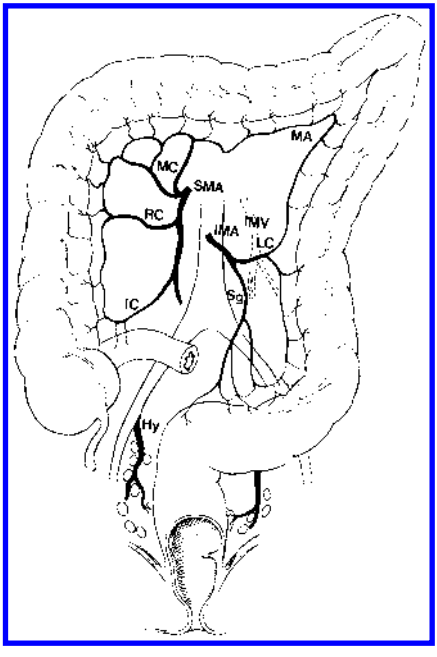

FIGURE 1 The arterial supply to the large bowel dictates the lymphatic distribution. Branches of the superior mesenteric artery (SMA) include the ileocolic (IC), right colic (RC), and middle colic (MC) arteries. The inferior mesenteric artery gives rise to the left colic (LC) and sigmoidal (Sg) branches, which terminate as the superior hemorrhoidal branches. The marginal artery of Drummond joins the SMA to the inferior mesenteric artery (IMA). The rectum is also supplied by the visceral branches of the hypogastric arteries (Hy). Each site represents a primary lymph node basin. (Figures 1–10 with permission from Enker, 1978.)

colic artery at its takeoff from the inferior mesenteric artery. A standard left hemicolectomy consists of removal of the descending colon down to the sigmoid (or may include the sigmoid in a radical left hemicolectomy). Most sigmoid cancers are managed by resection of the sigmoid colon and its draining mesentery with division of the inferior mesenteric artery at its origin on the aorta. The specifics will be discussed, but the basic concept is adequate removal of the bowel and its draining mesentery involved by the cancer.

Special Considerations

There are several philosophical issues that may impact on surgical management. The extent of the mesenteric resection and the value of no-touch technique will

be addressed in a discussion of resection of specific anatomical sites. Overall, although it is recognized that the mesenteric resection needs to adequately represent the drainage basin for the anatomical site, the use of extended resections beyond that mesenteric distribution is probably of no added value. Similarly, the no-touch technique as originally proposed by Turnbull and co-workers does not uniquely impact survival. The original concept was to minimize dissemination of malignant cells by not manipulating the primary lesion. The lymphovascular channels were ligated before the primary lesion was addressed. The concept was thought to improve survival rates for Dukes' C class lesions. Others, including Stearns in historical data reviews and Wiggins from clinical trial results, have examined this issue and demonstrated that wide-field resection rather than the unique effects of the no-touch technique were used in controlling the disease. Utilizing encircling tapes to occlude lumen of the bowel proximal and distal from the primary lesion and treatment of the wound edges to reduce implantation of malignant cells are considered by most surgeons, however, as practical ways of reducing recurrence. The utilization of intraluminal cytotoxic agents such as Dakin's solution or bichloride of mercury, or simply distilled water, as well as the use of iodized catgut, although of theoretical value, has not been demonstrated to be of benefit in clinical trials. A rational concept, however, suggests that careful attention to detail and utilization of techniques to reduce implantation on all wound edges, either of the bowel or abdominal wall, are prudent. The utilization of wound protectors to reduce implantation on wound edges, especially on the main incisional wound, is also important. This, again, has not been fully demonstrated in any clinical trial, but makes practical sense to minimize recurrence along the incision line—a formidable hazard to patients when it occurs. The effect of the wound healing on promoting tumor cell implantation and local recurrence is suggested from animal studies and merits further investigation.

Major issues include the identification of possible synchronous bowel lesions, which occur in 4–5% of the cases. In most cases, patients will have had a complete colonoscopy, but in the event that this was not done preoperatively, a colonoscopy at the time the patient is on the surgical table would make sense. This can be done using a prepared rigid scope (colotomy/coloscopy) or a flexible scope, which can be inserted via the edge of the bowel prior to or after resection. Careful use of drapes and plastic covers can obviate contamination. The potential of implanted disease at other sites also merits attention, with careful search for implantation such as peritoneal gutters or liver. Careful palpation of the liver even in the patient who has had a negative computerized tomography (CT) scan and a negative preoperative carcinoembryonic antigen (CEA) is very important. The resolution limits of the CT scan (about a centimeter) suggest that careful clinical examination augmented with intraoperative ultrasound, if available, to further assess the liver is important to adequately stage and manage the patient.

In the presence of demonstrated liver metastases, a plan can be made for either resection of the synchronous lesion or careful evaluation of the lesion with resection at subsequent surgery if it remains resectable. Other basic issues include the presence of ovarian metastases, which are found in approximately 7–8% of the cases. In many female patients who are past the childbearing age, permission for oophorectomy should be obtained to allow the surgeon to remove the ovary in the nonmenstruating woman (not only to avoid the metastatic potential at that site, but also to reduce the potential risk of a primary lesion for which the older woman is at risk).

Other issues include the demonstration of serosal implants by careful evaluation of serosal/serous surfaces, especially those around the liver, retroperitoneal gutters, pelvic floor, and suprahepatic diaphragmatic surfaces, which are favorite sites of implantation. Finding tumor here is indicative of Dukes' D tumor and further treatment of a palliative nature may be indicated.

Preoperative Assessment

All patients should have a careful preoperative assessment that includes a complete history and physical examination, an assessment of performance status and anesthetic risk, and notation of any special clinical conditions that warrant special care. The presenting symptom in colonic cancer may be cramping or colicky pain associated with complete or partial obstruction, melanotic or red blood per rectum, change in bowel habits, or the presence of an abdominal mass. High-risk features such as cardiopulmonary disease, chronic lung disease, past history of cardiac disease, hypertension, angina, requirement for cardiovascular medications, and history of thromboembolism need assessment. Male patients with obstructive uropathy may require evaluation. Strong histories of heavy smoking in patients with underlying cardiopulmonary disease may necessitate surgical delay to reduce smoking and make serious efforts to improve bronchopulmonary function under the direction of a pulmonologist, to minimize undue hazard to the patient and prolonged stay in the hospital. Baseline preoperative assessment in the older patient, including performance status, electrocardiogram, blood urea nitrogen, creatinine, and selected liver functions in patients with known liver disease, history of alcoholism, and so forth, may be necessary.

Clinical and radiological staging establishes stage of disease. The baseline assessment of the extent of disease should include a complete colonoscopy to eliminate second primary synchronous lesions, chest film to exclude pulmonary disease and identify the small percentage of those with pulmonary metastases, use of CT scan of upper abdomen (liver) in high-risk patients, i.e., those with large lesions or obstructing lesions, and pelvic CT in patients with rectal cancer. Determination of a preoperative CEA is frequently of value. Patients with CEA

levels over 20 should be considered at high risk for disease beyond the primary site and merit a careful CT scan of the abdomen including the primary disease site to exclude additional disease.

A careful pelvic examination in women to outline possible ovarian involvement or extension into the pelvis, even for colon lesions, should be considered a baseline requisite. A digital rectal examination even in the male patient with a colon lesion is performed to evaluate secondary extension into the pelvis and to evaluate for significant prostatic disease. A urological consultation at the time of primary surgery may be required, i.e., a cystoscopy, or placement of stents in patients with high-risk lesions impacting on the ureter.

Operative Technique

In patients with low-lying rectosigmoid tumors, the lithotomy position affords the opportunity for additional procedures, i.e., placement of the circular stapling unit, passing of the colonoscope under direct vision in selected patients, placement of ureteral stents, and an additional position for an assistant surgeon. For patients with right-sided or transverse colon lesions this position affords the opportunity of having an additional site for an assistant, as well as permitting access to the anorectum to perform on-table colonoscopy if necessary. The incision is a matter of surgical preference; whether midline or transverse incision, as suggested by some, is truly a matter of judgment of the surgeon. The placement of a wound protector once the abdomen has been opened and major adhesions taken down affords opportunity to protect the exposed surfaces of the wound and minimize chances for tumor cell implantation. The application of a self-retaining retractor facilitates necessary exposure for resection (right hemicolectomy). A lesion in the cecum, ascending colon, or hepatic flexure can be properly addressed by localizing the small bowel to the opposite side of the abdomen and packing with laparotomy tapes to ensure full access to the aorta, the right transverse colon, and the right side of the retroperitoneum with access to the right ureter in the ileocecal area. These maneuvers should be preceded by careful intraoperative examination with careful examination of peritoneal surfaces and palpation of the liver and pelvic structures, including the genitourinary structures in the woman. My own preference is to examine the mesentery of the right colon and transverse colon to make a determination of the planned line of resection in the mesentery (which can be marked out by incising the outer layer of the peritoneum) (Fig. 2). For a right-sided cecal lesion, the incision would extend from the left side of the transverse colon down to the level of the aorta and then along the aorta to the level of ileocolic vessels and then up to the line of the ileocolic vessels about 10 cm from the cecum. Resection of a cecal cancer would include approximately 10 cm of distal terminal ileum with emphasis more on the mesentery than on the luminal margin of excision.

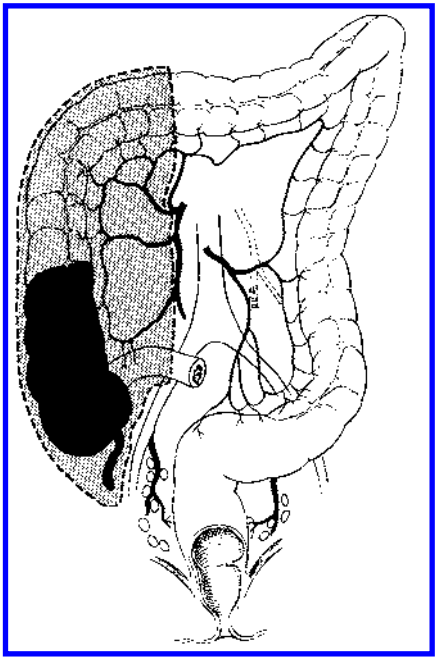

FIGURE 2 Anatomical limits of the right radical hemicolectomy. The site of the tumor is indicated by the solid area. The related resection surrounds the designated primary tumor. All vascular ligations are indicated at the true origin. Sufficient ileum is resected to clearly encompass the tumor and the entire ileocolic distribution.

Extended resections of the small bowel have consequences regarding vitamin B_{12} and folic acid absorption as well as bile salts, and greater resections are usually not indicated. Encircling the bowel with umbilical tape helps to minimize at least theoretical implantation of tumor cells. Those who practice the ''no-touch technique'' go through the steps of careful isolation of the ileocolic vessels, which can be carefully dissected in the root of the mesentery with care taken not to damage important structures such as underlying ureter, inferior vena cava, or superior mesenteric artery. Initial ligation of the middle colic artery and its vascular communication with the ileocolic, the right colic vessels, and the inferior mesenteric vein can be done in this fashion with very careful dissection in the mesentery.

Because there is little proof that the no-touch technique truly modifies the outcome and there is the potential hazard of vascular or ureteral misadventures, most surgeons proceed with the more classic isolation of the right colon by initially elevating the right colon from the right parities by incising the peritoneum

at the level of the terminal ileum and extending the incision more proximally along the abdominal wall up to the level of the duodenum. The initial incision can continue from the site of the terminal ileum that had been initially outlined, and by picking up the cecum at this level and dissecting the underlying structures carefully, one can identify the underlying ureter and colonic vessels. The right colon and its mesentery can be carefully dissected away with direct vision of the right ureter down to the level of the adjacent inferior vena cava and this dissection carefully continued until the right hepatic flexure is exposed and is prepared to be taken down. We frequently place a vascular loop around the ureter just to confirm its presence and have the ends fixed with a clip or small clamp to facilitate identification in the event that there is bleeding or to remind the operator doing final transection of the bowel that the ureter is close by.

At the level of the duodenum, the communication between the lesser sac can be carefully entered via a transparent opening in the gastric colic ligament. For proximal colon tumors, the resection of the omentum probably adds little oncological benefit, i.e., does not remove a significant drainage pathway for tumor cells, whereas for lesions more distal in the ascending colon, such as in the hepatic flexure, transverse colon, and splenic flexure, omentectomy probably has impact on adequate tumor removal. It is important to remove the omentum if there is identified seeding of tumor cells within the peritoneal cavity to minimize subsequent implantation on omentum and development of ascites. Once the lesser sac has been entered, one can carefully identify and protect the stomach and the transverse colon and continue bisection of the omentum between either clamps or ligatures clamping off the vascular arcades separating the omentum from its gastroepiploic vessel communication until one has reached the duodenum and the hepatic flexure. At this point, the hepatic flexure has been carefully mobilized from the retroperitoneum exposing the duodenum, the underlying inferior vena cava, and allowing full visualization of the arcades to the mesocolon. At this point, the site for incising the mesocolon near the middle colic vessels leading to transverse colon can be identified to allow removal of that portion of the mesentery with preservation of the left colonic vessel and facilitate the bisection of the right colic and ileocolic vessels. Pulling up on the colon will allow the surgeon to carefully identify the vascular arcades involved until one has carefully identified and bisected the ileocolic vessel and the right and mid branches of midcolic vessels. The site of the ligature should approximate the sites of the mesocolon that had been incised in a preemptory fashion (to ensure an adequate resection of the mesocolon). At this point, a stapler can be used to transect the ileum at the ileocolic level and the midtransverse colon and the resection is completed. The ileocolic anastomosis of the colon (near-splenic flexure) can be accomplished with either the stapler or suture technique.

A side-to-side stapled anastomosis with the terminal ileum to transverse colon can be accomplished by initially placing sutures near the mesenteric side of the terminal ileum and the transverse colon, which are positioned side by side,

and then placing sutures on the antimesenteric side to allow proper traction so that the linear stapler can be positioned to cut an adequate lumen. The site of the terminal ileum antimesenteric border and a similar site on the colon can be incised to allow placement of the stapler on the antimesenteric border either using the 60- or the 80-mm device (GIA stapler). The site of the placement of the stapler on its most proximal end can be formally closed with a second stapler transecting all of the devitalized tissue or with an end-firing stapler (TA50 device) with the extended end of the bowel formally excised with the knife. One then can easily place some sutures on the antimesenteric wall to prevent traction on the anastomosis. Openings in the mesentery are closed with sutures at this point.

The actual suture material is a matter of the surgeon's choice. For a hand suture closure, we usually use 2-0 or 3-0 mucosal or submucosal stitches, followed by carefully placed submucosal stitches with 5-0 silk. After any colon resection, the abdominal cavity is copiously irrigated with saline and in some cases distilled water to presumably lyse tumor cells (again perhaps to meet the preference of the surgeon, as there is no clinical trial proof of benefit of this method). Cleaning out the peritoneum with copious irrigation, however, is of value to remove blood clots, and any pieces of devitalized tissue and other material.

Resection of Transverse Colon

For lesions in the transverse colon an extended right hemicolectomy as described (Figs. 3 and 4) would include the area from the cecum to the splenic flexure. The splenic flexure needs to be taken down first by continuing the dissection of the gastrocolic omentum out to the spleen and transecting the omentum from the gastroepiploic arcade of the stomach (preserving the arcade to the stomach). Numerous attachments to the spleen must be carefully incised and, in some cases, suture-ligated to prevent tearing of the spleen. To the left side the lienocolic ligament can be incised along the line of Toldt, and with careful retraction, the splenic flexure (Fig. 5) can be retracted from the spleen. All adhesions to the spleen must be carefully incised by clamping and tying of small vessels to minimize any traction on the spleen.

Primary tumors at the splenic flexure may require a splenectomy for a very large lesion, or if there are obvious tumor attachments to the spleen. If there is no cancerous invasion, however, the usual anatomical attachments between the spleen and colon can carefully be taken down and the structures separated. For a splenic flexure lesion per se, either an extended right hemicolectomy, as shown in Figure 5, or a transverse colonic resection from the hepatic flexure to the sigmoid colon could be done with an anastomosis between the ascending colon and the sigmoid colon (Fig. 6). A full left hemicolectomy would include the middle colic and the left colic and the mesenteric vessel attachments to descending colon (Fig. 6). As described with the right colon, we would usually define the area of the mesentery to be excised by initially incising it after carefully

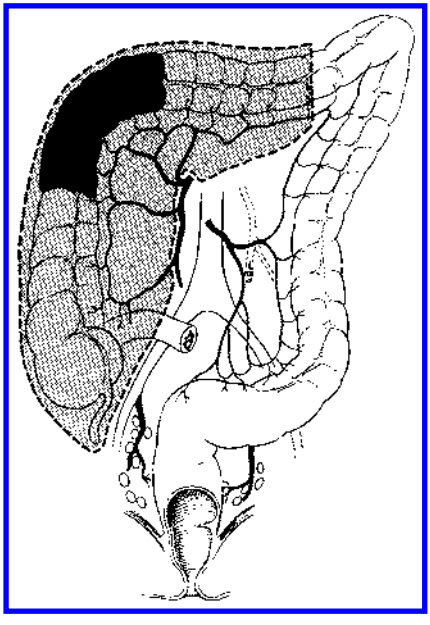

FIGURE 3 Extended right radical hemicolectomy allows for dissection of the middle colic artery at its origin from the superior mesenteric artery.

positioning the left side of the colon and packing off the right side of the colon so that the full mesentery can be visualized. In the case of a splenic flexure or a proximal descending colon cancer, a left hemicolectomy should be performed that extends from the midtransverse colon down to the root of the mesentery at the level of the ligament of Treitz and then continues along the aorta toward the level of the inferior mesentery artery (IMA), and then up to the level of the beginning of the sigmoid mesentery. The left colon can be mobilized by incising along the line of Toldt up to the splenic flexure and then taking down the various layers of the splenic flexure attachments including the lateral parietal peritoneum and the splenic attachments to the left colon as described above.

To avoid the possibility of injury to the left ureter, we usually mobilize the descending colon at the level of the splenic flexure, incise the parietal peritoneum of the sigmoid colon, and then carefully identify the ureter crossing the bifurcation of the iliac artery. A vascular loop can be placed around the ureter and attached to a hemostat or hemoclip for rapid access to it if necessary. The mesentery of the descending colon is carefully dissected at the level of the aorta with division of the inferior mesenteric artery (IMA) at its origin on the aorta, or preserving the root of the IMA and bisecting the left colic at its origin from

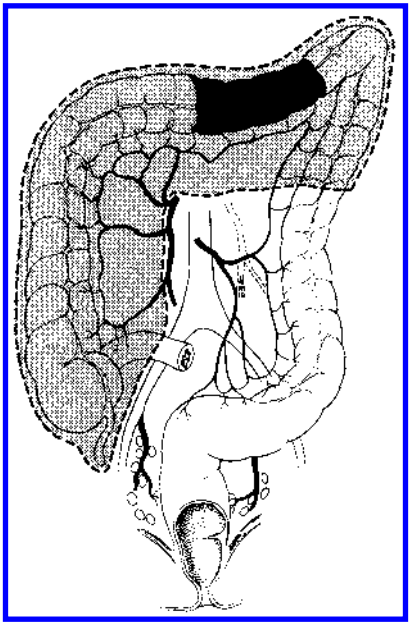

FIGURE 4 Lesions of the left transverse colon require wide mesenteric resection of the entire transverse colon together with the middle colic artery. The right colon is removed as a precaution to allow reconstruction by the safer ileodescending colon anastomosis.

the IMA. By picking up the colon and dissecting off the splenic flexure, one can then make final dissections of the vascular arcades. The left colic vessel can be taken at its origin from the inferior mesenteric artery, and its communicating branches to the sigmoid vessels can be maintained to ensure blood supply to the rectosigmoid. The watershed area between the sigmoid colon and the descending colon is a consideration, although rarely a clinical problem. Maintaining the IMA in this case does not take away from the oncological extent or effectiveness of surgery and maintains a good blood supply to the sigmoid and rectosigmoid. Following removal of the left colon again using staplers, the right side of the transverse colon can be reattached to the sigmoid. There is usually adequate mobility of both of these structures to safely perform an anastomosis using either the hand-sewn or the staple technique.

The more classic left-sided colon cancer in the descending colon will probably require a more extended resection including the full splenic flexure and the mesentery from the left side of the middle colic vessels plus the mesentery supplied by the left colic branch and continuing removal of mesentery down to the aorta, but preserving the IMA arcades supplying the sigmoid (Fig. 6). Sudeck's

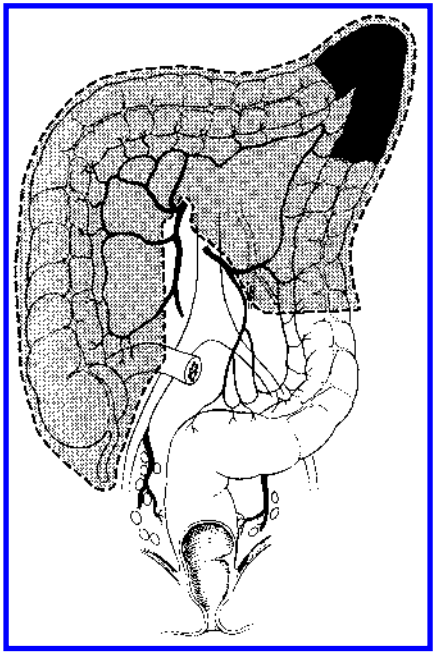

FIGURE 5 Lesions of the splenic flexure encompass the needs described in Figure 3 and 4 together with a dissection of the left colic artery. Reconstruction by ileodescending colostomy follows resection.

point describes the watershed between the sigmoid branches originating in the iliac vessels and the branches off of the IMA, which can rarely result in a devascularized segment (although this is unlikely, the sigmoid should be examined to ensure that there is adequate perfusion). At the completion of this resection, an anastomosis can be made between the transverse colon and the sigmoid, or in some cases the rectum, depending upon whether the tumor was near the sigmoid (in which case, the sigmoid resection should be included) or was located more proximally near the splenic flexure [in which case, a major portion (at least half) of the sigmoid and its mesentery can be maintained] (Fig. 7). In all of these cases, a primary anastomosis can be performed.

Primary cancers of the sigmoid are probably the easiest to resect (Figs. 7, 8). The sigmoid can be mobilized, and the mesentery incised along its serosal surface from the junction of sigmoid and descending colon to the aorta at the level of the IMA and from the rectosigmoid junction to the bifurcation of the aorta. The mesentery distal to the left colic vessels can be divided and ligated. One has to be very careful about the left ureter and gonadal vessels. Again, by

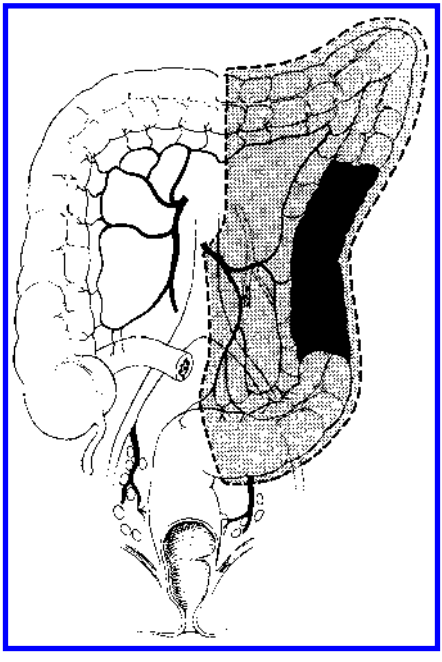

FIGURE 6 Left radical hemicolectomy is classically performed for lesions of the descending colon.

pulling up the sigmoid, one can incise the mesentery along the serosal surface overlying the mesentery down to the aorta, along the aorta to the bifurcation and extending from the bifurcation along the rectosigmoid vessels to the rectum. This will provide for adequate resection of the mesentery. An occasional sigmoid cancer will be attached to the midrectum, and because of its bulk may require an abdominoperineal resection to permit a curative resection (Fig. 9). Preoperative radiation would greatly facilitate resection by reducing bulk and lessening the chance of recurrence.

Complications of the Carcinoma

The major complications include obstruction, perforation, extension to adjacent organs, and associated metastases to the liver or peritoneum. Secondary complications to other organs include tumor extension or metastases that obstruct the ureter, lesions extending to major organs such as the pancreas, duodenum, and liver, or the full manifestations of advanced disease including ascites, multiple peritoneal implants, and multiple sites of obstruction.

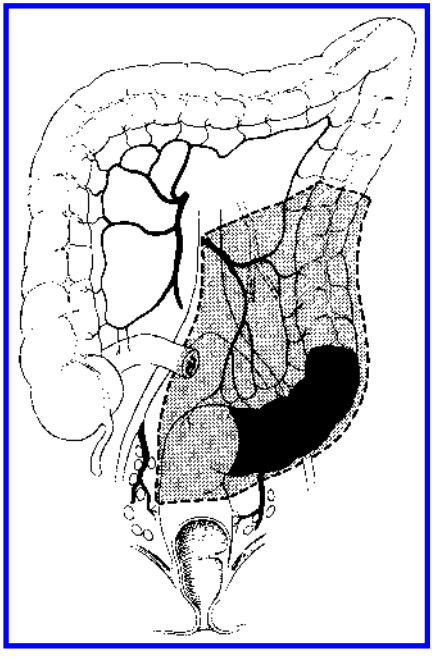

FIGURE 7 Some tumors of the sigmoid can be resected by high ligation of the inferior mesenteric artery and wide sigmoid resection.

The preoperative assessment will usually demonstrate the potential risks of obstruction so that appropriate planning can be undertaken. If a preoperative assessment shows a partially obstructed lesion of the colon, frequently the patient can have a very careful bowel prep with gentle cathartics, i.e., Haley's MO, or use of colonic irrigations or occasional mild purgatives to allow for a gentle cleanout with an antibiotic bowel prep to permit a resection and primary reconstruction. For an obstructing right-sided colon cancer, the accepted treatment of choice is resection and primary anastomosis involving the proximal or transverse colon (with an ileocolic anastomosis). Left-sided cancers involving the descending colon or sigmoid may require a subtotal colectomy with an ileorectal anastomosis. An isolated descending colon or rectosigmoid cancer in the younger patient may require special consideration. Although primary resection with ileorectosigmoid anastomosis is a relatively safe approach, other considerations would include resection with proximal colostomy and/or Hartman procedure. Some authors have recommended resection of the primary cancers with on-table lavage and primary anastomosis. In some instances, this may be associated with slightly improved outcome in 5-year survival in patients treated by primary resec-

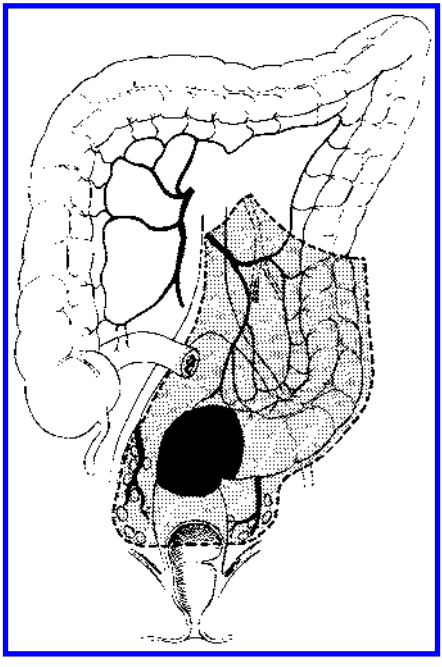

FIGURE 8 Lesions of the rectosigmoid are treated by low anterior resection. Note incorporation of the hypogastric lymph node dissection in addition to the mesenteric dissection, which begins at the origin of the inferior mesenteric artery.

tion as opposed to staged resection, but there may be a price of higher operative mortality. Other considerations are the use of an intracolonic bypass or primary resection with anastomosis and proximal diversion. Kronborg conducted a randomized trial comparing the traditional staged procedure with initial transverse colostomy followed by curative resection and subsequent colostomy closure with immediate resection and colostomy with subsequent anastomosis. There was no difference in mortality or survival between these two treatments.

A reasonable approach in the well-selected patient who is in good clinical condition would be to cleanse the bowel distal to the obstruction and perform a primary anastomosis between the ileum and the sigmoid colon. In the younger patient, consideration of preserving more of the colon proximal to the obstruction might prompt the performance of a primary resection with on-table lavage of the distal and proximal segment and primary anastomosis in the same procedure, but with a temporary loop ileostomy. Certainly in the high-risk patient, a staged procedure with an initial colostomy with resection of the involved colon (with or without anastomosis) followed by subsequent colostomy takedown may be

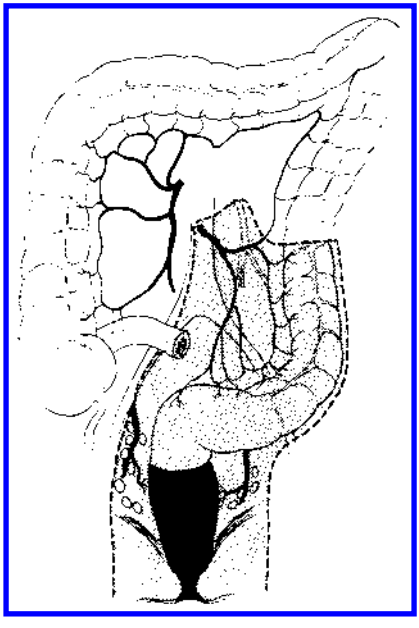

FIGURE 9 Abdominoperineal resection adds wide resection of the rectum and the levator ani to the same landmarks used in low anterior resection. Again hypogastric lymph node dissection is a vital element in the conduct of the operation.

indicated. Potential use of a laser to recanalize an obstructing carcinoma is appropriate for low-lying rectal cancers although less applicable and more hazardous in patients with obstruction of the colon. Another consideration for low-lying, obstructing left-sided or rectosigmoid cancers is the concept of performing a defunctionalizing colostomy or ileostomy and then treating with radiation and subsequent resection with primary anastomosis and takedown of the ileostomy or defunctionalizing colostomy at a subsequent date. In all instances, the primary concern should be to utilize the most effective procedure for the patient depending on the patient's functional status, the extent of disease, and potential for long-term survival with efforts to minimize morbidity.

Perforation

In the event of a free perforation of the carcinoma itself, an effort should be made to resect the perforated bowel with defunctionalization of the distal segment and a proximal colostomy. The distal colon may be brought out as a mucus fistula or closed as a Hartmann pouch. Resection of the perforated segment and performing a colostomy or a loop ileostomy would be the most reasonable approach. A secondary perforation of the right colon from an obstructing left-sided carci-

noma might include a resection and ileosigmoidostomy in the presence of limited peritoneal contamination.

Bleeding

Massive bleeding from a colon cancer is very unusual. In the event of this occurrence, the cathartic effect of the bowel probably cleans out the colon so that a resection and primary anastomosis can be done. Again, management should be dictated by the functional status of the patient and the risks of any ensuing morbidity from the procedure. It is always safer to come back another day if the surgeon is in doubt of a planned primary resection and reconstruction as opposed to a resection with a diverting ileostomy or colostomy.

Involvement of Adjacent Viscera

In patients with primary colon cancer, attachments to associated viscera occur perhaps up to 10% of the time. It is recommended to resect a portion of the attached organ and not to separate the adhesions, which may contain cancerous cells. Although occasionally these adhesions are inflammatory, the fact that they frequently involve lymphatic communications with the primary cancer suggests that the wisest maneuver is to remove the cancer and portion of the attached organ. The extent of the secondary organ resection would be dependent on the amount of involved area, the status of the patient, and technical issues regarding the organ and region to be resected. Areas of concern would be extension of the transverse colon cancer or perhaps even sigmoid cancer onto the duodenum or onto the pancreas. In such cases, a resection requiring a Whipple procedure may not be well tolerated by the patient. Another option would be to perform a bypass procedure, to administer radiation to the site, and to return subsequently for resection. Involvement or extension of the tumor to the bladder is frequently amenable to local en bloc resection of a portion of the bladder. A tumor attached to the dome of the bladder, which can be easily resected, has far different consequences than invading rectal cancer involving the bladder near the trigone.

Operations in the Face of Extensive Disease

Occasionally the surgeon is surprised by more extensive disease than anticipated from the initial workup. Even in patients with normal radiological imaging, normal CEA values prior to surgery, and an otherwise normal examination, extensive disease may be present. In such patients, the extent and type of advanced disease will have an impact on its treatment. In the event of metastatic liver disease, lesions that are unilobar or even bilobar, but limited, may be resectable. In such cases, it may be wise to resect the primary colon cancer and then to reimage the patient with subsequent treatment of the liver disease. Management of liver metastasis could include resection or performing a palliative maneuver, e.g., he-

patic artery cannulation and infusion. In the event that there is more extensive liver disease, one should just resect the primary tumor and consider the patient for a palliative protocol. In the event of ascites, a primary resection may be possible with perhaps a more limited resection. It is wise in both of these cases to avoid colostomy. In some cases, extensive involvement of the colon may necessitate some bypass maneuver. At any event, the objective should be to achieve the best palliation with minimal postoperative morbidity. In some patients with extensive cancer, palliative placement of a gastrostomy tube to allow for intermittent decompression may be necessary.

Complications Secondary to Colonic Surgery

Although the conventional colon anastomosis is generally uncomplicated and has less risks for anastomotic breakdown and other complications compared to rectal anastomoses, there are mitigating factors that may predispose to defects in anastomotic healing, e.g., malnutrition, hypoalbuminemia, severe blood loss, poorly prepared bowel, and local technical factors regarding blood supply. An early dehiscence within 48 hr usually presents with catastrophic findings, including peritonitis and leukocytosis, and requires urgent and early exploration with intestinal diversion. Attempts to repair the anastomosis are ill-fated and only add to the hazard. Copious irrigation of the abdominal cavity, formation of an ileostomy, which is perhaps more diverting than a colostomy, and irrigation of the distal and proximal segments of the involved bowel to help reduce continued fecal spillage are considerations. For an anastomotic leak after 48 hr or for a questionable staple line breakdown, an anastomotic breakdown may be confirmed by a gentle gastrograffin enema. The presence of anastomotic leak, with generalized peritonitis, may require taking down the anastomosis and formation of an end colostomy with closure of the distal end. If this is not possible, then a completely diverting transverse colostomy or ileostomy would be essential with drainage of the anastomotic site. In this case, surgical measures are lifesaving and should be expediently performed to save the anastomosis.

Anastomotic Bleeding

Anastomotic bleeding is occasionally a complication of colonic surgery. Often this type of bleeding is of low order and the use of techniques that will reduce the portal flow such as vasopressin could be considered. Correction of bleeding diathesis, i.e., with fresh frozen plasma or platelets, may be done if indicated. Operative intervention to correct anastomotic bleeding must be performed if conservative measures fail.

Other bleeding complications are more commonly related to the spleen. Approximately 20–40% of splenectomies in the United States are secondary to operative misadventures. In the event of early recognition of minor splenic injury,

such as a capsule tear, use of hemostatic plegetts, fibrin glue, or careful placement of packs containing hemostatic agents (e.g., Surgicel) can sometimes be effective.

Ureteral Injuries

The potential for ureteral injuries is high in the presence of severe adhesions, multiple previous surgeries, malignancy, inflammatory processes, or after previous radiation. The major sites of injury during colorectal procedures occur during performance of ligation of the vascular pedicles of the right colon or left descending colon. Isolation and ligation of the inferior mesenteric artery flush with the aorta may result in inadvertent ligation of the left ureter. The potential for ureteral involvement due to adhesions or even tumorous attachments during mobilization of the rectosigmoid on the left side or the ileocolic mobilization on the right side would be of particular concern. The best treatment for ureteral injury is prevention, identification, and isolation of the ureters during major right or left colon resections. In high-risk patients, the use of ureteral stents may facilitate the recognition of the ureter and help prevent injury (the ureter containing the ureteral stent is more easily palpated). If an injury does occur, it can often be primarily repaired. If the ureter has been crushed or transected, it will need to have either a pigtail catheter placed in the ureter, with ends in the bladder and the calyx of the kidney, or to undergo a primary anastomosis using absorbable sutures (dexon, vicryl, or gut).

Early recognition of ureteral injury may be difficult and intravenous injection of methylene blue may permit detection of such injuries in the lower abdomen or pelvis. Positioning the patient in the lithotomy position may facilitate placement of ureteral stents. In the event that ureteral injury recognition is postoperative, a percutaneous nephrostomy tube can be placed. Detection and identification of the site of injury is important so that early repair can be initiated. In some patients, a delayed ureteral injury is possible. In those who have had radiation and dissection with partial devascularization of the ureter, passage of a percutaneous nephrostomy or a retrograde, ureteral J tube may permit functioning of the ureter until the major operative procedure has healed with elective repair of the ureter at a later date. If there is concern of an inadvertent ligature of the ureter, early ultrasound of the kidney demonstrating a dilated urinary collection system followed by a retrograde study to demonstrate the level of blockage is indicated. Treatment includes percutaneous nephrostomy with passage of a ureteral stent through the ureter and planned early exploration with deligation and careful evaluation of the damage to the ureter. If the ureter is thought to be devitalized, a resection and end-to-end anastomosis would be indicated.

Survival Following Resection

The overall resectability for colon cancer ranges from 80 to 90% with an operative mortality of 3–5%. The overall 5-year survival ranges from 40 to 78%, de-

pending on disease stage. The crude survival range in selected series varies by stage: Dukes' A (64–81%), Dukes' B (51–65%), and Dukes' C (32–49%). Adjuvant therapy is an important consideration in high-risk patients. Its role is reviewed in the chapter on rectal cancer. Survival rates for patients with complications of colon cancer, including obstructing and perforating cancers, are worse. The operative mortality for obstructing cancers is high, ranging up to 23%, with survival expectations in the 25% range. For perforated cancers, mortality ranges between 14 and 38% with expectation of crude 5-year survival from 7 to 43%, depending on the series. The need for subsequent therapy in high-risk individuals is obvious, ideally by protocols designed for such high-risk patients.

RADIATION THERAPY

In contrast to rectal cancer, the role of adjuvant radiation therapy for cancers that arise above the pelvic peritoneal reflection has not been well established. Due to the anatomical locations of these cancers, particularly where the colon is attached to a mesentery, wide local excisions are commonplace. The primary failure pattern following potentially curative surgery is abdominal rather than local. However, distant metastases, particularly to the liver, without local or regional recurrence are rare. Gunderson et al. reported a reoperation series in which local or regional failure was a component of the failure pattern in 48% of the T3–4 or N1–2 patients who recurred. Other investigators have reported a somewhat lower locoregional recurrence rate.

Retrospective nonrandomized studies of radiation therapy following curative surgery of colon cancer with or without chemotherapy have suggested a potential benefit to both locoregional control and perhaps disease-free survival as well over surgical resection alone. Willett et al. at the Massachusetts General Hospital reported 203 patients who had undergone subtotal colectomy for their colon cancer (Table 1). Of those, 30 patients were found to have residual disease and underwent salvage postoperative radiation therapy with or without concurrent 5-FU chemotherapy. The other 173 patients who had no known residual disease were treated with adjuvant radiation therapy with or without 5-FU chemotherapy. These were compared with a historical control group of 395 patients who had undergone surgery only. Patients received 45 Gy in 1.8-Gy fractions to the tumor bed with approximately a 3–5-cm margin and the draining lymph nodes in selected cases. By a shrinking field technique, the tumor bed was boosted to 50.4 or 54 Gy depending upon the volume of small bowel irradiated. Sixty-three patients, including 11 of 30 patients with residual disease, received intravenous bolus of 5-FU with a variety of regimens.

There was a significant improvement in local control for patients with stage B3 and C3 disease ($p < 0.001$ and $p < 0.05$, respectively) and recurrence-free survival rates for patients with stage B3 disease ($p < 0.001$) treated with postop-

TABLE 1 Five-Year Actuarial Local Control, Recurrence-Free Survival Rates for Colon Cancer

	Surgery (historical control)			Surgery + radiation								
				Without 5-FU			With 5-FU			Total		
Stage	No. of patients	LC (%)	RFS (%)	No. of patients	LC (%)	RFS (%)	No. of patients	LC (%)	RFS (%)	No. of patients	LC (%)	RFS (%)
B2	163	90	78	16	87	69	7	100	80	23	91	72
B3	83	69	63	37[a]	94	78	16[a]	100	83	54[a]	93	79
C2	100	64	48	41	69	48	14	70	43	55	70	47
C3	49	47	38	24	67	53	15	79	52	39	72	53

LC = local control.
RFS = recurrence-free survival.
[a] The number of patients is internally inconsistent in the originally published data.
Source: Data from the Massachusetts General Hospital series adapted from Willett et al., 1993.

erative radiation therapy over the historical control surgical-only group. However, this benefit did not apply for the patients with stage B2 and C2 disease. The explanations could be either because postoperative radiation therapy simply does not provide a therapeutic gain for this group of patients or the bias of patient selection since most patients were referred owing to concerns of inadequate surgical treatment.

Thirty-eight of 173 patients had had perforation or fistula associated with their tumor but without documented residual disease. Postoperative radiotherapy improved local control and recurrence-free survival rates. Concurrent administration of 5-FU with the radiation therapy appeared to improve local control and recurrence-free survival compared to surgery plus radiation therapy only but the differences were not statistically significant. More cases will be needed to address the meaningfulness of this statistic. For the 30 patients with residual disease an impressive 37% 5-year disease-free survival was achieved when the patients were treated by high-dose postoperative radiation therapy. Additional data were regenerated from the report of the Massachusetts General Hospital to assess the impact of lymph node involvement (stage B vs. stage C) in the outcome of patients with colon cancer treated by two different modalities (Table 2). The 5-year local control and recurrence-free survival rates were significantly better for the patients with stage B disease than the patients with stage C disease regardless of treatment modalities ($p < 0.001$ for all). There was a significant improvement of local control and recurrence-free survival rates for patients with stage B disease ($p < 0.001$ for both) treated with postoperative radiation therapy over a historically controlled surgical-only group. However, for stage C disease postoperative radiation therapy only improved local control ($p < 0.001$) but offered no benefit for recurrence-free survival ($p < 0.1$). This implies that when lymph node involve-

TABLE 2 Five-Year Actuarial Local Control and Recurrence-Free Survival Rates by Lymph Node Involvement, Surgery and Postoperative Radiotherapy Versus Surgery Alone

	Surgery (historical control)			Surgery + radiation		
Stage	No. of patients	LC (%)	RSF (%)	No. of patients	LC (%)	RFS (%)
B	246	83	72	77[a]	92	78
C	149	58	44	94[a]	70	50

[a] The total number of patients is internally inconsistent in the originally published data.
Source: Data regenerated from the Massachusetts General Hospital series adapted from Willett et al., 1993.

ment in colon cancer is present, locoregional treatment is inadequate and more aggressive systemic chemotherapy is indicated to improve survival.

In view of the propensity for colon carcinoma to spread to the peritoneum, whole-abdomen radiotherapy has been used in a number of centers. It is difficult to assess these results in view of the small number of patients and the nonrandomized nature of the studies. The largest series was reported by Fabian et al. for the Southwest Oncology Group. Forty-one patients with completely resected T3N1–2M0 colon cancer were treated with continuous infusion 5-FU at a dose of 200 mg/m^2/day with concomitant whole-abdominal radiation of 30 Gy in 1 Gy per fraction. This was followed by a boost to the tumor bed with an additional 16 Gy in 1.6-Gy fractions and nine monthly cycles of maintenance continuous infusion 5-FU at a dose of 1000 mg/m^2. With a median follow-up of 5 years, the 5-year disease-free and overall survival were 58 and 67%, respectively. The 5-year disease-free and overall survival for the 19 patients with four or fewer nodes were both 61% and for the 20 patients with more than four involved nodes were 55% and 74%, respectively. There is no statistical difference between these two groups. The treatment appeared to be tolerable. The majority of toxicities were grade I and II. Seventeen percent of patients had severe and 7% had life-threatening toxicity of any kind. These results are encouraging and randomized studies are needed to confirm these results.

The North Central Cancer Treatment Group has just closed an intergroup phase III randomized study (INT-0130). Patients with completely resected adenocarcinoma of the colon at high risk for locoregional recurrence were randomized between radiation with 5-FU and levamisole versus 5-FU with levamisole alone. Over 200 patients were accrued to this study; the severe toxicities that occurred in more than 5% of the patients were leukopenia, nausea, diarrhea, and radiation enteritis. One patient died of peritonitis following the first course of chemotherapy. The local control and survival data must await final analysis, which will not be available for at least 2 or 3 years. This trial may clarify the role of adjuvant irradiation in the management of colonic cancer.

Other modalities have been used in conjunction with external radiation therapy. Intraoperative radiotherapy and hyperthermia plus external radiotherapy have shown promise in small groups of patients. However, these modalities, and brachytherapy as well, are more often used in rectal cancer rather than colon cancer. Further follow-up is needed to fully evaluate the indication of such modalities.

Liver Metastasis

The diagnosis of hepatic metastases represents an ominous event in the clinical course of a patient with colorectal cancer. Organ tolerance of the whole liver to radiation therapy is about 30 Gy at standard fractionation. At best, modest pallia-

tive benefit rather than control of intrahepatic disease can be expected. Liver metastases are frequently not painful, but if there is rapid enlargement of the liver with expansion of the capsule, which does contain sensory nerves, severe right hypochondrial pain can ensue. Such symptoms can be relieved with relatively low doses of radiation therapy. A useful treatment schedule that is well tolerated is 25 Gy in 10 fractions to the whole liver.

At the Rhode Island Hospital/Brown University, a total of 48 patients with liver metastases were treated. Of these eight received 5-FU intrahepatic artery infusion, 14 received hepatic irradiation, and 25 received combined intra-arterial chemotherapy plus total hepatic irradiation. An additional patient was initially treated with intra-arterial chemotherapy followed by hepatic radiation when she failed. The median survival was 140 days in the radiation-only group, 270 days in the intra-arterial chemotherapy group, and 376 days in the combined group. The treatment was well tolerated. The pretreatment performance level of the patient as determined by the Karnofsky Performance Score appeared to be the best indicator of potential response. Recent development of three-dimensional conformal radiation therapy has allowed radiation oncologists to deliver a higher dose locally to intrahepatic tumors and minimize the dose to the normal liver with an acceptable incidence of complications. Robertson et al. from the University of Michigan reported 22 patients who were treated with concurrent intra-arterial hepatic (IAH) fluorodeoxyuridine (FdUrd) (0.2 mg/kg/day) and conformal hepatic radiation therapy. The total dose of radiation of 48–72.6 Gy was delivered depending upon the volume of normal liver in the high-dose region. This regimen produced an objective response in 50% of patients and an actuarial freedom from hepatic progression in 25% of patients at 1 year. The acute toxicities were mild to moderate. For patients with two or three lesions who would otherwise be a candidate for surgical removal, this noninvasive technique is a useful alternative.

Other approaches such as radioactive implant and intraoperative radiotherapy were attempted to improve local control and survival of patients with liver metastases from colorectal cancer. However, despite the aggressive local treatment most of the patients with liver metastases will die of disease. Intensive local therapy is indicated only in selected patients but improvements in systemic chemotherapy are required to address the high rate of distant metastases.

SYSTEMATIC THERAPY

The role of systematic therapy in the management of patients with colon cancer is discussed in the chapter on rectal cancer.

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7

Rectal Cancer

Peter W.T. Pisters, Nora A. Janjan, Jean-Pierre Ayoub, and Richard Pazdur
The University of Texas M. D. Anderson Cancer Center, Houston, Texas

INTRODUCTION

Colorectal cancer is a significant public health problem in Western society. Carcinoma arising in the colon or the rectum represents the third leading cause of death from cancer in men and women. It is the third most common malignancy in men after prostate and lung cancers and is second only to breast cancer in American women. The natural history and treatment algorithms for rectal cancer are substantially different from those for colon cancer. For these reasons, these cancers are presented and reported separately.

In 1997, approximately 37,100 new cases of rectal cancer were expected to be diagnosed in the United States, and approximately 8300 Americans would die of the disease. Rectal cancer is slightly more prevalent in men than women (1.3:1.0).

The TNM staging system employed for staging rectal cancers is outlined in Table 1. T stage is optimally assessed by a combination of physical examination, including proctoscopy, and imaging [either transrectal ultrasonography or magnetic resonance imaging (MRI) with an intrarectal coil]. Patients with a T2 or greater primary tumor should also undergo computed tomography of the abdomen and pelvis. A chest x-ray suffices for staging of the chest in patients with localized disease.

The rectum is classically divided into three levels: the low rectum, midrectum, and upper (or proximal) rectum (Fig. 1). Because of variations in anatomy and body habitus, it is difficult to assign precise measurements to delineate each of these rectal segments. To complicate this, there is disagreement between various cooperative groups and the American College of Surgeons regarding the

Table 1 American Joint Committee on Cancer Staging System for Colorectal Cancer

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor invades submucosa		
T2	Tumor invades muscularis propria		
T3	Tumor invades through the muscularis propria into the subserosa or into nonperitonealized pericolic or perirectal tissues		
T4	Tumor perforates the visceral peritoneum or directly invades other organs or structures		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in 1–3 pericolic or perirectal lymph nodes		
N2	Metastasis in 4 or more pericolic or perirectal lymph nodes		
N3	Metastasis in any lymph node along the course of a named vascular trunk		
Distant metastasis (M)			
MX	Presence of distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage I	T1	N0	M0
	T2	N0	M0 Dukes' A
Stage II	T3	N0	M0
	T4	N0	M0 Dukes' B
Stage III	Any T	N1	M0
	Any T	N2–N3	M0
Stage IV	Any T	Any N	M1

T, primary tumor; N, regional lymph nodes; M, distant metastasis.

anatomical definition of the rectum. The American College of Surgeons has classified cancers extending from the anal verge to 15 cm as rectal cancers. Other groups, however, have recognized that the more proximal rectal cancers (12–15 cm from the anal verge) have a general biological behavior and recurrence rates that more closely resemble those of colon cancers than those of rectal cancers, and thus most cooperative groups have adopted a more stringent definition of rectal tumors as those 0–12 cm from the anal verge on rigid proctoscopy with the patient in the left lateral Sims' position.

The methods of measuring rectal cancers reported in the literature also have not been uniform, with some authors measuring lesions from the dentate line

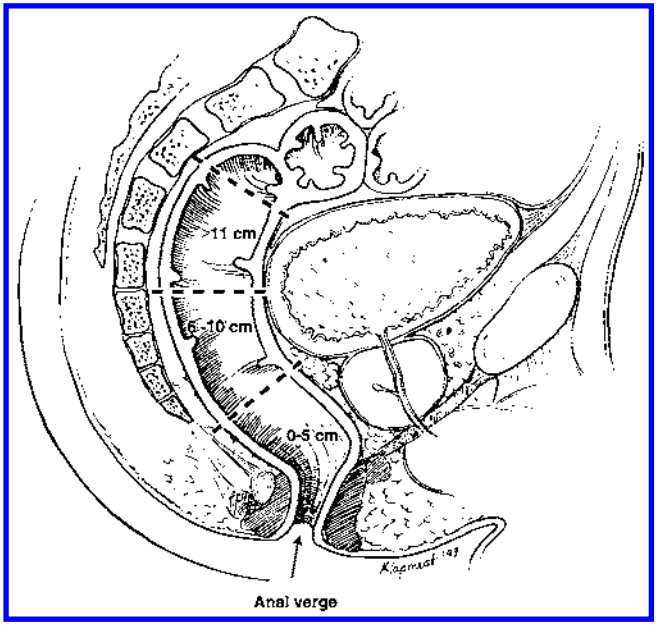


FIGURE 1 Cross-section of the anatomy of the rectum.

(which cannot be visualized by flexible or rigid sigmoidoscopy) and other authors using the anal verge as the reference point. This variability can introduce 1–3-cm discrepancies in the measurements of specific lesions. Thus, in an effort to standardize measurement and reporting, most cooperative groups have used the anal verge as the reference point, with measurement from the anal verge by rigid proctoscopy with the patient in the Sims' position. Universal adoption of this anatomical definition will be important to facilitate direct comparison of published series.

SURGICAL MANAGEMENT OF RECTAL CANCER

The general goals in the surgical management of patients with localized (T1–4, N1–2, M0) rectal carcinoma include (1) cure (prevention of distant recurrence), (2) local control (prevention of local recurrence in the pelvis), (3) sphincter preservation and preservation of integrated anorectal function, and (4) preservation of urinary and sexual function. Regrettably, these goals are not universally achievable. However, thorough understanding of basic surgical principles and attention to specific technical issues can optimize outcome for each of these goals.

Local Excision

Full-thickness local excision has emerged as a reasonable therapeutic option in a subset of patients with early-stage low rectal cancer. This treatment is predicated on a defined relationship between tumor thickness (T stage) and the risk of harboring regional lymph node metastases. Careful pathological studies have demonstrated that the risk of harboring occult metastasis within regional lymph nodes is approximately 10–12% for patients with T1 lesions and 20% for patients with T2 lesions. Stage T3 lesions, however, are associated with a 50–60% incidence of lymph node metastasis. Thus, assuming that T stage can be accurately assessed by the combination of physical examination and preoperative transrectal ultrasonography, there is a small subset of patients with early-stage cancer who may be considered candidates for initial local excision.

These patients must be carefully selected on the basis of preoperative physical examination and imaging. All patients should undergo transrectal ultrasonography or MRI with an intrarectal coil to confirm the clinical impression of T1 or T2 disease. With this background in mind, the generally accepted criteria for local excision include (1) the location of the lesion within the low rectum (0–5 cm from the anal verge), (2) tumor size less than 3 cm, (3) absence of ulceration, local fixation, or tethering of the lesion, (4) sonographic and physical examination findings consistent with T1 or T2 disease, and (5) absence of lymphatic, vascular, or perineural invasion on preoperative endoscopic biopsies.

The local excision should be considered as a full-thickness biopsy for complete pathological staging of the primary tumor. Further treatment, including more extensive surgery or adjuvant radiotherapy and/or chemoradiation, may be necessary based on the final pathological analysis of the full-thickness local excision specimen. The local excision specimen must be carefully anatomically oriented and the margins inked. Pathological evaluation should include determination of the pathological T stage, degree of differentiation of the lesion, the presence of vascular, lymphatic, or perineural invasion, and assessment of the circumferential microscopic surgical margins.

Subsequent treatment is based on careful assessment of the pathological findings. For patients with T1 lesions, the survival rate approaches 90% in the absence of additional adjuvant therapy, and thus no additional therapy may be necessary. For patients with T2 lesions, the pathological features of the lesion will indicate whether further therapy is required. Patients whose tumors show poor histological differentiation or other adverse histological features such as perineural or lymphatic invasion should be considered for additional local therapies such as completion resection (by abdominoperineal resection or low anterior resection with coloanal anastomosis) or for postoperative chemoradiation. Patients whose T2 tumors were excised with negative margins and show favorable histology may be treated with careful observation and follow-up. Patients who

are found to have pathological T3 lesions should undergo complete resection with total mesorectal excision in view of the significant risk (50–60%) of regional lymph node metastasis. Failure to further treat these tumors with adverse pathological features because of the patient's underlying medical condition or refusal to undergo more extensive surgery is associated with only a 60% 5-year survival rate. Thus, a policy of watchful waiting cannot be advocated for patients undergoing local excision in whom pathological analysis reveals significant adverse pathologic features such as T3 tumor thickness, poor histological differentiation, or lymphatic and/or neurovascular invasion.

The oncological results following local excision have been satisfactory, particularly when strict selection criteria are employed. In several published series, the local failure rate for selected patients with T1 or T2 lesions ranged between 0% and 26%, with an overall local recurrence rate of approximately 20%. The 5-year overall survival rate was 73%. When local recurrences do occur, approximately half of them are amenable to salvage surgery, usually by abdominoperineal resection.

Radical Resection

The majority of patients with rectal cancer will present with disease that is at least transmural (T3 or greater) and/or associated with local and regional lymphadenopathy (N1 or N2). These patients require radical resection with regional lymphadenectomy for local tumor control. The operative approach (low anterior resection, total proctectomy with coloanal anastomosis, or abdominoperineal resection with a permanent colostomy) will depend primarily on tumor location, tumor size, and experience of the surgeon. Irrespective of the surgical approach employed for resection of the tumor, all of these procedures require complete regional lymphadenectomy and satisfactory lateral tumor clearance to ensure satisfactory local tumor control. The pelvis is a frequent site of tumor recurrence, and such recurrences are a major cause of morbidity and death in patients with rectal cancer. This is frequently associated with debilitating pain from neural invasion, perineal breakdown, and obstruction with bleeding and/or fistulization.

Significant evidence suggests that incomplete surgical resection is a common cause of local tumor recurrence. Recent data have clearly established that involvement of the lateral radial margin of resection correlates with subsequent local recurrence, with 80% of patients with a microscopically positive radial surgical margin developing subsequent recurrence in the pelvis. In addition, investigators from Europe have demonstrated that the frequency of local recurrence is surgeon-dependent and varies from less than 10% to more than 50% among individual surgeons. These data emphasize the importance of surgical quality as factor in local tumor recurrence.

Fundamental understanding of the pelvic surgical anatomy is essential to

Table 2 Results of Total Mesorectal Excision for Rectal Cancer

First author	Year	Stage	No. of patients	No. treated with RT	Local failure (%)	Survival (%)
Cawthorn	1990	T1–3, N1–3	122	7	7	NR
MacFarlane	1993	T3 or N1–3	135	0	5	78
Enker	1995	T3 or N1–3	204	33%	6	77
Arbman	1996	T1–3, N1–3	128	3	7	68

RT, radiation therapy; NR, not reported.
Source: Modified from Guillem JG et al., 1997 (with permission).

ensure complete regional lymphadenectomy and minimize the risk of a positive radial surgical margin. The rectum and mesorectum from a single structure that is contained within an envelope of visceral pelvic fascia. The parietal layer of pelvic fascia covers the sacrum and presacral fascia, musculoskeletal boundaries of the pelvic side wall, pelvic autonomic nerves, and internal iliac vessels. The rectum and mesorectum can be completely resected as a single unit by sharp dissection along an areolar plane that separates the parietal and visceral fascia. This procedure is known as total mesorectal excision (TME). Radical resection with TME reduces the incidence of positive radial surgical margins and subsequent local recurrence. In several reported series from the United States and the United Kingdom, patients treated with radical resection and TME without radiation therapy had a 5–10% local failure rate. These encouraging results have been attributed to improved lateral tumor clearance, more complete removal of involved regional lymph nodes, and a minimized risk of tumor dissemination from disruption of the mesentery that frequently occurs when conventional blunt pelvic dissection is performed. TME has not been evaluated within the context of a randomized trial. However, the procedure has been evaluated prospectively in Sweden, where it was introduced using a formal preceptorship-based training program. Radical resection with TME was associated with a 7% local recurrence rate as compared to a 23% rate in historical controls.

Radical resection of the rectum has been combined with pre- or postoperative radiation or chemoradiation to reduce local recurrence and increase survival. Data from multiple trials confirm that the addition of radiation or chemoradiation improves local tumor control. Nine randomized trials have addressed this issue, with all studies confirming a local control advantage with combined-modality treatment. However, only one study, from the Swedish Rectal Cancer Trial Group, has shown a survival benefit for patients treated with preoperative radiation. The local recurrence rates in the surgery-only control arms of these randomized studies have ranged between 20% and 40%, significantly higher than those reported with radical resection and TME in single-institution series. It is certainly

possible that further improvements in local control could be achieved utilizing combined-modality therapy with radical resection and TME. A two-arm randomized study of TME with or without preoperative radiation therapy for resectable rectal cancer has been initiated in the Netherlands. This study will yield important data on the efficacy of TME and the relative benefits of surgery and radiation therapy in the local control of rectal cancer. Clear identification of the subsets of patients who may be optimally treated by surgery alone will be important in this era of cost containment and given the clear evidence that long-term anorectal and bowel function is compromised in patients receiving pre- or postoperative radiation therapy.

Sphincter-Preserving Operations

Sphincter-preserving operations for cancers of the rectosigmoid (greater than 12 cm from the anal verge) have been widely adopted in the surgical community over the past decades. However, sphincter preservation in selected patients with low rectal cancer has been less rapidly adopted. This reflects the outdated axiom that the operation of choice for all rectal cancers within reach of the examining finger is abdominoperineal resection with permanent colostomy. This dogma is a consequence of extrapolating concepts of what constitutes an adequate distal margin for resection of a colon cancer to cancers of the rectum and the mistaken belief that a specific length of residual rectum is essential for normal sphincter function. However, since fewer than 5% of rectal cancers have distal mural involvement beyond the edge of the tumor and only 2.5% have histological evidence of distal involvement beyond 2 cm, the traditional requirement for a 5-cm distal mucosal mural margin is unsubstantiated. Recent studies have demonstrated that distal mucosal margins of 1 cm are adequate for most low rectal cancers, except poorly differentiated or bulky lesions. In addition, distal margins greater than 2 cm do not appear to reduce the risk of local recurrence or suture line recurrence. In 1974, Stearns and colleagues reported a comparison of a large series of patients who had midrectal cancers and underwent sphincter-preserving operations versus abdominoperineal resection of the rectum. Sphincter preservation did not compromise local control or overall survival. Subsequent studies have confirmed these findings and have allowed for more widespread application of sphincter-sparing approaches for midrectal cancers. In addition, it is estimated that approximately 5–10% of patients with low rectal cancers may also be candidates for sphincter preservation with complete proctectomy and coloanal anastomosis.

The operative procedures employed for sphincter preservation in the setting of mid- or low rectal cancers include (1) standard low anterior resection with coloproctostomy, (2) total proctectomy with coloanal anastomosis, and (3) low anterior resection or total proctectomy with coloanal anastomosis and J-pouch

colonic reservoir reconstruction. A standard low anterior resection involves subtotal proctectomy with subsequent anastomosis between serosalized proximal colon and the extraperitoneal nonserosalized residual distal rectum. This involves an intrapelvic anastomosis situated anterior to the sacral hollow proximal to the muscular floor of the pelvis. In contrast, total proctectomy involves removal of the entire rectum with a subsequent extrapelvic anastomosis between the serosalized proximal colon and the anal canal either at the apex of the anal canal or lower in the anal canal at the level of the dentate line. By definition, total proctectomy involves complete removal of the rectum, with no subsequently remaining distal rectal pouch.

The technical details of these sphincter-sparing surgical procedures are beyond the scope of this chapter. However, an understanding of the general indications for total proctectomy and coloanal anastomosis is important. Total proctectomy with coloanal anastomosis may be utilized for the following: (1) for resectable midrectal cancers where a standard low anterior resection with intrapelvic coloproctostomy is technically difficult or impossible (e.g., significant obesity, narrow male pelvis, or prostatic hypertrophy), (2) as a satisfactory alternative to abdominoperineal resection for selected patients with low rectal cancers, and (3) as a substitute for abdominoperineal resection when used in combination with pre- or postoperative therapy (radiation therapy alone or with concurrent chemotherapy) within the setting of a clinical trial. This latter indication remains experimental. Minsky and colleagues have recently reported on a series of 30 patients with invasive resectable low rectal adenocarcinomas (28 of the patients had T3 lesions) that would have otherwise required abdominoperineal resection. These patients were treated with preoperative external-beam radiation to a total dose of 50.4 Gy with subsequent total proctectomy and coloanal anastomosis. The 4-year actuarial survival rate was 65%, and the local failure rate was 23%, emphasizing the importance of limiting this surgical procedure for low rectal cancers to clinical trials until more data are available.

RADIATION AND CHEMORADIATION THERAPY FOR RECTAL CANCER

Radiation therapy has three general roles in rectal cancer management. First, radiation therapy is used to enhance local-regional control by eliminating microscopic residual disease around the primary tumor and in the draining lymphatics. Second, significant tumor regression can result when radiation is administered preoperatively to locally advanced primary tumors. In these cases, an inoperable lesion can become resectable or amenable to a more conservative surgical approach with sphincter preservation. Third, radiation therapy can be used to palliate symptoms due to infiltration of pelvic structures or metastatic disease.

Indications for Adjuvant Radiation

With surgery alone, the overall 5-year disease-free survival rate is 55% for patients with rectal cancer. The identified prognostic factors after surgery alone reflect the risk of residual microscopic disease and include stage, tumor location, and serosal, lymphatic, and neurovascular invasion. In addition, the risk of local failure after surgery alone has been shown to increase as the tumor approaches the anus. Adjuvant radiation may eradicate microscopic residual tumor and eliminate local recurrence in approximately 90% of patients with these adverse prognostic factors.

Adjuvant radiation can be administered either preoperatively or postoperatively. Regardless of the sequencing of surgery and radiation, the primary goal is the same—to improve local-regional control by eradicating microscopic residual disease. Three clinical presentations result in a high risk of microscopic residual disease after surgical resection: locally advanced tumors, tumors arising in the low rectum, and preoperative evidence of nodal involvement. Extension of tumor into the perirectal fat or adjacent viscera (stage II; T3/T4, N0) can increase the rate of local recurrence to approximately 30% with surgery alone. Likewise, the radial surgical margin is often compromised in low rectal tumors. In either situation, the rate of local recurrence may be reduced to less than 10% with the addition of adjuvant radiation. Tumor in the regional lymphatics (stage III) can also be effectively treated with radiation, reducing the more than 50% rate of local recurrence after surgery alone.

Postoperative Radiation

The advantages of administering radiation postoperatively include the ability to plan treatment based on complete pathological staging of the primary tumor and a theoretical reduction in perioperative morbidity since surgery is performed in an unirradiated field. Pathological tumor staging assures that adjuvant radiation is indicated and allows more precision in defining the regions that are to be included in the radiation portal. For high rectal tumors, postoperative radiation is often used because sphincter-preserving surgery can routinely be performed in these cases without the need for tumor down-staging. In addition, prompt surgical intervention and postoperative radiation are indicated in cases in which there is significant bleeding or risk of obstruction.

The disadvantages of postoperative radiation include relative hypoxia within the operative bed, and potential growth of microscopic residual disease during postoperative healing. Hypoxia enhances resistance to radiation; approximately three times the radiation dose is required to kill hypoxic tumor cells as to kill the same number of well-oxygenated cells. Therefore, higher total doses of radiation are generally administered postoperatively than preoperatively. In

comparison to the 45–50 Gy generally prescribed with preoperative radiation, 53–55 Gy is usually administered postoperatively. However, the risk of radiation-related short- and long-term gastrointestinal toxicity increases precipitously as the total dose of radiation increases. The potential risk of radiation morbidity also increases with postoperative radiation because the small bowel is less mobile due to adhesions.

Results of postoperative radiation therapy demonstrate a reduction in the local relapse rate for high-risk rectal cancers from the 35–50% with conventional surgery (without TME) alone to 10–20% with the addition of postoperative radiation. The decrease in the rate of local failure with postoperative radiation, however, has not reduced the incidence of distant metastases; the risk of distant metastases is approximately 20% for stage II disease and 40–60% for stage III disease. The development of distant metastases directly affects survival, with 5-year survival rates of approximately 70–90% for stage II disease, 40% for T3N1 tumors, and 15–20% for T4N1 lesions. Because of this continued risk of distant disease despite improved rates of local control, systemic therapy is usually administered with postoperative radiation.

A number of prospective randomized studies have specifically evaluated these issues. The National Surgical Adjuvant Breast and Bowel Project (NSABP) in a three-arm trial compared (1) surgery alone, (2) surgery plus postoperative radiation, and (3) surgery plus postoperative chemotherapy. The chemotherapy administered included 5-fluorouracil (5-FU), semustine, and vincristine. The radiation dose was 46–47 Gy in 25–27 fractions; however, only 86% of the patients randomized to receive radiation received the total dose. The surgery-plus-postoperative-radiation arm had a decrease in the rate of local recurrence, but this did not affect survival. The addition of adjuvant chemotherapy significantly improved disease-free survival ($p = 0.006$) and marginally improved overall survival ($p = 0.05$), but the rates of local failure and distant metastases were not significantly different compared with those for surgery alone.

Two other randomized studies, the Gastrointestinal Tumor Study Group (GITSG) and the Mayo/North Central Cancer Treatment Group (NCCTG), also showed reductions in local recurrence rates and improvements in disease-free and overall survival when postoperative radiation and chemotherapy were administered. The GITSG trial randomized a total of 7175 patients among four arms: (1) surgery alone, (2) surgery and postoperative radiation (40–48 Gy), (3) surgery plus postoperative chemotherapy, and (4) surgery plus postoperative radiation (40–44 Gy) and chemotherapy. Similar to the NSABP trial, 5-FU and semustine were used for chemotherapy. Compared to surgery alone, all the arms that included some form of adjuvant therapy resulted in improvements in disease-free and overall survival. The improvements in disease-free ($p = 0.009$) and overall survival ($p = 0.005$) were highly significant when the surgery-alone arm was compared to the surgery, radiation, and chemotherapy arm. The addition of radia-

tion therapy decreased the incidence of local failure as the initial form of disease recurrence and reduced the risk of local failure to 11% in the surgery, radiation, and chemotherapy group. With a local failure rate of 27%, postoperative chemotherapy was not shown to reduce the risk of local recurrence; however, postoperative chemotherapy, either alone or with radiation, did decrease the rate of distant metastases.

The advantage of combined-modality therapy was also demonstrated in the Mayo/NCCTG trial that compared outcomes for postoperative radiation alone to the results achieved with postoperative radiation and chemotherapy. In this trial, higher radiation doses were administered (50.4 Gy in 28 fractions), and the chemotherapy included 5-FU and semustine. The addition of chemotherapy lowered the rate of local failure from 25% to 13.5% ($p = 0.04$) and the rate of distant metastases from 46% to 29% ($p = 0.01$). These factors improved the disease-free survival rate from 37% to 59% ($p = 0.002$) and the overall survival rate from 48% to 58% ($p = 0.025$). Subsequent randomized trials demonstrated that semustine failed to add any benefit over 5-FU administered as a single agent. Additionally, a protracted infusion of 5-FU as compared to bolus administration of the agent increased the time to relapse ($p = 0.01$), and improved survival rates ($p = 0.005$). These improvements were related to higher total doses of chemotherapy being administered and improved tolerance to therapy with the protracted infusion technique.

Approaches have been taken to minimize radiation- and chemoradiation-related side effects like hematological and gastrointestinal toxicities. Using a protracted infusion of 5-FU, a higher total dose of chemotherapy can be administered with fewer hematological effects. Radiation techniques such as the use of a belly board to displace the small bowel from the radiation portal also help to reduce gastrointestinal side effects (Figs. 2 and 3). Two factors, however, currently limit further improvement of postoperative combined-modality therapy. First are the limitations in available effective chemotherapeutic agents. Second are the treatment-related toxicities related to higher doses of 5-FU and radiation. Therefore, preoperative chemoradiation has been used with greater frequency to overcome some of the difficulties with postoperative therapy.

Preoperative Radiation

The advantages of administering radiation preoperatively capitalize on the disadvantages of postoperative radiation. One advantage of preoperative radiation is possible reduction in tumor size, allowing a greater chance for sphincter preservation, especially for lesions located in the distal rectum. Response to preoperative radiation also results in sterilization of potential sites of microscopic residual disease, such as the radial surgical margin and regional lymphatics. Because the blood supply has not been disrupted by surgery, the effects of both radiation

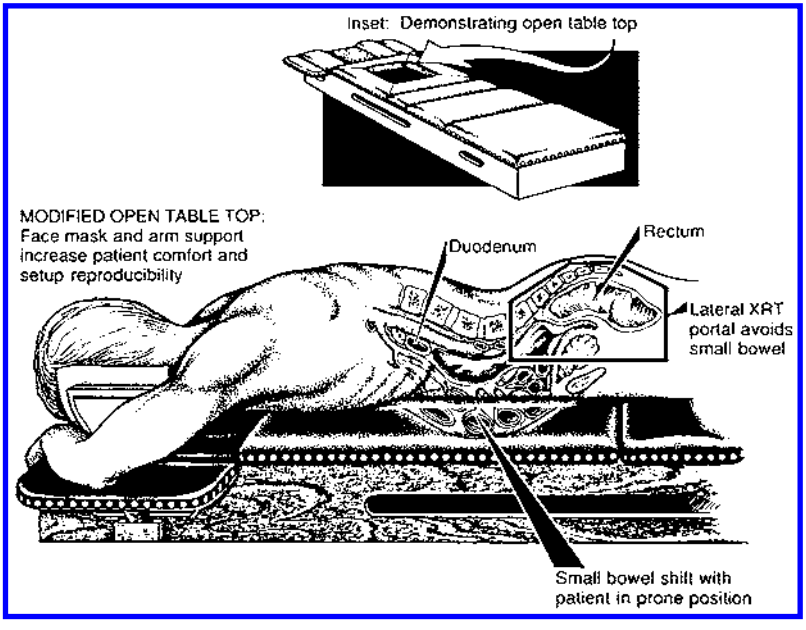
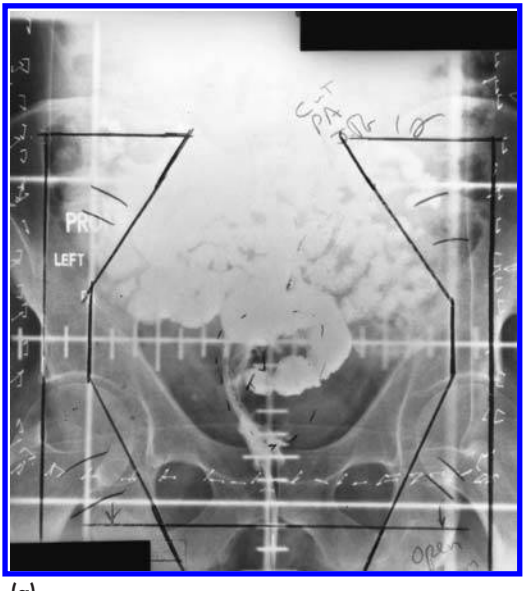


FIGURE 2 The belly board technique places the patient in the prone position and allows the small bowel to fall outside of and be completely excluded from the radiation fields.

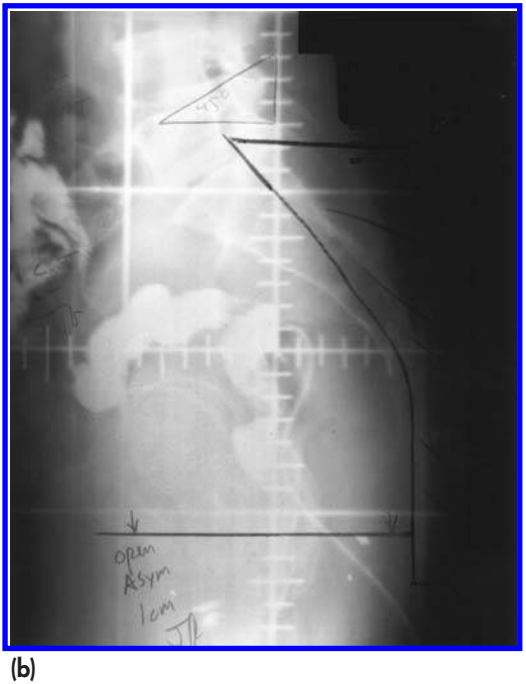
and chemotherapy are enhanced. Therefore, the total radiation dose administered preoperatively is lower, which also theoretically lowers the risk of radiation morbidity. In addition, the risk of radiation morbidity decreases with preoperative radiation because the small bowel is more mobile before surgery and can be displaced from the radiation field.

The disadvantages of preoperative radiation include the lack of pathological tumor staging and possibly higher rates of perioperative morbidity because surgical resection is performed in an irradiated field. Additionally, a two-stage surgical approach (stage 1, resection with fecal diversion; stage 2, reestablishment of intestinal continuity) may be necessary for sphincter preservation following preoperative chemoradiation.

Sphincter preservation is a major goal of preoperative radiation therapy. The current application of preoperative chemoradiation builds upon the experience with postoperative combined-modality therapy and the data demonstrating the efficacy of preoperative radiation alone. Compared with surgery alone, preoperative radiation achieved improvements at 5 years in local control ($p = 0.0001$), overall survival ($p = 0.0001$), and cause-specific survival ($p = 0.0001$). After



(a)



(b)

preoperative radiation, excellent rates of local control—more than 80% at 4 years—have been reported in conjunction with sphincter-preserving surgery for tumors in the distal 3–4 cm of the rectum.

With preoperative radiation, a 10% pathological complete response rate has been observed. Using infusional 5-FU and preoperative radiation, the pathological complete response rate increases to approximately 30%. In cases with pathological evidence of residual disease, 25% have only microscopic evidence of tumor. After preoperative chemoradiation, down-staging is evident in 70% of cases. Down-staging occurs in 53% of patients who present with invasion of the rectal wall and in 72% who present with lymph node invasion. Sphincter preservation is possible in more than two-thirds of patients with proximal low rectal lesions after preoperative chemoradiation. Local-regional control is accomplished with preoperative chemoradiation in up to 95% of cases of locally advanced rectal cancer, and survival benefits mirror response to therapy. In more advanced primary tumors (tethered T3 or T4 lesions), advantages in local control and survival have been observed with preoperative chemoradiation compared to preoperative radiation alone. Local recurrence rates were 10 times higher—33%—when preoperative radiation alone was administered in this group with locally advanced disease. Additionally, the 3-year survival rate increased to 82% with preoperative chemoradiation as compared to the 62% survival rate after preoperative radiation alone.

A prospective randomized trial by the Stockholm Colorectal Cancer Study Group compared preoperative radiation plus surgery to surgery alone. The study involved 285 patients with all stages of disease. Perioperative complications were seen with higher frequency in the preoperative radiation group ($p < 0.01$). Wound sepsis and postoperative mortality, primarily due to cardiovascular events in patients older than 75 years, occurred more commonly in the preoperative radiation group ($p < 0.01$). Local recurrence occurred in 16% of the group who received preoperative radiation and in 30% who underwent surgery alone ($p < 0.001$). The advantage was confined to patients with Dukes' B disease, although a trend ($p = 0.068$) for an advantage with radiation therapy was also observed

FIGURE 3 Simulation films using the three-field belly board technique. (a) Contrast material administered prior to simulation demonstrates the large volume of small bowel encompassed within the posterior portal. However, the doses to the small bowel and bladder are significantly less than if a four-field radiation technique, which includes an anterior portal, is used. (b) On the lateral projection, it can be seen that essentially all of the small bowel is excluded from the treatment fields. The presence of contrast material in the rectum helps demarcate the target volume.

in Dukes' C patients. With a median follow-up of 50 months, the rate of distant metastases was 19% after preoperative radiation and surgery as compared to 26% after surgery alone ($p = 0.02$), and this translated to a survival advantage for irradiated patients ($p = 0.02$). Although the disease-free interval was longer in the preoperative radiation group ($p < 0.01$), the lower rate of distant metastases and overall survival advantage after preoperative radiation were not durable with a longer follow-up of 107 months. The loss in the survival advantage, however, can be accounted for by the higher perioperative mortality rate in the preoperative radiation group because the disease-specific survival rate continued to show an advantage when radiation was administered ($p < 0.01$). With longer follow-up, a lower rate of distant metastases continued to be seen in patients with locally advanced tumors without associated lymph node metastases (Dukes' B) who received preoperative radiation ($p = 0.018$). This observation is not unexpected because control of local disease would be less likely to impact on the excess risk of distant metastases secondary to documented lymph node involvement.

Comparison of Pre- and Postoperative Radiation Therapy

The influence of technique on outcome is best illustrated in the Stockholm experience. In a prospective, randomized multicenter trial, 471 patients with resectable rectal cancer were randomized to receive either a short course of preoperative radiation or high-dose postoperative radiation. In the preoperative radiation arm, 236 patients received five 5.1-Gy/fractions to a total dose of 25.5 Gy over 5–7 days; surgical resection was performed 1 week later. In the postoperative radiation arm, radiation was initiated 4–6 weeks after surgery in 235 patients. Patients received 40 Gy at 2 Gy/fraction over 4 weeks; at this point, radiation was discontinued for 10–14 days, and then an additional 10 Gy was administered to the entire pelvis and another 10 Gy was administered to a reduced treatment volume. With the postoperative regimen, the pelvis received 50 Gy and the tumor bed received 60 Gy. Only patients who had evidence of transmural extension of disease or positive pelvic nodes at resection received postoperative chemotherapy. In all cases radiation was delivered using a three-field technique with the patient in the prone position.

Moderate to mild acute radiation effects were observed in essentially all patients receiving postoperative radiation. Acute radiation effects, like diarrhea and cystitis, were infrequent in the preoperative arm. The perioperative mortality rate after preoperative radiation was comparable to that in the postoperative radiation group, but the incidence of perioperative complications was higher in the preoperative radiation group. For example, perineal wound sepsis occurred after abdominoperineal resection in 33% of the preoperative radiation group and 18% of the postoperative radiation group. However, because of perioperative compli-

cations, half of the patients in the postoperative group could not start radiation therapy within the recommended 6 weeks after surgery.

With a mean follow-up of 6 years and minimum follow up of 3 years, the survival rates were comparable in the pre- and postoperative radiation arms. However, the local recurrence rate was lower in the preoperative radiation arm (13%) than in the postoperative radiation arm (22%; $p = 0.02$). The treatment-related complications included small bowel obstruction (diagnosed radiographically or requiring surgical intervention) in 6% after surgery alone, 5% after preoperative therapy, and 11% after postoperative radiation.

While the Stockholm trials identified advantages of combined modality therapy, significant morbidity was also observed. Peripheral nerves are relatively resistant to the late effects of radiation, but lumbosacral plexopathy has been reported with the preoperative radiation regimen used in this trial. Other late adverse effects of preoperative radiation therapy included thromboembolism ($p = 0.01$), femoral neck and pelvic fractures ($p = 0.03$), intestinal obstruction ($p = 0.02$), and postoperative fistulae ($p = 0.01$). No difference in genitourinary complications was observed. The mortality rates, which take into account late intercurrent disease, were the same for the surgery-alone and the preoperative-radiation groups.

Although the addition of radiation therapy significantly improved the local control and survival rates, the morbidity of radiation therapy was substantial enough to negate the impact of these results. It was recognized that refinement of radiation technique and more accurate patient selection were critical. Two key factors can increase the risk for morbidity due to radiation. First, the dose-fractionation schedules used are critical to morbidity and outcome. Second, the radiation technique used and the resultant volume of small bowel in the treatment portal are directly related to both acute and late radiation complications. Details of the specific dose-fraction schedules and the fundamental radiation techniques are critical determinants of toxicity, response, and long-term results but are beyond the scope of this chapter. The development of radiation techniques that more precisely localize the radiation dose and of new chemotherapeutic agents that more specifically increase tumor sensitivity to radiation without increasing normal tissue toxicity will allow further improvement in disease control.

Palliative Radiation

Achieving local-regional control is important in the management of rectal cancer. Local-regional failure occurs in approximately 75% of all patients who die from rectal cancer and results in significant symptoms, such as pain, bleeding, and obstruction, that are difficult to control. Palliative radiation can relieve the symptoms of pain and bleeding in about 70% of cases. However, obstructive symptoms

are often more difficult to relieve with palliative radiation, and a diverting colostomy is often required. Occasionally, urinary diversion may also be necessary. Palliative radiation temporarily relieves symptoms by causing partial regression of the recurrent tumor. With time and further tumor growth, however, symptoms will recur after palliative radiation unless the patient dies first of either intercurrent disease or distant metastases.

CHEMOTHERAPY FOR ADVANCED RECTAL CANCER

At the time of diagnosis, 19% of patients with colorectal cancer will have distant spread, and 40–50% of patients treated with a curative intent will eventually die of recurrent cancer. Like colon cancer, rectal cancer can spread hematogenously, most commonly to the liver and lungs. Selected patients with isolated recurrences in the liver or lungs may be cured by resection. Resection of liver metastases results in cure rates of 5–30%. Most patients with distant spread of rectal cancer, however, are not candidates for curative resection, and for these patients, chemotherapy should be considered.

Standard Agents

Since its synthesis by Heidelberger in 1957, 5-FU has remained the primary agent used in the treatment of advanced colorectal cancer. 5-FU exerts its cytotoxic effect by inhibiting tumor RNA synthesis through entry into the uridine metabolism pathway and also by interrupting DNA synthesis via thymidylate synthase inhibition. 5-FU may be administered as a bolus injection either weekly or daily for 5 days every 4–5 weeks. With these regimens, response rates in patients with advanced colorectal cancer have been approximately 10–15%.

5-FU has been administered using various dosage schedules and methods, including both bolus and short-term continuous intravenous infusion (750–1000 mg/m^2/day for 5 days) and protracted intravenous infusion via ambulatory infusion pumps (200–400 mg/m^2/day for up to 12 weeks). The pattern of 5-FU toxicity differs between bolus administration and continuous infusion. Bolus administration has pronounced myelotoxic effects, whereas the dose-limiting toxic effects of continuous-infusion 5-FU are mucositis and diarrhea. Palmarplantar erythrodysesthesia (hand-foot syndrome) has been reported with protracted infusions.

The paucity of new agents with activity against colorectal cancer has resulted in increased research into compounds that may enhance the activity of 5-FU. The most successful effort in biochemical modulation of 5-FU has been with folinic acid (calcium leucovorin). Preclinical studies demonstrated that leucovorin raises the level of N_5,N_{10},-methylenetetrahydrofolate and thus forms a stable tertiary complex of thymidylate synthase, the folate coenzyme, and 5-fluorodeoxyuridine, a metabolite of 5-FU. The enhanced stabilization of this tertiary

complex leads to enhanced inhibition of DNA synthesis. The combination of leucovorin and 5-FU, in various dosages and treatment schedules, has produced higher response rates than 5-FU alone in previously untreated patients with advanced colorectal cancers.

Two dosing schedules of leucovorin are approved by the U.S. Food and Drug Administration (FDA): (1) a ''low dose'' leucovorin regimen consisting of 20 mg/m^2/day leucovorin immediately followed by 425 mg/m^2/day 5-FU and (2) a ''high dose'' leucovorin regimen consisting of 200 mg/m^2/day leucovorin immediately followed by 370 mg/m^2/day 5-FU. With both schedules, leucovorin and 5-FU are administered by rapid intravenous injections daily for 5 consecutive days, with courses being repeated every 4–5 weeks. A third dosing schedule, 600 mg/m^2 5-FU plus 500 mg/m^2 leucovorin given weekly for 6 weeks with courses repeated every 8 weeks, offers response rates and survival rates similar to those with the above 5-FU-plus-leucovorin regimens. Diarrhea is more common with this third schedule, whereas myelosuppression is more frequently observed with the low-dose leucovorin regimen. Other attempts at biochemical modulation of 5-FU with agents such as alpha-interferon, methotrexate, and *N*-phosphonacetyl-L-asparate (PALA) have failed to show a consistent advantage in either response rate or survival, and the combinations are often more toxic than single-agent 5-FU.

Other agents examined for the treatment of colorectal cancer include the nitrosoureas (carmustine, lomustine, and semustine) and mitomycin. Response rates of 10–15% have been reported for these agents in previously untreated patients with metastatic colorectal cancer. Responses are short-lived (median duration 3 months), and are generally not observed in patients with 5-FU refractory disease. These agents have the potential for substantial hematological and renal toxicity. Furthermore, when these agents are combined with 5-FU, response rates have not exceeded those observed with 5-FU alone, and toxicity is additive.

New Agents

Irinotecan is a novel topoisomerase I inhibitor synthesized from the *Camptotheca acuminata*, a tree that is native to China. Response rates of 32% have been reported in previously untreated advanced colorectal cancer patients, with median survivals in excess of 12 months.

Irinotecan has some activity in patients whose disease progressed during 5-FU therapy. Reproducible 15–20% response rates in this patient population led to FDA approval of irinotecan for use in patients with 5-FU-refractory disease. The dosage schedules most commonly used are 125 mg/m^2 weekly for 4 weeks followed by a 2-week rest period (United States) and 350 mg/m^2 every 3 weeks (Europe). The primary toxicities of irinotecan are diarrhea and neutropenia. The intensive use of loperamide is important in the management of the former compli-

cation. Clinical evaluations of the combination of irinotecan and 5-FU with or without folinic acid are ongoing.

New agents under development for the treatment of advanced colorectal cancer include thymidylate synthase inhibitors and oral fluorinated pyrimidines. Raltitrexed (Tomudex) is a potent selective inhibitor of thymidylate synthase. This drug is polyglutamated and retained intracellularly for prolonged periods, allowing a convenient dosing schedule of a 15-min infusion repeated every 21 days. Preliminary studies indicate that raltitrexed has activity against advanced colorectal carcinoma and phase III trials are comparing this new agent to regimens of 5-FU plus leucovorin in the treatment of advanced colorectal carcinoma.

Two oral fluorinated pyrimidines are currently undergoing phase III testing in the United States and Europe. UFT, a combination of uracil and ftorafur (which is administered with oral leucovorin), and capecitabine are examples of oral fluorinated pyrimidines. These compounds are metabolized to 5-FU. Preliminary clinical trials indicate activity similar to that of intravenous 5-FU plus leucovorin regimens in the treatment of advanced colorectal carcinoma. The advantages over intravenous 5-FU include the convenience of oral administration and a favorable toxicity profile including reduction in neutropenia and mucositis.

Another oral regimen being studied for the treatment of advanced colorectal carcinomas is small oral doses of 5-FU combined with an inactivator of the enzyme dihydropyrimidine dehydrogenase. The inactivation of this enzyme allows predictable oral absorption of 5-FU so that 5-FU can be administered over prolonged periods without intravenous lines and infusion pumps.

Hepatic Intra-arterial Therapy

For patients with metastatic colorectal cancer confined to the liver, hepatic intra-arterial chemotherapy has been advocated. The delivery of chemotherapy agents by this route achieves a higher concentration of drug in the liver and potentially reduces systemic exposure to and toxicity of the agents. Floxuridine is the most commonly used chemotherapy agent delivered by the hepatic arterial route. The concomitant use of corticosteroids has reduced the hepatic toxicity of intra-arterial chemotherapy regimens. Increased response rates have been demonstrated with hepatic intra-arterial chemotherapy compared to intravenous chemotherapy regimens. In addition, recent trials have suggested that patients who have liver metastases refractory to intravenous 5-FU plus leucovorin regimens may respond to intra-arterial delivery of 5-FU with recombinant interferon alpha-2B. However, a conclusive survival benefit has not been demonstrated with the use of intra-arterial therapy, and the cost of delivery pumps, operative time, and hepatic toxicities must be carefully considered before prescribing this treatment.

In summary, despite the biochemical modulation of 5-FU and the activity

of irinotecan in 5-FU-refractory patients, the development of new systemic approaches is paramount to reducing mortality from colorectal cancer.

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8

Cancer of the Anal Canal

Paul J. McMurrick and Heidi Nelson
Mayo Clinic, Rochester, Minnesota

Richard M. Goldberg and Michael G. Haddock
Mayo Medical School and Mayo Clinic, Rochester, Minnesota

INTRODUCTION

Anal neoplasms are uncommon lesions, representing only 1–4% of all malignant tumors of the lower gastrointestinal tract. There exists a broad spectrum of malignant potential within this group of tumors. Benign lesions range from easily treated in situ Bowen's disease to locally aggressive verrucous lesions. Among malignant neoplasms, prognosis varies from early-stage squamous cell carcinoma, which generally responds favorably to treatment, to anal adenocarcinoma and malignant melanoma, which are rarely associated with long-term survival. In keeping with this diversity, favored treatment for each of these lesions is highly variable, and determined principally by histological subtype, location relative to the anal canal and margin, size, depth of penetration, the presence of metastases, and increasingly, the presence of any comorbidities, particularly AIDS.

Despite the pivotal importance of accurate staging of these tumors prior to determining therapy, there still exists no uniform approach to staging or even defining the location of lesions as being primarily within the anal canal or the anal margin. The following discussion helps to clarify these issues and place them in clinically meaningful perspective.

For the purpose of determining proper therapies, the anus must be divided into two parts; the *anal margin* and *anal canal*. Unfortunately, there is little agreement as to whether the line of differentiation should be the anal verge or

dentate line. Accordingly, there are two definitions of the anal canal; the *surgical* anal canal and the *anatomical* anal canal, each of which has its supporters.

The *surgical anal canal* is defined as the area between the anorectal ring and anal verge. The hair-bearing skin caudad to the anal verge is not included and is considered as the *anal margin*. This definition is incorporated in the TNM classification and is based on the observation that squamous and basaloid cancers between the verge and the anorectal ring present with similar distribution, grade of malignancy, depth of invasion, incidence of inguinal lymph node metastases, and overall long-term survival.

The *anatomical anal canal* is defined as that area between the dentate line and the anorectal ring. The area below the dentate line, to a point 5 cm caudad to the anal verge, is thus considered anal margin. This classification was originally described by Morson of St. Marks Hospital, London. It was based on consideration of the differential lymphatic drainage, that is, that lesions cephalad to the dentate tend to drain into the superior rectal lymphatics, into the inferior mesenteric nodes, and laterally along the middle and inferior rectal nodes, whereas lesions caudad to the dentate line preferentially drain to inguinal lymphatics. This differentiation is also supported by the histology of the normal epithelium, which is squamous caudad to the dentate line, but is transitional and then columnar cephalad to the dentate. Despite these compelling factors, the classification has shortcomings in that lesions frequently straddle the dentate line, and the lymphatic patterns cross both systems. Lesions cephalad to the dentate line can still metastasize to inguinal nodes (in up to 35% of cases), and lesions caudad to the line spread to the inferior mesenteric system.

Since a standard definition is lacking, it is imperative that clinicians and investigators make careful reference of the anatomical location relative to accepted anatomical landmarks (e.g., the anorectal ring, dentate line, and anal verge). Anal canal and margin tumors are discussed separately according to the classification outlined on Table 1.

Two major staging classifications have been described, the TNM and the Mayo staging classification. The TNM staging system is the most widely used (Table 2). Classification of primary tumor, ''T,'' stage is on the basis of measured tumor size, regardless of depth of penetration. Recent series have highlighted inherent weaknesses in this system, in that with current treatment modalities, there tends to be generally excellent long-term survival for stage I and II disease (90%) with little measurable difference between the two. Stage III disease has a far poorer outcome (50% 5-year survival), especially if the primary tumor is extensive. While this system is the most widely used, it ignores information regarding depth of penetration, which should be included in assessment of all tumors, as this is vital in defining those lesions that are amenable to local excision. The Mayo Staging Classification (Table 3) describes the primary tumor on the basis of invasion of anatomical layers. It is supported by a 1984 study of 188

Table 1 Classification of Anal Tumors According to Location

Anal margin
Bowen's disease
Perianal Paget's disease
Basal cell carcinoma
Squamous cell carcinoma
Verrucous carcinoma
Anal canal
Epidermoid tumors (includes squamous cell carcinoma, basaloid, cloacogenic, and mucoepidermoid tumors)
Melanoma
Anal adenocarcinoma

cases (all treated with surgical resection), which demonstrated differences in 5-year survival rate between stages when applied to squamous cell and nonkeratinizing basaloid surgical anal canal lesions: stage A 100%, stage B1 87%, stage B2 79%, stage B3 61%, stage C 40%, and stage D 23%. Of note, the increasing application of nonsurgical therapies renders pathological staging incomplete.

Table 2 TNM Definitions

Primary tumor (T)	
Tis: Carcinoma in situ	
T1: Tumor 2.0 cm or less in greatest dimension	
T2: Tumor more than 2.0 cm but not more than 5.0 cm	
T3: Tumor more than 5.0 cm	
T4: Tumor of any size that invades adjacent organ(s)	
Regional lymph nodes (N)	
N1: Metastasis in perirectal lymph node(s)	
N2: Metastasis in unilateral internal iliac and/or inguinal lymph node(s)	
N3: Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes	
Distant metastasis (M)	
M0: No distant metastasis	
M1: Distant metastasis	
Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
Stage II	T2, N0, M0 T3, N0, M0
Stage IIIA	T1, N1, M0 T2, N1, M0 T3, N1, M0 T4, N0, M0
Stage IIIB	T4, N1, M0 any T, N2, M0 any T, N3, M0
Stage IV	Any T, any N, M1

Table 3 Mayo Staging Classification

A	Tumor confined to anal epithelium and subepithelial connective tissue
B	Tumor penetration into the muscle or adjacent pelvic tissues
	B1 invasion into the internal sphincter
	B2 Invasion into the external sphincter
	B3 Invasion into adjacent pelvic tissues
C	Regional lymph node involvement (pelvic or inguinal)
D	Unresectable tumor or distant metastases

Pretreatment Evaluation of Lesions

A thorough history and physical examination should be complemented by laboratory investigations and radiological imaging where appropriate. Historical features of particular note include the length of symptoms, evidence of locally advanced tumor (incontinence, bowel obstruction), metastatic spread (weight loss, anorexia, fatigue), or the presence of risk factors (behavior at high risk for HIV, previous anogenital HPV infection). On examination, careful attention must be paid to assessment of the local extent of the tumor, and features suggesting malignancy (bleeding, local progression, adenopathy, fixation to or invasion of adjacent structures). The physical examination will establish whether the lesion is primarily of anal margin skin origin or of anal canal origin. On digital rectal examination, careful attention should be paid to the size of the lesion, the relationship to the anal verge, dentate line, and anorectal ring, and the presence of fixation to the sphincter mechanism, prostate, or vagina. Anoscopy and rigid proctoscopy will aid in defining the proximal extent of the lesion if it truly involves the canal, and in excluding rectal pathology in cases of Paget's disease. The relationship of the lesion to the anal verge is best determined by digital rectal examination and to the dentate line is usually best determined on anoscopy. The distance between the tip of the finger and the anal verge can be measured to determine both the proximal and distal extent of the lesion. Flexible endoscopy may be appropriate in selected cases when more proximal pathology is suspected. Endoanal ultrasound may be of assistance in determining more precise details of the submucosal dimensions of the lesion, the depth of invasion, relationship to the sphincters, and the presence of lymph node involvement. The accuracy of endoanal ultrasound is highly operator dependent and results should be carefully correlated with clinical findings.

To confirm histological diagnosis, biopsy under local or general anesthesia may be appropriate. When the lesion is confirmed as malignant, further assessment for the presence of metastases is appropriate to complete staging. Abdominal examination may reveal masses or liver metastases. The inguinal region

should be examined for the presence of lymph node metastases. Radiological imaging should be focused on the detection of pulmonary and hepatic metastases, specifically a CXR and abdominal computerized tomography (CT) scan.

SURGICAL THERAPIES

Anal Margin Tumors

Bowen's Disease

This is defined as an in situ intraepithelial squamous cell carcinoma. The disease is rare, and tends to present in women in their forties. Local invasion and metastatic behavior are uncommon, and occur in less than 5% of cases. The disease has a variable presentation; most typically it is asymptomatic. Symptoms when present include pruritus ani, or burning. The macroscopic appearance of these lesions is quite variable. In some cases, the lesion may be clinically inapparent, or an incidental finding at hemorrhoidectomy. The lesion may appear as reddened, thickened areas with fissuring or with patchy discoloration with or without nodules. Bowen's disease may be confused with other plaque-like pathology, including leukoplakia and eczema, or may present with an appearance similar to condyloma, skin tags, or external hemorrhoids. Diagnosis of the lesion is made by punch biopsy both centrally and at the periphery of the macroscopic lesion.

Early reports that Bowen's disease is commonly associated with further underlying malignancy have recently been challenged. Exhaustive investigation for internal malignancy is not indicated. However, the association with gynecological malignancy is strong enough that this diagnosis should be excluded in women.

Management is primarily surgical and dependent upon the local extent of the disease and/or the association with an invasive component. Surgery of noninvasive lesions involves full-thickness excision of all affected skin. ''Mapping'' of the lesion should be performed by taking serial punch biopsies in all four quadrants around the macroscopic lesion until a clear margin of at least 1 cm can be assured. Mapping needs to be performed at the peripheral margin of the lesion, as well as at the dentate line. Reconstruction may be by means of split skin grafting, or more preferably by VY advancement flap from the skin of the buttock. In all but the most extensive cases, primary closure can be obtained by this means. In cases where split skin grafting is required, a constipating agent may be administered for 6 days postoperatively to allow establishment of the grafts. Rarely, diverting colostomy may be necessary.

In locally invasive cases, abdominal perineal resection (APR) may be required. All patients should be followed for recurrence, which occurs in approximately 10% of patients, or for the development of invasive disease, which occurs in 6%.

Table 4 Summary of Surgical Therapy of Anal Tumors

Bowen's disease
Accurate lesion mapping
Wide local excision with flap repair as indicated
Exclude presence of locally invasive component and underlying gynecological malignancy
Paget's disease
Accurate lesion mapping
Wide local excision with flap repair as indicated
Exclude underlying malignancy
APR and chemoradiation if invasive adenocarcinoma present
Basal cell and anal margin squamous cell carcinoma
Local excision with clear margins
Radiation or chemotherapy in poor-prognosis lesions or recurrence as indicated
Verrucous carcinoma
Wide local excision; APR if very extensive.
Combined-modality therapy if transformation to SCC has occurred
Epidermoid cancer
Combined-modality, external-beam radiation therapy plus 5-FU + mitomycin
Local excision if favorable T1
APR if incontinent, or local treatment failure or recurrence after combined chemoradiation
Triple-modality therapy in bulky T3 and T4 lesions (role of APR controversial)
Adenocarcinoma
APR with 5-FU and radiation therapy as indicated
Melanoma
APR if potentially curable
Local excision if established metastases.

Perianal Paget's Disease

Similar to its mammary counterpart, perianal Paget's disease is an intraepithelial adenocarcinoma. The lesion is rare. Unlike in mammary Paget's disease, the perianal lesion is not universally associated with an underlying malignancy; however, a solid lesion can be identified in 50–86% of cases. In contrast to perianal Bowen's disease, the age group affected tends to be older, and the prognosis worse, particularly if an underlying malignancy is present. Macroscopic appearance is typically that of a well-demarcated plaque, which may be eczematoid and of variable coloration. Scaling may be present. Again, the lesion may be confused with a variety of other, more common dermatological conditions.

The origin of neoplastic cells in Paget's disease is unknown. The three most plausible theories of origin include that: (1) they arise in situ in the epidermis

from pleuripotent stem cells, (2) they arise from underlying carcinoma of the apocrine or sweat glands in continuity, or (3) they are metastatic from underlying adenocarcinoma. The malignancies most frequently associated with perianal Paget's disease are carcinomas of the apocrine or eccrine glands (36%), the rectum (22%), or the anus (11%). Of critical importance, therefore, is thorough assessment of the patient for an underlying malignancy. This can be achieved with a combination of clinical assessment, complemented as indicated by fiberoptic endoscopy, CT scanning, and gynecological assessment.

Treatment is similar to that of Bowen's disease for in situ lesions without an invasive component, that is, total excision confirmed by lesion mapping, with reconstruction either by skin grafting or preferably by primary closure (usually with a VY advancement flap). The presence of invasive adenocarcinoma in association with perianal Paget's disease is an indication for APR regardless of the level of the lesion, owing to the risk of disease in continuity. Any underlying lesion should be treated based upon its character, with the inclusion of adjuvant therapy where indicated.

Basal Cell Carcinoma

Basal cell carcinoma of the skin of the anal margin is rare. The lesion has the same macroscopic features as the common skin lesion, with raised edges and central ulceration. Even though the diagnosis is often delayed, these lesions are usually less than 2 cm in size at presentation. Treatment is as for any cutaneous basal cell carcinoma: full-thickness excision with a margin of 5–10 mm. Rarely, if the underlying sphincters are involved, APR may be indicated. The local recurrence rate is approximately 29%, depending on margins. Recurrence may be treated with reexcision if possible. Radiotherapy may have a role in this setting.

Squamous Cell Carcinoma (SCC)

Anal margin SCC behaves in a manner similar to its common cutaneous counterpart producing local symptoms of pruritus ani, bleeding, and a mass. The lesion may be associated with a long-standing cryptoglandular fistula. Size at presentation is generally between 2 and 5 cm. Many tumors are deeply penetrating at the time of presentation, and may involve the underlying sphincters. Between 5 and 10% of patients will have regional lymph node metastases at the time of presentation.

Wide local excision is recommended for most lesions just as it would be for skin lesions. Prognosis is worse for those lesions that encroach cephalad to the anal verge, supporting the concept of the surgical definition of the anal canal, demonstrating differing behavior for those lesions cephalad versus caudal to the anal verge. Lymphadenectomy is indicated for clinically involved inguinal nodes. Recurrence may be treated by reexcision or by APR as indicated. Long-term survival for primary tumors is estimated as being between 70 and 75%. Combined

modality therapy for anal margin SCC has not been prospectively evaluated, but may be appropriate in advanced-stage tumors.

Verrucous Carcinoma

The giant condyloma acuminata, or Buschke-Löwenstein tumor, may be regarded as intermediate in its malignant potential. While its potential for metastases is limited, it is frequently locally invasive, and recurrence rates after complete excision are high (65%). The tumor may transform into a locally invasive squamous cell carcinoma; thus the overall mortality for verrucous carcinoma is high at 30%. The lesion presents most frequently as a soft, cauliflower-like tumor that causes pain. Treatment is by complete local excision. If malignant transformation has occurred, or if the underlying sphincters are involved, APR may be indicated. Some lesions that have transformed to squamous cell carcinoma have responded to combined therapy with chemotherapy and radiation therapy.

Anal Canal Tumors

Epidermoid Tumors

Because squamous, basaloid, cloacogenic, and mucoepidermoid tumors of the anal canal tend to display similar clinical features, natural history, and response to therapy, they are commonly grouped together under the label ''epidermoid'' tumors. The typical clinical presentation is that of a mass, with associated pruritus, pain, and bleeding. At presentation, approximately 50% are between 1 and 3 cm in size, and 50% are more than 3 cm. In terms of depth of penetration, 24% are in situ, and 71% penetrate into muscle or fat. Of the deeply penetrating tumors, two-thirds are node negative and one-third node positive. Less than 10% have unresectable disease and 6% have distant metastases at the time of presentation. Hematogenous spread occurs preferentially to the liver, lung, and skin.

Historically, epidermoid carcinoma of the anus was treated with single-modality therapy, using either surgery or radiation. Early lesions were treated with local excision, and more advanced lesions with APR or radiation therapy, depending on institutional preference. Primary surgical resection was traditionally associated with variable results, with 5-year survival quoted as being between 20 and 75%, varying from center to center. The outcome in node-positive disease was dismal, with only 10% surviving 10 years. Introduction of the Nigro protocol of combined chemotherapy and radiotherapy for epidermoid carcinoma in the 1970s revolutionized therapy, producing outcome equal or superior to surgical resection with a high rate of functional sphincter preservation (70–75%). Current therapy is now focused on sphincter preservation, and includes local excision in early lesions and radiation therapy or combined-modality chemotherapy and radiation therapy for more advanced lesions. Major surgical resection is reserved

for recurrences and treatment failures after combined therapy, or patients in whom fecal incontinence is apparent at the time of presentation. A recent large retrospective series of more than 400 patients with anal cancer in the Veterans Affairs system in the United States found that 86% of patients were suitable for sphincter-preserving therapy. Only 14% required major surgical resection with stoma.

Local surgical excision remains an option for the treatment of early lesions. In particular, local excision is regarded as acceptable treatment of T1 lesions, or lesions limited to the subepithelial tissues. The extension of its application to include T2 lesions or its use in combination with radiation or combined-modality therapy remains controversial. Reported 5-year survival rates for the use of local excision vary widely, between approximately 60 and 90%. Clearly, this variation is in part due to differing selection criteria. Several studies reporting on local excision of lesions in the most favorable categories (lesions of less than 2 cm, with well-differentiated histopathology and which are confined to the epithelium) report cancer-specific long-term survival approaching 100%. Local excision in lesions with less favorable prognostic markers remains unproven. Patients should be regarded as unsuitable for local excision if significant poor prognostic factors are present, specifically, lesions larger than 2 cm, fixation to underlying sphincters or adjacent organs on either clinical examination or endoanal ultrasonography, or poorly differentiated histology. Those patients who have involved margins or invasion into underlying sphincter muscle after local excision should be considered for further treatment with chemoradiation.

The success of the Nigro protocol and the many variants it has spawned has relegated major surgical resection to a relatively minor role in the primary management of epidermoid anal cancer. There remain, however, certain subgroups of patients in whom APR may be considered for primary therapy, either alone or with combined-modality therapy. These patient groups would include (1) those for whom chemotherapy or radiation therapy is contraindicated (i.e., severely immunocompromised or previously radiated patients), (2) the fecally incontinent patient, or (3) any other patient who refuses combined-modality therapy. In addition, APR continues to play a pivotal role in salvage therapy after failed combined-modality therapy. Its role in the management of large primary tumors (extensive T3 and T4 lesions) remains under investigation.

While the success of combined modality therapy is impressive, local failure of primary or subsequent local recurrence will occur in between 10 and 35% of patients. The treatment of local failure remains controversial. Traditional wisdom dictated the use of APR in this setting. Again, the success of salvage APR varies markedly between series. Recently, prospective trials have included a protocol of chemotherapy for salvage after combined-modality therapy. The RTOG/ECOG trial published in 1996 examined the relative role of mitomycin in primary therapy of epidermoid cancer. As a second aim of this trial, the efficacy of salvage

therapy with repeat combined-modality therapy after failed primary therapy was assessed. This yielded modest results. Of 22 patients who underwent salvage therapy, 10 were biopsy positive after therapy, and underwent APR where appropriate. Of the remaining 12 who had a negative biopsy after salvage therapy, four later required APR and four died of progressive disease. Only four of the 22 remain disease free as a result of the salvage therapy, a success rate of only 18%. Hence, the claims of the authors that salvage chemoradiation should be attempted prior to surgical resection after failure of primary therapy seems a bit unjustified. Management of patients who fail sphincter-saving combined modality therapy or who develop locoregional recurrence remains controversial. A 1994 review of 204 patients from hospital in the Department of Veterans Affairs retrospectively compared the results of chemoradiation versus APR in this setting. Fifty-three percent of patients who underwent APR were subsequently alive at follow-up of 18 months, compared with only 19% of patients treated with chemoradiation. While it remains possible that high-toxicity salvage regimens with agents such as cisplatin may improve on these results, it appears that APR offers patients the best prospect of long-term survival after failure of primary therapy with chemoradiation. Future areas of research would include comparison of high-dose chemoradiation, surgery, and a combination of all modalities. Until these hypotheses can be tested, we would recommend surgical resection as the treatment of choice in the setting of local/regional recurrence or failure of primary therapy.

The treatment of locally advanced T3 and T4 primary lesions (those greater than 5 cm or invading local organs) remains controversial. While sphincter preservation with optimal oncological outcome remains the central focus of therapy, it needs to be noted that the rate of nodal metastases in these lesions is higher, and the locally extensive nature of the primary lesion implies that the underlying sphincter mechanism is often affected by the lesion itself, or is rendered incompetent after combined-modality therapy. Hence, consideration needs to be given to the possible role of surgery after combined-modality therapy in this setting. A recent retrospective French series, comparing radiation therapy alone versus radiation followed by surgery, indicates a possible role for APR in T4 lesions. While it may be argued that the absence of chemotherapy in this series represented suboptimal conservative therapy, the addition of surgery in T4 lesions improved the 10-year cancer-specific survival from 40 to 90%. This result was not significant, reflecting the small size of this series, but is clearly suggestive. Local control was also improved from 60 to 82%. While most contemporary centers would include chemotherapy in any conservative treatment arm for large or locally invasive primary lesions, this trial suggests that aggressive therapy of T3 and T4 lesions is indicated, and that prospective randomization to a variant of the Nigro protocol versus the addition of surgery is indicated.

In summary, combined-modality therapy remains the mainstay of the treatment of primary epidermoid cancer of the anus. Early lesions with favorable prognostic factors may be treated with local excision alone. Therapy of locally

advanced lesions may include both combined-modality therapy and APR. Local persistence and recurrence are optimally treated with APR. The addition of further combined-modality therapy warrants further evaluation.

Melanoma

Melanoma in the perianal region or anal canal is typically diagnosed late. In approximately one-third of patients, the lesion is nonpigmented, hindering diagnosis. The vast majority of lesions are diagnosed at a thickness of more than 2 mm, and the prognosis is almost uniformly grim, with less than 17% surviving 5 years and 10% surviving 10 years. The major controversy in the management of anal melanoma is the relative role of local excision versus APR. From a number of reports, no significant difference could be demonstrated between the two operations; however, the only long-term survivors have typically undergone APR. Hence, the authors recommend APR for node-negative disease.

Treatment of node-positive disease is more speculative. Wide local excision for local control may be appropriate when established metastases are present. A single case has been reported of long-term survival in a patient with inguinal nodal metastases treated with groin dissection.

Adenocarcinoma

True primary adenocarcinoma arising from the ductular epithelium of the anal canal is an exceedingly rare lesion. Because of this rarity, diagnosis is often late. Differentiation from low-lying rectal adenocarcinoma with extension into the anal canal may be difficult. The few published series of anal adenocarcinoma report a dismal outcome, with one series reporting 20 of 21 patients dead within 18 months.

Treatment options are not clearly defined owing to the rarity of the lesion. Small series support the treatment of T1N0M0 lesions with local excision only. More advanced lesions are usually treated with APR. Adjuvant therapy will generally employ a regimen similar to that for adenocarcinoma of the rectum, with 5-FU and radiation therapy. As it is often difficult to determine the true origin of anal canal adenocarcinomas, it seems most logical to treat with the regimen of success for rectal cancer, that is, with surgery plus chemoradiation. This approach may not benefit those with lesions arising in anal ducts, but gives the best chances possible for patients with rectal cancers extending to the anus.

THE ROLE OF VIRAL INFECTION AND IMMUNOCOMPROMISE IN THE GENESIS AND CLINICAL COURSE OF ANAL CANCER

There is significant evidence that infectious agents may play a role in the pathogenesis of anal neoplasia. Epidemiological studies have identified a number of

likely risk factors for the development of epidermoid cancer, including homosexuality, anal condylomata, human papilloma virus (HPV) infection, HIV infection, and a history of certain other sexually transmitted diseases. In addition, a marked increase in the incidence of anal cancer has been noted during the same time period as the spread of the AIDS epidemic. In the San Francisco area, the odds ratio for development of anal or anorectal cancer rose more than twofold during the period of time corresponding to rapid spread of HIV seropositivity. Studies have also indicated an increased risk of anal dysplasia and HIV positivity. The clinical significance of dysplasia is not defined.

An association between HPV and anal cancer is clear, with more than 60 variants of HPV having been identified. Subtypes 16 and 18 have been implicated in the pathogenesis of anal cancer. It has been suggested that there are two distinct populations of tumors in anal cancer, those that are HPV positive (mean age 63 years) and those that are HPV negative (mean age 72.5 years), although differences in the clinical behavior of these subtypes are currently lacking.

AIDS patients with CD4 counts of less than 200 represent a challenging clinical problem as they may respond unfavorably to radiation therapy with exaggerated radionecrosis of normal tissue. The increase in toxicity is also seen with chemotherapy, and in patients who are HIV positive. The optimum treatment modality for these patients is not clear, although it would appear that for HIV-positive patients who are not immunocompromised, treatment should not vary from the usual protocols, although longer treatment breaks may be indicated, and therapy must be tailored on an individual basis. For AIDS patients, treatment may well require a reduction in dose of both chemotherapy and radiotherapy, or replacement of combined-modality therapy by surgical resection. If the prognosis from the underlying HIV infection is poor, palliative surgical procedures may be indicated.

THE ROLE OF CHEMOTHERAPY IN THE TREATMENT OF ANAL CARCINOMA

Introduction

Information derived from the Surveillance and End Results (SEER) program indicates that anal canal carcinomas include four major histological subgroups. The most prevalent histology is squamous cell, which makes up 47% of cases, followed by 27% basaloid (cloacogenic), 20% adenocarcinoma, 1% melanoma, and 5% ''other.'' In general, squamous cell carcinomas are aggregated with basaloid/cloacogenic tumors when considering combined-modality therapy. This is due to similarities in the microscopic appearance (with the exception of the absence of keratinization in the latter group), frequent heterogeneity of the pathology observed within tumors such that both histologies are present simultaneously,

and the similar location of origin and patterns of spread. While the relevant information in the literature is sparse, some conflicting data exist as to whether there is a difference in outcome between these two most common histologies. In most reports and for purposes of this discussion, squamous and basaloid (cloacogenic) tumors are considered together.

This discussion on the role of chemotherapy will focus primarily on squamous and basaloid cancers as this subset of cancers is seen most commonly and its treatment has been best characterized. Adenocarcinomas and melanomas are less common and differ in both histology and behavior. Treatment of these two entities will be discussed briefly.

Chemotherapy in Squamous and Basaloid (Epidermoid) Anal Canal Cancer

Is Chemotherapy and Radiation Active Treatment for Squamous Anal Carcinoma?

Nigro and colleagues first reported on a regimen of preoperative therapy in a disease setting where APR had been the standard of practice. Their regimen, which became widely known as the ''Wayne State Regimen'' after the investigator's home institution, changed the focus of therapy from an emphasis on resection to an emphasis on preservation of the rectum and anus by providing alternative therapy to radical surgery, which had similar curative potential. As originally described, the combined-modality program consisted of radiation in the amount of 30 Gy given in 2-Gy fractions 5 days weekly with chemotherapy using 5-fluorouracil (5-FU) by 96-hr infusion at 1000 mg/m^2/day on days 1–4 (total dose per course 4000 mg/m^2) and 29–32 with mitomycin C (MMC) 15 mg/m^2/day on day 1. Four to six weeks later the first 12 patients in the series underwent APR. Because it was noted that 7/12 patients had no residual tumor at surgery, 14 additional patients treated were subjected to postchemoradiotherapy biopsy of the tumor bed, and only if the biopsy was positive or in the event of later recurrence was APR performed. At the time of the report 22/26 patients were alive and tumor free with 1–8 years of follow-up.

Over the next two decades various investigators reported sustained disease-free survival in 75–90% of over 500 similarly treated patients. Chemotherapy was traditionally given simultaneously with radiation, although there are no randomized trials in this disease setting that confirm that this approach is better than sequential use of the two modalities.

Results of the concurrent approach to the administration of chemotherapy and radiation are excellent. This approach has become established as standard. The individual contribution of the two modalities was not able to be discerned until randomized trials were performed.

Is Chemotherapy plus Radiation Therapy Better Than Radiation Alone?

Two large, well-conducted, prospectively randomized trials have been reported that have definitively answered this question. The European Organization for Research and Treatment of Cancer (EORTC) investigators, between 1987 and 1994, enrolled 110 patients with T3–4 N0–3 or T1–2 N1–3 anal cancer into a trial designed to compare radiation alone to radiation plus chemotherapy. The radiation component of therapy was more intensive than that of the Wayne State Regimen, reflecting greater experience with combination therapy and improved technology. In both study arms, patients were irradiated and subject to surgery as follows: 45 Gy was administered in 1.8-Gy fractions over 5 weeks. If partial or complete response was noted, a boost of 20 or 15 Gy was given after a 6-week rest. Surgical resection was performed when possible if patients either had not responded after the 6-week rest period or had residual disease after treatment was completed. Chemotherapy of 5-FU 750 mg/m^2/day as a 120-hr infusion on days 1–5 (total dose per course 3750 mg/m^2) and on days 29–33 accompanied by a single 15 mg/m^2 dose of MMC on day 1 was administered during radiation to 51 eligible patients. In 52 patients no chemotherapy was administered. Demographic factors were well balanced between arms.

Combined-modality therapy led to an 80% complete remission rate (CR) compared to 54% CR for radiation alone. Local-regional recurrence rates were significantly reduced by 18% with combined-modality treatment over radiotherapy alone. At 5 years, 32% more radiation-only patients had colostomies than did combined-modality patients ($p = 0.002$). While the progression-free survival was longer for combined-modality therapy, overall survival was not significantly different.

Patient and tumor characteristics such as age, performance score, maximum tumor length, proportion of the anal circumference involved by tumor, tumor thickness, and the presence or absence of skin infiltration were not prognostically important as endpoints. Three factors were prognostic: gender—women had better outcomes than men; nodal status—patients with positive nodes had higher rates of recurrence; and anal ulceration—patients with ulcerated tumors were more likely to have recurrence. Toxicities of therapy were not clearly different with the exception of an increased frequency of treatment-induced temporary anal ulceration among the combined-modality patients.

The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) Anal Cancer Trial Working Party also reported a definitive trial addressing this question. In this study, 585 patients (577 eligible) were entered. All were irradiated to 45 Gy. In 82% of patients an additional 15–20-Gy boost was given. The 295 patients randomized to the combined-modality treatment arm also received 5-FU 750 mg/m^2/day for 5 days (total dose per course 3750 mg/m^2)

during the first and last week of radiation and MMC 12 mg/m^2/day on day 1 of treatment. The local failure rate was much higher in the single-modality treatment group with 164 patients (59%) reoccurring versus 101 patients (36%) when combined-modality therapy was administered. This difference represented a 46% reduction in odds of local relapse. The risk of death from anal cancer was 0.71 when patients who received combined modality therapy were compared to those getting no chemotherapy ($p = 0.02$). There was no overall survival advantage between patients randomized to the two study arms.

The pertinent conclusions are that combined-modality therapy with 5-FU and mitomycin plus radiotherapy both reduces the need for colostomy and improves local-regional control without affecting overall survival when compared to radiotherapy alone. Most patients could survive, disease free, without loss of anal function or the need for radical surgery. The corollary of this conclusion is that patients who are not candidates for or do not wish to take chemotherapy can expect an equivalent survival rate but will more likely require colostomy.

Does MMC + 5-FU Improve Outcomes over 5-FU Alone?

Mitomycin is a drug with a broad spectrum of activity but response rates to single-agent therapy are usually limited, less than 15%. Acute toxicity is most often related to myelosuppression. Cumulative toxicity after repetitive dosing includes chronic myelosuppression, lung damage, and microangiopathic hemolytic anemia with renal compromise. The latter condition is often irreversible and commonly contributes to mortality in patients in whom it occurs. Therefore, the identification of the magnitude of incremental benefit, if any, arising from the administration of the MMC was an important issue. Identification of the incremental benefit was particularly relevant since the drug has not become a standard part of first-line regimens in any other disease site owing to its toxicity and its limited activity. Analysis comparing a number of individual series suggested that MMC did provide incremental benefit. One large, well-conducted trial that indicates that MMC does provide incremental benefit in this setting confirms this impression definitively.

In this trial, which enrolled patients between 1988 and 1991 and was conducted by investigators from the Radiation Therapy Oncology Group (RTOG) and Eastern Cooperative Oncology Group (ECOG), there were 291 assessable patients enrolled with epidermoid anal cancer who were randomized to one of two regimens. Therapy consisted of 45–50.4 Gy of pelvic radiation and continuous infusion 5-FU 1000 mg/m^2/day (total dose per course 4000 mg/m^2) for 96 hr either alone (145 patients) or with the addition of MMC 10 mg/m^2 (146 patients). When administered, MMC was injected twice, once in week 1 and once in week 5. On both study arms patients initially received 45 Gy in 1.8-Gy daily fractions but were boosted with an additional 5.4 Gy if tumor was palpable at the completion of the prescribed course of chemotherapy and radiation. At 6

weeks after completion of radiation and chemotherapy a full-thickness biopsy was performed, and if it was negative, the patient was observed for signs of recurrence.

In the group treated with two drugs 13 surgical procedures were considered indicative of treatment failure, i.e., colostomy, APR, or more extensive surgeries, compared to 32 such procedures in the single-agent group. At 4 years of follow-up the colostomy rate was 9% versus 23% and 73% versus 51% of patients were alive and disease free ($p = 0.0003$) for two- versus one-drug regimens, respectively. There was not a statistically significant difference in overall survival between arms.

Colostomies were most often required in patients with either T3–4 tumors or those with node-positive disease. Toxicities, particularly neutropenia and thrombocytopenia, were more common and more severe in the two-drug group. There were 23% grade 4 or worse toxicities in patients enrolled in the two-drug arm as compared to 7% in the single-drug group. Fatal sepsis was seen in 2.7% of two-drug and 0.7% of single-drug patients. Because of the increased incidence of treatment-related sepsis the investigators concluded that MMC should not routinely be administered to HIV-positive patients with anal cancer. However, in general the two-drug regimen did provide incremental benefit over single-drug treatment in combination with radiation.

Combined-Modality Therapy Using Radiation with 5-FU and Cisplatin

A phase II ECOG trial has been conducted to investigate whether 5-FU and cisplatin administered simultaneously with radiation had similar activity to that observed in squamous cell carcinoma of the esophagus. This trial was designed to generate activity and toxicity data as a prelude to incorporation into a randomized phase III study against standard therapy using 5-FU and MMC. Activity of 5-FU and cisplatin chemotherapy in anal carcinoma had been reported with a 55% response rate noted in locally recurrent disease. In the ECOG trial a total dose of 45 Gy radiation to a shrinking field followed by a 14.4-Gy tumor-directed boost was accompanied by chemotherapy. The chemotherapy was 5-FU 1000 mg/m^2/day infused over 96 hr on days 1–4 with cisplatin 75 mg/m^2 given on day 1. The chemotherapy was repeated on day 43. While 79% of patients had a complete remission there were 75% who had ≥grade 3 toxicity and one died of treatment-related complications of sepsis (antibiotic-associated *Clostridium difficile* colitis). Two large, prospectively randomized trials currently in progress, one sponsored by ECOG and the other by the UKCCCR, will compare radiotherapeutic strategies and 5-FU and either MMC or cisplatin.

Until the outcomes of the two randomized trials currently underway in which 5-FU and radiation given with either mitomycin or cisplatin become

known, the standard combined-modality treatment for epidermoid and carcinoma should be 5-FU plus MMC. The cisplatin and 5-FU combination therapy may have a role for locoregionally recurrent disease after initial standard combined-modality therapy in which the potential exists for resection if reduction in tumor size can be accomplished. While the 5-FU platinum regimen has not been formally tested in this setting, it provides the potential theoretical advantage of subjecting the recurrent tumor to a new drug.

Salvage Chemotherapy After Neoadjuvant Therapy Failure

Any discussion of salvage therapy in anal cancer must first emphasize that in a disease where local/regional recurrence predominates, resection may be curative and should be considered first. The use of radiation (including intraoperative and interstitial therapy) and chemotherapy to diminish the bulk of disease to the point where resection is possible can result in patient salvage.

In those patients with distant disease or disease beyond the scope of resection there is limited reported experience indicating drug activity. Single-agent activity has been reported with cisplatin, carboplatin, adriamycin, and for 5-FU given as bolus therapy or as a prolonged infusion. Combination regimens of 5-FU with cis- or carboplatin and of bleomycin plus vincristine given as a two-drug regimen or with cis- or carboplatin can result in complete and sustained remissions in some cases. Careful choice of drug, dose, and assessment of postinjection neutrophil and platelet counts is particularly necessary in patients who have had prior irradiation of the pelvis and been treated with MMC. Prior therapy with either or both treatments can result in long-lasting myelosuppression and predispose to profound neutropenia and/or thrombocytopenia. No one regimen has clearly been identified as standard or optimal. Although significant partial and even complete remissions can be observed, in most, if not all, cases such remissions are temporary.

Chemotherapy for metastatic or recurrent disease can result in meaningful remissions and disease palliation. Long-term remissions, while reported occasionally, are exceptional.

SPECIAL CONSIDERATIONS IN HIV-POSITIVE PATIENTS

Individuals with HIV infection and AIDS have clearly been identified as a group at higher risk of developing squamous and basaloid anal cancers. The largest series that identifies the outcomes of therapy of HIV-positive patients with anal carcinoma reported to date is that of Chadha. Among nine patients in this series, three had AIDS. The stages of the anal cancers were: stage 0: one, stage I: two, stage II: two, stage III: four patients. Seven patients received combined-modality therapy including 5-FU and MMC and two were treated with radiation alone.

Seven patients achieved complete clinical response, an outcome similar to that seen in HIV-negative patients. All stage I and II patients and one patient with stage III disease remained free of recurrence.

Skin toxicity exceeding grade 3 occurred in six patients. Despite the small number of patients in the series, this indicates a need for special vigilance in skin assessment during therapy for patients known to be HIV positive. The incidence and severity of myelosuppression was similar to that reported in patients not known to be HIV positive.

In summary, patients who are HIV positive can benefit from standard approaches to therapy for anal carcinoma with the caveat that there is almost no reported experience of toxicity or outcomes in patients with profound immunodeficiency and anal cancer or those with AIDS and advanced stages of anal cancer. The regimen of 5-FU plus cisplatin appears to be more myelotoxic than the 5-FU plus MMC program; therefore, the latter appears to be the treatment of first choice in this subgroup of patients as it is in the entire cohort of patients with squamous and basaloid anal carcinomas.

MEDICAL THERAPY OF ANAL ADENOCARCINOMA

Discerning the precise origin of distal rectal and anal tumors is often difficult. It seems likely that most adenocarcinomas noted in the anal canal are of rectal origin. The preliminary outcome of an intergroup CALGB, RTOG, ECOG, and SWOG phase II study of sphincter sparing treatment has been reported. Tumors within 10 cm of the dentate line that were clinically T1–2, less than 4 cm in diameter, and encompassed less than 40% of the bowel circumference were treated with full-thickness local excision in 164/180 registered patients. A total of 113 patients were eligible after exclusion of those with involved margins, inappropriate T stage, and size. The 60 patients with T1 tumors were simply observed. The 53 T2 patients were treated with 54 Gy in 30 fractions and given concomitant bolus 5-FU 500 mg/m^2/day for 3 days on days 1–3 and 29–31.

Grade 3 or greater neutropenia was noted in 10%, diarrhea in 18%, and skin irritation in 12%. After 24 months' median follow-up time, four patients had died of disease. Two of 113 patients who experienced isolated local recurrence were resected and remain disease free. The authors concluded that sphincter preservation and cancer control can be achieved in selected patients with superficial distal rectal cancers. For higher-stage tumors consideration should be given to use of an approach such as that described by O'Connell et al. for resection followed by postoperative adjuvant therapy with radiation combined with infusional 5-FU.

MEDICAL THERAPY OF ANAL CANAL MELANOMA

Little data on medical therapy for this rare tumor exists. In general, the approach to this entity has continued to focus on surgical extirpation of local or local-

regional disease. However, the natural history of melanoma is more commonly associated with distant metastatic disease than is squamous/basaloid anal cancer. Combined-modality adjuvant or neoadjuvant chemoradiation therapy is not known to be helpful in this setting. Adjuvant immunotherapy with interferon Alfa-2b, which has proven effective in improving the survival of patients with high-risk cutaneous melanoma, has not been tested in anal melanoma.

RADIATION THERAPY

Although anal neoplasms are rare, recent significant clinical and basic science research activities have led to important advances in the treatment of anal cancer. Sphincter-sparing approaches with radiation therapy and chemotherapy as the primary treatment modalities have replaced APR as initial therapy for most patients. Abdominal perineal resection continues to play a role in the management of recurrent disease and in selected cases as primary therapy. The optimal treatment regimen in terms of efficacy, functional outcome, and toxicity has not yet been determined and is the subject of ongoing research efforts.

The decision to use curative radiation therapy for epidermoid anal cancer is based on the location, locoregional extent, and distant metastatic spread of the tumor. Patients with epidermoid malignancies involving the perianal skin distal to the anal verge (anal margin) are preferably treated with sphincter-sparing primary surgical therapy, which is curative in 80% or more of cases. Candidates for curative radiation therapy should have no evidence of disease spread beyond the pelvic and inguinal lymph node regions.

The design of appropriate radiation fields is based on knowledge of the natural history and patterns of spread of the disease. Anal cancer may spread by direct extension to involve the anal sphincter or surrounding soft tissues in 50–55% of cases at diagnosis. The rectovaginal septum is a common site of tumor extension in women; invasion of the prostate in men, however, is rare and it is thought that Denonvilliers' fascia acts as a barrier to tumor spread. Lymphatic drainage of the region around the dentate line is to perirectal nodes and along the pathway of the inferior and middle hemorrhoidal vessels to the hypogastric and obturator nodes. The anal canal distal to the dentate line drains to superficial inguinal lymph nodes while the proximal anal canal and distal rectum drain to nodes along the superior hemorrhoidal vessels. Lymphatic connections exist to inguinal, external iliac, and presacral lymph nodes and these regions are at risk for nodal spread of disease.

Clinically detectable inguinal lymph node metastases are present in 10% of patients at initial diagnosis and 10–15% of those with clinically negative inguinal lymph nodes will have subsequent inguinal nodal failure after APR. The risk of inguinal node metastasis increases with increasing size of the primary tumor. Pelvic nodes are found to be metastatically involved in 25–45% of those who undergo APR. Spread of disease beyond the pelvis is uncommon, being detected

in only 5–10% of patients at diagnosis. Disease recurrence in sites beyond the pelvis occurs in 10–20% of those treated with primary radiation therapy.

The initial radiation treatment field should include the anal canal and inguinal and pelvic lymph node regions. More than 85% of inguinal lymph node recurrences are located within a rectangle defined by the following bony landmarks visible on an AP simulation film: superior border: top of the femoral head; lateral border: lateral femoral head; inferior border: 2.5 cm inferior to the ischial tuberosity; medial border: medial obturator foramen. Inclusion of the inguinal lymph nodes in AP:PA fields requires full-dose treatment of the femoral head and neck, which may place the patient at risk for subsequent fracture. In most patients, adequate coverage of the inguinal nodes may be achieved with techniques that minimize the femoral head and neck dose. This may be done by treating the patient in the supine position and including the pelvis and inguinal regions in the AP field while using a narrow PA field, which covers the pelvic nodes but excludes the majority of the femoral head and neck and therefore the lateral inguinal nodes. Electrons can be used to supplement the dose to the lateral inguinal nodes in the region that is included in the AP field but excluded from the PA field. The medial border of the electron field should be matched to the lateral exit border of the PA field on the anterior skin. This line can be determined at the time of simulation by placement of a wire on the anterior skin that matches the delineator wire for the PA field as seen on the fluoroscope. The choice of electron energy depends on the depth of the inguinal lymph nodes from the anterior skin. Although lymphangiography is the ideal method for determining this depth, this study is not universally available and the depth of nodes can be estimated from a CT scan by measuring the depth to the femoral vessels from the anterior skin. The use of anterior electron fields is feasible only in patients in whom the inguinal node depth is $\leq$5 cm.

Most patients with epidermoid anal cancer should be treated with combined radiation and 5-FU + mitomycin chemotherapy. Because the standard treatment regimen consists of a 4-day infusion of 1000 mg/m^2/24 hr 5-FU on days 1–4 and 29–32 in addition to 10 mg/m^2 mitomycin C on days 1 and 29, it is preferable to begin radiation therapy on a Monday or Tuesday to take full advantage of potential synergistic effects of chemotherapy and radiation on tumor cells.

In patients receiving combined modality therapy with both 5-FU and mitomycin, a reduction in the radiation field size to exclude clinically negative pelvic and inguinal lymph nodes may be made after the delivery of 30–36 Gy in 1.8-Gy fractions. The initial fields should extend from the L5–S1 interspace superiorly to a point 2.5–3.0 cm below the anus. After delivery of 3060 cGy, the upper border may be lowered to the greater sciatic notch at the inferior border of the sacroiliac joints. The final boost is delivered to a field that encompasses the primary tumor and any direct tumor extensions with a 2.5–3.0-cm margin. In the RTOG/ECOG combined-modality therapy trial the boost field consisted of a 10 cm $\times$ 10 cm

AP:PA field. Alternatively, the boost may be delivered with electrons using a direct perineal field. This is done by placing the patient in the lithotomy position with the table and gantry both rotated 90°. A 7-cm^2 or 8-cm^2 field is usually sufficient and the central axis is placed on the anus. The depth of the tumor must be measured in this position by rectal examination to determine the proper electron energy. Male patients should be instructed to elevate the penis and scrotum out of the field. The total dose to the anal tumor was 45–50.4 Gy in the RTOG/ECOG study.

Clinically positive inguinal or pelvic lymph nodes should receive the same total dose as the primary tumor. In patients who are not candidates for chemotherapy who are treated with radiation alone, the appropriate radiation dose is 45 Gy in 1.8-Gy fractions to the primary tumor and the pelvic and inguinal lymph nodes followed by a boost to the primary tumor to a total dose of 60–65 Gy.

Significant acute toxicity is associated with concomitant radiotherapy and chemotherapy, especially when mitomycin is included. Up to 25% of patients will experience severe or life-threatening toxicity and treatment-related death due to neutropenic sepsis has been reported in 3% of patients. Blood counts should be monitored twice weekly during radiotherapy and treatments withheld if the neutrophil count falls below 1000 or the platelet count below 50,000. Nearly all patients will experience a perineal skin reaction ranging from brisk erythema to confluent moist desquamation. Management consists of perineal hygiene with frequent bathing and analgesics. In severe cases a treatment break of 1–2 weeks may be required. The need for a treatment break must be balanced against the potential for decreased local control if the total treatment time is protracted.

Tumor response to radiotherapy ± chemotherapy may be slow; for larger tumors complete regression may take 3–12 months. In the RTOG/ECOG trial, 25 patients with positive biopsies received 9 Gy + 5-FU and cisplatin as salvage therapy; one-third of patients were rendered disease free without colostomy. However, some of the cases of successful salvage may have been attributable to the initial therapy with slow tumor response. Routine posttreatment biopsies are not recommended, especially in the early posttreatment period. A large tumor that continues to regress may be observed with frequent physical examination. Patients with an enlarging mass or new anal mass after complete clinical regression should be subjected to biopsy and considered for salvage APR if the biopsy is positive and there is no evidence of extrapelvic disease. Successful surgical salvage of local failures is possible in about 60% of cases. Patients with recurrence limited to the pelvis that is not surgically resectable for cure (i.e., due to pelvic sidewall involvement) should be considered for reirradiation + chemotherapy followed by resection and intraoperative radiation with electrons to boost sites of microscopic residual.

Selected patients with epidermoid anal carcinoma may be treated with APR; these may include those with large tumors who are not candidates for che-

motherapy or patients with fecal incontinence. A high rate of local failure after APR has been reported in patients with Mayo stage B2, B3, and C cancers. These patients should receive postoperative radiation therapy + 5-FU.

Long-term survival is achievable in 55–75% of patients treated with combined chemotherapy and radiation. Local control rates are in the 65–85% range and 90% of patients with local control can be expected to maintain a functional anus. Local control rates are higher in T1–2 cancers (75–100%) than in T3–4 cancers (55–75%). The probability of maintaining anal function is also higher in T1–2 tumors (>90%) than in T3–4 tumors (50–65%). Severe late treatment effects that require surgical intervention or affect social life occur in about 15% of patients and are usually diagnosed within 2 years from the time of treatment. The most common late complications include fecal incontinence, intestinal obstruction, chronic diarrhea, chronic pelvic pain, fistula, and femoral fracture. Up to 10% of patients with locally controlled disease may require colostomy to manage late effects of treatment.

As described in the text above, optimal management strategies for lesions such as anal adenocarcinomas and melanomas remain poorly defined. Although there is certainly room for improvement, as survival rates are low, the rarity of these lesions prohibits controlled trial evaluations. Still, attempts at improving success rates, such as with the application of interferon in melanomas post resection, are warranted. In contrast, using cooperative group mechanisms, epidermoid anal cancers can be investigated. Regarding anal canal epidermoid carcinomas, there are several clinical and basic research issues that deserve discussion and further study.

CLINICAL RESEARCH ISSUES

1. Will increasing the dose to the primary in the combined-modality setting result in improved local tumor control?

The local failure rate after combined-modality therapy with radiation and 5-FU + mitomycin is ≥20%. Two retrospective series of patients treated with radiation and 5-FU suggested improved local control in patients who received radiation doses >55 Gy. It is not known if increasing the dose above 50.4 Gy in patients who receive both 5-FU and mitomycin will result in improved local control with acceptable toxicity; higher doses of radiation are being evaluated in current prospective trials. An additional issue regards the best approach to salvage, surgery, or further radiation therapy.

2. Is there a subset of patients in whom radiation therapy without chemotherapy is preferred treatment?

A randomized EORTC trial of radiotherapy ± 5-FU and mitomycin in patients with T3–4 or node-positive anal cancer has demonstrated improved locoregional control and colostomy-free survival in patients who received chemo-

therapy. A second randomized trial from the United Kingdom compared radiation alone to radiation with 5-FU and mitomycin and included T1–4 tumors. Similar results were reported with improved locoregional control but no survival benefit to combined-modality therapy. The local control rates on the radiotherapy-alone arm in this trial may have been compromised by the 6-week delay from completion of 45 Gy to initiation of boost radiotherapy. Excellent results with radiation alone ± local excision for early-stage anal cancers have been reported.

3. What is the preferred treatment for HIV-positive patients?

HIV-positive patients are at increased risk for treatment complications with radiation and chemotherapy. Studies of combined-modality therapy in HIV-positive patients have reported an increased need for treatment breaks, hospitalization to manage acute toxicity, and chemotherapy dose reductions as well as worse survival in HIV-positive patients than in HIV-negative patients.

4. Are there equally effective but less toxic radiation-chemotherapy combinations?

Significant acute toxicity is associated with the addition of mitomycin to radiotherapy and 5-FU; treatment-related deaths have occurred in 2–3% of patients entered on randomized trials. Current research efforts are being focused on cisplatin as a potential substitute for mitomycin. An ECOG pilot study with radiation, 5-FU, and cisplatin reported grade 4 or 5 toxicity in 37% of patients, a rate comparable to that seen with mitomycin + 5-FU.

BASIC SCIENCE RESEARCH ISSUES

1. What is the biological basis for the clinically improved results seen with the addition of 5-FU and mitomycin to moderate-dose radiation therapy?

The addition of mitomycin to radiation therapy and 5-FU has been shown to result in improved colostomy-free survival, locoregional control, and disease-free survival, but no reduction in distant failure. Mitomycin has been shown to result in synergistic cytotoxicity when combined with radiation or 5-FU in mammalian cell lines. The mechanistic basis for this synergistic interaction is not known. Elucidation of this mechanism may allow for development of novel therapeutic strategies such as targeted gene therapy.

2. What role does human papilloma virus (HPV) infection play in the pathogenesis of anal cancer and what is the mechanism by which HPV infection predisposes to the development of anal cancer?

HPV DNA is detected in the majority of epidermoid anal cancers when studied using the polymerase chain reaction. It is not presently known how HPV infection predisposes to the development of anal cancer. HPV proteins have been shown to bind to the tumor suppressor gene p53 protein product and with the retinoblastoma tumor suppressor gene protein product. Determination of the exact mechanism may lead to novel therapies for prevention or treatment of anal cancer.

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Pancreatic and Periampullary Tumors

Blair M. Rowitz
Anderson Area Medical Center, Anderson, South Carolina

Douglas Brown, Barry C. Lembersky, and Mark S. Roh
Allegheny General Hospital, Pittsburgh, Pennsylvania

INTRODUCTION

Approximately 27,000 new cases of pancreatic cancer were expected to be diagnosed in the United States in 1997. Although the pancreas is the tenth leading site in terms of new cancer diagnoses, the pancreas represents the fourth most common site of cancers causing death. Exocrine malignancies account for 95% of all pancreatic malignancies. Owing to the vague and nonspecific nature of symptoms, these tumors generally present late in their course. In fact, the average time from onset of symptoms to diagnosis of pancreatic carcinoma is 8 weeks. Thus, less than 10% of patients present with disease confined to the pancreas while nearly 50% have locally advanced disease and 40% have visceral metastases. The overall survival rate for pancreatic cancers has risen from 1% in the 1960s to 5% between 1986 and 1992. To date, site of origin and resectability remain the most important predictors of survival.

Peripancreatic tumors can functionally be divided into periampullary/pancreatic head tumors and those occurring in the body and tail of the pancreas. In general, clinical presentation, diagnosis, and initial treatment of pancreatic tumors are more dependent on the anatomical site than on the pathological classification of the tumor. Nearly 70% of peripancreatic tumors are found in the periampullary and pancreatic head region while the remainder occur in the body and tail. Periampullary tumors may arise from the pancreas (85%), the distal common bile duct (10%), or the periampullary duodenum and ampulla of Vater (4.5%). The vast majority of body and tail tumors are pancreatic adenocarcinomas. Papillary

tumors, cystic tumors, neuroendocrine tumors, carcinoid tumors, lymphomas, and sarcomas may be found throughout the pancreas and will be discussed later in the text.

SURGERY

Tumors at or near the ampulla of Vater usually cannot be differentiated on the basis of clinical, radiological, or intraoperative assessments. Indeed, even histological diagnosis can be difficult. As a result, a common diagnostic approach and initial management is indicated for these neoplasms. The diagnostic goals are twofold. First, the presence of malignant neoplasm must be determined and differentiated from benign sources of biliary obstruction. Second, once the presence of neoplasm has been confirmed, the tumor must be staged to determine resectability. Currently no single screening test has proven to be effective in the diagnosis of ampullary tumors. Several imaging modalities are available for the assessment of symptomatic patients in whom there is a clinical suspicion of malignancy. Figure 1 represents an algorithm describing the diagnostic and staging strategies for periampullary tumors.

Transabdominal ultrasound (US) is an inexpensive, noninvasive, yet accurate diagnostic examination with a sensitivity reported as high as 78%. In general,

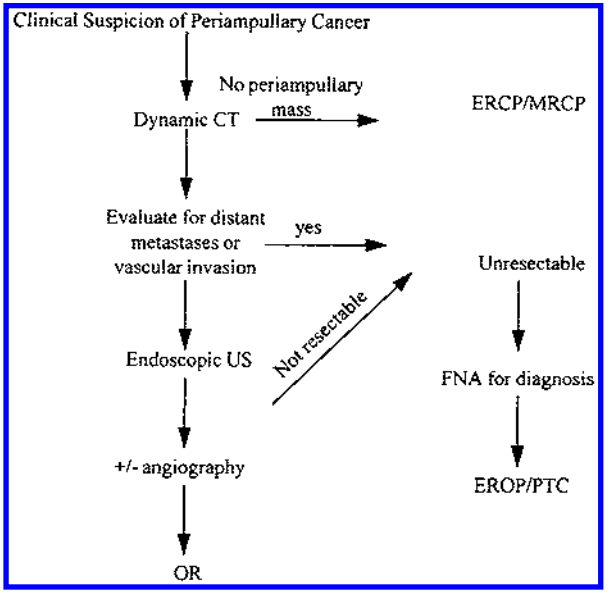

Figure 1 Diagnosis/staging of periampullary tumors.

neoplastic lesions will appear hypoechoic when compared to surrounding pancreatic tissue and other structures. Additionally, US allows the examiner to evaluate biliary or pancreatic duct dilatation, local extension of tumor, vascular involvement, lymphadenopathy, and liver metastases. US is operator dependent, however, with up to 15% of studies proving to be technically inadequate owing to overlying bowel gas or patient obesity. Additionally, a large number of false-positives occur secondary to the difficulty in differentiating neoplastic lesions from lesions of focal pancreatitis. Although lesions of focal pancreatitis are usually hyperechoic compared to surrounding structures, these findings are not uniform and thus may create a diagnostic dilemma.

Recent advances in the technique of dynamic computed tomography (CT) have led to the emergence of CT as the initial examination for visualization of the pancreas. Intermittent dynamic CT with 5-mm cuts is performed after intravenous iodinated contrast agents and oral iodinated or barium sulfate agents are administered. Owing to their hypovascular nature, lesions in the head of the pancreas are seen as lesions of diminished attenuation. Sensitivities as high as 80% have been reported. The most striking limitation of dynamic CT is the difficulty in detecting primary tumors or liver metastases less than 2 cm in size. Although CT and US provide similar information with regard to tumor size, ductal dilatation, lymphadenopathy, and metastatic disease, CT has replaced US in the diagnosis and staging of periampullary tumors as a result of the virtual absence of technical failures and the ability of CT to diagnose other intra-abdominal sources of presenting symptoms.

Until recently, angiography has been the procedure of choice to evaluate vascular invasion. Using digital subtraction techniques combined with delayed imaging for venous anatomy, the celiac axis, portal vein, superior mesenteric vein, and splenic vein can be evaluated for encasement or occlusion. Angiographic findings correlate very well with resectability. In a recent clinical review, 77% of patients without vascular encasement or invasion were found to be resectable, while no patients with celiac, portal, or SMV occlusion were found to be resectable. In the same series, 35% of patients with vascular encasement were found to be resectable. The emergence of endoscopic ultrasound has recently limited the role of angiography in many centers to the delineation of vascular anatomy. This vascular anatomy will be abnormal in roughly one-third of patients, thus identifying potential pitfalls during surgical resection. Experienced surgeons, on the other hand, can easily recognize the most common anatomical variants.

The recent development of endoscopic US (EUS) techniques represents a major advancement in the diagnosis and staging of periampullary tumors. In experienced hands, diagnostic sensitivity and specificity as high as 100% and 96%, respectively, have been reported. EUS is also useful for staging periampullary neoplasms, achieving significantly higher accuracy in terms of vascular and

lymph node invasion than CT, US, and angiography. EUS is also significantly more accurate in detecting smaller tumors than CT and US, including tumors as small as 0.5 cm. Limitations include difficulty in differentiating neoplasm from focal pancreatitis and a formidable learning curve with respect to training and diagnostic accuracy.

The main benefit of endoscopic retrograde cholangiopancreatography (ERCP) lies in the ability to differentiate between benign and malignant causes of biliary and pancreatic duct strictures. As ERCP allows the examiner to endoscopically visualize and potentially biopsy the major papilla, it is highly accurate in detecting periampullary tumors although little staging information can be provided. This accuracy is not without cost—major morbidity (pancreatitis, cholangitis, perforation, bleeding) occurs at a rate of 7% with a postprocedural mortality of 1%. Given its invasive nature, ERCP should be limited to cases of diagnostic uncertainty after CT and EUS or for therapeutic maneuvers to alleviate biliary obstruction in acutely ill or unresectable patients. Percutaneous transhepatic cholangiography is indicated for similar patient groups with dilated intrahepatic ducts in whom biliary cannulation cannot be accomplished via ERCP secondary to proximal obstruction.

Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive technique for delineating biliary and pancreatic ductal anatomy. Using heavily weighted T2 images, stationary fluids such as bile and pancreatic secretions have a high signal intensity while background structures and flowing blood have a low signal intensity. This combination of imaging characteristics allows for optimal imaging of the biliary tree and pancreatic ductal system. The major papilla is visualized in only 40% of cases under current imaging protocols, however. Hence, ampullary carcinomas remain a challenge to MRCP, limiting its current use to cases where nonneoplastic biliary obstruction or distal biliary carcinomas are suspected.

CT- or US-guided fine-needle aspiration (FNA) can achieve a sensitivity and specificity of 95% in the detection of pancreatic neoplasms. Concerns over the tumor seeding of needle tracts has limited the role of FNA to those patients with unresectable disease. Advances in EUS-guided FNA may revitalize FNA in the near future.

To date, surgical resection represents the only chance for cure of periampullary adenocarcinoma. Given the recent development of endoscopic and percutaneous biliary decompression, operative management is generally reserved for patients in whom surgical resection can be achieved. The primary goal of preoperative staging is to determine the extent of distant spread and local invasion. Although recent clinical data raise the possibility of palliative or more aggressive resections in the face of vascular involvement, it is generally accepted that patients with distant metastases or invasion of the portal or superior mesenteric veins are deemed unresectable. Microscopic lymph node involvement and

invasion of adjacent structures should not preclude resection if surgical margins can be cleared.

As discussed earlier, the anatomical proximity of ampullary, distal common bile duct, duodenal, and pancreatic head tumors mandates a similar approach to preoperative staging. Resectability rates of ampullary, distal common bile duct, and duodenal tumors are higher than those of their pancreatic counterparts, likely secondary to their earlier clinical presentation. These tumors are also less likely to invade proximal vascular structures. An algorithm for the operative management of periampullary tumors is proposed in Figure 2. A discussion of the operative options follows.

Laparoscopy plays an important role in the staging of peripancreatic tumors. Forty percent of patients without evidence of distant spread on CT or angiography will have hepatic, omental, or peritoneal metastases less than 2 cm in size found on laparoscopy. Pelvic metastases, which may be missed at laparotomy, may also be visualized laparoscopically. This allows for the avoidance of

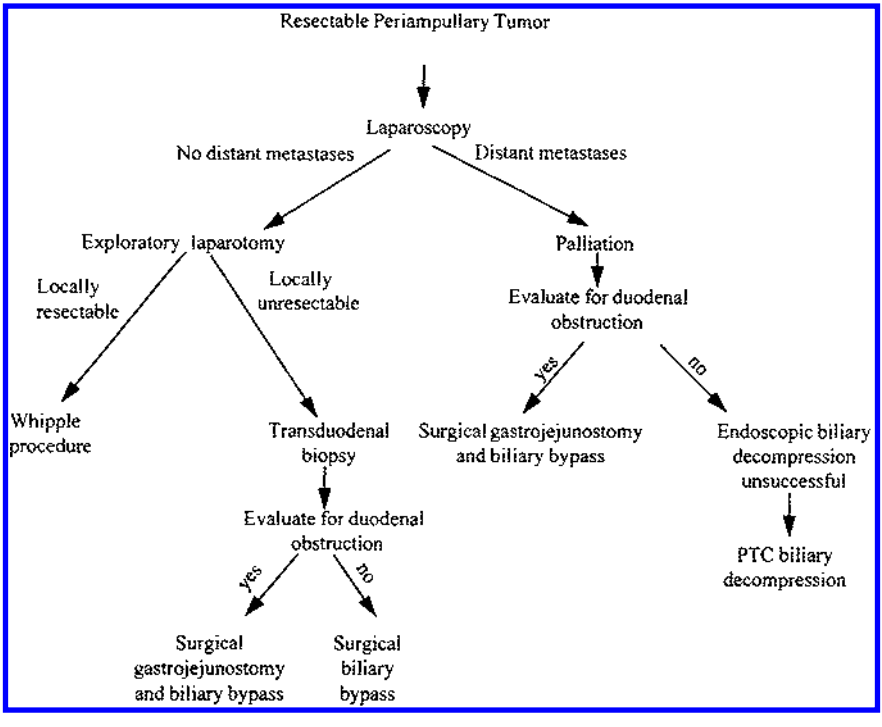

FIGURE 2 Operative management/palliation of periampullary carcinomas.

a laparotomy incision in the face of an extremely poor prognosis. The role of laparoscopic biliary bypass in this situation is not yet determined.

A one-stage pancreaticoduodenectomy, the Whipple procedure, is the procedure of choice for most patients with resectable tumors at or near the head of the pancreas. The procedure consists of an en bloc resection of the gallbladder, cystic duct, distal common bile duct, antrum, duodenum, proximal jejunum, head and neck of the pancreas, and the right half of the greater omentum. Literally dozens of techniques have been described for reestablishing intestinal and biliary continuity. Three anastomoses must be performed—pancreaticojejunostomy, gastrojejunostomy, and hepaticojejunostomy.

Perioperative mortality should be near or less than 5% at institutions experienced in the management of these patients. Deaths are usually caused by anastomotic leakage resulting in intra-abdominal sepsis progressing to multisystem organ failure. Delayed gastric emptying is the most common source of morbidity following the Whipple procedure, occurring in as many as 50% of patients. Management is conservative, including gastric decompression and promotility agents, as many patients will improve within the first few postoperative weeks. Between 5 and 20% of patients will develop leakage at the site of the pancreaticojejunostomy, resulting in the formation of pancreatic fistulae. Most patients can be managed nonoperatively with the careful placement of drainage tubes. Other surgical complications, including biliary fistulae, abscess, gastrojejunostomy leaks, and bleeding, are significantly less common. Only 1% of patients will require reoperative exploration.

Long-term survival data following the Whipple procedure are difficult to interpret, owing to differences in patient staging and selection for operation, resectability rates, and pathological stage of disease. Additionally, a significant number of patients who are alive at 5 years ultimately succumb to recurrent tumor. By far, the most important predictor of survival is the anatomical site of the tumor origin. Whereas 5-year survival for pancreatic ductal adenocarcinoma is a rare event, survival rates as high as 70% have been reported in patients with true ampullary carcinoma. Tumor size greater than 2 cm, regional lymph node involvement, residual tumor, perineural invasion, and advanced tumor grade have also been correlated with lower rates of long-term survival.

A one-stage pancreaticoduodenectomy in which the stomach, pylorus, and proximal 1–2 cm of duodenum are preserved was described by Longmire in 1978. This procedure potentially offers a decrease in postgastrectomy symptoms, operating times, and a theoretical improvement in gastrointestinal function. Follow-up reviews from the same institution revealed no improvement in operative times and an actual increase in the incidence of delayed gastric emptying in the immediate postoperative period. Another disadvantage lies in the possible compromise of tumor-free margin, especially in the case of tumors that invade the duodenum.

Pancreaticoduodenectomy with Portal Vein Resection

Inability to separate pancreatic tumor from the portal vein has until recently been a locoregional contraindication to resection. Frequently, this has been the only obstacle preventing resection. A number of recent retrospective reviews have demonstrated that resection of the portal vein with either primary anastomosis or placement of prosthetic grafts can be performed with complication and mortality rates similar to those of standard pancreaticoduodenectomy. These series suggest that there is a subset of patients who would benefit from resection despite adherence to or invasion of the portal vein. Given the dismal prognosis of these patients, pancreaticoduodenectomy is potentially a palliative resection at best.

Total Pancreatectomy

Total pancreatectomy offers the theoretical benefit of a more radical cancer operation in the face of a potentially multifocal disease process. Morbidity and mortality rates, including a very brittle and debilitating diabetes insipidus, are significantly higher, despite the avoidance of a pancreaticojejunostomy. There is no conclusive evidence that total pancreatectomy achieves improved survival rates. Thus this procedure cannot be recommended except in the instances of documented multifocal disease, resectable tumor extending into the distal pancreas, or an extremely friable distal pancreatic segment, which precludes a safe anastomosis.

Local resection of pancreatic tumors was first described by Halsted in 1899. The indications for local resection of ampullary tumors as opposed to the Whipple procedure remain controversial to this day. While local resection is clearly of benefit for benign tumors, opponents of local resection argue that malignancy is ultimately found in 40% of ampullary tumors. Even frozen-section examination fails in 14% of cases. Recent clinical evidence suggests that benign tumors less than 3 cm and carcinomas confined to the duodenal mucosa can be resected locally with acceptable outcomes as long as clear margins can be achieved. Patients who are prohibitive operative risks should also be considered for local excision. Clinical trials using EUS as a staging modality should shed further light on the indications for local resection.

PALLIATIVE TREATMENT

The majority of patients with periampullary cancers are unresectable either at the time of diagnosis or upon operative exploration. Therapeutic goals with regard to palliation include relief of biliary obstruction, relief of duodenal obstruction, and pain management.

Biliary Obstruction

Jaundice is the most common presenting symptom of periampullary carcinoma. Recently, nonoperative management of biliary obstruction has become available with the advent of percutaneous transhepatic and endoscopic stent placements. Several prospective, randomized trials have demonstrated results in terms of efficacy and morbidity of surgical versus nonsurgical interventions. Endoscopic and percutaneously placed stents must be changed periodically owing to infection and recurrent infections. It is therefore recommended that patients undergoing laparotomy for attempted resection or relief of duodenal obstruction be bypassed surgically. The technique of surgical bypass is variable and dependent upon the individual surgeon's experience. Biliary-duodenal anastomoses are contraindicated in the face of tumor proximity. Cholecystojejunostomy should be avoided in patients with tumors extending proximally along the bile duct near the junction of the cystic duct. This leaves choledochojejunostomy as the procedure of choice in most patients. The role of laparoscopic biliary bypass is yet to be determined.

Duodenal Obstruction

Patients who present with symptoms of duodenal obstruction should be palliated with an operative gastrojejunostomy if they are reasonable operative candidates. Fifteen percent of asymptomatic patients will go on to develop symptoms of duodenal obstruction. During exploration, a decision to proceed with a gastrojejunostomy should be made on an individual basis, taking into account the presence of symptoms and the extent of local tumor invasion. Historically, antecolic anastomoses have been performed to prevent delayed obstruction by tumor progression. More recently, advocates of posteriocolic anastomoses have claimed better gastric emptying with a reasonably low incidence of delayed obstruction (4%).

Pain

Intraoperative chemical celiac splanchnicectomy has been shown to be efficacious in 80% of patients undergoing a palliative procedure. Monoparesis and loss of sphincter control can occur secondary to splanchnic denervation. As most patients have pain refractory to pharmacological measures, percutaneous splanchnicectomy can be performed.

BODY AND TAIL TUMORS

Solid Tumors

Ductal adenocarcinomas of the body and tail represent 25–30% of exocrine pancreatic malignancies. Series reporting other histological tumor types are rare,

consisting primarily of case reports. Preoperative diagnosis and management of body and tail tumors is similar to that of periampullary tumors although jaundice is not commonly seen. When jaundice is present, it usually represents extensive hepatic involvement rather than biliary ductal obstruction.

Ductal Adenocarcinomas

Patients with adenocarcinomas of the pancreatic body and tail present with symptoms very late in their clinical course. Insidious symptoms such as vague abdominal discomfort and fatigue generally progress to back pain and extensive weight loss before the diagnosis is made. By the time a patient develops back pain, celiac plexus invasion has usually occurred, resulting in a tumor that is not resectable. If a high index of suspicion can lead to an early diagnosis, the clinician should proceed with evaluation for resection, recognizing that less than 10% of tumors are resectable and long-term survival is rare. Documented low morbidity and mortality rates for resections in experienced centers and the possibility of a tumor of a more favorable histological type obligate an evaluation for local extension and metastatic progression with the intention of treating a resectable lesion.

Pancreatic Lymphomas

Pancreatic lymphomas comprise less than 1% of pancreatic neoplasms and nearly always represent involvement of the pancreas secondary to a systemic hematological lymphoma. After tissue diagnosis is made with intraoperative or percutaneous needle biopsy, further treatment is nonoperative, consisting of chemotherapy with or without radiation treatment.

Other Solid Tumors

Other solid tumors of the pancreas are very rare, with no single center able to accumulate a significant series of patients. These tumors include acinar cell tumors, carcinoid tumors, sarcomas and connective tissue tumors, giant cell carcinomas, oat cell carcinomas, and adenosquamous carcinomas. As these tumors are very rare, therapeutic recommendations must be based on the pathophysiology of their histological counterparts in other organ systems.

Cystic Tumors

Cystic neoplasms constitute 10% of all pancreatic cysts and less than 1% of pancreatic neoplasms. They range from having benign or indolent courses to frank malignancy with or without metastatic disease. Once identified, these lesions are highly curable with surgical resection and therefore an aggressive approach is warranted. The radicalness of resection is dependent on the histological aggressiveness and tumor location. Differentiating cystic neoplasms from inflammatory pseudocysts is a difficult diagnostic dilemma, however. Given the

risk of tumor cell dissemination, needle aspiration is generally avoided whenever possible. Several clinical factors suggest neoplasia is present as opposed to inflammatory disease. Neoplastic cysts are more common in middle-aged women while pseudocysts usually follow an episode of acute pancreatitis, trauma, or a history of chronic pancreatitis. On CT, multiple cysts suggest an inflammatory process while lobulation and septa are characteristic of neoplasm. At operative exploration, pseudocysts commonly have thick walls and are adherent to the omentum and neighboring structures. During operation on symptomatic or persistent pseudocysts, the cyst wall should be biopsied for histological evaluation. If doubt remains, the pseudocyst should be resected rather than violating and draining a cystic neoplasm.

Mucinous Cystic Neoplasms

Mucinous cystadenomas are virtually impossible to differentiate from mucinous cystadenocarcinomas in the absence of gross metastatic disease or local extension without extensive histological sectioning and evaluation. Mucinous cystadenomas have a notoriously heterogeneous appearance and may have only one small focus of invasive epithelium. Thus, all mucinous cystic lesions should be considered malignant and treated with either a Whipple procedure or a distal pancreatectomy depending on tumor location. If a thorough pathological evaluation does not reveal invasion, 5-year survival approaches 95%. Roughly half of all patients with invasive mucinous cystic disease achieve long-term survival. These lesions occur predominantly in middle-aged women.

Serous Cystadenomas

Serous cystadenomas also occur predominantly in middle-aged women and have a characteristic honeycomb finding with ''sunburst'' calcifications on CT. They are benign and usually found incidentally but may become symptomatic owing to compression of surrounding tissues. Resection is recommended for both symptomatic and asymptomatic lesions as definitive diagnosis is difficult without obtaining tissue.

Mucinous Ductal Ectasia

Mucinous ductal ectasia, on the other hand, occurs most commonly in men and generally in the head of the pancreas. It is characterized by dilatation and filling of the main pancreatic duct with thick, viscous mucus by hyperplastic columnar epithelium. Growth occurs along the duct prior to invading surrounding parenchymal tissues. The lesions are premalignant and Whipple resection is recommended with frozen-section confirmation of surgical margins.

Papillary Cystic Neoplasms

Otherwise known as Hamoudi tumors, papillary cystic tumors are very uncommon and affect women between 15 and 35 years of age. These tumors may be

cystic, solid, or mixed. They follow an indolent but malignant clinical course, necessitating partial pancreatectomy.

Other Cystic Tumors

Endocrine and ductal adenocarcinomas may undergo necrosis with cystic degeneration. When resection is feasible, a Whipple procedure or distal pancreatectomy is recommended.

RADIATION THERAPY FOR PANCREATIC CANCER

The use of radiation therapy in the treatment of adenocarcinoma of the pancreas has proven to be one of the most difficult challenges for the radiation oncologist. This is related to the extreme biological aggressiveness of this tumor as well as the radiosensitivity of the surrounding normal tissues. Pancreatic cancer has a very high propensity for regional nodal, visceral, peritoneal, and hematogenous metastases, which make the likelihood of cure very small even with optimal local therapy. Local-regional control is difficult as the radiation oncologist is limited by the presence of stomach, duodenum, spinal cord, kidney, and liver, which are all located near the pancreatic tumor mass, and all with radiation tolerance less than total doses that would be needed to control the primary tumor. Radiation therapy is often the treatment recommended for adenocarcinoma of the pancreas as only 5–15% of the cases have long-term cures of their disease from either a Whipple resection or total pancreatectomy.

A large variety of radiation techniques have been explored for the primary treatment of pancreatic cancer. Neutrons have been tried because of their increased radiobiological effectiveness compared to conventional x-rays, but without any suggestion of a survival benefit compared to conventional (photons) treatment modalities. Median survival has generally been in the range of 6–9 months. Charged particles (protons) have been used because of the ability to better localize radiation dose, but these trials have likewise not shown a survival benefit. The radiation techniques that are still being used include conventional radiation therapy (often combined with at least 5-FU chemotherapy), radioactive implantation into the tumor mass, and intraoperative electron-beam radiation therapy (IORT).

External-beam irradiation is generally given with a four-field technique utilizing anterior, posterior, and right and left lateral fields to encompass the tumor mass and the regional nodal drainage areas. Although there is rationale to treat the entire pancreas because of the risk of multicentricity and because of the risk of peripancreatic nodal disease along the entire length of the pancreas, little seems to be gained by treating the entire gland in terms of either improved cure or palliation, and the patient morbidity is definitely increased. The AP-PA radiation fields will treat a portion of the right kidney (for tumors in the head of the pancreas), so care must be taken that the lateral fields do not treat an excessive amount of renal parenchyma (for anterior placed kidneys) and that the left kidney

is appropriately shielded. The dose to the spinal cord can easily be kept below 45 Gy (usual tolerance dose) by using lateral fields, although too much weighting from the laterals can often result in a higher-than-necessary dose to the liver. One must also ensure adequate coverage of the uncinate process, when indicated, and the porta hepatis to treat both nodal disease in this site and potential direct extension along the common bile duct.

Patients should generally be treated with high-energy x-rays of 10 MeV or greater, although little improvement in the dose distribution is seen when going to much higher x-ray energies. The radiation dose per fraction should be kept at 180–200 cGy to minimize the acute morbidity (primarily nausea) that occurs with therapy. The optimal radiation dose is not known, as one is trading increased toxicity for presumed improvement in local control. The Gastrointestinal Study Group (GITSG) has compared 40 Gy to 60 Gy, both combined with 5-FU, but using techniques generally inferior to those used today. However, this study suggests a small, nonstatistically significant advantage to the higher radiation dose. Typical radiation doses are 45 Gy to the tumor and nodal basins with a cone-down to the tumor mass with a margin to a total of about 60 Gy when radiation is used as primary therapy. The single most important management issue during radiation therapy is controlling nausea and maintaining the patient's weight. This will generally require antiemetics and intensive dietary counseling.

Postoperative Treatment

Radiation therapy is often employed postoperatively in an attempt to improve local control and survival. Although surgical resection is critical for the successful management of pancreatic adenocarcinoma, it is not usually curative. The rate of curative resectability (Whipple resection or total pancreatectomy) for patients with pancreatic adenocarcinoma ranges from 5% to 15%. Five-year survival among all patients is 0.4%, which is increased to just 4% among resected patients. This result is only slightly better than the survival of unresected patients of 0.2%. In a review from the Massachusetts General Hospital, only 20% of patients presented with tumors potentially treatable by surgical resection, an additional 30% of patients had local-regional disease, and the remainder had unresectable or metastatic disease. Even when patients are adequately resected, patients are at risk for local-regional recurrence.

It has been extremely difficult in multi-institutional studies to evaluate local-regional tumor control. Local-regional recurrence occurs in up to 70–80% of patients who undergo surgery alone. Data from the Massachusetts General Hospital (MGH) series reviewing recurrence patterns have shown that, of patients who have had a Whipple resection with curative intent, approximately 60% have clinical or pathological evidence of local tumor recurrence. This is presumably related to the minimal surgical margins that are often obtained on the portal vein, the

pancreatic resection margin, and in the areas of regional nodal extension. Therefore, it would seem possible that postoperative radiation therapy could sterilize microscopic residual disease left after resection. The GITSG studies have generally shown a 50% incidence of local failure with adjuvant 5-fluorouracil (5-FU) radiation. Among patients observed at the University of Pennsylvania, 85% recurred locally compared to 25–50% receiving adjuvant chemoradiation.

A number of studies have been performed to determine whether adjuvant radiation therapy and chemotherapy (with 5-FU) is superior to surgery alone and have consistently suggested an advantage to the combination following curative surgical resection. Data from the Mayo Clinic and from the GITSG have demonstrated an improvement in median survival and local control by the use of this combination.

The GITSG performed a study of patients who underwent curative resection and were then randomized between no further therapy versus irradiation and 5-FU chemotherapy. The GITSG trial used radiation therapy delivered in two courses of 2000 cGy each separated by a 2-week rest for a total dose of 4000 cGy given concurrently with 5-FU given as a 3-day bolus during weeks 1 and 5, at a dose of 500 mg/m^2/day. Fluorouracil was then continued on a once-weekly basis for 2 years or until recurrence was noted. Surgery consisted of a Whipple procedure or a total pancreatectomy. Of the patients who had curative surgery, approximately 33% had disease confined to the gland, 40% had contiguous invasion, and 30% had adjacent nodal involvement. Median survival for the treatment group (21 months) was significantly longer than that observed for the control (10.9 months). Two-year survival was 46% for patients randomized to treatment and 18% for the control group. In a subsequent analysis of nonrandomized patients who were treated with adjuvant regimen, 1- and 2-year survivals were 76% and 57%, respectively. Despite the small number of patients, these data suggest that the combination of adjuvant chemotherapy and radiotherapy following partial or total pancreatectomy for attempted cure may substantially prolong median survival time and improve local control.

Intraoperative Treatment/Implantation

IORT has been utilized for a number of years to increase the dose to the pancreatic mass and improve local control. This technique is used to avoid delivering the full radiation dose to normal tissues, which could otherwise be damaged by the radiation therapy. Advantages to IORT include substantially less radiation to the most sensitive normal structures (except for the c-loop of the duodenum). As the intraoperative dose is given in a single fraction, it is biologically much more effective than the same dose given in a fractionated regimen, although damage to normal tissue in the radiation field may be greater. Limitations of IORT include tumor thickness and diameters less than 8.0 cm. In this technique patients receive

a combination of approximately 45 Gy of conventional external-beam radiation, and then during surgery receive an additional dose of 15–20 Gy with high-energy electrons delivered to the primary tumor bed/mass.

A few single institutions have reported on their results with IORT including MGH and the Mayo Clinic. In groups of 73 patients from the MGH and 52 patients from the Mayo Clinic, median survivals of approximately 13 and 15 months, respectively, have been reported, which may be somewhat better than that obtained with external beam alone, with acceptable morbidity, and good palliation. Two-year survivals (15–25%) appeared no different than that obtained with external beam. In the analysis from the MGH, approximately 50% of the patients remained pain free for the rest of their life, and 75% of patients had good pain relief after completion of IORT.

Another approach that has generated significant interest is the use of intraoperative I^{125} implantation. I^{125} is an isotope with very limited tissue penetration, so the dose is tightly confined to the implanted volume. Reports from Thomas Jefferson Hospital suggest improved local control and survival compared to external beam alone, but the trial was not randomized and patient selection may have been quite different between the arms. It was reported that the addition of I^{125} (120 Gy) to external beam (55–60 Gy) improved local control from 22% to 80%, although median survival remained unchanged at 7 months. These investigators also noted an improvement in median survival by the addition of a variety of chemotherapy regimens from 7 to 14 months. The major theoretical problem with implantation is that it is usually indicated in the treatment of patients with disease unresectable because of tumor extension into the portal vein or superior mesenteric vessels. As these structures cannot be implanted, the dose to this portion of the tumor will be low.

Preoperative Irradiation

The role of preoperative radiation in carcinoma of the pancreas is in evolution. There are a number of potential advantages of preoperative radiation therapy for pancreatic carcinoma. These include biological (decreased tumor seeding at the time of laparotomy, thereby decreasing subsequent peritoneal tumor recurrence, and increased radiosensitivity due to better oxygenated cells not devascularized by surgery), physical (no postsurgical bowel fixation potentially increasing small bowel toxicity), and functional (potentially unresectable tumors may be downstaged to enable surgical resection). In addition, patients discovered to have disseminated disease subsequently on restaging studies after preoperative chemoradiation therapy would not be subjected to laparotomy. Potential disadvantages of preoperative therapy include treatment of patients with unrecognized metastatic disease. The primary disadvantage of postoperative chemoradiation therapy is the inability to deliver postoperative therapy to all patients in a timely manner

because of operative complications or delayed recovery after pancreaticoduodenectomy.

Fox Chase Cancer Center reported on 15 patients who received infusional 5-FU, bolus mitomycin C, and external-beam radiation therapy. Thirteen patients underwent surgical exploration approximately 1 month after completion of radiation therapy and three were found to have metastatic disease that was not detected by CT scan and precluded resection. Ten patients underwent resection and six remained free of disease to 40 months later. One patient had a pathologically complete response and one patient had recurrence at 19 months on last follow-up. Another study reported 28 patients with localized adenocarcinoma of the pancreatic head who received preoperative chemoradiation (5-fluorouracil 300 mg/m^2/day, and 50.4 Gy). Upon restaging prior to laparotomy, five patients were found to have metastatic disease. At laparotomy, three patients were found to have unsuspected metastatic disease, three patients had unresectable locally advanced disease, and the remaining 17 patients were able to undergo surgical resection.

The M. D. Anderson Center reported on preoperative chemoradiation and surgery in 41 patients compared with 19 patients who received pancreaticoduodenectomy and postadjuvant chemoradiation therapy. The median survival was 19.2 months in the 41 patients treated with preoperative radiation therapy and pancreaticoduodenectomy and 22 months in patients treated with postoperative chemoradiation. The preoperative chemoradiation therapy group contained a smaller percentage of patients with positive microscopic retroperitoneal margins as well as positive local regional lymph nodes. Twenty-six percent of the patients were found to have progressive disease on restaging prior to laparotomy and as a result, patients were spared a laparotomy.

UNRESECTABLE CANCER OF THE PANCREAS

Locally unresectable cancer of the pancreas often causes local symptoms including pain, biliary obstruction, and gastric obstruction for which local therapy is desirable. External-beam irradiation or external and intraoperative or interstitial radiation for unresectable pancreatic carcinoma is not curative, and has no impact on survival although local control is considered better. The major problems remain local-regional and distant failure (especially in the liver). Survival is 40–50% at 1 year and 20% at 2 years, and only occasionally are there survivors over 5 years.

Although it has not been extensively studied, there are data suggesting a role for local-field external-beam radiation therapy in patients with surgically unresectable disease who lack distant metastasis. The GITSG performed its first randomized trial with patients with surgically unresectable disease without distant metastases. Patients received high doses of radiation therapy (60 Gy administered

as a double split course), alone or in combination with 5-FU, compared with a more moderate dose of radiation therapy (40 Gy as a split course) combined with 5-FU. Patients who received 5-FU with radiation therapy were then maintained on weekly 5-FU for a total of 2 years. The median survival was 20 weeks for patients treated with 60 Gy alone, 36 weeks for patients treated with 40 Gy + 5-FU, and 40 weeks for patients treated with 60 Gy + 5-FU, indicating that median survival was prolonged in patients who received combined-modality therapy versus radiation therapy alone.

A second GITSG trial involving 42 patients randomized to supervoltage, continuous-course radiation therapy to 54 Gy with bolus 5-FU 350 mg/m^2 during the first 3 days and last 3 days followed by Senustine methotrexate and 5-FU (SMF) for 2 years versus SMF alone revealed an improved median survival for the combined-modality therapy (42 weeks) compared with the chemotherapy alone (32 weeks). Overall survival following this combined-modality treatment program (41% at 1 year) was significantly superior to that following SMF chemotherapy (19% at 1 year). Both studies suggest that patients with locally unresectable pancreatic cancer have superior median survivals with combined-modality therapy.

THERAPY OF METASTATIC PANCREATIC CANCER

Pancreatic cancer is frequently diagnosed at a relatively late stage and survival is generally extremely poor. The treatment of patients with unresectable or metastatic cancer of the pancreas is palliative. Optimizing the management of these patients requires a thorough understanding of the natural history of the disease, the pathophysiology and treatment options of cancer-associated pain and cachexia, and the current palliative role of systemic chemotherapy.

Pain Management

Pain is reported by approximately 90% of patients with advanced pancreatic cancer and is among the most dreaded symptoms associated with this disease. Adequate and durable pain control is one of the most important and challenging aspects of managing these patients. The various pain syndromes reflect the anatomy of the primary tumor and metastatic sites. Located in the upper retroperitoneal cavity, the pancreas is surrounded by numerous visceral organs including the stomach, duodenum, spleen, liver, and transverse colon. Pain can occur because of tumor infiltration of these structures and by obstruction of the hollow viscera. The pain is frequently described as crampy, intermittent, and somewhat generalized and may be accompanied by nausea, vomiting, and other manifestations of bowel obstruction. In addition, the pancreas is richly innervated by sympathetic and parasympathetic fibers. Inflammation and necrosis of the expanding

primary tumor mass produces a boring pain typically with radiation toward the back. Extensive hepatic metastases commonly cause pain by stretching the liver capsule. Bone metastases commonly cause pain and significant direct percussion tenderness. It is also important to recognize that pain may result from some of the primary treatment modalities. Surgical intervention can sometimes be complicated by nerve damage and cause persistent pain. Abdominal radiation therapy and chemotherapy-induced enteritis and diarrhea can also be associated with pain and other discomfort. At any given time the pain experienced by a patient may be multifactorial in origin and its perception and impact influenced by other factors including coexisting depression, anorexia, and fatigue.

Each specific complaint of pain should be thoroughly investigated. The primary objective is to identify the source of pain and to eliminate it. The pain of bowel and biliary obstruction is frequently prevented by initial surgical exploration accompanied by choledochojejunostomy and gastrojejunostomy. However, despite these procedures bowel obstruction may occur during the course of the disease. Conservative management with bowel rest, fluid hydration, and correction of electrolytes frequently results in symptomatic improvement. Surgical intervention may be indicated if conservative therapy is ineffective. Radiation therapy with or without chemotherapy provides symptomatic palliation of pain associated with the locally advanced primary tumor in 30–40% of patients. Unfortunately the pain relief is usually temporary.

Direct pharmacological block of the celiac plexus is frequently helpful for the palliation of pain. Afferent pain fibers from the pancreas traverse through the celiac ganglion and pass into the dorsal root ganglion. Alcohol or phenol may be injected into the celiac plexus either at the time of initial surgery or percutaneously under fluoroscopic or CT guidance. Side effects of postural hypotension and urinary retention are generally transient. The procedure is effective in approximately 50% of patients and often decreases the dosage of narcotic needed, thus minimizing narcotic-induced side effects.

For the majority of pancreatic cancer patients, narcotic analgesics are the most important component of a comprehensive pain management program. Several general principles should be followed. First, rather than administering the narcotic on an ''as needed'' basis, dosing should be with a sustained-release preparation given around the clock with rescue doses of immediate-release narcotic given for breakthrough pain. A stepwise approach to dosing is most commonly employed. Patients are started at a low dose of a sustained-release agent, which is then titrated upward until pain relief is achieved or intolerable side effects experienced. Second, while oral administration is usually preferable, narcotics may be given via the rectal, subcutaneous, transdermal, or epidural routes. Third, careful attention should be given to the side effects of narcotics. Constipation is the most frequent side effect and must be aggressively prevented with increased fluid and fiber intake and an adequate bowel regimen consisting of a

laxative and stool softener. Nausea is generally transient and usually well controlled with an oral antiemetic as needed. Confusion and lethargy may occur as the systemic dose of narcotic increases. Switching to the epidural route, while more invasive and cumbersome, significantly decreases the total narcotic dose required for pain control and thus minimizes these troubling side effects. Fourth, while patients develop tolerance to narcotics and require higher doses to achieve the same effect, they do not develop the behavior of narcotic addiction. Physicians and medical staff should counsel patients and their families accordingly and stress the value of narcotic analgesics in obtaining palliation of pain.

Systemic Chemotherapy

Until recently chemotherapy has been essentially ineffective for patients with metastatic pancreatic cancer. Phase II clinical trials in pancreatic cancer have been conducted for almost every chemotherapeutic agent ever investigated. Response rates for single agents range from 0% to 27%. Historically, the antimetabolite 5-FU was the most widely used agent for pancreatic cancer. When 5-FU is given as a bolus, the response rate is about 15%. To date, attempts to increase the activity of 5-FU such as administration by protracted venous infusion, biomodulation with leucovorin or interferon, or combining it with other minimally active chemotherapeutic agents have been unsuccessful.

The most promising agent in decades for pancreatic cancer is gemcitabine. Gemcitabine is a prodrug antimetabolite that requires intracellular phosphorylation to its active form. In initial phase II trials the drug demonstrated modest antitumor activity. The observation that many patients appeared to have symptomatic improvement even without objective tumor shrinkage prompted further investigation and, importantly, a refinement in the clinical trials process for patients with pancreatic cancer. Survival remains the most important study and clinical end-point when evaluating a new agent or therapy. For pancreatic cancer it is also critically important to define the palliative effect of any therapy. A new method to assess clinical efficacy was utilized in recent trials of gemcitabine. The investigators defined a clinical benefit as a composite measurement of pain (analgesic consumption and pain intensity), performance status, and weight gain. A clinical benefit response required a sustained improvement in at least one parameter without worsening in any others. In a phase III clinical trial of 126 patients with symptomatic pancreatic cancer, patients were randomly assigned to gemcitabine 1000 mg/m^2 or 5-FU 600 mg/m^2. Both drugs were given weekly. Clinical benefit response was observed in 24% of gemcitabine-treated patients compared to 5% of 5-FU-treated patients. The survival rate at 12 months was 18% for gemcitabine patients compared to 2% for 5-FU patients. In another study gemcitabine demonstrated a 27% clinical benefit response in 63 patients with pancreatic cancer previously refractory to 5-FU. Gemcitabine is generally well

tolerated with neutropenia as the only significant toxicity. Based on these studies the FDA recently approved gemcitabine for use as first- or second-line therapy for patients with pancreatic cancer and it is now the most widely used agent. Current clinical trials are investigating the combination of gemcitabine with 5-FU and other agents in an effort to further improve palliative therapy of pancreatic cancer.

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10

Pancreatic Endocrine Tumors

H. Richard Alexander, Jr. and Robert T. Jensen
National Institutes of Health, Bethesda, Maryland

John L. Doppman
Warren G. Magnuson Clinical Center and National Institutes of Health, Bethesda, Maryland

INTRODUCTION

Pancreatic endocrine (or neuroendocrine) tumors (PET) are uncommon neoplasms; the most common are insulinomas and gastrinomas, which have an incidence of approximately 0.5–1 per million people per year. Patients with PETs warrant special consideration because of the unique clinical features associated with these tumors. They are classified as APUDomas (amine precursor uptake and decarboxylation) and are cytochemically and structurally similar tumors thought to arise from neuroendocrine cells present throughout the body. Common to all APUD cells is the capacity to synthesize and secrete polypeptide products that have specific hormonal actions. The tumors appear cytostructurally similar under light microscopy and stain positive for chromogranin, a soluble protein present in neurosecretory granules, and for neuron-specific enolase (NSE). Pancreatic endocrine tumors are also referred to as ''islet cell tumors,'' which is not accurate as they most likely arise not from islet cells but from neuroendocrine stem cells present in the ductal epithelium of the exocrine pancreas.

PETs are classified as functional if they are associated with a clinical syndrome secondary to the unregulated secretion of a physiologically active polypeptide product or hormone such as gastrin, insulin, glucagon, vasoactive intestinal polypeptide (VIP), or somatostatin. Because functional PETs are usually diagnosed based upon the clinical sequelae of excess hormone production, the tumors

are small and frequently cannot be detected by routine imaging studies. Nonfunctional PETs do not produce any measurable secretory products based on currently available methods of detection or produce secretory products such as pancreatic polypeptide (PP) or chromogranin that do not result in any recognizable clinical syndrome. Nonfunctional PETs are more common than functional and patients generally present with symptoms referable to the large size of the tumor or their metastases.

PETs can occur in a sporadic form not associated with an inherited disease usually as a single tumor presenting in the fourth or fifth decade of life and with a slight female preponderance or as part of an inherited syndrome. Inherited syndromes frequently associated with PETs include MEN-1, and less commonly von Recklinghausen's disease, tuberous sclerosis, and von Hippel–Lindau disease. The autosomally dominant inherited syndrome MEN-1 has an equal predilection for males and females. In MEN-1 there are usually multiple tumors within the pancreas that are associated with multigland parathyroid hyperplasia and frequently pituitary adenomas. Of the more common PETs, gastrinoma and PPomas are most usually malignant and insulinoma is benign in approximately 85% of cases.

The first clinical recognition of a PET was made almost 100 years ago and various syndromes secondary to functional PETs have been described in the earlier part of this century. One of the most widely recognized of which is the Zollinger-Ellison syndrome (ZES) secondary to gastrinoma. The diagnosis, localization, and treatment of PETs have undergone considerable evolution since their recognition as a clinical entity. Recently, the gene for MEN-1 has been cloned and will provide an opportunity to understand the mechanisms of tumorigenesis not only in PETs associated with MEN-1 but possibly in sporadic tumors as well.

DIAGNOSIS AND PRESENTATION

Operative resection is the only curative modality for patients with localized PETs. The approach and success of the operation is dependent upon establishing the correct diagnosis of a functional PET, determining the possibility that the patient may belong to an MEN-1 kindred, performing appropriate radiographic imaging studies in an attempt to locate the primary tumor and extent of possible metastatic spread, and ensuring proper medical management of the functional sequelae of excess hormone production prior to surgery.

The clinical presentation of patients with functional PETs is a result of the symptoms associated with unregulated secretion of one polypeptide or hormone. The most common symptom in patients with ZES or gastrinoma is abdominal pain secondary to gastric hyperacidity. Because ZES is an unusual condition and the abdominal complaints are nonspecific, most patients are initially treated for other more common upper gastrointestinal disorders for 3–6 years before the

correct diagnosis is made. Up to two-thirds of patients have diarrhea as the initial symptom and in up to 20% it is the only symptom. Although rare, the initial presentation may be a catastrophic event such as severe bleeding or jejunal perforation in up to 10% of patients.

The biochemical confirmation of ZES is usually made on the basis of elevated basal gastric acid output (BAO) and fasting gastrin levels. A BAO of greater than 15 mEq/L or more than 5 mEq/L in a patient who has undergone a previous acid-reducing procedure and an elevated fasting serum gastrin will result in a sensitivity of 99% and a specificity of 90% in diagnosing gastrinoma. Although maximum acid output in response to pentagastrin stimulation is also elevated in patients with ZES, its use as a diagnostic criteria offers no advantage over BAO alone. Therefore, gastric acid hypersecretion resulting in a pH of less than 2.5 is an essential component of ZES. In a patient with a fasting gastrin level greater than 1000 pg/ml, a gastric pH of less than 2.5, and no history of a previous Billroth II gastrectomy, the diagnosis of ZES can be made without further studies. There are some conditions associated with elevated fasting serum gastrin levels without gastric acid hypersecretion including chronic gastritis with achlorhydria, pernicious anemia, gastric cancer, or patients who have previously undergone vagotomy.

On the other hand, there are other conditions associated with a low gastric pH and an elevated fasting serum gastrin such as retained gastric antrum, chronic gastric outlet obstruction, chronic *Helicobacter pylori* infection, G-cell hyperplasia of the gastric antrum, extensive small bowel resection, and chronic renal failure. Except for retained gastric antrum these conditions characteristically have fasting serum gastrin elevations between 100 and 1000 pg/ml. To distinguish these conditions from ZES several provocative tests have been developed that measure the serum response of gastrin following intravenous secretin or calcium or a meal. The secretin-stimulation test is the most commonly used provocative test because of its simplicity and high specificity, and high sensitivity. A positive secretin-stimulation test is defined as a rise in fasting serum gastrin by more than 200 pg/ml and is observed in almost 90% of patients with ZES. Moreover, a positive secretin-stimulation test can reliably exclude the above-mentioned conditions associated with mildly elevated fasting serum gastrins. If a diagnosis of ZES is strongly suspected and the secretin-stimulation test is negative, then a calcium-stimulation test administered as a 3-hr infusion should be performed.

In over 90% of cases, insulinomas result in symptoms caused by a level of hypoglycemia that is insufficient for normal cerebral function. Termed neuroglycopenic symptoms, these include visual disturbances, headache, confusion, irritability, weakness, and altered consciousness including seizures or coma. In up to half of patients with insulinoma, symptoms secondary to excess catecholamine secretion occur including sweating and tremors.

The diagnosis of insulinoma is made by documenting symptomatic hypo-

glycemia associated with inappropriately elevated serum insulin levels during a monitored fast. In over 97% of patients a supervised fast of 48 hr will be sufficient to document insulinoma with the development of clinical symptoms and/or a plasma glucose less than 45 mg/dl. In addition, patients with insulinoma will usually have serum insulin levels greater than 5 μU/ml; 97% will have levels greater than 10 μU/ml. An insulin-to-glucose ratio of greater than 0.3 is typical. Because endogenous insulin is synthesized as a precursor, proinsulin, quantification of the immunoreactive higher-molecular-weight component of insulin referred to as the proinsulin-like component (PLC) is also helpful in diagnosing insulinoma. More than 80% of patients with documented insulinoma have a PLC greater than 25%. The differential diagnosis of hypoglycemia and hyperinsulinemia includes other rare pancreatic causes of elevated insulin levels, insulin autoimmune hypoglycemia (insulin antibodies), administration of exogenous insulin, and oral sulfonylureas. In practice, the determination of proinsulin levels or C-peptide levels and a urine screen for sulfonylureas will eliminate the possibility of surreptitious insulin administration or factitious hypoglycemia.

Other functional PETs are rare and in the majority of cases malignant. Because initial symptoms can be intermittent, mild, and nonspecific, there is usually a significant delay between onset of symptoms and diagnosis. Metastases are present at the time of presentation in more than half of patients. On presentation, the manifestations of VIPomas (vasoactive intestinal polypeptide) can be severe and debilitating and include high volume (greater than 3–5 L/day), watery diarrhea leading to dehydration and severe hypokalemia. In addition, patients may have hypochlorhydria and hypercalcemia. The diagnosis is usually made on the basis of a pancreatic tumor associated with diarrhea and an elevated serum VIP concentration (greater than 170 pg/ml). Serum VIP levels may be episodic and fluctuate over time in individual patients. Therefore, VIP levels should be measured when the patient is having diarrhea. Glucagonomas are associated with a characteristic dermatitis termed migratory necrolytic erythema, which may be misdiagnosed as another dermatological condition initially. Because of the catabolic effects of glucagon, patients develop weight loss, anemia, glucose intolerance, and hypoaminoacidemia. The glucose intolerance reflects the gluconeogenic and glycogenolytic effects of glucagon in the liver. The diagnosis of glucagonoma is usually made on the basis of the characteristic skin rash, diabetes, weight loss, evidence of a pancreatic mass, and an elevated serum glucagon level. Serum glucagon levels are greater than 500 pg/ml and in 70% of patients are greater than 1000 pg/ml. The manifestations of somatostatinoma relate to the known generally inhibitory physiological effects of the hormone. It inhibits the release of multiple gastrointestinal hormones and decreases gallbladder contractility. However, symptoms are generally mild and nonspecific and include diabetes, gallbladder disease, weight loss, and diarrhea. Interestingly, despite its inhibi-

tory effects on intestinal motility, diarrhea occurs because of the inhibitory effect on secretion of pancreatic enzymes and bicarbonate. Tumors may be found incidentally when diagnostic imaging studies are being conducted to evaluate symptoms. Growth-hormone-releasing factor (GRF) can be elaborated by pancreatic endocrine tumors (GRFomas). GRF will result in growth hormone release from the pituitary causing clinical acromegaly. Therefore, a GRFoma should be suspected in an individual who has clinical features of acromegaly and a pancreatic tumor. Serum GRF levels greater than 300 mg/ml are consistent with the diagnosis.

LOCALIZATION OF PETs

Once a biochemical diagnosis of a functional PET has been made, imaging studies are usually performed to identify primary tumors, which are frequently small and may be difficult to identify intraoperatively, and to identify the presence of metastatic unresectable disease in the liver. In general, noninvasive studies are performed initially such as transabdominal ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and except in the case of insulinoma, somatostatin receptor scintigraphy (SRS). In addition, invasive localization studies may be performed such as endoscopic ultrasound (EUS), selective celiac and superior mesenteric angiography, and selective intra-arterial secretin or calcium stimulation with hepatic venous sampling. The latter tests are based on the principle that secretin and calcium are secretagogues for gastrinomas and insulinomas, respectively, and by selectively infusing branches of the celiac axis or superior mesenteric artery that supply discrete regions of the pancreas, a step-up in hormone release can be measured in the hepatic veins. In the past, transhepatic selective portal venous sampling has been used to directly measure hormone concentration gradients at different sites in the splenic and portal veins, but because of the need to perform transhepatic catheterization of the portal venous system and the complications associated with it, it has been largely replaced by the equally sensitive intra-arterial stimulation and venous sampling procedure.

Gastrinomas can be multiple in number and located in the duodenum, pancreas, regional lymph nodes, or rarely in ectopic sites such as the ovary, small bowel, bile duct, or liver. Most preoperative imaging modalities currently available have limited capacity to identify small primary duodenal gastrinomas. Insulinomas, on the other hand, are always located within the pancreatic parenchyma. It has been argued that the use of preoperative localization tests for patients with insulinoma is not necessary or cost-effective whereas others have found that preoperative localization of insulinomas is essential. US is the least useful test for localizing PETs with a sensitivity of about 25%; CT scan has only about a 50% sensitivity. Recent advances in MRI techniques have improved its sensitivity and,

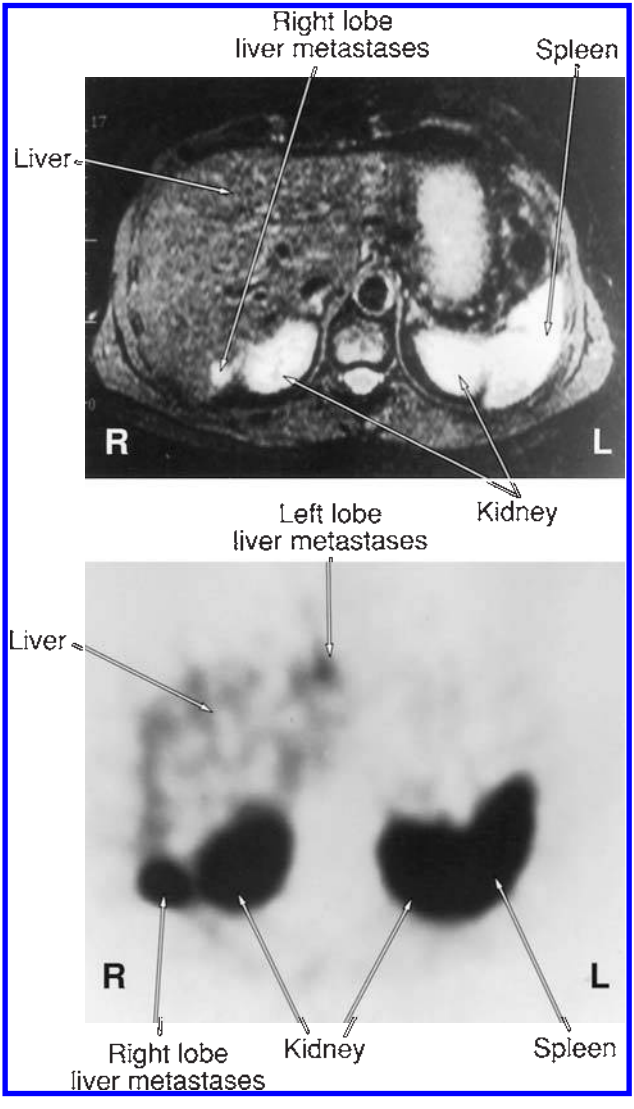

FIGURE 1 Sagittal MRI image (top) showing the high signal abnormality in the posterior aspect of the right lobe of the liver in a patient with Zollinger-Ellison syndrome, and sagittal SRS image (bottom) showing the same area in the posterior aspect of the right lobe of the liver and identifying a second otherwise occult left-lobe liver metastasis.

in the localization of gastrinomas, the combination of US, CT, and MRI has the same sensitivity as MRI alone. In addition, MRI and SRS are very sensitive tests for detecting metastatic disease in the liver. EUS has a sensitivity of up 82% and a specificity of 95%. It appears to be particularly useful for localizing PETs within the pancreatic parenchyma and has been advocated as the preoperative localization test of choice in patients with insulinoma. It can provide relatively precise information about the location of the PET within the pancreatic parenchyma and its relationship with the pancreatic duct. However, it is an invasive test and its

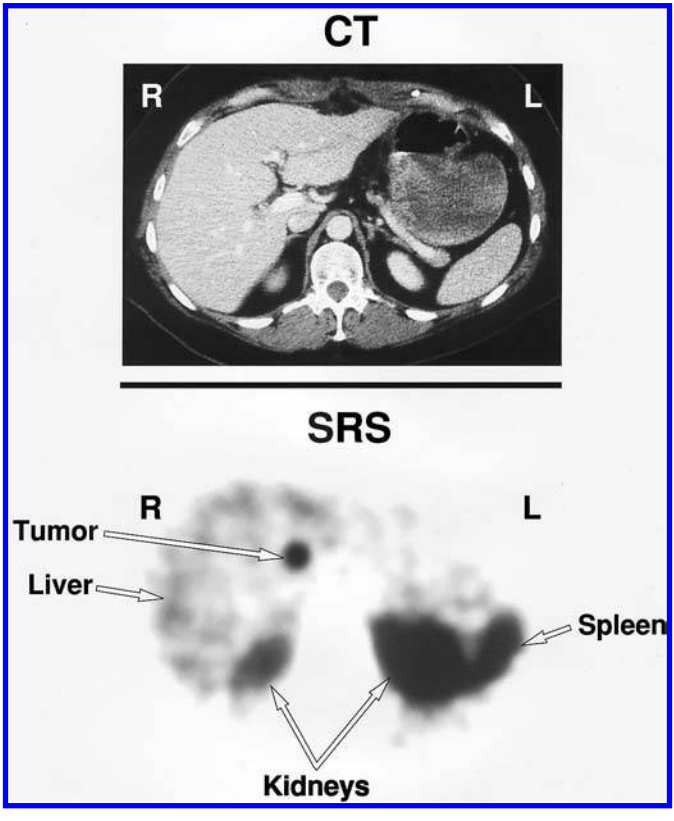

FIGURE 2 Sagittal contrast-enhanced CT scan (top) in a patient with a biochemically confirmed diagnosis of Zollinger-Ellison syndrome. The CT scan did not show any suspicious areas; however, SRS (bottom) showed a site of tumor that was subsequently found to be metastatic gastrinoma in a lymph node adjacent to the second portion of the duodenum.

success is dependent on the experience of the operator performing the procedure. SRS has a sensitivity of over 80% in localizing PETs except for insulinomas and has the advantages of being noninvasive and capable of imaging the entire body for sites of metastatic disease (Fig. 1). It will identify tumor in half the patients in whom all other conventional imaging studies are negative and is considered the initial localization procedure of choice for patients with ZES and other malignant PETs. However, it shares the same limitations as other imaging modalities in that it has limited ability to identify small lesions (less than 1 cm) or primary duodenal tumors in patients with ZES. In addition, it cannot provide the exact location of a tumor within the abdomen or pancreas (Fig. 2).

Because of the vascular nature of PETs, selective angiography is particularly sensitive in patients with PETs. However, because noninvasive imaging studies have been refined considerably, angiography should be used only in select cases and should be combined with intra-arterial stimulation using calcium (insulinoma) or secretin (gastrinoma). Intra-arterial stimulation angiography has a sensitivity of 90–95% and a specificity of 100% (Fig. 3).

In recent preoperative studies of patients with ZES angiography is less sensitive than SRS but will identify 10–15% of primary tumors not seen with SRS. In distinction to EUS, CT, and MRI but as with SRS, intra-arterial stimulation angiography does not provide a precise location of the PET but rather a region in which the tumor is confined.

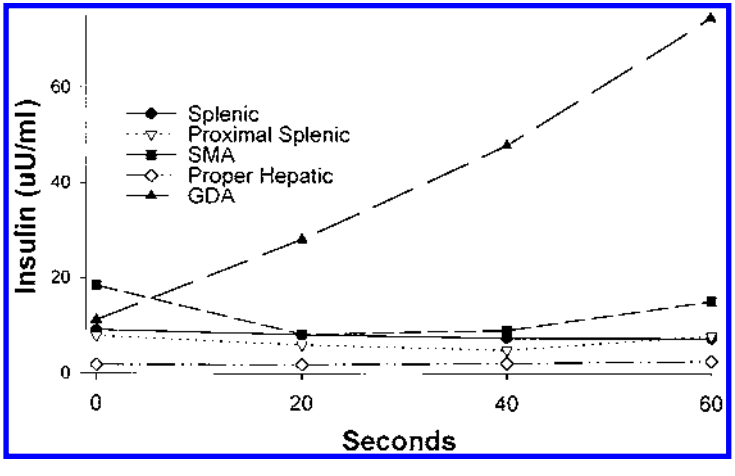

FIGURE 3 Results of a secretin stimulation angiogram in a patient with an occult biochemically confirmed insulinoma. A significant hormone gradient was observed in the hepatic veins after selective injection into the gastroduodenal artery (GDA). The patient was subsequently found to have a 6-mm insulinoma in the uncinate process.

As stated earlier, patients with a diagnosis of a nonfunctional PET are typically recognized as having a pancreatic tumor when routine studies are performed to evaluate vague or nonspecific abdominal symptoms. In this setting, the imaging studies are used to identify the presence of metastatic disease and to assess resectability of the primary lesion.

TREATMENT OF PETs

Gastrinoma

In patients with ZES the functional sequelae of gastric acid hypersecretion can be effectively controlled with medical management. Currently available antisecretory agents that inhibit H+-K+-ATPase can control gastric acid secretion in 100% of patients in most series. Relief of symptoms does not necessarily indicate adequate control of acid hypersecretion. In general, gastric acid analysis is used to document adequacy of medical therapy such that the amount of acid produced is less than 10 mEq/hr for the hour just prior to the next scheduled dose of medication. The role of surgery in ZES has fundamentally evolved in the face of having the capacity to medically control the gastric acid hypersecretion so effectively. Although total gastrectomy has been advocated as surgical *palliation* for patients with ZES as recently as 15 years ago, this approach has now been replaced by exploratory laparotomy performed with the *curative* intent of identifying and resecting the gastrinoma. The majority of gastrinomas are malignant and the role of surgery is primarily to control the malignant spread of gastrinoma. However, the malignant progression of gastrinoma is usually slow, and in previous series of ZES patients who underwent total gastrectomy without attempted gastrinoma resection or in those managed nonoperatively, the overall 5- and 10-year survival rates were approximately 75% and 50%, respectively (Fig. 4). In fact, in ZES patients who have no imageable disease operative exploration has not been uniformly advocated.

Gastrinoma tissue will be identified and resected in over 95% of patients undergoing exploration with curative intent including those who had no imageable disease on preoperative studies. Long-term biochemical cures are observed in about 40% of patients who undergo laparotomy and an additional 40% will have marked reduction in fasting serum gastrin and secretin stimulation gastrin levels. Recently it has been shown that routine operative exploration in ZES patients without MEN-1 with potentially curable lesions can prevent the development of hepatic metastases although it has not been shown to alter overall survival (Fig. 4). Even after successful resection of gastrinoma, patients continue to experience gastric acid hypersecretion for 6 months or longer and therefore must be maintained on medical antacid therapy postoperatively. Although antisecretory procedures such as vagotomy can reduce acid secretion in ZES patients by up

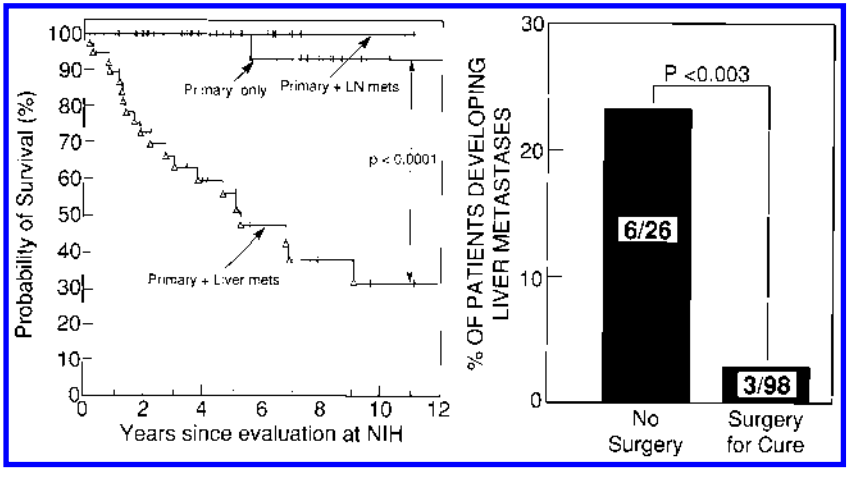

FIGURE 4 Survival in patients with different extent of gastrinoma. Data are from 31 patients who had a primary gastrinoma with no evidence of metastatic disease at surgical exploration, 24 patients who had a primary gastrinoma with lymph node metastases determined by surgical exploration, and 38 patients who had liver metastases in addition to an untreated primary gastrinoma determined on the basis of imaging studies. Survival was not different for patients with a primary tumor only versus a primary tumor with lymph node metastases. However, survival was significantly shorter in patients who had hepatic metastases. The bar graph shows that routine operative exploration in patients with potentially curable biochemically confirmed Zollinger-Ellison syndrome will significantly lower the incidence of subsequent hepatic metastases. Only three of 98 patients explored with curative intent subsequently developed hepatic metastases. However, six of 26 other patients who did not undergo laparotomy for medical or other reasons went on to develop subsequent metastatic gastrinoma in the liver.

to 60%, the benefit from the routine application of a procedure like this is not known.

ZES occurs in the setting of MEN-1 in approximately 20–25% of patients and the management of ZES under these circumstances deserves special comment. First, primary hyperparathyroidism secondary to multigland parathyroid hyperplasia is the first manifestation of MEN-1 in the majority of patients. Calcium is a known secretagogue for gastrin and control of hyperparathyroidism in ZES patients with MEN-1 can ameliorate the severity of the ZES as reflected in decreased fasting serum gastrin levels. Therefore, in patients with MEN-1 hyperparathyroidism should be corrected initially. Second, patients with MEN-1 have multiple PETs. The timing or role of surgery for resection of the pancreatic tumors is controversial. Furthermore, gastrinomas occur in the duodenum in 80%

of cases and are not amenable to simple enucleation. Therefore, operative exploration is offered more selectively in these circumstances. We recommend patients be explored when an imageable lesion is identified that measures 3 cm or greater because of the increased frequency of developing hepatic metastases with lesions greater than 3 cm.

The operative approach for a patient with potentially curable gastrinoma begins with an upper midline or bilateral subcostal incision. Initially, the abdomen is evaluated for sites of occult metastatic or ectopic disease. The liver is inspected and carefully palpated and suspicious lesions are either excised or biopsied. Intraoperative ultrasound is routinely used and can guide a core biopsy needle if necessary. The omentum, small intestine, liver, and ovaries are main sites of extrapancreatic, extraduodenal disease.

A systematic and uniform evaluation of the entire pancreas, duodenum, and associated lymph node basins is undertaken. The lesser sac is entered by dividing the gastrocolic omentum widely and the body and tail of the pancreas are mobilized from the retroperitoneum by incising the peritoneum along the inferior border of the gland. The splenic flexure of the colon can be reflected inferiorly to help expose the tail of the pancreas. The pancreas is mobilized from the retroperitoneum quite extensively by continuing the dissection along the posterior aspect of the gland. Attention is next directed to the duodeneum. If necessary, the hepatic flexure of the colon is reflected inferiorly. The peritoneum overlying the duodenum is incised and the duodenum from the porta hepatis structures extending inferiorly and medially to the mesenteric vessels is mobilized along with the pancreatic head. This enables the surgeon to inspect the anterior and posterior surfaces of the pancreatic head and palpate this region and the duodenum completely (Fig. 5). Along the neck of the pancreas, several small venous branches arise from the right gastroepiploic vein and communicate inferiorly with the middle colic veins. To prevent inadvertent traction injury to these vessels and to complete the exposure of this area, these veins must be carefully ligated and divided.

The intraoperative search for the gastrinoma should be guided by a knowledge of the findings of the preoperative localization studies and the fact that most gastrinomas arise from the head of the pancreas, the duodenum, or the associated regional lymph nodes. Gastrinoma, like other PETs, are firm to palpation and typically red-brown in color. Tumors arising in lymph nodes can usually be easily distinguished from benign mesenteric lymph nodes, which are typically pale yellow in color and soft in consistency. Lesions that arise in the pancreas and are present on the surface can usually be distinguished by their color against the pale-yellow background of the normal pancreatic parenchyma. Lesions arising deep within the pancreatic parenchyma can be difficult to identify by palpation even to the experienced surgeon. Primary duodenal lesions arise in the submucosa and are usually less than 10 mm in diameter. On palpation they are firm and

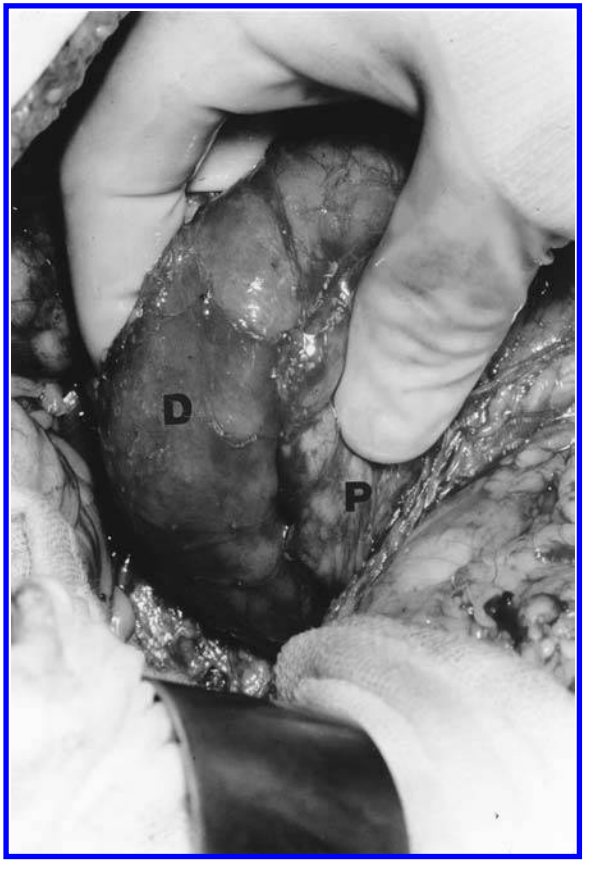

FIGURE 5 Intraoperative photograph illustrating the duodenum (D) and head of pancreas (P), after an extensive Kocher maneuver, being evaluated by palpation.

somewhat mobile. On direct inspection the overlying mucosa has a small punctate umbilication over the tumor.

In addition to careful inspection and palpation, intraoperative ultrasound (IOUS) is performed. A 10-mHz ultrasound probe is placed within a sterile plastic sheet and the upper abdomen is partly filled with saline. The ultrasound probe is gently applied to the pancreas and a systematic evaluation of the entire gland is undertaken. In addition, the lymph node basins around the pancreas including the celiac axis, portahepatis, periduodenal, and pancreatic lymph nodes can be carefully scanned. The normal tissue parenchyma of the liver or pancreas appears distinct sonographically from PETs and the uniform tissue background serves to

highlight the sonolucent properties of PETs. IOUS is most useful in identifying occult lesions deep within the hepatic or pancreatic parenchyma. IOUS is not particularly useful for the detection of extrapancreatic gastrinoma compared to palpation alone. Benign visceral lymph nodes can also appear sonolucent and difficult to distinguish from malignant sites of disease (Fig. 6). IOUS is not useful for identifying primary duodenal lesions; luminal fluid, bowel gas, and mucosal folds within the duodenum make a difficult background against which to identify a small primary gastrinoma with IOUS.

In general, PETs are encapsulated lesions that can be enucleated from the pancreatic parenchyma in most circumstances. To this end, IOUS serves two important additional purposes. The first is to demonstrate the relationship between the PET and other important structures including the pancreatic duct, the bile duct, and vascular structures. IOUS can be used to determine whether tumors arising from the body or tail of the pancreas can be enucleated or whether a distal pancreatectomy should be performed. Second, IOUS can be used during enucleation of the tumor to guide in the enucleation and reassess the proximity of the pancreatic duct. This is particularly useful for lesions arising in the head and for which a pancreaticoduodenectomy will otherwise be required.

Over the past several years the importance of a thorough and systematic evaluation of the duodenum to identify otherwise occult primary duodenal gastrinomas has been emphasized by several investigators. The evaluation of the duodenum is initially by inspection and palpation (Fig. 5). Subsequently, intraoperative endoscopy with duodenal transillumination can be performed. After an atraumatic bowel clamp is placed across the jejunum just distal to the ligament of Treitz, an upper gastrointestinal endoscope is advanced into the duodenum. The transilluminated duodenum is then inspected and primary duodenal gastrinomas as small as 2 mm can be identified. Any suspicious lesion that is observed is marked with a seromuscular suture. When a lesion is identified it can be successfully excised with an elliptical incision oriented longitudinally.

A duodenotomy is the most sensitive method of identifying primary duodenal gastrinomas and should be routinely performed as part of the evaluation of this site. A longitudal duodenotomy is made on the anterior lateral surface of the second portion of the duodenum. A finger is inserted into the duodenum and careful palpation of the duodenal wall is undertaken (Fig. 7). Complete evaluation of the duodenum is insured by palpating for the pylorus proximally and palpating as far distally in the duodenum as feasible. If a suspicious area is identified on the anterior, posterior, or antimesenteric surface of the duodenum, a submucosal excision is usually straightforward to perform. A musocal/submucosal stay suture is placed adjacent to the lesion to provide traction. The mucosa around the lesion is marked using a needle tip cautery. The mucosa and submucosa are then incised with cautery and the lesion is gently dissected from the underlying muscularis layer using careful dissection. The mucosa and submucosa are then approximated

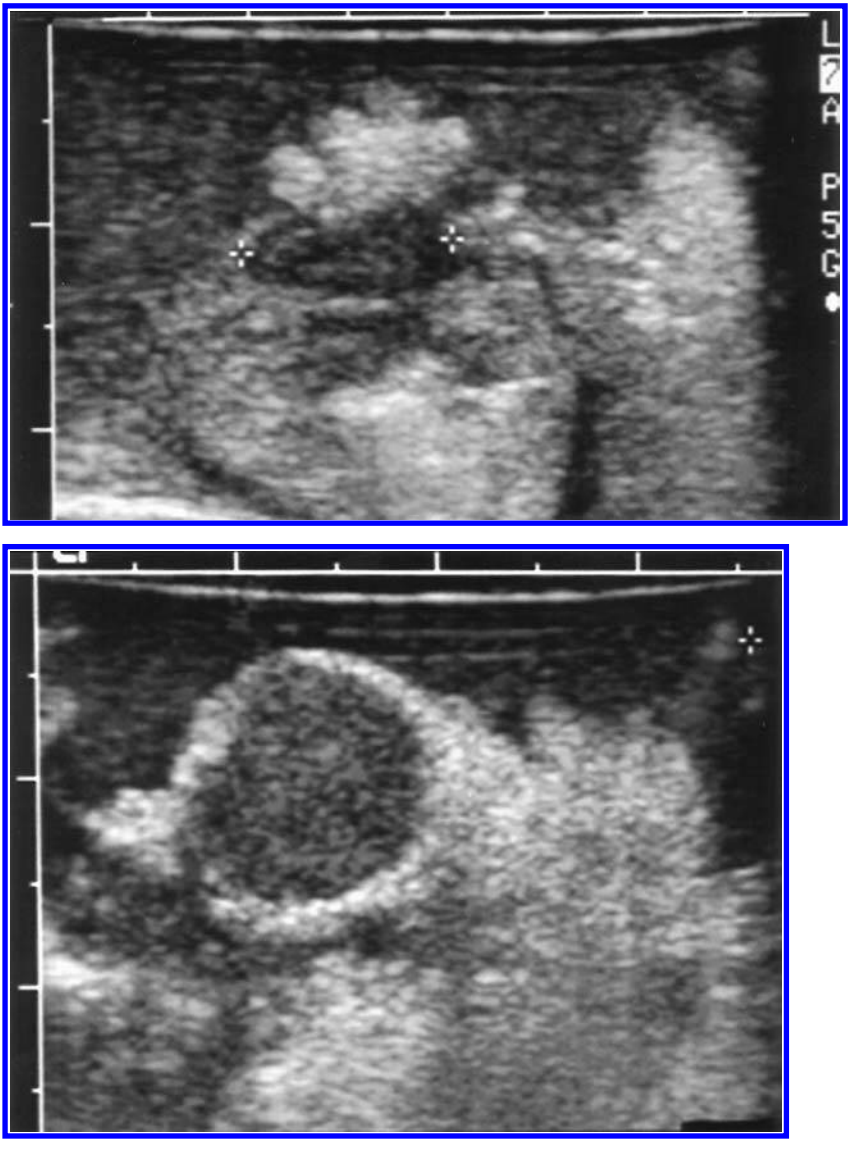

FIGURE 6 IOUS obtained in a patient with Zollinger-Ellison syndrome showing the characteristic appearance of a benign (top) and a malignant (bottom) lymph node. The benign lymph node is sonolucent and oval in shape. The malignant lymph node is sonolucent but has a more characteristic round shape, which frequently distinguishes it from a benign lesion.

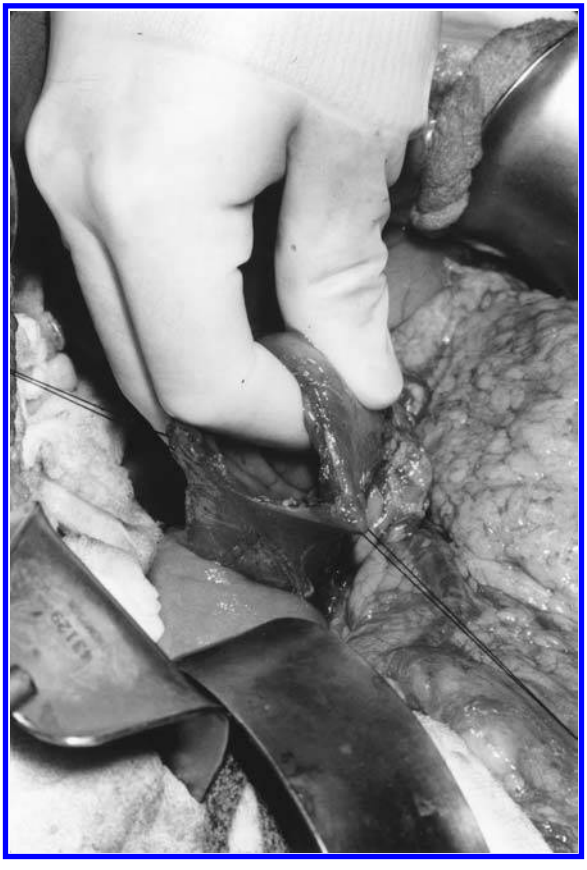

FIGURE 7 Intraoperative photograph of a patient with Zollinger-Ellison syndrome undergoing duodenotomy and palpation in an attempt to identify a primary tumor.

with a running absorbable suture (Fig. 8). If the duodenal lesion is difficult to reach via the duodenotomy, it can be excised using a separate full-thickness, elliptical duodenal excision.

Gastrinomas that are palpated on the medial wall of the duodenum pose a more difficult site for excision because of the potential for injury to the ampulla of Vater or the intrapancreatic bile duct. In those circumstances a small catheter can be positioned through the major ampulla or, if necessary, through the cystic duct after cholecystectomy to insure that the duodenal lesion is excised without injury to the adjacent duct. The duodenotomy is closed in a transverse orientation to avoid narrowing the lumen.

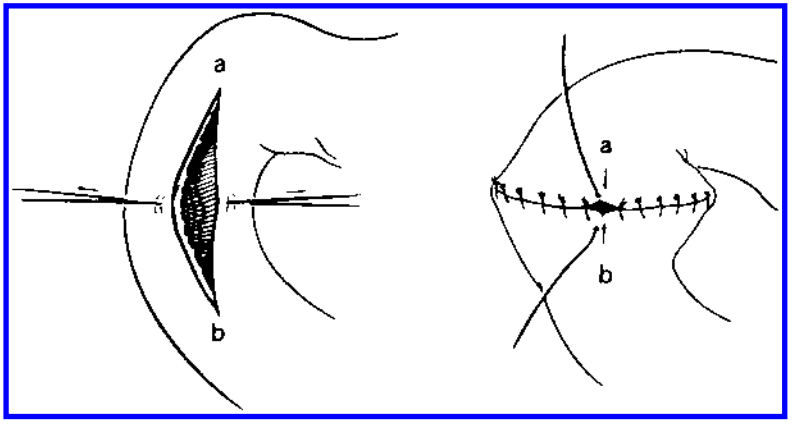

FIGURE 8 Typical position for a duodenotomy made during exploration for the purposes of identifying and resecting primary duodenal gastrinomas (left). The longitudinal duodenotomy is typically closed in a transverse fashion (right) to avoid narrowing of the lumen by approximating the superior (a) and inferior (b) aspects of the original incision.

In general, if a primary lesion is identified and resected in the pancreas or duodenum a diligent search for resectable metastatic disease in adjacent lymph nodes should be undertaken. Conversely, if disease is initially identified in lymph nodes, a search for the primary tumor in the duodenum or pancreas that may be drained by the affected lymph node should be undertaken. When only nodal tissue can be identified, a thorough resection of all pathological tissue should be undertaken as up to 40% of patients with disease apparently confined to lymph nodes will have a long-term biochemical cure of disease.

The perioperative management of patients undergoing exploration for resection of gastrinoma should include intravenous management of gastric acid hypersecretion with a continuous ranitidine infusion until they have resumed their usual oral antisecretory medication.

Insulinoma

Once the biochemical confirmation of insulinoma has been established an attempt to localize the tumor should be undertaken in preparation for surgical exploration. Most patients with insulinoma recognize that eating will control symptoms, and in milder cases, frequent small meals may be sufficient to control symptoms. Various medications have been used with variable success to reduce insulin levels in patients with insulinoma. The most commonly used agent is diazoxide and approximately 60% of patients will have improvement in symptoms with this

agent. Octreotide is also effective in inhibiting insulin release and can control symptoms in approximately 40% of patients; however, in some patients it can exacerbate symptoms. Other agents that have been used include verapramil, propranolol, and phenytoin. Although there is some debate about the extent of localization studies that are appropriate for patients with insulinoma, in practice most patients have some attempt at localization of the insulinoma in the pancreas. Because up to 10% of patients may present with metastatic disease particularly in the liver, studies to eliminate that possibility should be done prior to exploration.

Advocates of preoperative studies to localize the primary tumors in the pancreatic parenchyma argue that over 90% of insulinomas are less than 2 cm in diameter and they are usually located deep within the parenchyma of the gland, so they are not visible from the surface. With a combination of noninvasive and invasive imaging procedures, over 95% of tumors can be localized preoperatively. At centers that do not routinely use IOUS, preoperative imaging studies are considered essential to the successful surgical treatment in up to 30% of patients. In addition, preoperative localization studies allow the operative team to plan for the anticipated nature of the procedure in advance and counsel the patient regarding the nature of the procedure. Without any preoperative information about the location of the tumor, a complete pancreatic exploration is necessary. This includes an extended Kocher maneuver (mobilizing the duodenum and the head of the pancreas medially) to allow one to visually and manually examine the head and lateral aspect of the uncinate process (Fig. 5). To obtain further access to the more medial portion of the uncinate process small pancreatic branches from the superior mesenteric vein must occasionally be ligated and divided. To gain access to the body and tail of the pancreas the lesser sac is widely opened by dividing the gastrocolic omentum and reflecting the stomach cephalad. The peritoneum along the inferior surface of the pancreas from the superior mesenteric vein to the splenic hilum is divided and the pancreas is gently dissected from its retroperitoneal position. This allows for visual and manual examination of this portion of the gland (Fig. 9). Preoperative localization may allow one to avoid extensive mobilization of one or the other portion of the gland and allow for a more limited and directed exposure in the region of the anticipated insulinoma. With the increasing application of laparoscopic techniques to pancreatic procedures the use of preoperative imaging studies may become increasingly important in this context.

Others argue that extensive preoperative imaging studies in patients with biochemically confirmed insulinomas is not cost-effective nor does it improve operative outcome. Because sporadic insulinomas are almost always solitary tumors and are confined to the pancreatic parenchyma, careful intraoperative evaluation with palpation alone can identify these tumors in 50–80% of patients. The routine use of intraoperative ultrasound can further improve the intraoperative detection of insulinomas in up to 90–100% of patients. In one series of 19 patients

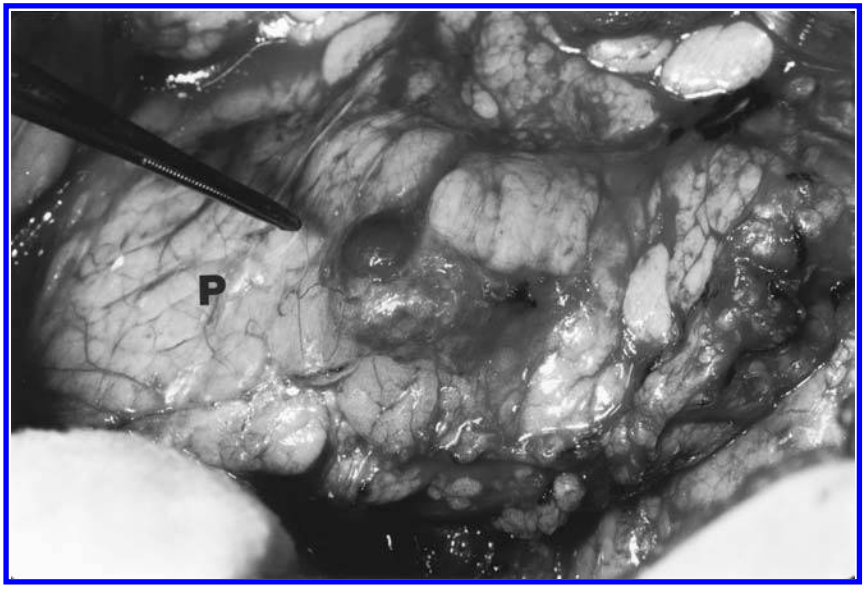

FIGURE 9 Intraoperative photograph of a patient with a biochemically confirmed diagnosis of insulinoma showing the typical reddish-brown appearance of an insulinoma against the pale-yellow color of the pancreas (P).

who had occult insulinomas that were not imageable on preoperative studies, all were identified with the use of IOUS. IOUS was particularly useful for the detection of occult tumors in the pancreatic head (Fig. 10). In one series of patients with insulinoma, nine were located in the head of pancreas. Six of these nine were not palpable and were identified only by IOUS.

The technique of enucleation commences with mobilization of the pancreas around the region of the tumor. This allows one to hold the gland and tumor with one hand to compress the gland and control blood loss during the enucleation procedure if necessary. Because of the vascular nature of these tumors attention to hemostasis is very important. If the tumor is visible on the surface of the pancreatic parenchyma, the dissection begins around the capsule of the tumor by isolating the pancreatic parenchyma over a fine hemostat and ligating the tissue sequentially with suture or staples. If the tumor is not visible on the surface of the gland, IOUS can be used to identify its precise location and the overlying pancreatic parenchyma can be divided directly over the lesion using ligature or staples for hemostasis. Once the tumor is visualized it can be dissected from the underlying pancreatic parenchyma in part using careful blunt dissection typically with a Penfield dissector or other instrument. Small feeding vessels are isolated

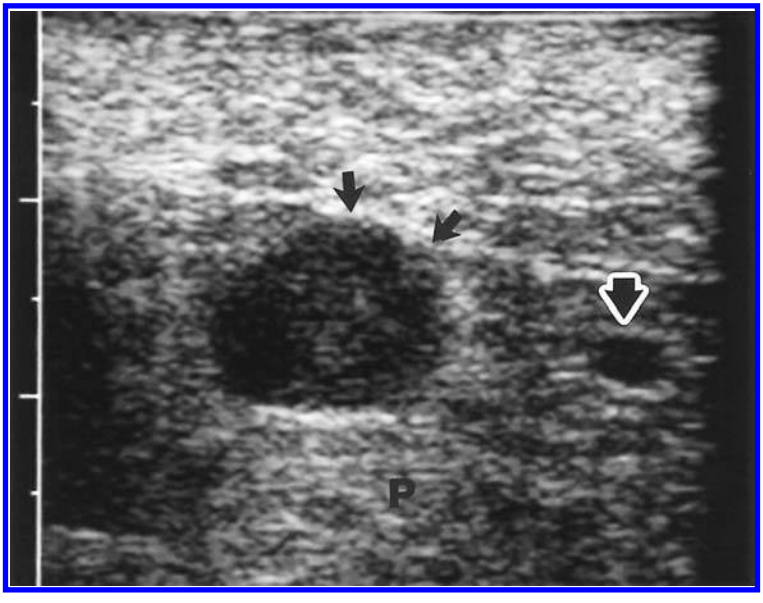

FIGURE 10 IOUS demonstrating the sonolucent character of an occult insulinoma in the pancreatic head (P). The black arrows are pointing to the insulinoma and the black-on-white arrow demonstrates the pancreatic duct.

and ligated as the tumor is progressively mobilized from the parenchyma staying on the capsule of the tumor. Once the lesion has been completely excised the bed of resection is carefully inspected and a closed suction drain is typically used.

Tumors that arise in the body or tail may abut the pancreatic duct making enucleation technically impossible without a high likelihood of injury to the duct. Under these circumstances a distal pancreatectomy should be performed. Although tumors in the head of the pancreas could theoretically present the same technical difficulties, in practice the need for a pancreaticoduodenectomy is extremely rare. Less than 5% of insulinomas are >3 cm and can safely be enucleated from the pancreatic head. Furthermore, by performing an extensive Kocher maneuver and using IOUS one can approach the tumor from either the anterior or posterior aspect of the pancreatic head to minimize potential injury to the intrapancreatic bile or pancreatic duct.

The question as to whether a blind distal pancreatectomy should be performed if no lesion can be identified intraoperatively deserves special comment. In the past blind distal pancreatectomy has been advocated if no insulinoma could be identified within the pancreas. The use of IOUS will identify some occult tumors that cannot be palpated. Calcium stimulation angiograms are being used

at an increasing number of centers. If there is a hormone gradient present in the splenic artery indicating the presence of a tumor in the region of the body or tail of the pancreas, then a distal pancreatectomy should be performed even though no discrete lesion can be identified because of the established sensitivity of the procedure. If there is a hormone gradient present following a gastroduodenal artery (GDA) injection of calcium, the wisdom of performing a blind pancreaticoduodenectomy must be carefully weighted against the potential morbidity of the procedure. Occult lesions that are present within the neck of the pancreas may also result in a hormone gradient following injection of the GDA. Depending upon the line of dissection across the pancreas during the pancreaticoduodenectomy it is possible that the lesion within the neck may not be encompassed within the specimen. Because most patients have a median duration of symptoms of over 2 years and can control symptoms with dietary manipulation or medication, the use of a truly ''blind'' pancreatic dissection should be abandoned. Interval evaluation with calcium stimulation angiography to regionalize the location of the tumor followed by reexploration should be considered.

Nonfunctioning or Other Rare PETs

Nonfunctioning or pancreatic polypeptide producing PETs (PPomas) and other rare functioning PETs (VIPoma, glucagonoma, somatostatinoma, GRFoma) are usually malignant and the majority of patients present with metastatic disease at the time of diagnosis. Because the symptom complex for most of these PETs is vague there is delay in diagnosis between 2 and 7 years from onset of symptoms. Surprisingly, this is also true for VIPomas in spite of the fact that the presenting manifestation of this condition is severe watery diarrhea with associated hypochorhydria, hypokalemia, and other electrolyte disturbances. For patients with nonfunctional PETs or PPomas the diagnosis may not be made preoperatively. With other rare PETs the presence of a pancreatic tumor in association with the characteristic symptom complex and elevated levels of the pertinent pancreatic peptide establishes the diagnosis.

VIPomas are almost always located in the pancreas and are solitary tumors in adults. In rare circumstances the syndrome may be caused by VIP-producing intestinal carcinoid tumors, pheochromocytomas, or ganglioneuromas. The initial treatment consists of fluid resuscitation and correction of electrolyte imbalance. Patients may require more than 350 mEq/day of potassium and should be carefully monitored during the fluid and electrolyte resuscitation. In the past, various agents have been used to control the amount of secretory diarrhea. However, currently the long-acting somatostatin analog octreotide is the agent of choice and can ameliorate the severity of diarrhea in over 90% of patients. In the majority of patients who have advanced metastatic disease not amenable to surgical extirpation, long-term therapy with octreotide has been shown to be effective for up

to 6 months. However, dose escalation may be necessary to maintain symptom relief. In patients who have become refractory to octreotide therapy, the addition of corticosteroids may improve the severity of symptoms. Although the majority of patients (up to two-thirds) may have metastatic disease at the time of presentation, after initial diagnosis and preoperative imaging studies are concluded, patients who have potentially resectable disease should undergo exploratory laparotomy. Approximately one-third of patients may be cured by surgical extirpation of the tumor, and because these tumors are often indolent, aggressive attempts at tumor debulking may provide symptomatic improvement. Occasionally, biochemically confirmed cases of VIPoma may be secondary to a small microadenoma in the pancreas. Because 80% of these possible tumors are present in the distal two-thirds of the pancreas, a two-thirds pancreatectomy should be considered if no pancreatic mass can be identified.

Like VIPomas, glucagonomas are large at the time of diagnosis and most are reported to arise in the body or tail of the pancreas. The pancreatic tumor is usually solitary in nature. However, metastatic disease is present at diagnosis in the majority of patients. Initial treatment consists of correction of the symptoms and signs associated with this condition. Patients may have a relatively poor metabolic status and anemia requiring hyperalimentation or blood transfusion. Correction of the hypoaminoacidemia is associated with improvement in the associated dermatitis in these patients. Octreotide has also been shown to improve the symptoms of weight loss and diarrhea. However, it appears to have little effect on the glucose intolerance in these patients. If the tumor can be surgically excised, the results may be profound with complete correction of the manifestations of the disease. As with other functional metastatic PETs, surgical debulking of the primary and metastatic disease can result in objective clinical improvement.

Somatostatinomas can occur throughout the pancreatic parenchyma with a predilection for the head and neck region. In addition, a small percentage of these tumors can occur in extrapancreatic sites especially in the duodenum in patients with von Recklinghausen's disease. At diagnosis, over 80% of the tumors have evidence of metastatic spread principally to the liver. Based upon the generally inhibitory nature of somatostatin, patients develop gallbladder disease with cholelithiasis, diarrhea, or steatorrhea, and diabetes. Weight loss and anemia can also occur. Patients may need correction of nutritional deficiencies at the time of diagnosis but in general, no good therapy has been developed for palliation of symptoms. Surgical resection should be contemplated in any patient who has resectable tumor although the benefit of this approach has not been definitively established.

GRFomas occur in younger patients and have a very strong female predominance. In a patient with acromegaly without a pituitary adenoma, the diagnosis should be considered. Octreotide will result in a decrease and frequently normalization of growth hormone levels in patients with GRFomas. Surgical resection of the primary tumor should be undertaken when feasible.

Because there is no hormone syndrome, nonfunctioning PETs typically present with advanced disease and frequently the diagnosis of a nonfunctioning PETs is not made prior to operation. Surgical resection is indicated for patients with a resectable pancreatic mass although the cure rate for these tumors is low.

MEDICAL THERAPY AND CHEMOTHERAPY FOR ADVANCED PETs

Patients with advanced metastatic PETs typically have disease predominantly in peripancreatic lymph nodes and liver. The liver is the sole or predominant site of progressive metastatic disease in a significant number of patients and regional therapeutic approaches directed toward controlling tumor growth within the liver have been under clinical evaluation. In general, patients with metastatic disease should be considered for exploration and resection if possible. In the face of unresectable metastatic disease, amelioration of symptoms can be achieved in patients with octreotide. Other treatment approaches include systemic combination chemotherapy, hepatic intra-arterial chemotherapy or chemoembolization, treatment with long-acting somatostatin analogs, interferon, and in rare circumstances, hepatic transplantation.

In general, metastatic progression in PETs is relatively slow and in the past, patients often succumbed to the complications of the functional syndromes rather than the results of tumor burden. However, because of the ability to control gastric acid secretion with long-term omeprazole therapy and other functional PETS with octreotide, progression of metastatic disease is becoming an increasingly important determinant of survival. Patients with MEN-1 are thought to have more indolent disease progression than patients with sporadic tumors, although this has not been conclusively demonstrated. In general, the natural history and biological behavior of metastatic PETs are similar and, therefore, proven approaches for these tumors are considered together.

Somatostatin analogs inhibit tumor growth in experimental models and somatostatin receptors are present in high density in all PETs except insulinomas. Treatment with octreotide in patients with metastatic PETs has been used primarily to control symptoms. The antineoplastic effects of octreotide are receiving increased attention although tumor regression occurs in less than 30% of patients. Stabilization of disease progression has been seen in one-third of patients in one series and the duration of the effect was variable lasting from 3 to over 12 months. Similar results have been obtained with interferon and octreotide may have an additive effect on tumor stabilization.

A number of studies have been conducted evaluating chemotherapy alone or in combination in patients with metastatic PETs. In the majority of these studies the patients had a variety of diagnoses including functional and nonfunctional PETs as well as carcinoid tumors. Streptozocin is an antibiotic derived from a

fungus species that produces specific islet cell toxicity in animal models. Currently, clinical uses of streptozocin produce the side effects of nausea, vomiting, nephrotoxicity, and hepatotoxicity. The Eastern Cooperative Oncology Group (ECOG) performed an initial random assignment trial comparing streptozocin alone to streptozocin plus fluorouracil and found that combination therapy had a significantly higher overall response rate compared to the single-agent regimen. The overall response rate was 62% and there was a complete response rate of 33%. However, it is important to note that some complete responses were scored by normalization of tumor markers. Subsequently, a phase II trial of streptozocin and doxorubicin was performed in 31 patients with metastatic advanced PETs. Using standard size criteria to assess response, 19% of patients achieved an objective partial response with a median duration of 9 months. Subsequently, ECOG conducted a second prospective random assignment trial comparing this combination to streptozocin and fluorouracil in patients with advanced metastatic PETs. The combination of streptozocin and doxorubicin had a significantly better overall response rate of 69% compared to 45% for the fluorouracil combination regimen. Furthermore, the median duration of response was 20 months compared to 9 months and conferred a significant survival advantage. The single-agent chlorozotocin alone produced a 30% regression rate. Therefore, for patients who have widespread metastatic disease the current recommended therapy of choice is a combination of streptozocin given by intravenous injection at a dose of 500 mg/m^2/day for 5 consecutive days plus doxorubicin given at a dose of 50 mg/m^2 on days 1 and 22. Each cycle is repeated every 6 weeks until a maximum dose of 500 mg/m^2 of doxorubicin has been administered. Other agents including DTIC alone or in combination have been used but are not considered as effective in causing significant tumor regression.

For patients who have metastatic disease confined to the liver, other regional therapies have been administered that may result in substantial tumor regression and improvement of symptoms. Hepatic artery occlusion resulted in objective regression in 60% of patients with hepatic-predominant metastases from PETs. When combination chemotherapy was administered after hepatic artery occlusion using alternating two-drug regimens of doxorubicin plus dacarbizine or streptozocin and fluorouracil, the overall response rate was 80%. Furthermore, the duration of the response with the addition of chemotherapy to hepatic artery occlusion was 18 months compared to 4 months with hepatic artery occlusion alone. Therefore, hepatic arterial therapy using a combination of occlusion and chemotherapy is effective in causing clinical meaningful regression of metastatic PETs to the liver. In another series of patients intra-arterial doxorubicin emulsified in iodized oil was administered into the hepatic artery followed by embolization with absorbable gelatin powder or pledglets. The overall response rate using this approach was 90% and the median survival after treatment was 24 months. The treatment was associated with low morbidity.

Liver transplantation has been performed in a small number of patients

who have metastatic PETs confined to the liver. It appears that long-term cure is not common and therefore the benefits of this aggressive approach for patients with this condition has not been proven. Bone metastases are being increasingly recognized in patients with metastatic PETs to the liver and, therefore, it is essential that patients be carefully evaluated prior to any therapy directed only to the liver. A recent study showed that SRS is the best method to establish the presence of osseous metastases.

CLINICAL RESEARCH QUESTIONS

There are a number of unresolved issues with respect to the management of patients with functional PETs. For patients with sporadic gastrinoma, long-term biochemical cures are seen after operation with curative intent in only 30–40%. This is primarily due to limitations in the ability to image gastrinomas preoperatively and to identify occult sites of disease intraoperatively. SRS has become the preoperative study of choice in patients with gastrinoma, although there are limitations with this imaging study's ability to detect lesions that are less than 2 cm in diameter. In general, the current operative approach for patients with potentially curable gastrinoma is to explore sites of primary disease within the pancreas, duodenum, or the associated regional lymph node basins (Fig. 11). When sites of disease are found, local excision of a tumor is undertaken. It is not known whether more aggressive extirpative procedures such as regional lymph node dissection or pancreaticoduodenectomy will improve cure rates or survival. The role and timing of pancreatic surgery in patients with ZES and MEN-1 remains controversial.

For patients who have insulinoma the cost-benefit analysis of preoperative imaging studies has not been definitively established. Imaging using MRI will exclude the possibility of unresectable metastatic disease in the liver. With a complete intraoperative evaluation of the pancreas, including the use of IOUS, the success in identifying tumors without the benefit of other preoperative studies is 95% or greater (Fig. 12). However, these results have been reported from institutions that have considerable experience and expertise in the management of patients with this diagnosis. For other centers that encounter patients with this diagnosis on a less frequent basis, the use of preoperative imaging studies may be of greater importance. Furthermore, the use of laparoscopic techniques for pancreatic procedures is gaining increasing application. Preoperative localization of tumors will be important if laparoscopy is contemplated.

BASIC SCIENCE RESEARCH QUESTIONS

Recently, the gene for MEN-1 has been identified on the long arm of chromosome 11 by positional cloning techniques. Multiple different mutations were identified

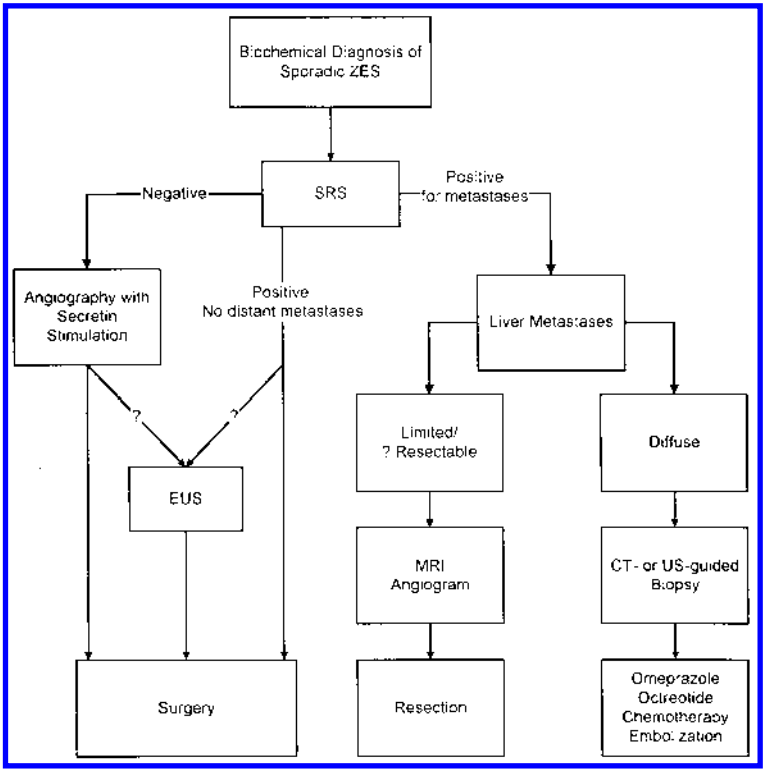

FIGURE 11 Flow diagram illustrating the general approach for patients with newly diagnosed sporadic Zollinger-Ellison syndrome at our institution. Patients who have metastatic disease on the basis of initial imaging studies are further evaluated to determine whether or not isolated liver metastases may be amenable to resection. In patients who have potentially curable lesions the sequence and role of EUS or secretin stimulation arteriography tests after SRS have not been clearly defined and are currently under clinical evaluation.

in 14 or 15 families with MEN-1 syndrome. Identification of this gene should improve our understanding of the mechanisms of endocrine tumorigenesis and facilitate accurate and early diagnosis. Furthermore, PETs are one of the central manifestations of the MEN-1 syndrome. It is not known whether or not PETs are caused by mutational inactivation of the MEN-1 gene. Somatic mutation of this gene has recently been found in 21% of patients with sporadic parathyroid adenomas and 40% of those with sporadic gastrinomas while the corresponding MEN-1 germline gene sequence was normal in each patient. Therefore, somatic gene mutations do appear to contribute to tumorigenesis in patients with sporadic

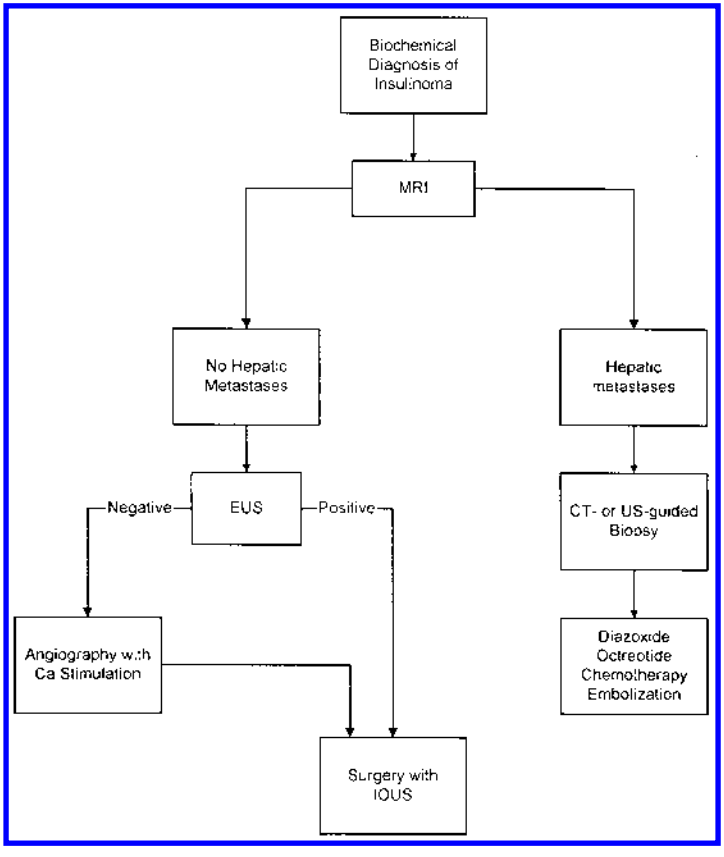

FIGURE 12 Flow chart illustrating the general approach to patients with biochemically confirmed insulinoma. At our institution MRI is obtained to eliminate the possibility, although rare, of metastatic disease. Subsequent localization studies are performed to identify the primary tumor and operative exploration is performed with IOUS. Patients with potentially resectable metastatic disease undergo exploration and tumor debulking with palliative intent.

parathyroid adenomas or gastrinomas and further study will be necessary to determine whether this gene mutation occurs with any significant frequency in other less common sporadic PETs.

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11

Liver and Proximal-Mid Biliary Cancer

Michael A. Choti
The Johns Hopkins Medical Institutions, Baltimore, Maryland

Ross A. Abrams
The Johns Hopkins Oncology Center, Baltimore, Maryland

Seamus O'Reilly
Waterford Regional Hospital, Waterford, Ireland

Floyd A. Osterman, Jr.
Aventura Hospital and Medical Center, Aventura, Florida

INTRODUCTION

This chapter deals with the management of primary liver and perihepatic malignancies. Included is a discussion of hepatocellular carcinoma, proximal and intrahepatic cholangiocarcinoma, and gallbladder cancer. Cholangiocarcinoma arising from the distal common bile duct will be discussed in other chapters. A unique feature about the management of liver and bile duct malignancies is the important therapeutic contribution of the interventional radiologist to that of the medical oncologist, radiation oncologist, and surgeon. For this reason, this chapter incorporates contributions from these four therapeutic disciplines.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is one of the most difficult and challenging malignancies the clinician faces. The overall prognosis is often poor, with a potential for rapid growth rate, multifocality, and association with underlying cirrhosis. Symptoms develop late in the majority of cases. Worldwide, HCC is the

seventh most common cancer in men and ninth in women, with more than 320,000 new cases per year. The geographical distribution is unique, with a high incidence in parts of Asia and Africa and paucity in other parts of the world, including North America and Europe. HCC commonly occurs in the background of ongoing hepatic injury and cirrhosis. While most causes of cirrhosis predispose to HCC, viral hepatitis B and C infections are the most common cause of HCC worldwide. Individuals with cirrhosis secondary to hepatitis B and C have a relative risk of developing cancer of 21 and 52, respectively. Alcoholic cirrhosis is an important cause of HCC in some countries including the United States. Other conditions, including exposure to myotoxins, hemachromatosis, and alpha-1-antitrypsin deficiency, are also associated with HCC.

Symptoms usually occur late in the clinical course of this disease. The most common complaint is upper abdominal pain or discomfort. When tumor rupture or hemorrhage occurs, sudden sharp pain can develop. Other symptoms include weight loss and cachexia. An abdominal mass can be felt or abdominal swelling can be present due to increased ascites. Most cases of small HCC are diagnosed with screening by ultrasonography and measurement of alpha-fetoprotein. Indeed, routine screening in such a way is advised in patients with a history of chronic liver injury and cirrhosis.

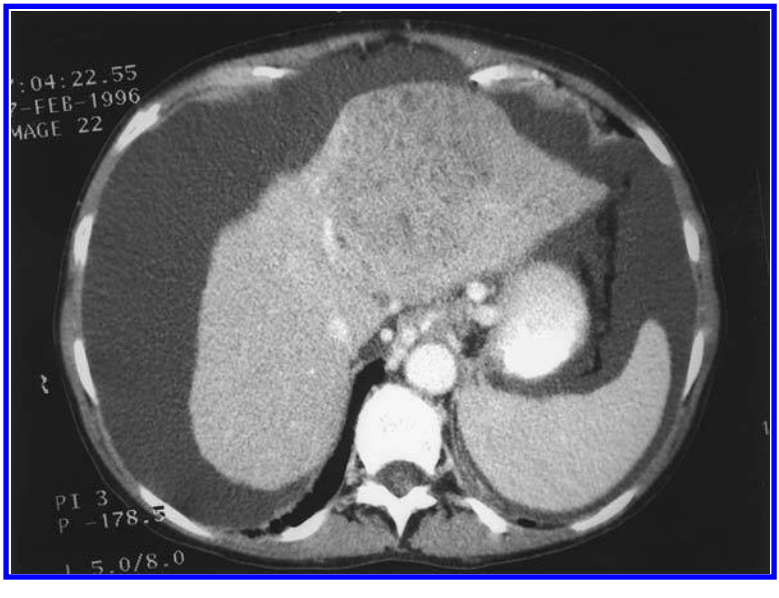

Figure 1 Computed tomography of liver demonstrating hepatocellular carcinoma in left lobe, as well as cirrhosis and ascites.

The most commonly used imaging modalities for HCC are ultrasonography, computed tomography (CT), and hepatic arteriography. Hepatic ultrasonography is simple, inexpensive, and noninvasive and most useful as a screening test in high-risk populations. CT is highly accurate at detecting HCC in most cases with sensitivity in excess of 80%. Tumors appear as hypodense lesions and may be heterogeneous due to necrosis. The extent of both intrahepatic and extrahepatic disease can be identified as well as the extent of cirrhosis, ascites, and the presence of portal vein thrombosis (Fig. 1). Newer techniques using helical CT with thin-section reconstruction and dual-phase contrast have improved the ability to visualize and stage these tumors. Hepatic arteriography, along with portovenography, can also be useful when imaging HCC. The appearance of these vascular tumors can often be diagnostic on arteriography (Fig. 2). CT arterial portography can also be used to improve the sensitivity of the preoperative evaluation. False-positive findings of up to 40% as well as the additional expense and morbidity associated with this procedure has resulted in a declining use of this study. Magnetic resonance imaging (MRI) using newer techniques has demonstrated similarly high sensitivity rates of 75–90%. MRI also provides better char-

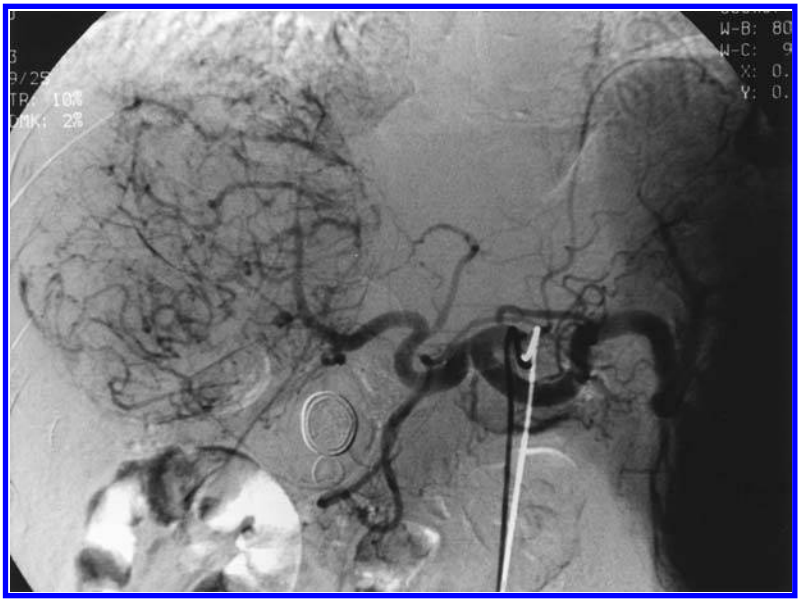

FIGURE 2 Celiac arteriogram showing a large vascular hepatocellular carcinoma of the right lobe of the liver. The tumor is supplied by branches from the right hepatic artery.

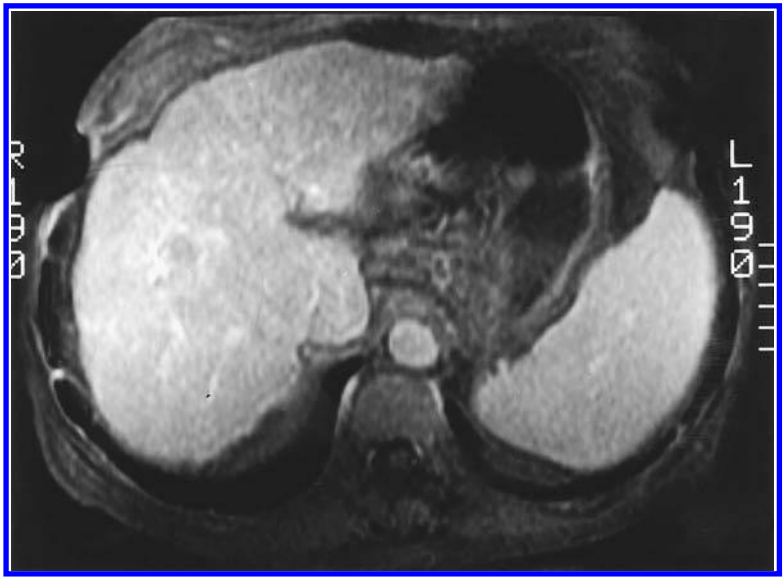

FIGURE 3 Magnetic resonance imaging (MRI) of small hepatocellular cancer.

acterization of lesions than CT and can clearly image intrahepatic vascular structures (Fig. 3).

CHOLANGIOCARCINOMA

Cholangiocarcinoma is less common than HCC and does not have the same variability in geographical distribution. In parts of the Far East, the increased incidence of this tumor has been causally related to chronic infestation of the biliary tree with liver flukes, *Clonorchis sinensis* and *Opisthorchis viverrini*. A strong association is also seen with intrahepatic stone disease. Recent series have demonstrated up to 10% risk of cholangiocarcinoma in patients with hepatolithiasis. Cholelithiasis, although more commonly associated with gallbladder carcinoma, is also associated with cholangiocarcinoma. Extrahepatic and hilar cholangiocarcinoma can be seen in patients with long-standing ulcerative colitis, Crohn's disease, congenital biliary atresia, or cystic dilatation of the biliary tree, including choledochal cyst disease and Caroli's disease.

The clinical presentation of cholangiocarcinoma varies depending on the location, intrahepatic or extrahepatic. Signs and symptoms of peripheral or intrahepatic cholangiocarcinoma are similar to those of hepatocellular cancer except that jaundice occurs more commonly. Extrahepatic or hilar bile duct cancers present with obstructive jaundice in up to 98% of patients. For this reason, extrahepatic tumors often present earlier than intrahepatic tumors.

Unlike HCC, these tumors rarely present with elevated levels of alpha-fetoprotein. Ultrasonography and CT are also useful with these tumors and, in addition to visualizing a mass lesion within the liver or hilum, can document evidence of bile duct dilatation. With hilar or mid–bile duct tumors, diagnostic evaluation should attempt to determine the level and extent of obstruction. Cholangiography via either the percutaneous transhepatic or endoscopic route is useful at making this determination, both within and outside the liver. The percutaneous transhepatic approach is favored in most cases of proximal biliary tumors because it defines the extent of proximal tumor involvement more easily. Percutaneous placement of a biliary stent can also be used, either for preoperative decompression in resectable patients or for palliation in those who are unresectable. In cases of bilateral duct obstruction, biliary stents can be placed in both the left and right lobes. The tissue diagnosis can be established in 45–85% of cases using percutaneous techniques, either preoperatively or in unresectable patients. Transhepatic scrape or brush biopsy, biliary cytology, or percutaneous fine-needle aspiration can be used.

GALLBLADDER CARCINOMA

Carcinoma of the gallbladder is an uncommon malignancy. The presence of gallstones is a clear associated factor, with cancer found in approximately 1% of gallbladders removed for cholelithiasis. As with gallstone disease, gallbladder carcinoma occurs in women three times more commonly than in men. The incidence increases with age and is most common in Latin America, and within the United States, the incidence in Hispanics and Native Americans is six times higher than in the general population.

Early diagnosis is the most important factor in improving prognosis. In early stages, gallbladder cancer is usually asymptomatic. Symptoms occur most commonly when the malignancy is found at advanced stages, including pain, jaundice, and weight loss. Physical findings can include jaundice, fever, abdominal mass, or tenderness. Ultrasonography is diagnostic in over 75% of patients with advanced gallbladder carcinoma. Findings include thickening of the gallbladder wall or the presence of a mass in the liver or the gallbladder. In the presence of cholelithiasis, diagnosis of early gallbladder cancer is difficult. CT can be useful in assessing the presence of spread into the adjacent liver, porta hepatis, or regional lymph nodes.

The majority of early gallbladder carcinomas are identified at the time of cholesystectomy for gallstone disease. In some cases, evidence of malignancy is suspected at the time of surgery, while in other cases carcinoma is found only after pathological examination of the gallbladder specimen. Therefore, it is important during cholecystectomy that the gallbladder is examined carefully, both at the time of operation and by microscopic examination.

SURGICAL THERAPY

Surgical resection is the only potentially curative form of therapy for patients with hepatic or biliary malignancies. Provided that the tumor is localized and sufficient viable liver remains, liver resection or partial hepatectomy can be performed safely in many cases. The role of total hepatectomy with orthotopic transplantation is controversial. In addition, other interstitial or regional surgical therapies can provide both palliative and potential curative options, including hepatic cryosurgery, radiofrequency ablation, ethanol injection, chemoembolization, and intra-arterial infusional therapy.

Liver Resection for Hepatocellular Carcinoma

Surgical resection is the treatment of choice for HCC. Although it is the best option, 70–90% of patients are not surgical candidates because of (1) the extent of disease within the liver, (2) the presence of metastatic disease, (3) the degree of cirrhosis and lack of parenchymal reserve, and (4) the overall medical condition. Contraindications include evidence of clinical jaundice in the absence of biliary obstruction, ascites, renal insufficiency, or prolonged prothrombin or partial thromboplastin times. The operative mortality is less than 3% for noncirrhotic patients compared with 5–25% for cirrhotic patients, and noncirrhotic patients are resectable in up to 60% of cases. While most patients with cirrhosis are unresectable, those with Child's class A or mild cirrhosis have significantly better outcomes after liver resection than patients with more severe child's B or C cirrhosis. Although the resectability rate is low and operative mortality higher compared to liver resection for metastatic liver cancer, the 5-year survival rate after resection for HCC ranges from 25 to 65%. Favorable prognostic factors include (1) well-differentiated or fibrolamellar histology, (2) absence of vascular invasion, (3) tumors less than 5 cm in diameter, and (4) unifocal disease.

Operative morbidity and mortality from liver resection have significantly improved in recent decades, principally because of a clearer understanding of anatomical considerations, newer surgical techniques, and improved postoperative care. A variety of types of surgical resections can be performed depending on the extent and location of disease. Minor hepatic resections include both nonanatomical wedge resections of peripheral lesions and anatomical resection of hepatic segments. Major resections include hepatic lobectomy or extended lobectomy. When major hepatic resection is performed, the vascular structures supplying the liver being removed are typically isolated extrahepatically prior to parenchymal dissection. Inflow occlusion at the porta hepatis can be useful in reducing bleeding during parenchymal dissection. The noncirrhotic liver can usually tolerate occlusion times beyond 60 min without irreversible damage. Such warm ischemia is less well tolerated in cirrhotic livers, however. In such cases of advanced

liver disease, total inflow occlusion should be used only intermittently and for brief periods. Total vascular isolation can also be used, incorporating both inflow occlusion and control of the infrahepatic and suprahepatic vena cava. This technique, however, can be associated with significant hemodynamic instability and should be used only selectively in complex cases.

Excessive blood loss during liver resection not only increases the need for blood transfusion with its associated problems but increases the risk of structural injury and suboptimal tumor margin clearance by obscuring the surgical field. New surgical techniques, including vascular isolation, intraoperative ultrasonography, and alternative methods of dividing the hepatic parenchyma, have significantly reduced the need for transfusion of blood and blood products in modern liver surgery.

Hepatic Transplantation

Total hepatectomy with orthotopic liver transplantation offers significant theoretical advantages over partial resection in patients with cirrhosis. Both the tumor and diseased liver are excised and replaced with a healthy organ. There are, however, limitations to this approach. Organ donor shortages result in ethical issues as well as long delay time between diagnosis and transplantation. There are also concerns about immunosuppression in patients with cancer and possible micrometastatic disease. In addition, high costs and operative mortality are associated with this approach.

Prognosis of patients treated with transplantation for HCC correlates with the size and stage of the malignancy. Reported 5-year survival rates after transplantation for HCC range from 20 to 45%, comparable to that of resection. Best results are seen in those patients in whom a small HCC was found incidentally during transplantation for liver failure. In cases where solitary or multiple (three or less) small (<5 cm) tumors are associated with significant cirrhosis, transplantation yields better results than resection. Therefore, only the small subset of patients with moderate to severe cirrhosis and small tumors should be considered candidates for transplantation.

Hepatic Tumor Ablation

Although surgical resection may afford the only potential for cure in patients with liver tumors, many patients may not be candidates for surgical resection for a variety of reasons. Novel methods for local ablation have been developed with a goal of increasing the number of patients eligible for surgical therapy. Hepatic *cryosurgery* is one such interstitial therapy that has gained popularity in recent years. This technique relies on the in situ destruction of a defined area within the liver using liquid nitrogen at subzero temperatures. Although cryosurgery has been used in the past for the treatment of a variety of surface malignancies, recent

advances in the ability to deliver liquid nitrogen deep within tissue using a closed-circuit insulated probe system as well as improved imaging with intraoperative ultrasound (IOUS) have provided the capability for safe hepatic cryoablation.

Relative indications for the application of these techniques include unresectable patients with multiple tumors, those with tumors in anatomical locations not amenable to formal resection, patients in whom limited hepatic reserve precludes major liver resection, and those with associated comorbid disease that may limit their ability to tolerate major liver resection. The upper limit of tumor size that can safely be treated with cryosurgery is approximately 6–8 cm. With radiofrequency ablation, the maximal diameter of ablation with each application is approximately 3.5 cm. However, multiple applications can be used per lesion in order to increase the treatment zone.

Early reported series of these ablative approaches suggest that these techniques can be performed safely and with few complications. With cryosurgery the follow-up of early uncontrolled series suggests the survival results are comparable to that of hepatic resection for both hepatocellular carcinoma and some metastatic tumors. When adequate cryoablation is performed with sufficient (>1 cm) margins, local recurrence in most series is less than 20%. The efficacy of radiofrequency ablation is less well established.

The major limitation with these ablative approaches is the ability to carefully document complete incorporation of the targeted lesion with adequate circumferential margins. In addition, major vascular structures within the liver, such as the main portal veins, vena cava, or proximal hepatic veins, provide a ''temperature sink'' that limits the ability to achieve complete ablation in these areas, either with heat or cold. Tumors located near these structures may not be optimal for treatment. When these techniques are used for curative intent, precise placement and adequate documentation of complete ablation are important. Until a well-controlled trial is carried out comparing these modalities, patients with resectable disease should be offered resectional therapy.

Surgical Therapy for Cholangiocarcinoma

Patients with peripheral or *intrahepatic cholangiocarcinoma* are approached surgically in a fashion similar to those with HCC, typically requiring hepatic lobectomy or segmentectomy without resection of a hepatic bifurcation. Because this entity is less common than extrahepatic or hilar cholangiocarcinoma, few studies with long-term prognosis are available. However, reports suggest that resectability rates are comparable to that of HCC and 5-year survival rates vary between 20 and 50%. Transplantation for intrahepatic cholangiocarcinoma has shown poor results and this tumor should be considered a contraindication to liver transplantation. Other modalities of interstitial and regional therapy, including local ablation and chemoembolization, can also be considered with this disease.

Resection of mid or proximal biliary duct cholangiocarcinoma should be offered to patients in whom the disease appears localized without evidence of extrahepatic metastatic disease or direct involvement of the portal vein. Preoperative cholangiography is useful in determining the extent of resection required. In some cases, the proximal bile duct with bifurcation and gallbladder may be resected without the need of concomitant hepatic lobectomy or caudate lobe resection. In other cases, when the tumor extends into the intrahepatic ducts on one side, en bloc hepatic lobectomy should be performed. Following resection, biliary reconstruction is performed using a roux-en-y hepaticojejunostomy. In patients in whom surgical exploration is performed and intraperitoneal tumor dissemination is found, resection is contraindicated in most cases. In this instance, operatively placed transhepatic catheters can be left in place to palliate biliary obstruction. The gallbladder should be removed to prevent acute cholecystitis from cystic duct obstruction and at times surgical biliary bypass can also be performed. Survival rates after resection of mid and proximal bile duct cancers depend largely on the ability to obtain negative margins at the time of surgical resection. In patients undergoing curative resection for hilar cholangiocarcinoma, 1-year, 3-year, and 5-year survival rates are approximately 70%, 30%, and 15%, respectively.

Surgical Treatment of Gallbladder Cancer

In patients with symptomatic gallbladder carcinoma, resectability rates range between 10% and 30%. In these patients the 5-year survival rate is typically less than 5%. Controversy exists regarding the role of surgical therapy in this disease. In patients with serosal invasion or extension of tumor into adjacent organs, it has been difficult to demonstrate any curative benefit of surgical therapy. The surgical therapy of early-stage gallbladder cancer is primarily related to the depth of invasion of the gallbladder wall. In patients with cancer limited to the mucosa, simple cholecystectomy appears to be sufficient therapy with 5-year survival rates exceeding 90%. The controversy exists regarding the surgical management of patients with involvement of the muscularis. Although some investigators feels there is limited benefit to radical surgery, many feel this is the subset in which more extensive surgical resection can improve survival. In this group of patients, resection of the liver adjacent to the gallbladder bed as well as hilar and celiac lymphadenectomy will significantly improve survival. More radical surgical therapy, including extensive hepatic resection and common bile duct resection, may also be indicated in some cases.

MEDICAL ONCOLOGY

Most patients with hepatic and biliary malignancies present in advanced stages or are associated with comorbid diseases precluding potentially curative surgical

therapy. The care of patients with these malignancies is particularly challenging owing to the high prevalence of such comorbidities as cirrhosis or tumor-related liver dysfunction, which will compromise drug clearance rates and increase the likelihood of treatment-related toxicity, and by the high incidence of biliary infections in those patients with biliary neoplasms. These issues are also compounded by the modest activity rates of systemically administered cytotoxic chemotherapy.

Systemic Chemotherapy for Hepatocellular Carcinoma

A large number of studies have been performed of most major classes of cancer chemotherapy agents, administered either alone or in combination for the treatment of hepatocellular cancer. Doxorubicin therapy, which has a response rate of 20%, is the single-agent standard for this disease. However, as demonstrated by a randomized clinical trial conducted in Hong Kong, such response rates have not translated into any survival benefit. In the latter study, no difference in overall survival was observed between patients receiving placebo or doxorubicin. In addition, the palliative benefits of this agent may be outweighed by treatment-related toxicity. Similarly, results from phase II evaluations of combination chemotherapy regimens have not demonstrated any improvements in survival when compared to control groups for these patients. Consequently, patients with this disease should be encouraged to enroll in phase II studies.

The ineffectiveness of conventional chemotherapy strategies in this condition has prompted several molecular biology studies to evaluate novel treatment approaches. Based on the observation that HCC tissue contains estrogen receptors, clinical trials with the antiestrogen tamoxifen have been undertaken. An initial study from Padua, Italy, demonstrated a significant survival advantage in a small group of patients receiving this agent. However, a subsequent study from the Mayo Clinic failed to confirm these findings. The results of a different study evaluating the antiestrogen Androlon and the luteinizing-hormone-receptor agonist Zoladex are pending. The use of systemic interferon therapy in this disease would seem attractive because of the agent's combination of both antitumor and antiviral effects. However, results from four studies of interferon therapy alone or in combination with systemic chemotherapy have demonstrated marginal effects at best. Moreover, two evaluations of the role of interleukin-2 have demonstrated low response rates.

Regional Chemotherapy for Primary Liver Cancer

Explanations for the refractoriness of HCC to chemotherapy include the heterogeneity of the tumor, multidrug resistance gene expression, or intrinsic drug resistance. These mechanisms may be partly overcome by increasing drug concentrations. In this regard, the unique anatomy of the liver blood supply has been

exploited. The blood supply to the liver is derived predominantly from the portal vein, whereas tumor blood supply is derived from the hepatic artery. Thus, hepatic arterial infusion may result in a high concentration of drug in the tumor, estimated to be 5–20 times greater than in normal surrounding hepatic tissue. These observations have prompted several studies examining the role of intra-arterial chemotherapy in this disease. A wide variety of single- and combination-chemotherapy regimens have been examined using this approach. Response rates as high as 57% have been achieved in some studies, and some patients have benefited with prolonged survival. Chemotherapy is usually by bolus injection. Some investigators have then gone on to treat with infusional chemotherapy with the placement of an implantable pump in responding patients. For patients under consideration for liver transplantation, pre- and postoperative chemotherapy is under evaluation at several centers. At the University of Pittsburgh, patients with stage III or IV HCC have been treated with intra-arterial cisplatin, doxorubicin, and subcutaneous interferon alpha. Pretransplant chemoembolization is also currently under investigation.

Chemotherapy for Cholangiocarcinoma

As with HCC, surgical therapy is the only curative option for patients with cholangiocarcinoma. In patients with unresectable disease, the use of 5-fluorouracil, alone or in combination with other agents, has not been proven to enhance survival. Combinations of chemotherapy with radiation have been attempted for many localized malignancies. In general, these regimens are well tolerated but require evaluation in randomized trials. Patients with these classes of tumors should be encouraged to participate in trials of novel therapeutic agents.

Chemotherapy for Gallbladder Cancer

Fluorouracil-based chemotherapy has been the main agent evaluated in the treatment of biliary malignancies with response rates of 10–24%. The use of this agent as a radiosensitizer with intraoperative or postoperative therapy is currently under evaluation.

RADIATION THERAPY

The fundamental challenge for the radiation oncologist is to use ionizing irradiation to produce a desired biological effect (tumor control or response) with a high probability and at the same time have only a low or modest probability of producing serious, undesired biological effect (life-threatening or compromising normal-organ toxicity). When dealing with primary hepatic and biliary neoplasms this challenge is quite severe. For example, using external-beam megavoltage irradiation with standard fractionation (180–200 cGy/treatment, one treatment

per day, treating 5 days/week) most epithelial malignancies arising within the gastrointestinal tract will require doses of 5000–6000 cGy to reliably control microscopic amounts of disease burden (e.g., as postoperative adjuvant management). Tumor burdens large enough to be visible to the surgeon's eye or by standard CT scan or MRI techniques require much higher doses, e.g., as high as 7000–8000 cGy or higher, to have even modest probabilities of control within the volume of irradiated tissue when radiation is used as the only modality of antitumor treatment. When measured against the stringent and limiting radiation tolerances of the organs of the upper abdomen where doses in excess of 5000–6000 cGy can only rarely be administered with safety (and then only to very restricted volumes of tissue), and of the liver itself where doses in excess of 2700–3000 cGy to the *whole* liver are associated with increased risk of potentially life-threatening radiation hepatitis, the limitations of radiation alone are quickly appreciated. Radiation oncologists have dealt with this challenge by utilizing partial liver irradiation when possible, limiting the dose required by combining radiation treatments with the use of other modalities (surgery, chemotherapy), by delivering radiotherapy by novel means (brachytherapy or radiolabeled antibodies), and by careful selection of clinical contexts and goals.

Radiotherapy for Hepatocellular Carcinoma

Treatment with Curative Intent

A curative approach to HCC management requires successful, surgical resection. This type of approach is best undertaken when there is reasonable probability of disease confined to anatomically and physiologically suitable volumes of liver as reflected by TNM staging (AJCC/UICC) and standard surgical parameters (e.g., Childs-Pugh criteria). In situations where initial indications are of only modest possibility of successful surgical exploration and resection based on extent or location of tumor volume in relation to lobar lines of resection or critical central structures or where underlying physiological reserve and clinical stability are unclear, preoperative regimens employing irradiation can be used to attempt to shrink tumor volumes away from critical structures and to more manageable proportions. Such treatment also provides a window of opportunity for observing the direction and tempo of the clinical course without leaving the patient untreated. Considering the biological heterogeneity of these tumor presentations (vide infra), such an opportunity can be of great value prior to undertaking the risks of major hepatic resection in patients who are often known to have significant confounding nonneoplastic hepatic pathology (cirrhosis, chronic active hepatitis B and/or C). In our experience patients successfully resected after preoperative chemoradiotherapy have done as well as patients directly taken to resection.

Conversion to resectability has been observed after various chemoradiation regimens and does not depend on the use of specialized techniques such as radiolabeled antibody therapy.

Treatment with Palliative Intent

The treatment of unresectable HCC is usually undertaken for one or more reasons, e.g., relief of tumor symptoms, shrinkage of tumor masses, or an effort to prolong survival. In these contexts, as the goals of therapy are more limited, the importance of minimizing the risk of serious morbidity is increased.

Stereotypically, unresectable presentations of HCC may bring to mind an image of severely painful illness, gross hepatic dysfunction, ascites, cachexia, and rapid demise. While such presentations are well described, it is also recognized that there is substantial variability in clinical severity and biology that impacts rather dramatically on survival and clinical course independent of the use of nonsurgical therapy. While some of this variability relates to characteristics associated with the tumor (tumor size, presence or absence of alpha-fetoprotein production, variant histology such as fibrolamellar), some also relates clearly to underlying hepatic reserve and the patient's ability to tolerate the tumor. For example, using readily measurable parameters such as performance status, the presence or absence of clinical ascites, and the presence or absence of abnormal levels of bilirubin, albumin, SGOT, and alkaline phosphatase with or without consideration of tumor size, patients can be readily stratified into prognostic groups with median survivals ranging from 11.5 months to 1 month and 1-year survivals ranging from 49% to 3%, respectively (Okuda stages I–III). Although initially reported in Asian patients, this approach has also been validated in North American patients where ''favorable'' (but unresectable) patients have been found to have median and 1-year survivals of 7–8 months and 30–35%, respectively, while ''unfavorable'' patients have median and 1-year survivals of 3 months and 3%, respectively. Clearly, the impact of these prognostic factors needs to be considered and incorporated into the process of assessing any therapeutic approach in the unresectable context.

Palliative Approaches with Irradiation

For many years the basic approach to the nonsurgical treatment of HCC at our institution, for patients felt to be reasonable candidates for antineoplastic therapy, included systemic chemotherapy in radiosensitizing doses administered intravenously during a brief course of hepatic irradiation (2100 cGy in seven fractions treated 4 days/week). This approach derived in part from known experience with this time dose fraction scheme to the liver in treating patients with extensive hepatic metastases where pain relief with modest morbidity was observed and from the desire to build a therapeutic foundation onto which additional treatment

modalities could be added safely. In initial trials this approach was then followed by further irradiation from ^{131}I conjugated polyclonal, heterologous antiferritin antibodies combined with sensitizing doses of chemotherapy or by chemotherapy alone. More recently, we have abandoned the use of the radiolabeled antibody therapy in favor of monthly cycles of intra-arterial cisplatinum directly administered in a selective regional fashion through the hepatic artery. In preliminary observations this approach appeared to be associated with better response and reduced toxicity and subsequent analysis has confirmed this impression.

Others have utilized twice-daily irradiation with intra-arterial FUDR and 3D treatment planning. This approach permits the delivery of much higher radiation doses with acceptable risk to surrounding hepatic parenchyma and may be most advantageous to relatively localized, nonresectable HCC.

Radiation Therapy for Gallbladder and Bile Duct Cancer

Radiation therapy can be safely administered to the hepatic hilum and adjacent tissues either primarily as palliative management or following surgical resection. When administered, radiation can be given both by external beam (linear accelerator) and through the use of intraluminal brachytherapy since direct access is often available through indwelling silastic stents. In addition, radiation can be combined with intravenous fluorouracil as has been done with other gastrointestinal malignancies. Nevertheless, most published reports contain relatively small patient numbers and unstated selection factors, although there has been report of increased survival with increased dose as part of 3D treatment with either photon (x-ray) or proton therapy. In our own institution we remain largely unconvinced that radiation therapy as usually administered, including intraluminal brachytherapy boosts, adds to survival. However, we are not sanguine about the limitations of results with surgery alone, and for favorable patients, resected with curative intent, we are adding systemic chemotherapy with 5-fluorouracil concurrently to postoperative irradiation.

INTERVENTIONAL RADIOLOGY

Interventional radiological techniques are useful in the management of patients with unresectable hepatic or biliary tract malignancy. These image-guided procedures are considered palliative and can be performed with limited risk and morbidity. It is often possible to use interventional radiological procedures to complement other forms of therapy. For example, chemoembolization has been used to enhance operability in patients who are marginal candidates because of tumor size. The purpose of this section is to describe interventional radiological procedures that are commonly used in hepatobiliary malignancy.

Chemoembolization

The concept of injecting an embolic substance through a selectively placed arterial catheter to devascularize and treat liver cancer with chemotherapy dates back to the earliest work with transcatheter embolization in the 1970s. Limited success was obtained with this technique in its earliest stages. It was not until the Asian experience of the 1980s with chemoembolization that renewed interest took place in the United States. The Japanese found that iodized poppyseed oil (Ethiadol), when selectively injected into the hepatic artery branches supplying a HCC lesion, was trapped within the tumor (Fig. 4). Chemotherapy, in its aqueous form and vigorously mixed with Ethiadol, forms an emulsion that suspends droplets of chemotherapy in the oil matrix and, when embolized to the tumor, is stopped at the hepatic arteriole and portal venule level. When embolic particles such as Ivalon (polyvinyl chloride), gel foam powder, or pledgets are added, the response of the tumor to chemoembolization is improved over the oil-and-chemotherapy emulsion alone. Chemoembolization delivers a high dose of chemotherapy to the target lesion, while at the same time the systemic dose is small and constitutional

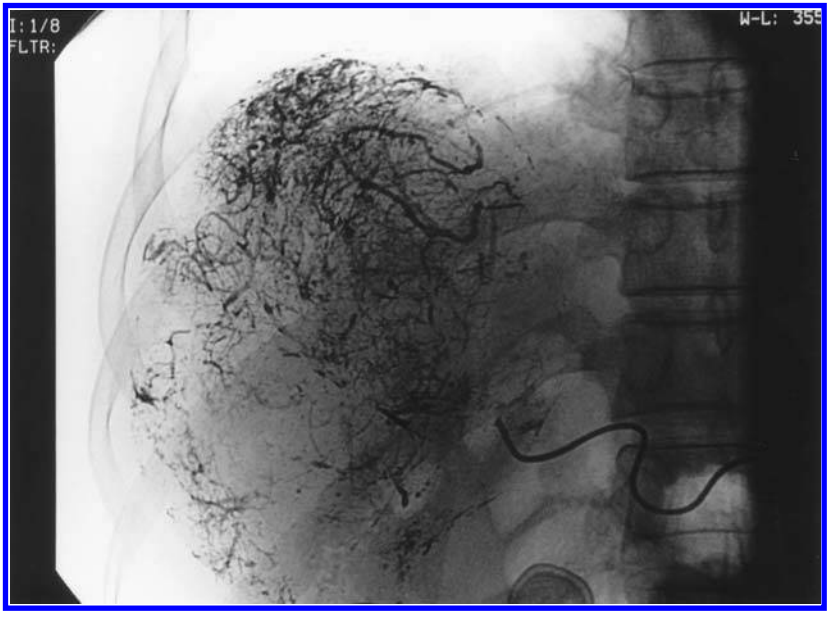

FIGURE 4 Postembolization with ethiodol, ivalon, cisplatin, doxorubicin, and mitomycin. The tumor vascular bed has been saturated with the embolic medium and is seen on the radiograph image because of the density of ethiodol.

symptoms are mild. The embolization causes impedance to arterial blood flow, which increases the time of target lesion exposure to the chemotherapeutic dose and also deprives the tumor of its nutritional support, which aids in tumor necrosis (Fig. 5). The combination of cisplatin (Platinol), doxorubicin (Adriamycin), and mitomycin C in aqueous solution is mixed with ethiadol to form a suspension of droplets within the oil medium. This mixture is well suited to transcatheter embolization. Doses range from 100 mg to 150 mg cisplatin, 50 mg to 75 mg doxorubicin, and 10 mg to 15 mg mitomycin C, mixed in a one-to-one or two-to-one oil-to-chemotherapy dilution.

Hepatocellular cancer, liver metastases from colorectal carcinoma, ocular melanoma, and carcinoid and neuroendocrine tumors have all shown response to chemoembolization (Figs. 6 and 7). These tumors are treated in patients who are not candidates for surgical resection and have lesions localized to the liver. Liver chemoembolization may be performed in patients with extrahepatic disease, but only if the liver lesions account for significant clinical morbidity. In some patients who may be borderline operative candidates, chemoembolization can be employed to reduce tumor size and improve resectability. Adequate liver functional reserve is necessary for effective chemoembolization. Patients with a serum

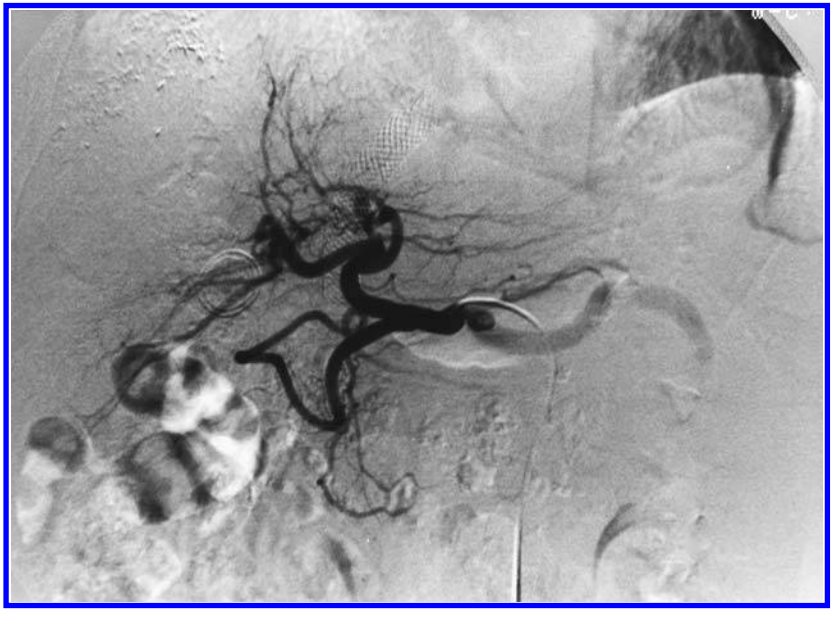

Figure 5 A digital subtraction arteriogram, postembolization, revealing complete obstruction of the tumor vascularity and preservation of blood flow to the hepatic artery.

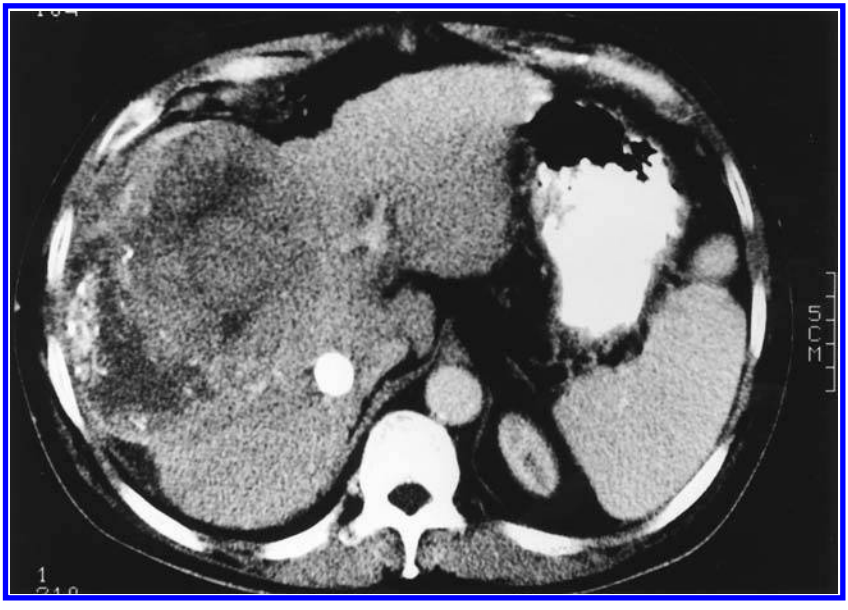

FIGURE 6 CT scan 1 month following embolization showing areas of necrosis. The radiopaque material is residual ethiodol from the chemoembolization.

bilirubin above 2.0, ALT and AST above 100 and 150, respectively, high alkaline phosphatase, and poor synthetic function respond poorly. Encephalopathy is a contraindication to chemoembolization. Cross-sectional imaging is useful in evaluating the lesion size and location, portal vein involvement, and bile duct obstruction. The risk of abscess formation and sepsis in a patient with biliary obstruction precludes the use of chemoembolization. While portal vein obstruction is a relative contraindication to hepatic artery occlusion by chemoembolization, selective therapy can be delivered to localized areas of the liver, and over time, some improvement in portal blood flow may occur with reduction in the size of the tumor.

Diagnostic angiography is useful for delineation of the arterial anatomy, presence of anomalous arterial supply to the liver, tumor vascularity, and portal vein involvement. The strategy for chemoembolization is based on the tumor arterial blood supply and distribution of the tumor in the liver on cross-sectional scans. A typical chemoembolization session includes selective catheterization of appropriate tumor feeding vessels, saturation of the target lesion with the oil/chemotherapy emulsion, and addition of gel foam or Ivalon to the emulsion based on the size of the tumor vascular network. The embolization is usually confined

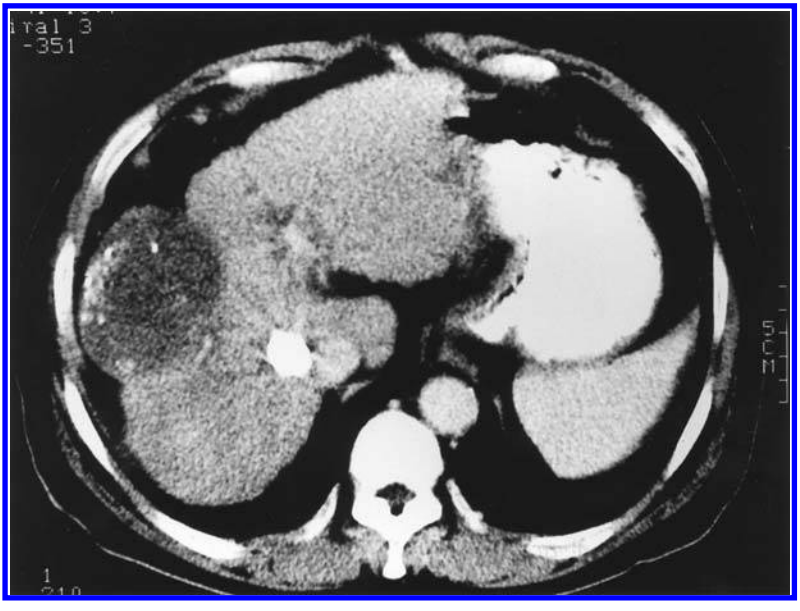

FIGURE 7 Same patient 1 year following chemoembolization showing significant reduction in the size of the tumor. The liver is small due to underlying cirrhosis.

to one lobe and continued until significant stasis of blood flow occurs. Total obstruction of the artery is usually avoided so as to maintain vascular access to the tumor should additional chemoembolization be required. The patient may be treated with multiple sessions at 3–6-week intervals. Most patients, however, require only two to three sessions for adequate response. The sophistication of modern catheter and guidewire technology allows precise selective catheterization of small and anatomically remote tumor arterial supply. Often such superselective catheterization is not necessary as the arterial network of the tumor is so significant that it acts as a hemodynamic sump, whereby nonselective embolization is preferentially drawn into the tumor with relative sparing of normal liver.

Tolerance to chemoembolization is quite varied among patients. Right upper quadrant or epigastric pain and/or nausea are the most frequent complaints following chemoembolization. Symptoms are self-limiting in the first 24–72 hr, and easily controlled by antiemetics and IV analgesics. Pre- and postprocedure antibiotics are given to reduce the risk of infection or abscess formation. Fever in the first 24–48 hr is common, but is attributed to the postembolization syndrome of fever, chills, leukocytosis, and pain, which may follow any peripheral embolization procedure. Blood cultures are usually not indicated unless fever is

persistent and significant constitutional symptoms are present. A postembolization noncontrast CT scan is obtained to evaluate the distribution of the chemoembolization and aid in planning future sessions. When discrepancies occur in the expected target saturation by chemoembolic material and the hepatic arterial supply, extrahepatic tumor vascular feeders arising from the aorta and intercostal arteries should be suspected.

A mild to moderate transaminase elevation routinely occurs following chemoembolization with return to baseline in 5–7 days post procedure. Follow up is conducted with physical examination, liver function tests, tumor markers, and cross-sectional imaging at 3–6 weeks following the procedure. A decision is made at that time to continue with another session or place the patient back in screening with cross-sectional studies and tumor markers at 3 months, and thereafter, at 6-month intervals.

Response to chemoembolization is difficult to accurately quantify, given the wide variability in the scientific literature, in study design, embolization techniques, response parameters, and lack of adequate controls. Survival data range from 60% to 80% for the first year, 40% to 60% for the second year, and 15% to 30% in year 3. Tumor response, as judged by reduction in size or tumor markers, is as high as 88%. While the exact mechanisms of chemoembolization have yet to be clearly defined, new technology in embolic media, which include improved binding of chemotherapeutic agents, controlled release, and better sizing of particle diameter to the tumor vascularity, offer promising areas of future research.

Direct Ethanol Injection

Direct percutaneous intervention in mass lesions of the liver involves image-guided placement of a small-caliber needle (CHIBA) and injection of absolute alcohol. This results in immediate disruption of cell membranes, cell death, and necrosis in a volume of tissue related to the amount of alcohol injected. Palliation can be achieved in multiple sessions (staged) where small volumes of alcohol are injected in different parts of the tumor based on cross-sectional images. Staged therapeutic injection of alcohol results in tumor ablation with less risk of leakage of alcohol from the injection site and less morbidity. A more aggressive approach is the injection of large volumes of alcohol (75–100 cc) in multiple sites using ultrasound guidance in one session. The patient will require general anesthesia owing to pain from the high-volume alcohol injection. Better response of the tumor to single large-volume ablation has been reported. Alcohol ablation by direct injection can be done in conjunction with chemoembolization, particularly when the arterial feeding vessels have become permanently occluded by the embolization. Owing to the complexity of the arterial anatomy, it is not always possible to achieve full embolization of a liver lesion. Cross-sectional studies

such as CT scanning can direct the CHIBA needle placement in viable areas of the tumor that has been poorly embolized. ETOH injection is then directed to these areas in 5–10-cc quantities by the CHIBA needle. Recently reported success with aggressive percutaneous ETOH ablation has been encouraging. One study of 754 cases has shown a 2-year survival of 48%, 31% at 3 years, 20% at 4 years, and 15% at 5 years.

Carcinoma of the Proximal and Mid Biliary Tree: Role of the Interventional Radiologist

Cholangiocarcinoma is the most notorious lesion occurring in the bile ducts near the liver hilum. Most frequently, the tumor occurs at the common hepatic duct bifurcation, which makes curative resection difficult. The lesion may infiltrate the intrahepatic ducts, causing segmental occlusion and isolation of dilated intrahepatic ducts. Although not as frequent, carcinoma of the gallbladder may cause an identical pattern of ductal obstruction. When ductal obstruction is caused by metastatic tumor, this lesion can be differentiated by cross-sectional imaging, and is characterized by tumor mass in the hilum in addition to bile duct obstruction.

The result of bile duct malignancy at the liver hilum is usually the same, regardless of the etiology. Varying degrees of bile duct occlusion by tumor lead to obstruction of the normal flow of bile, resulting in jaundice and a risk of cholangitis and sepsis. When severe, the obstruction causes significant bile duct dilatation, hepatocyte dysfunction, and cell death. In spite of normal hepatic functional reserve, at the outset of biliary obstruction, a central obstruction to the bile ducts leads to progressive and relatively rapid clinical deterioration. Death may come due to poor nutritional status, liver failure, and sepsis.

Percutaneous management of malignant biliary obstruction is directed exclusively to palliative relief of the ductal occlusion. Some intrahepatic forms of cholangiocarcinoma present as a liver mass and can be treated by chemoembolization. Hilar malignancy is especially difficult to palliate effectively, since extension into the right and left ducts creates problems in maintaining adequate drainage. Insertion of plastic or metallic stents across the neoplastic obstruction will restore the flow of bile, reduce the patient's jaundice, and often the accompanying pruritus, and decrease the likelihood of sepsis (Fig. 3b). When the common hepatic duct bifurcation is involved, both right and left ductal systems may require separate drainage by stents. While endoscopic stenting is effective in distal common bile duct malignancy, percutaneously placed stents are superior in dealing with hilar obstruction and multiduct obstruction. Stents may be inserted into each of the right and left obstructed ductal systems, from the periphery, often based on CT scanning, whereas endoscopic manipulation of retrograde stenting is less precise and may not completely cross the obstruction.

Prior to percutaneous access, cross-sectional imaging is useful in showing

the pattern of ductal obstruction and, therefore, the best site for access. Vascular compromise of the portal vein and resulting lobar atrophy is not unusual in hilar malignancies. Percutaneous access in this situation is usually avoided, as little will be gained by the drainage of an atrophied lobe of liver. CHIBA needle percutaneous transhepatic cholangiography will demonstrate the location of the obstruction and the feasibility of percutaneous drainage, and provides fluoroscopic visualization of the bile ducts for accurate placement of the biliary stent. The standard approach to drainage of the bile ducts is from the right lobe. The stent is located in such a way as to provide the most effective drainage of the obstructed bile ducts, to cross the site of central obstruction, and allow distal placement of the stent in unobstructed common bile duct or duodenum. More than one access may be required when both right and left systems are involved, and while additional percutaneous access substantially increases patient morbidity, all large undrained ductal systems should be stented. When the degree of neoplastic infiltration of the intrahepatic ducts is extensive, theoretically requiring three or more percutaneous access sites, the rationale for percutaneous management becomes less clear. When more than two percutaneous drainage catheters are employed, palliation becomes less effective, with increased risk of infection and hemobilia. A one-step insertion of a metallic endoprosthesis in each of the right and left duct systems, on the other hand, may offer better palliation and less risk from sepsis.

Metallic endoprostheses have been shown to be an effective method of palliation for malignant bile duct occlusion. Biliary metallic stents are of the self-expanding type, and can be delivered under fluoroscopic guidance with relatively small-caliber delivery systems. Before metallic stent insertion, the site of obstruction is balloon dilated by a percutaneous transluminal angioplasty catheter. Additional balloon inflations at high atmospheres of pressure may be required to obtain a satisfactory caliber in the stent lumen. When bleeding due to dilatation of the tumor is significant, temporary percutaneous drainage may be necessary by leaving a plastic catheter in the ducts above the stent. This catheter is often removed within 24–48 hr if the follow-up cholangiogram shows a patent endostent.

Causes of metallic stent failure are due to narrowing of the stent lumen by tumor overgrowth, through the interstices of the metallic stent or at the proximal or distal ends. Stent placement is directed to obtaining optimal bile duct coverage by the metal stent above and below the neoplastic lesion. Fabrication of covered stents may limit tumor growth through the stent interstices and prolong stent patency. When stent failure occurs, secondary patency can be achieved by repeating the process of percutaneous bile duct access, balloon dilatation, and restenting. The mean patency rate for large-caliber metallic endoprostheses is approximately 6–8 months. Lesions at the liver hilum are more problematic in terms of patency, owing to the smaller size of the right and left duct systems and the pattern of ductal arborization of the intrahepatic ducts.

Intracavitary radiation therapy or brachytherapy by placement of iridium

wire within percutaneous stents is another method of tumor palliation showing promise. Cholangiocarcinoma has been shown to be responsive to local external-beam radiation therapy. Brachytherapy avoids excessive radiation exposure to surrounding tissue but delivers a high level of exposure to the tumor by placement of ^{192}Ir wires within the percutaneously placed stents. Placement of the iridium wire within the tumor is based on cross-sectional imaging and fluoroscopic guidance. Following optimal exposure, the iridium wire is removed from the percutaneous stents and long-term percutaneous drainage is maintained for palliation of the ductal obstruction. Addition of brachytherapy to metallic stenting has improved stent patency in some studies. ^{192}Ir wire is placed percutaneously in the obstructed bile ducts before or after metallic stent insertion. External-beam irradiation has also been used effectively in conjunction with brachytherapy.

CLINICAL RESEARCH QUESTIONS

Surgical Resection Versus Transplantation for Hepatocellular Carcinoma

As discussed earlier, ongoing controversy remains regarding which patients with hepatocellular carcinoma should be offered hepatic transplantation. As most patients with HCC have severe cirrhosis, both the liver failure and malignancy may theoretically be treated by liver transplantation. Patients with severe cirrhosis and incidental or coincidental tumors less than 5 cm in size may have best results by transplantation. More advanced tumors, however, are associated with a significantly higher rate of recurrence. The difficulty in obtaining donor livers as well as the high mortality and cost of this procedure further add to the controversy of such therapy. Ongoing studies are examining whether combining preoperative local-regional techniques including ethanol injection, chemoembolization, or cryosurgery in combination with liver transplantation, as well as postoperative adjuvant systemic chemotherapy, may improve results with transplantation for liver cancer in the future. In addition, newer immunosuppressive agents may result in lower risk of recurrent extrahepatic disease.

Locoregional Techniques for Unresectable Hepatic Tumors

In patients who are not candidates for surgical therapy, a variety of physical and chemical agents are available. Considering the options available for producing objective responses in HCC (cryosurgery, radiofrequency ablation, ethanol injection, chemoembolization, external-beam radiation, regional chemotherapy) it is unclear whether any has particular advantage over the other. Reported phase II trials have generally not adequately considered the important prognostic factors in their descriptions of patient selection, confounding clear understanding of re-

sults from report to report. Treatment selection appears to be based more on institutional preference or expertise rather than any innate therapeutic advantage of one approach over another. Even in the few prospective randomized trials that compared one approach over another, even to best supportive therapy, no clear advantage has appeared.

Palliative Biliary Decompression for Unresectable Bile Duct Tumors

Although most patients with obstructive jaundice from unresectable cholangiocarcinoma derive benefit from palliative biliary decompression, the best method to achieve this goal remains in question. Endoscopic stenting, transhepatic stenting, and surgical bypass all have been advocated as the preferred approach in select circumstances. Several randomized trials comparing these modes of palliation have shown mixed results. Procedure-related complications, short-term mortality, biliary patency rates, and quality of life can vary with each approach and must be individualized according to the patient's performance status and local institutional expertise.

BASIC RESEARCH QUESTIONS

Hepatocellular Carcinogenesis

Although major risk factors for the development of HCC are known, factors involved in a molecular pathogenesis of this disease continue to be under investigation. Transformation of the hepatocyte to a malignant cell can occur through a variety of etiological agents by inducing chronic liver cell injury. This results in hepatocyte regeneration, which leads to genetic mutations and the subsequent development of HCC. Etiological agents such as alcohol, metabolic liver diseases, and probably hepatitis C virus may predispose to the development of cancer through such pathways of chronic hepatocyte injury. Hepatitis B virus may also have a direct carcinogenic effect, resulting in chromosomal alterations or the production of viral gene products that influence the control of growth regulation. Ongoing research suggests that other specific growth factors, oncogenes, and tumor suppressor genes may also play a role in the development of HCC. For example, evidence suggests that aflatoxins induce mutations in the p53 suppressor gene that may contribute to hepatocyte carcinogenesis. Discoveries in the molecular pathogenesis of HCC may result in better methods for the prevention and treatment of this disease.

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12

Adrenal Gland Carcinoma

David L. Bartlett, Brian Fuller, and Antonio T. Fojo
National Cancer Institute, National Institutes of Health, Bethesda, Maryland

INTRODUCTION

Adrenal tumors have clinical significance as both hormone-secreting neoplasms and malignant tumors. In addition, adrenal masses are commonly encountered as an incidental finding on abdominal imaging studies. It is essential for oncologists to be comfortable with the recognition of syndromes of adrenal hormone excess, the appropriate treatment of malignant adrenal neoplasms, and the management of incidentally discovered adrenal masses. The adrenal gland is unique in that within a single organ are combined two different histological types with distinct associated clinical entities. In this chapter the discussion of cortical neoplasms will be separated from that of medullary tumors.

INCIDENTAL ADRENAL MASSES

As abdominal computed tomography (CT) scans and ultrasound have become commonplace, incidental adrenal masses have become important clinical entities. Approximately 0.6% of CT scans of the abdomen demonstrate an incidental adrenal mass, and benign, hormonally silent adrenal adenomas are seen in 8.7% of autopsies. These masses are clinically important because they may represent a malignant tumor or they may have subclinical hormone production that will become significant in the future. The differential diagnosis includes adrenocortical carcinoma, pheochromocytoma, metastasis from a nonadrenal malignancy, adrenocortical adenoma, adrenal cyst or pseudocyst, ganglioneuroma, myelolipoma, and adenolipoma.

Diagnosis

The goal of workup is to differentiate lesions that require surgical resection for treatment (primary adrenal carcinoma, pheochromocytoma, functioning adrenocortical adenoma) from those lesions that can be safely observed. The algorithm for workup of an incidental mass is summarized in Table 1. A thorough history and physical examination are essential to screen for signs and symptoms of hormone excess. A summary of pertinent findings is shown in Table 2. It is also important to look for other signs of occult malignancy in case the adrenal mass represents a metastatic focus. Screening laboratory tests should consist of a 24-hr urine collection for levels of epinephrine, norepinephrine, metanephrine, and vanillylmandelic acid (VMA) to rule out a pheochromocytoma. In addition, the urine can be tested for free cortisol and 17-ketosteroids to rule out Cushing's syndrome or overproduction of sex hormones. Blood should be tested for electrolytes to rule out hypokalemia associated with excess aldosterone production. If any test is positive, further studies should be considered to confirm the diagnosis as shown in Table 2. Further radiographic workup should include a chest x-ray and mammograms to rule out a lung or breast primary tumor. The CT scan should be reviewed carefully for other indications of occult primary tumors or metastatic foci.

The CT appearance of the adrenal mass can provide clues to the diagnosis. Benign adrenal tumors are usually well-circumscribed, homogeneous spherical masses less than 6 cm in size. In contrast, malignant lesions are irregular in shape and inhomogeneous with central low-attenuation regions secondary to hemorrhage and necrosis. They may be associated with adjacent organ involvement, or lymph node metastasis. Adrenal cysts can be diagnosed by their characteristic CT appearance. Any suggestion of a thick, irregular wall or inhomogeneity con-

Table 1 Algorithm Summary for the Workup of an Incidental Adrenal Mass

1. CT scan and 24-hr urine collection for epinephrine, norepinephrine, metanephrine, vanillylmandelic acid (VMA), free cortisol, and 17-ketosteroid.
2. If >6 cm in diameter, suspicious for malignancy on CT scan, or functional, then the gland should be resected.
3. If 3–6 cm in size, then consider MRI scan. If suspicious for malignancy, then the gland should be resected.
4. If <6 cm and nonfunctional, not suspicious on CT or MRI, then follow the patient with CT scans and urine screening at 3 months, 9 months, and 18 months.
5. If significantly increases in size, changes occur that are suspicious for malignancy, or the mass becomes functional, then the gland should be resected.
6. If no significant change occurs after 18 months, then follow-up on an as-needed basis only.

TABLE 2 Summary of Presentation and Workup of Syndromes of Hormone Excess

Hormone	Signs and symptoms	Diagnosis
Cortisol (Cushing's)	Weight gain, truncal obesity, weakness, muscle wasting, buffalo hump, moon facies, ruddy complexion, striae, depression, psychosis, opportunistic infections, glucose intolerance	24-hr urinary free cortisol > 100 μg Low-dose dexamethasone suppression test—urinary cortisol > 20 μg/24 hr CT scan with 3–5-mm cuts through adrenal gland
Aldosterone (Conn's)	Weakness, muscle cramps, polyuria, polydypsia, hypertension, hypokalemia	On high-salt diet, 24-hr urinary K + >30 mEq 24-hr urinary aldosterone >15 μg Ratio of plasma aldosterone:plasma renin activity >30 CT scan with 3–5-mm cuts through adrenal gland
Androgens (virilizing)	Women: hirsutism, acne, amenorrhea, deep voice, temporal balding Men: nonspecific	24-hr urinary 17-ketosteroids >21 mg/day (male), >17 mg/day (female) Plasma DHEA >3500 Plasma testosterone >1200 (male), >80 (female) CT scan with 3–5-mm cuts through adrenal gland
Estrogens (feminizing)	Women: irregular menses, dysfunctional uterine bleeding Men: gynecomastia, decreased sexual drive, impotence, infertility	24-hr urinary 17-ketosteroids > 21 mg/day (male), > 17 mg/day (female) 24-hr urinary estrogens > 350 nmol/day CT scan with 3–5-mm cuts through adrenal gland
Catecholamines (pheochromocytoma)	Paroxysmal headaches, pallor, palpitations, diaphoresis, mild weight loss, labile hypertension	24-hr urinary metanephrine > 1.3 mg; VMA > 9 mg; epinephrine > 20 μg; Norepinephrine > 70 μg CT scan with 3–5-mm cuts through adrenal gland Consider MRI and MIBG scans

sistent with blood within the cyst should be worked up further to rule out a malignant lesion with extensive central necrosis. Magnetic resonance imaging (MRI) has proved helpful in differentiating benign adenomas, malignant tumors, and pheochromocytomas. Benign adenomas have a low signal intensity on T2-weighted images and show only mild enhancement and quick washout on dynamic contrast (gadolinium)-enhanced MRI. Malignant tumors and pheochromocytomas show a high signal intensity with T2 weighting and strong enhancement and slow washout with dynamic contrast imaging. Pheochromocytomas show the highest signal intensity on T2 weighting.

Needle biopsy of a nonfunctioning adrenal mass can provide a diagnosis in the majority of cases. Fine-needle aspiration can usually diagnose malignant adrenocortical cancers as well as metastatic malignancies. Patients with a history of a previous malignancy should undergo needle biopsy of any new adrenal mass identified on CT scan to rule out a metastatic tumor. The problem arises in differentiating adrenocortical adenomas from well-differentiated adrenocortical carcinomas. The pathological diagnosis of a well-differentiated adrenocortical carcinoma may rely on histological features such as vascular and capsular invasion, and may require histological examination of the entire mass. A small percutaneous core needle biopsy can also be done safely and may aid in differentiating a benign adenoma from a well-differentiated carcinoma. Further experience with core needle biopsy is required to make screening recommendations. As the negative predictive value for fine-needle aspiration is low, a negative aspirate cannot reliably rule out the presence of a carcinoma. If a benign diagnosis is not reliable, it does not make sense to perform this procedure to avoid surgical resection.

Treatment

Functioning adrenocortical adenomas and pheochromocytomas should be surgically removed. Special consideration of preoperative and postoperative management should be made for patients with hypercortisolism and pheochromocytomas as discussed in detail below. The best surgical approach is a laparoscopic adrenalectomy. Laparoscopic adrenalectomy has been shown to be safe and is associated with less postoperative pain, a shorter hospital stay, a shorter convalescent period, and improved cosmetic result compared to patients undergoing an open adrenalectomy via a flank or subcostal incision. Bilateral pheochromocytomas should be ruled out with a metaiodobenzylguanidine (MIBG) scan prior to laparoscopic removal of a single gland.

For nonfunctioning masses, those at risk for being malignant should be removed. Metastatic tumors to the adrenal gland diagnosed by a needle biopsy should be removed after an exhaustive search for other sites of systemic metastasis. Resection of isolated metastasis to the adrenal gland has been associated with long-term survival for a variety of histological types. Masses with CT scan

characteristics suspicious for malignancy should be resected. For lesions that appear benign, size is the most reliable predictor for the presence of malignancy. Recommendations regarding size criteria for surgical resection have ranged from anything greater than 3 cm to greater than 6 cm, based on different institutional reviews of adrenal cancers and size. Prior to the routine use of CT scans, adrenal cancers presented as large lesions when they became symptomatic. It is obvious that cancers begin as smaller lesions, and it is apparent that survival improves in an inverse relation to size. A reasonable recommendation is that all lesions greater than 6 cm be resected. Lesions between 3 cm and 6 cm that have malignant features on CT scan should be removed. If there are no significant malignant features, then the patient may undergo further workup with an MRI scan. Lesions that are suspicious for being malignant on MRI scan should be resected. Lesions that are considered benign should be followed with CT scans and hormone screening at 3, 9, and 18 months and resected if they become larger or hormonally active. If the lesion is stable for 18 months, then no further follow-up is necessary (a malignant tumor should grow within that period). The recommendation for resection should always take into consideration the patient's age, performance status, and concomitant illnesses. The surgical approach should be transabdominal for large lesions with a chance for regional spread. Small lesions (<6 cm) without evidence of vascular or regional invasion can be removed laparoscopically. The posterior approach is also described for smaller tumors, but the laparoscopic approach seems to be preferable.

FUNCTIONING ADRENOCORTICAL NEOPLASMS

Cushing's Syndrome

Adrenocortical tumors can produce cortisol (Cushing's syndrome), aldosterone (Conn's syndrome), sex hormones (virilization or feminization), or combinations of these. It is important to understand the differential diagnosis and workup for these clinical presentations. Cushing's syndrome is characterized by symptoms and signs summarized in Table 2, the most significant being weight gain, muscle wasting, and the characteristic moon facies. Cushing's syndrome can be caused by adrenal overproduction of cortisol, pituitary overproduction of ACTH (Cushing's disease), or an ectopic source of excess ACTH (e.g., bronchial carcinoid tumors).

Cortisol excess can be established by a 24-hr urinary free cortisol level. If there is any question regarding the presence of hypercortisolism, a low-dose dexamethasone test can be performed. The patient is given 0.5 mg dexamethasone every 6 hr for 48 hr, and urinary free cortisol is measured over the last 24 hr. If the urinary free cortisol remains above 20 μg/24 hr, then the diagnosis of cortisol excess is established. The source of the excess cortisol can be established by

measuring plasma ACTH levels and a high-dose dexamethasone test. Patients with an adrenal source of cortisol should have almost undetectable levels of ACTH. Patients with a pituitary source of ACTH hypersecretion have intermediate ACTH levels, whereas those with an ectopic source have very high levels. A high-dose dexamethasone test (2 mg every 6 hr for 48 hr) will differentiate a primary pituitary source of ACTH from an ectopic source. A pituitary source of ACTH will have suppression of urinary free cortisol to below 50% of baseline with high-dose dexamethasone treatment, whereas an ectopic source will not have suppression. Once an adrenal source is identified, the workup should proceed to a CT scan of the abdomen with 3–5-mm cuts through the adrenal glands. This will reliably differentiate bilateral primary adrenal hyperplasia from a unilateral adenoma or carcinoma.

Conn's Syndrome

Patients with hypokalemia (serum potassium <3.5 mEq/L) of unknown etiology and hypertension should be worked up for hyperaldosteronism or Conn's syndrome. Other signs and symptoms are summarized in Table 1. The causes of primary hyperaldosteronism include an aldosterone-producing adenoma, idiopathic adrenal hyperplasia, and adrenocortical carcinoma. In all cases, the plasma aldosterone level will be high and the plasma renin activity will be low. The diagnosis is made by measuring urinary potassium excretion (>30 mEq/day) and aldosterone (>15 μg/day) in a 24-hr urine collection after salt loading and potassium replacement. Plasma aldosterone and plasma renin activity are also measured, and the ratio of aldosterone to renin activity should be greater than 30. Once the diagnosis is established, a CT scan with 3–5-mm cuts through the adrenal gland should be performed. If the lesion is identified, with contralateral thinning of the adrenal cortex, then the patient should undergo unilateral adrenalectomy. If there is any question regarding the presence of a lesion, or an abnormal contralateral gland, then adrenal vein sampling for aldosterone should be performed to rule out idiopathic adrenal cortical hyperplasia (IAH), which is treated with spironolactone instead of surgery. Rarely, a postural stimulation test may be necessary to help differentiate between an adrenal adenoma and IAH.

Virilizing and Feminizing Tumors

Adrenal tumors associated with excess sex steroids are rare and often malignant. Virilization or feminization may be combined with excess cortisol secretion. For patients with symptoms of excessive virilization or feminization, workup should begin with a 24-hr urine collection for 17-ketosteroids and plasma measurements of dehydroepiandrosterone (DHEA) and testosterone or estrogen (depending on whether the symptoms are virilizing or feminizing). Once the diagnosis of excess production is made, a CT scan with 5-mm cuts through the adrenal gland should

be performed. If a mass is identified, then it should be removed carefully with the knowledge that it may be malignant.

ADRENOCORTICAL CANCER

Adrenocortical cancer is a rare malignancy with a poor prognosis. It accounts for 0.02–0.05% of all cancers, which translates into less than 2 cases per million in the world population. The peak age of incidence is in children less than 5 years and in adults in their 30s and 40s. Most series show a slight female preponderance. Approximately 50–80% of these cancers are considered hormonally functional, with the majority secreting multiple compounds. Clinical evidence of sex hormone production should heighten the suspicion for cancer. The combination of sex hormone and cortisol secretion is indicative of cancer. The etiology of adrenocortical carcinoma is unknown; however, it has been included as part of a complex hereditary syndrome with sarcoma, breast, and lung cancer. Childhood adrenocortical cancers are associated with hemihypertrophy and Li-Fraumeni syndrome.

Because of the retroperitoneal location of an adrenal tumor, if it is nonfunctional or minimally functional it can grow to a large size before becoming symptomatic. Functional adrenocortical cancers seem to be less efficient hormone producers than adenomas, allowing for large tumors to develop before a clinically apparent syndrome exists. Therefore, adrenocortical cancers tend to present at an advanced stage and have a poor prognosis. The clinical course overall, however, is quite variable even for some advanced tumors.

Diagnosis

The majority of patients present with flank pain, an abdominal mass, or a syndrome of hormone overproduction. Workup should consist of complete physical examination for signs of hormone excess or an abdominal mass, followed by urine and plasma hormone screening as discussed previously. In brief, this should consist of a 24-hr urine for catecholamines, metanephrines, VMA, cortisol, and 17-ketosteroids. Radiographic workup should begin with a CT scan of the abdomen with 3–5-mm cuts through the adrenal gland. An MRI can also be obtained, but it is more expensive and less readily available than the CT scan, and does not provide any increase in sensitivity. The advantage of the MRI is to help differentiate adrenocortical adenomas from carcinomas and pheochromocytomas as discussed previously.

The purpose of the radiographic workup is to assess the resectability of the mass. Tumors that cannot be completely resected recur quickly and have a poor prognosis. The morbidity of a large resection should be avoided in cases where the tumor is unresectable based on preoperative imaging studies. In general, syn-

chronous metastatic disease should be considered a contraindication to resection, although there have been some reports of prolonged survival after resection of lung metastasis. Adrenocortical cancers can be metastatic within the abdominal cavity and regionally invasive of surrounding organs, so attention should be given on the CT scan to evidence of lymph node involvement, liver metastasis, kidney invasion, pancreatic invasion (left tumors), and hepatic invasion (right tumors). In addition, vascular invasion and intracaval tumor thrombus formation are not uncommon (see Fig. 1). Further workup may include an arteriogram to assess encasement of the celiac axis and SMA, or a venogram to assess the inferior vena cava prior to surgical resection. Magnetic resonance angiography is a newer technique that provides good visualization of vascular structures noninvasively. This technique has been successful in reliably assessing the presence and extent of intracaval thrombus for these and similar tumors. A CT scan of the chest should be routinely performed to look for lung metastases or a lung primary tumor.

Surgery

Surgical resection of adrenocortical cancer is the most effective therapy. Since results of chemotherapy and radiotherapy have been disappointing, the goal of the surgeon must be to completely remove all of the tumor with an attempt at negative margins. The preoperative preparation is important and the patient may require medical treatment before surgery. For patients with excess aldosterone production, all electrolyte and acid/base problems should be corrected. Patients with florid Cushing's syndrome can be treated preoperatively with metyrapone, an 11-beta-hydroxylase inhibitor, to improve the patient's performance status prior to surgery. It is probably not wise to delay surgery while waiting for an effect from metyrapone, as the patient's condition may continue to deteriorate. Certainly if there is a delay in surgery for other reasons, the patient should be maintained on metyrapone until surgery.

The surgical approach is variable depending on the size of the mass, adjacent organ involvement, and the preference of the surgeon. For small incidentalomas the approach should be laparoscopic. Laparoscopic adrenalectomy can be performed safely with minimal postoperative morbidity. There exists a learning curve for this procedure as with any laparoscopic procedure, but after appropriate mentoring, anyone comfortable with laparoscopic techniques can become facile with laparoscopic adrenalectomy. The consequence of pneumoperitoneum in the presence of an intra-abdominal malignancy is still in debate. It is hypothesized that the pneumoperitoneum can cause diffuse seeding of tumor cells throughout the peritoneal cavity and into port sites. This has not been demonstrated clinically. Some surgeons advocate a posterior approach to small incidental masses with or without excision of the 11th and 12th ribs. This approach can provide good expo-

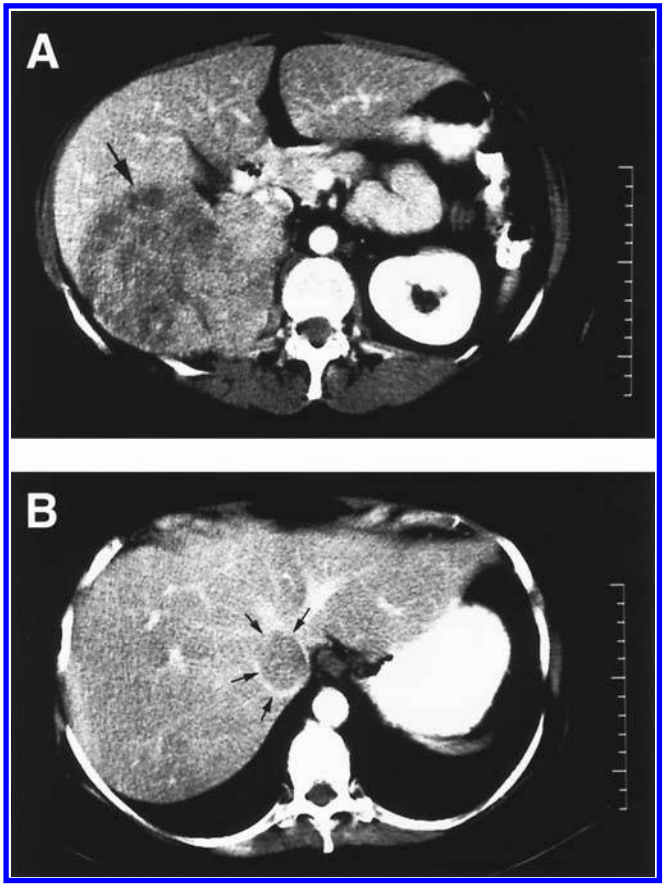

FIGURE 1 CT scan with intravenous contrast of a locally aggressive right adrenocortical cancer. The tumor appears to invade the right lobe of the liver (A) and is associated with a tumor thrombus in the inferior vena cava (B). The arrows in (B) outline the rim of the contrast-filled inferior vena cava around the tumor thrombus at the level of the insertion of the left and middle hepatic veins.

sure to the adrenal gland and allow for an easy excision. This is not recommended for patients suspected to have adrenal cancer, because of the risk for lymph node metastasis, adjacent organ involvement, and tumor thrombus. None of these can be managed adequately through this approach. In long-term follow-up of patients undergoing adrenalectomy with a posterior approach, they were found to have more chronic pain complaints and a delay in return to work compared to patients undergoing an open transabdominal approach.

For large lesions with or without adjacent organ involvement, the surgical approach should be either an anterior open laparotomy or a lateral thoracoabdominal approach. The anterior approach can be accomplished through a midline or bilateral subcostal incision. Large lesions requiring en bloc liver or pancreas resection can be best approached with a bilateral subcostal incision and superior midline extension, using a self-retaining retractor to retract the costal margin. Extension into the chest can be performed to improve exposure. For large left-sided lesions, the spleen, distal pancreas, stomach, and splenic flexure of the colon can be reflected medially prior to dissecting the adrenal gland. Smaller lesions can be approached by reflecting the splenic flexure of the colon inferomedially, and approaching the adrenal gland inferior to the pancreas, gently retracting the pancreas superiorly during the dissection.

For large right-sided lesions, the hepatic flexure of the colon should be mobilized medially, and peritoneal attachments of the right lobe of the liver need to be divided and the liver reflected medially. Smaller lesions can be approached by mobilizing the hepatic flexure and retracting the liver superiorly and the kidney inferiorly. Adjacent organs should be resected en bloc if there is any question of involvement. Most commonly this includes the distal pancreas and spleen for left-sided tumors and the posterior sector of the right lobe of the liver for right-sided tumors. Right-sided tumors may have tumor thrombus involving the inferior vena cava. This may be resected with the cancer en bloc. This requires division of caudate veins and control of the supra- and infrahepatic vena cava. Venoveno bypass may be necessary if the clamp time is going to be long or the patient cannot hemodynamically tolerate temporary interruption of inferior vena caval flow. Left-sided lesions that encase the celiac axis or SMA should be considered unresectable and only debulked when short-term palliation of symptoms is indicated. Intraoperatively and postoperatively, patients with cortisol-producing tumors need to have stress doses of glucocorticoids replaced, as normal contralateral adrenal tissue will be suppressed and unresponsive to ACTH stimulation. Similarly, patients with aldosterone-secreting tumors may have a large diuresis in the postoperative period.

Survival results after complete resection vary depending on the stage of the lesion. The TNM staging criteria are summarized in Table 3. Various modifications of this exist. It may be better to include locally advanced T4 lesions in a different category (stage III) than distant metastasis (stage IV) as the prognosis seems to be better for resectable T4 lesions. About 50% of patients present with stage III or IV disease, making the overall prognosis poor. The lymph nodes are involved in 20–30% of cases. The most frequent sites of distant metastasis in order are lung, liver, bone, and brain. Because of the rarity of disease, there are few large series of adrenocortical cancers for survival analysis. The clinical course is variable, and some patients can survive multiple recurrences over many years, while others die quickly of aggressively spreading tumors. Overall 5-year

Table 3 TNM Staging Criteria for Adrenocortical Cancer

	Tumor
T1	Tumor ≤5 cm, no local invasion
T2	Tumor >5 cm, no local invasion
T3	Tumor invading into adjacent adipose tissue
T4	Tumor invading into adjacent organs
	Lymph Nodes
N0	No lymph nodes involved with tumor
N1	Regional lymph nodes involved with tumor
	Metastases
M0	No distant metastases
M1	Distant metastases
	Stage grouping
I	T1, N0, M0—less than 5 cm with no local invasion, nodal or distant metastases
II	T2, N0, M0—greater than 5 cm with no local invasion, nodal or distant metastases
III	T1-2, N1, M0, T3, N0, M0—tumor with positive lymph nodes or local invasion
IV	Any T, any N, M1; T4, N0, M0; T3, N1, M0—advanced local or distant metastases

survival after complete resection of adrenocortical cancers is 45–50% whereas for incomplete resections it drops to less than 10%. Median disease-free survival after complete resection is about 2.5 years. Local and regional recurrences have been resected with a 5-year survival reported at 30%, and mean survival reported in another series at 56 months compared to a very poor outcome with chemotherapy alone. While anecdotal reports of prolonged survival after resecting metastatic disease exist, there are no series of cases that support this. Recommendations vary from aggressive resection of all disease if possible, to only resecting regionally confined disease. It is clear that subtotal resection is associated with a poor prognosis. In one series there was no difference in survival for patients undergoing palliative, incomplete resections compared to only a biopsy of the mass. Recommendations for aggressive surgical management should be made on a case-by-case basis, taking into consideration the patient's performance status, symptoms, sites of spread, and any clues as to the rate of disease progression.

Chemotherapy

Despite nearly 40 years of efforts aimed at developing chemotherapeutic strategies for the treatment of adrenocortical cancer, surgery still remains the therapy

of choice and the only curative option. Hampered largely by the rarity of this disease, and in part influenced by the success of surgery and the indolence of disease in some patients, significant advances have not been made in the chemotherapy of this disease since the introduction of mitotane in 1960. Although the infrequent occurrence of this disease will continue to preclude the conduct of large-scale studies, the future does seem brighter. The World Wide Web and databases such as the NCI's PDQ (Physician Data Query) have increased patient awareness of the existence of experimental therapies and the willingness of physicians to refer such rare patients for clinical trials. In addition, it is expected that the coming decade will see a larger number of agents with diverse mechanisms of action introduced, providing greater opportunities for the treatment of this disease.

Mitotane

The use of ortho, para′DDD (o,p′DDD, or mitotane) in the treatment of adrenocortical cancer arose from the observations of Nelson and Woodward that administration of the insecticide DDD to dogs results in necrosis and atrophy of the adrenal cortex. Systematic fractionation of DDD led to the identification of the isomer 1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)-ethane (o,p′DDD) as a less toxic and more active metabolite than crude DDD. Subsequent studies demonstrated that administration of o,p′DDD to dogs caused a marked decrease in secretion of 17-hydroxycorticosteroids, associated with the appearance of focal degenerative lesions in the zona fasciculata and zona reticularis, which was unresponsive to the administration of ACTH. In addition, o,p′DDD was shown to act as an inhibitor of enzyme systems responsible for the transformation of steroids in peripheral tissues. Encouraged by these observations, researchers began clinical trials in the late 1950s, and in 1960 Bergenstal and associates reported that the administration of o,p′DDD to patients with functional tumors resulted in a decrease in urinary steroid secretion and a reduction in the size of measurable lesions. This was followed by the general distribution of o,p′DDD to individual investigators under National Cancer Institute sponsorship and a series of reports that described the drug's activity, albeit in an era when tumor imaging was less sophisticated and criteria for response less stringently defined. Nevertheless, these early studies established mitotane as the single most active agent in adrenocortical cancer, a position it has held until the present time.

Any evaluation of mitotane must reconcile the results of early studies, in which the enthusiasm of clinical investigators was influenced by its antihormonal properties, with later trials that have found less antitumor activity. One must also carefully consider its toxicity. It is clear that more recent studies that have applied stricter criteria of antitumor response have found that the activity of mitotane is less than was originally reported. Nevertheless, physicians faced with a patient with adrenocortical cancer will almost invariably have to decide whether and

when to use mitotane in the management of this difficult disease; and this decision should be guided in part by the clinical setting.

For example, a frequently encountered clinical situation is that of a patient with a stage I, II, or III adrenocortical cancer who has undergone surgical resection, but in whom the size of the tumor or the difficulties in dissection increase concerns for a subsequent recurrence. While the experience (mostly anecdotal) of many suggests that mitotane may delay recurrence in such a patient, there is no evidence that mitotane in this situation is of value in improving survival. Consequently it seems prudent to withhold mitotane therapy in such patients. Indeed, as with most chemotherapeutic agents, this drug should not be used unless there is radiologically evaluable disease, or the tumor is producing measurable levels of a hormone. If therapy is instituted based on an elevated hormone level, and there is no measurable disease, serial scans should nevertheless be performed, as there can be complete dissociation of antihormonal and antitumor effects, and one should avoid the complacency that improvement in a hormonal level can engender.

Above all, one should avoid subtherapeutic mitotane treatment. Especially in patients in whom its use is debated, lower doses of mitotane are often administered, because higher doses bring difficult toxicities. This approach merely results in some toxicities, with an impact on quality of life, without the hope of any benefit. The observation that benefit is unlikely to occur is based on the experience of investigators who have measured mitotane levels and correlated these with response to therapy. These studies have shown that responses are rarely observed in patients with levels less than 10–14 μg/ml. For patients with stage III or IV disease who are unable to undergo a complete resection mitotane may be recommended. The dose administered depends on the individual patient, but should be guided by patient symptoms and measurement of blood levels. Barring side effects, the dose administered should be the highest dose tolerated by a patient. With the assistance of blood levels, an effort should be made to achieve the highest level possible, with a level above 10 μg/ml, and preferably one above 15 μg/ml, a goal that can be reached. While these levels can be achieved in a substantial fraction of patients, they often represent the levels at which side effects become difficult, or intolerable. Van Slooten observed progressive neurological toxicity when the plasma levels of o,p′DDD rose above 20 μg/ml, with a disappearance of symptoms after temporary discontinuation of therapy resulting in a fall in plasma levels of o,p′DDD.

While the use of mitotane in all stages is disputed, physicians caring for patients with inoperable adrenocortical cancer are invariably faced with having to decide whether to use this agent. The lack of other attractive alternatives, in a patient seeking any possible treatment options, frequently leads to a trial of this agent. In these cases it is recommended that treatment start gradually, and that the agent be pushed to its maximum tolerated dose. A starting dose of 2–3

g/day with increases in 1-g increments every week represents a viable alternative that can be modified according to patient tolerance. Increases should be attempted only after the patient adjusts to the current dose, and if accompanied by the appearance of severe side effects should be treated with a cessation of therapy for 1–2 days prior to resuming the previously tolerated dose. Every effort should be made to advance the dose again after a further period of adjustment, as this can prove successful even if a prior increase was accompanied by the occurrence of side effects. The schedule of drug ingestion can be flexible and should be left to the patient's discretion, with the recommendation that taking a larger portion of the dose at bedtime sometimes allows for better tolerance. Side effects can be treated symptomatically, with antiemetics and antidiarrheal agents prescribed liberally. In patients on long-term therapy, it is not unusual to find that the serum levels increase over time, and that a previously tolerated dose becomes intolerable as serum levels gradually increase, requiring a reduction in dose. For this and other reasons, measurement of serum levels monthly seems worthwhile. Van Slooten found a highly significant, semilogarithmic relationship between plasma and adipose tissue concentrations during therapy and at autopsy, as well as between levels in plasma and brain at autopsy. In addition, a linear relationship was found at autopsy between concentrations in adipose tissue and those in various other tissues, such as tumor and brain.

The evidence that higher levels are associated with a higher response rate suggests that levels of about 15 μg/ml or higher should be targeted. Although this represents the range at which side effects become intolerable for many patients, attempts should be made to achieve this, since some patients can tolerate even higher levels without side effects, although others experience intolerable symptoms at much lower levels. Because of the drug's long half-life, discontinuation of drug therapy for a couple of days does not significantly affect tissue levels. Recognition of this fact, and the observation that even a few days' respite in treatment can restore a sense of well-being, allows one to give patients on long-term therapy an occasional ''drug holiday'' during special occasions without compromising efficacy.

Mitotane's adrenolytic properties, which originally identified it as an agent for the treatment of adrenocortical cancer, usually lead to the development of adrenal insufficiency in patients receiving therapeutic doses. The onset of adrenal insufficiency can be insidious, and can vary depending on whether the patient's tumor is functional. Some physicians routinely begin replacement therapy at the start of mitotane treatment, but alternatively, patients can be followed carefully, and replacement therapy begun when indicated. The latter approach may be of greater value in the patient with a functional tumor. Finally, it should be borne in mind that mitotane's efficacy in reducing symptoms secondary to excess steroid production often exceeds its antitumor effects. Thus, it is not uncommon to have marked improvement and even resolution of the symptoms of excess hormone

production even as tumor volume increases. In such patients, when the decision is made to discontinue mitotane therapy, an aggressive alternative regimen with ketoconazole or other agents must be instituted, lest symptoms recur gradually, as mitotane is eliminated from the body, and become even more severe than at the start of therapy.

Other Chemotherapeutic Agents

While mitotane can be considered a chemotherapeutic agent, for the purpose of this discussion, the term ''chemotherapy'' will refer to the drugs that are also commonly administered to patients with other malignancies. The published experience using chemotherapy in this disease is best described as principally a large collection of anecdotes, as studies with more than a few patients are rare except for mitotane. The paucity of data in this disease is a result of several factors: (1) the rarity of this disease; (2) the fact that for almost three decades mitotane was viewed as the only viable treatment option; and (3) the fact that for many years adrenocortical carcinoma was viewed more as an endocrine than a neoplastic disease—consequently patients were usually seen and treated by an endocrinologist and often did not see an oncologist, or were referred to an oncologist because of far-advanced disease.

Although a review of the literature suggests that unlike other solid tumors this disease responds in some instances to available chemotherapeutic agents, there is likely to be among oncologists a reluctance to treat with chemotherapy. Consequently, it is probable that this field will continue to accrue a collection of anecdotes in the literature which, while often helpful, do not provide definitive answers. Unfortunately, the ''standard recommendation'' that these patients should be referred to clinical trials is difficult to administer in this disease, because studies are rare or often nonexistent. However, these patients are often young and have good performance status, and whenever possible, should be referred for phase I and II trials that evaluate newer chemotherapeutic agents.

Although the evidence is limited, some general principles that apply to solid tumors in general seem to apply to adrenocortical carcinoma: (1) large, bulky disease is less likely to respond to treatment than small-volume disease, although a handful of impressive responses have been reported in the literature; (2) response to therapy is usually slow; and progression or recurrence after a prior response make a second response less likely (with mitotane a possible exception as discussed below); (3) there is also one study that reported objective responses to doxorubicin in three of 16 patients with poorly differentiated, nonhormone-producing tumors but no responses in 15 patients whose disease did not respond to mitotane. In spite of the latter study, there is no conclusive evidence that a response to prior mitotane predicts a response to chemotherapy. Consequently, patients should be considered for chemotherapy regardless of their tumor's prior response to mitotane.

Numerous agents have been reported as active in adrenocortical cancer,

but for the majority, follow-up studies or documentation is lacking. While for many diseases as indirect evidence that attempts were unsuccessful, this may not be true for a disease like adrenocortical cancer which most oncologists see only rarely, if at all. Agents that have been reported to produce responses include: (1) adriamycin; (2) suramin; (3) carmustine (BCNU); (4) 5-fluorouracil; (5) methotrexate; (6) cisplatin; and (7) gossypol. Reports of combination regimens are even less common, and there is no evidence that these combinations are better than single agents. Combinations that have been reported include: (1) VP-16 with cisplatin with or without bleomycin; (2) adriamycin with cisplatin and cyclophosphamide; (3) intermittent streptozocin and continuous o,p′DDD; (4) 5-fluorouracil, adriamycin, and cisplatin; and (5) cisplatin and VP-16. There is anecdotal evidence that a response to prior mitotane, followed by a subsequent relapse, does not preclude a second response to mitotane. For this reason, regimens combining mitotane with other chemotherapeutic regimens should not be discouraged. However, they need to be more stringently evaluated as the addition of mitotane is almost certain to increase a regimen's toxicity.

Although the median survival of patients with metastatic adrenocortical carcinoma is less than 1 year, the literature and the experience of many physicians indicates that the natural history of adrenocortical carcinoma is similar to that of other endocrine tumors, with occasional patients experiencing prolonged survival. In these patients, chemotherapy appears to be less effective, and once patients with a more indolent course are identified, they should be followed without therapy, but with careful observation, until such a time as intervention is deemed necessary. Again, as with other patients, they should be considered candidates for phase I and II trials, with some of the newer agents with static properties appearing potentially attractive.

The refractory nature of the majority of adrenocortical cancers is a manifestation of its intrinsic drug resistance. A well-characterized mechanism of drug resistance is the drug efflux pump P-glycoprotein, which increases efflux of natural product chemotherapeutic agents. P-glycoprotein is encoded by the MDR-1 gene, and high levels of expression of this gene have been found in both the normal adrenal and the majority of adrenocortical cancers. Decreased drug accumulation mediated by P-glycoprotein can be overcome by clinically achievable concentrations of mitotane, at least in part by inhibiting drug export, with in vitro experiments demonstrating an increase in cytotoxicity when agents of the natural product class are used. This finding has provided a basis for exploring the use of mitotane in combination with natural product chemotherapeutic agents, and a clinical trial examining this is underway.

Summary

Nearly four decades after the introduction of mitotane, significant further progress has not been made in the chemotherapy of adrenocortical cancer. While the clinical evidence suggests that this is a malignancy that has a high degree of intrinsic

resistance to chemotherapy, the response to some agents in a small number of patients suggests that more effective therapies will likely emerge with time. Although mitotane is a difficult drug to administer, a trial of this agent in the majority of patients is indicated, with attention to side effects and monitoring of levels. However, mitotane need not be administered before experimental therapies, since in the majority of patients it is not curative. Consequently, every effort should be made to enroll these patients on experimental therapies, either those designed specifically for this disease or more general phase I and II studies.

Radiotherapy

Radiotherapy is effective against gross residual and metastatic adrenocortical carcinoma; however, the role of radiation as an adjuvant to surgical resection is unclear. Despite the need for effective adjuvant therapy as suggested by the presence of local invasion and lymph node involvement in the majority of cases and the 85% recurrence rate following resection alone, the use of adjuvant radiotherapy has been described only anecdotally. Analysis of local control following adjuvant radiation has been reported rarely for small numbers of patients in retrospective series. The low incidence of adrenocortical carcinoma has precluded a systematic evaluation of the role of adjuvant radiotherapy; however, the need for more thorough study of combined-modality treatment is clear.

Metastatic adrenocortical carcinoma is radiosensitive, and excellent palliation of painful bony metastases has been reported. The Yale University experience with radiotherapy for adrenocortical carcinoma was reviewed by Percarpio and Knowlton. This retrospective study analyzed a total of 14 patients, seven of whom required a total of 12 courses of palliative radiation therapy. Palliation was successfully achieved in all 12 courses, as determined by relief of pain and radiographic improvement of bony metastases. Separate episodes of rectal and colonic obstruction were relieved in one patient by radiotherapy.

Despite the development of recurrent disease in the majority of patients, a role for routine adjuvant radiotherapy in the treatment of adrenocortical carcinoma has yet to be demonstrated. Initial reports of small numbers of patients who received adjuvant radiation to the primary tumor bed in the presence of known metastatic disease indicated no benefit. In the most recent update of the Memorial Sloan-Kettering experience, 10 patients received adjuvant therapy following complete resection. Only three of these received from 3900 to 4500 centigray (cGy) of adjuvant external-beam radiotherapy to the adrenal fossa. The other seven patients received adjuvant chemotherapy. All 10 patients developed recurrent or metastatic disease. The pattern of recurrence was not described, nor was the impact of adjuvant radiation on locoregional failure analyzed.

In the report by Didolkar et al., 10 of 42 patients with adrenocortical carcinoma received adjuvant radiation to the tumor bed and adjacent areas involved

by tumor. Four of 10 patients with gross residual disease experienced a greater than 50% tumor reduction that lasted for 6 months or longer. Local control, metastatic recurrence, and survival were not analyzed separately for the subgroup receiving adjuvant radiation. Radiotherapy was recommended in that report for patients with incompletely resected tumor. In the Yale series, four patients received postoperative adjuvant radiotherapy to doses of 4000 cGy or less. All of these patients suffered local recurrence. However, one of two patients who received 4000-cGy preoperative radiotherapy for unresectable disease subsequently underwent resection and remained locally controlled for more than 5 years. In the Hahneman series reported by Markoe et al. five of eight patients received adjuvant radiotherapy for primary and in one case recurrent adrenocortical carcinoma. The median survival for these five patients was 6.9 months, with one patient who remained disease free for 14 years before developing metastatic recurrence. Two of the five patients failed locally following adjuvant radiotherapy, one of whom received less than the prescribed dose of 5000–6000 cGy.

Fifteen cases of adrenocortical carcinoma, including five pediatric patients, treated in Manchester, England were reported by Magee. Ten of the 15 patients received radiotherapy, one for metastatic disease, and nine were treated to the tumor bed. Radiation doses ranged from 2000 to 3000 cGy. Four patients had complete removal of tumor, two had partial removal, and four had biopsy only. Response was evaluable in six of 10 irradiated cases: two had no response, and four had partial responses. Three of 10 patients survived more than 10 years. All three 10-year survivors were female, less than 2 years of age at presentation, had complete resections of tumor, and received 3000 cGy of adjuvant radiotherapy. Two of these patients developed secondary osteogenic sarcoma and breast cancer, respectively, 11 and 14 years posttreatment.

In summary, the evidence supporting adjuvant radiotherapy for completely resected adrenocortical carcinoma is sparse, and at present its value awaits confirmation by a well-designed study. Preoperative radiation should be considered for patients with unresectable localized disease who may be more easily resected following a response to radiotherapy. Patients with incomplete resections may respond to postoperative radiation with a reduction in tumor bulk. However, a survival advantage from postoperative treatment has not been demonstrated. Adjuvant radiotherapy with or without chemotherapy for newly resected adrenocortical carcinoma deserves study in prospective trials, but the small number of patients with this rare disease will not allow such trials without considerable multi-institutional effort.

PHEOCHROMOCYTOMA

Pheochromocytomas are tumors arising from the adrenal medulla in chromaffin cells from neural crest origin. These tumors are quite rare, noted in less than

0.1% of autopsy studies and only 0.1% of patients with hypertension. Despite their rarity, these tumors are clinically very important. Unrecognized pheochromocytomas can lead to sudden death, cerebral vascular accidents, myocardial infarctions, and other life-threatening conditions. It was originally felt that only 10% of pheochromocytomas are malignant; however, recent reports show as many as 46% of these tumors are malignant. The varied incidence reports stem from the fact that these lesions are impossible to differentiate histologically as benign or malignant. Instead, long-term follow-up for the development of invasive recurrences or metastatic disease is required.

The pheochromocytomas play a prominent role in familial cancer syndromes. Bilateral adrenal pheochromocytomas are seen in MEN-IIA and MEN-IIB. In addition, 25% of patients with von Hippel–Lindau disease are diagnosed with pheochromocytomas, and approximately 1% of patients with neurofibromatosis and von Recklinghausen disease are found to have pheochromocytomas. It is important to recognize the patients with these cancer family syndromes so that screening for pheochromocytomas can begin at an early age. This will potentially avoid disastrous outcomes of catecholamine excess in response to stresses such as an operation for an unrelated indication.

Diagnosis

Pheochromocytomas produce catecholamines, and the symptoms and signs of this disease are a result of catecholamine excess. The most prominent symptom is paroxysmal headaches. This is usually associated with excessive sweating and palpitations. The patients may have sustained or paroxysmal hypertension. The levels of circulating catecholamines fluctuate during the day and in response to certain stimuli including physical exercise, micturition, laughing, or coughing, and even wearing tight clothing. Certain foods that are high in tyramine, such as beer, wine, and cheese, can cause an exacerbation of symptoms. Because of the high catecholamine secretion the patients' intravascular volume is low. This can cause symptoms of postural hypotension. In severe cases this can lead to lactic acidosis.

Screening for pheochromocytomas is important for patients with incidental masses of the adrenal gland, patients with a familial syndrome that includes pheochromocytomas, any patient who is undergoing a thyroidectomy for a medullary carcinoma of the thyroid, and patients with symptoms that could be attributable to catecholamine excess. Screening should consist of a 24-hr urine collection for metanephrine, vanillylmandelic acid (VMA), epinephrine, and norepinephrine. This test is highly sensitive and specific for the diagnosis of pheochromocytoma. Plasma norepinephrine and epinephrine levels can also be measured; however, these levels are less sensitive and specific. If there is any question about the diagnosis, a glucagon stimulation test can be performed (if the patient is normo-

tensive). A positive test is indicated by a threefold increase in plasma catecholamines or levels above 2000 pg/ml within 3 min of administration of glucagon.

Once the diagnosis is made, radiological imaging studies should be performed to localize the tumor. As chromaffin cells of neural crest origin are located in a variety of locations, pheochromocytomas can arise outside the adrenal glands. Extra-adrenal pheochromocytomas most commonly are located in the organ of Zuckerkandl, which is near the origin of the inferior mesenteric artery, immediately to the left of the aortic bifurcation. They can also occur in the carotid body, along the aorta, and within the urinary bladder. It appears that extra-adrenal pheochromocytomas are more commonly malignant. Bilateral adrenal pheochromocytomas can occur in the familial cancer syndromes. These are rarely, if ever, malignant. Radiological imaging for pheochromocytomas should consist first of a CT scan of the abdomen with 3–5-mm cuts through the adrenal glands. This will pick up the majority of lesions and will potentially avoid any other workup. The MRI scan is likely to be as sensitive as the CT scan, and the tumors tend to be hyperintense on T2-weighted images. If there is difficulty in localizing the gland, or there is suspicion of an extra-adrenal site, then a nuclear medicine scan using ^{131}I-labeled metaiodobenzylguanidine (^{131}I-MIBG) can be performed. This compound is taken up and concentrated in adrenergic tissue. It is helpful in identifying extra adrenal pheochromocytomas with a sensitivity of about 75–80% and a specificity near 100%. It is reasonable to use this scan to screen for bilateral pheochromocytomas in a patient who has a unilateral mass on CT scan and in whom the plan is to perform a laparoscopic adrenalectomy.

Surgery

The treatment of pheochromocytomas is surgical excision of the adrenal gland or extra-adrenal mass. Preoperative preparation is essential in these patients. Because of the catecholamine excess and low intravascular volume status, the patients can have problems with hypotension in the immediate postoperative period. In addition, the stress of the incision can lead to a severe surge of catecholamines, which can be life-threatening. It is recommended that patients undergo alpha-adrenergic blockade preoperatively. This can be done using phenoxybenzamine. The starting dose is 10 mg twice daily and this is increased by 10-mg increments every 3 days until the patient has postural hypotension. It may require as much as 200 mg/day to achieve effective blockade. The patient's hematocrit should fall as a result of the alpha-adrenergic blockade. If the patient has significant postural hypotension or the hematocrit has failed to fall, the patient can be volume-expanded with intravenous crystalloid over 24 hr prior to surgery. Beta blockade should be avoided as an initial treatment because this can lead to worsening hypertension. Patients who are tachycardiac after adrenergic blockade may be less symptomatic with the addition of beta-adrenergic blocking agents such

as propranolol. If symptoms are not controlled with phenoxybenzamine, the catecholamine synthesis blocker alpha methylparatyrosine (MPT) can be used.

Intraoperatively the patient's blood pressure needs to be monitored with an arterial line, and central venous pressure monitoring is also routine. Sodium nitroprusside can be used to control hypertension intraoperatively. It is important to avoid excessive pressure and retraction on the tumor during surgery as this can precipitate a hypertensive crisis. The approach for surgical resection of these tumors has been an anterior approach, which allows for inspection of both glands to rule out bilateral involvement. In patients who are not suspected of a familial syndrome and in whom the MIBG scan does not indicate bilateral disease, it is unlikely that bilateral adrenal tumors exist. Therefore, it is unnecessary to expose both of the glands. As with any small adrenal tumor, the laparoscopic adrenalectomy allows for the easiest postoperative recovery. There was initially some hesitation in performing laparoscopic adrenalectomies in patients with functioning pheochromocytomas, but this has been reported as a safe undertaking for these patients. As the pheochromocytomas are rarely greater than 5 cm in diameter, this technique is ideally suited for almost all of these lesions. Otherwise the technical aspects and various approaches to adrenalectomy are the same as described above for adrenocortical tumors. More care is required to avoid pressure on this tumor compared to adrenocortical tumors.

The postoperative management is significant for the possibility of a large fluid requirement. Depending on the effectiveness of the preoperative alpha blockade, the patients may continue to be hypovolemic and require large volumes of crystalloid in the postoperative period. Patients with familial syndromes that require bilateral adrenalectomies will require glucocorticoid replacement and ultimately mineralocorticoid supplementation once the corticosteroid replacement is down to maintenance levels.

The diagnosis of a malignant pheochromocytoma is based on clinical characteristics of regional organ invasion or metastatic disease. Histologically it is impossible to differentiate benign from malignant tumors. Benign tumors may demonstrate nuclear pleomorphism as well as mitoses and vascular and capsular invasion. The most significant differentiating factor is size and the presence of necrosis. Malignant pheochromocytomas tend to weigh more than 500 g whereas benign lesions are less than 200 g. As with functioning adrenocortical malignant tumors, malignant pheochromocytomas tend to be less efficient at producing catecholamines. Therefore, they can grow to a large size before presentation. It is difficult to define the natural history of malignant tumors (recurrence rate) after complete resection as often the only indication of malignancy is the presence of metastatic or locally invasive disease. Patients who have had locally recurrent or metastatic disease resected and patients who have resected primary tumors suspicious for malignancy based on size, number of mitoses per high-power field,

and the presence of necrosis within the tumor should all be followed approximately every 6 months with catecholamine screening and MIBG scans.

The treatment recommendation for metastatic or locally recurrent disease is repeated complete surgical resection when possible. This provides the best chance of palliation of the catecholamine excess. Patients with metastatic disease can achieve responses with chemotherapy as discussed below. Also, they can achieve significant palliation with alpha-adrenergic blockade as discussed above. The malignant lesions do not appear to be rapidly progressive and prolonged survival can be anticipated.

Chemotherapy

Because of the rarity of malignant pheochromocytomas and their indolent course, there is no large experience with chemotherapy for these tumors. Because of the initial success of streptozotocin in the treatment of neuroendocrine tumors, it was felt that this agent might be of use against malignant pheochromocytomas. While some patients with malignant pheochromocytomas may respond to streptozotocin therapy, the majority do not, and the treatment may be nephrotoxic. Because of similarities between pheochromocytomas and neuroblastoma, it was felt that malignant pheochromocytomas might respond to the chemotherapy combination of cyclophosphamide, vincristine, and darcarbazine (CVD), which has an 80% response rate against, metastatic neuroblastoma. An initial experience of three patients receiving this combination reported by Keiser et al. demonstrated a marked decrease in catecholamine secretion and a decrease in size of all tumors treated. A follow-up study by Averbuch et al. of 14 patients with pheochromocytoma treated with CVD showed a 50% response rate by imaging criteria and a 57% response rate by measurement of catecholamine levels. The median duration of response was greater than 18 months. The therapy is well tolerated, and overall the toxicity is minimal. Patients suffer approximately 2 days of malaise, nausea, and vomiting after receiving chemotherapy. There have been reports of patients suffering a hypertensive crisis after receiving cytotoxic chemotherapy in the presence of a pheochromocytoma. This can be prevented with appropriate alpha-adrenergic blockade. All patients with documented malignant pheochromocytoma and elevated catecholamine levels should be maintained on alpha-adrenergic blockade as discussed above.

Radiotherapy

The role of external-beam radiotherapy in the treatment of pheochromocytoma has been sparingly described in the literature. Irradiation of bone metastases from pheochromocytoma provides excellent palliation. Doses in the range of 3000–4000 cGy should be prescribed; however, some authors recommend external-

beam doses as high as 5000 cGy. Adjuvant postoperative radiation of primary pheochromocytoma finds little support in the literature.

In contrast to external-beam radiotherapy, radionuclide treatment of pheochromocytoma with MIBG has received considerable attention. MIBG is a guanethidine analog that was developed for imaging adrenomedullary tissues. MIBG binds specifically to neuroendocrine cell membranes and is actively transported into the cell by the norepinephrine uptake-1 mechanism. It has no adrenergic effects despite its long biological half-life, and is excreted primarily unchanged in the urine. MIBG scintigraphy is highly sensitive (85%) and specific (100%) for pheochromocytoma. The high specificity of MIBG led investigators to administer [^{131}I]-MIBG in clinical trials to patients with metastatic pheochromocytoma. Since the initial reports in the early 1980s, the use of MIBG has increased, and its apparent efficacy has improved with the delivery of higher doses and the development of radioconjugates with higher specific activity. A summary of responses to [^{131}I]-MIBG therapy was recently presented by Shapiro. Overall, approximately 60% of patients are reported to derive some benefit from MIBG resulting from improvements in symptoms, reduction of pain, and stabilization of blood pressure. Hormonal partial and complete responses occurred in 20% and 26%, respectively. Overall, radiographic responses were seen in approximately 20%: 13–19% were partial responders, and only 1–3% were complete responders. Toxicity from MIBG therapy is usually mild or absent, but can include transient diarrhea, changes in blood pressure, and transient elevations of urinary hormone levels. Severe toxicity from [^{131}I]-MIBG is rarely reported. However, patients with extensive bony metastases or a history of cytotoxic chemotherapy are at risk for marrow suppression and thrombocytopenia.

In summary, [^{131}I]-MIBG is active against metastatic pheochromocytoma, although response rates and the durability of response are far from optimal. Analysis of metastatic uptake of [^{131}I]-MIBG suggests that uptake diminishes with subsequent doses, implying that a larger initial dose may improve efficacy in multidose regimens. Although this therapy shows promise, it is still considered experimental and deserves further study.

CONCLUSIONS

In summary, adrenocortical cancer is associated with a poor prognosis because of late presentation and ineffective systemic chemotherapy. As early diagnosis is important, all incidental adrenal masses should be worked up as outlined in this chapter. Lesions showing radiographic signs suspicious for malignancy should be resected for a definitive diagnosis. Surgical resection remains the only curative modality against this cancer, so it is important to perform an optimal resection at the initial presentation with the goal of negative margins. This may require en bloc resection of adjacent organs. Locally recurrent disease should also be

managed surgically. Isolated metastatic disease, however, needs to be taken on a case-by-case basis taking into consideration the patient's performance status, the time between the primary resection and development of metastases, and the size and location of the metastases. Given the poor response rates with current chemotherapy for adrenocortical carcinoma, patients should be entered into clinical protocols so that newer agents can be explored against this tumor. Any agent that is shown to be effective against recurrent or metastatic disease could then be explored in an adjuvant trial after surgical resection of high-risk tumors.

Unlike adrenocortical cancers, pheochromocytomas tend to present early with symptoms of catecholamine excess. It is becoming apparent that the incidence of malignant pheochromocytomas is higher than originally reported. This emphasizes the importance of long-term follow-up of patients who have been resected for pheochromocytoma. Recurrent or metastatic disease should also be managed by surgical resection when possible as this appears to be associated with the best palliation. A trial of chemotherapy with CVD is indicated for unresectable metastatic disease. This is well tolerated with a significant chance for palliation. It is difficult to define the prognosis for metastatic and malignant pheochromocytoma. The 5-year survival has been reported between 36% and 60% with a median survival of approximately 3 years after the appearance of metastases. Metastatic lesions that take up [^{131}I]-MIBG may respond to treatment with high doses of this radioactive isotope.

QUESTIONS

1. What are the indications for resection of a nonfunctional adrenal mass?
   Answer: Masses larger than 6 cm should be resected because of the concern for malignancy. Lesions with radiographic signs of malignancy such as central necrosis, inhomogeneous appearance, or regional invasiveness should be resected. Lesions suspicious on MRI scan of malignancy based on a high signal intensity with T2 weighting should be resected. Lesions that show sign of increasing size within 18 months of follow-up CT scans should be resected.
2. What surgical approach to adrenalectomy is associated with the quickest postoperative recovery?
   Answer: Laparoscopic adrenalectomy is associated with the shortest hospital stay, the least requirement of narcotic pain medication, and the shortest duration of convalescence. It is controversial whether this approach is reasonable for malignant cancers because of the potential spread of cancer cells during insufflation. For small functioning adenomas it appears that the laparoscopic approach is the best.

3. What would be considered a contraindication to surgical resection of an adrenal cortical carcinoma?
   Answer: Any regional invasion of the tumor that would make a gross complete resection impossible is a contraindication to resection. This would include celiac access involvement or invasion of the aorta. Tumor thrombus within the inferior vena cava can often be resected. The presence of synchronous metastatic disease is also a contraindication unless the patient can be rendered disease-free with concurrent metastasectomy. This aggressive approach would be considered controversial.
4. What is the role of mitotane as an adjuvant to complete resection of adrenocortical carcinoma?
   Answer: There is no proof that adjuvant therapy with mitotane delays recurrence or improves survival after complete resection. Mitotane should be considered for patients with measurable disease in which the response to mitotane can be monitored and therapy discontinued if there is progression of disease.
5. What is the role of adjuvant radiation therapy after complete resection of adrenocortical cancer?
   Answer: There is currently no role for routine adjuvant therapy in the treatment of adrenocortical carcinoma after complete resection. It is reasonable to explore this further in prospective trials. Adrenal cancer is radiosensitive, and gross residual and metastatic cancer can be responsive to radiotherapy. Radiation therapy is also an excellent palliation for bone metastases.
6. What is the screening workup for a pheochromocytoma?
   Answer: A 24-hr urine collection for metanephrine, VMA, epinephrine, and neuroepinephrine is all that is required to screen for significant catecholamine excess. A glucagon stimulation test is a more sensitive indicator for the presence of a pheochromocytoma and can be used for screening in patients with von Hippel–Lindau disease or other familial predisposition to pheochromocytoma.
7. What is the recommended preoperative preparation for patients undergoing resection of a pheochromocytoma?
   Answer: The patients should undergo alpha-adrenergic blockade with phenoxybenzamine for 1–3 weeks prior to surgery (depending on the time it takes to achieve a response). The patients will be hypovolemic, and time must be given for the patient's blood volume to equilibrate. The patients should receive volume expansion with intravenous crystalloid prior to surgery. Beta blockade should be reserved for patients who remain tachycardic after adequate alpha blockade.

8. What is the role for radioactive ^{131}I-MIBG in the treatment of pheochromocytoma?
   Answer: Patients with metastatic pheochromocytoma not amenable to surgical resection should be considered for ^{131}I-MIBG therapy. The toxicity is minimal or absent, and treatment is associated with approximately 60% chance of palliation and 20% chance of a radiographic response.
9. What is the role for chemotherapy in the management of metastatic pheochromocytoma?
   Answer: The chemotherapy regimen of cyclophosphamide, vincristine, and darcarbazine (CVD) has been shown to have a 57% response rate by measurement of catecholamine levels and a 50% response rate by imaging criteria against metastatic pheochromocytoma. The median duration of response was over a year. It is reasonable to treat patients with the goal of palliation with this chemotherapy regimen.
10. What is the natural history of malignant pheochromocytoma?
    Answer: While almost all patients die of their disease, they can have a very protracted course. The 5-year survival is between 36% and 60%. Palliation can be achieved with chemotherapy and ^{131}I-MIBG.
11. What is the natural history of adrenocortical cancer?
    Answer: The majority of patients present with stage III or IV disease. The overall 5-year survival is between 40% and 50% after complete resection and drops to less than 10% for incomplete resection. The median disease-free survival after complete resection is about 2.5 years. Local and regional recurrences have been resected with a 5-year survival as high as 30%. Some palliation may be achieved with radiation therapy or mitotane chemotherapy.

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13

Thyroid and Parathyroid Cancer

Douglas L. Fraker
University of Pennsylvania, Philadelphia, Pennsylvania

Monica Skarulis
National Institutes of Health, Bethesda, Maryland

INTRODUCTION

Thyroid and parathyroid carcinoma are very unusual solid tumors for a variety of reasons. Thyroid neoplasms are not like other solid tumors as they are typically managed by endocrine surgeons, endocrinologists, and nuclear medicine physicians instead of surgical oncologists, medical oncologists, and radiation therapists. Well-differentiated thyroid cancer is relatively resistant to treatment with standard chemotherapy agents and with external-beam radiation therapy. The only effective treatment apart from surgical resection is radioactive iodine and this agent is administered by a team of endocrinologists and nuclear medicine physicians working together. The second reason that thyroid cancer is unusual is that although it is by far the most common endocrine neoplasm, it varies from other endocrine tumors in that it is not generally hormonally active. Neoplasms of the parathyroid, adrenal, endocrine pancreas, and pituitary generally manifest symptoms based on abnormal hormone production and regulation. Thyroid tumors are typically silent in terms of hormone production and proteins that are released (thyroglobulin and calcitonin) do not cause any symptoms. Instead of dividing the treatment of thyroid cancer into surgical, chemotherapy, and radiation therapy, it will be discussed in terms of surgery, treatment with radioactive iodine, with short sections on chemotherapy and external-beam radiation therapy.

Parathyroid cancer is notable for being extremely rare. The overall incidence of parathyroid cancer in primary hyperparathyroidism is on the order of

0.1% and there may be only 40–60 new cases of parathyroid cancer per year in the United States. On the other hand, primary hyperparathyroidism due to benign parathyroid adenoma is one of the more common endocrine neoplastic disorders. Again, because of the rarity of parathyroid carcinoma and the nonmalignant nature of the overwhelming majority of parathyroid tumors, chemotherapy and radiation therapy play very minor roles in the treatment of this disorder.

THYROID CANCER

Thyroid cancer is overwhelmingly the most common type of endocrine malignancy and accounts for the majority of the deaths due to endocrine cancers. It was estimated that in 1995 there would be 13,900 new cases of thyroid cancer (90% of the total new endocrine cancers) and 1120 deaths due to thyroid cancer, which is 63% of the total deaths due to endocrine cancers. The discrepancy between the total number of cases of all endocrine cancers arising in the thyroid (90%) and the total proportion of endocrine cancer deaths (63%) reflects the relative indolent nature and long-term survival with thyroid malignancies.

Within the broad category of thyroid cancers, there are many subtypes, each with a different epidemiology, natural history, treatment, and prognosis. The general categories of thyroid cancer are well-differentiated malignancies, anaplastic cancer, medullary thyroid cancer, lymphoma, and sarcoma and other rare malignancies. The normal thyroid is composed histologically of two main parenchymal cell types, follicular cells, which lead to well-differentiated and anaplastic tumors, and the parafollicular or C cell, which produces calcitonin and is the cell of origin for medullary thyroid cancer. Approximately 90% of malignant thyroid nodules are well-differentiated cancers, 5–9% are medullary thyroid cancer, 1–2% are anaplastic cancers, 1–3% are lymphoma, and $<1\%$ are sarcoma and other rare tumors.

Within the category of well-differentiated thyroid cancers, various histological subtypes have evolved over the past few decades. Previously, tumors were categorized as papillary, follicular, and mixed tumor with variable areas of both papillary and follicular cells. Several recent studies have documented that these mixed tumors with any features of papillary cells histologically behave like papillary thyroid cancer such that the category of mixed papillary and follicular should be grouped together with papillary carcinoma. A third category of well-differentiated thyroid cancer is Hürthle cell carcinoma, a subcategory of follicular tumors. The distribution of well-differentiated thyroid cancer subgroups in recent reports show that 80–85% of cases are papillary, with 10–15% of cases being follicular, and 3–5% Hürthle cell carcinomas. Therefore, since 90% of all thyroid cancers are well differentiated and 85% of all well-differentiated tumors are papillary, then papillary thyroid cancer accounts for 75–80% of all thyroid cancers and by incidence is the most important subtype.

Surgical Management

The vast majority of thyroid cancers present as thyroid nodules, yet only a minority of all thyroid nodules are malignant. The prevalence of thyroid nodules depends on the population under study; sex, age, and history of exposure to ionizing radiation strongly influence the incidence of detection of thyroid nodules. In one pathological study, up to 90% of women over 70 years and 60% of men over 80 years had nodular thyroid disease. In subjects between the age of 30 and 59 years examined in another study, 6.4% of women and 1.3% of men had clinically evident thyroid nodules. All studies show that women develop nodules more frequently than men although reports of female-to-male ratio vary from 1.2:1 to 4:1. A tendency to develop thyroid nodules is demonstrated in groups exposed to ionizing radiation especially during childhood as a third of patients develop thyroid nodules within 10 years of exposure.

The majority of clinically relevant thyroid nodules are found in asymptomatic patients at the time of physical examination of the neck. In general, there is a 5–10% chance of malignancy in all thyroid nodules for the total population. However, males and patients at the extremes of age, and patients exposed to radiation, are at higher risk for malignancy. Nodules found in a patient with a history of childhood neck irradiation carry a 33–37% chance of malignancy. The presence of a solitary nodule is of greater concern than a thyroid with multiple nodules; however, a dominant nodule or a nodule that changes size in the setting of a multinodular goiter may be neoplastic and malignant.

While not specific for malignancy, a history of rapid increase in size, pain in the region of the nodule, hoarseness, and the development of a Horner's syndrome are worrisome. A family history of thyroid cancer or pheochromocytoma should suggest medullary thyroid cancer in the setting of MEN-2A or MEN-2B of the neck; the firmness, mobility, size, adherence to surrounding structures, and the presence of adenopathy are important clues to the presence of carcinoma.

Laboratory tests are of little assistance in differentiating benign versus malignant thyroid tumors. Thyroid function testing should be performed to identify underlying thyroid pathology and not to differentiate benign from malignant nodules. Serum thyroglobulin levels are not helpful in distinguishing benign from malignant thyroid nodules. Routine measurement of serum calcitonin may be useful to identify patients with sporadic medullary carcinoma of the thyroid preoperatively; however, the rarity of this tumor makes this test non-cost-effective. Imaging studies are widely used to evaluate thyroid nodules but contribute little to the diagnosis of malignancy. The majority of both benign and malignant thyroid nodules are hypofunctional when compared to normal functioning thyroid tissue; thus, the finding of a ''cold nodule'' on ^{123}I or ^{99}Tc scanning is nonspecific. In a large study of 5000 patients with thyroid nodules who underwent preoperative radionuclide scanning, thyroid cancer was found in 16% of cold nodules, 9% of

warm nodules, and coincidentally found in the thyroids of 4% of the patients with hot nodules. Although clinicians are often very concerned about cold nodules, these results demonstrate a high majority of cold lesions are benign and this test does not discriminate between benign and malignant disease.

High-resolution ultrasonography is a useful adjunct to the clinical examination for size assessment of nodules, for the detection of multiple nodules not discerned by palpation, and for assisting in fine-needle biopsy of nodules. Ultrasound will identify whether a lesion is cystic or solid and the vast majority of cystic lesions are benign.

The single most important study in the evaluation of thyroid nodules is fine-needle aspiration (FNA) biopsy. The impact this procedure has had on clinical practice is reflected by a reduction of the total number of thyroid surgeries performed, a greater proportion of malignancies removed at surgery, and an overall reduction in the cost of managing patients with nodules. The accuracy of cytological diagnosis from fine-needle biopsy ranges from 70% to 97% and is highly dependent on the skill of the person performing the biopsy and primarily that of the cytopathologist reviewing the slides. The results of fine-needle biopsies are most commonly divided into the following categories: benign (colloid, minimal cells), suspicious or indeterminate (including all follicular neoplasms or those with extensive Hürthle cell changes), malignant (papillary, anaplastic, medullary, and lymphoma), and insufficient sample. Results typically obtained at the time of fine-needle biopsy of the nodules in large series are as follows: 70% are classified as benign, 4.% as malignant, 10% as suspicious, and 17% as insufficient sample.

Biopsies classified as benign or negative are safely followed medically with the caveat that false-negative results occur in 1–6% of cases. With experienced cytopathologists, this false-negative rate should decrease to $<1\%$. Clinical judgment should dictate the course of action in these cases. If a large, hard nodule is fixed to surrounding tissue and is painful, surgery should be performed despite a negative aspirate. Benign nodules on FNA should be followed regularly for changes in size or symptoms, or the development of lymph nodes.

Radiation exposure to the thyroid gland is the only risk factor known definitively to increase the incidence of well-differentiated thyroid cancer. Case-controlled studies of radiation administered for benign childhood conditions such as acne, enlarged tonsils, or enlarged thymus in the first half of the 20th century defined this association. The younger the age at exposure and the higher the dose, the greater the relative risk of thyroid cancer. The latent interval is at least 3–5 years and the increased risk appears to continue for several years. Currently, patients are exposed to thyroid radiation during treatment for curable diseases such as lymphoma or childhood malignancies and during environmental accidents such as occurred at Chernobyl. The overwhelming majority of thyroid cancers associated with radiation are papillary tumors with a natural history identical to

that of non-radiation-associated tumors. No common familial syndrome or genetic disease is associated with the development of well-differentiated thyroid cancer. This contrasts with medullary thyroid cancer, which has a variety of genetic syndromes now being defined at the molecular level.

The typical clinical presentation for a patient with well-differentiated thyroid cancer is development of an asymptomatic thyroid nodule noted on routine physical examination, or by the patient visually or by palpation. A small subset of patients will present with palpable cervical lymphadenopathy confirming metastatic carcinoma without an identifiable thyroid primary. Since most patients with well-differentiated thyroid cancer are euthyroid, complaints related to thyroid dysfunction are rare and thyroid function tests tend to be normal. Certain aspects of the clinical history are relevant to the differential diagnosis including a prior history of radiation exposure (increased risk of papillary cancer), family history (increased risk of familial medullary thyroid cancer), and rapid rate of growth of the thyroid nodule (increased likelihood of anaplastic thyroid cancer or thyroid lymphoma).

Any new palpable thyroid nodule or any lesion > 1.5 cm identified by neck imaging should be initially assessed by FNA as described above. Management decisions in these patients are based on the FNA results combined with the clinical history. Potential management options include careful observation, typically combined with thyroid suppression, alternative or repeat diagnostic studies, or surgical excisional biopsy. The goal of management of these patients is to not miss an enlarging carcinoma that could be potentially morbid to the patients if the disease is not recognized and treated, balanced against the goal of avoiding unnecessary surgical procedures for benign pathology. Decisions regarding patient management in three of the four categories of possible results from the FNA are relatively straightforward. Patients with malignant lesions identified by FNA should undergo surgical resection with the only controversy being the extent of this resection. Patients with a benign FNA result should be followed closely and nodules that enlarge or persist should be rebiopsied by FNA. One controversial management point regarding these patients is the use of thyroid suppression. Although common clinical practice is to suppress patients who have benign nodules by FNA using thyroid hormone, objective data that this practice alters the clinical course are lacking.

Patients with an inadequate biopsy should be rebiopsied as half of the time this will provide definitive results. Often patients with small lesions that are not discrete and are difficult to palpate, as well as patients with large lesions with areas of necrosis or hemorrhage, have inadequate sampling results. Repeat FNA with ultrasound guidance to make sure that the aspiration specimen is taken from a solid component of the lesion may increase the diagnostic yield. Cold solid nodules larger than 1.5 cm should undergo excisional biopsy if FNA two or three times does not yield diagnostic material.

Cystic lesions should be aspirated until all the fluid is removed. Following the cyst fluid aspiration, the area is studied with ultrasound and any residual solid component is biopsied by FNA using ultrasound guidance. Cyst with a complex cyst/solid component that are recurrent after three separate aspirations and are larger than 4 cm may warrant open biopsy as these conditions are more likely to be associated with malignancies.

Most investigators recommend surgical resection of lesions classified as indeterminate or suspicious by FNA to establish definitive diagnosis. In most large series, 20–25% of patients with suspicious FNA eventually were shown to have cancer. Any patients with an indeterminate or suspicious FNA with other risk factors such as prior radiation exposure or local symptoms should have nodules surgically resected.

The natural history and prognosis of well-differentiated thyroid cancer has been intensively studied over the past several decades. Clear definition of risk factors associated with poor outcome has allowed more selective and less morbid treatment recommendations primarily in terms of extent of surgery and the use of postoperative radioactive iodines. In general, well-differentiated thyroid cancer is a relatively indolent solid neoplasm with favorable long-term survival. However, a small proportion of patients with papillary and a slightly larger proportion of patients with follicular thyroid cancer succumb from their thyroid cancer. As opposed to other solid neoplasms, one major difference is that regional lymph node metastases appear to have no strong correlation with overall survival. Approximately 33–45% of patients with papillary thyroid cancer will have involved cervical lymph nodes at the time of diagnosis. The incidence of positive cervical lymph node metastases in follicular thyroid cancers is much less, ranging between 1% and 10%. If patients with papillary cancer have lymph nodes studied in great detail, the incidence of micrometastases in lymph nodes increases up to 80%. The clinical significance of these micrometastases in some ways parallels the significance of the microscopic foci of intrathyroidal disease as it is very common but does not progress and change clinical outcome.

Only a small minority of patients have distant metastatic disease at the time of diagnosis. In a large series from Mazzaferri, 1–2% of papillary thyroid cancer patients and 2–5% of follicular thyroid cancer patients had metastases outside of the neck or mediastinum at the time of diagnosis. Having distant metastases at the time of presentation is a strong predictor of very poor outcome as 50% and 90% of these patients die secondary to their thyroid malignancy.

Overall survival in well-differentiated thyroid carcinoma from various institutional series shows a better 10-year survival for papillary cancer ranging between 74% and 93% compared to follicular cancer with 10-year survivals of 43–94%. Although many institutions have reported their data based on these histological subcategories, a more meaningful system is to categorize patients according to defined risk factors more pertinent to generating prognostic informa-

tion. Both the group at the Lahey Clinic and the Mayo Clinic have large databases with long-term follow-up that define prognostic risk factors for well-differentiated thyroid cancer. Two dominant prognostic factors are the age at diagnosis and the presence of distant metastases. All systems also include some measurement of the size of the lesion and other factors, such as local invasion or grade of the tumor, that have impact on outcome. In general, younger patients do well with well-differentiated thyroid cancer. The Lahey Clinic system defined low-risk age categories as males < 40 years and females < 50 years. The Mayo Clinic takes age into account using a numerical factor in a formula calculating prognostic score that does not discriminate according to gender. Although historical data report follicular as having worse outcome compared to papillary thyroid cancer, if one corrects for age and other prognostic variables, then the outcome is similar within these two pathological subcategories.

The risk categorization schema developed by the Lahey Clinic group incorporating these components carries the acronym AMES for age, metastases, extent of tumor, and size. Using this system, low-risk patients can be identified who have a long-term overall survival of 98% and overall disease-free survival of 95% compared to 54% and 45%, respectively, for high-risk patients. The initial system developed by the Mayo Clinic group carried the acronym AGES to stand for age, tumor grade, tumor extent, and tumor size. A mathematical formula to produce a prognostic score (PS) with different weights on these factors was developed. The scoring system showed that patients with a PS < 4 had a 99% 20-year survival while patients with a PS > 6 had a 13% 20-year survival with graded categories in between. A more recent modification of this system is identified by MACIS, which is metastasis, age at diagnosis, extent subdivided into completeness of resection and invasion, and tumor size. Using this system, a score of <6 yields a 20-year survival of 99% and a score of >8 results in a 20-year survival of only 24%. On the basis of these scoring systems, which have been verified by other institutions, the aggressiveness of treatment can be balanced against the possible treatment risks and costs. Clearly, if subgroups of patients with 99% 20-year survivals can be prospectively identified, aggressive therapy with potential lifelong complications cannot be justified in this subpopulation.

The key decisions in the surgical management of thyroid nodules and/or cancers are for the endocrine surgeon to decide who to operate on and how extensive a resection to perform. The development of FNA cytology and the proven accuracy of those results over the past 15 years has significantly decreased the number of patients with thyroid nodules who need to undergo surgical exploration for diagnosis. Consequently, FNA has increased the proportion of nodules that are surgically excised that turn out to be cancer.

Prior to the development and widespread use of preoperative FNA of thyroid nodules, surgeons frequently relied on frozen-section results obtained during

the procedure to guide them. The utility of frozen-section diagnosis for thyroid nodules is controversial. The situations in which frozen section may theoretically be useful is for patients who have indeterminate FNA results. Specifically, patients with suspicious cytology or patients with a nodule in which an inadequate specimen was able to be obtained undergo surgical resection with an unknown diagnosis. Several investigators have reported benefit from obtaining frozen-section results on these patients with suspicious or indeterminate FNA pathology, but others have recently reported inaccurate reports in up to 31% of frozen sections in this category. Most of the lesions in the suspicious FNA category are follicular neoplasms, the majority of which are benign. Capsular and vascular invasion determines malignancy in this pathological category, and the ability to render an accurate interpretation on frozen section is very limited owing to sampling errors and frozen-section artifacts. In cases suspicious for papillary carcinoma, the presence of specific nuclear features necessary for the diagnosis often cannot be discriminated on frozen section and they are better determined by intraoperative cytology. A recent large series examined this patient population with suspicious FNA and demonstrated that 87% of frozen sections rendered no useful information while 5% gave inaccurate results. The current recommended approach in this group of patients is to do excision of the thyroid lobe harboring the nodule and wait for the definitive pathological report. If the lesion turns out to be a follicular carcinoma with characteristics that place a patient at high risk, a completion total or subtotal thyroidectomy is done during a second operation.

A long-standing controversy among endocrine surgeons has existed regarding the extent of surgical resection for well-differentiated thyroid cancer. Potential surgical procedures to remove a thyroid neoplasm include a lobectomy, a subtotal thyroidectomy, and a near-total or a total thyroidectomy. The entire thyroid lobe on the side of the primary site for the cancer is taken out as completely as possible for any of these procedures. The difference comes in the management of the contralateral lobe and how this choice relates to outcome as well as operative morbidity. In a thyroid lobectomy, the contralateral lobe is simply examined visually and by palpation for abnormalities but not biopsied or excised. A subtotal thyroidectomy leaves a rim of 2–4 g of tissue in the upper lateral portion of the contralateral thyroid lobe to minimize complications in two ways. First, the recurrent laryngeal nerve as it enters the larynx at the ligament of Berry is not dissected. Second, the blood supply to the upper parathyroid gland on that side is less likely to be disrupted by leaving a rim of tissue in this location. A near-total thyroidectomy leaves a much smaller amount of normal tissue ($<$1 g) immediately adjacent to the ligament of Berry. This maneuver may offer some protection to the recurrent laryngeal nerve, but it offers minimal benefit in terms of preserving the blood supply of the upper parathyroid. A total thyroidectomy implies every effort is made to excise all thyroid tissue leaving no gross or macroscopic residual tissue in either lobe.

The most significant risk of performing only a total thyroidectomy versus a lesser resection may be in the long-term incidence of hypocalcemia. A study from the Mayo Clinic spanning the years 1946–1970 reported a 32% incidence of permanent hypocalcemia after total thyroidectomy versus only a 0.3% incidence after a subtotal procedure. More recent series report much less permanent morbidity and show variable results comparing the patients undergoing subtotal versus total thyroidectomy. The incidence of recurrent laryngeal nerve injury is universally very low, and a more acceptable risk of hypocalcemia is 1–9% for total or near-total thyroidectomy. Most patients have some level of hypocalcemia postoperatively, which may or may not be symptomatic. Calcium replacement is so innocuous and inexpensive that it can be used routinely. Virtually all experienced surgeons who perform subtotal thyroidectomies can do so with very limited or near-zero morbidity.

The most compelling argument for performing a thyroid lobectomy is the data that comes from the definition of prognostic factors for this disease. If prognostic factors can accurately diagnose patients with such excellent outcome, then the added morbidity of a total thyroidectomy as well as postoperative iodine therapy may not be worth the cost. However, careful medical surveillance for cancer in the contralateral lobe as well as recurrence must be maintained as the incidence of thyroid recurrence may be 10–20%. Furthermore, in situations in which a small thyroid remnant is left, the true morbidity of treating this patient with ablative doses of ^{131}I, if indicated, is relatively minimal. Radioiodine ablation of an intact lobe of the thyroid lobectomy is associated with considerably more symptoms or pain and irritation in the neck. However, those symptoms do not necessarily translate to patients who have a much smaller sublobar remnant.

Variations in thyroid anatomy must be considered when deciding the extent of resection for a particular neoplasm. In some patients, the anatomy of the ligament of Berry as well as the upper parathyroid glands is such that a total thyroid lobectomy can be performed with very minimal risk. In other situations, the parathyroids are partly adherent to the thyroid capsule such that maintenance of the blood supply is technically difficult during dissection of these glands. In circumstances in which the parathyroid is adherent to the thyroid, the presumed parathyroid is excised and put in chilled sterile saline while awaiting a frozen-section diagnosis. Frozen-section diagnosis should always be obtained to confirm that it is a parathyroid and not a lymph node with metastatic thyroid carcinoma. If it is confirmed to be normal parathyroid, the tissue is minced into small 1–2-mm fragments and implanted in the sternocleidomastoid muscle as a parathyroid autograft. If this is the only remaining parathyroid tissue, the patient will become symptomatic and require calcium and possibly vitamin D supplementation, but should regain parathyroid function over 4–6 weeks. Experience and judgment must be used to individualize the extent of each thyroid resection if more than a thyroid lobectomy is indicated to avoid unnecessary morbidity.

The surgical management of lymph node metastases from well-differentiated thyroid cancer is also somewhat controversial. A procedure somewhere between ''berry picking'' of clinically positive nodes and a formal modified radical neck dissection is the ideal treatment. For patients who have bulky and obviously pathological lymph node metastases, a formal modified radical neck dissection is indicated. The presence of metastatic disease to lymph nodes does not carry the connotation of worse prognosis of other solid neoplasms. Although lymph node metastases correlate with increased local recurrence, they do not carry a worse prognosis per se in several series. Lymph node metastases may be a marker for systemic disease or tumor aggression and guide the use and dose of postoperative radioactive iodine.

Radiation Therapy—Radioactive Iodine

The postoperative treatment and follow-up of patients with well-differentiated thyroid cancer relating to radioiodine therapy is controversial.

All patients who have undergone a total or near-total thyroidectomy for a follicular carcinoma or a papillary carcinoma greater than 1.5 cm should be considered candidates for radioiodine ablation. ^{131}I ablation of residual normal thyroid is important after what is thought to be complete resection of the primary tumor to aid in the detection of metastatic disease and to destroy residual microscopic cancer. Normal thyroid tissue takes up ^{131}I more avidly than does cancer (the majority of thyroid tumors are cold nodules) and thus prevents full visualization of the true extent of disease. Furthermore, ^{131}I ablation removes the contribution of normal thyroid tissue to serum thyroglobulin, an important tumor marker in the follow-up of postoperative patients. Most importantly, large retrospective studies have documented that ^{131}I ablation decreases cancer death, tumor recurrence, and development of distant metastases. Despite such data for large patient populations, investigators at the Lahey Clinic observe that an enhanced survival has not been documented with the use of radioiodine ablation, particularly in ''low risk'' patients defined by AMES criteria.

The dose of ^{131}I for ablation is not standardized. Some recommend low-dose ablation with less than 30 mCi given on an outpatient basis. The Nuclear Regulatory Commission (NRC) and local regulators mandate that patients administered 30 mCi of ^{131}I or more must be kept in isolation until the measured whole-body activity falls below 30 mCi, meaning that higher doses require hospitalization in a lead-lined room.

Higher ablative doses should be used for high-risk patients, particularly those known to have an incomplete resection of the primary tumor, an invasive primary tumor, or metastases. No significant differences were noted when doses from 100 to 200 mCi or more were used, leading to a recommendation of an optimal ablative dose between 150 and 200 mCi. Further radioiodine therapies

are required in patients with incomplete resection of the primary tumor, or in those with lymph node involvement, distant metastases, capsular invasion, or evidence of recurrent carcinoma as demonstrated by postablative ^{131}I scanning.

The goal of dosimetry is to derive the dose of ^{131}I that will deliver no more than 200 cGy to the blood, with no more than 120 mCi retained at 48 hr or 80 mCi in the presence of pulmonary metastases. This decreases the risk of bone marrow damage and radiation fibrosis in patients with metastatic lung disease. Another method championed by Maxon and colleagues emphasizes the dose delivered to the tumor to assure successful therapy. The goal of quantitative dosimetry is based on calculations that account for tumor size, percentage uptake, and effective $t_{1/2}$ of ^{131}I over 72 hr to safely deliver 80–100 cGy to metastatic foci. One recommended approach is for all patients with metastatic disease treated with repeated therapeutic doses of ^{131}I to undergo dosimetric quantification of the highest safe dose, which may vary according to the site of uptake using a ceiling of 300 mCi. For example, a dose of 150 mCi is given for residual or recurrent thyroid bed carcinoma with or without metastases, up to 200 mCi for bone metastases, and a reduced dose of 75 mCi for diffuse pulmonary metastases to prevent radiation pneumonitis and fibrosis.

Lymph node metastases were found in up to 42% of patients at the time of initial therapy in one large retrospective study. The presence of lymph node metastases found at surgery or on radioiodine scanning is thought not to affect survival in thyroid cancer patients; however, there is a significant increase in recurrences. Radioiodine is indicated in these patients to decrease recurrences, which may have an impact on long-term survival.

Pulmonary metastases are frequently detected exclusively on radioiodine scanning with the rate of negative chest radiographs in patients with metastatic disease found to have increased recently from 13% to 43%. Earlier detection of pulmonary metastases prior to development of gross chest film abnormalities is thought to be due to the use of thyroglobulin screening and the enhanced sensitivity of ^{131}I scanning. Patients with metastatic disease that concentrates iodine have a much better prognosis than those whose tumors did not. In one study, a difference in 10-year survival rate of 70% versus 6% depended on whether the pulmonary disease concentrated iodine or not, respectively. Bone metastases may require several modalities for adequate therapy. Surgery may be needed for orthopedic stabilization or neurological palliation.

Ablation of residual thyroid is typically performed at 6 weeks after near-total or total thyroidectomy. Most centers perform a diagnostic scan followed by ablative ^{131}I therapy. To optimize uptake by both residual thyroid and thyroid cancer, patients are rendered hypothyroid with a goal of increasing thyroid-stimulating hormone (TSH). To accomplish this, replacement therapy is changed to triiodothyronine (T3) therapy 6 weeks prior to the scan and is discontinued after 4 weeks. While some clinicians simply discontinue thyroxine therapy for 4 weeks

prior to scanning, a preferred approach is to use T3 to shorten the duration and diminish the severity of hypothyroid symptoms. TSH must achieve levels of greater than 25–30 U/ml to obtain optimal uptake of radioiodine. A low-iodine diet is instituted 1–2 weeks prior to scanning to further enhance the uptake and retention of radioiodine.

Just as there is lack of consensus regarding ablation and therapeutic doses of ^{131}I, the use of a diagnostic scanning dose prior to the ablative dose is controversial. The ideal dose achieves high sensitivity in detecting residual thyroid tissue, thyroid cancer, and metastatic foci and reduces the potential for sublethal radiation ''stunning'' of thyroid tissue, which prevents optimal uptake of future ^{131}I therapy. While it is clear that higher scanning doses improve visualization of thyroid remnants and metastases, even conventional scanning doses of 4–5 mCi of ^{131}I were found to diminish therapeutic radioiodine uptake. One strategy is to use a 5 mCi ^{131}I diagnostic dose followed by a whole-body scan at 48 hr with treatment following in most cases 24–96 hours after whole-body scanning.

Patients receiving 30 mCi or more of ^{131}I are isolated until the total-body burden is less than 30 mCi. Thyroxine therapy is instituted at doses to suppress TSH to below normal levels after the patient is out of isolation. A posttherapy whole-body scan is obtained after 5–7 days to determine the extent of disease. Follow-up scanning should be performed at 6–12-month intervals and treatment should continue until there is no further uptake, the serum thyroglobulin is in the ''athyreotic'' range, or complications of ^{131}I therapy arise.

Medical management of malignant lesions includes thyroxine therapy to suppress TSH, which is invaluable in preventing tumor recurrences. The degree to which one suppresses TSH is a point of debate. It is advisable to keep the TSH at or below the normal range (range 0.5–5 U/ml) in patients thought to be without evidence of disease and maintain a lower TSH (0.1 U/ml) in patients with residual neck disease, metastases, or recurrent disease. The degree of thyroid suppression in these cases is dictated by the overall medical condition of the patient, particularly the cardiovascular status.

Thyroglobulin (Tg), the storage protein in colloid follicules for thyroid hormone, is an important tumor marker in the follow-up of thyroid cancer patients. Following successful thyroidectomy and ablation of residual normal or cancerous thyroid tissue by radioiodine, the thyroglobulin will be in the athyreotic range. Levels above the athyreotic range are indicative of persistent functioning residual thyroid tissue or carcinoma. If there is detectable serum Tg in the circumstance of suppressive thyroxine therapy, it is a true indicator of persistent or recurrent thyroid carcinoma. However, thyroxine may suppress Tg in patients with metastatic disease; therefore, the test is more sensitive when the thyroid hormone replacement is stopped and the patient is hypothyroid with an elevated TSH. Tg is used in conjunction with the diagnostic whole-body scan and may be more sensitive than the scan in detecting cancer as demonstrated by several investiga-

tors. Patients treated with high-dose ^{131}I with a negative diagnostic scan but an elevated thyroglobulin often have a positive posttreatment scan indicating residual disease.

The success of radioiodine therapy is dependent on residual thyroid tissue concentrating iodine avidly under the stimulation of elevated TSH. In some circumstances, stimulation by endogenous TSH is impossible, as in the case of hypopituitarism. In these cases, bovine TSH has been used prior to ^{131}I scanning; however, it is highly antigenic and not as effective as endogenous TSH.

Results from a phase I/II study of the use of recently available recombinant human TSH (rhTSH) for diagnostic scanning were reported. Studies are ongoing to test the safety and efficacy of rhTSH as an adjunct to radioiodine therapy in the follow-up of thyroid cancer patients. This recombinant hormone may eliminate the need to become hypothyroid with symptoms associated with thyroid hormone withdrawal.

The most common side effects from radioiodine therapy include sialadenitis, nausea, and temporary bone marrow suppression. Testicular function and spermatogenesis is transiently impaired but appears to recover with time. In a recent study comparing fertility rates, birth rates, and prematurity between women treated with ^{131}I and those not treated, there were no significant differences. There is a dose-dependent relationship between ^{131}I therapy and the development of leukemia. The incidence increases when the total cumulative dose is greater than 800 mCi and can be avoided by treating at widely spaced intervals (6–12 months) with activity between 100 and 200 mCi. A higher incidence of bladder carcinoma has been seen in patients who have received high cumulative doses of radioiodine.

Chemotherapy and External-Beam Radiation Therapy

The most effective nonsurgical treatment for well-differentiated thyroid cancer is, without question, ablation with radioiodine. Other conventional modes of neoplastic treatment, chemotherapy, and external-beam radiation therapy have much poorer results and consequently are much less studied. The best single chemotherapeutic agent for this tumor is adriamycin with partial response rates of 30% and up to 45% in some series. However, the very limited duration of the responses that are seen and lack of complete response limit the utility of this drug. Other agents that have been tried alone include cisplatin, VP16, and carboplatin. All of these agents do have response rates in the range of 22–30% including anecdotal reports of complete responses with VP16. Combination therapy with adriamycin and cisplatin has produced disappointing results. The results of these regimens were no better than those of single-agent trials, and the toxicity was worse.

For well-differentiated thyroid cancer, external-beam radiation therapy has relatively limited benefit. However, for surgically unresectable disease that has

not responded to radioiodine, the combination of hyperfractionated radiation treatments plus adriamycin has been reported to be successful. It is felt that the radiotherapy may act as a sensitizer to the action of the chemotherapeutics. Response rates of greater than 80% have been reported using this regimen, although even in this situation, complete responses are rare and limited in duration.

ANAPLASTIC THYROID CANCER

Anaplastic thyroid cancer (ATC) is one of the most aggressive and difficult to treat human malignancies, and subsequently is one of the most lethal. As opposed to the excellent long-term survival for well-differentiated thyroid carcinoma, ATC in most series has a median survival of 4–5 months from the time of diagnosis with rare long-term survivors.

Current epidemiological studies indicate that this lethal form of thyroid cancer has decreased to between 1% and 3% of the total number of cases. The decrease over time may be partially related to iodine prophylaxis and an overall decrease in endemic iodine-deficient goiter in North America. Patients with ATC differ epidemiologically from patients with well-differentiated thyroid neoplasms with a median age 2–3 decades greater and with a more equal gender distribution.

The majority of patients with ATC die from aggressive local-regional disease primarily with upper airway respiratory failure. At the time of diagnosis, 25–50% of patients may have synchronous pulmonary metastases. However, it is usually the local growth causing obliteration of the airway that causes the patient's demise. For this reason, aggressive local therapy is indicated in all patients who can tolerate it and in whom it is technically possible. Because of the high likelihood of local recurrence, aggressive primary resection should be undertaken including removal of surrounding strap muscles and any other structures locally invaded. Patients may need a tracheostomy at the initial procedure to accompany the resection and protect the airway. As opposed to well-differentiated thyroid cancer, ^{131}I plays no role in the treatment of recurrent or metastatic disease for this tumor. Therefore, total or near-total thyroidectomy is not as important in ATC except as needed to obtain local control.

Survival after the diagnosis of ATC is very poor. With the median survival in most series being less than 5 months from the time of diagnosis, this is one of the most rapidly lethal tumors known in clinical oncology. The majority of patients die owing to local recurrence raising the question of benefit of a local treatment such as radiation therapy, although distant metastases occur primarily in lung, bone, and liver. External radiation has been used with limited success to treat locally recurrent ATC. The combination of radiation therapy and relatively low-dose adriamycin has an apparent synergistic effect achieving responses in the majority of patients, although still having a median survival of only 12 months. Adriamycin is the single most effective chemotherapeutic agent for

ATC and it has been shown that adriamycin plus platinum is more effective than adriamycin alone. In favorable tumors, those less than 5–6 cm in size, there are patients who can have long-term survival. Early diagnosis with aggressive surgical therapy supplemented by external-beam radiation therapy and adriamycin-based chemotherapy is the most appropriate treatment for patients with anaplastic thyroid carcinoma.

MEDULLARY THYROID CANCER

In 1959, Hazard described medullary thyroid cancer (MTC) as a solid thyroid neoplasm without follicular histology, but with a high degree of lymph node metastases, which accounted for 3.5% of thyroid cancers. Since this description sequential pathological, biochemical, and molecular genetic studies have progressed to make this one of the best-characterized malignancies of the thyroid. In the 1960s investigators identified and described the parafollicular C cell, which produces calcitonin, which lowers serum calcium. Understanding of the familial associations of MTC with corollary genetic studies reported in the 1980s and early 1990s has defined molecular changes that are important for inherited MTC and may have implications for sporadic MTC as well.

MTC composes as low as 3% or as high as 12% of most institutional series of all thyroid cancers, and the actual proportion is estimated to be between 5% and 9% of cases. As opposed to well-differentiated thyroid cancer, MTC is not associated with radiation exposure but it does occur in distinct familial syndromes. Sporadic or nonfamilial MTC accounts for 60–70% of cases with three distinct familial syndromes accounting for the rest. MTC is the most prominent clinical diagnosis in MEN-2A and MEN-2B, which are multiple endocrine neoplasias and in 1986 non-MEN familial MTC was described. Appreciation of this syndrome has shifted the incidence of sporadic MTC of the total number of cases of MTC from 80% down to 60% and even lower in some recent series.

The clinical symptoms at the time of presentation vary depending upon the situation for each individual patient. Patients with a family history of MTC who are identified by screening with stimulation tests or with molecular analysis are universally identified prior to any macroscopic mass or lesion. Sporadic patients typically present with symptoms of a mass in the thyroid. Patients with advanced disease with extremely high levels of calcitonin may have severe secretory diarrhea as a principal symptom.

The most important tool in confirming diagnosis, screening potential patients with familial MTC, and following patients after treatment is the use of basal and stimulated serum calcitonin. Virtually all MTC produce abnormal levels of calcitonin and have characteristics of abnormal release of this hormone following stimulation with calcium and pentagastrin. The normal range for CT is typically less than 250–300 pg/ml. Stimulation tests in patients with normal basal calcito-

nin include injection of calcium gluconate (2 mg/kg/1 min), pentagastrin (0.5 μg/kg/5 sec), or a combination of these two agents given sequentially with calcitonin measured before and shortly after stimulation. Increases to >1000 pg/ml after stimulation are pathognomonic for MTC. Elevations to between 300 and 1000 pg/ml are borderline and these patients should be followed closely and retested sequentially. However, recent advances in genetic screening and diagnosis will likely make this type of testing obsolete when they become available. MTC does not concentrate iodine, so ^{131}I thyroid scans are of no utility but other nuclear medicine scans, including MIBG, somatostatin, and anti-CEA, have been evaluated with limited success.

Surgical resection is the definitive treatment for MTC as chemotherapy and external-beam radiation therapy are ineffective. For patients with sporadic MTC who are not identified by biochemical or genetic screening, the appropriate operation in most cases is total thyroidectomy with central node dissection because a small proportion of lesions may be bilateral. Also, in some cases, the patient is an index case of familial disease or family history is unknown. The only exception is a small tumor (<1.5 cm) with a definite negative family history in which a thyroid lobectomy is appropriate. Since all familial syndromes have a high propensity for bilateral tumors, total thyroidectomy is indicated in all. Combined with this thyroid resection, a central lymph node dissection is performed removing lymphoid tissue from the level of the hyoid bone to the innominate vessels inferiorly and laterally to the jugular vein. Lymph nodes lateral to the jugular vein are sampled and if there is any evidence of metastatic spread in this area, a formal modified radical neck dissection is performed. The incidence of positive lymph nodes correlates with the size of the primary lesion at the time of diagnosis. It has been reported that for lesions < 1 cm there can still be an 11% incidence of positive nodal disease while in tumors > 2 cm, 60% will have positive cervical lymph nodes. Taking all cases of MTC combined, between 15% and 75% have spread to the lymph nodes at the time of diagnosis. One approach is to perform a formal modified radical neck dissection for any lesion > 2 cm on the side in which it is located with a central node dissection on the contralateral side. The incidence of distant metastases at the time of diagnosis varies with the subtype of MTC. Twelve percent of patients with sporadic MTC have distant metastases, 20% of MEN-2B have metastatic spread, but only 3.3% of patients with MEN-2A and 2% of familial non-MEN MTC have distant metastases. The outcome of treatment of patients with sporadic MTC has improved over the past several decades, with 5-year survival improving from 50% to 80–90% and 10-year survival improving from 15% to 75%.

For patients with metastatic MTC, the results of treatment with external-beam radiation therapy or chemotherapeutics are disappointing. Radiation administered at a dose over 5000 rads to a large Y-shaped anterior field without laryngeal shielding necessary to treat these patients causes significant local toxicity.

Treatment with this radiation dose has not definitively been shown to decrease local recurrence. Chemotherapeutic agents used in treatment of medullary thyroid cancer include adriamycin, DTIC, streptozotocin, and 5-FU. Single-agent response rates are poor with aggressive adriamycin regimens producing 20–30% objective responses. A study of combination chemotherapy with 5-FU, streptozotocin, and DTIC produces objective responses in only 15% and no agent leads to durable responses. The poor outcome of treatment of metastatic disease validates the treatment recommendation to diagnose patients with MTC early and treat with initial aggressive surgery.

LYMPHOMA OF THE THYROID

Lymphoma of the thyroid is a relatively rare disease comprising less than 1% of all lymphomas and accounts for 2% of extranodal non-Hodgkin's lymphoma. Almost all of these thyroid lymphomas are non-Hodgkin's lymphoma with the majority being intermediate-grade and the remainder being high-grade. The majority of patients with thyroid lymphoma have all disease on one side of the diaphragm with a minority of patients with disease confined to the thyroid (stage IE) and the majority with thyroid disease plus cervical and/or mediastinal lymph nodes (stage IIE). The incidence of this disease may be changing primarily owing to improved recognition and diagnosis of thyroid lymphoma. One hypothesis to explain the incidence increase is that these patients were previously diagnosed as having anaplastic thyroid carcinoma and with better understanding and more sophisticated diagnostic tools such as immunohistochemistry, these patients are being correctly categorized as having thyroid lymphoma.

In most series, there is a strong female predominance and the median age in most series at diagnosis places patients in the 7th decade of life, similar to what is seen for anaplastic thyroid cancer and much older than patients with well-differentiated thyroid cancer. Between 10% and 30% of patients will report a symptom or combination of symptoms relating to local invasion including hoarseness, dyspnea with stridor, or dysphagia. Patients with thyroid lymphoma almost never have hyperthyroidism, but frequently have hypothyroidism in association with autoimmune thyroiditis or Hashimoto's thyroiditis.

The optimal treatment for thyroid lymphoma has evolved with the success of combination chemotherapy used in the treatment of non-Hodgkin's lymphoma and with the ability to obtain an accurate diagnosis without invasive surgery by large-needle or trucut biopsy. The primary role of surgery in this disease is simply to obtain adequate tissue for diagnosis and the primary treatment should be external-beam radiation combined with an adriamycin-based chemotherapy regimen. However in the minority of patients who have no extrathyroidal extension, excellent survival is achieved by surgical excision plus postoperative radiation therapy.

Patients with extrathyroidal disease either by direct extension or lymph node involvement should be considered to have systemic disease and not have formal thyroid resection.

PARATHYROID TUMORS

Benign parathyroid tumors are a common endocrine problem while parathyroid carcinoma is exceptionally rare. Parathyroid carcinomas, as opposed to other endocrine tumors that become less hormonally active when malignant, are hyperfunctional and characterized by severe elevations of serum calcium with associated renal and bone symptoms. The clinical course is variable, but typically follows a pattern of local recurrence in the neck with late distant metastases to lung, bone, and liver.

The vast majority of parathyroid cancers are functional with excess production of parathyroid hormone (PTH), which results in the clinical syndrome of primary hyperparathyroidism (HPT). The pathology of HPT can be grouped into three general categories: a single parathyroid adenoma (83–85% of cases), multiglandular hyperplasia (15%), and parathyroid cancer (0.5–3%). The true proportion of HPT patients who have parathyroid cancer is likely to be well under the 2% of cases recently quoted.

Pathology

The pathological criteria used to distinguish parathyroid carcinoma from benign parathyroid adenoma include thick fibrous bands, pleomorphic cells in a trabecular pattern, and a high incidence of mitotic figures as the chief distinguishing features. Invasion of the glandular capsule into surrounding tissue and vascular invasion also identify parathyroid carcinoma. As with other endocrine neoplasms, the diagnosis of parathyroid carcinoma strictly on historical evaluation using the criteria outlined above may be difficult. A spectrum of these changes is present in benign adenomas, atypical adenomas, and true carcinomas.

As almost all parathyroid carcinomas are functional, the presenting signs and symptoms of this disease relate primarily to the consequences of this hormone excess. Various manifestations of renal disease associated with hypercalcemia and hypercalcuria, such as renal stones, renal colic, nephrocalcinosis, and/or renal insufficiency, occur in up to 90% of cases. The incidence of bone disease and bone pain is much greater in parathyroid carcinoma than in patients with parathyroid adenoma with up to 70% of patients manifesting the symptoms. In nonmalignant parathyroid disease, it is unusual to have both renal and bone symptomatology documented at the time of diagnosis. However, these symptoms are present simultaneously at diagnosis in up to 50% of patients with parathyroid carcinoma.

These amplified symptoms reflect the increased magnitude of the biochemical disturbances seen with parathyroid carcinoma. The level of total serum calcium is significantly elevated in almost all series of parathyroid carcinoma with the mean values between 15 and 16 mg/dl compared to 11–12 mg/dl seen with parathyroid adenomas. Because of the extreme degree of hypercalcemia, it is very unusual for patients to be asymptomatic at presentation with parathyroid carcinoma compared to patients with benign causes of HPT who are asymptomatic in over 50% of cases in some series. Up to 14% of patients with parathyroid carcinoma may present with hypercalcemic crisis manifested by a depressed level of consciousness, dehydration, and extreme hypercalcemia. The size of the typical parathyroid carcinoma is much larger than benign lesions. The median maximal diameter in most series is between 3 and 3.5 cm, compared to approximately 1.5 cm for benign adenomas. This large mass translates into a significant number of patients who present with a palpable neck mass ranging between 22% and 50% of cases. Again, it is almost unheard of for patients with benign lesions to have palpable abnormalities in the neck and this clinical sign strongly suggests parathyroid carcinoma. In 10% of cases, patients with parathyroid carcinoma present with symptoms of hoarseness due to compression or invasion of recurrent laryngeal nerve and vocal cord paresis.

The natural history of parathyroid cancer reflects a locally invasive tumor compared to a widely metastatic malignancy. At initial presentation, very few patients with parathyroid carcinoma have metastases either to regional lymph nodes ($<5\%$) or distant sites ($<2\%$). A higher proportion of parathyroid carcinomas are locally invasive into the thyroid gland, overlying strap muscles, recurrent laryngeal nerve, trachea, or esophagus. Many patients are not identified preoperatively or intraoperatively as having parathyroid carcinoma and undergo parathyroid procedures as if to treat parathyroid adenoma. Only after review of the pathology following this resection, or when these patients recur locally or with metastases, is a correct diagnosis of parathyroid carcinoma made. The incidence of not recognizing parathyroid carcinomas at initial operation ranges between 11% and 86%.

After surgical treatment, 40–60% of patients will have recurrent disease at some point typically in the range of 2–5 years after the initial resection. Since parathyroid carcinomas are functional, serial measurement of calcium or PTH serves as an ideal tumor marker for this malignancy. In patients followed closely, hypercalcemia precedes physical evidence of recurrent disease in most cases. The most common location of recurrence is regionally either in the tissues of the neck or in cervical lymph nodes accounting for two-thirds of recurrent disease. Often local recurrences in the neck are difficult to identify as they may be small, multifocal, and involve the scar from the previous procedure and only recurrent elevations in PTH and calcium signify the return of microscopic disease. Use of ultrasound, sestamibi scanning, and more recently positron emission tomography

scanning may aid in this difficult diagnosis. Distant metastases occur in 25% of patients primarily in the lungs but also in the bone and liver.

Patients who succumb to parathyroid carcinoma typically die from metabolic consequences and not directly from malignant growth. For this reason, repetitive surgical operation to debulk parathyroid carcinoma, if possible, is indicated as medical management of the hypercalcemia of parathyroid carcinoma is difficult. The median survival after recurrent parathyroid cancer ranges between 3 and 5 years with isolated case reports of patients surviving several decades with intermittent surgical debulking.

The only effective treatment of parathyroid cancer is surgical resection. The most important component to achieve a favorable outcome is recognition by the operating surgeon that a lesion may be a parathyroid cancer, which allows performance of the appropriate en bloc resection of the tumor with all potential areas of invasion removed at the initial operation. A high level of suspicion of the possibility of parathyroid carcinoma in patients with extremely high serum calciums, very elevated PTH levels, and large lesions is appropriate. Parathyroid cancer often invades the ipsilateral thyroid lobe and resection of the tumor with one or both thyroid lobes is frequently required to perform an adequate operation. In most series, long-term results of decreased local recurrence are significantly improved when an en bloc excision including the thyroid is done as opposed to cases in which only the parathyroid cancer is removed. The recognition and diagnosis of parathyroid cancer preoperatively correlates strongly with a favorable outcome. The recurrent laryngeal nerve may be intimately involved or invaded by the parathyroid cancer. In these situations, patients frequently have preoperative hoarseness due to tumor invasion of the nerve. Because the nerve is at risk for loss of function owing to the malignant process itself, it is appropriate to resect the recurrent laryngeal nerve if necessary to perform an en bloc excision during the initial procedure for parathyroid cancer. The increased potential for long-term local control achieved by this approach outweighs the complication of postoperative vocal cord paralysis, which can be improved with techniques such as Teflon injection into the paralyzed cord.

For most cases of recurrent parathyroid carcinoma confined to the neck, the most appropriate treatment is aggressive reresection. However, as opposed to the initial procedure in which the success rate is up to 40–60%, it is unusual to obtain long-term cures in patients who have to undergo reresection. The benefit of sacrificing the recurrent laryngeal nerve is greatly decreased in patients undergoing reresection for recurrent parathyroid cancer as most recurrences are multifocal. If a recurrent nodule involves the recurrent laryngeal nerve, there are most likely other areas of parathyroid cancer that are adherent to the trachea, the esophagus, and the great vessels of the neck. As it is impossible to remove all of these vital structures, it is unlikely to obtain a cure by taking the nerve. However, in certain circumstances in which there is an isolated local recurrence that

is involving the nerve, it again should be sacrificed with an en bloc resection as those patients, in rare instances, may be salvaged by an aggressive surgical procedure.

Radiation Therapy and Chemotherapy

Nonsurgical forms of therapy for parathyroid carcinoma have generally poor results such that surgical treatment of distant metastases is appropriate in certain situations. Pulmonary metastases as well as bone metastases should be resected, if possible, primarily to debulk tumor to decrease the magnitude of hypercalcemia. However, occasionally long-term salvage is achieved in this group of patients with aggressive surgical treatment.

Radiation therapy, in general, does not result in meaningful antitumor responses. Isolated case reports of long-term control exist and radiation therapy should be used as a last resort in patients with unresectable recurrent cervical disease. Various chemotherapeutic agents alone or in combination have been utilized for treatment of parathyroid carcinoma with limited success. Dacarbazine alone or in combination with 5-fluorouracil and cyclophosphamide has been reported to result in objective responses including one complete response in a patient with pulmonary metastases. Other combination therapies have resulted in rare responses. Part of the problem with the medical treatment of parathyroid carcinoma is that the rarity of this disease does not allow systematic evaluation of various combination therapies.

The second aspect of medical management for metastatic parathyroid carcinoma relates to the treatment of the hypercalcemia. Acute therapy of patients with hypercalcemic crises or very high serum calciums is similar to that used for other causes of symptomatic hypercalcemia. Volume loading with loop diuretics causing a forced diuresis is the initial therapy. For patients with parathyroid carcinoma, the ultimate management of the hypercalcemia is directed at the tumor to decrease the level of PTH, if possible, by surgical treatment but when this is impossible, use of osteoclast inhibitors such as etidronate or pamidronate may be helpful.

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14

Carcinoid Tumors

Linda S. Callans, David J. Vaughn, R. Alex Hsi, and Eli Glatstein
University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Brenda E. Haynes
Delaware County Memorial Hospital, Drexel Hill, Pennsylvania

INTRODUCTION

Carcinoid tumors are part of the APUD system arising from Kulchitsky cells of the neural crest. Carcinoid tumors are rare, occurring with a frequency similar to that of small bowel carcinoma. They can occur at any age but the peak incidence is in the sixth decade. The most common site of carcinoid tumors is the appendix (44%), followed by the rectum (15%), ileum (11%), bronchus (10%), and colon (8%) (see Table 1). About 30% of ileal carcinoids are multifocal and 30% are associated with a second malignancy. Gastric carcinoids are rare but tend to be multifocal and occur in patients with atrophic gastritis. A small percentage occur in patients with MEN-I associated with the Zollinger-Ellison syndrome. Approximately 9% of patients with MEN-I have carcinoid tumors and over half occur in the bronchus or thymus.

Carcinoid tumors are generally slow-growing and follow an indolent course. Often, there is a 1–2-year delay in diagnosis due to the vague nature of symptoms and many carcinoids are not discovered until late in the course of disease. Both the incidence of lymph node metastases and survival rate are related to the site and size of the primary tumor. For example, appendiceal carcinoids have a more favorable prognosis than small bowel primaries. Most appendiceal primaries are less than 2 cm and are unlikely to have associated lymph node metastases. For tumors over 2 cm, carcinoids of the appendix have a lower incidence of lymph node metastases (33%) than small bowel carcinoids (90%).

Most patients with carcinoids are asymptomatic and the tumor is discovered incidentally. Other patients have vague abdominal symptoms or present more

Table 1 Common Sites of Carcinoid Tumors

Appendix
Rectum
IIeum
Bronchus
Colon
Other (Stomach, duodenum, thymus, etc.)

acutely with bowel obstruction or mesenteric ischemis. Only 7% of patients with carcinoid tumors actually present with the carcinoid syndrome and three-quarters of these patients have midgut tumors.

The typical carcinoid syndrome is attributed to serotonin secreted by the tumor cells. Since the liver clears serotonin that is secreted into the portal circulation symptoms of carcinoid syndrome usually indicate the presence of hepatic metastases when the primary tumor is located in the gastrointestinal tract. Primary carcinoid tumors with venous drainage directly into the systemic circulation can also cause the carcinoid syndrome—e.g., ovarian carcinoids, bronchial carcinoids, and tumors with extensive retroperitoneal venous drainage.

The symptoms of carcinoid syndrome include flushing, watery diarrhea, and abdominal colic. Less commonly, patients may have right-sided heart disease with valvular fibrosis, and bronchoconstriction. Foregut tumors have a more variable pattern of hormone secretion and may present with an atypical carcinoid syndrome. Classically, the diagnosis of carcinoid syndrome is made by measurement of 24-hr urinary 5-HIAA, a metabolite of serotonin. The patient should avoid serotonin-rich foods or medications that alter urinary 5-HIAA levels to prevent false-positive readings (Table 2).

The primary lesion can be localized using a variety of modalities including computed tomography (CT) scan, magnetic resonance imaging (MRI), chest x-ray, or endoscopy depending on the site of the tumor. Angiography may be useful to diagnose and localize small bowel primaries associated with carcinoid syn-

Table 2 Foods and Medications Altering Urinary 5-HIAA

Serotonin-rich foods		Medications
Bananas	Avocado	Salicylates
Pineapple	Walnuts	Acetaminophen
Plantains	Pecans	Cough medicine with guafanesin
Kiwi	Hickory nuts	L-Dopa

drome that are missed by other diagnostic modalities. Venous sampling may be helpful in certain circumstances. As over 80% of carcinoid tumors express the somatostatin receptor, nuclear scans using radiolabeled octreotide (a somatostatin analog) localize most primaries with high specificity. MIBG scans can also aid in localization. For staging purposes, CT scan and MRI are the most useful studies to assess liver metastases as well as periaortic or porta hepatis lymphadenopathy.

SURGICAL MANAGEMENT OF CARCINOID TUMORS

Surgery for Primary Lesions

The primary and curative modality of treatment for carcinoid tumors is surgery. The extent of resection depends on the size of the primary and the likelihood of lymph node involvement, which varies with the site of the primary tumor (Table 3). For small tumors with no lymph node involvement, local resection is adequate while a wide resection with draining mesenteric lymph nodes is appropriate for larger lesions with involved lymph nodes. Prognosis is improved if all disease can be resected. In addition, there may be a palliative role for debulking, particularly in the setting of liver metastases associated with severe carcinoid syndrome.

Of note, patients with carcinoid syndrome undergoing surgery are at risk of developing carcinoid crisis, which can be can be fatal if not recognized and treated appropriately. Carcinoid crisis presents with hypertension, tachycardia, profound hypotension, and even coma and can be precipitated by stressful situations including anesthesia, biopsy of hepatic disease, or chemotherapy. Carcinoid crisis can be treated and often prevented with octreotide, a somatostatin analog. If the patient's diagnosis is known, the patient can be given octreotide preoperatively to minimize the risk of carcinoid crisis intraoperatively.

The appendix is the most common site of carcinoid tumors and these are usually diagnosed by the pathologist following appendectomy for acute appendicitis. Appendiceal carcinoids occur at a rate of 1 per 2–300 appendectomies and over 90% are less than 1 cm in size. In this circumstance, appendectomy alone

TABLE 3 General Guidelines for Surgical Treatment of Carcinoid Tumors

Size of tumor	Tumor location	
	Appendix, rectum, bronchus	Ileum, ''sporadic'' gastric
<2 cm $\rightarrow$	Local resection	Extended resection with lymph nodes
≥ 2 cm $\rightarrow$	Extended resection with lymph nodes	Extended resection with lymph nodes

is adequate therapy. The incidence of lymph node metastases increases to 33% for appendiceal primaries larger than 2 cm, and formal right hemicolectomy is recommended. Surgery for appendiceal carcinoids is usually curative and the overall 5-year survival ranges from 95 to 100%. The operative mortality is less than 0.5% and complications such as anastomotic leak are rare. The incidence of wound infection is higher in the setting of acute or perforated appendicitis.

Most rectal carcinoids are discovered as small (less than 1 cm) mucosal nodules during proctoscopy and are rarely associated with lymph node metastases. Endoscopic resection or limited local transanal excision is appropriate for these small lesions. Patients with lesions larger than 2 cm should be carefully staged and a low anterior resection (LAR) or abdominoperineal resection (APR) performed if there is no evidence of distant disease. Perforation and bleeding are uncommon complications of endoscopic or transanal resections. Postoperative anal stricture or difficulty with fecal continence can occur following transanal resections usually associated with excessive anal dilatation. The operative mortality for LAR and APR is similar and ranges from 1.5 to 2.5%. Operative morbidity includes sepsis, pelvic abscess, and anastomotic leak (for LAR) as well as impotence and urinary retention.

Small bowel lesions may be found incidentally during exploratory laparotomy but more often patients present with vague abdominal symptoms, acute bowel obstruction or ischemia, or carcinoid syndrome. Small bowel carcinoids are associated with a dense desmoplastic reaction with foreshortening of the mesentery that leads to kinking and obstruction of the bowel. Rarely, intussusception occurs. Venous infarction can occur due to fibrosis and occlusion of regional vessels associated with the desmoplastic changes in the mesentery. Most ileal carcinoids are discovered late in the disease and the majority have lymph node metastases that are often unresectable owing to encasement of the main vessels at the root of the mesentery. Even with relatively small ileal carcinoids, lymph node metastases are common. Sixty to 80% of tumors between 1 and 2 cm and over 90% of tumors over 2 cm have lymph node involvement. Nonetheless, a segmental bowel resection with wide mesenteric resection should be performed, when possible, with care not to compromise the blood supply to the remaining small intestine. Distal ileal lesions require a right hemicolectomy. In addition, the surgeon should perform a careful abdominal exploration as about one-third of ileal carcinoids are multifocal and about 20% of patients will have a second primary malignancy. The overall 5-year survival for small bowel tumors ranges from 50 to 60%. If the disease is locally confined with no lymph node metastases, the 5-year survival approximates 75% whereas it drops to 59% if the lymph nodes are positive and 20–35% if there are liver metastases. The main complication of resection of small bowel carcinoids is devascularization of adjacent bowel.

The typical bronchial carcinoids, also known as Kulchitsky cell carcinoma-I (KCC-I), are usually detected by chest x-ray. Together with the atypical bron-

chial carcinoids (KCC-II), they account for about 10% of all carcinoids. Patients may be asymptomatic or present with cough, obstructive pneumonia, or hemoptysis. Bronchial carcinoids are also seen in a small subset of patients with MEN-I. Bronchial carcinoids are usually small; less than 10% of typical carcinoids and 30–50% of atypical carcinoids have lymph node metastases at presentation. In general, the prognosis following resection of typical bronchial carcinoids is excellent with close to 100% 5-year survival while atypical carcinoids behave more aggressively with a 5-year survival ranging from 38 to 74% in various studies.

Gastric carcinoid is rare and diagnosis is usually made by upper endoscopy. Two patterns are seen with gastric carcinoid. First, single or multiple small (<2 cm) mucosal nodules can be seen in patients with hypergastrinemia. The majority are associated with chronic atrophic gastritis though a small percentage are seen in the setting of Zollinger-Ellison syndrome. These carcinoids are usually benign and over 90% are limited to the mucosa or submucosa. They have an excellent prognosis and can usually be endoscopically resected, especially those less than 1 cm. Local excision should be considered for lesions between 1 and 2 cm and certainly for those larger than 2 cm. If the hypergastrinemic state persists, however, the gastric carcinoids may recur leading some to recommend antrectomy as the initial management. The second pattern of gastric carcinoid is the sporadic form that usually occurs as a single, large tumor that may be difficult to distinguish from gastric carcinoma. These carcinoids are usually more deeply invasive with over half presenting with lymph node and liver metastases. Most are well differentiated and follow an indolent course with the median survival reported as 69 months in a collected series. Poorly differentiated sporadic gastric carcinoids, however, are aggressive and have an extremely poor prognosis with over 75% of patients dying within 1 year. When the tumor is resectable, the recommended treatment for patients with sporadic gastric carcinoid is gastrectomy with lymph node dissection.

Overall, the survival of patients with small primaries and negative lymph nodes is equivalent to that of the general population following resection of the primary with a 5-year survival of 94%. When the lymph nodes are positive, the median survival approaches 15 years if the primary tumor and all involved lymph nodes can be completely resected. This compares with a median survival of 5 years if the lymph node metastases are unresectable. The median survival of patients with unresected liver metastases is 3 years with a 20% 5-year survival.

Surgical Management of Metastatic Disease

In most instances, metastatic disease is approached surgically only for palliation of symptoms. Liver metastases can be associated with incapacitating symptoms of carcinoid syndrome that are resistant to medical management. The different options for the management of liver metastases are listed in Table 4.

Table 4 Management of Hepatic Metastases from Carcinoid Tumors

Surgical resection	Chemoembolization
Cryosurgical ablation	Systemic chemotherapy
Liver transplantation	Radiation therapy
Hepatic artery ligation or embolization	

Debulking of metastatic disease by liver resection can provide effective and sustained relief of symptoms and reduce the need for additional therapy. The impact on survival is uncertain. An anatomical resection of the right or left lobe can be performed if the metastatic lesions are limited to a single lobe. Alternatively, wedge resections of multiple lesions can be performed. The reported perioperative mortality following liver resection is less than 5% in most series with a 25% morbidity rate. Major postoperative complications include hepatic failure, bleeding, abscess, and bile leak resulting in a bile fistula or biloma.

Cryosurgery is another option for the management of metastatic deposits using a probe inserted directly into the tumor. This is particularly useful in patients with significant cirrhosis or comorbid disease, numerous lesions, or bilobar distribution of metastases. When the cryoprobe is cooled to subzero temperatures by circulating liquid nitrogen, the tumor and surrounding tissue is ablated. At least three freeze-thaw cycles are recommended and multiple probes may be required for larger lesions. The operative mortality is less than 5% and the major morbidity rate ranges from 6% to 38%. Complications include severe coagulopathy, hepatic hemorrhage requiring reoperation, biliary fistula, subphrenic or hepatic abscess, and acute renal tubular necrosis. Myoglobinuria is common.

Occasionally, patients with carcinoid tumors metastatic to the liver are candidates for resection for cure. Patients with limited, unilobar liver disease may be considered for liver resection with a reasonable expectation of long-term survival. The primary site must be completely resected and no other extrahepatic site of disease identified. In general, a minimal surgical margin of 1.0 cm should be obtained with either a wedge or anatomical resection. Although the patient numbers are small, prolonged survival has been reported following curative resection in several retrospective series. Carcinoid tumors, however, are slowly progressive even after liver metastases have occurred and this information needs to be considered carefully. Because of the potential for long-term survival, on the other hand, liver transplantation has been considered an option for patients with isolated liver metastases from carcinoid. Patients with limited liver metastases who are not candidates for hepatic resection owing to cirrhosis or anatomical restrictions may be considered for liver transplantation.

Diffuse or extensive metastases are not amenable to local cytoreductive

surgery and are not considered candidates for liver transplantation owing to the high recurrence rate. Options for these patients include hepatic ischemia with hepatic artery ligation or, more commonly, occlusion by percutaneous catheter embolization. Chemoembolization is also being investigated. These approaches are discussed further in the next section.

MEDICAL ONCOLOGY IN THE MANAGEMENT OF CARCINOID TUMORS

Carcinoid tumors that are unresectable or metastatic are not curable. Although the pace of the disease may be slow, in most cases it is ultimately fatal. When the oncologist is evaluating a patient with advanced carcinoid tumor for therapy, many aspects must be considered. The individual patient should be evaluated with respect to pace of disease, tumor burden and location, severity of hormonal symptoms, and disability caused by the tumor. It is crucial to remember that these tumors often have an indolent course over several years and no treatment may be needed. In most cases, carcinoid tumors cause symptoms only after metastasizing to the liver. The type and severity of symptoms should be assessed so that treatment can be directed to provide the best palliation. In asymptomatic individuals, the best approach may be observation.

Treatment should be based on the severity of symptoms and incapacitation caused by these tumors (Table 5). Carcinoid syndrome is caused by secretion of serotonin and includes watery diarrhea, abdominal colic, malabsorption, flushing, heart disease, and bronchoconstriction. When symptoms are mild or moderate, use of common antidiarrheal agents should be considered first-line therapy. Drugs, such as opiates and/or lomotil, can control the hormonal effects without the need for more aggressive therapy. These agents, however, usually have no effect on the flushing that can occur with these tumors. More severe problems

Table 5 Management of the Carcinoid Syndrome

Resectable disease	→	Surgery
Unresectable disease	→	1. Symptomatic treatment
		a. Antidiarrheals
		b. Serotonin antagonists
		2. Octreotide
		3. Surgical debulking
		4. Chemotherapy
		a. 5-FU + streptozotocin
		b. Alpha-interferon
		5. ? Radiation

can be addressed with methysergide and cyproheptadine, which are peripheral serotonin antagonists that are effective in controlling severe diarrhea.

If these approaches are unsuccessful, the use of a somatostatin analog should be considered. Somatostatin is an endogenous peptide that can inhibit the release of many hormonal agents (growth hormone, insulin, glucagon, and gastrointestinal peptides). The native hormone has been shown to control the symptoms associated with the carcinoid syndrome, but it has a half-life of less than 2 min. Clinical use of this agent is not practical as it requires a continuous intravenous infusion. Octreotide, a somatostatin analog with a longer half-life, can block secretion of a wide range of endogenous peptides and is highly effective in controlling the symptoms from hormonal release. Almost 80% of patients with carcinoid syndrome obtain substantial or complete relief from flushing and diarrhea, along with objective decreases in 5-HIAA levels. Symptomatic improvement can occur within a few hours after administration of the first dose. Occasionally, reduction in tumor bulk is seen.

The side effects from octreotide are minimal but the drug is costly and must be administered three or four times a day by subcutaneous injection. Gallstones are a long-term complication due to inhibition of gallbladder contraction. Over time, many patients require increasing doses of octreotide to maintain control of symptoms. The majority of patients become resistant to therapy with a median duration of response of 1 year.

Systemic Chemotherapy

Systemic chemotherapy has poor results in advanced carcinoid tumors. Most single agents show less than 10% activity. Only patients with aggressive disease, discomfort due to tumor bulk, impending bowel obstruction, or symptoms not controlled by other means should be considered candidates for chemotherapy.

The most active single agents are fluorouracil (5-FU), streptozotocin, doxorubicin, and dacarbazine (DTIC). Investigations of combination chemotherapy from single institutions favor the use of 5-FU + streptozotocin with reported response rates of approximately 33%. Larger trials combining the most active agents have failed to show any one combination to be superior in activity. Cooperative group studies have evaluated regimens in a randomized fashion. ECOG compared the use of 5-FU + streptozotocin (FS) versus 5-FU + Adriamycin (FA) in the treatment of advanced carcinoid. The response rates were 16% for FS and 13% for FA, but the median survival for the patients treated with FS was 24 months and only 16 months for those treated with FA. Side effects associated with chemotherapy can include nausea, vomiting, diarrhea, mouth sores, and fatigue. Current investigations are underway using taxanes. Enrollment in clinical trials when possible should be encouraged.

Alpha-interferon has been shown to have modest single agent activity in advanced carcinoid tumors. Side effects are similar to ''flu'' symptoms with fever, muscle ache, and headaches being the most common complaints. Long-term side effects of interferon include the development of autoimmune disorders. In one study a response rate of 47% was reported, but this consisted mostly of a decrease in symptoms and 5-HIAA levels, rather than a reduction in tumor bulk, which was seen in only 12%. Further studies from the Mayo Clinic using recombinant alpha-interferon reported a 39% reduction in 5-HIAA levels and a 20% objective tumor regression. Symptom relief was only transient and responses lasted less than 2 months. Results from trials combining alpha-interferon and 5-FU have been mixed. One trial showed no superiority with the two drugs compared to the single agents alone. Another study, using continuous-infusion 5-FU and alpha-interferon, reported a 73% overall delay in tumor progression, 47% objective response, and disease stabilization by CT scan in 33%. Improved symptoms were reported in 67%. The striking results may have been due to the way the drugs were administered. It also appears that the addition of low doses of alpha-interferon to octreotide in patients who are refractory or not responding to octreotide may be beneficial in reducing symptoms.

Hepatic-directed Therapy

In patients with advanced disease and excessive symptoms from hormonal excretion, hepatic artery occlusion can result in an objective regression in 65% of patients. Unfortunately these responses are of short duration, lasting on average about 6 months with the major complication rate as high as 12%. Both surgical and embolization procedures have been used. Combining hepatic artery occlusion with chemotherapy has been attempted. The number of responses increased to 81% and the median duration of regression was almost 20 months. Regression in tumor size was seen in 75% and reduction in 5-HIAA secretion in 83%. The results are promising but a randomized trial has not been performed and therefore patient selection may have played a large role. Investigation of chemoembolization and continuous hepatic arterial infusion of chemotherapy is presently being performed.

RADIATION THERAPY FOR CARCINOID TUMORS

The role of radiation therapy (RT) in the treatment of carcinoid tumors is not well defined. This may be due at least in part to the relatively low incidence of this neoplasm and the high rate of cure with surgical resection alone. However, there are several reports in the literature of responses to irradiation for the treat-

ment of both primary and metastatic disease. The reported outcome after radiation therapy is variable but may be a function of the variable natural history of the disease.

Radiation for Treatment of Primary Carcinoid

Since the mainstay of treatment is surgical resection, the role of radiation therapy alone for the treatment of the primary tumor site has been reserved for locally advanced disease or gross residual disease after resection. There are case reports of tumor regression and occasionally cure in these situations, but the number of cases is small. There is no clear evidence that combining chemotherapy with radiation in such cases is of any benefit. Further, there are no data to support (or refute) the use of radiation therapy for residual microscopic disease.

Primary sites that have been treated include the thymus, lung, abdomen, and pelvis. Several case reports of treatment with radiation therapy for thymic carcinoids document tumor regression on chest x-ray, but in all cases the tumor recurred. However, the doses of radiation were low and the patients were not treated with modern megavoltage linear accelerators. In two modern series reporting the treatment of bronchial carcinoids, one-half to two-thirds of patients had a response to radiation therapy with doses of at least 35 Gy and several complete responses were noted in those receiving over 50 Gy. In the largest reported series of unresectable primary abdominal and pelvic carcinoids, seven patients were treated with a median dose of 25 Gy to the whole abdomen with 80% achieving a complete or partial response and 50% maintaining permanent in-field control.

However, there is still no documented overall survival benefit to radiation therapy as primary treatment for localized carcinoid tumors. This phenomenon is not surprising as small tumors only > 2 cm have an extremely high rate of distant metastases. For instance, small bowel carcinoids > 2 cm have a distant metastatic rate of 86–95% and nearly all rectal carcinoids of that size present with metastases. Even appendiceal carcinoids, which have an excellent prognosis, present with metastases in 33% of cases where the primary tumor is > 2 cm. With such a high rate of distant metastases, it would be difficult to show any survival benefit when treating large, locally advanced tumors with radiation therapy. On the other hand, the prognosis for small resectable tumors is so good (5-year survival about 94%) that the addition of radiation therapy in that situation would have a negligible impact. Therefore, the role of radiation therapy in the treatment of localized carcinoid tumors is rather limited but probably should be considered in cases of unresectable disease when tumor mass effect may cause serious local symptoms if left untreated.

Radiation for Metastatic Disease

The case for radiation therapy as a palliative treatment for carcinoid tumors is stronger than as a primary therapy. Overall response rates to radiation therapy in terms of symptomatic relief range from 25 to 80%. Situations where palliative treatment should be considered include brain metastases, bone metastases, spinal cord compression, superior vena cava syndrome, and massive liver and/or abdominal metastases. There are no clear factors that predict response to RT, although it has been reported that tumors causing the carcinoid syndrome are less responsive than nonfunctioning carcinoid tumors.

In most cases, substantial palliation can be achieved when adequate doses of radiation therapy are delivered. In such cases, the overall response rate is approximately 80% with response measured by the relief of clinical symptoms or radiographic evidence of tumor regression or resolution. In the largest reported series, analysis of response was reported by site—epidural, brain, bone, and abdominal metastases. The relief of neurological symptoms was observed in 92% (12/13) of cases involving the epidural space with a median dose of 30 Gy. Pain relief from bony metastases was noted in 89% (8/9) of cases with a median dose of 40 Gy. Regression of brain metastases was observed in 63% (5/8) of cases with a median dose of 33 Gy with no patients experiencing progression of tumor, although the median survival of these patients was only 4 months. Regression of abdominal/liver metastases was noted in 76% (16/21) of cases with a median dose of 27 Gy. Case reports documenting the relief of bronchial obstruction and symptomatic superior vena cava syndrome have also been reported. It appears that the response rates to radiation therapy of carcinoid metastases are, in general, similar to those reported in larger series with cancers of various histologies and thus radiation therapy seems to be a reasonable treatment option for symptomatic patients.

The treatment techniques used for carcinoid tumors are dependent upon body site. In general, radiation therapy is limited by the tolerance of normal tissues surrounding the tumor site. There is no clear dose-response relationship for carcinoid tumors, although the mean dose of irradiation has been reported as significantly lower in nonresponders (about 20–30 Gy) as compared to responding patients (about 40–50 Gy). Anterior mediastinal masses (i.e., thymic carcinoids) can be treated safely to a total dose of 45–50 Gy in 180–200-cGy fractions using opposed anterior and posterior fields possibly in combination with obliqued fields. Bronchial/lung tumors can also be treated in a similar fashion with similar or even higher doses (60–64 Gy) if the amount of normal lung tissue in the field can be limited. Treatment of the pelvis can be done using standard three- or four-field techniques depending on the location of the tumor. The dose-limiting structure in the pelvis is small bowel with an approximate tolerance of

45–50 Gy in 180–cGy fractions although small areas may be boosted to 54 Gy. Treatment of massive abdominal disease including liver metastases may require whole abdominal radiation, which can be delivered via anterior and posterior fields to a total dose of no more than 25–28 Gy in 100–125-cGy fractions using posterior kidney blocks to limit the kidney dose to less than 18–20 Gy. In treating metastases to brain, bone, and spinal cord, a typical course of 30 Gy in 10 fractions seems to be adequate but can be modified depending on life expectancy.

Complications of radiation therapy are related to the treatment site. Acute side effects such as esophagitis from mediastinal treatment, and nausea, vomiting, and diarrhea from abdominopelvic therapy can be treated symptomatically and usually resolve shortly after therapy is completed. Long-term complications such as esophageal stricture, pneumonitis, myelitis, or bowel stricture/obstruction are rare if radiation is delivered carefully and doses are kept under normal tissue tolerance levels as suggested above.

In summary, the role of radiation therapy in the primary treatment of carcinoid tumors is limited to unresectable or residual disease that may cause significant symptomatology if untreated. However, radiation therapy is quite effective in the palliative treatment of metastatic disease with response rates comparable to other cancers when standard doses are used.

CLINICAL RESEARCH QUESTIONS

Since surgery for localized primary disease is so effective and chemotherapy for disseminated disease so ineffective, most clinical research is focused on developing new approaches to the management of metastatic disease (Table 6). Peptide receptor radiotherapy using the radiolabeled somatostatin analogue [^{111}In-DTPA-D-Phe^{1}]-octreotide has been preliminarily investigated as a new treatment modality for carcinoid tumors. A single case report described a patient who received a series of injections of [^{111}In-DTPA-D-Phe^{1}]-octreotide with a resulting decrease in tumor volume of about 20% after a total cumulative dose of 550 mCi. Transient declines in serum hormone levels were also noted. It was felt that with the devel-

Table 6 Future Directions for the Management of Recurrent or Metastatic Carcinoid

[^{111}In-DTPA-D-Phe^{1}]-Octreotide
^{131}I-MIBG
Chemoembolization
Hepatic infusional chemotherapy
Photodynamic therapy (PDT)

opment of radionuclides with higher energies and longer particle ranges than ^{111}In, this therapy could hold promise.

A promising study was published evaluating the therapeutic effect of ^{131}I-labeled metaiodobenzylguanidine (^{131}I-MIBG) and unlabeled MIGB in patients with carcinoid tumors. The radioactive treatment led to symptomatic improvement in 60% of patients for a median duration of 8 months. The unlabeled MIBG resulted in the same percentage of improvement but the median duration of response was only 4.5 months. Unlabeled MIGB was easier to administer than the radioactive MIBG, especially in very ill patients. Further investigation of this treatment should be completed.

Photodynamic therapy (PDT) is another modality that may be effective in treating some carcinoid tumors. PDT involves injecting photosensitizing drugs into the patient and exposing tissue to specific wavelengths of light in the presence of oxygen to form cytotoxic oxygen species. The photosensitizers are preferentially retained by tumor cells versus normal tissue. Patients with intraperitoneal tumors that can be grossly resected can be treated intraoperatively with PDT to eliminate any small areas of residual disease after gross resection. A phase II trial of adjuvant intraperitoneal PDT is now underway. PDT can also be used for intraluminal disease such as in the bronchi or rectum where a fiberoptic light source can be introduced endoscopically. This treatment could be used repeatedly to relieve obstructing masses or as primary treatment for superficial tumors as an alternative therapy for nonsurgical candidates.

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15

Hodgkin's and Non-Hodgkin's Lymphomas

Brian J. Czerniecki, Hung Q. Nguyen, Kevin R. Fox, R. Alex Hsi, and Eli Glatstein
University of Pennsylvania, Philadelphia, Pennsylvania

HODGKIN'S DISEASE

Hodgkin's disease (HD) is a malignant neoplasm of lymphoid tissue. Although HD is uncommon, occurring in approximately 7500–8000 individuals per year in the United States, the approach to treatment serves as a model for a curative strategy in the treatment of adult malignancy.

Etiology, Pathogenesis, Epidemiology

The diagnosis of HD relies on the presence of the Reed-Sternberg cell within a lymphoid milieu of variable appearance. The diagnosis cannot be made in the absence of such cells in a background of accompanying lymphoid tissue. The cause of HD is unknown, and the exact cellular origin of the Reed-Sternberg cell is unknown, although an infectious cause is suspected. Although indirect molecular evidence suggests the presence of Epstein-Barr virus (EBV) genomic material in some Reed-Sternberg cells, an undeniable relationship between EBV and HD has never been conclusively proven.

There is a bimodal age peak in the incidence of HD, with the first peak occurring in young adulthood, the second peak in adults after age 45, with the peak incidence in the third decade of life. Although the disease occurs in virtually all demographic and socioeconomic groups, it is more common in urban dwellers, in higher socioeconomic strata, and in identical twins, siblings, and close relatives of affected patients.

Clinical Presentation

Patients may present in a variety of ways, with the most common presentation being that of a painless nodal mass in the neck, and less commonly the axilla or groin. Insofar as two-thirds of patients may present with intrathoracic disease, the diagnosis may be heralded by persistent cough or dyspnea, leading to a chest x-ray showing mediastinal, or less often hilar, adenopathy, or rarely discrete pulmonary nodules.

The patient may manifest B symptoms, which are systemic symptoms including fever (>38°C), affecting nearly one-third of patients, drenching night sweats requiring a change in bedclothes, or loss of more than 10% of body weight in the 6 months preceding the diagnosis. Patients may manifest only one of these B symptoms, however. Pruritus, while neither common nor prognostically a B symptom, is important in that the differential diagnosis of unexplained pruritus should always include HD, particularly in young adults. While HD patients may have subtle defects in cellular immunity at the time of diagnosis, clinical manifestations of such defects are rare before the diagnosis is made.

Diagnosis and Workup

Biopsy of the affected tissue should make the initial diagnosis. When possible, the entire involved lymph node should be excised. Reed-Sternberg cells are rarely abundant in HD, and the pathologist must be provided with a reasonable quantity of lymphoid tissue to find such cells. For this reason, fine-needle aspiration or core biopsy of suspicious masses may not be adequate and cannot be routinely recommended when HD is in the differential diagnosis. When patients are found to have incidental or symptomatic mediastinal or hilar masses on chest x-ray, a careful examination of the neck and axillae is required, and any enlarged peripheral nodes should be biopsied first in an attempt to spare the patient an unnecessary invasive mediastinal procedure.

The treatment of HD is somewhat stage-dependent, and thus the staging evaluation must be exhaustive. This should include, after thorough physical examination, routine laboratory studies including complete blood count, liver function tests, sedimentation rate, and electrolytes and tests of kidney function. Computed axial tomography (CAT) scans of the chest and abdomen, and usually bone marrow biopsies, should be performed. The traditional staging evaluation, although under question in many centers, requires that if the clinical presentation is above the diaphragm, which is usually the case, and if the abdominal CAT scan is normal, then a bipedal lymphangiogram should be done. If this study is nondiagnostic, a staging laparotomy should follow. Ongoing research trials are questioning the need for staging laparotomy, and this practice has been aban-

doned in many centers. The only reason to perform a staging laparotomy is if the resultant pathological findings will change therapy.

The patient is thus staged I–IV and A or B, according to the Ann Arbor Staging classification (Table 1). Approximately 25–35% of patients with disease confined to sites above the diaphragm after thorough radiological staging will have occult disease found at staging laparotomy.

The role of gallium scanning remains provocative in the evaluation of HD, and although gallium scanning should be considered in the staging workup, it should not be considered a staging procedure per se. Instead, sequential gallium scans may be useful, when the pretreatment scan is positive or gallium-avid, in assessing response to therapy. Conversion from positive to negative may predict a good outcome in most patients, while failure to attain gallium negativity may predict relapse.

Surgical Management

The surgeon's primary role in HD is to provide tissue for pathological diagnosis and to perform staging laparotomy in selected situations.

Lymph Node Biopsy

Biopsy for the initial diagnosis of HD requires adequate tissue for pathological examination. Asymptomatic lymphadenopathy is the most common presentation in HD involving most frequently cervical followed by axillary and then inguinal nodes.

Fine-needle aspiration (FNA) biopsy of an enlarged node is a quick and effective screening procedure that can be performed in an office setting. Its success, however, is primarily dependent on having adequate tissue and an experienced cytopathologist. In the patient with asymptomatic adenopathy, this technique is most useful in differentiating an inflammatory etiology from meta-

Table 1 Ann Arbor Staging Classification

Stage I	Single lymph node area involved
Stage II	Two or more sites of nodal involvement on same side of diaphragm
Stage III	Involvement of nodal sites on both sides of diaphragm
Stage IV	Involvement of any extranodal site (e.g., liver, lung, bone)
Subheadings	
A	Absence of B symptoms
B	Presence of B symptoms
E	Involvement of a single extranodal site

static cancers, i.e., adenocarcinoma or recurrent lymphoma. Its role in diagnosing primary HD is usually limited owing to the inability to obtain adequate tissue.

Excisional lymph node biopsy is the most commonly performed procedure to diagnose primary HD. The technique can be done under local anesthesia with or without intravenous sedation. Complications of excisional biopsy include seroma formation and wound infection while injury to the adjacent vital structures is rare.

The excisional biopsy is performed similarly for all superficially located nodes. An incision is made directly above the enlarged node. This incision is deepened into the subcutaneous tissue and the index node identified. The node should be excised in its entirety to preserve the original architecture and then sent fresh in saline with appropriate labeling and orientation for the pathologist. Meticulous hemostasis as well as ligation of both afferent and efferent lymphatics should be achieved prior to closure. Familiarity with the local anatomy is a prerequisite to avoid injuring adjacent neurovascular structures.

Staging Laparotomy

The role of staging laparotomy continues to be under scrutiny, although this is still considered the most accurate method of identifying occult abdominal disease. The H6 trial of the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Group (EORTC) demonstrated that freedom from disease progression and survival were similar in clinical and laparotomy staging for favorable HD patients. More recently, the Stanford G1 trial showed that VBM (vinblastine, bleomycin, methotrexate) plus involved-field radiation is equivalent to subtotal lymphoid irradiation for nonlaparotomized favorable clinical stage I and II disease. Thus with the continued evolution of more effective treatment strategy for HD, it is conceivable that future staging laparotomies will not be necessary.

Despite the continued controversy of staging laparotomy and increasing accuracy of nonoperative staging, there continues to be a 30% discrepancy between clinical and pathological staging, thus justifying the procedure. Laparotomy, however, is no longer routinely done in children. Factors that may contribute to downstaging of clinical stage III and IV patients include lack of B symptoms and mixed cellularity or lymphocyte depletion histology. Currently staging laparotomy is considered beneficial for any patient where a change in the clinical staging would result in an alteration of subsequent treatment. These are patients with clinical stage IA and IIA disease who lack hilar disease and whose mediastinal involvement is less than one-third of the chest diameter. Classic staging laparotomy for HD consists of splenectomy, liver, lymph node, and bone marrow biopsies along with bilateral oophoropexy.

Prior to any planned laparotomy, strong consideration should be given to administering Pneumovax to avoid the rare dreaded overwhelming postsplenectomy sepsis (OPSI). The actual laparotomy requires a systematic approach and begins with a midline incision from the xiphoid to the umbilicus. Upon entry into the peritoneal cavity, careful inspection of all abdominal viscera is made including bimanual palpation of the liver, bowel, mesentery, and major nodal groups. The liver biopsy is performed early to allow adequate time for hemostasis. This can be done via a wedge biopsy of one or both lobes followed with a Trucut needle biopsy for deeper tissue. The spleen is next mobilized into the operative field by dividing the gastrosplenic, splenocolic, lienorenal, and phrenosplenic ligaments. Vascular control can be obtained by individually ligating and dividing the short gastrics and the splenic vessels. Splenic hilar nodes should be searched for and sampled if not included in continuity with the spleen. Accessory spleen should also be searched for and removed. The splenic pedicle is marked with titanium clips for future reference.

The nodal stations likely to be involved in HD include splenic hilum, celiac, periportal, and para-aortic nodes. Each nodal group should be sampled, clearly marked, and sent separately in sterile saline. Likewise, any abnormal nodal group identified by preoperative lymphangiography should also be biopsied. Nodes along the hepatic artery and celiac axis are accessible by incising the gastrohepatic ligament. Periportal nodes are accessed by incising the lateral duodenal attachments and reflecting the duodenum medially. Para-aortic and celiac nodes are exposed after reflecting the transverse colon cephalad and the small bowel laterally to uncover the retroperitoneum overlying the aorta. The posterior peritoneum is incised and the para-aortic nodes are sampled. This peritoneum should be reclosed at the completion of nodal sampling. Finally, metal clips are used to identify each sampled nodal station for future reference.

Bilateral oophoropexy is now mostly reserved for patients suspected of having iliac nodal disease and those who wish to preserve fertility. Both ovaries can simply be attached to the uterus with a single transfixing, nonabsorbable suture.

Common perioperative complications of staging laparotomy are similar to other abdominal operations including upper respiratory complications and wound infection. The most common serious long-term complication is small bowel obstruction, which in most cases can be managed nonoperatively. Overwhelming postsplenectomy sepsis associated with staging laparotomy patients has been reported to be 6% in one study with the highest risk recorded in the first 5 years. This is compared to 0.3% of the general population. Preoperative administration of the polyvalent Pneumovax, however, has limited OPSI to the occasional high-risk patients with advanced disease (stage III or IV) or patients receiving combined modality therapy. Mortality directly relating to staging laparotomy occurs rarely at 0.4%.

Staging Laparoscopy

Since its introduction in the early 1900s, continual refinements have led to a plethora of clinical applications in laparoscopic surgeries over the past decade. Although laparoscopic procedures can be performed in just about every organ within the abdominal cavity, laparoscopic staging of lymphoma has yet to gain wide acceptance. A reason for this is the lack of any controlled comparison between staging laparoscopy and staging laparotomy. Thus the accuracy of staging laparoscopy cannot be truly determined. Proponents of laparoscopic surgery, however, advocate its use given the advantage of less postoperative pain, shorter hospitalization, and a quicker recovery to preoperative functional status. Another potential application for laparoscopy is in the second-look evaluation of recurrent lymphoma, although guidelines for this role have not been clearly defined. The principal contraindication to diagnostic laparoscopy is the inability of the procedure to contribute further information to the staging of the disease process. Relative contraindications include dense adhesions, bowel obstruction, and the patient's comorbid conditions.

Various techniques of port placement have been described for staging laparoscopy. One method involves placing a 10-mm camera port at the umbilicus while two 12-mm operating ports are placed in the midline between the umbilicus and the zyphoid process. Two other operating 12-mm ports are placed in a transverse line between the umbilicus and the anterior superior iliac spine. After induction of pneumoperitoneum, the peritoneal surface and omentum are initially examined for evidence of metastases. The liver can either be biopsied with an endoscopic needle or a wedge resection can be done with an Endo-GIA. The splenectomy is begun with division of the inferior attachments and proceeding cephalad. Hilar and short gastric vessels are divided sequentially with the Endo-GIA using vascular staples. The posterior attachments are divided last and the spleen can now be freely mobilized. Splenic removal is done by placing the spleen within a nylon specimen bag and removing it through extension of a midline incision. Lymphadenectomy can now be performed through this extended incision. Alternatively, the spleenic removal can be deferred until completion of the lymphadenectomy to preserve the pneumoperitoneum. Pelvic, mesenteric, and iliac nodes are easily accessible to the laparoscope with proper patient positioning and/or additional port placement for retraction. Retroperitoneal and periaortic nodes along with nodes surrounding the stomach and pancreas are more technically challenging. A careful review of the preoperative imaging studies would help in localizing the specific areas that would provide optimal yield.

Despite its unproven benefits, laparoscopic staging in lymphoma patients will continue to be an attractive alternative to formal celiotomy. The experience with this technique is still limited and its true efficacy would need to be proven in a controlled trial before its use can be considered a standard.

Medical Management

The treatment of early-stage HD is undergoing a general reevaluation in ongoing clinical trials that are questioning the role of radiation therapy alone, which for decades has been the mainstay of treatment in such patients. Traditional therapeutic approaches, however, utilize radiation therapy alone in early-stage patients (stage IA, IB, or IIA). Treatments are given to total doses of 3500–4500 cGy utilizing supervoltage sources, given to large fields encompassing many nodal groups. The mantle field includes the axilla, supraclavicular, infraclavicular, cervical, mediastinal, and hilar nodes, while the para-aortic field includes the para-aortic nodes and the splenic hilum, or the whole spleen if it has not been surgically removed. These two fields of radiation are usually given sequentially in early-stage patients.

In contrast, patients with stage IIIB or IV disease should be treated with chemotherapy. The standard chemotherapy for the treatment of HD of this stage is either ABVD alone, or some combination of MOPP and ABVD or MOPP and ABV given in an alternating fashion. Recent clinical trials suggest that MOPP and ABVD given in alternating monthly fashion is equivalent to the MOPP/ABV hybrid, while a separate clinical trial suggests the equivalence of ABVD alone with alternating monthly cycles of MOPP and ABVD. The true equivalence of ABVD to MOPP/ABVD combinations awaits the completion of confirmatory trials. Many clinicians have accepted ABVD as the new standard chemotherapy regimen for advanced-stage HD given the lower incidence of gonadal dysfunction and lower risk of long-term myelodysplastic or leukemic complications (Table 2).

Patients with stage IIB or IIIA disease may be treated with either radiation therapy alone, chemotherapy alone, or both, depending upon institutional habits, severity of illness, and bulk of nodal disease. Furthermore, the use of both chemotherapy and radiation therapy together, so-called combined-modality therapy, is gaining wider acceptance for the treatment of early-stage disease. This approach affords the possibility of smaller fields and doses of radiation therapy, thus reducing the possibility of late complications of treatment. Although the comparison of such combined-modality therapy (in clinically staged patients) to conventional radiation therapy alone (in pathologically staged patients) is being evaluated in

Table 2 Hodgkin's Disease: Chemotherapy Regimens

MOPP	Nitrogen mustard, vincristine, procarbazine, prednisone
ABVD	Adriamycin, bleomycin, vinblastine, DTIC
MOPP/ABVD	Alternating monthly treatments with the above
MOPP/ABV hybrid	Alternating weekly treatments with above, excluding DTIC

randomized trials, many institutions have accepted the combined use of abbreviated courses of ABVD with adjunctive radiation therapy in the treatment of clinically staged IA–IIB patients. A summary of treatment recommendations by stage is given in Table 3.

Radiation Management

Radiation therapy and combination chemotherapy play the central role in the management of HD today. The development of modern irradiation technique including the use of megavoltage linear accelerators, pretreatment simulation and portal imaging, as well as more precise radiographic and surgical staging with CT scan, bipedal lymphangiography, and staging laparotomy, has resulted in a high proportion of patients being cured with radiation therapy either alone or in combination with chemotherapy.

Early-Stage HD

Radiation therapy (RT) alone is an effective curative therapy for early (stage I, II) HD. In patients with a negative staging laparotomy who undergo mantle and para-aortic field irradiation, the 10-year overall survival rate is nearly 90% and the 10-year relapse-free survival rate is 75–80%. It is important to make a distinction, however, between the results of patients who are pathologically staged and those who are clinically staged as the clinically staged patients have an approximately 30% risk of harboring occult infradiaphragmatic disease. The ability to identify which subgroups of clinically staged patients are at low risk and high risk for occult infradiaphragmatic disease has been the subject of several studies. Data from Stanford and the Joint Center for Radiation Therapy suggest that patients in the following clinically staged subgroups have a low (<10%) risk of occult infradiaphragmatic involvement: (1) stage I with mediastinal disease only, (2) stage IA women, (3) stage IA men with lymphocyte-predominant subtype, and (4) stage IA men with ''high neck disease'' only. It has been suggested that

Table 3 Treatment Options for Hodgkin's Disease

Radiation therapy alone
Laparotomy-staged IA, IB, IIA, some IIB and IIIA
Non-laparotomy-staged IA, if nonbulky disease, particularly female
Chemotherapy alone
Any stage IIIB or IV, some IIB or IIIA
Chemotherapy and radiation therapy in combination
Bulky mediastinal masses, bulky stage III, possibly any early stage in non-laparotomy-staged patients

patients in these subgroups may be treated with RT alone without undergoing staging laparotomy and still achieve excellent overall and relapse-free survival rates. Currently, however, the standard of care remains surgical staging if RT alone is to be used as the only therapy for early-stage HD.

The standard treatment fields for HD are the mantle and para-aortic fields. The mantle field includes the cervical, supraclavicular, infraclavicular, axillary, mediastinal, and hilar lymph node regions and utilizes customized blocks to protect uninvolved tissues such as the lung. The para-aortic field includes the para-aortic nodes and splenic hilum or whole spleen if a splenectomy has not been performed. Although total nodal irradiation (mantle + para-aortic + pelvis ± inguinal nodes) has been used, subtotal nodal irradiation (mantle + para-aortic nodes) has been shown to be equally effective given the low risk of pelvic failure in HD. In addition, the omission of the pelvic and inguinal fields decreases bone marrow toxicity and risk of sterility.

The use of the mantle field alone, however, is more controversial. Both the EORTC and Joint Center for Radiation Therapy have shown that patients who meet certain criteria can achieve similar survival rates with mantle field irradiation alone compared to those undergoing subtotal nodal irradiation. The Joint Center criteria included pathological stage IA/IIA disease, nodular sclerosing or lymphocyte-predominant histology, and no disease below the carina. The EORTC criteria are the same with the additional requirement of age less than 40 and sedimentation rate less than 70. The use of the mantle field alone for a select group of clinical stage I and II patients is also currently under investigation by the EORTC.

The optimal dose of megavoltage radiation therapy that provides local control of HD has not been established with certainty. In the 1960s, Kaplan reviewed data from several series and found that local control increased with increasing dose delivered. Local control for doses above 40 Gy was nearly 99%. This analysis provided the rationale for the doses used in HD for many years. However, Kaplan's review included patients treated with kilovoltage and were staged in the pre-CT era raising the question of the dose in the modern era of megavoltage linear accelerators and CT scans. Indeed, more recent studies indicate that many patients can be cured with doses as low as 30–35 Gy. However, identification of which patients respond to lower doses is at this point unclear. Since a dose of 40–45 Gy in 180-cGy fractions using modern radiation technique is effective with acceptable morbidity, this still remains a reasonable dose recommendation.

In the last decade, investigations have been made to incorporate chemotherapy into the treatment of early-stage HD. Two large, randomized trials evaluated treatment for pathological stage I and II patients with RT alone (mantle and para-aortic fields) versus 6 months of MOPP chemotherapy. With 8-year follow-up, no significant differences were noted in freedom from relapse, although overall survival was found to be significantly better in the RT arm owing mainly to a

higher salvage rate for RT failures versus chemotherapy failures. Several studies comparing combined-modality therapy regimens (RT and combination chemotherapy) versus RT alone are underway incorporating lower chemotherapy doses and smaller RT fields in an attempt to reduce long-term complications of treatment without compromising cure rates. Further follow-up is necessary to determine the effectiveness of these approaches.

Advanced-Stage HD

The role of RT in advanced-stage HD is mainly as an adjunct to chemotherapy. Although some early reports suggested that a subset of patients with nonbulky pathological stage IIIA-1 disease with nodular sclerosing or lymphocyte-predominant histology could be treated with RT alone, longer follow-up showed a high rate of relapse. Most recommend chemotherapy as part of primary therapy even for these patients. For stage IIIB and IV patients, combination chemotherapy is standard primary treatment. The rationale for adding RT to chemotherapy lies in the fact that most relapses after chemotherapy occur in the original site(s) of disease. Thus involved-field RT (usually defined as the regions of gross involvement and the first echelon nodes beyond those regions) may improve local control. In addition, RT may help to convert some partial responders to chemotherapy into complete responders after combined therapy. There is no conclusive evidence, however, that RT in complete responders to chemotherapy is of any significant benefit. A final argument for the use of adjuvant RT in advanced HD is the possibility of reducing chemotherapy doses when used in combination with RT. A study by the National Cancer Institute of Canada showed that three cycles of MOPP and RT (20–30 Gy to a mantle and para-aortic field) resulted in slightly improved overall survival compared to six cycles of MOPP alone for stage III and IV patients. This therapeutic approach requires further investigation.

Irradiation Technique

The optimal technique for delivery of RT involves the use of opposed anterior and posterior fields, reproducible patient positioning, simulation, and careful treatment planning. Modern treatment tables and gantry rotation allow for treatment from the anterior and posterior positions without flipping the patient between the supine and prone positions. Patients are treated in the supine position with head extended and arms either placed above the head or at the sides (akimbo). If the arms are placed above the head, the axillary lymph nodes are pulled away from the chest wall laterally. Care must be taken to insure that these lymph nodes are not covered when drawing humeral head blocks. During simulation, the borders of the mantle and para-aortic fields are set. For the mantle field, the superior border lies at the tragus extending anteriorly just below the jaw line. Inferiorly, the border is placed at approximately the T10/T11 vertebral body interspace. The lateral borders should be wide enough to cover all the axillary

tissue. The top of the para-aortic field is matched to the bottom of the mantle field and extends downward to approximately the L4/L5 interspace. The lateral borders should cover the para-aortic lymph nodes. If the patient has undergone bipedal lymphangiography, residual contrast dye will remain (for up to 6 months) and this nodal group is easily seen under fluoroscopy during simulation. The splenic pedicle is also included in the upper portion of the para-aortic field although some feel this is unnecessary if the spleen is negative at laparotomy as this is not a commonly observed failure pattern. Typical mantle field blocks include humeral head blocks, lung blocks, and wing blocks that extend out laterally from the lung blocks to protect soft tissue below the axilla (which is particularly important in limiting dose to breast tissue in women). Additional blocks to cover the cervical spine, larynx, and lower mediastinum (heart) can be added during treatment depending on the original sites and extent of disease. A small partial transmission block can be added at the bottom of the mantle field to protect the spinal cord from dose overlap at the junction of the mantle and para-aortic fields.

Complications

Complications from RT for HD include xerostomia, hypothyroidism, Lhermitte's syndrome, cardiopulmonary toxicity, and second malignancies. Xerostomia can gradually improve over a period of months after RT and is treated symptomatically. Dental caries can develop as a result of xerostomia but can be minimized by fluoride supplementation and careful dental care. Hypothyroidism occurs in approximately one-third of patients receiving mantle field irradiation and can be treated with hormone replacement therapy. Lhermitte's syndrome is an acute, transient radiation myelopathy characterized by shock-like paresthesias down the back and extremities when the neck is flexed. Approximately 10–15% of patients are affected after mantle irradiation. This phenomenon occurs typically 6 weeks to 3 months after RT and is self-limited, resolving in weeks to months. Cardiopulmonary toxicity (pneumonitis, pericarditis, pericardial effusion, and accelerated coronary artery disease) is less common with modern RT techniques, but still represents a potential problem especially with the use of chemotherapeutics such as bleomycin and adriamycin. Symptomatic pneumonitis may occur in up to 5% of patients after mantle irradiation and must be treated with a prolonged steroid taper. The risk of second malignancy (solid tumors and leukemia) has been reported as approximately 7% at 15 years. The most common solid tumor is breast cancer.

Special Treatment Situations

Patients with large mediastinal masses that encompass more than one-third of the transverse chest diameter, although technically clinical stage I or II in most cases, are not suitable candidates for radiation therapy alone, and thus should

avoid laparotomy, and should be treated with some combination of chemotherapy followed by radiation.

Patients who relapse after radiation therapy alone may, in turn, receive conventional chemotherapy with curative intent. Patients who relapse after combination chemotherapy will usually be treated with second-line or salvage chemotherapy using drugs different from those initially employed. Patients who respond to such salvage chemotherapy may be referred for high-dose chemotherapy followed by stem cell or bone marrow rescue (or transplantation). Limited series of patients suggest that more than 50% of patients responding to salvage chemotherapy may enter long-term remission with this technique. There is no evidence to suggest the superiority of allogeneic transplantation to autologous transplantation in HD patients.

Treatment Goals

The goal of treatment in HD is cure. With conventional radiotherapeutic technique, approximately 80% of early-stage patients (stage I or II) will be cured. Early results of clinical trials suggest that combined-modality therapy or chemotherapy alone in patients who are early-stage but who did not undergo laparotomy may be equally effective. Patients with more advanced stage (IIIB–IV) disease may be cured up to 60% of the time by first-line chemotherapy alone, but this figure drops considerably for patients over the age of 50.

Late Complications

Both chemotherapy and radiation therapy may cause sterility, or may cause some risk of acute leukemia. Acute myelogenous leukemia or myelodysplasia may occur in up to 10% of patients, particularly those who received MOPP chemotherapy, and may not manifest itself until a decade after treatment. The exact contribution of radiation therapy to leukemia risk is uncertain. Sterility is virtually assured in men receiving MOPP chemotherapy, but is considerably less likely in men receiving ABVD alone. Sterility in women is closely tied to age in women, and is likely to occur in women receiving MOPP after the age of 30.

Hypothyroidism, either clinical or chemical, may occur in more than 30% of patients who received mantle radiation therapy, and patients should undergo regular measurements of serum thyroid stimulating hormone (TSH) after completion of such therapy.

The occurrence of second tumors, including cancers of lung, stomach, breast, skin, bone, and sarcomas, is increased in patients who received radiation therapy. A latency period of more than 10 years may occur before the appearance of such tumors, and the incidence may continue to rise beyond this point. Breast cancer risk may be markedly increased in women treated during childhood, adolescence, or before age 30 and should provoke the institution of aggressive screen-

ing programs beginning at age 30. Premature development of coronary artery disease has rarely been reported in young adults after receiving mantle radiotherapy. The present trend in clinical oncology away from conventional radiotherapeutic approaches in HD is a direct result of concern regarding these late effects.

NON-HODGKIN'S LYMPHOMA

The non-Hodgkin's lymphomas (NHL) are a diverse group of lymphoid neoplasms, which may arise anywhere in nodal or nonnodal tissue. Some types of NHL bear little similarity to others and do not lend themselves to easy categorization. Most adult NHL in the United States are of B-cell origin, but lymphomas of T-cell origin, macrophage/monocyte origin, and undifferentiated lymphomas are well described.

Etiology, Pathogenesis, Epidemiology

Although the etiology of certain types of lymphoma is known, such as the association of EBV and African Burkitt's lymphoma, and the association of virus HTLV-T with T-cell leukemia/lymphoma syndrome seen in Japan and the Caribbean, most lymphomas in the United States are of unknown cause. The association between *Helicobacter pylori* infection and low-grade lymphomas of the stomach has been well described. An increased risk of NHL has been reported in patients exposed to a variety of environmental agents, including phenoxyacetic acid herbicides, permanent hair dyes, organophosphates, and ionizing radiation from nuclear mishaps.

A variety of immunodeficiency states are associated with increased risk of the development of NHL. This increased risk is seen in congenital immunodeficiency states such as ataxia-telangiectasia and severe combined immunodeficiency disease, rheumatological diseases (Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, sprue, Hashimoto's disease), and the immunodeficiency state associated with HIV infection. Iatrogenic immunodeficiency states, particularly post-organ-transplant immunosuppression, are known to place patients at higher risk of NHL. Chromosomal translocations of a predictable type have been recognized in certain NHL, including translocations between chromosome 8 and either chromosomes 14, 2, or, 22 in Burkitt's lymphoma, and translocations between chromosomes 14 and 18 in follicular (low-grade) lymphomas. In general, these translocations involve the apposition of immunoglobulin light-chain or heavy-chain genes and a variety of regulatory genes such as *MYC*, *BCL*-1, and *BCL*-2. The etiological agent in effecting these translocations remains unknown.

Unlike HD, the NHL account for more than 45,000 cases in the United States per year, and this figure is increasing steadily. There is no bimodal age

peak for NHL, and they can occur at any time after age 1 year. Their peak incidence seems to be in the fifth and sixth decades of life, with the overall average age at diagnosis of 42 years. The increased incidence of NHL has been observed particularly in adults over 60 years of age, although the incidence is rising in all age groups. The increased risk of NHL in HIV-infected patients is accounting for much of the perceived increase in NHL.

NHL: Clinical Presentation, Diagnosis, and Staging Evaluation

The diversity of these lymphomas with respect to mode of presentation and type does not permit easily recognized patterns of presentation. Although NHL may present as painless adenopathy as in the case of Hodgkin's disease, NHL may arise virtually anywhere in the body. Presentation in extranodal sites such as brain, orbit, skin, sinus, and any visceral structure helps to differentiate NHL from HD. Furthermore, NHL may present in nodal sites not often seen in HD, such as Waldeyer's ring, mesenteric nodes, and lymphoid patches in the gastrointestinal tract. Waldeyer's ring involvement may herald simultaneous involvement of the gastrointestinal (GI) tract in 20% of cases. As in HD, B symptoms of fever, night sweats, or weight loss may be present, but are the exception rather than the rule.

The histological diversity of NHL and the reliance of the pathologist on nodal architecture as well as cell type mandate that incisional or excisional tissue biopsy of abnormal nodal sites or affected organs is always preferable to fine-needle aspiration. Core needle biopsy is occasionally helpful, but the optimum diagnosis is usually obtained by surgical removal of the greatest quantity of tissue within the confines of good clinical sense.

When the diagnosis is established, staging procedures are then undertaken. In addition to a history directed toward possible etiological factors (particularly HIV risk factors), B symptoms, and general organ-specific complaints, a thorough physical examination including inspection of Waldeyer's ring, all nodal sites, skin, and the testes is required. Routine laboratory studies, including complete blood count, liver chemistries, LDH, renal function, and calcium are required. CAT scans of chest (or alternatively chest-x-ray) and CAT scans of abdomen and pelvis should be obtained, as should bilateral bone marrow biopsies. Staging laparotomy is never required in the evaluation. Additional studies such as bone scans, magnetic resonance imaging (MRI) scans, and lumbar puncture should be reserved for special situations and do not constitute part of the routine staging evaluation. The value of gallium scans as a predictor of response to therapy appears to be similar to that seen in HD, with patients who convert from gallium-avid to gallium-negative after therapy tending to have a lower rate of relapse.

Staging of NHL

Treatment of NHL is much less driven by stage than by histological type. Nonetheless, the Ann Arbor Staging classification is usually ascribed to NHL (see section on HD), although this system lacks clinical relevance under many circumstances. Recently, a new international staging system has been devised specifically for patients with aggressive lymphomas (see Table 4). In this system, patients are evaluated according to Ann Arbor stage, age, performance status, serum LDH, and the number of involved extranodal sites. Age $>$ 60, a performance status greater than two, an elevated serum LDH, stage greater than II, and more than one extranodal disease site are considered to be negative prognostic factors, placing patients at greater risk for treatment failure. As expected, failure to achieve remission or survival increases with increasing numbers of these risk factors.

Pathological Classification of NHL

The Working Formulation for lymphoma classification, developed in 1982, remains the mainstay of pathological classification, although it fails to encompass many unusual types of lymphoma and does not take into account the molecular and immunochemical diagnostic aids used by modern pathologists. A new classification, the REAL classification, was recently introduced and attempts to reorganize lymphoma classification according to these diagnostic methods. Nonetheless, clinicians continue to rely heavily on the Working Formulation in making clinical decisions. A simplified version of the Working Formulation is presented in Table 5, and provides a framework for treatment considerations. For purposes of this text, one should consider lymphomas as low, intermediate, or high grade, as most treatment paradigms are chosen based on this distinction.

Table 4 NHL Staging System

International staging system—adverse prognostic features
Age $>$ 60
Ann Arbor stage $>$ II
Performance status $>$ 2
Elevated LDH
Extranodal involvement $>$ 1 site
Applies to aggressive lymphoma
Outcome worsens with higher number of adverse prognostic factors

TABLE 5 NHL Pathological Classification

Low-grade NHL
Small lymphocytic (5%)
Follicular, small cleaved cell (25%)
Follicular, mixed small cleaved, and large cell (15%)
Intermediate-grade NHL
Follicular, large cell (5%)
Diffuse, small cleaved cell (10%)
Diffuse, mixed small cleaved, and large cell (10%)
Diffuse large cell (cleaved or noncleaved) (30%)
High-grade NHL
Diffuse large cell, immunoblastic type (<5%)
Lymphoblastic (<5%)
Small, noncleaved cell (Burkitt or non-Burkitt) (<5%)

Surgical Management

Extranodal NHL occurs most commonly within the gastrointestinal tract where 60% are localized to the stomach followed by small bowel and colon. Most of these lymphomas are B cell in origin. The symptoms are usually vague and a preoperative diagnosis is often not available. Unlike HD, the surgical management of gastrointestinal NHL is more involved. In addition to obtaining tissue for diagnosis, the surgeon is more frequently faced with a lymphoma-related complication.

Gastric NHL

Primary gastric lymphoma (PGL) is the NHL that is localized to the stomach. The peak incidence occurs after the age of 50 with a male-to-female predominance of 2:1. The etiology remains unknown although patients with immunodeficiency disorders tend to be more at risk. An association between *H. pylori* and a subtype of gastric lymphoma, the mucosa-associated lymphoid tissue (MALT), has also been suggested. Eradication of the *H. pylori* infection has in some instances resulted in complete regression of the lymphoma.

Abdominal pain is the most frequent PGL symptom followed by nausea, vomiting, anorexia, and weight loss. Since PGL originates within the submucosa and spreads by submucosal extension, its diagnosis often eludes radiographic and endoscopic detection. Multiple deep biopsies along with brush cytology have been suggested to improve diagnostic yield. PGL is classified histologically by the Working Formulation and staging is stratified according to the Ann Arbor scheme as described above.

Surgical resection has been the traditional primary mode of therapy, where a curative resection requires removal of all gross disease along with the regional lymphatics and omentum. Accurate staging can also be performed intraoperatively by evaluating the extent of local involvement and ruling out intra-abdominal spread. Resection margins should be confirmed histologically. Since most gastric lymphomas localize to the distal third of the stomach, a subtotal gastrectomy is generally performed. Proximal disease may necessitate a total gastrectomy. Continuity is reestablished with a Roux-en-Y gastrojejunostomy. Radiation as adjuvant therapy is reserved for positive surgical margins, gross residual disease, or as salvage therapy for local recurrence. Various multiagent chemotherapeutic regimens have also been proposed for all patients with gastric lymphoma as well as patients at risk for relapse outside of the abdomen. It follows that in stage IE and IIE disease, a curative resection is performed when possible followed by postoperative chemotherapy with or without radiation. Stage IIIE and IVE patients who present with a gastric complication are treated first by attempted resection and then adjuvant therapy. Asymptomatic stage IIIE and IVE patients are treated primarily with chemoradiation while surgery is reserved for complications or persistent local disease.

Small bowel NHL

In the Western world, about 30% of the GI lymphomas are localized to the small bowel. Two-thirds of the primary small bowel lymphomas are of the B-cell type while the rest consist of T-cell tumors. Most of these tumors tend to high-grade and localize to a single site. T-cells tumors, however, are twice as likely to be multifocal. Common sites of occurrence include distal ileum, proximal ileum, and jejunum. The B-cell lymphomas tend to be exophytic or annular, while T-cell lymphomas ulcerate or form strictures. This possibly explains the higher perforation rate seen in the latter group versus their B-cell counterpart.

Presenting symptoms of small bowel lymphoma include abdominal pain, anorexia, weight loss, bowel obstruction, and abdominal mass. Less frequent symptoms that have been described are diarrhea, nausea and vomiting, and GI bleeding. Incidental finding is seen only in 3% of the cases. Small bowel lymphoma is rarely diagnosed preoperatively as these patients are most often explored for some acute abdominal conditions. Histological classification and staging are similar to the gastric lymphoma as described previously.

Treatment with curative intent requires resection of all gross disease with negative margins and the associated mesenteric lymphatic drainage. Continuity is reestablished by primary anastomosis. Large obstructing tumor that cannot be resected can be bypassed and left in situ to be treated by other modalities. Similar to gastric lymphoma, combined-modality treatment using chemoradiation as an adjunct to surgery appears to improve survival compared to noncurative resec-

tion. Stage of disease and resection for cure have been identified as independent predictors for survival.

Unusual Presentations of NHL

Pancreatic Lymphoma. Primary pancreatic lymphoma is an uncommon cause of pancreatic mass, which invariably is reported to represent 1–2% of patients with NHL. There are no specific distinguishing symptoms or radiographic features. However, the most prominent symptoms appear to be abdominal pain, weight loss, anorexia, and nausea. Surprisingly, jaundice is present in only one-third of the patients. A palpable abdominal mass is the most frequent physical finding.

Traditionally, surgery has been advocated to establish diagnosis while combination chemotherapy is used as the primary mode of treatment. More recently, the role of surgical resection or tumor debulking was again questioned in view of improved morbidity and mortality of pancreatectomy. Patients presenting with obstructive jaundice can undergo percutaneous decompression and be treated initially with cyclophosphamide and prednisone until resolution of the jaundice. Completion of treatment is continued with a doxorubicin-based regimen.

Thyroid Lymphoma. Lymphoma involvement of the thyroid comprises less than 2% of all thyroid malignancies and these are predominantly intermediate-grade NHL. This uncommon tumor should always be considered in the setting of a rapidly growing goiter or in the presence of Hashimoto's-induced hypothyroidism. As with the approach to all solitary thyroid nodules, a thorough history and physical examination followed by appropriate laboratory and imaging studies are mandatory. Fine-needle aspiration (FNA) biopsy can sometimes provide a diagnosis. When FNA is equivocal, surgical excision in the form of a lobectomy is required to obtain adequate tissue for histological confirmation. Staging can be performed with CAT scan or MRI examination.

Systemic chemotherapy with external-beam radiation to the neck and mediastinum is currently preferred in the treatment of thyroid lymphoma as even stage IE or IIE disease can harbor metastases. As survival is unaffected by the extent of resection, surgery is primarily relegated to performing biopsy or debulking a large compressive tumor mass.

Complications Relating to Treatment of NHL

Bleeding and Perforation. Surgery as emergency treatment of gastrointestinal lymphoma is occasionally required. The risk of bleeding and perforation from radiation and chemotherapy treatment has been variably reported at 10–20% and 0–20%, respectively. Contributing factors include ulceration and full-thickness involvement of the primary lesion. These patients are also likely to be thrombocytopenic and coagulopathic.

Management of these complications typically proceeds with the initial resuscitation and correction of underlying abnormalities. For bleeding, initial nonoperative measures such as heater probe or angiographic embolization can be tried while achieving stabilization. In most instances, however, some form of definitive surgical treatment will eventually be required. Surgical resection of the diseased bowel is preferred when conditions permit. For the stomach, a subtotal gastrectomy and for small bowel, a segmental resection is usually performed.

Surgery is mandatory for perforation except perhaps in the event of imminent death. Resection of the perforated segment is preferred when possible. In unstable patients, simple closure with omental patching may be all that can be tolerated.

Neutropenic Enterocolitis. This entity is seen in the setting of intense chemotherapy and severe neutropenia. The onset is typically 1 week after development of neutropenia where the absolute granulocyte count is less than 1000/mm^3. Bacterial invasion of the bowel wall causing ulceration and necrosis is felt to play a role in the pathogenesis of the disease. The cecum is most commonly affected.

Neutropenic colitis remains a diagnosis of exclusion. The diagnosis usually begins with a clinical suspicion in a patient who develops abdominal pain, distension, diarrhea, and fever in the presence of neutropenia and thrombocytopenia. However, other more common surgical pathologies such as acute appendicitis, diverticulitis, and pseudomembranous colitis and bowel obstruction must first be ruled out with appropriate diagnostic tests. Once this is done, the diagnosis can be confirmed by demonstrating ileus with a distended cecum or pneumatosis intestinalis and thickened bowel loops on abdominal CT scan.

As clinical improvement often occurs with normalization of the white count, the initial management is conservative. Bowel rest, nasogastric suction, broad-spectrum antibiotics, and total parenteral nutrition are often used. However, if the patient's condition does not improve after a few days of conservative treatment, then a laparotomy is warranted. This aggressive approach is preferred over waiting for perforation or bowel necrosis to develop given the patient's underlying medical illnesses. Bowel resection and enterostomy are the recommended treatment.

Pancreatitis. Acute pancreatitis can develop during chemotherapy, possibly as a result of an inhibitory effect on pancreatic protein synthesis. The presenting symptoms are similar to those of acute pancreatitis from other causes. Diagnosis can usually be made with an elevated amylase and lipase along with appropriate symptoms. An abdominal CT can both confirm the diagnosis and determine the severity of the inflammatory process.

Initial treatment consists of bowel rest, nasogastric tube, and intravenous (IV) hydration with nutritional support as indicated. Clinical progression can be

followed by monitoring hematocrit, electrolytes, and overall status. Surgery is reserved for managing complications such as pseudocyst, abscess, or hemorrhage.

Medical Management

Low-Grade Lymphomas

Under most circumstances, low-grade lymphomas will not be curable by any means. In general, treatment should be directed at symptom relief. Despite the fact that many, if not most, low-grade NHL patients will present with advanced stage (Ann Arbor III or IV) disease, treatment is not mandatory for asymptomatic patients. Patients with low-grade lymphoma treated by observation alone, reserving treatment for symptomatic indications, will usually respond well to therapy, and will have a median survival of 7–8 years. Chemotherapy, when given to asymptomatic patients, may cause rapid disease remission, but is not curative, and thus will not prolong survival when compared to patients first treated by observation alone. A possible exception to this approach rests with the rare patient with low-grade lymphoma presenting with stage I or II disease. These patients may enjoy prolonged disease-free survival when treated with radiation therapy alone. Such patients account for only 10% of all low-grade lymphoma patients.

When treatment is required for low-grade lymphoma, a variety of treatment options are available (Table 6). Oral alkylating agents such as chlorambucil or cytoxan will induce remissions in the majority of patients, while combination-chemotherapy programs such as CVP (cytoxan, vincristine, prednisone) may be reserved for patients who require more aggressive therapy. Newer agents such as fludarabine may have equivalent activity to oral alkylating agents, and may be used as first- or second-line therapy. Treatments of this type will produce remissions in the majority of patients, although the duration of these remissions will generally be less than 2 years. Younger patients with low-grade lymphoma, whose survival overall will necessarily be compromised despite the generally indolent behavior of their disease, may be considered for programs using high-

Table 6 Low-Grade NHL Treatment

Early stage
Radiation therapy
Advanced stage
Observation until symptoms
Oral alkylating agents
Combination chemotherapy
Fludarabine
Bone marrow transplant

dose chemotherapy with autologous or allogeneic stem cell or bone-marrow transplantation. Long-term results of this approach are not available, however, and the value of this approach as compared to traditional, less aggressive approaches remains to be proven.

Intermediate-Grade Lymphomas

These lymphomas should be treated with curative intent. Although some patients with stage I and II lymphomas are occasionally curable with radiation therapy alone, present care standards mandate that patients with early-stage lymphomas of this type receive some duration, between 3 and 6 months, of aggressive combination chemotherapy. A recent randomized trial of three cycles of standard CHOP chemotherapy followed by involved-field radiation versus eight cycles of the same chemotherapy without radiation in patients with nonbulky, limited-stage lymphoma suggested that the combined modality was at least equivalent to the extended chemotherapy course.

Although the optimum duration of CHOP chemotherapy in early-stage patients has not been determined, the addition of involved-field radiation therapy to areas of tumor involvement (rather than the large fields employed in the treatment of HD) should be considered standard management after chemotherapy in these patients.

Patients with more advanced-stage disease (stage II with bulky disease $>$ 10 cm, and all stage III and IV) should receive combination chemotherapy with CHOP, consisting of cytoxan, adriamycin, vincristine, and prednisone, for approximately 6 months. Although the optimum chemotherapy regimen has not been defined, the standard regimen remains CHOP. Although more complex and more aggressive regimens have been devised for the treatment of intermediate-grade NHL, none have clearly proven superior to CHOP in large, randomized trials. Table 7 summarizes treatment recommendations for intermediate-grade lymphoma patients.

TABLE 7 Intermediate-Grade NHL—Treatment

Early stage (I or nonbulky II)
Chemotherapy (CHOP) for three to eight cycles plus involved-field radiation
Advanced stage (bulky II, III, or IV)
Chemotherapy (CHOP) for eight cycles
Advanced-stage poor prognosis
Clinical trial randomizing between CHOP and high-dose chemotherapy plus autologous stem-cell transplant
Relapse after chemotherapy
Salvage chemotherapy (ESHAP or MINE) with high-dose chemotherapy and autologous stem cell transplant for responders

The results of treatment in intermediate-grade NHL are stage-dependent. Patients with early-stage disease may be cured in excess of 75% of the time, while cure rates for more advanced-stage patients will range from 30 to 50%.

The concept of high-dose chemotherapy with stem-cell support, while an accepted salvage treatment for patients with disease relapse after CHOP chemotherapy, is being utilized with increasing frequency as first-line therapy in patients with intermediate-grade lymphoma and negative prognostic features as identified by the International Staging System. Recent randomized trials from Europe suggest that this approach may be superior to conventional CHOP therapy in poor-prognosis patients. Randomized trials comparing CHOP to high-dose chemotherapy with autologous stem cell transplant are underway in other sites.

High-Grade Lymphomas

Treatment paradigms for high-grade lymphomas are modeled after treatment programs for pediatric patients, using more aggressive treatments, more frequent treatments, longer duration of therapy, and larger numbers of drugs than employed in the CHOP regimen. CHOP constitutes inadequate therapy in high-grade NHL.

The patterns of presentation of high-grade NHL are variable and usually related to the development of symptoms in the anatomical regions occupied by these aggressive, rapidly growing masses. One subtype of high-grade NHL, the lymphoblastic lymphoma, is a T-cell neoplasm, which usually presents with a mediastinal mass, and thus must be considered in the differential diagnosis of such masses along with HD and diffuse large-cell NHL of the intermediate-grade type.

All high-grade NHL have a propensity to present in or relapse in the central nervous system (CNS); therefore, prophylactic treatment of the CNS with intrathecal chemotherapy, or, less favorably, with radiation therapy, is a mandatory part of high-grade NHL management. Patients with poor prognostic features, such as bone marrow involvement or an elevated serum LDH, will often be subjected to high-dose chemotherapy and autologous or allogeneic stem cell or bone marrow transplantation.

Like intermediate-grade lymphomas, high-grade NHL should be treated with intent to cure. Although the overall cure rate for this disease subtype may approach 50%, patients with limited-stage disease may be cured up to 90% of the time with appropriate therapy.

Radiation Management

Low-Grade Lymphoma

Low-grade NHL, under the Working Formulation classification system, are generally considered to be incurable, although median survival even without treat-

ment is 8–10 years. Thus, a reasonable management approach, especially for the elderly patient, is watchful waiting with radiation therapy (RT) and/or chemotherapy held in reserve for symptomatic disease progression. For the patient who wishes to pursue a more aggressive management approach, RT has been used in stage I and II patients resulting in 10-year overall and disease-free survival rates of 70% and over 50%, respectively. RT doses of 35–40 Gy are usually sufficient to achieve effective local control. Extending field sizes beyond the nodal areas involved and their first echelon draining nodes (involved-field RT) has not proven to be of any benefit. The addition of chemotherapy may provide a slight improvement in relapse-free but not overall survival compared to RT alone.

The treatment of more advanced low-grade lymphomas (stage III and IV) is also not clearly defined. Many therapies including single- or multiagent chemotherapy, total lymphoid irradiation, total-body irradiation, and combined modality treatment have been used successfully to induce initial responses. However, relapse is common in the first 5 years of follow-up and continues thereafter at a rate of approximately 10–15% per year. In younger patients, the use of more aggressive therapy utilizing high-dose chemotherapy with stem cell or bone-marrow transplantation can be considered although long-term follow-up is needed to evaluate the effectiveness of this approach.

Intermediate- and High-Grade Lymphoma

Intermediate-grade lymphomas have a much more aggressive clinical course (1–2-year survival without treatment) than low-grade lymphomas and should be treated with multiagent chemotherapy with or without RT. Prior to the 1980s, RT alone had been used to treat stage I and II intermediate grade lymphomas with cure rates of 40–50%. However, recent reports seem to indicate that combined modality therapy is more effective in this group of patients. A phase III ECOG study randomizing stage I (bulky or extranodal) and II patients who were complete responders to CHOP chemotherapy to no further therapy or adjuvant RT (30 Gy involved field) showed significantly improved disease-free survival (73% vs. 58%, $p = 0.03$) and a trend toward improved overall survival (84% vs. 70%, $p = 0.06$) with combined-modality therapy (median follow-up 6 years). All partial responders were treated with adjuvant RT (40 Gy involved field) and had disease-free and overall survival rates of 54% and 60%, respectively. In addition, a randomized SWOG study indicated that three cycles of CHOP and involved-field RT resulted in slightly improved overall survival as compared to eight cycles of CHOP alone in stage I and II patients. For patients with stage III and IV disease, the mainstay of therapy remains combination chemotherapy. Survival rates are significantly lower (approximately 30%) than for stage I and II patients.

The role of RT in high-grade lymphoma is mainly for palliation of symptomatic disease and as part of conditioning regimens (total-body irradiation) for bone marrow or peripheral stem cell transplant.

Extranodal NHL

GI lymphomas are the most common extranodal NHL and the gastric site is the most common of the GI lymphomas. Regression of low-grade B-cell MALT lymphomas can be induced simply by treatment of the associated *H. pylori* infection. However, patients with more aggressive histologies, typically diffuse large cell, require treatment with a combination of surgery, RT, and/or chemotherapy. Surgical resection followed by adjuvant RT and chemotherapy has resulted in 5-year survival rates of greater than 75% for localized aggressive disease. In cases where surgery is not feasible, primary therapy with chemotherapy and RT is recommended although local control and survival rates are lower. RT is typically delivered via anterior and posterior fields to a total dose of 40–50 Gy. Care must be taken to exclude the right kidney from the treatment field as most of the left kidney will receive a dose in excess of its tolerance level.

Lymphoma of Waldeyer's ring (tonsil, base of tongue, and nasopharynx) can be treated with moderate doses of RT (35–50 Gy) to the involved areas and draining nodes. The majority of failures after RT occur outside of the RT fields and indicate the need to address occult systemic disease. Thus, RT in combination with chemotherapy has been used with good result. Local control rates in excess of 80% and overall survival rates of 60–75% have been reported.

Orbital lymphomas commonly present in the conjunctiva, as low-grade MALT lymphomas, or in the retro-orbital tissues, as intermediate-grade tumors. Conjunctival lesions can be treated with RT alone using orthovoltage x-rays or electron-beam therapy to provide adequate treatment of anterior lesions limited to the eyelid while sparing the more posterior orbital tissues. Local control in excess of 95% can be achieved for low-grade lymphomas. Retro-orbital tumors can be treated via opposed lateral or two oblique (wedged) fields with 4–6 MV photons taking care to exclude anterior structures such as the lens from the treatment volume. Doses of 30–35 Gy are recommended often in combination with chemotherapy for the aggressive histologies.

Primary central nervous system lymphoma is usually of intermediate grade and most often presents as intracranial nodules. Surgical management is primarily for histological confirmation and has no therapeutic role. Whole-brain RT to doses of 40–50 Gy results in median survival of 12–18 months. There is no added benefit to boost RT above these doses. Chemotherapy in combination with RT improves median survival in non-HIV-related disease to approximately 40 months. Patients with HIV-related CNS lymphoma do far worse, with median survivals of 3–6 months even with therapy.

Relapsed Disease

Disease relapses after treatment are expected in low-grade NHL, and are generally treated with alternative chemotherapies from the considerable therapeutic

armamentarium for these patients. Relapses after CHOP chemotherapy in intermediate-grade disease, however, portends a very poor prognosis, and this group of patients will often receive salvage chemotherapy with alternative agents such as ESHAP (cisplatin, etoposide, cytosine arabinoside, and methylprednisolone) or MINE (mitoxantrone, ifosfamide, etoposide, and mesna), and if they respond, may be subjected to high-dose chemotherapy with autologous stem cell transplantation. Long-term remission rates of up to 50% have been reported for such patients, although 20–30% long-term remissions may be a more realistic figure. The value of allogeneic bone marrow transplantation as an alternative to autologous stem cell transplantation has not been elucidated, although similar long-term remission figures have been reported.

Transformed Disease

Any low-grade lymphoma is capable of transformation to a higher histological grade. Such transformation is said to occur in 15–30% of low-grade NHL, and is unrelated to prior therapy for low-grade disease. Patients typically will transform to an intermediate-grade NHL, and will require treatment with CHOP chemotherapy or an equivalent regimen. Most of these patients will respond to appropriate treatment, and a subset of patients may sustain long-term remissions in excess of 6 years. The curability of such patients remains in question because of presumed persistence of low-grade lymphoma elements despite aggressive chemotherapy.

Gastric MALT Lymphoma

A particular subtype of low-grade B-cell lymphoma, known as MALT, may occur in the stomach, and is frequently associated with *H. pylori* infection. Some patients with gastric MALT lymphoma and associated *H. pylori* infection have been treated with antibiotic therapy alone, leading to regression of lymphoma in most cases. This situation is unique in medical oncology, and this unique treatment approach should not be extended to other MALT lymphomas in other aerodigestive tract sites. This approach is not applicable to other histologies of gastric lymphoma, of which diffuse, large cell lymphoma is the most common type.

HIV-ASSOCIATED LYMPHOMAS

The majority of lymphomas in the AIDS population are NHL, are of B-cell origin, and are of the intermediate- to high-grade type. Low-grade lymphomas and HD are rarely seen, and by themselves do not constitute an AIDS-defining illness.

Epidemiology, Etiology, Pathogenesis

The occurrence of an intermediate- or high-grade NHL in an HIV-infected patient is an AIDS-defining illness in the absence of opportunistic infection or Kaposi's sarcoma (KS). NHL is the second most common malignancy in the AIDS population, second to KS, and up to 10% of individuals with AIDS will ultimately develop NHL. The majority of these patients are homosexual and bisexual men, but unlike KS, HIV-associated NHL is known to occur in all AIDS risk groups, including IV drug users and hemophiliacs. In fact, the relative risk of developing NHL may be highest in HIV-infected hemophiliacs.

HIV infection per se is not the cause of NHL, but the consequences of the immunosuppressed state are responsible in a variety of possible ways. HIV-associated NHL are not exactly like those seen in other immunosuppressed groups, in that not all HIV-associated NHL are associated with Epstein-Barr Virus (EBV), that Burkitt lymphomas, while relatively common in HIV, are not seen in other immunosuppressed patient groups, and that HIV-associated NHL have an unusual tendency to present in extranodal sites. It is hypothesized that some combination of EBV-induced or other microbially induced B-cell polyclonal expansion, oncogene rearrangements, HIV-induced cytokine stimulation of B-cell proliferation, and suppression of T-cell surveillance will contribute to the development of NHL.

Clinical Manifestations, Diagnosis, Pathology, and Workup

Just as there exists no classic presenting pattern in non-HIV NHL, the same holds true in HIV-associated NHL, with the picture even more confounded by the unique ability of the latter NHL to present in extranodal sites. Approximately two-thirds of NHL patients will have an extranodal site at presentation, with bone marrow, central nervous system, GI tract, liver, anorectal mucosa, and oropharynx among the common sites, although virtually no site is spared. The central nervous system is the primary site of involvement in up to 20% of patients, including either brain parenchyma proper or the leptomeninges.

The predominant histological subtypes of lymphoma in the HIV population are the Burkitt (small noncleaved cell) lymphomas, and large cell lymphomas, either conventional or immunoblastic subtype. The various distributions of these subtypes varies among reports, but one can assume that 20–40% of lymphomas will be of the Burkitt type, while the remainder will be of the large cell variety. Virtually all of the primary CNS lymphomas are of the large cell or large cell immunoblastic subtype.

The diagnostic workup of these patients should follow patterns established for non-HIV NHL. However, the frequency of B symptoms in these patients (80%) will often be confused with symptoms produced by other AIDS manifesta-

tions. Tissue biopsy is mandatory for diagnosis; as most of these lymphomas have a diffuse pattern of growth, fine-needle aspirates may be of greater value than in non-HIV NHL. The staging evaluation should likewise follow that for other NHL patients, with the addition of particular attention to the CNS. Imaging studies of the brain for space-occupying lesions should be obtained routinely, and if they are negative, lumbar puncture for the presence of leptomeningeal disease should be performed. Blood CD4 counts will have some prognostic significance in these patients, and should also be obtained.

Patients with isolated CNS lesions present a particularly vexing problem in management, as most isolated CNS lesions in HIV patients will be caused by toxoplasmosis, not NHL. Patients with this finding as their only disease manifestation may be treated expectantly with antimicrobial therapy, with biopsy of the lesion encouraged within 2 weeks if clinical improvement does not occur.

Treatment

As HIV-associated NHL patients have an underlying incurable condition, treatment of NHL should be tempered by a thoughtful evaluation of comorbid conditions, opportunistic infections, and life expectancy. Untreated patients will usually die within 6 months of either lymphoma or other complications of AIDS. In general, conventional chemotherapeutic approaches have been disappointing because of drastically reduced response rates (20–30%) and exacerbation of opportunistic infections by the immunosuppressive effects of chemotherapy. In general, dose-intense approaches to treatment in these patients should be avoided. In fact, randomized trials have proven no advantage of conventional chemotherapeutic approaches over low-dose approaches specifically designed for these patients. Such a restrictive approach to treatment may not be appropriate, however, for patients with CD4 counts greater than 200 and with no other manifestations of AIDS.

The use of hematopoetic growth factors (G-CSF or GM-CSF) should be considered routine in these patients, as should infection prophylaxis with trimethoprim-sulfamethoxazole. For patients presenting with no evidence of CNS involvement (60–80% of patients), prophylactic therapy of the CNS with intrathecal chemotherapy (methotrexate or cytosine arabinoside) should be employed, particularly in patients with marrow involvement. Chemotherapy in standard doses should be used in patients with no other comorbid conditions, CD4 counts greater than 200, and good performance status. Patients otherwise should receive a low-dose approach to therapy, with the expectation that responses will be limited and their duration short. Finally, severely ill patients with significant comorbid conditions and CD4 counts under 100 may be candidates for supportive care without chemotherapy.

The same approach should be considered for patients with primary CNS lymphoma. These patients tend to be more compromised at diagnosis with lower CD4 counts (<100) and with more advanced underlying HIV disease. Their prognosis is generally poorer, and treatment should be restricted to steroids or radiation therapy designed to bring about short-term relief of CNS symptoms. The rare patient with CNS lymphoma and good performance status, with CD4 counts greater than 200, may be considered for a program of both radiation and chemotherapy.

It can be assumed that few patients with HIV-associated NHL will be cured. Patients with primary CNS lymphoma will have a median survival of less than 6 months, while patients with systemic lymphoma will have a median survival of less than a year. However, as response rates as high as 75% have been reported for good-risk patients, the palliative benefit of systemic chemotherapy remains a viable treatment option for many patients.

CLINICAL RESEARCH

The treatment of early-stage HD continues to trend toward using abbreviated chemotherapy with limited radiation. The recently published Stanford G1 trial is one of several exploring this prospect. In favorable clinical stage I and II disease, VBM plus involved-field radiotherapy can be substituted for the traditional extended-field radiotherapy without needing laparotomy. The advantage to the VBM regimen is that potential toxicities of infertility, secondary leukemia or solid tumors, and pulmonitis can be reduced or avoided. Further studies, however, are needed to determine an optimal treatment scheme that can maximize cure while minimizing complications.

In NHL, a different strategy using antitumor vaccine therapy is also undergoing intense research. The basis of this approach is to stimulate the native immune system to differentiate normal from neoplastic cells while leading to the eventual destruction of the abnormal cells. Various vaccine approaches have tried foreign carrier proteins, adjuvants, and viruses to deliver a tumor-specific antigen in an attempt to enhance immunogenicity.

Two recent clinical trials using the vaccine therapy have shown encouraging early success. The first is a pilot study from Stanford describing the use of dendritic cells to deliver the lymphoma-specific antigenic determinants. All four patients in this study developed measurable antitumor cellular immune response with one complete regression, one partial response, and a third without molecular evidence of residual disease. In a second study, an antitumor vaccine is made by emulsifying an immunological adjuvant with the tumor-specific protein. This much larger study has a median follow-up of 5 years. Half of the patients demonstrated specific antitumor response. Survival advantage and freedom from disease

progression (FFP) were shown to be significant in vaccinated patients comparing to case-matched historical controls. These preliminary clinical results thus provided an encouraging framework for other more effective antitumor vaccine therapy.

BASIC SCIENCE RESEARCH

Lymphomagenesis is recognized as a complex process integrating multiple factors. Overall, the molecular defects resulting from chromosomal translocations probably play a significant role in the eventual evolution of the malignant lymphomatous cells. These disordered translocations can result in activation of proto-oncogenes (c-myc) or abnormal regulatory genes for cell cycle (cyclin D1), differentiation (*bcl*-6), and apoptosis (*bcl*-2). Other factors that may contribute to the lymphoma pathogenesis include inactivation of tumor suppressor genes (p53, Rb, p16), chronic infections (EBV, HCV, HBV, *H. pylori*), and inflammatory cytokines such as Il-2, Il-4, IL-6, and IL-10.

Chromosomal translocation and loss of tumor suppressor gene are primary mechanisms for overexpression of the BCL-2 protein family and a common finding in NHL. BCL-2 typically leads to resistance of apoptosis or programmed cell death resulting in neoplastic expansion. Resistance to cytotoxic drugs and radiation is also believed to be mediated by BCL-2. Thus, BCL-2 antisense therapy and pharmacological manipulation of the cell death pathway are potential therapeutic strategies currently being investigated.

It is possible that through multiple complex steps a subset of B cells is immortalized and selected for clonal expansion and eventual transformation toward malignancy. Impaired immune function can lead to a defective clearance of abnormal B-cell clones that is persistently stimulated by exogenous or autoantigens. Interestingly, interaction with the reactive T lymphocytes may provide proliferative support to the clonal cell population instead of clearance. Overtime, the B-cell clone may evolve to a high-grade lymphoma while the T lymphocytes progressively decline. This observation was demonstrated in follicular lymphomas of the SLJ mouse model suggesting a possible dependency between different cell populations for growth in the early stages of the disease. Finally, tissue cytokines acting in an autocrine or paracrine fashion may also contribute to the lymphoproliferation.

The precise pathogenic mechanism of the B-cell lymphomas remains to be elucidated. However, continued advancement in molecular biology techniques and research will further define the surrounding initiation and proliferation events. It is through the understanding of these mechanisms that interventional strategies can evolve to prevent the development or control the clinical course of these lymphoproliferative disorders.

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Soft Tissue Sarcomas

Kelly K. Hunt, Shreyaskumar R. Patel, and Alan Pollack
The University of Texas M. D. Anderson Cancer Center, Houston, Texas

INTRODUCTION

The designation soft tissue sarcoma encompasses a wide diversity of more than 50 histiotypes of which about 6600 cases are diagnosed annually in this country. Tumor grade, size, depth, histological characteristics, and site of origin are important prognostic factors that influence the overall outcome in patients with soft tissue sarcoma. Patients with small ($<$5 cm, T1) primary tumors who have no evidence of distant metastatic disease are managed by local therapy consisting of surgery alone or in combination with radiation therapy. The use of systemic therapy is generally limited to patients with metastatic disease, those with small cell sarcomas of any size, or those patients with large ($\geq$5 cm, T2) high-grade or $\geq$10 cm intermediate-grade tumors who are at high risk of developing metastatic disease. The primary objective of multimodality treatment is to render patients free of disease. In patients for whom this endpoint is attainable, the therapeutic intent is cure; in patients for whom this is not accomplished, the intent is palliation of existing or potential symptoms.

Most clinicians have limited experience with the diagnosis and treatment of soft tissue sarcomas. In this review we will focus on the key issues the clinican faces in treating the more common high- and intermediate-grade neoplasms, with emphasis on the integration of surgery, radiotherapy, and chemotherapy.

NATURAL HISTORY

Of the approximately 6600 new sarcomas seen annually in the United States, roughly 60% occur in the extremities (Table 1). The patient often describes a

TABLE 1 Incidence of Soft Tissue Sarcomas and Anatomical Site (6286 cases)

Author	Year	Lower extremity	Upper extremity	Head and neck	Trunk[a]
Abbas	1981	81	42	24	90
Potter et al.	1986	152	59	12	84
Lawrence	1987	2110	594	406	1440
MDACC	1987	340	136	66	158
Torosian	1988	208	81	21	182
Total		2891	912	529	1954
		(46%)	(15%)	(8%)	(31%)

[a] Approximately one-half are retroperitoneal.

traumatic event at the involved site that preceded tumor development, but a direct relationship between trauma and the development of soft tissue sarcoma remains unproved. A painless mass is characteristic, although impingement on bone or neurovascular bundles may produce pain or edema and swelling, or all of these. Soft tissue sarcomas grow in a centrifugal fashion, if nearby structures such as bone permit, and they compress surrounding normal structures. A zone of compressed reactive tissue forms a pseudocapsule, which may mistakenly guide resection by the inexperienced surgeon. Tentacles of tumor that extend through and beyond the pseudocapsule for some distance must be considered in planning surgery and radiotherapy. The probability of local recurrence in the absence of appropriate surgery or combined-modality treatment with surgery and radiation is greater than 50%. With modern surgical and radiotherapy techniques, local failure rates of 10–20% are typical for soft tissue sarcomas of the extremity and trunk. Local failures are often reported to be more frequent for some histiotypes such as fibrosarcoma and malignant peripheral nerve tumors.

The majority of patients with soft tissue sarcomas present no evidence of distant metastases. The propensity for distant metastasis, and hence diminished survival, is highly dependent on tumor grade and histiotype, primary site, and tumor size; on average it is 50% for high-grade lesions. The most common sites of distant metastasis are the lungs (35%), bone (25%), and liver (15%). Lymph node metastasis is uncommon, typically $<4\%$, although lymph node involvement may be greater in cases of angiosarcoma, epithelioid sarcoma, synovial sarcoma, and rhabdomyosarcoma.

PATIENT EVALUATION AND TREATMENT PLANNING

Whenever possible, a patient with a deep soft tissue mass should be referred, even before a biopsy is done, to a tertiary treatment center that offers a team of

specialists with experience in treating sarcomas. Because such referral patterns are absent in the United States, some diagnostic procedures, which may ultimately affect treatment options and outcome, are often undertaken before definitive treatment is implemented.

Presentation of gross residual disease following incisional biopsy, core-needle biopsy, or fine-needle aspiration biopsy allows the treatment planning team the best opportunity to evaluate the tumor's proximity to vital structures and the likelihood of being able to perform surgical resection with negative histological margins. Even a simple diagnostic incisional biopsy can complicate planning if the scar is oriented incorrectly (horizontally across muscle groups instead of longitudinally) or is unnecessarily long. Surgical debulking rarely, if ever, provides any treatment benefit to the patient and may result in postoperative complications that delay the use of chemotherapy or radiation therapy. Debulking is frequently seen in cases of large pelvic or abdominal tumors; it precludes the opportunity to optimize the sequencing of surgery and radiotherapy. A pelvic sarcoma, for example, might best be treated with preoperative external-beam radiotherapy or postoperative external-beam radiotherapy after small bowel displacement with a sling. Histological characteristics, location, size, depth, involvement of nearby structures (e.g., bone, bowel), necessity for skin grafting or autogenous tissue reconstruction, and the patient's performance status may influence the selection of treatment technique.

In a tertiary treatment center, the most typical presentation of soft tissue sarcoma is after gross total excision. Often this has been performed without adequate pretreatment imaging studies. Magnetic resonance imaging (MRI) has supplanted computed tomography (CT) scans in the work up of soft tissue sarcomas. A CT scan may be useful if bone involvement is suspected, although with state-of-the-art MRI this is rarely necessary. Wide en-bloc excision is seldom performed as a diagnostic procedure; when it is done, the margin status is often not even described in the pathological assessment of the specimen. Unless detailed descriptions of the surgical procedure and pathological specimen are provided, the margins should be classified as uncertain or unknown, which carries the same prognosis as resection margins that are positive for tumor cells. Recurrence rates are in the range of 30–40% when margins are positive or uncertain. Reexcision may not be possible in some cases, like those involving the hands and feet, so that radiotherapy alone may be considered the best option for limb preservation.

Additional diagnostic studies should include a chest x-ray and a chest CT for grade 2 or 3 lesions > 5 cm. CT scans of the abdomen and pelvis should be obtained when the histological assessment reveals myxoid liposarcoma, because this subtype is known to metastasize to the abdomen. Except in the case of hemangiopericytoma, bone scans are rarely useful.

HISTOLOGICAL TUMOR GRADE AND PATHOLOGICAL CLASSIFICATION

Tumor grade, firmly established to have prognostic significance, has been incorporated into the staging of soft tissue sarcomas (Table 2). Tumor grade is based on histological features including cellularity, differentiation, pleomorphism, mitotic index, and necrosis. Although some studies have suggested that necrosis is the most important of these, other researchers have found that when nonhistological factors such as tumor size are considered as well, necrosis loses significance. Evans and colleagues at the M. D. Anderson Cancer Center (MDACC) have suggested that pathological classification is far more important than grade when other pretreatment variables are taken into account. In this schema, the only feature of the grading system that seems to provide prognostic information that su-

TABLE 2 American Joint Committee on Cancer Stage Groupings of Soft Tissue Sarcomas

Stage I	
Stage IA	G_1, T_1, N_0, M_0
Stage IB	G_1, T_2, N_0, M_0
Stage II	
Stage IIA	G_2, T_1, N_0, M_0
Stage IIB	G_2, T_2, N_0, M_0
Stage III	
Stage IIIA	$G_{3/4}$, T_1, N_0, M_0
Stage IIIB	$G_{3/4}$, T_2, N_0, M_0
Stage IV	
Stage IVA	G_{1-4}, T_{1-2}, N_1, M_0
Stage IVB	G_{1-4}, T_{1-2}, N_{0-1}, M_1

G	Grade
G_1	Well differentiated
G_2	Moderately differentiated
G_3	Poorly differentiated
G_4	Undifferentiated
T	Tumor size
T_1	<5 cm
T_2	>5 cm
N	Nodal metastases
N_0	No evidence of nodal metastases
N_1	Nodal metastases
M	Distant metastases
M_0	No evidence of distant metastases
M_1	Distant metastases

Table 3 Histiotype and Tumor Aggressiveness

Low metastatic potential	High metastatic potential
Desmoid tumor	Malignant fibrous histiocytoma (nonmyxoid)
Atypical lipomatous tumor	Pleomorphic liposarcoma
Dermatofibrosarcoma protuberans	Dedifferentiated liposarcoma
Hemangiopericytoma	Synovial sarcoma (mono- and biphasic)
	Rhabdomyosarcoma (all types)
Intermediate metastatic potential	Leiomyosarcoma
Myxoid liposarcoma	Neurogenic sarcoma (malignant schwannoma)
Myxoid malignant fibrous histiocytoma	Angiosarcoma
	Alveolar soft part sarcoma
Extraskeletal chondrosarcoma	Epithelioid sarcoma
	Clear cell sarcoma (melanoma of soft parts)
	Extraskeletal Ewing's sarcoma
	Extraskeletal osteosarcoma

persedes pathological classification is the degree of cellularity in myxoid liposarcomas. Table 3 shows the relationship of histiotype to tumor aggressiveness. Tumors with little or no metastatic potential include desmoids, atypical lipomatous tumors (also called well-differentiated liposarcoma), dermatofibrosarcoma protuberans, and hemangiopericytomas. Those with an intermediate risk of metastatic spread usually have a significant myxoid component (e.g., myxoid liposarcoma). Highly aggressive tumors that have a substantial likelihood of metastasizing include malignant fibrous histiocytoma (MFH), liposarcoma, and synovial sarcoma. The classification of aggressiveness by tissue type is more constrained than tumor grading, as this system includes no intermediate MFHs without myxoid features. Yet the use of tissue type as a corollary grade is highly predictive of clinical outcome.

LOCAL THERAPY—SURGICAL RESECTION

Historically, local excision of soft tissue sarcomas resulted in local failure rates as high as 50–70%, even when a cuff of normal tissue was taken around the tumor. As a consequence, radical surgery consisting of radical resection or amputation became the standard. Because sarcomas usually spread along fascial planes or within muscle bundles, radical resection encompasses the removal of all muscles in the involved compartment, including nerves, vessels, and involved bone. Amputation was often required to fulfill these stipulations. The use of radical surgical techniques resulted in local recurrence rates of about 10% in multiple series. The addition of radiotherapy to less radical surgical resection made limb

Table 4 Surgical Resection Series

Author	Year	No. of patients	Primary amputations	5-yr. local recurrence rate (%)	5-yr. survival rate (%)
Shiu	1975	297	139 (47%)	18	55
Simon	1976	54	29 (54%)	17	62
Abbas	1981	123	51 (41%)	31	50
Markhede	1982	97	15 (15%)	22	59
Berlin	1990	137	35 (26%)	18	63
Total		708	269 (38%)	21	57

salvage possible in many cases. The local recurrence rate of 19% with wide local excision plus radiotherapy compares favorably to that of series employing radical surgery. Table 4 lists the results of several surgical series including amputation rates, local recurrence rates at 5 years, and survival rates at 5 years.

The doctrine that radiotherapy is required for nonradical surgical procedures that avoid amputation or removal of the entire muscle compartment (radical excision), such as en-bloc wide local excision with myectomy, has been challenged by some groups, mostly European. These physicians argue that the purported recurrence rates of 30–50% with less than radical surgery alone are based on older series that preceded the advent of MRI scans and other advances in surgical and pathological methods. These investigators have used wide en-bloc excision with a wider than 2–3-cm cuff of fat or muscle, or the entire muscle for intramuscular tumors, and radial margins including fascial planes or bone, and they have reported local failure rates of less than 20%. Certainly, for tumors < 5 cm, regardless of grade, the utility of radiotherapy must be questioned. Until recently, our policy at the MDACC was to administer radiotherapy as an adjunct to surgery for all patients with intermediate and highly aggressive tumors of any size. In general, tumor size has not been shown to be associated with local recurrence; however, physicians should not hesitate to use radiation after excision of tumors < 5 cm when margins are close, positive, or uncertain, and reexcision is not practical.

CONSERVATIVE SURGERY PLUS RADIOTHERAPY: THE IMPORTANCE OF LOCAL CONTROL

The oft-quoted randomized National Cancer Institute (NCI) trial in which amputation alone was compared with limb-sparing surgery plus radiotherapy would be difficult to perform today. The design was a 2:1 randomization scheme, and

approximately one of three eligible patients were entered in the study, which is not unreasonable. Thus, 27 patients were in the limb-sparing arm and 16 in the amputation arm. Median follow-up was 4 years and 8 months. Despite the small number of patients, a borderline significant difference ($p = 0.06$) in actuarial local control was reported, with four local failures in the combined-modality arm versus none in the surgery-alone arm. In a subsequent report from the NCI, the authors reported no significant difference in disease-free or overall survival between the two groups. The study lacked the power to detect a survival difference, however, and the small number of patients enrolled combined with the unequal randomization makes further interpretation difficult.

The 1986 report by Potter and colleagues reviewed the entire NCI experience and included the patients in the randomized trial. A total of 123 patients were treated with conservative surgery plus radiotherapy, and 83 were treated with amputation. The difference in local control was highly significant, with 10 failures (8%) in the surgery and adjuvant radiotherapy arm and none in the amputation arm. The survival rate was better for those in the amputation arm, although the difference was not statistically different ($p = 0.13$). The conclusion that conservative surgery plus radiotherapy controls soft tissue sarcomas as effectively as amputation was not supported by the data, nor was the suggestion that local recurrence does not influence survival. The practical issue is whether the risk of local recurrence and possibly shorter survival in those treated conservatively outweighs the benefits of limb preservation; the limited data available indicate that limb preservation carries minimal, if any, detriment to survival, whereas quality of life is substantially improved. Local failures are generally less than 20% with conservative treatment, and not all of these patients are destined to develop metastatic disease. Several groups contend that local recurrence does not affect survival and that, by virtue of inherent tumor biology, the development of metastasis is predetermined.

There are two methods for determining whether local recurrence predisposes to distant metastasis and subsequent reduction in survival. In one, the relationship of local failure to distant metastasis or death is assessed, while any unequal distribution of prognostic factors is corrected for by multivariate analysis. In several studies of this type, local recurrence has been found to be an independent correlate of reduced survival. Another approach is to examine the association of local failure with survival in patients randomized between two treatments, one of which enhances local recurrence. The breast cancer literature provides examples of such an approach; in a randomized trial with sarcoma patients performed at Memorial Sloan-Kettering Cancer Center such analyses are described. In that study, 164 patients were randomized during wide local en-bloc resection either to receive postoperative brachytherapy (BRT) to 42–45 Gy over 4–6 days, or not. Local control was significantly better in the 78 patients who received BRT (82% vs. 69%). The authors emphasized that the absence of correlation of treat-

ment (surgery alone vs. surgery plus BRT) with survival demonstrated that local recurrence does not affect the generation of distant metastasis or survival. As was true of the NCI trial in which patients were randomized between amputation and conservative surgery plus radiation, the power of the Memorial BRT series is inadequate to accurately address this question. There were 13 local recurrences in the BRT arm (16.7%) and 25 in the surgery-alone arm (29.1%). The difference in local failure was only 12.4% ($n = 12$). The relationship of local recurrence to survival could not be addressed in a trial with so few patients because not all patients who develop local recurrence are destined to experience distant metastasis, and death caused by local tumor progression in the absence of distant metastasis is rare.

Data from MDACC research indicated that about 50% of patients with local recurrence were salvaged with surgery, and that death as a consequence of local recurrence only was uncommon. Thus, only about six patients, or fewer than 4% of those in the Memorial Sloan-Kettering BRT study, would be expected to die as a consequence of not receiving BRT. Even if one were to assume that every patient with local recurrence died, a conservative estimate is that 335 patients, or 167 per arm, would be needed to provide the power necessary to demonstrate a survival difference (one-sided $p = 0.05$, power = 0.8). If one-half of the patients who experienced local recurrence were salvaged, 1163 patients would be needed before a significant difference in survival would be observed. Clearly, these data do not repudiate the dictum that local control is a decisive factor in determining survival.

RADIOTHERAPY TECHNIQUE

CT scanning, as part of radiotherapy treatment planning, is integral to determining adequate coverage and avoiding excessive radiation doses to vital normal anatomy. Prechemotherapy and presurgical tumor volumes, ideally based on findings from pretreatment physical examination by the radiotherapist and diagnostic MRI scans, should be covered with an at least 5-cm margin. A 5–7-cm margin is typical, although some centers advocate wider margins for tumors $>$ 15 cm. In cases of postoperative radiation, the scar and drain sites should be included and bolused, so that a near-full dose is given to the superficial skin. A brisk skin reaction is desirable in most cases. An inadequate dose to the superficial skin using unbolused 6-MeV photons probably would increase the risk of local failure. At the MDACC, the radiotherapist routinely mixes electrons and photons (e.g., about 4:1 electrons:photons) in treating superficial tumors to prevent severe skin reaction, although with lower-energy electrons a $<$12-MeV bolus may be required. Raising the contralateral leg facilitates placement of laser lines on the medial aspect of the tumor-bearing leg without immobilizing the limb with cradles. For lesions of the proximal thigh, laser alignment of the hips and both

thighs makes the three-point setup more exact. Tumors in the antecubital fossa, popliteal fossa, and ankles are more apt to benefit from immobilization. Long laser setup lines are used to ensure positioning. Care is taken to avoid an exit dose to surrounding normal structures, such as the contralateral extremity, gonads, kidney, liver, lungs, and heart.

To assure lymphatic drainage, one-third of the circumference of the extremity, one-half of joints, and one-half of the circumference of long bones should be spared from radiation exposure. The dose to major tendons (e.g., patellar, Achilles) should be limited to >45 Gy to avoid rupture. Each patient presents unique treatment challenges, and adherence to these treatment principles may be difficult. In our experience, the risks of edema and fracture are greater in the lower extremity and should be discussed with the patient in detail. We prefer to use preoperative radiotherapy to 50 Gy in 25 fractions in cases of bulky lesions for which the treatment volume is large or, as in the case of inguinal or axillary involvement, the risk of edema is high. Doses of 60–70 Gy are generally necessary for postoperative treatment.

RESULTS OF EXTERNAL-BEAM RADIOTHERAPY AT MDACC

The policy at our institution has been to deliver 60–64 Gy postoperatively (postop) or 50 Gy preoperatively (preop) in 2-Gy fractions. The outcomes for patients treated at MDACC in recent years for synovial sarcomas, malignant fibrous histiocytomas (MFH), and liposarcomas have been described. These are the most common soft tissue sarcoma histiotypes, and because the patients were treated in a uniform manner, the data were pooled to investigate determinants of external beam efficacy. The data presented here concern 293 patients whose grade 2 or 3 tumors were treated at MDACC with either preop or postop radiotherapy. The series included 18% ($n = 54$) with recurrent disease; patients with retroperitoneal tumors were excluded. Table 5 displays the distribution of patients by various potential prognostic factors and type of treatment (preop vs. postop radiation). The patients' median age was 51 years (range 6–88 years) and the ratio of men to women was 0.74:1.0. There were 86 (29%) patients with grade 2 tumors and 207 (71%) with grade 3 tumors. Approximately 75% were tumors in extremities, with a median tumor size of 8.4 cm (range 0.8–30 cm); 62% of the tumors were >5 cm and 28% >10 cm. The mean and median doses for those receiving postop were 62 and 64 Gy, respectively (range 45–72 Gy). The mean and median dose for those receiving preop was 50 Gy (range 6–70 Gy). To determine their appropriate treatment strategies, patients were presented at a multidisciplinary conference for review by pathologists, radiologists, surgeons, medical oncologists, and radiation oncologists specializing in sarcoma treatment. Patients presented with gross residual disease after subtotal resection, incisional

TABLE 5 Patients with Soft Tissue Sarcomas Treated at M.D. Anderson Cancer Center with Preoperative or Postoperative Radiotherapy

Factor		Preop: S + XRT % (*n*)	Postop: XRT + S % (*n*)	*p*
Age	≤32 years	18 (29)	16 (20)	
	>32 years	82 (136)	84 (108)	0.66
Gender	Male	43 (71)	42 (54)	
	Female	57 (94)	58 (74)	0.88
Tumor grade	2	27 (44)	33 (42)	
	3	73 (121)	59 (86)	0.25
Histology	MFH	67 (111)	41 (76)	
	Synovial sarcoma	15 (25)	14 (18)	
	Liposarcoma	18 (29)	27 (34)	0.18
Tumor size	≤5 cm	47 (77)	25 (32)	
	>5 cm	53 (87)	75 (96)	0.0001
Tumor site	Extremity	71 (117)	82 (105)	
	Other	29 (48)	18 (23)	0.03
Recurrence	No	77 (127)	88 (112)	
	Yes	23 (38)	12 (16)	0.02
Disease status (at referral)	Gross disease	54 (89)	65 (83)	
	Micro + marg	2 (4)	12 (15)	
	Uncertain marg	41 (68)	22 (28)	
	Neg marg	2 (4)	2 (2)	0.0002
Chemotherapy	No	64 (106)	60 (77)	
	Yes	36 (59)	40 (51)	0.47
XRT dose	≤50 gy	7 (12)	81 (104)	
	>50 Gy	93 (152)	19 (24)	<0.0001
MDACC Margins	Negative	82 (136)	93 (119)	
	Positive	18 (29)	7 (9)	0.008

S, surgery; XRT, radiotherapy; MFH, malignant fibrous histiocytoma; Micro + marg, microscopic positive margins; Neg marg, negative margins; MDACC marg, final surgical margin produced by MDACC procedures. (*p*-value determined by chi-squared analysis.)

biopsy, or needle biopsy ($n = 172$), or after excisional biopsy with microscopically positive margins ($n = 19$), uncertain margins ($n = 96$), or negative margins ($n = 6$). All of these patients underwent resection at MDACC; those who did not have gross disease at referral underwent a second wide local resection before or after radiotherapy.

Several factors correlated with actuarial local control, including the status of the final surgical margin attained by the MDACC team, whether a primary or

recurrent tumor was being treated, and whether the tumor was located in the extremity. Patients who received neoadjuvant or adjuvant chemotherapy had a significantly greater risk of local recurrence at 10 years (69% vs. 84%, $p = 0.02$). No difference in local control was seen in relation to treatment (preop vs. postop), radiotherapy dose, tumor size, grade, gender, or histological classification. As already noted, tumor size was a more accurate predictor of distant metastasis than local recurrence.

According to Cox proportional hazards analyses, the final margin status was a strong predictor of local tumor recurrence for the entire patient group independent of treatment technique, as has been corroborated by other investigators. Interestingly, for the 20 patients with primary tumors, the 5-year local control rate was 80% when the MDACC margin was positive after preoperative treatment. Although the rate was much lower for the nine patients treated postoperatively, the difference was not significant.

The group that stands to benefit most from dose escalation are patients with positive margins whose local recurrence rate averages 40%. Higher doses seem to be particularly necessary for patients treated postoperatively or whose tumor is recurrent. The Memorial Sloan-Kettering physicians advocate 66 Gy for positive margins and 70 Gy for gross disease. A number of techniques have been used to boost the high-risk volume in patients with positive margins, including sandwiching preop and postop, with postop given by either implant or external beam. A note of caution concerning the use of brachytherapy after 50 Gy preop: placement of catheters in close proximity to bone or neurovascular bundles, especially along these structures' long axes, has a high complication rate. A sandwich technique with external beam seems to be safer; however, from the standpoint of radiation biology, a break of 4–6 weeks between the preop and boost treatment courses seems pointless. Recently, Alekhteyar et al. reported on a small group of patients treated with BRT to 15–20 Gy over 1.5–3 days, followed by 45- to 50-Gy external-beam radiotherapy. Nine of 10 patients with positive margins experienced local tumor control with this technique. Although the technique looks promising, more experience is needed to establish its advantage.

PREOP VERSUS POSTOP EXTERNAL-BEAM RADIOTHERAPY

Use of pre- and postoperative external-beam radiotherapy is one approach to treating soft tissue sarcomas. There is no consensus on the sequencing of radiation with surgery because each method has advantages and drawbacks. Preoperative radiotherapy usually involves lower doses and smaller fields; however, pathological assessment of margins is more complicated because of artifacts, and wound healing complications are more pronounced. In some studies, preoperative radiotherapy was seen as advantageous, especially for large lesions, while others concluded that postoperative radiotherapy is the treatment of choice. As delineated

above, no difference was seen in local control among patients treated with preop and postop radiotherapy when the entire MDACC cohort was studied. We reasoned that a possible influential factor might be tumor status at presentation. In patients examined after excision, the remaining tumor cells are left in an avascular, hypoxic environment, so a preop dose might be insufficient, despite reexcision after radiotherapy. Under these conditions, the extent of the previously created surgical bed is difficult to define, and radiotherapy has a key role in sterilizing the peripheral tumor cells. In patients presenting with gross residual disease, a preop dose might be adequate because the vascular supply is left largely intact and the surgical field is better defined. Under these conditions, lower doses could be used to eradicate peripheral tumor cells.

BRACHYTHERAPY

The potential advantage of BRT is that the treatment is usually completed in 4–6 days. Since the catheters are not loaded for 5–6 days to avoid complications, the patient must remain in the hospital for nearly 2 weeks in some cases. Suitable placement of catheters depends on the level of expertise of both surgeon and radiotherapist. In the Memorial Sloan-Kettering BRT series, the local control rate was analogous to that achieved with external-beam radiotherapy. The radiotherapy margin around the surgical bed is, however, much smaller than with external-beam radiation and the risk of marginal failures is enhanced. Overall, external-beam radiotherapy is at least as effective as BRT, perhaps more so in some cases. BRT may be best suited for those patients who present with recurrent disease and have already been treated with external-beam radiation. The applicability of BRT for salvage depends on the surrounding normal tissue structures.

RETROPERITONEAL SARCOMAS

Retroperitoneal sarcomas are typically large (nearly half are >20 cm) at diagnosis and positioned so close to vital structures that radiotherapy dose is limited and surgical resection may be compromised. Local recurrence rates of more than 60% have been reported, with many in the 40% range. Survival at 5 years is typically 40–50%. A recent publication from Memorial Sloan-Kettering Cancer Center reported that only 25% of patients were alive >5 years from the time of surgical resection. As expected, incomplete gross resection increased the risk of tumor-related mortality. Patients who received radiation therapy had a reduction in local recurrence. Our policy at M. D. Anderson Cancer Center has been to deliver preoperative radiotherapy to 44 Gy with oblique off-cord boost fields to 50 Gy, depending on the amount of small bowel in the field. This is followed by complete surgical resection.

SARCOMAS OF LOW METASTATIC POTENTIAL (GRADE 1)

Although desmoid tumors do not metastasize, they are very invasive locally (hence the name ''aggressive fibromatoses'') and, depending on location, may cause death. They are associated with several genetic diseases such as Gardner's syndrome. Although the tumors may originate in any location, their classic presentation is in the anterior abdominal wall of postpartum women. The primary treatment of desmoid tumors is surgical resection. In some cases, the anatomical location may limit resectability and preop or postop radiotherapy may be employed. Sherman et al. reviewed 45 patients treated at MDACC with radiation therapy and concluded that, above 50 Gy, there was not a significant dose response. The median dose was 60.4 Gy, and four of the seven recurrences occurred at doses of 57–66.4 Gy. The actuarial local control rate was 80% at 5 years, similar to that of 14 patients treated with primary radiotherapy for gross disease. Control rates with radiotherapy alone were similar to those of surgery plus radiotherapy; patients with recurrent disease should be evaluated carefully, therefore, to determine the appropriate treatment.

Atypical lipomatous tumors (ALT), dermatofibrosarcoma protuberans (DMFSP), and hemangiopericytomas are tumors of low metastatic potential that are frequently treated by surgical excision alone. Since their local recurrence with surgery alone is probably similar to that of other soft tissue sarcomas, radiotherapy may be employed to ensure local control. The classic presentation of ALT is in the abdomen, but extremity lesions are also seen. Radiation therapy for ALT of the abdomen is not advocated, but disease at other sites, such as pelvis only, extremity, and buttock may be treated with the same techniques as other soft tissue sarcomas. Zagars et al. described a 10-year actuarial local control rate of 92% for 15 patients.

Recently, Suit et al. described the results of radiotherapy for DMFSP. Of the 18 patients analyzed, three were treated with radiation alone and all experienced tumor control. The overall local control rate at 10 years was 88%. The experience at MDACC is similar, with only one local treatment failure among 18 patients treated.

The results with hemangiopericytomas are equally encouraging, indicating that these tumors are also radiosensitive. Staples et al. found that local control was achieved in all four patients treated with surgery plus radiotherapy versus only one of seven treated with surgery alone. Jha et al. reviewed 14 patients treated at MDACC, mainly for positive margins or gross disease. Three were treated palliatively, and of the remaining 11 none suffered local recurrence. Although the dose-response has not been defined because of small patient numbers, most were controlled with doses in excess of 50 Gy. Our current policy is to deliver 60 Gy when possible.

EARLY AND LATE SEQUELAE OF RADIOTHERAPY

Wound Healing

A report from Massachusetts General Hospital revealed that wound healing was complicated in 37% of 202 patients after preop radiotherapy. The complications most often reported were delayed primary closure, dehiscence, ulceration, need for debridement, and cellulitis. Sixteen percent of the patients required a second operation. Cheng et al. found that 31% had wound complications with preop and only 8% with postop irradiation. In our experience, wound healing complications were seen in 25% of patients who received preop and 11% who received postop irradiation. Grafts and flaps must be well healed before postop radiation is initiated. Postoperative treatment of free flaps with radiation is often complicated, and the patient should be warned that secondary surgical repair may be necessary.

Late Reactions

Late effects including fibrosis, necrosis, fracture, edema, neurovascular compromise, contracture, and the need for amputation are moderate to severe in relatively few patients. In the MDACC experience with synovial sarcoma, MFH, and liposarcoma discussed here (includes all grades) the 10-year actuarial rate of moderate to severe complications was about 7% and not dependent on treatment technique (radiotherapy alone vs. preop vs. postop radiotherapy).

ISOLATED LIMB PERFUSION FOR SOFT TISSUE SARCOMA IN THE EXTREMITY

Limb salvage therapy combining surgery and radiation therapy for soft tissue sarcomas in an extremity has resulted in local control rates similar to those for amputation, and without adverse impact on survival. These results have led to the exploration of other methods that would allow limb salvage in patients with large tumors that anatomically make margin-negative surgical resection difficult because of their proximity to bone or neurovascular structures.

Isolated limb perfusion (ILP) with cytotoxic agents was first used in patients with in-transit disease from melanoma confined to the extremity. After McBride of the M. D. Anderson Cancer Center first reported ILP for extremity sarcomas, several other investigators used hyperthermic isolated limb perfusion (HILP) for soft tissue sarcomas. Many of these reports that followed concerned the results of ILP or HILP for melanoma; only a minority of patients had soft tissue sarcomas. Because of the heterogeneous nature of the patients included in these studies and the wide variety of chemotherapeutics (melphalan, nitrogen

mustard, cisplatin, doxorubicin) used in the perfusion circuit, response rates vary from 18% to 60%, with reported 5-year survival rates of 50–69%.

More recently, Lienard et al. reported excellent response rates in recurrent extremity sarcomas using melphalan in combination with tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ). They noted four complete responses (CR) and one partial response (PR), one patient having a pathological CR (no histological evidence of tumor at surgical resection) after repeat perfusion. This study was followed by a European multicenter trial reporting on 55 patients with primary or recurrent soft tissue sarcomas and utilizing the same regimen of melphalan, TNF-α, and IFN-γ in the perfusion circuit. The median tumor size in this group was 18 cm, and 84% of patients achieved limb salvage. Local recurrence developed in 13% of the patients who underwent resection and 31% of the patients who did not. As the authors noted, limb salvage was possible in many patients who did not undergo resection because they died of systemic disease before local recurrence was evident.

Although melphalan has been reported to have minimal activity against soft tissue sarcomas when used as a systemic agent, it has been shown to result in significant PR and occasional CR when used alone or in combination in an ILP circuit. In addition, its local-regional toxicity has been minimal. Doxorubicin has been the most effective systemic agent for soft tissue sarcomas, but concerns about potential local-regional toxicity have limited its use in ILP. Recently, Rossi and colleagues published the results of both a phase I and phase II trial using HILP with doxorubicin for extremity sarcomas. They reported a limb salvage rate of 91% without any increase in local-regional toxicity over that of other regimens.

The use of ILP or HILP for extremity sarcomas remains investigational, and the appropriate cytotoxic agents have not yet been defined. This modality appears, however, to be a useful tool for achieving limb salvage in selected patients with otherwise unresectable tumors.

SYSTEMIC THERAPY

Adriamycin (doxorubicin) and ifosfamide are the two most active agents in soft tissue sarcoma. Both these drugs have a positive dose-response curve. O'Bryan et al. of the Southwest Oncology Group have reported that the response rate to single-agent adriamycin doubles from 18% at a dose of 45 mg/m^2 to 36% at 75 mg/m^2. A randomized trial conducted by the Southwest Oncology Group showed that cardiac toxicity from adriamycin can be significantly minimized by administering the drug as a prolonged continuous infusion, instead of bolus, without compromising response rates. Concomitant use of cardioprotective agents like dexrazoxane (Zinecard) and bolus doxorubicin in adult sarcoma patients can provide similar cardioprotection without the often dose-limiting mucositis; however,

the potential for concomitant tumor protection has to be considered until more data become available. A randomized crossover phase II study of cyclophosphamide versus ifosfamide in adult soft tissue sarcoma patients conducted by EORTC investigators revealed ifosfamide to be a better alkylating agent with a higher response rate and less myelosuppression than cyclophosphamide. Sequential studies at the M. D. Anderson Cancer Center revealed a dose-response relationship for ifosfamide in sarcomas. Response rates at doses of 6, 8, 10, and 14 g/m^2 were 10%, 14%, 21%, and 45%, respectively, in patients with previous exposure to adriamycin. Other chemotherapeutic agents, including dacarbazine, cisplatin, and methotrexate, have minimal activity in soft tissue sarcomas. Actinomycin D, vincristine, and VP-16 are active only in small cell sarcomas including Ewing's, rhabdomyosarcoma, primitive neuroectodermal tumor (PNET), and neuroblastoma.

ADJUVANT CHEMOTHERAPY

The average 5-year disease-free survival rate of patients with localized disease who have undergone surgical excision of the primary tumor is approximately 50%, ranging from 28% to 83% as reported in several randomized trials. This number decreases to less than 20% for tumors with specific histological characteristics like rhabdomyosarcoma and extraskeletal Ewing's sarcoma because these tumors have a much higher propensity for systemic micrometastasis. The latter two responded very well to chemotherapy, with a resultant survival advantage, so that adjuvant chemotherapy is considered standard therapy for these two soft tissue sarcomas. The issue of adjuvant chemotherapy in all other soft tissue sarcomas remains controversial and generates a great deal of debate and discussion. Over the last 10–15 years, several prospective randomized trials have been conducted to evaluate the role of adjuvant chemotherapy in localized soft tissue sarcomas. Only two of these 12 studies showed a statistically significant overall survival advantage when patients received chemotherapy; adjuvant chemotherapy for soft tissue sarcomas is therefore considered investigational. The major criticism of these trials was that the chemotherapy regimen studied in most of them was single-agent adriamycin used at suboptimal dose intensity, which was ineffective chemotherapy. Second, the sample size in each study was too small for a meaningful difference to be detected and the study population was believed to be inappropriately selected since patients with low risk of metastases (small tumors, <5 cm, low-intermediate grade) were mixed with those at high risk of micrometastases (large tumors, ≥ 5 cm, high grade), which could have diluted any potential benefit to the high-risk subset. Despite these problems, the published data from most studies demonstrate a slight numerical advantage, without statistical significance, in disease-free and overall survival in favor of chemotherapy. A recent report of pooled data from 11 prospective studies of randomized

adjuvant chemotherapy revealed a disease-free (68% vs. 53%, $p < 0.00001$) and overall survival advantage (81% vs. 71%, $p = 0.0005$) for patients with soft tissue sarcomas. A formal meta-analysis of 14 adjuvant chemotherapy trials conducted between 1973 and 1990 including 555 patients was performed by the Sarcoma Meta-Analysis Collaboration, Medical Research Council, United Kingdom. The data revealed a significant improvement in local recurrence-free interval ($p = 0.024$), distant recurrence-free interval ($p = 0.0003$), overall recurrence-free interval ($p = 0.000008$), overall recurrence-free survival ($p = 0.00008$), and a trend toward improved survival ($p = 0.087$) in patients who received chemotherapy.

One major deterrent to the use of adjuvant chemotherapy has been the drugs' toxic effects and the unjustifiable risk to the nonresponding patient population. The universal belief is that, in the best of circumstances, 30–50% of patients with soft tissue sarcomas will not respond to standard chemotherapy. A better approach, therefore, would be the use of neoadjuvant or primary chemotherapy, which would enable us to identify patients whose disease is responsive. We could treat these patients aggressively, with some hope of improving their ultimate outcome, and conversely sparing the nonresponding patients the toxic effects of prolonged chemotherapy. In addition, continually improving supportive care with growth factors, antiemetics, and antibiotics has significantly diminished the morbidity of chemotherapy, making it reasonable and justifiable to treat the high-risk population in a controlled clinical research setting.

CHEMOTHERAPY FOR LOW- AND INTERMEDIATE-GRADE SOFT TISSUE TUMORS

Desmoid tumors are locally aggressive neoplasms that have no metastatic potential and are cured in most cases with local therapy comprised of surgery with or without radiation therapy. In selected situations, when the tumor presents as a huge primary requiring surgical procedures that may impose significant functional limitations on the patient, or when it recurs locally within a previously operated and irradiated field, or when it presents as part of Gardner's syndrome with mesenteric fibromatosis that encases the mesenteric vasculature, chemotherapy has been shown to reduce tumor size and thus make less radical surgical procedures possible. Hormonal therapy with tamoxifen, toremifene—a triphenylethylene derivative chemically related to tamoxifen—and progesterone has been reported active in desmoid tumors. Precise response rates are difficult to ascertain because of the small numbers of patients treated and the varying definitions of response used by the investigators; however, response rates seem to range between 15% and 25%. Systemic chemotherapy with doxorubicin and dacarbazine resulted in response rates in excess of 60%, and similar results have been reported with weekly administration of methotrexate and vinblastine.

Intermediate-grade tumors like myxoid liposarcoma, myxoid malignant fibrous histiocytoma, and extraskeletal myxoid chondrosarcoma have a definite metastatic potential, but they fortunately tend to be indolent, having a longer natural history than high-grade sarcomas. Like other soft tissue sarcomas, myxoid liposarcoma and malignant fibrous histiocytoma respond to standard adriamycin-based chemotherapy. In contrast, extraskeletal myxoid chondrosarcoma seems to be refractory to standard chemotherapy.

CHEMOTHERAPY FOR ADVANCED DISEASE

For the vast majority of soft tissue sarcomas, the most common initial site of metastases is the lung. Resection of pulmonary metastases is indeed a valid option for a select group of patients who have few nodules and have had a long disease-free interval, indicating a favorable prognosis. This approach has been reported to result in a 5-year disease-free and overall survival rate of 10–30%. For the majority of patients, the only available treatment modality continues to be combination chemotherapy, which has a complete response rate of approximately 10% and a limited potential for cure. Several investigators have attempted to improve these results by combining ifosfamide and adriamycin with or without dacarbazine, with varying degrees of success. An initial report from the Dana Farber Cancer Institute revealed a response rate of 47% for the three-drug combination MAID; however, subsequent phase II studies with standard and high-dose schedules, with or without growth factors, showed a variable response rate ranging from 22% to 63%. Results from two prospective randomized cooperative group trials indicated that overall response rates were significantly better with the combination of adriamycin and ifosfamide with or without dacarbazine; however, neither complete response rates nor survival rates improved significantly. The results of the EORTC study, however, indicate no difference in response rates to either single-agent adriamycin or the combination of adriamycin and ifosfamide. Severe myelosuppression, which seemed to be the dose-limiting toxic effect of these combinations, required dose reductions and further compromised the already compromised dose intensity of the individual active drugs; this may, in turn, have been responsible for the lack of improvement in complete responses and overall survival. The major thrust of clinical research over the last few years has been focused, therefore, on dose intensification of the commercially available agents with growth factors. The basic rationale of trials evaluating higher dose intensity lies in the linear dose-response relationship of adriamycin and ifosfamide. The ultimate goal one would hope to achieve is an incremental response rate, together with improvement in the quality of response sufficient to influence survival. The advent of growth factors like granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) has helped minimize the morbidity related to neutropenia. The issue of dose-limiting

thrombocytopenia has therefore become the most important hurdle for the medical oncologist. At the M. D. Anderson Cancer Center, we are currently evaluating the dose-intensive combination of adriamycin at 90 mg/m^2 and ifosfamide at 10 g/m^2 in conjunction with G-CSF and thrombopoietin, a platelet-specific growth factor. Preliminary analysis of the first 43 patients with soft tissue sarcomas (excluding leiomyosarcomas of gastrointestinal origin, which tend to be refractory to these two drugs) reveals a response rate of 70%, which is extremely encouraging. Although the strategy of dose intensification with growth factor support seems promising, its ultimate effect on survival is anxiously awaited.

The enthusiasm for marrow-ablative doses of chemotherapy with or without total-body irradiation, followed by autologous bone marrow rescue, seems to have waned. The results of early studies performed in the mid- to late 1980s were uniformly disappointing, with short durations of response, extremely high cost, substantial treatment-related morbidity and mortality, and a lack of improvement in survival rate. Among others, the most apparent reason seems to be the absence of an effective, cytoreductive regimen with minimal extramedullary toxicities. A more appealing approach may be to deliver higher chemotherapy dose intensity on multiple occasions with reinfusion of the growth factor–stimulated and harvested peripheral blood progenitor cells. This approach has the advantage of not requiring general anesthesia, and platelet recovery is generally more rapid than after autologous marrow transplantation.

NEW DRUGS AND APPROACHES

Although current areas of research, including dose intensification with growth factor support, seem promising, newer, more effective drugs offer the best hope for future progress. At M. D. Anderson, we have studied paclitaxel (Taxol) in patients with previously treated bone and soft tissue sarcomas and did not observe responses in any of the trials. A recent report of using paclitaxel in patients with previously untreated advanced soft tissue sarcomas showed a response rate of 12.5%. In a phase II study of Topotecan, a topoisomerase I inhibitor, investigators from the NCI in Canada found two partial responses in the first 16 evaluable soft tissue sarcoma patients. Docetaxel (taxotere) is another interesting drug with broad-spectrum activity. An initial report from the EORTC phase II study described five partial responses among 29 evaluable patients who were previously treated with chemotherapy, adding up to a response rate of 17% (95% CI, 6–36%), with a median response duration of 5 months. Another study of Docetaxel conducted by the North Central Cancer Treatment Group in previously untreated patients with soft tissue sarcomas resulted in a disappointing response rate of 5.9% (95% CI, 0.15–28.7%).

Immunotherapy trials in sarcomas have been limited. In two phase II studies at our institution of alpha interferon alone and in combination with 5-fluorouracil

the response rates were <10%. Hyperthermic isolated limb perfusion with TNF-α, INF-γ, and melphalan has been reported to result in extremely high response rates in patients with localized extremity soft tissue sarcomas. This approach does not address the systemic micrometastases, which are a major problem in most high-risk patients. Clinical research efforts should be aimed at better selection of candidates for therapy, identification of newer drugs, and improving the methods of implementing the currently available therapeutic armamentarium.

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Melanoma

Alfred E. Chang, Timothy M. Johnson, David C. Smith, and Howard M. Sandler
University of Michigan, Ann Arbor, Michigan

GENERAL INFORMATION

Incidence and Mortality

New knowledge and guidelines regarding the genetics, biology, and treatment of melanoma continue to rapidly change and develop. The incidence of melanoma is increasing at a greater rate than any other human cancer in the United States and the increase in the mortality rate is second only to lung cancer. Since 1973, the incidence rate has been rising 4–6% each year. In 1995, approximately 34,100 new cases were reported in the United States resulting in 7200 deaths, or one death every hour and 13 minutes. Nearly half of these new cases occurred in people younger than 40 years of age. Melanoma is presently the seventh most common type of cancer overall. It is the most common cancer in women between 25 and 29 years of age, and second only to breast cancer in women 30–35 years of age. Lifetime analysis reveals that approximately one in 75 persons born in the year 2000 will develop melanoma during their lifetime. Despite the rapidly increasing incidence of melanoma over the past five decades, the overall 5-year survival rate increased from 40% in 1940 to the present 80%. Earlier detection, diagnosis, and surgical excision are probably the most significant factors accounting for the increase in overall survival rates during the past decades.

Predisposing Factors

Since early detection, diagnosis, and surgical removal of such lesions is desirable, efforts should be particularly directed toward identifying individuals who are at

an increased risk of developing melanoma. Risk factors include a history of light complexion, blue eyes, red or blonde hair, tendency to freckle, and tendency to sunburn. A personal or family history of melanoma, atypical nevi, or many nevi, or a history of significant sun exposure (especially blistering sunburns even in childhood) also puts the individual at higher risk for developing melanoma. Familial melanoma occurs in as high as 10% of cases. One predisposing gene has clearly been linked to chromosome 9, while a second linkage to chromosome 1 is still uncertain. The most common early signs of melanoma are a change in size, shape, or color of a skin lesion. The earliest symptom is persistent pruritus of a lesion. Later signs and symptoms include bleeding, crusting, erosion, ulceration, and tenderness.

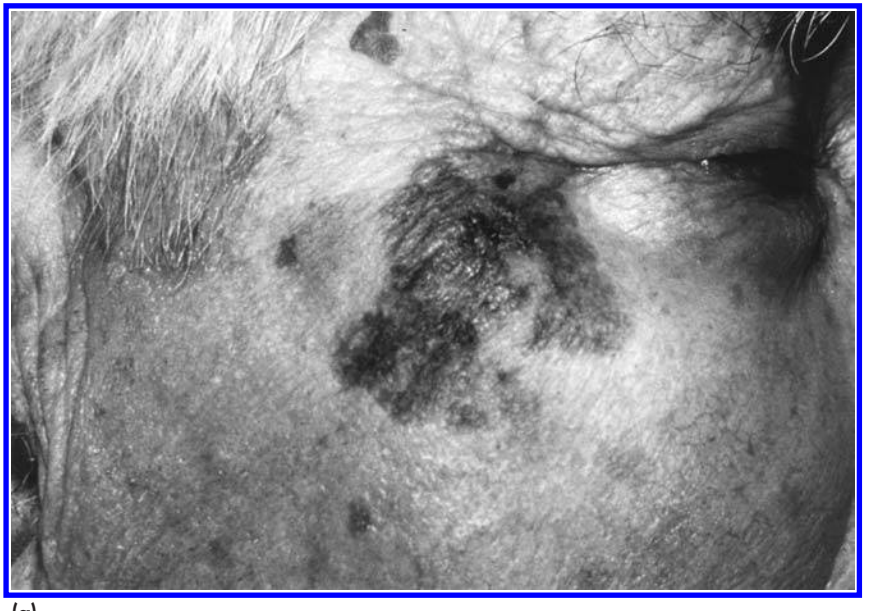
SURGERY

Introduction

Surgical excision remains the mainstay of definitive therapy in those melanoma patients presenting with disease confined to the primary skin site and regional nodal basins [American Joint Committee on Cancer (AJCC) stages 0–III]. Over 90% of patients diagnosed with primary cutaneous melanomas will present with these stages of disease. Recent prospective, randomized clinical studies have defined acceptable guidelines for excisional margins, based on tumor thickness and other prognostic factors. Modifications of surgical technique may be indicated, based upon the anatomical location and histology of the primary tumor.

Diagnosis and Biopsy

A biopsy is indicated for any lesions suspected for melanoma. Lesions that are asymmetrical, display variegated borders, demonstrate several different colors (i.e., brown, red, black, blue, and white), and are $>$6 mm are common features of melanomas. Nevertheless, early melanomas may lack these signs. Based on growth patterns and clinical characteristics, melanomas can be classified into four major categories: lentigo maligna melanomas, superficial spreading melanomas, nodular melanomas, and acral lentiginous melanomas (Fig. 1). Lentigo maligna melanomas constitute 10–15% of cutaneous melanomas. These melanomas typically occur on sun-exposed areas of the head and neck and are more prevalent in the older population. Superficial spreading melanomas account for about 70% of melanomas, making them the most common subtype. These lesions are typified by variation in color, irregular borders, and irregular surfaces. Nodular melanomas occur in 15–30% of patients with melanoma and often present as thick lesions; hence, they are the most aggressive lesions. In general, nodular melanomas are bluish black, more uniform in coloration, and have smooth borders. Acral



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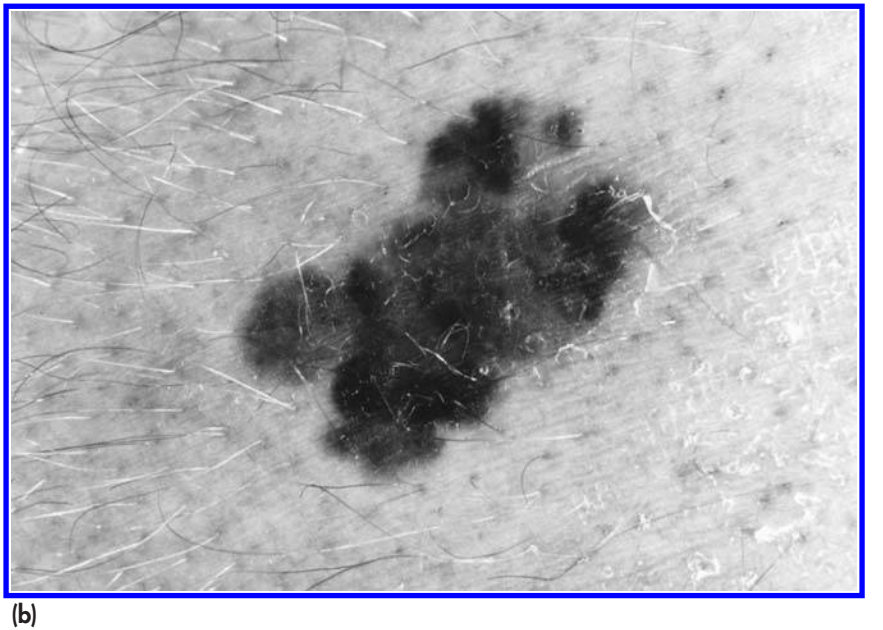
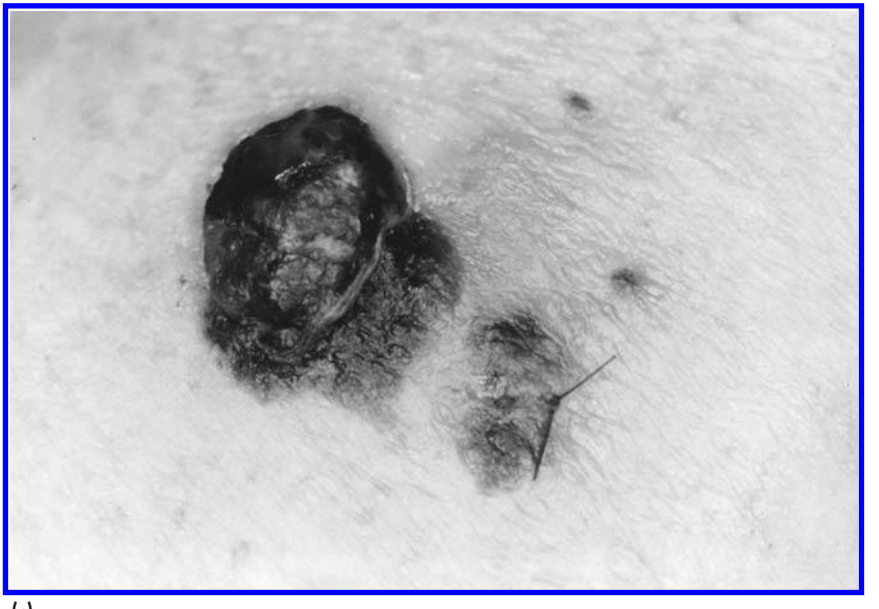


(b)

FIGURE 1 Examples of different categories of melanoma. (a) A lentigo maligna melanoma of the facial area. (b) A superficial spreading melanoma. (c) A nodular melanoma. (d) An acral lentiginous melanoma located on the plantar surface of the foot.



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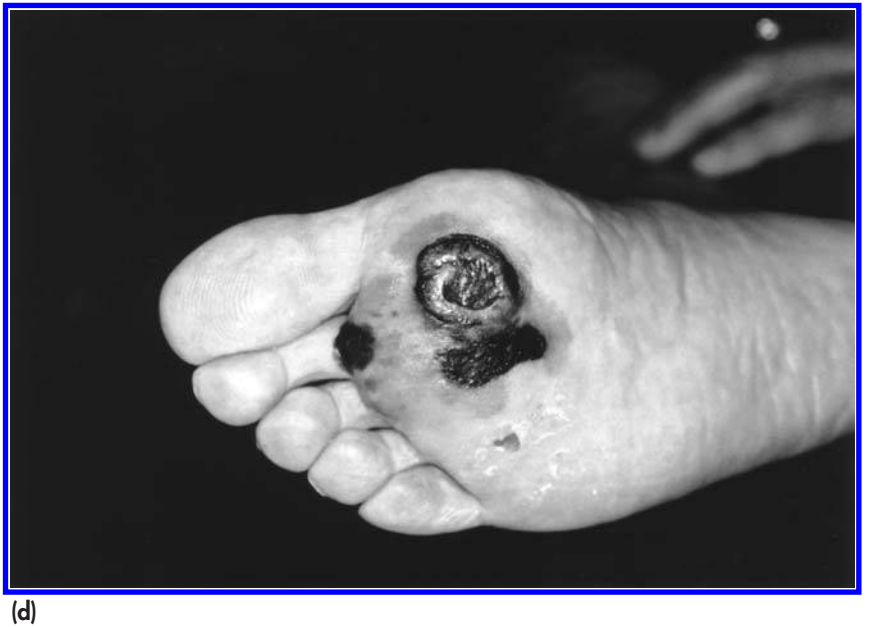


(d)

lentiginous melanomas occur in the palms, soles, and subungual locations. These lesions occur in only 2–8% of whites with melanoma, as opposed to 35–60% of dark-pigmented individuals (i.e., blacks, Hispanics, Asians) who develop melanoma.

Tumor thickness measured in millimeters (Breslow depth) is the strongest predictor and single most important factor that ultimately determines treatment, prognosis, and follow-up recommendations for melanoma. For this reason, a shave biopsy through the dermis is never recommended for melanoma owing to the risk of transecting the lesion and preventing an accurate measurement of the Breslow depth of invasion. If the lesion is small, complete excision with a 2-millimeter (mm) margin is desirable and can be done under local anesthesia. A portion of the underlying subcutaneous fat should be included for accurate microstaging (Fig. 2). Excisional biopsies for very small lesions can be accom-

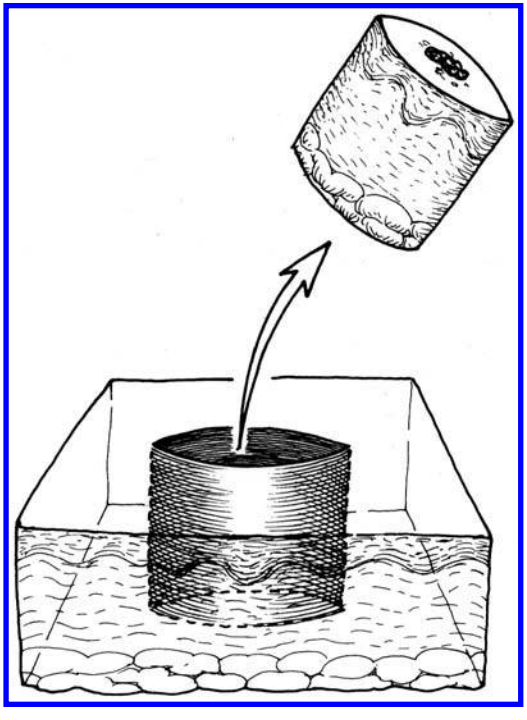


FIGURE 2 An excisional biopsy with 1–2-mm margins is the preferred biopsy method for small suspicious pigmented lesions. To provide the pathologist with a total specimen for histological evaluation, the incision should be extended into the subcutaneous adipose tissue. (Reprinted with permission from Arca et al., 1995.)

plished using a punch biopsy tool, which is available in various sizes (Fig. 3). The excisional biopsy represents the first of a two-stage procedure if the lesion is, in fact, a melanoma. The second stage consists of a wide local excision with margins ranging from 0.5 to 3.0 cm with or without lymphatic mapping, depending primarily on the final tumor thickness (see below). The preferred method of excisional biopsy is a standard elliptical excision parallel to the lymphatics. Alternatively, a deep saucerization to the underlying fat allowing the wound to granulate secondarily may be performed.

If the lesion is too large for total excision or located anatomically where complete excision is difficult or undesirable, then an incisional biopsy through the thickest and darkest part of the lesion may be performed (Fig. 4). Incisional biopsies do not increase the risk of metastasis for melanoma. The punch biopsy tool can be used for obtaining incisional biopsies.

Subungual melanomas can be confused with subungual hematomas. More than three-fourths of subungual melanomas involve the great toe or thumb. They generally arise at the base of the nail bed and present as an irregular, tan-brown streak. In the absence of a trauma history to the nail, irregular pigmented lesions of the nail bed should be biopsied. This requires removal of a portion of the nail to biopsy the nail bed, which can be performed under a digital block.

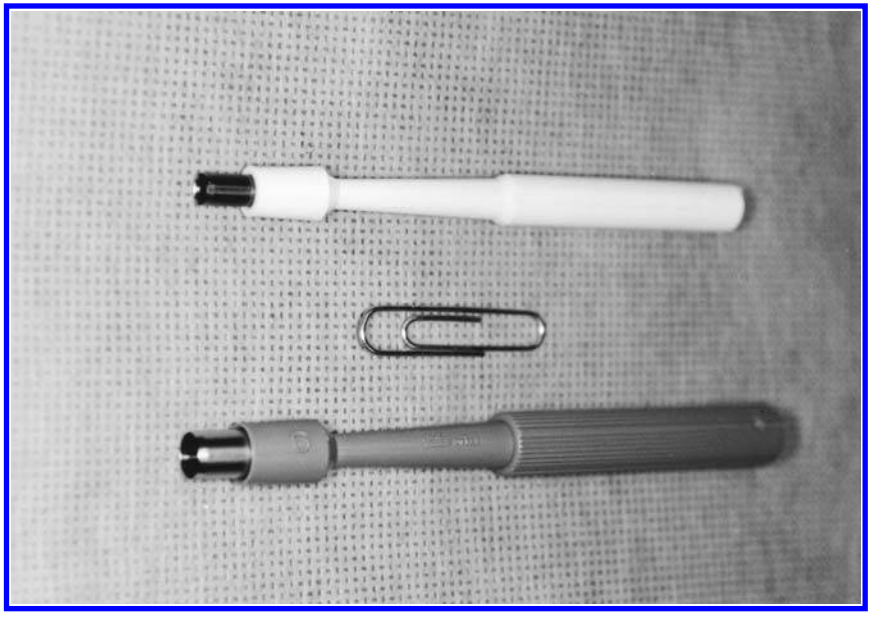


Figure 3 A 4- and 6-mm punch biopsy tool used for skin biopsies.

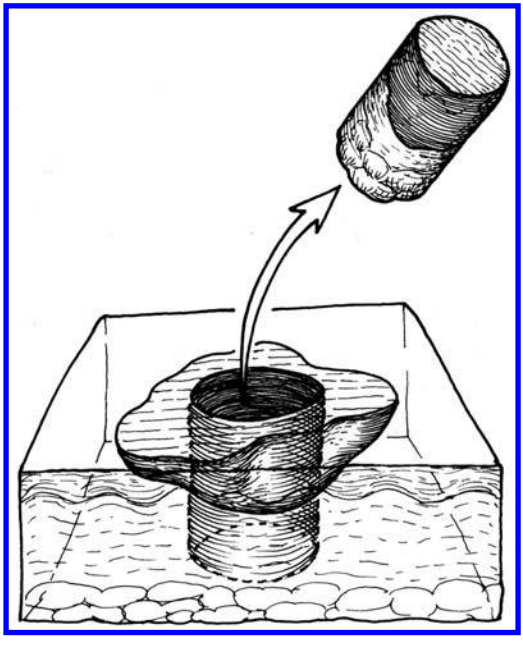


FIGURE 4 An incisional biopsy may be performed for suspicious pigmented lesions that are too large for complete excision simply because of size or anatomical location. A punch biopsy shown here removes a circular specimen. The most elevated or suspicious area of the lesion is removed to include a portion of subcutaneous tissue. (Reprinted with permission from Arca et al., 1995.)

Staging

Accurate histopathological interpretation of the biopsy specimen is the cornerstone for treatment and prognosis of melanoma. A histopathology report for melanoma should include the diagnosis, thickness of the lesion in millimeters as defined by Breslow (measured from the granular layer to the deepest portion of the tumor), and status of the margins. Additional histological factors that may provide important prognostic and treatment information include the presence or absence of ulceration, microsatellitosis, angiolymphatic invasion, neurotropism, and extensive regression. The histological subtype pattern (i.e., superficial spreading, lentigo maligna, nodular), Clark level of invasion, mitotic rate, and growth phase (radial or vertical) may also provide valuable information in select cases.

The most current American Joint Commission on Cancer staging system is given in Table 1. Stages I and II represent localized disease $\leq$ 1.5 mm (I) and

TABLE 1 American Joint Commission on Cancer (AJCC) Staging System (1992)

TNM Staging of Melanoma

Primary tumor (pT)

pTX	Primary tumor cannot be assessed
pTO	No evidence of primary tumor
pTis	Melanoma in situ (atypical melanocytic hyperplasia, with severe melanocytic dysplasia, not an invasive lesion) (Clark level I)
pT1	Tumor 0.75 mm or less in thickness and invading the papillary dermis (Clark level II)
pT2	Tumor more than 0.75 mm but not more than 1.5 mm in thickness and/or invades to the papillary-reticular dermal interface (Clark level III)
pT3	Tumor more than 1.5 mm but not more than 4 mm in thickness and/or invades the reticular dermis (Clark level IV)
PT3a	Tumor more than 1.5 mm but not more than 3 mm in thickness
PT3b	Tumor more than 3 mm but not more than 4 mm in thickness
pT4	Tumor more than 4 mm in thickness and/or invades the subcutaneous tissue (Clark level V) and/or satellite(s) within 2 cm of the primary tumor
pT4a	Tumor more than 4 mm in thickness and/or invades the subcutaneous tissue (Clark level V)
pT4b	Satellite(s) within 2 cm of the primary tumor

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis 3 cm or less in greatest dimension in any regional lymph node(s)
N2	Metastasis more than 3 cm in greatest dimension in any regional lymph node(s) and/or in-transit metastasis[a]
N2a	Metastasis more than 3 cm in greatest dimension in any regional lymph node(s)
N2b	In-transit metastasis
N2c	Both (N2a and N2b)

Distant metastasis

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis in skin or subcutaneous tissue or lymph node(s) beyond the regional lymph nodes
M1b	Visceral metastasis

	Stage Grouping		
Stage I	pT1	N0	M0
	pT2	N0	M0
Stage II	pT3	N0	M0
	pT4	N0	M0
Stage III	Any pT	N1	M0
	Any pT	N2	M0
Stage IV	Any pT	Any N	M1

[a] In-transit metastasis involves skin of subcutaneous tissue more than 2 cm from the primary tumor not beyond the regional lymph nodes.

> 1.5 mm (II) thick, respectively; stage III is regional lymph node disease; and stage IV is distant disease.

Wide Excision

For melanoma in situ (stage 0), excision of normal skin 0.5 cm around the lesion or previous biopsy site is acceptable for local control. For invasive cutaneous melanoma, wider excision of the primary tumor or biopsy site is necessary. The extent of the wide excision has evolved from the results of prospective, randomized trials conducted within the last 10 years. Prior to these trials, the routine approach was to excise all primary cutaneous melanomas with 3–5-cm margins, often requiring skin grafts or rotation flaps for coverage. The rationale for such large excisions was to avoid local recurrences. In retrospective analyses, it became apparent that the risk of local recurrence correlated more with the thickness of the melanoma than with the margin of excision. Local recurrence after excision of melanomas less than 1 mm thick is rare regardless of the extent of the margin. Hence, the margin of excision is based upon the Breslow thickness of the lesion.

The extent of the wide excision margins is summarized in Table 2. For thin lesions less than 1 mm thick, a margin of 1 cm is adequate. Almost all of these excisions can be closed primarily without the need for grafting. For thick lesions measuring greater than 4 mm, a 3-cm margin should be obtained. In these cases, skin grafting is often necessary for coverage. These excisions should be taken down to the underlying muscle fascia. Whether the fascia is taken or not has not been demonstrated to be a critical factor in achieving local control.

Despite these recommendations, the site of melanoma can sometimes affect the extent of the excision. Facial lesions usually cannot be excised with more than a 1-cm margin because of the adjacency of vital structures. Special mention must be made concerning the treatment of the lentigo maligna melanoma, a com-

Table 2 Surgical Guidelines for Patients with Localized Melanoma Based on Tumor Thickness

Breslow depth (mm)	Excision margin (cm)	5-year disease-free survival (%)
In situ	0.5	99+
≤1.0	1	90–99
1.1–4.0	2[a]	60–90
>4.0	3	<50

[a] For lesions 1.1–2.0 mm, a margin of 2 cm is preferable. However, if primary closure can not be obtained, then a margin of 1 cm is acceptable.

mon lesion in the head and neck region. A Wood's lamp is useful to identify the extent of pigmentation in the skin that is not clinically apparent in normal light. Excision margins of at least 1 cm are considered acceptable for treatment for lentigo maligna melanoma. However, if margins reveal residual atypical melanocytic hyperplasia, reexcision to obtain clear margins is mandatory.

Subungual melanomas should always be treated with amputation. In general, a margin of at least 1 cm of normal skin must be maintained between the tumor edge and the level of amputation. The goal of the amputation is to achieve an adequate margin while preserving digit function, which can be accomplished by amputating at the level of the interphalangeal joint in the thumb or toe.

Regional Lymphadenectomy

Surgical excision of the metastases to regional lymph nodes is the only potentially curative therapy for stage III disease. Only 10% of patients who first present with a diagnosis of melanoma will have clinically evident nodal disease; about 85% will have disease confined to the primary site (stage I or II); and the remaining 5% will have distant metastases (stage IV). Of those patients who present with nodal disease, less than 15% will have a diagnosis of melanoma made in the absence of a definable primary lesion. If patients present with isolated nodal disease from an unknown primary site, the results of lymphadenectomy are similar to those with known primary tumors (see Results).

The surgical excision of clinically positive lymph nodes is referred to as a therapeutic lymph node dissection (TLND). Some surgeons prefer to perform lymphadenectomy when the patient presents without clinically suspicious nodal enlargement. This procedure is known as an elective node dissection (ELND) or prophylactic dissection. Until recently, the application of ELND was one of the most controversial procedures in surgical oncology. Advocates of ELND claimed that resection of occult microscopic metastases in the regional nodes resulted in better cure rates than taking the ''wait and watch'' approach where patients undergo TLND only when clinically suspicious nodes become evident. The drawback to ELND is that a majority of patients would end up having no evidence of disease in their resected lymph nodes, and would have undergone an unnecessary procedure.

To address this controversy, several prospective randomized trials have been performed. These are summarized in Table 3 and include patients with stages I and II disease who are randomized to receive ELND versus routine follow-up with use of TLND when indicated. A total of 1464 patients were included in these studies, which demonstrated that there was no survival advantage between randomized treatment arms. In the most recent study that entered only patients with melanomas 1–4-mm thick, a subgroup analysis revealed that indi-

TABLE 3 Prospective Randomized Clinical Trials Evaluating ELND versus TLND in Stage I and II Melanoma

Trial[a]	No. of patients	Median follow-up (years)	Results
World Health Organization	553	10.4	No difference
Mayo Clinic	171	4.5	No difference
Intergroup Study, U.S.	740	7.4	No difference in overall groups; individuals ≤60 yrs. old had improved survival with ELND
Total	1464		

[a] See reference list for citations.

viduals 60 years of age or younger had an improved survival if subjected to an ELND. Taken in the aggregate, the results of the randomized studies indicate that ELND has a minimal role in the therapy of melanoma.

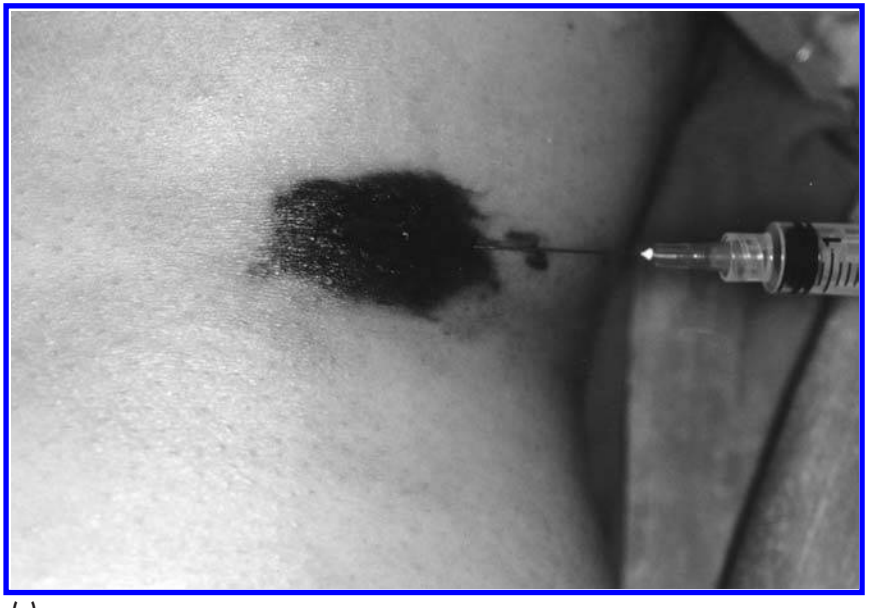
Despite these conclusions regarding ELND, more recent findings regarding adjuvant therapy for resected node-positive patients have raised the issue of mandatory staging of melanoma patients to determine therapeutic options. In the past, there were no known systemic therapies proven to be efficacious in improving survival in patients with stage III disease. As will be described later, interferon-alpha (IFN-α) has been shown to enhance survival in patients with node-positive disease. This finding provides a rationale to subject patients to ELND for staging purposes to determine subsequent therapy. The development of selective lymphatic mapping to identify the ''sentinel'' lymph node draining a primary melanoma has helped address the issue of whether or not a lymphadenectomy should be performed.

Lymphatic Mapping

An attractive alternative to ELND for staging patients with clinically localized melanoma would be to restrict the use of lymphadenectomy to patients in whom microscopic nodal metastases are known to be present. This information would reduce the number of unnecessary lymphadenectomies and allow the application of the surgical procedure to those patients most likely to benefit. A technique called intraoperative lymphatic mapping has been developed to identify the first draining lymph node adjacent to a cutaneous melanoma, known as the sentinel lymph node. It has been hypothesized that melanoma involvement of a nodal

basin develops in an orderly fashion and that involvement of the sentinel node is the first step of this process. By injection of a blue dye intradermally around the site of the primary melanoma, the sentinel lymph node can be identified by exploration of the nodal basin through a small incision and retrieved for pathological examination. The dye is taken up by afferent lymphatics, which initially drain to the sentinel lymph node, and mimics how melanoma cells spread to regional nodal basins (Fig. 5). With this blue dye technique, patients with clinically localized melanomas have been found to have tumor involvement of the sentinel node about 20% of the time. Formal lymphadenectomy is then performed only if histological examination confirms metastatic disease. Moreover, it has been shown that a negative sentinel node accurately predicts whether the remaining nodes in the basin are negative. Usually the formal lymphadenectomy is performed as a separate procedure several days later to allow thorough pathological assessment of the sentinel node. This approach can replace ELND and is referred to as selective lymph node dissection. There are several advantages to incorporating lymphatic mapping in the routine management of clinically localized melanoma: (1) the technique can be performed as an outpatient procedure; (2) only patients with histological proof of nodal disease would be subjected to lymphadenectomy; (3) patients requiring adjuvant systemic therapy can be identified with less invasive procedures. An important aspect of adequate lymphatic mapping is the thoroughness of the pathological evaluation. It has been shown that single sections of the sentinel lymph node are inadequate to assess the presence of microscopic involvement. Multiple sections for routine histological assessment are required. Moreover, the employment of immunohistochemical staining is also key to identify melanoma cells (i.e., S100 and HMB-45 staining) within the sentinel lymph nodes. Lymphatic mapping cannot be employed after a wide excision has been performed. A wide excision interrupts a large area of dermal lymphatic drainage and can potentially alter flow to the sentinel node. Lymphatic mapping can only be performed with an intact primary lesion or a lesion that has been excisionally biopsied.

An important adjunct to the use of lymphatic mapping is lymphoscintigraphy. This technique employs the intradermal injection of technetium sulfur colloid around the site of the primary lesion to help determine the sites of lymphatic drainage of melanomas located in ambiguous areas where multiple drainage sites are possible (i.e., head and neck region, midback region). In addition, this technique can be combined with the blue dye method to help the surgeon localize the sentinel node intraoperatively utilizing a hand-held gamma-detector probe. The combination of both techniques can decrease the operation time as well as minimize the incision made to localize the sentinel node. An algorithm for the surgical approach to treatment of cutaneous melanomas is outlined in Figure 6. It is apparent that for lesions < 1 mm in thickness, the lymphatic mapping tech-



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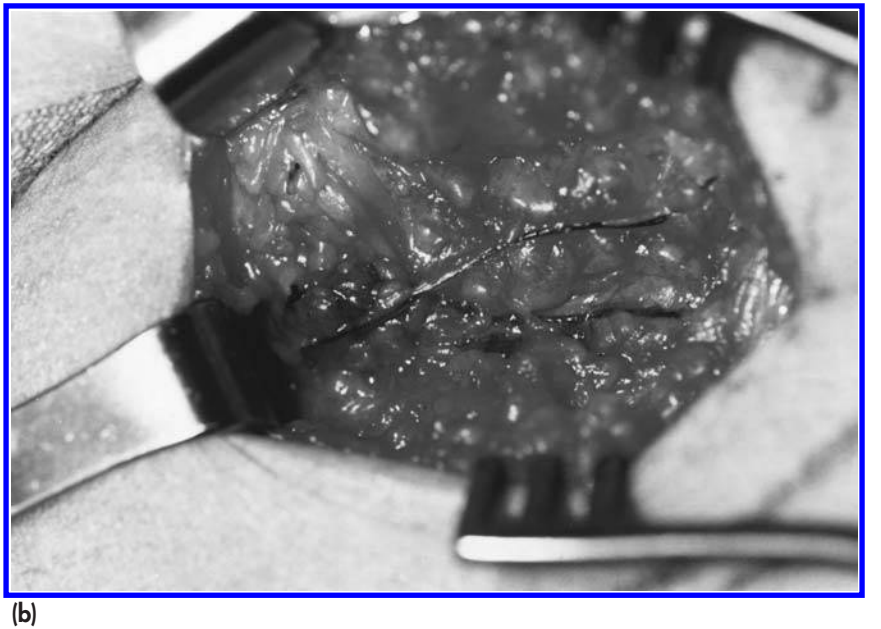

(b)

FIGURE 5 Lymphatic mapping technique with blue dye. (a) Injection of 1.5–2.0 ml of blue dye (Lymphozurin) intradermally at the site of a melanoma that has been excisionally biopsied. (b) Identification of two lymphatic vessels in a nodal basin tracking toward the blue-stained sentinel lymph node.

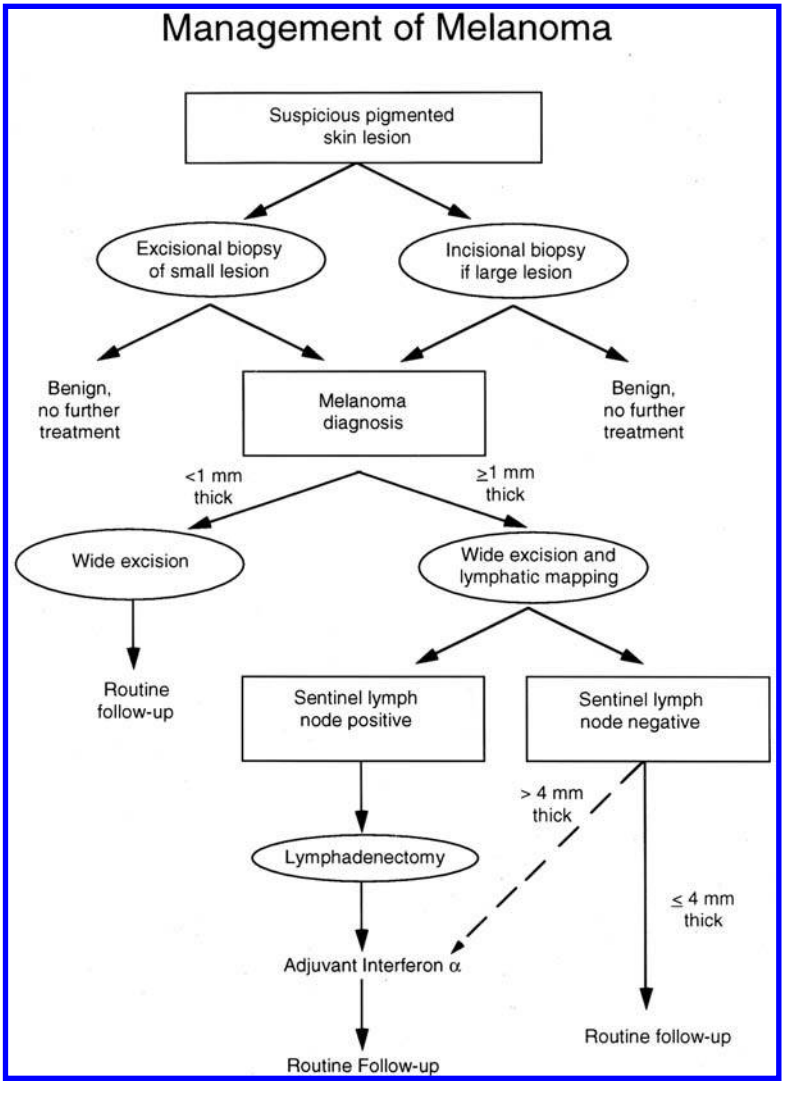

FIGURE 6 An algorithm for the management of cutaneous melanoma confined to the skin or regional lymph nodes (stages I–III).

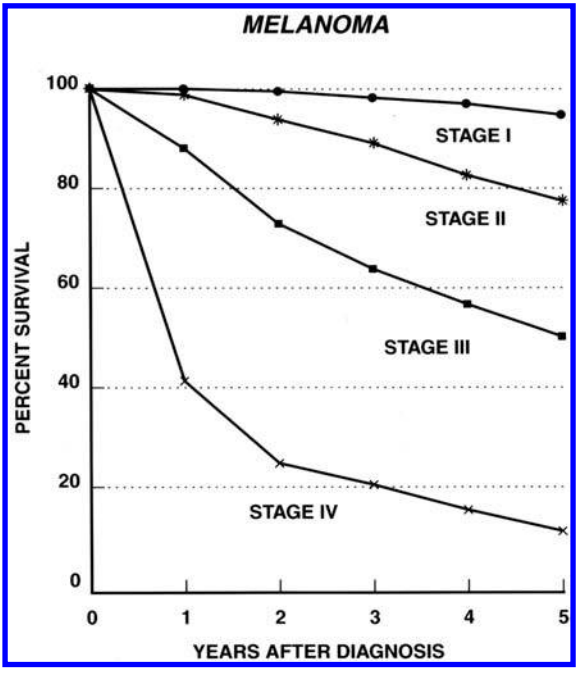

FIGURE 7 Five-year survival rates of cutaneous melanoma correlated with the AJCC stages.

nique is not required as the incidence of occult nodal metastases would be exceedingly low. For lesion $\geq$ 1 mm, and where the draining lymph nodes are clinically negative, lymphatic mapping is recommended for complete surgical staging.

Results and Complications

The correlation of survival with staging is shown in Figure 7. In general, patients with melanoma in situ (stage 0) are not considered to have a malignant tumor and will be cured 100% of the time with adequate wide excision. Patients with stage I, II, and III disease have 5-year survivals of >80%, 50–80%, and 25–50%, respectively. For patients with stage I or II disease, there is a direct correlation with the thickness of the primary lesion in millimeters and the survival rate. Therefore, within stages I and II, a range of survival rates is observed. For stage III patients, the survival rate diminishes directly with the number of involved lymph nodes. Overall, the survival of patients with stage IV disease is dismal with a 5-year rate of 25%. Therapies for stage IV disease are reviewed in later sections.

Complications associated with surgical therapy are mainly confined to individuals undergoing lymphadenectomy. For individuals with head and neck melanomas, the major complications associated with nodal dissections are associated with nerve damage. These include injuries to the facial nerve, spinal accessory nerve, or stellate ganglion. The incidence of these complications should not exceed 1–2%. For individuals undergoing axillary dissection upper extremity edema may occur in up to 5% of patients along with symptoms related to division of the intercostal brachialus nerve bundles. Injuries of the long thoracic nerve leading to the ''winged scapula'' or thoracodorsal nerve are rare. Superficial groin dissections in the femoral triangle can be associated with lower extremity edema in 5–25% of individuals. The employment of a deep groin dissection to remove the external iliac lymph nodes in conjunction with a superficial groin dissection is associated with a higher incidence of lower extremity edema. The rarity of involvement of the deep inguinal lymph nodes when the superficial nodes are not palpably enlarged or only microscopically involved does not warrant a deep dissection. When the highest superficial groin node is grossly enlarged (also known as Cloquet's node) or there is computed tomography scan evidence of iliac lymph node enlargement, a deep groin dissection should be performed. Skin separation and cellulitis are more common after inguinal lymph node dissections than after lymphadenectomies in other sites. Because of the extensive skin flaps that are raised with inguinal dissections, trimming the wound skin edges at highest risk for ischemia should be performed.

MEDICAL ONCOLOGY

Introduction

Early in its natural history, melanoma has the ability to spread throughout the body. Common sites of metastatic disease are the skin, subcutaneous tissues, lymph nodes, bone, brain, and viscera. At a very early stage, melanoma is thus a systemic disease. Systemic therapy consisting of immunological or chemotherapeutic approaches is indicated in concert with surgery and radiation therapy to deal with metastatic lesions. This section will discuss the systemic approaches used in the treatment of patients with melanoma.

Interferon for Adjuvant Therapy

Patients who present with thick primary melanomas (>4.0 mm Breslow depth) or melanoma metastatic to regional lymph nodes are at high risk for systemic relapse and mortality. Several studies suggest that more than 75% of patients with node-positive melanoma (stage III) will develop metastatic disease within 5 years. Based on documented response rates of 15–20% in patients with metastatic

melanoma treated with interferon-alpha2b (α2b), the Eastern Cooperative Oncology Group embarked upon a randomized phase II study of adjuvant high-dose interferon α2b in patients with deep or node-positive melanomas. Patients were randomized between no treatment and maximally tolerated doses given intravenously daily for 5 days a week $\times$ 4 weeks, followed by subcutaneous administration three times weekly for 48 weeks. The initial induction dose was 20 million units/m^2 followed by maintenance at 10 million units/m^2/dose. High-dose interferon treatment resulted in a significant reduction in the incidence of melanoma recurrence, as well as a significant delay in the time to relapse. Thirty-seven percent of the patients in the treatment arm were disease-free at a median follow-up of 6.9 years versus 26% in the observation arm. This represents a 42% improvement in the fraction of patients who were continuously disease-free after treatment. Expressed in a somewhat different fashion, disease recurrence was prevented in approximately one in six patients who are destined to recur following surgery.

The toxicity associated with this regimen is significant. Typically, patients have marked fatigue during the initial induction phase, which results in significant disability. Fevers, chills, myalgias, nausea, and vomiting are also common, but are generally fairly well controlled with current regimens designed to prevent these complications. Significant myelosuppression and hepatotoxicity occur in the majority of patients. This often results in dose reduction, or dose delay. In the initial study, fully two-thirds of the patients had severe toxicity at some point during the year of treatment, and nearly 10% had life-threatening toxicity. The most common toxicities during the maintenance phase are anorexia, which may result in significant weight loss, and gradual alopecia. Treatment with this regimen requires close attention to the need for dose modification, but with appropriate dose modification, 75% of patients can complete a full year of therapy.

Based on the results of this study, high-dose interferon α2b has become the standard adjuvant therapy for high-risk melanoma. Owing to the toxicity associated with this regimen, there are several limiting factors for this therapy. Patients with comorbid conditions that result in a limited life expectancy, or that would predispose them to excessive toxicity (e.g., coronary artery disease, active hepatitis), are not good candidates for this therapy. Similarly, this therapy should be used with caution in patients with deep melanomas ($>$4.0 mm Breslow depth) who have no evidence of nodal involvement by either clinical examination or sentinel node biopsy. The randomized study showed that node-positive patients had the most significant benefit for therapy with interferon-α2b, and that this effect was independent of whether they presented with palpable adenopathy or disease detected on node biopsy. In contrast, there was no impact of therapy on the small number of patients with deep melanomas ($>$4.0 mm) who did not have nodal involvement. Thus, in practice, adjuvant therapy with high-dose interferon is recommended for all patients with node-positive disease who are capable of

tolerating the therapy, and only for selected patients with deep melanomas without evidence of nodal involvement. These latter patients should definitely not be treated with interferon if comorbid conditions exist.

Biological Response Modifiers for Metastatic Disease

Interferon has also been studied extensively in patients with metastatic disease. Individual phase II studies have reported response rates ranging from 10 to 25%, and the overall response rate appears to be near 15% with a 5% complete response. Prognostic factors indicate that patients with nonvisceral disease are more likely to respond. Some patients will respond to relatively low doses of interferon, and there is no evidence that response rates are higher with high-dose regimens. Interferon therapy is associated with typical toxicities including fatigue, fever, chills, myalgias, arthralgias, and anorexia. These side effects appear to be dose-related. Combinations of interferon with chemotherapy have not shown a significant improvement in response rates or survival in large randomized trials, although one small trial of dacarbazine (DTIC) alone versus DTIC with interferon suggested an increase in response rate and median survival with the combination.

Interleukin-2 (IL-2) is another biological agent that has been used to treat metastatic disease. The mechanism of action IL-2 is unique in that it possesses no direct antitumor activity. IL-2 exerts its effect via the immune system, although the exact immune mechanisms that are activated by IL-2 resulting in tumor regression are not entirely clear. High-dose bolus IL-2 has been shown to have a 17% overall response rate with a 7% complete response rate in the largest study published to date. These data indicate that IL-2 alone can produce meaningful remissions that are often long-lived in patients with metastatic melanoma. However, the response rate is low, and the significant toxicity associated with this regimen limits its use. High-dose IL-2 is associated with a capillary leak syndrome, which can result in renal and cardiac toxicity. The high-dose regimen requires placement of a central venous access device. With close monitoring and judicious use of pressors and fluids, appropriately selected patients can usually be safely treated outside of the intensive care unit setting. In addition to the cardiac and renal toxicities, fever, malaise, and anorexia are common. Specific deficits in immune function are also included, which predispose patients to bacterial infections. Despite these toxicities, dramatic tumor responses have been demonstrated in both previously untreated and chemotherapy-refractory patients. High-dose IL-2 remains an option for the treatment of patients with metastatic melanoma with good performance status.

Biological agents have also been combined with chemotherapy in a variety of trials. In general, these combinations have been disappointing. IL-2 has been used with combination chemotherapy with marginal increases in response rates over chemotherapy alone in several trials. A trial based at M. D. Anderson Cancer

Center did show an apparent improvement in median survival when compared to the chemotherapy regimen alone; however, this was not in a randomized trial. Similarly, combinations of interferon with DTIC alone and in various combinations have shown slight increases in response rate, but have not demonstrated any significant increase in survival in the few randomized trials that have been conducted.

Chemotherapy for Metastatic Disease

DTIC is the mainstay of chemotherapy for metastatic melanoma. Single-agent trials have demonstrated response rates ranging from 15 to 30%. Overall, it appears that approximately 20% of patients will respond to DTIC alone. Visceral metastases are the most likely to respond, while bone and brain metastases appear to be ineffectively treated by this agent. A variety of schedules and doses have been utilized. These range from 10-day regimens to once-a-month dosing. Most investigators have settled on 3- or 5-day courses as the most tolerable regimens. Hematological toxicity is generally mild. Dose-limiting toxicity is gastrointestinal, and this varies with the intensity of the regimen. Patients who receive large single doses can also develop photosensitivity. A rare and potentially fatal complication is hepatic veno-occlusive disease.

Nitrosoureas including carmustine (BCNU) and lomustine (CCNU) also have single-agent activity in the treatment of melanoma. Response rates range from 10 to 18% with an overall response rate of approximately 15%. Like other chemotherapeutic agents, these drugs are most active against visceral disease. They are associated with significant marrow suppression, which can be prolonged. Cisplatin also has activity as a single agent in melanoma, with reported response rates of approximately 15%. The major toxicities associated with this drug include renal and neurotoxicity, as well as nausea, vomiting, and alterations in hearing. Cisplatin is currently used primarily as a component of the combination regimens described below.

Temozolamide is a new antineoplastic agent that has shown significant single-agent activity in the treatment of melanoma. This agent is an oral DTIC analog, which has relatively modest toxicity. This is primarily manifested as marrow suppression. In a large phase II trial conducted in the United Kingdom, 21% of patients had a significant response, including a 5% complete response rate. This preliminary investigation suggests that temozolamide is comparable to DTIC in its activity in the treatment of melanoma.

Other single agents that have shown some activity in melanoma include procarbazine, the vinca alkaloids, doxorubicin, paclitaxel, and dibromodulcitol. Each of these agents has shown some activity in single-agent trials. However, none of them has been shown to be superior to DTIC alone.

The majority of these agents have been incorporated into multidrug combinations. DTIC has been the backbone of these combination regimens. Two-drug combinations with DTIC and any of the other potential agents have not shown a significant improvement over DTIC alone. Three- and four-drug combinations have shown marginal improvements in response rate. Although the combinations have been promising in single-institution trials, multi-institutional and randomized trials have not shown a significant improvement over DTIC alone for these combinations.

The need for these large multi-institutional randomized trials is perhaps best illustrated by the history of the ''Dartmouth regimen.'' This regimen consists of a combination of DTIC, carmustine, cisplatin, and oral tamoxifen, which was initially reported to have a response rate of approximately 50%. Based on subsequent nonrandomized, single-institutional studies, the combination therapy was felt to be more effective than DTIC alone, and it was felt that tamoxifen was an important component of the combination regimen. By itself, tamoxifen has little or no activity against melanoma. Unfortunately, this observation has not been borne out in multicenter randomized trials. A randomized Italian trial comparing DTIC alone to DTIC plus tamoxifen did demonstrate a higher overall response rate and survival for the combination arm. In this trial, however, the response rate to the DTIC-alone arm was inferior to that in other DTIC-alone trials. In a phase II trial conducted by the Southwest Oncology Group, tamoxifen was added to DTIC and cisplatin. This regimen had previously produced a 13% response rate in patients with metastatic melanoma. When tamoxifen was added to this regimen, the response rate was 18%. This was not a statistically significant difference, and the impact on survival was unclear. A large randomized, double-blind, placebo-controlled trial conducted by the National Cancer Institute of Canada Clinical Trials Group compared carmustine, DTIC, and cisplatin with and without tamoxifen. The study was designed to detect a 20% difference in response rate. There was no significant difference in response between the two groups with the tamoxifen group having a 30% response rate, and the placebo group a response rate of 21%. The complete response rate was actually higher in the placebo group (6% vs. 3%), and there was no significant difference in the incidence of deep venous thrombosis or pulmonary embolus between the two groups. This study is open to essentially the same criticism as the Italian study in that the tamoxifen arm had a significantly lower response rate than has previously been reported for the regimen. However, the number of trials reporting a 20% response for DTIC alone dwarfs the number that have reported the 50% response rate for the combination plus tamoxifen.

The conclusions that can be drawn from these data are extremely limited. It appears that the combination regimens, particularly the Dartmouth regimen, may have a higher response rate than single-agent therapy. Whether this translates

into improved survival will have to await the completiton of an ongoing randomized trial that compares the Darthmouth regiment to DTIC. Based on current data, tamoxifen does not appear to contribute significantly to inproving the response rate or survival of patients with metastatic melanoma. Patients presenting with metastatic disease should be considered first for ongoing clinical trials of new agents, or new immunotherapeutic approaches. If a standard therapy is to be used, the Dartmouth regimen could be considered based on its higher reported response rates, but the basic chemotherapy for metatatic disease should probably be DTIC alone.

Regional Perfusion for Recurrent Limb Disease

Regional limb perfusion with chemotherapy agents has been the therapy of choice for intransit metastases for many years. Melphalan has been the primary agent used for this approach. Extensive experience with this agent has shown response rates ranging from 50 to 70%, with numerous complete responses. The principal advantages of regional perfusion include the ability to deliver relatively high doses of chemotherapy with limited systemic toxicity. A retrospective analysis of patients treated with this approach has shown that improved prognosis is associated with multiple versus single perfusions, the absence of regional nodal involvement, and leg involvement versus other tumor sites. Single lesions and complete remission after perfusion, as well as female gender, appear to have a predictive effect for freedom from recurrence within the limb. Toxicities associated with isolated limb perfusion with melphalan include neuropathy and myopathy. This is typically confined to the perfused limb. Systemic toxicities, including marrow suppression, are typically mild and limited in extent. At least one randomized trial has suggested a benefit in terms of survival following isolated limb perfusion with melphalan for intransit metastases, although this has not been confirmed by subsequent studies.

Other single agents that have been used for isolated limb perfusion include tumor necrosis factor (TNF) and cisplatin. Each of these has a significant response rate; however, they have not been shown to be definitively better than melphalan alone. Melphalan has also been used as a single agent in combination with hyperthermia with a suggestion of an improvement in response rate.

European studies have reported a $>$90% response rate with the combination of melphalan, tumor necrosis factor (TNF), and interferon-gamma. This approach allows the administration of high doses of TNF and prevents the severe hypotension associated with systemic circulation of this agent. A recent trial conducted by the Surgery Branch of the National Cancer Institute confirmed the high response rates for this approach. Twenty-six patients were treated with 4 mg of TNF and 12 patients received 6 mg of TNF in this dose escalation study. The complete response rate in the 4-mg group was 76% with a complete response

rate of 36% in the 6-mg group. However, the overall objective response rate was 92% in the 4-mg group and 100% in the 6-mg group. Regional toxicity was dose-limiting at the 6-mg dose level, while systemic toxicity was short-lived, and reportedly easily managed. This combination is being compared in a randomized fashion with regional perfusion of melphalan alone.

RADIATION THERAPY

Introduction

Radiation therapy (RT) has a role in malignant melanoma therapy that, in contrast to its role in many other malignancies, is relatively limited. The primary reason for this attenuation has been the success of surgical resection in securing local control. Thus, RT tends to be involved in the palliation of advanced or metastatic disease or, potentially, in the treatment of regional disease. A secondary reason for RT's limited role is the historical impression that melanoma is a radioresistant lesion and not responsive. These impressions are based upon older historical case reports and on laboratory experiments exploring in vitro survival of cultured melanoma cells after single fractions of RT. The large shoulder observed on the survival curve generated in multiple experiments, implying relative resistance of the cells to RT at relatively low doses, added to the clinical impression of radioresistance. These experimental findings also initiated clinical exploration of larger dose per fraction treatment regimens to overcome the shoulder of the curve.

RT for Adjuvant Therapy in Stage III Patients

The role of RT in the treatment of regional nodal disease has not been well defined. The two issues of significance for patients with regional disease are local control and survival. Local recurrence after lymphadenectomy for patients who present with palpable lymphadenopathy can become a major clinical problem, even though most of these patients will ultimately die owing to complications of distant disease spread. RT can reduce the likelihood of regional recurrence when used postoperatively in this situation; however, no proven overall survival benefit can be demonstrated.

The use of RT for stage III disease was studied in a small, prospective, randomized trial from the Mayo Clinic published in 1978. Patients received surgery with or without postoperative RT using conventional fraction sizes to a total dose of 50 Gy. For both disease-free survival and overall survival, the survival curves tended to favor the RT arms with median times until disease recurrence in the control arm and the RT arm of 9 months and 20 months ($p = 0.07$) and median times to death of 22 months and 33 months ($p = 0.09$), respectively. The authors attributed the differences in the survival curves to imbalances between

the two arms in various prognostic factors and concluded that RT did not add significantly to clinical management in this setting.

An alternate view has been supported by a group from M. D. Anderson Hospital in particular for the management of regional disease affecting patients with primary head and neck melanomas. A phase II study was conducted involving patients who were of various stages. Some were treated with RT if the primary melanoma was relatively deep ($\geq$1.5 mm or Clark level $\geq$3) even if the regional lymph nodes were clinically negative (group 1). Other patients were treated following resection of stage III disease (group 2) or upon resection of regional recurrences (group 3). The RT that was employed used a large dose per fraction scheme. Patients were treated to 24–30 Gy in four to five fractions, two fractions per week. The investigators selected this treatment regimen after a literature review indicated a potential benefit to large dose per fraction RT, especially for nodal metastatic disease. In this series, locoregional control at 2 years was 95% for group 1, 90% for group 2, and 83% for group 3. It was concluded that these local control data were superior to the results of surgery alone for similar patients for whom there was an estimated 50% risk of locoregional recurrence.

The M. D. Anderson experience has generated an Intergroup Phase III study coordinated by the Radiation Therapy Oncology Group (RTOG). This ongoing clinical trial is designed to evaluate the effectiveness of the radiotherapy described above (30 Gy in five fractions of 6 Gy given twice per week) in preventing regional failure in patients with pathologically confirmed lymph node metastasis. This study, when completed, should objectively define the role of postoperative RT, at least for local control benefit for head and neck melanomas. Although this study is limited to head and neck melanomas, the results, either positive or negative, could presumably be extrapolated to other regional lymph node sites.

RT for Bone or CNS Metastasis

The major role of RT in melanoma therapy is for the palliation of metastatic disease. Also, it is apparent from many reports that metastatic melanoma lesions respond favorably to palliative RT. Thus, in general, standard RT indications for palliation apply to patients with metastatic melanoma and RT should be used when necessary to treat painful bone lesions, soft tissue metastases, brain metastases, and other similar circumstances.

The issue of which dose per fraction regimen is superior—large fraction or conventional fraction—continues to be raised concerning palliation of melanoma lesions. This issue raised enough interest that it resulted in a phase III RTOG trial designed to evaluate the effectiveness of high dose per fraction RT in the palliative treatment of metastatic melanoma. The study randomized patients with measurable lesions to a standard palliative regimen of 2.5-Gy daily fractions to a total of 50 Gy or to 8-Gy fractions given once weekly to a total of 32 Gy.

Despite slightly greater toxicity in the 8 Gy per fraction arm, there was no difference in the response rate. The total response rate (complete responders plus partial responders) was 60% in the large fraction arm and 58% in the standard fraction size arm. This study concluded that large dose per fraction schemes are unlikely to be superior to conventional treatment regimens, despite the earlier retrospective studies. The total response rate was felt to be encouraging in this study—even for tumors $\geq$ 5 cm, the response rate was 60%. These data seem to indicate that melanoma is not fundamentally a radioresistant malignancy.

Regarding RT for central nervous system (CNS) metastases, there are older literature sources that suggest relative radioresistance of brain metastases to RT. However, more recent data, especially studies using radiosurgery, are more encouraging.

Two studies using radiosurgery and whole-brain RT for solitary metastases have recently been reported. These studies were multi-institutional compilations of data to create relatively large databases. The patient population consisted of various primary malignancies, including melanoma. In one of the studies, 16 patients with solitary melanoma metastasis were treated and only one developed a subsequent local recurrence, yielding a control rate of 94%. In the other study, melanoma histology was significantly associated with better local control compared to other histologies (mostly lung and breast cancers) in a multivariate analysis. Thus, it is apparent that melanoma is not necessarily a radioresistant histology when palliative treatments are indicated and RT should not be avoided on that presumption, even in the setting of brain metastases.

CLINICAL RESEARCH QUESTIONS

Vaccine Therapy

Melanoma represents a disease where there have been significant advances in the identification and cloning of tumor-associated antigens. There are now several defined antigens (i.e., MAGE-1, MAGE-2, MART-1, gp 100, tyrosinase, gangliosides, etc.) that are expressed by melanoma tumor cells and elicit cellular immune responses. These antigens, which represent small peptides, are currently being assessed as vaccines in patients with micrometastatic disease (i.e., resected stage III and IV patients) and may offer a nontoxic immunotherapy. Another approach to vaccine development has been cell-based. One approach has been to utilize whole tumor cells that can express a variety of known as well as undefined tumor antigens, which are genetically engineered to be more ''immunogenic.'' The genetic modification commonly entails introducing genes encoding for cytokines or costimulatory molecules. Another approach is the use of dendritic cells, which are potent antigen-presenting cells that can be retrieved from the peripheral circulation. Dendritic cells can be ''pulsed'' with antigenic peptide or whole tumor

cells ex vivo enabling them to sensitize naïve T cells. The use of genetically modified tumor cells or pulsed dendritic cells is being evaluated in clinical studies for their efficacy in generating immune responses.

Molecular Diagnostics

The polymerase chain reaction (PCR) represents a powerful molecular biology tool to replicate segments of DNA. A modification of the PCR technique utilizing reverse transcriptase (RT-PCR) can amplify messenger RNA and is being investigated to detect tumor cells at the molecular level. Using RT-PCR, tumor-associated messenger RNA can allow detection of a single tumor cell within a million normal cells. In melanoma, techniques to identify message for tyrosinase are being investigated as a tool to evaluate for micrometastases in the peripheral blood and sentinel lymph nodes. The prognostic and clinical implications of identifying tissue samples that are positive for tumor-associated messenger RNA are being defined in clinical studies currently underway.

BASIC RESEARCH QUESTIONS

The molecular biology of melanoma from its inception, growth, invasion, and metastatic potential are areas of active investigation. In the very near future, the gene(s) responsible for the familial predisposition of melanoma will be identified. It is anticipated that such genes will also be associated with the genesis of sporadic melanomas as well. The subsequent characterization of the function of the proteins encoded by these genes will provide valuable information as to how melanomas are initiated and provide targets for the development of prevention and therapeutic strategies. For example, mutated oncogenes and tumor suppressor genes are being examined as tumor-associated antigens in other tumor histologies. The mechanisms involved in the metastatic process of melanoma have their basis at the genetic level. It is anticipated that such genes will be identified for melanoma. These genes may provide valuable prognostic markers for patients who are at high risk of recurrence even though they have early-staged melanomas, and thus may benefit from adjuvant therapy.

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Lung Cancer

Jamie Brown
University of Colorado Health Sciences Center and the Department of Veterans Affairs VA Medical Center, Denver, Colorado

Alden H. Harken
University of Colorado, Denver, Colorado

Rachel Rabinovitch
University of Colorado Health Sciences Center, Denver, Colorado

Ariel F. Soriano and Paul A. Bunn, Jr.
University of Colorado Cancer Center, Denver, Colorado

INTRODUCTION

The incidence of lung cancer yearly in the United States is now estimated to be greater than 170,000 new cases per year. Twenty percent of these will be small cell carcinomas (SCLC) and 80% will be non–small cell lung cancers (NSCLC). Twelve percent will be cured. More than five billion dollars will be spent on direct medical care of lung cancer annually in the United States. Lung cancer will cost an additional 40 billion dollars in years of productive life lost or unmeasured family expenses. Insurers measure the value of medical care in terms of outcomes divided by cost. The cost to deliver care to lung cancer patients will be tracked for individual surgeons and new treatments will be evaluated in terms of cost per year of life saved. In this regard, efficiency in the management of a lung cancer patient will be necessary. Although improved screening procedures, new chemotherapeutic agents, and molecular biological techniques have ad-

vanced, the death rate and years of potential life lost to lung cancer continue to increase. This fact distinguishes lung cancer from other carcinomas in which improvements in survival have been made. It will be incumbent on the practitioner to streamline the preoperative, operative, and postoperative care of the lung cancer patient.

Smoking is the most common etiology associated with lung cancer. Cigarette smoke contains over 4000 different substances. Its carcinogenic potential relates to these contents as well as its vapor and its particulate phase. It is the most significant preventable contributing etiological factor related to lung cancer. Notwithstanding the contribution of smoking, 25% of lung cancers occur in nonsmokers, because of exposure to factors such as passive smoke and environmental factors such as air pollution, radon gas, and white asbestos fibers. Genetic factors interact with the foregoing environmental factors and play a role in lung cancer risk although no direct role of a specific gene has been elucidated in the prediction of lung cancer in an individual.

Twenty years ago in reported series of cancer, squamous cell carcinoma predominated. However, adenocarcinoma has been increasing especially in nonsmokers and young women. This is important because of the biologically more aggressive nature of adenocarcinoma compared to squamous cell carcinoma. New chemotherapeutic agents have been developed and seem to be associated with better response rates. However, there has been no proof of enhanced survival in lung cancer patients. Molecular biological techniques have provided insight into the pathogenesis of the disease on the cellular level. For example, the contribution of angiogenesis and tumor suppressor genes to tumorigenesis has been elucidated. These techniques have provided means to identify patients at risk for lung cancer, develop new therapies, and aid in the prognosis of a lung cancer. Their full benefit has not yet been realized.

SURGERY

Lung cancer remains a surgical disease. Of the one-third of lung cancer patients who present with resectable disease, the best 5-year survival is obtained with surgery. Neoadjuvant or preoperative chemotherapy trials have provided hope for improvements in the survival of advanced-stage disease. An aging population, the presence of other disease processes, the large number of the patients who present with advanced-stage tumors, and cost pressures in the current managed care environment will require an efficient, cost-effective management of lung cancer. It is our proposal that a simplified consideration of the lung cancer patient that focuses on the diagnoses, staging, and risk assessment will aid in the expedient and cost-effective workup and management of this disease (Fig. 1).

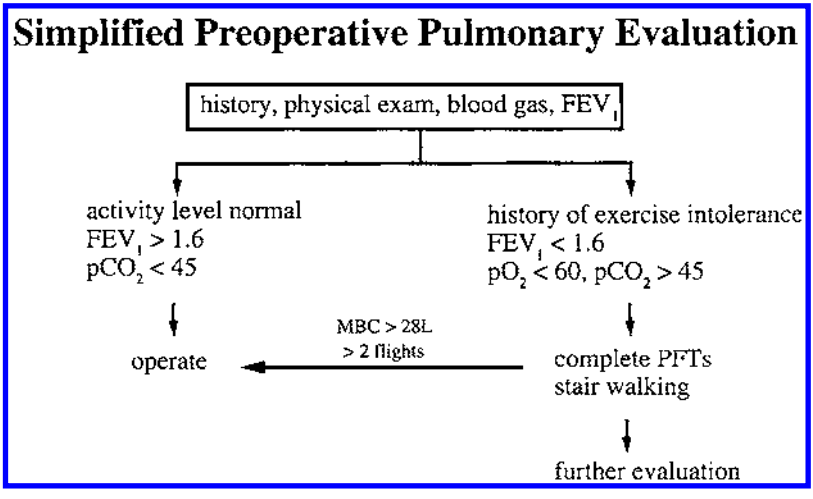

FIGURE 1 Schematic of clinical thought process used to work up and manage the lung cancer referral. In the current managed care environment an elderly patient with multiple comorbidity factors may arrive in the surgeon's clinic with only a chest radiographic. Keeping this simplified flow of thought and the relation of tests and procedures to outcome will help simplify and streamline the process of care.

Cell Type/Presentation

Twenty percent of lung cancer is small cell. The majority of these will be advanced disease. The rare locally confined small cell cancer can be considered NSCLC. Although these tumors require more preoperative staging and postoperative chemotherapy, 5-year survivals in the 20% range can be achieved. The main cell types that comprise the NSCLC are adenocarcinoma and squamous cell carcinoma, which now occur with equal incidence with adenocarcinoma predominating in younger patients and in women. Large cell carcinoma comprises between 5 and 10% of lung cancers. It is biologically more aggressive than squamous or adenocarcinoma. Bronchoalveolar lung cancer is a subtype of adenocarcinoma. It can present as a nodule or as involvement of an entire lobe or lung because of its propensity to spread over alveolar surfaces. In 10% of cases, the presentation of lung cancer is an incidental finding but because two-thirds of patients present with stage III or IV disease, most have symptoms referable to the tumor (for example, cough) or metastases (for example, bone pain). Ten percent of lung cancer patients have a paraneoplastic syndrome, which is a neuromusculoskeletal or endocrine symptom complex related to a primary tumor. Peripheral neuropathy, cerebral ataxia, hypertrophic osteoarthropathy, Cushings

syndrome, and hypersecretion of antidiuretic hormone are examples of paraneoplastic syndromes. The important point about paraneoplastic syndromes is that they are not a contraindication to operation and resection.

Staging

A revision in the original staging of lung carcinoma has been adopted by the American Joint Committee on Cancer (AJCC). In this staging system stage I cancers have no metastases to any lymph nodes. Stage II cancers have metasteses to inter, intra, or hilar lymph nodes or the tumor invades the chest wall without lymph node involvement otherwise. Stage IIIA tumors are the same as the previous classification except chest wall involvement with involvement of lymph nodes other than mediastinal lymph nodes is included. Stage IIIB and stage IV are unchanged. (See Table 1.)

In the management of lung cancer, one question is ''How much expense and effort should be made in the process of staging lung cancer patients?'' In this regard, staging will predict the outcome in populations of patients although not in individual patients. A rigorous attempt at clinical staging will, however, aid in a more accurate decision process for intervention. Furthermore, accurate staging is necessary for any ongoing clinical trials. Routine modalities employed for clinical staging include a careful history and physical examination aimed at elucidating evidence of stage IV disease typified by weight loss of greater than 20 lb or markedly diminished performance status. A computed tomography (CT)

Table 1 New Lung Cancer Staging

O	Carcinoma in situ	
IA	$T_1N_0M_0$	T_1 = tumor $\leq$ 3 cm in size
IB	$T_2N_0M_0$	T_2 = tumor $>$ 3 cm or involving visceral pleural surface
IIA	$T_1N_1M_0$	N_1 = interlobar, intralobar, or hilar node involvement
IIB	$T_2N_1M_0$	
	$T_3N_0M_0$	T_3 = tumor invading chest pericardium or proximal 2 cm of mainstem bronchus
IIIA	$T_3N_1M_0$	
	$T_1N_2M_0$	N_2 = ipsilateral mediastinal lymph nodes
	$T_3N_2M_0$	N_3 = contralateral mediastinal lymph node involvement or suprapubicular lymph node involvement
IIIB	T4 any N	T_4 = tumor invading carina or mediastinal structures such as heart or great vessels
	N_3 any T	
IV	M_1 any T any N	

scan of the chest is performed routinely. CT scanning is accurate for tumor size and location but it is inaccurate for invasion of chest wall or mediastinal structures. CT scanning is sensitive for the presence of mediastinal lymph nodes with enlargement being recognized as nodes greater than 1 cm. Unfortunately, CT scanning is not specific for mediastinal lymph nodes. Given a negative CT scan, there is a 10% chance that a patient will still have cancer in mediastinal lymph nodes at thoracotomy. Given an enlarged mediastinal lymph node on CT scan, there is a 30% chance that the patient will have a negative mediastinal node exploration. Mediastinoscopy also has a false-negative rate of 9%. Therefore, CT scanning is as sensitive as mediastinoscopy but not as specific. A contemporary staging strategy for lung cancer that incorporates this knowledge is presented in Figure 2. It includes history, physical examination, and CT scan of the chest followed by mediastinoscopy to evaluate enlarged lymph nodes. Magnetic residence imaging (MRI) should not be performed routinely in lung cancer patients. Indications for MRI include a superior sulcus tumors, a question of chest wall or diaphragm invasion, or a question of great vessel invasion.

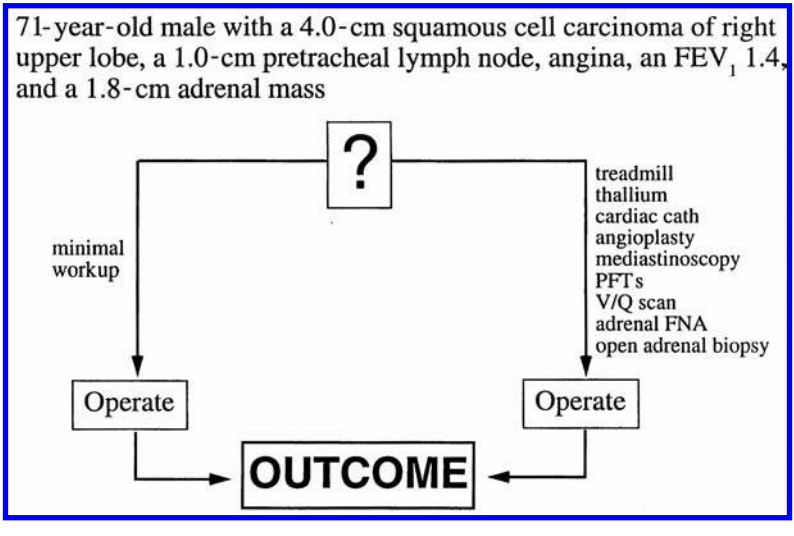

FIGURE 2 Clinical lung cancer staging. Histroy and physical examination should provide valuable information relevant to advanced disease such as weight loss or poor performance status. Otherwise a computed tomography (CT) scan of the chest should be used as the initial screening tool. It gives information about the tumor, mediatinal nodes, and metastases status. Mediastinoscopy is indicated if the CT scan demonstrates mediastinal adenopathy.

Preoperative Risk Assessment

Risk assessment in the lung cancer patient prior to thoracotomy is a central issue, because risk is correlated with cost and outcome. Older patients with advanced disease have potentially enhanced morbidity, lengthy hospital stays, and high costs. The key in management currently is to efficiently order only tests that will alter behavior and correlate with different outcomes. An exaggerated example of an expensive algorithm compared to a simplified algorithm culminating in the same outcome is shown in Figure 3 to illustrate this point. Data from highly selected studies of lung cancer patients suggest that the mortality for lobectomy should be in the range of 2.9% and for pneumonectomy 6.2%. Morbidity ranges between 10% and 50%. Morbidity includes pulmonary infections, superventricular tachycardias, and other cardiac events. These events correlate with hospital stay and cost. The main factors to consider in risk assessment are: age, pulmonary system, and cardiac system.

The risk of operatin doubles every 10 years in age such that the risk for a lobectomy for a patient under 60 is 1% but the risk for a lobectomy in an 80-year-old is roughly 6%. The morbidity for lobectomy in octogenarians, however, approaches 50%.

The pulmonary system evaluation can be lengthy and should include a history, physical examination, arterial blood gas, complete set of pulmonary function studies, exercise or stress testing, and ventilation perfusion scanning. Our simpli-

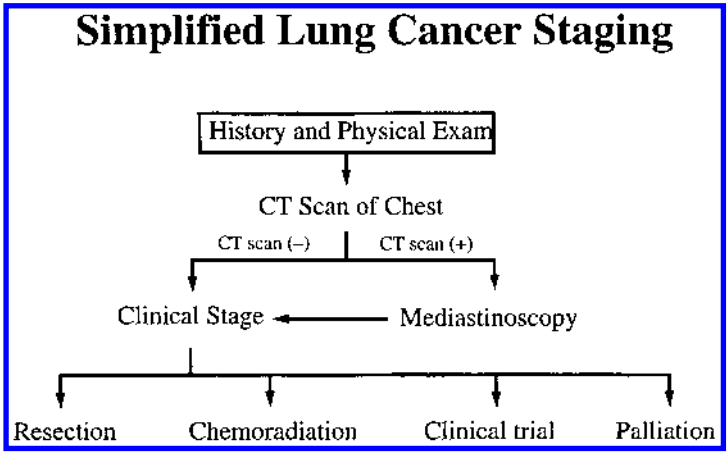

FIGURE 3 Example of workup overkill. This patient followed the left-sided pathway. All testing resulted in an uneventful right upper lobectomy. The value (cost divided by outcome) of all these procedures was minimal. Such workups are to be avoided.

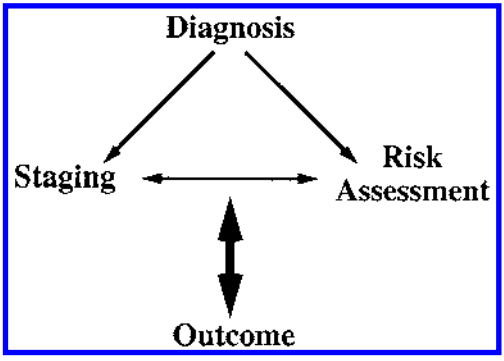

FIGURE 4 Simplified preoperative pulmonary evaluation. A history, physical examination, room air arterial blood gas, and an FEV_1 are used as screening procedures. In patients with near-normal activity level, normal P_{CO_2} values, and FEV_1 greater than 1.6 minimal other workup is justified. However, historical or physical examination factors such as wheezing, elevated P_{CO_2}, decreased P_{O_2}, or low FEV_1 are red flags and justify further simple investigations such as exercise tolerance testing or complete pulmonary function testing.

fied approach is presented in Figure 4. A careful history and physical examination should reveal the presence of severe emphysema, for example. A room air blood gas and a forced expiratory volume in 1 sec (FEV_1) are additional objective criteria that will help predict risk. No single test accurately predicts morbidity and mortality. However, there are several accepted contraindications to pulmonary resections (Table 2). Diminished pulmonary function studies, specifically an

TABLE 2 Contraindications to Pulmonary Resection

Absolute
Pulmonary hypertension: pulmonary vascular resistance (PVR) $>$ 190 dyne/sec^{-5} or PVR increases with exercise
$PCO_2 > 50$ torr or PCO_2 increases with exercise
Maximum O_2 consumption $<$ 10 ml/kg/min
Relative
Predicted postop $FEV_1 < 800$ cc
$PCO_2 > 45$
DLCO $<$ 60%
MBC $<$ 28 L
$PO_2 < 60$

FEV_1 of less than 1.6 preoperatively or a predicted postoperative FEV_1 of 800 cc, are suggestive of a high-risk patient. They do not and should not, however, accurately preclude patients from resection because these tests are not specific. Preoperative borderline pulmonary function studies should be considered indicative of a higher risk category and should prompt further investigation. They are therefore good screening tools. We suggest beginning with a history, physical examination, an arterial blood gas, and an FEV_1 to be followed with further evaluation based on other factors such as extent of resection (lobectomy vs. pneumonectomy), age, and cardiac disease. For example, a 70-year-old patient with an FEV_1 of 1.4 who is scheduled for lobectomy might receive a complete set of pulmonary functions to evaluate maximum breathing capacity or maximal midexpiatory flow, which should be greater than 28 L and 600 cc, respectively. On the other hand, in patients at higher risk, such as a 75-year-old with heart disease who is to undergo pneumonectomy, preoperative evaluation should be more deliberate. This examination can include stair walking or Reichal stress testing, which has been shown to predict mortality after pneumonectomy. Furthermore, although formal exercise stress testing and oxygen consumption can be accomplished at great cost, walking one flight of stairs (18 steps) correlates with an oxygen consumption of 7.9 ml/kg/min and walking four flights of stairs correlates with an oxygen consumption of greater than 20 ml/kg/min. Patients undergoing pneumonectomy should be able to climb four flights of stairs. Preoperatively, patients who can climb more than two flights of stairs should tolerate lobectomy.

The final issue in risk assessment is the cardiac system. The guidelines published by the American Heart Association and American College of Cardiology in 1996 jointly recommended that preoperative cardiac evaluation be kept simple. Red flags that should prompt further investigation include malignant arrhythmias, uncompensated congestive heart failure, severe stenotic valvular lesions, and an unstable anginal pattern. Otherwise, expensive testing and intervention is to be discouraged.

Preoperative Planning and Strategy

Preoperative incentive spirometry, exercise, and cessation of smoking should be strongly encouraged. The benefit of these measures cannot be overstated. In the operating room after single-lumen endotracheal intubation and inspection with a bronchoscope, a double-lumen endotracheal tube is placed into the left mainstem bronchus under bronchoscopic guidance. An arterial line is used routinely. A central venous line is placed for patients over 70 or patients who are receiving pneumonectomy. Swan-Ganz catheters are used for patients with pulmonary hypertension or congestive heart failure. Full thoracotomy and open lobectomy or pneumonectomy is our recommended procedure. Video-assisted techniques have not been proven in lung cancer as of yet and are not recommended except in the arena of

diagnosis. Incisions should be planned to spare muscle groups wherever possible. When entering the chest, we take down the inferior pulmonary ligament, mobilize the hilum, and perform a complete node sampling. Standard techniques of pulmonary resection have been previously described. The posterior ''bronchus first'' approach should be considered for redo operations, prior radiation, or in the setting of thick infected secretions for right upper lobe or pneumonectomy resections.

Numerous circumstances can be encountered unsuspectedly in the operating room. These include chest wall invasion, carcinomatous mediastinal adenopathy, phrenic nerve involvement, or involvement in the superior vena cava. In all the above circumstances, if simple maneuvers will allow complete resection, it should be performed. In cases of chest wall invasion or adherence, partial chest wall excision results in better survival than simple parietal pleurectomy. Preoperative special circumstances include presence of metastatic disease, such as single metastases to the brain or the adrenal gland, which can be first resected followed by resection of the lung tumor after adequate staging. These procedures in highly selected patients result in 5-year survivals in the range of 20%. Malignant pleural effusions should be treated palliatively by video-assisted drainage and pleurodesis with a sclerotic agent or 4 g of aerosolized sterile talc if available. Life span in these circumstances is less than 6 months. Malignant pericardial effusions can be treated with percutaneous catheter drainage or open pericardial window. Tumors located at the superior sulcus, known as Pancoast tumors, should be diagnosed by fine-needle aspiration and treated by preoperative radiation followed by lobectomy, and chest wall resection including the first three ribs. In the situations where the tumor is located at the lobar orifice in patients with limited pulmonary reserve, sleeve lobectomy and reanastomosis of the distal bronchus to the mainstem bronchus should be considered.

Outcome Targets

Targets for mortality are 3% for lobectomy and 6% for pneumonectomy. Morbidity should be less than 25%. Hospital stay in uneventful cases should be roughly 6 days and hospital charges per case in the range of $12,000. Five-year survival for completely resected lung cancer with no positive nodes should be in the range of 65%. With positive lobar nodes (stage II) that have been resected survival should be in the range of 35%. For completely resected mediastinal nodes found at thoracotomy 5-year survival should be in the range of 20%. For T1 coin lesion lung cancers, the lung cancer study group's reevaluation of its data from Study 821 suggested that the local recurrence rate is increased with a wedge and segmentectomy although differences in 5-year survival between lobectomy and limited resection are more difficult to prove and less than originally thought. We recommend that lobectomy be the standard treatment for T1 lung carcinoma although in high-risk patients with peripheral and easily accessible lesions, wedge excision can be considered. Early (less than 30 days) complications after pulmo-

nary resection include respiratory failure and pneumonia (10%), supraventricular tachycardia (20%), wound infection (5%), and residual space on chest x-ray (10%). Late (greater than 30 days) postoperative complications include bronchial dehiscence usually from recurrent cancer (1%), postthoracotomy pain syndrome (10%), residual air spaces (<5%), postpneumonectomy syndrome (1%), and chronic respiratory inefficiency requiring oxygen therapy or resulting in limited life-style (10%). Follow-up of lung cancer patients is best kept simple and inexpensive ($500/year), including a chest x-ray and minimal laboratory tests and clinic visits. No studies have shown altered outcomes by more intensive postoperative surveillance.

RADIATION THERAPY

Radiation therapy (RT) has a well-established role in the primary management of lung cancer. Its indications vary with tumor histology (small cell vs. non–small cell), stage of disease, and general medical condition of the patient.

Non–Small Cell Lung Cancer

The standard indications for RT in the treatment of NSCLC include:

1. Medically inoperable patients with early-stage disease
2. Patients status/post (s/p) radical resection with incidentally noted N2 disease
3. Patients s/p resection with positive margins
4. Patients with locally advanced (stage IIIA and some IIIB) disease
5. Superior sulcus tumors (special T3–4)
6. Symptomatic metastases

Medically Inoperable Patients with Early-Stage Disease

Although surgery is the preferred local treatment for lung cancer, not all patients are medically fit for definitive resection. Careful medical evaluation is essential in this population with a high incidence of tobacco-related cardiopulmonary disease.

Medical contraindications to surgical resection include:

Poor performance status, i.e., ambulatory <50% of daytime hours
Myocardial infarction within the last 3 months
Uncontrolled multifocal PVCs
Complete heart block
Uncontrolled congestive heart failure
FEV_1 <1 L
Predicted postoperative FEV_1 < 0.8 L
Elevated CO_2
Other major illness

In a patient with early-stage resectable lung cancer (T1–2 N0–1 M0) and a medical contraindication to surgical resection, radiation substitutes as the local treatment modality. Series evaluating the effectiveness of radiation alone in treating such patients demonstrate a small but consistent cure rate. Five-year survival rates range from 16 to 32%. Both intercurrent disease and lung cancer are responsible for the poor outcome in this group of patients when compared to the 60–80% 5-year survival rate in matched healthy resected patients.

These studies have used a wide variety of fractionation schemes, including split-course, hyperfractionation, and accelerated-fractionation treatment. RTOG studies 73-01 and 73-02 established 6000 cGy in 6 weeks as the benchmark against which other fractionation schemes were to be compared. These studies, performed on patients with inoperable stage II–III disease, demonstrated an improved local control rate (73%) with this dose level when compared to 4000 cGy (in split or continuous course) or 5000 cGy. No improvement in median survival, however, was achieved despite superior thoracic tumor control demonstrating the systemic nature of most lung cancers. Distant metastases developed in 80% of patients. Given the poor performance status of many medically inoperable patients, accelerated treatment is not an unreasonable approach (i.e., 3000 cGy in 2 weeks, with an additional 2500 in 2 weeks following a 2-week rest).

RT has been greatly affected by new computor technology. Conformal or 3D radiotherapy is a powerful treatment planning tool that facilitates evaluation of the relationship between anatomical structures, the geometry of treatment beams, and the subsequent distribution of dose. This technology provides more complex treatment planning options that result in decreased dose delivery to normal tissues, and therefore the potential to treat target areas to higher total doses. RTOG 93-11 is designed to test the impact of treating inoperable lung cancers with escalating doses of RT using conformal treatment planning.

An area that has yet to be explored is the value of concomitant chemotherapy in this group of patients. Combined-modality therapy has clearly shown an advantage for patients with more advanced disease. Medically inoperable patients often, but not always, have medical contraindications to chemotherapy delivery as well.

There is no definitive evidence that prophylactic treatment of clinically negative hilar or mediastinal nodal stations has any impact on ultimate outcome. Treatment of rediographically evident disease only is worth considering in the context of sparing potential toxicity.

N1 or Incidentally Noted N2 Disease s/p Radical Resection

Two randomized trials have evaluated the role of adjuvant RT following definitive resection. Both the EORTC and the Lung Cancer Study Group (LCSG) found a significant improvement in local control (LC) for patients with node-positive disease who received adjuvant RT. No survival benefit, however, was rendered. The LCSG study did demonstrate an improved disease-free survival in the subset of patients with N2 disease.

To avoid the morbidity of mediastinal recurrence, it is considered standard in most U.S. oncology centers to add mediastinal RT to resected N2 patients. Although the data are just as strong in the N1 setting, positive hilar adenopathy has not been as well accepted as an indication for adjuvant RT. Doses of 4500–5000 cGy are employed; esophagitis is the primary toxicity.

Positive Resection Margins

Despite the intuitive conclusion that patients left with positive margins following radical resection require further therapy, there is a paucity of literature directly addressing this issue. Although no study has directly addressed the value of adjuvant RT in this setting, basic principles lead to the recommendation of such treatment. Doses of 4500–5400 cGy in standard fractionation delivered to the area of concern are appropriate.

The LCSG randomized patients with positive margins or disease within the highest sampled mediastinal lymph node to RT or RT with CAP (cyclophosphamide, doxorubicin, and cisplatin) chemotherapy. The addition of systemic therapy did not decrease the thoracic recurrence rate when compared to chest irradiation alone.

The utility of treating microscopic residual disease at a resection margin with chemotherapy, which is designed to address occult microscopic systemic disease in the adjuvant setting, instead of RT has never been investigated.

Locally Advanced Disease (Stage IIIA and IIIB)

Patients with clearly documented mediastinal adenopathy (N2–3) or T3–4 tumors are considered to have locally advanced disease. In the past, RT alone was employed as the sole treatment modality. Exceptions included patients with malignant pleural effusions who are not candidates for definitive RT owing to the intolerable toxicity of whole-pleural irradiation, and tumors of the superior sulcus/chest wall where surgery remains an important component of their overall management (see below). Definitive RT in this group of patients results in an average median survival of 10 months and 2-year survival rates of 15–20%. Standard fractionation in the United States consists of 6000 cGy in 6 weeks. Novel fractionation schemes have been tested to improve upon these statistics. RTOG 83-11, for example, suggested an improved LC and survival rate with treatment of 120 cGy twice daily to a total of 6960 cGy, but only for good-risk patients (weight loss $< 5\%$, hemoglobin > 10, and Karnofsky performance status 80 or better).

Combined-modality therapy (CMT), i.e., chemoradiation, has evolved over the past decade as the standard treatment approach for locally advanced lung cancer owing to the superior results reported in multiple randomized trials. These studies demonstrate a small but consistent and significant survival advantage of CMT compared to RT alone, yielding median survival times of approximately

14 months and 2-year survival rates of 26%. The four most commonly quoted trials used a myriad of RT fractionation schemes, drug combinations, and sequencing schedules, leaving no clear advantage of one over another.

The role of surgery in stage IIIA–IIIB patients is investigational and should be employed only in a protocol setting (this again excludes patients with T3 N0–1 tumors by virtue of chest wall invasion/superior sulcus location). Intergroup 0139 is a National Cancer Institute (NCI) high-priority trial designed specifically to address this question. Patients with T1–3 N2 disease are treated with upfront chemoradiation and randomized to either completion doses of radiation (standard arm) or surgical resection (experimental arm).

Questions that remain unresolved for this group of patients despite the numerous published trials include:

What is the ideal fractionation scheme for CMT?
What is/are the best systemic agent(s)?
Should chemotherapy be delivered prior to and/or concomitantly with radiotherapy?
Should chemotherapy, when delivered concurrently with RT, be delivered on a daily, weekly, or monthly basis?

One trial attempting to address some of these questions is RTOG 94-10 which compares (1) vinblastine/cisplatin chemotherapy followed by 6000 cGy in standard fractionation, (2) vinblastine/cisplatin with concurrent RT to 6000 cGy, and (3) cisplatin/oral etopiside with concurrent hyperfractionated RT to 6960 cGy (120 cGy BID).

Superior Sulcus Tumors

Superior sulcus or Pancoast tumors (SST) comprise a unique subset of advanced lung cancer. These tumors of the thoracic inlet locally invade adjacent structures, such as ribs, brachial plexus, vertebral bodies, and so forth. They are therefore always classified as T3–4 lesions. The Pancoast syndrome is characterized by shoulder pain radiating down the ulnar aspect of the arm, Horner's syndrome, and wasting of the hand musculature. Compared to other T3 tumors, SSTs have a lower incidence of nodal involvement and therefore better long-term outcome.

Complete surgical resection is difficult to achieve in many of these patients; therefore, preoperative radiotherapy has been employed to enhance tumor resectability. Most of these series, though not randomized, demonstrate an improvement in the complete resection rate. When compared to retrospective series of such patients treated with RT alone, preoperative treatment improves 5-year survival from approximately 20% to 30%. When positive margins or gross residual disease is left at the time of resection, permanent brachytherapy implants and/or further external-beam radiation therapy can be delivered postoperatively.

The largest series using this approach was published by Hilaris et al. in which 82 of 129 patients with Pancoast tumors were treated with preoperative RT. Multivariate analysis revealed improved survival for patients treated with preoperative RT and negative mediastinal lymph nodes.

Current standard treatment consists of preoperative megavoltage irradiation via AP/PA fields encompassing the tumor, crossing midline, and extending superiorly to the thyroid notch. Standard fractionation to 4500 cGy or an accelerated schema such as 3000 cGy in 2 weeks is acceptable. Surgery generally follows a 4-week break at which time response and resectability are reassessed. An additional 1500–2000 cGy can be delivered for gross residual disease.

The role of chemotherapy in this subgroup has not been specifically evaluated and deserves further investigation. Even with aggressive local therapy, a majority of these patients will develop distant failure. A current Intergroup trial (INT 0139) is testing the value of preoperative chemoradiation followed by surgical resection. Patients with T3 N2 lesions of the superior sulcus are eligible for enrollment.

Metastatic Disease

RT plays a central role in the palliation of focal symptomatic metastases. Numerous randomized trials have evaluated the effectiveness of palliative RT for brain and bone metastases, demonstrating the equivalency of numerous fractionation schemes. The compassionate radiotherapist will not obligate a patient with a limited life expectancy to endure 4 weeks of palliative treatment when 3000 cGy in 2 weeks or 2000 cGy in 1 week is equally efficacious. Treatment schemes of even shorter duration are commonly used in Europe. If a patient, however, is expected to have a prolonged life expectancy, slower fractionation for whole-brain radiotherapy is indicated to minimize late neurotoxicity. The relative roles of radiosurgery and surgical resection of symptomatic brain metastases continue to be evaluated.

RT is also an excellent treatment for thoracic symptoms secondary to uncontrolled local disease. Indications for palliative RT include large volume and persistent hemoptysis, postobstructive pneumonia, and dysphagia secondary to esophageal obstruction. Accelerated fractionation schemes are indicated as outlined above.

Small Cell Lung Cancer

Limited-Stage Disease

Patients with SCLC can be divided into limited- and extensive-stage disease. The definition of these two groups was first proposed by a report from the Veterans Administration and was specifically designed to differentiate patients whose disease can be reasonably encompassed within a single radiation field (limited stage)

from those in whom treatment of all known tumor would result in prohibitive toxicity or require multiple portals (extensive stage). Limited stage includes patients with mediastinal and even contralateral hilar or supraclavicular adenopathy, and any tumor limited to one hemithorax. Malignant pleural effusion is considered extensive-stage disease.

Value of Chest Radiation

A minimum of 16 randomized trials have evaluated the role of thoracic irradiation in addition to chemotherapy in patients with limited-stage disease. Nearly all of these trials demonstrated a significant improvement in local control and median survival with the addition of thoracic RT, with an average of 13 months. Radiation doses ranged from 4000 cGy in 10–20 fractions to 5000 cGy in 25 fractions. The value of thoracic irradiation continued to be somewhat controversial until the publication of two meta-analyses, both confirming a 5% survival advantage to patients receiving combined-modality therapy. Combined-modality therapy is clearly the standard treatment for limited-stage disease because of the significant improvement in thoracic tumor control and the small but real improvement in survival.

In vitro studies have demonstrated that SCLC is more radiosensitive than NSCLC. This observation presents the opportunity to decrease the toxicity of chest RT by decreasing the delivered dose when compared with non–small cell lung tumors. The challenge, however, is to do so without compromising tumor control. Several authors have evaluated for a dose response and have demonstrated higher local failure rates when doses of less than 4500–5000 cGy are delivered in standard fractionation. Although doses of 4500–5400 cGy are routinely prescribed, tumor recurrence within the chest continues to be a significant component of overall failure (30–75%).

Alternative approaches include delivery of chest RT in a twice-daily schema, using smaller doses per treatment (hyperfractionation). This approach has the theoretical advantages of improved tumor cell kill in a rapidly growing tumor, decreased late toxicity with a given total dose, and earlier completion of RT, which facilitates earlier delivery of further chemotherapy cycles. Results using this approach have been mixed. Turrisi et al. has published impressive 4-year survival and local control rates of 46% and 84%, respectively. An identical fractionation scheme at Memorial Sloan-Kettering Cancer Center yielded poorer survival rates for those treated with hyperfractionated RT (19% vs. 42% at 2 years).

The timing of chest RT relative to the initiation of chemotherapy appears to have significant impact on ultimate outcome. The NCI of Canada elegantly evaluated this issue by comparing the outcome of patients treated with alternating CAV and EP chemotherapy and randomized to receive chest RT (4000 cGy in 3 weeks) beginning with either the 2nd or 6th cycle. Median and 5-year survival rates were significantly better for patients treated with early chest RT. The inci-

dence of brain metastases was significantly higher in the late-RT arm. Concomitant delivery of chemoradiation with early delivery of chest RT in the sequence of chemotherapy has evolved as a standard approach.

Volumes requiring irradiation are shrinking. The South West Oncology Group demonstrated in a randomized trial the ability to treat postchemotherapy volumes in patients achieving a partial response, without negatively impacting upon thoracic failure or survival. Choi demonstrated that elimination of uninvolved supraclavicular regions and contralateral hila does not compromise local control in these anatomical subsites and likely decreases treatment toxicity. Furthermore, treatment margins of only 1–1.5 cm beyond gross disease were adequate. Elimination of RT from patients achieving a CR does, however, result in increased chest recurrence rates.

Prophylactic Cranial Irradiation (PCI)

Brain metastasis (BM) is a frequent and problematic event in the natural history of SCLC. Ten percent of patients at diagnosis, 25% during treatment, and 50% at autopsy have metastatic disease to brain parenchyma. To avoid the potential negative impact on mortality and neurological performance status, RT as prophylaxis for the development of brain metastases has been evaluated.

Numerous randomized trials have revealed a significant decrease in the development of BM when patients receive PCI (6% vs. 20%). No improvement in overall survival, however, is rendered owing to the high frequency of both chest failure and other systemic sites of recurrence. Patients who achieve a durable complete response to CMT are the most likely to benefit from this treatment. Treatment generally consists of 2500 cGy in 10 fractions.

Extensive-Stage Disease

Chemotherapy is the primary treatment for extensive-stage disease. Chest RT clearly decreases the local recurrence rate, but has no impact on median survival. The value of delivering thoracic RT to these patients should be considered in the context of response to chemotherapy, and evaluation of other sites of symptomatic disease.

CHEMOTHERAPY

Small Cell Lung Cancer

SCLCs have a high propensity for early metastatic spread and are rarely found locally. More than 90% of patients with SCLC have mediastinal lymph node metastases and more than two-thirds of patients have distant organ metastases at the time of diagnosis. SCLC has the most aggressive clinical course of any type of pulmonary tumor, with median survival from diagnosis of only 2–4 months

without treatment. Because of its propensity for distant metastases, localized forms of treatment such as radiotherapy or surgical resection rarely produce long-term survival. SCLC cells are initially sensitive to many chemotherapeutic agents, so response rates approximate 90% with complete response rates of 10–50% depending on the stage. Combination chemotherapy thus is the cornerstone of treatment.

SCLC is classified as either limited- or extensive-stage disease. Limited-stage disease is disease confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes, which is encompassable within a ''tolerable'' radiotherapy port. Radiation therapy cannot be delivered to an entire hemithorax, so patients with malignant pleural effusions are included in extensive stage. Approximately one-third of patients at time of diagnosis will have limited-stage disease. Patients with tumor that has spread beyond the supraclavicular area are said to have extensive-stage disease and have a worse prognosis than patients with limited stage. Median survival of 6–12 months is reported with current available therapy, but long-term disease-free survival is rare. Prognostic factors, in addition to stage, include performance status, LDH, and female gender.

Therapy for Limited-Stage SCLC

For the rare stage I patient without nodal involvement or distant metastases (T1 N0, T2 N0), the treatment of choice appears to be surgery followed by chemotherapy. Cure rates exceeding 60% are expected in these instances. Most 2-year disease-free survivors come from this group. Other patients are treated with both chemotherapy and radiotherapy. In limited-stage disease, the combined use of chest irradiation and combination chemotherapy was shown to be superior to either modality alone, resulting in increased complete response rates, decreased local recurrence, and improved survival. A recent meta-analysis of 13 randomized trials, which compared chemotherapy alone with chemotherapy/chest irradiation, showed a modest but significant 14% reduction in the relative mortality rate of patients receiving combined-modality therapy versus those given chemotherapy alone. The absolute survival difference was about 5.5% at 3 years in favor of the combined-modality approach. Patients receiving chemotherapy/chest irradiation were at greater risk of early mortality than were patients given chemotherapy alone. After 1 year of follow-up, however, survival was consistently better in combined-modality patients.

The optimal means of combining the chemotherapy and radiotherapy remains undefined. Most believe that giving sequential radiotherapy and chemotherapy is not optimal. The most frequent ways of combining the modalities are to give them concurrently or to give them in an alternating manner. The radiotherapy may be started at the initiation of chemotherapy or after a few chemotherapy cycles. Three trials by SWOG utilized different sequences of administration for etoposide/cisplatin and chest irradiation in SCLC. The best 4-year survival rate,

30%, was obtained in the trial in which etoposide/cisplatin was given concurrently with chest irradiation as initial therapy. The other two trials in which patients either did not receive etoposide/cisplatin or did not receive these drugs in proximity to chest irradiation and chemotherapy discontinued during irradiation had a 4-year survival of approximately 10%.

More recent studies have altered the radiotherapy by reducing volumes using ports designed by CT scans and by using postchemotherapy volumes or shrinking fields. These studies suggest volume reductions have reduced toxicity but have not adversely affected outcome. Increasing the frequency of delivery of the radiotherapy by giving it twice daily in standard or reduced fraction size (accelerated-hyperfractionated and hyperfractionated radiotherapy) has been evaluated. A randomized trial of ECOG showed that this approach increased toxicity and produced a small but insignificant improvement in survival. Thus, these approaches remain experimental. Limited-stage SCLC patients receiving combined-modality therapy still have a high relapse rate at both local and distant sites. Thus, we must continue to develop new therapeutic strategies.

Therapy for Extensive-Stage SCLC

Single-agent chemotherapy prolongs the survival of these patients and active agents produce responses in the 20–70% range. Combinations of two or three active drugs routinely produce objective responses in 80–90% of patients and complete responses in 10–50% of patients depending on disease stage. Thus, combination chemotherapy is the cornerstone of treatment. During the 1970s, most patients were treated with cyclophosphamide- and/or adriamycin-based regimens. The three-drug CAV regimen (cyclophosphamide, adriamycin, and vincristine) became one of the most commonly used regimens in both limited and extensive stages. This regimen produced responses in 80–90% of patients and markedly prolonged survival (median survival 8–10 months) compared to no treatment or single-agent chemotherapy. This therapy produced long-term survivors in a small fraction of patients (2–10%). A relatively high rate of grade 4 myelosuppression, pulmonary toxicity, and neuropathy was noted however. The response and survival after failure on CAV were very dismal. Most second-line drugs alone or in combination produced responses in less than 10% of patients and survival is generally 8–12 weeks.

During the late 1970s, cisplatin and etoposide (VP-16) were shown to be active in SCLC. The combination of cisplatin and etoposide (PE) produced response rates in 90% of patients with complete responses in 10–50% depending on stage. This combination was also active in patients who failed CAV therapy producing responses in up to 50% of such patients. The PE regimen's toxicity consisted primarily of myelosuppression, nephrotoxicity, ototoxicity, and peripheral neuropathy. The incidence of neuropathy was similar to that of CAV but

the myelosuppression was less severe. Carboplatin can be substituted for cisplatin with no loss of efficacy and with reduced toxicity. Carboplatin has the advantage of producing less renal and ototoxicity, less neuropathy, less nausea and vomiting, and is easier to administer. Two randomized trials showed carboplatin to be equivalent in efficacy and less toxic compared to cisplatin. Because of the low toxicity, the PE and carboplatin/etoposide regimens are the most commonly used in the United States.

A major clinical problem in SCLC was the high relapse in nearly all responding patients. It was recognized that acquired drug resistance developed. Alternating active and non-cross-resistant regimens were tried to prevent the development of drug resistance and relapse. When PE was found to be active in patients who failed CAV therapy, it was thought that the two regimens might be non-cross-resistant, leading to randomized trials comparing the regimens alone to the regimens given in a sequential or alternating manner. Some early randomized trials suggested that there might be some advantage to the alternating approach, especially in limited-stage disease. Two large randomized studies showed no significant difference in the response rates, complete response rates, and survival. The PE arm was, however, associated with the least myelosuppression and was only given for four cycles compared to six cycles of CAV or alternating CAV/EP. Thus, PE given for four to six cycles has reduced toxicity compared to other regimens, especially when given for longer periods or in higher doses.

Attempts to increase the efficacy of the CAV or EP regimens by increasing the dose or increasing the frequency of drug delivery have largely been unsuccessful. Individual randomized trials have been performed comparing standard-dose CAV to dose-intensified CAV and standard-dose PE to dose-intensified PE. The results of these trials revealed that increasing the doses increased the toxicity without improving survival. Growth factors such as G-CSF and GM-CSF have been used to increase the dose of standard regimens such as CAE (cyclophosphamide, adriamycin, and etoposide). The G-CSF reduced the myelosuppression but did not improve response rates or survival. These growth factors should not be given with concurrent radiotherapy because they produce a significant increase in thrombocytopenia and other toxicities. A number of trials attempted to improve results by marked increases in drug doses, which required support with autologous bone marrow cells. Some of the studies gave the intensified therapy initially, while most used intensification therapy after response to standard therapy. In general, these studies showed marked increases in toxicity while the survival results were not better than with standard approaches. Thus, an international consensus panel concluded that this approach remains experimental. Increasing the frequency of drug delivery led to the testing of weekly regimens. Randomized trials reported to date have failed to show an advantage for weekly regimens compared to standard regimens.

There has been some debate over the optimal number of chemotherapy cycles and the role of maintenance therapy. The optimal chemotherapy regimen for combined-modality approaches has not been defined. Three large randomized trials showed that the time to progression was longer in the group receiving maintenance chemotherapy but there were no differences in survival. Toxicity was greater in patients receiving the maintenance therapy. Both the continued exposure to the toxicities of chemotherapy and the fact that patients given continuous chemotherapy who progress tend to fare poorly under salvage treatment make discontinuing chemotherapy after four to six cycles a preferred approach at present. Randomized trials using interferons as maintenance therapy showed an increase in cost and toxicity without an effect on survival.

Many elderly and unfit patients with SCLC often have other comorbid diseases especially because of their smoking histories. It has often been unclear whether these patients should be treated with chemotherapy. Several groups evaluated the role of oral VP-16 in these patients. The studies showed that single-agent oral VP-16 was tolerated by the elderly/unfit patients and that response rates and survival were similar to those reported in younger and more fit patients. These observations led to randomized trials comparing oral VP-16 to standard combinations in elderly and unfit SCLC patients. These results showed single-agent oral etoposide to be more toxic and slightly less effective than the standard combination regimens. Thus, these patients should be offered chemotherapy regimens.

Unfortunately, the vast majority of SCLC patients eventually relapse and die from progressive disease. Extensive-stage SCLC patients who receive chemotherapy have a 5-year survival rate of only 1%. Thus it was reasonable to study new agents in untreated extensive-stage patients. In some trials where ineffective agents were studied in untreated patients, the patients receiving the ineffective agent had a worse outcome than patients receiving standard therapy. In other instances, where patients were crossed over rapidly to standard PE regimens if there was no response to the new agent, there was no negative impact from the study of the new agent in these untreated patients. Thus, it is reasonable to study new agents in either setting if attention to study crossover is built into studies in untreated patients.

In studies of patients who progress after initial standard therapy, highly important prognostic variables have been identified. The response to the initial therapy and the duration of response between the end of chemotherapy and progression are extremely important prognostic variables. Patients who fail to respond to initial therapy and patients who relapse after short periods have much lower response rates than patients who have an initial complete response and who have a long initial response duration.

Several new agents, with novel mechanisms of action, have been tried in SCLC to improve cure rate and overall survival. These include the taxanes, pacli-

taxel and docetaxel; the topoisomerase I inhibitors, CPT-11 (irinotecan) and topotecan; another vinca alkaloid, navelbine; and gemcitabine, and antimetabolite.

Paclitaxel, unlike the vinca alkaloids, which prevent microtubule assembly, stabilizes microtubules against depolymerization. Paclitaxel inhibits proliferation of cells by inducing a sustained mitotic block at the metaphase/anaphase boundary. Two phase II trials of paclitaxel given as a 24-hr continuous infusion at a dose of 250 mg/m^2 every 3 weeks with G-CSF support showed response rates of about 60%. The first study conducted by ECOG showed a confirmed response rate of 34%, but the confirmed plus unconfirmed rate, which most likely represents the true response rate, was 53%. The other trial by the North Central Cancer Treatment Group (NCCTG) treated 37 patients with an overall response rate of 68%. When the studies were combined, there were 42 responses among 71 evaluable patients (59%).

In the study from the EORTC, docetaxel, another taxane, at a dose of 100 mg/m^2, resulted in an objective response rate of 25% among 28 patients, most of who had received prior therapy. Ninety percent of the patients, however, developed grade 4 neutropenia and a significant minority of patients developed clinically significant effusions, ascites, and edema.

The topoisomerase I inhibitors, CPT-11 and topotecan, have considerable activity in SCLC. Two studies from Japan using CPT-11 showed an objective response of 40% in previously treated patients. This included 5% CRs and 35% PRs. Topotecan also showed considerable activity in both previously treated (35%) and previously untreated (39%) patients.

Navelbine, a vinca alkaloid, was reported to have a response rate of 13% in pretreated SCLC patients. Because of its myelosuppressive properties, its ability to be combined with other myelosuppressive agents is limited. Gemcitabine was reported to have a response rate of 36% in 26 patients.

Combinations of these new agents with established agents such as cisplatin, carboplatin, and etoposide in SCLC revealed impressive results. The group from the Sarah Cannon Cancer Center using the combination of carboplatin, paclitaxel, and daily etoposide showed a 95% response rate among the first 22 patients, including 10 complete responses (45%). The combination of paclitaxel, cisplatin, and etoposide gave a response rate of 100% and a complete response rate of 20% in a University of Colorado study. The median survival was 11 months. ECOG reported a response rate of 88% and a complete response rate of 13% with the same combination of paclitaxel, etoposide, and cisplatin. The group from the NCI reported four partial responses in the first six patients treated with continuous-infusion paclitaxel and carboplatin. Thus, in these four trials, there was a complete response rate of 34%, warranting further study of paclitaxel combinations in SCLC.

Because of the high frequency of development of brain metastases in SCLC, prophylactic cranial irradiation (PCI) was evaluated as a means to reduce

CNS metastases and prolong survival. Prospective randomized studies have shown that PCI reduces the frequency of clinically detected brain metastases, particularly in patients with a complete response to therapy, but has not shown improvement in overall survival. There are reports of significant neurological, mental, and psychometric deficits in long-term survivors treated with PCI. A review of seven studies in which PCI was employed revealed that in 96 long-term survivors, neuropsychological impairment was noted in 76% of examined patients as compared to 15% in a group of 20 long-term survivors not treated with PCI.

Most likely, the explanation for the failure to affect survival is the fact that brain metastases are rarely the sole site of metastatic spread. Thus, the major issue is whether a delay and reduction in brain metastases by PCI in a small fraction of patients is justified by the toxicity and the treatment of patients.

Non–Small Cell Lung Cancer

The most important prognostic factors in NSCLC are stage and performance status. Determination of stage has a critical role in the selection of therapy. The stage of disease is based on a combination of clinical (physical examination, radiological, and laboratory studies) and pathological (biopsy of lymph nodes, bronchoscopy, mediastinoscopy, or other type of thoracotomy) staging. The TNM classification endorsed by the American Joint Committee was revised in 1997. In NSCLC, surgery is the major potentially curative therapeutic option for this disease and is used in all patients with operable stages without medical contraindication.

Role of Adjuvant Chemotherapy for Stages I–IIIA (non-N2) NSCLC

Surgical therapy provides excellent results with cure rates exceeding 70% only for stage IA (T1 N0 M0) NSCLC. There is no evidence that any adjuvant therapy including immunotherapy, radiotherapy, or chemotherapy improves survival for these patients. Because the majority of these patients are cured by surgery, it is probably best to reserve further study of adjuvant chemotherapy until such adjuvant therapy shows value in NSCLC patients at higher risk of relapse.

Lung cancer patients resected for cure have a high risk of developing second primary tumors as well as a risk of disease recurrence. After 2 years, the risk of developing a second lung cancer exceeds the risk of recurrence. Because of this, patients should be encouraged to stop smoking. These patients also serve as excellent subjects for chemoprevention studies. In fact, one such study was conducted in Europe where completely resected patients were randomized to receive high-dose vitamin A (retinol) or placebo. There was a reduction in the rate

of developing second primary lung cancers in the group randomized to retinol. However, the benefit was of borderline statistical significance, possibly owing to the small numbers of patients in the trial. Overall survival rates were no different. Because of this, two follow-up randomized trials have been conducted. One was an intergroup study in the United States where patients were randomized to receive 13-cis-retinoic acid or placebo and one was an EORTC study in Europe where patients were randomized to receive retinol or placebo. The results of these studies should be available in a few years.

Large surgical series evaluating the sites of relapse in completely resected NSCLC patients demonstrated that the vast majority (about 80%) of relapses occurred in distant sites. Systemic therapies are the only way to decrease these relapses making adjuvant chemotherapy a logical adjuvant approach. The earliest studies used alkylating agents alone or in combination. The Veterans Administration (VA) Lung Cancer Study Group amassed the largest experience in adjuvant chemotherapy during this early period. In this series examining 2348 patients undergoing curative resection, patients were treated with either nitrogen mustard, methotrexate, or methotrexate plus cyclophosphamide depending on the study. The 5-year survival rates were 26% and 25% in the adjuvant-chemotherapy and surgery-alone groups, respectively. A later VA Lung Cancer study Group examined resection alone versus resection followed by lomustine plus hydroxyurea. No improvement in survival was seen. Instead, a trend toward reduced survival was seen in the adjuvant-chemotherapy group: 35% 5-year survival compared to 46% 5-year survival with surgery alone. These studies showed no benefit for the postoperative chemotherapy and in several studies, including the one above, survival was actually shortened. These therapies were also relatively toxic and these facts led to considerable support for the role of adjuvant chemotherapy.

When cisplatin-based chemotherapy was shown to have activity in advanced NSCLC, it was evaluated as postoperative therapy in resected patients. The largest number of trials used the CAP regimen consisting of cyclophosphamide, adriamycin, and cisplatin. The cisplatin was usually given in low dosage (40 mg/m^2). This therapy was relatively toxic and the amount of drug delivered was usually considerably less than what was planned. Some of these studies showed survival advantages for the chemotherapy, while others did not. Because of this, a meta-analysis showed that the cisplatin therapy was associated with an absolute increase of 5% in the 5-year survival rate, which was a 13% reduction in the hazard rate of death. This increase was of borderline statistical significance. When physicians in the United Kingdom were surveyed after being shown these data, less than 5% indicated that they would recommend such a therapy for their patients. In contrast, when such data were explained to patients, more than 90% wished to be offered chemotherapy, which would increase the cure rate by 1%. Fortunately, we now have much superior chemotherapy, which also has less tox-

icity. Whether patients should be offered such chemotherapy is a matter of considerable debate. Resolution of the issue will require phase II and III studies of new chemotherapy regimens.

Role of Adjuvant Chemotherapy for Stage IIIA N2 NSCLC

The 5-year survival rates for patients with clinical stage IIIA N2 NSCLC determined by massive mediastinal node enlargement on chest x-ray or by biopsy and treated with surgery alone is dismal (<15%). Postoperative radiotherapy fails to improve survival. This made studies of preoperative chemotherapy logical. Phase II studies of such an approach were conducted by the following groups and provided encouraging results. The Memorial Sloan-Kettering Cancer Center evaluated 136 patients with stage IIIA (N2) disease treated with neoadjuvant mitomycin, vinblastine, and cisplatin chemotherapy (two to three cycles). The objective response rate to chemotherapy was 77% and the complete resection rate was 78%. The pathological complete response rate was 14%. The 5-year survival rate was 17% with a median survival of 19 months, whereas the corresponding values in the subgroup of patients undergoing complete resection were 26% and 27 months, respectively. The group in Toronto using the same chemotherapy regimen reported a 71% response rate and a 51% complete resection in a study of 55 patients. Median survival was 21.3 months. The preoperative chemotherapy, which consisted of MVP (mitomycin C, vinblastine, and cisplatin), produced a high objective response rate (about 70%) and the majority of patients were able to undergo subsequent complete resections. The 5-year survival rates were very encouraging (>20%). A large phase II trial by the CALGB evaluated 74 patients with stage IIIA NSCLC treated with two cycles of vinblastine/cisplatin prior to complete resection, followed by chest irradiation in patients who had incomplete resection or no response to chemotherapy. The objective response plus stable disease was 88%. Eight-six percent of patients were treated with surgery and 36% had complete resection. The 3-year overall survival rate was 33%, with median survivals of 20.9 months in patients undergoing complete resection and 17.8 months in those with incomplete resection compared with 8.5 months in patients who were not resected.

These studies led to two prospective phase III randomized trials, which both showed a statistically significant survival improvement for neoadjuvant chemotherapy. The Spanish trial compared cisplatin + ifosfamide + mitomycin C for three cycles followed by surgery to surgery alone. The median (26 months vs. 8 months) and the 3-year survival (25% vs. 0%) favored the chemotherapy. In the study from the M. D. Anderson Cancer Center, the preoperative chemotherapy consisted of cisplatin + cyclophosphamide + etoposide for three cycles before surgery or surgery alone. Postoperative chemotherapy was also administered and postoperative radiotherapy was allowed at the discretion of the physician. Survival results again favored the chemotherapy with improved median (64 months

vs. 11 months) and 3-year survival (56 vs. 15%). Both of these studies had a very small number of patients (60 in each study) because the statisticians closed the studies at an early stopping rule because of the highly statistically significant improvement in survival. Many physicians concluded that these studies showed that single-modality surgical therapy for preoperatively defined N2 disease can no longer be justified.

The early experience with the neoadjuvant approach and the high local relapse rate after combined therapy with chemotherapy and radiotherapy led to phase II trials combining all three modalities. The majority of these trials gave concurrent induction therapy with chemotherapy and radiotherapy and followed these with surgery for patients who did not progress. The entry criteria varied considerably in these studies with some confined to IIIA N2 and others including patients with IIIB and/or some with T3 N0 or T3 N1 disease. These studies showed a response rate in the 50–70% range, a complete surgical resection rate in the range of 60–85%, a pathological complete response rate of 20%, and a surgical mortality rate of about 6–8%. The 5-year survival in many of these studies was about 20%. The long-term survival rate was similar to many of the studies using only two modalities including chemotherapy with radiotherapy and chemotherapy with surgery.

A Southwest Oncology Group (SWOG) phase II study was done to assess the feasibility of concurrent chemotherapy and irradiation followed by surgery in locally advanced NSCLC. This study reported an 85% resectabiltiy for the stage IIIA (N2) group and an 80% resectability for the IIIB group. Two- and 3-year survival rates were 37% and 27%, respectively. An intergroup study is currently in progress to determine whether all three modalities are better than combined modality with radiotherapy. Future trials should also address whether chemotherapy + radiotherapy or chemotherapy + surgery is preferred for stage IIIA N2 NSCLC patients.

Role of Chemotherapy in the Treatment of Stage IIIB NSCLC

Radiotherapy was the primary therapy for stage IIIB NSCLC for many years because it alleviated symptoms and because about 5% of patients experienced 5-year survival. Survival of patients with locally advanced, unresectable, NSCLC treated with radiotherapy is poor with a median survival of only 9–10 months. The addition of chemotherapy was tested to evaluate its ability to improve local control and eliminate or delay the emergence of metastatic disease. Multiple randomized trials of radiotherapy alone versus radiotherapy plus chemotherapy have been completed, most of which showed survival advantage for the combined approach. For example, an EORTC phase III trial in inoperable, nonmetastatic NSCLC compared split-course radiation therapy alone with split-course radiation therapy combined with cisplatin, given either weekly or daily. A total of 331 patients were evaluated. Survival was significantly improved in the combination

group compared with the radiotherapy-only group ($p = 0.009$). Patients' median length of survival was prolonged by several months by daily cisplatin/radiotherapy and the 2- and 3-year survival rates were double or triple the radiotherapy-only survival rates (3-year survival rate for daily cisplatin/radiotherapy 16%, weekly cisplatin/radiotherapy 13%, and radiotherapy alone 2%). Also noted was improved local control in the daily cisplatin/radiotherapy group (13 vs. 11 months) ($p = 0.003$), suggesting that this schedule results in maximal radiation enhancement.

The CALGB, using sequential chemotherapy-radiotherapy, compared two cycles of cisplatin and vinblastine induction chemotherapy followed by definitive chest irradiation with the same radiotherapy alone in 155 patients with stage III NSCLC. The median duration of survival was 13.8 months for the combined-modality group and 9.7 months for the radiotherapy-alone group ($p = 0.0066$). Survival rates at 2 and 3 years were 24% and 23%, respectively, for the combined-modality group compared with 14% and 11%, respectively, for the radiotherapy-alone group. After more than 7 years of follow-up, the median survival remains greater for the CT-RT group (13.7 months) than for the RT group (9.6 months) ($p = 0.012$).

A French group used an approach with chemotherapy alternating with radiotherapy. They compared thoracic irradiation alone (65 Gy) to the same radiotherapy preceded and followed by three monthly cycles of vindesine, cyclophosphamide, cisplatin, lomustine (VCPC) chemotherapy in 353 patients. In the radiotherapy group, 20% of patients achieved CRs as did 16% in the combined-modality group. The rate of distant metastases at 2 years was 64% in the radiotherapy group compared to 43% in the combined-modality group ($p < 0.001$). Combined-modality therapy was associated with significant improvement in length of survival (median survival, 12 months vs. 10 months) and reduced distant disease.

A meta-analysis of 14 randomized trials of combination therapy and radiotherapy alone in locally advanced, unresectable NSCLC was subsequently done. Compared with radiotherapy, the combination of chemotherapy and radiotherapy reduced the risk for death by 12% at 1 year, 13% by 2 years, and 17% by 3 years. This corresponds to a mean gain in life expectancy of about 2 months from 10.3 months to 12.0 months. When considered separately, trials of concurrent and sequential chemotherapy yielded similar treatment effects. The addition of chemotherapy to radiotherapy was associated with a 10–20% decrease in the risk for death.

Therapy of Stage IIIB with Pleural Effusions

Malignant pleural effusions indicate incurable disease by a surgical approach and are usually treated with primary chemotherapy or palliative measures such as thoracentesis or chest tube insertion with pleurodesis. Without chemotherapy, the

average survival from the time of diagnosis carcinomatous involvement of pleura by lung cancer is only about 2.2 months. Radiotherapy cannot be delivered to the entire chest cavity and is not used in these patients. Thus, these patients are usually treated in the same manner as patients with stage IV disease.

Current Therapy for Stage IV NSCLC

Until the last several years, there was great pessimism about the role of chemotherapy in advanced NSCLC: no agent consistently produced objective responses in more than 25% of patients, and no evidence showed that chemotherapy prolonged the survival of these patients. Prior to the introduction of six new agents for the therapy of advanced NSCLC, the most widely used agents were the platinum compounds cisplatin and carboplatin; the topoisomerase 2 inhibitor etoposide; and the vinca alkaloids, vinblastine and vindesine. Cisplatin produced objective responses in about 15–20% of NSCLC patients. Cisplatin increased the survival of lung cancer patients as shown by several randomized trials and by meta-analyses of all randomized trials. For example, in the randomized study of the Canadian National Cancer Institute, patients in the best supportive care arm had a median survival of 17 weeks compared to 33 weeks for patients receiving chemotherapy. The 1-year survival was more than doubled from 10% to 20% and symptoms improved in responding patients. All of these studies showed improved survival in patients receiving the chemotherapy although the differences were not always statistically significant. In the meta-analysis, cisplatin-based combinations significantly improved survival by about 2 months at the median with about a 10% (from 10% to 20%) increase in the percent of patients alive at 1 year. Because of the low response rates and minor impact on survival, better agents and combinations are needed.

Six new chemotherapeutic agents in phase I and II studies have been approved by the Food and Drug Administration for various indications over the past 2 years. These agents include the two taxanes, paclitaxel and docetaxel; two topoisomerase 1 inhibitors, irinotecan (CPT-11) and topotecan; a novel antimetabolite, gemcitabine; and a novel vinca alkaloid, vinorelbine.

Two initial phase II studies of paclitaxel as 24-hr infusions of a high dose (200–250 mg/m^2) showed a response rate of 22% among the 49 patients. Subsequent phase II studies of paclitaxel used 1–3-hr infusions and showed similar efficacy with an overall response rate of 21%. The survival rates from paclitaxel were even more impressive than the response rates. In studies with both schedules, the 1-year survival rates were 40% and the 2-year survival rates were about 20%.

Docetaxel (taxotere) also was shown to be active in NSCLC. In phase II studies, the response rate varied from 18% to 38% with an average of 25%. In previously treated patients, docetaxel appears to be nearly as active. One report reported a response rate of 33% with an estimated 1-year survival rate of 45%.

The topoisomerase I inhibitors have also been shown to be effective. Phase II studies of CPT-11 in advanced untreated NSCLC patients reported response rates of 32–41% with an average of 34% among 161 patients. Gemcitabine has been shown to have an overall response rate of 20% among 332 patients in several phase II trials. Gemcitabine alone was shown to have equivalent efficacy to the two-drug combination of etoposide and cisplatin and to be less toxic.

Vinorelbine (navelbine) is a novel vinca alkaloid with substantially less neurotoxicity than other vinca alkaloids. As a single agent, vinorelbine was shown to have a response rate ranging from 14% to 29% with median survival time of about 32 weeks. In a large European study, vinorelbine alone was shown to have similar median survival times to the combination of vindesine and cisplatin (32 vs. 31 weeks), with substantially less toxicity. A U.S. study showed single-agent vinorelbine to have a 12% response rate and a median survival of 29 weeks, with 25% of patients alive at 1 year.

Combination Chemotherapy in NSCLC

Because of the impressive results of these new single agents, attempts were made to combine some of these drugs. A large experience is reported with the combination of paclitaxel plus carboplatin or cisplatin. Many studies evaluated varying doses of paclitaxel given as a 24-hr infusion with a carboplatin dosed based on the Calvert formula using an area under the curve (AUC) of 6–7.5. In these studies, the overall response rate varied from 27% to 63% with an average of 48%. Survival was also impressively long with a median of 62 weeks in the largest study.

There is also considerable experience with the more convenient 3-hr infusion of paclitaxel combined with carboplatin without G-CSF support. Response rates varied from 33% to 47% with an average of 41%. The recommended dose appears to be 225 mg/m^2 of paclitaxel and an AUC of 6 of carboplatin. This combination is being compared to the navelbine-cisplatin combination in an ongoing SWOG study.

There is evidence that the combination of paclitaxel with a platinum agent is superior to prior cisplatin combinations. The Eastern Cooperative Oncology Group (ECOG) completed a randomized study comparing their standard etoposide-cisplatin combination to the paclitaxel-cisplatin combination with paclitaxel over 24 hr at 135 mg/m^2 without G-CSF support or 250 mg/m^2 with G-CSF support. Both of the paclitaxel arms were superior to the etoposide-cisplatin arm with respect to response and survival. Giving paclitaxel as a 3-hr infusion in combination with cisplatin showed a 47% response rate. The European Organization for Research on Treatment of Cancer (EORTC) compared a short infusion of paclitaxel plus cisplatin to teniposide plus cisplatin. The paclitaxel arm was superior with respect to response rate, toxicity, and quality of life. In both of

these randomized trials, 37–40% of patients on the paclitaxel arms were alive at 1 year. This compares to 10% alive at 1 year in all best supportive care studies.

Docetaxel was also combined with cisplatin in many phase II studies in advanced NSCLC. In these studies, the response rate was 35% and the average median survival was 39 weeks. These response and survival rates are slightly inferior to those reported with paclitaxel combined with either cisplatin or carboplatin. The ECOG is conducting a four-arm randomized study comparing docetaxel/cisplatin to paclitaxel/cisplatin, paclitaxel/carboplatin, and gemcitabine/cisplatin. Phase II studies of gemcitabine and cisplatin reported an overall response rate of 47%. The average median survival was 48 weeks with an average 1-year survival rate of 48%. Phase II trials with irinotecan and cisplatin have shown an average response rate of 50% among 120 patients.

Phase III trials using the combination of vinorelbine and cisplatin reported longer median survival times compared to other cisplatin-based regimens. A large European study reported a 30% response rate for the combination with a median survival of 40 weeks. A significantly higher rate of neutropenia was, however, noted. A randomized study comparing a three-drug regimen of cisplatin, mitomycin, and vincesine versus cisplatin, mitomycin, and vinorelbine reported a 25% response rate for the vinorelbine arm and overall median survival time of 33 weeks. For stage IIIB patients, median survival rate was 46 weeks compared to the vindesine arm and 1-year survival rate of 40%. The SWOG is currently doing a study comparing carboplatin and paclitaxel with cisplatin and navelbine in stage IIIB and stage IV NSCLC.

Because chemotherapy, especially new agents, costs money and because it prolongs survival, the costs per year of life gained can be determined and compared to those of other medical therapies. In a Canadian study cited above, the survival benefit of 8 weeks in favor of patients receiving chemotherapy was associated with an economic saving of $949.49 (in Canadian dollars) when compared to best supportive care. This translated into a savings of $6171 per year of life gained. It can be considered that chemotherapy improved quality of life compared to palliative treatment resulting in reduced hospitalization costs. The majority of costs were related to hospitalization and not to the use of chemotherapy since chemotherapy costs accounted for only a small proportion of the total hospitalization costs. Other studies showed similar results. Compared to the 16- or 17-week median survival of patients who receive best supportive care, patients treated with new agents alone or in combination have median survival of about 39–48 weeks, a gain of about 26 weeks. Currently, new therapies may cost as much as $2500 per cycle, or $10,000 per four cycles. This equates to $20,000 per added year of life. Thus, the cost of therapy for advanced NSCLC is well within the range of other accepted medical therapies and will be lowered considerably when generic agents become available.

Conclusions

Chemotherapy can be now viewed as a major component of therapy for both SCLC and NSCLC patients. Meta-analyses of randomized trials showed that chemotherapy prolongs the survival of patients with stage III and stage IV SCLC and NSCLC. The guidelines of lung cancer therapy of the American Society of Clinical Oncology (ASCO) reflect this contribution of chemotherapy to prolonging the survival of these patients.

For patients with stage III N2 lung cancer, one modality of therapy is not sufficient. Randomized trials have shown that combined chemotherapy and radiotherapy is superior to either modality alone in both SCLC and in NSCLC. In stage IIIA NSCLC, chemotherapy plus surgery has also been shown to be superior to surgery alone. In stage III SCLC, all three modalities (chemotherapy + radiotherapy + surgery) are not superior to chemotherapy + radiotherapy. In stage III NSCLC, this question is currently being addressed in a randomized intergroup study.

For stage I SCLC (a rare occurrence), surgery is usually preferred before chemotherapy. For resectable NSCLC, stage IB, II and T3 N0–1 stage IIIA non-N2, postoperative radiotherapy reduced local failures, which occur in about 20% of patients, but does not improve survival. Old randomized studies with low-dose cisplatin (40 mg/m^2) based postoperative chemotherapy showed a 13% reduction in the hazard rate of death, which translated into a 5% absolute increase in 5-year survival. Since modern chemotherapy regimens are markedly superior to both low-dose and high-dose cisplatin combinations, it is likely they will further increase the cure rate when given preoperatively to these NSCLC patients.

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19

Malignant Mesothelioma

Sunil Singhal
Johns Hopkins University School of Medicine, Baltimore, Maryland

Mitchell Machtay and Larry R. Kaiser
University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

INTRODUCTION

Mesotheliomas are primary neoplasms of the serosal membranes of the body cavities. Eighty percent of mesotheliomas originate in the pleural space. Other sites of origin for this tumor include the peritoneum, pericardium, tunica vaginalis testis, and ovarian epithelium. Most reports describe a ratio of pleural to peritoneal mesotheliomas of 10:1, with the other serosal membranes affected only rarely. Malignant pleural mesotheliomas account for only 5% of intrapleural tumors with the other 95% accounted for by tumors metastatic to the pleural space.

Mesotheliomas can be classified into three general categories: diffuse malignant, localized benign, and localized malignant mesotheliomas. Diffuse mesotheliomas account for 90% of cases seen. They are of special interest because of their increasing frequency, dismal prognosis, and issues of asbestos exposure. Localized mesotheliomas, now referred to as solitary benign fibrous tumors of the pleura, are rare and can be quite large at the time of presentation. Ten percent of localized pleural lesions prove to be malignant.

Asbestos inhalation is an established cause of malignant pleural mesotheliomas (MPM). It is estimated that 80% of cases are caused by asbestos. Hundreds of cohort studies and case reports have reported an association between asbestos and pleural malignancies. Together, these epidemiological studies have analyzed

over 50,000 male and female asbestos-related workers and come to the same conclusion: asbestos unequivocally is related to the development of MPM.

Pleural mesotheliomas occur much more commonly in men than in women with a ratio of 5:1. This reflects the increased occupational exposure of men to asbestos. Incidence rates rise steadily with age and are approximately 10-fold higher in men between ages 60 and 64 than among those between ages 30 and 34. Patients usually present in the sixth or seventh decade of life, though MPM has been seen in individuals ranging in age from 4 years to over 90. There is also a significant geographical variation in the incidence of MPM with sections of New England, Philadelphia, Seattle, San Francisco, and Hawaii (all locations of large shipbuilding and asbestos use in World War II) having up to fivefold higher rates of the disease.

Until recently it has been difficult to ascertain the number of deaths caused by MPM because physicians were reluctant to diagnose serosal-based tumors and rarely coded them separately from other pulmonary carcinomas. Death certificates were rarely accurate when there was a question of mesothelioma. The incidence of mesothelioma was estimated at 2.7/million people in 1972 and has been trending upward. More recent statistics suggest that MPM currently accounts for 20 deaths/million male population in industrialized nations. There are approximately 2200 new cases/year in the United States alone. Various epidemiological estimates based on data from the Surveillance, Epidemiology, and End Results (SEER) program suggest that a peak of 3000–4000 new cases/year should be reached at the turn of the century and then decline over the next 40 years. Approximately 75,000 new cases are expected to occur over the next 20 years. The incidence of MPM in women remains flat at 3 cases/million women. In developing countries, mesothelioma incidence rates are predicted to continue to rise indefinitely because of poor regulation of asbestos mining and continued widespread industrial and household utilization of asbestos.

Smoking is an established risk factor in the development of primary bronchogenic carcinomas; however, epidemiological studies have failed to show any association between tobacco and mesothelioma development. There is significant danger in asbestos-exposed smokers where the increased risk of developing lung cancer is 90-fold higher than from smoking or asbestos exposure alone. Animal experiments and epidemiological studies have confirmed this synergistic effect of asbestos exposure and cigarette smoking on lung cancer development.

Seemingly not all MPM is mesothelioma attributable to asbestos exposure. Even with a thorough history and review with family members, 20% of patients are unable to recount prior asbestos exposure, but is is well recognized that a trivial exposure, enough to cause MPM in a susceptible individual, may not be recalled 30–40 years after the fact. Regardless of etiology, however, the natural history and prognosis is uniformly dismal.

DIAGNOSTIC APPROACH

History/Physical Examination

The typical patient with MPM presents in the seventh decade of life. Children of asbestos workers may present under 50 years of age, reflecting the 30-year latency period. The most important data of medical history to obtain are history of asbestos exposure and tobacco use. A comprehensive history must focus on the period 20–40 years before diagnosis and should include the occupations of family members living with the patient at the time.

At presentation, most patients with MPM are in surprisingly good general health. There is an average 3-month delay following onset of symptoms before patients seek medical consultation, but the delay often is considerably longer. The most common presenting symptoms are dyspnea (60–70%) and insidious onset of chest pain (50–70%). At later stages, patients will begin experiencing weight loss (25–30%), cough (27%), fever (33%), weakness (33%), and anorexia (10%). Other symptoms noted at presentation have included stridor, nausea, headache, and perceived tachycardia. Five percent of patients will present with complaints of acute onset of excruciating chest pain and dyspnea. Emergency evaluation will reveal a hemothorax or spontaneous pneumothorax. Approximately 10% of patients will be referred due to asymptomatic abnormalities on routine chest roenteogram. Rarely will the patient present with nonspecific constitutional symptoms or evidence of metastatic disease. Another rare presentation of malignant mesothelioma is bilateral lymphangitic spread within the lung.

The symptoms of MPM are secondary to the effects of the tumor within the pleural cavity: the enlarging mass, invasion of adjacent structures, and production of fluid by mesothelial cells. At the time the patient presents, the tumor often has become bulky and restricts movement within the hemithorax (Fig. 1). The patient experiences dyspnea because the tumor encases the lung and restricts ventilation and normal chest wall mechanics. Pleural effusion with compression of lung parenchyma and decreased oxygenation occurs commonly. A dry cough may be elicited when the patient is asked to breathe deeply. In later stages, patients develop significant weight loss due to the extensive thoracic involvement and creation of a hypermetabolic state.

The chest pain ranges from a heavy feeling to a dull aching sensation in the posterolateral chest to a severe pain that frequently radiates to the upper abdomen, shoulder, and arms. While the pain may be pleuritic, it is more commonly unrelated to respiratory or other chest wall movements. The pain, when severe, is characteristically persistent and resistant to analgesics. When powerful narcotics fail to provide relief, intercostal and paravertebral block may be necessary.

The most common (80%) physical findings usually are secondary to the pleural effusion or pleural mass: decreased ipsilateral chest wall movement, dull-

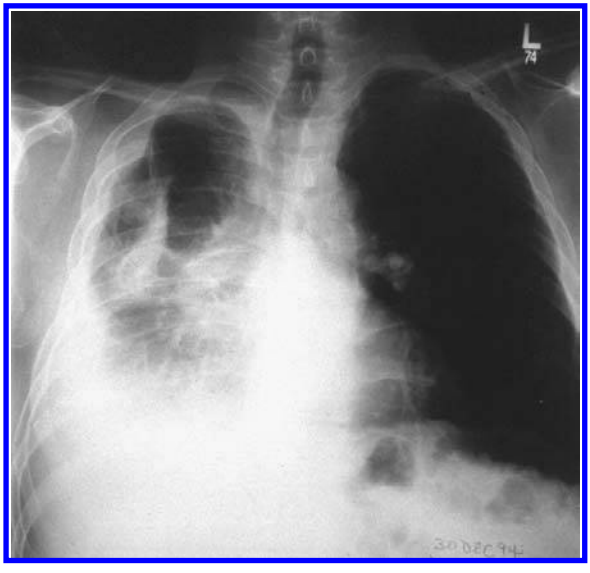

FIGURE 1 Typical chest radiograph of a patient presenting with shortness of breath and chest pain secondary to a mass in the pleural space.

ness to percussion over involved lung fields, and decreased intensity of breath sounds. The right side is more commonly affected, while bilateral involvement at presentation is rare. If the tumor has eroded through the chest wall, focal tenderness or a palpable mass may be felt. In late stages of disease, there may be signs of compression or invasion of the mediastinal structures such as superior vena cava syndrome or diaphragm paralysis. There may also be digital clubbing, cachexia, and muscle wasting. Signs of extrathoracic involvement are uncommon at presentation, occurring in less than 10% of cases. Though metastatic disease is uncommon at presentation, patients may have cervical lymphadenopathy and hepatomegaly.

Laboratory Studies

Patients with malignant mesothelioma have no pathognomonic laboratory abnormalities. The most common finding is thrombocytosis ($>400{,}000/mm^3$) noted in 60–90% of patients. Approximately 15% of patients have platelet counts over $1{,}000{,}000/mm^3$. Occasionally, patients will develop anemia of chronic disease. Elevated sedimentation rate (>100 mm/hr) is noted early in the disease, but is nonspecific. Some patients develop hypergammaglobulinemia, eosinophilia, and hypoglycemia, though these are more common in rare instances of solitary benign

fibrous tumors of the pleura. There have been occasional reports of hypercalcemia, nephrotic syndrome, and hemolytic anemia.

Imaging Studies

The first radiographic changes associated with asbestos were described by Pancoast 80 years ago. To differentiate tuberculosis from dust inhalation, he described increased thickness of the prominent linear shadows that uniquely extended from the hilum to the base. Since then, chest roentograms, ultrasonography, and computed tomography have changed the approach to diagnosis and staging of malignant mesothelioma. The radiological diagnosis of MPM requires a high degree of clinical suspicion. The major pathological features of mesothelioma are well demonstrated by conventional chest radiography and computed tomography (CT). CT, however, demonstrates the findings more frequently and in greater detail. Ultrasound and magnetic resonance imaging (MRI) are additional imaging modalities with helpful but limited application in studying malignant mesotheliomas (Fig. 2).

The most common radiological presentation is a large, unilateral pleural effusion, seen in greater than 50% of patients. Only 10% of patients present with bilateral effusions. The effusion at presentation can be quite large with near-complete opacification of the hemithorax. Fluid may be loculated and surrounded by areas of thickened or nodular pleura and there may be only a small amount of free-flowing pleural fluid. The concave upper boundary of the fluid shadow may be distorted by adhesions. Since CT scans are performed in the supine posi-

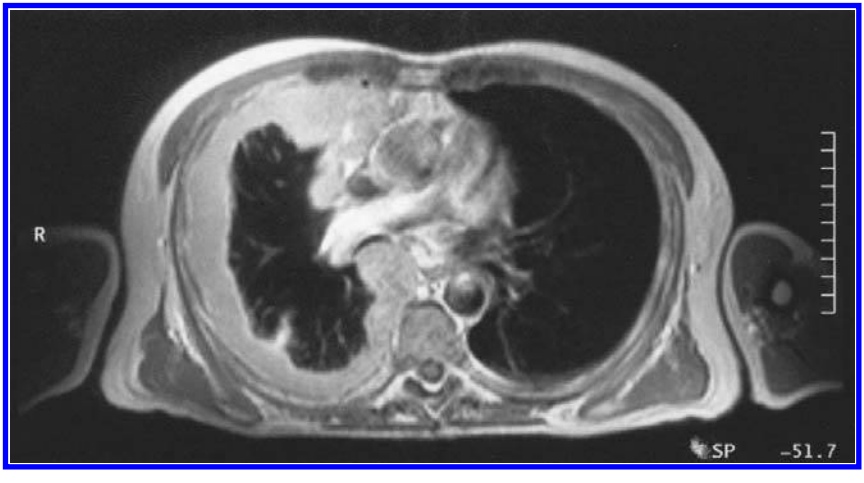

Figure 2 MRI axial image on a patient with malignant pleural mesothelioma.

tion, it is difficult to distinguish free-flowing pleural fluid from loculated effusions, pleural thickening, or pleural-based mass. The patient can be placed in the lateral decubitus position for differentiation.

Aspiration of the fluid may reveal an underlying tumor radiographically, particularly if a pneumothorax is produced at the same time. The production of a pneumothorax can sometimes be used as a diagnostic aid. A shadow that persists after removal of the fluid is highly suggestive of an underlying tumor.

Mediastinal shift is a variable finding, both before and after aspiration of the effusion. Shift may occur, either toward the affected side (suggesting invasion and fixation of tissue by tumor) or to the contralateral side (''tension effusion,'' a relatively late manifestation). The presence of a large pleural effusion in the absence of a contralateral shift may indicate three possibilities: atelectasis secondary to bronchial obstruction by the primary tumor or lymph node metastases, fixation of the mediastinum as a result of direct invasion or spreading along lymphatic channels, or growth into the ipsilateral lung or pleural space, mimicking a large effusion.

Asbestos pleurisy should be part of the differential diagnosis in a patient with a pleural effusion and history resembling malignant mesothelioma. Asbestos pleurisy occurs in 3–5% of asbestos workers and is usually recurrent and bilateral. Also associated with chest pain, 33% of the effusions secondary to asbestos pleurisy are bloody.

The other common radiographic finding in MPM is diffuse, circumferential pleural thickening (60–100%), usually associated with plaques and effusions. Neoplastic growth is usually unilateral at presentation and two-thirds of tumors are on the right side. This may reflect the larger surface area of the right pleural cavity as well as the anatomical distinction of the more vertical right bronchial tree. Pleural thickening commonly extends along pleural spaces into the pleural fissures and medially to involve the mediastinal pleura. The major fissure toward the basal region becomes markedly thickened owing to a combination of fibrosis, tumor, and associated fluid. A thick rind of neoplasm results in restriction of the involved hemithorax and resultant decrease in size, which is obvious on the CT scan. The lower hemithorax tends to be more affected by the tumor than the upper, a phenomenon termed ''gravitational metastasis.'' Additionally, the mediastinum frequently becomes fixed in position by the rigid rind of disease. The nodular densities can become quite large and a mass lesion can predominate with only minimal pleural thickening. Calcification is uncommon.

Up to one-third of patients with mesothelioma have evidence of pleural or parenchymal asbestosis (pulmonary fibrosis). The severity of asbestosis does not seem to correlate with the incidence of mesothelioma. Asbestosis presents as an interstitial infiltrate characterized by irregular linear densities, septal lines, and parenchymal bands. Often there are fine nodular opacities, honeycombing, and

a ''ground-glass'' appearance. Both lungs will reveal pleural thickening with fibrous or calcified plaques.

Parenchymal disease is present in approximately 50% of patients. Nodules are the most common finding, usually seen as multiple discrete tumor masses under the serosal membranes. They are often large, greater than 5 cm when first detected. These nodular masses represent either parenchymal extension from pleural based masses that have become surrounded by lung parenchyma or, more uncommonly, metastatic disease. While intraparenchymal extension has little diagnostic significance, metastases portend a poor outcome. Diffuse pulmonary parenchymal metastases in a miliary pattern should also be recognized as a possible presentation of pleural mesothelioma. Lung nodules must be differentiated from rounded atelectasis that can be caused by localized fibrous thickening of the pleura with lung folded around it and associated with curving vessels and bronchi, producing a cochlea-like appearance. It is a response of the lung to scarring of visceral pleura. As this scar retracts, it causes successive pleating of the pleura resulting in an area of atelectatic lung held collapsed by the pleural scar. Radiological features that can differentiate rounded atelectasis from mesothelioma include blurring of the border by entering vessels causing a tail or comet sign, chronic pleural thickening near the mass, and a stable appearance on serial films.

Involvement of the chest wall and rib destruction is not uncommon (up to 20%) and can be best demonstrated by CT scan. Degrees of involvement include ''roof tiling'' deformities due to periosteal reaction secondary to the pressure exerted by the tumor or complete destruction of ribs usually along the axillary line.

There are a variety of other findings on radiological examinations of the thorax. Up to 25 or 30% of patients present with radiological evidence of mediastinal lymph node involvement. Other findings include pericardial infiltration and transdiaphragmatic invasion.

Chest Roentograms

On plain roentograms, a large pleural effusion, pleural thickening, and nodularity with decreased volume of the involved hemithorax are sufficiently classic to permit a consideration of the diagnosis of mesothelioma. The tumor grows rapidly, so typically the mass can be easily identified radiographically. The most common findings on chest roentograms include pleural thickening (25–75%), localized masses (15%), and loss of hemithorax volume (15%). In many cases, there is blunting of costophrenic angle. The tumor may flatten the dome of the thorax. A composite picture of lowered shoulder, elevated diaphragm, contracted intercostal spaces, and curvature of the spine is often seen. With advanced disease, scoliosis may develop with contracture of the chest toward the ipsilateral side.

Bony structures may be eroded. The appearance of tumor shadows is not very characteristic and they are hard to distinguish from other intrathoracic tumors. Only 20% of patients with pleural mesothelioma demonstrate characteristic signs of asbestosis—a low diaphragm, interstitial fibrosis, or pleural plaques. Lateral and oblique films are extremely helpful in radiographic screening for pleural plaques.

Computed Tomography

A CT scan should be obtained for staging purposes and to aid in planning therapy. CT is the most accurate noninvasive method for assessing stage and progression of mesothelioma, and results may alter staging and therapy in up to 40% of cases. The initial study should always be performed with contrast medium though subsequent follow-up studies can be performed without contrast.

The prime importance of CT lies in its ability to define the extent of disease and follow response to treatment. CT can detect minute progression of disease and is also used to look for metastatic disease to the contralateral lung and liver. Serial CT has demonstrated increased accuracy over conventional radiography in determining the extent of pathology and response to treatment.

A CT scan is helpful in differentiating benign from malignant pleural thickening. The most common finding on CT scans in mesothelioma is unilateral thickening with irregular pleuropulmonary contours. There are a spectrum of appearances of malignant mesothelioma on CT scans: focal nodular masses or lesions, pleural effusions, diffuse pleural thickening extending circumferentially around the hemithorax, spread of the tumor within the ipsilateral or contralateral parenchyma, through the ribs, into the mediastinum, or across the diaphragm, or distant hematogenous spread. Information provided from a CT scan includes contralateral pleural abnormalities, parenchymal nodules, chest wall abnormalities, pericardial thickening, lymph node enlargement, liver metastasis, vertebral column involvement, and subpleural nodules.

Ultrasound

Ultrasound has wide application in surveillance and for percutaneous needle aspiration of mesotheliomas. Ultrasound is ideal for demonstrating encysted fluid versus solid tumor mass. Ultrasound can be used to drain cysts as small as 2 ml. Ultrasound is excellent for determining pleural mesothelioma extension into the pericardium. Ultrasound has several advantages over CT. It is less expensive, there is no need for intravenous contrast, it is easy to repeat, and there is increased patient comfort and no radiation risk; however, it is less commonly used than CT.

Magnetic Resonance Imaging

MRI provides additional information in mesothelioma primarily because of the ability to reconstruct images in the coronal and sagittal planes (Fig. 3). Malignant

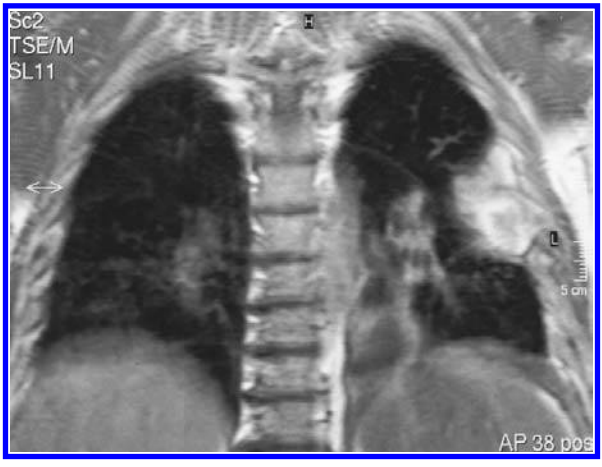

FIGURE 3 MRI image (coronal) of malignant pleural mesothelioma.

pleural mesothelioma infiltration and pleural fluid is seen as a high-intensity signal on T2-weighted images. MRI is useful in defining the extent of chest wall disease by demonstrating signal alterations caused by contiguous extension of tumor from the pleura; 3-D reconstruction may allow for volumetric determination of extent of disease. The greatest use of MRI in mesothelioma is to determine whether the tumor invades through the hemidiaphragm, an assessment best made utilizing the coronal and sagittal reconstructions.

Invasive Diagnostic Studies

The single most important variable in making a correct diagnosis is an appropriate clinical presentation, including a history of asbestos exposure, recurrent pleural effusions, chest pain, and pleural thickening. Imaging studies can provide an excellent description of the extent of disease and invasion of pulmonary tissues. However, encasement of the lung with tumor is not pathognomonic for malignant mesothelioma. Pleural thickening with a circumferential distribution or lung encasement, nodular morphology, pleural thickening of more than 1 cm, and involvement of the mediastinal pleura are all suggestive of malignant disease, with specificites of 100%, 94%, 94%, and 88%, respectively; the sensitivities of these findings are 41%, 51%, 36%, and 56%, respectively. As none of these imaging findings are reliable indicators, tissue sampling must be completed to correctly diagnose malignant pleural mesothelioma. The most reliable measure of diagnostic accuracy is the method of sample collection. Available techniques are pleural fluid cytology (0–64%), needle biopsy (5–60%), thoracoscopy (93%), and open biopsy (100%).

To balance optimal diagnostic sensitivity with minimal invasiveness, a practical approach to pathological examination would be to start with thoracentesis. Fluid cytology can be examined for malignant cells and hyaluronic acid. A closed-needle biopsy under imaging guidance can be attempted next. Unfortunately, it is common to miss the lesion or sample only thickened fibrotic pleura that does not contain neoplasm. Even if sufficient material is obtained, it is difficult to differentiate mesothelioma from benign reactive mesothelial proliferation. Thoracentesis and needle biopsy each provides 40–60% accuracy; combined they are 90% accurate in making the diagnosis. If a large effusion is present and no dominant mass is visible on imaging studies, it may be preferable to use video-assisted thoracoscopy (VATS) as the preferred method of obtaining tissue for diagnosis.

The main problem associated with less invasive diagnostic techniques is the size of the tissue sample obtained. Malignant pleural mesotheliomas vary in differentiation, cell type, and histological pattern from one anatomical region to another; therefore, thorough sampling is often needed. The size of the tumor specimen influences the diagnosis. More biphasic mesotheliomas are diagnosed with larger (thoracotomy, autopsy) than smaller (thoracoscopy, closed needle) biopsy techniques. Sarcomatoid mesotheliomas account for 20% of the tumors regardless of the method the tissue is obtained, indicating the increased incidence of the biphasic variant is due to the epithelial type.

The most worrisome complication of invasive biopsy techniques, whether effusion analysis, needle biopsy, or thoracoscopy, is seeding of the needle tract, chest tube site, or incision with malignant cells. Ten to 50% (median 20%) of patients develop seeding of the chest wall that develops into a painful site of tumor invasion. Boutin routinely waits 10–12 days to allow the incision to heal and then performs radiotherapy on the chest wall to prevent chest wall seeding. Using this technique, Boutin has eliminated mesothelioma invasion at incision sites. Radiation treatment should be performed early, preferably within the first 2 weeks following an incision.

Thoracentesis

Up to 80% of patients present with an effusion and 95% will develop one at some point in the course of their disease. Whenever an effusion is suggestive of malignancy, a thoracentesis should be performed to aid in pathological diagnosis. Aspiration and removal of the fluid also improves dyspnea.

Mesothelial cells synthesize collagen, laminin, elastin, and proteoglycans including hyaluronic acid into the pleural space. In malignant mesothelioma, the fluid is frequently serosanguinous, and 50% of effusions are bloody. The consistency is sometimes viscous or gelatinous. Fluid chemistry is usually exudative (protein $>$ 30g/L). Pleural fluid has an LDH of 36–600 IU and glucose of 21–155 mg/dl (which is inversely correlated with the number of malignant cells present). Pleural effusion with a low pH ($<$7.30) may be an indicator of poor

prognosis. Hyaluronic acid (HA) is consistently elevated in patients with malignant mesothelioma. It is 70–90% sensitive for malignant mesotheliomas. Close to 20% of nonmalignant inflammatory diseases also have elevations of equal level. Other neoplasms retain near-normal values. Some authors report hyaluronic acid levels greater than 0.8 mg/ml are diagnostic for malignant mesothelioma.

Fluid cytology has some value in the diagnosis of malignant mesotheliomas with success that ranges from 30 to 70%, with the negative results coming from sampling and not interpretative error. When looking at fluid cytology, the most important finding indicative of malignant mesothelioma is numerous cell aggregates of varying size (Fig. 4). Clumps composed of 5–200 or more cells are frequently irregular with protruding edges. They may also be frond-like and appear to be papillary fragments. Metastatic adenocarcinoma, on the other hand, has rounded, smooth-appearing cell aggregates. Reactive mesothelial processes also have cellular aggregates of smaller, less complex size. The other features to look for are the characteristic cytoplasm with cell enlargement, specialized cell borders, multinucleation, cell-to-cell apposition, and a uniform cell population.

Fine-Needle Aspiration

An alternative means of obtaining diagnostic material is closed fine-needle aspiration of the tumor. In closed-needle biopsy, malignant mesothelioma is often hard to distinguish from reactive mesothelial proliferation. In diffuse pleural thick-

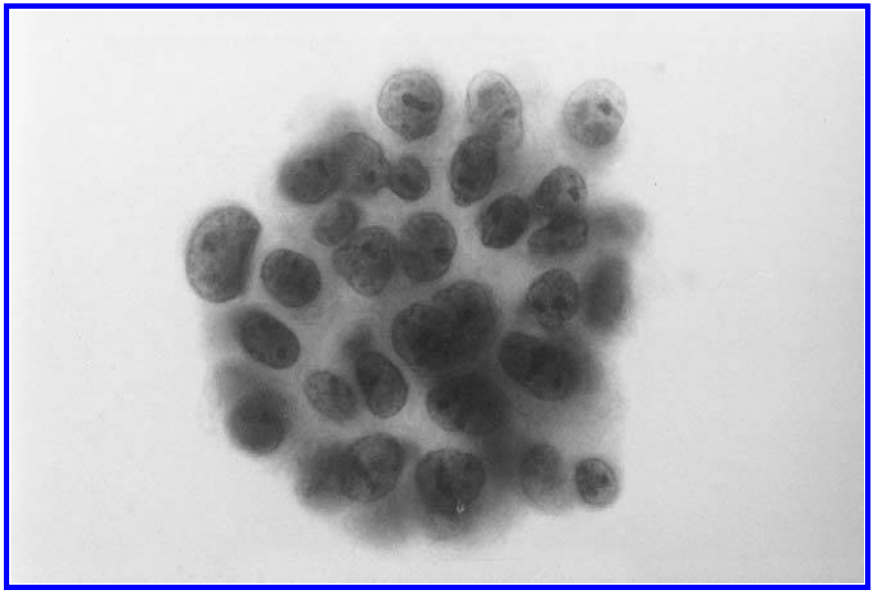

FIGURE 4 Typical pleural fluid cytology of malignant pleural mesothelioma.

ening there may be only a small, localized focus of malignant cells within dense fibrotic tissue. Some physicians prefer to use an Abram's or Cope needle in the presence of pleural fluid as the likelihood of a parenchymal stick is less. Musk recommends a cutting needle such as Trucut to obtain sufficient pleural tissue for histopathological examination. The addition of mechanically operated biopsy instruments has improved the ease and speed of biopsy while producing high-quality specimens without shear artifacts. The most common complications are pneumothorax, focal pulmonary hemorrhage, and local seeding of the tumor.

Video-Assisted Thoracoscopic Surgery

VATS is the best way to obtain a prompt diagnosis with close to 100% diagnostic sensitivity and specificity. It permits complete visualization of the pleural cavity and the opportunity for thorough sampling of various sites. It also allows the surgeon to better stage the disease and can be combined with a pleurodesis utilizing talc insufflation. The procedure can be done under local anesthesia with the patient spontaneously breathing or under general anesthesia with a double-lumen tube and single-lung ventilation. Suspicious areas may be sampled under direct vision (Fig. 5). Complications of thoracoscopy are minimal and the procedure carries a very low incidence of mortality (<0.02%). The most common problems are subcutaneous emphysema, local pleural infection, hemorrhage of < 100 ml,

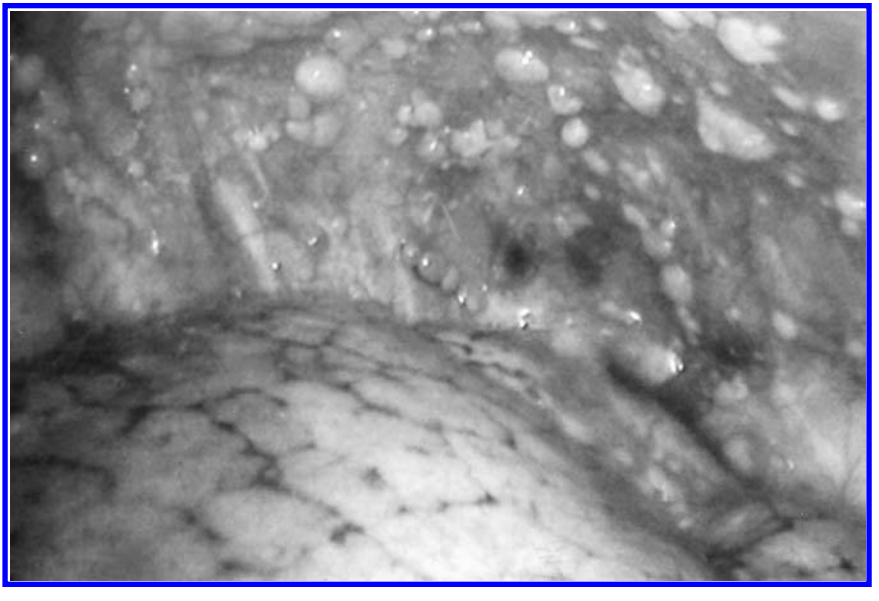

Figure 5 Thorascopic view of malignant pleural mesothelioma.

and a low-grade fever. Thoracoscopy may not be possible if dense adhesions are encountered between the visceral and parietal pleura.

Diagnostic Thoracotomy

If repeated attempts to obtain diagnostic material have failed or more tissue is needed, a limited thoracotomy remains the only alternative. However, open biopsy should rarely be required to make a diagnosis of mesothelioma.

STAGING

Because of the lack of a single staging system, it has been difficult to predict survival and guide management because different clinical trials have lacked uniform descriptors to classify treatment and mortality rates. In the past, the fundamental problem with staging malignant mesothelioma was twofold. Owing to the long latency period of the disease, we lacked knowledge regarding the natural history of the disease. Second, our ability to image mesothelioma was limited owing to the unique plate-like growth pattern exhibited by the tumor.

To solidify these staging systems, the International Mesothelioma Interest Group Consensus Meeting was held in June 1994 during the Seventh World Conference of the International Association for the Study of Lung Cancer. The meeting included originators of the previously proposed staging systems. The new staging system was based on analysis of emerging information about the impact of tumor and nodal status on survival (Table 1). It incorporates very specific TNM descriptors based on recently acquired information on the natural history of the disease.

The new staging system is better at delineating early disease and, in particular, recognizing the improved survival of T1N0 disease. T1 is separated into T1a and T1b. The key feature between T1a and T1b is involvement of the visceral pleura, which in many cases is assessed thoracoscopically. Tumor tends to arise in the parietal and diaphragmatic pleura and later progresses to the visceral pleura. Patients usually have a free pleural space and present with a large pleural effusion. T1 disease is amenable to resection by pleurectomy with decortication. Another key aspect is distinction between T1b and T2. T2 disease extends into the pulmonary parenchyma and thus tumor cannot be resected without taking part of the underlying parenchyma. Usually the diaphragm is involved as well and an extrapleural pneumonectomy may be required to remove all gross disease. T3 disease describes a locally advanced tumor that may not be a candidate for an extrapleural pneumonectomy. By this point, the tumor involves the entire ipsilateral pleural space and has extended into the extrathoracic fascia, mediastinal fat, focally localized soft tissues of the chest wall, or the pericardium. T4 disease designates a locally advanced and technically unresectable tumor. It involves all of the ipsilateral pleural surfaces and there is advanced thoracic invasion.

Table 1 Staging Classification for Malignant Mesothelioma

T1	T1a Tumor limited to the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura No involvement of the visceral pleura
	T1b Tumor involving the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura Scattered foci of tumor also involving the visceral pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: involvement of diaphragmatic muscle confluent visceral pleural tumor (including the fissures) or extension of tumor from visceral pleura into the underlying pulmonary parenchyma
T3	Describes locally advanced but potentially resectable tumor Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: involvement of the endothoracic fascia extension into the mediastinal fat solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall nontransmural involvement of the pericardium
T4	Describes locally advanced technically unresectable tumor Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with at least one of the following features: diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction direct transdiaphragmatic extension of tumor to the peritoneum direct extension of tumor to the contralateral pleura direct extension of tumor to one or more mediastinal organs direct extension of tumor into the spine tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium

N—Lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral, or contralateral supraclavicular lymph nodes
M—Metastases	
MX	Presence of distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Stage	*Description*
Stage I	
Ia	T1aN0M0
Ib	T1bN0M0
Stage II	T2N0M0
Stage III	Any T3M0
	Any N1M0
	Any N2M0
Stage IV	Any T4
	Any N3
	Any M1

Stages I–IV are based primarily on surgical and pathological findings, which may be staged by CT and aided by MRI. Up to 85% of tumor staging established by CT corresponds to that found at thoracotomy or autopsy. Neither CT nor MRI can always distinguish among T1a, T1b, and T2 because these techniques cannot differentiate parietal from visceral pleural involvement. However, CT can image a significant pleural effusion (T1 disease) and usually can differentiate extension of the tumor through the visceral pleura to involve the lung parenchyma (T2 disease). CT frequently can distinguish between T3 and T4 disease by defining involvement of soft tissues of the chest wall and pericardium. CT provides little information regarding involvement of lymph nodes except size. Two factors account for this: involved nodes may not be enlarged and large portions of the hilum and mediastinum often are obscured by bulky tumor. If anything, CT tends to understage the true extent of MPM.

Even with the new International Staging System, a problem remains in assigning the correct stage to individual patients. CT remains poor at distinguishing invasion of adjacent structures from abutment. Ideally, complete assessment includes thoracoscopy and mediastinoscopy for suspicious nodes. As well, laparoscopy has been demonstrated to be safe and accurate for detecting transdiaphragmatic tumor extension when CT fails to do so and MRI is equivocal.

The new TNM staging system promises to aid future studies in mesothelioma. Unfortunately, none of the staging systems recognizes the pathological and biological variables that affect survival: histology, age, gender, performance status, type of symptoms, weight loss, and platelet count. If the new system is used routinely, it will provide an opportunity to stratify patients and predict survival and treatment options accurately. It will aid in resolving the controversy over the choice of operation for patients who have potentially resectable malignant pleural mesothelioma. To make rational treatment plans for patients with mesothelioma, accurately staged groups must be analyzed to obtain the best prognostic data.

THERAPEUTIC APPROACH

Strategy

For patients with limited disease, particularly stage I, pleurectomy with decortication remains the best option. Mesotheliomas tend to remain confined to the pleural space early in their course and can remain in this cavity for long periods, making them suitable for radical surgery. Once the tumor has penetrated the parietal pleura, radical surgical approaches add little to the overall outcome and provide little symptom relief. Chemotherapy or radiotherapy should be considered for more advanced disease, though results have been uniformly poor. Finally, for stages III and IV, palliative treatment is the recommended approach.

With the new staging system, it may be easier to decide the best therapeutic options after delineating the extent of disease. Specific variables such as nodal status and extrapleural as well as extrathoracic involvement should be identified. Patients should be carefully followed after any therapeutic intervention. A chest CT scan should be performed every 3 months after extrapleural pneumonectomy or pleurectomy with decortication to monitor disease progression in the hemithorax.

Chemotherapy

Chemotherapy has limited beneficial effects against pleural mesotheliomas. Over the past 45 years, scores of controlled studies, case reports, and retrospective analyses have compared single-drug and combination therapies. Often these studies have been part of large phase II studies of patients with sarcomas.

The best response of any single chemotherapeutic agent has been approximately 20%. The average response rate varies from 9 to 12%. Combinations of drugs have not improved this rate. The most promising cytotoxic drugs against pleural mesothelioma have included doxorubin, epirubicin, cyclophosphamide, and mitomycin.

In many of these clinical trials, there are problems in assessing the efficacy of treatment. First, studies use variable criteria to define response as opposed to standard accepted criteria, i.e., PR $\geq$ 50% shrinkage as measured by the product of two diameters. Second, the patient population in many of these studies is variable or unclear. Some studies appear to selectively choose patients based only on good prognostic indicators while others do not define their inclusion criteria. In addition, there are only a handful of studies with large cohorts of patients. Many studies base results on 15 patients or less making any conclusions regarding efficacy of treatment uncertain.

Anthracyclines have shown the greatest promise of agents used against mesothelioma. Doxorubicin, the most extensively studied agent, has a partial response rate in the range of 10–40%, with an average of about 20%. In one study, 35 patients were given doxorubicin at 40 mg/m^2 for 3 days every 3 weeks for up to five cycles. Two patients achieved a complete response, seven a partial response, and 18 patients had some relief of chest pain. Median response was 19 months, one of the longest reported to date.

Cisplatin appears to be more effective in combination with other drugs. Carboplatin, a cisplatin analog, has been shown to have some activity against mesothelioma when used as a single agent and has the advantage of being less nephrotoxic and better tolerated than cisplatin.

A number of trials have shown vincristine and vinblastine to be inactive against mesothelioma. Some isolated cases of partial response to paclitaxel have been suggested; however, there is a high association of cardiac arrhythmias and

painful peripheral neuropathy. Alkylating agents such as ifosfamide, mesna, cyclophosphamide, and mitomycin have been studied in over 400 patients in numerous studies. One of the most promising agents is mitomycin. In a single phase II trial, 21% of patients were found to have some degree of response; however, this was associated with significant pulmonary toxicity. Ifosfamide and cyclophosphamide had only meager activity against pleural mesotheliomas. Methotrexate was found to have a response rate ranging from 35 to 45% in various studies, while fluorouracil, at best, shows a 15% response rate over many studies. Trimetrexate has also been evaluated in a multi-institution phase II trial.

A large number of combination drug trials have attempted to improve on the 20% response rate for doxorubicin. Combined chemotherapeutic regimens have not resulted in improvement in overall survival. There have been over 20 different multidrug trials since 1978, the majority combining anthracyclines (doxorubicin) with alkylating agents (cyclophosphamide, mitomycin, ifosfamide) or platinum (cisplatin, carboplatin). The Cancer and Leukemia Group B has carried out four phase II and phase III studies in mesothelioma since 1985, with no notable improvement on single-agent therapy. One of the most promising trials compared doxorubicin and cisplatin, but objective response rates were similar (9% vs. 12%, respectively). The combination of doxorubicin, cisplatin, bleomycin, and mitomycin has produced response rates of 44% in one study; however, this has not been repeated.

Intracavitary treatment is being evaluated as a potential delivery route for chemotherapeutic agents. High local tissue concentrations of drug are the goal but achieving these concentrations often is limited to patients with early-stage disease. Minimal to moderate tumor burden seems to be required to assure adequate uptake and penetration of chemotherapeutic agents into the neoplasm. In advanced disease the pleural space often is obliterated preventing optimal distribution of drug. Agents that have been evaluated for intracavitary treatment to date include cisplatin, cytosine arabinoside, doxorubicin, and mitomycin C. One of the first attempts at intrapleural chemotherapy without surgery for malignant mesothelioma involved 21 patients who received 20–30 mg of doxorubicin weekly for 4 weeks and then were treated monthly. Average survival was 21 months. Cisplatin has been the most extensively studied agent for intracavitary use.

Radiation Therapy

Radiation therapy may be of benefit in the treatment of mesothelioma, but its role is unclear. Laboratory studies show that mesothelioma is not ''radioresistant'' and a number of clinical reports demonstrate efficacy to radiation therapy. However, effective irradiation for mesothelioma may require enormous field sizes, essentially encompassing an entire hemithorax and the mediastinum. The

risks of acute and chronic radiation toxicity to the heart, spinal cord, adjacent normal lung, and even intra-abdominal structures and bone marrow function become considerable. This is the major limitation to the use of radiation therapy for this locally invasive disease.

Nonetheless, radiation therapy may be used for a variety of indications in mesothelioma. The treatment indications and techniques may be broadly divided into ''radical'' radiotherapy and ''palliative'' radiotherapy. Radical radiotherapy is an attempt to achieve local control and/or prolong survival and consists of whole-hemithorax irradiation either postoperatively or after biopsy alone. It is sometimes combined with multiagent chemotherapy both to act as a radiosensitizer and to attempt to control disease outside of the radiation portals. Palliative radiotherapy consists of localized irradiation of a painful chest wall mass and/or prophylactic irradiation of a thoracoscopy or chest tube site to prevent tract seeding.

Indications and Techniques

Radical Radiotherapy. Radical radiation therapy is rarely indicated outside of the clinical trial setting. Most commonly it is employed following extrapleural pneumonectomy for early-stage disease. Radiotherapy may be combined with chemotherapy in this setting. Because of the risks of severe, even life-threatening toxicity, careful patient selection is needed. Only patients with excellent performance status and healthy cardiac, hepatic, renal, and bone marrow reserve should be considered for such an intensive multimodality program.

Patients who are candidates for adjuvant radiotherapy (± adjuvant chemotherapy) are given a dose of 4000–4500 cGy in 180–200-cGy daily fractions directed to the entire hemithorax and mediastinum. Occasionally, it may be feasible to identify an isolated area(s) of special concern for residual disease, which may be given a boost dose of radiotherapy to 5500–6000 cGy. Given the usual situation of very close or positive margins, higher doses than these would be desirable; however, toxicity limits the potential for dose escalation. Sometimes, however, there are multiple areas of close (or positive) margins and it is not possible to isolate a small area for boost treatments.

The treatment fields are generally AP-PA (anterior and posterior opposed photon fields) and are typically 20 cm or more in length. Both the entire diaphragm and the region of resected apical portion of the lung must be included in the treatment fields and CT target planning is indicated. Because of the long field length and the shape of the chest surface as it slopes from inferiorly to superiorly, it is necessary to use radiation beam-modifying compensators to avoid significant ''hot spots'' within the superior portion of the spinal cord. Given the large field size, we recommend limiting the spinal cord dose to 4000 cGy (in standard fractionation), particularly if chemotherapy is given with radiotherapy.

Other critical organs must be considered in the planning of radical radio-

therapy for mesothelioma. Left-sided hemithorax irradiation will encompass essentially the entire heart while right-sided hemithorax irradiation will include a substantial portion of the liver. In addition, in either case, there will be some scattered dose of irradiation to the remaining contralateral lung. Three-dimensional CT target planning allows the radiation oncologist to calculate dose-volume histograms (DVHs) for these and other critical structures. DVHs provide a graphical plot of radiation dose versus percentage of a target organ receiving that radiation dose, offering valuable information about the relative safety of a radiation treatment plan. For example, in the treatment of a right-sided mesothelioma, a DVH analysis may determine that 50% of the liver parenchyma will receive 3000 cGy or more, which would be an unacceptable risk of serious radiation hepatitis. Field modification (or in extreme cases abandonment of radiotherapy altogether) would thus be indicated.

Treatment similar to that described above has been administered after limited surgery or for unresectable disease. Although it is endorsed in some major academic centers, we have not generally offered radical radiotherapy to patients who have not undergone extrapleural pneumonectomy. The chance for local control appears to be minuscule compared to the potential for toxicity, and there is little or no evidence of radiotherapy improving survival. Most patients with unresectable disease have worse performance status and/or organ function than those with successfully resected disease referred for adjuvant radiotherapy. In addition, in the absence of a pneumonectomy, the ipsilateral lung becomes yet another radiation-dose-limiting structure.

Radical radiotherapy for unresectable disease presents an added challenge to treatment, compared with radiotherapy after extrapleural pneumonectomy. Although in most cases of mesothelioma the ipsilateral lung is not contributing significantly to the patient's breathing function, it is still capable of developing symptomatic radiation pneumonitis, with further decline in the patient's quality of life. In severe cases, through an unknown mechanism, ipsilateral radiation pneumonitis can progress to full-blown bilateral adult respiratory distress syndrome. Some investigators have attempted to minimize the risk to the underlying lung by using partial transmission blocks or shields overlying the midportion of the treated hemithorax. The anterior and posterior chest wall that is shielded by these blocks can then be ''boosted'' with direct electron-beam irradiation, which treats superficial surfaces without any significant falloff dose to the deeper lung parenchyma. This extremely complex radiation technique irradiates virtually all of the pleural surface, with the interlobar fissures being a notable exception. It has the disadvantage of significant dose inhomogeneity near the interfaces between the standard (anterior and posterior opposed photon) and directed electron fields, with ''hot'' and ''cold'' spots not uncommon.

Another option for the treatment of patients who are not candidates for extrapleural pneumonectomy is surgical debulking with pleurectomy followed by placement of temporary or permanent brachytherapy sources. This is com-

bined with external-beam radiotherapy as described above. Outside of Memorial Sloan-Kettering Cancer Center, there has been little use of this form of combination therapy, and very limited information has been reported on the results of this treatment.

Palliative Radiotherapy. Patients with unresectable mesothelioma may still be candidates for palliative radiotherapy administered to an area(s) of painful disease, particularly if clinical trials are not available. The field sizes may still be considerable, but are less than whole-hemithorax irradiation. In patients who are not preterminal, CT target planning should be considered for these palliative situations as is the case for radical radiotherapy. CT target planning may be used to devise radiation fields that encompass irregularly shaped tumor while minimizing irradiation to the underlying lung, heart, esophagus, liver, and spinal cord (Fig. 6). With proper planning, palliative radiotherapy of masses 10 cm or

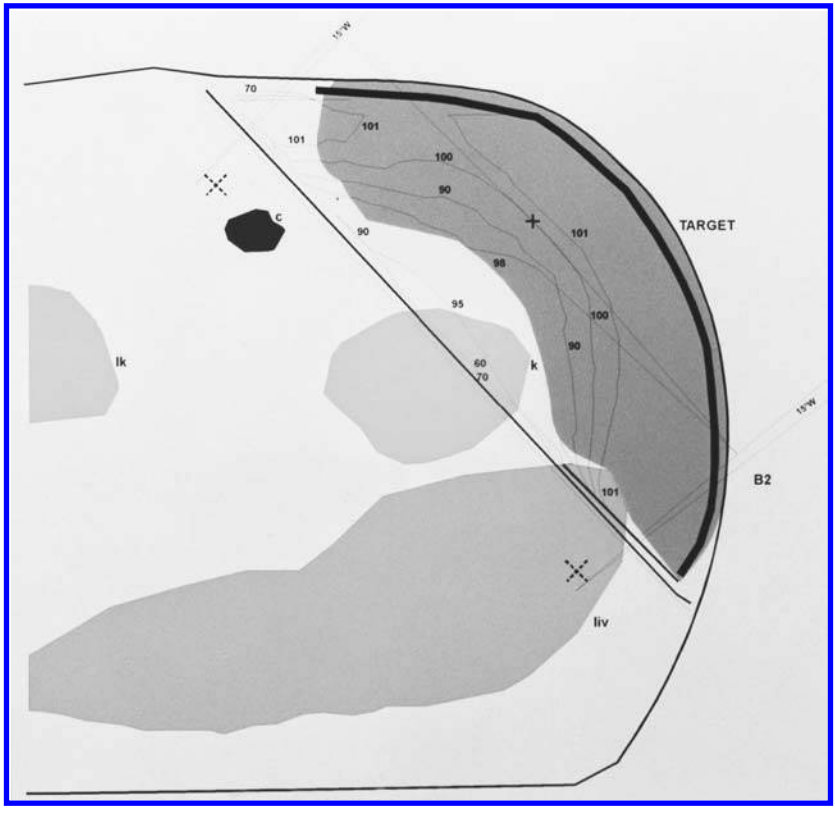

FIGURE 6 Dosimetry plan for radiation therapy of tumor mass with minimal radiation to surrounding normal structures.

smaller in size may be achieved successfully with minimal risks of toxicity. A typical field arrangement consists of two oblique or tangentially directed radiation fields similar to that used for breast cancer or chest wall sarcomas. The radiation dose may range from an accelerated course of 2000 cGy in five fractions to a more definitive dose of 5000 cGy in 20 fractions. One of the most commonly used schedules is 3000 cGy in 10 fractions, although it is not clear that this regimen reliably achieves durable palliation (see below). The decision on dose fractionation is based primarily on the patient's overall status and life expectancy. A patient with a relatively good performance status and life expectancy would be expected to benefit from a more intensive, higher-dose course of radiotherapy than a patient who is preterminal. Significant shrinkage of a chest wall mass during radiotherapy is usual; maximal response may require 1 month after the completion of treatment.

A recently developed indication for radiotherapy is its use as prophylactic treatment after invasive procedures such as thoracoscopy or chest tube placement. After such procedures, there is a significant risk of tumor seeding along the instrumentation tract, ultimately growing into exquisitely painful and unsightly masses on the chest wall or skin. A short course of relatively modest dose irradiation can be administered to the tract site with minimal morbidity. The typical treatment consists of three fractions of 700 cGy each given 10–15 days after thoracoscopy. This may be given with small-field direct electron-beam irradiation to field sizes of approximately 10 $\times$ 10 cm. The use of electron-beam therapy (9–15 MeV energy) offers sparing of underlying critical normal tissue such as lung, liver, and spinal cord.

Results: Radical Radiotherapy

The most extensive experience with adjuvant radiotherapy (plus chemotherapy) in the literature is from the Brigham and Women's Hospital, reported several times by Sugarbaker. This series consists of approximately 100 patients over the past 15 years. In their cohort of carefully selected patients, 45% 2-year survival and 22% 5-year survival was noted, with a median survival of 21 months. Patients with epithelial subtype had better outcome than patients with sarcomatous or mixed histology mesothelioma. There were no 5-year survivors among the non-epithelial subgroup. Lymph node status and margin positivity were also predictive of survival. In this prospective, nonrandomized series of patients, there is no control group of patients treated with surgery alone. While the results with this trimodality therapy appear superior to historical controls consisting of surgery alone, it is unclear whether this benefit is due to adjuvant therapy or merely a reflection of improved patient selection and surgical techniques in the last decade. Even if one accepts the results from the Sugarbaker series as clearly superior to surgery alone, it is uncertain as to whether the benefit of adjuvant therapy is primarily from radiation or from chemotherapy.

It is similarly uncertain whether radical hemithorax irradiation with or without chemotherapy for unresectable disease alters the natural history of mesothelioma. There are no randomized trials comparing radiotherapy or chemoradiotherapy with best supportive care. Median survival for unresectable disease treated with radical radiotherapy or chemoradiotherapy ranges in various series from 5 to 17 months. While some series have reported improvement with treatment compared to untreated patients, there are obvious selection bias factors that may explain any differences.

Combining chemotherapy with radiotherapy may improve the duration of tumor control, although at the expense of toxicity. Doxorubicin has been the most commonly used drug with radiotherapy, despite its well-known potentiation of radiation toxicity. Newer chemotherapeutic agents may better enhance the therapeutic ratio of radiotherapy. A small report from the National Cancer Institute of the combination of infusional paclitaxel with high-dose radiotherapy (5760–6300 cGy) showed seven of eight patients achieving local control, with an acceptable toxicity profile.

Despite all the concerns about the issue of late toxicity, there are relatively few data on this issue. Undoubtedly this is due to the short median survivals of patients with malignant mesothelioma; the pool of patients eligible for analysis of late radiation toxicity is thus quite limited. Cases of fatal radiation hepatotoxicity and radiation myelopathy after radical radiotherapy have been reported, however, and serial pulmonary function testing shows significant decline after radiotherapy.

Results: Palliative Radiotherapy

Most reports on the use of radiotherapy for palliation of painful chest wall masses show tumor response and/or pain improvement in 50% or more of patients irradiated. This is lower than the response rates for radiotherapy in the treatment of bony metastases from epithelial malignancies, though substantially better than the palliative effects of chemotherapy for malignant mesothelioma. The durability of this effect remains unclear. A small series by Bissett reported that although pain decreased in 13 of 19 patients by 1 month after radiotherapy, nine of 12 patients had progressive pain 3 months later. The dose used in this report was fairly modest (300 cGy $\times$ 10); also, it is possible that recurrent pain may be due to progressive intrathoracic disease outside of the radiation portal. A series from Harvard noted that only one of 23 patients treated with doses of 4000 cGy or less achieved significant palliation, compared with four of six patients treated with doses above 4000 cGy.

The ability of radiotherapy to effectively prevent malignant tract seeding has been demonstrated. A randomized trial of radiotherapy after thoracoscopy was performed by Boutin et al. in Marseille, France. After follow-up, eight of 20 patients (40%) not irradiated developed malignant tumor at thoracoscopy sites,

compared with none of 20 patients given moderate-dose irradiation after thoracoscopy. Similar results have been obtained at other institutions, with nonrandomized series. It is left to institutional preference whether or not to proceed with prophylactic irradiation after thoracoscopy compared with therapeutic irradiation upon the development of palpable nodules at the tract site, as with either approach survival will not be affected.

While radiotherapy is very appropriate treatment for pain, it is unlikely to be beneficial for the palliation of dyspnea. This is because any lung tissue irradiated to doses effective for palliation will be rendered nonfunctional by radiotherapy. unfortunately, there is probably no treatment effective for the severe dyspnea caused by advanced mesothelioma.

Surgery

Only about 20% of all patients with malignant mesothelioma are surgical candidates. There are several indications for surgical management. First, open thoracotomy for biopsy is necessary if other invasive diagnostic techniques have failed. Second, attempts at cure are possible with early, potentially resectable disease. Third, if cure is unattainable, surgical palliative measures should be considered. Palliation would entail controlling any effusions or decreasing discomfort by debulking to relieve pain or organ compression.

Usually the determination of resectability is made at the time of operation. A tumor of any size may be resectable if it is confined to one hemithorax, demonstrates only superficial invasion of the diaphragm or visceral pericardium, has localized invasion of the chest wall limited to a previous biopsy site, and no penetration of tumor through the hemidiaphragm. The CT and MRI criteria for resectability include (1) preserved extrapleural flat planes, (2) normal CT attenuation values and MR signal intensity characteristics of structures adjacent to the tumor, (3) absence of extrapleural soft tissue masses, and (4) absence of transdiaphragmatic spread on sagittal and coronal MRI images. Patz concluded the most reliable indicator of resectability was a clear, flat plane between the inferior surface of the diaphragm and adjacent abdominal organs and a smooth inferior diaphragmatic contour.

Any tumor that has extended through the diaphragm, diffusely invaded the chest wall or focal chest wall beyond the biopsy site, or has invaded essential mediastinal structures such as the great vessels, esophagus, trachea, aorta, or heart is surgically unresectable. As well, patients with distant metastases are not surgical candidates. Criteria for unresectability on CT or MRI include tumor encasement of the diaphragm, invasion of the extrapleural soft tissues or fat, infiltration or displacement or separation of rib by tumor, and bone destruction.

Although there are numerous reports that include over 800 patients, it is difficult to assess the outcome of surgical resection because of the diversity of

the procedures. The two main surgical procedures are parietal pleurectomy with decortication and extrapleural pneumonectomy.

Perioperative Management

Before a patient is considered for operation, preoperative evaluation should assess whether the patient will be able to withstand a pleurectomy or pneumonectomy. The patient's overall health and nutritional status should be considered. Cardiac status should be routinely evaluated by electrocardiogram and history of heart disease should be pursued. Both surgical procedures are associated with potentially large blood loss and could produce significant cardiac stress. Any patient with a myocardial infarct in the past 3 months or having an arrhythmia requiring medication should not be considered for extrapleural pneumonectomy.

Furthermore, results of pulmonary function tests should ensure that adequate pulmonary reserve remains following the operation. Decreased pulmonary function could be present secondary to high asbestos burden, smoking history, patient's age, or degree of lung trapped by fluid. The degree of pulmonary dysfunction, specifically restriction, correlates with the degree of costophrenic angle involvement, width and length of pleural fibrosis, and presence of either circumscribed plaque or diffuse pleural thickening. Forced expiratory volume (FEV_1) should be greater than 2 L/sec. If less, a quantitative ventilation-perfusion scan should be performed to predict if FEV_1 after pneumonectomy will be greater than 1 L/sec. Relative contraindications include $FEV_1 < 1$ L/sec, $Pao_2 < 55$ mmHg, or $Pco_2 > 45$ mmHg.

Procedures

A parietal pleurectomy involves stripping of the entire parietal pleura and pericardium from the apex of the lung to the diaphragm. The extrapleural plane of dissection is entered after a generous posterolateral thoracotomy incision is made. Most of the mediastinum and chest wall pleura can be removed, but the diaphragmatic pleura usually cannot be completely resected. An attempt is made to strip any tumor off the visceral pleura and preserve the integrity of the underlying lung (i.e., decortication). Hemostasis is achieved as the procedure is performed, and blood replacement is frequently necessary. At the conclusion of the operation, two large intercostal catheters are used to drain blood and to manage peripheral air leaks. Large leaking areas are suture-ligated to allow maximal expansion of the underlying lung with underwater seal drainage. Operative mortality should be less than 1–2%. Various studies using this approach have reported median survival ranging from 9.0 to 18.3 months (Table 2).

Complications reported include prolonged air leaks, hemorrhage, and subcutaneous emphysema. The most common complication (10%) is prolonged air leaks (>7 days). On average, chest tubes can be removed in approximately 5.5 days. Other postoperative complications include pneumonia and respiratory fail-

Table 2 Selected Trials of Pleurectomy With or Without Decortication

Year	Author	N	Median Survival (mo)	2-yr Survival %
1997	Pass	39	14.5	—
1996	Rusch	51	18.3	40
1994	Allen	56	9	8.9
1989	Achatzy	46	10	11
1984	Law	28	20	32
1982	Chahinian	30	13	27
1976	Wanebo	33	16.1	—
	Totals	525	13.4	

ure and rarely empyema and hemorrhage. Vocal cord paralysis also has been reported.

Extrapleural pneumonectomy is a significantly more radical procedure that includes en bloc removal of the entire parietal pleura, lung, pericardium, and hemidiaphragm (Fig. 7). It removes essentially all of the disease, particularly from the diaphragmatic and visceral pleural surfaces. It is necessary to include the pericardium to accomplish as complete a resection as possible as the pleura will not ''strip'' off this surface. This procedure is indicated for stage I, technically resectable tumors that are confined to the parietal pleura and do not invade the underlying chest wall or have not penetrated through the diaphragm. Studies of extrapleural pneumonectomy have reported median survival ranging from 4 to 21 months (Table 3). As this procedure is associated with higher morbidity and mortality rates, it should, ideally, be performed in institutions with significant experience with this procedure.

Expert anesthetic management is key to the success of this operation. Patients should receive broad-spectrum antibiotics prior to the start of the procedure, have arterial blood pressure monitored by a radial artery catheter, and have pneumatic compression stockings placed because the operation may be prolonged. A double-lumen endobronchial tube should be verified in position by auscultation and bronchoscopy before the thoracotomy is begun. A nasogastric tube should be placed and preparations made to deal with up to 3 L of blood loss. A thoracic epidural catheter for analgesia allows the patient to wake up at the conclusion of the procedure with minimal pain, a situation that greatly facilitates coughing and deep breathing as well as other respiratory maneuvers designed to limit postoperative complications.

The most common complication is supraventricular arrhythmia requiring medical treatment, which occurs in up to 25–40% of patients. A small number of

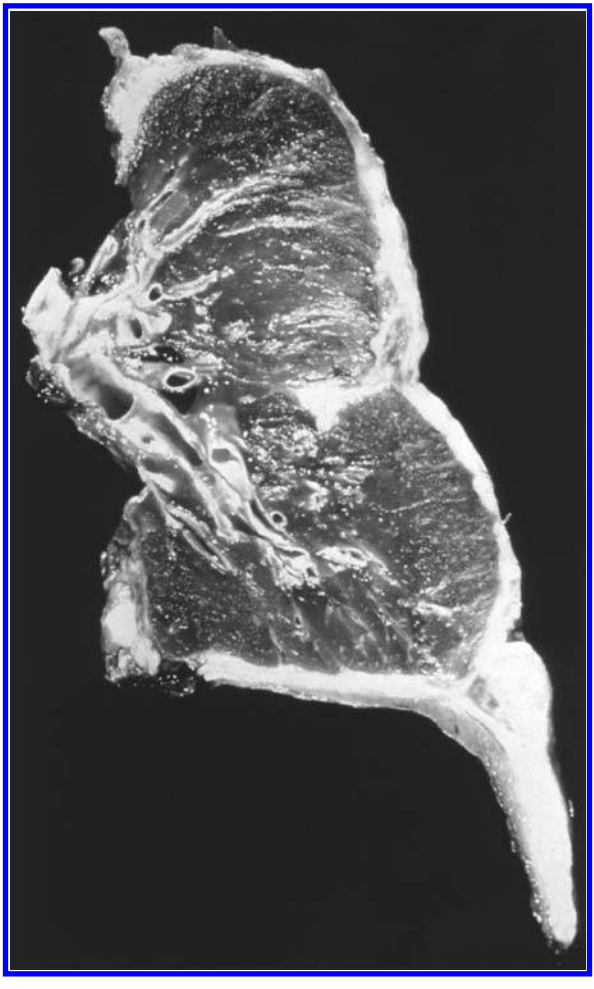

FIGURE 7 Extrapleural pneumonectomy specimen.

patients develop bronchopleural fistulas, especially with right-sided extrapleural pneumonectomies. This should be treated with open thoracostomy drainage with or without muscle flap interposition. Other complications that can occur include empyema, vocal cord paralysis, chylothorax, arrhythmia, myocardial infarct, congestive heart failure, and respiratory insufficiency.

Butchart and associates examined 29 patients in one of the first major reports of the role of extrapleural pneumonectomy for pleural mesothelioma. Though median survival was approximately 4 months and perioperative mortality

Table 3 Selected Trials of Extrapleural Pneumonectomy

Year	Author	N	Median Survival (mo)	2-yr Survival %
1997	Pass	39	9.4	—
1996	Sugarbaker	120	21	45
1996	Rusch; Faber	50	9.9	—
1994	Allen	40	13.3	22.5
1982	Chahinian	6	18	33
1976	Butchart	29	4.5	10.3
	Totals	376	12.9	

hovered around 30%, three major lessons were learned from this study. First, there were two long-term survivors. Second, the histology was analyzed and epithelial histology emerged as a positive prognostic indicator. And finally, the Butchart staging system was presented.

Allen and Faber have reported results of a trial at the Rush-Presbyterian-St. Luke's Medical Center in Chicago. In their series, 40 patients were treated with extrapleural pneumonectomy and 56 patients underwent pleurectomy and decortication only. Most patients were treated additionally with postoperative adjuvant chemotherapy and/or radiotherapy. They reported similar operative mortality rates, 7.5% for extrapleural pneumonectomy and 5.4% for pleurectomy. While the extrapleural pneumonectomy group had a 13.3-month median survival and 22.5% 2-year survival, pleurectomy patients had a 9.0-month median survival and a 8.9% 2-year survival. However, this trend did not reach statistical significance.

A third major series was reported by the Lung Cancer Study Group (LCSG). From 1985 to 1988, 83 patients were entered into this trial. The first mesothelioma trial, LCSG 851, defined the patient population seen by the LCSG, and the feasibility of performing surgical resection by extrapleural pneumonectomy in a multi-institutional setting. Only 20 of the 83 patients (24%) actually underwent extrapleural pneumonectomy. Patients who were not extrapleural pneumonectomy candidates had a more limited operation with or without adjuvant therapy or had nonsurgical management. Three of these 20 patients (15%) died postoperatively. The recurrence-free survival was significantly longer for the patients undergoing extrapleural pneumonectomy than for the other two groups ($p = 0.03$), but there was no difference in overall survival among the three groups. This experience prompted the LCSG to explore combining a potentially less morbid operation, pleurectomy/decortication, with adjuvant therapy. The results of another LCSG trial (LCSG 861) and of a small, single-institution pilot study demonstrated the feasibility of intrapleural cisplatin-based chemother-

apy and led to the development of LCSG 882, which combined pleurectomy/decortication with postoperative intrapleural, and subsequent systemic, cisplatin-based chemotherapy.

Another report from Memorial Sloan-Kettering Cancer Center in 1996 described 131 thoracotomies, resulting in 101 resections of which 72 were complete. Extrapleural pneumonectomy was carried out in 50 patients and pleurectomy/decortication in 51. Local recurrence occurred mainly after pleurectomy/decortication. Median survival was 9.9 months and 18.7 months for extrapleural pneumonectomy and pleurectomy, respectively.

Multimodality Therapy

Single-modality treatment for pleural mesothelioma, whether chemotherapy, radiation, surgery, or immunotherapy, is unlikely to effect a cure or prolong life for more than several months at best. Operation rarely is used as the exclusive mode of therapy. In fact, only a small handful of reports exist of surgical therapy with no further treatment. Adjuvant therapies and combined modalities are being utilized to work synergistically to improve efficacy with some reason for guarded optimism.

Bimodal and trimodal treatment plans have been tried: chemotherapy with radiation, surgery with chemotherapy, surgery with radiation, as well as all three modalities combined. Rare studies of chemotherapy with radiation have met with only very limited success.

For over a decade at the Dana Farber Cancer Institute, trimodality protocols combining extrapleural pneumonectomy with sequential postoperative chemotherapy (doxorubicin at 60 mg/m^2, cyclophosphamide at 600 mg/m^2, cisplatin at 70 mg/m^2) for four to six cycles, and then up to 5500 cGy adjuvant radiotherapy to the postoperative hemithorax, have been used. Overall median survival of 44 stage I patients improved to 16 months (Fig. 8). The most common site of failure was the ipsilateral hemithorax. A similar approach was used in Germany. Aggressive surgical management in low-risk patients was followed by doxorubicin, vindesine, and cyclophosphamide. Those patients who demonstrated partial remission received 4500–6000 cGy using a rotating tangential technique. Overall median survival was 13 months. In a series of 26 patients, Alberts reported only a 10.9-month median survival after maximal pleural cytoreduction followed by 4500 cGy and doxorubicin, cyclophosphamide, and procarbazine.

Investigators at Memorial Sloan-Kettering Cancer Center combined surgery with brachytherapy. After debulking by partial pleurectomy, gross residual tumor was treated with ^{125}I, ^{192}Ir, or ^{32}P radioactive colloids, which deliver approximately 3000 cGy over 3 days to a volume within 1 cm of the site of implantation. This was followed by external-beam radiation to 4500 cGy over 4.5 weeks. Forty-one patients received external-beam irradiation after pleurectomy and de-

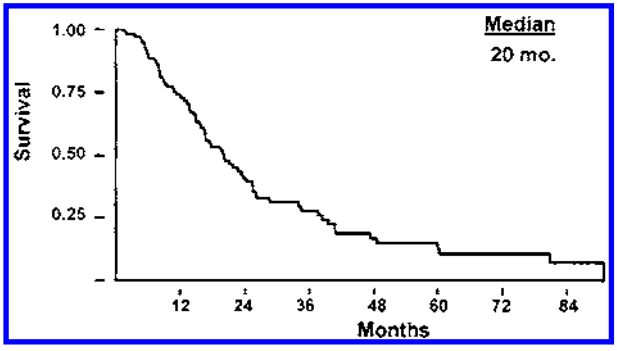

FIGURE 8 Survival curve for Sugarbaker study. (From Sugarbaker et al., 1996.)

cortication, and 54 patients received an implant and external-beam therapy. Median survival for the entire group was 12.6 months, with a 2-year survival rate of 35%. Those with pure epithelial histology and who did not require an implant had a median survival of 22.5 months and a 2-year survival of 41%. The majority of the complications were secondary to radiotherapy—pneumonitis, pulmonary fibrosis, esophagitis, and pericardial effusion.

Another common treatment protocol has involved pleurectomy with intracavitary chemotherapy with or without postoperative systemic chemotherapy. Cytoreduction and other debulking techniques have been utilized prior to administration of intrapleural chemotherapy. Intrapleural chemotherapy achieves high local tissue levels with the most notable toxicity being acute renal insufficiency. Rusch combined intrapleural chemotherapy with cisplatin and cytosine arabinoside following pleurectomy and decortication and systemic cisplatin chemotherapy. In a subsequent phase II trial, pleurectomy and decortication were followed by immediate postoperative intrapleural cisplatin and mitomycin. Two cycles of systemic cisplatin and mitomycin were given starting 4–6 weeks postoperatively. Of the 36 patients entered on study, 28 had pleurectomy/decortication and intrapleural chemotherapy. The median survival was 17 months and locoregional disease was the most common location of relapse. Other investigators have utilized intrapleural cisplatin and mitomycin after pleurectomy followed by systemic chemotherapy. Median survival ranges from 13 to 17 months. This approach likely has a limited role for palliation of symptoms and occasional long-term disease-free survival. Others claim this approach is inadequate and produces high toxicity.

Chemoimmunotherapy has been studied as an alternative form of therapy. Various combinations of chemotherapy (doxorubin, mitomycin, cisplatin) with immunomodulators (interferon alpha) have been tried. No significant differences

in survival or relapse rates have been observed in comparison to single modalities; however, later results need to be evaluated.

Immunotherapy

Like the majority of human malignancies, mesothelioma is frequently resistant to multiple effector mechanisms. This phenomenon appears to represent active immune evasion or deviation mediated in part by mesothelioma-derived cytokines. Also, multiple mesothelioma-derived cytokines appear to be involved at several levels of tumorigenesis. Recent research has focused on how proliferation-related and other tumorigenic cytokine-mediated processes may be inhibited by some of the agents that are already partially successful against mesotheliomas. Trials have been designed using systemic administration of interferon alpha, beta, gamma, interleukin-2, and lymphokine-activated killer cells.

Interferon alpha (IFN-alpha) has immunoregulatory effects on antibody production, macrophage functions, and delayed-type hypersensitivity, and is an effector of major histocompatability complex antigen expression in leukocytes and parenchymal stromal cells. IFN-alpha may also potentiate the effects of chemotherapy. It has been consistently shown to inhibit the cellular proliferation of mesothelioma and has demonstrated additive or synergistic inhibition of growth when combined with other chemotherapeutic agents. However, IFN-alpha alone has recorded only a 12% response rate in some of the most promising studies.

IFN-beta is unlikely to be useful because it is associated with significant toxic side effects. The Southwest Oncology Study Group has noted no response after 6 weeks of IFN-beta treatment in 14 patients.

IFN-gamma is a lymphokine produced by T lymphocytes in response to specific antigenic or mitogenic stimuli. Transient partial response has been noted in early disease, but not in late disease. Attempts at intrapleural delivery of recombinant IFN-gamma have been studied. IFN-gamma shares the antiproliferative effect of other interferons and, in addition, is a potent activator of macrophage cytotoxicity as demonstrated against tumor cell lines. In a study of 89 patients over 46 months, an overall partial response of 15–20% was seen in early disease with good tolerance of the agent. Eight patients had histologically confirmed complete remissions and nine had partial responses with greater than 50% reduction in tumor volume. Overall, patients with stage I disease had a response rate of 45%. IFN-gamma was found to have limited efficacy in stage I disease especially if the tumor was confined to the parietal and diaphragmatic pleura.

Human mesothelial cells grown in tissue culture have been shown to be susceptible to lysis by lymphokine-activated killer cells (LAK), an effect enhanced by interleukin-2 (IL-2). Intrapleural administration of IL-2 has been associated with good tolerance, moderate toxicity, and 90% initial response rate. Administration of IL-2 in patients with malignant mesothelioma, either alone or in

combination with autologous IL-2 activated killer cells, has been evaluated by several groups. Intrapleural recombinant IL-2 has been infused with little to no improved efficacy over other modalities. The median survival of the largest intrapleural IL-2 study ($n = 15$) was 21 months.

Gene Therapy

The localized nature of MPM and the lack of consistent response to any regimen make this tumor an ideal target for early trials of gene therapy. The use of a so-called ''suicide gene'' is a technique of gene therapy that delivers a gene into a neoplastic cell and sensitizes the cell to killing by a prodrug. Herpes simplex virus type 1 is a common human virus that produces a thymidine kinase (tk) unique only to herpes viruses. Inserting this herpes simplex virus thymidine kinase (HSV-tk) gene into neoplastic cells using an adenovirus vector renders the HSV-tk-positive cells exquisitely sensitive to the antiviral drug ganciclovir.

Ganciclovir is an antiviral agent in the same class as acyclovir and famciclovir. This agent is a guanosine nucleoside analog that is phosphorylated by the protein product of the HSV-tk gene. The HSV-tk enzyme is over 1000-fold more effective at phosphorylating ganciclovir than the cellular tk gene. This is ordinarily the rate-limiting step for activating ganciclovir. Once phosphorylated into a monophosphate form, normal cellular guanylate kinases can diphosphorylate and triphosphorylate the drug. The end result is a toxic triphosphate moiety that can be incorporated into DNA and, thereby, inhibit DNA polymerase. In a dose-escalating phase I clinical trial, 26 patients were treated with a replication-deficient adenovirus containing the HSV-tk gene at the University of Pennsylvania. A maximal tolerated dose (MTD) was not achieved even at a dose of 1.0×10^{12} pfu. Gene transfer was accomplished in every patient at the higher dosage levels and all patients were treated with ganciclovir for 14 days. A significant immune response, both humoral and cellular, was generated against the adenoviral vector. Additional trials exploring the efficacy of this promising approach are set to begin.

Emerging Modalities

Regardless of the modality used, conventional forms of treatment for malignant mesothelioma have proven disappointing. Only 20% of tumors can be approached surgically, chemotherapy has limited results, and the neoplasm presents difficulties for radiation therapy. Immunotherapy and gene therapy offer new approaches to treatment. Other modalities for treatment include photodynamic therapy, immunoconjugate therapy, and chemohyperthermia.

Photodynamic therapy is a technique based on administering light-sensitive porphyrin molecules followed by direct intracavitary photodynamic therapy aimed at destroying the porphyrin-containing tumor cells. The photosensitizing

agent is taken up preferentially by tumor cells. When 630-nm light is used to activate the molecule, it generates free radicals that selectively lyse neoplastic cells. Moderate success has been achieved in good-risk patients with low tumor burden. Attempts at using photodynamic therapy as a surgical adjuvant show limited results with a series of early reports suggesting a high rate of esophagopleural fistulae and esophageal perforations.

A phase I trial of surgery and photodynamic therapy to determine the optimal light dose was completed after enrolling 54 patients. Patients with isolated hemithorax pleural malignancy (mesothelioma or lung adenocarcinoma) were prospectively entered into the trial in groups of three to receive light doses of 15–35 J/cm^2 2 days after delivery of the porphyrin molecules. Another arm of the trial delivered light doses of 30–32.5 J/cm^2 after a day. The MTD was determined to be 30 J/cm^2 1 day after receiving the sensitizer molecule. Additional trials are being conducted to determine efficacy, and new photosensitizing agents with better selectivity and less toxicity are now available.

Immunoconjugate therapy makes use of monoclonal antibodies targeted toward specific tumor antigens, usually conjugated to a toxin or radioactive particle. Clinical trials have been slow in development because of absence of mesothelial specific target cells. Chemohyperthermia combines intracavitary chemotherapy with intracavitary hyperthermia. Although it has proven to be safe, no survival advantage has been demonstrated yet.

Palliative Management

Unfortunately, palliative treatment is often the only help the thoracic surgeon can offer patients and their families. Palliation involves two facets: control of the pleural effusion and pain management.

Once an effusion has developed, it is persistent and returns rapidly following thoracentesis. Several liters may be removed in a matter of weeks. The effusion usually is unilateral early in the disease course but progresses to bilateral involvement with time. Most people come to tolerate aspiration of 1–2 L of fluid at a time at intervals of 1–2 weeks. Diuretics do not prevent reaccumulation. With repeat drainage, thickening of the pleura with loculation of fluid begins to occur leading to difficulty in complete aspiration. The pleural space begins to contract as the tumor spreads over the mediastinum and visceral pleura causing progressive disappearance of the pleural space. Ultrasound or CT may be required at this stage to localize these sites. The heart, mediastinum, and trachea are drawn toward the affected side with crowding of the ribs and scoliosis concave to that side.

Complete drainage and full reexpansion of the lung are necessary before any of the common intrapleural agents can be expected to induce pleural adhesions. Full reexpansion is often difficult to achieve in advanced mesothelioma

because the thick rind of tumor on the surface of the lung prevents it from expanding sufficiently to appose the chest wall. Decortication may be required if the patient is well enough to undergo the procedure. Talc, especially by insufflation, is considered more effective than bleomycin or tetracycline in promoting pleural adhesions.

If a chest tube can be placed, full expansion of the lung is attempted followed by doxycycline or talc slurry sclerotherapy. If a chest tube cannot be placed, thoracoscopy may be necessary for direct lysis of adhesions and intrapleural application of powdered talc. Another option involves placement of a pleuroperitoneal shunt when pleural apposition proves to be impossible.

A number of modalities exist to manage pain in patients with malignant mesothelioma. Radiation therapy has been successful in palliating the pain from tumor involvement of the chest wall. Radiation in moderate doses of 4000–5000 rad has demonstrated relief of symptoms of pain, superior vena cava obstruction, dyspnea, and dysphagia in up to two-thirds of cases.

Narcotics usually are needed in late-stage disease to control the pain associated with malignant mesothelioma invasion of the chest wall. Intradermal narcotic (Fentanyl) delivery has excellent efficacy and is easy for the patient to use. Chronic indwelling epidural catheters may be placed as well for continuous narcotic delivery.

PROGNOSIS

The overall prognosis of MPM remains poor. As the tumor progresses, dyspnea on exertion is followed by shortness of breath at rest. The tumor encases the lung and obliterates the pleural space. Significant ventilation-perfusion mismatching occurs as deoxygenated blood is shunted into lung trapped by tumor and effusions. This leads to hypoxemia that is refractory to supplemental oxygen.

Symptoms begin to develop secondary to tumor invasion of thoracic structures. Compression of the esophagus leads to dysphagia, which results in rapid weight loss and death. Infiltration of the vertebral column may cause spinal cord compression and paraplegia. Invasion of the sympathetic and thoracic nerves can cause recurrent laryngeal nerve paralysis, brachial plexopathy, Horner's syndrome, and Pancoast syndrome. The superior vena cava may become compressed and ultimately blocked. Growth into the epicardium leads to right-sided heart failure and arrythmias causing death in 10% of patients. Any biopsy, trocar, or chest tube sites are highly susceptible to being seeded by tumor and are sites of significant chest pain. Transdiaphragmatic involvement usually results in peritoneal spread of disease often with ascites production.

Distant metastatic disease is an end-stage complication of malignant mesothelioma and is rarely the cause of death, though at least 50% of patients at necropsy have evidence of hematogenous spread. The sarcomatous MPM resem-

ble sarcomas clinically in that they are more commonly associated with extrathoracic metastasis, little or no effusions, and shorter survival. Epithelial variants are similar to carcinomas in that they are associated with local invasion causing large pleural effusions, contralateral pleural effusions, ascites, and metastasis to regional lymph nodes. In a review of 143 autopsies, Henderson reported that intrathoracic spread occurs most commonly to the pericardium and contralateral pleura and lung. Trandiaphragmatic spread and hilar, mediastinal, retroperitoneal, and cervical lymph node metastasis are other common locations of invasion. The most common sites of distant metastasis are the liver (25%), bone (16%), adrenal gland (14%), and kidney (13%). Hilar and mediastinal lymph node involvement is present in approximately 50% of patients; however, extrathoracic lymph node involvement is particularly uncommon (<1%). Brain metastases are rare, but have been reported. Lymphangitic spread within the pulmonary parenchyma is also occasionally seen.

Most patients die of complications of local disease. Progressive tumor bulk compromises pulmonary function and chest wall invasion requires high doses of narcotics to control pain. Death often occurs from respiratory failure, pulmonary infections, and small bowel obstruction. Sudden death can occur secondary to occlusion of the pulmonary blood supply leading to gangrene of the affected lung due to growth infiltrating the vessels in the hilum. Also there have been reports of pulmonary embolus from leg and pelvic veins.

In most large series, the mean age of death is 58–60 years. In a review of 11 studies encompassing 560 patients receiving supportive care or treatment, median survival was 8.6 months. Most authors present similar statistics; however, there is occasionally wide variation. It is difficult to interpret exact mean survival because some reports measure survival from diagnosis while others measure survival from the development of symptoms. Long-term survivors (>10 years) of the disease are occasionally seen.

In a retrospective analysis of 131 patients at Memorial Sloan-Kettering Cancer Center, using the new staging system from the International Mesothelioma Interest Group, survival was calculated based on clinical stage. Stage I disease had a 35-month median survival. T1a had a 32.7-month median compared to 7 months associated with T1b. Patients with stage I disease tend to have spread intrapleurally and can remain in this stage for a prolonged period. Stage II patients had a 16-month survival, Stage III, an 11.5-month survival, and Stage IV, a 5.9-month median survival. Until the new staging system comes into common use, it will be difficult to assess survival based on staging. Prior studies based survival analysis on Butchart's staging criteria and a large range of median survival has been reported, reflecting the nonspecific lumping of wide degrees of disease into the same stages.

Multiple prognostic indicators have been identified. Certain factors correlate with better survival: epithelioid histology, stage I disease by Butchart's stag-

ing system, and age < 60. Epithelioid histology has been consistently found to be the best prognostic indicator of survival with a 10–17-month median, whereas sarcomatous variants have a median survival of only 4–7 months. There is some disagreement as to which is the worse prognostic indicator: sarcomatous or biphasic histology. Survival in older patients is significantly worse than younger patients, reflecting the poorer overall health of older patients or the increased likelihood of higher total asbestos load due to longer exposure in this subset of patients. Other important prognostic indicators include performance status less than or equal to 1, absence of weight loss at any time during the diagnosis, absence of chest pain, and an interval greater than 6 months from the onset of symptoms and presentation. Absence of chest pain reflects lack of chest wall invasion. Although some authors suggest females have longer survival, this may merely reflect that females are more likely to have an epithelioid histology. Fever of unknown origin and thrombocytosis are associated with poor prognosis.

CONCLUSION

Though in the overall context of malignant disease MPM causes only a relatively small number of deaths (approximately 2000 per year), the tumor has garnered a great deal of attention because of the link to asbestos. Billions of dollars per year are spent in asbestos removal solely for the purpose of preventing this tumor. The amount of money paid by the asbestos industry in compensation to victims of this disease is staggering and the litigation continues today. MPM remains one of the few malignancies where no therapy to date has made a significant impact. The efforts continue, however, to improve the therapy for this devastating disease. The tendency of this tumor to remain localized makes it an excellent target for emerging treatment strategies such as gene therapy. There is reason for optimism as we approach the new century.

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Mediastinal Tumors

W. Roy Smythe
The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Kevin R. Fox
Hospital of the University of Pennsylvania and University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

INTRODUCTION

The mediastinum is a relatively small anatomical region with a tightly packed constituency that includes the heart and great vessels, conducting airways, esophagus, and spinal cord with associated neural structures. As one might expect, a myriad of tumor types may arise in this high-density region of progenitor tissues. Although the variety of tumors that may arise in the confines of the mediastinum is impressive, this diversity is easily matched and perhaps even surpassed by differing methods of proper treatment for these lesions. For this reason, the mediastinum could be considered one of the areas of the body with the greatest potential and necessity for meaningful therapeutic collaboration between the surgical, medical, and radiation oncologist.

Anatomical Considerations

The mediastinum is bounded by the thoracic inlet superiorly, the diaphragm inferiorly, the pleurae laterally, the sternum anteriorly, and the vertebral column and paravertebral sulci posteriorly. Although a number of schemas have been proposed by various authors over the years, the simplest system divides the mediastinum into anterior, superior, middle, and posterior compartments (Fig. 1).

The anterior and superior compartments extend from the manubrium and first ribs (thoracic inlet) to the diaphragm and are bounded posteriorly by the

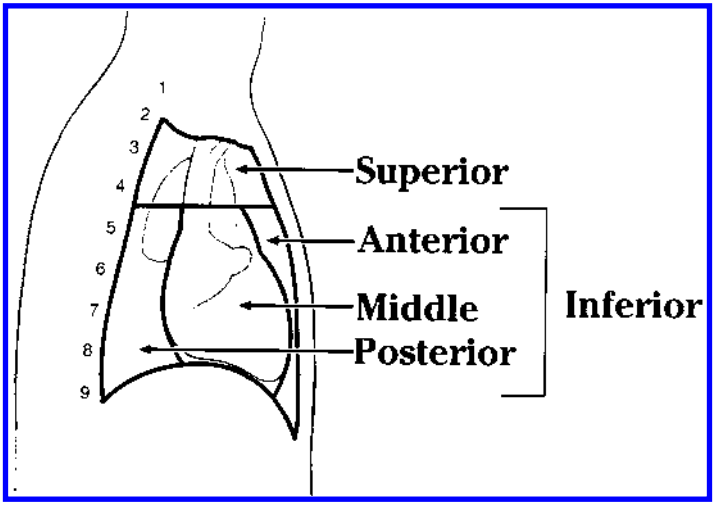


FIGURE 1 Anatomical divisions of the mediastinum. (From Fishman AP. Pulmonary Diseases and Disorders. New York: McGraw-Hill, 1998.)

anterior pericardium, aortic arch, and great vessels. The middle or visceral compartment is bounded anteriorly and superiorly by the superior pericardial reflection and anterior surfaces of the great vessels, inferiorly by the diaphragm, and posteriorly by the vertebral bodies. The posterior compartment extends from the superior first vertebral body down to the diaphragm anteriorly and then posteriorly to the most posterior curvature of the ribs (paravertebral sulci or costovertebral region). Although considered a part of the mediastinum proper, intramural and intraluminal tumors of the trachea and esophagus are more appropriately covered elsewhere.

Epidemiology and Incidence

In children, the majority (60–70%) of tumors occur in the posterior mediastinum; therefore, those of neurogenic origin predominate. In adults, the distribution is more equitable, with slightly more lesions found in the anterosuperior compartment. Recent studies have shown the percentage of thymic, neurogenic, and lymphoid-origin tumors to be fairly similar in adults (15–25%); however, the incidence of lymphoma specifically and malignant lesions of any type in general seems to be on the increase.

If a patient presents with an indeterminate mediastinal mass, the risk of malignancy is approximately 30%. Risk of malignancy correlates directly with presence of symptoms. Adults present with symptoms related to a mediastinal mass approximately 50% of the time, and children present with symptomatic

lesions in approximately 65% of cases. Therefore, a child presenting with a mediastinal mass is more likely to have a malignancy.

SURGICAL MANAGEMENT OF MEDIASTINAL TUMORS

Diagnosis

Gross mismanagement can result from an incorrect or assumed clinical diagnosis of a mediastinal tumor, and the need for an accurate diagnosis cannot be overemphasized. That being stated, the combination of clinical symptomatology, laboratory investigation, radiological investigation, and, if necessary, tissue examination should readily allow the clinician the opportunity to make a firm diagnosis and treatment plan. The surgeon is commonly expected to coordinate the diagnostic workup as the final step in the algorithm may often involve an invasive procedure to obtain tissue for histological examination.

SIGNS AND SYMPTOMS

As previously stated, the mediastinum is an area of highly compacted vital anatomical structures; therefore, it is not surprising that space-occupying lesions arising here are often symptomatic. If large enough, a mediastinal tumor may produce compressive cardiorespiratory symptoms regardless of its compartmental origin.

Symptoms of chest pain, dyspnea, and cough are most common. Other common manifestations include dysphagia, hemoptysis, facial cyanosis, and/or venous engorgement, chest heaviness, and hemoptysis. A number of systemic or constitutional manifestations may be noted with mediastinal tumors due to endocrinological, immunological, or other paraneoplastic effects.

NONINVASIVE DIAGNOSTIC TECHNIQUES

Plain Film

The plain chest roentgenogram should still be considered the initial test of choice for suspected mediastinal pathology, and is usually the means by which asymptomatic lesions are initially noted. A mediastinal lesion must project at least in part over radiolucent lung tissue to be noted, and both a posterior-anterior as well as a lateral film are necessary to maximize the chance that this will occur. It should be possible for an experienced radiologist to detect over 90% of abnormal mediastinal densities on plain film. If the degree of suspicion is high for mediastinal pathology based on symptoms in a patient with a negative plain film, cross-sectional imaging should be performed.

Anterosuperior and middle compartment tumors that appear smooth and spherical suggest benignity, such as encapsulated thymoma, benign teratoma, or cysts. Lobulation, especially in a mass that is rapidly growing, is more suggestive of a malignant process, with invasive thymoma and malignant germ cell tumors being illustrative. Calcification may occur in all common anterosuperior tumor types as well as in substernal thyroid goiter. Posterior compartment tumors tend to be well-defined, rounded densities projecting into the apparent pleural space.

Computed Tomography (CT)

The chest CT examination should be considered the gold standard for evaluation of mediastinal masses. Unless contraindicated, intravenous contrast to more carefully evaluate vascular structures should be administered, and both lung (parenchymal) and mediastinal windows should be utilized. Vascular abnormalities such as congenital malformations (i.e., right aortic arch), aneurysms, and great vessel tortuosity may mimic masses. In addition, it is important to delineate, if possible, whether any vascular invasion or compression by tumor exists as this may alter the treatment plan. The CT scan may also give important information regarding associated mediastinal lymphadenopathy, pleural effusion, or metastatic lesions to the lung parenchyma. It is important to note that the differentiation between solid and cystic masses is not always possible with CT evaluation. Invasion may be suggested by obliteration of fat planes; however, CT scan is not reliable for evaluating tumor involvement of chest wall or spinal structures such as vertebral body and intervertebral foraminae.

Magnetic Resonance Imaging (MRI)

MRI is more useful than CT in evaluation of mediastinal masses when vascular, neural, bony spinal, or transdiaphragmatic invasion is suspected. It is particularly helpful in distinguishing whether or not posterior mediastinal tumors have invaded the intervertebral foramina, epidural space, or spinal cord proper. It may also be of use when sagittal or coronal images would be helpful. The use of T1- and T2-weighted images usually precludes the need for gadolinium administration. Electrocardiographic gating makes evaluation of images below the aortic arch and those involving the heart proper much more accurate as cardiac motion artifact is minimized.

Radionuclide Studies

Radionuclide studies may be of use in diagnosis of mediastinal masses, especially those in the anterosuperior compartment. ^{131}I and ^{123}I have been helpful in the diagnosis of substernal goiter. Gallium 67 has been used as an adjunct to the diagnosis of lymphoma; however, its best use is as a follow-up examination.

Approximately 50% of indolent and most aggressive lymphomas take up this radionuclide. Following treatment, a loss of gallium uptake portends a better prognosis, and gallium scanning may allow for a diagnosis of recurrent disease prior to the ability of conventional imaging studies to resolve a lesion. Finally, although somewhat rare, mediastinal pheochromocytoma may be imaged with the help of metaiodobenzyguanidine (MIBG).

Fluoroscopy/Contrast Esophagram

These techniques have been largely supplanted by modern cross-sectional imaging studies. Upward movement of a mass with deglutition suggests tracheal, thyroid, or laryngeal association, and medial movement with inspiration suggests primary lung pathology invading the mediastinum secondarily. Esophageal duplication cysts, often difficult to distinguish from mediastinal masses by computed-tomography scan owing to density of luminal material, may rarely exhibit delayed filling with contrast.

Biochemical Markers

Serum markers specific for germ cell tumors should be routinely checked in young patients with anterior mediastinal masses. Useful in this regard are tests for levels of alphafetoprotein (AFP), beta human chorionic gonadotropin (βHCG), and carcinoembryonic antigen (CEA). Although elevations of these markers may suggest a diagnosis of teratoma or germ cell tumor, they have greatest use in following patients for posttreatment recurrence or effectiveness of therapy. Posterior mediastinal neurogenic tumors may express catecholamines; however, these have not been found to be clinically useful except for pheochromocytoma.

INVASIVE DIAGNOSTIC TECHNIQUES

General Considerations

A variety of invasive techniques are available to the clinician for sampling of mediastinal tumor masses. However, the dilemma regarding invasive procedures is rarely which method to use, but rather whether or not invasive biopsy is safe and necessary. One of the more regrettable errors that can be made is invasive biopsy of thymoma with resultant seeding of pericardial or pleural surfaces. This may result in clinical upstaging of an encapsulated tumor with poorer anticipated treatment results. In general, the decision whether or not to proceed with an invasive diagnostic procedure will be determined by (1) the location of the mass, (2) the presence or absence of symptoms, and (3) the results of noninvasive tests (i.e., tumor markers and gallium scan).

Prior to considering biopsy of mediastinal lesions, a careful physical examination is indicated to rule out the presence of an enlarged supraclavicular or scalene lymph node that may be locally sampled. Asymptomatic, well-localized anterior mediastinal masses with negative tumor markers and no gallium uptake need not be biopsied prior to removal. One important caveat here, however, is to question the patient carefully regarding the possible presence of systemic symptoms referable to lymphoma (night sweats, weight loss, pruritus, etc.). If lymphoma is suspected on this basis, biopsy is warranted. Any lesion that has invasive or significant compressive symptoms (pleural or pericardial effusion, pain, cough, dysphagia, superior vena caval compression) requires biopsy owing to a high likelihood of malignancy and low likelihood of benefit from resection alone. Obvious nodal disease, often localized to the anterosuperior and middle mediastinum, always requires biopsy whether related to a primary lesion in the mediastinum or not. Lymphoma will often have both a nodal and larger primary mediastinal mass component. If nodal disease represents metastasis from non–small cell carcinoma, patients may require preoperative therapy for stage IIIA disease (positive ipsilateral mediastinal node positive) or primary medical therapy alone for stage IIIB disease (contralateral mediastinal node positive). Small cell carcinoma must also be ruled out as chemotherapy is the treatment of choice. In addition, numerous benign processes such as sarcoid, histoplasmosis, tuberculosis, and Castleman's disease may mimic neoplastic nodal processes.

Tumor marker positive masses (AFP, CEA, βHCG) should also be biopsied as primary medical or adjuvant therapy may be indicated in germ cell tumors.

Biopsy Techniques

Listed in order of least to most invasive biopsy modalities, the options for sampling mediastinal lesions include the following: bronchoscopy/esophagoscopy, transthoracic fine needle aspiration (FNA) or core biopsy, mediastinoscopy, anterior mediastinotomy (Chamberlain procedure), thoracoscopy, and strernotomy/thoractomy.

For any patient with new respiratory symptoms (cough, wheezing, or hemoptysis, etc.) and/or dysphagia, endoscopic examination of the airway and/or esophagus should be mandatory. Invasion and endoluminal involvement of either of these structures by mediastinal masses may allow for a simple flexible fiberoptic-guided forceps biopsy and obviate the need for other procedures. Transtracheal needle biopsy can often be of use, especially when either small cell or non–small cell carcinoma is suspected, as cytopathology may more reliably yield a diagnosis in these tumor types than in cases of suspected thymoma or lymphoma. FNA may be diagnostic in 75–90% of mediastinal masses, but the accuracy of this method depends greatly on the skill of the radiologist and cytopathologist involved. FNA can be performed with either fluoroscopic or CT guidance and

can be performed for masses in all compartments. If a lesion is thought equivocal for thymoma, this modality is a viable initial option as needle track seeding is uncommon. Core biopsy via this approach may yield more information; however, an unequivocal diagnosis of lymphoma with adequate histological classification usually requires more tissue. FNA is quite safe, with the incidence of significant hemorrhage very rare and the risk of pneumothorax considerably less than transthoracic biopsy of parenchymal lung lesions. As is true for all methods of biopsy, if a pheochromocytoma is thought likely, biopsy is contraindicated.

Mediastinoscopy is a procedure commonly performed by thoracic surgeons for staging of non–small cell lung carcinoma, but it can also be of great utility in the diagnosis of both anterior and middle mediastinal masses. The mediastinoscope is placed posterior to the innominate artery and aorta and anterior to the trachea (Fig. 2a) and paratracheal as well as subcarinal regions may be accessed. An extended version of this technique, allowing biopsy of lesions in the anterior compartment via placing the mediastinoscope anterior to the aortic arch, has met with some success as well; however, this should be considered an advanced technique for experienced operators. Significant complications such as life-threatening hemorrhage, injury to the airway, or recurrent laryngeal nerve (especially the left as it lies just adjacent to the distal trachea) have occurred in less than 1% of cases in large published series.

Anterior mediastinotomy, or the Chamberlain procedure, is useful for biopsy of anterior lesions not easily accessible to the mediastinoscope. It involves removal of a small segment of costosternal cartilage in the subperichondrial plane and may often be performed extrapleurally as the internal thoracic vessels are divided or swept medial and the true pleura swept lateral to expose the mass (Fig. 2b).

Thoracoscopic biopsy can be performed for mediastinal lesions in any location, but has been especially useful for lesions in the subaortic window, posterior subcarinal, and posterior mediastinal locations where mediastinoscopy and conventional mediastinotomy may not suffice.

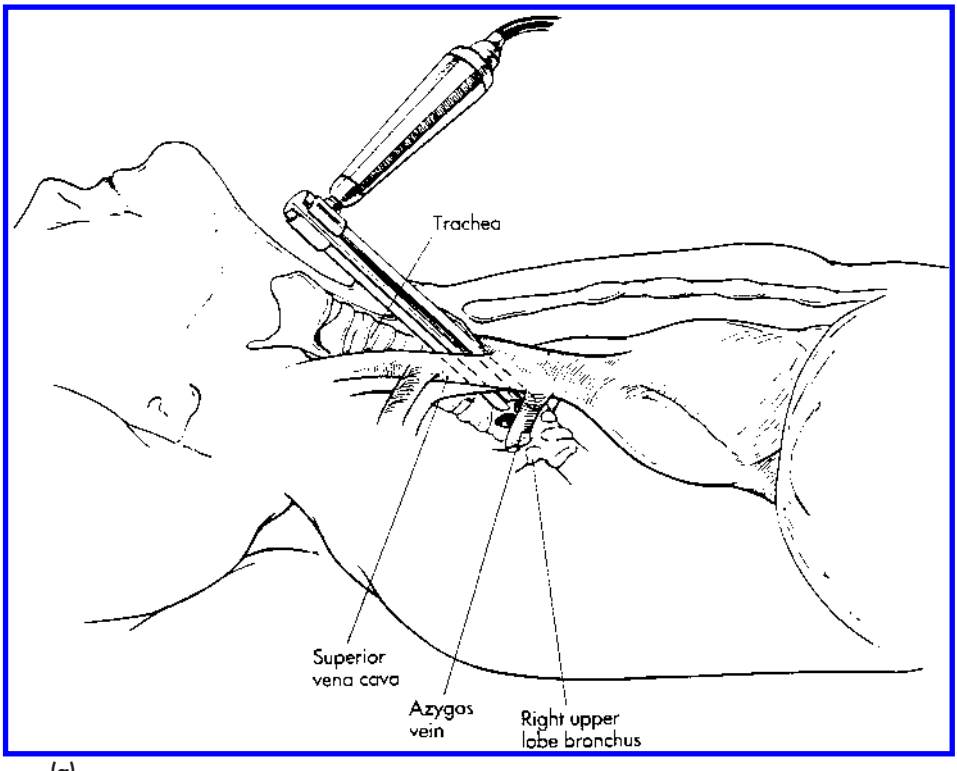
SURGICAL THERAPY BY BIOLOGICAL CLASSIFICATION

Discussion of surgical therapy for primary mediastinal tumors will be limited here to those arising from the thyroid, thymus, lymphatic tissues (lymphoma), and germ cell tissues, and those of neurogenic origin.

Thyroid

Retrosternal Thyroid

General. Although not usually a neoplasm per se, retrosternal thyroid is a ''tumor'' with which both general surgical oncologists and general thoracic surgeons alike must frequently deal. Females predominate at a ratio of 2–3:1, and the appearance of these lesions is most frequent in the fifth to seventh decade.



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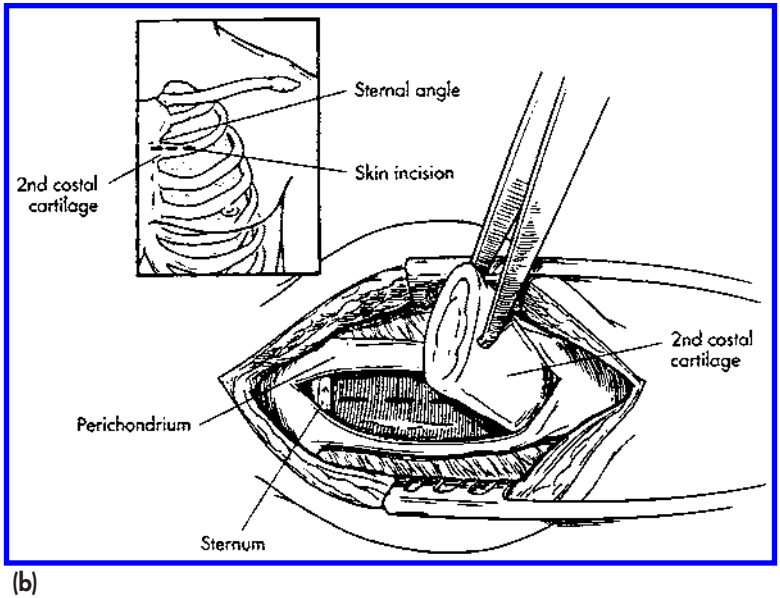


(b)

FIGURE 2 Routine surgical approaches to biopsy of mediastinal masses. (a) Cervical mediastinoscopy; (b) anterior mediastinotomy, or Chamberlain procedure. (From Kaiser LR. Atlas of General Thoracic Surgery. St. Louis: CV Mosby, 1997.)

Pathophysiology and Histopathology. The vast majority (75–85%) of mediastinal thyroid masses are substernal multinodular goiters, with a minority of follicular adenomata and rare Hashimoto's thyroiditis with enlargement (<3%). The presence of retrosternal thyroid tissue usually implies that a multinodular goiter originating from either lobe of the cervical thyroid has extended into the mediastinum; however, rare intrathoracic masses may arise from heterotopic mediastinal thyroid tissue. Most of the lesions descend on the right side of the mediastinum owing to the left-sided aortic arch. Most are found in the anterior mediastinum, but they may descend into the posterior mediastinum posterior to the trachea and great vessels (Fig. 3).

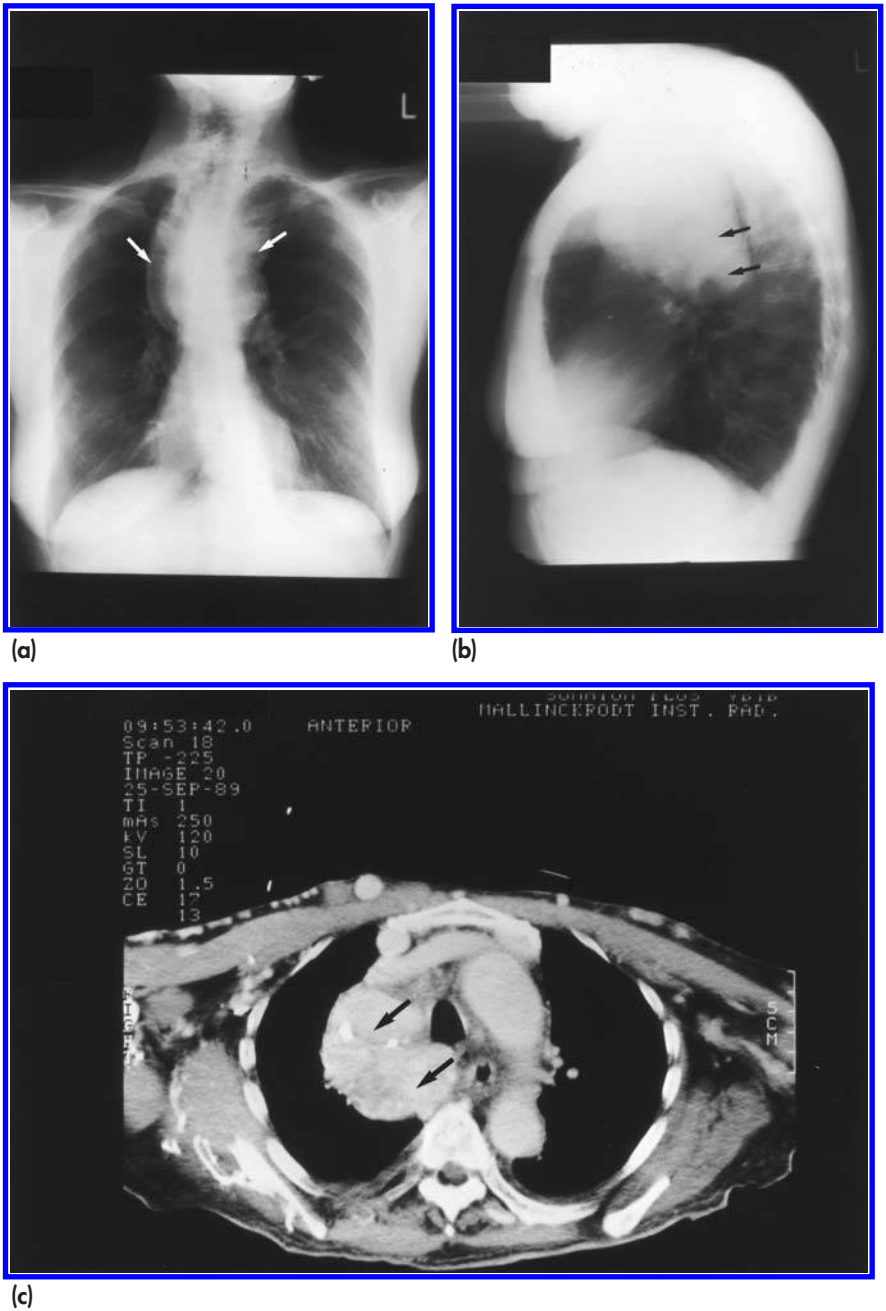
The presence of papillary or follicular carcinoma is infrequent in most series of cases (3–15%), but may be nearly impossible to rule out prior to extirpation owing to the large size of most of these glands and the likelihood of sampling error with biopsy.

Signs and Symptoms. Most patients (<50%) present with the gradual onset of respiratory symptoms (stridor, wheezing, cough, etc.) due to tracheal compression. An occasional patient may present in extremis from precipitous loss of an airway following hemorrhage into a retrosternal thyroid at the relatively restrictive thoracic inlet. Dyspnea may be somewhat positional, as with any mass compressing the trachea. Dysphagia may occur, especially if the goiter descends into the posterior mediastinum. Retrosternal thyroid is one of the few benign masses that may lead to a superior vena caval syndrome. The majority of patients (>85%) are euthyroid, and up to 15% of patients with retrosternal goiter are completely asymptomatic.

Diagnosis. A combination of a plain film of the chest, CT scan, and/or MRI is most often all that is necessary to make a diagnosis of retrosternal goiter. However, ^{131}I radionuclide scanning may help to substantiate the diagnosis (see above). Needle biopsy may be performed and sampling the cervical portion of the mass may obviate the need for radiological guidance.

Surgical Treatment. In the opinion of many, with the combined risks of airway compromise (acute: hemorrhage; chronic: compressive tracheomalacia) and foci of carcinoma, the mere presence of retrosternal thyroid tissue indicates a need for surgical removal.

Preoperative induction of anesthesia and positioning are important. In many cases, it is prudent to intubate the patient awake and in the sitting or slightly reclined position, as this may avoid loss of a compressed tracheal airway with muscular relaxation. As is the case for all tracheal pathology, a rigid bronchoscope should be in the operating room during induction in case of need for emergency airway control (Fig. 4). The patient is positioned supine with a shoulder elevation and neck extension.



(a) (b)

(c)

FIGURE 3 Mediastinal goiter. (a and b) Plain films of large mediastinal goiter. (c) CT scan of mediastinal goiter with extension of the mass lateral and posterior to the trachea (arrows = goiter).

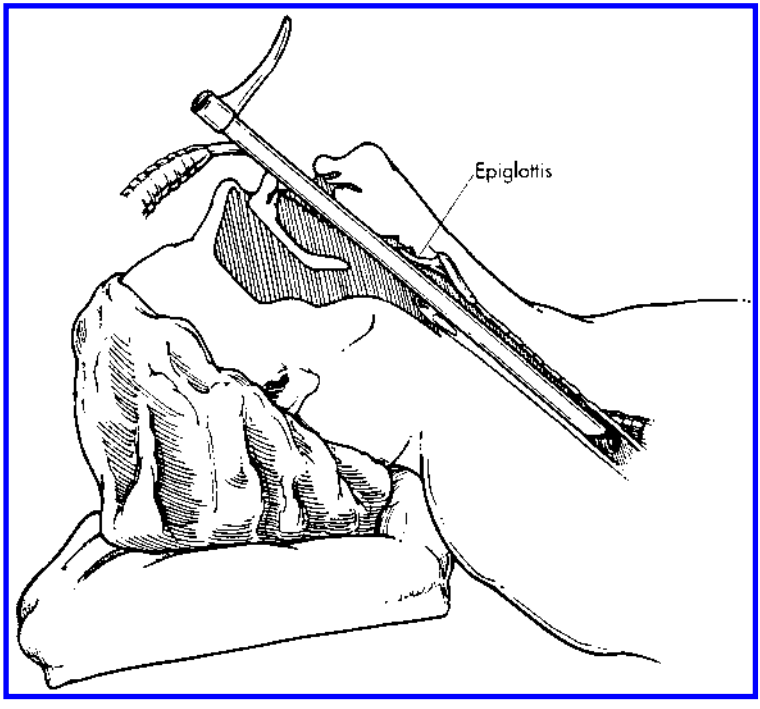


FIGURE 4 Insertion of the rigid bronchoscope for airway control. Note the position of the patient's head with shoulder elevation and neck extension. Ventilation can be established via a sidearm and connector to a ventilatory source. (From Kaiser LR. Atlas of General Thoracic Surgery. St. Louis: CV Mosby, 1997.)

Most of these lesions should be approachable via a cervical collar incision, as the blood supply originates in the neck. Only on rare occasions will a mediastinal mass originate from heterotopic tissue and be fed via a mediastinal vessel. The goiter is usually not avidly adherent to mediastinal structures, and may be lifted out of the mediastinum via a collar incision with a combination of blunt and sharp dissection. A sternotomy or thoracotomy is indicated only when the mass is avidly applied to the great vessels or recurrent laryngeal nerve, is engendering a superior vena cava (SVC) syndrome, contains known carcinoma, or presents as acute airway compromise. More relative indications for sternotomy or thoracotomy would include diagnostic uncertainty, a history of previous mediastinal thyroid tissue removal, or a posterior mediastinal goiter. As a large potential space often results from removal, a closed suction drain may be indicated. If the mass originates from one pole of the gland, a complete unilateral lobectomy

is performed; if bilobar involvement is noted, a lobectomy with partial contralateral lobectomy or a subtotal thyroidectomy is performed.

Complications. In addition to the complications common to thyroidectomy (recurrent laryngeal nerve injury, compressing tracheal hematoma, hypothyroidism, hypoparathyroidism), pneumothorax, hemothorax, and postoperative pleural effusion should be ruled out with serial plain films of the chest.

Results and Follow-up. Recurrence of substernal goiter is rare with complete resection. The use of thyroid supplementation for avoidance of recurrence of goiter is controversial, but such supplementation is necessary in patients rendered hypothyroid.

Thymus

Thymoma

General. Thymomas are the most common neoplasm of the anterior mediastinum, representing about 20% of all mediastinal malignancies. They are unique by virtue of their often indolent course, lack of histological evidence of malignancy in most cases, and frequent association with a systemic neurological disease in myasthenia gravis. They are rare in children and are most common in adults in the fourth and fifth decades of life. The sex distribution is equal except in the case of associated myasthenia gravis where females predominate.

Pathophysiology and Histopathology. A number of clinical and histopathological classification schema for thymoma have been proposed, but the most widely accepted are the clinical staging system of Masaoka and the histological classification of Marino and Muller-Hermelink (Tables 1 and 2). Complicating any discussion of the malignant potential of thymoma is the fact that the tumor often looks relatively bland without an abundance of the usual histopathological negative prognostic markers of nuclear or cytoplasmic pleomorphism and mitotic

Table 1 Thymoma Staging System (Masaoka)

Stage	Description	10-year survival (%)
I	Encapsulated tumors without gross or microscopic invasion	85–100
II	Capsular or pleural invasion	60–84
III	Macroscopic invasion of surrounding tissues (lung, pericardium, vena cava, or aorta)	21–77
IV	Disseminated disease within the chest	26–47
V	Distant metastases	Unknown

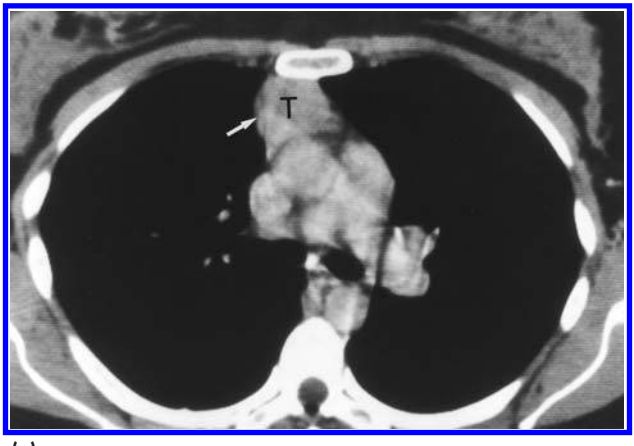
Table 2 Thymoma Classification System by Histological Characteristics (Marino and Muller-Hermelink)

Medullary thymoma
Mixed thymoma
Predominantly cortical thymoma
Cortical thymoma
Well-differentiated thymic carcinoma

figures. Certain trends associated with histology have been noted, however. Medullary and mixed tumors may be more benign in behavior. The cortical and predominantly cortical histology carries with it a possibly poorer prognosis, and is associated with a more invasive phenotype. Grossly, thymomas often appear well encapsulated, with the tumor mass localized anywhere in the gland, but when small often in the horn. Approximately one-third of the time, regardless of gross appearance, the thymoma is invasive into either the capsule or surrounding mediastinal structures (Fig. 5). Tumoral metastatic implants noted at the time of surgery are most often pericardial or subpleural and less commonly involve the pulmonary parenchyma (Fig. 6). Late metastasis is more common than at diagnosis. Extrathoracic metastasis is much less common than intrathoracic, but has been reported in bone, liver, spleen, supraclavicular nodes, brain, and peritoneum.

Signs and Symptoms. Although the association with systemic conditions such as myasthenia gravis is common, between one-third and one-half of all patients with thymoma present asymptomatically with a mediastinal mass noted on plain film. In several series evaluating the presence of myasthenia gravis in resected thymoma, the incidence ranged from 35 to 70%. The incidence of thymoma in patients with a primary diagnosis of myasthenia is lower, ranging from 10 to 25%. Although rare, a myriad of other paraneoplastic syndromes have been noted with thymoma, with hypogammoglobulinemia, pure red cell aplasia (erythroblastopenic anemia), and systemic lupus erythematosus being the most common. Interestingly, up to one-third of patients with evidence of paraneoplasia

Figure 5 Thymoma. (a) Well-encapsulated small thymoma noted on chest CT. (b) Large invasive thymoma with aortic involvement. Note the lack of a fat plane between the mass and the vascular structures. (c) Thymoma invading tumor capsule. Arrow = thymoma; arrowhead = capsular invasion; T = thymoma; L = adjacent normal lung; A = aorta.



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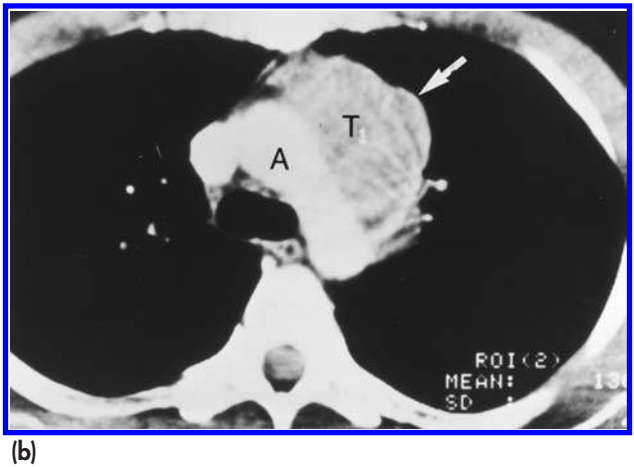

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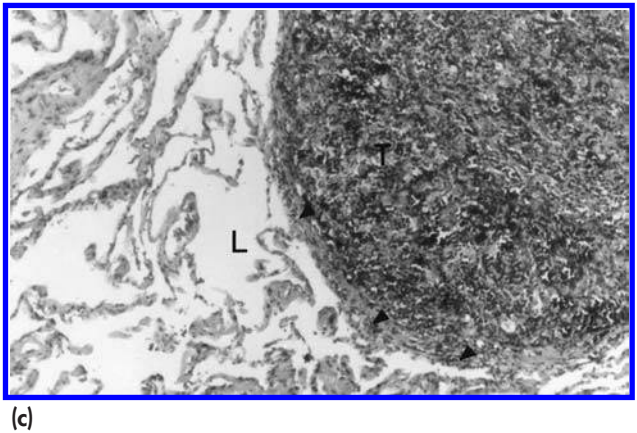

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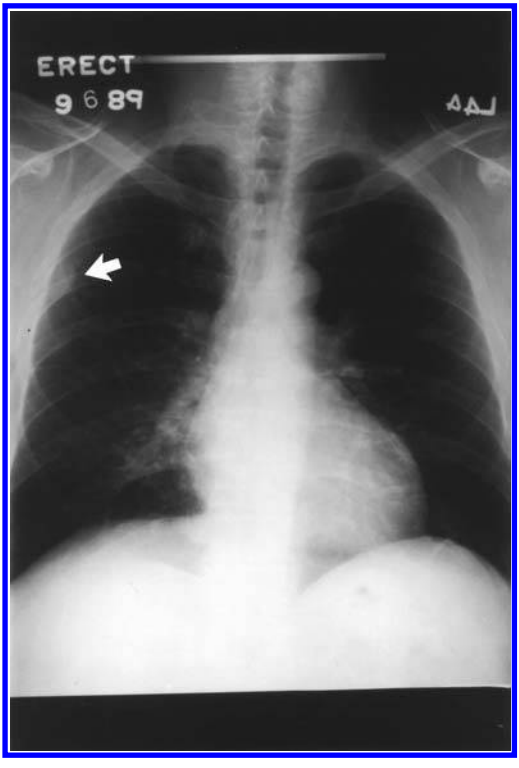


FIGURE 6 Pleural-based metastases from thymoma. Arrow = metastases.

have two or more of these syndromes when carefully evaluated. Compressive syndromes with thymoma are similar in incidence to other lesions in the anterior compartment.

Diagnosis. If a patient presents with new-onset myasthenia gravis or hypogammaglobulinemia and an anterior mediastinal mass on plain film, the diagnosis is not difficult. The radiographic presentation of thymoma is unfortunately not that specific. The radiographic appearance of a normal thymus is related to the age of the individual. In younger patients, the thymus may be large (greatest size during puberty) with convex margins and have a CT density roughly equivalent to that of muscle. As the individual ages, the gland is gradually replaced with fat. This transformation is most marked during the third decade, and by age 40 most glands appear entirely fatty. Owing to the increased density, tumors in the substance of the thymus gland are more difficult to identify in younger patients. Fatty replacement actually improves the ability of CT scan and MRI to

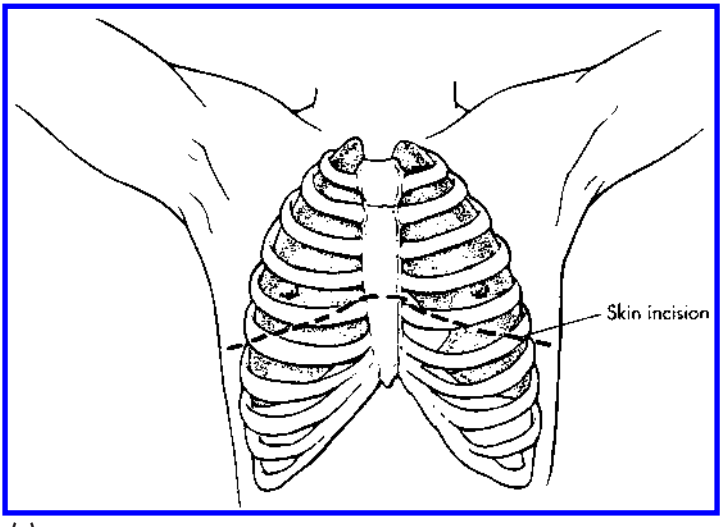
delineate these lesions. Calcification and cystic regions may be noted by cross-sectional imaging; however, these are not specific to thymoma. The enlarged appearance of a thymus gland with thymic hyperplasia should not be confused with a thymoma. Thymic hyperplasia is most commonly associated with a primary diagnosis of myasthenia gravis, and the enlargement correlates with the development of germinal centers within the gland. During the administration of either chemotherapy or corticosteriods, atrophy of the thymus is common, and ''rebound'' hyperplasia and enlargement of the thymus may be seen frequently following the cessation of these agents.

Capsular or surrounding mediastinal structure invasion by thymoma may be suggested by CT scan or, more likely, MRI; however, this is only assessed unequivocally at the time of surgical exploration and pathological examination. It is important to carefully image the lungs and pleurae, as metastases are likely in these regions and may help determine (or obviate) the operative approach.

Tissue diagnosis may be necessary in patients with anterior mediastinal masses and absolutely no referable symptoms, or in very large and obviously unresectable anterior mediastinal masses (obvious invasion of heart, etc.). When indicated, biopsy can be problematic as thymoma may occasionally be spread to exposed pleural and pericardial surfaces. FNA has been sensitive in approximately 90% and specific in about 85% of cases. If FNA is equivocal, anterior mediastinotomy should be considered before mediasinoscopy if thymoma is suspected as both the pleural and pericardial space may be avoided.

Surgical Treatment. Two general concepts are of paramount importance in considering surgical therapy of thymoma: the chance for cure is greatest if complete resection (including structures involved by invasion) is performed, and the entire thymus (not just the tumor) must be carefully removed. This latter recommendation is supported by the fact that (1) patients with myasthenia or other autoimmune syndromes may not experience amelioration of symptoms without complete removal of the gland, and (2) occult multiple small thymomas are not uncommon.

The operative approach should be dictated by fulfillment of the above recommendations. With all approaches it must be remembered that the horns of the thymus may extend up into the neck to at least the level of the inferior thyroid. Most surgeons prefer a median sternotomy or partial sternotomy and, if necessary, an intercostal extension. Other approaches could include the hemiclamshell or formal clamshell incision (should be considered only for larger lesions) (Fig. 7). Small thymomas and larger lesions without evidence of mediastinal structure invasion can be approached via a transcervical incision, and thoracoscopic removal has been reported (Fig. 8). The latter two approaches require a great deal of experience, and the likelihood of residual thymic tissue being left behind is theoretically greater. In addition, the patient should always be informed of the



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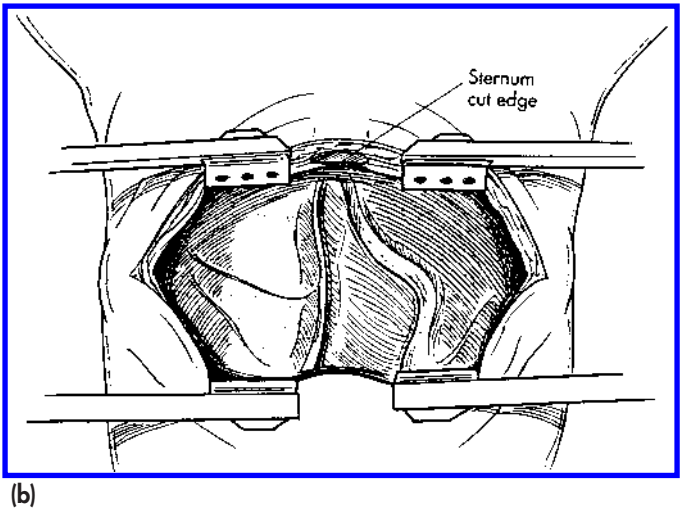
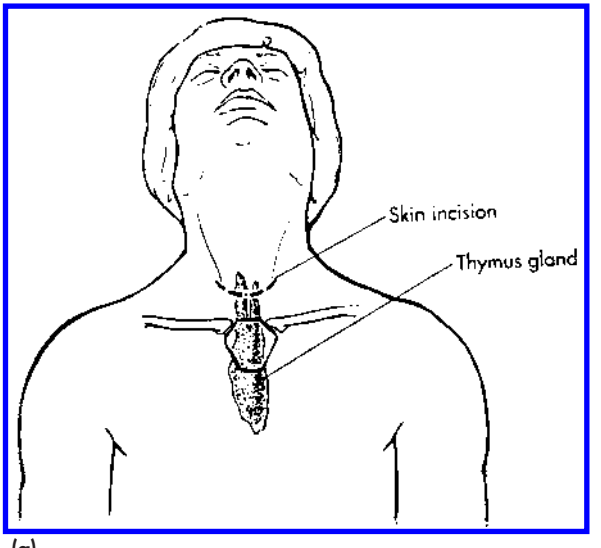
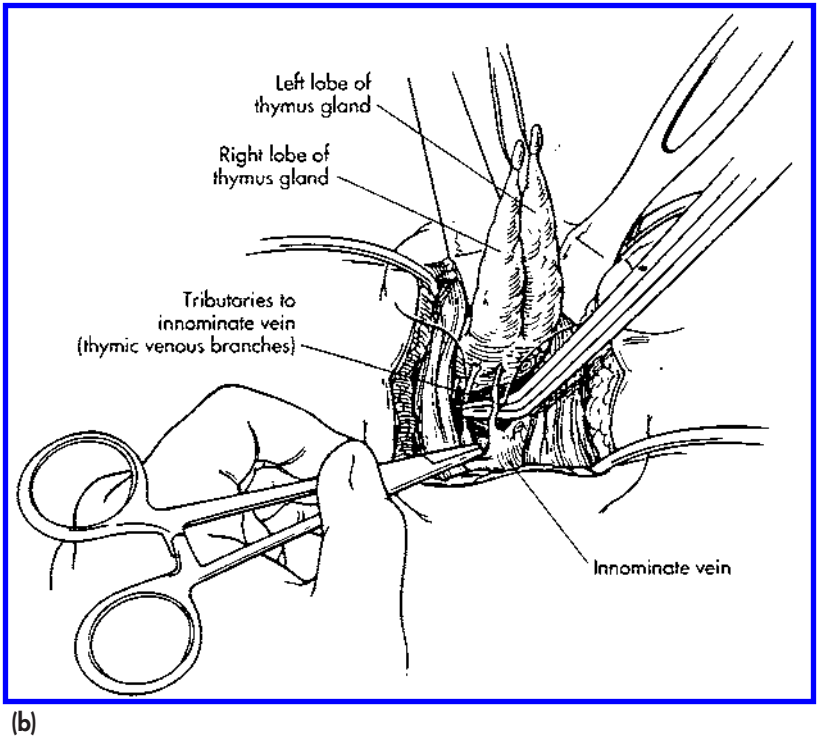


(b)

FIGURE 7 Thoracosternotomy "clamshell" approach for large mediastinal tumors. (a) Placement of skin incision—midpoint should approximate 4th or 5th intercostal space on sternum. (b) Thoracosternotomy exposure with bilateral chest retractors in place. (From Kaiser LR. Atlas of General Thoracic Surgery. St. Louis: CV Mosby, 1997.)



(a)



(b)

FIGURE 8 Transcervical thymectomy. (a) Placement of skin incision overlying cervical horns of the thymus. (b) Thymus being delivered via cervical incision. Small tributaries of the innominate vein must be ligated. (From Kaiser LR. Atlas of General Thoracic Surgery. St. Louis: CV Mosby, 1997.)

possibility of the need to convert a less invasive approach to a formal sternotomy or thoracotomy.

Surgical removal is the primary treatment of choice for thymomas ranging from stage I to IVA. Stage IVB is best treated with chemotherapy ± radiation therapy followed by surgery if downstaged appropriately. Care should be taken to avoid the phrenic nerve in stages I and II (especially in myasthenics), and stage IVA lesions should be tackled only if the pleural and pericardial lesions are isolated enough to realistically remove them completely. Postoperative radiation therapy should be administered to all invasive thymomas. The use of chemotherapy with radiation therapy in lower-stage disease is controversial.

Patients with thymoma and myasthenia gravis should be managed with a multidisciplinary team approach. Adequate dosing of anticholinesterase medication is necessary, and continuation of these medications in the immediate postoperative period is essential, as myasthenic symptoms will not improve following thymectomy for an unpredictable period ranging from several weeks to a year or more. At our institution, plasmapheresis (removal of anti-AChR antibody) is routinely performed a week or two prior to surgery in an effort to avoid a dangerous myasthenic crisis, maximize postoperative mobilization, and minimize the chance of prolonged ventilation. In addition, it is important to recognize the myriad of indications for and possible side effects related to the use of certain drugs in myasthenic patients (e.g., the importance of use of shorter-half-life paralytic agents during the operative procedure).

Complications. The majority of complications related to surgical therapy of thymoma are engendered by either the necessity to remove mediastinal structures adherent to or invaded by the tumor or the complications of myasthenia gravis in the postoperative patient.

It is imperative that the phrenic nerve be spared in all noninvasive thymomas with associated myasthenia gravis as unilateral diaphragmatic paresis or paralysis can lead to an inability to wean from postoperative ventilatory support. The nerve should be identified early in these cases, and sharp dissection should supplant electrocautery in the vicinity of this structure.

Occasionally a myasthenic crisis can occur in the postoperative period, and is manifested by life-threatening exacerbation of muscular weakness that can lead to respiratory failure or aspiration. Infection often triggers these events, and perioperative antibiotic coverage as well as good pulmonary toilet are essential. Repeat plasmapheresis may be helpful in addition to supportive care.

Results and Follow-up. The reported survival following recommended therapy for thymoma by stage is shown in Table 1. Although reports of both negative and positive impact on survival have been reported for a number of preoperative characteristics, studies utilizing careful statistical methods have not noted differences in prognosis or survival based on sex, age, or presence of myas-

thenia gravis. Some studies suggest that the medullary histology carries a more favorable prognosis with treatment than does cortical. The only variables that are undeniably related to outcome are stage (i.e., invasiveness) and completeness of resection. For stage III tumors especially, complete resection may more than double the survival at 10 years (70% complete resection vs. 28% incomplete resection). Although studies differ, it appears as if the chance that myasthenic symptoms will resolve or at least improve following complete thymectomy is less likely for thymoma than for thymic hyperplasia. As for other autoimmune symptoms, hypogammaglobulinemia rarely responds to thymectomy and pure red cell aplasia responds only about 30% of the time. A return of myasthenic symptoms following resection and resolution of the same indicates a strong possibility of tumor recurrence.

Uncommon Thymic Tumors

Thymic carcinoma is a tumor that arises from the epithelial cells of the thymus and retains more histological and cytoarchitechural features of malignancy than thymoma. Several subtypes exist and are divided into well-differentiated or low-grade (basaloid, squamous, and mucoepidermoid) and high-grade (lymphoepitheliod, small cell, clear cell, sarcomatoid, and anaplastic) categories. The treatment of choice is aggressive surgical resection followed by chemotherapy. Prognosis is considerably poorer than for thymoma, with long-term survival rates of only 15–30%. Classically, this tumor has been staged utilizing the Masaoka thymoma staging system; however, some studies do not substantiate correlation between survival and Masaoka stage. Vascular invasion may be the most useful measure of prognosis. Local recurrence is extremely common, and distant metastases are noted in the liver, lung, and bone.

Thymic carcinoid is an extremely uncommon lesion that may be associated with the multiple endocrine neoplasia (MEN) syndromes. It usually occurs in men and is likely to present with a paraneoplastic syndrome, often ectopic ACTH production. Bland carcinoid histology may require only extirpation.

Thymolipoma is a benign fatty tumor of the thymus. Appearance on CT is pathognomonic: a huge, well-encapsulated tumor with fat density and islands of normal-appearing thymus. These do not necessarily require surgical excision, but may be removed for compressive symptoms. Neoplastic transformation has not been reported.

Germ Cell Tumors

General

The mediastinum is the most common site for extragonadal germ cell tumors in adults, accounting for 50–70% of these lesions. These tumors are most commonly

located in the anterior mediastinum and constitute 10–15% of all mediastinal tumors. Only 3–8% of germ cell tumors of the mediastinum are found in the posterior compartment.

In children, all extragonadal germ cell tumors are equally distributed between sexes. In adults, extragonadal germ cell tumors classified as benign are equally distributed, but 90% of tumors classified as malignant are found in men. Although the majority of tumors occur during the third decade of life, they may occur in patients of all ages.

Pathophysiology and Histopathology

Germ cell tumors have been subdivided into benign and malignant categories. Benign tumors include mature teratomas and teratomas with immature components of less than 50%. Malignant tumors include seminomas and nonseminomatous tumors. Nonseminomatous tumors include teratocarcinoma, yolk sac tumor, embryonal carcinoma, and teratoma with more than 50% immature component (immature teratoma). Midline tumors of uncertain histogenesis are tumors that are often deemed carcinoma with unknown primary site and may at times represent a form of germ cell tumor that would respond to similar therapies. It is pertinent to note that with careful pathological examination, tumors harboring more than one histological subtype are fairly common. The presumption is that extragonadal germ cell tissue that has assumed an abnormal position during migration forms these tumors.

Signs and Symptoms

Approximately one-half of patients with benign mediastinal germ cell tumors are asymptomatic; however, 90–100% of those with malignant tumors present with symptoms. Local symptoms include cough, chest pain, and dyspnea and are related to rapid expansion of tumor in the mediastinum with secondary involvement of mediastinal structures. Weight loss and fever are common constitutional symptoms for malignant tumors, and patients may also present with symptoms related to metastasis to the lungs, bone, or liver.

Diagnosis

The importance of an accurate diagnosis in germ cell lesions of the mediastinum cannot be understated. One must rule out the possibility of a gonadal metastasis as the mediastinum is a common location for such lesions. In addition, histological type determines whether primary therapy will be medical or surgical.

Careful testicular examination should always be performed, and if an abnormality is palpated, testicular ultrasound should be obtained with biopsy of the suspicious lesion. In addition to chest imaging, abdominal CT should be performed to rule out metastatic lesions to the liver or retroperitoneal adenopathy, the presence of which would argue for a gonadal primary.

In 95% of cases an abnormal plain film of the chest is noted with an anterior mass. Calcification is fairly common in mature teratomas due to retained ossified structures such as teeth and bone and may be noted on both plain film and CT (Fig. 9). Unfortunately, other specific cross-sectional imaging characteristics do not exist that could differentiate germ cell tumors from other anterior mediastinal masses. One distinguishing characteristic of germ cell tumors, however, is the secretion of tumor markers. Serum levels of alpha fetoprotein (AFP), human chorionic gonadotropin (βHCG), and lactate dehydrogenase (LDH) should be routinely obtained, especially in young male patients. Patients with benign teratomas are marker negative, and seminomas are likely to secrete βHCG, but not AFP. Nonseminomatous tumors secrete both of these markers (AFP 60–80%, βHCG 30–50%). In addition to tumor markers, there have been a few notable associated syndromes that could aid in the differentiation of germ cell tumors from others. Klinefelter's syndrome, characterized by the XXY karyotype, hypogonadism, developmental delay, and musculoskeletal abnormalities, may be seen in up to one-fourth of male patients with nonseminomatous mediastinal germ cell tumors. In addition, a number of hematological malignancies have been associated with these tumors.

Tissue diagnosis is essential and can be obtained by either FNA or more formal surgical procedures. FNA may yield adequate material for immunohisto-

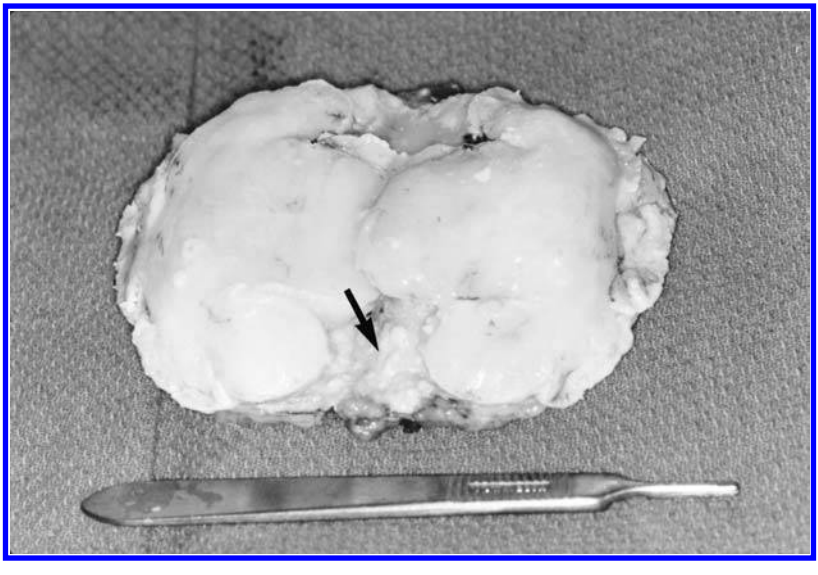


FIGURE 9 Mature teratoma. Note the calcified structures (rudimentary teeth) in the bisected specimen (arrow = teeth).

chemical evaluation cytology and some tumor or cell surface markers, but larger amounts of tissue may be necessary to examine both tissue architecture and a full battery of immunohistochemical markers. Common markers examined include βHCG, human placental lactogen (HPL), AFP, LDH, and placental alkaline phosphatase (PLAP). An anterior mediastinotomy (Chamberlain procedure) may be the procedure of choice. A chromosomal abnormality often associated with germ cell tumor is the presence of an isochromosome of the short arm of chromosome 12, designated i(12p). This abnormality may be seen in up to 60% of germ cell tumors and is more common in the nonseminomatous types. It may be of particular benefit in designating midline tumors of uncertain histogenesis as germ cell tumors that may respond to similar therapy.

Surgical Treatment

Mature (Benign) Teratoma. Surgical resection is the treatment of choice for these lesions and may be curative in most cases. Although benign, this tumor tends to be densely adherent to mediastinal or pulmonary structures. For this reason, formal sternotomy or thoracotomy is often necessary rather than a minimally invasive approach; however, eccentric lesions may first be attempted via the thoracoscope. Complete resection is recommended as the true immature component of the tumor may not be known (making recurrence more likely), degeneration of benign lesions to carcinomatous or sarcomatous variants is possible, and regrowth and invasion of mediastinal structures can occur.

Seminoma. Surgical therapy for these tumors is reserved for residual disease following primary treatment with either radiation or radiation and chemotherapy, and is rarely indicated as the tumor is so sensitive to available medical therapies. This approach is controversial, and an argument has been made for observation only. Residual masses often consist entirely of a dense schirrous reaction/scar (85–90% of cases); however, if the lesion is greater than 3 cm in diameter, there is a greater chance of true residual tumor. Isolated residual masses greater than or equal to 3 cm should be completely resected. Surgical debulking (incomplete resection) of extensive or diffuse disease has not been shown to be beneficial.

Nonseminomatous Tumors. Primary therapy of these tumors is medical (chemotherapy), and recent advances in this regard have improved survival. However, 40–50% of patients will require ''adjunctive'' surgery following chemotherapy to achieve disease-free status. The current recommendation is to explore and resect all residual disease in these patients following therapeutic chemotherapy and disappearance of serum tumor markers. Any areas that demonstrate an obvious mass on postchemotherapy radiographic studies, in addition to areas that were suspicious on radiographs prechemotherapy, must be explored. The proper surgical approach should be planned to give access to all these regions. If the

patient is relatively young, a more aggressive exposure such as a thoracosternotomy (''clamshell'') may be considered as a sternotomy may not adequately expose such areas as the superior-lateral mediastinum or paratracheal and subcarinal regions. Care must be taken not to compromise or resect normal structures such as major blood vessels or the phrenic nerve unless definitive malignancy is present. Frozen section examination should direct these decisions when necessary. Residual masses may represent simply residual fibrosis or scar (~40% of residual lesions) and, as many of these lesions are mixed, residual benign teratoma (~40% of residual lesions) that was unresponsive to the chemotherapy. Survival is best when no lesions are identifiable at follow-up radiological exam, or when all areas resected show only fibrosis. Even when residual tumor is found (~20% of residual lesions), survival may be improved, but only if complete resection is possible. ''Salvage'' surgery may be suggested when tumor markers do not return to normal following one or even two cycles of chemotherapy, with the same goals in mind as with responsive tumor. The results of any form of additional therapy, surgical or medical, for nonresponsive nonseminomatous tumor are poor.

Complications

Complications related to surgical therapy of germ cell malignancies are relatively nonspecific and include all those that could be anticipated for removal of masses adjacent to or invading mediastinal structures such that partial removal or compromise of these structures might be anticipated. Procedures with a high likelihood for threat to life or quality of life designed to resect fully mature teratoma should be considered carefully, as the prognosis may not be altered by a small amount of unresectable disease. Major vascular invasion necessitating planned major vascular revision for removal of residual nonseminomatous germ cell tumor should also be weighed carefully as the poor prognosis associated with this finding will most likely not be improved.

Results and Follow-up

Benign teratoma carries an excellent prognosis, and near-universal cure rates should be anticipated with complete resection. Several general statements regarding prognosis are pertinent for patients with malignant germ cell tumor: (1) 70–80% of patients with malignant lesions can anticipate cure with chemotherapy $\pm$ surgical adjunctive therapy, (2) level of preoperative tumor markers and rate of drop (slower drop = poorer prognosis) with treatment have prognostic value, (3) a larger number of multiple lesions have a poorer prognosis, (4) pure seminoma responds more favorably to all therapy than nonseminomatous lesions, and (5) effective salvage regimens may exist for those that do not respond to first-line treatment.

Disease-free seminoma survival following conventional treatment has been reported in approximately 67% of patients at 24 months. Conversely, similar

survival in patients with nonseminomatous lesions should be anticipated in only 24% of patients. Midline tumors of uncertain histogenesis may respond much like nonseminomatous lesions when they harbor the 12p isochromosome; however, three-quarters of these tumors are i(12p) negative, and these may be relatively unresponsive to conventional therapy. Close follow-up with frequent CT scan and serum tumor marker evaluation is important as recurrent tumor can appear and quiescent lesions thought to represent fibrosis may ''degenerate'' into ''new'' malignant lesions.

Neurogenic Tumors

General

Neurogenic tumors are by far the most common of the posterior mediastinum. These lesions are the most common neoplasm in children and make up approximately 15% of all mediastinal masses in adults. Although almost exclusively found in the posterior mediastinum, lesions may also arise along the course of the phrenic or vagus nerves as they travel through the middle mediastinum (Fig. 10). These tumors are broadly characterized as either nerve sheath or neuronal cell/neuroendocrine tumors. Nerve sheath tumors are usually benign, but the neuronal cell–derived tumors may be either benign or malignant. Adults are more likely to present with benign lesions, with malignant tumors found in less than 10% of cases. In contrast, children are likely to present with malignant tumors in this category more than 50% of the time.

Histopathology and Histogenesis

Neurogenic tumors originate from the neural crest, and differentiate along either a nerve sheath or neuronal cell/neuroendocrine pathway (Fig. 10). The neuronal cell tumors are further subdivided into either the autonomic ganglia (sympathetic) or paraganglionic system (parasympathetic). As stated above, malignant behavior is more common in the neuronal cell tumor category. A detailed description of the varied and rather complicated histopathology of these lesions is beyond the scope of this chapter, but pertinent comments will be made for specific lesions. An interesting association between radiation exposure and late development of malignant schwannoma has been noted.

Signs and Symptoms

Most patients with posterior mediastinal neurogenic tumors are asymptomatic, with serendipitous findings on radiological examinations for other reasons. Occasionally, patients will present with such symptoms as spinal cord or spinal nerve compression (motor/sensory deficits or radicular pain), chest wall pain (intercostal nerve involvement), hoarseness (recurrent laryngeal nerve involvement), dys-

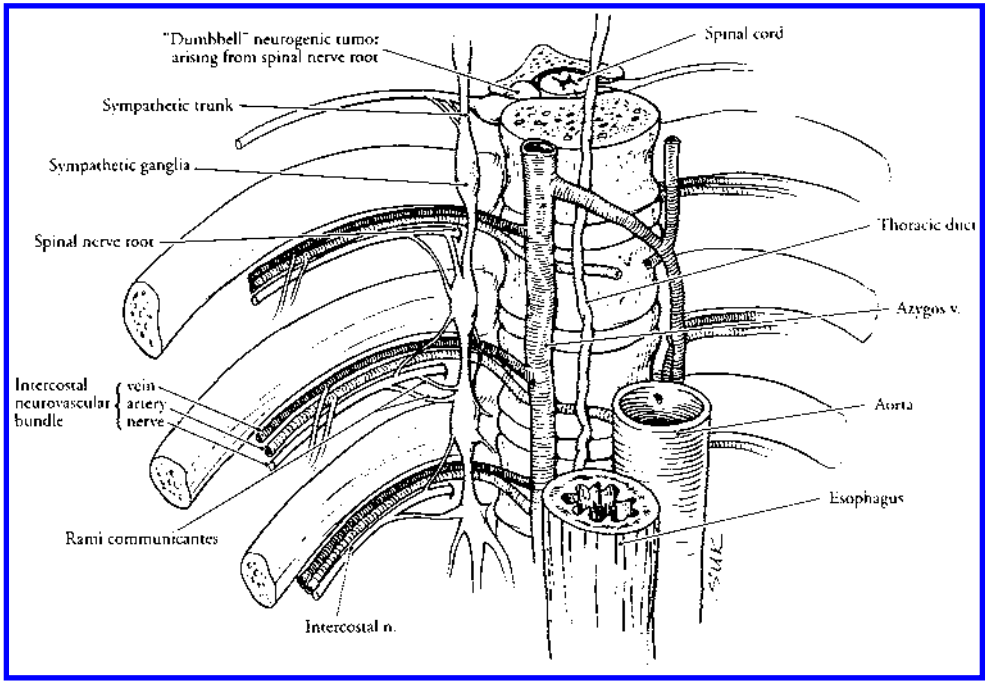
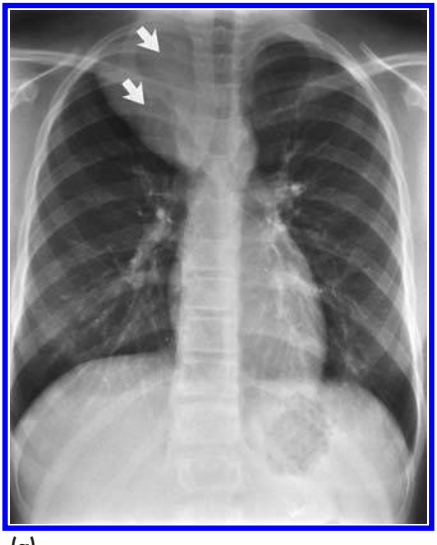


FIGURE 10 Structures in the posterior mediastinum from which neurogenic tumors may arise. (From Fishman AP. Pulmonary Diseases and Disorders. New York: McGraw-Hill, 1998.)

pnea (phrenic nerve involvement), and Horner's syndrome (cervical ganglion involvement).

Diagnosis

As previously stated, most neurogenic tumors are found on routine plain film of the chest. Posterior compartment tumors tend to be well-defined rounded densities projecting into the apparent pleural space (Fig. 11). Those arising from the sympathetic ganglia tend to be more elongated longitudinally than those arising from the proximal peripheral nerve sheaths, rendering them more difficult to see in the lateral view. Unlike anterosuperior and some middle mediastinal masses, calcification is rare in posterior compartment neurogenic tumors. Oblique views and other procedures such as plain film tomography have been supplanted by cross-sectional technology. CT scan is useful in determination of spatial location and likelihood of spinal involvement. The MRI scan is of paramount importance in making a preoperative diagnosis and planning resection of a so-called ''dumbbell'' tumor. The extension of a neurogenic tumor into the intervertebral foramen



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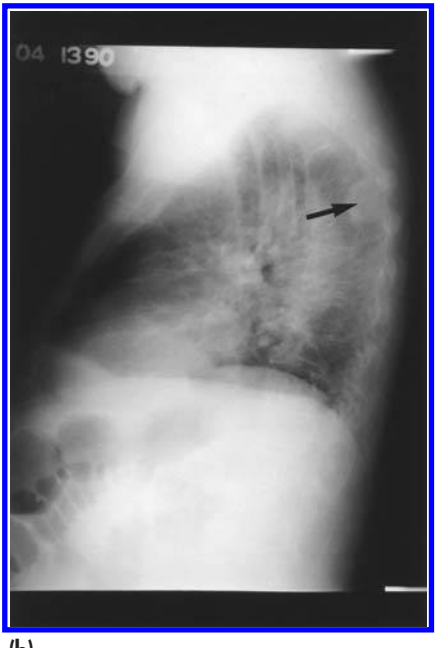

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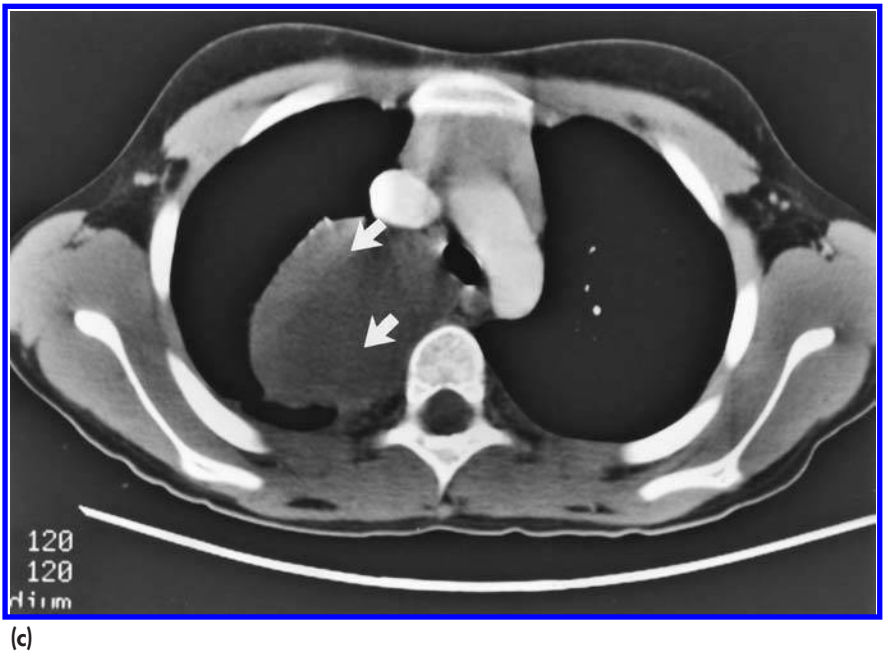

(c)

and extent of intraspinal involvement may be noted by the use of coronal and sagittal views provided by this method. Noting this preoperatively can provide for discussion and collaboration with a neurosurgical consultant and possible prevention of an egregious neurological complication. Fine-needle aspiration may be attempted for pathological diagnosis; however, larger amounts of tissue are usually necessary for evaluation.

A previous diagnosis of von Recklinghausen's disease or findings consistent with this disorder (café au lait spots, cutaneous fibromata, iris hamartomas) may lend support to a diagnosis of neurofibroma or neurilemoma of the mediastinum, especially if lesions are multiple. Malignant schwannoma is associated with von Recklinghausen's disease in 40% of cases, but when a primary diagnosis of von Recklinghausen's disease is made, these tumors are noted only 4% of the time. CT scan of the abdomen should be performed as some malignant neurogenic lesions in the posterior mediastinum may represent metastases from adrenal primary tumors.

Surgical Treatment—Nerve Sheath Tumors

Neurilemoma (Schwannoma) and Neurofibroma. Both of these lesions may be easily excised via a number of approaches, but perhaps the procedure of choice for those without intraforaminal extension is thoracoscopic removal as these lesions tend to ''shell out'' from their surrounding structure and do not routinely have large feeding vessels. To prevent recurrence, clear margins should be obtained. Neurofibromas may present problems when they are multiple in the setting of von Recklinghausen's disease and when they involve the brachial plexus. In contrast to neurilemoma, these lesions may also be unencapsulated and more densely adherent to adjacent structures. If direct brachial plexus involvement exists, these lesions are termed plexiform neurofibroma, and resection should be tempered by consideration of loss of upper extremity function and the fact that major vascular structures may be involved as well. Even though these lesions may continue to grow, they will not metastasize unless malignant transformation occurs. At times these tumors may be associated only externally with the plexus structures and therefore be resectable. Negative intraoperative nerve stimulation may be useful in making this distinction.

Malignant Schwannoma. Tumors associated with von Recklinghausen's disease may be situated more centrally and be more difficult to resect than de

FIGURE 11 Neurogenic tumors in the posterior mediastinum. (a) Gangioneuroblastoma. Although larger masses such as this may be noted on a PA plain film of the chest, smaller lesions (b) may be best seen in the lateral view. (c) Chest CT of the lesion noted in (a) Arrows = tumor. [(a) and (c) from Fishman AP. Pulmonary Diseases and Disorders. New York: McGraw-Hill, 1998.]

novo tumors. They should, if possible, be completely resected to prevent recurrence and metastasis.

Surgical Treatment—Neuronal Cell Tumors

Ganglioneuroma and Ganglioneuroblastoma. Ganglioneuromas are fully differentiated neuroendocrine tumors located in the paravertebral sulcus or retroperitoneum. These tumors are common in children; however, 50% occur in adolescents and young adults. Treatment is surgical resection. Ganglioneuroblastomas are transitional tumors with ganglioneuroma and neuroblastoma components. They are less common in adults than ganglioneuroma. All tumors that do not represent adrenal metastases or primary tumors that have metastasized elsewhere should be resected.

Dumbbell Tumors. Up to 10% of posterior mediastinal tumors are categorized as dumbbell tumors due to the presence of extension of the mass into the intervertebral foramen. In adults these are most often neurilemomas or neurofibromas. As stated above, collaboration with a neurosurgeon is imperative. Surgical resection can be undertaken by one of two methods. The neurosurgeon may elect to remove the intraforaminal/paraspinal portion of the mass via a laminectomy and microsurgical dissection. Following recovery from this procedure, a thoracotomy or a thoracoscopic procedure is performed to remove the mediastinal component. Alternatively, a posterior thoracotomy adjacent to the spine may be performed overlying the interspace occupied by the mass following the development of a skin flap, and the tumor dissected free without disturbing the intraforaminal component (Fig. 12). The neurosurgeon may then perform a laminectomy and microsurgical dissection. With this approach, if the dura is opened, the paraspinal surgical field should be buttressed with a pleural, pericardial fat pad or intercostal muscle flap to prevent a cerebrospinal fluid–pleural fistula.

Complications

Complications resulting from resection of posterior mediastinal neurogenic tumors are uncommon, but can be devastating. Most severe complications result from careless removal of dumbbell lesions or inadvertent damage to various neural structures. Spinal cord compression and resultant neurological deficits can result from hemorrhage into the intervertebral foramen following removal of intrathoracic dumbbell tumors without prior laminectomy. This can also result from placing hemostatic materials into the intervertebral foramen area in an attempt to stem bleeding. This can be avoided either by laying this material over the defect rather than within or by judicious use of bipolar electrocautery taking care to remain outside the foraminal area. As mentioned above, a cerebrospinal fluid–pleural fistula may result if the dura is opened at the same setting of thoracotomy or thoracoscopy, and a vascularized pedicle flap may help prevent this. Removal

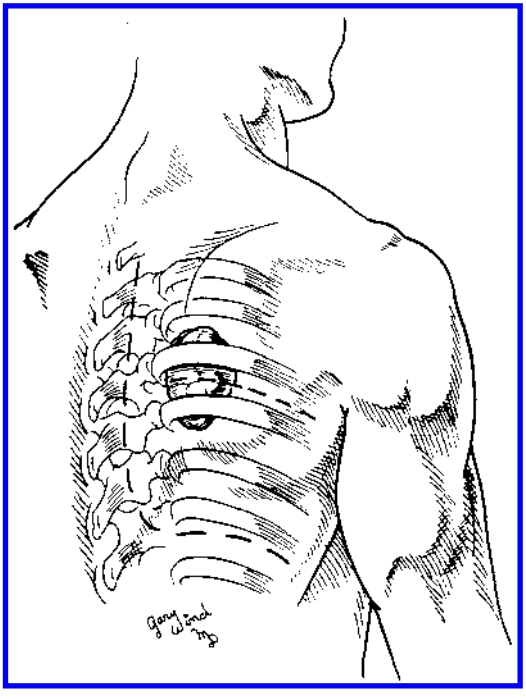

FIGURE 12 Posterior approach to "dumbbell" tumor in posterior mediastinum. (From Aisner J. Comprehensive Textbook of Thoracic Oncology. Williams & Williams, 1996.)

of several vertebral bodies or pedicles for a multilevel tumor may result in scoliosis, especially in children, if immediate reconstruction is not performed. When benign neural sheath tumors are removed, involved neural structures, especially the phrenic and brachial plexus, should be spared to prevent serious motor deficits.

Although this tumor is being covered in another chapter, one must be aware of the rare mediastinal pheochromocytoma. Manipulation of the tumor may lead to hypertensive crisis if the diagnosis is not expected and the patient is not placed on appropriate alpha and beta blockade preoperatively. One must always include in the history and physical examination questions regarding new onset of paroxysmal autonomic symptoms (headache, flushing, palpitations, diarrhea, etc.) in patients with middle and posterior mediastinal tumors.

Results and Follow-up

The prognosis of patients with benign neural sheath tumors is excellent, with virtually 100% cure with complete resection. The prognosis for malignant

schwannoma is much poorer as these tumors may be difficult to completely resect, are prone to local recurrence, and may metastasize.

Patients with the neuronal cell tumor ganglioneuroma have an excellent chance for cure with resection, and local recurrence is uncommon. The prognosis for ganglioneuroblastoma patients is actually very good with multimodality therapy for invasive phenotypes. Later age, poorer differentiation, and diffuse histology portend a poorer outcome; however, the 5-year actuarial survival with conventional therapy is still approximately 88% for all patients with this diagnosis

Tumors of Lymph Node Origin

Mediastinal lymphoma should not be considered an isolated entity, nor are there therapies specific to this location. The surgeon's role in this disease is to establish a diagnosis, as treatment consists of chemotherapy and/or radiotherapy.

MEDICAL ONCOLOGICAL MANAGEMENT OF MEDIASTINAL TUMORS

The medical oncologist will be called upon to treat patients with mediastinal tumors when surgery is not able to effect a cure. This situation will arise either due to the fact that the tumor type is by definition not surgically curable, as in the case with germ-cell tumors or lymphoma, or because the surgeon simply cannot extirpate the entire tumor volume, as is the case with some thymomas and with carcinoma of the lung. These four tumor types will account for the vast majority of patients with mediastinal tumors referred to the medical oncologist.

Lymphoma

Although any type of lymphoma might theoretically arise in or present in the mediastinum, Hodgkin's disease and two subtypes of non-Hodgkin's lymphoma, diffuse, large-cell type and lymphoblastic lymphoma, comprise the majority of lymphomas of the mediastinum. Although these lymphomas are capable of arising in any number of sites, mediastinal presentations will typically be anterior, and mediastinal lymphomas will account for approximately one-fourth of anterior mediastinal masses encountered in clinical practice.

Each of these lymphomas is managed somewhat differently in accordance with treatment guidelines specific to each subtype of lymphoma. Hodgkin's disease will present with mediastinal involvement in nearly two-thirds of cases, although a minority of these cases will be truly confined to the mediastinum. In fact, in most cases of Hodgkin's disease presenting with mediastinal involvement, other sites of disease, such as supraclavicular or cervical lymph nodes, will be apparent and thus more accessible for diagnostic purposes. On occasion, however,

Hodgkin's disease will be apparent, after an appropriate staging evaluation, only in the mediastinum, and will be considered stage I disease by the Ann Arbor staging classification.

The treatment of early-stage Hodgkin's disease is outlined in the chapter on lymphoma and, as stated in that chapter, is undergoing an evolution of sorts. As outlined in that chapter, small mediastinum-only masses of Hodgkin's disease can be treated with supervoltage radiation therapy to a ''mantle'' field with a high expectation for cure in more than 75% of patients. However, the long-term toxicities of mediastinal and mantle radiation therapy have led to the emergence of treatment programs that use chemotherapy regimens with drugs such as doxorubicin (Adriamycin), bleomycin, vinblastine, and DTIC (ABVD) for 2–6 months, followed by supervoltage radiation to more confined fields that encompass only the tumor site, avoiding the larger ''mantle'' field with its contiguous nodal sites. Such ''combined modality'' therapy appears to produce long-term results at least equivalent to those rendered by radiation therapy alone. Mediastinal masses of Hodgkin's disease that encompass more than one-third of the width of the thoracic cavity are considered too large for treatment with radiation therapy alone, and should be treated with combined chemotherapy-radiotherapy programs as outlined above, with expected cure rates in excess of 70%.

Non-Hodgkin's lymphomas of the diffuse, large-cell type of the anterior mediastinum represent a distinct clinical entity. Most diffuse, large-cell lymphomas do not present in the mediastinum and the real incidence of such mediastinal lymphomas within the larger spectrum of large-cell lymphoma is not known. These lesions present almost exclusively in the anterior mediastinum and are more capable than Hodgkin' disease of provoking airway compromise and superior vena cava obstruction. If, after an appropriate staging evaluation, the lymphoma is indeed confined to the mediastinum, patients may be treated with an abbreviated course of CHOP chemotherapy (see chapter on lymphoma) for three or four cycles, followed by supervoltage radiation to the involved mediastinal field. However, a subset of patients with mediastinal, large-cell lymphoma may have a decreased likelihood of survival, particularly when the mediastinal mass is ''bulky'' (greater than 10 cm), or accompanied by ''B'' symptoms (fever, night sweats, or loss of more than 10% of body weight). Such patients should be treated with a more extended course of chemotherapy (six to eight cycles of CHOP) with or without supplemental involved-field radiation. Radiation therapy alone does not constitute adequate therapy for patients with mediastinal large-cell lymphoma unless extreme medical circumstances forbid the safe use of chemotherapy.

Lymphoblastic lymphoma, or T-cell lymphoblastic lymphoma, is a high-grade malignant lymphoma that is uncommon in adults, and typically afflicts adolescent or young adult men. As is the case with large-cell lymphomas, these tumors are capable of producing symptoms of airway obstruction and superior

vena compression at the time of diagnosis more frequently than Hodgkin's disease. The cell of origin of this particular type of mediastinal tumor is indistinguishable from that of T-cell acute lymphoblastic leukemia. For this reason, treatment programs fashioned after those for acute lymphoblastic leukemia, utilizing complex, multidrug regimens and extended periods of ''maintenance'' chemotherapy and chemotherapeutic treatment of the central nervous system, have produced excellent long-term results in these patients. If there exists at the time of diagnosis no involvement of the bone marrow or central nervous system, up to 90% of these patients will be disease-free at 5 years. Standard CHOP chemotherapy does not constitute adequate therapy for these patients. And the value of supplemental radiation therapy in the overall management of patients with mediastinal lymphoblastic lymphoma is not known.

Germ-Cell Tumors

Germ-cell tumors arise most frequently in gonadal tissues, but the mediastinum remains the most common site of extragonadal presentation of germ-cell malignancies, accounting for 2–5% of these tumors. Germ-cell tumors account for 10–13% of mediastinal neoplasms, making them less frequent than thymoma or lymphoma, but posing a particular challenge to the medical oncologist. The mediastinal germ-cell tumor is a disease predominantly of men, with the majority of these men under age 40, most of whom will be symptomatic at the time of diagnosis.

The curative management of mature teratoma is surgical, and the medical oncologist is not typically called upon to treat these patients. However, the curative therapy of malignant germ-cell tumors of the mediastinum (seminoma in one-third of cases and nonseminoma in two-thirds) will involve the radiation oncologist in some cases and the medical oncologist in others. Mediastinal seminoma is a highly curable neoplasm when treated either with radiation therapy (with tumor doses ranging from 20 to 45 Gy) or conventional cisplatin-based chemotherapy as outlined in Table 3. When the seminoma is truly confined to the mediastinum, radiation therapy with curative intent remains the standard of care, with long-term survival of patients approaching 80%. However, when dis-

Table 3 A Representative Chemotherapy Regimen for the Treatment of Mediastinal Germ-Cell Tumors

Cisplatin 20 mg/m^2 IV daily for 5 days
Etoposide 100 mg/m^2 IV daily for 5 days
Bleomycin 30 units IV weekly on day 2, 9, 16
Four cycles of the above are administered at 21-day intervals

ease is locally extensive into adjacent lung tissue as to make radiation portals dangerously large, or when the seminoma has metastasized to extramediastinal sites, chemotherapy should be employed, with expectations for long-term survival in at least 80% of patients. Except for the incidental resection of small mediastinal seminomas, the role of surgery in the curative treatment of seminoma is doubtful.

Nonseminomatous germ-cell tumors of the mediastinum are a more virulent counterpart of mediastinal seminoma, with approximately 90% of patients having distant metastases at the time of diagnosis, as opposed to approximately 60% of mediastinal seminoma patients. The treatment of nonseminomatous germ-cell tumors requires chemotherapy utilizing a cisplatin-based chemotherapeutic regimen as shown in Table 3. The conventional application of four cycles of such therapy will bring about complete responses and long-term survival in up to half of patients. Patients who have persisting radiological abnormalities in the mediastinum, however, pose a particular challenge to the medical oncologist and thoracic surgeon. In patients who had elevated serum tumor markers at the time of diagnosis whose markers have subsequently normalized, or in patients who had no elevation of these markers, who have persisting radiological abnormalities in the mediastinum following chemotherapy, complete surgical extirpation of these persisting abnormalities should be considered. If such a resection should yield residual, viable tumor, two additional cycles of chemotherapy are recommended. Surgical resection of residual mediastinal abnormalities in seminoma patients is generally not necessary. Radiation therapy plays no role in the management of nonseminomatous mediastinal germ-cell tumors.

Thymoma

Surgical resection remains the standard approach in the curative therapy of thymoma. When completely resected thymomas are seen to invade the tumor capsule, surrounding fat, or adjacent pleura microscopically or macroscopically (stage II) or invade adjacent organs (stage III), postoperative adjuvant radiation therapy is indicated, with disease-free recurrence rates of greater than 60% at 5 years from diagnosis. In fact, radiation therapy alone may succeed in obtaining 5-year survival rates of 30–70% when tumors are only partially resected or are only biopsied and no resection is attempted. Radiation doses of 30–60 Gy have been employed in most instances, but the optimum radiation dose has not been defined. The value of chemotherapy in the treatment of invasive thymoma is less clear. The bulk of chemotherapy data has been derived in patients who have developed metastatic disease. In general, platinum-based regimens, typically including doxorubicin (Adriamycin) and cyclophosphamide as shown in Table 4, bring about responses of greater than 50%, with median survivals in responding patients of more than 3 years. The use of ‘‘neoadjuvant’’ chemotherapy prior to surgical resection has been investigated less extensively, but has confirmed the

TABLE 4 A Representative Chemotherapy Regimen in the Treatment of Locally Recurrent or Metastatic Thymoma

Cisplatin 50 mg/m^2 IV
Doxorubicin 50 mg/m^2 IV
Cyclophosphamide 500 mg/m^2 IV
Each agent is administered once every 21 days up to eight cycles

chemosensitivity of thymoma, with chemotherapy responses observed in more than 80% of patients, and median survival of more than 5 years in patients who could be completely resected. In general, chemotherapy is reserved for the palliative management of patients who have relapsed after local curative therapy or who have developed metastatic disease.

Lung Cancer

The diagnosis of non–small cell lung cancer in the mediastinum implies either direct invasion of the mediastinum (stage IIIB disease) or involvement of ipsilateral (stage IIIA) or contralateral (stage IIIB) mediastinal lymph nodes. While chemotherapy and/or radiation therapy remain the care standard for unresectable (stage IIIB) disease, the use of preoperative or postoperative chemotherapy and radiation therapy in locally advanced but resectable (stage IIIA) disease is gaining widespread acceptance. These facets of the treatment of non–small cell lung cancer are discussed in greater detail in another chapter. Likewise, the presentation of small cell lung cancer in the mediastinum, whether by direct tumor extension or mediastinal lymphadenopathy, mandates the application of systemic chemotherapy, with or without radiation therapy, as outlined in that chapter.

Other Tumor Types

The mediastinum can play host to a wide variety of neoplasms, the management of which is largely a function of surgical resectability. The medical oncological management of mediastinal tumors, which do not lend themselves to surgical resection or palliation by radiation therapy, is dictated largely by the chemotherapeutic guidelines specific to the histological type of tumor found in the mediastinum.

FUTURE DIRECTIONS

Tumors of the mediastinum present a number of future challenges to the basic scientist and clinician. Some specific examples of translational basic research

applications include the use of molecular diagnostic techniques as well as the possibility of gene therapy for mediastinal lesions.

The finding of consistent abnormalities of chromosome 12 in germ-cell tumors may yield both diagnostic and therapeutic benefit. Most germ-cell tumors possess an isochromosome of the short arm of chromosome 12 [i(12p)]. This has been noted in at least 70% of germ-cell tumors and is possibly more frequent with nonseminomatous lesions. This knowledge alone [presence of i(12p)] should now be useful as a molecular diagnostic marker in difficult-to-classify mediastinal tumors. Even though i(12p) may not exist in every germ-cell tumor, other investigators have noted uniform abnormalities in i(12p) negative tumors suggestive of a distinct overrepresentation of short arm sequences on chromosome 12. This raises the very real possibility of the presence of a dominant oncogene or some other discrete genetic lesion on chromosome 12 that could become a target for gene therapy techniques in the future.

A more traditional future trend in the treatment of mediastinal tumors is the application of new, more aggressive multimodality approaches to mediastinal tumors. In early stages, thymoma has classically been a tumor amenable to cure with surgical removal alone. However, recent reports suggest that patients previously thought unresectable can now be successfully treated with a combination of induction chemotherapy and radiation, followed by surgical resection. In a report from M. D. Anderson Cancer Center, 12 patients with Masaoka stage III or IVA tumors were treated with three courses of cyclophosphamide, doxorubicin, cisplatin, and prednisone, followed by 50–60 Gy of radiation. Eleven patients then underwent resection. All patients are alive at 7 years (median follow-up of 43 months), and in 10, no evidence of recurrence has been noted. One should maintain optimism that the future holds great promise for similar clinical results with other mediastinal malignancies as well.

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21

Oncological Emergencies

Lori Jardines
Medical College of Pennsylvania, Philadelphia, Pennsylvania

Douglas Fein
Texas Oncology, PA, Austin, Texas

Jamie Siegel
Robert Wood Johnson Medical School, New Brunswick, New Jersey

INTRODUCTION

By definition, oncological emergencies require management as soon as they are identified. A wide range of emergency conditions can occur in cancer patients and may be a direct result of the tumor, whether primary, metastatic, or recurrent disease. In addition, patients may experience toxicities of cancer treatment that manifest themselves as emergency situations. When evaluating a patient with an acute problem who has a diagnosis of cancer, it is helpful to understand the natural history of the disease and the treatment-related toxicities. The problem may not be recognized in a timely fashion so that treatment can be instituted to minimize further complications as might be seen with an unrecognized spinal cord compression. The urgency of the situation may not be appreciated soon enough to avoid an irreversible complication for the patient as might be seen with a patient who has a necrotizing soft tissue infection. In the present health care climate where cancer patients are receiving their care through general internists or family physicians, it is now necessary that a broad range of physicians and other

health care providers recognize the critical signs and symptoms of oncological emergencies.

OBSTRUCTION

The symptoms of obstruction vary with the location of the obstructive process in the gastrointestinal tract. Patients who present with esophageal or gastric obstruction require intervention but, generally, not on an emergency basis. Those who present with either a small bowel or colonic obstruction require prompt surgical evaluation and possibly emergency surgery based upon the clinical scenario.

The most common etiologies of intestinal obstruction in patients treated for intra-abdominal or pelvic malignancies are adhesions, radiation enteritis, and recurrent cancer. Patients with extra-abdominal malignancies can develop metastatic disease to the abdominal cavity manifesting as obstruction. It is important to remember that many of these patients who present with intestinal obstruction will have a benign etiology as the underlying cause of the obstruction. One cannot presume that the obstruction is secondary to recurrent cancer or carcinomatosis based solely on their history. An intestinal obstruction will be secondary to malignancy in approximately 60–75% of patients with a past history of cancer.

The most common intra-abdominal malignancy associated with intestinal obstruction is colon cancer. Other etiologies include ovarian, gastric, and pancreatic cancers as well as non-Hodgkin's lymphomas. Many of these patients have undergone previous abdominal surgery as well as radiation therapy to the abdomen or pelvis. Metastatic extra-abdominal malignancies that cause obstruction include melanoma as well as lung and breast cancers. Intussusception is an unusual cause of intestinal obstruction and has been associated with tumors that metastasize to the small bowel and include melanoma, sarcomas, renal cell carcinoma, and carcinoma of the lung.

Patients with small bowel and/or colonic obstructions may present with nausea, vomiting, abdominal distension, crampy abdominal pain, hyperactive bowel sounds, obstipation, and/or lack of flatus. The first step in the evaluation is a thorough history, physical examination, and abdominal x-rays, which include supine and erect views as well as an upright chest radiograph. When a patient cannot sit in the upright position, a left lateral decubitus film may be obtained. The diagnosis of obstruction versus ileus is made when air fluid levels are identified. In the case of long-standing obstruction, the abdomen may appear gasless as the loops of intestine are fluid filled. If the patient is obstructed and has evidence of peritonitis, leukocytosis, unexplained tachycardia, acidosis, temperature elevation, cecal dilatation measuring 10–14 cm, or free intraperitoneal air on x-ray, (s)he should have a nasogastric tube placed for decompression, receive

broad-spectrum antibiotics, be volume-resuscitated with correction of electrolyte abnormalities, and be taken to the operating room for exploration. When there is evidence of obstruction and no evidence of the above factors, the location of the obstruction should then be determined. A gastrograffin enema can be obtained to determine whether the obstruction is located in the colon and, if so, the location. The majority of patients with colonic obstruction require surgical intervention. When the obstruction is partial, a complete evaluation and bowel preparation can be performed prior to surgery. Patients with a complete colon or small bowel obstruction should be explored without delay after fluid resuscitation and correction of electrolyte abnormalities. An uncomplicated partial small bowel obstruction may resolve after a trial of nasogastric tube decompression. In the face of an unresolving partial small bowel obstruction or a history of repeated small bowel obstructions, an upper gastrointestinal (GI) series using barium may be helpful in the decision-making process. A gastrograffin upper GI series is not helpful owing to the dilution of water-soluble contrast in the fluid-filled small intestine. Patients with a past history of extra-abdominal malignancy and no history of previous abdominal surgery who present with intestinal obstruction should undergo exploratory laparotomy as there is a high likelihood the obstruction is due to metastatic disease.

At the time of exploration, the surgical interventions include lysis of adhesions, bowel resection with primary anastomosis, creation of ostomies, and/or intestinal bypass. If possible, the entire gastrointestinal tract should be evaluated as approximately 8% of patients will have both small and large bowel obstructions. When the patient has been treated with previous radiation therapy, it may only be possible to bypass the involved segment of bowel. When diffuse carcinomatosis is identified at the time of exploration, the surgical options to relieve the obstruction are limited. When no other option is available to relieve the obstruction, a palliative gastrostomy can be placed. It is controversial as to whether a feeding jejunostomy should be placed in patients with carcinomatosis or advanced cancer and in most instances, probably, should not due to the poor prognosis of the patient.

Operative mobidity ranges from 15 to 49%, and on average, the obstruction is not relieved or recurs shortly after the laparotomy in 15% (range 4–45%). Only 35% of patients with malignant obstruction will obtain lasting relief and the vast majority of them have a life span of only months. On average, operative mortality is 19% with a range of 9–35%. Over half of the patients in whom the obstruction is relieved and who are discharged from the hospital report good to excellent quality of life. In patients who undergo exploration for obstruction with a known diagnosis of carcinomatosis, the operative mortality is higher; therefore, those patients would be better served with a percutaneous endoscopic gastrostomy tube if palliation from obstruction is necessary. Some have advocated the use of home parenteral nutrition when the obstruction could not be relieved.

INTESTINAL PERFORATION

In most instances, patients with a perforated viscus have a dramatic presentation with severe abdominal pain. On physical examination, the abdomen is generally distended and quiet and there are peritoneal findings. In addition, the patient may have fever and tachycardia and hypotension secondary to hypovolemia due to third space losses. Either an upright chest x-ray or a left lateral decubitus film will most often demonstrate the presence of free intra-abdominal air. Patients who are neutropenic or taking steroids may have a more subtle presentation of a perforated viscus and one must have a high index of suspicion when evaluating this population. When the diagnosis of intestinal perforation is made, nearly all patients should be explored after fluid resuscitation and correction of electrolytes.

In patients with a diagnosis of cancer, intestinal perforation may be secondary to benign disease or treatment-related toxicities as well as primary, recurrent, or metastatic disease. When the perforation is due to a benign etiology, it is most often due to either peptic ulcer disease or diverticulitis. Approximately 3–8% of patients with colon cancer develop intestinal perforation and an obstructing lesion involving the left colon may present as a cecal perforation. Patients with mural involvement of non-Hodgkin's lymphoma may spontaneously perforate an involved area of the gastrointestinal tract or the perforation can occur as the disease responds to chemotherapy. Neutropenic enterocolitis may progress and lead to intestinal perforation, which can be difficult to diagnose. In addition, immunocompromised patients can develop severe viral or bacterial infections involving the gastrointestinal tract, resulting in perforation. Metastatic cancers, such as breast, lung, kidney cancers, and melanoma, can spread to involve the bowel wall and ultimately perforate.

Broad-spectrum antibiotics should be administered prior to exploration. When the abdomen is entered, aerobic and anaerobic swabs should be obtained for gram stain and culture with bacterial sensitivities. The surgical therapy will depend upon the intraoperative findings and the segment of perforated bowel should be resected. When a benign condition such as a perforated duodenal ulcer or diverticular disease is encountered, it should be treated in the standard fashion. The decision to restore continuity of the gastrointestinal tract should be weighed against many factors, including the general condition of the patient (including nutritional status), the degree of intra-abdominal contamination, whether the patient is receiving steroids, and the stability of the patient intraoperatively. After resection, ostomies can be created when it is not safe to perform a primary anastomosis. A gastrostomy can be placed at the time of surgery to avoid the use of a long-standing nasogastric tube seconary to prolonged ileus. In addition, in the appropriate clinical situation, a feeding jejunostomy should be placed to begin early enteral feedings and avoid the prolonged use of hyperalimentation or the

use of nasoduodenal feeding tubes. This can often be accomplished by placing a combined gastrostomy-jejunostomy tube. These tubes may also be used to decompress the bowel prior to beginning enteral feedings.

At the completion of the surgical procedure, the abdomen should be copiously irrigated to reduce contamination and carefully inspected for bleeding. Hemostasis may be difficult to achieve particularly when the patient is thrombocytopenic or has a coagulopathy. Consideration should be given to utilizing retention sutures to avoid evisceration as many of these patients are nutritionally depleted and are at higher risk for wound complications. The skin should be allowed to heal by a delayed primary closure to reduce the likelihood of wound complications. Operative mortality ranges from 30 to 40% and is related the degree of peritonitis, sepsis, and stage of the disease.

HEMORRHAGE

Massive hemorrhage secondary to cancer is an uncommon event, and when it occurs in a patient with a known diagnosis of cancer, it is usually secondary to a benign cause. Hemorrhage is also seen as a complication of cancer therapy, which includes thrombocytopenia secondary to chemotherapy or invasive procedures, such as a percutaneous liver biopsy. Hemorrhage secondary to malignancy can occur as a consequence of the primary tumor, such as a lymphoma involving the gastrointestinal tract, or from metastatic deposits to the gut mucosa. Tumors may erode into blood vessels and may first manifest themselves by a sentinel bleed followed by massive hemorrhage. Hemorrhage into the free peritoneal cavity is seen with hepatomas and presents as cardiovascular instability and abdominal distension. Retroperitoneal bleeding may also be seen in patients with a diagnosis of cancer and should be considered when there is evidence of blood loss that is not from the gastrointestinal tract.

Generally, the approach to a patient with a known diagnosis of cancer and spontaneous massive hemorrhage is similar to that of a patient with no history of malignancy and depends upon the stability of the patient. For those patients receiving chemotherapy or with advanced disease, thrombocytopenia or clotting factor coagulopathy should be considered and the appropriate blood work should be sent to determine the platelet count and PT/PTT. The hemorrhage may be controlled by replacing platelets or clotting factors.

Large-bore intravenous lines should be placed to volume-resuscitate the patient with crystalloid and, if necessary, blood products should be administered. Hematemesis or bloody nasogastric tube aspirate suggests bleeding proximal to the ligament of Treitz, which should prompt upper GI endoscopy for diagnosis and possible treatment. When findings are suggestive of a colonic source, colonoscopy may be helpful in localizing the lesion. Angiography or a nuclear medicine–tagged red blood cell scan may be necessary to localize the source of bleed-

ing, particularly from a colonic or small bowel source. In some instances, hemorrhage can be controlled with angiography and embolization of the bleeding site or the administration of vasopressin. The decision to use nonoperative measures to manage hemorrhage will depend upon the patient and the clinical situation.

INFECTION/SEPSIS

Catheter-Related Sepsis

Semipermanent indwelling catheters are a necessity for patients undergoing cancer treatment. They are most commonly used for the delivery of chemotherapy, blood products, total parenteral nutrition, and hydration as well as for patients who require frequent laboratory studies. Hickman catheters are more commonly used in patients requiring bone marrow transplantation/autologous stem cell reinfusion and with hematological malignancies. Patients with solid tumors are more likely to have a port inserted. The incidence of infection is higher in Hickman-type sialastic tunneled catheters when compared to completely implanted subcutaneous ports. The most common complication of indwelling catheters is bacteremia or fungemia, which is most often manifested by sepsis. Other sites of infection include the port pocket, exit site, and tunnel tract.

When a patient with an indwelling catheter manifests signs of sepsis, the catheter site must be carefully evaluated. Blood cultures should be drawn via the catheter and from a peripheral vein. A wide variety of organisms have been associated with catheter-related infections. Gram-negative rods account for 55% of Hickman catheter–associated bacteremia whereas coagulase-negative staphylococci cause 65.5% of the port-related bacteremias. Gram-positive bacilli, fungi, and mycobacteria have been isolated from the blood of patients with ports and Hickman-type catheters. The most common organism seen in port pocket infections is *Staphylococcus aureus*. Catheter site infections without associated bacteremia are most commonly caused by gram-positive cocci.

A 10–14-day course of intravenous antibiotic through the infected line is commonly used to treat catheter-related bacteremia with success in over three-quarters of the cases. Infections involving the tunnel of a Hickman catheter required removal in 94% of patients. With infections associated with subcutaneous ports, 52% required removal for sepsis, 33% for port pocket cellulitis, and 100% for port pocket infection.

In the face of infection, an indwelling catheter should be removed when there is evidence of a port pocket infection, failure of culture-specific antibiotics, hemodynamic instability in suspected sepsis or fulminant sepsis, or evidence of septic emboli. Rarely, necrotizing soft tissue infections are seen with indwelling catheters and are most often associated with patients who are severely immuno-

suppressed. In those instances, the catheter should be removed and the insertion site debrided. With recurrent infection with the same organism or fungal infection without fungemia or sepsis, consideration should be given to removing the subcutaneous intravenous access device.

Fulminant Soft Tissue Infections

Necrotizing soft tissue infections are not common in the cancer patient and occur most often in patients being treated for lymphoproliferative or myeloproliferative diseases. The presence of a necrotizing soft tissue infection is a surgical emergency as this process progresses rapidly. Death may occur hours after the diagnosis is made secondary to the infection and the underlying malignancy.

Physical examination generally underestimates the extent of the problem. When the patient is profoundly neutropenic, no pus will be formed despite the active infection. For these reasons, the diagnosis may not be made in a timely fashion adding to the morbidity. Crepitation in the soft tissue may be present when there are gas-forming organisms and may alert the examiner to the presence of a serious soft tissue infection.

Broad-spectrum antibiotics should be administered preoperatively and should cover aerobic and anaerobic gram-positive and gram-negative organisms. Simultaneously, the patient should be fluid-resuscitated and then taken to the operating room for wide debridement. The debridement must extend to viable tissue and patients most often return to the operating room for dressing changes and additional debridement. These infections can occur after minor trauma, as a consequence of an anorectal infection, at the site of an indwelling venous access catheter, or after laparotomy. The risk for developing Fournier's gangrene is increased in the face of neutropenia, pelvic irradiation, diabetes mellitus, and atherosclerosis. In some instances, no obvious cause can be identified other than the underlying malignancy and neutropenia.

Anorectal Disease

Anorectal disease is not uncommon in patients with a diagnosis of cancer secondary to altered bowel habits and can be managed in the usual way unless the patient is neutropenic (absolute neutrophil count $<500/mm^3$). The diagnosis and treatment of anorectal problems becomes more complex in the face of neutropenia. The patient may complain of severe pain in the perirectal area. On examination, there may be evidence of a thrombosed hemorrhoid, an anal fissure, or edema; however, in many neutropenic patients, the examination of the region is often unremarkable. Computerized tomography (CT) of the region can be helpful in the evaluation. When there is evidence of inflammation on CT scan without evidence of abscess formation, high-dose broad-spectrum intravenous antibiotics

are indicated. When an abscess is identified, surgical incision and drainage is required.

NEUTROPENIC ENTEROCOLITIS

Neutropenic enterocolitis, necrotizing enteropathy, ileocecal syndrome, and typhlitis are all terms that describe the same clinical entity. It is seen in patients with severe neutropenia related to the disease or its treatment. Neutropenic enterocolitis has most often been associated with leukemia but has also been seen in patients with myelodysplastic syndrome, multiple myeloma, aplastic anemia, AIDS, and following organ or bone marrow transplantation. It has recently been described as a complication of paclitaxel and doxorubicin chemotherapy for metastatic breast cancer. Neutropenic enterocolitis may also be the cause of recurrent bacterial sepsis in the neutropenic patient during the course of therapy.

The true incidence of neutropenic enterocolitis is not known and the incidence has ranged from 10 to 46% in autopsy series in patients with leukemia. The pathology is often limited to the terminal ileum, cecum, appendix, and the ascending colon. The initial presentation of neutropenic enterocolitis may mimic appendicitis and patients may have fever, nausea, vomiting, abdominal distension, diarrhea, and right-sided abdominal pain with tenderness. Abdominal x-rays often reveal an ileus pattern and are useful in excluding the presence of free intra-abdominal air. A CT scan of the abdomen is useful to exclude other intra-abdominal pathology and may demonstrate only edema and thickening of the bowel wall. Abdominal ultrasound has also been used as an imaging modality in neutropenic enterocolitis and may be most useful for follow-up of known cases. When diarrhea is present, stool cultures and a stool sample for *Clostridium difficile* toxin should be evaluated to exclude other diagnoses.

The treatment, ranging from supportive care with bowel rest and decompression, intravenous antibiotics, and total parenteral nutrition to surgical resection, will depend upon the clinical situation; however, most patients respond to medical management. Recovery is most often associated with resolution of the neutropenia. Surgery is indicated when there is evidence of perforation, uncontrolled sepsis despite aggressive medical management, or when the diagnosis is questionable. At the time of surgery, the affected bowel is removed and an ileostomy is created. No attempt should be made to restore gastrointestinal continuity.

SPINAL CORD COMPRESSION

Spinal cord compression develops in 1–5% of patients with metastatic disease. A total of 18,000–20,000 cases of spinal cord compression are diagnosed in the United States each year. Cord compression is second to brain metastases as the most frequent neurological complication of cancer. It is regarded as an oncologi-

cal emergency as a delay in diagnosis and treatment may result in irreversible bowel and bladder dysfunction as well as paralysis. Most cases of spinal cord compression are due to extramedullary metastases. The metastatic deposit produces occlusion of the venous and arterial vessels of the spinal cord leading eventually to spinal cord edema, ischemia, and infarction. The most frequent tumors causing spinal cord compression in decreasing order of frequency are: breast, lung, lymphoma, prostate, sarcoma, myeloma, and kidney. It involves the thoracic spine in approximately 70% of cases, the lumbosacral spine in 20%, and the cervical spine in 10%.

The most frequent presenting sign and symptom is pain, which can often be localized to the spine on physical examination. Muscle weakness is the second most common presenting sign and most often affects the proximal muscles. Eventually symptoms of bladder and bowel dysfunction, as well as paralysis, are recognized, which often suggests the irreversible nature of the spinal cord compression. The pretreatment neurological status is the most important predictor of outcome. Physical findings often include vertebral body discomfort, muscle spasticity, and sensory loss below the level of the cord compression, which may be helpful in diagnosing the level of impingement. Recognition of the sensory dermatome level is essential if one is to clinically determine the level of spinal cord compression.

In general, spinal cord compression can be divided into two distinct types of presenting symptoms with dramatically different outcomes. In one type of presentation the sensory radiculopathy precedes the muscle weakness by a significant period of time, i.e., months. This slow onset of symptoms tends to lead to a more favorable outcome following the administration of steroids and radiation therapy. In the second type of presentation, which is markedly more ominous, both sensory and motor dysfunction occur rapidly. As a result, the patient often presents with paraplegia as well as bowel and bladder dysfunction. Paraplegia often signifies spinal cord infarction, which is irreversible.

The initial step in evaluating the patient should be a thorough history and physical examination with particular attention paid to the neurological evaluation. The gold standard and the study of choice in the diagnosis and localization of spinal cord compression is the magnetic resonance imaging (MRI) scan, which has now replaced both the CT scan and myelogram. The sensitivity and specificity of MRI for extradural masses causing spinal cord compression are 92% and 90%, respectively. At institutions where an MRI is not available, a CT scan or myelogram should be performed. Multiple levels of spinal cord compression are appreciated in 20% of patients.

Following the diagnosis of spinal cord compression, all patients should be started on a course of corticosteroids such as dexamethosone 4 mg every 6 hr, which may lead to both an immediate improvement in neurological dysfunction and a reduction in pain. Some clinicians advocate the use of high-dose steroids,

although there has not been sufficient investigative effort to determine whether high-dose or low-dose steroids are more beneficial. Some investigators have demonstrated a more rapid decrease in discomfort with the use of high-dose steroids. The steroids should be tapered during the course of treatment, particularly if improvement is noted. If the patient's symptoms progress following discontinuation of steroids, this therapy should be reinstituted. It is not necessary to continue steroids throughout treatment with radiation therapy.

The goal of treatment is the recovery of normal neurological function as well as relief of pain. The treatment of choice is radiation therapy, which often provides rapid relief of both the discomfort and neurological compromise. The histology and radiosensitivity of the tumor are also important in determining outcome as both the response and the duration of the response have been correlated with histology. Radiosensitive tumors, which include breast, prostate, lymphoma, seminoma, small cell carcinoma, and myeloma, are associated with a more rapid reversal of neurological symptoms as well as improved survival when compared to radioresistant tumors, which include renal cell carcinoma and melanoma. Lymphomas and myelomas respond more quickly and predictably to a course of radiation therapy than do carcinomas.

The results of treating a patient with spinal cord compression are primarily associated with the degree of symptoms at presentation. When patients with cord compression have minimal neurological symptoms, the vast majority maintain their ability to walk and their sphincter function. In cases where there is neurological impairment, treatment improves motor and sphincter function. When patients present with muscle weakness, approximately 35% of them will have sufficient resolution of their symptoms to become ambulatory again after treatment. In patients who present with paraplegia, only 10% regain their ability to ambulate. The clinical outcome is also largely dependent not only upon the severity of symptoms but also the rapidity of onset. Recovery of motor function is greater in patients who experience a slow, rather than rapid, loss of motor function. Therefore, the primary goal of the radiation oncologist must be to irradiate the patient before paraplegia occurs, which is often dependent on other clinicians recognizing the cord compression and referring the patient for evaluation and treatment. As paraplegia is reversed in a small fraction of patients, this condition clearly represents a true emergency situation for radiation oncologists. Approximately one-quarter of patients will be alive at 1 year and the median survival is approximately 6 months after radiation therapy for spinal cord metastases. In addition, it has been reported that 7.5% of patients with a history of spinal cord compression develop a second episode of spinal cord compression in new locations within the spinal canal.

For treatment of a patient with spinal cord compression, the radiation volume should include the area of spinal cord or epidural compression plus two vertebral bodies both inferiorly and superiorly as 64% of patients who suffer a

recurrence within 3 months of radiation therapy experience it within two vertebral bodies of the spinal cord compression. Ideally, an MRI of the entire spine should be obtained prior to initiation of treatment as in 10–30% of cases there is an additional area of spinal cord compression. The radiation dose and fractionation scheme must take into account the size of the field irradiated as well as the radiosensitivity of the tumor. Larger field sizes are typically irradiated with a lower dose per fraction than smaller field sizes owing to an increase in acute toxicity associated with the larger irradiated volume.

In general, cord compression of the cervical spine should be treated with lateral opposed fields to spare the larynx and as much pharyngeal mucosa as possible. Lesions of the thoracic spine may be treated with a single posterior field (unless a ''hot'' spot of greater than 110% results in which case it would be better treated with opposed anterior and posterior fields) while compression of the lumbosacral spine is best treated with opposed anterior and posterior fields. Photons should be used as they typically provide the most homogeneous dose distribution. In order not to underdose the area of cord compression it is customary to prescribe the dose to the anterior edge of the vertebral body. The depth of the anterior extent of the vertebral body, as well as the depth of spinal cord, can be determined by obtaining a lateral film of the treatment area. Typical doses with small to moderate size fields include 3000 cGy in 10 fractions as well as a more abbreviated regimen of 2000 cGy in five fractions. To minimize acute morbidity larger field sizes may be irradiated with smaller doses per fraction to a total of 4000 cGy in 20 fractions or 4500 cGy in 25 fractions. Histology should also be considered when deciding on the total radiation therapy dose as well as the dose per fraction. The more radiosensitive tumors such as lymphoma and seminoma may be adequately treated with doses of 2500 cGy while the more radioresistant tumors such as melanoma may require a higher total dose. Overall, radiation therapy is successful in reducing pain in 70% of cases and improving motor dysfunction in 50% of cases.

An alternative to radiation therapy is surgical decompression, although radiation therapy does remain the treatment of choice in most situations. In particular, surgical resection should be entertained if (1) the patient has already received the maximum tolerable dose to the spinal cord and further radiation would place him at significant risk of transverse myelitis, (2) he has no history of cancer, (3) he has a tumor that has previously been demonstrated in the same individual to be radioresistant, or (4) a CT scan or MRI reveals a bony fragment(s) in the spinal canal or a collapsed vertebral body. For cases in which there is no pathological diagnosis of cancer one should consider a fluoroscopic or CT-guided percutaneous vertebral body biopsy. This may be effectively accomplished with minimal morbidity by using a paraspinal or transpedicular approach to place the needle.

The tumor typically compresses the anterior aspect of the spinal cord as the tumor usually involves the vertebral body. An important surgical premise is

that the surgical decompression should be managed from the side of the cord compression. Laminectomy should be confined to posterior tumors only as they offer poor exposure and very little benefit for anterior tumors. For anteriorly located tumors anterior decompression with mechanical stabilization has replaced laminectomy as the surgical treatment of choice in this situation. Usually this procedure is accomplished via a thoractomy or retroperitoneal approach. The involved vertebral body is removed, replaced with methylmethacrylate, and a metal prosthesis that attaches to adjacent vertebral bodies is placed for additional stabilization. Although results with anterior decompression with mechanical stabilization have been very good, it is limited to patients in good overall medical condition who present with spinal cord compression from anteriorly located tumors. In addition, attaching the metal prosthesis to adjacent vertebral bodies requires that they are strong and not completely infiltrated with tumor.

In the past, some groups have advocated using a combination of laminenctomy and radiation therapy. The retrospective studies and single prospective study have not indicated an advantage to laminectomy and radiation therapy over radiation therapy alone. There has been one prospective study involving only 29 patients, which suggests that laminectomy does not add to the efficacy of radiation therapy in the setting of spinal cord compression.

In some instances treatment with chemotherapy may be the treatment of choice. The use of chemotherapy in the treatment of spinal cord compression is largely confined to young children where physicians are concerned about the development of radiation-induced neoplasms or impaired bone growth. Chemotherapy has been used with excellent results to treat neuroblastoma and Ewing's sarcoma, both of which are chemosensitive tumors. If the symptoms progress, the patient should be treated with radiation therapy or laminectomy.

SUPERIOR VENA CAVA SYNDROME

Superior vena cava syndrome (SVCS) is a common and well-recognized occurrence among cancer patients and can result in such life-threatening events as cerebral or laryngeal edema. It is caused by the obstruction of blood through the superior vena cava, which begins at the innominate veins and extends to the right atrium. The superior vena cava is located in the middle of the mediastinum and is surrounded by rigid, immobile structures such as the right mainstem bronchus, the hilar nodes, trachea, aorta, and pulmonary artery. Of significance, the azygous vein enters the superior vena cava posteriorly and provides an important venous collateral pathway for decompression. Nodes surround the superior vena cava and can produce SVCS by external compression. These nodes include the subcarinal, perihilar, and paratracheal nodes, which serve to drain the right lung and the lower lobe of the left lung.

The cause of SVCS has changed significantly. Forty years ago, 67% of

SVCS cases were associated with benign conditions while one-third were secondary to malignancy. Currently, 85–95% of cases of SVCS are due to malignancy while benign conditions are responsible for only 5–15% of cases. Intrathoracic malignancies account for 80–90% of cases of SVCS and lung cancer accounts for 70% of them. Among the lung cancers, small cell carcinoma accounts for 40% of cases, squamous cell carcinoma accounts for 25%, adenocarcinoma accounts for 15%, and large cell carcinoma accounts for 10%.

In 2.4% of all lung cancers, SVCS is the initial presentation. This compares to a 10–20% rate of SVCS seen at presentation among patients with small cell carcinoma. Lymphomas account for approximately 10% of the cases of SVCS. The non-Hodgkin's lymphomas are a far more frequent cause of SVCS than Hodgkin's disease. The most common non-Hodgkin's lymphoma causing SVCS is diffuse large cell responsible for 65% of cases. The malignancy is typically in the anterior mediastinum and causes SCVS by extrinsic compression. Solid tumors that have metastasized to the mediastinum have also been associated with SVCS at presentation.

Overall, SVCS develops in 3–15% of patients with a history of lung cancer and it is about 4 times more common in right-sided tumors than in left-sided ones. The SVCS is more frequently caused by nodal disease rather than the primary tumor. In 3–8% of cases, lymphomas can cause SVCS and this is most often secondary to disease involving the anterior mediastinum. Of the solid tumors that metastasize to the mediastinum the most common are breast and testicular carcinoma, which comprise approximately 5% of all cases of SVCS.

Thrombosis may be the cause of SVCS in up to 7% of cancer patients. Thrombosis may occur secondary to indwelling central venous catheter, obstruction, decreased flow, the associated hypercoagulable state of malignancy, or any combination of these factors. Other nonmalignant causes of SVCS include idiopathic causes, silicosis, sarcoidosis, syphilis, infection, actinomycosis, dermoid cyst, benign teratoma, mediastinal fibrosis sometimes secondary to radiation therapy, histoplasmosis, aortic aneurysm, thyroid goiter, and cystic hygroma. In some series, SVCS has been attributed to nonmalignant causes in up to 20% of cases.

Typical presenting symptoms from SVCS in decreasing frequency include dyspnea (60%), facial edema (50%), and cough (20%). Other symptoms include orthopnea, hoarseness if there is compression of the recurrent laryngeal nerve, dysphagia if there is compression of the esophagus, syncope, dizziness, headaches, and tachypnea. Common physical findings include venous distention of the neck (65%), venous dilatation of the chest wall due to collateral vein filling (55%), facial edema (45%), cyanosis (20%), plethora of the face (20%), and edema of the arms (15%). The degree of symptoms is related to the extent of obstruction. Life-threatening complications include laryngeal or cerebral edema. Some patients report that symptoms are exacerbated by bending over.

The tumor is best localized by CT scan and chest x-ray. The classic findings

on chest x-ray are superior mediastinal widening, the presence of a pleural effusion, and a right hilar mass. The CT scan is able to depict the extent and probable cause of the SVCS including extrinsic compression, intraluminal thrombosis, or encasement. In addition, the CT scan will typically reveal collateral circulation including the internal mammary, azygous, or thoracic wall veins. A CT scan also enables the radiation oncologist to more accurately plan the radiation therapy portals to ensure that all disease is encompassed. MRI should still be considered experimental in the workup of SVCS as sufficient data have not been acquired to date. The cause of the SVCS cannot be demonstrated by either venography or scintiangiography. Venography does offer the advantage of enabling the clinician to determine whether the vena cava is completely or only partially obstructed, which cannot be determined by a CT scan. It may also play a role if surgical bypass is considered. Another essential feature of CT is that it can help determine the least invasive means of obtaining histological diagnosis. Verification of tumor histology is essential and should be accomplished in the least invasive manner. The diagnosis may be confirmed by sputum cytology, supraclavicular node biopsy, bronchoscopy, bone marrow biopsy particularly for small cell carcinoma and non-Hodgkin's lymphoma, CT-guided biopsy, thoracentesis in the presence of a pleural effusion, or mediastinoscopy. Thoracotomy is sometimes necessary to obtain a definitive diagnosis and rule out nonmalignant causes, particularly if all other procedures have failed to produce a diagnosis.

Treatment options are numerous and depend primarily on the etiology of the SVCS. It is imperative that the physician understands that SVCS is an emergency and that treatment must be initiated as soon as possible. In cases where there is no definitive pathology one should consider steroids or diuretics, which are often successful in delaying disease and symptomatic progression until a definitive diagnosis can be obtained. As the types of available treatments are so variable it is usually prudent to wait until pathology is available before embarking on treatment. One should only consider emergent radiation therapy without a definitive pathological diagnosis if life-threatening cerebral or laryngeal edema is present. Traditional treatment for SVCS has included chemotherapy and/or radiotherapy. Other treatment options depending on the causative etiology include surgical bypass, balloon angioplasty, thrombolytic therapy, and expandable wire stents.

Once a diagnosis of cancer is obtained the decision to treat with radiation therapy and/or chemotherapy is in large part dependent on the pathology and the tumor sensitivity to either chemotherapy or radiation therapy. Tumors, such as non-small cell lung cancer, that are more resistant to immediate tumor reduction with chemotherapy should be considered for emergent treatment with radiation therapy. On the other hand, tumors that are exquisitely chemosensitive such as lymphomas should be treated with the appropriate drug therapy $\pm$ radiation therapy. Patients with small cell lung cancer should be considered for aggressive

treatment with combination chemoradiation. Studies have demonstrated that presence of SVCS in small cell carcinoma does not lead to a worse prognosis over patients who do not present with SVCS.

Interventional radiological techniques have been successful in treating patients with SVCS. If the SVCS is secondary to thrombosis, thrombolytic therapy with streptokinase, urokinase, or tissue plasminogen activator has been successful. Treatment with a thrombolytic agent should be initiated as soon as possible after the diagnosis is made. The use of endovascular stenting for palliation of the symptoms of SVCS has also been effective. Its use will likely be for patients who have tumor unresponsive to chemotherapy or radiation therapy. The response to stenting is more immediate and may be necessary for patients with extreme symptoms and/or those who cannot tolerate the time required for the effects of specific antitumor therapy to occur. The use of anticoagulation after stenting remains controversial but appears to prevent stent thrombosis in patients who present with clot or have significant residual narrowing. The complications associated with stenting are few.

When the decision is made to employ radiation therapy for cure, the setting doses should be similar to that which would be employed without SVCS for the appropriate histology. The radiation oncologist should consider several high doses per fraction (i.e., 300–400 cGy) followed by a more conventional fractionation scheme (180–200 cGy per fraction). This treatment approach was applied in 125 patients with 79% having a diagnosis of lung cancer. Forty-six patients received 300–400 cGy per fraction for the first three treatments while 79 patients were treated at 200 cGy per fraction. Patients treated at the higher dose per fraction responded quicker with 70% demonstrating a good response within 2 weeks compared to 56% of patients who were treated at the lower dose per fraction. Patients should receive conventional total doses of radiation therapy. For instance, doses for non-small cell carcinoma should be approximately 6000 cGy, while doses for small cell carcinoma should be around 5000 cGy. Lymphomas are typically irradiated to doses of 3000–4000 cGy. Palliative doses typically range from an abbreviated course of 2000 cGy in 1 week to a more prolonged fractionation scheme of 5000 cGy in 5 weeks. Most patients experience a very rapid response to radiation therapy with quick resolution of the venous distention and edema as well as a clear radiographic response.

Treatment with chemotherapy $\pm$ radiation therapy should be considered the treatment of choice for small cell carcinoma and non-Hodgkin's lymphoma. One should utilize typical drug regimens such as CHOP for non-Hodgkin's lymphoma and etoposide/cisplatin for small cell carcinoma with typical dose intensity. When appropriate, such as in the treatment of small cell carcinoma, concurrent radiation therapy should be employed.

The prognosis for individuals who present with SVCS is largely dependent upon the underlying cause or histology of the condition producing the syndrome.

THROMBOTIC COMPLICATIONS

The association between thrombosis and malignancy has been recognized at least since 1865 when Armand Trousseau described the association between migratory thrombophlebitis and occult malignancy. A report in the 1960s described one hospital's population of patients; 6% of the patients admitted with venous thrombosis were found to have a malignancy. In 1981, the first report of an unusually high incidence of thrombosis in women receiving adjuvant chemotherapy for breast cancer was published. Thrombosis was also later shown to occur at a high rate in women with metastatic breast cancer receiving chemotherapy. Tamoxifen added to chemotherapy has been shown to increase the risk of thrombosis from 1.4% to 12.5%.

The pathophysiology of thrombosis was characterized by Rudolf Virchow as a triad: hypercoagulability of blood, venous endothelial damage, and venous stasis. Malignancy may result in changes in the blood composition, result in damage to the vessel wall, and contribute to blood flow disturbances because of tumor compression, immobilization, or hyperviscosity. Additional risk factors for thrombosis include surgery, chemotherapy, hormonal therapy, and central venous catheters. Management principles in venous and arterial thromboembolism in patients with malignancy are undergoing modification. Previous concerns about the risks of bleeding, while valid, are now balanced against concerns regarding the morbidity and mortality of untreated thrombosis.

The malignancies classically associated with coagulation system abnormalities leading to either thrombosis or disseminated intravascular coagulation (DIC) include the mucin-secreting adenocarcinomas, prostatic carcinoma, and primary central nervous system cancers. In promyelocytic leukemia, malignant promyelocytes release procoagulant substances. Patients may present with venous thromboembolism or bleeding from the thrombocytopenia associated with DIC or marrow infiltration. The myeloproliferative disorders, essential thrombocytosis, polycythemia vera, and paroxysmal nocturnal hemoglobinuria may present with or be complicated by the Budd-Chiari syndrome (hepatic vein thrombosis).

Venous Thromboembolism

The clinical diagnosis and subsequent evaluation of deep venous thrombosis (DVT) and pulmonary embolism in patients with malignancy may be complicated by the underlying condition. Lower extremity edema may have already been present secondary to malignant obstruction or nutritional deficiencies. A change in symptoms or physical examination would alert the clinician to pursue the diagnosis further with radiographic studies. Acute onset of shortness of breath or chest pain needs to be differentiated from a new rib fracture, congestive heart failure, or pleural effusion. A chest x-ray should be obtained to rule out other etiologies

of the symptoms. If the chest film is negative or if the index of suspicion for pulmonary embolism is high, a ventilation-perfusion scan should be obtained to aid in the diagnosis. In some instances, it is necessary to proceed with pulmonary angiography to establish the diagnosis and this study remains the gold standard.

The optimal therapy for venous thromboembolic disease (VTE) is to begin heparin at a dose that would achieve a therapeutic aPTT within 24 hr. Weight-based dosing is the preferred method of prescribing heparin and is ideal in patients with malignancy who may have had considerable weight loss. The weight-based dosing regimen is an intravenous heparin bolus of 80 units/kg, followed by an infusion at 18 units/kg/hr. An aPTT must be checked 6 hr after the bolus and every 6 hr until it is first stable in the therapeutic range and then confirmed again 6 hr later. Heparin is continued for at least 5 days to overlap with the warfarin; it is continued longer for massive pulmonary embolism or ileofemoral thrombosis.

Warfarin is started only after the aPTT is in the therapeutic range and should be given in a dose no greater than 5 mg. Long-term therapy with warfarin is then continued. There is no increased rate of bleeding complications in patients with malignancy as compared to patients without malignancy when the international normalized ratio (INR) is maintained in the therapeutic range. The therapeutic INR to be achieved is between 2.0 and 3.0. Warfarin should be continued as long as the original stimulus remains present, whether it is the cancer, chemotherapy, or hormonal therapy.

Low-molecular-weight heparin (LMWH) may replace the use of unfractionated heparin as it can be given on an outpatient basis and is administered by subcutaneous injection in a weight-based dose. The dosage is different for different formulations of the drug and the dispensing pharmacy should be consulted for the proper dose. Preliminary information reveals a subset of patients with cancer who received LMWH had a lower overall mortality rate not attributable to bleeding or thrombosis when compared to patients receiving unfractionated heparin. This is now being investigated further.

Recurrent thrombosis on therapeutic doses of warfarin occurs more often in patients with malignancy than in patients without malignancy. Optimal management of these patients has not been determined. Alternatives include LMWH or dose-adjusted subcutaneous unfractionated heparin. Vena caval interruption may be necessary.

Management of VTE in patients with malignancy in the central nervous system is controversial. Excessive bleeding in these patients remains a concern but the high rate of VTE in these patients and the unexpected rate of complications from the vena caval filter needs to be considered. One retrospective review in patients with brain tumors demonstrated a high rate (62% with a 95% CI) of recurrent embolism, progressive thrombosis, or other complication from the vena caval filter. Low-dose heparin or low-molecular-weight heparin should be consid-

ered. The exception would be patients with hemorrhagic brain metastases, usually seen with melanoma and renal cell cancer. Further study is necessary to determine the optimal therapy in this group of patients.

The use of inferior vena cava filters should be reserved for situations when heparin cannot be given either because of bleeding present, because of a clearly documented and recognizable risk for bleeding, or if heparin thrombocytopenia is suspected and lower extremity thrombosis is documented. Inferior vena cava filters are also indicated when recurrent thrombosis or embolization occurs despite adequate anticoagulation.

Thrombolytic therapy is absolutely contraindicated when an intracranial lesion or active bleeding is present. Other contraindications include pericardial tumor, the postoperative state, recent thoracentesis or paracentesis, gastrointestinal lesions, and an underlying bleeding diathesis including thrombocytopenia.

Prevention of Venous Thromboembolism

Patients with malignancy have an increased risk of developing VTE after major surgery. The general recommendation for patients who are older than 40 years, undergoing major operations, and have additional risk factors is unfractionated heparin at a dose of 5000 units subcutaneously every 8 hr (LMWH). In very high risk patients, it is recommended that intermittent pneumatic compression (IPC) be added to the prophylactic regimen. It is also recommended that the anticoagulant be given preoperatively. IPC can be used as an alternative for patients who cannot receive heparin anticoagulation. Heparin anticoagulation would be contraindicated if there is a history of heparin-associated thrombocytopenia or if the patient has an active bleeding site.

While DVT prophylaxis for surgery has been well demonstrated and is widely used, the use of warfarin for catheter thrombosis prevention is now prevalent. One milligram per day of warfarin is recommended when a patient has a central venous catheter placed for a prolonged period. In patients with metastatic breast cancer, warfarin starting at 1 mg daily for 6 weeks, then adjusting the dose to achieve an INR of 1.3–1.9 until 1 week after the completion of chemotherapy resulted in a significant reduction in the rate of VTE with no increase in bleeding complications. Further studies are needed before this regimen can be generalized to other patients with cancer.

Heparin-Induced Thrombocytopenia

Heparin may cause paradoxical heparin thrombocytopenia (HIT) and heparin thrombocytopenia and thrombosis syndrome (HITTS). Recognizing this complication may be difficult in a patient with malignancy. The incidence of HIT in patients receiving therapeutic doses is 5% for bovine heparin and 1% for porcine heparin, and lower in patients receiving prophylactic doses of heparin or heparin

flushes. HIT should be considered when there is a decrease in the platelet count to less than 150,000 or a decrease in the platelet count to less than 50% of the baseline during heparin treatment in patients who originally had normal platelet counts.

Other additional criteria used in the diagnosis of HIT include normalization of the platelet counts within several days after the heparin is stopped, no other potential etiology for thrombocytopenia, and new or recurring thromboembolic events while on heparin therapy. Some believe that developing resistance to heparin therapy, i.e., decreasing aPTTs on the same dose of heparin or increasing doses of heparin to achieve the same aPTT, is a prodrome to the syndrome. This heparin-induced form of resistance must be differentiated from true heparin resistance, which occurs when there is an increase in heparin-binding proteins. This requires higher doses of heparin to increase bioavailability and achieve a therapeutic heparin level. It is extremely important to recognize this syndrome because the incidence of thrombosis in patients with HIT is estimated to be 20%, but may be even higher. The thrombotic complications include limb-threatening acute arterial thrombosis, myocardial infarction, strokes, and venous thrombosis. In patients who develop thrombosis the mortality rate is estimated to be close to 50%.

HIT is antibody mediated and therefore will take 4–15 days to develop in a patient who has never been exposed to heparin but may take less than a day in a patient who has been previously exposed. Recent evidence suggests that the antibodies in HIT react with complexes formed between platelet factor 4 (PF4) and heparin or heparin-like molecules on the endothelial surface. The heparin-IgG complex binds to the platelet Fc receptors and the platelets are activated.

The gold standard for the diagnosis remains clinical. Confirmatory laboratory testing is far from perfect. The best test, the serotonin release assay, can still give false-negative results in 15% of patients. The principle of the test is antibody-mediated, heparin-dependent, platelet activation and granule release in the presence of therapeutic doses of heparin. Use of the assay is to confirm the clinical diagnosis or to determine safety of reexposure. The assay should not be used to rule out the diagnosis if negative.

The immediate management decision when the diagnosis is suspected is to stop the heparin and remove all hidden sources of heparin exposure including heparin-coated catheters. A vena cava filter or even surgical embolectomy may be necessary if thrombolytic therapy is contraindicated. Alternative anticoagulants available include the heparinoid Lomoparan. This drug cross-reacts in less than 10% of patients but should, nevertheless, be used with caution. Direct thrombin inhibitors, hirudin, Hirulog, and Argatroban, are effective but not yet available for general use in the United States. Ancrod, a defibrinogenating agent, is available in Canada but not in the United States. Low-molecular-weight heparin should not

be used because of the high rate of cross-reactivity with unfractionated heparin. Warfarin is contraindicated because of the subsequent development of venous gangrene.

BLEEDING DISORDERS

Bleeding disorders were traditionally seen as the major hematological problem in patients with malignancy. Now that treatment has become more effective for control of bleeding, the thrombotic complications have taken precedence. Nevertheless, there are important issues to identify and address to either prevent or effectively treat bleeding in patients with malignancy. Localized abnormalities or tumor sites will bleed whether or not there is an underlying hemorrhagic diathesis. GI bleeding may occur from tumor, stress ulceration, or gastritis. Management should be directed toward the anatomical site but also to treat an identified coagulopathy if present (see Hemorrhage).

Thrombocytopenia has multiple etiologies in malignancy. The most likely cause is chemotherapy or radiation therapy. Other etiologies of thrombocytopenia include sepsis, bone marrow infiltration by tumor or infection, disseminated intravascular coagulation, and drugs (other than chemotherapy) including heparin.

The recommendation for routine transfusion of platelets when the platelet count is 20,000/μl or less has changed. Routine prophylactic transfusion may only be necessary when the count is below 5000/μl, or if the count is below 10,000/μl and there is fever or minor hemorrhage. If the patient requires heparin, has an additional coagulation disorder, or has an anatomical abnormality, then platelets would be indicated at or above the 20,000/μl level.

The malignancy classically associated with DIC is promyelocytic leukemia. The promyelocytes contain and release procoagulant substances that activate the coagulation system. Optimal management is with platelet and fresh-frozen plasma transfusions as needed. Heparin had been universally recommended in the past but is now reserved for patients with evidence of ongoing thrombin activity or thrombosis. DIC has also been diagnosed in patients with prostate carcinoma as well as other diffuse metastatic adenocarcinomas. When DIC occurs in association with adenocarcinomas, it is often in the face of advanced disease. Management is to treat the underlying disease if possible. Recommendations to use heparin, cryoprecipitate, plasma, and platelet transfusions should be made after careful consideration of the underlying disease state and prognosis of the patient.

Plasma factor deficiency may occur if there are nutritional deficiencies, biliary disease, and malabsorption. In addition, there may be an unexpected warfarin sensitivity in patients with liver metastases. Prophylactic transfusion for prolonged clotting times is no longer recommended and should be reserved for

a patient who is bleeding or who has a demonstrated factor deficiency. If a patient on warfarin sodium becomes deficient and bleeds or requires emergency surgery, then fresh-frozen plasma may be indicated to achieve immediate hemostasis.

Acquired bleeding disorders in patients with malignancy most often occur with the dysproteinemias, multiple myeloma, and Waldenström's macroglobulinemia. There is an associated platelet function defect and, much less commonly, disordered ability to activate fibrinogen to fibrin clot. Treatment necessitates management of the underlying disorder and control of the abnormal protein production. Hyperviscosity syndrome is caused by IgM accumulation in the plasma resulting in increased whole blood or serum viscosity. The symptoms resulting from this include dizziness, blurred vision, and bleeding from the mucous membranes. Management requires treatment of the underlying disorder after emergent plasmapheresis reduces the elevated IgM paraprotein.

TUMOR LYSIS SYNDROME/HYPERURICEMIA

Tumor lysis syndrome results when a rapidly proliferating tumor undergoes necrosis either spontaneously or after chemotherapy or radiation therapy is administered. The result of the necrosis of these tumor cells is life-threatening release of intracellular chemicals including uric acid, phosphorus, and potassium. The extreme high levels of these chemicals can be organ or life threatening. Renal failure is a major risk and results from hyperuricemia, hyperphosphatemia, and dehydration. The very high phosphorous level may also cause a secondary severe hypocalcemia, which needs to be monitored and treated. Recognition and emergent management are essential.

Tumor lysis syndrome should be suspected in any patient presenting with a rapidly proliferating malignancy. The high-grade lymphomas, particularly Burkitt's lymphoma, are classically associated with this syndrome. Other hematological malignancies include the acute and chronic leukemias. Rarely, other solid tumors, such as germ cell neoplasms, oat cell carcinoma, and even breast cancer, have been reported to result in the tumor lysis syndrome with excellent response to chemotherapy.

Tumor lysis syndrome must be considered when planning the treatment of a bulky, rapidly proliferating tumor. A markedly elevated lactate dehydrogenase (LDH) can be a predictor. Prevention includes administering allopurinol, hydration, and urine alkalinization. In addition, careful clinical and laboratory monitoring is essential. Clinical manifestations are the classic signs of hypocalcemia, including Chvostek's sign: tapping the facial nerve and producing a contraction of the facial muscles; and Trousseau's sign: carpopedal spasm in response to increased venous pressure on the arm usually occurring after application of a blood pressure cuff. Laboratory studies include uric acid, phosphorus, potassium,

and calcium. In addition, renal function with blood urea nitrogen (BUN) and creatinine must be followed closely to monitor the patient for impending renal failure and the possible need for dialysis.

If tumor lysis syndrome presents with renal failure, arrhythmias, or neuromuscular symptoms such as cramps, tetany, confusion, or seizures, management must be immediate and aggressive. Patients should be admitted to an intensive care unit where they can be monitored closely, preferably with telemetry. Patients with this condition must have frequent checking of vital signs, daily weights, and strict accounting of intake and output. Laboratory monitoring should include sodium, potassium, calcium, and phosphorus every 6–8 hr, creatinine, blood urea nitrogen, and uric acid every 12 hr, and daily LDH. This monitoring can be modified when the patient has stabilized and shows no evidence of continued tumor lysis. Immediate venous access is necessary to accomplish aggressive hydration using isotonic saline or hypotonic saline with the addition of sodium bicarbonate. Alkalinization is recommended to keep the urine pH close to 7.0 and in some cases, the addition of acetazolamide may be necessary to achieve this. Allopurinol, 300 mg once or twice a day, should be started immediately. If the patient has inadequate urine output, central venous monitoring is indicated. When the patient is adequately hydrated and urine output is low, mannitol, furosemide, or low-dose dopamine may be necessary to improve urine production. Hemodialysis should be used if a patient presents with or develops acute renal failure. Other indications for dialysis include hyperkalemia, volume overload, hyperphosphatemia, hypocalcemia, hyperuricemia, and control of uremia. Hemodialysis may be necessary every 12 hr with tumor lysis syndrome. Treatment of the hypocalcemia with intravenous calcium is discouraged because of increased tissue precipitation of calcium phosphate in the face of the hyperphosphatemia and the concern of metastatic calcification. Therefore, only those patients with severe symptoms of hypocalcemia should be treated. Phosphate binders may be helpful in controlling the phosphate level.

HYPONATREMIA

Hyponatremia may present as a laboratory abnormality, with the insidious onset of lethargy and confusion or acutely with muscle twitching, irritability, psychotic behavior, and seizures. The typical differential must first be examined and underlying metabolic abnormalities that are identified should be treated. Pseudohyponatremia, seen with hyperproteinemia, hyperlipidemia, and hyperglycemia, must first be ruled out. This is done by calculating the osmolality of the extracellular body fluid and simultaneously measuring the true serum osmolality. The osmolality is calculated using the formula:

$$2 \times \text{Na} + \text{glucose}/18 + \text{BUN}/2.8$$

Normal plasma tonicity is 285 mosm/kg of water. Pseudohyponatremia is a discrepancy between the calculated and measured values. If true hyponatremia exists, then the patient's volume status must be determined. This will categorize the condition into one of three categories:

1. Hyponatremia and decreased volume
2. Hyponatremia and increased volume
3. Hyponatremia and euvolemia

If there is volume depletion, then gastrointestinal loss, abdominal sequestration of fluid, as well as renal loss need to be investigated. Addison's disease must be considered, particularly if the patient is hypovolemic and hyperkalemic. Hyponatremia and increased volume are seen with congestive heart failure, cirrhosis, nephrotic syndrome, and renal failure. The differential for hyponatremia and euvolemia includes glucocorticoid deficiency, hypothyroidism, stress, drugs, reset osmostat, and psychogenic polydipsia. The syndrome of inappropriate antidiuretic hormone secretion (SIADH), also called humoral hyponatremia of malignancy, is then a diagnosis of exclusion.

Humoral hyponatremia of malignancy is associated with the ectopic production of arginine vasopressin as well as atrial natriuretic peptide. This was previously called the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Ectopic production is seen with both malignant disorders and nonmalignant disorders. The latter includes pulmonary disease, central nervous system disorders, drugs, and hyperthyroidism. The most common malignancy is small cell lung cancer but the syndrome is seen with other cancers. Chemotherapeutic drugs associated with hyponatremia and likely with the syndrome SIADH include cyclophosphamide, vincristine, vinblastine, cisplatin, carboplatin, ifosfamide, interferon, interleukin-2, levamisole, and monoclonal antibodies.

Treatment for hyponatremia and decreased volume requires volume replacement with isotonic fluids. Mineralocorticoid and potassium replacement may also be necessary. The treatment for hyponatremia and increased volume is guided by the underlying disease process. Treatment of euvolemic hyponatremia must be directed at the underlying tumor. Additional therapies include fluid restriction although hypertonic saline may be necessary with addition of intravenous furosemide. Medical therapy for chronic management is best achieved with demeclocycline at a dose of 600–1200 mg/day with a response after 5–8 days of treatment. Correction of serum sodium must be slow to prevent the occurrence of osmotic demyelinating syndrome and central pontine myelinolysis, which is an irreversible neurological complication of rapid correction of severe hyponatremia.

HYPERCALCEMIA

Hypercalcemia is the most common metabolic complication of cancer. Malignancies associated with hypercalcemia include breast, lung, head and neck, kidney,

lymphoma, and multiple myeloma. The human T-cell lymphotropic virus type I (HTLV-I)-associated leukemia/lymphoma is almost always associated with hypercalcemia. Hypercalcemia of malignancy is often a poor prognostic sign.

The hypercalcemia of malignancy can be classified into two major categories. The first, humoral hypercalcemia of malignancy, occurs when there is no evidence of bony disease but the tumor cells produce parathyroid hormone–related protein (PTHrP). PTHrP is similar to parathyroid hormone in biological activity. It increases renal tubular reabsorption of calcium and osteoclastic bone resorption as well as decreasing renal phosphate uptake. This paraneoplastic hormone has been found with squamous carcinomas and breast and renal carcinomas. The second type of hypercalcemia of malignancy occurs when tumor cells cause localized osteolysis. This occurs most often in patients with metastatic breast cancer and multiple myeloma.

Despite these categorizations, in metastatic bony disease there still appears to be mediation of the bone destruction by osteoclastic activity possibly stimulated by local hormonal production. The mediator in breast cancer may also be PTHrP and the mediator in myeloma may be interleukin-1, interleukin-6, and tumor necrosis factors (TNF) alpha and beta. In addition, in a particular patient both classifications may be overlapping. In lymphoma there may be increased production of 1,25-dihydroxyvitamin D with resultant increased calcium absorption from the gut and increased bone turnover. In some breast cancers, prostaglandins have been associated with increased bone resorption after hormonal therapy.

Hypercalcemia is usually a late manifestation of disease but it should be considered in any patient with a malignancy who presents with vague symptoms of fatigue, malaise, weakness, anorexia, nausea, vomiting, polyuria, polydipsia, abdominal pain, constipation, and central nervous system impairment. Constipation can easily be attributed to narcotic use, but if there is a marked change in bowel habits, hypercalcemia needs to be considered. Patients will also complain of anorexia and vomiting and may have mental status changes. This symptom complex should have a differential diagnosis of both brain metastases and hypercalcemia. Electrocardiographic changes occur and may lead to arrythmias including bradyarrhythmias, AV block, asystole, and cardiac arrest may occur if the calcium level is above 18 mg/dl.

Hypercalcemia is defined as a serum calcium level above 11.0 mg/dl (>5.5 mEq/L or 2.74 mmol/L). The general recommendation for therapeutic intervention is when a patient is symptomatic or if the calcium is greater than 12.0 mg/dl (>6.0 mEq/L or 2.99 mmol/L). Correction of the calcium level is necessary if the patient's serum albumin is low. The accepted correction is:

> For each gram per deciliter decrease in serum albumin (<4.0 g/dl) serum calcium concentrations are corrected by adding 0.8 mg/dl (0.4 mEq/L or 0.2 mmol/L) to the measured serum calcium value.

This correction is necessary because it is actually the ionized or free fraction of calcium that is physiologically significant.

Diagnosis of the cause of hypercalcemia is not difficult in a patient with known metastatic cancer, a history of malignancy, or evident bony metastases. Less commonly, evaluation of the cause of hypercalcemia is necessary to differentiate cancer versus primary hyperparathyroidism, which can be differentiated by the PTH level. PTH is increased or normal with hyperparathyroidism but decreased or undetectable in hypercalcemia of malignancy.

Prevention of the symptoms of hypercalcemia may be possible. Patients can be given guidelines to take in adequate fluid and salt. Appropriate medication can be given for nausea and vomiting. Walking and increased mobility should be encouraged and adequate analgesia administered to support this effort. Dietary calcium restriction is usually unnecessary. Thiazide diuretics must be avoided because of their effect on renal calcium reabsorption. Hormonal therapy with tamoxifen, estrogen, or androgenic steroids may also precipitate hypercalcemia and patients with metastatic disease should be closely monitored when the drug is first given and counseled concerning the prevention of hypercalcemia.

Management of patients with hypercalcemia must be immediate and the initial treatment is volume repletion to enhance renal calcium excretion. Often 3–6 L of 0.9% sodium chloride over 24 hr is necessary. Loop diuretics (furosemide, bumetanide, and ethacrynic acid) will induce hypercalciuria but should be withheld until euvolemia has been restored. Treatment is then targeted at inhibiting bone resorption. Pamidronate, a bisphosphonate, inhibits osteoclastic function, is safe and effective, and has dramatically improved the management of hypercalcemia. It is administered early in therapy and given by intravenous infusion over 4–24 hr using 60–90 mg. Normocalcemia is achieved by 4 days and lasts for 28 days. If the hypercalcemia must be reduced immediately, then calcitonin can be administered acutely until the pamidronate takes effect. Calcitonin has a rapid onset of action of 2–4 hr, has few toxic reactions, and can be used regardless of renal function or hydration status. Its major drawback is the occurrence of tachyphylaxis. Calcitonin is administered in a dose of 6–8 IU/kg IM or SC every 6–8 hr. Other treatments include gallium nitrate, plicamycin, glucocorticoids, phosphate, and dialysis. Definitive treatment of the underlying condition is administered if available.

Pamidronate has also now been approved to be used in patients with osteolytic lesions who are not hypercalcemic. In patients with multiple myeloma it was shown to reduce the incidence of pathological fractures, requirement for radiation to the bone, spinal cord compression, and development of hypercalcemia. It alleviated bone pain and improved quality of life. In patients with breast cancer there was a significant reduction in skeletal complications and bone pain.

Hypercalcemia associated with malignancy is a poor prognostic indicator unless the underlying malignancy can be effectively treated with specific chemo-

therapy. Treatment of the hypercalcemia otherwise is palliative only and does not affect survival.

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22

Cancer Vaccines: Medical and Surgical Implications

David Berd and John Kairys
Thomas Jefferson University, Philadelphia, Pennsylvania

PRINCIPLES OF IMMUNOTHERAPY

There are three requirements for successful immunotherapy of a malignant tumor, whether a transplanted tumor in an experimental animal or a spontaneous cancer in a human patient: (1) Immunogenic tumor, (2) intact cell-mediated immunity, and (3) low tumor burden.

The term *immunogenic tumor* means a tumor that is capable of eliciting an immune response under the proper circumstances. Immunogenicity implies that the tumor is composed of cells that express one or more antigens that could be recognized by the cells of the immune system. In experimental animals, a tumor is designated immunogenic if immunization with the tumor cells prepared as a vaccine (e.g., by irradiating the cells and/or mixing them with an immunological adjuvant) results in protection against a subsequent challenge with live tumor cells. As experiments of this type cannot be done in humans, the definition of immunogenicity of human cancers is unclear and somewhat controversial. For example, some investigators argue that immunogenicity can be determined by in vitro tests, while others insist on the demonstration of immunologically mediated antitumor effects in vivo.

Surprisingly little is known about the antigens expressed on cells that comprise an immunogenic tumor. In virus-induced tumors, the viral antigens may elicit a destructive immune response, but at present, very few human cancers are considered to be virally induced. It seems likely that many human cancers are induced by chemical carcinogens (e.g., those found in cigarette smoke), but the

Table 1 Concept of Tumor Burden

	Mouse Tumor system	Clinical setting
10^6 tumor cells	Prophylaxis experiments	Clinically undetectable
10^7 tumor cells	Therapy experiments	Clinically undetectable
10^8 tumor cells	Therapy experiments	Clinically undetectable
10^9 tumor cells	Rarely curable by immunotherapy	1.5 cm diameter mass
10^{10} tumor cells	Beyond range of testing	Advanced metastatic cancer
10^{11} tumor cells	Beyond range of testing	Terminally ill

tumor antigens that might be newly expressed as a consequence of carcinogenesis have not been well characterized, even in experimental systems.

Intact cell-mediated immunity is critical because it is clear that tumor rejection is mediated predominantly by T lymphocytes. Other immunological cells, such as natural killer (NK) cells and macrophages, are much less important. There is little experimental or clinical evidence that tumors are destroyed by antibodies. T-cell immunity can be impaired by anticancer therapies (radiation therapy or chemotherapy); other immunosuppressive drugs, particularly corticosteroids; or HIV infection. Progressive tumor growth can cause depressed T-cell immunity, but significant immunosuppression is usually not apparent until the cancer is extensive enough to cause deterioration of the patient's general health.

The concept of *low tumor burden* is illustrated in Table 1. Cure of transplanted tumors in mice rarely has been accomplished with total-body tumor burdens of $>10^8$ cells. In contrast, patients with advanced metastatic cancer may have total-body tumor burdens of 10^{10}–10^{11} cells, and a ''low'' tumor burden of 10^8 cells is clinically undetectable (unless a sensitive tumor marker, such as CA-125, is available). It seems unlikely that vaccine therapy will be effective against a tumor burden of $> 5 \times 10^9$ cells, which is likely to be found in a patient with small, asymptomatic metastases. The chances of success should be much greater in patients with clinically undetectable metastases, e.g., tumor burden $< 10^9$ cells.

EXPERIMENTAL BASIS FOR CANCER VACCINE THERAPY

It is important for the clinician to have some understanding of the experimental basis of the clinical approaches to cancer vaccines. Most of this work has utilized

transplantable tumors that had been originally induced by chemical carcinogens. Such tumors were injected into mice that had become genetically identical by years of inbreeding. The classic experiment of this type, and perhaps the classic experiment of tumor immunology, was performed by Richmond Prehn in the mid-1950s. He transplanted chemically induced sarcomas subcutaneously into mice and allowed them to grow for several weeks. At that point, when they were 1–2 cm in diameter but had not metastasized, the tumors were excised. Several weeks to months later, these mice, along with a control group that had not been treated, were injected with the same tumor, and its subcutaneous growth was monitored by serial measurements. The most common result of such experiments was that the sarcomas failed to grow, or grew much more slowly, in mice that previously had been surgically cured of the same tumor. The protection was proven to be immunological by demonstrating that it required an intact immune system and that it could be transferred to a naive mouse by intravenous injection of ''immune'' T lymphocytes.

This Prehn experiment is characterized as *immunoprophylaxis*, as the immunization was performed before tumor challenge. Subsequently there have been hundreds of experiments published that represented variations on this theme. For example, immunological protection could be obtained by the prior injection of inactivated (usually irradiated) tumor cells as well as with viable cells. It is also possible, although more difficult, to achieve positive results in an *immunotherapy* system in which the therapy is begun *after* the live tumor challenge, a situation that is more clinically relevant. For example, Gerald Bartlett and Berton Zbar injected guinea pigs with 10^6 live tumor cells from a chemically induced hepatoma. Beginning 1 hr later, the animals were inoculated with a vaccine consisting of irradiated tumor cells mixed with BCG. Initially the tumors grew, reaching a diameter of 5–10 mm by 7 days; then they regressed completely, and the animals were cured. Thus eradication of an experimental tumor by administration of a vaccine requires the immunotherapy to be started at an early stage of tumor growth.

CLINICAL APPROACHES TO TUMOR VACCINES

Intact Tumor Cells

The simplest way to make a cancer vaccine is to use intact, but inactivated tumor cells, as described in animal systems. One may use autologous tumor cells (i.e., from the patient who is to be treated) or allogeneic tumor cells (i.e., same histological type from different patients). To prepare an allogeneic cell vaccine, the investigator establishes tissue culture lines from the metastatic tumors of several patients and grows them in large batches. An example is the work of Donald Morton at John Wayne Cancer Center. The various cell lines are mixed and inacti-

vated, usually by irradiation. Autologous cell vaccines require a tumor specimen to be processed for each patient to be treated. Most commonly, single cell suspensions are prepared from each tumor by enzymatic digestion and then cryopreserved. When needed, the cells are thawed and inactivated by irradiation.

Autologous vaccines are certainly more difficult to prepare. Moreover, studies are limited to patients who have surgically accessible metastases that are large enough to obtain enough cells (about $50–100 \times 10^6$) to prepare vaccine; generally, a mass of 2.5 cm diameter is required. However, they have two theoretical advantages over allogeneic vaccines: (1) As noted above, very little is known of the nature of human cancer antigens. Allogeneic vaccines depend on the existence of antigens that are shared by many or all tumors of the same histological type. It is not clear whether such ''common antigens'' are immunogenic in humans, and there is little evidence that they make effective vaccines in animal models. (2) It is an established immunological principle that antigen recognition by T lymphocytes requires that they be presented by cells with a matching HLA profile. This phenomenon is known as major histocompatibility complex (MHC) restriction. By definition, allogeneic tumor cells have an HLA profile that is foreign to the responder T cells. There are ways of overcoming this problem, for example, by macrophage ''processing'' of the allogeneic tumor cell.

Crude Extracts of Tumor Cells

An approach that is technically a bit more complex is the preparation of crude extracts of tumor cell themselves (as per the work of Malcolm Mitchell at University of California at San Diego) or of the supernatant fluid in which the tumor cells have been cultured (as per the work of Jean Claude Bystryn at New York University). These materials are usually prepared from allogeneic cells. They have the advantage of not requiring inactivation by irradiation. Moreover, the samll particles or proteins in these preparations are more likely than intact cells to be phagocytosed and processed by macrophages, perhaps leading to amplification of the immune response.

Purified Extracts

Several investigators have been able to identify chemical components found on the surface of cancer cells and to prepare vaccine consisting of purified or synthesized preparations of them. Generally, these chemical components are not cancer-specific but are found, often to a lesser extent, on nonmalignant cells as well.

The most intensively studied is the ganglioside developed by Philip Livingston at Memorial Sloan-Kettering Cancer Center, which is known as GM2. This material is found in the cell membrane of virtually all melanoma cells and is a normal component of several other tissues, especially in the central nervous system. For vaccine preparation, GM2 is extracted from animal sources and exten-

sively purified. Other gangliosides, especially GD3, are also under investigation by the Sloan-Kettering research group.

Olivera Finn at the Pittsburgh Cancer Institute has shown that mucin derived from human adenocarcinomas can be immunogenic. Although all normal gastrointestinal lining cells contain mucin, tumor mucin has a subtle chemical difference from normal mucin in that it is underglycosylated.

Finally, Michael Longenecker at the University of Alberta in Edmonton has been working with a purified carbohydrate antigen. Although this material is a component of a blood group antigen, it is found in high quantitites in a variety of human tumor cells, especially adenocarcinomas.

A conventional immunologist might argue that to attempt to immunize patients to any of these chemicals is futile because they are normal components of nonmalignant cells that just happen to be present in large amounts on cancer cells. Thus, normal immunoregulatory mechanisms would prevent the development of immunological responses against them. However, the investigators working with these vaccine have been able to induce antibody responses against these materials, so it is possible that antitumor responses might follow.

Peptides

One of the more exciting recent developments in basic immunology has been the discovery that intracellular proteins can be expressed on the cell surface in the form of small peptides. The proteins undergo intracellular processing that breaks them down into units as short as eight amino acids, which are then carried to the cell surface and bind to the MHC complex. Because of their simple structure, these MHC-bound peptides can be easily characterized, synthesized, and used as vaccines.

The most interesting examples of peptide vaccines are those derived from a series of melanoma-associated proteins encoded by the MAGE genes, discovered by Thiery Boon in Belgium. MAGE proteins (named MAGE-1, MAGE-2, MAGE-3, etc.) were originally found in melanoma cells, but subsequently identified in some lung, gastrointestinal, and breast cancers. These materials are not cancer specific, but since they are found on a very limited array of normal tissues (particularly testicular cells) they are considered highly selective for malignant tumors. Several small peptides processed from MAGE-encoded proteins have been identified and synthesized for clinical vaccine trials.

Another set of peptides, found on the surface of most melanoma cells, is derived from proteins involved in the synthesis of melanin. By definition these materials are not cancer-specific but are differentiation proteins found on normal melanocytes in the skin and the choroid of the eye. They include tyrosinase, gp100 (related to HMB45, a marker used for the immunohistochemical detection of melanoma cells in tissues), and MART-1 (discovered by Steven Rosenberg's

group at the National Cancer Institute). As noted above in the discussion of gangliosides, it should be difficult to immunize patients to these normal materials because of the barrier of physiological tolerance. However, they have been reported to induce the development of cytotoxic T cells, at least in vitro.

Heat Shock Proteins

The use of heat shock proteins as cancer vaccines is a new development, but one that merits the clinician's consideration because of theoretical interest and therapeutic potential. Work in this field was pioneered by Pramod Srivastava, who now works at the University of Connecticut. As the name implies, heat shock proteins are produced by cells as a response to heating or other stresses. What makes them relevant to cancer vaccines is that they serve as carriers for peptides that are processed within the cell. Thus, a heat shock protein may have bound to it hundreds or thousands of peptides, some of which may have been derived from tumor proteins. Srivastava has extracted heat shock proteins from a number of murine tumors and shown that they served as vaccines that protect the animals from challenge with those tumors. Such vaccines are autologous (the term *syngeneic* is more accurate when applied to inbred mice), because the heat shock proteins extracted from a given tumor provide immunological protection only against that tumor and not against other tumors of a similar histology. It is relatively easy to extract heat shock proteins from human cancer cells and thereby to create a noncellular autologous vaccine.

ADJUNCTS TO TUMOR VACCINES

It is often possible to achieve protective immunity in experimental tumor systems by immunizing with tumor cells alone. However, it is usually advantageous to administer an immunological stimulant simultaneous with, before, or after the vaccine administration. Since human cancers are decidedly less immunogenic than transplanted animal tumors, such adjuncts will probably be necessary to induce a meaningful antitumor immune response.

Immunological Adjuvants

An adjuvant is defined by immunologists as a material that boosts the response to an antigen when mixed with or administered simultaneously with that antigen. Despite years of investigation, the mechanism of action of immunological adjuvants has not been delineated, but it probably involves stimulation of macrophages and consequent production of stimulatory cytokines at the vaccine sites. The most useful adjuvants have been mycobacteria or chemicals extracted from them. For example, Freund's adjuvant, the classic adjuvant for experimental use, consists of killed mycobacteria suspended in oil. Because of its toxicity, Freund's

adjuvant is seldom used in humans. Instead, many investigators have used bacille Calmette Guérin (BCG), which is an attenuated strain of *Mycobacterium bovis*. BCG has been used for over 50 years as a prevention for human tuberculosis, and it has an excellent safety record.

Recently, a number of synthetic adjuvnts have been developed. These appear to work as well as BCG, but have the obvious advantage of not containing living microorganisms. Two examples are Detox, which is ''detoxified'' bacterial endotoxin, and QS-21, a glycoside material extraced from tree bark.

Immunopotentiating Drugs

About 30 years ago, Henry Maguire, now on the faculty at Thomas Jefferson University, made a peculiar observation on the cytotoxic drug cyclophosphamide. That drug, often used as cancer chemotherapy, was a known immunosuppressive because of its toxicity to lymphocytes. However, Maguire found that when cyclophosphamide was administered to animals prior to injection of a vaccine, the cell-mediated immune response was actually *augmented* rather than suppressed. This observation has been repeated by hundreds of investigators and is now an immunological ''fact.'' The factor that determines whether cyclophosphamide augments or suppresses an immune response is the time of administration of the drug and the vaccine. Cyclophosphamide given after vaccine causes suppression of the immune response, whereas cyclophosphamide given before vaccine causes augmentation. The dose of cyclophosphamide is much less important, so very low (i.e., nontoxic) doses can be immunopotentiating.

Our group at Thomas Jefferson University (including Michael Mastrangelo, Maguire, and Berd) extended this observation to humans in 1982. Thus, the administration of low-dose (300 mg/m^2) cyclophosphamide prior to a vaccine greatly increased the development of cell-mediated immunity. Consequently, cyclophosphamide pretreatment has been incorporated into all of our cancer vaccine programs and is used by other investigators as well. Cyclophosphamide is not unique as a cytotoxic drug, since a number of similar compounds (e.g., melphalan, adriamycin) have the same immunopotentiating effect when given in the right way.

Cytokines

This term refers to a family of proteins produced by the cells of the immune system whose function is to modulate immune responses. The most well-known cytokines are the interleukins, e.g., interleukin-2 (IL-2), a series that currently extends to IL-18; the interferons—alpha, beta, and gamma; tumor necrosis factor (TNF); and the colony-stimulating factors, particularly GM-CSF. When administered simultaneously with or following vaccines, some of these cytokines can

potentiate the subsequent immune response, while others can suppress it (e.g., IL-10).

Transfection with Cytokine Genes

It is now possible to use the techniques of molecular genetics to take full advantage of the immunopotentiating effects of cytokines. This is commonly done by altering tumor cells so that they begin to produce a given cytokine in large quantities; then the cells are used as a tumor vaccine. Even though the tumor cells may have been inactivated, they produce high concentrations of the cytokine at the injection site, which theoretically could booster the induction of antitumor immune response.

In animal systems, this approach has been used successfully with the cytokines IL-1, IL-2, IL-4, IL-6, and IL-10, gamma interferon, and GM-CSF. However, whether such genetically engineered vaccines are superior to standard vaccines given with conventional immunological adjuvants is still the subject of controversy. Human cancer vaccines transfected with cytokine genes have been prepared and tested. This approach is most easily applied to allogeneic vaccines, because of the technical difficulty of genetically altering an autologous vaccine for individual patients.

MEASUREMENT OF EFFECTIVENESS OF TUMOR VACCINES

Clinical endpoints—tumor regression and survival—are certainly the most important criteria of the effectiveness of any cancer treatment, including vaccines. However, they may require lengthy follow-up times, which delays assessment of comples and costly new immunological treatments. Moreover, particularly in the early stages of testing of a new approach, tumor regression and prolongation of survival may be unachievable. Clearly it would be helpful to have immunological tests to determine a vaccine's effectiveness, to obtain dose-response data, and to develop useful modifications.

Unfortunately, there are no immunological criteria that are universally accepted as surrogate markers of a treatment's effectiveness. Instead each investigator has his own favorite, influenced perhaps by the degree to which that test supports the validity of his chosen therapeutic approach.

Antibody

As discussed previously, evidence from animal systems overwhelmingly supports the idea that tumor rejection is dependent on cellular immune responses and that antibody responses are of little significance. However, it is easy to serially collect serum, and a number of established serological techniques are available. Therefore, a number of investigators monitor their vaccines by measurement of the

appearance of antitumor antibodies. For example, Livingston's GM2 vaccine induces antibodies that bind to the ganglioside.

Delayed-Type Hypersensitivity (DTH)

DTH measurement is accepted as an indicator of a cell-mediated immune response to an antigen. It is well known to clinicians-that a positive DTH response indicates present or past exposure to a microorganism, the best example being the PPD response in tuberculosis. For this reason our group has used the DTH response to autologous tumor cells as an indicator of effectiveness of autologous tumor vaccine in patients with melanoma. DTH testing is performed by injecting small numbers of inactivated (usually by lethal irradiation) tumor cells intradermally into the ventral forearm. After 48 hr DTH responses are apparent as urticaria-like reactions, which are quantitated as diameter of the area of induration. An example of DTH responses in a patient receiving autologous melanoma vaccine is shown in Figure 1.

In a recent study of a hapten-modified autologous melanoma vaccine as postsurgical adjuvant treatment of clinical stage III melanoma (see details below), we found that the development of a positive DTH to autologous, unmodified melanoma cells was a statistically significant prognostic indicator. However, interpretation of DTH tests may be obscured by some notorious artifacts. For example, many human vaccines are prepared by dissociating tumors with the enzyme collagenase, which is quite immunogenic. Thus a positive DTH response to collagenase-dissociated tumor cells might indicate nothing more than a clinically useless response to the enzyme itself.

In Vitro Tests of T Lymphocyte Function

Using well-established techniques, any state of the art immunology laboratory can extract human T lymphocytes from blood or tumors, propagate them in tissue culture, and test them for ability to respond to tumor cells in vitro (as measured by tumor cell killing or by production of critical cytokines). The most sophisticated laboratories, e.g., Rosenberg's at the National Cancer Institute (NCI), Michael Lotze's in Pittsburgh, and Boon's in Belgium, are using these tests to measure the effectiveness of their vaccines. Many other investigators, however, have found them to be troublesome, because the results are unreproducible or artifactual. One example of a troublesome result is the observation by several laboratories that T lymphocytes from normal human subjects are strongly reactive to tyrosinase; as noted above, this protein is a normal constituent of cutaneous and ocular melanocytes. It is difficult to square this observation with the facts that few people have in vivo evidence of immune destruction of their melanocytes,

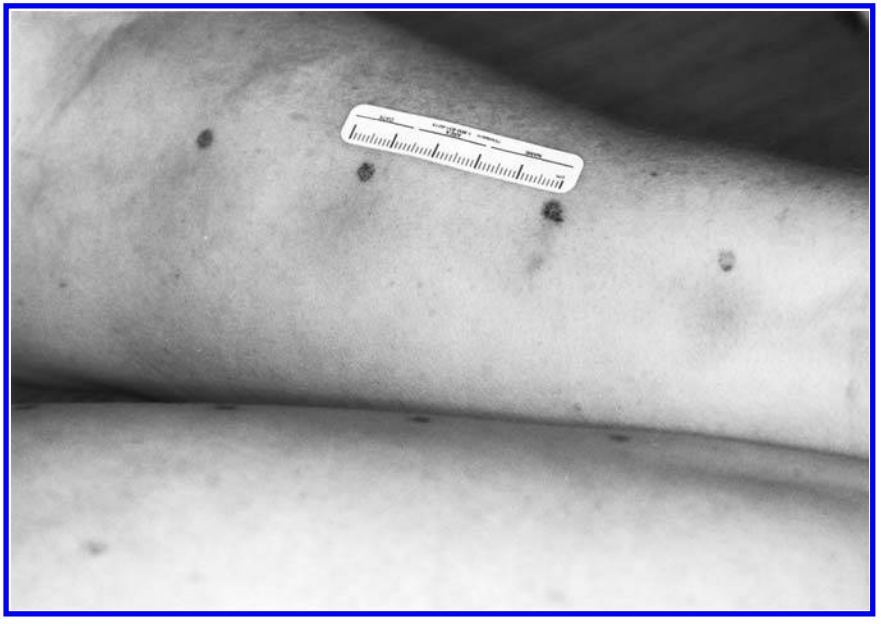

FIGURE 1 Delayed-type hypersensitivity (DTH) responses in a patient treated with autologous, DNP-modified melanoma vaccine. DTH responses were measured after a 6-week course of vaccine injections. The reactions were to the following materials, left to right: (1) autologous melanoma cells, enzymatically dissociated, hapten modified; (2) autologous melanoma cells, enzymatically dissociated, unmodified; (3) autologous melanoma cells, mechanically dissociated, unmodified; (4) autologous melanoma cells, mechanically dissociated, hapten modified. Control DTH reactions (not shown) indicated no response to normal, autologous lymphocytes or to lymphocytes treated with the enzymes.

as indicated by vitiligo. Thus it seems fair to conclude that the correlation of in vitro T cell tests with clinical phenomena remains the subject of controversy.

CLINICAL RESULTS OF CANCER VACCINES

Melanoma

Most of the clinical trials of human cancer vaccines have been directed at one disease—melanoma. Although some investigators consider melanoma to be immunologically unique, the reason for its predominance as an immunological target are probably more practical than theoretical. Melanomas commonly metastasize to superficial sites, so the tumors often can be removed with simple surgery.

The cells are relatively easy to extract from tumors and to grow in vitro. Finally, melanoma is traditionally thought of as a cancer that is resistant to traditional therapies (although this should be reconsidered in light of recent promising results with combination chemotherapy), so treatment with an experimental immunotherapy is considered early in the course of the disease.

Autologous, Hapten-Modified Cells

Our group at Thomas Jefferson University has conducted clinical trials of autologous, intact melanoma vaccines since 1982. Tumor cells are obtained by enzymatic digestion of freshly excised surgical specimens, most commonly lymph node metastases. At least 60×10^6 tumor cells must be obtained for a full course of vaccine administration, which requires a tumor of at least 5 g. The cells are cryopreserved in liquid nitrogen until needed. On the day that a patient is to receive a vaccine injection, an aliquot of his cells is thawed and irradiated and mixed with BCG (as an immunological adjuvant) just before injection. The mixture is injected intradermally on the upper dorsal arm, but sites ipsilateral to a lymph node dissection are avoided. For reasons discussed above, patients receive a one-time intravenous bolus of low-dose cyclophosphamide 3 days before vaccine injections are begun.

In 1988, we discovered that modification of the tumor cells with the hapten dinitrophenyl (DNP) greatly enhanced their immunogenicity. The theoretical basis of and experimental support for this phenomenon are beyond the scope of this chapter, but have been extensively described in many publications (see references). Thus, the autologous DNP vaccine mixed with BCG and with cyclophosphamide pretreatment has become our standard approach to melanoma immunotherapy.

Administration of DNP vaccine to patients with surgically incurable metastatic melanoma produces an interesting and unique result—the development of inflammatory response in metastatic sites. By clinical examination, superficial metastases become erythematous, tender, soft, and warm, sometimes with the development of frank necrosis. Immunohistochemistry and flow cytometric analysis of the inflamed tumors shows infiltration with T lymphocytes. Analysis of these tissues using the polymerase chain reaction (PCR) indicates that the T cells produce the important cytokine gamma interferon. Recently we, in collaboration with Giorgio Parmiani's group at the Istituto Nazionale in Milan, have reported that the infiltrating T cells represent expansion of particular clones that were not present in pretreatment metastases. This implies that immunization with DNP-modified autologous melanoma induces a T-cell response at the tumor site that is driven by yet-to-be-identified melanoma antigens.

Despite the inflammatory responses, patients with advanced metastatic disease only occasionally exhibit clinically defined tumor regression after receiving DNP vaccine. The reasons for this are not completely clear, but to some extent

must be due to excessive tumor burden. As indicated in Table 1 and the associated discussion, it should be possible to obtain a better clinical result in patients with a lower tumor burden.

To that end we have conducted a postsurgical adjuvant trial. The subjects have been patients with melanoma metastatic to regional lymph nodes with at least a single large (≥2.5 cm diameter) palpable mass. Following standard lymphadenectomy, the patients started the vaccine program, provided computed tomography studies showed no evidence of residual metastases. Several schedules of administration of DNP vaccine have been tested, and the optimum appears to be as follows: low-dose cyclophosphamide, followed 3 days later by six weekly vaccine injections, with vaccine boosters at 6 months after surgery.

The results of our initial studies appeared quite promising: Of 62 patients with metastasis in a single lymph node bed (stage III), 36 are alive after a median follow-time of 55 months (29–76 months); the projected 5-year relapse-free and overall survivals are 45% and 58%, respectively (Fig. 2). In contrast, the 5-year

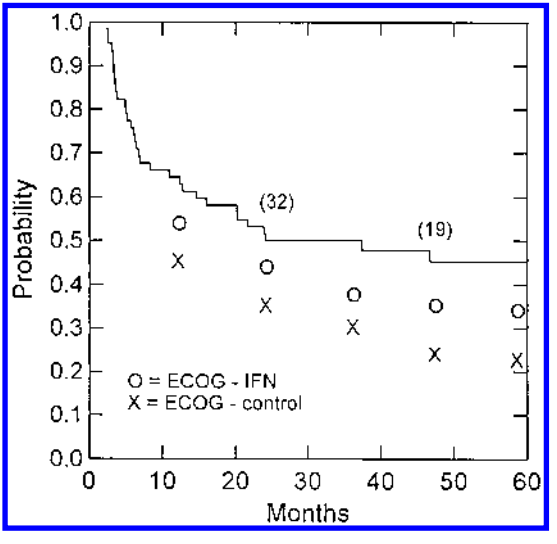

FIGURE 2 Relapse-free survival of patients with stage III melanoma treated with autologous, DNP-modified vaccine. The solid line indicates probability of being relapse-free. The numbers in parentheses indicate the size of the cohort followed for 24 months and 47 months, respectively. X,O = relapse-free survival at selected time points of clinical stage III patients treated in the Eastern Oncology Cooperative Oncology Group (ECOG) adjuvant study: O = surgery alone; X = surgery + high-dose interferon. (Reprinted from Berd et al., 1997, with permission of the publisher.)

survival after surgery only is 20–25% in most series (e.g., Daniel Coit's large surgical series from Memorial Sloan-Kettering). Moreover, administration of high-dose alpha interferon for 1 year produced a 5-year relapse-free survival of only 35% in the East Cooperative Oncology Group study headed by John Kirkwood (Fig. 2). An unexpected finding in our studies has been the significantly better survival of older patients; the projected 5-year survivals of patients >50 versus ≤50 were 71% and 47%, respectively. Finally, the development of a positive DTH response to unmodified autologous melanoma cells was associated with significantly longer 5-year survival (71% vs. 49%, respectively).

Because of these positive clinical results, we have initiated a randomized trial comparing DNP vaccine with interferon. The trial is being conducted by AVAX Technologies.

Autologous Gene-Transfected Cells

Dranoff and his colleagues at Johns Hopkins Cancer Center have reported a phase I trial with autologous melanoma cells transfected with the gene for GM-CSF. No serious toxicity was encountered. It can be expected that clinical efficacy trials of this vaccine will be forthcoming.

Allogeneic, Intact Cells

Donald Morton at the John Wayne Cancer Center has been a leader in the development and testing of a melanoma vaccine consisting of allogeneic, intact cells. In a published phase II trial, he reported that patients with disseminated, surgically incurable metastases who received this vaccine had a prolonged survival compared with historical controls.

Allogeneic Cells Lysed with Vaccinia Virus

Mark Wallach has a long record of testing a vaccine consisting of allogeneic melanoma cells that have been lysed by infecting them with vaccinia virus (the virus used for smallpox vaccination). These so-called viral oncolysates are thought to contain antigens that are not exposed on intact cells. A randomized controlled trial of this material in patients with resected nodal metastases (clinically positive and clinically negative nodes combined) did not show a significant survival advantage for the vaccine.

Melacine

Malcolm Mitchell at the University of California at San Diego developed a vaccine prepared by chemical extraction of melanoma proteins that are mixed with the adjuvant Detox. The final product is known as Melacine. In a large randomized trial Melacine was compared with a standard combination chemotherapy regimen in patients with surgically incurable metastases. Although a higher per-

centage of the patients in the chemotherapy arm experienced tumor regression, the overall survival of the two groups was similar. Furthermore, quality-of-life analysis showed a marked advantage for the vaccine group.

Ganglioside GM2

Livingston has published a randomized trial of the GM2 vaccine in patients with resected regional lymph node metastases (clinically positive or negative). There was no significant difference in the relapse-free or overall survival in the vaccine group compared with the surgery-alone group. However, patients who developed an antibody response to the ganglioside had longer survival times than those who did not. Based on these results, the Eastern Cooperative Oncology Group has undertaken a large trial comparing GM2 vaccine with high-dose interferon in high-risk, resected melanoma patients.

MAGE-3 Peptide

In a European study of a small group of patients, several were reported to have exhibited tumor regression after injection of a MAGE-3 peptide without an adjuvant. Immunological responses (e.g., DTH) were not detected. Obviously, there will be a number of follow-up studies to try to corroborate this interesting result.

MART-1 Peptide

Rosenberg's group at NCl has conducted a series of phase I studies with this peptide in patients with clinically evident metastases. They reported the induction of cell-mediated immunity against the peptide as shown by T cell responses in vitro. Clearly, many trials of this and related peptides will follow.

Kidney Cancer

Autologous Cells

In the early 1980s Craig McCune, working at the University of Rochester, conducted a series of trials in patients with metastatic adenocarcinoma of the kidney. His vaccine consisted of irradiated, autologous tumor cells mixed with an immunological adjuvant. Several patients exhibited partial regression of metastases, which was well documented in the publications. Unfortunately, there appears to have been no follow-up to this work.

Autologous Gene-Transfected Cells

The Hopkins group has reported a phase I trail of a vaccine identical to that described above for melanoma. One patient exhibited regression of pulmonary metastases.

Colon Cancer

Autologous Cells

Michael Hannah and Herbert Hoover pioneered the use of an autologous cell vaccine (without hapten modification or cyclophosphamide) as postsurgical adjuvant treatment of Dukes' B and C adenocarcinoma of the colon. BCG was used as an adjuvant. The final analysis indicated no significant difference in survival between vaccine-treated patients and surgical controls. However, a subsequent study, recently reported from Europe, suggested that this vaccine produced clinical benefit.

Autologous Cells Modified with a Virus

Volker Schirrmacher in Heidelberg, Germany developed a vaccine prepared by treating autologous tumor cells with the Newcastle disease virus (NDV). This virus does not lyse the tumor cells, but appears to modify their cell surface to make them more immunogenic. This material was tested in patients with liver metastases from colon adenocarcinoma who had undergone hepatic resection. Patients who received NDV vaccine had a somewhat lower rate of tumor recurrence than patients who received surgery only.

Ovarian Cancer

Autologous Hapten-Modified Cells

Recently, our group has extended the use of autologous, DNP-modified vaccine to adenocarcinoma of the ovary. Patients with stage III disease underwent debulking surgery; tumor tissue was obtained and cells were cryopreserved. After six cycles of standard chemotherapy, DNP-vaccine was administered by the dosage schedule found to be optimal for melanoma. DTH testing showed that 8/9 patients developed cell-mediated immunity to their own ovarian cancer cells. A larger study with clinical endpoints is planned.

Lung Cancer

There have been few attempts to test vaccine therapy in patients with lung cancer. However, Hannah treated a small group of patients with small cell carcinoma with an autologous, whole-cell vaccine following radiation therapy. Because of the small sample size, the clinical results were not definitive.

Summary

This review is not meant to be comprehensive, but it does include most of the major approaches to human cancer vaccine that have been subjected to clinical

trials. One cannot help but be impressed by the number of studies and the diversity of technologies. However, with the exception of melanoma, an overall assessment does not suggest that vaccines have produced a great deal of clinical benefit in any tumor type. Some of these approaches appear promising, and their further development could lead to improved efficacy. Our bias is that autologous vaccines have the highest chance of producing breakthrough results, and we believe that the results with autologous, DNP-modified cells stand out from the rest. However, the newer approaches—synthetic peptide vaccine and gene-transfected cells—are in their infancy. Whether or not they are therapeutically successful, they will provide new insights into the human tumor-host relationship.

PRACTICAL ISSUES FOR SURGICAL ONCOLOGISTS

Importance of Complete Lymph Node Dissections

It is easy to be pessimistic when dealing with patients with resectable, but bulky lymph node metastases, especially in difficult diseases, such as melanoma. Faced with a patient whose surgical prognosis is poor, the surgeon may be tempted to simply remove clinically evident masses or to stop short of complete nodal dissections to minimize morbidity. However, the availability of vaccines as postsurgical adjuvant therapy provides new justification for aggressive surgery of regional metastases. As repeatedly stated in this chapter, vaccines are more likely to work if the residual tumor burden is low. Conversely, the presence of residual tumor in a lymph node bed may doom a vaccine to failure.

Palliative Surgery of Incurable Metastases

In only a few clinical situations do surgeons consider surgery for disseminated metastases. These include resection of solitary pulmonary metastases (especially melanomas, kidney adenocarcinoma, and sarcomas) and resection of hepatic metastases of colon carcinoma. The availability of vaccines, particularly autologous vaccines, provides additional justification for these procedures and some reason to pursue them more aggressively. For example, it might be reasonable to remove a large lung metastasis even in the presence of several other small, nonresectable metastases if postsurgical vaccine trial is a possibility.

Importance of Needle Biopsies

The preoperative fine-needle aspiration biopsy is the tumor immunologist's friend. By making the diagnosis prior to definitive surgery, the surgeon is free to give all or most of the resected tissue to the laboratory for vaccine preparation. Since counts of positive nodes are important prognostic criteria, we recommend

Table 2 Handling of Surgical Specimens for Autologous Vaccine Preparation

1. Immediately after excision, place the tumor mass into a sterile container with sterile saline or other sterile isotonic solution without formalin.
2. If possible, the bulk of the tumor specimen should be made available for vaccine preparation. A small, representative piece of the tissue should be submitted to the pathology laboratory if a diagnosis has not been made preoperatively.
3. If a formal lymph node dissection is being done, the residual tissue should be sent to the pathology laboratory so that the degree of microscopic nodal involvement can be determined.
4. The tumor tissue should be put on wet ice immediately and kept at 4° until it is delivered to the laboratory.

that our collaborating surgeons send us the largest lymph node masses in toto and send the remaining resected material for pathological examination.

Handling Tissues Intended for Autologous Vaccine Preparation

As described previously, preparation of autologous vaccine requires a large amount of tumor tissue. Our laboratory's experience indicates that the yield from enzymatic digestion of a melanoma metastasis is $10–20 \times 10^6$ cells per gram. Assuming that $50–100 \times 10^6$ cells are required for a series of treatments, at least 5 g of tumor tissue is generally required. Currently technologies require that the tissue is both viable and sterile. Freezing tumors or exposing them to formaldehyde kills the cells and makes them unsuitable for vaccine preparation. Our suggested method for handling tumors is shown in Table 2.

''Think Vaccine''

It is not unusual for a melanoma patient to present with a mass in the axilla or inguinal area. There may have been no history of a primary cutaneous melanoma, or the primary tumor may have been treated many years before so the patient does not consider it relevant to his present problem and fails to inform his physician. An open biopsy is likely to result in the discarding of the residual specimen and loss of the opportunity to prepare an autologous vaccine. In evaluating such patients, surgeons are already ''thinking cancer.'' Perhaps they should begin to ''think vaccine'' as well.

Surgery and Immunotherapy—The Old and the New

Surgery is the oldest form of cancer treatment, and, arguably, it is still the most effective. It is a strange irony that the success of a 21st-century treatment such as

tumor vaccine should depend so heavily on the skill and dedication of individuals practicing a 19th-century art. We hope that surgical oncologists will relish their new roles as facilitators of biological therapies and will incorporate immunological concepts into their training and their thinking.

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23

Nutritional and Life-Style Modification to Augment Oncology Care

Charles B. Simone
Simone Protective Cancer Institute, Lawrenceville, New Jersey

INTRODUCTION

By the year 2000, cancer will emerge as the number one cause of death in the United States. Despite the enormous effort to combat cancer, the number of new cases of nearly every form of cancer has increased annually over the last century. Still worse: from 1930 to the present, despite the introduction of radiation therapy, chemotherapy, and immunotherapy with biological response modifiers, despite computed tomography scans, magnetic resonance imaging scans, and all the other new medical technology—life spans for almost every form of adult cancer except cervical cancer and lung cancer have remained constant, which means that there has been no significant progress in cancer treatment. The successes in the treatment of cancer plateaued in the 1970s, and no real advances have been made since then. However, chemotherapy and radiation therapy continue to have a role in cancer treatment but produce morbidity. Nutritional modification, including the use of certain nutrients, and proper life-style can dramatically decrease the morbidity and side effects of chemotherapy and radiation therapy. There have even been some reports that nutritional and life-style modification actually increase survival. Numerous studies show that nutrients used with chemotherapy and radiation therapy can enhance tumor killing and preserve normal tissue.

VITAMINS AND MINERALS IN CHEMOTHERAPY AND RADIATION THERAPY

Do vitamins or minerals interfere with chemotherapy and/or radiation therapy? This is a question I am asked frequently by patients because they have been

advised not to take supplements during treatment. Many studies have been done to address this. The early clinical studies were performed at the National Cancer Institute using an antioxidant called *N*-acetyl cysteine, which can protect the heart from the cardiac toxicity of adriamycin. The heart was protected and there was no interference with the tumor-killing capability of adriamycin. Another antioxidant called dexrasonane (formerly called ICRF-187) offered significant protection against cardiac toxicity caused by adriamycin without affecting the antitumor effect. Many cellular studies and animal studies demonstrate that vitamins A, E, and C, as well as beta-carotene and selenium, all protect against the toxicity of adriamycin and, at the same time, actually enhance its cancer-killing effects.

Animal Studies

Vitamins and minerals have also been studied with other chemotherapies and radiation. Studies using beta-carotene and other retinoids, vitamin C, or vitamin K show that normal tissue tolerance was improved in animals undergoing both chemotherapy and radiotherapy and that tumors regressed. Vitamin E produced similar findings: Tumors in animals showed regression when either radiation or chemotherapy was used concomitantly with vitamin E. Animals given both beta-carotene and vitamin A with radiation and chemotherapy had more tumor killing than with chemotherapy and radiation alone, normal tissues were more protected, and there was a longer period without tumor recurrence. Selenium and cysteine also heighten tumor killing by chemotherapy and radiation, and at the same time protect normal tissue.

Cellular Studies

All cellular studies using vitamins (C, A, K, E, D, B_6, B_{12}), beta-carotene, minerals (selenium), and cysteine concomitantly with chemotherapy, or tamoxifen, or interferon alpha-2b, or radiation, or combinations of these modalities show the same effect: increased tumor killing and increased protection of the normal tissues.

Human Studies

In human studies, vitamin E reduced the toxicity without affecting the cancer-killing performance of 13-*cis*-retinoic acid, used in the treatment of patients with head and neck, skin, and lung cancers. At 1600 IU of vitamin E per day, hair loss in patients receiving chemotherapy was reduced from the expected 30–90%. Treatment of 190 head and neck cancer patients with vitamin A, 5-FU, and radiation resulted in greater-than-expected tumor killing while preserving normal tissue. And vitamin A combined with chemotherapy for postmenopausal patients with metastatic breast cancers significantly increased the complete response rate. In 13 patients with different cancers receiving 42 different chemotherapies, vita-

min K decreased tumor resistance. Vitamin B_6 at 300 mg/day decreased radiation therapy toxicity. In 20 patients receiving chemotherapy with vitamins A, C, and E, there was a greater response rate. Glutathione, part of the selenium complex, protected 150 women with ovarian cancer against cisplatin toxicity with no loss of anticancer effects as shown in double-blind studies at nine British oncology centers. In fact, more women treated with glutathione had an objective response (73% vs. 62%) and completed more cycles of cisplatin (58% vs. 39%) than those who were not so treated. And studies show that amifostine (WR-2721), an antioxidant, protects against the harmful side effects of chemotherapy and radiation without the loss of antitumor activity.

An increase in survival for cancer patients, which is uncommon with any treatment, has been shown using antioxidants combined with chemotherapy or radiation. In fact, 11 patients who were given beta-carotene and anthaxanthin while undergoing surgery, chemotherapy, and radiation lived longer with an increase in disease-free intervals. And antioxidant treatment with chemotherapy and radiation prolonged survival for patients with small cell lung cancer compared with patients who did not receive antioxidants.

The effects of one chemotherapeutic agent, methotrexate, can be reversed with folinic acid, which is an analog of the vitamin folic acid. Folic acid itself does not reverse methotrexate's effects. To reverse the effects of methotrexate, folinic acid has to be given in high doses. Folinic acid cannot be obtained over the counter, it must be prescribed.

Studies of supplements all show that vitamins and minerals do not interfere with the antitumor effects of chemotherapy or radiation therapy. In fact, on the contrary, some vitamins and minerals used in conjunction with chemotherapy and/or radiation therapy have been shown to protect normal tissue and potentiate the destruction of cancer cells.

BREAST CANCER TREATMENT USING ADJUNCTIVE THERAPEUTIC LEVELS OF NUTRIENTS

Using quality-of-life scales, 50 patients with early-stage breast cancer evaluated treatment side effects of radiation and/or chemotherapy while taking therapeutic doses of nutrients. Quality-of-life scales are an acceptable way of evaluating any treatment or side effect not by the physician, but rather by the patient. The patient decides whether the treatment is beneficial or not in terms of side effects incurred. These scales have been successfully used to evaluate treatments for cardiovascular disease, cancer, and other chronic illnesses.

The scoring system for the quality-of-life scales is simple. The patient decides if the nutrients used during the radiation and/or chemotherapy treatments improved, worsened, or made no change in her life during the treatment period.

The qualities of life tested were: physical symptoms, performance, general well-being, cognitive abilities, sexual dysfunction, and life satisfaction.

Fifty consecutive patients with early-stage infiltrating ductal adenocarcinoma of the breast were treated with lumpectomy (reexcisional lumpectomy if indicated), axillary node dissection, and radiation therapy. Depending upon the nodal status, chemotherapy was used. In group I, 25 women with T1 or T2, N1, M0 were treated with primary radiation therapy, receiving 4500 cGy to the whole breast, and a total dose of 6000 cGy to the tumor bed. In group II, 25 patients with T1 or T2, N1, MO were treated with primary radiation therapy to the same doses as with group I and also received modified CMF chemotherapy consisting of cytoxan and 5-FU (methotrexate was omitted until radiation was completed). A total of six cycles of this modified regimen was given.

Each patient was instructed to follow the aspects of the Simone Ten-Point Plan pertinent as an adjunct to treatment. These points are:

Point 1. Nutrition.
Maintain an ideal weight—lose even 5 or 7 lb if necessary.
Low-fat (about 20% of calories), high-fiber (25 g) diet.
Micronutrients taken 30 min before each therapeutic modality: beta-carotene 30 mg, vitamin A 5000 IU, vitamin D 400 IU, vitamin E 400 IU, vitamin C 350 mg, folic acid 400 mcg, vitamin B_1 10 mg, vitamin B_2 10 mg, niacinamide 40 mg, vitamin B_6 10 mg, vitamin B_{12} 18 μg, biotin 150 μg, pantothenic acid 20 mg, iodine 150 μg, copper 3 mg, zinc 15 mg, potassium 30 mg, selenium (organic) 200 μg, chromium (organic) 125 μg, manganese 2.5 mg, molybdenum 50 μg, inositol 10 mg, and L-cysteine 20 mg.

In addition, the women took the following at bedtime: calcium carbonate 1000 mg, magnesium 280 mg, potassium bicarbonate 100 mg, boron 2 mg, L-lysine 2 mg, L-threonine 2 mg, and silicon 2 mg.

Eliminate salt, food additives, and caffeine.

Point 2. Tobacco. Do not smoke, chew, snuff, or inhale other's smoke.

Point 3. Alcohol. Avoid all alcohol.

Point 4. Radiation. Avoid unnecessary x-rays; sunscreens to be used. Avoid electromagnetic fields.

Point 5. Environment. Keep air, water, and workplace clean.

Point 6. Hormones, drugs. Avoid all estrogens and unnecessary drugs.

Point 7. Know the seven warning signs of cancer: lump in breast, nonhealing sore; change in wart/mole; change in bowel or bladder habits; persistent cough or hoarseness; indigestion or trouble swallowing; unusual bleeding.

Table 1 Patient Responses Regarding Qualities of Life

	Group I[a]			Group II[a]		
Life quality	Improve	Change	Worsen	Improve	Change	Worsen
Physical symptoms	25			24	1	
Skin reaction						
Fatigue						
Mouth sores						
Nausea/vomiting						
Dizziness, vertigo						
Lightheadedness						
Muscle cramps						
Performance	23	2		23	2	
General well-being	25			25		
Cognitive abilities	25			22	3	
Sexual dysfunction	25			15	10	
Life satisfaction	25			25		

[a] Group I patients had radiation only; group II had radiation and chemotherapy.

Point 8. Exercise.
Point 9. Stress modification, spirituality, and sexuality.
Point 10. Have executive physical annually.

The majority of the nutrients ingested were free radical scavengers (antioxidants) in high doses, combined with the B vitamins, and other important minerals. The rationale for this combination has been previously outlined. Radiation and many chemotherapeutic agents exert their killing effects and morbidity by generating free radicals.

Table 1 presents the responses of the 50 patients. Patients generally indicated improvement, a few indicated no change, and none indicated worsening. Numerous in vitro and animal and human studies have addressed this question. Vitamins and minerals do not interfere with the tumor-killing effects of radiation and chemotherapy, and they actually enhance tumor kill while at the same time they protect normal cells. In summary, this study demonstrates that patients who followed the Ten-Point Plan and used certain vitamins and minerals had few side effects from chemotherapy and radiation therapy.

THE HOFFER-PAULING STUDY

Researchers Hoffer and Pauling asked whether therapeutic nutrition helped cancer patients. All 129 cancer patients in their study were to follow a low-fat diet supplemented with therapeutic doses of vitamins C, E, A, niacin, and a multiple vitamin/mineral supplement, in addition to following the advice and treatment

of traditional oncology care. Those who did not follow nutritional modification (31 patients) lived an average of 6 months less. The other 98 patients fell into three categories: Females with breast, ovarian, cervix, and uterus (32 patients) cancer had an average life span of over 10 years; patients who had leukemia, lung, liver, and pancreas cancer (47 patients) had an average life span of over 6 years; and patients with end-stage terminal cancer (19 patients) lived an average of 10 months.

OTHER CLINICAL STUDIES

Other studies show similar findings: Patients who undergo conventional oncology therapy and modify life-style, which includes diet and nutrient supplementation, generally live longer. It has also been found that patients who undergo chemotherapy, in fact, have lower serum levels of vitamins and minerals, which return to near baseline levels thereafter.

JAPANESE EXPERIENCE

The older generation of Japanese women rarely get breast cancer, but when these women do, they live longer than American women stage for stage because of only two factors: (1) they are less obese, and (2) they eat a low-fat, high-fiber diet with vitamins and minerals. This is not necessarily true for younger Japanese women, who have now adopted a more Western culture and diet.

Obese breast cancer patients have a greater chance of early recurrence and a shorter life span compared to non-obese patients (99–103). And breast cancer patients who have a high-fat intake and an high serum cholesterol also have a shorter life span than patients with normal or low-fat intake and low serum cholesterol (104). Fat can initiate and also promote a cancer, especially a dietary cancer like breast cancer. If cholesterol intake is dramatically limited, cancer cell growth is severely inhibited (105).

NATIONAL CANCER INSTITUTE EFFORT

Armed with this information, the National Cancer Institute (NCI) attempted a research protocol in the mid-'80s to see if a low-fat diet would increase the life span of breast cancer patients. However, in January 1988, after only a brief time and an expenditure of about $90 million, the Board of Scientific Counselors of NCI's Division of Cancer Prevention and Control decided to end the proposed 10-year study because: (1) physicians did not ''believe'' that there was a relationship between breast cancer and fat or other nutritional factors and, subsequently, did not refer patients to the study; and (2) once a woman was enrolled in the protocol, she subsequently ''failed out'' because she did not want to give up pizza, ice cream, and other high-fat foods. In 1991, NCI decided to try, in the near future, another low-fat cancer study in women aged 45 and 69.

CONCLUSION

Many of the nutrients used in the above studies are antioxidants. Antioxidants neutralize free radicals. Most cancer modalities exert their cancer-killing effects by generating free radicals. Therefore, it would seem inconsistent that these nutrients can help the cancer patient. In vitro and in vivo studies, including many clinical studies, have repeatedly shown that certain vitamins and minerals can enhance the killing capabilities of cancer therapeutic modalities while at the same time they protect normal tissues and decrease side effects from these modalities.

It has been postulated that cancer cells accumulate excessive amounts of antioxidants owing to a loss of the homeostasis control mechanism for the uptake of these nutrients. Normal cells do not have this membrane defect and do not accumulate large amounts of antioxidants. The accumulation of excessive nutrients in cancer cells can:

Shut down the oxidative reactions necessary for generating energy
Inhibit protein kinase C activity, which normally increases cell division and increases cell proliferation
Inhibit oncogene expression
Increase the amount of growth inhibitory growth factors

With higher levels of cancer intracellular accumulation of nutrients, more of these cellular alterations occur. These changes can lead to a higher rate of cancer cell death and a reduction in the rate of cell proliferation and induction of differentiation. These acquired changes of cancer cells due to high doses of nutrients actually override any protective action that antioxidants have against free radical damage on cancer cells.

Therefore, it behooves cancer patients to modify their life-styles, which includes modifying nutritional factors and taking important vitamins and minerals in doses outlined, especially if they receive chemotherapy and/or radiation.

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Molecular Biology in the Management of Solid Tumors: Breast, Colon, and Prostate Cancer

Sofia D. Merajver, Stephen B. Gruber, and Kathleen A. Cooney
University of Michigan Medical School and School of Public Health, Ann Arbor, Michigan

INTRODUCTION

The application of molecular biology principles and techniques to the understanding of the carcinogenesis process has produced a revolutionary and ever-expanding body of knowledge that is poised to impact prevention, diagnosis, and treatment of solid tumors. Already, knowledge of genes expressed at different stages of cancer development and progression helps determine the clinical significance and prognosis of certain premalignant and early cancerous lesions of the breast and colon. Perhaps the greatest contribution of molecular biology to the present management of cancer is in the risk assessment and surveillance of asymptomatic clients through accurate and targeted predictive testing of individuals at increased risk.

The psychosocial, ethical, and legal implications of knowledge of cancer susceptibility continue to be studied avidly and legislation aimed at protecting clients from discrimination is underway at the national and state level. A major clinical consequence of the Human Genome Project is the ability of individuals and populations to gain access to and more accurately understand their risk for cancer and other diseases. The fair and unbiased representation of the true capabilities of genetic testing and molecular biology is likely to result in beneficial applications of this knowledge for the management and surveillance of individual patients. In this chapter, we summarize those concepts emanating from molecular

genetics of cancer that either already impact or are at the verge of influencing the care of breast, colon, and prostate cancer patients, which together accounted for 46% of new cases of cancer (965, 904 individuals) and for 50% of cancer deaths (392,900 individuals) in the United States in 1997.

BREAST CANCER

Clinical Implications of Prognostic and Predictive Factors

Breast cancer is a major public health concern worldwide, with over 1,500,000 new cases per year. Because breast cancer lesions are highly heterogeneous, an impressive array of prognostic and predictive factors has become available to help manage treatment decisions and surveillance. These include the basic evaluation of tumor histology and stage accompanied by cellular and molecular features that reflect different clinical phenotypes. The potential for dysregulated proliferation in the presence of steroid or growth factor ligands, potential for invasiveness and new blood vessel growth, and aberrations of cell cycle regulation and apoptosis possibly associated with alterations in tumor suppressor genes have all been targeted as predictive markers in breast cancer. Table 1 outlines these factors, their clinical impact, and whenever known, the 5-year recurrence rate for patients with lymph-node-negative breast cancer who have the factor. This information is often used by clinicians in presenting therapeutic options to patients. However, for each of these categories, knowledge is still rudimentary about the exact sequence of events resulting in a given phenotype. Below we summarize the usefulness and applications of a subset of these molecular markers for clinical breast cancer management.

Nodal status and tumor size are by far the most important predictors of survival in breast cancer. Although these two factors are predictive of survival independently when considered separately, the probability of nodal metastases incrases with increasing tumor size. Within a TNM stage, a wide range of potential tumor biological behavior may impact survival. Although histological grade is not an independent predictor of survival beyond nodal status, for a given TN stage, the higher histological grade tumors are more likely to respond to high-dose chemotherapy and are therefore more likely to be treated aggressively.

One important indicator of the degree of differentiation in breast cancer is the level of expression of estrogen (ER) and progesterone (PR) receptors. These parameters are very important because higher ER and PR titers correlate with increasing quality and length of response of tumors to adjuvant and primary hormonal therapy. In the case of node-negative tumors, especially those considered of ''borderline'' size (between 1 and 2 cm), the histological grade and the ER/PR status help determine the course of adjuvant therapy. This is especially true in perimenopausal or postmenopausal women with node-negative, ER-negative

TABLE 1 Prognostic and Predictive Factors in Breast Cancer

Factor	Favorable	Unfavorable	5-year recurrence rate
Stage and histology			
Axillary lymph nodes			
0 positive nodes	Yes	No	10–15%
1–3 positive nodes	No	Yes	17%
>4 positive nodes	No	Yes	35%
DCIS (noninvasive)	Low-grade	Comedo type	1%
Invasive tumor size			
<1 cm	Yes	No	6%
1–2 cm	No	Yes	11%
>2 cm	No	Yes	13–34%
Bloom-Richardson grade			
I	Yes	No	7%
II	No	Yes	26%
III	No	Yes	28%
Growth and differentiation			
ER +	Yes	No	27%
pS2	High	Low	
ER−	No	Yes	33%
PR	Positive	Negative	
HER-2/Neu expression			
Low	Yes	No	
			55% (T > 3
High	No	Yes	cm)
EGF-R expression	Low	High	
Genome integrity, cell cycle, tumor suppressor gene dysfunction			
Ploidy			
Diploid	Yes	No	12%
Aneuploid	No	Yes	25%
S-phase fraction			
Low	Yes	No	10%
High	No	Yes	30%
Ki-67/PCNA	Low	High	
TLI	Low	High	
p53	Negative staining	Positive staining	
ATM, BRCA1, BRCA2	Unknown	Unknown	
Invasiveness and angiogenesis			
Cathepsin D	Low	High	
uPA	Low	High	
Microvessel density	Low	High	

DCIS = ductal carcinoma in situ; ER = estrogen receptor; PR = progesterone receptor; PS2 = estrogen-stimulated secreted protein; EGF-R = epidermal growth factor receptor; PCNA = proliferating cell nuclear antigen; T = tumor size; TLI = thymidine labeling index; ATM = ataxia-telangiectasia gene; BRCA = breast cancer gene; uPA = urokinase plasminogen activator.

tumors. A tumor of higher histological grade, even one of small size (<2 cm) is more likely to be treated with chemotherapy. Therefore, in node-negative cases, ER and PR status are key determinants of whether chemotherapy is to be given as part of the initial therapeutic plan. For most tumors, both node positive and negative, ER/PR status helps guide postchemotherapy hormonal therapy and the decision on systemic therapy following local-regional recurrence.

Recurrences in the breast, chest wall, or draining lymph node chains such as the supraclavicular fossa are primarily treated with excision and radiotherapy. The decision to treat further with hormonal or cytotoxic therapy often rests on pathological evaluation of the aggressiveness of the recurrence. An ER-negative local-regional recurrence of high histological grade is thus very likely to be treated further with a few courses of chemotherapy followed by close observation. Other markers of growth and differentiation also play important roles in determining adjuvant and primary therapies in breast cancer.

Overexpression of the HER-2/Neu oncogene occurs in 25% of breast cancers; its negative correlation with survival is limited almost exclusively to node-positive patients. In these patients overexpression is, as a single variable, associated with shorter disease-free and overall survival. An important clinical application of this prognostic factor is that those tumors found to overexpress HER-2/Neu are more likely to respond to high-dose chemotherapy, thereby improving the survival in that subset of patients (node positive, HER-2/Neu overexpressing). However, the absence of HER-2/Neu overexpression should not be construed as a reliable predictor of good outcome because the power of this marker is limited. For example, it is never overexpressed in lobular carcinomas and these recur at the same rate, stage for stage, as ductal carcinomas. Most importantly, fewer than 40% of the recurrent cancers show HER-2/Neu amplification, thereby further weakening the predictive power of this marker. However, used in the context in which it has been studied, HER-2/Neu can be a useful adjunct to therapeutic planning.

Overexpression of another oncogene, EGF-R (also called HER-1), has important prognostic implications in breast cancer. EGF-R overexpressing tumors are nearly always ER-negative and occur most often in premenopausal women. Unlike HER-2/Neu, overexpression of EGF-R protein is not due to gene amplification and is a negative prognostic factor independent of HER-2/Neu expression. A better understanding of the alterations in signaling that lead to EGF-R overexpression may help establish the role of this marker in the progression of breast cancer, thereby enhancing its clinical application in the future.

Markers associated with loss of cancer cell genome integrity and dysregulated passage through the cell cycle, such as ploidy (DNA content and number of chromosomes) and S-phase fraction (SPF), are important predictors of outcome, especially in node-negative tumors where the 5-year disease-free survival is approximately double for diploid and low-S-phase tumors. However, as the determi-

nation of these indices in archival specimens is inconsistent across laboratories, only frozen-section-derived values should be used clinically. In this context, this marker may be useful in the clinic in weighing decisions about cytotoxic treatment in tumors of borderline size, weakly positive or negative ER/PR status, and high histological grade. Other adjunct markers of mitotic activity such as Ki67/PCNA and thymidine labeling index (TLI) are less often used in the clinic and require specialized handling and expertise. Whereas the predictive power of Ki67/PCNA has been inconsistent, TLI may be a more robust marker than either ploidy or SPF. Except for medullary carcinomas for which the TLI is uncorrelated with prognosis, low TLI is an independent predictor of good outcome. At present, TLI is used mainly in further stratifying node-negative, ER-negative tumors.

Tumor suppressor gene mutations and protein product expression are actively under study for p53, ATM, BRCA1, and BRCA2, with p53 studies being the farthest along. Several independent studies using different antibodies have shown predictive significance for p53 expression in ductal carcinomas of the breast. However, standardized guidelines for interpretation of immunohistochemical staining for p53 are not yet available, thereby limiting its usefulness outside research protocols. It is expected, however, that knowledge of the role of these genes in sporadic carcinogenesis will provide robust avenues for diagnosis and therapy in the future.

In summary, the heterogeneity of breast cancer lesions is amenable to study and characterization by context-specific markers. Awareness of the limitations of the measurements and the clinical boundaries within which the markers have been studied allows for the rational application of this knowledge in therapeutic decisions in the clinic.

Hereditary Breast and Ovarian Cancer Syndrome

Familial breast cancer was described by physicians in ancient Rome. In modern times, the recognition that a positive family history is, after age, the most important risk factor has been fostered by epidemiological and genetic research. Other important nonheritable familial factors also affect risk, such as culturally derived dietary and reproductive habits, life-style variables such as exercise and diet, and environmental exposures. Genetically similar individuals are also likely to share multiple inherited factors that modulate the effect of a particular environmental risk on tumor suppressor genes. Increasing knowledge about the identity and function of genes responsible for hereditary breast cancer syndromes is leading to a better understanding of the interactions between these factors in the pathways leading to carcinogenesis.

Inherited breast cancers have several clinical characteristics that may help distinguish them from sporadic breast cancers. The age of onset is younger, bilaterality is more common, and associated tumors at other sites in affected individu-

als are noted in many families. Associated tumors may include ovarian, colon, prostate, and endometrial cancers, and sarcomas. Inherited and sporadic breast cancers have otherwise been found to be indistinguishable by histological type, grade, metastatic behavior, detectability by clinical or radiographic means, or response to therapy. Large correlative studies will be needed to provide a more accurate clinical picture of the natural history of inherited tumors. Based on that knowledge, the tailored management of affected breast cancer susceptibility gene carriers will be possible. In the meantime, most of our knowledge derives from epidemiological studies of population cross-sections and of high-risk families, primarily from North America and Western Europe.

Epidemiological Studies

Several population-based studies in the United States and Sweden have attempted to estimate the contribution of a positive family history to breast cancer risk. A standardized relative risk of 1.7 was found for women with a first-degree relative with breast cancer compared to controls without a family history. Higher risks were reports in studies involving large cohorts of volunteers who may have been more inclined to participate if they had a family history of breast cancer, thereby biasing the studies.

Populations enriched with high-risk families proved especially useful for the detection of a strong association between family history and breast cancer risk present only in a limited subset of the population. Factors that were shown to increase risk within families were premenopausal status at diagnosis and bilateral disease in relatives. Additionally, first-degree relatives of probands were found to be at higher risk than second-degree relatives. More strikingly, calculation of risk in individuals with two affected first-degree relatives (such as mother-daughter or sister-sister) with premenopausal, bilateral disease yielded a 50% lifetime breast cancer risk. These data suggested the presence of one or more autosomal dominant susceptibility gene(s), with nearly complete penetrance, responsible for the development of breast cancer in this subgroup of families. In contrast, the calculated risk of 7% in first-degree relatives of women with postmenopausal diagnosis and unilateral disease hardly differs from the general population risk. The isolation of three major tumor suppressor genes, *BRCA1*, *BRCA2*, and *TP53*, contributed to the understanding of the molecular bases for these epidemiological observations.

BRCA1

Since 1990, it has been known that a single locus on chromosomal region 17q12–21, termed *BRCA1*, is responsible for most cases of hereditary early-onset breast/ovarian cancer. Approximately 60% of families with breast cancer diagnosed before age 45 and 95% of families with breast and ovarian cancer appear to be linked to *BRCA1*. The penetrance or lifetime risk of breast cancer conferred by

a disease-associated germline *BRCA1* mutation is approximately 50–70%, by age 80, whereas the risk for ovarian cancer is approximately 45%. These estimates of risk continue to change as different types of families are studied for the presence of *BRCA1* mutations.

Among the family characteristics most likely to correlate with a *BRCA1* mutation are age of onset less than 45 years and breast and ovarian cancer in the same woman. Significant increases in the relative risks for colon (4.11, 95% CI 2.36–7.15) and prostate cancer (3.33, 95% CI 1.78–6.20) in *BRCA1* mutation carriers prompt reinforcement of the need for surveillance for these important diseases in both female and male carriers. In contrast to the general population in which only 10% of breast cancers occur in women under 60 years of age, for *BRCA1* mutation carriers, 60% of the risk of breast cancer has been realized by age 50. For this reason, screening for early detection of breast and ovarian cancer typically starts 5–10 years earlier than the earliest case of cancer in the family.

The BRCA1 protein comprises 1862 amino acids and is a putative transcription cofactor that may participate in genome preservation during mitosis. Studies of BRCA1 protein function in inherited and sporadic breast and ovarian carcinogenesis may suggest novel therapies based on this gene in the future. Seventy percent of the germline mutations in *BRCA1* encountered so far give rise to a truncated and/or qualitatively altered protein product. Approximately 10–15% of the disease-related mutations detected so far produce missense changes at codons interspersed throughout the gene; at present, these alterations can only be detected by detailed analyses of the germline DNA sequence. Although all *BRCA1* truncating mutations appear to be disease-associated, the specific risk a given mutation confers to a particular individual cannot be answered with certainty at this time. Given these complicating factors, thorough and reliable predictive testing for *BRCA1* is neither available nor warranted for the general population at *mildly* increased risk. In certain ethnically segregated populations, a few mutations have been found to account for a large number of at-risk individuals. In Ashkenazi Jews in the United States and Israel, three mutations in *BRCA1* account for nearly all of the *BRCA1*-linked families. Ethnicity is therefore an important factor in the eligibility criteria for genetic testing protocols.

Individuals from breast/ovarian families interested in risk assessment or in participating in research related to *BRCA1* may be referred to risk evaluation centers. Most centers have a contact person or toll-free number through which an informal preliminary consultation can advise the practitioner on whether referral is appropriate. Innovative methods of screening and counseling high-risk women and of training genetic counselors and nurse practitioners for the assessment and long-term follow-up of these patients are being developed at some specialized centers. In addition, it is anticipated that in the near future, prevention trials for mutation carriers will be opening in the context of risk assessment clinics

and community networks. Participation of primary care professionals in these trials will be key to achieving adequate accrual of diverse populations.

Mutations in *BRCA1* have so far been found to be present only rarely in sporadic ovarian cancers. However, loss or alteration in the function of the BRAC1 protein may be involved in sporadic breast and ovarian carcinogenesis and remains an area of active investigation.

BRCA2, Familial Male Breast Cancer, and Other Breast Cancer Genes

Germline mutations in *BRCA2* are likely to account for approximately 40–70% of the site-specific breast cancer families not linked to *BRCA1*. *BRCA2* mutations also appear to confer approximately 40–60% lifetime risk of breast cancer and an elevated (approximately 6%) risk of male breast cancer. Ovarian cancer cosegregates with breast cancer in *BRCA2*-linked families, but it tends to occur at a more advanced age than in *BRCA1* families. Approximately 5% of breast and ovarian families are found to be linked to *BRCA2*. The *BRCA2* gene is located on chromosome 13q and encodes for a 320-kDa protein whose function has not yet been ascertained, but like BRCA1, may be related to the monitoring of double-stranded genomic integrity. Most breast/ovarian *BRCA2* families exhibit mutations within the large exon 11 of *BRCA2*, but in other families, mutations are also interspersed throughout this large gene. Truncation of the extreme C-terminal amino acids of *BRCA2* does not appear to increase cancer risk, and is likely to represent a normal variant. This is in contrast to *BRCA1*, for which all truncating mutations appear to be disease-associated. This is an important difference that impacts on the counseling of *BRCA2* families.

Male breast cancer is extremely rare and the familial form probably accounts for only a small proportion of cases. Only a few dozen families with two or more cases of male breast cancer were reported in a 100-year period. More than half of these families show that first-degree relatives of male breast cancer cases have other types of cancers including oropharyngeal, ovarian, and female breast cancer, suggesting an inherited component to familial clustering of male breast cancer. *BRCA2* is thought to be responsible for the increased susceptibility to male breast cancers and other cancers observed in many of these families.

An interesting association between germline mutations in the androgen receptor gene and familial male breast cancer may provide the molecular basis for the increased susceptibility to breast cancer in men with relative androgen deficiency manifested by gynecomastia, orchitis, testicular atrophy, and Klinefelter's syndrome.

The *PTEN* gene on chromosome 10q has recently been isolated and is responsible for the familial Cowden's syndrome of cancer susceptibility, which involves excess of breast cancer (see Table 2). Families that fulfill the characteris-

TABLE 2 Hereditary Syndromes Associated with Breast and Ovarian Cancer

Tumor	Syndrome	Other malignancies or characteristics
Breast	BRCA associated	Breast, ovary, prostate
	Ataxia-telangiectasia	Telangiectasia, spinocerebellar degeneration
	Li-Fraumeni disease	Sarcomas, brain tumors, leukemia
	Cowden disease	Trichilemmomas, GI polyposis, uterine leiomyomata
	Muir-Torre disease	Basal cell carcinoma, GI tumors
Ovary	Lynch II	Uterine, colon, genital-urinary cancers
	Gonadal dysgenesis	46 XY
	Peutz-Jeghers syndrome	Oral pigmented lesions, GI polyposis
	Ollier's disease	Enchondromatosis
	Basal nevus syndrome	Basal cell carcinomas, jaw cysts
	Familial ovarian fibromatosis	Ovarian hyperplasia

tics of this relatively rare syndrome may be referred for appropriate studies of the *PTEN* gene in specialized centers, as this kind of testing is not offered commercially at this time.

In spite of increasing sensitivity in predictive testing for *BRCA1* and *BRCA2*, it is clear that over 30% of breast cancer families are not accounted for by these genes. Other genes are being actively sought on candidate loci on chromosomes 17p, 17q distal to the *BRCA1* locus on 17q23 and 17q25, 18q, 8p, 10q, and 3p, which may be responsible for most of the remaining autosomal dominant breast cancer families.

TP53

The *TP53* gene is located on chromosome 17p13.1 and codes for a 393-amino-acid nuclear phosphoprotein. Somatic mutations of this gene are observed in 50–60% of a wide variety of human cancers, in a nonrandom pattern, which preferentially involves regions of highly conserved sequence motifs. Intriguing phenotype-genotype correlations have arisen from comparison of the patterns and types of mutations present in different kinds of cancers. ''Hot spots'' of missense mutations are observed in sporadic tumors of many organs and in certain viral- or toxin-associated cancers leading to the hypothesis that the production of faulty TP53 protein may lead to uncontrolled growth in these cases. In contrast, virtually all the alterations seen in osteosarcomas and chronic myelogenous leukemias involve rearrangements and homologous deletions resulting in the absence of TP53 protein. *TP53* mutations are also found in the germline of some families affected with the Li-Fraumeni syndrome (LFS). These kindreds have at least one

member affected with an osteosarcoma, and relatives with brain, breast, adrenocortical, stomach, and other carcinomas. Early-onset breast cancer is common, with 77% of cases occurring between 22 and 45 years; the breast cancer cases in LFS are distinguished from the *BRCA1* and *BRCA2* families by the striking incidence of a wide variety of other types of cancer. These families are rare and the diverse clinical concerns they elicit may warrant early referral to a specialized cancer genetics clinic. Mutation testing is available for families at risk; genetic testing and counseling are used to guide individuals into appropriate surveillance protocols for early detection of cancer.

Other Syndromes Associated with Increased Risk of Breast Cancer

The Mendelian inheritance of a germline mutation plays a major role in the development of breast cancers in the important familial syndromes listed in Table 2. In some cases, the genes affected are known, such as *MSH2* and *MLH1* in Muir-Torre syndrome, which is characterized by skin tumors and multiple benign and malignant tumors of the upper and lower gastrointestinal and genitourinary tracts.

Ataxia-telangiectasia (AT) is an autosomal recessive disorder characterized by cerebellar ataxia, oculocutaneous telangiectasias, radiation hypersensitivity, and an increased incidence of malignancies. The genetic defect that underlies the clinical syndrome of AT has recently been elucidated and it is believed to result in chromosomal fragility. AT homozygotes have a risk of cancer that is 60–180 times greater than that of the general population, manifested by a nearly 100% lifetime risk of non-Hodgkin's lymphoma and somewhat lower risks of developing breast and ovarian cancer, lymphocytic leukemia, head and neck, stomach, pancreas, and bladder cancer. In particular, the breast cancer risk in AT mutation carriers is much lower than the risk observed in women with germline mutations in *TP53* or *BRCA1*. AT heterozygotes do not demonstrate the neurological symptoms of AT, but may have an increased incidence of breast cancer, although the exact risk has not yet been determined.

The recognition of the features and distribution of lesions associated with these syndromes will expedite referrral to a specialized cancer genetics clinic for recommedations on a surveillance program, which should most often be implemented at the patient's community.

Risk Assessment for Breast Cancer in the Clinic

Dissemination of information by advocacy groups, the media, medical professional organizations, and the government has increased public awareness of the high incidence of breast cancer in the United States. Recent advances in the genetics of breast cancer have received considerable attention. As a result, clients are more informed about issues surrounding risk factors and are concerned about their individual risk of developing breast cancer. These patients are bringing their

concerns to primary care practitioners and requesting specific risk assessment. Recognition of the contribution of heritable factors to the development of breast cancer has resulted in an important role for genetic counseling when available in the care of women with a family history of the disease. The task of risk assessment for women and families concerned about breast cancer consists of: the collection of a detailed medical history of the extended family, interpretation of this history in light of current information to assess individual risk, clear communication of this information to patient and family, and discussion of options for minimizing the risk.

Family history information constitutes the main focus around which all subsequent tasks revolve. It is initially collected in the community by concerned practitioners. A thorough history should include the characteristics (organ of origin, laterality, histological type, age of onset) of all cancers in blood relatives as well as the positions of these relatives within the family pedigree. The positions of unaffected relatives within the family are essential to the assessment of inheritance patterns. Whenever possible, family history data should be confirmed by medical and pathology records to ensure accuracy. Patients have been shown to identify correctly the sites of primary cancer in first-degree relatives 83% of the time, with significant declines in accuracy as the distance of relationship increases.

Following the isolation of breast cancer susceptibility genes such as *BRCA1* and *BRCA2*, breast and ovarian cancer families are being studied to develop more accurate estimates of the risks conferred by specific mutations. The estimation of the risk of ovarian cancer is especially challenging owing to variability in the penetrance of this disease.

Another important challenge is presented by the large number of families with apparent autosomal dominant inheritance of breast cancer where *BRCA1* or *BRCA2* mutations are not detected in affected family members or where linkage to *BRCA1* or *BRCA2* cannot be determined. For these families, issues related to autosomal dominant inheritance of breast cancer susceptibility are discussed and estimates of risk derived from epidemiological studies can be provided. Research is underway on the contribution of *BRCA1*, *BRCA2*, and other breast cancer genes to the risk of breast cancer in families with apparent autosomal dominant transmission but fewer cases of breast cancer.

Most of the patients seeking risk assessment do not have a family history consistent with a highly penetrant breast cancer susceptibility gene. The breast cancer risk of an individual can be estimated by empirical data on the frequency of breast cancer in a large population of women with an equivalent family history. This method of risk assessment makes no assumptions regarding the mode of transmission of breast cancer among the relatives and these estimates are subject to the design limitations of the study from which they derive.

An alternative approach, termed analytic, is based on a specific model of

transmission to estimate risk of breast cancer in these ''small families.'' Although the estimation of analytic risk is standard practice in genetic counseling of many inherited disorders, it has not been routinely employed for breast cancer because of the absence of a widely accepted model of disease transmission. As more genetic information becomes available, it is expected that these models will be refined and may prove useful in the assessment of individual risk.

The information derived from risk assessment for breast cancer is of great importance for the patient and the family. The individual receives risk information in a medical setting, regardless of whether an actual genetic test is performed. This may inspire in patients assumptions of high accuracy and sound scientific backing, which need to be discussed by the counselor in a realistic light commensurate with the present molecular understanding. Therefore, in addition to research efforts on the molecular genetics of breast cancer, important studies are being conducted on the methodology and ethics of risk assessment, counseling, and decision making. Interested patients should be encouraged to participate in approved protocols conducive to acquiring this clinically important knowledge.

COLORECTAL CANCER

The care of patients with colorectal cancer (CRC) has been revolutionized by advances in the study of molecular genetics. The pathogenesis of CRC is determined by a series of molecular events that transform cells from normal, epithelial mucosa into malignant tumors with the potential to metastasize. Detailed molecular studies of CRC have changed the screening, diagnosis, and management of patients with rare syndromes such as familial adenomatous polyposis (FAP), and now the impact of these advances is being realized in the management of patients with sporadic CRC. This section reviews the major molecular events in CRC, describes criteria for recognizing hereditary forms of CRC, and outlines the clinical application of this technology in the screening, diagnosis, and treatment of patients with CRC.

In the 1980s several groups showed that normal cellular homologs of oncogenes existed in human cells, and that the activated version of these genes (oncogenes) could transform cell lines into cancer. The idea that accumulated genetic changes were responsible for the development of neoplasia and that these changes could be correlated to identifiable pathological transitions from normal tissue to cancer was first described in CRC (Fig. 1). The details of this model and its confirmation in subsequent studies demonstrated the importance of oncogenes and tumor suppressor genes in common human cancers. Subsequently the discovery and characterization of *APC* as a gatekeeper gene regulating the development of polyps provided a molecular description of how CRCs are initiated. CRC also served as a molecular model for understanding tumor promotion through the mismatch repair genes that are altered in hereditary nonpolyposis colorectal can-

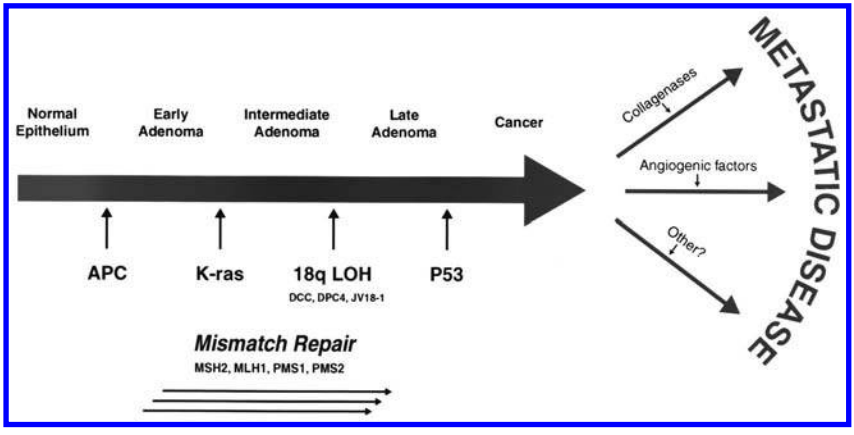

FIGURE 1 The molecular pathogenesis of CRC can be described as a series of genetic events that are responsible for the transition of normal colonic epithelium into polyps, invasive cancer, and metastatic disease. (Adapted from Cell 1990; 61:759–767.)

cer (HNPCC). These genes accelerate the rate of progression of benign adenomas to cancer by failing to repair a particular kind of error in DNA replication. Mismatch repair genes do not increase the number of adenomas, but greatly increase the likelihood that an adenoma will progress to cancer. Other mechanisms of cancer development continue to be identified in colorectal cancer, including a very common mutation in *APC* first identified in Ashkenazi Jews. This particular mutation, I1307K, increases the mutation rate of *APC* itself and predisposes to a form of colon cancer that is virtually indistinguishable from sporadic CRC.

Hereditary Colorectal Cancer

At least 15% of all CRC is hereditary, and hereditary colorectal cancer can usually be recognized by analyzing the family history. The two best characterized syndromes are FAP and HNPCC. Several other polyposis syndromes are associated with a very high risk of CRC, including Peutz-Jeghers syndrome (PJS) and juvenile polyposis. The molecular pathogenesis of cancer arising in each of these syndromes is distinct, although some features are common to all.

FAP

FAP accounts for $<1\%$ of all CRC and is inherited in an autosomal dominant pattern. This debilitating syndrome is rare, with an incidence of 1 in 10,000. FAP is recognized by the presence of hundreds to thousands of polyps that carpet the

colon. These polyps typically begin to develop in early adolescence, and the increased risk of cancer is probably explained by a normal, low somatic mutation rate applied to an overwhelming number of polyps. If untreated, nearly all patients with FAP develop colon cancer by the age of 40. The treatment for FAP is total colectomy, which eliminates the risk of colon cancer by removing the organ at risk. Often patients and surgeons opt to leave the rectum in place, and it is imperative that these patients continue to be followed with serial sigmoidoscopic evaluations.

Extracolonic manifestations of FAP are fairly common, and include benign desmoid tumors, osteomas, and congenital retinal hypertrophy of the pigmented epithelium (CHRPE). Desmoid tumors tend to arise at surgical wound sites and can become quite large and difficult to manage. Even though desmoid tumors are benign, they can lead to local problems such as pain or small bowel obstruction. The fact that surgical exploration increases the likelihood of desmoid formation and the observation that these tumors tend to recur argues for minimizing surgery as much as possible among patients who form desmoids. Osteomas are benign bony outgrowths commonly identified in the mandibles of FAP patients that usually do not require specific management. CHRPEs (also called pigmented ocular fundus lesions, POFLs) can be an important clinical sign of FAP. Rare complications of FAP include thyroid cancer, hepatoblastoma, and brain tumors.

The molecular basis of FAP is attributable to mutations of the *APC* gene on chromosome 5q. The clinical features are not uniform, despite the fact that all patients with FAP have shortened C-terminal proteins. Mutations have been identified throughout *APC*, and some strong relationships between specific genetic changes (genotype) and clinical manifestations (phenotype) are becoming clear. For example, the most common mutation in *APC* is found at codon 1309, leading to a classic picture of innumerable adenomas lining the colon. Some, but not all, patients with a 1309 mutation also have extracolonic features of FAP such as desmoid tumors or CHRPEs. However, mutations between codons 1403 and 1578 of APC are much less likely to be associated with CHRPEs. Other areas seem to be hot spots for extracolonic manifestations. Finally, truncating mutations proximal to codon 157 lead to an attenuated form of FAP with far fewer polyps than the classic syndrome. The study of APC and colorectal cancer clearly demonstrates that all mutations are not created equal, and future studies will be required to define the subtleties of specific mutations.

The mechanism of how the APC protein participates in the regulation of colorectal neoplasia is becoming clear (Fig. 2). Normally *APC* is thought to serve two functions. It directly signals cells to migrate from their point of origin in the epithelial crypts to the villi, where they die by apoptosis. *APC* also regulates β-catenin levels, normally degrading catenin to keep intracellular levels low. When *APC* is mutated and is not working properly, intracellular catenin levels rise. High levels of β-catenin then bind to APC, and this complex seems to directly

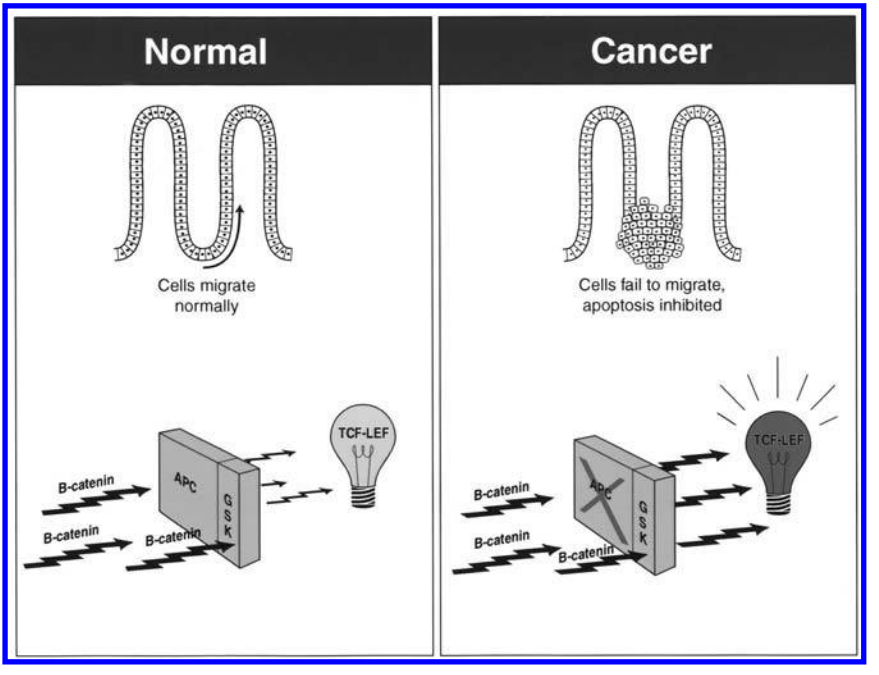

FIGURE 2 APC regulates the development of adenomatous polyps in the colon. APC normally forms a complex with GSK, and this complex lowers the intracellular levels of β-catenin by breaking down β-catenin. APC provides a direct signal to cells in epithelial crypts to migrate to the villi, where they slough and die. When APC is mutated, this direct signal is interrupted and cells fail to migrate appropriately. In addition, mutated APC cannot break down β-catenin, and intracellular β-catenin levels rise. β-catenin then stimulates the TCF-LEF family of proteins to activate gene expression, further signaling epithelial cells to stop migrating and stop dying through apoptosis. (Adapted from Science 1997; 275:1752.)

inhibit normal cell migration. In addition, high β-catenin levels can then reach the nucleus where β-catenin cooperates with a family of proteins called TCF (for T-cell factor) to activate gene expression and inhibit apoptosis. Several different mutations of *APC* have been studied, and all that have been examined work through this mechanism. But it is not yet clear how phenotypic variations of FAP are explained by different mutations in *APC*.

Gene testing has changed the care of patients with FAP. For many hereditary cancer syndromes it is difficult to demonstrate the benefits of incorporating genetic testing into clinical care; that is not the case for FAP. Because FAP is inherited in an autosomal dominant manner, has a penetrance of 100%, can be

treated effectively, and leads to cancer in all untreated patients, gene testing has become standard in the management of patients and families with FAP. Without gene testing, yearly sigmoidoscopy is recommended beginning around age 10 for all family members at risk. As soon as polyps begin to form, prophylactic colectomy is recommended. When a family's mutation is known, a negative test in a child at risk can result in a very different management plan. Instead of annual endoscopy, the gene test is repeated to confirm the negative result, or sigmoidoscopy is recommended at ages 18, 25, and 35 with one negative gene test result. A positive test permits children and families to anticipate colectomy and to prepare for something already quite familiar to the family. In addition, presymptomatic children who test positive are eligible for a chemoprevention trial of sulindac designed to test whether this nonsteroidal anti-inflammatory agent will delay the onset of polyps beyond the formative years of adolescence.

HNPCC

HNPCC is an autosomal dominant cancer syndrome related to mutations in mismatch repair genes that accounts for 5–10% of all CRC. This clinical syndrome was first described in 1912 by Alfred Warthin, and later studied by Henry Lynch. Lynch's detailed clinical and familial descriptions led to the common nomenclature of familial CRC without other cancers (Lynch syndrome I) and familial CRC in association with cancers of the endometrium, ovary, stomach, small bowel, ureter, and renal pelvis (Lynch syndrome II). Diagnostic criteria for HNPCC were established by an International Collaborative Group that first met in Amsterdam. The ''ICG'' or ''Amsterdam Criteria'' are met when there is no evidence of familial polyposis and: (1) at least three family members have CRC, two of whom are first-degree relatives, (2) at least two generations have been diagnosed with CRC, and (3) at least one family member has been diagnosed before the age of 50. These criteria were especially helpful in identifying the research families that led to the discovery of the molecular basis of HNPCC, but the criteria are overly restrictive as clinical tools as they do not incorporate other tumor sites and miss some families.

The molecular basis of HNPCC is related to mutations in a family of genes integral to mismatch repair. Linkage studies demonstrated that genes responsible for HNPCC were located on the short arm of chromosome 2 in some families and the short arm of chromosome 3 in others. The search for these proposed tumor suppressor genes took an unexpected turn when new microsatellite alleles were observed in areas of the genome that contained dinucleotide and trinucleotide repeats. Investigators expected that DNA from tumors in HNPCC families would show a loss of one of the two alleles seen in normal tissue, as this ''loss of heterozygosity'' had been the rule for all previously discovered tumor suppressor genes. What was actually observed was exactly the opposite. Additional alleles were seen instead of the loss that was expected. The molecular basis of these

extra bands became clear when researchers discovered that HNPCC is due to an inherited mutation of any one of a family of genes responsible for the repair of mismatched DNA sequences. Repeated sequences such as dinucleotide and trinucleotide repeats are especially vulnerable to mismatch, and mutated mismatch repair genes lead to ''extra bands'' that are not properly recognized, excised, and repaired.

The clinical management of families with HNPCC has lagged behind molecular advances. There are no good clinical data to support one screening and management strategy over another. For families that meet the strict clinical criteria for HNPCC, most approaches have recommended yearly fecal occult blood testing and colonoscopy every 1–3 years beginning at either age 25 or 5–10 years earlier than the earliest at age which CRC was first diagnosed in the family, whichever is younger. For families with histories less impressive than that of classic HNPCC, most specialist providers relax the screening recommendations to colonoscopy every 3–5 years, beginning at age 35–40, or 5–10 years earlier than the earliest age at diagnosis of CRC. Screening recommendations for other tumors in the HNPCC spectrum vary considerably, from no additional screening to transvaginal endometrial ultrasound with or without biopsy.

Genetic testing for HNPCC is thought to provide a clinical benefit, but has not been shown to provide an unequivocal clinical advantage. Several high-risk clinics incorporate molecular workups of patients and families as shown in Figure 3. In families that carry a known mutation of a mismatch repair gene, genetic testing of at-risk individuals can be helpful in planning screening strategies by directing frequent screening to those who carry a mutation, and avoiding unnecessary screening procedures in those who do not. Families who do not carry a known mutation can be tested in several ways, and the relative efficiencies of each approach have not been studied. Several clinical trials assessing the risks and benefits of genetic testing for HNPCC are underway.

Other Familial CRC Syndromes

Approximately 5–6% of all CRC among individuals of Ashkenazi Jewish descent is attributable to a novel mutation in *APC* that predisposes to colorectal cancer and polyps, but does not cause the hundreds to thousands of polyps observed in FAP. This mutation appears to double a person's risk of CRC, and is found in 6% of Ashkenazi Jews, and 28% of Ashkenazim with a family history of CRC. This newly described mutation, I1307K, predisposes to CRC by creating a hypermutable tract in the *APC* gene itself, and this short hypermutable region is especially vulnerable to further mutations that predispose to CRC.

The hamartomatous polyposis syndromes, PJS, juvenile polyposis, and Cowden disease, are rare polyposis syndromes that carry an increased risk of CRC. PJS is an autosomal dominant disorder characterized by benign hamartomatous polyps of the gastrointestinal tract and mucocutaneous pigmentation on the

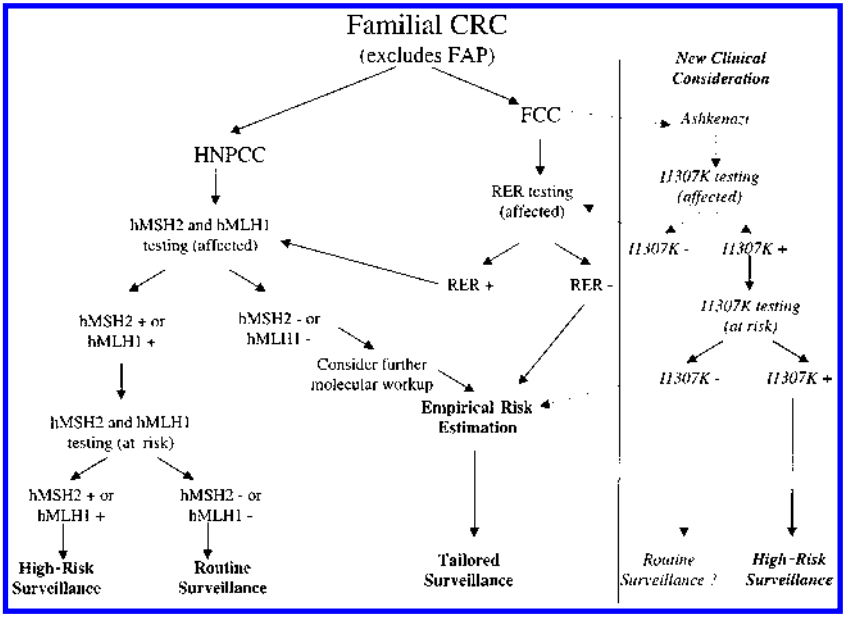

FIGURE 3 The molecular diagnostic workup of familial colorectal cancer (FCC) depends on the strength of the family history of cancer. Families that meet the ICG criteria for HNPCC are likely to carry a mutation in a mismatch repair gene, and hMSH2 and hMLH1 account for more than 60% of these cases. Families that have FCC, but do not meet all aspects of the ICG criteria, may also carry a mutation in a mismatch repair gene. Testing tumor specimens of an affected individual for the replication error (RER) phenotype can help identify whether gene testing for mismatch repair genes is likely to be useful. Individuals who carry a mutation in a mismatch repair gene are likely to benefit from high-risk surveillance. When a molecular diagnostic workup is uninformative, clinicians need to rely on empirical risk estimates from epidemiological studies. Families of Ashkenazi descent may carry a mutation called 11307K that predisposes to CRC. When identified within a family, this mutation may be helpful in directing some family members to high-risk surveillance.

lips, buccal mucosa, eyelids, and fingertips. The most common complication of PJS is small bowel obstruction due to enlarging hamartomas, but individuals with PJS are also at increased risk of cancer, especially of the small bowel and colon. Several studies have shown that the locus for PJS is located at the distal end of the short arm of chromosome 19 (19pter), but the gene has not yet been cloned.

Cowden disease, an autosomal dominant disorder also known as multiple hamartoma syndrome, is extremely rare and carries a greater risk of breast and thyroid cancer than gastrointestinal malignancy. Like PJS, the gastrointestinal

tumors arising in Cowden disease are usually benign hamartomas, but can progress to malignancy. The gene for Cowden disease, *PTEN*, was identified in 1997 and is located on the long arm of chromosome 10. Gene testing for *PTEN* has not yet been incorporated into clinical practice. Similarly, the gene for juvenile polyposis has not yet been localized or cloned, and therefore clinicians do not yet have molecular diagnostic tools to guide the management of patients and families with juvenile polyposis. Surveillance for the early detection of cancers in each of these hamartomatous polyposis syndromes is recommended by most groups, but no screening guidelines have been adopted uniformly.

Molecular advances have led to remarkable changes in the understanding of the biology of CRC and its clinical management. Genetic testing is an important component of the management of patients with FAP, and is becoming increasingly useful in the management of familes with HNPCC. It is likely that the screening, chemoprevention, diagnosis, and management of CRC will all become increasingly reliant on molecular technology as new information about the genetic epidemiology of CRC, including common mutations such as the I1307K mutation among Ashkenazi Jews, becomes available.

PROSTATE CANCER

Prostate cancer is the most common cancer affecting men in the United States. However, compared to breast and colon cancer, the contribution of molecular biology to our understanding of prostate cancer is comparatively less. This section will review the two areas in which molecular biology has contributed substantially, however, to the field of prostate cancer, namely the early detection of prostate cancer and inherited prostate cancer susceptibility.

Early Detection of Prostate Cancer Using PSA

Prior to the mid-1980s, most cases of prostate cancer were detected based on clinical symptomatology. This included alterations in urinary function due to local prostate cancer and bone and/or abdominal pain due to metastatic disease. The diagnosis of asymptomatic prostate cancer can now be accomplished in some patients through detection of an elevated serum-prostate-specific antigen (PSA) level. This molecule was first isolated from seminal fluid in 1972. The gene encoding PSA (termed *APS*) is located on chromosome 19q13.3. PSA is a kallikrein-like serine protease. A commercial test to identify this 237-amino-acid glycoprotein in plasma has been available since 1987. A large number of studies have subsequently appeared in the literature over the past decade in which measurement of PSA was utilized for the early detection of prostate cancer. In general, a serum PSA value of greater than 4.0 ng/ml using a polyclonal assay has

been considered abnormal and indicative of the need for additional diagnostic evaluation.

PSA is a tissue-specific marker rather than a cancer-specific marker with expression primarily restricted to the prostate gland. Thus a number of benign conditions and other factors may confound the use of PSA as a tumor marker. For example, both benign prostatic hypertrophy and acute and chronic prostatitis have been associated with serum PSA levels above the normal range. Furthermore, manipulation of the prostate gland via transurethral resection or biopsy can result in markedly elevated serum PSA values.

A number of investigators have attempted to improve the sensitivity and specificity of serum PSA measurements for the diagnosis of prostate cancer. This has included measurement of PSA density (concentration of serum PSA/prostate gland size) and PSA velocity (change in PSA/time). While studies continue to assess the utility of these measures, neither has been formally incorporated into the routine standard of care of patients being evaluated for prostate cancer. A more recent area of investigation has involved the measure of various molecular forms of PSA. PSA is primarily bound to serum proteins, namely α-2-macroglobulin (A2M) and α-1-antichymotrypsin (ACT). When PSA is complexed to these serum proteins, it varies in its immunoreactivity as well as its enzymatic activity. The minority of PSA is noncomplexed or free in the serum ($<$10%); free PSA is biologically inactive. Many laboratories have been developing antibody-based detection assays to distinguish between free and complexed forms of PSA for clinical indications. This research has developed from the observation that the percentage of free PSA is lower in patients with prostate cancer compared to patients without prostate cancer. Thus, measurement of the ratio of free/total (where total = free + complexed) PSA has been widely investigated to determine its ability to improve the specificity of PSA measurements for the diagnosis of prostate cancer. While most studies suggest that use of free PSA measurements may be helpful in determining the existence of cancer in patients with a mildly elevated PSA, additional work must be done to determine the optimal cutoffs before this test can be carried into widespread clinical use.

Randomized clinical trials are currently ongoing to determine whether screening for prostate cancer will result in an overall decrease in prostate cancer mortality. For example, the National Cancer Institute is sponsoring the PCLO trial in which men and women between the ages of 60 and 74 are routinely screened for prostate, colorectal, lung, and ovarian cancer. Unfortunately, the results of trials such as this will not be available until well after the year 2000. In the meantime, physicians must make decisions based on the current data whether or not to screen asymptomatic men for prostate cancer. While some groups such as the U.S. Preventative Health Services Task Force have not supported routine screening, the American Cancer Society has recently revised their recommendations for the early detection of prostate cancer (see References).

They recommended that physicians offer a PSA test and a digital rectal examination annually to men between the ages of 50 and 69 years who have an estimated life expectancy of greater than or equal to 10 years. Men at increased risk for the disease such as African-American men and/or those with a strong family history may be offered screening at an earlier age although that age has not been determined. An important part of this recommendation includes a discussion between the physician and patient regarding the risk and benefits of prostate cancer early detection for the individual in question.

Development of Novel Prostate Cancer Markers

Given the potential problems with PSA as a molecular screening tool for prostate cancer, a number of investigators have attempted to define additional molecules that more accurately detect the asymptomatic presence of cancer within the prostate gland. Other molecules may provide clues about the potential biological behavior of a tumor that would improve our ability to diagnose clinically significant cancers. One such molecule is prostate-specific membrane antigen (PSMA), which can be detected in the serum of prostate cancer patients. Several studies have suggested that elevated serum levels of PSMA may correlate with a poorer prognosis, although this finding has not been uniformly observed. Another molecule that is under active investigation as a potential prostate tumor marker is human kallikrein 2 (hK2). hK2 is a kallikrein with approximately 80% homology to PSA and expression limited primarily to the prostate gland.

Inherited Predisposition to Prostate Cancer

While the effects of age and race on the incidence of prostate cancer are well documented, the contribution of family history to prostate cancer risk has been recognized only within the last decade. At least eight large epidemiological studies have now demonstrated that men with a family history of prostate cancer are at increased risk of the same disease. In fact, some studies indicate that the familial clustering of prostate cancer is greater than that observed with breast and colon cancer, diseases for which multiple site-specific cancer predisposition genes have been defined. Segregation analyses performed using several independent data sets have demonstrated that the most likely explanation for the observed familial clustering of prostate cancer is autosomal dominant inheritance of a rare prostate cancer susceptibility gene(s). This gene(s) has been hypothesized to contribute to a significant percentage of early-onset cancer but a much smaller percentage of the total number of prostate cancer cases. From this work, the following clinical definition of hereditary prostate cancer has been proposed by Carter et al.: (1) three or more affected individuals within one nuclear family, (2) affected individuals occurring in three successive generations (maternal or paternal lineage), or (3) a cluster of two or more relatives each affected before the age of 55. Patients

who have at least one family member affected with prostate cancer but do not meet the criteria above are said by these investigators to have familial prostate cancer. Using these definitions, approximately 20% of families with more than one case of prostate cancer may be considered to have hereditary prostate cancer. Others studies have suggested there may also be autosomal recessive or X-linked prostate cancer susceptibility genes.

Many groups have developed research programs to identify and collect DNA samples from affected and unaffected individuals from families with multiple cases of prostate cancer in order to identify prostate cancer susceptibility genes. However, successful identification of these genes will require analysis of a large number of prostate cancer kindreds due to complicating factors for this late-onset disease. These factors include the changing incidence of disease attributable to early detection programs and the inability of investigators to distinguish genetic and nongenetic forms of the disease based on clinical features alone. Finally, prostate cancer is extremely common in the general population with a one in five lifetime probability that an individual will develop prostate cancer. This high phenocopy rate further contributes to the difficulty in distinguishing inherited from sporadic cases.

Identification of the First Prostate Cancer Susceptibility Locus

Investigators from Johns Hopkins and the National Institutes of Health reported the first genetic locus that may contribute to the inherited predisposition to prostate cancer in November 1996. This locus, termed *HPC1*, has been mapped to the long arm of chromosome 1q. Identification of this locus resulted from genome scanning of individuals from a large number of high-risk prostate cancer families identified in North America and Sweden. Additional statistical analyses of these families suggested that the *HPC1* gene may contribute to prostate cancer in only one-third of families studied. These data suggest the likely presence of additional prostate cancer susceptibility genes. While one report has confirmed linkage of prostate cancer to markers that map to the *HPC1* candidate region using an independent set of families, others have been unable to confirm the contribution of this gene to prostate cancer susceptibility. Other studies suggest that families with prostate cancer due to mutations in *HPC1* may have an earlier age of onset of prostate cancer and more advanced disease at presentation. These subtle clues may accelerate the identification of families with potential defects in *HPC1* and therefore facilitate the positional cloning of this potential disease gene.

Other Genetic Alterations that May Contribute to Prostate Cancer Susceptibility

Genes similar to *HPC1* are hypothesized to be highly penetrant. For example, individuals who inherit a mutant *HPC1* allele may have an 80–100% chance of

developing prostate cancer in their lifetime. However, these *HPC1* (and perhaps *HPC2*, *HPC3*) alleles are likely to be relatively rare. In contrast, there are a number of genetic alterations that may be more common in the population but do not appear to be highly penetrant. Since these genetic alterations are so prevalent, the attributable risk associated with these genetic loci may be significant.

Alterations in the CAG trinucleotide repeat in exon 1 of the androgen receptor (*AR*) gene is an example of a genetic variation that is associated with minor alterations in prostate cancer risk. This trinucleotide repeat is polymorphic in the population. Furthermore, it was observed that African-American men have shorter *AR* CAG repeats compared to Caucasian men. Asian men have significantly longer *AR* CAG repeats compared to those observed in either racial group. Interestingly, this finding corresponds to the observed variation in prostate cancer incidence between men in different racial groups (African-American men $>$ Caucasian-American men $>$ Asian men). Functional studies have demonstrated that shorter *AR* CAG repeats result in increased transcriptional activity of the *AR*. Recent case-control studies within the Caucasian population have indicated that shorter CAG repeats may be associated with an approximately 1.5–2.0-fold increased relative risk of prostate cancer. One study also suggested that shorter *AR* CAG repeat lengths are associated with a greater likelihood of distant metastatic cancer and death from prostate cancer. While these studies are preliminary, measurement of the *AR* CAG repeat length may be important in determining men who are at increased risk for the development of clinically significant prostate cancer. Similar studies have suggested that there may be high-risk alleles of the steroid 5-α-reductase-2 and the vitamin D receptor genes.

The increasing understanding of the molecular genetics of breast, colorectal, and prostate cancer is impacting the practice of oncology and the care of families with high prevalence of these cancers. As this new knowledge reaches the clinic, the methods for using these advances for improving public health are also being investigated, with the hope that the merging of the bench and the clinic will improve survival and quality of life for patients with cancer and contribute to prevention.

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