FOURTH EDITION

Cancer Management: A Multidisciplinary Approach

Medical, Surgical, & Radiation Oncology

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Library of Congress Catalog Card Number 99-075070
ISBN Number 1-891483-05-6

For information on obtaining additional copies of this volume, contact the publishers, PRR, Inc., 48 South Service Road, Melville, NY 11747

Printed on acid-free paper

PRR
MELVILLE, NY

Publishers of
ONCOLOGY
Oncology News International
Managed Care & Cancer
Primary Care & Cancer
InTouch—*The Good Health Guide to Cancer Prevention and Treatment*
Cancer Consultations

CHAPTER 6

Non–small-cell lung cancer and mesothelioma

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In the United States, lung cancer has been the leading cause of cancer death in men for years, and since 1988 it also has become the number one cause of cancer death in women. It is estimated that, in 2000, 171,600 new cases of lung cancer will be diagnosed, and 158,900 deaths due to this disease will occur. This exceeds the combined number of deaths from the second, third, and fourth leading causes of cancer (breast, prostate, and colon cancer, respectively).

Lung cancer appears to develop from a stem cell that can differentiate along multiple lines. Although multiple cell types are often found within a single lung tumor, one type usually predominates. Based on therapeutic approach, there are two major subdivisions of lung cancer: SCLC, for which chemotherapy is the primary treatment, and NSCLC, which, in its early stages (I and II), is treated primarily with surgery.

This chapter will focus on the diagnosis, staging, pathology, and treatment of NSCLC, including carcinoid tumors of the lung, while chapter 7 will provide information on the staging, pathology and pathophysiology, and treatment of the far less common SCLC. In addition, this chapter will also provide basic information on the epidemiology, etiology, screening and prevention, and signs and symptoms of lung cancer in general, as well as the pulmonary evaluation of lung cancer patients. This chapter will conclude with a brief discussion of mesothelioma.

NON-SMALL-CELL LUNG CANCER

Non–small-cell tumors account for approximately 80% of all lung cancers. The three major tumor types included under this category are adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma.

Epidemiology

Gender In 1984, there were 87 cases of lung cancer per 100,000 men, and in 1994 this number decreased to 74 cases per 100,000 men. Although lung cancer

incidence had been rising in women, the rate of increase has begun to slow recently. In 1995, there were 43 cases of lung cancer per 100,000 women.

Age Although the age at which lung cancer patients are diagnosed varies widely, the median age at diagnosis is approximately 60 years.

Race In the United States, the highest incidence of lung cancer is found in Hawaiians and African-Americans.

Geography There are geographic variations in the incidence of lung cancer, with the highest rates worldwide observed in Scotland and Wales, and the highest rates in the United States found in northern urban areas and along the southern coast from Texas to Florida.

Survival The overall 5-year survival rate for lung cancer is 14%.

Etiology and risk factors

Cigarette smoking Approximately 87% of all cases of lung cancer are related to cigarette smoking. There is a relatively strong dose-response relationship between cigarette smoking and the development of this cancer. An individual who smokes one pack of cigarettes daily has a 20-fold increased risk of developing lung cancer compared to a nonsmoker. The greater the number of cigarettes smoked on a daily basis and the greater the number of years of smoking, the greater is the risk of developing lung cancer.

Overall, there has been a decrease in the incidence of cigarette smoking from 1974 through 1992. Smoking cessation decreases the risk of developing lung cancer, but a significant decrease in risk does not occur until approximately 5 years after stopping. In addition, the risk of developing lung cancer in former smokers remains higher than the risk in nonsmokers for at least 25 years. The benefit of smoking cessation is greater if it occurs at a younger age.

Smoking cessation is difficult. Recent data have suggested that certain individuals have an increased risk of addiction to nicotine based on a variety of hereditary factors. Nevertheless, millions of former smokers have quit successfully. Smoking cessation programs that address both physical withdrawal from nicotine and psychological dependence appear to be more effective than either of these approaches alone. In addition, continued efforts are needed to prevent adolescents and preadolescents from beginning to smoke or to encourage them to quit after a brief period of experimentation.

Several cancer centers have recently reported that more than half of their patients with newly diagnosed lung cancer are former smokers, having quit more than a year before diagnosis. Healthy exsmokers represent a large group of individuals who may benefit from effective tools for early detection and/or chemoprevention of lung cancer.

Second-hand smoke Not only is smoking risky for those who smoke, but it also poses a hazard to nonsmokers who either live or work with smokers. It is

estimated that approximately 3,000 lung cancer deaths per year in the United States are due to second-hand smoke. Individuals who live in a household with a smoker have a 30% increase in the incidence of lung cancer compared to nonsmokers who do not live in such an environment.

Asbestos exposure is another risk factor for lung cancer. Cigarette smokers who are exposed to asbestos develop lung cancer at an extremely high rate. Exposure to asbestos also is a major risk factor for the development of mesothelioma (see discussion of this cancer below).

Radioactive dust and radon exposure Uranium miners who have been exposed to radioactive dust and radon gas also have an increased incidence of lung cancer. Although there has been some controversy about the risk posed by exposure to residential radon gas, a recent study conducted in Sweden showed an increased incidence of lung cancer in individuals who were exposed to a high level of radon in their homes.

Screening and prevention

Screening

Three randomized screening trials conducted in the United States in the 1970s failed to show a survival advantage for individuals who were screened by sputum cytology for lung cancer. Despite the fact that these US trials were not designed to evaluate chest x-ray as a screening tool, the results led most experts to conclude that screening for lung cancer was not worthwhile. In addition, most investigators recommended that research efforts and resources be allocated to the prevention of lung cancer.

A more recent, randomized, prospective trial from Czechoslovakia showed that screening with a chest x-ray increased the diagnosis of early-stage lung cancer and reduced mortality from lung cancer. Studies are currently underway to evaluate chest CT scan for lung cancer screening. Several recent reports from Japan, Germany, and the United States have documented the ability of low-dose spiral CT scans to detect lung cancer at an early stage. Kaneko screened male smokers > 50 years. Of the 15 cancers detected by CT scan, only 4 were seen on chest x-ray; 14 of the 15 cancers were stage I with an average diameter of 1.6 cm. Ohmatsu found 35 lung cancers (37% detection rate) with 9,452 CT scans. Of these, 27 were stage IA. These patients had a 3-year survival rate of 83%.

Also, consideration has recently been given to conducting a larger trial to evaluate screening with long-term annual chest x-rays. It has been estimated that this type of study could result in a 13% reduction in lung cancer mortality, which would translate into approximately 18,000 lives saved on an annual basis. Despite the renewed interest in screening for lung cancer, at present routine screening is not recommended.

The lack of demonstrated benefit for the older screening approaches should not be misinterpreted as nihilism about the early detection of patients with

lung cancer. Patients at risk (current and former smokers) who present with symptoms consistent with lung cancer deserve appropriate evaluation. The lack of resolution of radiographic abnormalities on a chest x-ray obtained after the completion of empiric antibiotic therapy for pneumonia should prompt further evaluation for possible lung cancer. Failure to do so constitutes inappropriate therapeutic nihilism.

Chemoprevention

Second primary lung tumors develop at the rate of 1%-3% annually for the first 5 years following resection of stage I lung cancer. The retinoid 13-c*is*-retinoic acid (isotretinoin) has reduced the incidence of second primary cancer in head and neck cancer patients.

This observation served as the basis for an intergroup randomized trial that is assessing the ability of 13-*cis*-retinoic acid to prevent the occurrence of a second primary cancer in patients with completely resected stage I lung cancer. This trial has completed accrual (1,486 patients have been enrolled). Although final results are not yet available, early findings have demonstrated a higher-than-expected recurrence rate in patients with early-stage lung cancer.

Two recent randomized trials evaluating the administration of β-carotene in heavy smokers have shown that, contrary to expectation, the risk of death from lung cancer was increased in the treated population. Prior epidemiologic data had suggested a correlation between low dietary β-carotene intake and an increased risk of lung cancer. The reason for the apparent discrepancy between these findings and the results of the randomized trials is unknown. One possibility is that dietary substances other than or in addition to β-carotene are the active chemopreventive agents.

In any event, these therapeutically negative trials have demonstrated a proof of principle that it is possible to modify lung cancer risk in smokers; what is needed now are agents that will reduce rather than increase this risk.

Educational programs While the information from the intergroup randomized chemoprevention study is being collected, it is important to continue educational efforts to prevent adolescents from starting to smoke cigarettes and to advocate smoking cessation in active smokers. Some experts believe that educational programs must begin during childhood, probably between the ages of 6 and 10 years.

Signs and symptoms

The clinical manifestations of lung cancer depend on the location and extent of the tumor. In patients who have localized disease, the most common symptoms are related to obstruction of major airways, infiltration of lung parenchyma, and invasion of surrounding structures, including the chest wall, major blood vessels, and viscera.

Cough is a major manifestation of lung cancer. However, it is important to remember that the majority of lung cancer patients are current or former smokers, and may have a cough related to chronic irritation of the upper and/or lower airways from cigarette smoke. Therefore, smokers should be asked whether there has been a change in their cough, such as an increase in frequency or severity.

Dyspnea and hemoptysis Increasing dyspnea and hemoptysis may be signs of lung cancer.

Pneumonia Postobstructive pneumonia secondary to partial or complete bronchial obstruction occurs relatively frequently in association with lung cancer. It is important to obtain repeat chest x-rays in adults who have been treated for pneumonia to be certain that the radiographic abnormalities have cleared completely.

Pleural effusion Lung cancer may spread to the pleural surface, resulting in pleural effusion and increased dyspnea.

Chest pain Approximately 5% of lung tumors invade the chest wall. The resultant pain is a better predictor of chest wall invasion than are chest CT findings. An individual who complains of persistent chest pain should have a chest x-ray to exclude the presence of peripheral lung cancer that has invaded the chest wall.

Shoulder and arm pain Apical tumors that infiltrate surrounding structures (also called Pancoast's tumors) produce shoulder and/or arm pain as a result of brachial plexus compression. Tumors in the apical lung segments may be difficult to detect on a routine chest x-ray; therefore, a person who complains of persistent shoulder pain, particularly with signs of neurologic involvement, should have a CT scan of the chest to look for an apical tumor. It is also important to examine the lung apex in bone films obtained to evaluate shoulder pain.

Horner's syndrome Invasion of the sympathetic ganglion by an apical lung tumor causes Horner's syndrome (ptosis, myosis, and ipsilateral anhydrosis).

Hoarseness secondary to vocal cord paresis or paralysis occurs when tumors and lymph node metastases compress the recurrent laryngeal nerve. This situation is more common on the left side, where the recurrent laryngeal nerve passes under the aortic arch, but it may also occur with high lesions on the right side of the mediastinum.

Other symptoms of tumor compression Lung tumors may also cause dysphagia by compression or invasion of the esophagus or superior vena cava syndrome by compression or invasion of this vascular structure.

Some tumors may result in wheezing or stridor secondary to compression or invasion of the trachea, and may also cause signs of cardiac tamponade secondary to involvement of the pericardial surface and subsequent accumulation of pericardial fluid.

Signs and symptoms of metastatic disease Lung cancer can metastasize to multiple sites, the most common of which are bone, liver, brain, lung (contralateral or ipsilateral), and adrenal glands.

Lung cancer patients who have brain metastases may complain of headaches or specific neurologic symptoms, or family members may notice a decrease in the patient's mental acuity. Also, metastatic lung cancer may cause spinal cord compression, resulting in a characteristic sequence of symptoms: pain, followed by motor dysfunction, followed by sensory symptoms. The patient may have any or all of these symptoms.

It is important to note that patients who complain of band-like pain encircling one or both sides of the trunk may have spinal cord compression. In addition, coughing and sneezing may cause significant exacerbation of pain from spinal cord compression.

Bone x-rays and/or a bone scan are warranted in lung cancer patients who complain of persistent pain in the trunk or extremities. MRI of the spine is the most effective way to evaluate suspected spinal cord compression.

Lung cancer frequently metastasizes to the adrenal glands, and occasionally, this may cause flank pain. However, in general, adrenal metastases are asymptomatic. It is relatively uncommon for adrenal metastases to result in adrenal insufficiency.

Systemic paraneoplastic symptoms Lung cancer is commonly associated with systemic manifestations, including weight loss (with or without anorexia). In addition, patients frequently complain of fatigue and generalized weakness.

Specific neurologic syndromes, such as Lambert-Eaton syndrome (see chapter 46), cortical cerebellar degeneration, and peripheral neuropathy, may occur in lung cancer patients, but these are relatively rare.

Clubbing Although clubbing may occur in a variety of conditions, it is important for the clinician to evaluate a patient's hands, because if clubbing is noted, obtaining a chest x-ray may result in the early diagnosis of lung cancer.

Hypertrophic osteoarthropathy A relatively small percentage of patients with lung cancer may present with symptomatic hypertrophic osteoarthropathy. In this syndrome, periosteal inflammation results in pain in affected areas, most commonly, the ankles and knees.

Carcinoid syndrome is extremely uncommon in patients who have a bronchial carcinoid tumor. Most of these patients are asymptomatic (tumors are found by x-ray), and a few have cough from an endobronchial lesion.

Staging and prognosis

Staging

The staging of lung cancer must be conducted in a methodical and detailed manner in order to permit appropriate therapeutic recommendations to be

made and to allow treatment results from different institutions to be compared. The TNM staging system, recently updated by Mountain (Table 1), applies equally well to all histologies. However, TNM staging is generally not utilized in SCLC, as it does not predict well for survival. Rather, SCLC is generally staged as limited (M0) or extensive (M1) disease.

Stage is commonly reported as either clinical or pathologic. The former is based on noninvasive (or minimally invasive) tests, while the latter is based on tissue obtained during surgery (see "Diagnosis and preoperative staging evaluation" below).

Prognostic factors

Stage The most important prognostic factor in lung cancer is the stage of disease.

Performance status and weight loss Within a given disease stage, the next most important prognostic factors are performance status and recent weight loss. The two scales used to define performance status are the Eastern Cooperative Oncology Group (ECOG) performance status system and the Karnofsky system (see Appendix 3). In short, patients who are ambulatory have a significantly longer survival than those who are nonambulatory. Similarly, patients who have lost > 5% of body weight during the preceding 3-6 months have a worse prognosis than patients who have not lost a significant amount of weight.

Molecular prognostic factors Several studies published over the last decade have indicated that mutations of *ras* proto-oncogenes, particularly K-*ras*, portend a poor prognosis in individuals with stage IV NSCLC. Accordingly, research has focused on developing molecularly targeted therapeutic approaches to the *ras* proto-oncogenes, in particular, the farnesyl transferase inhibitors (see "Promising novel agents" page 113).

Of equal relevance was the completion of large studies by Pastorino et al and Kwiatowski et al evaluating the prognostic importance of immunocytochemical and molecular pathologic markers in stage I NSCLC. The findings of these two studies suggest that pathologic invasion and extent of surgical resection may yield the most critical prognostic information, but mutation of the K-*ras* oncogene and absence of expression of the H-*ras* p21 proto-oncogene may augment the pathologic information obtained.

Diagnosis and preoperative staging evaluation

History and physical examination

The diagnosis and preoperative staging of lung cancer begin with a good history and physical examination. When obtaining the history, the clinician should keep in mind the tendency for lung cancer to involve major airways and other central structures. Similarly, the patterns of metastatic dissemination and systemic manifestations must be considered when conducting the physical examination.

TABLE 1: TNM staging of lung cancer

Primary tumor (T)	
TX	Tumor proven by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically, or any tumor that cannot be assessed, as in pretreatment staging
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3.0 cm in greatest dimension, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy
T2	Tumor > 3.0 cm in greatest dimension, or tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region (but involving less than the entire lung). At bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina.
T3	Tumor of any size with direct extension into the chest wall (including superior sulcus tumors), diaphragm, or mediastinal pleura or pericardium without involving the heart, great vessels, trachea, esophagus, or vertebral body; or tumor in the main bronchus within 2 cm of, but not involving, the carina
T4	Tumor of any size with invasion of the mediastinum or involving the heart, great vessels, trachea, esophagus, vertebral body, or carina; or presence of malignant pleural effusion
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No demonstrable metastasis to regional lymph nodes
N1	Metastasis to lymph nodes in the peribronchial and/or ipsilateral hilar region, including direct extension
N2	Metastasis to ipsilateral mediastinal and subcarinal lymph nodes
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping			
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T3	N1	M0
	T1-3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

From Mountain CF: Revisions in the international system for staging lung cancer. Chest 111(6):1710-1717, 1997.

Patients should be questioned specifically about the presence of palpable masses, bone pain, headache, or changes in vision. Careful auscultation and percussion may suggest the presence of atelectasis or a pleural effusion. Also, auscultation of the chest may show evidence of large airway obstruction and pulmonary consolidation. An enlarged liver may indicate hepatic metastases.

Examination of supraclavicular fossa Clinicians should be careful to examine the supraclavicular fossa, as detection of an enlarged lymph node in this area may provide the means for establishing a tissue diagnosis.

In addition, identification of supraclavicular lymph node metastases has important therapeutic and prognostic implications. In particular, supraclavicular nodal metastases immediately eliminate the patient from consideration for surgery.

Imaging studies

Chest x-rays should always be done in a high-risk patient with new respiratory symptoms. Not only are PA and lateral chest x-rays of fundamental importance in assessing the local extent of the primary tumor, but also they may provide valuable information regarding metastatic disease.

The chest x-ray should be inspected for the presence of a pleural effusion or synchronous pulmonary nodules, and the bones should be examined for evidence of osseous metastases. A widened mediastinum usually indicates metastatic disease within the mediastinal lymph nodes. Comparison with previous x-rays is frequently helpful and well worth the effort expended in their retrieval.

Chest CT A CT scan of the chest, including the liver and adrenal glands, is performed routinely to further define the primary tumor and to identify lymphatic or parenchymal metastases. Metastatic tumor is found in approximately 8% of mediastinal lymph nodes < 1 cm in greatest diameter, 30% of nodes 1-2 cm in greatest diameter, and 60% of those > 2 cm. Benign enlargement of mediastinal nodes is more common in patients with postobstructive infection. Histologic documentation of the presence or absence of tumor within the mediastinal lymph nodes is necessary whenever this information will change treatment recommendations.

It is important to remember that patients with persistent symptoms, such as cough and dyspnea, who have a normal chest x-ray may be harboring a central lesion that is not obvious on chest x-ray but can be easily detected by chest CT. Also, as mentioned above, apical tumors (Pancoast's tumors) may be difficult to detect on a chest radiograph but are usually readily apparent on a CT scan.

PET Current data suggest that PET may be very helpful for the evaluation of lung masses, lymph nodes, and distant metastases. When a lung mass "lights up" on a PET scan, there is a 90%-95% chance that it is cancerous. The positive predictive value of a PET scan is lower in areas with a high prevalence of granulomatous disease. If the mass is at least 1 cm and cannot be imaged by PET scanning, there is only a 5% chance that it is malignant. Both the sensitivity and specificity of PET for detecting nodal metastases are approximately 90%.

Several trials have evaluated the prognostic significance of fluorodeoxyglucose (FDG) uptake on PET scan in NSCLC. Most of these studies used a standardized uptake value (SUV), a semiquantitative measurement of FDG uptake. Utilizing multivariate Cox analysis, these studies noted that SUV, particularly when > 7, was a highly important prognostic factor. Other studies indicated that the use of PET combined with chest CT was almost as sensitive as surgery alone in the evaluation of pathologically positive mediastinal lymph nodes.

Adrenal gland biopsy The adrenal gland may be the sole site of metastatic disease in as many as 10% of patients with NSCLC. Therefore, an enlarged or deformed adrenal gland should be biopsied. Patients should not be assumed to have metastatic disease and denied a potentially curative operation on the basis of a scan; histologic confirmation must be obtained.

Obtaining a tissue diagnosis

The next step is to try to obtain a histologic or cytologic diagnosis of the radiologic lesion, although preoperative histologic diagnosis need not be obtained in a patient with a new, peripheral lung mass and no evidence of distant or locoregional metastases (see below).

Central lesions Although collecting sputum cytologies for 3 consecutive days frequently provides a cytologic diagnosis for central lesions, most clinicians proceed directly to bronchoscopy. In centrally located lesions, this procedure establishes a cytologic and/or histologic diagnosis in 80%-85% of cases. In addition, bronchoscopy may provide important staging information, such as whether the tumor involves the distal trachea or carina, and may help plan the appropriate operation (lobectomy or sleeve resection vs pneumonectomy).

Peripheral lesions Bronchoscopy is less likely to yield a diagnosis in patients with peripherally located lesions. The false-negative rate in such cases may range from 20% to 50%.

A CT-guided needle biopsy may diagnose up to 90% of peripheral lung cancers. However, needle biopsy is usually reserved for patients who are not candidates for an operation due to distant metastatic disease or poor performance status. If the patient is a candidate for surgery, resection is generally recommended for any suspicious mass whether the needle biopsy is positive or nondiagnostic. Therefore, for patients with a suspicious peripheral lesion that is not invading the chest wall and is not associated with mediastinal adenopathy, it is reasonable to proceed directly to surgery.

Mediastinoscopy provides not only a histologic diagnosis but also yields important staging information. If multiple lymph node levels contain tumor, most thoracic surgeons would not proceed directly to operation, but rather, would offer these patients neoadjuvant therapy as part of a clinical trial. Alternatively, such patients could receive nonoperative primary therapy. However, if only one ipsilateral nodal level is positive for metastatic tumor, many surgeons will perform a pulmonary resection and lymph node dissection and advise participation in an adjuvant therapy trial. Involvement of contralateral

TABLE 2: Selective indications for mediastinoscopy

Enlarged N1 or N2 lymph nodes on chest CT scan
Centrally located tumors
Poorly differentiated tumors
T3 tumors
Patients who are marginal candidates for resection

mediastinal lymph nodes (stage IIIB) is generally thought to contraindicate surgery even when preceded by neoadjuvant therapy. Table 2 lists selective indications for mediastinoscopy.

Thoracentesis and thoracoscopy Individuals who have pleural effusions should undergo thoracentesis. Video-assisted thoracoscopic surgery (VATS) is being used increasingly in patients with such effusions if thoracentesis does not show malignant cells. VATS permits direct visualization of the pleural surface, enables one to directly biopsy pleural nodules, and also may facilitate biopsy of ipsilateral mediastinal lymph nodes.

Measurement of serum tumor-associated antigens has no current role in the staging of NSCLC.

Evaluation for distant metastases

Once a tissue diagnosis has been established, the possibility of distant metastases should be assessed. Again, this process starts with a careful history and physical examination.

Clinical stage I-II patients Patients with clinical stage I or II lung cancers based on chest x-ray and CT scan, no evidence of skeletal or neurologic metastases, and normal blood chemistries and blood counts do not require brain or bone scans.

Symptomatic, clinical stage I-II patients, including those who have lost $> 5\%$ of their usual body weight and those who cannot work on a regular basis due to decreased performance status (ECOG performance status ≤ 2), should have bone and brain scans. Although these patients do not require an abdominal CT scan per se, CT scans of the chest should routinely include the adrenal glands and virtually all of the liver.

Clinical stage III patients Patients who have physical findings, laboratory findings (such as an elevated alkaline phosphatase), or symptoms suggestive of distant metastases should undergo appropriate scans to evaluate these areas. In addition, most clinical trials of combined-modality therapy for stage III disease require radiologic imaging of the brain and bone. Thus, it seems reasonable to perform these imaging studies in clinical stage III patients who are receiving potentially curative therapy (high-dose radiation therapy or combined-modality therapy). If brain and bone are to be investigated, brain MRI with gadolinium and a technetium radionuclide bone scan should be performed.

Diagnosis and evaluation of suspected carcinoid tumor

A carcinoid tumor of the lung may be suspected in a patient with a slowly enlarging pulmonary mass and a prolonged history of respiratory symptoms. Patients in whom a primary carcinoid tumor of the lung is suspected or documented should be evaluated in a manner identical to that used in patients with NSCLC. The diagnosis is usually made during bronchoscopy.

Pulmonary carcinoid tumors rarely produce 5-hydroxyindoleacetic acid (5-HIAA). Therefore, it is only necessary to measure urinary 5-HIAA excretion prior to surgery in symptomatic patients.

Intraoperative staging

Intraoperative staging represents an integral part of any operation for lung cancer. In addition to a thorough visual and tactile inspection of the lung, diaphragm, and pleura, the ipsilateral mediastinal lymph nodes must be either completely removed or, at a minimum, sampled.

The American Thoracic Society has assigned numbered levels to locations in which lymph nodes are regularly found, defined by their relation to constant anatomic structures. For instance, right level IV lymph nodes are those that are found between the cephalic border of the azygous vein and the caudal border of the innominate artery where it crosses the trachea. A complete mediastinal lymph node dissection is associated with little morbidity and lengthens the operation only slightly.

Pulmonary evaluation

In order to determine the volume of lung that can be removed without rendering the patient a pulmonary cripple and to identify those individuals at risk for postoperative complications, each patient must undergo pulmonary function testing.

Forced expiratory volume in 1 second Postoperative respiratory failure occurs rarely if the post-resection forced expiratory volume in 1 second (FEV_1) is > 800 mL. Regardless of the extent of the scheduled resection, if the preoperative FEV_1 is < 2 L, a split-function perfusion scan should be obtained to determine the contribution of each lung to overall pulmonary function. This information may be critical when an unplanned pneumonectomy is required to achieve complete tumor resection.

Other pulmonary function tests A diffusing capacity of the lung for carbon monoxide (D_LCO) $< 60\%$ of the predicted value or a maximum voluntary ventilation (MVV) $< 35\%$ is associated with increased postoperative morbidity. Similarly, an arterial $pO_2 < 60$ mm Hg or a $pCO_2 > 45$ mm Hg has been linked to increased operative morbidity and mortality.

Measurement of oxygen consumption during exercise has also proved useful in determining which patients can tolerate a pulmonary resection. Oxygen consumption values > 15 mg $\cdot$ kg^{-1} $\cdot$ min^{-1} have been associated with minimal morbidity.

Pathology

Three major types of tumors are included under the NSCLC category: adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma.

Adenocarcinoma is currently the most common type of NSCLC, accounting for approximately 40% of cases. Of all the types of lung cancer, adenocarcinoma is most likely to occur in nonsmokers or former smokers. In addition, it is the most common tumor in women.

Typically, adenocarcinoma presents as a small peripheral lesion that has a high propensity to metastasize to both regional lymph nodes and distant sites. Because of the tendency of the primary tumor to occur in peripheral locations, it frequently produces no symptoms.

Bronchoalveolar adenocarcinoma During the last decade, it has become apparent that the incidence of the bronchoalveolar type of adenocarcinoma is increasing. This tumor appears to rise from type 2 pneumocytes, and it may present as a pneumonic infiltrate, as multiple nodules scattered throughout the lung, and, occasionally, as a single nodule.

Squamous cell tumors comprise approximately 30% of all cases of lung cancer. This tumor tends to occur in a central location and tends to spread to regional lymph nodes; it is the most likely of all the lung cancers to remain localized and to cavitate. In fact, autopsy studies have shown that about 15%-30% of patients with squamous cell carcinoma may expire from local disease without evidence of distant metastases.

Large-cell carcinoma accounts for approximately 10%-15% of all lung cancers. It tends to be a relatively large peripheral lesion, and like adenocarcinoma, it has a high propensity to metastasize to regional lymph nodes and distant sites.

Carcinoids These neoplasms, which contain neurosecretory granules and neural filaments, are relatively rare. The classic carcinoid tumor presents as an endobronchial lesion, tends to be quite indolent, and rarely metastasizes. Some carcinoid tumors spread to regional lymph nodes and distant sites. These tumors are classified as atypical carcinoids or anaplastic carcinoids. More recently, some investigators have suggested that the more aggressive carcinoids be called well-differentiated neuroendocrine carcinoids.

Treatment

All investigators agree that patients with clinically staged IA, IB, IIA, and IIB NSCLC should undergo resection of their tumors. There is a similar consensus that, except for the rare individual with a solitary brain metastasis, patients with stage IV disease should be treated nonoperatively. The treatment of stage IIIA and IIIB disease remains controversial.

SURGICAL APPROACH

The appropriate treatment of NSCLC is resection of the lobe containing the tumor. Occasionally, a bilobectomy or pneumonectomy is required. Mortality

following lobectomy and pneumonectomy approximates 3% and 7%, respectively. A wedge or segmental resection has a 3-5 times higher incidence of local recurrence and a lower 5-year survival than a lobectomy. Therefore, if the patient can tolerate the procedure, the standard operation should be a lobectomy, rather than a wedge resection or segmentectomy.

Patients with pathologic stage IA disease have an 80% 5-year survival rate after resection, whereas 5-year survival rates are 60% in those with stage IB disease and 40%-50% in those with stage IIA/IIB disease. Patients found to have N2 (stage IIIA) disease located at a single nodal level have a 25%-30% 5-year survival rate.

Mediastinal lymph node involvement The standard lung cancer operation should include sampling or dissection of mediastinal lymph nodes. The presence of metastases in any of the mediastinal lymph nodes (N2 disease) is indicative of advanced disease and is thought by some to represent a contraindication to surgery. However, resection of N2 disease has prognostic significance, implications for postoperative care, and, probably, therapeutic value. Some series of patients with N2 disease have shown a 5-year survival rate of 20%-30%, but patients in these series are highly selected.

The American College of Surgeons is currently conducting a randomized, prospective study comparing survival following mediastinal lymph node sampling vs dissection. Also, clinical trials are currently testing preoperative chemotherapy or chemoradiation in patients with mediastinal node involvement.

Preoperative histologic assessment of the mediastinal lymph nodes is essential if multilevel metastases are suspected, as there have been few long-term survivors among patients with metastatic disease at more than one level. Such patients should be treated nonsurgically or offered participation in a trial designed to assess the benefits of neoadjuvant therapy. Although patients with stage IIIB tumors are usually treated with radiation and chemotherapy (see discussions below), the occasional patient with isolated involvement of the vena cava or atrium can undergo resection.

Carcinoid tumors Although the majority of carcinoid tumors remain localized, regional lymph node metastases are identified in a significant percentage of patients. The surgical approach, therefore, should be similar to that used in NSCLC; namely, resection. If a small tumor in a proximal airway is identified and there is no histologic evidence of lymph node disease, a bronchoplastic procedure with preservation of lung tissue can sometimes be performed. Rates of survival at 10 years are $> 90\%$ for patients with stage I disease and 60% for patients with stage II disease.

ADJUVANT THERAPY

Radiation therapy

A trial conducted by the Lung Cancer Study Group (LCSG) clearly showed that, in patients with squamous cell carcinoma of the lung and resected N1-N2 disease, administration of postoperative radiation reduced the risk of recur-

rence in the chest from 20% to 3% but did not significantly improve disease-free or overall survival. A trial by the British Medical Research Council reached similar conclusions.

These results created a lack of consensus about treatment recommendations, with some experts advocating the use of postoperative radiation therapy to reduce local recurrence, and others avoiding it because of the absence of an effect on survival. Unfortunately, present studies have not established either the toxicities of such adjuvant treatment or the efficacy of radiation in controlling locally recurrent disease.

A recently published meta-analysis of nine randomized trials assessing postoperative radiation therapy in lung cancer reported a 21% increase in mortality in patients receiving this therapy. However, many of the patients in these trials had N0 disease, for whom few would advocate radiation therapy. Also, most of the patients were treated with cobalt-60 beams and technically limited treatment planning, not with modern radiation therapy techniques.

At present, therefore, the appropriate role of postoperative radiation therapy remains ill defined. However, it should be seriously considered in patients at high risk for locoregional relapse (ie, those with multiple positive lymph nodes, extracapsular extension, or close or microscopically positive margins).

Chemotherapy

Classic post-surgical adjuvant chemotherapy also has been tested in three randomized trials conducted by the LCSG.

Stage I disease In one trial, adjuvant therapy with 6 courses of cyclophosphamide, Adriamycin, and Platinol (CAP) failed to produce a significant survival advantage in patients with stage I lung cancer. Therefore, at present, adjuvant chemotherapy is not recommended for stage I disease.

Stage II-III disease In two earlier trials, postoperative adjuvant chemotherapy with 6 courses of CAP, given alone in one study and following postoperative radiation therapy in the other, resulted in a modest improvement in median survival but had no impact on long-term survival. Adjuvant chemotherapy is not recommended for these patients.

A randomized intergroup trial of adjuvant therapy for patients with resected T2 N0, T1 N1, or T2 N1 NSCLC is now accruing patients under the direction of the National Cancer Institute of Canada. Following operation, patients are being randomized to receive cisplatin and vinorelbine (Navelbine) or no further treatment.

An intergroup, randomized, prospective trial of adjuvant therapy for patients with resected stage II or IIIA NSCLC recently reported results. Patients with histologically proven metastases to N1 or N2 lymph nodes were randomized to receive either postoperative mediastinal radiation therapy alone (50 Gy) or 4 cycles of concomitant cisplatin (Platinol) and etoposide plus radiation therapy. The study demonstrated no benefit from the addition of chemotherapy to mediastinal radiation in the adjuvant setting.

NEOADJUVANT CHEMOTHERAPY OR CHEMORADIATION

During the last decade, numerous phase II trials showed that, in general, it is feasible to perform pulmonary resection following chemotherapy or chemoradiation. Although surgery was difficult after preoperative treatment, morbidity and mortality were generally acceptable.

Stage IIIA-IIIB disease The greater effectiveness of current chemotherapeutic regimens in settings of reduced disease bulk suggested that their use prior to surgery, either alone or in combination with radiation therapy, might increase both resectability and survival in patients with stage IIIA or IIIB NSCLC. Multiple phase II trials have shown such an approach to be feasible; however, it is not clear that, among patients who initially have more than minimal N2 disease, such a strategy improves median or long-term survival over best non-surgical chemoradiotherapy.

Based on these initial observations, three groups conducted small randomized trials testing preoperative therapy. Two of these studies showed significantly improved survival among patients who received three courses of cisplatin-containing chemotherapy prior to surgery. In the third trial (reported in abstract form only), Brazilian investigators observed significantly higher rates of resection and significantly longer survival in patients who received preoperative chemoradiation than in those given preoperative chemotherapy alone.

Current recommendations There is increasing evidence that preoperative treatment has a favorable effect on survival in selected stage III NSCLC patients. However, since aggressive neoadjuvant approaches have treatment-associated mortality in the range of 5%-12% and unproven benefits, they are still considered investigational.

Stage I-IIIA disease Neoadjuvant chemotherapy may even play a role in early-stage disease. A multicenter trial from France randomized 373 stage I-IIIA NSCLC patients to either surgery alone or chemotherapy (mitomycin [Mutamycin; 6 mg/m^2 on day 1], ifosfamide [Ifex; 1.5 g/m^2 on days 1-3], and cisplatin [Platinol; 30 mg/m^2 on days 1-3]) at 3-week intervals for 3 cycles followed by surgery. Disease-free survival was significantly longer in the patients randomized to receive neoadjuvant chemotherapy than in those treated with surgery alone ($P = .02$). The most striking benefit of chemotherapy was seen in patients who had minimal lymphadenopathy (either N0 or N1; $P = .008$). No excessive complications were seen in the chemotherapy-treated patients.

TREATMENT OF MEDICALLY INOPERABLE PATIENTS WITH STAGE I-II DISEASE

Some patients with resectable stage I or II NSCLC are high-risk operative candidates because of poor cardiopulmonary function, other medical problems, or advanced age. Other patients refuse to undergo surgery despite the recommendation of their treating physicians. In such patients, an attempt should be made to optimize pulmonary function by encouraging smoking cessation and initiating vigorous treatment with bronchodilators, corticosteroids, and antibiotics.

Radiation therapy

Several institutions have reported their experience with definitive radiation therapy for such patients (Table 3). Although the results are not as good as those reported in patients selected for surgery, medically inoperable patients with early-stage NSCLC clearly should be offered radiation therapy, with reasonable expectation of cure.

TREATMENT OF PATIENTS WITH STAGE IIIA-IIIB DISEASE

Radiation therapy

In the past, radiation therapy was considered the standard therapy for patients with stage IIIA or IIIB disease. Long-term survival was poor, in the range of 5%-10%, with poor local control and early development of distant metastatic disease.

Altered fractionation schedules Recent randomized trials have compared standard daily radiation therapy (60 Gy) with twice-daily treatment of a higher total dose (69.6 Gy) and with an accelerated regimen that delivered 54 Gy over 2½ weeks, rather than the usual 5-6 weeks. Both of these altered fractionation schedules resulted in improved survival. Efforts are currently underway to combine such fractionation schedules with chemotherapy.

Chemoradiation

Chemoradiation vs radiation alone At least 11 randomized trials have compared thoracic irradiation alone to chemoradiation in patients with stage III NSCLC. Several meta-analyses have demonstrated a small, but statistically significant, improvement in survival with the combined-modality regimens. Indeed, six randomized trials have demonstrated a statistically significant survival advantage favoring chemoradiation; three of these trials employed sequential chemoradiation and three, concurrent chemoradiation.

In the three trials using sequential chemoradiation, the combination of cisplatin with a vinca alkaloid (either vinblastine or vindesine [Eldisine]) significantly improved survival rates over radiation therapy alone.

The first of the concurrent chemoradiation trials, the European Organization for Research and Treatment of Cancer (EORTC) trial 08844, compared radiotherapy alone to radiotherapy and concomitant (daily or weekly) low-dose cisplatin therapy. This study demonstrated a significant survival advantage for daily cisplatin and radiotherapy compared to radiotherapy alone (3-year survival rates, 16% vs 2%); the weekly cisplatin/radiation arm produced intermediate results (3-year survival rate, 13%).

A three-arm, randomized study comparing hyperfractionated radiotherapy (1.2 Gy twice daily to a total dose of 64.8 Gy) alone to a combination of hyperfractionated radiotherapy and carboplatin (Paraplatin) plus etoposide (administered weekly or every other week) demonstrated 3-year survival rates of 6.6%, 23%, and 16%, respectively ($P = .003$).

TABLE 3: Definitive radiation therapy for patients with stage I-II NSCLC

Series	Number of patients	Stage (clinical)	Radiation (Gy)	Median survival (mo)	Survival rate at ≥2 years (%)
Morrison	28	Operable	45/4 wk	NA	14
Smart	40	Operable	50-55 (250 kV)	~ 30	~ 50
Coy	141	T1-3 NX	50-57.5	NA	31
Cooper	72	T1-3 N0-1	Variable	9	NA
Haffty	43	T1-2 N0-1	54-59	28	60
Noordijk	50	T1-2 N0	60	25	56
Zhang	44	T1-2 N0-2 (80% N0)	55-70	> 36	~ 55
Talton	77	T1-3 N0	60	17	36
Sandler	77	T1-2 NX	60	20	30
Ono	38	T1 N0	60-70	~ 40	68
Dosoretz	152	T1-3 N0-1	50-70	17	40
Dosoretz	44	T1	50-70	Not reached	~ 60
Dosoretz	63	T2	50-70	~ 12	~ 30
Dosoretz	41	T3	50-70	~ 12	~ 30
Hayakawa	17	Stage I	60-80	NA	75
Hayakawa	47	Stage II	60-80	NA	44
Rosenthal	62	T1-2, N1	18-65 (median, 60)	18	33
Kaskowitz	53	T1-2, N0	50-70 (median, 63)	21	43

NA = Data not available

Modified from Wagner H: Radiotherapeutic management of stage I-II lung cancer, in Pass HI, Mitchell JB, Johnson DH, et al (eds): Lung Cancer: Principles and Practice. Philadelphia, Lippincott-Raven, 1996.

In the third phase III concurrent chemoradiation trial, the combination of hyperfractionated radiation and low-dose daily chemotherapy (carboplatin plus etoposide) was superior to hyperfractionated radiation alone (to 69.6 Gy), with 4-year survival rates of 22% vs 9% ($P = .02$).

Analyses of these positive randomized trials favoring chemoradiation over radiation alone suggest a difference in the patterns of failure that relates to the method of combining chemotherapy with thoracic radiotherapy. In the three trials employing sequential chemoradiation, the improvement in survival rates

over radiation alone appeared to be linked to a decrease in the development of distant metastases. In contrast, in the three positive trials employing concurrent chemoradiation, the survival advantage appeared to be associated with an improvement in locoregional control.

It may be that the use of high-dose induction chemotherapy combats systemic disease, whereas the simultaneous delivery of low-dose chemotherapy (cisplatin or carboplatin) with radiation may be necessary to improve local tumor control. Such a construct fits well with prior observations that platinum–based chemotherapy can act as a radiosensitizer.

Concurrent vs sequential chemoradiation A recent phase III trial has reported, for the first time, an advantage of concurrent over sequential chemoradiation (see box). Hopefully, this important sequencing issue (concurrent vs sequential therapy) will be resolved by a large, randomized Radiation Therapy Oncology Group trial (RTOG 94-10), which completed accrual in 1998 with over 600 patients. In this trial, the "gold-standard" arm of induction chemotherapy (with cisplatin and vinblastine) followed by standard radiotherapy is being compared to the exact same chemotherapy and radiotherapy delivered concurrently. This study also includes a third arm of hyperfractionated radiotherapy and concomitant cisplatin and oral etoposide, based on preliminary results of a phase II trial (RTOG 91-06) demonstrating a median survival of approximately 20 months.

Furuse et al evaluated mitomycin, vindesine, and Platinol (MVP), either concurrent with or prior to thoracic radiation (56 Gy), in patients with unresectable stage III NSCLC. With over 300 patients randomized, survival favored concurrent over sequential therapy (median survival, 16.5 vs 13.3 months, and 5-year survival rates, 15.8% vs 8.9%; $P = .04$) *(Furuse K, Fukuoka K, Takada Y, et al: Proc Am Soc Clin Oncol 18:458a[abstract], 1999).*

New chemotherapeutic agents plus radiation Several recent phase I-II trials evaluated relatively low doses of carboplatin and paclitaxel (Taxol) given concurrently with thoracic radiation. These studies showed acceptable toxicity and relatively high response rates, and in one of the studies the 3-year survival rate was quite high (39%).

In addition to paclitaxel and carboplatin, many other chemotherapeutic agents with activity in NSCLC have emerged in the 1990s, including docetaxel (Taxotere), vinorelbine (Navelbine), gemcitabine (Gemzar), and irinotecan (CPT-11 [Camptosar]). The Cancer and Leukemia Group B (CALGB) recently reported the preliminary results of a randomized phase II trial of gemcitabine, paclitaxel, or vinorelbine combined with cisplatin as induction chemotherapy, followed by concomitant chemoradiotherapy, in patients with unresectable stage III NSCLC. Although the response rates in all of the arms appeared to be similar, the gemcitabine-cisplatin arm seemed to have the highest rate of grade 3-4 thrombocytopenia (53% vs 6% or 0% in the other arms) and esophagitis (49% vs 31% and 25%). The median survival duration for all patients was promising at 18 months, with a 1-year survival rate of 66%.

Current treatment recommendations

At present, it is reasonable to consider sequential chemoradiation as standard treatment in stage III lung cancer patients who are ambulatory (ECOG performance status, 0-1) and who have not lost more than 5% of their usual body weight.

Data accrued to date in stage III and IV NSCLC suggest that amifostine (Ethyol) effectively reduces cisplatin-related nephrotoxicity and, possibly, neurotoxicity without compromising response or survival (*Tannehill SP, Mehta MP, Larson M, et al: J Clin Oncol 15(8):2850-2857, 1997*). This radioprotective agent is currently being tested as a strategy to reduce chemoradiation-induced esophagitis in a phase III study (RTOG 98-01).

Common approaches are either induction chemotherapy for several cycles followed by radiation therapy or concurrent chemoradiation. If cisplatin-vinblastine is used prior to radiation, cisplatin is given at a dose of 100 mg/m^2 IV over 30-60 minutes on days 1 and 29, and vinblastine is administered at a dose of 5 mg/m^2 IV weekly for 5 weeks.

Radiation alone is appropriate for patients with stage III NSCLC who are otherwise not good candidates for chemoradiation, eg, those with ≥ 5% weight loss and/or those whose ECOG performance status is ≥ 2. The dose of radiation used in this setting ranges widely, from short courses of 30 Gy in 10 fractions over 2 weeks (in the palliative setting) to 60 Gy in 30 fractions over 6 weeks (in the definitive setting).

TREATMENT OF PATIENTS WITH STAGE IV DISEASE

Until recently, there was considerable controversy over the value of treating stage IV NSCLC patients with chemotherapy. Treatment with older cisplatin-containing regimens, such as cisplatin-etoposide, showed only a modest effect on survival, improving median survival by approximately 6 weeks, according to a meta-analysis, and yielding a 1-year survival rate of approximately 20% (as compared with a rate of approximately 10% for supportive care).

However, several new chemotherapeutic agents have produced response rates in the range of 15% in NSCLC. The potentially useful new agents include the taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine, and irinotecan. Several of these new drugs have unique mechanisms of action compared to the mechanisms of agents that have previously shown some effectiveness against NSCLC. For instance, paclitaxel and docetaxel cause increased polymerization of tubulin, gemcitabine is an antimetabolite, and irinotecan is a topoisomerase I inhibitor.

Paclitaxel plus a platinum agent

The combination of paclitaxel and a platinum agent, either cisplatin or carboplatin, appears to be particularly promising. Although results with paclitaxel plus cisplatin have varied somewhat, multiple phase II studies using this combination have reported response rates of 31%-56% (mean, 42%), which are significantly higher than rates observed with paclitaxel or cisplatin alone. The few phase II studies that reported survival found paclitaxel-cisplatin to be only slightly superior to paclitaxel alone (median survival, 44 weeks; 1-year survival

rate, 38%). However, survival with paclitaxel-cisplatin appeared to be markedly superior, compared with the older cisplatin combinations.

Randomized trials Based on these results, four large randomized studies were performed to compare paclitaxel plus either cisplatin or carboplatin vs the older cisplatin-based combinations.

Paclitaxel-cisplatin An ECOG study compared three regimens: (1) a 24-hour infusion of high-dose paclitaxel (250 mg/m^2) with granulocyte colony-stimulating factor (G-CSF [Neupogen]) plus cisplatin (75 mg/m^2); (2) a 24-hour infusion of standard-dose paclitaxel (135 mg/m^2) without G-CSF plus cisplatin (at the same dose); and (3) a control arm of etoposide plus cisplatin. The two paclitaxel regimens produced significantly higher response rates than etoposide-cisplatin (27%-32% vs 12%), as well as significantly longer survival (median survival, 41-43 vs 32 weeks). Rates of survival at 1 year also were improved in the two paclitaxel arms (40% and 37%, respectively) compared to the etoposide-cisplatin arm (32%). Marked thrombocytopenia and neuropathy were more common in the high-dose paclitaxel arm, whereas severe neutropenia appeared to occur at a similar frequency in the three arms.

The second study, conducted by the EORTC, compared the combination of a short (3-hour) infusion of paclitaxel and cisplatin vs teniposide (Vumon) plus cisplatin (one of the standard regimens in Europe). The paclitaxel arm produced a significantly higher response rate than the standard arm (47% vs 29%). However, median survival durations were 41 weeks with paclitaxel-cisplatin and 42 weeks with teniposide-cisplatin. The absence of a survival benefit contrasted with quality-of-life assessments, which showed a clear advantage for the paclitaxel-cisplatin arm. Also, major toxicities, including myelosuppression, were significantly more common in the teniposide arm.

Paclitaxel-carboplatin In the third randomized trial, the combination of paclitaxel (225 mg/m^2 infused over 3 hours) and carboplatin (dosed to achieve an area under the time-concentration curve [AUC] of 6 mg/mL · min) was compared with etoposide (100 mg/m^2 on days 1-3) plus cisplatin (75 mg/m^2). The overall response rate was higher in the paclitaxel-carboplatin arm than in the cisplatin-etoposide arm (23% vs 14%; $P = .046$). However, 1-year survival rates for the two arms were 32% and 37%, respectively. This slightly superior survival for the cisplatin-etoposide arm, which was not statistically significant, remains difficult to explain, although patient selection, better supportive care, and superior second-line chemotherapy with taxanes or other novel agents may explain the discrepancy.

Most recently, the Southwest Oncology Group (SWOG) conducted a randomized, phase III trial of paclitaxel plus carboplatin vs vinorelbine plus cisplatin in patients with untreated advanced NSCLC and good performance status (World Health Organization [WHO], or Zubrod, scale 0-1). The 408 eligible patients were randomized to receive either (1) paclitaxel (225 mg/m^2 infused over 3 hours on day 1) and carboplatin (dosed to achieve an AUC of 6 mg/mL · min on day 1) every 21 days; or (2) vinorelbine (25 mg/m^2 weekly) and cisplatin (100 mg/m^2 on day 1) every 28 days.

Overall partial response rates were 27% in both groups. Median survival times also were identical in the two groups (8 months), and 1-year survival did not differ appreciably (approximately 34%). Furthermore, while nausea, vomiting, and infection appeared to be less common in patients treated with paclitaxel and carboplatin, neurotoxicity and cost were both substantially higher in this group.

This study attests to the improved options now available for the initial treatment of patients with stage IV NSCLC. A median survival of 8-9 months has been achieved with several regimens (cisplatin-paclitaxel, carboplatin-paclitaxel, cisplatin-vinorelbine, and gemcitabine-cisplatin), and 1-year survival rates of 33%-39% are now attainable. These results compare favorably with studies of best supportive care of the 1980s, which achieved a median survival of approximately 17 weeks and 1-year survival rates of 10%-14%. However, no clearly superior front-line regimen exists at present, and we await results of the randomized ECOG trial, which evaluates four different chemotherapeutic regimens as front-line treatments for NSCLC.

Vinorelbine-cisplatin

Vinorelbine also has been studied extensively in phase III trials. In three studies, vinorelbine combined with cisplatin was compared to either vinorelbine alone or cisplatin alone. In each of these studies, the two-drug combination produced significantly higher response rates. In addition, significantly longer survival was observed in patients treated with vinorelbine-cisplatin in two of the trials. Perhaps more important, vinorelbine-cisplatin prolonged survival compared with vindesine-cisplatin.

Docetaxel

Docetaxel is another taxane that has produced relatively high response rates in patients with previously untreated, advanced NSCLC. In addition, two phase II trials have shown that docetaxel has activity in patients whose disease has progressed after treatment with cisplatin-containing chemotherapy.

Two large phase III trials of docetaxel in the second-line setting have been completed. The first trial, conducted by multiple US investigators, compared docetaxel (75 or 100 mg/m^2) vs vinorelbine or ifosfamide in NSCLC patients who had been treated previously with platinum-based chemotherapy. Response rates in patients treated with docetaxel were significantly higher than rates in patients in the vinorelbine-ifosfamide control group; this difference was seen with both the 100-mg/m^2 dose of docetaxel (response rate, 12%; $P = .001$) and the 75-mg/m^2 dose (response rate, 8%; $P = .036$). Although median survival was identical in the three groups (approximately 5.6 months), the 1-year survival rate was superior in the group given 75 mg/m^2 of docetaxel than in those treated with vinorelbine-ifosfamide (32% vs 19%; $P = .046$).

Approximately 35% of patients in each treatment arm received further chemotherapy after completion of the study, including 21% of patients in the vinorelbine-ifosfamide arm, who later received subsequent taxanes (either docetaxel or paclitaxel). An intention-to-treat analysis, in which patients were

censored for subsequent chemotherapy, revealed significant differences in 1-year survival favoring docetaxel (either dose) over vinorelbine-ifosfamide (32% vs 10%; $P = .012$).

A trial by Shepherd et al randomized patients to docetaxel (75 or 100 mg/m^2) vs best supportive care. Median survival was 9 months in the patients who received 75 mg/m^2 of docetaxel vs 4.6 months in those treated with best supportive care, and 1-year survival in these docetaxel-treated patients was superior (40% vs 16%; $P = .016$). Improvements favoring the 75-mg/m^2 docetaxel arm were also seen with respect to quality of life; a reduction in both narcotic and nonnarcotic analgesic usage was noted as well.

These results, along with an analysis of the toxicities observed in the two phase III trials, suggest that a 75-mg/m^2 dose of docetaxel may be an acceptable second-line chemotherapeutic regimen in the platinum-refractory or -resistant patient. Docetaxel combined with cisplatin is being evaluated in the current phase III ECOG trial.

Gemcitabine

Gemcitabine, a fluorine-substituted cytarabine (Ara-C) analog, is a prodrug that requires intracellular phosphoration (by deoxycytidine kinase) to generate its active forms, gemcitabine diphosphate and triphosphate. Gemcitabine has greater membrane permeability and enzyme affinity than Ara-C and is a potent compound in several solid tumors.

Gemcitabine, in combination with cisplatin, was approved by the FDA in July 1998 for the front-line treatment of NSCLC, based on several randomized trials. The most prominent of these, by Sandler et al of the Hoosier Oncology Group, randomized over 500 patients to treatment with either gemcitabine (1,000 mg/m^2 on days 1, 8, and 15) followed by cisplatin (100 mg/m^2 IV infused over 4 hours), or cisplatin alone (same dose). Response rates were significantly higher in the gemcitabine arm (31% vs 12%; $P < .0001$), and time to progression was also significantly longer (5.6 vs 3.7 months; $P = .0013$). Most importantly, median survival was significantly better in the gemcitabine-cisplatin group than in the cisplatin-alone group (9.1 vs 7.6 months; $P = .004$).

Irinotecan

This topoisomerase I inhibitor produced a 32% response rate in a phase II trial conducted by Japanese investigators. Combined with cisplatin, irinotecan appeared to have acceptable toxicity and produced a 54% response rate. However, in a follow-up trial conducted in the United States, irinotecan produced a 15% response rate in previously untreated patients.

Promising novel agents

Several novel agents are being developed for the treatment of solid tumors, including lung cancer. For example, farnesyl transferase inhibitors target prenylation of the *ras* family of proto-oncogenes. Farnesylation causes the *ras* oncogene to be constitutively active.

Other novel agents include signal transduction inhibitors, such as tyrosine kinase inhibitors, and antiangiogenic agents. Many of these novel agents are being tested in combination with chemotherapeutic agents, as their mechanisms of action suggest that these agents may be far more effective as chronic inhibitors of cancer progression than as classic cytotoxics.

To date, most phase I studies of these various compounds have suffered from a difficulty in developing pharmacologically or molecularly driven end points that will serve as reasonable intermediate biomarkers of efficacy or even surrogates for toxicity.

Current treatment recommendations

It is important to note that patients who have lost significant amounts of weight or who have poor performance status are at greater risk for toxicity, including a higher likelihood of lethal toxicity, when they are treated with modest doses of chemotherapy. Based on currently available data, a reasonable approach for stage IV NSCLC patients who have good performance status (ECOG performance status, 0-1) and have not lost a significant amount of weight (≥ 5% of usual weight) would be to encourage them to participate in a clinical trial.

However, it would also be appropriate to treat this group of patients with etoposide plus cisplatin or with one of the newer combination regimens, such as gemcitabine-cisplatin, vinorelbine-cisplatin, paclitaxel-cisplatin, paclitaxel-carboplatin, or docetaxel-cisplatin (Table 4).

ROLE OF PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT), a treatment that combines Photofrin (a hematoporphyrin derivative in which the less active porphyrin monomers have been removed) with an argon-pumped dye laser, has been explored in a variety of different tumors, with varying results. Several investigators have reported excellent results with PDT in early-stage head and neck cancers, as well as intrathoracic tumors. However, initial studies have involved a limited number of patients.

Although this novel technique seems to be extremely promising, it appears to be applicable to only a small minority of NSCLC patients. Nevertheless, PDT appears to be particularly useful for the treatment of early-stage lung cancer for a variety of reasons. First, it appears to effectively preserve lung function and can be repeated as additional tumors appear—an important consideration since such patients appear to be at high risk for developing other new tumors. Furthermore, this technique does not preclude ultimate surgical intervention when deemed necessary.

Results in early-stage NSCLC Perhaps most striking are the results reported by Furuse et al, who treated 54 patients with 64 early-stage lung cancers using Photofrin (2.0 mg/kg) and 630-nm illumination of 100-200 J/cm^2. Of 59 accessible tumors, 50 responded completely and 6 showed partial responses. Five of the complete responders developed recurrences 6-18 months after treatment.

TABLE 4: Chemotherapeutic regimens for NSCLC

Regimen	Dose	Schedule
Etoposide	100 mg/m^2/d	Days 1-3 q3wk
Cisplatin	60 mg/m^2	Day 1 q3wk
Paclitaxel	225 mg/m^2	Infused over 3 h
followed by		
Carboplatin	Dosed to produce AUC of 6 mg/mL · min	
Vinorelbine	30 mg/m^2	Weekly
Cisplatin	120 mg/m^2	Days 1 and 29 and then q42d
Docetaxel	75 mg/m^2	Day 1 q3wk
Cisplatin	75 mg/m^2	Day 1 q3wk

AUC = area under the curve

The major predictor of response in this study was tumor length. The likelihood of achieving a complete response was 97.8% if the tumor was < 1 cm, as opposed to only a 42.9% if the lesion was > 1 cm. The overall survival rate in these patients was 50% at 3 years.

A similar study by Kato et al also indicated a 96.8% complete response rate for tumors < 0.5 cm but only a 37.5% rate for tumors > 2 cm. The overall 5-year survival rate for the 75 patients treated in this study was 68.4%, which is quite acceptable by current standards.

Further work by Lam et al supported these promising results of PDT in early-stage NSCLC.

Results in advanced-stage NSCLC Two prospective, randomized trials (European; US/Canada) compared PDT vs the neodymium–yttrium-aluminum-garnet (Nd:YAG) laser for partially obstructive, advanced NSCLC. Investigators analyzed results from the two trials both individually and collectively. Collective analysis included data from 15 centers in Europe and 20 centers in the United States and Canada, and involved a total of 211 patients. In the European trial, 40% of the patients had received prior therapy, whereas in the US/Canada trial all of the patients had been received previous treatment.

Tumor response was similar for both therapies at 1 week. However, at 1 month, 61% and 42% of the patients treated with PDT in the European and US/Canada trials, respectively, were still responding, as compared with 36% and 19% of patients who underwent laser therapy in the two trials.

PDT also produced more dramatic improvements in dyspnea and cough than did Nd:YAG therapy in the European trial, but the two treatments had similar effects on these symptoms in the US/Canada trial. Both sets of investigators concluded that PDT appears to be superior to laser therapy for the relief of dyspnea, cough, and hemoptysis. Also, the overall incidence of adverse reactions was similar with the two therapies (73% for PDT vs 64% for Nd:YAG therapy).

PALLIATION OF LOCAL AND DISTANT SYMPTOMS

Radiation therapy

Many patients with lung cancer experience distressing local symptoms at some time. These may arise from airway obstruction by the primary tumor, compression of mediastinal structures by nodal metastases, or metastatic involvement of distant organs. Radiation therapy is quite effective in palliating most local symptoms, as well as symptoms at common metastatic sites, such as bone and brain. For selected patients with a solitary brain metastasis and controlled disease in other sites, resection followed by radiation appears to be superior to radiation therapy alone in improving both survival and quality of life.

Doses In the United States, most radiation oncologists use doses in the range of 30 Gy in 10 fractions for palliative treatment. Data from the United Kingdom suggest that similar efficacy without greater toxicity may be achieved with more abbreviated schedules, such as 17 Gy in 2 fractions 1 week apart or single fractions of 11 Gy (see Table 5). Such schedules may facilitate the coordination of radiation and chemotherapy and also reduce patient travel and hospitalization.

Endobronchial irradiation with cobalt-60 or iridium-192 has been used to palliate symptoms arising from partial airway obstruction, including cough, dyspnea, and hemoptysis. The dosimetric advantage of being able to deliver a high radiation dose to the obstructing endobronchial tumor while sparing adjacent normal structures, such as lung, spinal cord, and esophagus, has clear appeal, particularly in the patient whose disease has recurred following prior external-beam irradiation. Although good rates of palliation have been reported with endobronchial irradiation, significant complications, including fatal hemoptysis, are seen in 5%-10% of patients.

Endobronchial irradiation should be considered as only one of several approaches (including laser excision, cryotherapy, and stent placement) that can be used in the management of patients with symptomatic airway obstruction, and management should be individualized. All of these approaches are more suitable for partial rather than complete airway obstruction.

Chemotherapy

Several recent trials have explored the use of chemotherapy to palliate specific symptoms in patients with lung cancer. In general, these trials have found that rates of symptomatic improvement were considerably higher than objective response rates and were not dissimilar to symptomatic response rates with local radiation therapy.

Thus, while radiation therapy remains the most appropriate modality for the treatment of such problems as superior vena cava obstruction, spinal cord compression, brain metastases, or localized bone pain, patients who have more extensive disease without these local exigencies may be considered for palliative chemotherapy, which may both relieve local symptoms and prolong survival.

TABLE 5: Palliation of symptoms of NSCLC with external-beam irradiation (percentage of patients with symptoms palliated)

Symptom	Standard RT (24-30 Gy in 6-10 fractions)	17 Gy in 2 fractions (first trial/second trial)	1 fraction of 10 Gy
Cough	56	65/48	56
Hemoptysis	86	81/75	72
Chest pain	80	75/59	72
Anorexia	64	68/45	55
Depression	57	72/NA	NA
Anxiety	66	71/NA	NA
Breathlessness	57	66/41	43

NA = data not available, RT = radiation therapy

Data from Bleehen NM, Girling DJ, Fayers PM, et al: Br J Cancer 63:265-270, 1991; Bleehen NM, Bolger JJ, Hasleton PS, et al: Br J Cancer 65:934-941, 1992.

Follow-up of long-term survivors

At present, no standard follow-up protocol exists for patients with cured NSCLC or SCLC. However, at a minimum, long-term follow-up should include serial physical examinations once the patient has reached the 5-year mark. Controversy currently exists about the value of utilizing CT scanning or even chest x-rays for the long-term follow-up of these patients.

In this vein, retrospective reviews of the literature have revealed that SCLC patients appear to have the highest rate of second primary tumor development–as high as 30% over the course of their lifetime, with some studies reporting annual second primary tumor rates of 5%-10%. Therefore, the concept of chemoprevention appears to have particular merit in these patients.

A recently completed, randomized chemoprevention study of patients with stage I NSCLC showed a surprisingly high annual recurrence rate of 6.5% in patients with T1 tumors, as opposed to 11.2% in patients with T2 tumors. Whether retinoids are effective chemopreventive agents remains to be seen. Nevertheless, there is clearly a need for effective chemoprevention for both of these tumor subsets, as well as the establishment of consistent guidelines for routine long-term follow-up. Given the current controversy over lung cancer screening, however, it is unlikely that this issue will be resolved without the performance of another prospective screening trial.

MESOTHELIOMA

Mesotheliomas are uncommon neoplasms derived from the cells lining the pleura and peritoneum. Currently, 2,000-3,000 new cases are diagnosed in the United States each year.

Epidemiology

Gender Males are affected five times more commonly than females.

Age The median age at diagnosis is 60 years.

Etiology and risk factors

Asbestos exposure The relationship between asbestos exposure and diffuse pleural mesothelioma was first reported by Wagner, who documented 33 pathologically confirmed cases from an asbestos mining region in South Africa. Selikoff and colleagues documented a 300-fold increase in mortality from mesothelioma among asbestos insulation workers in the New York metropolitan region when compared to the general population. The interval between asbestos exposure and tumor formation is commonly 3-4 decades.

Asbestos fibers are generally divided into two broad groups: serpentine and amphibole. The latter includes crocidolite, the most carcinogenic form of asbestos. The inability of phagocytic cells to digest the fiber appears to initiate a cascade of cellular events that results in free-radical generation and carcinogenesis.

Diagnosis

Patients with mesothelioma usually seek medical attention while the disease is limited to a single hemithorax and commonly complain of dyspnea and pain. Dyspnea results from diffuse growth of the tumor on both the parietal and visceral pleura, which encases the lung in a thick rind. Pain is caused by direct tumor infiltration of intercostal nerves.

Chest x-ray and CT Chest x-ray demonstrates pleural thickening, pleural-based masses, or a pleural effusion. Chest CT scan more accurately portrays the extent of disease and frequently reveals chest wall invasion, as well as pericardial and diaphragmatic extension.

Thoracentesis and thoracoscopy Thoracentesis and pleural biopsy usually are sufficient to establish the diagnosis of malignancy, but a thoracoscopic or open biopsy is often required to provide enough tissue to make an accurate histologic diagnosis of mesothelioma.

Distinguishing mesothelioma from other neoplasms Light microscopy is often insufficient for differentiating among mesothelioma, metastatic adenocarcinoma, and sarcoma. Immunohistochemistry and electron microscopy are frequently necessary to establish the diagnosis.

Although adenocarcinomas stain positive for carcinoembryonic antigen (CEA), Leu-M1, and secretory component, mesotheliomas are negative for these markers. Mesotheliomas stain positive for cytokeratin, whereas sarcomas do not. Mesotheliomas have characteristic long microvilli that are well demonstrated by the electron microscope; adenocarcinomas have short microvilli.

TABLE 6: Staging of mesothelioma according to Butchart

Stage	Description
Stage I	Tumor confined within the "capsule" of the parietal pleura, ie, involving only ipsilateral pleura, lung, pericardium, and diaphragm
Stage II	Tumor invading chest wall or involving mediastinal structures, eg, esophagus, heart, opposite pleura; lymph node involvement within the chest
Stage III	Tumor penetrating diaphragm to involve peritoneum; involvement of opposite pleura; lymph node involvement outside the chest
Stage IV	Distant blood-borne metastases

Pathology

Mesotheliomas may contain both epithelial and sarcomatoid elements and are classified by the relative abundance of each component. Epithelial mesotheliomas are most common (50%), followed by mixed (34%) and sarcomatoid (16%) tumors. Survival for the epithelial type is 22 months, compared to only 6 months for the other types.

Staging and prognosis

The most commonly utilized staging system for mesothelioma, that of Butchart, is based on inexact descriptions of the extent of local tumor growth or distant metastases (Table 6). Other, more detailed staging systems based on TNM criteria have been proposed.

Median survival following diagnosis ranges from 9 to 21 months. Although autopsy series have demonstrated distant metastases in as many as 50% of patients with mesothelioma, death usually results from local tumor growth.

Treatment

Treatment rarely results in cure and should be considered palliative.

Surgical options include chest tube insertion and pleurodesis to control the pleural effusion. Currently, there is renewed interest in aggressive treatment that includes extrapleural pneumonectomy with concomitant resection of the diaphragm and pericardium, followed by chemotherapy and radiotherapy. Subtotal pleurectomy is a less extensive surgical procedure that debulks the majority of tumor, permits reexpansion of the lung, and prevents recurrence of the pleural effusion.

Chemotherapy and radiotherapy appear to offer no survival benefit. Radiation therapy is useful in relieving symptoms due to local tumor invasion, however.

Although the median survival of patients treated with aggressive multimodality regimens that include surgery appears to be superior to survival of patients

treated with chemotherapy and radiotherapy alone, the apparent improvement may be the result of selection bias.

Innovative treatments for this recalcitrant disease, such as PDT and gene transfer therapy, are under investigation.

SUGGESTED READING

ON NON-SMALL-CELL LUNG CANCER

Albain K, Rusch V, Crowley J, et al: Long-term survival after concurrent cisplatin/etoposide (PE) plus chest radiotherapy (RT) followed by surgery in bulky, stages IIIA (N2) and IIIB non–small-cell lung cancer (NSCLC): 6-Year outcomes from Southwest Oncology Group Study 8805 (abstract). Proc Am Soc Clin Oncol 18:467a, 1999.

This study demonstrated that long-term survival plateaus at 20% and is identical for bulky IIIA (N2) and IIIB substages.

Belani CP, Natale RB, Lee JS, et al: Randomized phase III trial comparing cisplatin/etoposide vs carboplatin/paclitaxel in advanced and metastatic non-small-cell lung cancer (NSCLC) (abstract). Proc Am Soc Clin Oncol 17:455a, 1998.

This trial demonstrated higher response rates for carboplatin/paclitaxel vs cisplatin/etoposide (24% vs 13%) but no survival benefit.

Clamon G, Herndon J, Cooper R, et al: Radiosensitization with carboplatin for patients with unresectable stage III non-small-cell lung cancer: A phase III trial of the Cancer and Leukemia Group B and the Eastern Cooperative Oncology Group. J Clin Oncol 17:4–11, 1999.

This randomized trial found no benefit to the addition of weekly carboplatin (100 mg/m^2/wk) concurrently with thoracic radiotherapy when preceded by induction chemotherapy (vinblastine and cisplatin). Of note, the results of this trial, using the same strategy as CALGB 84-33 by Dillman et al (which had reported a 5-year survival of 17% with induction chemotherapy followed by radiotherapy), demonstrated a 4-year survival rate of only 10%, closer to the 5-year results (of 8%) seen with the same regimen in the RTOG 88-08 trial.

Dougherty TJ, Gomer CJ, Henderson BW, et al: Photodynamic therapy. J Natl Cancer Inst 90:889–905, 1998.

An outstanding review of the state of the art in PDT.

Fossella FV, DeVore R, Kerr R, et al: Phase III trial of docetaxel 100 mg/m^2 or 75 mg/m^2 vs vinorelbine/ifosfamide for non–small-cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy (PBC) (abstract). Proc Am Soc Clin Oncol 18:460a, 1998.

This study showed that docetaxel, particularly at a dose of 75 mg/m^2, offers an advantage in terms of 1-year survival, as opposed to the vinorelbine-ifosfamide alternative.

Furuse K, Fukuoka M, Kato H, et al: Prospective phase II study on photodynamic therapy with Photofrin II for centrally located early-stage lung cancer: The Japan Lung Center. J Clin Oncol 11:1852–1857, 1993.

The first published prospective, phase II trial of PDT.

Giaccone G, Postmus P, Debruyne C, et al: Final results of an EORTC phase III study of paclitaxel vs teniposide in combination with cisplatin in advanced NSCLC (abstract). Proc Am Soc Clin Oncol 16:460a, 1997.

Randomized comparison of paclitaxel-cisplatin vs a standard European regimen of teniposide-cisplatin, suggesting the superiority of the taxane-based regimen.

Grilli R, Oxman ADF, Julian JA: Chemotherapy for advanced non–small-cell lung cancer: How much benefit is enough? J Clin Oncol 11:866–871, 1993.

The authors describe the results of a meta-analysis that included 635 NSCLC patients entered into six trials in which supportive care was compared to chemotherapy. Chemotherapy was associated with a mean survival gain of 6 weeks.

Harpole DH, Feldman JM, Buchanan S, et al: Bronchial carcinoid tumors: A retrospective analysis of 126 patients. Ann Thorac Surg 54:50–55, 1992.

Analysis of the survival of 126 patients with bronchial carcinoids treated at Duke University Medical Center during a 20-year interval.

Hayman JA, Martel MK, Randall K, et al: Dose escalation in non–small-cell lung cancer (NSCLC) using conformal 3-dimensional radiation therapy (C3DRT): Update of a phase I trial (abstract). Proc Am Soc Clin Oncol 18:459a, 1999.

In this trial of conformal three-dimensional radiotherapy, the radiation dose was escalated based on the effective volume of irradiated lung (up to 102.9 Gy). Such doses produced acceptable toxicity, and no cases of isolated failures were observed in purposely unirradiated, clinically uninvolved nodal regions.

Kato H, Okunaka T, Shimatani H: Photodynamic therapy for early stage bronchogenic carcinoma. J Clin Laser Med Surg 14:235–238, 1996.

This report confirms the promise of PDT in (very) early lung cancer.

Keller SM, Adak S, Wagner H, et al: Prospective randomized trial of postoperative adjuvant therapy in patients with completely resected stages II and IIIA non–small-cell lung cancer: An intergroup trial (E3590) (abstract). Proc Am Soc Clin Oncol 18:465a, 1999.

This study showed no benefit to adjuvant chemoradiation therapy vs radiotherapy.

Kelly K, Crowley J, Bunn PA, et al: A randomized phase III trial of paclitaxel plus carboplatin (PC) versus vinorelbine plus cisplatin (VC) in untreated advanced non–small-cell lung cancer (NSCLC): A Southwest Oncology Group (SWOG) trial (abstract). Proc Am Soc Clin Oncol 18:461a, 1999.

Two of the newer chemotherapy combinations showed no difference with regard to response rates or survival in stage IV NSCLC.

Kwiatkowski DJ, Harpole DH Jr, Godleski J, et al: Molecular pathologic substaging in 244 stage I non-small-cell lung cancer patients: Clinical implications. J Clin Oncol 16:2468–2477, 1998.

A prospective survey of different molecular prognostic markers in stage I NSCLC. Pathologic and surgical factors are also evaluated.

Lippman SM, Lee JJ, Karp DD, et al: Phase III intergroup trial of 13-cis-retinoic acid to prevent second primary tumors in stage I non–small-cell lung cancer (NSCLC) (abstract). Proc Am Soc Clin Oncol 17:456a, 1998.

An early analysis of the intergroup lung chemoprevention trial, indicating the higher-than-expected likelihood of recurrence in stage I NSCLC.

Martini N, Burt ME, Bains MS, et al: Survival after resection of stage II non–small-cell lung cancer. Ann Thorac Surg 54:460–466, 1992.

Analysis of survival in 214 patients with stage II NSCLC who underwent resection and mediastinal lymph node dissection at Memorial Sloan-Kettering Cancer Center during a 16-year period.

Miller DL, McManus KG, Allen MS, et al: Results of surgical resection in patients with N2 non-small-cell lung cancer. Ann Thorac Surg 57(5):1095–1101, 1994.

In a study of 167 patients with NSCLC, researchers concluded that when N2 disease is found at thoracotomy, complete resection is warranted to achieve long-term survival.

PORT Meta-Analysis Trialists Group: Postoperative radiotherapy in non–small-cell lung cancer: Systemic review and meta-analysis of individual patient data from nine randomized controlled trials. Lancet 352:257–263, 1998.

A highly controversial meta-analysis indicating that cobalt-based radiotherapy can actually be harmful in early stage NSCLC patients without nodal involvement. An important initial study that highlighted the rate-limiting neurotoxicity observed with this regimen.

Sause WT, Scott C, Taylor S, et al: Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: Preliminary results of a phase III trial in regionally advanced unresectable non–small-cell lung cancer. J Natl Cancer Inst 87:198–205, 1995.

This trial confirmed the results of the CALGB trial showing a survival advantage of giving induction chemotherapy (cisplatin-vinblastine) prior to radiation (60 Gy/30 fractions/6 weeks) in favorable patients with stage IIIA-IIIB NSCLC. A third arm using twice-daily radiation to 69.6 Gy produced intermediate results that did not differ significantly from the standard radiation therapy arm.

Schiller JH, Storer B, Berlin J, et al: Amifostine, cisplatin, and vinblastine in metastatic non–small-cell lung cancer: A report of high response rates and prolonged survival (abstract). J Clin Oncol 14:1913–1921, 1996.

Amifostine was combined with cisplatin and vinblastine in 25 patients with metastatic NSCLC. While median survival was estimated at 17 months, the promise of this regimen has yet to be confirmed in randomized trials.

Thomas P, Rubinstein L, and the Lung Cancer Study Group: Cancer recurrence after resection: TI N0 non–small-cell lung cancer. Ann Thorac Surg 49:242–247, 1990.

The incidence of cancer recurrence, the appearance of second primary lung cancers, and the patterns of metastatic spread are analyzed in 907 carefully staged patients with NSCLC treated in LCSG trials.

Van Raemdonck DE, Schneider A, Ginsberg RJ: Surgical treatment for higher stage non-small-cell lung cancer. Ann Thorac Surg 54:999–1013, 1992.

A comprehensive review of treatment regimens for stages IIIA, IIIB, and IV NSCLC that contain surgery as one component. The authors describe surgical procedures, neoadjuvant or adjuvant chemoradiation, and patient survival.

Vansteenkiste J, Stroobants S, Dupont P, et al: Prognostic importance of fluorodeoxyglucose-uptake (FDG) on PET-scan in non–small-cell lung cancer (NSCLC): An analysis of 125 cases (abstract). Proc Am Soc Clin Oncol 18:464a, 1999.

PET scan was shown to be an important prognostic factor in this analysis of 125 patients with operable lung cancer.

Vokes EE, Keopold KAS, Herndon II JE, et al: Cancer and Leukemia Group B: A randomized phase II study of gemcitabine or paclitaxel or vinorelbine with cisplatin as induction chemotherapy (Ind CT) and concomitant chemoradiotherapy (XRT) for unresectable stage III non–small-cell lung cancer (NSCLC) (CALGB study 9431) (abstract). Proc Am Soc Clin Oncol 18:459a, 1999.

Vokes et al demonstrate a promising median survival for chemoradiation with different novel agents.

Walsh GL, Morice RC, Putnam JB Jr, et al: Resection of lung cancer is justified in high-risk patients by exercise oxygen consumption. Ann Thorac Surg 58:704–711, 1994.

A cohort of 66 patients with NSCLC and "high-risk" standard pulmonary function tests were further evaluated by measuring oxygen consumption during exercise.

ON MESOTHELIOMA

Albelda SM: Gene therapy for lung cancer and mesothelioma. Chest 111:144S–149, 1997.

An innovative approach to the treatment of mesothelioma, in which an adenovirus vector is utilized to introduce the thymidine kinase gene into tumor cells. Patients are treated with the nontoxic nucleoside ganciclovir (Cytovene), which is converted, in the body, into a tumoricidal triphosphate form.

Selikoff IJ, Churg J, Hammond E: Relation between exposure to asbestos and mesothelioma. N Engl J Med 272:560–565, 1965.

This seminal publication firmly established the link between asbestos exposure in the workplace and later development of mesothelioma. A subsequent publication by these authors linked concomitant cigarette smoking and asbestos exposure to a greatly increased risk of lung cancer.

Sugarbaker DJ, Garcia JP, Richards WG, et al: Extrapleural pneumonectomy in the multimodality therapy of malignant pleural mesothelioma. Ann Surg 224:288–296, 1996.

The largest series of extrapleural pneumonectomies for mesothelioma. Patients were treated with adjuvant chemoradiotherapy. Median survival was 21 months.

CHAPTER 7

Small-cell lung cancer

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Lung cancer has been the leading cause of cancer death in US men for years, and since 1987 it also has become the number one cause of cancer death in American women. It is estimated that, in the year 2000, 171,600 new cases of lung cancer will be diagnosed, and 158,900 deaths due to this cancer will occur.

Lung cancer appears to develop from a stem cell that can differentiate along multiple lines. Although it is not uncommon to find multiple cell types within a single lung tumor, one type usually predominates. Based on therapeutic approach, there are two major subdivisions of lung cancer: small-cell carcinoma (SCLC), for which chemotherapy is the primary treatment, and non–small-cell carcinoma (NSCLC), which, in its early stages (I and II), is treated primarily with surgery. Approximately 20% of all lung cancers are small-cell carcinomas.

This chapter will focus on the staging and prognosis, pathology and pathophysiology, and treatment of SCLC. Chapter 6 covers NSCLC, including carcinoid tumors of the lung, and also discusses mesothelioma. In addition, chapter 6 provides information on the epidemiology, etiology, screening and prevention, signs and symptoms, and diagnosis and staging evaluation of lung cancer in general, as well as the pulmonary assessment of lung cancer patients and the follow-up of long-term survivors.

Staging and prognosis

Unlike NSCLC, in which the TNM staging system is used for all patients, the TNM staging classification is generally not utilized in SCLC, as it does not predict well for survival. Rather, SCLC is usually described as either limited (M0) or extensive (M1), although these general terms are inadequate when evaluating the role of surgery. For surgical staging, the TNM system is usually used (see chapter 6, Table 1). Patients with SCLC who have stages I-III disease, excluding those with a malignant pleural effusion, are classified as having limited disease. These patients constitute approximately one-third of all SCLC patients. The remaining SCLC patients fall into the extensive-disease category, which includes any patient with a malignant pleural effusion or any site of distant disease—brain, liver, adrenal gland, bone, bone marrow, and others.

The staging of lung cancer must be conducted in a methodical and detailed manner in order to permit appropriate therapeutic recommendations and to allow comparison of treatment results from different institutions.

Stage is commonly reported as either clinical or pathologic. The former is based on noninvasive (or minimally invasive) tests, while the latter is based on tissue obtained during surgery (see chapter 6).

The most important prognostic factor in lung cancer is the stage of disease. Within a given disease stage, the next most important prognostic factors are performance status and recent weight loss. The two scales used to define performance status are the Eastern Cooperative Oncology Group (ECOG) performance status system and the Karnofsky system (see Appendix 3). In short, patients who are ambulatory have a significantly longer survival than those who are nonambulatory. Also, patients who have lost ≥ 5% of body weight during the preceding 3-6 months have a worse prognosis.

Pathology and pathophysiology

SCLC tumors tend to be large central masses with extensive mediastinal lymph node metastases and also have a high likelihood of spreading to distant sites; two-thirds of patients have detectable distant metastases at the time of diagnosis. SCLC has characteristic electron microscopic features that include the presence of neurosecretory granules and neurofilaments.

These tumors contain enzymes that can decarboxylate amino acids, resulting in biologically active amines, and also promote the synthesis of polypeptide hormones, such as antidiuretic hormone and adrenocorticotrophic hormone. Overproduction of polypeptide hormones may result in a syndrome of inappropriate antidiuretic hormone (SIADH), which occurs in approximately 10% of SCLC patients (see chapter 46 for a more extensive discussion of this syndrome), or clinically apparent signs of hypercortisolism, which is relatively rare, occurring in approximately 1% of patients.

Treatment

TREATMENT OF DISEASE LIMITED TO LUNG PARENCHYMA

Surgery

The majority of patients with SCLC present with advanced-stage disease. In the 5%-10% of patients whose tumor is limited to the lung parenchyma, very often the diagnosis is established only after the lung mass has been removed. If, however, the histology has been determined by bronchoscopic biopsy or fine-needle aspiration and there is no evidence of metastatic disease following extensive scanning, examination of the bone marrow, and biopsy of the mediastinal lymph nodes, resection should be performed. Adjuvant chemotherapy is recommended because of the high likelihood of the development of distant metastases following surgery.

The surgical approach is similar to that used in NSCLC: A lobectomy or pneumonectomy should be followed by a thorough mediastinal lymph node dissection. Tumor resection in SCLC should be limited to patients who have no

evidence of mediastinal or supraclavicular lymph node metastases. SCLC patients who have pathologic stage I disease have a survival rate similar to that of stage I NSCLC patients.

TREATMENT OF DISEASE LIMITED TO THE THORAX

As mentioned above, approximately one-third of SCLC patients present with disease that is limited to the thorax and can be encompassed within a tolerable radiation portal. In early studies in which either radiation therapy or surgery alone was used to treat such patients, median survival was only 3-4 months and the 5-year survival rate was in the range of 1%-2%. The reason for the failure of these therapies was rapid appearance of distant metastases.

Chemotherapy

During the 1970s, it became apparent that SCLC was relatively sensitive to chemotherapy. Various combination chemotherapy regimens were used to treat limited SCLC. Although none of the regimens was clearly superior, median survival was approximately 12 months and the 2-year survival rate was approximately 10%-15%.

It appears that maintenance chemotherapy adds little to survival in patients with limited SCLC.

Chemotherapy plus thoracic irradiation

There has been considerable controversy over the value of thoracic irradiation in conjunction with chemotherapy in limited SCLC. However, two meta-analyses of randomized trials comparing chemotherapy alone to chemotherapy plus thoracic irradiation show that the addition of radiation provides a clear benefit in terms of improving both local control and survival. Further data suggest that the timing of the combination is important.

An intergroup trial directly compared once-daily to twice-daily fractionation (45 Gy/25 fractions/5 weeks vs 45 Gy/30 fractions/3 weeks) given at the beginning of concurrent chemoradiation with PE. Initial analysis showed excellent overall results, with median survival for all patients of 20 months and a 40% survival rate at 2 years. With a minimum follow-up of 5 years, survival was significantly better in the twice-daily than in the once-daily radiation group (26% vs 16%). The only difference in toxicity was a temporary increase in grade 3 esophagitis in patients receiving twice-daily radiation therapy *(Turrisi A, Kim K, Blum R, et al: N Engl J Med 340:265-271, 1999).*

Current recommendations While important questions remain as to the optimal radiation doses, volumes, and timing with regard to chemotherapy, a reasonable present standard is to deliver thoracic radiation concurrent with chemotherapy consisting of PE (Platinol, 60 mg/m^2 on day 1, and etoposide, 120 mg/m^2 IV daily for 3 days). The PE regimen is repeated every 21 days for a total of 4 courses. Excellent results have been achieved with 2 courses of chemotherapy during radiation and 2 courses following radiation. A sequence of completing 4-6 cycles of chemotherapy and then delivering similar radiation doses has appeared less promising and should not be used based on current data.

If patients are to receive radiation after completing chemotherapy, higher radiation doses may be required to achieve local control. However, the survival benefits of such an approach are speculative.

A randomized trial of concurrent vs sequential thoracic radiotherapy in combination with PE in over 200 patients with limited-stage SCLC demonstrated a benefit to concurrent therapy, with 3-year survival rates of 31% (concurrent arm) vs 21% (sequential arm). Thoracic radiation therapy consisted of 45 Gy over 3 weeks, starting either with the first cycle of PE in the concurrent arm or after the fourth cycle in the sequential arm *(Goto K, Nishiwaka Y, Takada M, et al: Proc Am Soc Clin Oncol 99:468a[abstract], 1999).*

Results of an intergroup trial indicate that radiation therapy strategies that increase biological dose can improve local control and survival (see box on previous page). Further exploration of accelerated fractionation or of doses > 45 Gy is warranted and is currently being investigated in prospective trials.

Prophylactic cranial irradiation

Recognition that patients with SCLC were at high risk for the development of brain metastases led to the suggestion that they be given "prophylactic" cranial irradiation (PCI) to prevent the clinical manifestation of previously present but occult CNS disease. The role of PCI has been controversial. Most trials have shown a reduction in CNS relapse rates but little effect on survival. There also has been concern about the contribution of prophylactic irradiation to the late neurologic deterioration seen in some patients with SCLC, although recent studies show neurologic impairment in many patients with SCLC prior to any treatment.

Model calculations from data on patterns of failure in patients achieving a systemic complete response suggest that the greatest gain in survival to be expected with PCI is in the range of 5%. To demonstrate this convincingly would require randomized trials of about 700 patients—substantially larger than trials conducted to date or likely to be feasible. However, a recent meta-analysis of randomized trials of PCI in SCLC patients showed a survival improvement of this magnitude with PCI.

A recent meta-analysis of all randomized trials of PCI in patients with SCLC who achieved a complete or near-complete response to induction chemotherapy (alone or combined with thoracic radiation) showed a statistically significant improvement in survival in patients treated with PCI (20.7% at 3 years, vs 15.3% in those not given PCI). The survival improvement with PCI was seen in all patient subgroups, regardless of age, stage, type of induction treatment, or performance status *(Aupérin A, Arriagada R, Pignon J-P, et al: N Engl J Med 341:476-484, 1999).*

Current recommendations When PCI is to be used, patients should be treated only if they have achieved a complete or near-complete remission of disease outside of the CNS. Use of chemotherapeutic agents with known CNS toxicity (eg, methotrexate, procarbazine [Matulane], nitrosoureas) should be avoided, and chemotherapy should not be given during or after the administration of radiation.

Radiation doses for PCI should probably be in the range of 25-30 Gy with a daily fraction size of 2-3 Gy, although recent data suggest that such doses delay and reduce rates of CNS relapse but may not eliminate it; thus, higher doses may warrant exploration. Larger

fraction sizes would be expected to produce greater toxicity. Smaller fractions given twice daily may reduce toxicity, but trials of this approach have not been reported.

TREATMENT OF EXTENSIVE DISEASE

As mentioned above, two-thirds of SCLC patients have extensive disease at diagnosis. Without treatment, median survival in this group of patients is 6-8 weeks. Treatment with combination chemotherapy increases median survival duration to approximately 8-10 months.

Combination chemotherapy

No regimen has been shown to be clearly superior, but the two most commonly used regimens are PE or cyclophosphamide, Adriamycin, and vincristine (CAV). In the PE regimen, Platinol (60 mg/m^2 IV) is given on day 1 and etoposide (100 mg/m^2 IV) is given daily for 3 days; courses are repeated every 21 days. The cyclophosphamide dose used in the CAV regimen is 1,000 mg/m^2 IV, the Adriamycin dose is 40 mg/m^2, and the vincristine dose is 1 mg/m^2 (maximum total dose, 2.0 mg). Courses of this combination are repeated every 21 days.

New agents

A variety of novel agents have been investigated in SCLC. Of these, the taxanes and topoisomerase I inhibitors, particularly topotecan (Hycamtin), have demonstrated the greatest efficacy.

Taxanes Because of their novel mechanism of action and clinical activity in other solid tumors, including NSCLC, the taxanes—paclitaxel (Taxol) and docetaxel (Taxotere)—are particularly attractive agents for evaluation in the treatment of SCLC.

Paclitaxel Ettinger et al reported that single-agent paclitaxel produces an overall response rate of 34% in untreated patients with SCLC. This taxane is currently being evaluated in combination with a variety of different agents, including etoposide and cisplatin (or carboplatin [Paraplatin]), in SCLC patients.

Docetaxel Compared with paclitaxel, docetaxel appears to have a slightly lower response rate of 26% (12 out of 46), even when administered at a dose of 100 mg/m^2, as reported by the Southwest Oncology Group (SWOG). This lower response rate with docetaxel was offset somewhat by the fact that median survival was promising at 9 months, similar to that obtained with combination chemotherapy. Disturbingly, however, median time to progression was only 3 months.

Topoisomerase I inhibitors The topoisomerase I inhibitors—topotecan and irinotecan (CPT-11 [Camptosar])—are clearly active in SCLC, with single-agent response rates of 40%-60%. Due to their novel mechanism of action, the

topoisomerase I inhibitors are currently being tested in patients with recurrent or refractory disease, as many of these patients have been previously exposed to topoisomerase II inhibitors (epipodophyllotoxins/anthracyclines) during the induction phase of therapy. Furthermore, preclinical data suggest that topoisomerase I levels are upregulated in cells resistant to topoisomerase II inhibitors, via downregulation of topoisomerase II levels.

Topotecan A randomized, phase III trial compared topotecan vs CAV in patients who had a response to initial therapy and a minimum drug-free interval of 60 days. Overall response rates were 24% for topotecan alone vs 18% for CAV ($P > .05$). Time to progression and median survival also were similar in the two arms. However, topotecan offered superior palliation for many disease-related symptoms, including dyspnea, fatigue, and hoarseness, and also improved patients' abilities to carry out daily activities. Moreover, topotecan had toxicities similar to those of CAV, with the exception of a slight increase in grade 4 thrombocytopenia.

Irinotecan also has been investigated in recurrent or refractory SCLC in a limited number of patients. Like topotecan and other new agents, irinotecan produced a disappointingly low response rate among patients with SCLC resistant to primary chemotherapy, with only 1 of 27 patients exhibiting a response. In contrast, the response rate to irinotecan among patients with initially sensitive disease that later recurred was 29%.

Other agents, such as gemcitabine (Gemzar) and vinorelbine (Navelbine), have shown activity in SCLC, but this has been less impressive than that reported for the taxanes and topoisomerase I inhibitors.

Phase II trials of new combinations, such as PET (Platinol, etoposide, and Taxol) and TP (topotecan and paclitaxel), have yielded promising median and 2-year survival rates in patients with extensive disease. The contribution of these regimens, relative to standard PE, is being evaluated in ongoing phase III trials.

Experimental approaches

A variety of experimental approaches have been tested in SCLC. These include high doses of chemotherapy and autologous bone marrow transplantation (BMT), alternating regimens of chemotherapy, and weekly administration of chemotherapy.

High-dose chemotherapy plus BMT Most phase II trials using high doses of chemotherapy plus BMT appear to show no advantage of the high-dose approach over standard doses of chemotherapy.

Alternating chemotherapy regimens have been used in an attempt to overcome drug resistance. In randomized trials, alternating chemotherapy regimens have shown a slight improvement in terms of median survival (4-6 weeks) when compared to a single chemotherapeutic regimen but no impact on long-term survival.

PALLIATION OF LOCAL AND DISTANT SYMPTOMS

Radiation therapy

Many patients with lung cancer have distressing local symptoms at some point in their disease course. These may arise from airway obstruction by the primary tumor, compression of mediastinal structures by nodal metastases, or metastatic involvement of distant organs. Radiation therapy is quite effective in palliating most local symptoms, as well as symptoms at common metastatic sites, such as bone and brain. For selected patients with a solitary brain metastasis and controlled disease in other sites, resection followed by radiation appears to be superior to radiation therapy alone in improving both survival and quality of life.

Doses In the United States, most radiation oncologists use doses in the range of 30 Gy in 10 fractions for palliative treatment. Data from the United Kingdom suggest that similar efficacy without greater toxicity may be achieved with more abbreviated schedules, such as 17 Gy in 2 fractions 1 week apart or single fractions of 11 Gy (see Table 4, chapter 6). Such schedules may facilitate the coordination of radiation and chemotherapy and also reduce patient travel and hospitalization.

Endobronchial irradiation with cobalt-60 or iridium-192 has been used to palliate symptoms arising from partial airway obstruction, including cough, dyspnea, and hemoptysis. The dosimetric advantage of being able to deliver a high radiation dose to the obstructing endobronchial tumor while sparing adjacent normal structures, such as lung, spinal cord, and esophagus, has clear appeal, particularly in the patient whose disease has recurred following prior external-beam irradiation. Although good rates of palliation have been reported with endobronchial irradiation, significant complications, including fatal hemoptysis, are seen in 5%-10% of patients.

Other local approaches

Endobronchial irradiation should be considered as only one of several approaches (including laser excision, cryotherapy, and stent placement) that can be used in the management of patients with symptomatic airway obstruction, and management should be individualized. All of these approaches are more suitable for partial rather than complete airway obstruction.

Chemotherapy

Several recent trials have explored the use of chemotherapy to palliate specific symptoms in patients with lung cancer. In general, these trials have found that rates of symptomatic improvement were considerably higher than objective response rates and were not dissimilar to symptomatic response rates with local radiation therapy. Thus, while radiation therapy remains the most appropriate modality for the treatment of such problems as superior vena cava obstruction, spinal cord compression, brain metastases, and localized bone pain, patients who have more extensive

disease without these local exigencies may be considered for palliative chemotherapy, which may both relieve local symptoms and prolong survival.

SUGGESTED READING

Cormier Y, Eisenhauer EA, Muldal A, et al: Gemcitabine is an active new agent in previously untreated extensive small-cell lung cancer (SCLC). Ann Oncol 5:283–285, 1994.

Treatment with gemcitabine resulted in a response rate of 27% in 29 previously untreated patients with SCLC.

Elias AD, Ayash L, Frei E III, et al: Intensive combined modality therapy for limited stage small-cell lung cancer. J Natl Cancer Inst 85:559-566, 1993.

This phase III study of high-dose therapy with stem-cell support demonstrated high response rates and the suggestion of a survival benefit in patients with extensive-stage SCLC. However, these patients were highly selected, with excellent performance status and few poor prognostic indicators.

Heyne KH, Lippman SM, Lee JS, et al: The incidence of second primary tumors in long-term survivors of small-cell lung cancer. J Clin Oncol 10:1519–1524, 1992.

This paper outlined the high likelihood of developing second primary NSCLC tumors in patients previously treated for SCLC.

Jeremic B, Shibamoto Y, Acimovic L, et al: Initial versus delayed accelerated hyperfractionated radiation therapy and concurrent chemotherapy in limited small-cell lung cancer: A randomized study. J Clin Oncol 15:893–900, 1997.

In this phase III trial, initial integration of thoracic radiation in cycle 1 of chemotherapy yielded superior median- and long-term survival compared to chemoradiation in cycle 3 (median survival, 34 vs 26 mo).

Lassen U, Østerlid K, Hansen M, et al: Long-term survival in small-cell lung cancer: Post-treatment characteristics in patients surviving 5 to 18+ years—an analysis of 1,714 consecutive patients. J Clin Oncol 13:1215–1220, 1995.

One of several analyses that have reported similar problems with late relapse and second malignancies in patients with SCLC, who, by virtue of increasingly effective therapy of their initial malignancy, are living long enough for the onset of late complications of treatment of further tobacco-induced malignancies.

Pignon J-P, Arriagada R, Ihde DC, et al: A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 327:1618–1624, 1992.

This international collaboration collected individual patient data from 13 randomized trials comparing chemotherapy alone to chemotherapy plus thoracic irradiation in patients with limited SCLC. The overall analysis showed a significant improvement in 3-year survival for patients receiving thoracic irradiation compared with those receiving chemotherapy alone (14.3% vs 8.9%). This survival improvement was not seen in patients over age 70.

Shah SS, Thompson J, Goldstraw P: Results of operation without adjuvant therapy in the treatment of small-cell lung cancer. Ann Thorac Surg 54:498–501, 1992.

In this study of complete resection and mediastinal lymph node dissection without adjuvant therapy, actual 5-year survival rates were 57% for the 14 patients with stage I disease and 56% for the 11 patients with stage IIIA disease. No patient with lymph node involvement survived 4 years.

Tucker MA, Murray N, Shaw EG, et al: Second cancers are related to smoking and treatment of small-cell lung cancer. J Natl Cancer Inst 89(23):1782–1788, 1997.

This study indicated that extent of smoking before, during, and after treatment of SCLC influences the rate of second primary cancers.

Von Pawel J, Schiller JH, Shepherd FA, et al: Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 17:658–667, 1999.

For this randomized study of patients with recurrent SCLC and a minimal 60-day drug-free interval, topotecan and CAV were equally effective; however, topotecan resulted in greater symptomatic improvement.

CHAPTER 8

Breast cancer overview

Risk factors, screening, genetic testing, and prevention

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Breast cancer is the most common malignancy in women, accounting for 32% of all female cancers. Breast cancer also is responsible for 18% of cancer deaths in women, making it the number two cause of cancer death. An estimated 175,000 new breast cancer cases will be diagnosed in the United States in the year 2000, and 43,700 women will die from this cancer. With improved awareness on the part of both women and health-care providers, however, more breast cancers are being diagnosed while still in situ.

This chapter provides an overview of breast cancer, with discussions of epidemiology, etiology and risk factors, genetic cancer risk assessment, signs and symptoms, screening and diagnosis, prevention (including lifestyle changes and chemoprevention), staging, and prognosis. The three chapters to follow focus on the management of stages 0 and I, stage II, and stages III and IV breast cancer, respectively.

Epidemiology

Gender Breast cancer is relatively uncommon in men; the female to male ratio is approximately 100:1.

Age The risk of developing breast cancer increases with age. The disease is uncommon in women under the age of 40 years; only about 0.8% of breast cancers occur in women < 30 years old and approximately 6.5% develop in women between 30 and 40 years old.

Race White women have a higher overall rate of breast cancer than African-American women; however, this difference is not apparent until age 40 and is marked only after menopause. The incidence of breast cancer in US Asian and Hispanic women is approximately half that in US Caucasian women. Breast cancer risk is extremely low in Native American women.

Geography There is at least a fivefold variation in the incidence of breast cancer among different countries, although this difference appears to be narrowing. The incidence of breast cancer is significantly lower in Japan, Thai-

land, Nigeria, and India than in Denmark, the Netherlands, New Zealand, Switzerland, the United Kingdom, and the United States. It has been suggested that these trends in breast cancer incidence may be related, in some way, to dietary influences, particularly dietary fat consumption (see "Etiology and risk factors" section below).

Socioeconomic status The incidence of breast cancer is greater in women of higher socioeconomic background. This relationship is most likely related to lifestyle differences, such as age at first birth.

Disease site The left breast is involved more frequently than the right, and the most common locations of the disease are the upper outer quadrant and retroareolar region.

Survival Survival rates for patients with nonmetastatic breast cancer (all stages) have improved in recent years (Table 1). These improvements may be secondary to advances in adjuvant chemotherapy and radiation therapy. In addition, early detection of recurrent disease after breast-conservation therapy allows for salvage surgery.

Etiology and risk factors

Numerous risk factors have been associated with the development of breast cancer, including genetic, environmental, hormonal, and nutritional influences. Despite all of the available data on breast cancer risk factors, 75% of women with this cancer have no risk factors.

Genetic factors Hereditary forms of breast cancer constitute only 5%-7% of breast cancer cases overall. However, the magnitude of the probability that a woman will develop cancer if she inherits a highly penetrant cancer gene mutation justifies the intense interest in predictive testing. Commercial testing is available for several genes (*BRCA1, BRCA2,* and *p53)* that are associated with a high risk for breast cancer development (see "Genetic cancer risk assessment" below).

Elevated risk for breast cancer is also associated with mutations in the *PTEN* gene in Cowden's syndrome (described below), and modest increased risk (relative risk of 3.9-6.4) may be seen in women who are heterozygous for a mutation

TABLE 1: Survival of women with breast cancer, according to stage

Stage	Survival rate at 8 years (%)
Stage I	90
Stage II	70
Stage III	40
Stage IV	10

in the *ATM* gene, which is associated with the recessive disease ataxia-telangiectasia in the homozygous state. It has been suggested that other *BRCA* genes will be discovered as well.

BRCA1 *gene* The *BRCA1* gene is located on chromosome 17. This gene is extremely large and complex, and more than 500 different mutations have been discovered, distributed along the entire gene. *BRCA1* mutations are inherited in an autosomal-dominant fashion and are associated with an increased risk for breast, ovarian, and to a lesser degree, prostate cancers. A *BRCA1* mutation carrier has a lifetime risk of developing breast cancer on the order of 56%-85%, and a 15%-45% lifetime risk of developing ovarian cancer.

The incidence of *BRCA1* mutations in the general breast cancer population is unknown since most of the data concerning *BRCA1* have come from studies of high-risk populations. In one study of women with breast cancer, only 6.2% of women < 35 years of age at the time of diagnosis and 7.2% of women < 45 years old who also had a first-degree relative with breast cancer had germline *BRCA1* mutations. However, a 40-year-old woman of Ashkenazi Jewish ancestry who has breast cancer has a greater than 20% probability of bearing a *BRCA* gene mutation.

Further research is necessary to determine the impact that *BRCA1* and other genetic alterations have on the development of breast cancer in the general breast cancer population.

BRCA2 *gene* The *BRCA2* gene has been localized to chromosome 13. *BRCA2* is approximately twice as large as *BRCA1,* and similarly complex.

Alterations in *BRCA2* have been associated with an increased incidence of breast cancer in both women (similar to *BRCA1)* and men (6% lifetime risk). Increased risk for ovarian cancer, pancreatic cancer, and melanoma has also been reported. Together, *BRCA1* and *BRCA2* account for most hereditary breast and ovarian cancer families, and approximately half of hereditary breast cancer families.

Li-Fraumeni syndrome This rare syndrome is characterized by premenopausal breast cancer in combination with childhood sarcoma, brain tumors, leukemia and lymphoma, and adrenocortical carcinoma. Tumors frequently occur in childhood and early adulthood, and often present as multiple primaries in the same individual. Germline mutations in the *p53* gene on chromosome 17p have been documented in persons with this syndrome. Inheritance is autosomal dominant with a penetrance of at least 50% by age 50.

Cowden's syndrome is inherited as an autosomal-dominant trait and is manifested primarily by mucocutaneous lesions. Patients with this uncommon syndrome have a higher incidence of GI polyps and thyroid disorders; lifetime estimates for breast cancer among women with this syndrome range from 25% to 50%. Germline mutations in the *PTEN* gene, located on chromosome 10q23 are responsible for this syndrome.

Family history The overall relative risk of breast cancer in a woman with a positive family history in a first-degree relative (mother, daughter, or sister) is 1.7. Premenopausal onset of the disease in a first-degree relative is associated with a three-fold increase in breast cancer risk, whereas postmenopausal diagnosis increases relative risk by only 1.5. When the first-degree relative has bilateral disease, there is a fivefold increase in risk. The relative risk for a woman whose first-degree relative developed bilateral breast cancer prior to menopause is nearly nine.

No increased risk has been demonstrated when only a second-degree relative (aunt, cousin, or grandmother) has had breast cancer.

Proliferative breast disease The diagnosis of certain conditions after breast biopsy is also associated with an increased risk for the subsequent development of invasive breast cancer. These include moderate or florid ductal hyperplasia and sclerosing adenosis, which pose only a slightly increased risk of breast cancer (1.5-2 times); atypical ductal or lobular hyperplasia, which moderately increases risk (4-5 times); and lobular carcinoma in situ (LCIS), which markedly increases risk (8-11 times; see more detailed discussion of LCIS in chapter 9). Patients who have a family history of breast cancer along with a personal history of atypical epithelial hyperplasia have an eight-fold increase in breast cancer risk when compared to patients with a positive family history alone and an 11-fold increase in breast cancer risk when compared to patients who do not have atypical hyperplasia and have a negative family history.

Personal cancer history A personal history of breast cancer is a significant risk factor for the subsequent development of a second, new breast cancer. This risk has been estimated to be as high as 1% per year from the time of diagnosis of an initial sporadic breast cancer. The risk for development of a second primary breast cancer is significantly higher for women with hereditary breast cancer, approximately 5% per year (50%-60% lifetime risk). Women with a history of endometrial, ovarian, or colon cancer also have a higher likelihood of developing breast cancer than those with no history of these malignancies.

Menstrual and reproductive factors Early onset of menarche (< 12 years old) has been associated with a modest increase in breast cancer risk (two-fold or less). Women who undergo menopause before age 30 have a two-fold reduction in breast cancer risk when compared to women who undergo menopause after age 55. A first full-term pregnancy before age 30 appears to have a protective effect against breast cancer, whereas a late first full-term pregnancy or nulliparity may be associated with higher risk. There is also a suggestion that lactation protects against breast cancer development.

Radiation exposure An increased rate of breast cancer has been observed in survivors of the atomic bomb explosions in Japan, with a peak latency period of 15-20 years. More recently, it has been noted that patients with Hodgkin's disease who are treated with mantle irradiation, particularly women who are

under age 20 at the time of radiation therapy, have an increased incidence of breast cancer.

Exogenous hormone use The data on the possible association between use of oral contraceptives or hormone replacement therapy and breast cancer are controversial. Some data suggest that prolonged use of oral contraceptives by nulliparous women or the use of oral contraceptives before a first full-term pregnancy heightens breast cancer risk. In addition, the literature concerning the possible breast cancer risk posed by prolonged use of estrogens in perimenopausal and postmenopausal women is inconclusive.

There are clear benefits of exogenous hormone replacement for menopausal women, which include reductions in cardiovascular disease and osteoporosis, as well as alleviation of menopausal symptoms. Patients considering hormone replacement therapy should carefully weigh the risks and benefits.

Alcohol Moderate alcohol intake (two or more drinks per day) appears to modestly increase breast cancer risk.

High-fat diet Diets that are high in fat have been associated with an increased risk for breast cancer. As mentioned previously, it has been suggested that differences in dietary fat content may account for the variations in breast cancer incidence observed among different countries.

Obesity Alterations in endogenous estrogen levels secondary to obesity may enhance breast cancer risk.

Genetic cancer risk assessment

Dramatic advances in our understanding of the genetic bases for cancer have led to the development of new technologies and tools for genetic cancer risk assessment. Tests for *BRCA1* and *BRCA2* mutations, responsible for the majority of hereditary breast and ovarian cancer (HBOC) families, are now available commercially.

Genetic testing clearly has the potential to benefit carefully selected and counseled families. Education and adequately trained health care professionals are key elements in the successful integration of genetic cancer risk assessment into clinical practice.

The genetic risk assessment process begins with an assessment of perceived risk and the impact of cancer on the patient and her family. This information forms the framework for counseling.

Comprehensive personal and family history Detailed information regarding personal, reproductive, and hormonal risk factors is noted. Family history, including age at disease onset, types of cancer, and current age or age at death, is obtained for all family members in going back at least three generations.

Documentation of cancer cases is crucial to accurate risk estimation. Pathology reports, medical record notes, and death certificates may all be used in determining the exact diagnosis.

Pedigree construction and evaluation The family pedigree is then constructed and analyzed to determine whether a pattern of cancer in the family is consistent with genetic disease. Sometimes, small family structure or lack of information about the family limits assessment of a hereditary trait; other times, clues, such as ancestry or early age at diagnosis, influence risk assessment and the usefulness of genetic testing.

Individual risk assessment Empiric cancer risk estimates are derived from the information gathered, as well as an estimate of the likelihood that a detectable *BRCA1* or *BRCA2* mutation is responsible for the disease in the family.

Education about the principles of genetics and hereditary cancer patterns is provided. Information on the application of genetic testing (appropriateness, limitations, advantages, and disadvantages) is also given.

The BRCAPRO computer program is a new cancer risk assessment tool that uses a family history of breast or ovarian cancer in first- and second-degree relatives, and includes a Bayesian calculation to account for age-specific penetrance differences, to calculate the probabilities that either a *BRCA1* or *BRCA2* mutation is responsible for the disease. At present, this model has not been validated *(Parmigiani G, Berry DA, Agiular O: Am Hum Genet 62:145-158, 1998).*

Genetic counseling and testing Informed consent is obtained before genetic testing is performed. For individuals who decide to undergo testing, a post-test counseling session is scheduled to disclose and explain the results in person.

Customized screening and prevention recommendations Regardless of whether or not the woman undergoes genetic testing, a customized management plan is delineated, with the goal of prevention or early detection of malignancy, within the context of her personal preferences and degree of risk.

Follow-up care and support The genetic cancer risk assessment service also provides follow-up care and support. This may include cancer surveillance measures, as well as assistance with family dynamics and advising patients about sharing information with at-risk relatives.

Models for predicting the likelihood of a BRCA *mutation*

Several studies have assessed the frequency of *BRCA1* or *BRCA2* mutations in women with breast or ovarian cancer from clinical referral centers. These data are likely to be subject to some selection biases. Personal and family characteristics that are associated with an increased likelihood of a *BRCA1* or *BRCA2* mutation are summarized in Table 2.

Table 2: Features indicating an increased likelihood of a *BRCA* mutation

Multiple cases of early-onset breast cancer
Ovarian cancer (with a family history of breast or ovarian cancer)
Breast and ovarian cancer in the same woman
Bilateral breast cancer
Ashkenazi Jewish heritage
Male breast cancer

Laboratory methods

Several techniques/strategies for detecting mutations in cancer genes have been adopted by different researchers and commercial vendors. Current technology misses 8%-10% of pathologic alterations in *BRCA1* and *BRCA2.*

Directed assays are available for specific founder or ancestral mutations that are common in a gene population. Among Ashkenazi Jews, 1 in 40 individuals bear one of three founder mutations (185delAG and 5382insC in *BRCA1,* and 6174delT in *BRCA2),* and these mutations account for 25% of early-onset breast cancer in this population.

Limitations All of the approaches to detecting mutations have limitations. In general, discovery of an inactivating or "deleterious" mutation of either *BRCA1* or *BRCA2* indicates a high probability that the person will develop breast and/or ovarian cancer.

One of the greatest challenges is the interpretation of missense mutations. These mutations are more likely to be significant if located in an evolutionarily conserved or functionally critical region of the protein. In the absence of a clear disease association, it is often difficult to exclude the possibility that a given missense alteration simply represents a rare polymorphism. A testing service may designate such changes as "genetic variants of uncertain significance."

Testing strategies

In general, testing should be initiated with the youngest affected individual in a given family. Even if one is convinced that a family has HBOC based on clinical criteria, there is only a 50% chance that an offspring or sibling of an affected patient will have inherited the deleterious allele. Therefore, only a positive test (detection of a known or likely deleterious mutation) is truly informative.

Until the "familial mutation" is known, a negative test result could mean either that the unaffected person being tested did not inherit the cancer susceptibility mutation, or that the person inherited the disease-associated gene but the mutation was not detectable by the methods used.

In many cases, no affected family members are available for testing. In that case, one may proceed with genetic testing of an unaffected person, but only after she has been thoroughly counseled regarding its risks, benefits, and *limitations.*

Unless there is suggestive family history, cancer susceptibility testing is not considered appropriate for screening unaffected individuals in the general population. However, it may be reasonable to test unaffected persons who are members of an ethnic group in which specific ancestral mutations are prevalent and whose family structure is limited (ie, the family is small, with few female relatives or no information due to premature death from noncancerous causes).

Impact of genetic cancer risk status on initial management

Data from the Breast Cancer Linkage Consortium (BCLC) suggest that the cumulative risk of developing a second primary breast cancer is approximately 5% per year (up to 65% by age 70) among *BRCA* gene mutation carriers who have already had a breast cancer. Thus, knowledge of the genetic status of a woman affected with breast cancer might influence the initial surgical approach (eg, bilateral mastectomy might be recommended for a mutation carrier instead of a more conservative procedure). Moreover, since ovarian cancer risk may be markedly increased in women with *BRCA1* mutations (and to a lesser degree with *BRCA2* mutations), additional measures, such as surveillance for presymptomatic detection of early-stage tumors or consideration of oophorectomy, may be warranted.

Potential benefits and risks of genetic testing

The ability to identify individuals at highest risk for cancer holds the promise of improved prevention and early detection of cancers. Patients who are *not* at high risk can be spared anxiety and the need for increased surveillance. Recent studies suggest a better emotional state among at-risk relatives who undergo testing than among those who choose not to know their status. The patient's perception of risk is often much higher than risk estimated by current models.

Potential risks Potential medical, psychological, and socioeconomic risks must be addressed in the context of obtaining informed consent for genetic testing.

Concerns about insurance Fear about adverse effects of testing on insurability remains the premier concern among patients. Close behind that is concern about the costs of analyzing large complex genes ($2,400 for *BRCA1* and *BRCA2)* in an uncertain insurance coverage and reimbursement environment.

Legal and privacy issues The legal and privacy issues surrounding genetic testing are as complex as the testing technologies. Although several state laws regarding the privacy of medical information, genetic testing, and insurance and employment discrimination have been passed, they vary widely.

The 1996 Health Insurance Portability and Accountability Act (US public law 104-191) stipulates that genetic information may not be treated as a preexisting

TABLE 3: BI-RAD classification of mammographic lesions

BI-RAD class	Description	Probability of malignancy (%)	Follow-up
0	Needs additional evaluation	I	Diagnostic mammogram, ultrasound
I	Normal mammogram	0	Yearly screening
2	Benign lesion	0	Yearly screening
3	Probably benign lesion	< 2	Short interval follow-up
4	Suspicious for malignancy	20	Biopsy
5	Highly suspicious for malignancy	90	Biopsy

BI-RAD = Breast Imaging Reporting and Data System

condition in the absence of a diagnosis of the condition related to such information. It further prohibits group medical plans from basing rules for eligibility or costs for coverage on genetic information. However, the law does not address genetic privacy issues and doses not cover individual policies.

ASCO recommendations for genetic testing

The American Society of Clinical Oncology (ASCO) recommends that cancer predisposition testing be offered only when: (1) the person has a strong family history of cancer or very early onset of disease; (2) the test can be adequately interpreted; and (3) the results will influence the medical management of the patient or family member.

Signs and symptoms

Mammographic findings Increasing numbers of breast malignancies are being discovered in asymptomatic patients through the use of screening mammography. Mammographic features suggestive of malignancy include asymmetry, microcalcifications, a mass, or an architectural distortion (see Figures 1-5, pages 144-146).

When these features are identified on a screening mammogram, they should, in most cases, be further evaluated with a diagnostic mammogram (and, in some cases, with a breast ultrasound), prior to determining the need for a tissue diagnosis. Often, pseudolesions, such as those caused by summation artifact, dust on the mammographic cassettes, and dermal calcifications, are correctly identified in this manner. All mammographic lesions (and the examinations themselves) must be unambiguously categorized according to one of the six

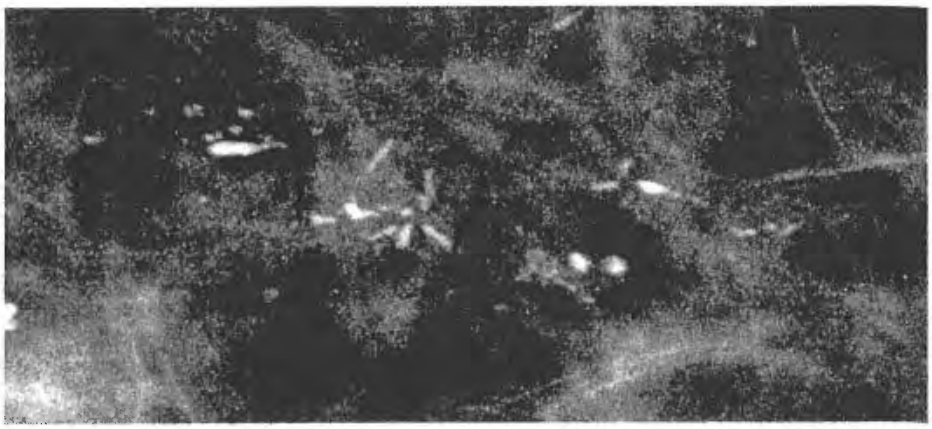

FIGURE 1: Malignant calcifications (comedocarcinoma) in a classic linear dot and dash configuration (BI-RAD 5 lesion). BI-RAD = Breast Imaging Reporting Data System.

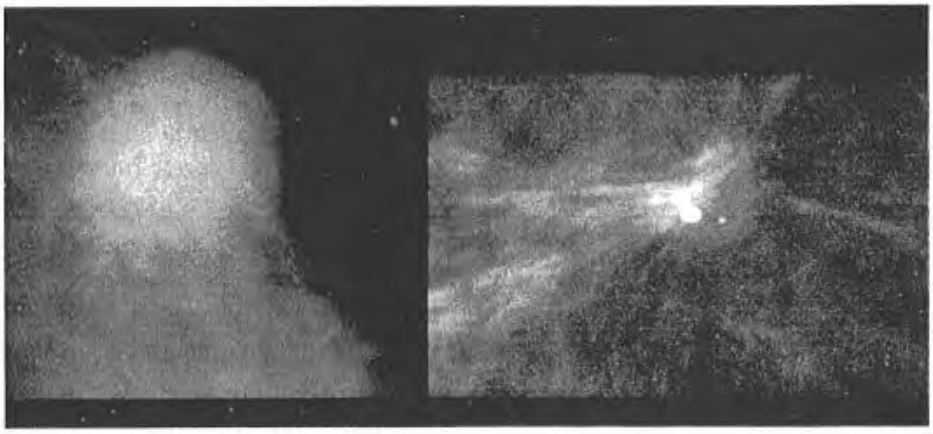

FIGURE 2: Left panel: A dense mass with partially unsharp margins, (BI-RAD 4 lesion), which proved to be a fibroadenoma. Right panel: A small, spiculated mass (BI-RAD 5 lesion), which has engulfed a coarse, benign calcification. This lesion proved to be an invasive ductal carcinoma, not otherwise specified (NOS). BI-RAD = Breast Imaging Reporting Data System.

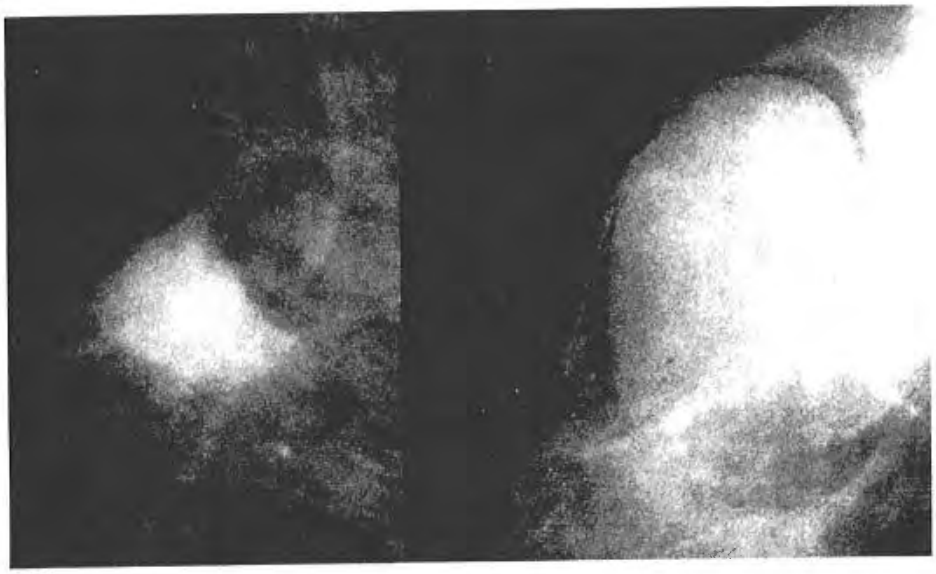

FIGURE 3: Left panel: This focal mass with truly nonsharp margins (BI-RAD 4 lesion) was diagnosed as a tubular carcinoma on stereotactic core biopsy. Right panel: A well-circumscribed lesion containing fat (BI-RAD 2 lesion), which is pathognomonic for a breast hamartoma (fibroadenolipoma). BI-RAD = Breast Imaging Reporting Data System.

FIGURE 4: Focal architectural distortion may be difficult to see, but, if confirmed, it has the highest positive predictive value for breast carcinoma. This BI-RAD 4 lesion proved to be an invasive lobular carcinoma, which often has a subtle mammographic appearance. BI-RAD = Breast Imaging Reporting Data System.

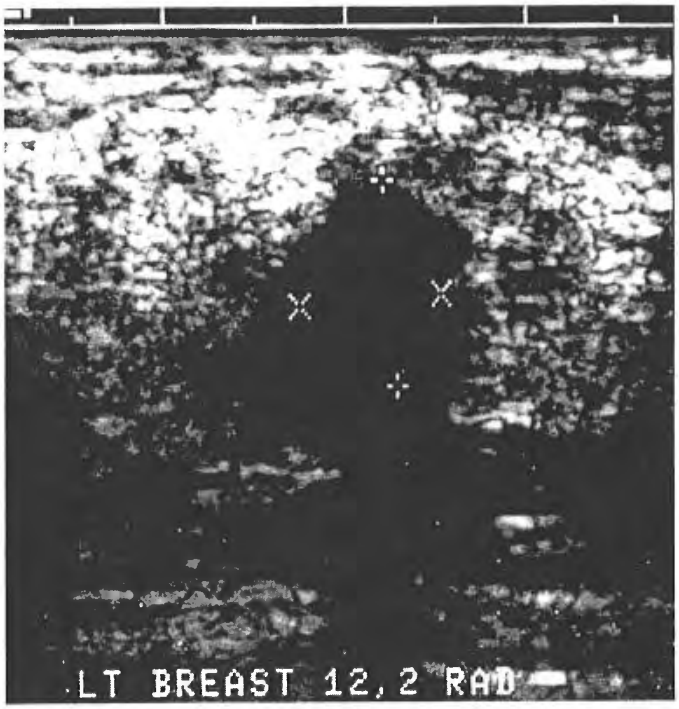

FIGURE 5: This breast ultrasound demonstrates a hypoechoic, solid mass, which exhibits posterior shadowing and is taller than wide. This BI-RAD 4 lesion proved to be an invasive ductal carcinoma, not otherwise specified (NOS). BI-RAD = Breast Imaging Reporting Data System.

Breast Imaging Reporting and Data System (BI-RAD) classifications developed by the American College of Radiology (Table 3).

Breast lump When signs or symptoms are present, the most common presenting complaint is a lump within the breast. The incidence of this complaint can range from 65% to 76%, depending on the study.

Paget's disease has been associated with intraductal carcinoma involving the terminal ducts of the breast and may have an associated invasive component. It presents as an eczematoid change in the nipple, a breast mass, or bloody nipple discharge. Cytology may be helpful in establishing the diagnosis; however, negative cytologic results should not preclude a biopsy.

Other local symptoms Breast pain is the presenting symptom in ~5% of patients, breast enlargement in 1%, skin or nipple retraction in ~5%, nipple discharge in ~2%, and nipple crusting or erosion in 1%.

Screening and diagnosis

Screening

Breast self-examination A recent meta-analysis of 12 studies involving a total of 8,118 patients with breast cancer correlated the performance of breast self-examination with tumor size and regional lymph node status. Women who performed breast self-examination were more likely to have smaller tumors and less likely to have axillary node metastases than those who did not.

A major problem with breast self-examination as a screening technique is that it is rarely performed well. Only 2%-3% of women do an ideal examination a year after instruction has been provided.

Clinical breast examination should be performed and a complete breast history obtained when a woman presents for routine health care. The clinical examination should include inspection and palpation of the breast and regional lymph nodes. Between 14% and 21% of breast cancers are detected by clinical breast examination.

Screening mammography is performed in the asymptomatic patient to detect an occult breast cancer. This contrasts with diagnostic mammography, which is performed in a patient with a breast abnormality (palpable mass, bloody nipple discharge, or some other clinical finding) to further identify the etiology of the problem.

Physical examination and mammography are complementary. Mammography has a sensitivity of 85%-90% and, thus, would miss 10%-15% of clinically evident tumors, while detecting the majority of cases an average of 2 years prior to any perceptible clinical signs or symptoms.

Screening recommendations for average-risk patients After a protracted national debate, a consensus has emerged concerning the age guidelines for screening mammography. The American Cancer Society (ACS), National Cancer Institute (NCI), and American College of Radiology all recommend that women without significant known risk factors for breast cancer begin regular (every 1-2 years) screening mammography at 40 years of age, with universal agreement on yearly screening by age 50. No upper age limit has been suggested, and the previous recommendation for a "baseline" mammogram between the ages of 35 and 40 has been withdrawn.

Screening recommendations for high-risk patients Based on epidemiologic evidence that premenopausal familial breast cancer often presents at similar ages among affected family members, many breast imaging centers recommend that yearly screening for such high-risk individuals begin 5-10 years prior to the youngest age at which their first-degree relative was diagnosed with breast cancer. For example, according to this algorithm, a woman whose mother developed breast cancer at age 45 could begin yearly screening at age 35, in addition to biannual clinical breast examinations. Screening for women at genetic risk may begin at age 25.

Evaluation of a cystic mass

Fine-needle aspiration (FNA) When a dominant breast mass is present and the history and physical examination suggest that it is a cyst, the mass can simply be aspirated with a fine needle. Aspiration of a simple benign breast cyst should yield nonbloody fluid and result in complete resolution of the lesion.

Ultrasonography can also be used to determine whether a lesion is solid or cystic, and also whether a cyst is simple or complex. A complex cyst does not meet the strict criteria of a simple cyst. For example, a complex cyst may demonstrate low level echoes within the cyst fluid or a thickened cyst wall. These features may also be caused by cyst aspiration (presumably due to postaspiration bleeding).

Biopsy A biopsy is indicated if the cyst fluid is bloody, the lesion does not resolve completely after aspiration, or the cyst recurs after repeated aspirations. Cytologic examination of the fluid is not routinely indicated, as the yield for positive cytology is so low. Cystic carcinoma accounts for $< 1\%$ of all breast cancers. However, an intraluminal solid mass is a worrisome sign suggesting (intra) cystic carcinoma, and should be biopsied.

Evaluation of a solid mass

A solid mass can be evaluated in a variety of ways. The decision to observe a patient with a breast mass that appears to be benign should be made only after careful clinical, radiologic, and cytologic examinations.

Mammography is used to assess the radiologic characteristics of the mass and is important for the evaluation of the remainder of the ipsilateral breast as well as the contralateral breast.

FNA is a simple, easy-to-perform method for obtaining material for cytologic examination. The overall incidence of false-positive results ranges from 0%-2.5% (0.7% when done by experienced technicians) and the incidence of false-negatives varies from 3% to 27% (3%-9% in experienced hands). Reasons for false-negative readings include less-than-optimal techniques in preparing the cytologic material, missing the lesion on aspiration, tumor necrosis, and incorrect cytologic interpretation.

Biopsy A core biopsy (18 gauge or larger needle biopsy) can be advantageous since architectural as well as cellular characteristics can be evaluated. An excisional biopsy, in which the entire breast mass is removed, definitively establishes the diagnosis. When the mass is extremely large, an incisional biopsy (which entails removal of only a portion of the mass) may be more appropriate.

Evaluation of nonpalpable mammographic abnormalities

Excisional biopsy Prior to 1991, almost all nonpalpable mammographic lesions were diagnosed by surgical excision, and this remains a major diagnostic tool today. Prior to surgery, a breast imager places a hook-wire at the lesion in

order to guide the surgeon to it accurately. After the target lesion has been excised, a specimen film is then obtained to ensure that it was successfully removed and, in some cases, to assess the gross adequacy of the margins around the lesion.

Stereotactic- and ultrasound-guided core biopsies have revolutionized the management of nonpalpable mammographic lesions, and currently the majority of these lesions can be diagnosed with these percutaneous techniques. At various facilities around the United States, the percentage of benign (false-positive) breast biopsies with these techniques ranges from 60% to 93%.

Stereotactic-guided core biopsy Several different biopsy devices are available, from a 14-gauge core biopsy needle, to an 11-gauge vacuum-assisted biopsy gun (Mammotome and MIB), to a 20-mm wide percutaneous excisional cannula (ABBI). With each device, the lesion is accurately localized in three dimensions by the use of a stereotactic table, which takes a pair of mammographic images at a fixed angle to each other for lesion triangulation.

Numerous studies comparing the sensitivity and specificity of stereotactic biopsy vs biopsy have consistently found the two procedures to be statistically equivalent. A recent large series demonstrated a false-negative rate of 1.4% for stereotactic core biopsy after long-term follow-up, which equals best published results with surgical biopsy.

Up to 80% of nonpalpable mammographic lesions are candidates for stereotactic core biopsy. Lesions near the chest wall or immediately behind the nipple often cannot be reached on the stereotactic table. Diffuse lesions, such as scattered calcifications or a large asymmetric density, are subject to undersampling with the percutaneous approaches. Some patients are unable to lie prone on the stereotactic table for the duration of the examination. Finally, stereotactic units and trained personnel are not universally available.

Ultrasound-guided core biopsies are another accurate percutaneous technique, useful for lesions best imaged by ultrasound. Since the biopsy gun is hand-held and guided in real time by the ultrasound imager, there is more variability in performance, depending on the experience and skill of the practitioner. The overall reported accuracy rate of ultrasound-guided biopsy is comparable to rates achieved with stereotactic and surgical biopsies.

Ultrasound- or stereotactic-guided FNA is another biopsy option. Although somewhat less invasive than core biopsy, FNA provides only cytologic (not histologic) pathology results. This technique can result in both false-positive and false-negative results, whereas a false-positive has not been reported to date for core breast biopsies. FNA is most successful in centers that have an experienced cytopathologist, who, ideally, is available on site to review smears for adequacy during FNA procedures.

Breast MRI is a sensitive tool for detecting occult breast cancer foci. Due to its limited specificity and high cost, however, MRI is not likely to become a screening tool.

MRI is currently used primarily to search for a subtle primary breast carcinoma in a patients with metastatic disease, to evaluate the extent of disease in a biopsy-proven breast carcinoma (useful if breast conservation is being considered), or to screen very high-risk women with dense mammograms. If an occult lesion is discovered by MRI, localization of the lesion may be problematic, unless a MRI localization device is available.

Ultrasound Stavros et al have described ultrasound features of solid masses that suggest benign or malignant disease, such as sharp margins (benign) and taller-than-wide lesions (malignant). Although these features are useful for clinical decision-making, their utility in increasing the specificity of the breast lesion work-up has not been verified.

Sestamibi nuclear medicine scanning can help differentiate benign from malignant mammographic asymmetries, and may play a role in evaluating palpable masses. Due to its limited spatial resolution and scatter, this technique is not reliable for lesions 1 cm or smaller.

Prevention

In the Multiple Outcomes of Raloxifene Evaluation (MORE), 7,705 postmenopausal women with osteoporosis were randomized to placebo or raloxifene (Evista), 60 or 120 mg/d. Over a median follow-up period of 40 months, 12 invasive breast cancers were diagnosed in the raloxifene-treated patients vs 27 in the placebo-treated patients—a 75% reduction in risk ($P < .001$). At the time of presentation of the updated study results at the 1999 ASCO meeting, the raloxifene group showed a 3.1 increase in the relative risk of thromboembolic disease but no difference in endometrial cancer rate, compared with the placebo group *(Cauley J, Krueger K, Eckert S, et al: Proc Am Soc Clin Oncol 18:87a [abstract], 1999).* The MORE trial will continue for 4 more years to determine the long-term effects of raloxifene. A second NSABP prevention trial, the Study of Tamoxifen and Raloxifene (STAR), will compare 5 years of tamoxifen vs raloxifene in 22,000 postmenopausal women at high risk of breast cancer.

LIFESTYLE CHANGES ASSOCIATED WITH BREAST CANCER RISK REDUCTION

There is increasing evidence that lifestyle changes may alter an individual's breast cancer risk.

Physical activity has been associated with a reduction in breast cancer risk. The benefit was greatest in premenopausal women, as compared with postmenopausal women, and was larger in younger as opposed to older women. The activity can be related to leisure or work time activities.

It has been suggested that women who exercise 3½-4 times per week have a reduced incidence of breast cancer, as compared with women who do not exercise. The protective effect of exercise may be associated with a reduction in the frequency of ovulatory cycles and circulating estrogen and progesterone levels.

Alcohol consumption Numerous studies that have evaluated the effects of alcohol consumption on breast cancer risk and the results of a

TABLE 4: Examples of eligible risk profiles used in the Breast Cancer Prevention Trial

Age (yr)	Risk profile
35	Two affected first-degree relatives plus personal history of biopsy
40	Two affected first-degree relatives plus no live births
45	Two affected first-degree relatives *or*
	One affected first-degree relative plus personal history of biopsy

cohort study addressing this issue were recently published. When compared to nondrinkers, women who consumed 2.3-4.5 bottles of beer per day, 2.5-5.6 glasses of wine per day or 2-4 shots of liquor per day had a 41% higher risk of developing invasive breast cancer. Therefore, a reduction in alcohol consumption is likely to reduce breast cancer risk.

The biological basis for the association between alcohol consumption and an increased risk of breast cancer is unclear. It has been proposed that there is a positive correlation between alcohol and estrogen levels.

Alterations in diet and tobacco use A reduced incidence of breast cancer has been observed in countries where the populations' diet is typically low in fat. However, no reduction in breast cancer risk has been observed in the United States when women followed low fat diets. An association between red meat consumption or tobacco use and breast cancer risk has not been demonstrated.

Lactation Although it has been suggested that lactation may protect against breast cancer, it is unclear whether lactation reduces breast cancer risk. A recent study failed to demonstrate any breast cancer risk reduction in women who breast-fed and showed no dose-response effect in women who breast-fed for longer time periods.

TABLE 5: Number of breast cancer events among BCPT participants[a]

Type of event	Placebo	Tamoxifen	Total
Invasive breast cancer	154 (5)	85 (3)	239 (8)
Noninvasive breast cancer	59	31	90
Total	**213 (5)**	**116 (3)**	**329 (8)**

[a] Numbers in parentheses indicate the number of deaths due to breast cancer.

TABLE 6: Number of fracture events among BCPT participants

Type of fracture	Placebo	Tamoxifen	Total
Hip	20	9	29
Colles'	12	7	19
Spine	39	31	70
Total	**71**	**47**	**118**

CHEMOPREVENTION

Breast Cancer Prevention Trial

The National Institutes of Health (NIH) and NCI have publicized the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT). Women who had a risk of developing breast cancer equivalent to that of women 60 years of age qualified as participants in this double-blind, randomized trial. (For representative eligibility profiles, see Table 4.) A total of 13,388 women were randomized to tamoxifen (Nolvadex) or placebo.

Benefits of therapy The summary results indicate that tamoxifen prevented about half of both invasive and noninvasive breast cancers in all age groups (Table 5). In addition to this reduction in invasive and noninvasive breast cancer, a secondary benefit of tamoxifen appeared to be a reduction in the incidence of hip fracture (Table 6).

At present, no survival advantage has been shown for participants in this trial.

Side effects Tamoxifen-treated women under age 50 had no apparent increase in side effects. However, women over age 50 experienced serious side effects, including vascular events and endometrial cancer. Particularly worrisome was

TABLE 7: Number of all invasive cancer events among BCPT participants

Type of cancer	Placebo	Tamoxifen	Total
Breast	154	85	239
Endometrial	14	33	47
All other	88	85	173
Total	**256**	**203**	**459**

TABLE 8: Number of vascular events among BCPT participants

Vascular event	Placebo	Tamoxifen	Total
Fatal stroke	3	4	7
Nonfatal stroke	21	30	51
Transient ischemic attack	21	18	39
Fatal pulmonary embolism	0	2	2
Nonfatal pulmonary embolism	6	15	21
Deep vein thrombosis requiring hospitalization	3	3	6
Deep vein thrombosis not requiring hospitalization	16	27	43
Total	**70**	**99**	**169**

the increased incidence of endometrial cancer in the tamoxifen-treated patients (Table 7). In addition, a significant increase in pulmonary embolism and deep vein thrombosis was noted, especially in women over age 50 (Table 8).

Current recommendations

Based on results of the BCPT, the FDA recently approved tamoxifen for use in women at high risk of breast cancer.

The NCI and NSABP are in the process of developing risk profiles based on age, number of affected first-degree relatives with breast cancer, number of prior breast biopsies, presence or absence of atypical hyperplasia or LCIS, age at menarche, and age at first live birth. These risk profiles may help guide women in making the decision of whether or not to take tamoxifen.

An ASCO working group recently published an assessment of tamoxifen use in the setting of breast cancer risk reduction. All women older than 35 years with a Gail model risk of $> 1.66\%$ (or the risk equivalent to that of women 60 years of age) should be considered candidates for this treatment strategy. Comorbid conditions, such as a history of deep venous thrombosis, must be a part of the consent process and treatment decision.

Staging and prognosis

Staging system The most widely used system to stage breast cancer is the American Joint Committee on Cancer (AJCC) classification, which is based on tumor size, the status of regional lymph nodes, and the presence of distant metastasis (Table 9).

TABLE 9: TNM staging system for breast cancer

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraductal carcinoma, LCIS, or Paget's disease of the nipple with no tumor
T1	Tumor ≤ 2 cm in greatest dimension
Tmic	Microinvasion ≤ 0.1 cm in greatest dimension
T1a	Tumor > 0.1 but not < 0.5 cm in greatest dimension
T1b	Tumor > 0.5 cm but not >1 cm in greatest dimension
T1c	Tumor > 1 cm but not > 2 cm in greatest dimension
T2	Tumor > 2 cm but not > 5 cm in greatest dimension
T3	Tumor > 5 cm in greatest dimension
T4	Tumor of any size, with direct extension to (a) chest wall or (b) skin only, as described below
T4a	Extension to chest wall
T4b	Edema (including peau d'orange) or ulceration of the skin or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed (eg, previously removed)
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph node(s)
N2	Metastasis to ipsilateral axillary lymph node(s) fixed to one another or to other structures
N3	Metastasis to ipsilateral internal mammary lymph node(s)

Clinical staging is done initially and is determined after the physical examination and appropriate radiologic studies have been performed.

Pathologic staging Pathologic stage is determined following surgery for operable breast cancer. Pathologic tumor size may differ from clinical tumor size. In addition, axillary nodal metastases that were not clinically evident may be detected after pathologic examination.

Prognostic factors Numerous prognostic factors for breast cancer have been identified.

Lymph node status Axillary nodal metastases are the most important prognostic factor. Axillary node involvement and survival were evaluated in patients with breast cancer. Survival was examined relative to the number of nodes involved and the location of nodes that contained metastatic deposits. For any given number of positive nodes, survival was independent of the *level* of involvement but was directly related to the *number* of involved nodes.

Distant metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis, including metastasis to ipsilateral supraclavicular lymph node(s)

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1*	N0	M0
Stage IIA	T0	N1	M0
	T1*	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1-2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

**Note: T1 includes Tmic*

Adapted, with permission, from Fleming ID, Cooper JS, Henson DE: AJCC Cancer Staging Manual, 5th ed. Philadelphia, Lippincott-Raven, 1997.

Overall, patients who are node-negative have a 10-year survival rate of 70% and a 5-year recurrence rate of 19%. As the number of positive nodes increases, so does the likelihood of relapse. Patients with > 10 positive lymph nodes have a recurrence rate of 72%-82%. The majority of patients who develop recurrence after initial curative treatment for early-stage breast cancer will have distant metastases.

Tumor size and hormone-receptor status also correlate with outcome.

Other factors that have been utilized to predict outcome are histologic grade, lymphovascular permeation, S-phase fraction, and ploidy.

More recently, molecular prognostic factors have been evaluated to determine their utility in predicting outcome. These include the growth factor receptors (epidermal growth factor receptor and c-*erb*B-2/*neu*), tumor-suppressor genes *(p53)*, proteolytic enzymes that may be associated with invasion and metastasis (cathepsin D), and metastasis-suppressor genes *(nm23)*.

SUGGESTED READING

ON RISK FACTORS AND GENETIC CANCER RISK ASSESSMENT

Dupont WD, Parl FF, Hartmann WH, et al: Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. Cancer 71(4):1258–1265, 1993.

Reviews the risk of breast cancer associated with proliferative breast disease, with or without atypia.

Ford D, Easton DF, Stratton M, et al: Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet 62:676–689, 1998.

This article nicely summarizes the most complete analysis to date of the BCLC cohort that was so instrumental in the identification of *BRCA1* and *BRCA2*, including a reappraisal of estimated penetrance in this highly selected group. The article also raises the issues of genetic heterogeneity and the possible existence of a *BRCA3* gene.

Malone KE, Daling JR, Thompson JD, et al: BRCA1 mutations and breast cancer in the general population: Analyses in women before age 35 years and in women before age 45 with first-degree family history. JAMA 279:922–929, 1998.

Study analyzing the presence of *BRCA1* mutations in young women with breast cancer.

Parmigiani G, Berry DA, Agiular O: Determining carrier probabilities for breast cancer susceptibility genes *BRCA1* and *BRCA2*. Am J Hum Genet 62:145–158, 1998.

The paper describes a model for calculating the probability that a woman is a carrier of a *BRCA1* or *BRCA2* mutation, on the basis of first- and second-degree family history. The model incorporates a Bayesian calculation to take into account intrafamily relationships and ages of both affected and unaffected members. The lead author builds on previous work of one of his coauthors, Donald Berry, yielding new tools for cancer risk assessment.

Struewing JP, Harge P, Wacholder S, et al: The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* in Ashkenazi Jews. N Engl J Med 1401–1408, 1997.

A population-based estimate of breast cancer risk for Jewish patients with *BRCA1* and *BRCA2* founder mutations.

ON PREVENTION

Stuver SO, Hseih C-C, Bertone E, et al: The association between lactation and breast cancer in an international case-control study: A reanalysis by menopausal status. Int J Cancer 71:166–169, 1997.

A reanalysis of two large, international, case-controlled studies, which demonstrates no reduction in breast cancer risk associated with lactation.

Thunn I, Brenn T, Lund E, et al: Physical activity and the risk of breast cancer. N Engl J Med 336:1269–1275, 1997.

This study demonstrates that modest physical activity is associated with a reduction in breast cancer risk.

ON SCREENING AND DIAGNOSIS

Jackman RJ, Nowels KW, Rodriguez-Soto J, Marzoni FA, et al: Stereotactic, automated, large-core needle biopsy of non-palpable breast lesions: False negative and histologic underestimation rates after long term follow-up. Radiology 210(3):799–805, 1999.

This article confirms the low false-negative rate of stereotactic core breast biopsy, which has been consistently reported in the literature since 1991.

Kaufman CS, Delbelcq R, Jacobson L: Excising the reexicision: Stereotactic core-needle biopsy decreases the need for reexcision of breast cancer. World J Surg 22(10):1023–1027, 1028 (discussion), 1998.

Percutaneous breast biopsy provides the surgeon with accurate presurgical information. This article documents a reduction in the number of surgical reexcisions performed when such information is obtained.

Leitch AM, Dodd GD, Constanza M, et al: American Cancer Society guidelines for the early detection of breast cancer. CA Cancer J Clin 47:150–153, 1997.

Highlights of the ACS workshop concerning breast cancer screening guidelines.

Orel SG, Schnall MD, Powell CM, et al: Impact of MR imaging and MR-guided biopsy on the staging of breast cancer. Radiology 196:115–122, 1995.

Using a specially designed breast coil, this University of Pennsylvania team reports on state-of-the-art MRI breast imaging and its impact on the clinical staging of difficult breast cancer cases.

CHAPTER 9

Stages 0 and I breast cancer

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This chapter focuses on the diagnosis and management of "minimal" breast cancer, ie, stages 0 and I disease. This is an important area since more noninvasive and small breast cancers are being diagnosed due to the increasing use of screening mammography. Treatment of these malignancies continues to evolve and will continue to change as the results of clinical trials lead to further refinements in therapy.

STAGE 0 BREAST CANCER

Stage 0 breast cancer includes noninvasive breast cancer—lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS)—as well as Paget's disease of the nipple when there is no associated invasive disease.

LOBULAR CARCINOMA IN SITU

LCIS is nonpalpable, produces no consistent mammographic changes, and is most often an incidental finding after breast biopsy performed for another reason. The apparent incidence of LCIS is increasing as more breast biopsies are performed and pathologists examine specimens more thoroughly. Since there are no clinical or radiographic findings associated with LCIS, it is difficult to accurately determine its incidence.

The current consensus is that LCIS should not be treated as a cancer. Rather, it is considered to be a marker for increased breast cancer risk. It has been suggested that a more appropriate term for this pathologic entity may be "lobular neoplasia."

Epidemiology and etiology

LCIS affects only women, has a peak incidence at age 45 years, and decreases in incidence after menopause.

It has been estimated that as many as 90% of women with LCIS are premenopausal, and estrogen receptors are found in most lesions. Therefore, the development of LCIS may be related to hormonal influences.

Signs and symptoms

As mentioned above, LCIS is nonpalpable and has no consistent mammographic features. Often, LCIS is found in association with an independent mammographic abnormality.

Risk of invasive cancer

A woman diagnosed with LCIS has a risk of developing an invasive breast cancer 8-11 times that of the general population. The absolute risk of invasive breast cancer development is 20%-25% in the 15 years after the diagnosis of LCIS is made.

Pathology

LCIS appears to arise from the terminal duct–lobular apparatus, and the disease tends to be multifocal, multicentric, and bilateral.

DUCTAL CARCINOMA IN SITU

DCIS is being encountered more frequently with the expanded use of screening mammography. In some institutions, DCIS accounts for 25%-50% of all breast cancers.

Epidemiology

DCIS, like invasive ductal carcinoma, occurs more frequently in women, although it accounts for approximately 5% of all male breast cancers. The average age at diagnosis of DCIS is 54-56 years, which is approximately a decade later than the age at presentation for LCIS.

Signs and symptoms

The clinical signs of DCIS include a mass, breast pain, or bloody nipple discharge. On mammography, the disease most often appears as microcalcifications.

Risk of invasive cancer

The risk of developing an invasive carcinoma following a biopsy-proven diagnosis of DCIS is between 25% and 50%. Virtually all invasive cancers that follow DCIS are ductal and ipsilateral and generally present in the same quadrant within 10 years of the diagnosis of DCIS. For these reasons, DCIS is considered a more ominous lesion than LCIS and appears to be a more direct precursor of invasive cancer.

Pathology

A variety of histologic patterns are seen with DCIS, including solid, cribriform, papillary, and comedo. Some researchers have divided DCIS into two subgroups: comedo and noncomedo types. As compared with the noncomedo subtypes, the comedo variant has been associated with a higher proliferative rate, overexpression of HER-2/*neu*, and a higher incidence of local recurrence and associated microinvasion.

DCIS is less likely to be bilateral and has approximately a 30% incidence of multicentricity.

Treatment of noninvasive breast carcinoma

LOBULAR CARCINOMA IN SITU

Treatment options

Since the risk of invasive breast cancer in patients with LCIS is equal for either breast, the treatment options for LCIS are bilateral mastectomy, biopsy followed by close follow-up, or participation in a breast cancer chemoprevention trial. Ablative surgery may be indicated in patients with LCIS who have other risk factors. In these cases, bilateral total mastectomy is indicated. Patients undergoing this procedure can be offered immediate reconstruction.

DUCTAL CARCINOMA IN SITU

Breast-conserving surgery

Breast-conservation surgery, followed by radiation therapy to the intact breast, is now considered the standard treatment for patients with DCIS. Since the incidence of positive lymph nodes after axillary lymph node dissection for DCIS is ~1%-2%, axillary dissection is not indicated in most instances.

Adjuvant radiation therapy

Retrospective series of patients with DCIS, as well as subsets of patients with early invasive cancer, have been treated with conservative surgery alone, omitting radiation therapy to the intact breast. In addition, several prospective, randomized trials have attempted to address this issue of omission of breast irradiation for both invasive cancer and DCIS. It is clear from all of these series that omission of breast irradiation results in a significantly higher ipsilateral breast tumor recurrence rate but has not, as yet, had an impact on overall survival.

A recently published study demonstrated acceptable local control in patients with DCIS treated by excision alone, provided that wide negative margins were obtained. In this retrospective series of 469 patients, radiation therapy did not lower the local recurrence rate in patients with wide (≥ 10 mm) negative margins but did produce a significant benefit in patients with close (≤ 1 mm) margins. The authors concluded that radiation therapy is unlikely to benefit patients with wide negative margins. These findings need to be confirmed in prospective, randomized trials *(Silverstein NJ, Lagio MD, Groshen S, et al: N Engl J Med 340:1455-1461, 1999).*

Although there may be some patients in whom wide excision alone is appropriate therapy, the available literature has not consistently identified a specific subgroup of patients in whom radiation therapy should routinely be omitted. Clearly, the omission of radiation therapy in subsets of patients remains a controversial issue worthy of further investigation. Hopefully, ongoing randomized studies will help resolve some of the controversy generated by selective, retrospective studies (see box).

Adjuvant tamoxifen therapy

Although adjuvant therapy is not routinely employed in patients with DCIS, the use of tamoxifen (Nolvadex) for the prevention of secondary breast cancers in women at high risk for breast cancer, which includes women previously diagnosed with DCIS, has led some clinicians to consider the use of tamoxifen in women diagnosed with DCIS. A recent controlled clinical trial, employing tamoxifen in patients with DCIS treated by lumpectomy and radiation therapy, demonstrated a significant benefit with respect to reductions in ipsilateral and contralateral breast cancers (see box).

In a National Surgical Adjuvant Breast Project trial (NSABP-24), 1,804 women with DCIS treated with lumpectomy and radiation were randomly assigned to placebo or tamoxifen. At a median follow-up of 74 months, women in the tamoxifen group had fewer breast cancer events than those in the placebo group (8.2% vs 13.4%; $P = .0009$). Tamoxifen decreased the incidence of both ipsilateral and contralateral events. The risk of ipsilateral invasive cancers was reduced by tamoxifen, irrespective of the presence or absence of comedonecrosis or margin involvement (*Fisher B, Dignam J, Wolmark N: Lancet 353:1993-2000, 1999*).

Clearly, based on these results, tamoxifen may be considered as an adjuvant therapy in women with DCIS. The role of tamoxifen or other estrogen receptor modulators is likely to evolve rapidly over the next decade.

STAGE I BREAST CANCER

Stage I breast cancer includes small primary malignancies (≤ 2 cm in greatest dimension that have not spread to the lymph nodes), as well as microinvasive tumors ≤ 0.1 cm in greatest dimension.

Pathology of invasive breast cancer

Ductal carcinoma Most cases of invasive carcinomas of the breast are ductal in origin. Of the different histologic subtypes of ductal carcinoma that have been described, tubular, medullary, mucinous (colloid), and papillary subtypes have been associated with a favorable outcome.

Lobular carcinoma Approximately 5%-10% of invasive breast cancers are lobular in origin. This histology has been associated with synchronous and metachronous contralateral primary tumors in as many as 30% of cases.

Treatment of stage I breast cancer

SURGICAL AND RADIATION TREATMENT

Multiple studies have demonstrated that patients with stage I breast cancer who are treated with either breast-conservation therapy (lumpectomy and radiation therapy) or modified radical mastectomy have similar disease-free and overall survival rates.

Breast-conservation therapy

Extent of local surgery The optimal extent of local surgery has yet to be determined and, in the literature, has ranged from excisional biopsy to quadrantectomy. A consensus statement on breast-conserving therapy issued by the National Cancer Institute (NCI) recommended that the breast cancer be completely excised with negative surgical margins and that a level I-II axillary lymph node dissection be performed. The patient should subsequently be treated with adjuvant breast irradiation.

Patient selection Specific guidelines must be followed when selecting patients for breast conservation. Patients may be considered unacceptable candidates for conservative surgery and radiation therapy either because the risk of breast recurrence following the conservative approach is significant enough to warrant mastectomy or the likelihood of an unacceptable cosmetic result is high. Absolute and relative contraindications to breast-conserving surgery are listed in Table 1.

Risk factors for ipsilateral recurrence For patients undergoing conservative surgery followed by radiation therapy to the intact breast, the risk of ipsilateral breast tumor recurrence has been reported to range from 0.5% to 2% per year, with long-term failure rates varying from 7% to 20%. Risk factors for ipsilateral breast tumor recurrence include, but are not limited to, young age (< 35-40 years), extensive intraductal component, major lymphocytic stromal reaction, peritumoral invasion, presence of tumor necrosis, and positive resection margins.

Patients whose tumors have an extensive intraductal component who undergo adequate surgical therapy with negative surgical margins do not have a higher local failure rate than those with lesions that do not have an extensive intraductal component. Although it is desirable to achieve negative surgical margins, the available data do not preclude the use of conservative treatment, provided that adequate radiation doses (> 6,000 cGy) to the tumor bed are employed. The role of the remaining risk factors cited above in predicting recurrence is unclear, and patients should not be denied breast conservation because of their presence.

TABLE 1: Contraindications to breast-conservation therapy

Absolute contraindications	Relative contraindications
Multicentric disease[a]	Tumor size vs breast size
Diffuse malignant microcalcification	Tumor location
Pregnancy	Collagen vascular disease (excluding rheumatoid arthritis)
Persistently positive surgical margins	
Previous breast or mantle irradiation	

[a] If a satisfactory cosmetic outcome is anticipated, multicentric disease is considered to be a relative contraindiation.

Cosmetic considerations include primary tumor size and location, overall breast size, total body weight, and a history of preexisting collagen vascular disease.

The primary tumor is excised with a margin of normal breast tissue (no absolute margin has been defined). Therefore, tumor size and breast size are important in determining whether the patient will have an acceptable cosmetic outcome after surgical resection.

Obese women with large, pendulous breasts may experience marked fibrosis and retraction of the treated breast, making a good to excellent cosmetic outcome less likely.

Patients with collagen vascular disease may develop marked fibrosis and bone necrosis following adjuvant radiation therapy. Most patients with active collagen vascular disease are not candidates for conservative therapy; however, patients with minimal manifestations of the disease or those with rheumatoid arthritis may be considered for breast-preserving treatment.

Patients with centrally located tumors Traditionally, patients who have centrally located tumors requiring excision of the nipple-areolar complex have not been offered the option of breast conservation. However, the cosmetic result achieved after local tumor excision that includes the nipple-areolar complex may not differ significantly from that obtained following mastectomy and reconstruction.

Furthermore, conservatively treated patients with subareolar lesions do not necessarily need to have the nipple-areolar complex sacrificed as long as negative surgical margins can be achieved. However, if the complex is not removed, the remaining breast tissue and overlying skin remain sensitive. Recent studies also indicate that the incidence of local recurrence is not increased when primary tumors in this location are treated conservatively.

Role of axillary node dissection The role of axillary lymph node dissection in the management of breast cancer has been questioned, particularly when a patient with a clinically negative axilla is undergoing breast-conservation therapy. In most instances, the breast surgery is performed under local anesthesia and sedation and the patient does not require hospital admission. When axillary lymph node dissection is added, the surgery is performed under general anesthesia and the patient is admitted to the hospital.

It has also been suggested that if the status of the nodes will not change therapy, the dissection is unnecessary and the axilla can be treated with radiation. On the other hand, if an axillary lymph node dissection is not performed, the patient will not be accurately staged and important prognostic information will be unavailable.

Sentinel lymph node biopsy The sentinel lymph node is the first node in the draining lymphatic basin that receives primary lymph flow. The technique of sampling the first draining lymph node was first described in the management of patients with melanoma who would benefit from a regional lymph node dissection, and was performed using a vital blue dye. The same technique has been used in patients with breast cancer, and sentinel lymph node biopsy represents a minimally invasive way to determine whether the axilla is involved

with disease. If the sentinel lymph node is negative for metastatic disease, the patient may be spared from undergoing an axillary lymph node dissection. The precise role of this technique is under investigation.

Patients who have undergone a previous incisional or excisional biopsy, are pregnant or lactating, have received prior breast irradiation, or have noninvasive breast cancer are not candidates for sentinel lymph node biopsy.

Technique used in breast cancer In breast cancer, lymphatic mapping has been performed using a vital blue dye and/or lymphoscintigraphy. The primary tumor site is injected with the blue dye or a radioactive tracer, usually technetium-labeled sulfur colloid. When a vital dye is used, the axillary dissection is carefully carried out to identify the blue-stained afferent lymphatic vessels that lead to the sentinel node. When the radioactive tracer is injected peritumorally, a handheld gamma counter is used to determine the location of the sentinel node.

Once the sentinel node (or nodes) is identified and biopsied, it is sent to pathology for frozen-section analysis. The diagnosis of the primary breast cancer is made by fine-needle aspiration (FNA) for cytology or core biopsy.

Sensitivity and specificity The sentinel lymph node can be identified 92%-98% of the time. The sensitivity and specificity of the procedure are high, and the likelihood of a false-negative result is extremely low. In one series, in 18% of the cases where the frozen-section evaluation of the node was negative, the final pathologic evaluation revealed metastatic disease, and the patient ultimately required a lymph node dissection. This potential result can be distressing to patients; however, they should be informed of this possibility at the time of the sentinel lymph node biopsy.

Radiation therapy after breast-conserving surgery

Based on the results of a number of retrospective single-institution experiences, as well as several prospective randomized clinical trials, breast-conserving surgery followed by radiation therapy to the intact breast is now considered a standard treatment for the majority of patients with stage I or II invasive breast cancer.

Radiation dose and protocol Radiation therapy after breast-conservation surgery should employ careful treatment planning techniques that minimize treatment of the underlying heart and lung. In order to achieve the optimal cosmetic result, efforts should be made to obtain a homogeneous dose distribution throughout the breast. Doses of 180-200 cGy/d to the intact breast, to a total dose of 4,500-5,000 cGy, are considered standard.

A radiation boost to the tumor bed is frequently administered, although its necessity is controversial and is the subject of a number of completed and ongoing randomized trials (see box). When used, a

In a randomized clinical trial, patients who received a radiation boost of 10 Gy to the tumor bed after 50 Gy to the whole breast achieved a statistically significant reduction in local recurrence, as compared with those who received 50 Gy of whole-breast irradiation only (3.6% vs 4.5%; $P = .044$), with no significant difference in the self-assessment cosmesis score *(Romestaing P, Lehingue Y, Carrie C, et al: J Clin Oncol 15:964-968, 1997).*

boost consists of an electron beam or interstitial implant to bring the tumor bed to a total dose of 6,000-6,600 cGy.

Regional nodal irradiation For patients who do undergo axillary dissection and are found to have negative nodes, regional nodal irradiation is no longer routinely employed. For patients with positive nodes, radiation therapy to the supraclavicular fossa and/or internal mammary chain may be considered on an individualized basis (see chapter 10).

MEDICAL TREATMENT

Medical management of local disease depends on clinical and pathologic staging. Systemic therapy is indicated only for invasive (infiltrating) breast cancers.

In the past, systemic therapy was not offered to patients with stage I disease (tumors up to 2.0 cm in size). However, adjuvant chemotherapy and hormonal therapy have been shown to improve disease-free and overall survival in selected node-negative patients.

The sequence of systemic therapy and definitive radiation therapy in women treated with breast-conserving surgery is a subject of continued clinical research. The use of concomitant chemotherapy and radiation is not recommended due to radiomimetic effects of chemotherapy and the potential for increased locoregional toxicity. Delaying chemotherapy up to 8-10 weeks after surgery does not appear to have a negative impact on the development of metastasis or survival.

Treatment regimens

Multiagent therapy with cyclophosphamide, methotrexate, and fluorouracil (5-FU; CMF regimen); cyclophosphamide, methotrexate, 5-FU, and prednisone (CMFP); and sequential methotrexate and 5-FU (MF) have been used in node-negative patients (Table 2). Hormonal therapy with tamoxifen (10 mg PO bid for 5 years) has been shown to be of value in women ≥ 50 years of age with estrogen-receptor–positive tumors.

The role of the taxanes, ie, paclitaxel (Taxol) and docetaxel (Taxotere), in adjuvant therapy is being investigated in clinical trials.

Node-negative tumors < 1 cm The reduction in the odds of recurrence and death with adjuvant therapy is similar in node-negative and node-positive patients. Therefore, patients who have the lowest risk of recurrence are least likely to benefit from systemic treatment when the attendant risks of treatment are considered. None of the reported trials in node-negative breast cancer included women with tumors < 1.0 cm, and because of the low risk of recurrence (≤ 10%) in this group, systemic adjuvant therapy should not be used.

Node-negative tumors ≥ 1.0 cm The selection of a specific treatment program and the characteristics that predict risk of recurrence and death in women with node-negative breast cancer require further delineation and clari-

TABLE 2: Adjuvant chemotherapy regimens in node-negative breast cancer

Regimen	Dose and frequency
MF	
Methotrexate	100 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 IV on days 1 and 8 (1 h after methotrexate)
Folinic acid	10 mg/m^2 PO q6h × 6 doses (24 h after methotrexate)
Repeat every 4 weeks for 12 cycles.	
CMF (Bonadonna regimen)	
Cyclophosphamide	600 mg/m^2 IV on day 1
Methotrexate	40 mg/m^2 IV on day 1
5-FU	600 mg/m^2 IV on day 1
Repeat every 3 weeks for 9 cycles.	
CMFP	
Cyclophosphamide	100 mg/m^2 PO on days 1-14
Methotrexate	40 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 IV on days 1 and 8
Prednisone	40 mg/m^2 PO on days 1 and 14
Repeat every 4 weeks for 6 cycles.	

fication in clinical trials. At present, women with tumors ≥ 1.0 cm that have poor histologic or nuclear differentiation, negative estrogen receptors, high S-phase percentage, or high Ki-67 can be considered appropriate candidates for adjuvant systemic therapy.

An update of the NSABP B-20 trial indicated a significant advantage in the estrogen-receptor–positive, node-negative population when chemotherapy with CMF or sequential MF is added to tamoxifen in the adjuvant setting. Patients receiving CMF plus tamoxifen appeared to derive the greatest benefit. Benefits with respect to both disease-free and overall survival have been reported for patients given chemotherapy and tamoxifen.

Other tumors in the breast

Lymphomas Primary breast lymphomas are very rare, accounting for 0.04%-0.5% of all breast malignancies and < 3% of extranodal non-Hodgkin's lymphomas.

Soft-tissue sarcomas of the breast also are uncommon; they account for < 1% of all breast malignancies. The most common histologic types of soft-tissue sarcomas of the breast, excluding angiosarcoma, are malignant fibrous histiocytoma, liposarcoma, and fibrosarcoma.

Follow-up of long-term survivors

There is no consensus among oncologists as to the optimal follow-up routine for long-term breast cancer survivors. For patients with stage I disease, follow-up physical examinations typically are performed at 6- to 12-month intervals, and mammograms are obtained every 12 months. All other follow-up evaluations are dictated by the development of symptoms.

SUGGESTED READING

Cowen D, Jacquemier J, Houvenaegal G, et al: Local and distant recurrences after conservative management of "very low-risk" breast cancer are independent events: A 10-year follow-up. Int J Radiat Oncol Biol Phys 41:801–807, 1998.

Review of factors associated with recurrence in node-negative patients after conservative surgery.

Fisher B, Anderson S, Redmond C, et al: Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 333:1456–1461, 1995.

Reanalysis and 12-year follow-up of a prospective randomized trial comparing mastectomy to lumpectomy, with or without adjuvant breast irradiation, in the treatment of stage I-II invasive breast cancer.

Fisher B, Redmond C, Dimitrov N, et al: A randomized clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node-negative breast cancer who have estrogen-receptor-negative tumors. N Engl J Med 320:473–478, 1989.

Mansour E, Gray R, Shatila A, et al: Efficacy of adjuvant chemotherapy in high-risk node-negative breast cancer: An intergroup study. N Engl J Med 320:485–490, 1989.

These two papers focus on adjuvant therapy for node-negative patients.

Fisher ER, Dignam J, Tan-Chu E, et al: Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) eight-year update of Protocol B-17. Cancer 86:429–438, 1999.

Update on a prospective, randomized trial comparing lumpectomy vs lumpectomy and radiation therapy for the conservative treatment of DCIS.

Haffty B, Ward B, Pathare P, et al: Reappraisal of the role of axillary lymph node dissection in the conservative treatment of breast cancer. J Clin Oncol 15:691–700, 1997.

This study concludes that, for selected patients, axillary lymph node dissection appears to have little influence on subsequent management and long-term outcome. The data suggest that it is time to reassess the role of axillary node dissection in patients who undergo conservation surgery and radiation therapy.

Hill AD, Tran KN, Akhurst T, et al: Lessons learned from 500 cases of lymphatic mapping for breast cancer. Ann Surg 229:528–535, 1998.

The authors examine the ability of lymphatic mapping, using blue dye and technetium-labeled sulfur colloid, to identify sentinel lymph nodes in 500 consecutive biopsy procedures. They are successful in more than 90% of cases, and conclude that sentinel node biopsy is a safe, effective alternative to routine axillary node dissection in early breast cancer. Both blue dye and radioisotope are recommended to maximize accuracy.

Krag D, Weaver D, Ashibaga T, et al: The sentinel node in breast cancers: A multicenter validation study. N Engl J Med 339:941–946, 1998.

A multicenter study of lymphatic mapping, indicating a 93% rate of identifying the sentinel nodes, 97% accuracy rate with respect to the positive or negative status of the axillary nodes, specificity of 100%, and positive predictive value of 100%. This study concludes that the procedure is technically challenging and that the success rate can vary, depending on the surgeon and patient characteristics. Caution is advised, therefore, when initiating a sentinel node biopsy as the only approach to primary breast cancer, excluding axillary lymph node dissection.

Loomer L, Brockschmidt JK, Muss HB, et al: Postoperative follow-up of patients with early breast cancer. Cancer 67:55–60, 1991.

Results of a survey of 80 clinical oncologists concerning follow-up protocols for early-stage breast cancer patients.

Meyer JS: Sentinel lymph node biopsy: Strategies for pathologic examination. J Surg Oncol 69:212–218, 1998.

A practical review of the issues related to pathologic specimen preparation and analysis of sentinel lymph node biopsies.

Paszat L, MacKillip W, Groome PL, et al: Mortality from myocardial infarction after adjuvant radiotherapy for breast cancer in the Surveillance, Epidemiology, and End-Results Cancer Registries. J Clin Oncol 16:2625–2631, 1998.

This analysis found that, in women < 60 years old, adjuvant radiation therapy for left-sided breast cancer was associated with a higher risk for fatal myocardial infarction than was adjuvant radiation for right-sided cancers.

Silverstein MJ, Lagio MD, Groshen S, et al: N Engl J Med 340:1455–1461, 1999.

This is a retrospective study of 469 patients with ductal carcinoma in situ of the breast treated by lumpectomy alone or lumpectomy with radiation. The authors conclude that margin width is an important determinant of local control, and that selected patients with wide excision margins may be treated by wide excision without radiation therapy, regardless of tumor size, nuclear grade, or the presence of comedonecrosis.

Solin L, Kurtz J, Fourquet A, et al: Fifteen-year results of breast-conserving surgery and definitive irradiation for ductal carcinoma of the breast. J Clin Oncol 4:754–763, 1996.

A multi-institution, collaborative study analyzing the long-term outcome of over 200 patients with DCIS treated by conservative surgery followed by radiation to the intact breast.

Tamoxifen for early breast cancer: An overview of the randomised trials: Early Breast Cancer Trialists' Collaborative Group. Lancet 351:1451–1467, 1998.

An updated overview analyzing the results of 55 randomized trials of adjuvant tamoxifen vs no tamoxifen in 37,000 women with early breast cancer.

Veronesi U, Paganelli G, Galimberti V, et al: Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph nodes. Lancet 349:1864–1867, 1997.

Results of a large study evaluating the role of sentinel lymph node biopsy in breast cancer.

CHAPTER 10

Stage II breast cancer

Lori Jardines, MD, Bruce G. Haffty, MD, Richard L. Theriault, DO, and James H. Doroshow, MD

This chapter focuses on the treatment of stage II breast cancer, which encompasses primary tumors > 2 cm in greatest dimension that involve ipsilateral axillary lymph nodes, as well as tumors up to 5 cm without nodal involvement.

Stage II breast cancer is further subdivided into stages IIA and IIB. Patients classified as having stage IIA breast cancer include those with T0-1, N1, and T2, N0 disease. Stage IIB breast cancer includes patients with T2, N1 and T3, N0 disease. Therefore, this patient population is more heterogeneous than the populations with stage 0 and stage I disease. The pretreatment evaluation and type of treatment offered to patients with stage II breast cancer are based on tumor size, nodal status, and estrogen receptor status.

Treatment

SURGICAL AND RADIATION TREATMENT

Multiple studies have demonstrated that patients with stage II breast cancer who are treated with either breast-conservation therapy (lumpectomy and radiation therapy) or modified radical mastectomy have similar disease-free and overall survival rates.

Breast-conservation therapy

The optimal extent of local surgery has yet to be determined and, in the literature, has ranged from excisional biopsy to quadrantectomy. A consensus statement issued by the National Cancer Institute (NCI) recommended that the breast cancer be completely excised with negative surgical margins and that a level I-II axillary lymph node dissection be performed. The patient should subsequently be treated with adjuvant breast irradiation.

Patients with tumors > 4-5 cm may not be candidates for breast conservation due to the risk of significant residual tumor burden and the potential for a poor cosmetic result following lumpectomy (or partial mastectomy). A more detailed discussion of patient selection criteria, axillary dissection, and the role of sentinel node biopsy can be found in chapter 9.

Radiation therapy after breast-conserving surgery

Based on the results of a number of retrospective single-institution experiences, as well as several prospective randomized clinical trials, breast-conserving surgery followed by radiation therapy to the intact breast is now considered a standard treatment for the majority of patients with stage II invasive breast cancer.

Radiation dose and protocol Radiation dose to the intact breast follows the same guidelines as are used in patients with stage 0-I disease, described in chapter 9.

Regional nodal irradiation For patients who do undergo axillary lymph node dissection and are found to have negative lymph nodes, regional nodal irradiation is no longer employed routinely. For patients with positive lymph nodes, radiation therapy to the supraclavicular fossa and/or internal mammary chain may be considered on an individualized basis.

Regional nodal irradiation should be administered using careful treatment planning techniques so as to minimize the dose delivered to the underlying heart and lung. Prophylactic nodal irradiation to doses of 4,500-5,000 cGy results in a high rate of regional nodal control and may improve disease-free survival in subsets of patients.

The Danish Cancer Cooperative Group trial randomized 1,708 premenopausal patients receiving CMF (cyclophosphamide, methotrexate, and fluorouracil [5-FU]) to receive or not to receive post-mastectomy radiation therapy. This trial demonstrated a statistically significant improvement in locoregional control and in disease-free and overall survival in patients given radiation therapy *(Overgaard M, Hanson P, Overgaard J, et al: N Engl J Med 337:949-955, 1997)*. The British Columbia trial randomized 318 premenopausal women with node-positive breast cancer who were receiving cytotoxic chemotherapy to receive or not to receive post-mastectomy radiation therapy. At 15 years of follow-up, this trial also demonstrated a 33% reduction in the rate of recurrence and a 29% reduction in breast cancer mortality with post-mastectomy radiation therapy *(Ragaz J, Jackson SM, Nhu L, et al: N Engl J Med 337:956-962, 1997)*.

Given the widespread use of systemic therapy for both node-negative and node-positive patients, the role of axillary dissection has recently come into question. In patients with clinically negative axillae who do not undergo axillary dissection, radiation therapy to the supraclavicular and axillary regions at the time of breast irradiation results in a high rate (> 95%) of regional nodal control with minimal morbidity.

Radiation therapy after mastectomy

Available data suggest that, in patients with positive post-mastectomy margins, primary tumors > 5 cm in size, or involvement of four or more lymph nodes at the time of mastectomy, the risk of locoregional failure remains significantly high enough to consider post-mastectomy radiation therapy. Even with the use of high-dose chemotherapy, locoregional failure is a significant problem in these patients without the use of post-mastectomy

radiation. Most ongoing trials evaluating dose-intensive chemotherapy, with or without bone marrow or stem-cell transplantation, routinely include post-mastectomy radiation therapy to the chest wall and/or regional lymph nodes to minimize locoregional recurrence.

Several prospective randomized trials have evaluated the role of post-mastectomy radiotherapy in addition to chemotherapy. Most of these trials have been limited to patients with pathologic stage II disease or patients with T3 or T4 primary lesions. All of these trials have shown an improvement in locoregional control with the addition of adjuvant radiation, and two recent trials (see box on previous page) demonstrated a disease-free survival and overall survival advantage in selected patients.

Several other trials have not consistently demonstrated a benefit, however, and controversy regarding a disease-free or overall survival benefit of post-mastectomy radiation continues. The significant improvements noted in local control, particularly in patients with four or more positive nodes and/or T3 primary tumors, have been consistent, and justify consideration of post-mastectomy radiation in these patients.

Current recommendations There is no clearly defined role for post-mastectomy radiation in patients with small (T1 or T2) primary tumors and negative nodes. Patients with T3 or T4 tumors and node-negative disease may be treated on an individualized basis.

For patients with four or more positive lymph nodes, with or without a large primary tumor, post-mastectomy radiation should be considered to lower the rate of local relapse and improve disease-free survival. For patients with T1 or T2 tumors and one to three positive nodes, post-mastectomy radiation may have a benefit with respect to disease-free and overall survival. However, controversies and uncertainties regarding this issue remain, and individualized decision-making, based on the patient's overall condition and specific risk factors, is reasonable.

Currently in the planning stages, an intergroup randomized trial will randomize post-mastectomy patients with one to three positive nodes treated with current chemotherapy regimens to postoperative radiation vs observation. Hopefully, this trial will define subgroups of patients who will derive the greatest benefit from post-mastectomy radiation.

Minimizing pulmonary and cardiac toxicity Early trials employing post-mastectomy radiation showed that the modest improvements in breast cancer mortality were offset by an excess risk of cardiovascular deaths, presumably due to the radiation treatment techniques used, which resulted in delivery of relatively high radiation doses to the heart. Recent trials employing more modern radiation therapy techniques have *not* demonstrated an excess of cardiac morbidity and, hence, have shown a slight improvement in overall survival due to a decrease in breast cancer deaths. Thus, in any patient being

considered for post-mastectomy radiation therapy, efforts should be made to treat the areas at risk while minimizing the dose to the underlying heart and lung.

Radiation dose and protocol The available literature suggests that doses of 4,500-5,000 cGy should be sufficient to control subclinical microscopic disease in the post-mastectomy setting. Electron-beam boosts to areas of positive margins and/or gross residual disease, to doses of ~6,000 cGy, may be considered.

In patients who have undergone axillary lymph node dissection, even in those with multiple positive nodes, treatment of the axilla does not appear to be necessary in the absence of gross residual disease. Treatment of the supraclavicular and/or internal mammary chain should employ techniques and field arrangements that minimize overlap between adjacent fields and minimize the dose to underlying cardiac and pulmonary structures.

MEDICAL TREATMENT

Medical management of local disease depends on clinical and pathologic staging. Systemic therapy is indicated only for invasive (infiltrating) breast cancers.

The sequence of systemic therapy and definitive radiation therapy in women treated with breast-conserving surgery is a subject of continued clinical research. The use of concomitant chemotherapy and radiation is not recommended due to radiomimetic effects of chemotherapy and the potential for increased locoregional toxicity. Delaying chemotherapy up to 8-10 weeks after surgery does not appear to have a negative impact on the development of metastasis or survival.

Epirubicin HCl (Ellence) recently received FDA approval for use in combination with cyclophosphamide and 5-FU (CEF regimen) in the adjuvant treatment of patients with early-stage, node-positive breast cancer who have undergone resection. In a pivotal trial conducted by the National Cancer Institute of Canada that compared CEF with CMF in 716 premenopausal women, CEF lowered the relative risk of breast cancer recurrence by 24% and the relative risk of death by 29%. Estimated 5-year disease-free survival rates were 62% and 53% in the CEF and CMF groups, respectively, and estimated 5-year overall survival rates were 77% and 70%, respectively.

Treatment regimens

Multiagent therapy with cyclophosphamide, methotrexate, and fluorouracil (5-FU; CMF regimen); cyclophosphamide, methotrexate, 5-FU, and prednisone (CMFP); and sequential methotrexate and 5-FU (MF) have been used in node-negative patients (Table 1). Hormonal therapy with tamoxifen (10 mg PO bid for 5 years) has been shown to be of value in women ≥ 50 years of age with estrogen-receptor–positive tumors.

The role of the taxanes, ie, paclitaxel (Taxol) and docetaxel (Taxotere), in adjuvant therapy is being investigated in clinical trials.

TABLE 1: Adjuvant chemotherapy regimens in node-negative breast cancer

Regimen	Dose and frequency
Methotrexate	100 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 IV on days 1 and 8 (1 h after methotrexate)
Folinic acid	10 mg/m^2 PO q6h × 6 doses (24 h after methotrexate)
Repeat every 4 weeks for 12 cycles.	
CMF (Bonadonna regimen)	
Cyclophosphamide	600 mg/m^2 IV on day 1
Methotrexate	40 mg/m^2 IV on day 1
5-FU	600 mg/m^2 IV on day 1
Repeat every 3 weeks for 9 cycles.	
CMFP	
Cyclophosphamide	100 mg/m^2 PO on days 1-14
Methotrexate	40 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 IV on days 1 and 8
Prednisone	40 mg/m^2 PO on days 1 and 14
Repeat every 4 weeks for 6 cycles.	

Stage II disease

All patients with stage II breast cancer should be considered for systemic adjuvant therapy.

Age ≤ 49 years old Among women 49 years of age or younger, multiagent chemotherapy affords the greatest benefit with respect to reductions in the risk of recurrence and death from breast cancer. Reductions of 25%-50% in the odds of death from breast cancer have been reported for patients treated with CMF, A-CMF (Adriamycin, cyclophosphamide, methotrexate, and 5-FU), FAC (5-FU, Adriamycin, and cyclophosphamide), or CAF (cyclophosphamide, Adriamycin, and 5-FU).

Recent preliminary data from a Cancer and Leukemia Group B (CALGB) study indicated that the addition of 4 cycles of paclitaxel to 4 cycles of the AC (Adriamycin and cyclophosphamide) regimen substantially improved disease-free and overall survival in patients with axillary node-positive breast cancer. This study did not show any substantial benefit from dose escalation of doxoru-

A randomized trial comparing preoperative paclitaxel therapy with preoperative FAC reported comparable antitumor activity of the two regimens when assessed by pathologic analysis of surgical specimens. After 4 cycles of preoperative chemotherapy, 33% of FAC-treated patients and 40% of paclitaxel-treated patients had < 1 cm of residual disease *(Buzdar A, Hortobagyi G, Theriault R, et al: Proc Am Soc Clin Oncol 18:73a [abstract], 1999).*

TABLE 2: Adjuvant chemotherapy regimens in node-positive breast cancer[a]

Regimen	Dose and frequency
CMF	
Cyclophosphamide	100 mg/m^2 PO on days 1-14
Methotrexate	40 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 IV on days 1 and 8
Repeat every 28 days.	
or	
Cyclophosphamide	600 mg/m^2 IV on day 1
Methotrexate	40 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 IV on day 1
Repeat every 21-28 days.	
FAC	
5-FU	500 mg/m^2 IV on days 1 and 8
Adriamycin	50 mg/m^2 IV by continuous 72-h infusion on days 1-3
Cyclophosphamide	500 mg/m^2 IV on day 1
Repeat at 21-day intervals if hematologic recovery occurs.	
CAF	
Cyclophosphamide	600 mg/m^2 IV on day 1
Adriamycin	60 mg/m^2 IV on day 1
5-FU	600 mg/m^2 IV on day 1
Repeat every 21-28 days.	
AC	
Adriamycin	60 mg/m^2 IV on day 1
Cyclophosphamide	600 mg/m^2 IV on day 1
Repeat every 21-28 days depending on hematologic recovery.	
AC → T	
Adriamycin	60 mg/m^2 IV on day 1
Cyclophosphamide	600 mg/m^2 IV on day 1 × 4 cycles
followed by	
Taxol	175 mg/m^2 IV by 3-h infusion q3wk × 4 cycles
FEC (CEF) [a]	
Cyclophosphamide	75 mg/m^2 PO on days 1-14
Epirubicin	60 mg/m^2 IV on days 1 and 8
5-FU	500 mg/m^2 IV on days 1 and 8 every month × 6
A-CMF	
Adriamycin	75 mg/m^2 IV on day 1
Repeat every 3 weeks for 4 courses.	
Cyclophosphamide	600 mg/m^2 IV on day 1
Methotrexate	40 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 on day 1
Repeat every 3 weeks for 8 courses.	

[a] Doses from Levine MN, Bramwell VH, Pritchard KI, et al: J Clin Oncol 16:2651-2658, 1998.

bicin. Thus, it is reasonable to consider the regimen of AC × 4 with sequential paclitaxel × 4 as a primary adjuvant therapy.

The NSABP B-18 trial showed that preoperative doxorubicin-based chemotherapy decreases tumor size by > 50% in approximately 90% of operable breast cancers. This results in a greater frequency of lumpectomy but has no reported survival advantage.

In addition, data from the Early Breast Cancer Trialists' Collaborative Group overview analyses demonstrated a significant advantage afforded by the addition of tamoxifen to the adjuvant therapy regimen of women of all ages with estrogen-receptor–positive tumors. Sequential tamoxifen (20 mg/d PO) for 5 years is recommended.

The dosages, schedules, and frequencies of these combination regimens are detailed in Table 2. Doxorubicin-containing regimens are being used with greater frequency and have been shown to be of greater value, ie, decreasing disease recurrence and improving survival, in patients treated in the adjuvant setting. Risk reductions for polychemotherapy are proportionately the same in patients with node-negative and node-positive disease.

Recent results suggest, furthermore, that patients with HER-2/*neu*-expressing breast cancers that are associated with axillary lymph node metastases benefit significantly from intensive, doxorubicin-containing adjuvant chemotherapy.

The optimal duration of systemic therapy is unknown, but 4-6 cycles is considered to be the minimum length of therapy for providing benefit. Chemotherapy cycles are repeated every 21-28 days or as soon as hematologic recovery (absolute granulocyte count ≥ 1,500/μL) permits.

Age ≥ 50 years old Treatment for women ≥ 50 years of age is similar in content to that of women < 50 years old.

Estrogen-receptor–positive tumors In women with estrogen-receptor–positive tumors (estrogen receptor ≥ 10 fmol), the estrogen agonist/antagonist tamoxifen (10 mg PO bid for 5 years) has been shown to reduce the risk of recurrence and death from breast cancer. An overview analysis showed a reduction in risk of death of ~20% for women treated with tamoxifen. The benefit of tamoxifen is independent of menstrual status and has been demonstrated in women from 50 to > 70 years of age. Recent data from the Early Breast Cancer Trialists' Group indicate that the use of combination chemotherapy adds significant benefit in reducing the risk of recurrence and affording a survival advantage in this group of women.

Estrogen-receptor–negative tumors Systemic therapy for women ≥ 50 years of age with hormone-receptor–negative tumors consists of a chemotherapy program, as outlined above for women ≤ 49 years of age. Very limited data are available from randomized trials regarding women ≥ 70 years of age. However, in the absence of comorbidity, such as heart or renal disease, systemic adjuvant therapy can be offered as for women ≥ 70 years old.

High-dose chemotherapy Because of the higher rate of recurrence in patients with stage IIB breast cancer, high-dose chemotherapy can also be considered as part of a clinical trial. See chapter 11 for a discussion of the current status of this approach.

Toxic effects of medical therapy

Chemotherapy The most frequent acute toxicities are nausea/vomiting, alopecia, and hematologic side effects, such as leukopenia and thrombocytopenia. Neutropenia, with its attendant risk of infection, is a potentially life-threatening complication that requires prompt medical attention and broad-spectrum antibiotics until hematologic recovery occurs.

Other toxicities may include amenorrhea, cystitis, stomatitis, myocardial failure, and nail/skin changes. Amenorrhea is drug- and dose-related and is often permanent in women over 40 years of age. Cardiac failure, while rare, is potentially life-threatening and may be irreversible.

Tamoxifen Toxicities of tamoxifen include hot flashes, menstrual irregularities, thrombophlebitis, and endometrial hyperplasia or cancer.

Follow-up of long-term survivors

There is no consensus among oncologists as to the appropriate and optimal follow-up routine for long-term breast cancer survivors. Recommendations for follow-up testing are quite variable. The vast majority of relapses, both locoregional and distant, occur within the first 3 years, when surveillance is the most intensive. After this initial period, the frequency of follow-up visits and testing is reduced (Table 3).

TABLE 3: Follow-up recommendations for the asymptomatic long-term breast cancer survivor

Intervention	Interval
History and physical examination	Every 6 months or annually
Mammogram	Annually
Chest x-ray	?Annually
Liver function tests	?Annually
Bone scan	Not routinely recommended
Tumor markers	Not routinely recommended
Liver imaging	Not routinely recommended
Brain imaging	Not routinely recommended

History and physical examination Surveillance methods include a detailed history and physical examination at each office visit. Patients who have been treated by mastectomy can be seen in the office annually after they have been disease-free for 5 years. Patients who were treated with breast-conserving surgery and radiotherapy can be followed at 6-month intervals until they have been disease-free for 6-8 years, and then annually.

Approximately 71% of breast cancer recurrences are detected by the patients themselves, and they will report a change in their symptoms when questioned carefully. In patients who are asymptomatic, physical examination will detect a recurrence in another 15%. Therefore, a patient's complaint on history or a new finding on physical examination will lead to the detection of 86% of all recurrences.

Mammography should be performed annually in all patients who have been treated for breast cancer. The risk of developing a contralateral breast cancer is approximately 0.5%-1.0% per year. In addition, approximately one-third of ipsilateral breast tumor recurrences in patients who have been treated by conservation surgery and radiotherapy are detected by mammography alone. As the time interval between the initial therapy and follow-up mammogram increases, so does the likelihood that a local breast recurrence will develop elsewhere in the breast rather than at the site of the initial primary lesion.

Chest x-ray Routine chest radiograms detect between 2.3% and 19.5% of recurrences in asymptomatic patients and may be indicated on an annual basis.

Liver function tests detect recurrences in relatively few asymptomatic patients, and their routine use has been questioned. However, these tests are relatively inexpensive, and it may not be unreasonable to obtain them annually.

Tumor markers The use of tumor markers, such as carcinoembryonic assay (CEA) and CA 15-3, to follow long-term breast cancer survivors is not recommended.

Bone scans Postoperative bone scans are also not recommended in asymptomatic patients. In the NSABP B-09 trial, in which bone scans were regularly performed, occult disease was identified in only 0.4% of patients.

Liver and brain imaging Imaging studies of the liver and brain are not indicated in the asymptomatic patient.

SUGGESTED READING

Clarke DH, Martinez AA: Identification of patients who are at high risk for locoregional breast cancer recurrence after conservative surgery and radiotherapy: A review article for surgeons, pathologists, and radiation and medical oncologists. J Clin Oncol 10(3):474–483, 1992.

Excellent review that evaluates risk factors associated with a high failure rate after conservative surgery and radiotherapy for invasive breast cancer.

Fisher B, Dignam J, Wolmark N, et al: Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. J Natl Cancer Inst 89:1673–1682, 1997.

This paper focuses on adjuvant therapy for node-negative patients.

Fowble B: Results of prospective randomized trials evaluating post-mastectomy radiation for axillary node positive patients receiving adjuvant systemic therapy. ASCO Educational Book (spring), pp 623–628. Philadelphia, Lippincott Williams & Wilkins, 1999.

This presentation provides a succinct review of the survival advantages of post-mastectomy radiation therapy in node-positive patients and compares these advantages to those of multiagent chemotherapy, as noted in randomized, published trials. Dr. Fowble presents a cogent, persuasive argument for post-mastectomy radiation therapy.

Overgaard M, Hanson P, Overgaard J: Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med 337:949–955, 1997.

In this large Danish Breast Cancer Cooperative Group trial, post-mastectomy patients treated with CMF chemotherapy were randomized to receive or not to receive radiation therapy. Patients given radiotherapy showed a significant improvement in locoregional control and in disease-free and overall survival.

Paik S, Bryant J, Park C, et al: erbB-2 and response to doxorubicin in patients with axillary lymph node positive, hormone receptor-negative breast cancer. J Natl Cancer Inst 90:1361–1370, 1998.

Thor AD, Berry DA, Budman DR, et al: erbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer. J Natl Cancer Inst 90:1346–1360, 1998.

These two papers review the evidence suggesting that treatment with doxorubicin-containing chemotherapeutic programs is beneficial in women whose primary breast cancer overexpresses the HER-2/*neu* (erbB-2) oncogene.

Ragaz J, Jackson SM, Nhu L, et al: Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 337:956–962, 1997.

In this trial, 318 premenopausal node-positive patients were randomly assigned, after modified radical mastectomy, to receive chemotherapy plus radiotherapy or chemotherapy alone. After 15 years of follow-up, the women assigned to chemotherapy plus radiotherapy had a 33% reduction in the rate of recurrence and a 29% reduction in breast cancer mortality.

CHAPTER 11

Stages III and IV breast cancer

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This chapter addresses the diagnosis and management of locally advanced, locally recurrent, and metastatic breast cancer, ie, stages III and IV disease.

Approximately 20%-25% of patients present with locally advanced breast cancer. Inflammatory breast cancer is a particularly aggressive form of breast cancer that falls under the heading of locally advanced disease and accounts for 1%-3% of all breast cancers.

Locoregional recurrence of breast cancer remains a major clinical oncologic problem. Rates of locoregional recurrence may vary from < 10% to > 50%, depending on initial disease stage and treatment.

Metastatic disease is found at presentation in 5%-10% of patients with breast cancer. The most common sites of distant metastasis are the lung, liver, and bone.

The optimal therapy for stage III breast cancer continues to evolve. Recently, the use of neoadjuvant chemotherapy has been very effective in downstaging locally advanced breast cancer disease prior to surgical intervention. The optimal neoadjuvant chemotherapeutic regimens continue to evolve, and studies are being performed to evaluate new agents and delivery methods.

Diagnosis

Locally advanced disease

Patients with locally advanced breast cancer do not have distant metastatic disease and are in this group based on tumor size and/or nodal status. Such patients often present with a large breast mass or axillary nodal disease, which is easily palpable on physical examination. In some instances, the breast is diffusely infiltrated with disease and no dominant mass is evident.

Patients with inflammatory breast cancer often present with erythema and edema of the skin of the breast (peau d'orange) and may not have a discrete mass within the breast. These patients often are treated with antibiotics unsuccessfully for presumed mastitis.

Mammography is beneficial in determining the local extent of disease in the ipsilateral breast, as well as in studying the contralateral breast.

Fine-needle aspiration (FNA) or biopsy The diagnosis of breast cancer can be confirmed by either FNA cytology or core biopsy. When FNA is utilized to establish the diagnosis, material can be sent for determination of hormone-receptor status.

Search for distant metastasis The presence of distant metastatic disease should be ruled out by physical examination, chest radiography, CT of the liver, bone scan, and CT of the chest.

Locoregional recurrence

Biopsy or FNA Locoregional recurrence of breast cancer can be diagnosed by surgical biopsy or FNA cytology. Whichever modality is appropriate, material should be sent for hormone-receptor studies, since there is only an 80% concordance in hormone-receptor status between the primary tumor and recurrent disease. When the suspected recurrent disease is not extensive, the biopsy procedure of choice is a negative margin excisional biopsy. For an extensive recurrence, an incisional biopsy can be used.

Search for distant metastasis Prior to beginning a treatment regimen for a patient with locoregional recurrence, an evaluation for distant metastasis should be instituted, since the findings may alter the treatment plan.

Distant metastasis from the breast

Metastatic breast cancer may be manifested by bone pain, shortness of breath secondary to a pleural effusion, parenchymal or pulmonary nodules, or neurologic deficits secondary to spinal cord compression or brain metastases. In some instances, metastatic disease is identified after abnormalities are found on routine laboratory or radiologic studies.

Assessment of disease extent by radiography, CT, and radionuclide scanning is important. Organ functional impairment may be determined by blood tests (liver/renal/hematologic) or may require cardiac and pulmonary function testing. Biopsy may be required to confirm the diagnosis.

Metastasis to the breast

The most common source of metastatic disease to the breast is a contralateral breast primary. Metastasis to the breast is more commonly seen in women. The average age at diagnosis ranges from the late 30s to 40s. Treatment depends on the status and location of the primary site.

Mammographic findings Mammography in patients with metastatic disease to the breast most commonly reveals a single lesion or multiple masses with distinct or semidiscrete borders. Less common mammographic findings include skin thickening or axillary adenopathy.

FNA or biopsy FNA cytology has been extremely useful in establishing the diagnosis when the metastatic disease has cytologic features that are not consistent with a breast primary. When cytology is not helpful, open biopsy may be necessary to distinguish a primary breast cancer from metastatic disease.

Treatment

TREATMENT OF LOCALLY ADVANCED DISEASE

The optimal treatment for patients with locally advanced breast cancer has yet to be defined, due to the heterogeneity of this group. There are approximately 40 different substage possibilities with the different combinations of tumor size and nodal status. Between 66% and 90% of patients with stage III breast cancer will have positive lymph nodes at the time of dissection, and approximately 50% of patients will have four or more positive nodes.

Patients with locally advanced breast cancer have disease-free survival rates ranging from 0% to 60%, depending on the tumor characteristics and nodal status. In general, the most frequent type of treatment failure is due to distant metastases, and the majority of these appear within 2 years of diagnosis.

With the increased utilization of multimodality therapy, including chemotherapy, radiation therapy, and surgery, survival for this patient population has improved significantly.

Neoadjuvant systemic therapy

Neoadjuvant therapy with cytotoxic drugs permits in vivo chemosensitivity testing, can downstage locally advanced disease and render it operable, and may allow breast-conservation surgery to be performed. Preoperative chemotherapy requires a coordinated multidisciplinary approach to plan for surgical and radiation therapy. A multimodality treatment approach can provide improved control of locoregional and systemic disease. When neoadjuvant therapy is used, accurate pathologic staging is not possible.

Active regimens Preoperative chemotherapy regimens reported to result in high response rates (partial and complete responses) include CAF (cyclophosphamide, Adriamycin, and fluorouracil [5-FU]), AC (Adriamycin and cyclophosphamide), CMF (cyclophosphamide, methotrexate, and 5-FU), and CMFVP (cyclophosphamide, methotrexate, 5-FU, vincristine, and prednisone). Combination chemotherapy with an anthracycline-based regimen—CAF or AC—is used most often. The doses of these combination chemotherapy regimens are given in Table 1.

Recent preliminary data have shown that docetaxel (Taxotere) plus doxorubicin, given either sequentially or concomitantly, can result in high clinical response rates, including pathologic complete responses, in patients with noninflammatory stage II breast cancer *(Miller KD, McCaskill-Stevens W, Sisk J, et al: Proc Am Soc Clin Oncol 18:72a [abstract], 1999).*

Neoadjuvant chemotherapy results in complete response rates ranging from 20% to 53% and partial response rates (≥ 50% reduction in bidimensionally measurable disease) ranging from 37% to 50%, with total response rates ranging from 80% to 90%. Patients with large lesions are more likely to have partial responses. Pathologic complete responses do occur and are more likely to be seen in patients with smaller tumors.

Patients should be followed carefully while receiving neoadjuvant systemic therapy to determine treatment response. In addition to clinical examination,

TABLE 1: Chemotherapy regimens commonly used for locally advanced breast cancer

Regimen	Dose and frequency
CAF	
Cyclophosphamide	500 mg/m^2 IV on day 2
Adriamycin	50 mg/m^2 by continuous IV infusion on days 1-3 (72 hours)
5-FU	500 mg/m^2 IV on days 1 and 8
Repeat every 21-28 days depending on hematologic recovery.	
or	
Cyclophosphamide	600 mg/m^2 on day 1
Adriamycin	60 mg/m^2 on day 1
5-FU	600 mg/m^2 on day 1
Repeat every 21-28 days depending on hematologic recovery	
AC	
Adriamycin	60 mg/m^2 on day 1
Cyclophosphamide	600 mg/m^2 on day 1
Repeat every 21-28 days depending on hematologic recovery.	

it may also be helpful to photographically document the response of ulcerated, erythematous, indurated skin lesions. A 1997 report by Herroda et al indicated that physical examination and mammography are best for assessing primary breast tumor response, while physical examination and sonography of axillary nodes are optimal for determining regional nodal disease response.

Multimodality approach

A multimodality treatment plan for locally advanced breast cancer (stage IIIA and IIIB, M1 supraclavicular nodes) is shown schematically in Figure 1. This approach has been shown to result in a 5-year survival rate of 84% in patients with stage IIIA disease and a 44% rate in those with stage IIIB disease. The most striking benefit has been seen in patients with inflammatory breast cancer, with 5-year survival rates of 35%-50% reported for a multimodality treatment approach including primary chemotherapy followed by surgery or radiation therapy and additional adjuvant systemic therapy. The same chemotherapy drugs, doses, and schedules used for single-modality therapy are employed in the multimodality approach.

Surgery Traditionally, the surgical procedure of choice for patients with locally advanced breast cancer has been mastectomy. In recently published studies, some patients with locally advanced breast cancer who responded to treatment with neoadjuvant chemotherapy became candidates for breast-conservation therapy and were treated with limited breast surgery and adjuvant breast irradiation. However, at present, this is not the standard of care, and patients treated with this approach should be enrolled in a clinical trial.

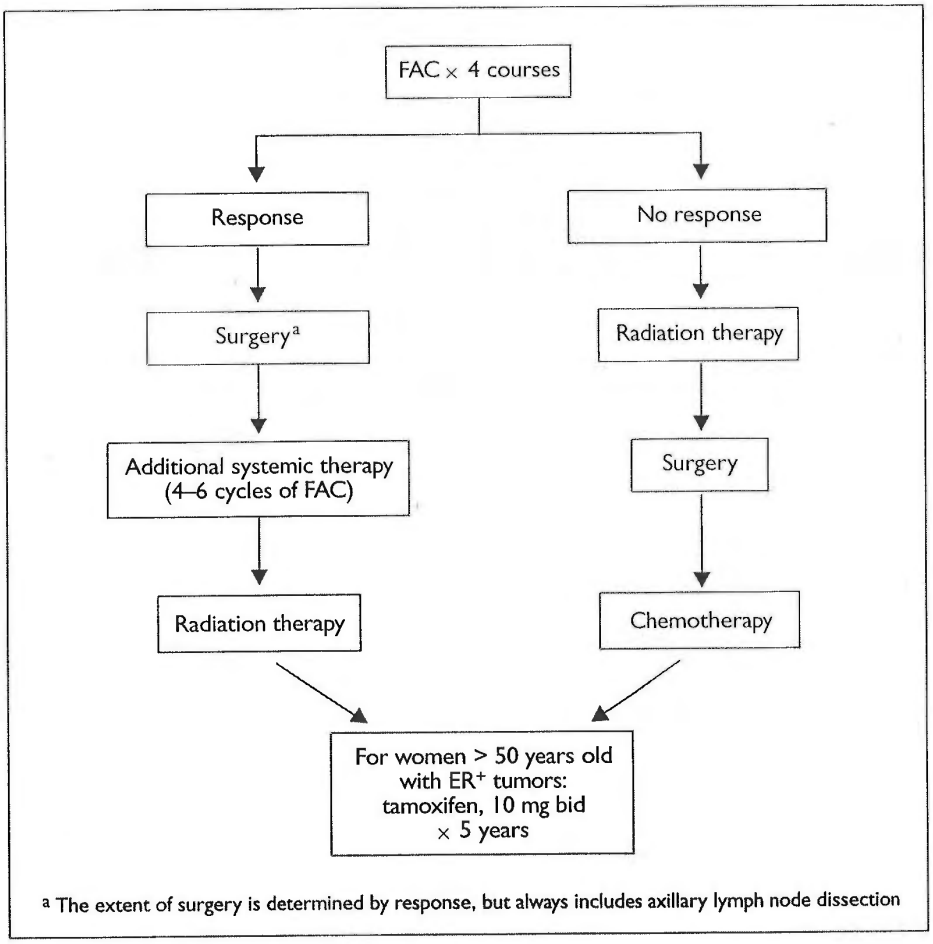

FIGURE 1: Multimodality approach to locally advanced breast cancer

Radiation therapy remains an integral component of the management of patients with locally advanced breast cancer. For patients with operable breast cancer undergoing mastectomy, radiation therapy to the chest wall and/or regional lymph nodes (to a total dose of 5,000-6,000 cGy) is usually employed, as discussed in chapter 10. Recent randomized trials suggest that post-mastectomy patients with any number of positive nodes derive a disease-free and/or overall survival benefit from post-mastectomy radiation.

Available data do not suggest a problem in delaying radiation therapy until the completion of systemic chemotherapy. Even in patients undergoing high-dose chemotherapy with autologous bone marrow or stem-cell transplantation, radiation is generally indicated following mastectomy for patients with locally advanced disease (primary tumors ≥ 5 cm and/or ≥ 4 positive axillary nodes).

For patients whose disease is considered to be inoperable, radiation therapy may be integrated into the management plan prior to surgery.

High-dose chemotherapy Patients with locally advanced breast cancer and those with multiple positive nodes may be candidates for protocol treatment

with high-dose chemotherapy plus autologous stem-cell support. Preliminary results from three prospective, randomized trials of high-dose chemotherapy with autologous stem-cell support in women with high-risk primary breast cancer were recently presented. All three trials are summarized in Table 2, and two of the trials are discussed in more detail below.

A trial from South Africa compared standard treatment with 6 cycles of cyclophosphamide (Cytoxan, Neosar), doxorubicin (or epirubicin [Ellence]), and 5-FU with 2 cycles of high-dose cyclophosphamide, mitoxantrone (Novantrone), and etoposide with hematopoietic stem-cell support. With a total of 154 patients with high-risk primary breast cancer (at least seven involved lymph nodes or stage III disease) enrolled and after more than 5 years of follow-up, patients receiving tandem cycles of high-dose chemotherapy experienced a 25% relapse rate, as compared with a 66% rate in those given standard chemotherapy. Survival also was improved following high-dose chemotherapy. No treatment-related deaths were reported. *[Editors' Note: As this text went to press, the University of Witwatersrand, Johannesburg, announced the launch of an investigation into alleged serious scientific misconduct in the South African trial. This action was taken after an independent US team auditing the trial's data found significant deviations from standard conduct with respect to the trial's protocol.]*

The largest trial evaluating the high-dose chemotherapy was conducted by the Cancer and Leukemia Group B (CALGB) in patients with stage II or III breast cancer involving 10 or more axillary lymph nodes. This trial examined the value of consolidation high-dose therapy with cyclophosphamide, cisplatin (Platinol), and carmustine (BCNU) with autologous stem-cell support following adjuvant therapy with cyclophosphamide, doxorubicin, and 5-FU. Preliminary results of this study, with 783 participants, showed a 3-year survival rate of 68% in patients treated with high-dose chemotherapy vs a 64% rate in those who received intermediate-dose consolidation therapy with the same drugs. However, follow-up is not yet long enough to define the ultimate benefit of this approach. Moreover, toxicity to date has been significantly higher and the relapse rate significantly lower in the high-dose group.

Nonrandomized studies of high-dose chemotherapy plus autologous stem-cell support have shown a disease-free survival of ~70%, as compared with historical data showing a 30% 5-year disease-free survival rate with conventional-dose chemotherapy.

TABLE 2: Randomized studies of high-dose chemotherapy in primary breast cancer

Investigators	Number of patients	Follow-up (median)	Survival benefit?	*P* value
Bezwoda	154	278 wk	Yes	< .05
Peters et al	783	36 mo	No	NS
Scandinavian Breast Cancer Study Group	525	20 mo	No	NS

A more recently initiated prospective, randomized trial is examining the value of combination alkylating agent chemotherapy (cyclophosphamide, cisplatin, and BCNU) with autologous stem-cell support in patients with four to nine involved axillary lymph nodes. Accrual to this study should be completed within the next 18-24 months.

To date, the results of available clinical trials have not all shown improved disease-free and overall survival in patients treated with dose-intensive regimens. However, trial design, power, and strategy have all been questioned. Outside of the context of a clinical trial, high-dose chemotherapy cannot be recommended for patients with primary or metastatic breast cancer.

PRIMARY CHEMORADIATION

Several studies have evaluated the role of primary chemotherapy (neoadjuvant chemotherapy), followed by radiation to the intact breast, as initial treatment in patients with newly diagnosed breast cancer. At present, this approach should be considered experimental in patients with early-stage disease and, in more advanced disease, should be reserved for patients who are not candidates for surgery due to comorbidity or metastatic disease.

TREATMENT OF LOCOREGIONAL RECURRENCE AFTER EARLY INVASIVE CANCER OR DCIS

When a patient develops a local failure after breast-conservation treatment for early invasive cancer or ductal carcinoma in situ (DCIS), it is generally in the region of the initial primary tumor. The risk of ipsilateral breast tumor recurrence after conservative treatment in patients with early invasive cancer ranges from 0.5% to 2% per year, with long-term local failure rates plateauing at about 15%-20%. Local failure rates after wide excision alone for DCIS vary from 10% to 63%, as compared with rates between 7% and 21% after wide excision plus radiation therapy. Most patients whose disease recurs after conservative treatment for DCIS can be treated with salvage mastectomy. In one study, 14% of patients who developed a local recurrence had synchronous distant metastatic disease.

The optimal treatment of a local or regional recurrence after mastectomy has yet to be defined. Locoregional recurrences are associated with initial nodal status and primary tumor size. Appropriate treatment may result in long-term control of the locoregional disease. In many instances, these patients develop simultaneous distant metastasis or distant disease develops some time after the locoregional recurrence manifests itself.

Recurrence of invasive cancer after breast conservation

Recurrence after wide excision and breast irradiation For patients with early invasive cancer who have undergone conservative surgery followed by radiation and whose cancer recurs in the ipsilateral breast, salvage mastectomy is the most common treatment modality. The same is true for ipsilateral recurrence (of invasive or in situ disease) after conservative treatment for DCIS, when there is no evidence of distant metastatic disease.

Some studies with limited follow-up have reported acceptable results with repeat wide local excision for ipsilateral breast tumor relapses following conservative surgery and radiation therapy. Selection criteria for this approach are unclear, however, and use of this salvage procedure remains controversial. Although the use of limited-field reirradiation has been reported, selection criteria for this management option and long-term follow-up data are lacking.

Recurrence after wide excision alone In patients initially treated with wide local excision alone who sustain an ipsilateral breast tumor recurrence, small series with limited follow-up suggest that wide local excision followed by radiation therapy to the intact breast at the time of local recurrence may be a reasonable treatment alternative. In this situation, standard radiation doses would be employed.

Chest wall recurrence after mastectomy

In general, patients who develop minimal recurrent disease in the chest wall after a long disease-free interval may be treated by excision alone, although this approach is controversial and may not be ideal. Locoregional control obtained by radiation therapy alone is related to the volume of residual disease and may not be durable. When possible, disease recurring in the chest wall or axillary nodes should be resected and radiation therapy should be delivered to aid in local control.

Radiation treatment techniques are generally similar to those employed for patients treated with standard post-mastectomy radiation, and consist of photon- and/or electron-beam arrangements directed at the chest wall and adjacent lymph node regions. Treatment planning should strive for homogeneous dose distributions to the target areas while minimizing the dose to the underlying cardiac and pulmonary structures.

Radiation dose and protocol Conventional fractionation of 180-200 cGy/d to the area of locoregional recurrence and immediately adjacent areas at risk, to a total dose of 4,500-5,000 cGy, is indicated. A boost to the area of recurrence or gross residual disease, to a dose of approximately 6,000 cGy, results in acceptable long-term locoregional control.

Radical chest wall resection A select group of patients with local chest wall recurrence secondary to breast cancer may be candidates for a radical chest wall resection, which may include resection of skin, soft tissue, and bone. Flap coverage or prosthetic chest wall reconstruction is required. Appropriate candidates would include patients who do not have distant metastases and who have persistent or recurrent chest wall disease after chest wall irradiation and patients who present with a chest wall recurrence after a long disease-free interval.

ADJUVANT SYSTEMIC THERAPY FOR LOCOREGIONAL RECURRENCE

Ipsilateral breast tumor recurrence

Limited data support the use of adjuvant systemic therapy at the time of ipsilateral breast tumor recurrence. Retrospective studies have suggested a

20%-50% risk of systemic metastases in patients who sustain an ipsilateral breast tumor recurrence. A recent study conducted at Yale found that ipsilateral breast tumor recurrence was a significant predictor of distant metastases, particularly among women who relapsed within 4 years of the original diagnosis; these women had a rate of distant metastasis of approximately 50%. Similar findings were noted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) investigators.

These data suggest that women whose tumors recur in the ipsilateral breast within the first few years following the original diagnosis may be considered for adjuvant systemic therapy. Given the lack of prospective, randomized data, specific treatment recommendations for these women remain highly individualized.

Regional nodal recurrence and post-mastectomy chest wall recurrence

Although there are limited data addressing the use of adjuvant systemic therapy at the time of locoregional relapse following mastectomy, given the high rate of systemic metastasis in this population, these patients may be considered for adjuvant systemic therapy. A recently reported randomized trial demonstrated a disease-free survival benefit with the use of adjuvant tamoxifen (Nolvadex) following radiation therapy at the time of post-mastectomy chest wall recurrence in estrogen-receptor–positive patients. The 5-year disease-free survival rate was increased from 36% to 59%, and median disease-free survival was prolonged by > 4.5 years.

Patients with estrogen-receptor–negative tumors and aggressive locoregional recurrences may also be considered for systemic cytotoxic chemotherapy, given their relatively poor prognosis and high rate of metastasis.

MEDICAL TREATMENT OF METASTATIC BREAST CANCER

Patients with metastatic cancer can be divided into two groups: those with stage IV disease at presentation and those who develop metastases after primary treatment. The management of stage IV disease depends on the site and extent of metastases, comorbid conditions, and clinical tumor characteristics.

Patients with delayed metastatic disease can be divided into two groups, ie, so-called low risk and intermediate/high risk, based on the biological aggressiveness of the disease. As shown schematically in Figure 2 (page 194), the management approach to these two groups differs.

Low-risk patients

The low-risk group includes patients who develop metastatic disease after a long disease-free interval (ie, a long disease-free interval from primary breast cancer diagnosis to presentation with metastasis), those whose tumors are positive for hormone receptors (estrogen and progesterone), those with bone-only disease, and those without extensive visceral organ involvement.

Hormone therapy Low-risk patients may be treated with a trial of hormone therapy.

TABLE 3: Doses and schedules of hormonal agents commonly used in patients with metastatic breast cancer

Agent	Dose and schedule
Postmenopausal	
Tamoxifen	20 mg PO qd
or	
Toremifene	60 mg PO qd
Anastrozole	1 mg PO qd
or	
Letrozole	2.5 mg PO qd
Megestrol acetate	40 mg PO qid
Fluoxymesterone	10 mg PO tid
Aminoglutethimide	250 mg PO qid
Premenopausal	
Tamoxifen	20 mg PO qd
Luteinizing-hormone–releasing-hormone analogs	7.5 mg IM depot q28d
Megestrol acetate	40 mg PO qid
Fluoxymesterone	10 mg PO tid

First-line hormonal therapy consists of antiestrogen therapy, such as tamoxifen or toremifene (Fareston), with careful serial assessment of clinical and disease response.

Hormone therapy may be associated with a "flare" response, a temporary worsening of signs and symptoms of disease within the first few weeks of treatment. This response generally means clinical benefit will follow.

If the tumor initially responds to first-line hormone therapy and then progresses, a second hormonal manipulation is warranted. Various hormonal agents are available (Table 3). These may be used sequentially and may provide disease palliation for prolonged periods in some patients.

Second-line hormonal agents The most commonly used second-line hormonal agents had been progestational drugs, such as megestrol acetate (Megace). Recent randomized trials have indicated that the aromatase inhibitors, such as anastrozole (Arimidex) and letrozole (Femara), are equally effective for palliation of metastatic disease, have less toxicity, and may provide a survival advantage compared to megestrol acetate. Therefore, they are the drugs of second choice following tamoxifen administration.

Hormonal therapy continues until evidence of disease progression or drug-related toxicity precludes further therapy with the same agent. If a partial or complete response to the first hormonal treatment is documented at the time of disease progression, a second hormonal agent may provide further palliation of symptoms and avoid the initiation of systemic chemotherapy. However, subsequent hormonal responses tend to be of

TABLE 4: Doses and schedules of chemotherapy agents commonly used in patients with metastatic breast cancer

Drug/combination	Dose and schedule
CAF	
Cyclophosphamide	500 mg/m^2 IV on day 1
Adriamycin	50 mg/m^2 by continuous IV infusion on day 1
5-FU	500 mg/m^2 IV on days 1 and 8
Repeat every 3-4 weeks.	
Paclitaxel	175 mg/m^2 by 3-h IV infusion 80-100 mg/m^2/week
Docetaxel	60-100 mg/m^2 by 1-h IV infusion 40 mg/m^2/week
Repeat every 3-4 weeks if hematologic recovery has occurred (ie, absolute granulocyte count ≥ 1,500/μL and platelet count ≥ 100,000/μL).	
Capecitabine	2,510 mg/m^2 PO bid (divided dose, AM and PM) for 14 days
Repeat after 7-day rest.	
Vinorelbine	15-25 mg/m^2 by IV infusion weekly (for heavily pretreated patients)
Repeat weekly for 4-6 weeks; resume cycle after 1-2 week rest if hematologic recovery has occurred (as defined above).	

shorter duration, and, ultimately, the disease will become refractory to hormone treatment.

Cytotoxic agents Hormone-refractory disease can be treated with systemic cytotoxic therapy. FAC, paclitaxel (Taxol), or docetaxel may be used in this situation. (For a more detailed discussion of these agents, see "Intermediate- or high-risk patients," below. For doses, see Table 4).

Intermediate- or high-risk patients

Intermediate- or high-risk patients include those with rapidly progressive disease or visceral involvement, as well as those with disease shown to be refractory to hormonal manipulation by a prior therapeutic trial.

Anthracycline-containing combinations, such as CAF (see Table 4), are preferred for these patients. However, newer combinations of doxorubicin and a taxane are gaining favor for use in patients who have not received > 450 mg/m^2 of an anthracycline and whose relapse has occurred more than 12 months after the completion of adjuvant therapy.

Single agents Many single cytotoxic drugs have shown some activity in metastatic breast cancer (Table 4). These include vinblastine, mitomycin (Mutamycin), and thiotepa (Thiotepa), capecitabine (Xeloda), and vinorelbine (Navelbine).

Paclitaxel One of the most active new agents is paclitaxel. It has demonstrated antitumor activity in patients with anthracycline-resistant disease, as well as in those who have received three or more prior chemotherapy regimens for metastatic disease.

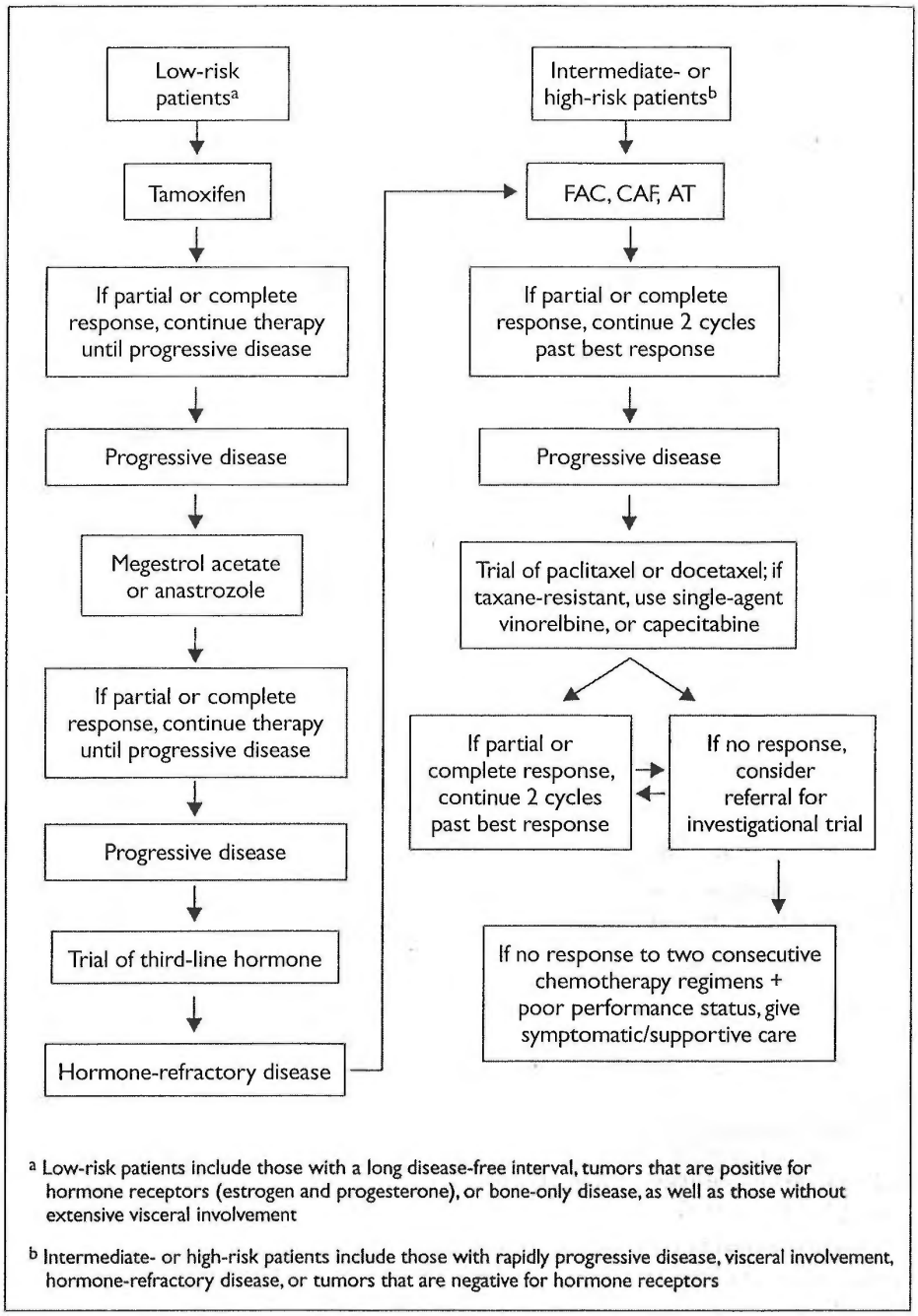

FIGURE 2: Treatment approach to metastatic breast cancer

High-dose paclitaxel (250 mg/m^2 over 3 hours) has not been shown to be superior to 175 mg/m^2 over 3 hours. The higher-dose regimen is associated with greater toxicity, both hematologic and neurologic.

Docetaxel, approved by the FDA for anthracycline-resistant locally advanced or metastatic breast cancer, has demonstrated overall response rates of 41% in

doxorubicin-resistant disease. It has been shown to be superior to mitomycin/vinblastine in patients whose disease progressed after an anthracycline-based chemotherapy regimen.

The recommended starting dose of docetaxel—100 mg/m^2 as a 1-hour IV infusion—requires premedication with dexamethasone to avoid fluid retention and the capillary leak syndrome. The usual regimen of dexamethasone is 8 mg bid for a total of 3 days beginning 24 hours prior to the administration of docetaxel.

Although 100 mg/m^2 is the dose of docetaxel approved by the FDA, many recent trials have demonstrated a high rate of grade 4 hematologic toxicity at this dose level; a dose of 60-70 mg/m^2 may achieve equivalent therapeutic benefit with improved safety. As with paclitaxel, docetaxel dosage must be modified in patients who have hepatic impairment, manifested by elevated transaminase or alkaline phosphatase levels.

Capecitabine, an orally active fluorinated pyrimidine carbonate, has been shown to have substantial antitumor effect in patients whose disease has recurred or progressed after prior anthracycline chemotherapy and has progressed after taxane therapy. Prolonged survival, limited toxicity, and response in visceral as well as soft-tissue disease add to the benefit of capecitabine. Toxicities include diarrhea, stomatitis, and hand-foot syndrome.

New approaches Multiple new approaches to treating metastatic breast cancer are being explored. Weekly docetaxel and paclitaxel have been reported to produce high response rates and lower toxicity than 3-week schedules. Combinations of doxorubicin with paclitaxel or docetaxel have also shown substantial antitumor activity. These newer combinations need to be compared with standard AC or FAC (CAF) in phase III trials.

Monoclonal antibody therapy

Trastuzumab (Herceptin), a humanized monoclonal antibody to the HER-2/*neu* protein, has been approved for use as a single-agent in second- and third-line therapy for metastatic breast cancer and in combination with paclitaxel as first-line therapy in this setting. A randomized trial in 469 women showed that the combination of trastuzumab with chemotherapy yielded a 45% overall response rate, as compared with a 29% rate with chemotherapy alone—a 55% increase. The addition of trastuzumab had the greatest impact on response when combined with paclitaxel. Among the study group as a whole, 79% of women treated with trastuzumab-chemotherapy were alive at 1 year, as compared with 68% of those given chemotherapy alone.

A recent update of those data has shown a superior median overall survival with chemotherapy plus trastuzumab compared to chemotherapy alone (25.4 vs 20.9 months). The survival advantage was seen with both AC plus trastuzumab and paclitaxel plus the monoclonal antibody.

In another single-arm trial involving 222 women who had not responded to prior chemotherapy, trastuzumab shrunk tumors by 50% in 14% of women, with a median duration of response of 9 months. Overall, trastuzumab was well tolerated in both trials. Due to an increased risk of cardiac dysfunction

observed in women treated with trastuzumab plus an anthracycline, trastuzumab should not be used in combination with this drug class.

It is important to point out that trastuzumab also produces cardiac toxicity when administered by itself, particularly in patients who have had extensive prior exposure to an anthracycline. Finally, essentially all of the clinical benefit of trastuzumab (alone or in combination) is confined to patients whose breast cancers express high (3+) levels of the HER-2/*neu* oncoprotein.

High-dose chemotherapy

Patients who present with or subsequently develop distant metastasis may be candidates for high-dose intensive chemotherapy programs with autologous stem-cell support. Multiple feasibility and phase II studies of this approach have been undertaken. The majority of programs include the use of multiple alkylating agents. The role of high-dose chemotherapy in metastatic disease remains controversial, and analysis and observation of ongoing clinical trials continue to be important.

The results from multiple centers indicate an overall 5-year disease-free survival rate of 25% in patients with metastatic disease treated with high-dose chemotherapy. However, it must be remembered that these results were obtained in a select patient population—generally individuals < 60 years of age with good performance status, chemotherapy-sensitive disease, and normal cardiac, pulmonary, renal, and hepatic function. The use of intensive supportive outpatient care, such as colony-stimulating factors and antibiotics, has significantly reduced the morbidity and mortality associated with the high-dose chemotherapy approach.

In recently presented randomized trials of high-dose chemotherapy in patients with metastatic breast cancer (Table 5), it appears that most of the benefit occurs in women with low-bulk disease, especially those in complete clinical remission. This therapeutic modality remains investigational for patients with stage IV disease, however; women referred for high-dose therapy should be enrolled in a clinical trial.

Adjunctive bisphosphonate therapy

Multiple published reports have now confirmed the benefit of bisphosphonates, such as IV pamidronate (Aredia), as an adjunct to chemotherapy and hormonal therapy for metastatic breast cancer with osteolytic disease in bone. Hortobagyi et al have reported a significant reduction in skeletal-related events, including bone pain, pathologic fracture, and the need for radiation therapy to bone, in patients treated with chemotherapy and pamidronate for metastatic disease. Long-term data showed that this benefit persists for up to 24 months of pamidronate treatment.

Theriault et al also reported on the long-term results of hormonal therapy. They observed a substantial reduction in skeletal-related events during up to 24 months of bisphosphonate treatment.

TABLE 5: Randomized studies of high-dose chemotherapy in metastatic breast cancer

Investigators	Number of patients	Median follow-up (yr)	Survival rate (%)		P value
			High-dose treatment	Standard treatment	
Stadtmauer et al	553	3	32	38	NS
Lotz et al	61	5	29.8	18.5	NS

The standard dose of pamidronate is 90 mg in 250 mL of 5% dextrose-and water infused IV over 2 hours. This dose is repeated every 3-4 weeks, depending on the schedule of chemotherapy or hormone therapy.

Minimal toxicity has been reported in patients treated with pamidronate, but bone pain, fever, and conjunctivitis may be seen occasionally. Symptomatic hypocalcemia, while relatively rare, requires frequent monitoring of calcium and phosphate levels during treatment.

ROLE OF RADIATION THERAPY IN METASTATIC DISEASE

Radiation remains an integral component of the management of metastatic breast carcinoma. Although bone metastases are the most commonly treated metastatic sites in patients with breast cancer, brain metastases, spinal cord compression, choroidal metastases, endobronchial lung metastases, and metastatic lesions in other visceral sites can be effectively palliated with radiation.

Radiation dose and schedule Depending on the disease site and volume of the radiation field, fractionation schedules ranging from 20 Gy in 5 fractions to 30 Gy in 10 fractions are used most commonly. In some situations, more protracted courses using lower daily doses may be indicated.

Bone metastasis For patients with widespread bone metastasis, hemibody radiation (6-7 Gy in one fraction to the upper body or 8 Gy to the lower body) has been shown to be effective. Strontium-89 (Metastron) and other systemic radionuclides also provide effective palliation for widespread bone disease.

Consolidation after high-dose chemotherapy Since patients with metastatic disease treated with high-dose chemotherapy and autologous bone marrow or stem-cell transplantation often develop disease failure in previously involved sites, studies have suggested the use of "consolidative radiation therapy" for patients undergoing high-dose chemotherapy. Although this approach appears to be well tolerated and preliminary data are encouraging, whether it will affect survival remains to be determined.

ROLE OF SURGERY IN METASTATIC DISEASE

There are selected indications for surgical intervention in patients with metastatic breast cancer, and the role of surgery at this point is generally

palliative. Most commonly, palliative surgery is offered to patients with brain metastases, spinal cord compression, fractures, or symptomatic pleural or pericardial effusions not controlled by other means. It is also used for GI complications stemming from metastatic deposits. The curative benefit of surgery in the treatment of metastatic disease to the lung or liver is not proven, but, in highly selected cases, surgery may be beneficial.

Spinal cord compression Patients with cord compression who have progressive symptoms during radiation, disease recurrence after radiation, or spinal instability or who require diagnosis are candidates for surgery.

Solitary brain metastasis Patients with a long disease-free interval and a solitary brain metastasis may be candidates for resection. Evidence suggests an improved disease-free survival, overall survival, and quality of life in this subset of patients when treated with surgery combined with postoperative cranial irradiation, as compared with radiation therapy alone.

Chest wall resection It is extremely rare for a patient with distant metastatic disease to be a candidate for a chest wall resection; however, patients with a symptomatic chest wall recurrence who have limited distant disease and have a life expectancy of > 12 months may be appropriate candidates.

Follow-up of long-term survivors

For recommendations on the types and timing of follow-up evaluations, see chapter 10.

SUGGESTED READING

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Three good reviews of chemotherapy approaches.

Lotz JP, Curé H, Janvier M, et al: High dose chemotherapy with hematopoietic stem cell transplantation for metastatic breast cancer: Results of the French protocol PEGASE 04 (abstract). Proc Am Soc Clin Oncol 18:2a, 1999.

Stadtmauer EA, O'Neill A, Goldstein LJ: Phase III randomized trial of high-dose chemotherapy and stem cell support shows no difference in overall survival or severe toxicity compared to maintenance chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil for women with metastatic breast cancer who are responding to conventional induction chemotherapy: The "Philadelphia" Intergroup Study (PBT-1) (abstract). Proc Am Soc Clin Oncol 18:1a, 1999.

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Powles TJ, Hickish TF, Makris A, et al: Randomized trial of chemoendocrine therapy started before or after surgery for treatment of primary breast cancer. J Clin Oncol 13:547–552, 1995.

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Valero V, Holmes F, Walters R, et al: Phase II trial of docetaxel: A new, highly effective antineoplastic agent in the management of patients with anthracycline-resistant metastatic breast cancer. J Clin Oncol 13:2886–2894, 1996.

Includes response and toxicity data on docetaxel in anthracycline-resistant disease, and highlights the premedications needed prior to docetaxel therapy.

CHAPTER 12

Esophageal cancer

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While still relatively uncommon in western countries, esophageal cancer is fatal in the vast majority of cases. An estimated 12,500 new cases will be diagnosed in the year 2000, and 12,200 deaths will result from the disease. This high percentage of deaths rivals that of pancreatic cancer and is more than four times that of rectal cancer.

The esophagus extends from the cricopharyngeal sphincter to the gastroesophageal (GE) junction and is commonly divided into the cervical, upper to mid-thoracic, and thoracic portions. This can be important, as histology and optimal treatment approaches may vary considerably based on the site of the cancer. It may not be possible to determine the site of origin if the cancer involves the GE junction itself.

Epidemiology

Gender Esophageal cancer is 2.7 times more common and slightly more lethal in men than in women.

Age The incidence of squamous cell cancer of the esophagus increases with age and peaks in the seventh decade of life. However, adenocarcinoma of the esophagus is now more common in the United States than the squamous cell type, with the greatest frequency in white males 40-50 years old.

Race The incidence of squamous cell esophageal cancer is three times higher in blacks than in whites, while adenocarcinomas are increasingly more common in whites.

Geography Evidence for an association between environment and diet and esophageal cancer comes from the profound differences in incidence observed in different parts of the world. Esophageal cancer occurs at a rate 20-30 times higher in China than in the United States. An esophageal "cancer belt" extends from northeast China to the Middle East.

Survival While the overall outlook for patients diagnosed with esophageal cancer has improved in the last 30 years, most patients still present with advanced disease and their survival remains poor. Between 1983 and 1990, only 25% of patients with esophageal cancer presented with localized disease.

Disease site The rate of cancer of the distal esophagus is about equal to that of the more proximal two-thirds. In general, squamous cell carcinoma

is found in the body of the esophagus, whereas adenocarcinoma predominates in lesions closer to the GE junction.

Etiology and risk factors

Cigarettes and alcohol Most cases of squamous cell carcinoma of the esophagus can be attributed to cigarette smoking or excessive alcohol intake. Furthermore, these two habits can act synergistically and produce very high relative risks in heavy tobacco and alcohol users.

Patients with squamous cell carcinoma of the esophagus have an increased incidence of second primary tumors of the head and neck and/or lung. These second primaries may be detected prior to, after, or at the time of diagnosis of the esophageal carcinoma. The association of these tumors may reflect a cancer "field" defect associated with smoking and alcohol use.

A population-based, case-control study from Sweden showed a strong, probably causal relationship between gastroesophageal reflux and esophageal adenocarcinoma *(Lagergron J, Bergstrom R, Lindren A, et al: N Engl J Med 340:825-831, 1999).*

Diet High-fat, low-protein, and low-calorie diets have also been shown to increase the risk of esophageal cancer. A common etiology may be exposure to nitrosamines, which has been proposed as a factor in the development of both squamous cell carcinoma and adenocarcinoma of the esophagus.

Barrett's esophagus and other factors Barrett's esophagus (adenomatous metaplasia of the distal esophagus), tylosis, Plummer-Vinson syndrome, and achalasia have also been associated with a higher-than-normal risk of developing esophageal cancer.

Signs and symptoms

Few esophageal cancers are diagnosed at an early stage, suggesting that symptoms do not alert the patient until the disease is advanced. This, along with the high incidence rate, is the justification for the screening procedures considered routine in parts of the world, such as China.

Dysphagia The most common presenting complaint is dysphagia, which generally is not noted until the esophageal lumen is narrowed to one-half to one-third of normal, due to its elasticity.

Weight loss is common and often significant (> 10% of total body weight).

Cough that is induced by swallowing is suggestive of local extension into the trachea with resultant tracheo-esophageal fistula.

Pain Patients who describe pain radiating to the back may well have extraesophageal spread. Supraclavicular or cervical nodal metastases may be appreciated on examination.

Hoarseness may be a sign of recurrent laryngeal nerve involvement due to extraesophageal spread.

Metastatic disease may present as malignant pleural effusion or ascites. Bone metastasis can be identified by pain involving the affected site or by associated hypercalcemia.

Screening and diagnosis

Routine screening for esophageal cancer is not generally practiced in western countries because the disease is relatively uncommon. Mass screening is appropriate in high-risk areas, such as China and Japan.

High-risk patients Individuals at increased risk for esophageal cancer, in whom close screening endoscopy or barium swallow is justified, include patients with Barrett's esophagus and patients diagnosed with squamous cell carcinoma at another site in the upper aerodigestive tract. Screening examinations also should be considered in immigrants from high-risk regions.

Endoscopic ultrasound (EUS) is a relatively new staging technique that complements information gained by CT. Specifically, depth of tumor invasion can be assessed more accurately by EUS than by CT. EUS also can detect local tumor recurrence at an early stage.

Endoscopy and barium x-rays The diagnosis of esophageal cancer in a patient presenting with any constellation of the symptoms described above revolves around the use of upper endoscopy or double-contrast barium x-rays. The advantage of endoscopy is that it allows for direct visualization of abnormalities and directed biopsies. Barium x-rays do not facilitate biopsies but are less invasive and also can identify small abnormalities.

Bronchoscopy should be performed to detect tracheal invasion in all cases of esophageal cancer except adenocarcinoma of the distal third of the esophagus.

CT scan Once a diagnosis has been established and careful physical examination and routine blood tests have been performed, a CT scan of the chest, abdomen, and pelvis should be obtained to help assess tumor extent, nodal involvement, and metastatic disease.

PET Numerous studies report the accuracy of PET scanning in determining the presence of metastatic disease, with sensitivity approaching 90% and specificity over 90%. As PET becomes more widely available, its use will probably become an important part of the preoperative evaluation of these patients.

Bone scan A bone scan should be obtained if the patient has bone pain or an elevated alkaline phosphatase level.

Pathology

Adenocarcinoma The incidence of esophageal adenocarcinoma involving the GE junction has risen 4%-10% per year since 1976 in the United States and Europe. As a result, adenocarcinoma is now the predominant

histologic subtype of esophageal cancer. The distal one-third of the esophagus is the site of origin of most adenocarcinomas.

Squamous cell carcinomas, previously the most common histologic subtype in the United States, occur most often in the proximal two-thirds of the esophagus. Squamous cell carcinoma is still the most prevalent histologic subtype worldwide.

Other tumor types Other, less frequently seen histologic subtypes include mucoepidermoid carcinoma, small-cell carcinoma, sarcoma, adenoid cystic carcinoma, and primary lymphoma of the esophagus. Occasionally, metastatic disease from another site may present as a mass in the esophagus.

Metastatic spread The most common sites of metastatic disease are the regional lymph nodes, lungs, liver, bone, adrenal glands, and diaphragm. Adenocarcinoma can also metastasize to the brain.

Staging and prognosis

Based on data demonstrating that the depth of penetration has important prognostic significance, the American Joint Committee on Cancer (AJCC) TNM staging system for esophageal cancer was changed from a clinical one (1983) to a pathologic one in 1997. Both the clinical and pathologic staging systems are shown in Table 1, as the curative approach may or may not be primarily an operative one.

The initial endoscopic biopsy specimens of 112 patients treated with fluorouracil (5-FU), cisplatin (Platinol), and concurrent radiation followed by esophagogastrectomy were subjected to immunohistochemical analysis. Markers studied included *p53*, HER-2/*neu*, and P-glycoprotein. The analysis suggested improved overall survival in patients whose tumors were HER-2/*neu*-positive (26.8 vs 14.5 months) and P-glycoprotein-*negative* (20.9 vs > 60 months) *(Harpole DH, Moore M-B, Aloia TA, et al: Proc Am Soc Clin Oncol 18:387a [abstract], 1999).*

Pathologic information obtained from an esophagectomy specimen is of significant prognostic importance. Immunohistochemical analysis of the initial biopsy specimen may also have prognostic relevance (see box). Clinical staging has also been shown to be of prognostic importance, particularly in patients managed with primary radiotherapy or chemoradiation.

EUS, mediastinoscopy, and laparoscopy are being used to clinically stage patients prior to treatment. CT is accurate in determining liver and abdominal node metastasis in 98% and 78% of cases, respectively. EUS correlates with final pathologic T- and N-stages in 85% and 75% of cases, respectively.

Histology and grade Neither histology nor grade has been shown to be of prognostic importance in esophageal carcinoma.

Other prognostic factors Patient age, performance status, and degree of weight loss are of prognostic importance. The prognostic implications of tumor-suppressor genes and oncogenes are an area of active investigation.

TABLE 1: 1983 and 1998 AJCC TNM staging systems for esophageal cancer

1983 Classification (clinical)				1997 Classification (pathologic)		
Primary tumor (T)						
Tis	Carcinoma in situ			Noninvasive		
T1	Tumor involves ≤ 5 cm of esophageal length, produces no obstruction, and has no circumferential involvement			Tumor invades lamina propria or submucosa		
T2	Tumor involves > 5 cm of esophageal length, causes obstruction, or involves the circumference of the esophagus			Tumor invades muscularis propria		
T3	Extraesophageal spread			Tumor invades adventitia		
T4	NA			Tumor invades adjacent structures		
Regional lymph nodes (N)						
NX	Regional nodes cannot be assessed			Same		
N0	No nodal metastases			No regional nodal metastasis		
N1	Unilateral, mobile, regional nodal metastases (if clinically evaluable)			Regional nodal metastasis		
N2	Bilateral, mobile, regional nodal metastases (if clinically evaluable)			Not applicable		
N3	Fixed nodes			Not applicable		
Distant metastases (M)						
M0	No distant metastases			Same		
M1	Distant metastases			Distant metastases		
				Tumors of lower thoracic esophagus: M1a Metastasis in celiac lymph nodes M1b Other distant metastasis		
				Tumors of mid-thoracic esophagus: M1a Not applicable M1b Nonregional lymph nodes and/or other distant metastasis		
				Tumors of upper thoracic esophagus: M1a Metastasis in cervical nodes M1b Other distant metastasis		
Stage grouping						
Stage I	T1	N0 or NX	M0	T1	N0	M0
Stage II	T2	N0 or NX	M0			
Stage IIA				T2-3	N0	M0
Stage IIB				T1-2	N1	M0
Stage III	T3	Any N	M0	T3 T4	N1 Any N	M0 M0
Stage IV	Any T	Any N	M1	Any T	Any N	M1
Stage IVA				Any T	Any N	M1a
Stage IVB				Any T	Any N	M1b

TABLE 2: Treatment options and survival by stage in esophageal cancer

Stage[a]	Standard treatment	5-Year survival rate (%)
Stage 0 (Tis N0 M0)	Surgery, radiation	> 90
Stage I (T1 N0 M0)	Surgery Chemoradiation	> 50
Stage IIa (T2-3 N0 M0)	Surgery Chemoradiation	15-30
Stage IIb (T1-2 N1 M0)	Surgery Chemoradiation	10-30
Stage III (T3 N1 M0 or T4 Any N M0)	Chemoradiation Palliative resection of T3a tumors	< 10
Stage IV (Any T Any N M1)	Radiation therapy ± intraluminal intubation and dilation ± chemotherapy	Rare

[a] According to the AJCC TNM system definitions (see Table 1)

Note: Surgical results are based on the pathologic staging system, while patients treated with combined-modality therapy or neoadjuvant chemoradiation are clinically staged.

Treatment

Treatment options for the various disease stages are given in Table 2, along with 5-year survival rates.

TREATMENT OF LOCALIZED DISEASE

Only 40%-60% of patients with esophageal cancer present with clinically localized disease. This group of patients have been treated predominantly with surgical resection as primary therapy. Even in these patients, however, resection often is not curative. The overall 5-year survival rate after surgery is between 5% and 20%, except in the rare patients with pathologic stage I disease, in whom 5-year survival can exceed 50%.

Chemoradiation as primary management of localized or locoregionally confined esophageal cancer has been shown to be superior to radiation alone. No randomized trial of chemoradiation vs esophagectomy as primary therapy has ever been completed; thus, both have been used as initial management of localized esophageal cancer.

Surgery

Preoperative evaluation helps determine the patient's risk of developing postoperative complications and mortality. In a study of 800 patients, a risk score was developed based on general status; pulmonary, hepatic, renal, and cardiac function; and tumor staging. Using those risk scores, the investigators were able to reduce 90-day mortality from 16% to 6% in the last 250 patients.

Patient selection The indications for esophagectomy in esophageal cancer are very controversial. The use of EUS has improved the staging of esophageal lesions, with better determination of the depth of tumor invasion.

Clearly, patients with distant metastases, evidence of nodal metastases in more than one nodal basin, or tumor extension outside of the esophagus (airway, mediastinum, vocal cord paralysis) are candidates for palliative surgery only, or are probably better treated with combined chemotherapy and radiation. Patients with disease limited to the esophagus and no evidence of nodal metastases (stages I and IIa) may be treated with esophagectomy, although these patients can also be considered for chemoradiation. Patients with disease limited to the esophagus and N1 disease (stage IIb) do not do well with esophagectomy alone.

Esophagectomy following chemoradiation Considerable controversy exists regarding the need for esophagectomy following chemoradiation. To date, no study has compared patients treated with chemoradiation alone vs those treated with chemoradiation followed by surgery. The incidence of residual disease in patients who have a complete response to chemoradiation is 40%-50%; half of these patients are long-term survivors, supporting the use of esophagectomy. CT and EUS findings correlate poorly with pathologic stage and response following chemoradiation (see "Chemoradiation" below).

A total of 199 patients (94% of whom had squamous cell carcinomas) underwent radical esophagectomy with three-field (cervical, mediastinal, and abdominal) lymphadenectomy. Tumors invaded at least to the submucosa, and patients had no evidence of nodal metastases. Mortality was 1.6%; 45% of patients developed vocal cord paralysis. Overall survival at 5 years was 78% for N0, 49% for N+ (1-4 nodes), and 6% for N+ (> 4 nodes) disease. There were no long-term survivors among patients with metastases in the three fields, metastases to > 5 nodes, or distal-third tumors with cervical lymph node metastases *(Nishimaki T, Suzuki T, Kuwabara S, et al: Am Coll Surg 186(3):306-312, 1998).*

Extent of resection The extent of the resection depends on the location of the primary tumor, histology of the tumor, and nature of the procedure (palliative vs curative). For tumors of the intrathoracic esophagus (squamous cell carcinomas) and tumors with extensive Barrett's esophagus (adenocarcinomas), it is necessary to perform a total esophagectomy with cervical anastomosis in order to achieve reasonable disease-free margins. For distal lesions of the abdominal esophagus (adenocarcinomas) and cardia, it is often possible to perform an intrathoracic esophageal anastomosis above the azygous vein, although many surgeons would prefer to perform a total esophagectomy.

The resected esophagus may be replaced with tubularized stomach in patients with tumors of the intrathoracic esophagus or with a colon interposition in patients with tumors involving the proximal stomach, since such involvement makes this organ unsuitable for esophageal reconstruction. The esophageal replacement is usually brought up through the posterior mediastinum, although the retrosternal route is often used in palliative procedures.

Method of resection Considerable controversy exists among surgeons regarding the method of resection. To date, two randomized studies have compared transhiatal esophagectomy (without thoracotomy) with the Ivor-Lewis (transthoracic) esophagectomy (with thoracotomy). These studies failed to show differences between the two procedures with regard to operative morbidity and mortality. The studies were too small to detect a difference in survival.

Lymphadenectomy Considerable controversy exists regarding the need for radical lymphadenectomy in esophageal disease. Much of the controversy is due to the fact that different diseases are being compared.

Japanese series include mostly patients with squamous cell carcinomas of the intrathoracic esophagus, with 80% of the tumors located in the proximal and middle sections of the esophagus. Americans report combined series, with at least 40%-50% of patients with distal esophagus adenocarcinomas. Skinner and DeMeester favor en bloc esophagectomy with radical (mediastinal and abdominal) lymphadenectomy, based on 5-year survival rates of 40%-50% in patients with stage II disease, as compared with rates of 14%-22% in historical controls.

To date, only one randomized study has compared a three-level lymphadenectomy (cervical, mediastinal, and abdominal nodes) vs a two-level procedure (mediastinal and abdominal nodes). In this 62-patient study, there was a significantly higher incidence of complications in the group undergoing a three-level dissection. The 5-year overall survival rates for the extended and conventional lymphadenectomy groups were 65% and 48%, respectively ($P = .19$) *(Nishiihira T, Hirayama K, Mori S: Am J Surg 175(1):47-51, 1998).*

In a retrospective study, Akiyama found a 28% incidence of cervical node metastases in patients with squamous cell carcinomas located in the middle and distal portions of the esophagus, as opposed to 46% in those with tumors of the proximal third. Overall survival at 5 years was significantly better in patients who underwent extended lymphadenectomy (three fields) than in those who had conventional lymphadenectomy (two fields); this was true in patients with negative nodes (84% and 55%, respectively) and in those with positive nodes (43% and 28%, respectively). Extended lymphadenectomy afforded no survival advantage in patients with tumors in the distal third of the esophagus.

In summary, radical lymphadenectomy may confer a survival advantage in patients with esophageal cancer. Cervical lymphadenectomy should be reserved for patients with squamous cell carcinoma of the proximal two-thirds of the esophagus.

Chemoradiation

Preoperative chemoradiation Initial trials of preoperative chemoradiation reported unacceptably high operative mortality (~ 26%). Subsequent trials reported 4%-11% operative mortality, median survival as long as 29 months, and 5-year survival rates as high as 34%. In general, 25%-30% of patients have no residual tumor in the resected specimen, and this group tends to have a higher survival rate than those who have a residual tumor discovered by the pathologist.

The superiority of preoperative chemoradiation over surgery alone in esophageal adenocarcinoma has been demonstrated in a prospective trial. This trial included 113 patients with adenocarcinoma of the esophagus. These patients were randomized either to preoperative chemoradiation (2 courses of 5-FU and cisplatin given concurrently with 40 Gy of radiotherapy in 15 fractions) or to surgery alone. Median survival was statistically superior in the combined-modality arm than in the surgery-alone arm (16 vs 11 months). Rates of 3-year survival again statistically favored the combined-modality arm (32% vs 6%). Toxicity was not severe.

A similar study in esophageal squamous cell carcinoma showed improved disease-free survival and a higher frequency of curative resection among patients treated with preoperative chemoradiation, but this did not alter overall survival, which was 18.6 months for both groups. This study used low total doses of split-course radiation.

Primary chemoradiation In light of the significant rate of complete pathologic response to moderately aggressive chemoradiation regimens administered preoperatively, the role of this treatment in a more intense form as primary management remains an area of active investigation.

In a nonrandomized, single-institution trial, patients with stage I or II cancers were treated with 60 Gy concurrent with 5-FU and mitomycin (Mutamycin). Median disease-specific survival duration was 20 months, with a 5-year actuarial disease-specific survival rate of 29%. Most patients had excellent preservation of swallowing function after treatment. Surgical resection as salvage was successful in patients with local failure only.

Randomized trials have demonstrated a survival advantage for chemoradiation over radiotherapy alone in the treatment of esophageal cancer. In a Radiation Therapy Oncology Group (RTOG) randomized trial involving 129 esophageal cancer patients, radiation (50 Gy) with concurrent cisplatin and 5-FU provided a significant survival advantage (27% vs 0% at 5 years) and improved local control over radiation therapy alone (64 Gy). Median survival also was significantly better in the combined-therapy arm than in the radiation arm (14.1 vs 9.3 months).

Numerous recently published phase I and II studies have demonstrated excellent response rates to chemoradiation regimens utilizing taxanes. Future trials will continue to explore these combinations.

Patient selection Patients with disease involving the mid- to proximal esophagus are excellent candidates for definitive chemoradiation. This is because resection in this area can be associated with greater morbidity than resection of more distal tumors.

Most of the trials demonstrating the efficacy of chemoradiation have had a high proportion of patients with squamous cell cancers. Chemoradiation has thus become a standard treatment for locoregionally confined squamous cell cancer of the esophagus. It is essential that chemotherapy be given concurrently with radiation when this approach is chosen as primary treatment for

esophageal cancer. A typical regimen is 50-60 Gy over 5-6 weeks with cisplatin (75 mg/m^2) and 5-FU (1 g/m^2/24 h for 4 days) on weeks 1, 5, 8, and 11.

The literature also supports offering patients with adenocarcinoma primary surgery, preoperative chemoradiation, or primary chemoradiation with surgical salvage if necessary. Entering these patients on protocols will allow us to further define standard treatment.

Radiotherapy

Radiotherapy alone is inferior to chemoradiation in the management of locoregionally confined esophageal cancer.

Preoperative radiotherapy has been shown to be of little value in converting unresectable cancers into resectable ones or in improving survival. However, it decreases the incidence of locoregional recurrence.

Postoperative radiotherapy (usually to 50 or 60 Gy) can decrease locoregional failure following curative resection but has no effect on survival.

Brachytherapy Intraluminal isotope radiotherapy (intracavitary brachytherapy) allows high doses of radiation to be delivered to a small volume of tissue. Retrospective studies suggest that a brachytherapy boost may result in improved rates of local control and survival over external-beam radiotherapy alone. This technique can be associated with a high rate of morbidity if not used carefully.

In an intergroup study, patients were randomized either to 3 cycles of 5-FU and cisplatin followed by esophagectomy or to esophagectomy alone. Median survival was 14.9 months in patients given preoperative chemotherapy vs 16.1 months in those treated with surgery alone, while the 2-year survival rates were 35% and 37%, respectively. There were no differences in survival between patients with squamous cell carcinoma or adenocarcinoma. Chemotherapy did not decrease the rate of locoregional or distant failure *(Kelsen DP, Ginsberg R, Pajak TK, et al: N Engl J Med 339:1979-1984, 1998).*

Preoperative chemotherapy

Of three small randomized trials comparing surgery alone with chemotherapy followed by surgery for esophageal cancer, only one study showed a significant improvement in survival rate in the chemotherapy arm among the subgroup of patients who responded. An intergroup randomized study of preoperative chemotherapy vs surgery alone involving over 440 patients showed no difference in median survival or 2-year survival between the two groups (see box). At present, therefore, preoperative chemotherapy should not be recommended outside of the context of a clinical trial.

TREATMENT OF ADVANCED DISEASE

As mentioned previously, the majority of patients with esophageal cancer present with locally advanced (extraesophageal spread) or metastatic disease. The goal of treatment in this group is generally palliative, as reports of long-term cure are rare. Therapeutic approaches should temper treatment-related morbidity with the overall dismal outlook.

Local treatment In patients with a good performance status, the combination of 5-FU, mitomycin, and radiotherapy (50 Gy) results in a median survival of

7-9 months. This regimen renders most patients free of dysphagia until death and produces few severe treatment-related complications.

Photodynamic therapy (PDT) Porfimer sodium (Photofrin) and an argon-pumped dye laser can provide effective palliation of dysphagia in patients with esophageal cancer. A prospective, randomized multicenter trial comparing PDT with neodymium/yttrium-aluminum-garnet (Nd:YAG) laser therapy in 236 patients with advanced esophageal cancer found that improvement of dysphagia was equivalent with the two treatments.

Other approaches include external-beam radiotherapy with or without intracavitary brachytherapy boost, simple dilatation, placement of stents, and laser recannulization of the esophageal lumen.

Chemotherapy Single-agent chemotherapy is rarely used. Agents with reported activity in esophageal carcinoma include bleomycin (Blenoxane), cisplatin, 5-FU, methotrexate, mitoguazone (methyl-GAG), mitomycin, paclitaxel (Taxol), vindesine (Eldisine), and irinotecan (CPT-11 [Camptosar]). Paclitaxel as a single agent has been reported to produce a 34% response rate in patients with esophageal adenocarcinoma and a 28% response rate in those with squamous cell carcinoma.

The most commonly used combination regimen for esophageal carcinoma has been 5-FU (usually administered at 750-1,000 mg/m^2/d as a continuous IV infusion for 4-5 days) combined with cisplatin (75-100 mg/m^2). A recent study combined paclitaxel with cisplatin and 5-FU. A total of 46 patients were treated, with an overall response rate of 44%.

Patients with advanced disease should be encouraged to participate in well-designed trials exploring novel agents and chemotherapy combinations.

Palliative resection for esophageal cancer is rarely warranted, although in some patients it does provide relief from dysphagia.

SUGGESTED READING

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Step-by-step guidelines from experts in the field for the work-up and treatment of carcinomas arising in the upper GI tract.

Al-Sarraf M, Martz K, Herskovic A, et al: Progress report of combined chemoradiotherapy vs radiotherapy alone in patients with esophageal cancer: An intergroup study. J Clin Oncol 15:277–284, 1997.

This multi-institution, prospective, randomized trial showed the superiority of primary therapy with 5-FU and cisplatin and concurrent radiation (50 Gy) over radiation alone (64 Gy) in patients with carcinoma of the thoracic esophagus.

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Use of a risk score helps reduce mortality from resection.

Block MI, Patterson GA, Sundaresan RS, et al: Improvement in staging of esophageal cancer with the addition of positron emission tomography. Ann Thorac Surg 64(3):770–776, 1997.

PET is superior to CT in the evaluation of distant metastases.

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Cooper JS, Guo MD, Herskovic A, et al: Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of a prospective randomized trial (RTOG 85-01). JAMA 281:1623–1627, 1999.

Updated results of an important study, showing superior results for chemoradiation over radiotherapy alone in locally advanced esophageal cancer.

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Excellent review of current controversies in the management of esophageal cancer from the perspective of a US surgeon.

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Kane JM, Shears LL, Ribeiro U, et al: Is esophagectomy following upfront chemoradiotherapy safe and necessary? Arch Surg 132(5):481–486, 1997.

This study on the results of esophagectomy following chemoradiation includes a good outline and review of the rationale for esophagectomy in patients with complete responses following chemoradiation.

Kelsen DP, Ginsberg R, Pajak TF, et al: Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 339(27):1979–1984, 1998.

This randomized study found no survival advantage of preoperative cisplatin and 5-FU chemotherapy over surgery alone in operable esophageal cancer.

Lagergron J, Bergstrom R, Lindgren A, et al: Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 340:825-831, 1999.

Case-control study from Sweden showing a strong, probably causal link between GE reflux and esophageal adenocarcinoma.

Laterza E, de Manzoni G, Guglielmi A, et al: Endoscopic ultrasonography in the staging of esophageal carcinoma after preoperative radiotherapy and chemotherapy. Ann Thorac Surg 67(5):1466–1469, 1999.

EUS correlates poorly with pathologic stage and response of esophageal cancer following chemoradiation.

Nesbitt J, Ajani JA, Komaki R, et al: Preoperative Taxol-based chemotherapy followed by chemoradiation therapy in patients with potentially resectable esophageal carcinoma (abstract). Proc Am Soc Clin Oncol 18:282a, 1999.

This phase I study suggests that preoperative treatment with paclitaxel, 5-FU, and radiotherapy may be a promising method of treating esophageal cancer.

Nishiihira T, Hirayama K, Mori S: A prospective randomized trial of extended cervical and superior mediastinal lymphadenectomy for carcinoma of the thoracic esophagus. Am J Surg 175(1):47–51, 1998.

Randomized trial comparing three- vs two-field lymphadenectomy in the treatment of squamous cell carcinoma of the esophagus.

Nishimaki T, Suzuki T, Kuwabara S, et al: Outcomes of extended radical esophagectomy for thoracic esophageal cancer. J Am Coll Surg 186(3):306–312, 1998.

Results of 190 patients with squamous cell carcinoma of the esophagus treated with three-field lymphadenectomy. Emphasis is given to indications and pitfalls.

Walsh TN, Noonan N, Hollywood D, et al: A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 335:462–467, 1996.

The authors of this prospective, randomized trial concluded that multimodality treatment was superior to surgery alone in patients with resectable adenocarcinoma of the esophagus.

CHAPTER 13

Gastric cancer

Steven R. Bonin, MD, Lawrence R. Coia, MD, Paulo M. Hoff, MD, and Roderich E. Schwarz, MD, PhD

Gastric cancer is more common than esophageal cancer in western countries but is less fatal. An estimated 21,900 new cases of gastric cancer will be diagnosed in the United States in the year 2000, with 13,500 deaths attributable to this cancer. The incidence of gastric cancer has decreased by approximately 60% between the 1930s and '70s. During the past 20 years, the incidence has remained relatively stable or has increased slightly.

Gastric cancer is defined as any malignant tumor arising from the region extending between the gastroesophageal (GE) junction and the pylorus. It may not be possible to determine the site of origin if the cancer involves the GE junction itself, a situation that has become more common in recent years.

Epidemiology

Gender Gastric cancer occurs more frequently in men, with a male-female ratio of 1.7:1. Once this cancer is diagnosed, however, mortality is approximately equal in the two genders.

Age The incidence of gastric cancer increases with age and peaks in the seventh decade of life.

Race Gastric cancer occurs 1.5 times more frequently in blacks than whites.

Geography Evidence for an association between environment and diet and gastric cancer comes from the profound differences in incidence seen in different parts of the world. Gastric cancer occurs nearly 10 times as frequently in Japan as in the United States.

Disease site The antrum and lower third of the stomach remain the predominant sites for gastric neoplasms. Proximal gastric cancers have become increasingly common, however. In fact, the increased incidence of proximal gastric adenocarcinomas and distal GE junction adenocarcinomas in young males suggests a possible common etiology.

Multicentricity is seen in up to 20% of gastric cancers.

Survival Most patients still present with advanced disease and their survival remains poor. From 1983 to 1990, only 17% of patients with gastric cancer presented with localized disease. The relative 5-year survival for gastric cancer of all stages is 21%.

Etiology and risk factors

Diet and environment Studies of immigrants have demonstrated that high-risk populations (eg, the Japanese) have a dramatic decrease in the risk of gastric carcinoma when they migrate to the West and change their dietary habits. Low consumption of vegetables and fruits and high intake of salts and nitrates have been associated with an increased incidence of gastric carcinoma.

Occupational exposure in coal mining and processing of nickel, rubber, and timber have been reported to increase the risk of gastric carcinoma.

Intestinal metaplasia, a premalignant lesion, is common in locations where gastric cancer is common, and is seen in 80% of resected gastric specimens in Japan.

Individuals with blood group A may have a greater risk of developing gastric carcinoma than do individuals with other blood groups. The risk appears to be for the infiltrative type of gastric carcinoma (rather than the exophytic type).

Helicobacter pylori infection has been associated with gastric lymphomas (see discussion of mucosa-associated lymphoid tissue [MALT] lymphomas in chapter 30) and with the occurrence of gastric adenocarcinomas. The infection may act as a contributing factor for gastric carcinogenesis, and *H pylori* has been designated a class I carcinogen *(Scheiman JM, Cutler AF: Am J Med 106:222-226, 1999).* The odds ratio for gastric cancer in *H pylori* infected patients varies, depending on age, between 9.29 and 1.05 *(Huang JG, Sridhas S, Chen Y, et al: Gastroenterology 114:1169-1179, 1998).* The prognostic relevance of *H pylori* infection for survival in gastric cancer patients has not been established.

Gastric resection Although reports suggesting that patients undergoing gastric resection for benign disease (usually, peptic ulcer disease) are at increased risk of subsequently developing gastric cancer, this association has not been definitely proven. Gastric resection may result in increased gastric pH and subsequent intestinal metaplasia in affected patients.

Pernicious anemia Although it has been widely reported that pernicious anemia is associated with the subsequent development of gastric carcinoma, this relationship also has been questioned.

Genetic abnormalities The genetic abnormalities associated with gastric cancer are still poorly understood. Abnormalities of the tumor-suppressor gene *p53* are found in over 60% of gastric cancer patients and the adenomatous polyposis coli *(APC)* gene in over 50%. The significance of these findings is not completely clear at present.

Signs and symptoms

Most gastric cancers are diagnosed at an advanced stage. Presenting signs and symptoms are often nonspecific and typically include pain, weight loss, vomiting, and anorexia.

Hematemesis is present in 10%-15% of patients.

Physical findings Peritoneal implants to the pelvis may be palpable on rectal examination (Blumer's shelf). Extension to the liver may be appreciated as hepatomegaly on physical examination. Nodal metastases can be found in the supraclavicular fossa (Virchow's node), axilla, or umbilical region. Ascites can accompany advanced intraperitoneal spread.

Screening and diagnosis

Routine screening for gastric cancer is generally not performed in western countries because the disease is so uncommon. Mass screening is appropriate in high-risk areas, such as Japan.

Endoscopy and barium x-rays The diagnosis of gastric cancer in a patient presenting with any constellation of the symptoms described above revolves around the use of upper endoscopy or double-contrast barium x-rays. The advantage of endoscopy is that it allows for direct visualization of abnormalities and directed biopsies. Barium x-rays do not facilitate biopsies but are less invasive.

Japanese investigators studied outcome parameters and clinicopathologic findings in patients who underwent resection for gastric carcinoma between 1969 and 1995. They separated patients into three "generation" groups: 1969-1977, 1978-1986, and 1987-1995. The investigators found a significant increase in the incidence of early-stage gastric carcinoma over time. This had a significant impact on the overall survival rate over the "generations." The 5-year survival rate in patients diagnosed with gastric cancer between 1969 and 1977 was 36%, as compared with a rate of 68.6% in those diagnosed between 1987 and 1995. The investigators also noted a general trend toward improved survival in patients with stage I, II, and III cancers over those time periods. This trial demonstrates the importance of effective screening measures in high-risk populations *(Kitamura K, Yamaguchi T, Sawai K, et al: J Clin Oncol 15:3471-3480, 1997).*

CT scan Once a diagnosis has been established and careful physical examination and routine blood tests have been performed, a CT scan of the chest, abdomen, and pelvis should be obtained to help assess tumor extent, nodal involvement, and metastatic disease. CT may demonstrate an intraluminal mass arising from the gastric wall or focal or diffuse gastric wall thickening. It is not useful in determining the depth of tumor penetration unless the carcinoma has extended through the entire gastric wall. Direct extension of the gastric tumor to the liver, spleen, or pancreas can be visualized on CT, as well as metastatic involvement of celiac, retrocrural, retroperitoneal, and porta hepatis nodes. Ascites, intraperitoneal seeding, and distant metastases (liver, lung, bone) can also be detected.

Endoscopic ultrasound (EUS) is a relatively new staging technique that complements information gained by CT. Specifically, depth of tumor invasion can be assessed more accurately by EUS than by CT. Furthermore, perigastric regional nodes are more accurately evaluated by EUS, whereas regional nodes further from the primary tumor are more accurately evaluated by CT.

Laparoscopy Laparoscopic staging procedures are being used more commonly. This is especially true in patients being considered for preoperative chemoradiation.

Bone scan A bone scan should be obtained if the patient has bone pain or an elevated alkaline phosphatase level.

Pathology

Adenocarcinoma is the predominant form of gastric cancer, accounting for approximately 95% of cases. Histologically, adenocarcinomas are classified as intestinal or diffuse; mixed types occur but are rare. Intestinal-type cancers are characterized by cohesive cells that form gland-like structures and are often preceded by intestinal metaplasia. Diffuse-type cancers are composed of infiltrating gastric mucous cells that infrequently form masses or ulcers.

Primary lymphoma of the stomach is increasing in frequency and, occasionally, may be difficult to distinguish from adenocarcinoma.

Other histologic types Infrequently, other histologic types are found in the stomach, such as squamous cell carcinomas, small-cell carcinomas, carcinoid tumors, and leiomyosarcomas. Metastatic spread from primaries in other organs (ie, breast and malignant melanoma) are also seen occasionally.

Metastatic spread Gastric carcinomas spread by direct extension (lesser and greater omentum, liver and diaphragm, spleen, pancreas, transverse colon); local, regional, and distant nodal metastases; hematogenous metastases (liver, lung, bone, brain); and peritoneal metastases.

Staging and prognosis

At present, gastric cancers are most commonly staged by the TNM system. The most recent update of this staging system (Table 1) allows for a more precise nodal classification based on the number of lymph nodes involved.

A more detailed Japanese staging system has been shown to have prognostic importance in gastric cancer. However, these results have not yet been duplicated in the United States, and this system is not widely used around the world.

Prognostic factors Aneuploidy may predict a poor prognosis in adenocarcinoma of the distal stomach. The prognostic implications of tumor-suppressor genes and oncogenes are an area of active investigation. Patients with cancers of the diffuse type fare worse than those with intestinal-type lesions.

Treatment

PRIMARY TREATMENT OF LOCALIZED DISEASE

Management of gastric cancer relies primarily on surgical resection of the involved stomach, with reconstruction to preserve intestinal continuity, as resection provides the only chance for cure. Radiotherapy and chemotherapy are currently being tested as adjuncts to surgery in patients with unresectable tumors and in individuals with locally advanced or disseminated disease. Preoperative chemoradiation is a very active area of current investigation.

TABLE 1: TNM staging system for gastric cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor with invasion of the lamina propria
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria or subserosa[a]
T3	Tumor penetrates the serosa (visceral peritoneum) without invasion of adjacent structures[b,c]
T4	Tumor invades adjacent structures[b,c]
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-6 regional lymph nodes
N2	Metastasis in 7-15 regional lymph nodes
N3	Metastasis in > 15 regional lymph nodes
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Stage grouping	
See Table 2	

Adapted from Fleming ID, Cooper JS, Henson DE, et al (eds): AJCC Cancer Staging Manual, 5th ed. Philadelphia, Lippincott-Raven, 1998.

[a] *Note:* A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified as T2. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified as T3.

[b] *Note:* The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

[c] *Note:* Intramural extension to the duodenum or esophagus is classified by the depth of greatest invasion in any of these sites, including the stomach.

Surgery

The objectives of operative treatment for potentially curable gastric cancers are: confirmation of resectability, performance of a complete resection, facilitation of appropriate pathologic staging, and reestablishment of GI continuity and function.

Confirmation of resectability Laparoscopy has emerged as an excellent tool to assess the extent of disease and resectability, before the surgeon performs an open laparotomy. Laparoscopy adds to the accuracy of preoperative imaging primarily in cases of peritoneal spread or small liver metastases. As a result, morbidity, hospital stay, and costs have been reduced significantly in patients with unresectable lesions.

The initial experience with laparoscopic ultrasonography has shown that its value lies in identifying lesions with a high risk of recurrence (T3-4), for which a preoperative chemotherapy protocol may be available.

Extended lymphadenectomies (D2 dissections or greater) have been associated with more precise staging, improved locoregional control, and enhanced survival in comparison to historical controls. Retrospective data had shown that D2 lymphadenectomies are safe and do not increase morbidity. In two recent European multicenter trials that compared limited (D1) with extended (D2) lymphadenectomy, higher postoperative morbidity and mortality occurred in the D2 group. This was largely related to a higher rate of splenectomy and/or partial pancreatectomy performed in association with the D2 dissections. The long-term survival in both studies showed no significant differences between D1 and D2 dissection groups *(Bonenkamp JJ, Hermans J, Sasako M, et al: N Engl J Med 340:908-914, 1999; Cuschieri A, Weeden S, Fielding J, et al: Br J Cancer 79:1522-1530, 1999)*. Since the improvement in survival after gastrectomy seen in larger western centers during recent decades was usually associated with the performance of extended lymph node dissections, this practice appears to be sensible if performed with acceptable complication rates *(Brennan MF, Karpeh M Jr: Semin Oncol 23:352-359, 1996)*.

Extent of resection The extent of gastric resection depends on the site and extent of the primary cancer. Subtotal gastrectomy is preferred over total gastrectomy, since it leads to comparable survival but lower morbidity. A 5-cm margin of normal stomach appears to be sufficient in proximal and distal resections. For lesions of the GE junction or the proximal third of the stomach, proximal subtotal gastrectomy can be performed. If a total gastrectomy is necessary, transection of the distal esophagus and proximal duodenum are required, and an omentectomy is performed.

Extent of lymphadenectomy The extent of lymph node resection at the time of gastrectomy continues to be controversial (see box). Preferably, lymphadenectomy includes the lymphatic chains along the celiac, left gastric, splenic, and hepatic arteries, which allows for more precise lymph node staging. This dissection of the second-echelon lymph nodes has been termed a D2 lymphadenectomy. Accordingly, a D1 dissection would include only the removal of pericardial or perigastric lymph nodes. The exact level designation of lymph nodes varies with the site and intragastric location of the primary tumor. Based on the new TNM staging criteria, 15 or more lymph nodes should be obtained and examined for an accurate N classification.

Reconstruction methods After a distal gastrectomy, a Billroth I gastroduodenostomy or, more commonly, Billroth II gastrojejunostomy is an appropriate method for reconstruction. Reflux esophagitis is a common problem when the gastric reservoir is too small. After total or subtotal gastrectomy, a Roux-en-Y esophagojejunostomy is commonly performed.

Resection of extragastric organs may be required to control T4 disease. Such a resection can be associated with long-term survival. Splenectomy should be avoided unless indicated by direct tumor extension, as it significantly increases the rate of complications.

NEOADJUVANT THERAPY

Prompted by the promising results and acceptable toxicity of preoperative (neoadjuvant) chemoradiation in other parts of the GI tract (ie, esophagus, rectum), there is growing interest in neoadjuvant therapy for gastric cancer. Neoadjuvant treatment may be done in an attempt to convert an initially unresectable cancer to resectable status, or it may be used in advanced but resectable disease.

Results of neoadjuvant therapy are preliminary but encouraging (see top box). Further randomized trials are needed to confirm the utility of preoperative chemoradiation in advanced gastric carcinoma.

A phase II study examined the toxicity of concurrent paclitaxel (Taxol) and radiotherapy in patients with T2-4, N0-3 adenocarcinoma of the stomach. In lesions that were subsequently deemed resectable, surgery was performed. Patients whose tumors remained unresectable received another cycle of paclitaxel and a radiotherapy boost (50.4 Gy total). The overall response rate was 63%, with acceptable toxicity *(Safran HJ, Wanebo PJ, Hesketh P, et al: Proc Am Soc Clin Oncol 18:273a, [abstract], 1999).*

ADJUVANT THERAPY

The 5-year survival rate after "curative resection" for gastric cancer is only between 30% and 40%. Treatment failure stems from a combination of local or regional recurrence and distant metastases. This has stimulated interest in adjuvant treatment in the hope of improving treatment results. Unfortunately, no form of adjuvant treatment has yet been convincingly demonstrated to alter the survival rates achieved with surgery alone for stage I-III gastric cancer (Table 2). This issue is being addressed in a large randomized trial, which was recently closed to patient accrual.

Radiotherapy

Patients with T3-T4 any N M0 tumors are at highest risk for locoregional recurrence after potentially curative surgery (surgery in which all macroscopic tumor has been resected with no evidence of metastatic disease) for gastric cancer. Even patients with node-negative disease (T3 N0) have a gastric cancer–related mortality of about 50% within 5 years. Mortality is significantly worse in node-positive patients.

A total of 38 patients with unresectable gastric cancer were treated with radiotherapy (median dose, 40Gy). Complications from the radiotherapy were minimal. Overall, the median survival was 9.5 months. Patients who underwent surgical resection at some point tended to have the longest survival *(Windham TC, Feig BW, Rich TA, et al: Proc Am Soc Clin Oncol 18:305a [abstract], 1999).*

The potential for patients with these adverse features to benefit from postoperative treatment has been evaluated in numerous trials. In general, these trials have demonstrated a local control advantage with the addition of radiotherapy or chemoradiation but not a survival advantage. Unfortunately, the trials probably had insufficient statistical power to demonstrate a survival benefit. Nevertheless, at many centers, postoperative

moderate-dose radiotherapy (45 Gy) in conjunction with fluorouracil (5-FU) chemotherapy is frequently used in patients with serosal involvement, positive margins, or positive nodes.

Chemotherapy

The role of adjuvant systemic therapy for gastric carcinoma after "curative resection" is still not clearly defined. Numerous prospective, randomized trials have been conducted in the United States and Europe, with contradictory results. Hermans et al, in a meta-analysis of 123 trials, 11 of which could be analyzed for crude mortality odds, showed no improvement in survival after adjuvant chemotherapy. However, at the 1998 American Society of Clinical Oncology (ASCO) meeting, Earle et al presented a reanalysis of the literature. Twelve trials met eligibility criteria to be included in this meta-analysis. A small survival benefit was seen in the group treated with adjuvant chemotherapy. At present, there is no definitive answer to this issue.

Thus, in the United States, it is appropriate to offer patients with resected gastric cancer who are at high risk of recurrence the option of either observation or adjuvant treatment, preferably in the context of a clinical trial. The risks of treatment, as well as the uncertainty regarding a survival benefit, must be discussed with patients beforehand.

TREATMENT OF UNRESECTABLE TUMORS

Patients with unresectable gastric cancers and no evidence of metastatic disease can be expected to survive 5-6 months without any treatment.

Palliative surgery Palliative resection or bypass may be appropriate for some patients with obstructive lesions. Palliative resection may also be suitable for patients with bleeding gastric cancers that are not resectable for cure.

Radiotherapy Radiation therapy alone can provide palliation in patients with bleeding or obstruction who are not operative candidates. Radiotherapy may convert unresectable cancers to resectable tumors (see boxes on previous page).

Chemoradiation Patients with locally advanced disease may be appropriately treated with chemoradiation. This can provide relatively long-lasting palliation and may render some unresectable cancers resectable.

In a phase II study conducted in Japan, the new oral fluorinated agent S-1 showed impressive activity against advanced gastric cancer. In the 28 patients treated with the drug, a response rate of 53.6% was reported, with modest toxicity *(Horikoshi N, Mitachi Y, Sakata Y, et al: Proc Am Soc Clin Oncol 15:206 [abstract], 1996).*

MEDICAL TREATMENT OF ADVANCED GASTRIC CANCER

When possible, all newly diagnosed patients with disseminated gastric cancer should be considered candidates for clinical trials. Even though neither survival prolongation nor cure are expected with chemotherapy, such treatment may provide palliation in selected patients and sometimes durable remissions.

TABLE 2: Treatment and survival by stage in gastric carcinoma patients

Stage			Treatment	5-Year overall survival rate[a] (%)
Stage 0 (in situ)			Surgery	> 90%
Tis	N0	M0		
Stage IA			Surgery	60%-80%
T1	N0	M0		
Stage IB			Surgery ± chemoradiation	50%-60%
T1	N1	M0		
T2	N0	M0		
Stage II			Surgery ± chemoradiation	30%-40%
T1	N2	M0		
T2	N1	M0		
T3	N0	M0		
Stage IIIA			Surgery ± chemoradiation	~ 20% (distal tumors)
T2	N2	M0		
T3	N1	M0		
T4	N0	M0		
Stage IIIB			Palliative chemotherapy, radiation therapy, and/or surgery, neoadjuvant chemoradiation	~ 10%
T3	N2	M0		
Stage IV			Same as for stage IIIB	< 5%
T4	N1-2	M0		
Any T	N3	M0		
Any T	Any N	M1		

Sources of data: American College of Surgeons Commission on Cancer and American Cancer Society

[a] Some US centers are reporting superior 5-year survival rates to those presented above. Confirmation of these results on a national level may be forthcoming.

Single-agent chemotherapy

Compared to other disease sites, the number of agents with established activity in gastric cancer is small. These have included 5-FU, cisplatin (Platinol), mitomycin (Mutamycin), etoposide, and the anthracyclines; 5-FU and cisplatin have been used most commonly. The responses seen with single-agent chemotherapy have been traditionally partial and mostly short-lived, with little, if any, impact on overall survival.

Recently, several new agents have demonstrated significant activity in gastric cancer. These include the taxanes; irinotecan (Camptosar); and S-1, the combination of tegafur chloro-2,4-dihydropyridine, and potassium oxonate. In Japan, S-1 has been reported to produce a response rate approximating 50% using Japanese gastric response criteria (see box on previous page).

Combination chemotherapy

Response rates are consistently higher when combination chemotherapy regimens are used in gastric cancer. Therefore, despite no demonstrated survival advantage, combination therapy has been generally preferred over single agents.

In the 1980s the combination of 5-FU, Adriamycin, and mitomycin (FAM) was considered the standard regimen in the treatment of advance gastric cancer. However, the North Central Cancer Treatment Group (NCCTG) randomly compared this regimen to 5-FU plus Adriamycin and single-agent 5-FU and found no difference in survival among the patients treated with the three regimens.

Several different regimens including FAMTX (5-FU, Adriamycin, and methotrexate), ECF (etoposide, carboplatin, and 5-FU), and ELF (etoposide, leucovorin, and 5-FU) have been tested. No combination has demonstrated superiority over any other regimen. The search for the optimal combination regimen continues, with the promising newer agents being introduced in combination regimens.

Gastric cancer patients should be encouraged to participate in well-designed clinical trials. Outside of experimental regimens, the recommended therapy for patients with good performance status is a 5-FU–or cisplatin-based regimen.

SUGGESTED READING

Ajani JA, Mansfield PF, Janjan P, et al: Preoperative chemoradiation therapy (CTRT) in patients with potentially resectable gastric carcinoma: A multi-institutional pilot (abstract). Proc Am Soc Clin Oncol 17:283a, 1998.

Preliminary results of this trial of neoadjuvant chemoradiation in gastric cancer are encouraging. Furthermore, at the time of publication, toxicity was acceptable, and no treatment-related deaths were reported.

Bonenkamp JJ, Hermans J, Sasako M, et al: Extended lymph node dissection for gastric cancer. N Engl J Med 340:908–914, 1999.

A large-scale, prospective, randomized, well-controlled Dutch trial comparing limited with extended lymphadenectomy at the time of gastrectomy for gastric cancer. Extended lymphadenectomy led to a significantly higher mortality and complication rate, due, in part, to a higher incidence of splenectomy and partial pancreatectomy. Survival and relapse rate were not significantly different. The accompanying editorial by Brennan (pp 956-958) is recommended.

Cushieri A, Weeden S, Fielding J, et al for the Surgical Cooperative Group: Patient survival after D1 and D2 ressections for gastric cancer: Long-term results of the MRC randomized surgical trial. Br J Cancer 79:1522–1530, 1999.

This British multicenter trial demonstrates higher complications after D2 lymphadenectomy but suggests the possibility of enhanced survival after D2 dissection when the survival analysis controls for splenectomy and pancreatectomy.

Kitamura K, Yamaguchi T, Sawai K, et al: Chronologic changes in the clinical pathologic findings and survival of gastric cancer patients. J Clin Oncol 15:3471–3480, 1997.

This retrospective review demonstrated the effectiveness of screening in the detection of earlier stages of gastric carcinoma over ~25 years in Japan. A significant increase in overall survival over the same time period was due primarily to malignancies being found at an earlier stage. Nonetheless, there seemed to be some effect of more modern treatment.

Lee KH, Lee JS, Lee M-S, et al: Prognostic value of DNA flow cytometry in stomach cancer: A five-year prospective study (abstract). Proc Am Soc Clin Oncol 17:263a, 1998.

DNA flow cytometry was performed on specimens from 217 patients treated for gastric cancer. High S-phase fraction (over 17%) was associated with inferior survival. Tumor ploidy status was not predictive of survival, however.

NCCN practice guidelines for upper gastrointestinal carcinomas. Oncology 12(11a):179–223, 1998.

Step-by-step guidelines for the work-up and treatment of carcinomas arising in the upper GI tract, from experts in the field.

CHAPTER 14

Pancreatic, neuroendocrine GI, and adrenal cancers

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PANCREATIC CANCER

Pancreatic cancer is the fifth leading cause of cancer death in the United States. In the year 2000, an estimated 28,600 new cases will be diagnosed, and 28,600 deaths will be ascribed to this cancer.

Incidence and epidemiology

Gender The incidence of pancreatic cancer is slightly higher in males than in females. These gender differences are most prominent among younger individuals.

Age The peak incidence of pancreatic carcinoma occurs in the seventh decade of life. Two-thirds of new cases occur in people > 65 years old.

Race Incidence is higher in the African-American population, with an excess risk of 30%-40% over whites. Perhaps more importantly, the African-American male probably has the highest risk of pancreatic cancer worldwide.

Survival Cancer of the pancreas is a highly lethal disease historically, with few reports of 5-year survivors. However, more recent series have shown a decrease in both operative mortality and overall morbidity. There has also been a significant increase in 5-year survival after curative resection (21%-25%). Factors that appear to be important in predicting long-term survival after resection include improved pancreatectomy technique, earlier detection, reduced perioperative mortality, and decreased blood transfusions.

Adenocarcinoma of the pancreas, the most common histologic type, has a median survival of 9-12 months and an overall 5-year survival rate of 3% for all stages. At the time of diagnosis, over four-fifths of patients with pancreatic adenocarcinoma have clinically apparent metastatic disease. Among patients whose disease is considered to be resectable, 80% will die of recurrent tumor within 2 years.

Etiology and risk factors

The specific risk factors for pancreatic cancer are not as striking as those for other GI malignancies, such as esophageal and gastric carcinomas. There does appear to be a significant relationship between pancreatic cancer and environmental carcinogens, however.

Cigarette smoking Cigarette smoke is one of the carcinogens directly linked to the causation of pancreatic malignancies. Heavy cigarette smokers have at least a twofold greater risk of developing pancreatic carcinoma than nonsmokers. In Japan, cigarette smoking carries an even greater risk, which can be as much as 10-fold in men consuming one to two packs of cigarettes daily.

N-nitroso compounds, found particularly in processed meat products, reliably induce pancreatic cancer in a variety of laboratory animals. No study has directly linked dietary carcinogens to pancreatic cancers in humans.

Caffeine The contribution of caffeine consumption to the development of pancreatic carcinoma is controversial. A case-control study showed a correlation between caffeine consumption and pancreatic cancer. However, other studies have been unable to confirm this relationship.

Alcohol Likewise, a clear-cut relationship between alcohol use and pancreatic carcinoma has not been clearly shown.

Diabetes does not seem to be a risk factor for pancreatic cancer. However, 10% of all patients with pancreatic carcinoma present with new-onset diabetes.

Genetic factors Cancer of the pancreas is a genetic disease. To date, more than 80% of resected pancreatic cancers have been found to harbor activating point mutations in K-*ras*. In addition, the tumor-suppressor genes *p16, p53,* and *DPC4* are all frequently inactivated in this cancer.

The National Familial Pancreas Cancer Registry has amassed data on over families with pancreatic cancer in two first-degree relatives connected by a person with any malignancy. When familial pancreatic cancer cases are compared to sporadic cases, age at onset is similar. The number of non–pancreatic cancer–associated malignancies, such as bladder, colon, lung, prostate, and breast cancers, and melanoma, is also similar in familial and sporadic pancreatic cancers. However, the risk of having first-degree relatives with pancreatic cancer is twice as high in the familial as in the sporadic group.

Familial pancreatic carcinoma has been associated with the following genetic syndromes: hereditary pancreatitis, ataxia-telangiectasia, hereditary nonpolyposis colorectal cancer (HNPCC), familial atypical mole-melanoma (FAMM) syndrome, Peutz-Jeghers syndrome, and familial breast cancer.

Families with *p16* germline mutations may be at higher risk for developing pancreatic cancer. In addition, there is interest in angiogenic factors as prognostic indicators. For example, survival may be decreased in pancreatic cancer patients with vascular endothelial growth factor *(VEGF)* gene expression.

Signs and symptoms

Early disease The initial clinical features of pancreatic carcinoma include anorexia, weight loss, abdominal discomfort or pain, and nausea. The nonspecific, vague nature of these complaints may delay diagnosis for several months.

Pain Specific symptoms usually relate to localized invasion of peripancreatic structures. The most common such symptom is pain, which stems from tumor invasion of the splanchnic plexus and retroperitoneum. This pain is described as severe, gnawing, and radiating to the mid or low back.

Jaundice In > 90% of cases, patients with pancreatic cancer present with epigastric or back pain and/or jaundice. True painless jaundice is unusual but does occur. Jaundice as a presenting symptom is most commonly related to compression of the common bile duct by tumors in the head of the pancreas.

GI symptoms Invasion of the duodenum or gastric outlet may give rise to nausea or vomiting as a presenting symptom. This is rare early in the course of the disease. Changes in bowel habits related to pancreatic insufficiency may also be present, along with associated steatorrhea.

Glucose intolerance Recent onset of glucose intolerance in an elderly patient associated with GI symptoms should alert the physician to the possibility of pancreatic carcinoma.

A palpable gallbladder occurring in the absence of cholecystitis or cholangitis suggests malignant obstruction of the common bile duct until proven otherwise. This so-called Courvoisier's sign is present in about 25% of all pancreatic cancer patients.

Other physical findings Other associated findings include Trousseau's syndrome (migratory superficial phlebitis), ascites, Virchow's node (left supraclavicular lymph node), a periumbilical mass (Sister Mary Joseph's node), or a palpable pelvic shelf on rectal examination (Blumer's shelf). These findings are usually indicative of distant metastases.

Screening and diagnosis

Early diagnosis of pancreatic carcinoma is difficult but is essential if surgical resection and cure are to remain possibilities. Defining early lesions at a resectable stage remains a diagnostic challenge.

Serum markers The use of serologic tumor markers for pancreatic carcinoma, such as CA19-9, was originally thought to be appropriate as a screening tool. However, since the prevalence of pancreatic carcinoma in the general population is extremely low (0.01%), many false-positive screening results are generated. Nevertheless, CA19-9 may be a useful marker for screening patients at high risk, such as men over the age of 60 years, smokers, African-Americans, or recent-onset diabetics. This marker also is useful in following disease and in assessing the adequacy of resection.

No currently available serum marker is sufficiently accurate to be considered reliable for screening asymptomatic patients.

Laparoscopy is useful for staging patients with pancreatic carcinoma and for formulating treatment plans. Approximately 25% of patients thought to have resectable disease are found at laparoscopy to have intra-abdominal disease that would preclude curative resection. The false-negative rate of laparoscopy is < 10%.

Peritoneal cytology also is being explored for the diagnosis of pancreatic carcinoma. Cytology is positive in ~ 15% of patients who are thought to have localized disease. However, the clinical/prognostic value of this test is not yet known.

Imaging techniques

Imaging for pancreatic carcinoma is best performed with conventional ultrasound and CT.

There is growing interest in the use of positron emission tomography with 2[18F]-fluoro-2-deoxy-D-glucose (18 FDG-PET) in the evaluation of patients with pancreatic cancer. This imaging modality may be useful in detecting small primaries and metastatic disease and in differentiating between cancer and pancreatitis.

Ultrasound The limit of sonographic resolution for early pancreatic carcinoma is a diameter on the order of 1-1.5 cm. A mass located in the pancreatic head will produce dilatation of the common bile duct. The actual sensitivity of ultrasonography in the diagnosis of pancreatic carcinoma is ~70%.

CT provides better definition of the tumor and surrounding structures than does ultrasonography and is operator-independent. CT correctly predicts unresectable tumors in 85% of patients and resectable tumors in 70% of patients. Findings of tumor unresectability on CT scanning include regional lymphadenopathy, encasement or occlusion of the superior mesenteric or celiac artery, portal vein involvement, liver metastasis, invasion of adjacent organs, or peritoneal spread.

Spiral CT More recently, spiral CT has emerged as a preferred technique for increasing the accuracy of detecting pancreatic carcinoma in general and vessel encasement in particular. This technique permits rapid data acquisition and computer-generated three-dimensional (3D) images of the mesenteric arterial and venous tributaries in any plane. Spiral CT is quicker and less expensive and uses less dye than angiography.

MRI At present, MRI is not as accurate as CT in diagnosing and staging pancreatic carcinoma.

Endoscopic ultrasound (EUS) is an important modality for the diagnosis of pancreatic carcinoma, with an overall diagnostic accuracy rate of approximately 90%. For the assessment of regional lymph node metastases, the accuracy of EUS is 50%-70%. This technique is also important in the evaluation of portal vein involvement by tumor. In addition, EUS-guided fine-needle cytology of periampullary tumors may yield new information with respect to the diagnosis of pancreatic cancer.

In a comparison of EUS and spiral CT, both techniques showed comparable efficacy in detecting tumor involvement of lymph nodes and the superior mesenteric and portal veins. However, EUS may be less helpful in the evaluation of the superior mesenteric artery.

Endoscopic retrograde cholangiopancreatography (ERCP) may someday be supplanted as a diagnostic tool by EUS, although, at present, ERCP is used in many clinics. Also, if a patient presents with jaundice and the CT scan reveals dilatation of the common bile duct without an obvious mass, ERCP may be complementary to spiral CT. ERCP findings of pancreatic cancer include an abrupt cutoff of both the main pancreatic and common bile ducts.

Magnetic resonance cholangiopancreatography (MRC) is being used to evaluate bile and pancreatic duct pathology. As yet, MRC is not a standard test for the diagnosis of pancreatic carcinoma, but it may become helpful in the future.

Pathology

Adenocarcinoma arising from the exocrine gland ductal system is the most common type of pancreatic cancer, accounting for 95% of all cases. Two- thirds of these cancers originate in the pancreatic head, and the remainder arise in the body or tail. Most ductal carcinomas are mucin-producing tumors and usually are associated with a dense desmoplastic reaction.

Although most pancreatic adenocarcinomas arise from the ductal epithelium, pancreatic acinar carcinomas and cystadenocarcinomas are also found.

Multicentricity, which is usually microscopic, is not unusual.

Metastatic spread Perineural invasion occurs in the majority of patients with pancreatic carcinoma. In addition, pancreatitis distal to and surrounding the tumor is usually present. Most patients present with lymph node metastases in the region of the pancreaticoduodenal drainage basins. Subpyloric and inferior pancreatic head lymph node groups also may be involved.

Staging and prognosis

Pancreatic adenocarcinoma is staged according to local spread, nodal status, and distant metastatic involvement using the American Joint Committee on Cancer (AJCC) TNM system (Table 1). The T-staging of the primary tumor includes an analysis of direct extension to the duodenum, bile duct, or peripancreatic tissues. In addition, a T4 advanced cancer may extend directly to any of the following: stomach, spleen, colon, or adjacent large vessels.

Independent prognostic factors Lymph node metastases and tumor size and differentiation each have independent prognostic value in patients with pancreatic carcinoma. Significantly improved survival is seen in patients with smaller lesions, lymph node–negative tumors, and well-differentiated lesions.

TABLE 1: TNM staging of pancreatic tumors

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the pancreas ≤ 2 cm in greatest dimension
T2	Tumor limited to the pancreas > 2 cm in greatest dimension
T3	Tumor extends directly into any of the following: duodenum, bile duct, peripancreatic tissues
T4	Tumor extends directly into any of the following: stomach, spleen, colon, adjacent large vessels
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
pN1a	Metastasis in a single regional lymph node
pN1b	Metastasis in multiple regional lymph nodes
Distant metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1-2	N0	M0
Stage II	T3	N0	M0
Stage III	T1-3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

Adapted from Fleming ID, Cooper JS, Henson DE, et al (eds): AJCC Cancer Staging Manual, 5th edition. Philadelphia, Lippincott-Raven, 1997.

Lymph node status In most series, lymph node metastases appear to be the most significant predictor of survival (Figure 1). Numerous authors have reported actuarial survival rates between 25% and 30% at 36 months for node-negative patients. In sharp contrast, the median survival of patients with positive lymph nodes is 6-8 months regardless of treatment.

Treatment

SURGICAL TREATMENT OF RESECTABLE DISEASE

The rate of resection for curative intent ranges from 10% to > 75%, with the higher percentage resulting from both a more aggressive approach and better preoperative staging for resectability. Also, there is growing evidence that patients with potentially resectable pancreatic cancer have a shorter hospital stay, reduced surgical mortality, and an overall better outcome if the surgery is performed at "high-volume" medical centers staffed by experienced surgeons (approximately 20 operable cases per year).

Determination of resectability

The initial approach to surgery for pancreatic carcinoma includes a determination of resectability. Careful examination of the liver, porta hepatis, and portal and superior mesenteric vessels is necessary. The head of the pancreas and uncinate process are mobilized by an extensive Kocher maneuver to evaluate the head of the pancreas. The pancreas is elevated away from the superior mesenteric and portal veins. The hepatic artery and celiac trunk are examined to make certain there is no vascular encasement.

Criteria for unresectability include metastases to the liver, peritoneal surface, Virchow's node, Blumer's shelf, and umbilicus. Involvement of the superior mesenteric and/or portal vein may preclude resection in some patients and for some surgeons. However, recent data suggest that patients with portal or superior mesenteric vein involvement alone may have overall survival to similar to that of patients without involvement of these veins.

A recent analysis of 200 patients who underwent resection of pancreatic adenocarcinoma found that the most important factors influencing long-term survival were the diameter of the primary tumor, status of the resected lymph nodes, and status of the resected margins. Patients with tumors < 3 cm in diameter had significantly longer median survival and 5-year survival rates (21 months and 28%, respectively) than those with tumors ≥ 3 cm (11.5 months and 15%). Patients with no lymph node involvement had a 5-year survival of 36%, as compared with < 5% for those with positive nodes. Patients who underwent resections with negative margins had a 5-year survival rate of 26% vs 8% for those with positive margins. The type of resection (pylorus-preservation vs standard Whipple procedure) did not influence survival *(Yeo CJ: Surg Clin North Am 1(7):143-155, 1998).*

Extent of resection

Whipple vs pylorus-preserving procedure If the tumor is deemed to be resectable, a standard pancreaticoduodenectomy (Whipple procedure) or pylorus-preserving Whipple procedure (PPW) is performed. The PPW theoretically eliminates the nutritional problems caused by a reduced gastric reservoir and gastric dumping. Some groups advocate PPW in all patients with pancreatic tumors, except those involving the duodenal mucosa.

Intraoperative biopsy Most patients with resectable periampullary tumors can successfully undergo pancreaticoduodenectomy without an intraoperative biopsy. A time-consuming frozen section interpretation may not be informative, and histologic confirmation may be impossible with small lesions associated with peritumor pancreatitis. Although fine-needle aspiration has been used by some surgeons, it has not been widely accepted as an intraoperative means of making the diagnosis of pancreatic cancer. Most large series of pancreaticoduodenectomy for carcinoma include resections of benign pathology based on clinical judgment. A negative fine-needle cytology should not deter an experienced surgeon from proceeding with resection.

Reconstruction technique The most common reconstruction technique after a Whipple resection requires a single retrocolic jejunal loop to complete the pancreaticojejunostomy, which is followed by a hepaticocholangiojejunostomy and gastrojejunostomy.

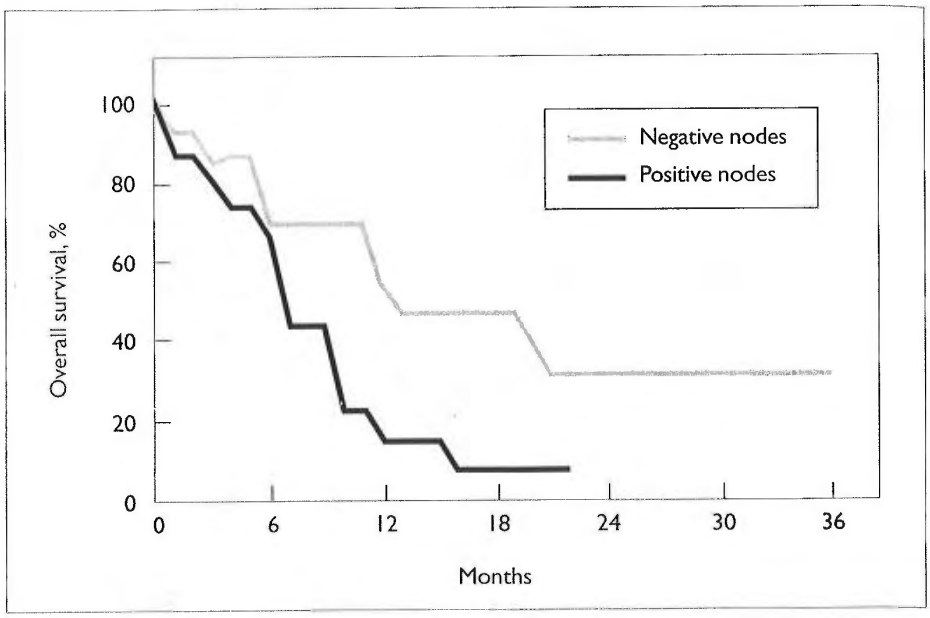

FIGURE 1: Actuarial survival as a function of regional lymph node status in patients with pancreatic cancer.

Postsurgical complications Operative mortality of pancreaticoduodenectomy is currently < 6% in major surgical centers. The leading causes of postoperative mortality include postoperative sepsis, hemorrhage, and cardiovascular events.

In many series, early delayed gastric emptying is the leading cause of morbidity. The number two cause of morbidity, seen in 5%-15% of all patients, is a leak or fistula from the pancreatic anastomosis. Today, most fistulas close spontaneously with the addition of somatostatin analog treatment. Pancreatic fistulas heal with conservative measures in approximately 80% of patients.

SURGICAL PALLIATION

Surgical palliation is also considered in patients undergoing exploration with curative intent. Jaundice, gastric obstruction, and pain may be alleviated by surgical palliation.

Biliary tract obstruction Either a choledochojejunostomy or cholecystojejunostomy can be used to bypass the biliary obstruction. Recurrent jaundice and cholangitis are less likely to develop when the common duct is used for decompression.

Duodenal obstruction Although duodenal obstruction is rare as a presenting symptom, duodenal involvement may occur eventually in 25% of patients. Some authors feel that prophylactic bypasses are safe and should be performed in all patients.

Pain relief Severe back pain may be an incapacitating symptom. Pain relief may be achieved by chemoablation of the celiac plexus or by alcohol injection, which may be performed intraoperatively or percutaneously. An intraoperative

injection of 25 mL of ethanol (95%) on both sides of the celiac axis will ablate tumor pain. (For further discussion of these techniques, see chapter 36 on pain management.)

NEOADJUVANT AND ADJUVANT THERAPY

Radiation therapy

Even with apparently adequate surgical resection, pancreatic cancer has a high risk of locoregional recurrence. Moreover, most lesions are unresectable even when there is no apparent distant metastatic disease. Thus, there is a theoretical rationale for the adjunctive use of radiation therapy, either before or after surgery, in almost all patients. Preoperative (neoadjuvant) radiation may help render locally advanced lesions resectable. Postoperative (adjuvant) radiation may help eliminate residual microscopic disease in the tumor bed and/or regional lymphatics.

A new Radiation Therapy Oncology Group (RTOG)/Southwest Oncology Group (SWOG)/Eastern Cooperative Oncology Group (ECOG) intergroup trial, the largest of its kind, is comparing infusional 5-FU to gemcitabine (Gemzar), both agents given before and after chemoradiation, in patients with resected pancreatic cancer. Radiation is being administered without a treatment break and is being given with continuous-infusion 5-FU in both arms. End points include quality of life, as well as survival.

The use of adjuvant radiation has been limited by concerns about potential morbidity, however. Since there is already a substantial risk of toxicity from surgery alone, it is important to demonstrate that adjuvant radiation is safe as well as efficacious. For the majority of patients who will succumb to their disease regardless of treatment, it is important that any adjuvant therapy used does not have too adverse an impact on quality of life.

The dose of external-beam radiation to the upper abdomen is limited by the tolerance of the small bowel and stomach. If a patient has undergone surgery, doses > 4,500-5,000 cGy can lead to a high risk of severe enteritis, bowel obstruction, or GI bleeding.

Given the limitations on radiation dose, most trials of adjuvant radiotherapy in pancreatic carcinoma have also included chemotherapy. If an effective chemotherapeutic agent can be found, there is a greater potential for adequate locoregional cytotoxicity—as well as control of subclinical distant disease—than could be obtained with limited doses of adjuvant radiation alone.

Preoperative chemoradiation Several single-institution studies have evaluated the role of preoperative radiation in conjunction with fluorouracil (5-FU)–based chemotherapy. In these studies, approximately 60% of the lesions were completely resected 1-1.5 months after the completion of chemoradiotherapy. An ECOG phase II trial of preoperative mitomycin (Mutamycin), 5-FU, and radiation resulted in disease resection in 24/53 patients with a median survival of 15.7 months. Preoperative radiation therapy, to 4,500-5,000 cGy, in conjunction with chemotherapy should be considered for patients with pancreatic adenocarcinoma who are medically fit but who have marginally resectable disease.

Postoperative chemoradiation A small Gastrointestinal Tumor Study Group (GITSG) trial demonstrated a significant prolongation of survival (median survival increase, 7-10 months) among patients with pancreatic adenocarcinoma who received radiation plus bolus 5-FU chemotherapy after curative resection, as compared with those given no adjuvant treatment. A possible improvement in the long-term cure rate also was observed among those given chemoradiation.

The GITSG study utilized 4,000 cGy of radiation delivered in a split-course fashion—with a planned 2-week break midway through the treatment. However, single-institution studies indicate that 4,500-5,000 cGy can be safely delivered in 5-5½ weeks without a treatment break.

The European Organization for Research and Treatment of Cancer (EORTC) recently completed a trial similar to that of the GITSG but without maintenance chemotherapy. Preliminary data suggest no significant difference between split-course radiation with bolus 5-FU and observation only after curative resection.

Careful attention to field size is important. The GITSG allowed portals as large as 20 × 20 cm. However, ports that are approximately 12 × 12 cm are usually sufficient to cover the tumor bed with a 2- to 3-cm margin. The use of multiple beams and high-energy photons is also important.

TREATMENT OF UNRESECTABLE DISEASE

Radiation can prolong and/or improve quality of life in some patients with unresectable adenocarcinoma of the pancreas. Long-term survival is, unfortunately, highly unusual. Median survival is approximately 6-10 months.

Chemoradiation The addition of chemotherapy to radiation therapy has been shown to improve the survival of patients with unresectable pancreatic adenocarcinoma, with moderate doses of radiation only slightly less effective than higher doses. In a GITSG trial of unresectable disease, moderate-dose radiation (4,000 cGy) with 5-FU chemotherapy significantly improved survival, as compared with higher doses of radiation (6,000 cGy) and no chemotherapy (median survival, 9.6 vs 5.2 months). The GITSG has also compared chemotherapy plus radiation with chemotherapy alone and demonstrated a significant improvement with combined-modality therapy (median survival, 42 vs 32 weeks).

Based on these data, except in a protocol setting, the palliative management of a patient with unresectable pancreatic adenocarcinoma should probably consist of moderate doses of radiation (4,000-5,000 cGy) in conjunction with 5-FU–based chemotherapy. As in adjuvant treatment, carefully shaped portals approximately 12 × 12 cm in size should be used.

Approaches under investigation At present, numerous trials are exploring a variety of chemoradiation approaches, including single-agent or combination therapy with oral or infusional 5-FU, cisplatin (Platinol), and gemcitabine. The dose of gemcitabine, when combined with radiation, is significantly lower than the standard 1,000-mg/m^2 dose because of concerns over toxicity. Combined-modality studies utilizing conformal radiation and hyperfractionated radiotherapy also are being conducted.

TREATMENT OF METASTATIC ADENOCARCINOMA

Pancreatic adenocarcinoma is still one of the most frustrating, resistant solid neoplasms to treat, and therapy for metastatic disease remains palliative. Few agents have demonstrated activity of > 10%. Moreover, most of the reported series have been small, and not all encouraging results have been duplicated.

Chemotherapy

As metastatic pancreatic carcinoma is incurable, the anticipated risks of chemotherapy, which are often substantial, must be balanced against the gains that may be achieved. Unfortunately, these are few. Patients who are debilitated due to their underlying or comorbid disease should not be offered chemotherapy, as their likelihood of deriving any benefit is exceedingly slim. However, patients who desire therapy and who, while symptomatic, still have a good performance status, may be offered "standard" chemotherapy or, if possible, should be encouraged to participate in a clinical trial.

5-FU Historically, single-agent 5-FU has been associated with a response rate of 25% in pancreatic cancer. FAM (5-FU, Adriamycin [doxorubicin], and mitomycin) and 5-FU plus doxorubicin offer no advantage over 5-FU alone. 5-FU plus leucovorin appears to be ineffective.

Gemcitabine is indicated for the treatment of locally advanced or metastatic pancreatic adenocarcinoma. Gemcitabine was compared to 5-FU in a group of 126 previously untreated patients, and showed a small, but statistically significant improvement in response rate. Median survival in the gemcitabine group was 5.7 months, with 18% of patients alive at 12 months, as compared with a median survival of 4.4 months in the group receiving 5-FU, with 2% of patients alive at 12 months. Perhaps more importantly, clinical benefit response (a composite measurement of pain, performance status, and weight) occurred in 23.8% of the gemcitabine-treated group, as compared with 4.8% of the 5-FU–treated group. Due to its palliative potential, gemcitabine has become the standard of care for patients with unresectable pancreatic adenocarcinoma.

A recent randomized, phase II trial of dose-intense gemcitabine administered by standard infusion vs a fixed dose rate (10 mg/m²/min) suggested an improved 1-year survival with the fixed dose rate *(Tempero M, Plunkett W, Ruiz van Haperin V, et al: Proc Am Soc Clin Oncol 18:273a [abstract], 1999).*

Promising combinations and single agents Promising combinations include cisplatin plus gemcitabine, cisplatin plus 5-FU, and irinotecan-containing combinations. The ECOG is conducting a randomized trial comparing gemcitabine with or without 5-FU. The investigational drug 9-nitro-20(S)-camptothecin-9NC (RFS 2000) has demonstrated significant activity in metastatic pancreatic adenocarcinoma and is under further evaluation in three randomized, phase III clinical trials.

Agents with marginal activity include mitomycin, doxorubicin, ifosfamide (Ifex), streptozocin (Zanosar), and docetaxel (Taxotere). To date, monoclonal antibody therapy and hormonal manipulation have also been ineffective.

Novel approaches A progressively better understanding of the molecular biology of pancreatic cancer has revealed numerous new therapeutic targets. Areas of active current research include attempts to replace tumor-suppressor genes (ie, *p53*) and to inhibit ras protein function.

A recent randomized trial comparing marimastat, a broad-spectrum matrix metalloproteinase inhibitor, to gemcitabine did not demonstrate any significant difference between the survival curves. Similarly, in randomized trials exploring the efficacy of the long-acting somatostatin analog, SMS 201-995 pa LAR (octreotide pamoate LAR), no significant activity was demonstrated.

ISLET-CELL TUMORS

Islet-cell tumors cover a spectrum of neoplasms, many, although not all, of which originate from the pancreatic islets of Langerhans. Rarely, some islet-cell tumors are found within the pancreas, notably, gastrinomas; the majority of these neoplasms arise from the proximal small bowel.

Islet-cell neoplasms are not rare. Autopsy studies have documented an incidence as high as 1.5%. Most of these lesions are clinically silent.

The normal islet contains α-, β-, and γ-cells, as well as enterochromaffin cells, which primarily secrete glucagon, insulin, somatostatin, and serotonin, respectively. All of these hormones may be secreted in excess by islet-cell neoplasms. Other hormones that may be secreted by these tumors include vasoactive intestinal peptide (VIP), gastrin, pancreatic polypeptide (PP), and calcitonin. The aggressiveness of an islet-cell lesion in terms of its metastatic potential appears to be due to the cell of origin.

Types of tumors

Insulinomas are β-cell tumors of the pancreatic islets that produce insulin. Four-fifths of insulinomas occur as a solitary lesion, and < 10% of these tumors demonstrate malignant potential (in terms of invasiveness or the development of metastases). In patients with the multiple endocrine neoplasia type 1 (MEN-1) syndrome, insulinomas are multicentric (10% of patients). In addition, a small group of insulinomas are associated with diffuse islet-cell hyperplasia or nesidioblastosis.

Approximately 20% of patients with ZES develop the syndrome in the setting of the MEN-I syndrome. MEN-I is inherited as an autosomal-dominant trait and is characterized by tumors of multiple endocrine organs, including the pituitary, pancreas, and parathyroid. The gene for MEN-I, which has been localized to the long arm of chromosome 11, was recently identified and named *MENIN*.

Gastrinomas are gastrin-secreting tumors associated with the Zollinger-Ellison syndrome (ZES). These tumors can be either sporadic or familial. Sporadic gastrinomas do not have associated endocrinopathies, whereas hereditary gastrinomas occur in patients with multiple endocrine adenopathy type 1 syndrome (MEA-1). Patients with the sporadic form of ZES may have single or multiple gastrinomas.

This contrasts with patients with hereditary MEA-1 islet-cell tumors, who generally have a more diffuse tumor process within the pancreas.

It is known that 80%-90% of gastrinomas are located within the "gastrinoma triangle," defined as the junction of (1) the cystic and common duct, (2) the second and third portion of the duodenum, and (3) the neck and body of the pancreas. Although tumors most characteristically are located within the pancreas, a significant percentage of patients with ZES demonstrate primary tumors of the duodenal wall. Extrapancreatic and extraintestinal locations occur in approximately 10% of patients.

More than 90% of gastrinomas are malignant. The spectrum of clinical progression includes localized tumors, regional lymph node metastases, and widespread metastatic disease.

Other types Approximately three-quarters of VIPomas and approximately half of all glucagonomas and somatostatinomas are malignant.

"Nonfunctional" tumors Although many islet-cell carcinomas cause considerable morbidity due to the inappropriately elevated levels of the hormones that they secrete, even "nonfunctional" islet-cell carcinomas, ie, those without an associated demonstrable hormone-related syndrome (such as PPomas, neurotensinomas, and nonsecretory islet-cell carcinomas), may be aggressive. Nonfunctional tumors account for up to 30% of all islet-cell carcinomas. Two-thirds of these nonfunctional tumors will demonstrate metastatic lesions at some point during the patient's lifetime.

Signs and symptoms

The symptom complex that is observed depends on which hormone or hormones are secreted in excess.

Insulinomas are associated with symptoms of recurrent hypoglycemia. Diagnosis of these tumors is made by the demonstration of inappropriately elevated levels of insulin, proinsulin, and C-peptide at the time of hypoglycemia.

Gastrinomas Symptoms of gastrinoma-ZES are due to the effect of elevated levels of circulating gastrin. Ulceration of the upper GI tract is seen in $>$ 90% of patients. Diarrhea is the second most common symptom. Approximately 25% of gastrinomas occur in the context of MEN-1 and are associated with parathyroid hyperplasia and hypercalcemia.

The diagnosis of ZES is established by the demonstration of hypergastrinemia (fasting serum gastrin concentration $>$ 1,000 pg/mL) and gastric acid hypersecretion in a patient with ulcer disease.

VIPomas VIP excess causes a profuse, watery diarrhea, hypokalemia, hypophosphatemia, and hypochlorhydria.

Glucagonomas are associated with a rash (described as a necrotizing migratory erythema), glossitis, cheilosis, constipation and ileus, venous thrombosis, and hyperglycemia. Not all of these manifestations are secondary to elevated glucagon

levels alone. The etiology of these signs and symptoms remains unknown, but some patients respond to supplemental zinc and amino acid infusions.

Somatostatinomas, which are quite rare, are associated with elevated blood glucose levels, achlorhydria, cholelithiasis, and diarrhea.

Tumor localization

Insulinomas Ultrasonography, CT, MRI, and selective arteriography with portal vein sampling have been utilized for the preoperative localization of insulinomas. The sensitivity of these preoperative imaging tests ranges from approximately 30% to 60%. This is because 40% of insulinomas are ≤ 1 cm and two-thirds of these tumors are < 1.5 cm.

In a study of 10 patients with insulinoma, EUS correctly identified the tumor preoperatively in 70% of patients. Current studies suggest that EUS has a sensitivity of 50%-75% and a specificity of 95% for imaging islet-cell tumors *(Thompson NW, Czako PF, Frith LL, et al: Surgery 116:1131-1138, 1994).*

Because the success of preoperative localization tests is disappointing and because 90% of these tumors will be found and successfully resected by an experienced endocrine surgeon, there is a general trend toward less testing. Some centers utilize preoperative ultrasonography if the patient has not undergone prior pancreatic surgery. Other centers still routinely employ portal vein catheterization and angiography.

More recently, intraoperative sonography has been shown to greatly aid the surgeon. In one series, 84% of tumors not localized preoperatively were correctly located by surgical exploration and intraoperative sonography. Many lesions not discovered by surgical palpation may be found by this technique. At present, there is much less reliance on blind distal resection than was previously advocated. Obviously, the technique of intraoperative ultrasonography may not be as helpful in the MEN-1 syndrome, in which multiple small insulinomas may be found.

Gastrinomas CT, ultrasonography, selective abdominal angiography, selective venous sampling of gastrin, intraoperative ultrasonography, endoscopic ultrasonography, and octreotide scans have all been reported to be helpful in localizing gastrinomas.

Treatment

Surgery for insulinomas

For larger insulinomas in the body or tail of the pancreas, a distal pancreatectomy may be preferable to enucleation. For tumors in the head of the pancreas, enucleation of the tumor is usually possible. Patients with MEN-1 or islet hyperplasia may benefit from an 80% distal pancreatectomy. If the insulinoma is not found at surgery, a blind pancreatectomy is not warranted. Further imaging and venous sampling studies may reveal the exact location of the tumor.

A surgical cure results in normal values on subsequent provocative testing, during which blood insulin and glucose concentrations are measured simultaneously. Some insulinoma recurrences actually represent persistent disease after incomplete tumor excisions or overlooked secondary multiple tumors.

Surgery for gastrinoma-ZES

The ideal treatment for gastrinoma-ZES is surgical excision of the gastrinoma. However, this is possible in only 20% of patients, most of whom have a sporadic tumor. With the development of effective antisecretory agents and preoperative localization with octreotide scanning, the majority of patients demonstrating gastrinoma metastatic to the liver can be identified and spared from surgical exploration. In addition, some series report that patients with nonmetastatic sporadic gastrinoma may have a greater incidence of extrapancreatic sites than was previously thought. One series has reported that two-thirds of gastrinomas are extrapancreatic.

Patients with sporadic gastrinoma All patients with sporadic gastrinoma should undergo localization studies and be considered for exploratory laparotomy, with the goal of potential cure of ZES. Recent evidence suggests that resection of primary gastrinoma decreases the incidence of liver metastases and ZES. Overall, surgery produces complete remission in approximately 60% of patients with sporadic ZES, and subsequent survival is excellent.

Patients with ZES and MEN-1 Some experts believe that surgery should not be used in the management of patients with MEN-1 and ZES. Instead, they recommend treatment with antisecretory medications. This is somewhat controversial, as some authors believe that all patients without demonstrated liver metastases should undergo surgery to remove duodenal and pancreatic gastrinomas.

Moreover, since many patients with ZES and MEN-1 die from metastatic gastrinoma at a young age, a surgical approach may be warranted. This should be performed only if imaging studies localize the tumor. Although radical surgery may not provide a cure, removal of large tumors may decrease metastatic potential and increase survival.

Surgical procedure At surgery, the entire pancreas should be mobilized and scanned with ultrasound to permit a thorough examination of the pancreatic head, duodenum, stomach, mesentery, liver, and splenic hilum. In general, enucleation is the treatment of choice, except for lesions within the duodenal wall, which may require pancreaticoduodenectomy. If no tumor is found, blind distal pancreatectomy should be avoided, since 90% of gastrinomas are located within the gastrinoma triangle.

Radiation therapy for islet-cell tumors

Adjuvant therapy The role of adjuvant radiation in the treatment of islet-cell carcinomas of the pancreas is unclear. Because of the rarity of these lesions and their often indolent behavior, the role of this therapy will probably never be demonstrated. However, postoperative radiation can be considered for patients with positive nodes or microscopically close margins. Concurrent

chemotherapy with such agents as 5-FU and/or streptozocin also can be considered. Radiation doses are the same as are used in adjuvant treatment of pancreatic cancer.

Palliative therapy Anecdotal reports indicate that pancreatic islet-cell tumors can respond to palliative doses of irradiation. Long-term control of unresectable disease has been reported.

Chemotherapy for islet-cell tumors

Islet-cell carcinomas are more sensitive to chemotherapy than carcinoid tumors.

Single agents Agents that have demonstrated antitumor activity include recombinant human interferon-alfa 2a and 2b (Intron A, Roferon-A), 5-FU, doxorubicin, dacarbazine (DTIC), streptozocin, and its newer analog chlorozotocin.

Combination regimens Combination chemotherapy is often more effective than monotherapy. For example, in an ECOG study, the combination of 5-FU and streptozocin demonstrated a higher response rate than streptozocin alone (63% vs 36%) in islet-cell tumors, as well as a better complete response rate (33% vs 12%) and median survival duration (26 vs 16.5 months). Doxorubicin plus streptozocin was superior to both 5-FU plus streptozocin and single-agent chlorozotocin in terms of response and survival and is the combination most widely used in the United States. Etoposide combined with cisplatin is active in poorly differentiated neuroendocrine malignancies but is marginally effective in well-differentiated lesions.

TREATMENT OF SYMPTOMS

Octreotide

Octreotide (Sandostatin) is often successful in palliating symptoms in patients with islet-cell carcinomas, although this depends somewhat on the cell type. For example, insulinomas are marginally responsive to octreotide, whereas gastrinomas and VIPomas often respond. However, compared with carcinoid tumors, the median duration of response of islet-cell neoplasms to octreotide is significantly shorter (~ 10 weeks).

As discussed more fully in the section on carcinoid tumors below, a promising experimental approach for patients whose tumors express somatostatin receptors is the use of octreotide conjugated to a therapeutic radioisotope.

Other agents

Omeprazole (Prilosec), an inhibitor of the function of the parietal cell hydrogen pump, is more effective than H_2-receptor antagonists in blocking gastric acid production and is useful in the symptomatic management of gastrinomas.

Other agents available for symptomatic treatment of insulinoma include diazoxide, an insulin-release inhibitor, and, more recently, glucagon by continuous infusion through a portable pump. Both of these agents are used in conjunction with frequent high-carbohydrate meals.

Patients with the glucagonoma syndrome are treated symptomatically with insulin, high-protein meals, supplemental zinc, amino acid infusions, and anticoagulants.

Hepatic arterial embolization

Hepatic arterial embolization, with or without chemotherapy (chemoembolization), is an alternative palliative therapy for patients with either carcinoid tumors or an islet-cell carcinoma who have predominant liver metastases or who are symptomatic. Embolization is best reserved for patients with $< 75\%$ tumor involvement of the liver, bilirubin < 2 mg/dL, and an ECOG performance status of ≤ 2.

CARCINOID TUMORS OF THE GI TRACT

Carcinoid tumors typically arise from components derived from the primitive gut and lung, and rarely, the gonads. Approximately 85% of all carcinoids originate from the gut, predominantly the appendix, followed by the small bowel and rectum.

These tumors have the propensity to cause considerable morbidity by virtue of creating a syndrome of hormonal excess. For example, while the majority of carcinoids are hormonally inert, these neoplasms may produce excessive amounts of serotonin (from dietary tryptophan), prostaglandins, kinins (secondary to kallikrein release), and a variety of other hormones, which may account for the "carcinoid syndrome."

Signs and symptoms

Flushing The most common sign of the carcinoid syndrome is flushing, which is often triggered by alcohol, catecholamines, or emotional stress. It ranges in severity from a minor annoyance to profound vasodilatation with near-syncope and hypotension.

Diarrhea is also common, and is due to GI hypermotility. It usually occurs after meals and is rarely voluminous, bulky, or foul-smelling.

Abdominal cramps Diarrhea may be associated with crampy pain, although other etiologies for the pain must be considered, including bowel obstruction due to tumor or mesenteric fibrosis.

Bronchospasm Patients may also develop bronchospasm, which may be mediated by histamine. This is often associated with (although less common than) flushing.

Valvular heart disease A late finding is right-sided valvular heart disease, although left-sided lesions may be noted occasionally. The fibrous deposits that form may lead to tricuspid insufficiency and/or pulmonary stenosis. Valve replacement is rarely necessary, however.

Symptom triad If there is sufficient shunting of dietary tryptophan from niacin to serotonin synthesis, patients may develop diarrhea, dermatitis, and dementia, although this symptom triad is quite rare if patients maintain adequate intake of a balanced diet.

Diagnosis

Diagnostic studies include CT/MRI of the abdomen and a 24-hour urine test for 5-hydroxyindoleacetic acid (5-HIAA). Some radiologists prefer to obtain a triple-phase CT scan of the liver to detect these highly vascular liver metastases.

Octreotide scanning [Indium-111]-octreotide scintigraphy (Octreoscan) has been shown to have a higher sensitivity for detecting pancreatic tumors and is superior to CT or MRI for detecting metastatic disease, particularly extrahepatic disease. One study suggests that [indium-111]-octreotide scintigraphy can reduce costs by avoiding unnecessary surgeries. Also, a positive scan may predict which patients may benefit from treatment with somatostatin analogs (eg, octreotide acetate). Initial studies with a new peptide tracer, [indium-111]-DOTA-lanreotide, suggest high tumor uptake and a more favorable dosimetry than is seen with [indium-111]-DTPA-D-Phel-octreotide.

Prognosis

Site and size of tumor The site of tumor origin is potentially prognostic, as most appendiceal carcinoids (75%) are < 1 cm when found and are usually cured by resection. Similarly, rectal carcinoids are usually small and completely resectable for cure.

In contrast, small bowel carcinoids tend to present at a more advanced stage, and approximately one-third have multicentric primary lesions. However, if the disease is completely resectable, patients have a 20-year survival rate of 80%; patients with unresectable intra-abdominal or hepatic metastases have median survival durations of 5 and 3 years, respectively.

Treatment

The management of carcinoid tumors focuses not only on treating the bulk disease, in common with other solid malignancies, but also on managing the complications of hormonal excess.

TREATMENT OF BULK DISEASE

Surgery

Appendiceal carcinoids For tumors that are found incidentally in the appendix and that are probably between 1 and 2 cm, appendectomy is the treatment of choice. For tumors > 2 cm, a right hemicolectomy and lymph node dissection are appropriate.

Small intestine and rectal carcinoids should be resected with a wedge lymphadenectomy to evaluate nodal disease.

Tumor debulking Liver resection or ablation of liver metastases with cryotherapy or radiofrequency techniques is useful in patients with limited extrahepatic disease and/or asymptomatic carcinoid syndrome. Tumor debulking can protect liver functional reserve and improve quality of life.

Liver transplantation may be of benefit in selected patients without extrahepatic disease whose disease progresses after other therapeutic interventions.

Radiation therapy

Carcinoid tumors are responsive to radiation and frequently are well palliated with this modality. Overall, treatment with higher radiation doses (29-52 Gy) has been associated with higher response rates (40%-50%) than have been seen with lower doses (10%).

Chemotherapy

Since carcinoid tumors tend to be resistant to most chemotherapeutic agents, there are no standard regimens for the treatment of unresectable tumors.

Single agents Agents that have reported activity include 5-FU, doxorubicin, and recombinant human interferon-alfa 2a and 2b. However, response rates with these agents are in the range of 10%-20%, responses are < 6 months in duration, and complete remissions are rare.

Combination regimens Combination chemotherapy regimens represent little improvement over single-agent therapy, with response rates ranging from 25% to 35%, response durations < 9 months, and rare complete remissions.

TREATMENT OF SYMPTOMS

Somatostatin analogs

Octreotide The most active agent is the somatostatin analog, octreotide acetate. Even though native somatostatin is effective in controlling many symptoms, due to its short half-life (< 2 minutes), this agent would have to be administered via continuous infusion to be clinically useful. However, octreotide may be administered subcutaneously every 8-12 hours, facilitating outpatient therapy. The initial dose of octreotide is 100-600 μg/d in 2-4 divided doses, although the effective dose varies between patients and must be titrated to the individual patient's symptoms.

Octreotide not only is useful in managing the chronic problems of the carcinoid syndrome but also is effective in treating carcinoid crisis (volume-resistant hypotension), which may be precipitated by surgery or effective antitumor treatment.

Octreotide is well-tolerated, although chronic treatment may be associated with cholelithiasis, increased fecal fat excretion, fluid retention, nausea, and glucose intolerance. Occasional objective antitumor responses have been observed in

patients who have received octreotide; the median duration of symptomatic improvement is 1 year. One report evaluating the cost-effectiveness of octreotide suggested that it may double survival time.

SMS 201-995 pa LAR is a long-acting somatostatin analog that allows for monthly dosing, avoiding the need for three daily injections. This new agent improves quality of life while apparently maintaining the same activity seen with daily octreotide. The usual monthly dose is 20 or 30 mg.

Somatostatin analog–radioisotope conjugates A promising experimental treatment approach involves the use of octreotide or other somatostatin analogs conjugated to therapeutic radioisotopes (eg, yttrium-90) in patients whose tumors express somatostatin receptors (eg, those with a positive [indium-111]-octreotide scintigram).

Other agents

Other agents that have been used for symptomatic management include H_1- and H_2-receptor antagonists, methoxamine (Vasoxyl), cyproheptadine, and diphenoxylate with atropine. The symptom complex of diarrhea, dermatitis, and dementia may be prevented or treated with supplemental niacin.

Hepatic arterial embolization

Hepatic arterial embolization with such agents as Ivalon or Gelfoam, with or without chemotherapy (chemoembolization), is an option for patients with either a carcinoid tumor or an islet-cell carcinoma who have predominant liver metastases or who are symptomatic. These lesions often are hypervascular, and thus, peripheral hepatic embolization may provide symptomatic relief in some patients. It is unclear whether this therapy has any effect on patient survival.

ADRENOCORTICAL CARCINOMA

Adrenocortical carcinoma is a rare, highly malignant neoplasm that accounts for about 0.2% of cancer deaths. Long-term survival is dismal overall; the survival rate is 23% at 5 years and 10% at 10 years.

Etiology

The etiology of adrenocortical cancer is unknown, but some cases have occurred in families with a hereditary cancer syndrome.

Signs and symptoms

Approximately half of adrenocortical neoplasms produce hormonal and metabolic syndromes of hormone hypersecretion (such as Cushing's syndrome, virilizing or feminizing syndromes, and hyperaldosteronism). In children, Cushing's syndrome is rare but is often due to adrenal carcinoma. Mixed syndromes, such as Cushing's syndrome and virilization, strongly suggest adrenal carcinoma. The combination of hirsutism, acne, amenorrhea, and rapidly

progressing Cushing's syndrome in a young female is a typical presentation. In men, estrogen-secreting tumors are associated with gynecomastia, breast tenderness, testicular atrophy, impotence, and decreased libido.

Often the diagnosis of adrenocortical carcinoma is not evident until the discovery of metastases or until the primary tumor becomes large enough to produce abdominal symptoms. Smaller tumors may be discovered incidentally when unrelated abdominal complaints are investigated radiographically.

Treatment

Surgery

Complete surgical resection is the treatment of choice in patients with localized disease, as it offers the best chance of extending the disease-free interval and survival.

Medical therapy

Mitotane (o,p'-DDD [Lysodren]) is one of only a few effective agents; it exerts a specific cytolytic effect on adrenocortical cells and has been used to treat unresectable or metastatic adrenocortical carcinoma. Only 15%-30% of patients experience objective tumor regression, with a median duration of about 7 months. Mitotane is given at a dose of 4-8 g/d as tolerated, although the dose is variable.

Chemotherapy Doxorubicin has been of benefit in a limited number of patients, and combination chemotherapy is under investigation.

Suramin, a sulfonated drug that is cytotoxic to human adrenocortical carcinoma cell lines, has been evaluated but has not proven useful in inoperable adrenocortical cancer. Innovative chemotherapy programs are clearly needed for this disease.

Controlling hormone hypersecretion Hormone hypersecretion can be controlled medically in most cases. Agents that are effective in reducing steroid production and in palliating associated clinical syndromes include the antifungal drug ketoconazole (Nizoral), 800 mg/d; aminoglutethimide (Cytadren), 1-2 g/d; and metyrapone (Metopirone), 1-4 g/d or higher as needed to control cortisol levels. These agents may be used alone or with mitotane.

PHEOCHROMOCYTOMA

Pheochromocytomas are catecholamine-secreting tumors that arise from chromaffin cells in the adrenal medulla or extra-adrenal sympathetic ganglia. These tumors constitute a surgically correctable cause of hypertension in 0.1%-1% of hypertensive persons.

Only about 10% of pheochromocytomas are considered to be malignant. The vast majority (90%) of pheochromocytomas are found in the adrenal medulla,

and 97% are located below the diaphragm. Approximately 10% each of pheochromocytomas are bilateral, malignant, multifocal, extra-adrenal, found in children, or associated with a familial syndrome.

Pheochromocytomas in patients with familial syndromes, such as MEN-2 and von Hippel–Lindau syndrome (VHL), are less likely to be malignant. In contrast, pheochromocytomas in patients with a family history of malignant pheochromocytoma are more apt to be malignant.

Epidemiology and etiology

Pheochromocytomas occur in all age groups, but incidence peaks in the third to fifth decades of life. Most pheochromocytomas (90%) are sporadic. Approximately 10% of cases are inherited as an autosomal-dominant trait, either independently or as a part of the MEN-2 syndrome; bilateral tumors are more common in this setting.

Both MEN-2A and MEN-2B include medullary thyroid carcinoma and pheochromocytoma. MEN-2A includes hyperparathyroidism, whereas MEN-2B includes ganglioneuromas and marfanoid habitus. In MEN-2 families, pheochromocytoma occurs in 5.5%-100% (mean, 40%), depending on the kindred studied. Bilateral medullary hyperplasia is almost always present. Pheochromocytomas are bilateral in 70% and usually multicentric, but they are rarely extra-adrenal or malignant.

Signs and symptoms

Patients can present with various symptoms, ranging from mild labile hypertension to hypertensive crisis, myocardial infarction, or cerebral vascular accident, any of which can result in sudden death. The classic pattern of paroxysmal hypertension occurs in 30%-50% of cases; sustained hypertension may also occur and resembles essential hypertension. A characteristic presentation includes "spells" of paroxysmal headaches, pallor or flushing, tremors, apprehension, palpitations, hypertension, and diaphoresis.

Diagnosis

The diagnosis of pheochromocytoma relies on an appropriate history and documentation of excessive catecholamine production.

Catecholamine measurements Measurement of 24-hour urinary catecholamines and their metabolites, vanillylmandelic acid and metanephrine, is commonly used; the metanephrine level is considered to be the most specific single test. Serum catecholamine measurements are more susceptible to false elevations due to stress-related physiologic fluctuations. The evaluation of serum catecholamines after clonidine suppression, however, provides a very useful diagnostic tool that is more convenient than urine collections. Dynamic provocative tests are very rarely indicated.

Radiologic studies Almost all pheochromocytomas are localized in the abdomen, mostly in the adrenal medulla; other locations include the posterior mediastinum or any distribution of the sympathetic ganglia. After the diagnosis is established biochemically, radiologic methods may be needed for preoperative localization of the lesion; CT and MRI are most widely used. Iodine methyl-iodobenzyl guanidine (MIBG) and somatostatin scintigraphy provide a "functional" image; they are most helpful in the detection of occult contralateral or extra-adrenal lesions.

Differentiating benign from malignant tumors The histologic differentiation between benign and malignant lesions is extremely difficult and often impossible to make; this distinction often requires the development of lymph node, hepatic, bone, or other distant metastases. Recurrent symptoms of pheochromocytoma, often emerging many years after the original diagnosis, are suggestive of malignancy. Biochemical confirmation of recurrent catecholamine hypersecretion and localization of metastatic lesion(s) with iodine-131-MIBG scan constitute diagnostic proof.

Treatment

PREOPERATIVE MEDICAL MANAGEMENT

Phenoxybenzamine (Dibenzyline), an oral, long-acting, noncompetitive α-adrenoceptor blocker, is a widely used, very helpful first drug; it is given at a dose of 10-40 mg/d. Propranolol, a β-blocker (20-80 mg/d), is usually added after a few days to prevent tachycardia or arrhythmias. The use of β-blockers alone is hazardous because they may precipitate a paradoxical rise in blood pressure. The tyrosine hydroxylase inhibitor metyrosine (Demser) may be added in patients whose blood pressure is not well controlled with the combination of an α-blocker and a β-blocker.

SURGERY

The principles of pheochromocytoma resection are complete tumor resection, avoidance of tumor seeding, and minimal tumor manipulation. Adrenalectomy can be performed by means of an open anterior transabdominal, open posterior retroperitoneal, laparoscopic lateral transabdominal, or laparoscopic posterior retroperitoneal approach. In the past, an open anterior approach was the standard because it allowed for complete exploration and inspection for potential tumor foci. However, with the improved accuracy of preoperative imaging and increased experience with laparoscopic procedures, there is little need for exploration in areas in which a tumor has not been identified.

In one of the largest series of laparoscopic adrenalectomy, the results in 67 patients were analyzed. The most common indication for lateral transabdominal laparoscopic adrenalectomy was pheochromocytoma. Conversion to open surgery was necessary in only one patient. The overall mean postoperative stay was 3 days. Indications for bilateral laparoscopic adrenalectomy included malignant pheochromocytoma *(Gagrer M: Surg Clin North Am 76(3):523-537, 1996).*

Except for tumors < 6 cm, the laparoscopic approach to pheochromocytoma is probably the technique of choice. In the absence of obvious local invasion or metastatic disease, a laparoscopic procedure is acceptable to many experienced endocrine surgeons.

The most critical intraoperative aspect of surgery is control of blood pressure immediately after removal of the tumor, when all agonistic effects are abolished and the effects of α- and β-blockers are still present. Close cooperation with the anesthesiologist to expand fluid volume and prepare the appropriate infusions of agonists to support vascular stability is critical.

TREATMENT OF METASTATIC MALIGNANT PHEOCHROMOCYTOMA

The treatment of choice for metastatic malignant pheochromocytoma remains problematic.

Medical and radiation therapy

Medical therapy with α- or β-blockers, as well as metyrosine, is almost always required to maintain hemodynamic stability. Chemotherapy utilizing streptozocin-based regimens or the combination of cyclophosphamide (Cytoxan, Neosar), vincristine, and dacarbazine has yielded promising responses. Treatment with iodine-131-MIBG or (in Europe) with radiolabeled somatostatin has met with only limited success. In most cases, uncontrolled catecholamine hypersecretion eventually escapes biochemical blockade, and fatal hypertensive crisis ensues.

Surgery

In those cases in which limited and resectable lesions can be identified, surgery can effect complete and lasting remission of the disease.

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CHAPTER 15

Liver, gallbladder, and biliary tract cancers

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HEPATOCELLULAR CANCER

Hepatocellular carcinoma is one of the most common malignancies in the world, with approximately 1 million new cases recorded annually.

Epidemiology

Gender Hepatocellular carcinoma is the most common tumor in males worldwide, with a male to female ratio of 4-7:1 in Asia and 2:1 in the United States.

Geography Tumor incidence varies significantly, depending on geographical location. In the United States, hepatocellular carcinoma represents < 2% of all tumors and has an incidence of 1-4 cases per 100,000 population, whereas in the Far East and sub-Saharan Africa, this neoplasm occurs at an incidence of 150 per 100,000 and comprises almost 50% of all diagnosed tumors.

Age The incidence of hepatocellular cancer increases with age. The mean age at diagnosis is 53 years in Asia and 62 years in the United States.

Race The incidence of hepatocellular tumors is higher in Asians and blacks. These racial differences are attributed to geographical differences in incidence.

Survival In patients with moderate to advanced cirrhosis, hepatocellular carcinoma is a lethal disease since these patients are not candidates for surgical resection. In patients who undergo curative resection, the 5-year survival rate is approximately 25%. Recurrence is common, with metastases arising in the remaining liver, lungs, bone, kidney, and heart. Untreated patients rarely live for more than 3-6 months.

Etiology and risk factors

Hepatitis B The close geographic relationship between hepatitis B incidence and hepatocellular carcinoma rates is well recognized. In endemic areas of hepatitis B, approximately 90% of all patients with hepatocellular carcinoma are positive for hepatitis B surface antigen (HBsAg). In addition, fragments of viral DNA are frequently found within the genome of the hepatocellular carci-

noma, although the sites of integration are not consistent and do not occur near any known oncogenes or tumor-suppressor genes. The most compelling evidence of a causal relationship between hepatitis B infection and hepatocellular carcinoma is the observation of a significant decline in the incidence of childhood hepatocellular carcinoma after the introduction of a national immunization program in Taiwan.

Hepatitis C has also been implicated in hepatocellular carcinoma development, although the lower rates of coexistent cirrhosis and viral DNA integration suggest alternate pathways of carcinogenesis.

Cirrhosis Worldwide, over 70% of hepatocellular tumors arise in cirrhotic livers, and the incidence is higher when the cirrhosis is due to hepatitis.

Other possible etiologies include aflatoxin, hemochromatosis, hepatic venous obstruction, thorotrast (a contrast agent no longer used for radiologic procedures), androgens, estrogens, and α_1-antitrypsin deficiency.

Signs and symptoms

Nonspecific symptoms Patients usually present with abdominal pain and other vague symptoms, including malaise, anorexia, weight loss, and jaundice.

Physical findings An abdominal mass is noted on physical examination in one-third of patients. Less common findings include splenomegaly, ascites, tenderness, muscle wasting, and spider nevi. Up to 10% of patients may present with an acute abdomen due to a ruptured tumor.

Screening and diagnosis

α-Fetoprotein is produced by 85% of hepatocellular carcinomas. The normal range for this serum marker is 0-20 ng/mL, and a level > 400 ng/mL is diagnostic for hepatocellular cancer. Levels between 20 and 400 ng/mL may represent either an exacerbation of hepatitis or the presence of a small, potentially curable tumor. Most symptomatic lesions are associated with α-fetoprotein values > 1,000 ng/mL. False-positive results may be due to acute or chronic hepatitis, germ-cell tumors, or pregnancy.

Hepatitis B and C Given the association between hepatitis B and C and hepatocellular cancer, blood should be sent for hepatitis B and C antigen and antibody determinations.

Ultrasound The initial diagnostic test in the symptomatic patient may be ultrasonography, as it is noninvasive, highly accurate, and can detect lesions as small as 1 cm. The diagnosis is nonspecific and the mass identified rarely can be documented as a hepatocellular carcinoma.

CT Comparative studies have found dynamic CT with portography to be superior to ultrasound, MRI, and angiography in detecting hepatocellular carcinoma. However, CT predicts resectability in only 40%-50% of cases and does not accurately determine the extent of cirrhosis.

Laparoscopy allows for the evaluation of small tumors, the extent of cirrhosis, peritoneal seeding, and the volume of noninvolved liver and, therefore, may be used prior to open laparotomy for resection. Laparoscopic or intraoperative ultrasound should be used to confirm preoperative imaging tests; results of the former studies may change surgical management in up to one-third of patients. This is particularly true in males over the age of 40.

High-risk patients Patients who are HBsAg carriers or who have chronic active hepatitis B or cirrhosis should be screened with an α-fetoprotein level every 4 months and ultrasound every 12 months.

Pathology

Three patterns of hepatocellular carcinoma have been described: nodular, diffuse, and massive. Diffuse and massive types account for > 90% of cases. The nodular type usually has multiple lesions in both lobes.

Histologic arrangements Several histologic arrangements have been identified: trabecular, compact, pseudoglandular or acinar, clear cell, and a fibrolamellar variant, which is associated with a more favorable prognosis.

Staging and prognosis

The staging system for hepatocellular cancer is based on the number and size of lesions and the presence or absence of vascular invasion (Table 1).

Of the 5%-30% of patients who can undergo resection, factors associated with improved survival include curative resection, small tumor size, well-differentiated tumors, and normal performance status. Cirrhosis, nodal metastases, and an elevated prothrombin time are indicative of a poor prognosis, as are male sex, age > 50 years, poor performance status, duration of symptoms < 3 months, tumor rupture, aneuploidy, high DNA synthesis rate, hypocalcemia, and high serum α-fetoprotein level.

Treatment

SURGERY

Surgery is the only form of treatment that offers the potential for cure, even though only a small minority of patients will actually be cured. Unfortunately, many patients whose disease is thought to be resectable are clinically understaged.

Only stage I or II tumors have a significant likelihood of being resectable for cure. A large tumor may still be potentially resectable, however. Moreover, contiguous involvement of large vessels (including the portal vein and inferior vena cava) or bile ducts does not automatically mitigate against a resection, especially in patients with a fibrolamellar histology, although such resections are considerably more difficult.

TABLE 1: TNM staging of liver and intrahepatic bile duct tumors

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤ 2 cm in greatest dimension without vascular invasion
T2	Solitary tumor ≤ 2 cm in greatest dimension with vascular invasion; or multiple tumors limited to one lobe, none > 2 cm in greatest dimension, without vascular invasion; or solitary tumor > 2 cm in greatest dimension without vascular invasion
T3	Solitary tumor > 2 cm in greatest dimension with vascular invasion; or multiple tumors limited to one lobe, none > 2 cm in greatest dimension, with vascular invasion; or multiple tumors limited to one lobe, any > 2 cm in greatest dimension, with or without vascular invasion
T4	Multiple tumors in more than one lobe, or tumor(s) involve(s) a major branch of the portal or hepatic vein(s), or invasion of adjacent organs other than the gallbladder, or perforation of the visceral peritoneum

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

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
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1-3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

Adapted from Fleming ID, Cooper JS, Henson DE, et al (eds): AJCC Cancer Staging Manual, 5th edition. Philadelphia, Lippincott-Raven, 1997.

Bilobar disease may be addressable with formal resection, tumor ablation techniques (eg, cryoablation, radiofrequency ablation, and ethanol injection ablation), or a combination of the two modalities.

Contraindications to resection include imminent clinical hepatic failure (jaundice in the absence of biliary obstruction), hypoalbuminemia, ascites, renal insufficiency, hypoglycemia, prolongation of the prothrombin and partial thromboplastin times, extrahepatic metastatic disease, or other comorbid diseases that would preclude surgery of any kind.

Noncirrhotic vs cirrhotic patients Resection should be performed in all noncirrhotic patients when feasible. Resection of hepatocellular carcinoma in the presence of cirrhosis is more controversial due to its increased morbidity in this setting. This has been a major deterrent to resection in western nations.

Resectability rates vary from 0% to 43% for cirrhotic patients, whereas up to 60% of patients without cirrhosis undergo resection. Use of the modified Child's classification aids in the selection of best-risk patients.

When resection is performed in the presence of cirrhosis, Child's class A patients fare better than Child's class B or C patients. Survival rates at 5 years following resection vary from 4% to 36%, with noncirrhotic patients living longer than cirrhotic patients.

Transplantation Due to the risk of hepatic failure following resection in cirrhotic patients, transplantation has become an option for patients with hepatocellular cancer and cirrhosis. In a study of 181 patients with hepatocellular carcinoma, Starzl and Iwatsuki found similar overall 5-year survival rates in patients treated with transplantation vs resection (36% vs 33%). Survival rates were similar in the two groups when tumors were compared for TNM stage. However, survival was significantly improved in patients with concomitant cirrhosis if they were treated with transplantation. Tumor recurrence rates for stage II and III tumors were significantly lower after transplantation than after resection, but no differences were seen for stage IV tumors.

Patients with cirrhosis and tumors < 5 cm can be treated with transplantation alone, while larger tumors may be treated with chemoembolization followed by transplantation.

NONRESECTIONAL THERAPIES

Given the high risk of recurrence after resection, the multifocal nature of hepatocellular carcinoma, and its association with chronic liver disease, nonresectional therapies can play an important role in management.

Radiation therapy

Adjuvant treatment Intrahepatic recurrence has been observed in up to two-thirds of patients treated with partial hepatectomy for hepatocellular carcinoma. Such a recurrence may represent growth at the resected edge, metastatic disease, or a new primary tumor. There is no evidence, however, that adjuvant radiation therapy can reduce this risk.

Unresectable disease Whole-liver radiation therapy can provide palliation in patients with unresectable tumors but is limited to a total dose of ≤ 30 Gy due to the risk of radiation-induced liver disease. Whole-liver radiation has been combined with chemotherapy, with an objective response rate of approximately 40%.

Radiation therapy has also been delivered using yttrium-90 microspheres infused via the hepatic artery. This approach has achieved an objective response rate of 50% and a median survival duration of 9.4 months.

There is recent evidence that three-dimensional conformal radiation therapy treatment planning can allow patients with nondiffuse disease to be safely irradiated to doses well above the whole-liver tolerance dose. In a pilot experience in which up to 72.6 Gy of conformal radiation was

delivered, the hepatic control rate was 50%, median survival time was 16 months, and the actuarial 4-year survival rate was approximately 20%.

Vascular ablation

As most patients with hepatocellular carcinoma have unresectable disease at presentation, dearterialization has been utilized in an attempt to downstage intrahepatic tumors and to palliate malignancies that are unresectable but symptomatic. The concept of depriving a hepatic tumor of its arterial supply is based on the observation that while the liver has two sources of vascular inflow (the portal vein and hepatic artery) and normal hepatocytes receive most of their blood supply from the portal vein, hepatocellular tumors derive nearly all of their influx from the hepatic artery.

Most patients, including those with extrahepatic disease, may undergo arterial embolization to palliate hemorrhage or tumor-related pain or to decrease tumor-related hormone production and paraneoplastic syndromes. Approximately two-thirds of patients will demonstrate some degree of tumor necrosis, and half will have an objective tumor response. Randomized studies will be necessary to determine what impact this therapy may have on patients with locally advanced hepatocellular cancer without extrahepatic spread.

Hepatic artery ligation, a surgical procedure in which the proper hepatic artery or a lobar branch distal to the takeoff of the gastroduodenal artery is ligated, is only temporarily effective, as collateral blood vessels usually form rapidly, often in less than a week. Thus, hepatic artery ligation or even more extensive dearterialization procedures have not demonstrated any impact on patient survival and are not routinely recommended.

Hepatic artery embolization Temporary dearterialization with hepatic arterial embolization has been developed as an alternative to arterial ligation. In this procedure, a percutaneous catheter is advanced as peripherally as possible within the hepatic artery. A variety of materials have been used, including starch, polyvinyl alcohol, iodized oil, Gelfoam, and collagen, none of which appears to be truly superior to the others at present. A randomized study of Lipiodol chemoembolization (an iodized oily agent given with cisplatin and Gelfoam) found reduced tumor growth in treated patients, but was associated with frequent acute liver dysfunction and no significant improvement in survival.

Although peripheral embolization does lead to collateral vessel formation, this occurs to a lesser extent than after hepatic artery ligation. Also, peripheral embolization produces a greater degree of tumor ischemia.

Chemoembolization Some embolizations have also included intra-arterial chemotherapy (ie, chemoembolization), based on the observation that embolization is associated with an increase in the area under the curve within the tumor bed for chemotherapy infused into the hepatic artery. However, there is no evidence that the addition of any chemotherapeutic agent is more effective than embolization alone.

Intratumoral ethanol injection

The direct injection of 95% ethanol into a neoplastic lesion causes cellular dehydration and coagulation necrosis. Intratumoral ethanol ablation may be employed via a percutaneous route under ultrasound guidance or via laparoscopic techniques. Other methods currently being developed include radiofrequency ablation with or without ethanol ablation. Percutaneous intratumoral ethanol injection is best suited for use in patients with few lesions, each < 5 cm, although larger lesions may be injected multiple times.

Selected patients with hepatocellular cancer may do well with intratumoral ethanol injection. However, malignant cells often survive in the periphery of the lesion, and this therapy cannot be used to treat tumors that are too small to be accurately detected by ultrasound. Thus, although intratumoral ethanol injection is an excellent palliative modality in certain patients, its effect on patient survival is unclear.

Chemotherapy

Systemic chemotherapy At present, there is no evidence that any systemically administered single chemotherapeutic agent or combination regimen reproducibly produces response rates > 20% in unselected patients with hepatocellular cancer. Moreover, systemic therapy has no effect on the rate or duration of survival.

Doxorubicin Although initial trials indicated that doxorubicin had significant activity in hepatocellular cancer, subsequent trials failed to confirm single-agent activity > 15%.

Other agents, such as etoposide (VePesid), cisplatin (Platinol), mitoxantrone (Novantrone), recombinant human interferon-alfa 2b or 2a (IFN-α [Intron A, Roferon-A]), or fluorouracil (5-FU) with leucovorin or epidoxorubicin (Epirubicin), have also been marginally effective as single agents.

Combination chemotherapy Thus far, no clear survival benefit of combination chemotherapy regimens has been documented.

5-FU–interferon A combination of 5-FU and recombinant human IFN-α produced a response rate of 18% in patients with small-volume, low–α-fetoprotein (< 50 ng/mL) hepatocellular carcinoma.

Hormonal manipulation with tamoxifen (Nolvadex) or ketoconazole (Nizoral) has been unrewarding. A recent large Italian study confirmed the lack of benefit of tamoxifen in this setting (see box).

A large, randomized, multicenter trial compared 1-year survival in patients with hepatocellular cancer treated with tamoxifen vs those given best supportive care. From January 1995 to January 1997, 496 patients were randomized in 30 institutions. Median survival was 16 months in the control group and 15 months in the tamoxifen-treated group. This trial effectively rules out tamoxifen as an alternative therapy for patients with hepatocellular *carcinoma (Pignata S, Izzo F, Farinati G, et al: Proc Am Soc Clin Oncol 17:257a [abstract], 1998).*

Intra-arterial chemotherapy In contrast to the lack of activity with systemic chemotherapy, intra-arterial chemotherapy reliably produces response rates of 30%-50%. Unfortunately, many, if not most,

trials involve embolization of some or all of the patients, making it difficult to determine the contribution of each modality to the reported patient responses.

Patients who may be offered intra-arterial chemotherapy should have unresectable disease that is limited to the liver and adequate hepatic and renal function. Drugs that have demonstrated activity when given intra-arterially include doxorubicin, cisplatin, mitomycin (Mutamycin), and the fluoropyrimidines, along with various combinations. No regimen is clearly superior at present.

BILIARY TRACT CANCERS

Malignancies of the biliary tract are uncommon in the United States, with approximately 8,000 cases reported annually; nearly two-thirds of these arise in the gallbladder, while the remainder (cholangiocarcinoma) originate from the bile ducts and periampullary region.

Gallbladder carcinoma is diagnosed approximately 5,000 times a year in the United States, making it the most common biliary tract tumor and the fifth most common GI tract cancer. Approximately 4,500 cases of bile duct tumors occur each year in the United States.

Epidemiology

GALLBLADDER CANCER

Gender Women are more commonly afflicted than men, with a female to male ratio of 2.7:1.

Age The median age at presentation of gallbladder cancer is 73 years.

Race An incidence five to six times that of the general population is seen in southwestern Native Americans, Mexicans, Hispanics, and Alaskans.

BILE DUCT CANCER

Gender Bile duct tumors are found in an equal number of men and women.

Age Extrahepatic bile duct tumors occur primarily in older individuals; the median age at diagnosis is 70 years.

Etiology and risk factors

GALLBLADDER CANCER

The risk of developing gallbladder cancer is higher in patients with cholelithiasis or calcified gallbladders and in typhoid carriers.

BILE DUCT CANCER

Ulcerative colitis is a clear risk factor for bile duct tumors. Patients with ulcerative colitis have an incidence of bile duct cancer that is 9-21 times higher than that of the general population.

Other risk factors Primary sclerosing cholangitis, congenital anomalies of the pancreaticobiliary tree, and parasitic infections are also associated with bile duct tumors. No association of bile duct cancer with calculi, infection, or chronic obstruction has been found.

Signs and symptoms

GALLBLADDER CANCER

Early disease In the early stages, gallbladder cancer is usually asymptomatic.

Late disease Later, symptoms similar to those of benign gallbladder disease arise; these include right upper quadrant pain, nausea, vomiting, fatty food intolerance, anorexia, jaundice, and weight loss. This nonspecificity of symptoms delays presentation for medical attention and contributes to the low curability of gallbladder cancer.

Physical findings may include tenderness, an abdominal mass, hepatomegaly, jaundice, fever, and ascites.

BILE DUCT CANCER

Jaundice is the most frequent symptom found in patients with high bile duct tumors; it is present in up to 98% of such patients.

Nonspecific signs and symptoms Patients who do not present with jaundice have vague complaints, including abdominal pain, weight loss, pruritus, fever, and an abdominal mass.

Diagnosis

GALLBLADDER CANCER

Gallbladder carcinomas are often diagnosed at an advanced stage, such that by the time symptoms have developed, most tumors are unresectable.

Laboratory values in patients with gallbladder carcinoma are nonspecific but may include anemia, leukocytosis, and an elevated bilirubin.

Ultrasound is useful for defining a thickened gallbladder wall and may show tumor extension into the liver.

CT is more helpful in assessing adenopathy and spread of disease into the liver, porta hepatis, or adjacent structures.

Endoscopic retrograde cholangiopancreatography (ERCP) or transhepatic cholangiography (THC) may be useful in the presence of jaundice to determine the location of biliary obstruction and involvement of the liver.

BILE DUCT CANCER

Cholangiocarcinoma may present earlier than gallbladder cancer by virtue of the development of biliary obstruction with jaundice, which may be

painless. The goals of the diagnostic evaluation include the determination of the level and extent of obstruction, the extent of local invasion, and the identification of metastases.

Many patients with cholangiocarcinoma are thought to have metastatic adenocarcinoma of an unknown primary, although occasionally the metastatic lesion may produce biliary dilatation without the primary lesion itself being radiographically visualized.

Ultrasound It is generally accepted that ultrasonography should be the first imaging procedure in the evaluation of the jaundiced patient.

CT is a complementary test to ultrasonography, but both tests are accurate for staging in only 50% of patients and for determining resectability in $< 45\%$.

Cholangiography is essential to determine the location and nature of the obstruction. Percutaneous transhepatic cholangiography (PTC) is used for proximal lesions and ERCP for distal lesions. Magnetic resonance cholangiopancreatography (MRCP) may replace invasive studies in the near future. Histologic confirmation of tumor can be made in 45%-85% of patients with the use of exfoliative or brush cytology during cholangiography.

Pathology

GALLBLADDER CANCER

Histologic types Over 85% of gallbladder neoplasms are adenocarcinomas and the remaining 15% are squamous cell or mixed tumors.

Route of spread The major route of spread of gallbladder cancer is locoregional rather than distant, with 25% of patients having lymphatic involvement and 70% having direct extension into the liver.

BILE DUCT CANCER

Adenocarcinoma Morphologically, more than 90% of bile duct tumors are adenocarcinomas. Three macroscopic appearances have been identified: The papillary and nodular types occur more frequently in the distal bile duct, whereas the sclerosing type is found in the proximal bile duct. Papillary lesions have the best prognosis.

Other histologic types Unusual malignant diseases of the biliary tract include adenosquamous carcinoma, leiomyosarcoma, and mucoepidermoid carcinoma.

Route of spread Most bile duct tumors grow slowly, spreading frequently by local extension and rarely by the hematogenous route. Nodal metastases are found in up to one-third of patients.

Staging and prognosis

GALLBLADDER CANCER

Gallbladder cancer is staged primarily at the time of surgery, and staging is determined by lymphatic involvement and extension into adjacent structures (Table 2).

Stage Survival of gallbladder carcinoma is directly related to disease stage. The 5-year survival rate is 83% for tumors that are confined to the gallbladder

TABLE 2: TNM staging of gallbladder cancer

Primary tumor (T)		
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ
T1		Tumor invades the lamina propria or muscle layer
	T1a	Tumor invades the lamina propria
	T1b	Tumor invades the muscle layer
T2		Tumor invades the perimuscular connective tissue; no extension beyond the serosa or into the liver
T3		Tumor perforates the serosa (visceral peritoneum), directly invades one adjacent organ, or both (extension ≤ 2 cm into the liver)
T4		Tumor extends > 2 cm into the liver and/or into two or more adjacent organs (stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts, any involvement of the liver)
Regional lymph nodes (N)		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in cystic duct, pericholedochal, and/or hilar lymph nodes (ie, in the hepatoduodenal ligament)
N2		Metastasis in peripancreatic (head only), periduodenal, periportal, celiac, and/or superior mesenteric lymph nodes
Distant metastasis (M)		
MX		Presence of distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis

Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1-3	N1	M0
	T3	N0	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

Adapted from Fleming ID, Cooper JS, Henson DE, et al (eds): AJCC Cancer Staging Manual, 5th edition. Philadelphia, Lippincott-Raven, 1997.

mucosa; this rate decreases to 33% if the tumor extends through the gallbladder. For patients who have involvement of the lymph nodes or metastatic disease, 5-year survival rates range from 0% to 15%.

Type of therapy Median survival is also improved in patients who have undergone a curative resection, as compared with those who have had palliative procedures or no surgery (17 months vs 6 and 3 months, respectively).

BILE DUCT CANCER

Over 70% of patients with cholangiocarcinoma present with local extension, lymph node involvement, or distant spread. The AJCC staging system for extrahepatic tumors is shown in Table 3.

Stage Survival for these patients is poor and is directly related to disease stage. Median survival is 12 months for patients with disease limited to the bile ducts and ≤ 8 months when the disease has spread.

TABLE 3: Staging of bile duct tumors

Primary tumor (T)		
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ
T1		Tumor invades the subepithelial connective tissue or fibromuscular layer
	T1a	Tumor invades the subepithelial connective tissue
	T1b	Tumor invades the fibromuscular layer
T2		Tumor invades the perifibromuscular connective tissue
T3		Tumor invades adjacent structures: liver, pancreas, duodenum, gallbladder, colon, stomach
Regional lymph nodes (N)		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in the cystic duct, pericholedochal, and/or hilar lymph nodes (ie, in the hepatoduodenal ligament)
N2		Metastasis in the peripancreatic (head only), periduodenal, periportal, celiac, and/or superior mesenteric and/or posterior pancreaticoduodenal lymph nodes
Distant metastasis (M)		
MX		Presence of distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis

Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1-2	N1	M0
	T1-2	N2	M0
Stage IVA	T3	Any N	M0
Stage IVB	Any T	Any N	M1

Adapted from Fleming ID, Cooper JS, Henson DE, et al (eds): AJCC Cancer Staging Manual, 5th edition. Philadelphia, Lippincott-Raven, 1997.

Tumor location Survival is also related to tumor location, with distal lesions doing better than mid or proximal tumors.

Success of therapy Curative resections and negative margins result in improved survival.

Treatment

Relatively few patients with gallbladder cancer are diagnosed prior to surgery, and only 1%-2% of cholecystectomy specimens are found to contain malignancy.

SURGERY FOR GALLBLADDER CANCER

Surgical management of gallbladder carcinoma is based on the local extension of the tumor.

Early-stage disease Tumors that invade the mucosa, those that do not penetrate the muscularis, and those that penetrate full thickness but do not abut the liver or muscularis require cholecystectomy alone. If there is direct extension to or through the serosa, the resection should include the gallbladder bed (segments IVb and V) and a porta hepatis lymphadenectomy. Patients with involvement of the gallbladder node are particularly curable and should be resected. Nodal disease beyond the pericholedochal nodes defines the surgically incurable patient.

SURGERY FOR BILE DUCT CANCER

The rate of resectability is 15%-20% for high bile duct tumors and up to 70% for distal lesions.

Assessing resectability Hepatic arteriography and portal venography or duplex imaging should be obtained preoperatively to assess resectability.

Preoperative treatments Three randomized trials have shown no benefit to preoperative decompression of the biliary tree in patients with obstructive jaundice. Some authors advocate the preoperative placement of biliary stents to facilitate dissection of the hilus. This should be performed immediately prior to resection to reduce the risk of cholangitis and maintain the duct at its maximally dilated size.

Proximal tumors Local excision is often possible for proximal lesions. Hepatic resection is indicated for high bile duct tumors with quadrate lobe invasion or unilateral intrahepatic ductal or vascular involvement. Resection is not indicated in situations in which a clear surgical margin cannot be obtained.

Mid-ductal and distal tumors Mid-ductal lesions can often be removed by skeletonization of the bile duct. Distal or mid-ductal lesions that cannot be locally excised should be removed by pancreaticoduodenectomy.

Reconstruction techniques Biliary-enteric continuity is usually reconstructed with a Roux-en-Y anastomosis for high lesions and with a jejunal loop after pancreaticoduodenectomy.

Liver transplantation has been attempted for unresectable tumors, but early recurrence and poor survival have prevented the widespread application of this approach.

Surgical bypass For patients found to have unresectable disease at surgical exploration, operative biliary bypass may be performed using a variety of techniques. Bypass results in excellent palliation and obviates the need for further intervention.

ADJUVANT RADIATION THERAPY FOR BILIARY TRACT CANCER

Local recurrence after cholecystectomy for gallbladder cancer has been reported to occur in 86% of patients, who die within 5 years after surgery. Resected bile duct tumors have a 25% to 40% rate of local recurrence.

Despite these observations, there are no good prospective data to define the role of adjuvant treatment with radiation or chemoradiation. Given the role of adjuvant chemoradiation in pancreatic cancer, it would seem reasonable to recommend similar therapy for patients with resected biliary tract cancer if transmural invasion is present or the regional lymph nodes are involved.

TREATMENT OF UNRESECTABLE DISEASE

Like pancreatic adenocarcinoma, unresectable biliary tract carcinoma has a poor prognosis.

Stenting

Patients whose disease is deemed unresectable on preoperative evaluation should undergo percutaneous or endoscopic stenting.

Radiation therapy

There are little data on radiation therapy for unresectable gallbladder cancer, other than reports of intraoperative radiation therapy. External-beam radiation therapy would be anticipated to provide a palliative benefit.

There is considerable experience using brachytherapy alone or combined with external-beam radiation for unresectable bile duct tumors. Median survival times range from 10 to 24 months and 5-year survival rates are approximately 10% with these approaches.

Chemotherapy

Due to the relative infrequency of biliary tract malignancies, only a limited number of clinical trials that describe chemotherapy regimens for advanced disease have been published. However, drug activity in these cancers appears to be similar to that in adenocarcinoma of the pancreas. Clearly, additional trials with larger numbers of patients are required to establish a role for chemotherapy in this disease.

5-FU appears to be the most active single agent, although response rates are on the order of 10%-15%, and there are no published reports of either prolonged infusional administration or modulation of 5-FU as a single agent.

Gemcitabine (Gemzar) shows promise as a new agent in the treatment of biliary tract cancers. In a recent phase II trial, 7 out of 19 patients had an objective response to gemcitabine therapy. Additional controlled trials of this agent are needed.

Other agents that have reported activity in biliary tract cancer are mitomycin, doxorubicin, and the nitrosoureas, although the numbers of patients are too small to reliably assess the rate of response.

Combination regimens Reports of combination chemotherapy regimens are likewise hampered by small numbers. The FAM (5-FU, Adriamycin, and mitomycin) regimen, as designed for gastric cancer, produced responses in 4 of 13 patients, while the combination of the 5-FU prodrug tegafur (Ftorafur), doxorubicin, and carmustine (BCNU [BiCNU]) produced responses in 3 of 7 patients.

More recent trials have involved larger numbers of participants. The combination of 5-FU, leucovorin, and mitomycin resulted in objective responses in 5 of 20 patients and produced stable disease in another 6 patients. The regimen was generally well tolerated but needs further study.

Another study combining a continuous infusion of 5-FU with cisplatin produced 6 partial remissions out of 24 patients, 1 of whom was still alive 6 years after the initiation of therapy.

Hepatic arterial chemotherapy There is limited experience with hepatic arterial chemotherapy for locally advanced or metastatic biliary tract disease.

Treatment recommendations In the absence of a clinical trial, patients should be offered 5-FU, with or without leucovorin. Other agents, such as doxorubicin, may be added, but, as noted, there is no evidence that combination chemotherapy produces any substantial benefits in terms of improving a patient's quality of life or survival.

SUGGESTED READING

ON HEPATOCELLULAR CARCINOMA

Allgaier HP, Deibert P, Blum HE, et al: Survival benefit of patients with inoperable hepatocellular carcinoma treated by a combination of transarterial chemoembolization and percutaneous ethanol injection–a single center analysis including 132 patients. Int J Cancer 79(6):601–605, 1998.

This group prospectively analyzed the clinical factors determining the prognosis of 132 patients with inoperable hepatocellular carcinoma and assessed the feasibility, therapeutic efficacy, and safety of percutaneous ethanol injection, transarterial chemoembolization, and a combination of the two. Multivariate analysis revealed that patients treated with the combination of transarterial chemoembolization and ethanol injection have a significantly better survival than patients receiving either PEI or TACE alone ($P = .001$).

Lai ECS, Fan ST, Lo CM, et al: Hepatic resection for hepatocellular carcinoma: An audit of 343 patients. Ann Surg 221:291–298, 1995.

A review of a 22-year experience resecting hepatocellular carcinoma in 343 patients. Improvements in morbidity, mortality, and survival rates over time are due to recent changes in the management strategy and technological advances.

Liu CL, Fan ST: Nonresectional therapies for hepatocellular carcinoma. Am J Surg 173(4):358–365, 1997.

Percutaneous ethanol injection and transarterial chemoembolization result in 3-year survival rates of 55%-70% and about 20%, respectively, according to this extensive review.

Patt YZ, Charnsangavej C, Yoffe B, et al: Hepatic arterial infusion of floxuridine, leucovorin, Adriamycin, and cisplatin for hepatocellular carcinoma: Effects of hepatitis B and C viral infection on drug toxicity and patient survival. J Clin Oncol 12:1204–1211, 1994.

Although this is an active regimen, this study illustrates the enhanced toxicity of chemotherapy in patients who are positive for hepatitis B or C.

Robertson JM, Lawrence TS, Andrews JC, et al: Long-term results of hepatic artery fluorodeoxyuridine and conformal radiation therapy for primary hepatobiliary cancers. Int J Radiat Oncol Biol Phys 37:325–330, 1997.

The combination of three-dimensional conformal radiation therapy (to doses of 48-72.6 Gy) and hepatic artery chemotherapy was associated with a median survival of 16 months and an actuarial 4-year survival rate of about 20% in patients with nondiffuse unresectable hepatobiliary cancer.

Tzoracoleftherakis EE, Spiliotis JD, Kyriakopoulou T, et al: Intra-arterial vs systemic chemotherapy for nonoperable hepatocellular carcinoma. Hepatogastroenterology 46(26):1122–1125, 1999.

Ernst O, et al: Treatment of hepatocellular carcinoma by transcatheter arterial chemoembolization: Comparison of planned periodic chemoembolization and chemoembolization based on tumor response. Am J Roentgenol 172(1):59–64, 1999.

Seno H, Ito K, Kojima K, et al: Efficacy of an implanted drug delivery system for advanced hepatocellular carcinoma using 5-fluorouracil, epirubicin, and mitomycin C. J Gastroenterol Hepatol 14(8):811–816, 1999.

Each of these trials demonstrate that hepatic arterial infusion is a method for treating advanced hepatocellular carcinoma that improves performance status, but produces only small differences in overall survival.

ON GALLBLADDER TUMORS

Bartlett DL, Fong Y, Fortner JG, et al: Long-term results after resection for gallbladder cancer: Implications for staging and management. Ann Surg 224(5):639–646, 1996.

Large retrospective study that defines surgically curable and incurable patients.

Ducreaux M, Rougier P, Armand JP: Effective treatment of advanced biliary tract carcinoma using 5-fluorouracil continuous infusion with cisplatin. Ann Oncol 9(6):653–656, 1998.

This phase II trial demonstrates the synergistic effect of the combination of 5-FU and cisplatin in inoperable biliary tract tumors, producing an overall response rate of 24% with tolerable toxicity profile.

Falkson G, MacIntyre JM, Moertel CG: Eastern Cooperative Oncology Group experience with chemotherapy for inoperable gallbladder and bile duct cancer. Cancer 54:965, 1984.

Combination chemotherapy with 5-FU and an alkylating agent was no more effective than 5-FU alone.

Raderer M, Hejna MH, Scheithauer W: Two consecutive phase II studies of 5-fluorouracil/leucovorin/mitomycin and of gemcitabine in patients with advanced biliary cancer. Oncology (Basel) 56(3):177–180, 1999.

These two consecutive trials examine the feasibility of systemic therapy in advanced biliary cancer. Both regimens were mild and produced partial response rates in the range of 16%-25%. The second regimen used gemcitabine in this setting, which may have better tolerability. More controlled studies will be needed to define its role in this entity.

ON BILE DUCT TUMORS

Foo ML, Gunderson LL, Bender CE, et al: External radiation therapy and transcatheter iridium in the treatment of extrahepatic bile duct carcinoma. Int J Radiat Oncol Biol Phys 39:929–935, 1997.

A 5-year survival rate of 14% was found in 24 patients with extrahepatic bile duct cancer treated with brachytherapy combined with external-beam radiation.

CHAPTER 16

Colorectal and anal cancers

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COLORECTAL CANCER

Colorectal carcinoma is a major public health problem in western countries. An estimated 129,400 new cases will be diagnosed in the United States in the year 2000, and some 56,600 people will die of the disease.

Colorectal carcinoma is the third leading cause of death from cancer in both males and females. It also is the third most common malignancy in both men (after prostate and lung cancers) and women (after breast and lung cancers).

Colon cancer is more than 2.5 times as common as rectal cancer. Rectal cancer is defined as cancer arising below the peritoneal reflection or < 12-15 cm from the anal verge. Because it has a different natural history, colon cancer is treated and reported separately from rectal cancer.

Epidemiology

Gender The overall incidence of colorectal cancer is nearly identical in men and women; tumors of the colon are slightly more frequent in women than in men (1.1:1), whereas rectal carcinomas are more common in men than in women (1.3:1).

Age The risk of developing colorectal tumors begins to increase at age 40 years and rises with age. The mean age at presentation is 60-65 years.

Race The incidence of colon carcinomas has increased by 30% in blacks since 1973 and is now higher than in whites.

Geography The incidence of colorectal carcinoma is higher in industrialized regions (the United States, Canada, the Scandinavian countries, northern and western Europe, New Zealand, Australia) and lower in Asia, Africa (among blacks), and South America (except Argentina and Uruguay).

Disease site Colon carcinomas constitute approximately 70% of all cancers in the large bowel, with occurrence on the right side of the proximal colon becoming more common.

TABLE 1: Five-year survival in colorectal cancer[a]

Time of detection	5-Year survival rate (%)
In early, localized stage	91
After spread to adjacent organs or lymph nodes	66
After spread to distant sites	8

[a] Source: Cancer Facts & Figures—1999. Atlanta, American Cancer Society, 1999.

Survival Five-year survival rates (Table 1) for patients with stage I, II, or III colorectal carcinomas have improved in recent years. This may be due to wider surgical resections, modern anesthetic techniques, and improved supportive care. In addition, better pathologic examination of resected specimens, preoperative staging, and abdominal exploration reveal clinically occult disease and allow treatment to be delivered more accurately. Survival also has improved through the use of adjuvant chemotherapy for colon cancer and adjuvant chemoradiation for rectal cancer.

Etiology and risk factors

The specific causes of colorectal carcinoma are unknown, but environmental, nutritional, genetic, and familial factors, as well as preexisting diseases, have been found to be associated with this cancer.

Environment Asians, Africans, and South Americans who emigrate from low-risk areas assume the colon cancer risk of their adopted country, suggesting the importance of environmental factors in colorectal cancer.

Diet Diets rich in fat and cholesterol have been linked to an increased risk of colorectal tumors. Dietary fat causes endogenous production of secondary bile acids and neutral steroids and increases bacterial degradation and excretion of these acids and steroids, thereby promoting colonic carcinogenesis. In contrast, diets rich in cereal fiber or bran and yellow and green vegetables are said to have a protective effect. A protective role also has been ascribed to calcium salts and calcium-rich foods, because they decrease colon-cell turnover and reduce the cancer-promoting effects of bile acid and fatty acids.

Genetic factors Several genetic premalignant polyposis syndromes are associated with a high risk of colorectal cancer (Table 2). Colorectal cancer risk also is increased in patients with positive family histories.

Familial adenomatous polyposis (FAP) is inherited as an autosomal-dominant trait with variable penetrance. Patients develop pancolonic and rectal adenomatous polyposis in the mid-teenage years and may develop colorectal carcinoma if a prophylactic total colectomy is not done. The risk of colorectal carcinoma is almost 100% if the patient lives long enough.

Recently, a gene predisposing to FAP (adenomatous polyposis coli, or *APC)* was identified on the long arm of chromosome 5. Mutations in the APC gene and other tumor-suppressor genes (*p53* and the "deleted in colorectal cancer"

TABLE 2: Hereditary polyposis syndromes

Adenomatous polyposis

Familial adenomatous polyposis (FAP)

Characterized by hundreds or thousands of sessile or pedunculated polyps, each < 1 cm, throughout the large intestine; histologic examination reveals microscopic adenomas; average age at onset of polyps, 25 years; at onset of symptoms, 33 years; at diagnosis, 36 years; at diagnosis of colon cancer, 42 years; extracolonic features include mandibular osteomas, upper GI polyps, and congenital hypertrophy of the retinal pigment epithelium

Gardner's syndrome

Same colonic manifestations as FAP; extracolonic features more evident and varied, including osteomas of the skull, mandible, and long bones; desmoid tumors; dental abnormalities; neoplasms of the thyroid, adrenal glands, biliary tree, and liver; upper GI polyps; and congenital hypertrophy of the retinal pigment epithelium; fibromatosis of the mesentery is a potentially fatal complication (8%-13% of patients)

Turcot's syndrome

Rare, compared with above syndromes; associated with malignant brain tumors; after index patient is identified, potentially affected family members should be screened with colonoscopy and CT or MRI

Hamartomatous polyposis

Peutz-Jeghers syndrome

In infancy and childhood, melanin deposits manifest as greenish-black to brown mucocutaneous pigmentation (which may fade at puberty) around the nose, lips, buccal mucosa, hands, and feet; polyps (most frequent in small intestine; also found in stomach and colon) are unique hamartomas with branching bands of smooth muscle surrounded by glandular epithelium; may produce acute and chronic GI bleeding, intestinal obstruction, or intussusception; 50% of patients have cancer (median age at diagnosis, 50 years); ovarian cysts and unique ovarian sex-cord tumors reported (5%-12% of female patients)

Juvenile polyposis

Three forms: familial juvenile polyposis coli (polyps limited to the colon), familial juvenile polyposis of the stomach, and generalized juvenile polyposis (polyps distributed throughout the GI tract); polyps are hamartomas covered by normal glandular epithelium, found mostly in the rectum in children and sometimes in adults; may produce GI bleeding, obstruction, or intussusception; mixed juvenile/adenomatous polyps or synchronous adenomatous polyps may lead to cancer, but gastric cancer has not been reported in patients with familial juvenile polyposis of the stomach

Cowden's disease (multiple hamartoma syndrome)

Multiple hamartomatous tumors of ectodermal, mesodermal, and endodermal origin; mucocutaneous lesions are prominent and distinctive; also reported: breast lesions ranging from fibrocystic disease to cancer (50% of patients), thyroid abnormalities (10%-15%), cutaneous lipomas, ovarian cysts, uterine leiomyomas, skeletal and developmental anomalies, and GI polyps; no associated risk of cancer in GI polyps; probably does not warrant clinical surveillance

Neurofibromatosis

May include submucosal neurofibromas in the GI tract, with symptoms of abdominal pain or bleeding; malignant transformation into neurofibrosarcomas has been reported

gene, or *DCC)* combined with mutational activation of proto-oncogenes, especially c-Ki-*ras*, occur sequentially in the neoplastic transformation of bowel epithelium in FAP.

Hereditary nonpolyposis colorectal cancer Some families without adenomatous polyps in the large intestine are also at higher risk of developing colorectal tumors. The familial aggregations of these diseases are now known as hereditary nonpolyposis colorectal cancer (HNPCC) types a and b. HNPCC type a denotes a familial, site-specific, nonpolyposis colon cancer. HNPCC type b describes nonpolyposis colon cancer in association with other forms of cancer, such as breast, endometrial, gastric, and ovarian carcinomas.

Recently, mutations in the human homologs of the bacterial *mutHLS* gene complex *(hMSH2, hMLH1, hPMS1,* and *hPMS2)* were found to predispose to the development of HNPCC. Such mutations lead to genetic instability, which is reflected in errors in DNA replication (replication errors or microsatellite instability).

Flat adenoma syndrome The flat adenoma syndrome, in which families are at higher risk of developing flat adenomas and colorectal cancer, has also been described by Lynch and colleagues. Table 3 compares the clinical features of hereditary colon cancer syndromes, with and without polyposis.

Inflammatory bowel disease Patients with inflammatory bowel disease (ulcerative colitis, Crohn's disease) have a higher than normal incidence of colorectal carcinoma. The risk of colorectal carcinoma in patients with ulcerative colitis is associated with the duration of active disease, extent of colitis, development of mucosal dysplasia, and duration of symptoms.

The risk of colorectal cancer increases exponentially with the duration of colitis, from approximately 3% in the first decade to 20% in the second decade to > 30% in the third decade. Colorectal cancer risk also is increased in patients with Crohn's disease, although to a lesser extent.

Adenomatous polyps Colorectal tumors develop more often in patients with adenomatous polyps than in those without polyps. There is approximately a 5% probability that carcinoma will be present in an adenoma; the risk correlates with the histology and size of the polyp. The potential for malignant transformation is higher for villous and tubulovillous adenomas than for tubular adenomas. Adenomatous polyps < 1 cm have a slightly greater than 1% chance of being malignant, in comparison with adenomas > 2 cm, which have up to a 40% likelihood of malignant transformation.

Cancer history Patients with a history of colorectal carcinoma are at increased risk of developing a second primary colon cancer or other malignancy. Women with a history of breast, endometrial, or ovarian carcinoma also have an increased chance of developing colorectal cancer.

Prior surgery Following ureterosigmoidostomy, an increased incidence of colon cancer at or near the suture line has been reported. Cholecystectomy also has been associated with colon cancer in some studies but not in others.

TABLE 3: Clinical features of inherited colon cancer syndromes

Feature	Flat adenoma syndrome	HNPCC
Onset	Late	Early
Number of polyps	0-100	<10
Polyp histology	Flat adenomas	Tubular adenomas
Polyp distribution	Mainly on the right side	Mainly on the right side
Cancer distribution	Mainly on the right side	Mainly on the right side
Other cancer(s)	Periampullary hepatoblastoma of unknown significance	Endometrial, other

Adapted, with permission, from Lynch HT, Smyrk T, Watson P, et al: Hereditary colorectal cancer. Semin Oncol 18:337-366, 1991.

HNPCC = Hereditary nonpolyposis colorectal cancer

Chemoprevention

Chemoprevention aims to block the action of carcinogens on cells before the appearance of cancer. The most well-studied agents in the prevention of colorectal cancer include the antioxidants β-carotene, vitamin C, and vitamin E; calcium; and nonsteroidal anti-inflammatory drugs (NSAIDs). End points evaluated include changes in adenomatous polyps, alterations in mucosal proliferation, and colorectal cancer incidence.

Antioxidants and calcium Controlled trials of vitamins C and E and calcium have produced mixed results. In two randomized studies, β-carotene did not demonstrate a protective effect.

A recent study in carcinogen-treated rats showed that administration of celecoxib (Celebrex), a specific cyclooxygenase-2 (COX-2) inhibitor, inhibited the incidence and multiplicity of colon tumors by about 93% and 97%, respectively *(Kawamori T, Rao CV, Seibert K, et al: Cancer Res 58:409-412, 1998).*

NSAIDs inhibit colorectal carcinogenesis possibly by reducing endogenous prostaglandin production through cyclooxygenase inhibition. Sulindac has induced regression of large bowel polyps in patients with FAP. Controlled studies have shown a reduction in the incidence of colorectal cancer with regular, long-term use of aspirin.

A study on tissue from human colorectal adenomas and adenocarcinomas showed that the expression of COX-2 messenger RNA is enhanced, Thus, selective COX-2 inhibition may reduce the formation of adenomatous polyps.

Signs and symptoms

Early stage During the early stages of colorectal cancer, patients may be asymptomatic or complain of vague abdominal pain and flatulence, which

may be attributed to gallbladder or peptic ulcer disease. Minor changes in bowel movements, with or without rectal bleeding, are also seen; these are frequently ignored and/or attributed to hemorrhoids or other benign disorders.

Left colon Cancers occurring in the left side of the colon generally cause constipation alternating with diarrhea; abdominal pain; and obstructive symptoms, such as nausea and vomiting.

Right colon Right-sided colon lesions produce vague, abdominal aching, unlike the colicky pain seen with obstructive left-sided lesions. Anemia resulting from chronic blood loss, weakness, weight loss, and the abdominal mass may also accompany carcinoma of the right side of the colon.

Rectum Patients with cancer of the rectum may present with a change in bowel movements; rectal fullness, urgency, or bleeding; and tenesmus.

Pelvic pain is seen at later stages of the disease and usually indicates local extension of the tumor to the pelvic nerves.

Screening and diagnosis

Screening

Fecal occult blood testing Guaiac-based fecal occult blood tests are, in themselves, inexpensive but have been associated with many false-positive and false-negative results. Almost all colonic polyps and > 50% of all colorectal carcinomas go undetected because they are not bleeding at the time of the test. The newer fecal occult blood tests, including a guaiac-based product called Hemoccult SENSA and immunochemical tests for hemoglobin (HemeSelect), appear to have better sensitivity than the older tests without sacrificing specificity. Three large randomized controlled clinical trials have demonstrated decreased colorectal cancer mortality associated with detection of earlier-stage cancer and adenomas by fecal occult blood testing.

Digital rectal examination is simple to perform and can detect lesions up to 7 cm from the anal verge.

Sigmoidoscopy Flexible proctosigmoidoscopy is safe and more comfortable than examination using a rigid proctoscope. Almost 50% of all colorectal neoplasms are within the reach of a 60-cm sigmoidoscope.

Colonoscopy provides information on the mucosa of the entire colon, and its sensitivity in detecting tumors is extremely high. Colonoscopy can be used to obtain biopsy specimens of adenomas and carcinomas and permits the excision of adenomatous polyps. Limitations of colonoscopy include its inability to detect some polyps and small lesions because of blind corners and mucosal folds and the fact that sometimes the cecum cannot be reached.

Barium enemas can accurately detect colorectal carcinoma; however, the false-negative rate associated with double-contrast barium enemas ranges from 2% to 18% because of misreading, poor preparation, and difficulties in detecting smaller lesions. A barium enema should be viewed as complementary to colonoscopy.

Recommendations for low-risk patients The American Cancer Society recommends that asymptomatic patients with no risk factors should have a digital rectal examination annually beginning at age 40 and, starting at age 50, fecal occult blood tests yearly plus flexible sigmoidoscopy every 3-5 years. A case-control study suggests that screening sigmoidoscopy can reduce mortality from cancer of the rectum and distal colon; however, screening once every 10 years may be nearly as efficacious as more frequent screening. Combining fecal occult blood testing with flexible sigmoidoscopy appears to be the most cost-effective strategy for reducing mortality from colorectal cancer.

Recommendations for high-risk patients There is no proven screening recommendation for high-risk patients, but it is not unreasonable to start screening family members of patients with familial polyposis with annual flexible sigmoidoscopy between the ages of 10 and 12 years.

Patients with one or more first-degree relatives (parents, siblings) who developed colorectal cancer by age 55 should have an annual fecal occult blood test and either a colonoscopy or double-contrast barium enema every 5 years, beginning at age 35-40.

Members of families with a history of HNPCC should have annual fecal occult blood testing and full colonoscopic examination every 2 years beginning at age 24, or beginning at an age 5 years younger than the age of the family member with the earliest colon cancer diagnosis. Colonoscopy should be done annually in these patients after age 35.

Surveillance of the entire remaining large intestine 1 year after resection has been recommended for patients with one or more adenoma(s) > 1 cm in size and/or adenomas with villous changes; if the initial findings are normal, such surveillance should be repeated every 3-5 years thereafter. A recent Memorial Sloan-Kettering Cancer Center study suggests that performing follow-up colonoscopic examination 3 years after a polypectomy is as effective as performing such examinations at 1 and 3 years.

Follow-up colonoscopic examinations are also warranted in patients with tubulovillous, villous, or large (≥ 1 cm) adenomas in the rectosigmoid colon, particularly if multiple adenomas are present. However, in patients with only a single, small tubular adenoma, surveillance colonoscopy may not be cost-effective, because the risk of cancer is low.

Patients with more than an 8-year history of ulcerative colitis with pancolitis who have not undergone proctocolectomy require colonoscopy, with multiple random biopsies every 1-2 years to detect dysplasia.

Individuals with a personal history of colorectal cancer are also at high risk for developing another colorectal cancer and need surveillance of the large bowel, as well as regular follow-up for metastatic disease.

Better screening methods are needed for both average- and high-risk patients. Stool DNA analysis for mutations of the K-*ras* gene and other genetic abnormalities may be utilized for this purpose in the future.

Diagnosis

Initial work-up An initial diagnostic work-up for patients suspected of having colorectal tumors should include:

- digital rectal examination and fecal occult blood test
- colonoscopy
- biopsy of any detected lesions

Adequate staging prior to surgical intervention requires:

- chest x-ray
- CT scan of the abdomen and pelvis
- CBC with platelet count
- liver and renal function tests
- urinalysis
- measurement of carcinoembryonic antigen (CEA) level

Immunoscintigraphy Two newer diagnostic imaging agents are now available for selective use in colorectal cancer. Although not usually recommended in the evaluation of primary disease, these modalities can aid in the staging of recurrence.

Satumomab pendetide (Oncoscint) is indicated for determining the extent and location of extrahepatic malignant disease in colorectal cancer patients. Immunoscintigraphy using this agent and CT have demonstrated similar sensitivity (69% and 68%, respectively) and specificity (77% for both methods). Although CT is able to detect a greater proportion of liver metastases (84% vs 41%), immunoscintigraphy is more sensitive in detecting pelvic tumors and extrahepatic abdominal metastases (84% vs 41%).

CEA-Scan The CEA-Scan, an anti-CEA Fab′-antibody fragment labeled with technetium, received approval in 1996 for use in the staging of colorectal cancers. In a phase III trial in patients with colorectal cancer, the CEA-Scan was injected intravenously, after which external scintigraphy was performed. Imaging with conventional diagnostic modalities (primarily CT) was also performed, and findings were confirmed by surgery and histology.

The sensitivity of the CEA-Scan was superior to that of conventional modalities in evaluating the extrahepatic abdomen (55% vs 32%) and pelvis (69% vs 48%). The CEA-Scan complemented the findings of conventional imaging in evaluating the liver. The positive predictive value was significantly higher when both modalities were positive (98%), compared with either alone, perhaps obviating the need for histologic confirmation when both tests are positive. In patients with occult cancer, combining the CEA-Scan with conventional imaging significantly increased diagnostic accuracy (61% vs 33%).

Pathology

Adenocarcinomas constitute 90%-95% of all large bowel neoplasms. These tumors consist of cuboidal or columnar epithelium with multiple degrees of differentiation and variable amounts of mucin.

Mucinous adenocarcinoma is a histologic variant characterized by huge amounts of extracellular mucus in the tumor.

Signet-ring-cell carcinoma is another variant that contains large quantities of intracellular mucin elements that cause the cytoplasm to displace the nucleus.

Other tumor types Squamous cell carcinomas, carcinoid tumors, and adenosquamous and undifferentiated carcinomas also have been found in the colon and rectum. Nonepithelial tumors, such as sarcomas and lymphomas, are exceedingly rare.

Metastatic spread Colorectal carcinoma has a tendency for local invasion by circumferential growth and for lymphatic, hematogenous, transperitoneal, and perineural spread. Longitudinal spread is usually not extensive, with microscopic spread averaging only 1-2 cm from gross disease, but radial spread is common and depends on anatomic location.

By the time they are diagnosed, some 25% of colon cancers will have extended through the bowel wall, whereas cancers of the rectum will have spread through the wall in 50%-70% of patients and metastasized to lymph nodes in 50%-60%.

The most common site of extralymphatic involvement is the liver, with the lung the most frequently affected extra-abdominal organ. Other sites of hematogenous spread include the bones, kidneys, adrenal glands, and brain (cerebellum).

Staging and prognosis

The TNM staging classification, which is based on the depth of tumor invasion into and through the intestinal wall, the number of regional lymph nodes involved, and the presence or absence of distant metastases, is largely replacing the older Dukes' classification scheme (Table 4).

Pathologic stage is the single most important prognostic factor following surgical resection of colorectal tumors. The prognosis for early stages (I and II) is favorable overall, in contrast to the prognosis for advanced stages (III and IV).

Histologic grade may be correlated with survival. Five-year survival rates of 56%-100%, 33%-80%, and 11%-58% have been reported for grades 1, 2, and 3 colorectal tumors, respectively.

Other prognostic factors (such as age at diagnosis, presurgical CEA level, gender, presence and duration of symptoms, site of disease, histologic features, obstruction or perforation, perineural invasion, venous or lymphatic invasion, ploidy status, and S-phase fraction) have not consistently been correlated with overall disease recurrence and survival. Furthermore, the size of the primary le-

TABLE 4: TNM staging of colorectal cancer

TNM stage	Primary tumor[a]	Lymph node metastasis[b]	Distant metastasis[c]	Modified Astler-Coller
Stage 0	Tis	N0	M0	
Stage I	T1	N0	M0	A
	T2	N0	M0	B1
Stage II	T3	N0	M0	B2
	T4	N0	M0	B3
Stage IIIA	Any T	N1	M0	C[d]
Stage IIIB	Any T	N2, N3	M0	
Stage IV	Any T	Any N	M1	D

[a] 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 nonperitoneal pericolic or perirectal tissues; T4 = tumor perforates the visceral peritoneum or directly invades other organs or structures

[b] N0 = no regional lymph node metastasis; N1 = metastases in one to three pericolic or perirectal lymph nodes; N2 = metastases in four or more pericolic or perirectal lymph nodes; N3 = metastases in any lymph node along the course of a named vascular trunk

[c] M0 = no distant metastasis; M1 = distant metastasis

[d] C1 = T2 N1, T2 N2, T2 N3 C2 = T3 N1, T3 N2, T3 N3 C3 = T4 N1, T4 N2, T4 N3

sion has had no influence on survival. The expression of thymidylate synthase (TS) may be an independent prognosticator of survival. Patients with high TS levels may have inferior survival compared to patients with low TS levels.

The status of chromosome 18q appears to have prognostic value in patients with stage II colorectal cancer. The prognosis of stage II patients with chromosome 18q allelic loss in their tumors is similar to that of stage III patients, who may benefit from adjuvant chemotherapy. In comparison, patients with stage II disease who do not have chromosome 18q allelic loss have a survival rate similar to those with stage I disease, and may not require adjuvant therapy.

Treatment

PRIMARY TREATMENT OF LOCALIZED DISEASE

Management of colorectal carcinoma relies primarily on resection of the bowel. The need for adjuvant systemic or local chemotherapy or immunotherapy, with or without concurrent radiation, depends on tumor location (colon vs rectum) and stage of disease.

Surgery

Colon The primary therapy for adenocarcinoma of the colon is surgical extirpation of the bowel segment containing the tumor, the adjacent mesentery, and draining lymph nodes. The type of resection depends on the anatomic loca-

tion of the tumor. Right, left, or transverse hemicolectomy is the surgical treatment of choice in patients with right, left, or transverse colonic tumors, respectively. Tumors in the sigmoid colon may be treated with wide sigmoid resection. The length of colon resected depends largely on the requirement for wide mesenteric nodal clearance.

A review of the long-term results of TME for 405 resectable rectal cancers, conducted by a pioneering group in the field, revealed a 10-year local recurrence rate of 4% and a 10-year disease-free survival rate of 78%. The majority of patients had full-thickness rectal cancers or lymph node involvement. Fewer than 10% received adjuvant therapy. These results with TME for rectal cancer are considerably better than those reported for standard surgical resection followed by radiotherapy with or without chemotherapy *(Heald RJ, Ryall RDH, Sexton R, et al: Arch Surg 133:894-899, 1998)*. Long-term results of TME performed at the University of Vienna indicated that R0 resections were performed in 85.7% of patients. Among these patients, the 5-year local recurrence rate was 12% *(Jatzko GR, Jagoditsch M, Lisborg PH, et al: Eur J Surg Oncol 25(3):284-291, 1999)*. Operative complications are also increased.

Rectum For rectal carcinoma, the distal surgical margin should be at least 2 cm and include the node bearing mesorectum surrounding the rectum. This procedure, which is termed total mesorectal excision (TME), is accomplished using a sharp dissection technique. Posteriorly, the mesorectal dissection is carried out along the presacral fascia. Anteriorly, the dissection follows the posterior vaginal wall in females or Denonvillier's fascia in males, both of which are resected in the presence of an anterior wall rectal cancer.

Although the local control rates with TME in selected series appear excellent, TME alone is not the standard of care for stage II or III rectal cancer. It is not clear whether these low local failure rates of TME are reproducible, or whether the complication rate is less than that of postoperative adjuvant chemoradiation when modern conformal techniques are used.

Sphincter-sparing approaches New technologies (eg, circular stapling devices) and the application of newer surgical techniques, such as coloanal anastomosis and creation of intestinal pouches, are employed to maintain anal sphincter function. If the tumor is located proximally between 6 and 15 cm from the anal verge, a low anterior resection with end-to-end anastomosis may be performed.

The National Cancer Data Base Report on Patterns of Care for Adenocarcinoma of the Rectum, observed four trends during 1985-1995: (1) stage I disease was diagnosed with decreasing frequency; (2) local excision was used more often for stage I disease; (3) the use of abdominoperineal resection was on the decline; and (4) chemoradiation was used with greater frequency for stage II/III disease *(Cancer 83:2408-2418, 1998)*.

Abdominoperineal resection, removing the anus and sphincter muscle with permanent colostomy, may be necessary if the tumor is located in the distal rectum and other characteristics of the tumor (eg, bulky size, proximity to the sphincter musculature) preclude an oncologically adequate sphincter-sparing approach. An alternative procedure for tumors 2-5 cm from the anal verge is to resect the entire rectum, sparing the anoderm and anal sphincter musculature, and to perform a coloanal anastomosis. Either procedure can be performed with autonomic nerve preservation, minimizing bladder and sexual function morbidity.

Local excision alone may be indicated for selected patients who have small (< 3-4 cm), T1, well- to moderately differentiated rectal cancers without histologic evidence of lymphovascular involvement, provided that a full-thickness negative margin can be achieved. For T2 or T3 tumors, the standard therapy remains a transabdominal resection because of the risk for mesorectal nodal spread. Preoperative transrectal ultrasound is very useful in defining lesions that that can be resected by local excision alone.

Neoadjuvant therapy For rectal cancers approaching the anal sphincter, preoperative (neoadjuvant) radiation or the combination of chemotherapy and radiation, will significantly reduce the size of the majority of tumors. This approach allows for sphincter-preserving surgery in many patients. In addition, the long-term morbidity of radiation therapy for rectal cancer may be reduced if it is administered prior to surgery. The use of preoperative chemotherapy and radiation therapy is particularly important for patients presenting with locally advanced, unresectable rectal cancer, as the majority will be rendered resectable following neoadjuvant therapy.

Laparoscopic colonic resection The use of laparoscopic colonic resection is being evaluated as an oncologically acceptable method of treating cancers of the colon. The advantages include shorter hospital stay, reduced postoperative ileus, and decreased time away from work. The potential disadvantages include incomplete resection (inadequate nodal resection), longer operative time, inability to palpate intra-abdominal organs, and technical considerations related to operative skills.

Patterns of failure

The natural history and patterns of failure following "curative" resection are different for colon and rectal carcinomas. Locoregional failure as the only or major site of recurrence is common in rectal cancer, whereas colon cancer tends to recur in the peritoneum, liver, and other distant sites, with a lower rate of local failure. As a result, a local therapy, such as radiation, may play a significant role in the treatment of rectal tumors but is not used routinely for colon cancers.

ADJUVANT THERAPY FOR COLON CANCER

Approximately 75% of all patients with colorectal carcinoma will present at a stage when all gross carcinoma can be surgically resected. Nevertheless, despite the high resectability rate, almost half of all patients with colorectal adenocarcinoma die from metastatic disease, primarily because of residual disease that is not apparent at the time of surgery. These individuals are candidates for adjuvant local or systemic therapies.

Systemic chemotherapy

Systemic chemotherapy or immunotherapy (ie, with levamisole [Ergamisol]) is the principal adjuvant therapy for colon cancer. The administration of single-agent fluorouracil (5-FU) or floxuridine (fluorodeoxyuridine [FUDR]) in patients with stage II or III tumors following surgical resection has failed to show a survival advantage over postsurgical observation.

Levamisole plus 5-FU Levamisole, an anthelmintic agent with nonspecific immunostimulating properties, plus 5-FU was the first adjuvant regimen to demonstrate a decrease in recurrence rate and increases in disease-free and overall survival in patients with stage III colon cancer. These beneficial results, reported in a randomized, controlled study, have been updated at 7 years and demonstrate the effectiveness of this regimen in stage III colon cancer.

Adjuvant therapy for patients with stage III colon carcinoma using 5-FU plus levamisole should be initiated 3-5 weeks after surgery. The suggested dosage of 5-FU is 450 mg/m^2 by rapid IV injection, daily for 5 days, then weekly for 48 weeks, starting on day 28 following surgery. Levamisole, 50 mg orally, 3 times daily for 3 days every 2 weeks for 1 year, is recommended in this adjuvant schedule. Although generally well tolerated by patients, levamisole has been shown to be associated with progressive multifocal leukoencephalopathy in rare patients.

5-FU plus leucovorin Other studies have suggested the benefits of 5-FU plus leucovorin calcium (folinic acid) in the adjuvant treatment of colon carcinomas. Acceptable adjuvant regimens of 5-FU plus leucovorin for colon cancer include:

- a "low-dose" leucovorin regimen, consisting of leucovorin (20 mg/m^2) immediately followed by 5-FU (425 mg/m^2), both given by rapid IV injections daily for 5 consecutive days, with courses repeated every 4 weeks for 6 months
- a "high-dose" weekly leucovorin regimen, consisting of 5-FU (500 mg/m^2) by rapid IV injection given at 1 hour during a 2-hour infusion of leucovorin (500 mg/m^2) weekly for 6 weeks, with courses repeated every 8 weeks for 4 cycles

A recent analysis of survival data from patients with stage II or III disease treated in four consecutive National Surgical Adjuvant Breast and Bowel Project (NSABP) adjuvant chemotherapy trials showed similar relative reductions in disease recurrence and mortality as well as similar improvements in overall survival in stage II and III patients. A recent report on an NSABP trial comparing 5-FU plus leucovorin, 5-FU plus levamisole, and the combination of all three drugs in patients with stage II or III colon cancer found no significant differences among the three treatment groups with respect to disease-free or overall survival.

Monoclonal antibody 171A A recent placebo-controlled, randomized study showed that patients with stage III colon cancer treated adjuvantly with monoclonal antibody (MoAb) 171A had significant reductions in recurrence and mortality. A trial that recently completed patient accrual is comparing adjuvant therapy with standard 5-FU plus leucovorin or 5-FU plus levamisole in combination with MoAb 171A vs standard 5-FU–based adjuvant therapy alone.

Perioperative administration Future adjuvant therapy trials should determine whether the administration of chemotherapy in the perioperative setting has a positive impact on patient survival.

Portal vein infusion The liver is the sole site of recurrence in 25% of patients who ultimately develop metastatic colorectal carcinoma. Micrometastatic hepatic disease derives its vascular supply from the portal vein, and delivery of chemotherapeutic agents directly by this route is being investigated.

To date, the results of clinical trials of adjuvant portal vein infusion of chemotherapy for colorectal tumors have not consistently shown a survival benefit, and such therapy is not recommended outside of clinical trials.

Radiation therapy

Postoperative radiation to the tumor bed may be useful in patients with T4 (B3 or C3) tumors of the colon, since more than 30% of these patients develop a local recurrence, and retrospective studies suggest improved local control with radiation.

ADJUVANT THERAPY FOR RECTAL CANCER

Local recurrence alone or in combination with distant metastases occurs in 25%-50% of patients with rectal carcinoma. Nodal metastases and deep bowel wall penetration are significant risk factors for locoregional failure.

In the absence of nodal metastases, the rate of local recurrence may be as low as 5%-10% for stage I rectal cancer and 25%-30% for stage II tumors. In stage III disease, the incidence of pelvic failure increases to 50% or more.

The randomized Swedish Rectal Cancer Trial showed that a short-term regimen of high-dose preoperative radiotherapy (25 Gy delivered in 5 fractions over 1 week) reduced rates of local recurrence and improved survival among patients with resectable rectal cancer *(Swedish Rectal Cancer Trial: N Engl J Med 336:980-987, 1997).*

Local recurrence in the pelvis is complicated by involvement of contiguous organs, soft and bony tissue, and deep nodal disease. Presenting symptoms vary from vague pelvic fullness to sciatica related to mass effect in the fixed space of the bony pelvis and invasion of the sciatic nerve.

Because local recurrence in the absence of metastatic disease is more common in rectal cancer than in colon cancer, aggressive resections, such as pelvic exenteration (anterior and posterior), sacral resection, and wide soft-tissue and pelvic floor resection, have been employed to treat these recurrences. Modern techniques of pelvic floor reconstruction, creation of continent urinary diversion, and vaginal reconstruction may be required for functional recovery.

Radiation therapy

Radiation therapy has been used to reduce the locoregional recurrence rate of rectal tumors. Preoperative radiation therapy has been demonstrated to reduce local tumor recurrence, but, with the exception of one recent study, has not affected overall survival in patients with stage II or III rectal cancer. An improvement in local control also has been observed with postoperative irradiation, but again with no benefit with regard to disease-free or overall survival.

Chemoradiation

Postoperative chemoradiation North Central Cancer Treatment Group (NCCTG) trials have shown that postsurgical 5-FU–based chemotherapy combined with pelvic irradiation is superior to either modality alone in reducing locoregional failures and improving disease-free and overall survival of patients with stage II or III rectal carcinoma. Combined therapy reduced the rate of cancer-related deaths by 36%.

The most effective combination of drugs, optimal mode of administration, and sequence of radiation and chemotherapy still need to be determined. Radiation doses of 45-55 Gy are recommended in combination with 5-FU–based chemotherapy. Postoperative bolus 5-FU administration with radiation is inferior to protracted venous infusion, resulting in lower 3-year rates of both overall survival (68% vs 76%) and disease-free survival (56% vs 67%).

An adjuvant treatment combining chemotherapy and pelvic irradiation in patients with stage II or III disease used the following regimen: 5-FU, 500 mg/m^2/d administered as a rapid IV infusion on days 1-5 and 450 mg/m^2/d on days 134-138 and days 169-173. Patients received a protracted IV infusion of 5-FU, 225 mg/m^2/d, by portable ambulatory infusion pump during the entire period of pelvic irradiation. Pelvic radiation therapy began on day 64 with a multiple-field technique to the tumor bed and nodal groups. A total of 4,500 cGy in 180-cGy fractions was administered over a 5-week period. Patients received a minimal boost dose of 540 cGy to the entire tumor bed, adjacent nodes, and 2 cm of adjacent tissue. A second boost dose of 360 cGy was allowed in selected patients with excellent displacement of the small bowel.

Preoperative vs postoperative chemoradiation Preoperative chemoradiation may be preferred to postoperative adjuvant treatment, particularly in patients with T3 or T4 lesions. Such treatment may enhance resectability and may have a lower frequency of complications compared with postoperative treatment. The relative value of preoperative vs postoperative treatment is being examined in a number of randomized trials.

A recent randomized trial showed improvements in time to hepatic recurrence and overall survival in patients given a hepatic arterial infusion of FUDR plus dexamethasone and systemic 5-FU plus leucovorin after resection of hepatic metastases from colorectal cancer, as compared with patients who received systemic chemotherapy alone *(Kemeny N, Cohen A, Huang Y, et al: Proc Am Soc Clin Oncol 18:263a [abstract], 1999).* A second randomized trial demonstrated a longer time to hepatic recurrence and a reduced incidence of liver recurrences in patients who received a continuous hepatic artery infusion of FUDR followed by systemic infusional 5-FU, as compared with patients who received no adjuvant therapy. Overall survival was not affected in this study, however *(Kemeny MM, Adak S, Lipsitz S, et al: Proc Am Soc Clin Oncol 18:264a[abstract], 1999).*

TREATMENT OF ADVANCED COLON CANCER

Surgery

Local recurrences from colon cancers usually occur at the site of anastomosis, in the resection bed, or in the contiguous and retroperitoneal (para-aortic, paracaval) lymph nodes. Anastomotic recurrences heralded by symptoms are the most curable, followed by local

soft-tissue recurrences. Regional and retroperitoneal lymph node recurrences portend a poor prognosis and systemic disease.

Metastasectomy Metastases to the liver and lungs account for nearly all nonnodal systemic disease in colorectal cancer. Resection of metastases, or metastasectomy, has gained recognition as a viable treatment. Resection of liver metastases results in cure rates of 5%-30%, depending on the number of metastases and stage of disease. Resection of solitary metastases in stage I or II patients results in a 5-year survival rate of 25%-30%.

Adjuvant therapy after resection of hepatic metastases is currently being studied (see box on previous page). Intra-arterial (IA) therapy has significant hepatobiliary toxicity. Intraportal therapy, although it has reduced complications, has not been evaluated in a prospective, randomized trial.

Chemotherapy

5-FU, synthesized by Heidelberger in 1957, remains the primary agent used in the treatment of advanced colon carcinoma. 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 have been approximately 10%-15%. The development of permanent venous access devices and portable infusion pumps has permitted the continuous infusion of 5-FU on an outpatient basis. Commonly used continuous-infusion regimens of 5-FU are 750-1,000 mg/m^2/d for 5 days. Protracted infusions have administered 5-FU at 200-400 mg/m^2/d for up to 12 weeks.

The pattern of 5-FU toxicity differs depending on whether it is administered as a bolus or continuous infusion. Bolus administration has pronounced myelotoxic effects, whereas the dose-limiting toxic effects of continuous infusion 5-FU are mucositis and diarrhea. Palmar-plantar erythrodysesthesia (hand-foot syndrome) has been reported with protracted infusions.

5-FU has been combined with other agents, such as mitomycin (Mutamycin) and semustine. At best, response rates have not exceeded 25%, similar to those observed with 5-FU alone. Toxic effects are additive.

Biochemical modulation of 5-FU Interest in the biochemical modulation of 5-FU by leucovorin is based on preclinical studies demonstrating that leucovorin raises the level of N_5,N_{10}-methylenetetrahydrofolate and, thus, forms a stable tertiary complex of thymidylate synthase (TS), the folate coenzyme, and 5-FU (in the form of 5-fluorodeoxyuridine). The use of 5-FU with leucovorin results in higher response rates than 5-FU alone and may prolong survival.

According to an NCCTG randomized trial, a low-dose leucovorin regimen appeared to have a superior therapeutic index to a weekly 5-FU plus high-dose leucovorin (5-FU, 600 mg/m^2 IV push, plus leucovorin, 500 mg/m^2 as a 2-hour infusion, weekly for 6 weeks, with courses repeated every 8 weeks) in metastatic colon carcinoma patients, based on response rate and survival. In addition, the low-dose leucovorin regimen was associated with lower cost and less need for hospitalization to manage chemotherapy toxicity.

Although there is no agreement as to the optimal dose of leucovorin, two dosing schedules have been approved by the FDA:

- a low-dose leucovorin regimen, consisting of leucovorin, 20 mg/m^2/d, immediately followed by 5-FU, 425 mg/m^2/d
- a high-dose leucovorin regimen, consisting of leucovorin, 200 mg/m^2/d, immediately followed by 5-FU, 370 mg/m^{2}d.

With both schedules, leucovorin and 5-FU are administered by rapid IV injections daily for 5 consecutive days. Courses of both schedules are repeated at 4 weeks, 8 weeks, and every 5 weeks thereafter. There is no survival difference between these two regimens.

Irinotecan (CPT-11 [Camptosar]), a novel topoisomerase I inhibitor synthesized from *Camptotheca acuminata,* a tree that is native to China, has significant clinical activity in metastatic colorectal cancer patients whose disease has recurred or spread after standard chemotherapy. Its approval was based on two phase III trials showing that irinotecan (350 mg/m^2 once every 3 weeks) significantly increased survival, compared with best-supportive care (Figure 1) and infusional 5-FU, respectively, in patients with recurrent or progressive cancer following first-line 5-FU therapy. Irinotecan increased median survival by 27% and 41%, respectively, in the two trials.

Irinotecan is active in patients whose disease progressed while they were receiving 5-FU. Reproducible 15%-20% response rates in this patient population led to the 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).

In a North American trial, response rates and time to progression were substantially improved in metastatic colorectal cancer patients treated with weekly irinotecan (125 mg/m^2 for 4 out of every 6 weeks), leucovorin (20-mg/m^2 bolus), and 5-FU (500-mg/m^2 bolus), as compared with patients who received either irinotecan alone or low-dose leucovorin and 5-FU *(Saltz LB, Locker PK, Pirotta N, et al: Proc Am Soc Clin Oncol 18:233a[abstract], 1999).* Similar results were observed with the addition of oxaliplatin to infusional 5-FU regimens. The addition of irinotecan to those regimens improved survival, response rate, and symptoms *(Douillard JY, Cunningham D, Roth AD, et al: Proc Am Soc Clin Oncol 18:233a [abstract], 1999).* In both studies, toxicity of the combination arm was predictable and manageable.

The primary toxicities of irinotecan are diarrhea and neutropenia. Intensive loperamide is important in the management of the former complication. An initial 4-mg loading dose is given at the first sign of diarrhea, followed by 2-mg doses every 2 hours until diarrhea abates for at least a 12-hour period.

Preliminary results of two randomized trials comparing standard regimens of 5-FU and leucovorin to irinotecan, 5-FU, and leucovorin in the front-line treatment of metastatic colorectal cancer were recently reported (see box). Randomized trials are currently studying the role of irinotecan and 5-FU plus leucovorin in the adjuvant treatment of stage III colon cancer patients.

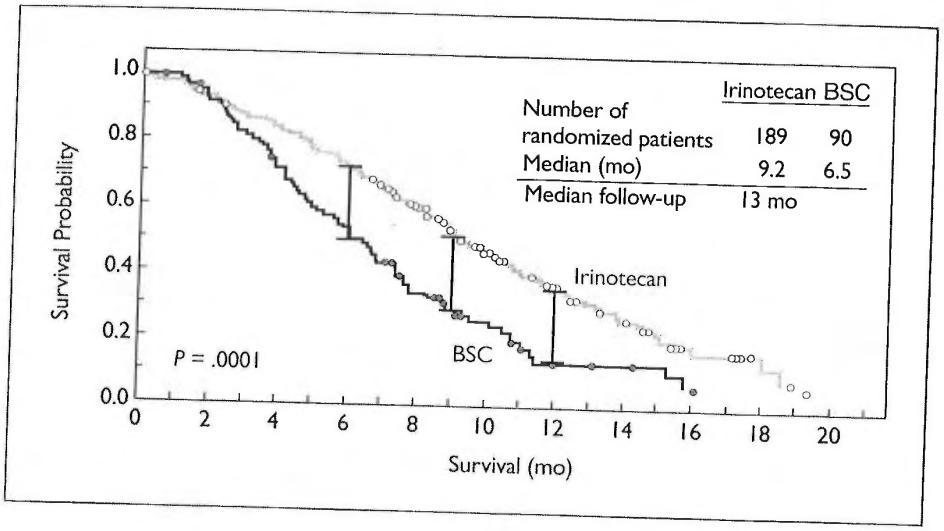

FIGURE 1: Overall survival: Irinotecan vs best supportive care (BSC)

At a median follow-up of 13 months, median survival of 189 patients with 5-FU–refractory advanced colorectal cancer randomized to treatment with irinotecan was 9.2 months, as compared with 6.5 months for 90 patients randomized to BSC alone ($P = .0001$; log-rank test). Source of data: Lancet 352:1413-1418, 1998.

Intrahepatic FUDR administration Renewed interest in regional delivery of FUDR into the liver has followed the introduction of effective implantable infusion pumps. These pumps allow chemotherapeutic agents to be delivered in higher concentration directly into the hepatic artery.

Randomized trials have shown a considerably higher therapeutic response rate with intrahepatic administration of FUDR than with systemic therapy. A recent meta-analysis of studies comparing IV vs IA fluorinated pyrimidines in patients with unresectable, liver-confined, metastatic disease has indicated a small advantage for IA therapy.

Intrahepatic chemotherapy is costly and associated with gastroduodenal mucosal ulceration, hepatitis, and sclerosing cholangitis. The addition of dexamethasone to FUDR infusions appears to decrease biliary sclerosis.

New agents New agents under development for the treatment of advanced colorectal cancer include TS inhibitors, oral fluorinated pyrimidines, and a new platinum analog.

Raltitrexed (Tomudex) is a potent, selective inhibitor of TS. It is polyglutamated and retained intracellularly for prolonged periods, allowing for a convenient dosing schedule of a 15-minute infusion repeated every 21 days.

Oral fluorinated pyrimidines Two oral fluorinated pyrimidines have undergone phase III testing in the United States and Europe: (1) UFT, a combination of uracil and tegafur, which is being administered together with oral leucovorin (the combination of UFT plus leucovorin is known as Orzel); and (2) capecitabine (Xeloda). Both of these compounds are metabolized to 5-FU.

Preliminary results of phase III studies comparing these two oral fluorinated pyrimidines to IV regimens of 5-FU and leucovorin have shown at least comparable efficacy in terms of response rates and survival. The advantages of these oral fluorinated pyrimidines over 5-FU include the convenience of oral administration and a favorable toxicity profile, including reductions in neutropenia and mucositis. Capecitabine has been found to cause hand-foot syndrome, a toxicity commonly seen with infusional 5-FU.

Eniluracil (776C85) plus oral 5-FU Eniluracil is a potent inactivator of dihydropyrimidine dehydrogenase (DPD), the initial catabolic enzyme of 5-FU. The coadministration of eniluracil with 5-FU allows consistent absorption of 5-FU from the GI tract. Phase II multiinstitution trials of eniluracil and 5-FU have demonstrated response rates over 25%. Phase III testing comparing this completely oral regimen to IV 5-FU and leucovorin has completed patient accrual.

Oxaliplatin is a new diaminocyclohexane platinum compound that is undergoing clinical investigation in Europe and the United States. Oxaliplatin has demonstrated activity in patients with pretreated, 5-FU–resistant colorectal cancer when used alone (10% response rate) or in combination with 5-FU (45% response rate). In patients with untreated metastatic colon carcinoma, response rates of 27% have been reported with oxaliplatin alone and rates as high as 57% when the drug was combined with 5-FU. Oxaliplatin's toxicity profile includes nausea/vomiting and cumulative, reversible neuropathy.

A recent randomized trial of bimonthly leucovorin and 5-FU with or without oxaliplatin demonstrated a substantially improved response rate and progression-free survival in patients with metastatic colorectal cancer treated with the oxaliplatin-containing regimen *(de Gramont A, Figer M, Seymour M, et al: Proc Am Soc Clin Oncol 17:257[abstract], 1998).* Although overall survival did not differ significantly between the two groups, an analysis showed treatment with oxaliplatin to be an independent prognostic factor for survival. This suggests that the lack of a survival improvement with oxaliplatin may have been related to post-study crossover to effective second-line chemotherapy *(Figer A, Louvet C, Homerin M, et al: Proc Am Soc Clin Oncol 18:239a[abstract], 1999).*

TREATMENT OF ADVANCED RECTAL CANCER

Radiation therapy

Radiation therapy is moderately effective in palliating advanced rectal cancer symptoms. Pain is decreased in 80% of irradiated patients, although only 20% report complete relief. Bleeding can be controlled in over 70% of patients. Obstruction cannot be reliably relieved by radiation, and diverting colostomy is recommended. Only 15% of patients with recurrent rectal cancers achieve local disease control with radiation, and median survival is < 2 years.

Chemoradiation may be useful to convert fixed unresectable lesions into resectable lesions. These regimens have generally used protracted infusions of 5-FU (200-250 mg/m^2/d) delivered via a portable infusion pump during pelvic radiation therapy (450 cGy over 5 weeks).

Intraoperative radiotherapy (localized radiation given to the tumor or tumor bed at the time of resection) is under active investigation in advanced and locoregionally recurrent rectal cancer.

Laser photoablation

Laser photoablation is occasionally employed for temporary relief of obstructive rectal cancer in patients who are not surgical candidates because of the presence of distant metastases, surgical comorbidity, or extensive intra-abdominal disease.

Follow-up of long-term survivors

Patients who have completed therapy for colorectal cancer require monitoring for potential treatment-related complications, recurrent disease, and new metachronous cancers. Specific follow-up recommendations for these patients are quite controversial at present. Guidelines for post-treatment surveillance/monitoring adopted by the National Comprehensive Cancer Network (NCCN), a consortium of 17 US cancer centers, are shown in Table 4.

ANAL CANAL CARCINOMA

Epidemiology, etiology, and risk factors

In the United States, anal canal carcinoma occurs more frequently in women than men. More than 80% of anal canal tumors occur in individuals > 60 years of age. Recent epidemiologic studies suggest that receptive anal intercourse is strongly related to anal cancer.

The incidence rate of anal cancer for single men is reported to be six times that for married men. In people < 35 years old, anal carcinoma is more common in men than women. A history of genital warts has been observed, suggesting that papillomavirus may be an etiologic factor.

Signs and symptoms

The diagnosis of anal canal carcinoma is usually delayed because the symptoms (bleeding, pain, and sensation of mass) are so often attributed to benign anorectal disorders, such as hemorrhoids or anal fissures.

Diagnosis

Evaluation should include a careful rectal examination, endoscopic examination with description of lesion size, and assessment of whether there is invasion into adjacent organs (vagina, urethra, or bladder). Reexamination under general anesthesia may be necessary. A diagnostic incisional biopsy is required.

TABLE 4: NCCN recommendations for post-treatment monitoring/surveillance

- Physical examination, including digital rectal examination with stool occult blood test, every 3 months for 2 years, then every 6 months to 5 years[a]
- CBC plus chemistries every 3 months for 2 years, then every 6 months to 5 years[a]
- If CEA was elevated at diagnosis or within 1 week of colectomy, repeat CEA every 6 months for 2 years, then annually for 5 years[a]
- Chest x-ray[a]:
  Every 12 months for 5 cycles if stage B2 or C *or*
  Every 6 months for 10 cycles if resected liver or abdominal metastases *or*
  Every 3 months for 20 cycles if resected lung metastases
- Abdominal CT[a]:
  Every 6 months for 4 cycles, then annually for 3 years if resected liver or abdominal metastases *or*
  Every 6 months for 4 cycles, then annually for 3 years if resected rectal tumor
- Chest CT[a] every 6 months for 4 cycles if resected lung metastases
- Colonoscopy[a] in 1 year; repeat in 1 year and every 3 years if:
  Negative for multiple synchronous polyps *or*
  Patient with new polyp on surveillance colonoscopy

Reprinted, with permission, from NCCN colorectal cancer practice guidelines. Oncology 10(11;suppl):140-175, 1996.

[a] Recommendations that are somewhat controversial

CEA = Carcinoembryonic antigen; NCCN = National Comprehensive Cancer Network

Pelvic CT is suggested to evaluate pelvic nodes. Although distant metastases are uncommon at diagnosis, a chest x-ray and liver function tests are recommended. Suspicious inguinal nodes discovered on physical examination must be assessed pathologically. The incidence of inguinal nodal metastases at diagnosis varies from 13% to 25%. The presence of perirectal, inguinal, and pelvic lymph node involvement correlates with tumor size and is unusual for tumors < 2 cm in diameter. Formal groin dissection is not advised; needle aspiration should be performed, with limited surgical biopsy done if results of aspiration are inconclusive.

Pathology

Squamous cell carcinomas Most anal canal malignancies are squamous cell carcinomas. These have been classified as cloacogenic carcinomas, basaloid carcinomas, transitional cell carcinomas, or mucoepidermoid carcinomas. However, there is little difference in the natural history of these various types.

Unusual tumors arising in the anal canal include small-cell carcinomas, anal melanomas, and lymphomas.

Small-cell carcinomas of the anal canal are aggressive neoplasms similar in natural history to bronchogenic small-cell carcinomas. If such a histology is

TABLE 5: TNM classification of anal canal tumors

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm in greatest dimension
T2	Tumor > 2 cm but not > 5 cm in greatest dimension
T3	Tumor > 5 cm in greatest dimension
T4	Tumor of any size that invades adjacent organs (eg, vagina, bladder, urethra; involvement of sphincter muscle[s] *alone* is not classified as T4)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
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)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Grade (G)	
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Stage groupings			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage IIIA	T1-3	N1	M0
	T4	N0	M0
Stage IIIB	T4	N1	M0
	Any T	N2-3	M0
Stage IV	Any T	Any N	M1

Adapted, with permission, from Sobin LH, Wittekind C (eds): UICC International Union Against Cancer: TNM Classification of Malignant Tumors, 5th ed. New York, John Wiley & Sons, 1997.

identified, the clinician should be alerted to the possibility of early distant metastases, and treatment should include chemotherapeutic regimens used in bronchogenic small-cell carcinomas.

Anal melanomas Although advanced anal melanomas generally are associated with a dismal survival, prognosis may be related to depth of penetration. Early anal melanomas < 2.0 mm in depth can be cured with wide excision. Abdominoperineal resection is indicated only rarely in the management of anal melanoma.

Staging

Size of the primary tumor is the most important clinical predictor of survival for patients with anal carcinomas. Both the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) have agreed on a unified staging system (Table 5). The TNM classification distinguishes between anal canal carcinoma and anal margin tumors, since the latter exhibit biological behavior similar to that of other skin cancers (Table 6).

Treatment

Surgery

In selected individuals with small superficial tumors, local excision has achieved adequate local control and survival. However, most studies of local excision have been retrospective, with small numbers of patients. Prior to the advent of primary radiotherapy and combined-modality treatment (see below), abdominoperineal resection was considered to be the conventional treatment for patients with invasive anal canal cancer. Unfortunately, even with radical surgical procedures, local recurrences are frequent. Currently, radical extirpative surgery is indicated only after the failure of combined-modality treatment.

Radiation therapy

Trials of primary external-beam radiotherapy in patients with anal canal carcinomas have used doses varying between 4,500 and 7,550 cGy. Local control rates of 60%-90%, with 5-year survival rates of 32%-90%, are similar to the results of surgical series when the trials are controlled for tumor size.

Interstitial radiation therapy alone has been used primarily in Europe for early-stage lesions. A relatively high radiation dose is delivered to a small volume. This modality carries a high potential for radiation necrosis and fails to incorporate treatment of the inguinal nodes.

Combined-modality treatment

Chemoradiation is the preferred therapy for most patients with anal canal cancer. Investigators from Wayne State University pioneered the use of simultaneous pelvic irradiation and chemotherapy in the treatment of patients with anal canal carcinomas, and demonstrated that the majority of such patients could be treated with this combination, obviating the need for an abdominoperineal resection. The original study design used 3,000 cGy over 3 weeks with 5-FU (1,000 mg/m^2/d) as a continuous infusion on days 1-4 and then repeated on

TABLE 6: TNM classification of anal margin tumors

Primary tumor (T)[a]			
T4	Tumor invades deep extradermal structures		
Regional lymph nodes (N)			
N1	Metastasis in ipsilateral inguinal nodes		
Distant metastasis (M)			
M1	Distant metastasis		
Stage groupings[b]			
Stage III	T4	N0	M0
	Any T	N1	M0

[a] Designation as for anal canal tumors, except T4

[b] Stage groupings as for anal canal tumors, except stage III (no stage IIA or IIIB)

Adapted, with permission, from Sobin LH, Wittekind C (eds): UICC International Union Against Cancer: TNM Classification of Malignant Tumors, 5th ed. New York, John Wiley & Sons, 1997.

days 29-32. Mitomycin (15 mg/m^2) was administered as an IV bolus on day 1. Four to 6 weeks after the completion of therapy, patients had a deep muscle biopsy of the anal canal scar.

An updated analysis of this experience demonstrated that 38 (84%) of 45 patients were rendered disease-free after chemotherapy and irradiation. Individuals who had positive biopsies underwent an abdominoperineal resection.

A randomized trial from the Radiation Therapy Oncology Group (RTOG) showed that the use of mitomycin with radiation and 5-FU increased complete tumor regression and improved colostomy-free survival over radiation and 5-FU alone. At 4 years, the colostomy-free survival rate was higher in the mitomycin arm than in the 5-FU–alone arm (71% vs 59%), as was the disease-free survival rate (73% vs 51%) ***(Flam MS, John M, Pajak T, et al: J Clin Oncol 114:2527-2539, 1998).***

Because of the success of the above experience, other investigators have attempted to implement infusional 5-FU and mitomycin with radiation as definitive therapy. Most studies have used similar schedules of 5-FU and mitomycin, but have used higher doses of pelvic irradiation (4,500-5,700 cGy). Five-year survival rates > 70% have been reported.

Several investigators have compared the results of irradiation alone vs irradiation plus chemotherapy. Cummings et al found that, with identical radiation doses and techniques, the local control rate for cancers > 2 cm in size rose from 49% with radiation therapy alone to 85% when 5-FU and mitomycin were combined with radiation. Papillon and Montbarbon found an increase in the rate of local control with a combined-modality approach, as compared with pelvic irradiation alone (81% vs 66%). Two recent randomized studies have shown improved local control with chemoradiation over radiation.

Chemotherapy

Reports of other chemotherapeutic agents in anal cancer have been relatively anecdotal, with limited phase II studies. Because of the activity of cisplatin (Platinol) in other squamous cell carcinomas, this agent has been employed as a single agent or combined with infusional 5-FU in advanced disease.

SUGGESTED READING

ON COLORECTAL CARCINOMA

Cunningham D, Purhonen S, James RD, et al: Randomized trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 352:1413–1418, 1998.

This study demonstrated that patients receiving irinotecan had prolonged survival, improved quality of life, and fewer disease-related symptoms, as compared with those given best supportive care.

Heald RJ, Moran BJ, Ryall RDH, et al: The Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg 133:894–899, 1998.

This recent review details the excellent long-term results of TME for rectal cancer.

Hyams DM, Mamounas EP, Petrelli N, et al: A clinical trial to evaluate the worth of preoperative multimodality therapy in patents with operable carcinoma of the rectum: A Progress report of National Surgical Breast and Bowel Project Protocol R-03. Dis Colon Rectum 40:131–139, 1997.

This preliminary review of data from NSABP R-03 reveals that preoperative chemoradiotherapy is associated with acceptable morbidity and helps avoid the need for sphincter ablative surgery.

Moffat FL, Pinsky CM, Hammershaimb L, et al: Clinical utility of external immunoscintigraphy with the IMMU-4 technetium-99m Fab' antibody fragment in patients undergoing surgery of the colon and rectum: Results of a pivotal phase III trial. J Clin Oncol 14:2295–2305, 1996.

Phase III trial leading to the approval of the CEA-Scan for the staging of colorectal cancer.

O'Connell MJ, Laurie JA, Kahn M, et al: Prospectively randomized trial of postoperative adjuvant therapy in patients with high-risk colon cancer. J Clin Oncol 16:295–301, 1998.

This randomized trial demonstrated that the duration of adjuvant chemotherapy with selected regimens can be reduced from 12 to 6 months.

Riethmuller G, Holz E, Schlimock G, et al: Monoclonal antibody therapy for resected Dukes' C colorectal cancer: Seven-year outcome of a multicenter randomized trial. J Clin Oncol 16:1788, 1998.

A randomized, multicenter trial demonstrating that 171A antibody administered after surgery prevents the development of distant metastases in approximately one-third of patients. This therapeutic effect is maintained for at least 7 years.

Rougier P, Bugat R, Douillard JY, et al: Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naive patients and patients pretreated with fluorouracil-based chemotherapy. J Clin Oncol 15:251–260, 1997.

Summarizes the European experience with irinotecan, demonstrating the activity of this agent as first-line therapy, as well as second-line treatment.

Rougier P, Van Cutsem E, Niederle N, et al: Randomized trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 352:1407–1412, 1998.

The results of this prospective, nonblinded, multicenter, randomized, phase III trial comparing irinotecan to infusional 5-FU as second-line chemotherapy for metastatic colorectal cancer show a survival advantage associated with irinotecan, with a comparable effect on quality of life and control of disease-related symptoms.

Rustgi AK: Hereditary gastrointestinal polyposis and nonpolyposis syndromes. N Engl J Med 331:1694–1702, 1994.

Excellent state-of-the-art review on GI polyposis and nonpolyposis syndromes. Provides clinical and genetic screening tests for these syndromes.

Tepper JE, O'Connell MJ, Petrom GR, et al: Adjuvant postoperative 5-FU modulated chemotherapy combined with pelvic radiation therapy for rectal cancer: Initial results of intergroup 0114. J Clin Oncol 15:2030–2039, 1997.

This intergroup study finds no evidence at present for a beneficial effect of levamisole in the adjuvant treatment of rectal cancer. Definitive evaluation of the effect of the addition of leucovorin with 5-FU and pelvic radiation will require further follow-up.

Winawer SJ, Zauber AG, Ho MN, et al: Prevention of colorectal cancer by colonoscopic polypectomy. N Engl J Med 329:1977–1981, 1993.

Results of the National Polyp Study demonstrated that colonoscopic polypectomy resulted in a lower than expected incidence of colorectal carcinoma, supporting the concept that colorectal adenomas progress to adenocarcinomas.

ON ANAL CANAL CARCINOMA

Cummings B: Anal cancer—radiation alone or with cytotoxic drugs? Int J Radiat Oncol Biol Phys 27:173–175, 1993.

Confirmation that chemotherapy plus pelvic irradiation provides superior results to irradiation alone.

Flam MS, John M, Pajak T, et al: The role of mitomycin C in combination with 5-FU and radiotherapy and of salvage chemoradiation in the definitive nonsurgical management of epidermoid cancer of the anal canal. J Clin Oncol 14: 2527–2539, 1998.

In this randomized RTOG trial, mitomycin plus radiation therapy and 5-FU produced higher rates of complete tumor regression and colostomy-free survival than radiation therapy plus 5-FU.

Roelofsen F, Bosset J, Eschevege F, et al: Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: Results of a phase III randomized trial of the EORTC Radiotherapy and GI Cooperative Group (abstract). Proc Am Soc Clin Oncol 14:194, 1995.

European randomized trial demonstrating the superiority of chemoradiation over radiation alone in locally advanced anal cancer. The complete remission rate was 55% with radiation alone compared to 77% with chemoradiation.

UKCCCR Anal Cancer Trial Working Party: Epidermoid anal cancer: Results from the UKCCCR randomized trial of radiotherapy alone vs radiotherapy, 5-FU, and mitomycin. Lancet 348:1049–1054, 1996.

Another randomized trial demonstrating the superiority of chemoradiation over radiation alone in anal cancer. This was a 46% reduction in the risk of local failure and a 29% reduction in the risk of death from anal cancer with chemoradiation.