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Cancer Management: A Multidisciplinary Approach

Medical, Surgical, & Radiation Oncology

Edited by

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US Food and Drug Administration

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Note to the reader

The information in this volume has been carefully reviewed for accuracy of dosage and indications. Before prescribing any drug, however, the clinician should consult the manufacturer's current package labeling for accepted indications, absolute dosage recommendations, and other information pertinent to the safe and effective use of the product described. This is especially important when drugs are given in combination or as an adjunct to other forms of therapy. Furthermore, some of the medications described herein, as well as some of the indications mentioned, had not been approved by the US Food and Drug Administration at the time of publication. This possibility should be borne in mind before prescribing or recommending any drug or regimen.

The views expressed are the result of independent work and do not necessarily represent the views or findings of the US Food and Drug Administration or the United States.

CHAPTER 6

Non–small-cell lung cancer

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Lung cancer has been the leading cause of cancer death among men in the United States for years, and since 1988, it has become the number-one cause of cancer death among women. An estimated 172,570 new cases of lung cancer are expected in 2005, and 163,510 deaths due to this disease are expected to occur. This exceeds the combined number of deaths from the leading causes of cancer (breast, prostate, and colon cancer). It accounts for 6% of all deaths in the United States.

Lung cancer develops from pulmonary parenchymal or bronchial supportive tissues. 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: small-cell lung cancer (SCLC), for which chemotherapy is the primary treatment, and non–small-cell lung cancer (NSCLC), which in its early stages (I and II) is treated primarily with surgery. Nearly all cures in NSCLC involve surgery.

This chapter provides basic information on the epidemiology, etiology, screening, prevention, and signs and symptoms of lung cancer in general, and then focuses specifically on the diagnosis, staging, pathology, and treatment of NSCLC and carcinoid tumors of the lungs, as well as the pulmonary evaluation of lung cancer patients and follow-up of long-term survivors.

Chapter 7 provides information on the staging, pathology and pathophysiology, and treatment of the far less common SCLC and concludes with brief discussions of mesothelioma and thymoma.

Epidemiology

Gender From 1995 to 1999, there were 86 cases of lung cancer per 100,000 men and 57 cases of lung cancer per 100,000 women. Although the incidence of lung cancer had been rising in women, the rate of increase has begun to slow recently.

Age The age at which lung cancer patients are diagnosed varies widely, but the median age at diagnosis is approximately 70 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 12%.

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. 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 lung cancer. An individual who smokes one pack of cigarettes daily has a 20-fold increased risk of lung cancer compared to a nonsmoker.

The overall incidence of cigarette smoking decreased from 1974 through 1992. Smoking cessation decreases the risk of lung cancer, but a significant decrease in risk does not occur until approximately 5 years after stopping, and the risk remains higher in former smokers than 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 a variety of hereditary factors increase the risk of addiction to nicotine among some individuals. 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 1 year before diagnosis. Healthy ex-smokers represent a large group of individuals who may benefit from effective tools for early detection and/or chemoprevention of lung cancer.

Secondhand 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 secondhand 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 is also a major risk factor for the development of mesothelioma (see discussion of this cancer in the following chapter).

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

Currently, screening for lung cancer among asymptomatic individuals at elevated risk due to smoking history or occupational exposures is not recommended, and the US strategy for diagnosis and treatment of lung cancer is to do nothing until the patient presents with symptoms. An unfortunate result of this policy is that most patients present in advanced stage, and cure rates have improved little over the past 30 years. Only 7% of NSCLC patients are diagnosed in stage IA.

Three randomized screening trials conducted in the United States in the 1970s failed to show a reduction in lung cancer mortality among the smokers who were screened by sputum cytology and chest x-ray for lung cancer. Despite the fact that these American 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 but failed to reduce the mortality from lung cancer.

The potential to screen for lung cancer has received renewed interest due to the superior performance of low-dose helical CT compared with chest radiography in detecting small lesions. Although there is insufficient evidence to establish policy related to routine screening for lung cancer with spiral CT, there is a growing trend toward promoting screening with this new technology to individuals at increased risk for lung cancer.

Numerous studies are currently under way 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. In some recent trials, more than 80% of lung cancers detected by screening were diagnosed in stage I.

Kaneko screened male smokers > 50 years of age. 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 (0.37% detection rate) with 9,452 CT scans. Of these cancers, 27 were stage IA. These patients had a 3-year survival rate of 83%.

The International Early Lung Cancer Action Project (I-ELCAP, http://www.ielcap.org/professionals.htm) is a single-arm prospective study that has accrued more than 26,000 study subjects and documented that a high percentage of lung cancers are detected in stage I, a stage in which long-term survival can reasonably be anticipated in more than 60% of patients. These studies provide early evidence to suggest that CT lung cancer population screening has the potential to reduce lung cancer mortality in the near future.

Henschke et al recently reported encouraging results from ELCAP of screening with spiral CT scan. Included in the initial report were 1,000 symptom-free volunteers, aged 60 years or older, with at least 10 pack-years of cigarette smoking and no previous cancer who were medically fit to undergo thoracic surgery. Noncalcified pulmonary nodules were detected in 233 participants (23% [95% CI: 21-26]) by low-dose CT at baseline, compared with 68 (7% [95% CI: 5-9]) by chest radiography. Lung cancer was detected by CT in 27 patients (2.7% [95% CI: 1.8-3.8]) and by chest radiography in 7 patients (0.7% [95% CI: 0.3-1.3]).

Of the 27 CT-detected cancers, 26 were resectable. Stage I cancers were diagnosed in 23 of 27 patients (85%) by CT and 4 of 7 patients (57%) by chest radiography. In addition, low-dose CT detected four more nonparenchymal cases of lung cancer: two with endobronchial lesions and two in the mediastinum. These cases show an added benefit of low-dose CT over chest radiography, although the data were not included in the analysis. (The study primarily focused on malignant disease in noncalcified pulmonary nodules detected by low-dose CT or radiography.) It remains to be seen, however, whether lung cancer screening with low-dose spiral CT will reduce the lung cancer mortality of the study population or only improve the 5-year survival rate of the patients diagnosed with lung cancer.

Based on growing evidence that spiral CT may truly provide for a successful early detection strategy, the National Cancer Institute (NCI) launched the National Lung Screening Trial (NLST, http://www.nci.nih.gov/NLST) in September 2002. NLST has fully accrued 50,000 current and former smokers (aged 55-74) into a prospective trial, randomizing participants to receive annual spiral CT or annual chest x-rays. Survival data will not be available for a number of years.

The efficacy of lung cancer screening is also being evaluated as part of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO). Men and women were randomized to receive annual chest x-ray vs usual care. Eligibility was not based on risk of lung cancer because given the large size of the study (> 100,000 participants), it was expected that there would be appreciable numbers of current and former smokers among the participants.

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. Individuals 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.

Chemoprevention

Second primary lung tumors develop at a rate of 1%-3% annually for the first 5 years following resection of stage I NSCLC. The retinoid 13-*cis*-retinoic acid (isotretinoin [Accutane]) has reduced the incidence of second primary cancer in head and neck cancer patients in one small randomized trial.

The intergroup randomized trial that assessed the ability of 13-*cis*-retinoic acid to prevent the occurrence of a second primary cancer in patients with completely resected stage I NSCLC showed no impact of treatment on the incidence of second primary tumors. Furthermore, patients who continued to smoke and who received isotretinoin had a higher risk of recurrence of their index cancer. The early findings have demonstrated a higher-than-expected recurrence rate in patients with early-stage lung cancer who received 13-*cis*-retinoic acid and continued to smoke. Also, there was no reduction in second primary tumors in the 13-*cis*-retinoic acid-treated group.

Educational programs Although 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 and is present in nearly 80% of patients with symptomatic lung cancer. It is important to remember, however, that most 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. Although in the case of hemoptysis, 70% of patients are bleeding from nonmalignant causes, mostly infection and more frequently bronchitis. In patients who present with hemoptysis, are older than age 40, and have a history of smoking and chronic obstructive pulmonary disease without abnormality on chest radiograph, lung cancer should be considered in the differential diagnosis.

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 or may obstruct segmental or lobar lymphatics, 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. An MRI scan of the chest apex may be beneficial. 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 anhidrosis).

Hoarseness secondary to vocal cord paresis or paralysis occurs when tumors and lymph node metastases compress, cause dysfunction in, or invade 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, most commonly to bone, liver, brain, lungs (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 patients' 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.

Patients who complain of bandlike 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. If performed in the evaluation of lung cancer, ^{18}F-fluorodeoxyglucose (FDG)-PET supplants the need for bone scanning in most patients. PET appears to be more sensitive but less specific for bone metastases. If plain films are normal or equivocal for metastases, CT and/or MRI may be helpful to evaluate suspicious areas. MRI of the spine is the most effective way to evaluate suspected spinal cord compression.

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. SCLC is associated with hormone production, which causes endocrine syndromes in a subset of patients, such as SIADH (syndrome of inappropriate antidiuretic hormone secretion) and via secretion of ACTH (adrenocorticotropic hormone) hypercortisolism.

Specific neurologic syndromes, such as Lambert-Eaton syndrome (see chapter 45), cortical cerebellar degeneration, and peripheral neuropathy, may occur in lung cancer patients but 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. 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.

TUMOR BIOLOGY

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.

Staging and prognosis

Staging

The staging of lung cancer must be conducted in a methodical and detailed manner. The TNM staging system, updated by Mountain (Table 1), applies equally well to all histologies of NSCLC, but TNM for SCLC is less helpful. Most patients have advanced disease at the time of presentation.

Stage is commonly reported as either clinical or pathologic, designated as c or p, respectively. Clinical stage is based on noninvasive (or minimally invasive) tests, whereas pathologic stage is based on tissue obtained during surgery (see section on "Diagnosis and staging evaluation").

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 unexplained 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 1). Simply, 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 past 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 section on "Promising novel agents").

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.

Diagnosis and 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.

Patients should be questioned specifically about the presence of palpable masses, dysphagia, bone pain, headache, or changes in vision. Careful auscultation and percussion may suggest the presence of atelectasis or pleural effusion. Auscultation of the chest also may provide evidence of large airway obstruction and pulmonary consolidation. Ronchi and wheezing may provide some helpful treatment planning information. An enlarged liver may indicate hepatic metastases.

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TABLE I: 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
TI	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 (whether cytology positive or negative)

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed
N0	No demonstrable metastasis to regional lymph nodes
NI	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
MI	Distant metastasis

Stage grouping

Occult carcinoma	Tx	N0	M0
Stage 0	Tis	N0	M0
Stage IA	TI	N0	M0
Stage IB	T2	N0	M0
Stage IIA	TI	NI	M0
Stage IIB	T2	NI	M0
	T3	N0	M0
Stage IIIA	T3	NI	M0
	TI-3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	MI

Palpation of the neck and supraclavicular fossa Discovery of neck and supraclavicular fossa adenopathy may allow both diagnosis and staging, by needle or open biopsy.

Imaging studies

Chest x-rays provide initial helpful information in patients with new respiratory symptoms. Posteroanterior (PA) and lateral chest x-rays are fundamental in assessing the local extent of the primary tumor and also 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 helpful and well worth the effort expended in their retrieval.

Chest CT, including the entire liver and adrenal glands with 5-10 mm slices, is performed routinely to further define the primary tumor and to identify lymphatic or parenchymal metastases. In a review of 20 studies that assessed the value of CT scan to determine mediastinal lymph node involvement, with an average prevalence of 28%, CT had a pooled sensitivity of 57%, a specificity of 82%, and a negative predictive value (NPV) of 83%. Benign enlargement of mediastinal nodes is more common in patients with postobstructive infection. Histologic confirmation of the presence or absence of tumor within the mediastinal lymph nodes is necessary whenever this information will change treatment recommendations. In patients who are considered surgical candidates, metastatic tumor is found in approximately 15%-20% of mediastinal lymph nodes < 1 cm in greatest diameter.

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 previously mentioned, apical tumors (Pancoast tumors) may be difficult to detect on a chest radiograph but are usually readily apparent on a CT scan.

PET For lung masses, FDG accumulation on PET implies a significant likelihood of malignancy.

Standardized uptake value (SUV) of 2.5 optimizes the sensitivity and specificity of PET in assessing suspicious lung lesions larger than 1 cm. FDG-PET accumulation is not diagnostic for cancer, nor does it exclude a cancer diagnosis. Bronchioalveolar and carcinoid are two cell types that do not readily accumulate FDG. Furthermore, higher SUV lesions do not imply a greater likelihood of cancer; the highest SUVs have been found in inflammatory lesions, such as granulomas and infections.

A review of 18 studies of the utility of PET to assess the mediastinal lymph nodes demonstrated a pooled sensitivity of 84% and a specificity of 89%, with a positive predictive value (PPV) of 79% and an NPV of 93%. Combining the results of CT and PET, the PPV and NPV were 83%-93% and 88%-95%, re-

spectively. Thus, FDG-PET is superior to CT scanning in staging the mediastinal lymph nodes. Fifteen to 20% of patients with a known or suspected diagnosis benefit from a preoperative FDG-PET, because previously unrecognized metastatic disease will be discovered.

Several trials have evaluated the prognostic significance of FDG uptake on PET scan in NSCLC. Utilizing multivariate Cox analysis, these studies noted that SUV, particularly when > 7-10, was an independent prognostic factor.

PET scanning may also prove a valuable tool for evaluation of patients with NSCLC treated with chemoradiotherapy or irradiation. In a study by MacManus et al, the PET response was found to be a powerful predictor of survival.

Adrenal gland The adrenal gland may be the sole site of metastatic disease in as many as 10% of patients with NSCLC. Patients should not be assumed to have metastatic disease and denied a potentially curative operation on the basis of a scan alone. Adrenal masses at least 1 cm that are negative on CT and FDG-PET were found to indicate a low likelihood of malignancy, whereas FDG-PET–positive masses on visual inspection were found to be more likely malignant. Contrast-enhanced MRI-weighted images may assist in achieving a diagnosis. Suspicious adrenal masses should be either biopsied or resected in potentially operable patients to confirm the stage of disease.

Obtaining a tissue diagnosis

The next step is to obtain a histologic or cytologic diagnosis of the radiologically revealed lesion, although preoperative histologic diagnosis need not be obtained in a highly suspicious lung mass without evidence of distant or locoregional metastases (see below).

Central lesions Collecting sputum cytologies for 3 consecutive days provides a cytologic diagnosis for central lesions 71% of the time and for peripheral lesions 49% of the time. A negative sputum cytology result warants further clinical investigation. Flexible bronchoscopy is commonly required to achieve a diagnosis. For central lesions that are exophytic, at least three direct forceps biopsies should be performed to achieve a 74% sensitivity. Washings and brushings add to the sensitivity but by themselves have a sensitivity of 48% and 59%, respectively. Further improved sensitivity is obtained with bronchoscopic fluoroscopically directed transbronchial needle aspiration biopsies. For central lesions, the overall sensitivity for flexible bronchoscopy is 88% in experienced hands.

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). Determining the degree of bronchial involvement assists surgical planning. Bronchoscopy-directed biopsies should be performed to assist in determining the intended line of resection, especially when evaluating for submucosal involvement.

Peripheral lesions Bronchoscopy is less likely to yield a diagnosis in patients with peripherally located lesions. Bronchoscopic ability to make a diagnosis of

TABLE 2: Selective indications for mediastinoscopy

Enlarged N1, N2, or N3 lymph nodes on chest CT scan

FDG-PET–positive mediastinal disease

Centrally located tumors

T2-T4 tumors

malignancy in peripheral lesions is dependent upon the size; for those less than 2 cm, the sensitivity is 33%, and for lesions greater than 2 cm, it is 62%. If a bronchiole is seen traversing or extending to the mass on CT, the sensitivity is reported to be twice as high, nearly 60%.

A CT-guided needle biopsy may diagnose up to 90% of peripheral lung cancers but is dependent on the quality of the CT scan and the experience of the radiologist performing the procedure. The false-negative rate is 20%-30%. Needle biopsy is usually reserved for patients who are not candidates for an operation due to distant metastatic disease or poor health or performance status. If the patient is a candidate for surgery, resection is generally recommended for any suspicious mass whether the result of needle biopsy is positive or nondiagnostic. Therefore, for patients with a suspicious peripheral lesion that is not associated with pleural effusion or mediastinal adenopathy, it is reasonable to proceed directly to surgery.

Mediastinoscopy Mediastinoscopy is a time-tested technique whereby the middle (cervical mediastinoscopy) and the anterior mediastinum may be assessed for direct or metastatic lymph node involvement. In the hands of a specialist, the risk of death; biopsy trauma of local structures such as the great vessels, trachea, or esophagus; bleeding; recurrent nerve paresis; or infection is minimal. Whole-node biopsies may be taken, achieving a great deal of information about the location, degree of nodal involvement, and capsular invasion. There is no evidence that mediastinoscopic biopsy spreads tumor within the mediastinum, worsens the prognosis, or renders eventual surgical mediastinal dissection difficult.

Mediastinoscopy may be performed for the following indications (Table 2): enlarged nodes on CT, positive nodes on PET, centrally located tumors, and T2-T4 tumors. To assess response to therapy, repeat mediastinoscopy has been performed with few complications. Patients with N2 disease may potentially benefit from neoadjuvant treatment. Patients with N3 disease are considered to be stage IIIB and less likely to benefit from surgical resection. There have been a few retrospective reports that have demonstrated survival from induction therapy in patients with microscopic N3 involvement.

Thoracentesis and thoracoscopy Individuals who have pleural effusions should undergo thoracentesis. Video-assisted thoracoscopic surgery (VATS) should be used to assess patients who have cytology-negative effusions. Sixty percent of patients with known pleural disease and effusions will have cytology-negative effusions. However, lung cancer patients with exudative cytol-

ogy-negative effusions and their cytology-positive counterparts appear to have equally poor survival. 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. The role of VATS to assess effusions remains to be elucidated.

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, 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 $\geq$ 2), should have a brain scan. An FDG-PET should be performed to assess for metastatic disease as well as to evaluate the primary and the mediastinum.

Clinical stage III patients Patients who have physical findings, laboratory findings, 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.

To reliably assess for metastatic brain lesions, a high-dose gadolinium (double to triple) brain MRI on a greater than 1.5 T machine with appropriate conformal analysis is far superior to a brain CT and should be used in any patient who can tolerate the procedure.

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 usually have no symptoms. Most tumors are located centrally and exist endobronchially. When they occur, symptoms may include wheezing, recurrent pneumonia, dyspnea, and potentially paraneoplastic syndromes. Bronchoscopy frequently assists in diagnosing the lesion. The finding of a polypoid, pale, firm mass should not lull the bronchoscopist into taking a large-forceps biopsy. First, these masses are frequently vascular, and massive bleeding has been reported; second, the entire mass can be accidentally removed, making it difficult to identify the location of the orgin of the polyp.

Given the bleeding potential, rigid bronchoscopy may be a better way to assess these lesions. Especially with cytology, carcinoid tumors may be difficult to differentiate from small-cell and atypical carcinoid tumors. Carcinoid tumor

should be suspected when a small-cell tumor diagnosis by fine-needle aspiration does not respond to therapy. True carcinoids will have metastatic nodal disease in 5%-10% of patients and have an excellent prognosis with surgical resection. Atypical carcinoid tumors are differentiated from typical tumors in that they have more than two mitotic figures per high-powered field and areas of necrosis.

Unlike its infradiaphragmatic counterpart, pulmonary carcinoid tumors rarely present with paraneoplastic syndromes, including carcinoid, acromegaly, and Cushing syndromes. Therefore, it is only necessary to measure urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion prior to surgery in symptomatic patients. Fewer than 3% of all patients with pulmonary carcinoid tumors can be found to have any detectable urinary 5-HIAA.

Intraoperative staging

Intraoperative staging is an integral part of any operation for lung cancer. In addition to the thorough visual and tactile inspection of the lungs, 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, 4R 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

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 may undergo pulmonary function testing, spirometry, and potentially a diffusing capacity. The results of pulmonary testing should be referenced to the normal values for ethnicity, height, age, and sex.

Forced expiratory volume in 1 second Postoperative respiratory failure rarely occurs if the postresection forced expiratory volume in 1 second (FEV_1) is > 800 mL or > 30% of predicted. Regardless of the extent of the scheduled resection, if the preoperative FEV_1 is < 2 L or < 60% of predicted, 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_tCOa; a= adjusted for the patient's hemoglobin) < 60% of the predicted value or a maximum voluntary ventilation (MVV) < 35% is associ-

ated with increased postoperative morbidity. Patients with a baseline oximetry saturation of less than 90% and those who desaturate with exercise more than 4% have a greater likelihood of postoperative complications. Arterial blood gas $pCO_2 > 45$ mm Hg is an independent risk factor for increased operative morbidity and mortality.

In patients with borderline lung function, further physiologic testing may be required to better estimate pulmonary reserve prior to and after surgery. Quantitative pulmonary effusion scanning may assist in this endeavor. The perfusion portion is used to calculate the percentage of lung to be removed and the estimated postoperative percentage of normal. An additional test is exercise pulmonary function testing. Patients are monitored for heart rate, rhythm, blood pressure, and oxygen consumption. Patients who reach their target heart rate and exercise capacity and who have a maximal oxygen consumption > 1.5 mL/kg/min are less likely to have a postoperative complication.

Pathology

The World Health Organization and the International Association for the Study of Lung Cancer have devised guidelines for the histologic classification of lung cancer, which are revised as necessary (Table 3). The different cell-type classifications are performed using light microscopy and do not require electron microscopy or immunohistochemistry. There are variations in the natural history of the different cell types and potential differences in response to treatment and survival. Overall, 90%-95% of NSCLC is adenocarcinoma, squamous, or large cell, with 3%-4% being mixed tumors, such as adenosquamous carcinoma. Three major types of tumors are included under the NSCLC category: adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma.

Adenocarcinoma is the most common type of NSCLC, accounting for approximately 30%-40% of cases. Of all the types of lung cancer, adenocarcinoma is most likely to occur in nonsmokers or former smokers. It is also 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. In contrast with their metastatic lesions, the primary adenocarcinoma tumor is histologically heterogeneous in 80% of patients, consisting of numerous histologic subtypes, and is classified as "mixed-" or "indeterminate-adenocarcinoma."

Bronchioloalveolar adenocarcinoma (BAC) During the past decade, it has become apparent that the incidence of BAC is increasing. This tumor originates from type II pneumocytes, and it may present as a pneumonic infiltrate, as multiple nodules scattered throughout the lungs, and, occasionally, as a single nodule.

Squamous cell tumors comprise approximately 30% of all cases of lung cancer. These tumors tend to occur in a central location and tend to spread to regional lymph nodes; they are the most likely of all 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 die of local disease without evidence of distant metastases.

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

Treatment

In operable candidates, clinically staged IA, IB, IIA, and IIB NSCLC should undergo anatomic complete surgical resection. Primarily, patients with stage IIIB and IV disease are treated nonoperatively. Although multimodality therapy is routinely recommended for stage IIIA disease, it is recommended that it be performed within a clinical trial.

SURGICAL APPROACH

The appropriate treatment of NSCLC is resection of the lobe containing the tumor. Occasionally, a bilobectomy or pneumonectomy is required. Mortality approximates 3% following lobectomy and 7% following pneumonectomy. A wedge or segmental resection has a three to five 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. Segmentectomy, though, was not studied separately from wedge resection, and more recent evaluation demonstrates that in selected tumors, when the bronchus and vascular supply are individually ligated with a regional node resection, survival appears to be comparable, yet salvages lung parenchyma.

VATS Traditionally, lung cancers have been resected through a posterolateral thoracotomy incision. Muscle-sparing incisions may reduce pain. The current trend is toward an even less invasive approach: lobectomy and lymph node dissection with VATS. This approach appears to offer the same cancer operation and survival with perhaps lower morbidity.

Two VATS methods have been described: the mass hilar ligation technique and individual ligation of the vasculature and airway. Patients with peripheral tumors up to 4-6 cm without clinical hilar or mediastinal adenopathy appear to be good candidates for a VATS procedure. Conversion rates to open thoracotomy are 10%, and hospital stays are usually 3-5 days.

The results of several VATS series show lower complication rates than reported series for thoracotomy, granted a selection bias may have occurred. One small randomized trial showed a significant benefit favoring VATS. Patients have better shoulder function, better performance on the 6-minute walk, and less impairment of vital capacity after VATS than after a thoracotomy. A VATS approach may be better tolerated than other approaches for older patients.

Patients with pathologic stage IA disease have a 70%-80% 5-year survival rate

TABLE 3: WHO and IASLC guidelines for the histologic classification of lung cancer

I	**Adenocarcinoma**
	i. Adenocarcinoma with mixed subtypes
	1. Well-differentiated fetal adenocarcinoma
	2. Mucinous adenocarcinoma
	3. Mucinous cystadenocarcinoma
	4. Clear cell adenocarcinoma
	5. Signet ring adenocarcinoma
	ii. Acinar
	iii. Papillary
	iv. Bronchioloalveolar carcinoma
	1. Mucinous
	2. Nonmucinous
	3. Mixed mucinous and nonmucinous
	v. Solid adenocarcinoma with mucin
II	**Squamous**
	i. Papillary
	ii. Small-cell
	iii. Clear cell
	iv. Basaloid
III	**Large-cell**
	i. Large cell neuroendocrine carcinoma
	ii. Basaloid carcinoma
	iii. Lymphoepithelioma-like carcinoma
	iv. Mixed large-cell neuroendocrine carcinoma
	v. Clear cell carcinoma with rhabdoid phenotype
IV	**Adenosquamous carcinoma**
V	**Carcinomas with pleomorphic, sarcomatous characteristics**
	i. Carcinosarcoma
	ii. Pulmonary blastoma
	iii. Carcinomas with spindle and/or giant cells
	1. Giant cell carcinoma
	2. Spindle cell carcinoma
	3. Pleomorphic carcinoma
	iv. Other
VI	**Carcinoid**
	i. Typical carcinoid
	ii. Atypical carcinoid
VII	**Carcinomas of salivary gland origin**
	i. Adenoid cystic carcinoma
	ii. Mucoepidermoid carcinoma
	iii. Others
VIII	**Unclassified**

Adapted from the World Health Organization. Histologic typing of lung tumors. In: International Classification of Tumors. Geneva, Switzerland: WHO, 1991; Travis WD, Colby TV, Corrin B, et al: World Health Organization: Histological Typing of Lung and Pleural Tumours, 3rd ed. Berlin: Springer-Verlag, 1999.

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 and/or N3 disease) is indicative of advanced disease and is thought by some to represent a contraindication to surgery. Resection of mediastinal disease may have prognostic significance, implications for postoperative care, and potential 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 has completed accrual to a randomized, prospective study comparing survival following mediastinal lymph node sampling vs dissection. Data are still being collected. Also, clinical trials are currently testing preoperative chemotherapy and chemoradiation therapy 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. Nonsurgical treatment appears preferable, or patients should be offered participation in a trial designed to assess the benefits of neoadjuvant therapy. Although patients with stage IIIB tumors are usually treated with irradiation and chemotherapy (see later discussions), 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 5%-15% of patients. The surgical approach, therefore, should be similar to that used in NSCLC. 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

Chemotherapy

Classic postoperative adjuvant chemotherapy has been tested in three randomized trials conducted by the Lung Cancer Study Group (LCSG). For almost 20 years, the relative value of adjuvant chemotherapy for resectable NSCLC has been disputed and debated. In a randomized, prospective study involving 488 patients, Keller et al showed no benefit to adjuvant chemotherapy. The ALPI (Adjuvant Lung Project Italy) study of 1,209 patients also showed no survival benefit. In contrast, the International Adjuvant Lung Cancer Trial (IALT) randomized 1,867 patients to receive cisplatin-based, adjuvant chemotherapy or no treatment. At 5 years, the treatment arm showed a survival advantage of 4.1% ($P = .003$), compared with the observation arm.

Two recently presented trials, the Canadian BR-10 and Cancer and Leukemia Group B (CALGB) 9633, both demonstrated clinically significant improvement in survival, with minimal chemotherapy side effects; cisplatin and vinorelbine were used in the BR-10 trial and carboplatin and paclitaxel were

used in CALGB 9633. These results, in combination with the recent positive findings of the adjuvant trial of UFT (a drug composed of tegafur and uracil mixed at the ratio of 1:4) in patients with stage IB NSCLC, increase the likelihood of adjuvant platinum-based therapy becoming the standard of treatment for patients with stages IB-IIIB NSCLC.

Further data from two subsequent positive adjuvant chemotherapy trials support this new standard. Based on these data, the standard of practice has shifted to chemotherapy for operable NSCLC, either adjuvant or in the induction setting. The potential benefits are higher efficacy of chemotherapy early in the natural history of disease, facilitation of subsequent local therapy, and early eradication of distant micrometastases. Despite these positive data, not all patients benefit from adjuvant chemotherapy.

Stage I disease In one trial, adjuvant therapy with six courses of CAP (cyclophosphamide [Cytoxan, Neosar], Adriamycin [doxorubicin], and Platinol [cisplatin]) failed to produce a significant survival advantage in patients with stage I lung cancer. The IALT demonstrated that modern adjuvant chemotherapy could be provided with a survival advantage. In patients with stage IB disease, CALGB 9335 compared postoperative carboplatin and paclitaxel with surgery alone and found a clinically and significant survival advantage, with minimal morbidity. The Canadian BR-10 trial demonstrated similar results using cisplatin and vinorelbine; patients with stage II disease were included as well.

The current trend is to provide continued observation for stage I patients and involvement in a chemopreventive clinical trial for stage IA patients. For patients with stage IB disease, platinum-based adjuvant chemotherapy (cisplatin or carboplatin combined with a taxane or vinorelbine) should be strongly considered.

Stage II/III disease In two earlier trials, postoperative adjuvant chemotherapy with six 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. In contrast, the IALT and Canadian BR-10 trials demonstrated a clinically significant survival advantage, justifying consideration for adjuvant chemotherapy. There does not appear to be any survival advantage to adding adjuvant mediastinal radiotherapy to chemotherapy, unless there are particularly high risk factors for local recurrence.

Radiation therapy

A trial conducted by the LCSG showed that in patients with squamous cell carcinoma of the lungs and resected N1/N2 disease, administration of postoperative radiation reduced the risk of recurrence in the chest from 20% to 1%. Although there was no improvement in overall survival, postoperative irradiation was associated with a significant improvement in disease-free survival for patients with N2 disease. A trial by the British Medical Research Council reached similar conclusions. In contrast, a prospective, randomized European trial comparing 60 Gy of adjuvant radiation therapy with surgery alone found a survival advantage for the surgery-only arm (50% vs 24%), with no difference in local control.

The preliminary results of the intergroup trial 0139 (RTOG 93-09) have been reported. In this trial, 429 patients with pathologic N2 (stage IIIA) disease were randomized to receive either induction chemoradiation therapy (cisplatin and etoposide and 45 Gy) followed by surgical resection vs definitive chemoradiation therapy (cisplatin and etoposide and 61 Gy). The pathologic complete response rate on the surgical arm was 36%. More treatment-related deaths occurred on the surgical arm (7% vs 1.6% on the chemoradiation arm). The 3-year disease progression-free survival was superior on the surgical arm (29% vs 19%, $P = .02$). The median survival for each arm was 22 months ($P = .51$). There were more early noncancer deaths on the surgical arm, but overall survival curves crossed so that by year 3, overall survival was 15% better on the surgical arm (absolute: 38% vs 33%). Longer follow-up will be needed to determine whether surgery significantly prolongs survival in patients with stage III (pN2) NSCLC (Albain KS, Scott CB, Rusch VR, et al: Proc Am Soc Clin Oncol [abstract] 22:621, 2003).

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.

A 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 controversial. Such therapy should be seriously considered, however, in patients at high risk for locoregional relapse (ie, those with hilar or mediastinal disease, squamous histology, multiple positive lymph nodes or lymph node stations, extracapsular extension, bulky nodal disease, or close or microscopically positive margins). In patients who are receiving adjuvant chemotherapy, it is reasonable to administer the chemotherapy first (as it has been associated with a survival benefit) followed by radiation therapy (for enhanced local control).

Moreover, in a randomized trial by Keller et al, no benefit was shown for concurrent chemoradiation over radiation therapy when in the adjuvant setting for completely resected patients with stage II/IIIA NSCLC. An exception may be in patients with microscopic residual disease (ie, positive margins or extracapsular extension), for whom a delay in radiation therapy may be detrimental. Radiotherapy may be less advantageous if provided more than 6-7 weeks after surgery, and a higher rate of complication is expected in elderly patients with numerous comorbidities, such as chronic obstructive pulmonary disease.

NEOADJUVANT CHEMOTHERAPY OR CHEMORADIATION THERAPY

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

Stage IIIA/IIIB disease The greater effectiveness of current chemotherapeutic regimens to reduce 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 NSCLC. Multiple phase II trials have shown such an approach to be feasible; however, it is not clear that such a strategy improves median or long-term survival over best nonsurgical chemoradiotherapy among patients who initially have more than minimal N2 disease.

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 therapy than in those given preoperative chemotherapy alone.

In an analysis of 686 patients who underwent surgical resection of N2 NSCLC, preoperative chemotherapy was associated with a better survival outcome in a subgroup of patients with clinically evident N2 disease ($P < .0001$) than in those who did not receive preoperative chemotherapy. The 5-year survival rate was 18% for patients treated with preoperative chemotherapy, compared with 5% for those not treated.

Current recommendations In selected patients, preoperative treatment may have a favorable effect on outcome in surgically resectable stage IIIA NSCLC. Although aggressive neoadjuvant approaches may have treatment-associated mortality in the range of 5%-12%, in experienced institutions, potential benefits seem to outweigh the risks. The results of the intergroup randomized trial (see box) comparing preoperative chemoradiation therapy with definitive chemoradiation therapy (in pathologic N2 disease) showed a significant improvement in disease progression-free survival (but not overall survival) in the surgical arm ($P = .02$). Patients with persistently positive N2 disease after induction therapy do not appear to benefit from resection.

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 undergo either surgery alone or chemotherapy (mitomycin [Mutamycin, 6 mg/m² on day 1], ifosfamide [Ifex, 1.5 g/m² on days 1-3], and cisplatin [30 mg/m² on days 1-3]) at 3-week intervals for three 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.

A phase III trial comparing neoadjuvant chemotherapy with paclitaxel/carboplatin vs surgery alone in early-stage NSCLC (the Bimodality Lung Oncology Team [BLOT] vs NOT study) did not reach accrual, and the results are being analyzed. The phase II 3-year survival rates of 64% with this strategy appear promising.

SPECIAL CIRCUMSTANCES

Chest wall invasion and/or bulky hilar disease

Invasion of the chest wall has a poorer prognosis than invasion of the parietal pleura. Patients with chest wall invasion may present with chest wall pain, either constant or pleuritic. Confirmation of chest wall involvement is associated with the presence of pain in the location of involvement, visualization of the tumor transgressing normal chest wall plains, or the demonstration of rib destruction/involvement on plain radiograph, CT, MRI, or bone scan. Patients presumed or found to have chest wall involvement should undergo a full metastatic evaluation, including a chest CT, FDG-PET, brain MRI, and mediastinoscopy. Pretreatment thoracoscopy may be helpful to assess the degree of chest wall and pleural space involvement.

Bulky hilar disease should be evaluated similarly, given the high prevalence of clinically unrecognized metastatic disease in these patients. Furthermore, bronchoscopy is often helpful to detect an endobronchial component, evaluate the bronchial anatomy (given the possibility of carinal or sleeve resection), determine the presence of synchronous or metastatic cancer, and assess submucosal spread to determine the potential line of bronchial resection.

Preoperative radiation or chemoradiation therapy may decrease the tumor bulk and thus decrease the amount of vital tissue necessary for complete resection. In the case of a hilar mass, removing a lobe rather than performing a pneumonectomy will reduce the operative mortality by more than 50%. Radiation doses of 30-64 Gy have been used along with radiation chemosensitizers.

T4 N0/I (nonpleural disease) tumors

Some patients with T4 disease may be surgical candidates and thus have a curative potential. The more commonly involved structures are the carina, left atrium, superior vena cava, vertebral body and aorta. Patients should be thoroughly evaluated for metastatic disease. Those who are not surgical candidates may be considered for chemoradiotherapy without surgery, with a survival rate of approximately 10%-15%.

Satellite nodules

Satellite nodules may occur within the same lobe, a different lobe, or the opposite lung. For patients who have undergone complete resection and possess a satellite nodule within the same lobe and no nodal involvement, survival is between 54% and 70%, nearly the same as for patients with stage I disease without a satellite nodule. However, the survival is significantly worse with a satellite nodule in a separate lobe, with a 5-year survival rate averaging 10%. Most CT-identified satellite lesions in patients with NSCLC are benign. Thus, there should be no attempt to preoperatively diagnose the second lesion in patients with a satellite nodule in the same lobe, but investigation should be considered when satellite leisons are found in different lobes. It is inappropriate to assume that there is metastatic disease.

For patients with suspicious lesions in other lobes or on opposite sides of the chest, there should be a thorough metastatic evaluatinon. In fact, the likelihood that the second lesion is benign or there is a second primary is higher than that of an isolated pulmonary metastasis. In these patients, a core-needle biopsy with histologic confirmation should be performed.

These patients should undergo preoperative chest CT, FDG-PET, and potentially brain MRI to rule out the possibility of metastatic disease. They should then undergo thorough mediastinal evaluation, given the increased likelihood of mediastinal involvement. If the nodules are operable and the histologies appear to be different, complete resection of each of the two separate primaries can be performed, preserving the pulmonary parenchyma. Segmentectomy and even possibly wedge resection may be necessary, although not ideal. The prognosis is associated with the stage of the more advanced of the two primaries and is slightly worse than that for patients with nonsynchronous disease, stage for stage.

Brain metastases

The brain is one of the more common sites of metastatic disease in NSCLC. The median survival in patients treated with steroids alone is approximately 2 months and in those with whole-brain radiation therapy, 6 months. Surgical resection of brain metastases and the primary lung cancer may be considered in selected patients. A thorough evaluation for other metastatic disease should be performed with a chest CT scan, FDG-PET, and an additional brain MRI if the patient has had a brain CT scan. If there is no evidence of metastatic disease, the patient should undergo mediastinoscopy to determine whether there is N2 or N3 disease. If surgery is performed, it should be an R-0 resection to achieve a survival advantage.

Stereotactic radiotherapy may be an alternative to brain surgery, with a similar cure rate. Usually, patients with three or fewer lesions that are peripheral, supratentorial, less than 3 cm, and mediastinal node-negative are more likely to benefit from surgical resection of the brain metastasis(es) and the primary. The role of whole-brain radiation therapy (WBRT) in these patients is controversial, given the morbidity associated with WBRT and the fact that less than half of patients will have further brain recurrence after adequate treatment. Furthermore, the quality of MRI allows for close and detailed follow-up, permitting early detection of recurrence or other new lesions.

The brain lesion should be treated first, and if mediastinoscopy is used, it should precede chemoradiotherapy. The role of induction chemoradiotherapy before lung resection is controversial. The determination and the amount of lung reesected should be the same as those for nonmetastatic patients. The 5-year survival rate is between 16% and 30%.

TREATMENT OF PATIENTS WITH MEDICALLY INOPERABLE STAGE I/II DISEASE

Some patients with resectable stage I or II NSCLC are high-risk operative candidates because of poor cardiopulmonary function or other medical problems. 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. Although the results are not as good as those reported in patients selected for surgery (possibly due to differences in patient selection and between clinical vs pathologic staging), patients with medically inoperable early-stage NSCLC clearly should be offered radiation therapy, with reasonable expectation of cure. Timmerman et al reported the results of a phase I study of extracranial stereotactic radioablation (ESR) in patients with medically inoperable stage I NSCLC. ESR was delivered in 3 fractions over 2 weeks, with a starting dose of 800 cGy per fraction. The dose was escalated to 2,000 cGy per fraction for 3 fractions (6,000 cGy total). Of 36 patients, 1 developed grade 3 hypoxemia and another, symptomatic radiation pneumonitis. The maximum tolerated dose was not reached.

Radiofrequency ablation

Patients who are not operative candidates may be treated with radiofrequency ablation (RFA). There is considerable experience with RFA for cancer in other organs, and its use for lung cancer is growing. It can be performed either intraoperatively or percutaneously with CT guidance. The preliminary findings show these radiologic results: complete response (0%), partial response (50%), stable disease (30%), and disease progression (20%).

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%, with poor local control and early development of distant metastatic disease.

Altered fractionation schedules A randomized trial compared standard daily radiation therapy (66 Gy) with a continuous hyperfractionated accelerated radiation therapy regimen [CHART] that delivered 54 Gy over 2½ weeks. The altered fractionation schedule resulted in improved 2-year survival.

Various efforts are under way to look at combining altered fractionation schema with chemotherapy. Although the preliminary results of Radiation Therapy Oncology Group (RTOG) 94-10 do not favor altered fractionation (see section on "Concurrent vs sequential chemoradiation therapy"), the long-term results of another study support this strategy. Jeremic et al compared hyperfractionated

radiation therapy (bid to 69.6 Gy) and concurrent low-dose daily carboplatin/etoposide with or without weekend carboplatin/etoposide in a randomized trial of approximately 200 patients. Although investigators found no benefit with the addition of weekend carboplatin/etoposide, both arms demonstrated promising median survival times of 20 and 22 months and excellent 5-year survival ratios of 20% and 23%.

Conformal radiation therapy

Hayman et al reported updated results of the Michigan phase I dose-escalation trial of three-dimensional (3D) conformal radiation therapy for NSCLC. In this study, 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 in purposely unirradiated, clinically uninvolved nodal regions. This strategy is beginning to be integrated with chemotherapy.

Socinski et al reported a dose-escalation radiotherapy (from 60-74 Gy) trial, using 3D computer-assisted planning techniques, in patients receiving induction carboplatin and paclitaxel and concurrent weekly carboplatin/paclitaxel. Ninety-seven percent (31 of 32) of the patients completed therapy to 74 Gy, as planned. The grade 3/4 esophagitis rate overall was relatively low at only 11%. Moreover, the results found a promising median survival of 26 months and 3-year survival of 47%.

Interestingly, investigators at M. D. Anderson Cancer Center found that the maximum tolerated dose (MTD) of gemcitabine (Gemzar) administered weekly concurrent with conventional (two-dimensional) thoracic irradiation was only 125 mg/m²/wk × 7 weeks vs 190 mg/m²/wk × 7 weeks utilizing 3D conformal radiotherapy. Further escalation of the radiation therapy dose in the context of chemotherapy will need to be evaluated.

Chemoradiation therapy

Chemoradiation vs radiation therapy alone At least 11 randomized trials have compared thoracic irradiation alone with chemoradiation therapy 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 therapy: Three of these trials employed sequential chemoradiation therapy and the other three employed concurrent chemoradiation therapy.

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

The first of the concurrent chemoradiation therapy trials, the European Organization for Research and Treatment of Cancer (EORTC) trial 08844, compared radiotherapy alone with radiotherapy and concomitant (daily or weekly) low-dose cisplatin therapy. This study demonstrated a significant survival advantage for daily cisplatin and radiotherapy compared with radiotherapy alone

(3-year survival rates, 16% vs 2%); the weekly cisplatin/radiation therapy 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 with a combination of hyperfractionated radiotherapy and carboplatin plus etoposide (administered weekly or every other week) demonstrated 3-year survival rates of 7%, 23%, and 16%, respectively ($P = .003$).

In the third phase III concurrent chemoradiation therapy trial, the combination of hyperfractionated radiation therapy and low-dose daily chemotherapy (carboplatin plus etoposide) was superior to hyperfractionated radiation therapy 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 therapy 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 therapy, the improvement in survival rates over irradiation alone appeared to be linked to a decrease in the development of distant metastases. In contrast, in the three positive trials employing concurrent chemoradiation therapy, 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 irradiation 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 therapy Furuse et al evaluated mitomycin, vindesine, and Platinol (MVP), administered either concurrently or prior to thoracic irradiation (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 et al also reported the patterns of failure, which demonstrated a benefit of concurrent chemoradiotherapy in improving the local relapse-free survival ($P = .04$) but not the distant relapse-free survival ($P = .6$).

Curran et al recently presented the long-term results of a larger randomized trial (> 600 patients) comparing sequential vs concurrent chemoradiotherapy (RTOG 9410). The 4-year survival with concurrent cisplatin/vinblastine and once-daily irradiation was 21% vs 12% with sequential treatment ($P = .04$). The third treatment arm (concurrent cisplatin/oral etoposide and hyperfractionated irradiation) was intermediate, with a 4-year survival of 17%.

The role of altered radiation therapy fractionation, though, deserves further study. ECOG 2597 randomized patients after induction chemotherapy (with carboplatin and paclitaxel) to receive either standard radiation therapy (64 Gy/ 2 Gy fraction) vs hyperfractionated accelerated radiation therapy (HART), 57.6 Gy delivered 1.5 Gy tid over 2.5 weeks. Although the study closed prematurely

due to poor accrual (only 111 patients were eligible), the median survival in the investigational arm appeared promising (22 months).

Movsas et al reported the results of a quality-adjusted time without symptoms of toxicity (QTWiST) analysis of RTOG 94-10. Despite the increase in reversible nonhematologic toxicities in the concurrent arms, the overall mean toxicity was highest in the sequential arm, which involved the longest treatment time. The concurrent once-daily arm had the optimal QTWiST, further supporting concurrent chemoradiation therapy as a new treatment paradigm.

Recently, two randomized phase II trials also appear to support the use of concurrent chemoradiation therapy for locally advanced NSCLC. Choy et al performed a randomized phase II study in 276 patients of three chemoradiation therapy regimens with paclitaxel, carboplatin, and thoracic irradiation in their locally advanced multimodality protocol (LAMP). They found that concurrent chemoradiation therapy followed by adjuvant chemotherapy appeared to have the best therapeutic outcome, with a median survival of 16.1 months, compared with either induction chemotherapy followed by concurrent chemoradiation therapy (median survival, 11 months) or sequential chemotherapy followed by irradiation (median survival, 12 months).

Similarly, in another randomized phase II study, Zatloukal et al studied 102 patients treated with concurrent chemoradiation therapy and sequential chemotherapy followed by irradiation. The chemotherapy consisted of four cycles of cisplatin and vinorelbine (Navelbine). The investigators reported a median survival in the concurrent arm of ~20 months, vs ~13 months in the other arm ($P = .02$).

Movsas et al reported the results of the first Patterns of Care Study (PCS) for lung cancer, which was conducted to determine the national patterns of radiation therapy practice in patients treated for nonmetastatic lung cancer. As supported by clinical trials, the PCS for lung cancer demonstrated that patients with clinical stage III NSCLC received chemotherapy plus radiation therapy more than radiation therapy alone ($P < .0001$). In clinical stage I NSCLC, though, radiation therapy alone was the primary treatment ($P < .0001$). Factors correlating with increased use of chemotherapy included lower age ($P < .0001$), histology (SCLC > NSCLC, $P < .0001$), increasing clinical stage ($P < .0001$), increasing Karnofsky performance status ($P < .0001$), and lack of comorbidities ($P = .0002$) but not academic vs nonacademic facilities ($P = .81$). Of all patients receiving chemotherapy, approximately three-quarters received it concurrently with radiation therapy. Only 3% of all patients were treated on Institutional Review Board-approved trials, demonstrating the need for improved accrual to clinical trials.

New chemotherapeutic agents plus irradiation Several recent phase I/II trials evaluated carboplatin and paclitaxel given concurrently with thoracic irradiation. 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, including docetaxel (Taxotere),

vinorelbine, gemcitabine, UFT, and irinotecan (CPT-11, Camptosar). A trial from Japan tested induction chemotherapy with irinotecan and cisplatin followed by radiation therapy with weekly irinotecan (30 mg/m^2 during radiation therapy). The study reported a response rate of 65% and a median survival rate of 16.5 months, with a grade 3/4 esophagitis rate of only 4%.

Typically, it can be difficult to deliver systemic doses of chemotherapy following concurrent chemoradiotherapy. However, the Southwest Oncology Group (SWOG) recently reported a phase II study of concurrent chemoradiation therapy (cisplatin/etoposide) followed by consolidation docetaxel (75-100 mg/m^2 q21d × 3). This group of patients with pathologically documented stage IIIB NSCLC (pleural effusion excluded) had a promising median survival of 27 months. Toxicity during consolidation consisted primarily of neutropenia (56% grade 4).

Current treatment recommendations

At present, it is reasonable to consider concurrent chemoradiation therapy (with once-daily radiation therapy) as a new treatment paradigm in stage III (inoperable) lung cancer patients with an ECOG performance status of 0/1 who have not lost more than 5% of their usual body weight.

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 newer chemotherapeutic agents have produced response rates in excess of 20% in NSCLC (Table 4). 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. Paclitaxel and docetaxel increase polymerization of tubulin; gemcitabine is an antimetabolite; and irinotecan is a topoisomerase I inhibitor.

Furthermore, randomized trials demonstrated that a combination of a newer agent plus cisplatin significantly improves the response rate over cisplatin monotherapy (historically considered the most active agent for NSCLC). This increase in response rate translates into significant, although modest, improvement in survival (Table 5).

Optimal chemotherapy for advanced NSCLC

Until the early 1990s, regimens of cisplatin plus a vinca alkaloid or etoposide were most common. More recently, regimens that employ newer agents are more widely used. However, choosing one regimen from many options is a difficult task because there is no survival advantage documented for one regimen over another or standard regimen vs regimens containing newer agents.

Table 6 summarizes the results of selected randomized trials in which combination regimens containing a newer agent are compared with old "standard" regimens or regimens containing another newer agent. Subtle differences in the eligibility criteria (eg, inclusion of patients with stage III tumors or those with poor performance status) make it difficult to directly compare the trial results. Nevertheless, there is a trend indicating that regimens containing newer agents show higher response rates and also better survival outcome in some series than do older regimens.

Vinorelbine plus cisplatin combination
Vinorelbine was the first agent that demonstrated improved activity against NSCLC in combination with cisplatin. The European multicenter trial reported by LeChevalier showed the results favoring cisplatin plus vinorelbine combination (vinorelbine, 30 mg/m^2 weekly; cisplatin, 120 mg/m^2 on days 1 and 29, then every 6 weeks) over a vindesine plus cisplatin combination (vindesine, 3 mg/m^2 weekly; cisplatin, 120 mg/m^2 on days 1 and 29, then every 6 weeks) and vinorelbine alone (30 mg/m^2 weekly). The median survival duration of 40 weeks in the vinorelbine/cisplatin treatment arm was significantly longer than the 32 weeks in the vindesine/cisplatin arm ($P = .04$) and 31 weeks in the vinorelbine monotherapy arm ($P < .001$). This trial, however, did not confirm the role of vinorelbine in NSCLC therapy, even though it confirmed the role of cisplatin.

To address this issue, SWOG conducted a study comparing cisplatin alone (100 mg/m^2 every 4 weeks) with vinorelbine/cisplatin combination (cisplatin, 100 mg/m^2 every 4 weeks; vinorelbine, 25 mg/m^2 weekly × 3 every 4 weeks). Survival outcome was analyzed for 415 patients, 92% with stage IV tumors. The vinorelbine/cisplatin treatment significantly improved the disease progression-free survival (median, 2 vs 4 months; $P = .0001$) and overall survival (median, 6 vs 8 months; 1-year survival 20% vs 36%; $P = .0018$).

Recently, Comella et al reported interim analysis results of a phase III trial of the Southern Italy Cooperative Oncology Group. A three-drug regimen (cisplatin, gemcitabine, and vinorelbine) was associated with a substantial survival gain over the cisplatin and vinorelbine regimen (median survival time, 51 and 35 weeks, respectively).

Movsas et al reported the results of RTOG 98-01, a phase III study of amifostine (500 mg IV 4×/wk) in patients with locally advanced NSCLC receiving chemotherapy and hyperfractionated radiation therapy. Seventy-three percent received amifostine per protocol or with minor deviation. On the amifostine arm, there were significantly higher rates of low-grade acute nausea and vomiting, acute cardiovascular toxicity, mostly transient hypotension, and episodes of acute infection/febrile neutropenia. The rate of grade ≥ 3 esophagitis was 30% with amifostine vs 34% without amifostine ($P = .9$). Based on daily patient diaries, though, the swallowing dysfunction area under the curve was lower with amifostine ($P = .03$). Overall, amifostine did not reduce grade ≥ 3 esophagitis per the NCI-CTC criteria. However, direct patient assessment suggests a possible advantage to amifostine that is being explored with modified dosing/route strategies (Movsas B, Scott C, Langer C, et al: Proc Am Soc Clin Oncol [abstract] 22:636, 2003).

TABLE 4: Active newer agents for NSCLC chemotherapy

Agent	Number of studies	Number of patients	Response rate (%) (range)
Irinotecan	3	150	34 (32-37)
Docetaxel	7	257	33 (21-54)
Paclitaxel	4	151	22 (10-24)
Gemcitabine	7	566	21 (20-26)
Vinorelbine	4	501	21 (12-32)

Paclitaxel plus platinum compound A number of studies demonstrate promising results with paclitaxel in combination with cisplatin or carboplatin and other agents. Two large randomized trials compared paclitaxel plus cisplatin with standard regimens. In a three-arm, randomized ECOG trial (ECOG 5592) reported by Bonomi et al, 600 eligible patients with chemotherapy-naive stage IIIB to IV NSCLC were randomly assigned to receive a combination of cisplatin (75 mg/m^2) plus etoposide (100 mg/m^2 daily on days 1 to 3) vs either low-dose (135 mg/m^2 over 24 hours) or high-dose (250 mg/m^2 over 24 hours with growth factor) paclitaxel plus cisplatin (75 mg/m^2). The response rates for the low-dose and high-dose paclitaxel arms were 26.5% and 32.1%, respectively, significantly better than the cisplatin/ etoposide arm (12.0%). Superior survival was observed with the combined paclitaxel regimens (median survival time, 9.99 months; 1-year survival rate, 39.1%) compared with etoposide plus cisplatin (median survival time, 7.69 months; 1-year survival rate, 31.6%; $P = .048$). Comparing survival rates for the two dose levels of paclitaxel revealed no significant differences.

In a European trial of similar design reported by Giaccone et al, cisplatin/ paclitaxel improved the response rate and quality-of-life parameters. There was no improvement in overall survival, however, compared with a standard regimen of cisplatin/teniposide (Vumon).

Paclitaxel/carboplatin has been the most widely favored regimen for first-line chemotherapy in all NSCLC stages among US medical oncologists, mainly due to promising phase II trial results and the ease of administration as outpatients, with manageable toxicity profiles compared with cisplatin-containing regimens. One of the early phase II trials, for example, reported a response rate of 62%, a median survival duration of 53 weeks, and a 1-year survival rate of 54%. However, a randomized trial sponsored by the manufacturer of paclitaxel failed to demonstrate a survival advantage over the standard cisplatin plus etoposide regimen. Nevertheless, paclitaxel plus carboplatin may remain a community standard because a recently completed SWOG trial reported results equivalent to the time-tested vinorelbine/cisplatin regimen (see Table 6).

Second-line chemotherapy A randomized phase III study conducted by the CALGB further supported the superiority of combination chemotherapy over

TABLE 5: Results of selected randomized trials of chemotherapy comparing cisplatin alone vs cisplatin plus a newer agent in advanced NSCLC

Investigator	Chemotherapy regimen	Pts (n)	Response rate (%)	Median survival (mo)	1-yr survival (%)
Klastersky (1989)	Cisplatin	81	19	6.0	NA
	Cisplatin + etoposide	81	26[a]	5.	NA
Wozniak (1998)	Cisplatin	209	12	6	20
	Cisplatin + vinorelbine	206	26	8[a]	36[a]
Gatzemeier (1998)	Cisplatin	206	17	8.6	NA
	Cisplatin + paclitaxel	202	26[a]	8.1	NA
Sandler (1998)	Cisplatin	262	10	7.6	28
	Cisplatin + gemcitabine	260	26[a]	9.0[a]	39[a]
Von Pawel (1998)	Cisplatin	219	13.7	6.3	21
	Cisplatin + tirapazamine	218	27.5[a]	8.5[a]	33[a]

[a] The difference between the groups was statistically significant ($P < .05$).

NA = data not available

single-agent therapy. Previous trials had indicated that a platinum plus a novel agent was superior to a platinum alone. Lilenbaum et al demonstrated that for patients with stage IIIB-IV NSCLC, carboplatin and paclitaxel are superior to paclitaxel alone, even for patients with a performance status of 2. This randomized trial showed a median survival advantage for the combination therapy.

Gemcitabine plus cisplatin Gemcitabine is also approved by the FDA for use against NSCLC based on a series of successful phase II trials of cisplatin/gemcitabine and three major phase III trials. The Hoosier Oncology Group study, reported by Sandler et al, compared gemcitabine/cisplatin with cisplatin alone and showed a modest improvement in median and 1-year survival comparable to that seen in the vinorelbine trials (Table 5). The Spanish and Italian trials, reported by Cardenal et al and Crino et al, compared gemcitabine plus cisplatin with standard-regimen cisplatin plus etoposide and mitomycin plus ifosfamide plus cisplatin, respectively. Although there was a significant improvement in overall response, these two studies failed to demonstrate a survival benefit.

Since gemcitabine is relatively well tolerated without dose-limiting myelosuppression, it is being evaluated for use as a single agent or in combination with other agents in older or medically compromised patients. Italian investigators report that gemcitabine combined with vinorelbine regimen is associated with significantly better survival than single-agent vinorelbine in elderly patients with NSCLC.

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NON–SMALL-CELL LUNG CANCER

Other combination regimens that contain cisplatin plus newer agents, such as docetaxel or irinotecan, also showed similar results when compared with other two-drug regimens of either two newer or two older agents (Table 6).

Major randomized trials comparing new regimens

To identify a better chemotherapy regimen for advanced-stage NSCLC, the US cooperative study groups conducted large phase III trials. The SWOG investigators compared paclitaxel/carboplatin with vinorelbine/cisplatin (the time-tested regimen in previous European and SWOG trials). A total of 404 evaluable patients were randomized to receive either paclitaxel (225 mg/m^2 over 3 hours) plus carboplatin (at an area under the curve [AUC] of 6 mg/mL × min on day 1) every 21 days or vinorelbine (25 mg/m^2 weekly) plus cisplatin (100 mg/m^2 on day 1) every 28 days. Overall response rates were 27% for both groups. The median survival times were also identical (8 months), with virtually identical 1-year survival rates (35% and 33%, respectively). Although both regimens provided effective palliation for advanced NSCLC, the investigators identified paclitaxel/carboplatin for future studies because of a favorable toxicity profile and better tolerability and compliance.

The ECOG 1594 trial compared three platinum-based regimens containing new agents in the treatment of NSCLC with a control arm of cisplatin and paclitaxel. The regimens were gemcitabine (1,000 mg/m^2 on days 1, 8, and 15) plus cisplatin (100 mg/m^2 on day 1) every 4 weeks, docetaxel (75 mg/m^2) plus cisplatin (75 mg/m^2 on day 1) every 3 weeks, and paclitaxel (225 mg/m^2 over 3 hours) plus carboplatin (at AUC of 6 mg/mL × min on day 1) every 21 days; the reference regimen was paclitaxel (175 mg/m^2 over 24 hours) plus cisplatin (75 mg/m^2 on day 1) every 21 days.

Analysis of 1,163 eligible patients showed no statistically significant differences in overall response rates, median survival, and 1-year survival rates when compared with the control arm, paclitaxel and cisplatin. Gemcitabine plus cisplatin was associated with a statistically significant prolongation of time to disease progression when compared with the control arm (4.5 vs 3.5 months, $P = .002$) but was also associated with a higher percentage of grade 4 thrombocytopenia, anemia, and renal toxicity.

Since all the regimens showed similar efficacy, quality of life becomes a critical issue in choosing a particular regimen. The decision to use one regimen over another will depend not only on ease of administration and side effects, but also on the personal preference and experience of the treating oncologist.

Second-line chemotherapy for NSCLC

Before the new generation of more effective agents became available, few, if any, significant benefits were expected from second-line chemotherapy. As a result, reports in the literature seldom address this issue specifically or systematically. The most experience with second-line chemotherapy in NSCLC is with docetaxel, which has received FDA approval for this indication based on two randomized phase III trials confirming the promising phase II results of docetaxel monotherapy in patients with advanced NSCLC previously treated with platinum-based chemotherapy.

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TABLE 6: Results of selected randomized trials evaluating chemotherapy regimens of newer agents in advanced NSCLC

Investigator	Chemotherapy regimen	No. of patients	Response rate (%)	Median survival	1-yr survival rate (%)
LeChevalier (1994)	Vinorelbine + cisplatin	206	30	40 wk	35
	Vindesine + cisplatin	200	19	32 wk	27
	Vinorelbine	206	14	31 wk	30
Bonomi (1996)	Etoposide + cisplatin	600	12.0	7.69 mo	31.6
	Paclitaxel + cisplatin	(total)	26.5	9.56 mo	36.9
	Paclitaxel + cisplatin + G-CSF		32.1	9.99 mo	39.1
Giaccone (1997)	Teniposide + cisplatin	157	28	9.9 mo	41
	Paclitaxel + cisplatin	152	41	9.7 mo	43
Belani (1998)	Etoposide + cisplatin	179	14.0	9.9 mo	37
	Paclitaxel + carboplatin	190	21.6	9.5 mo	32
Crino (1998)	Mitomycin + ifosfamide + cisplatin	152	28	38 wk	NA
	Gemcitabine + cisplatin	154	40	35 wk	NA
Georgoulias (1999)	Docetaxel + cisplatin	152	32	10 mo	42
	Docetaxel + gemcitabine	144	34	9 mo	34
Masuda (1999)	Irinotecan + cisplatin	378	43	50.3 wk	47.5
	Vindesine + cisplatin	(total)	31	47.4 wk	37.9
	Irinotecan		21	46.1 wk	40.7
Kelly (1999)	Paclitaxel + carboplatin	184	27	8 mo	36
	Vinorelbine + cisplatin	181	27	8 mo	33
Schiller (2000)	Paclitaxel + cisplatin	1,163	21.3	7.8 mo	31
	Gemcitabine + cisplatin	(total)	21.0	8.1 mo	36
	Docetaxel + cisplatin		17.3	7.4 mo	31
	Paclitaxel + carboplatin		15.3	8.2 mo	35
Frasci (2000)	Gemcitabine + vinorelbine	60	22	29 wk	30
	Vinorelbine	60	15	18 wk	13
Lilenbaum (2002)	Paclitaxel + carboplatin	292	29	10 mo	NA
	Paclitaxel	290	17	8.6 mo	NA

G-CSF = granulocyte colony-stimulating factor; NA = data not available

In a multicenter US trial reported by Fossella et al, 373 patients were random-ized to receive either docetaxel, 100 mg/m² (D100) or 75 mg/m² (D75) vs a control regimen of vinorelbine (30 mg/m²/wk) or ifosfamide (2 g/m² × 3 days) every 3 weeks. Overall response rates were 10.8% with D100 and 6.7% with D75, each significantly higher than the 0.8% response of the control arm ($P = .001$ and $P = .036$, respectively). Although overall survival was not significantly different among the three groups, the 1-year survival was significantly higher with D75 than with the control treatment (32% vs 19%; $P = .025$).

The second trial reported by Shepherd et al compared single-agent docetaxel with best supportive care. The initial docetaxel dose was 100 mg/m^2, which was changed to 75 mg/m^2 midway into the trial because of toxicity. A total of 204 patients were enrolled; 49 received D100, 55 received D75, and 100 received best supportive care. Treatment with docetaxel was associated with significant prolongation of survival (7.0 vs 4.6 months; log-rank test, $P = .047$) and time to disease progression (10.6 vs 6.7 weeks, $P < .001$).

Duration of chemotherapy

The American Society of Clinical Oncology (ASCO) has recommended that no more than eight cycles of chemotherapy be administered to patients with stage IV NSCLC. However, therapy should be individualized depending on the quality of tumor response and the patient's tolerance.

Novel and promising 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 (eg, erlotinib [Tarceva], gefitinib [Iressa]), antiangiogenic agents, and monoclonal antibodies (C225 [antiepidermal growth factor receptor antibody] and trastuzumab [Herceptin]). Many of these novel agents are being tested in combination with chemotherapeutic agents, as their mechanisms of action suggest that they 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. Further research has focused on the novel small molecule tyrosine kinase inhibitors erlotinib and gefitinib. Two phase II trials of gefitinib in the second- and third-line settings were conducted in Europe and Japan. Patients were randomized to receive either 250 mg/d or 500 mg/d. The drug was found to be active, with an 11%-18% response rate, and there was no superiority for the higher dose. Similar data were seen for erlotinib.

Unfortunately, randomized combination trials of gefitinib at 250 and 500 mg/d with cytotoxic chemotherapy, either paclitaxel and carboplatin in one trial or gemcitabine and cisplatin in the other study vs placebo in front-line therapy, failed to demonstrate any survival advantage. These results have cast a pall over the development of tyrosine kinase inhibitors in combination with chemotherapy. Regardless, the question of whether or not to approve these new agents for third-line therapy of lung cancer in cisplatin/docetaxel-refractory patients remains open for debate.

The activity demonstrated by the tyrosine kinase inhibitors gefitinib and erlotinib as single agents in advanced NSCLC generated much optimism, including a

recent trial indicating that erlotinib improved survival (by a median of 2 months) in the second- and third-line treatment of NSCLC, with a substantial increase in 1-year survival ($P < .001$). After the initial successes with chemotherapy and promising results from targeted tyrosine kinase inhibitors in stages IIIB and IV NSCLC, several large phase III trials of either gefitinib or erlotinib in combination with conventional platinum-based chemotherapy were conducted as the INTACT 1 and INTACT 2 trials or the TALENT and TRIBUTE trials.

Unfortunately, these large trials indicated no benefit to adding the tyrosine kinase inhibitors to conventional chemotherapy. A phase III trial combining the farnesyl transferase inhibitor lonafarnib (Sarasar) with paclitaxel and carboplatin in unselected, untreated patients with stage IIIB/IV NSCLC also failed to yield a survival advantage, despite promising phase I and II data. There was evidence that the combination of the chemotherapy with the signal transduction inhibitors was potentially detrimental. The placebo plus chemotherapy results initially showed a survival benefit over the first 6 months in two of these four trials. Survival data after 6 months from the INTACT II and the TRIBUTE trial indicate that from that point forward, patients who remained on erlotinib or gefitinib appeared to have a significant survival benefit, when compared with placebo.

In general, there appears to be little to favor triplet cytotoxic drug combinations vs doublet combinations in NSCLC. An area of great excitement, however, has been the addition of novel biologically or molecularly targeted agents to cytotoxic chemotherapy combinations. Several recent trials have demonstrated the potential advantages of adding a small molecule targeted to either the epidermal growth factor receptor (EGFR) or *ras* (namely the farnesyl transferase inhibitors). The interest in these agents in advanced NSCLC appears to have superseded the new cytotoxic agents with activity in other diseases, such as oxaliplatin (Eloxatin), tirapazamine, and UFT. A phase III combination of farnesyl transferase with paclitaxel and carboplatin failed to show superiority over paclitaxel and carboplatin.

The mechanisms of action of these new small molecules are widely divergent, and their combinations with the cytotoxics may not necessarily lead to an enhanced response rate. Khuri and colleagues demonstrated, however, that the combination of cisplatin, vinorelbine, and bexarotene (Targretin, a retinoid-X-receptor [RXR]-specific novel retinoid) resulted in substantial median and 2-year survival rates in patients with stage IIIB NSCLC with malignant pleural effusion or stage IV NSCLC. Median survival in this multicenter study was 14 months in the phase II portion; 2-year survival was 32%; and 3-year survival was 18%. The combination yielded modest response rates (25%), not markedly superior to what was expected with cisplatin and vinorelbine alone.

This finding has led to an uncoupling of the requirement for higher response rates when adding cytotoxic agents to one another in the belief that adding these novel biologic agents may lead to enhanced survival. There now appears to be a great deal of promise associated with several small molecules, either alone or combined with chemotherapy. Novel agents such as gefitinib or the farnesyl transferase inhibitor lonafarnib have shown promising efficacy in small

A phase III trial of 731 patients conducted by the National Cancer Institute of Canada Clinical Trials Group sought to determine whether erlotinib (Tarceva) prolonged survival in patients with advanced NSCLC whose disease had progressed after first- or second-line chemotherapy. The overall response rate to erlotinib was 8.9% ($P < .001$), with a median response duration of 34.3 weeks. Overall survival (6.7 vs 4.7 mo, $P = .001$) and disease progression-free survival (2.23 vs 1.84 mo, $P < .001$) were significantly greater in the erlotinib arm than in the placebo arm. (Shepherd FA, et al: Proc Am Soc Clin Oncol [late-breaking abstract 7022] 23, 2004). Tarceva was approved for second-line treatment of advanced NSCLC in November 2004.

trials that have included patients with NSCLC; gefitinib alone resulted in an 18% response rate in second- or third-line therapy for NSCLC in a study population recruited across several continents.

Some provocative phase I and II data with both bexarotene and lonafarnib in combination with chemotherapy have led to the recent launch of phase III trials of both agents in combination with cytotoxic chemotherapy. These trials are ongoing and are expected to accrue between 600 and 800 patients over the next 2 years. The trials will test whether the preclinical and clinical synergy seen with these compounds and either platinums or taxanes is vindicated in phase III front-line trials of NSCLC.

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 patients with stage IV NSCLC 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 (Tables 7 and 8).

ROLE OF PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT), which 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 patients with NSCLC. Nevertheless, PDT appears to be particularly useful for the treatment of early-stage lung cancer for a variety of reasons. First, it appears to 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. Second, 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.

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 42.9% if the lesion was > 1 cm. The overall survival rate in these patients was 50% at 3 years.

In a phase III trial led by Hanna et al, 572 previously treated patients were randomized to receive pemetrexed (Alimta) with vitamin B_{12}, folic acid, and dexamethasone or docetaxel (Taxotere) with dexamethasone. The overall response rate in the pemetrexed arm was higher, 9.1% vs 8.8%. The median disease progression-free survival was 2.9 months for each arm, and the median survival favored pemetrexed (8.3 vs 7.9 mo). The 1-year survival for each arm was 29.7%. Adverse reactions (grade 3/4) were more severe with docetaxel (Hanna N, Shepherd FA, Fossella FV, et al: J Clin Oncol 22:1589-1597, 2004).

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 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/Canadian) compared PDT with 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/Canadian trial, all of the patients had 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/Canadian trials, respectively, were still responding, 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/Canadian 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). Early-stage lung cancer, most specifically endobronchial squamous cell carcinomas smaller than 1 cm, is effectively treated, with a complete response rate of 75% and a recurrence rate of 30% over 5 years.

TABLE 7: Single-agent chemotherapy regimens for NSCLC

Drug	Dose and schedule
Vinorelbine	30 mg/m^2 IV weekly

LeChevalier T, Brisgand D, Douillard J-Y, et al: J Clin Oncol 12:360–367, 1994.

Drug	Dose and schedule
Vinorelbine	For patients 70 years old or older: 30 mg/m^2 IV on days 1 and 8, every 21 days

Gridelli C, Perrone F, Cigolari S, et al: Proc Am Soc Clin Oncol [abstract] 20:308a, 2001.

Drug	Dose and schedule
Docetaxel	75 mg/m^2 IV on day 1 every 3 weeks

Shepherd FA, Dancey J, Ramlau R, et al: J Clin Oncol 18:2095–2103, 2000.

Drug	Dose and schedule
Pemetrexed	500 mg/m^2 IVPB every 3 weeks

Dexamethasone (4 mg by mouth twice daily) should be started a day before and a day after pemetrexed. All patients should also receive folic acid (350-1,000 mg/d) started about a week before and thereafter while taking pemetrexed. Vitamin B$_{12}$ (1,000 mg IM) should be started about 1 to 2 weeks before pemetrexed and every 9 weeks while taking pemetrexed.

Hanna N, Shepherd F, Fossella FV, et al: J Clin Oncol [abstract] 22:1589–1597, 2004.

Drug	Dose and schedule
Gefitinib	250 mg orally once a day

Kris MG, Natale RB, Herbst RS, et al: JAMA 290:2149–2158, 2003.

Drug	Dose and schedule
Gemcitabine	1,000 mg/m^2 IV on days 1, 8, and 15 every 4 weeks

Vansteenkiste J, Vandebroek J, Nackaerts K, et al: Proc Am Soc Clin Oncol [abstract] 19:1910a, 2000.

Table prepared by Ishmael Jaiyesimi, DO

PALLIATION OF LOCAL AND DISTANT SYMPTOMS

Radiation therapy

Many patients with lung cancer experience distressing local symptoms at some time. They 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 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 irradiation appears to be superior to radiation therapy alone in improving both survival and quality of life.

Recent studies have demonstrated varying degrees of benefit for strategies beyond palliative whole-brain radiation therapy (WBRT) in the management of brain metastases. Sperduto et al reported the results of RTOG 95-08, a randomized trial comparing WBRT (3,750 cGy in 250 cGy fractions) vs WBRT

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and stereotactic radiosurgery (SRS) in 333 patients with one to three brain metastases. They found a statistically significant survival advantage with WBRT and SRS for the stratified group of patients with solitary brain metastases (mean survival, 6.5 vs 4.9 months; $P=.04$). Other subsets that appeared to benefit included those with NSCLC. Patients in the WBRT and SRS group were more likely to have a stable or improved performance status than those in the WBRT-alone group.

In another randomized trial, 401 patients with unresected brain metastases (Karnofsky performance score > 70) were randomized to receive WBRT (30 Gy) with or without the redox mediator motexafin gadolinium (MGd). Overall, there was no improvement in survival, but time to neurologic disease progression (as determined by investigators) was significantly prolonged with MGd ($P=.02$). Interestingly, the benefit of MGd was primarily seen in lung cancer (which made up 63% of the cases). This has led to a trial of this agent specifically for patients with brain metastases from NSCLC.

A large prospective trial of gefitinib (Iressa) in patients with bronchoalveolar carcinoma (BAC) conducted by the Southwest Oncology Group (SWOG S0126), found that 19% of 102 previously untreated patients with measurable disease responded to the drug. Among 67 chemotherapy-naive patients with measurable disease, the response rate was 21%. In 21 previously treated patients, the response rate was 10%. The median survival was 12 months and 10 months for chemotherapy-naive and previously treated patients, respectively. The 1-year survival in each group was about 50%. Adverse events included acneiform rash and diarrhea (*West H, Franklin WA, Gumerlock PH, et al: Proc Am Soc Clin Oncol [abstract] 23:618, 2004*).

In another randomized trial, Antonadou et al compared WBRT with or without temozolomide (TMZ, Temodar), 75 mg/m^2 daily during WBRT and 1 month afterward (at 200 mg/m^2) on days 1-5 q 28 days × six cycles. A total of 134 eligible patients were randomized to undergo treatment, 82% with lung primaries. Median survival was 8.3 months in the TMZ plus WBRT arm and 6.3 months in the WBRT arm ($P=.18$). Of note, a significantly higher response rate was observed in the combined-modality arm (53%) than in the WBRT arm (33%, $P=.04$). The optimal management of patients with brain metastases should be tailored to the individual situation.

Doses In the United States, radiation oncologists often use doses of ~30 Gy in 10 fractions for palliative treatment in lung cancer. 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 10 Gy (see Table 9). Such schedules may facilitate the coordination of irradiation and chemotherapy and also reduce patient travel and hospitalization.

Recently, just over 400 patients with inoperable NSCLC (stage III/IV) were randomized to receive three different fractionation regimens (8.5 Gy × 2, 2.8 Gy × 15, or 2.0 Gy × 25). Using the EORTC Quality-of-Life Questionnaire (QLQ) C-30 with the lung cancer-specific module (LC-13), Sundstrom et al found the effect of hypofractionated irradiation (17 Gy in 2 fractions) was comparable to that with longer fractionation schemes with regard to symptom relief and survival.

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TABLE 8: Combination chemotherapy regimens recommended for NSCLC

Regimen	Agents	Dose and schedule	Treatment interval
PE	Platinol Etoposide	60 mg/m^2 IV on day 1 120 mg/m^2 IV on days 1-3	3 weeks
MIC	Mitomycin Ifosfamide Cisplatin	6 mg/m^2 IV on day 1 3 g/m^2 IV on day 1 100 mg/m^2 IV on day 2	4 weeks
PT	Platinol Taxol	75 mg/m^2 IV on day 2 135 mg/m^2 IV on day 1 (24-h infusion)	3 weeks
CP	Carboplatin Paclitaxel	AUC of 6 IV on day 1 225 mg/m^2 IV on day 1 (3-h infusion)	3 weeks
PG	Platinol Gemcitabine	100 mg/m^2 IV on day 1 1,000 mg/m^2 IV on days 1, 8, and 15	4 weeks
PD	Platinol Docetaxel	75 mg/m^2 IV on day 1 75 mg/m^2 IV on day 1	3 weeks
PV	Platinol Vinorelbine	100 mg/m^2 IV on day 1 25 mg/m^2 IV on days 1, 8, 15, and 22	4 weeks
GV	Gemcitabine Vinorelbine	1,200 mg/m^2 IV on days 1 and 8 30 mg/m^2 IV on days 1 and 8	3 weeks

AUC = area under the curve

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 the lungs, 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. It remains unclear, however, how often this complication is actually due to the irradiation vs the underlying disease itself.

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 than for complete airway obstruction.

TABLE 9: Percentage of patients with symptoms of NSCLC palliated by external-beam irradiation

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.

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.

A randomized phase II study suggests that rhuMAb vascular endothelial growth factor (VEGF; 15 mg/kg) in combination with carboplatin/paclitaxel chemotherapy may increase response rates and prolong time to disease progression in patients with previously untreated NSCLC when compared with carboplatin/paclitaxel chemotherapy alone. Patients with progressive disease who received carboplatin/paclitaxel alone were allowed to cross over to receive rhuMAb VEGF. The median survival time was 7.7 months with high-dose rhuMAb VEGF (15 mg/kg q3wk) and 4.9 months with carboplatin/paclitaxel alone. Although sudden and life-threatening hemoptysis occurred in six rhuMAb VEGF-treated subjects and was fatal in four, survival data are encouraging, and a phase III trial is in progress without crossover to rhuMAb VEGF.

Thus, although 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 emergencies may be considered for palliative chemotherapy, which may relieve local symptoms and prolong survival.

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Bisphosphonates

Approximately 30%-65% of patients with advanced lung cancer develop bone metastases. The median survival following development of bone metastases is 6 months. Bone disease is associated with significant morbidity, including severe pain, hypercalcemia of malignancy, pathologic fracture, and spinal cord or nerve root compression. Treatment of bone metastases may include surgical intervention, radiation therapy, and chemotherapy. Bisphosphonate treatment can decrease skeleton-related complications, delay progressive disease, and relieve bone pain.

Bisphosphonates such as clodronate, pamidronate (Aredia), and zoledronic acid (Zometa) exhibit strong affinity for the hydroxyapatite crystal of bone and preferentially accumulate at sites of active bone remodeling, where they prevent bone resorption. They provide effective treatment for hypercalcemia of malignancy and have been shown to delay the onset of progressive bone disease and relieve bone pain in studies largely performed in patients with metastases secondary to breast cancer, multiple myeloma, and prostate cancer. Nitrogen-containing bisphosphonates, such as pamidronate and zoledronic acid, appear to exert antitumor effects. Zoledronic acid has also been found to have pronounced antinociceptive effects, which have been absent with other bisphosphonates in preclinical studies. Zoledronic acid is the only bisphosphonate shown to be effective in reducing skeletal complications in patients with bone metastases from lung cancer and solid tumors other than breast and prostate cancers.

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 patients with SCLC 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 screeing trial.

SUGGESTED READING

American College of Chest Physicians; Health and Science Policy Committee: Diagnosis and management of lung cancer: ACCP evidence-based guidelines. Chest 123(1 suppl):D-G, 1S–337S, 2003.

Belani CP, Wang W, Johnson DH, et al: Induction chemotherapy followed by standard vs thoracic radiotherapy vs hyperfractionated accelerated radiotherapy for patients with unresectable stage III A + B NSCLC: Phase III study of the Eastern Cooperative Oncology Group (ECOG 2597) (abstract). Proc Am Soc Clin Oncol 22:622, 2003.

Curran WJ Jr, Scott C, Langer CJ, et al: Long-term benefits observed in a phase III comparison with sequential vs concurrent chemoradiation for patients with unresected stage III NSCLC: RTOG 9410 (abstract). Proc Am Soc Clin Oncol 22:621, 2003.

Fukuoka M, Yano S, Giaccone G, et al: Final results from a phase II trial of ZD 1839 (Iressa) for patients with advanced non–small-cell lung cancer (IDEAL 1) (abstract). Proc Am Soc Clin Oncol 21:298a, 2002.

Gandara DR, Chansky K, Albain KS, et al: Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non–small-cell lung cancer: Phase II Southwest Oncology Group Study S9504. J Clin Oncol 21:2004–2010, 2003.

Giaccone G, Johnson DH, Manegold C, et al: A phase III clinical trial of ZD 1839 (Iressa) in combination with gemcitabine and cisplatin in chemotherapy-naive patients with advanced non–small-cell lung cancer (INTACT 1) (abstract). Ann Oncol 13:2, 2002.

Ichinose Y, Tada H, Koike T, et al: A randomized phase III trial of postoperative adjuvant chemotherapy in patients with completely resected stage IIIA-N2 non–small-cell lung cancer: Japan Clinical Oncology Group (JCOG 9304) trial (abstract). Proc Am Soc Clin Oncol 20:311, 2001.

Johnson DH, Herbst R, Giaccone G, et al: ZD 1839 (Iressa) in combination with paclitaxel and carboplatin in chemotherapy-naive patients with advanced non–small-cell lung cancer (NSCLC) (abstract). Ann Oncol 13:127, 2002.

Kato H, Tsuboi M, Ohta M, et al: A randomized phase III trial of adjuvant chemotherapy with UFT for completely resected pathological stage 1 adenocarcinoma of the lung (abstract). Proc Am Soc Clin Oncol 22:621, 2003.

Kawahara M, Hosoe S, Fukuoka M, et al: A phase II study of induction chemotherapy with CPT-11 and cisplatin followed by thoracic radiotherapy combined with weekly CPT-11 in patients with unresectable stage III NSCLC: Final results of Japan Clinical Oncology Group protocol 9706 (abstract). Proc Am Soc Clin Oncol 21:316, 2002.

Kris MG, Natale RB, Herbst RS, et al: A phase II trial of ZD 1839 (Iressa) in advanced non–small-cell lung cancer (NSCLC) patients who had failed platinum- and docetaxel-based regimens (IDEAL 2) (abstract). Proc Am Soc Clin Oncol 21:292, 2002.

LeChevalier T, for the IALT Investigators: Results of the randomized International Adjuvant Lung Cancer Trial (IALT): Cisplatin-based chemotherapy (ct) vs no ct in 1,867 patients with resected non-small cell lung cancer (abstract). Proc Am Soc Clin Oncol 22:2, 2003.

Lilenbaum RC, Herndon J, List M, et al: Single-agent vs combination chemotherapy in advanced NSCLC (abstract). Proc Am Soc Clin Oncol 21:1, 2002.

Martelli M, Clerici M, Cognetti F, et al: Adjuvant Lung Project Italy/European Organisation for Research Treatment of Cancer–Lung Cancer Cooperative Group Investigators: Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non–small-cell lung cancer. J Natl Cancer Inst 95:1453–1461, 2003.

Movsas B, Moughan J, Komaki R, et al: Radiotherapy (RT) Patterns of Care Study (PCS) in lung carcinoma. J Clin Oncol 21:4553–4559, 2003.

Movsas B, Scott C, Langer C, et al: A phase III study of amifostine in patients with locally advanced NSCLC receiving chemotherapy and hyperfractionated radiation: Radiation Therapy Oncology Group 98-01 (abstract). Proc Am Soc Clin Oncol 22:636, 2003.

Pisters K, Ginsberg R, Giroux D, et al: Phase II Biomodality Lung Oncology Team (BLOT) trial of induction paclitaxel/carboplatin (PC) in early-stage non–small-cell lung cancer (NSCLC): Effect of number of induction cycles, sites of relapse, and survival (abstract). Proc Am Soc Clin Oncol 20:323, 2001.

Rosen LS, Bordon D, Tchekmedyian S, et al: Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: A phase III, double-blind, randomized trial–The Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. J Clin Oncol 21:3150–3157, 2003.

Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non–small-cell lung cancer. N Engl J Med 2:92–98, 2002.

Sperduto P, Scott C, Andrews D, et al: Stereotactic radiosurgery with whole-brain radiation therapy improves survival in patients with brain metastases: Report of Radiation Therapy Oncology Group Phase III Study 95-08. Int J Radiat Oncol Biol Phys 54:3, 2002.

Strauss GM, Herndon J, Maddaus MA, et al: Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small-cell lung cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) protocol 9633 (abstract). Proc Am Soc Clin Oncol 22(14S):621, 2004.

Sundstrom S, Bremnes RM, Aasebo U, et al: Effect of hypofractionated palliative radiotherapy (17 Gy/2 fractions) is comparable with standard fractionation in advanced NSCLC: Results from a national phase III trial (abstract). Proc Am Soc Clin Oncol 21:300, 2002.

Timmerman R, Papiez L, Likes R, et al: Extracranial stereotactic radioablation: Results of a phase I study in medically inoperable stage I non–small-cell lung cancer patients (abstract). Proc Am Soc Clin Oncol 21:317, 2002.

Winton TL, Livingston R, Johnson D, et al: A prospective randomized trial of adjuvant vinorelbine (VIN) and cisplatin (CIS) in completely resected stage IB and II non small cell lung cancer (NSCLC) Intergroup JBR-10 (abstract). Proc Am Soc Clin Oncol 22(14S):621, 2004.

Stages III and IV breast cancer

Lori Jardines, MD, Bruce G. Haffty, MD, Melanie Royce, MD, PhD, and Ishmael Jaiyesimi, MD

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 lungs, liver, and bone.

The optimal therapy for stage III breast cancer continues to evolve. Recently, the use of neoadjuvant chemotherapy has been effective in downstaging locally advanced breast cancer 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.

STAGES III-IV BREAST

Fine-needle aspiration (FNA) or biopsy The diagnosis of breast cancer can be confirmed by either FNA cytology or core biopsy. Core biopsy is preferred to perform the wide variety of marker analyses.

Search for 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. [18]Fluorodeoxyglucose-positron emission tomography (FDG-PET) has moderate accuracy for detecting axillary metastasis. It is highly predictive for nodal tumor involvement when multiple intense foci of tracer uptake are identified but fails to detect small nodal metastasis. The addition of FDG-PET to the standard workup of patients with locally advanced breast cancer may lead to the detection of unexpected distant metastases. Abnormal PET findings should be confirmed to prevent patients from being denied appropriate treatment.

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 breasts

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 of metastasis; this is especially important when only a single distant lesion is identified.

Metastasis to the breasts

The most common source of metastatic disease to the breasts is a contralateral breast primary. Metastasis from a nonbreast primary is rare, representing < 1.5% of all breast malignancies. Some malignancies that could metastasize to the breast include non-Hodgkin's lymphoma, leukemias, melanoma, lung cancer (particularly small-cell lung cancer), gynecologic cancers, soft-tissue sarcomas, and GI adenocarcinomas. Metastasis to the breasts from a nonbreast pri-

mary is more common in younger 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 breasts 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, core biopsy or even open biopsy may be necessary to distinguish 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 them 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 [Cytoxan, Neosar], doxorubicin [Adriamycin], and fluorouracil [5-FU]), FAC (5-FU, Adriamycin, and cyclophosphamide), CMF (cyclophosphamide, methotrexate, and 5-FU), and CMFVP (cyclophosphamide, methotrexate, 5-FU, vincristine, and prednisone). Combination chemotherapy with

TABLE 1: Doses and schedules of chemotherapy agents commonly used in patients with metastatic breast cancer

Drug/combination	Dose and schedule
FAC	
5-FU	500 mg/m^2 IV on days 1 and 8
Adriamycin	50 mg/m^2 IV on day 1
Cyclophosphamide	500 mg/m^2 IV on day 1
Repeat cycle every 3-4 weeks.	
TAC	
Taxotere	75 mg/m^2 IV on day 1
Adriamycin	50 mg/m^2 IV on day 1
Cyclophosphamide	500 mg/m^2 IV on day 1
Repeat cycle every 21 days.	
FEC	
5-FU	500 mg/m^2 IV on day 1
Epirubicin	100 mg/m^2 IV on day 1
Cyclophosphamide	500 mg/m^2 IV on day 1
Repeat cycle every 21 days. _Note: An absolute granulocyte count < 1,500/mm^3 and/or platelet count <100,000/mm^3 on day 21 will cause a treatment delay of at least 1 week. Treatment wil be terminated if hematology recovery takes more than 3 weeks._	
Paclitaxel	175 mg/m^2 by 3-h IV infusion every 3 weeks or 80-100 mg/m^2/week
Docetaxel	60-100 mg/m^2 by 1-h IV infusion every 3 weeks or 40 mg/m^2/week
Repeat if hematologic recovery has occurred (ie, absolute granulocyte count ≥ 1,500/μL and platelet count ≥ 100,000/μL).	
Capecitabine	2,000 to 2,500 mg/m^2 PO bid (divided dose, AM and PM) for 14 days, followed by 1-week rest
Repeat cycle every 21 days.	
Capecitabine + docetaxel	
Capecitabine	1,000 to 1,250 mg/m^2 orally twice daily on days 1 to 14, followed by 1-week rest
Docetaxel	75 to 100 mg/m^2 IV infusion over 1 hour
Repeat cycle every 3 weeks.	
Vinorelbine + trastuzumab	
Vinorelbine	25 mg/m^2 IV on day 1 every week
Trastuzumab	4 mg/kg IV loading dose, then 2 mg/kg IV every week

an anthracycline-based regimen—FAC or AC—is used most often. Recently published data suggest that the AT regimen of Adriamycin and docetaxel (Taxotere) given concomitantly may produce equivalently high response rates. Combination agents for metastatic breast cancer also include paclitaxel plus trastuzumab (Herceptin) with carboplatin (Paraplatin), gemcitabine (Gemzar)

Drug/combination	Dose and schedule
Docetaxel or paclitaxel + carboplatin + trastuzumab (every-3-week dosing)	
Docetaxel	75 mg/m^2 IV on day 1 every 21 days
	OR
Paclitaxel	175 mg/m^2 IV on day 1 every 21 days
	PLUS
Carboplatin	AUC of 5 to 6 on day 1 every 21 days
	PLUS
Trastuzumab	4 mg/kg IV loading dose on day 1, followed by 2 mg/kg weekly
Note: Patients must be premedicated with dexamethasone prior to docetaxel.	
Trastuzumab	4 mg/kg IV loading dose, then 2 mg/kg weekly
	8 mg/kg IV loading dose, then 6 mg/kg every 3 weeks
Paclitaxel or docetaxel + carboplatin + trastuzumab (weekly dosing)	
Paclitaxel	80 mg/m^2 IV on day 1 every week
	OR
Docetaxel	35 mg/m^2 IV on day 1 every week
	PLUS
Carboplatin	AUC 2 IV on day 1 every week
	PLUS
Trastuzumab	4 mg/kg IV loading dose, then 2 mg/kg every week
Gemcitabine + paclitaxel	
Gemcitabine	1,250 mg/m^2 IV on days 1 and 8 (as a 30-minute infusion) every 21 days
Paclitaxel	175 mg/m^2 IV on day 1 (over 3 hours) every 21 days
Note: Standard paclitaxel premedications should be given.	
Pegylated doxorubicin	
Doxil	30 to 50 mg/m^2 IV on day 1 every 21 to 28 days

and paclitaxel, and capecitabine (Xeloda) and docetaxel (Table 1). Although not yet definitive, recent data indicate that enhancing dose density may increase the pathologic complete response rate for women with locally advanced disease. The doses of these combination chemotherapy regimens are given in Table 1, chapter 10.

There seems to be no difference in survival in women with locally advanced disease who receive chemotherapy before or after surgery. Neoadjuvant chemotherapy results in complete response rates ranging from 20%-53% and partial response rates ($\geq$ 50% reduction in bidimensionally measurable disease) ranging from 37%-50%, with total response rates ranging from 80%-90%. Patients with large lesions are more likely to have partial responses. Pathologic complete responses (pCRs) do occur and are more likely to be seen in patients with smaller tumors. A pCR in the primary tumor is often predictive of a com-

plete axillary lymph node response. Patients with locally advanced breast cancer who have a pCR in the breast and axillary nodes have a significantly improved disease-free survival rate compared with those who have less than a pCR. However, a pCR does not entirely eliminate the risk for recurrence.

Patients should be followed carefully while receiving neoadjuvant systemic therapy to determine treatment response. In addition to clinical examination, it may also be helpful to document photographically the response of ulcerated, erythematous, indurated skin lesions. Physical examination, mammography, and breast ultrasonography are best for assessing primary tumor response, whereas physical examination and ultrasonography are used to evaluate regional nodal involvement.

The role of MRI in evaluating response to preoperative chemotherapy is still evolving. Dynamic contrast-enhanced MRI performed at baseline, during chemotherapy, and before surgery has yielded more than 90% diagnostic accuracy in identifying tumors achieving a pCR and can potentially provide functional parameters that may help to optimize neoadjuvant chemotherapy strategies. However, despite its high sensitivity, a large number of patients still may have either false-negative or false-positive results on MRI scanning.

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 and 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. Patients who have been downstaged using neoadjuvant chemotherapy should be evaluated carefully before proceeding with conservative treatment. It may be helpful to mark the site of the primary tumor with the placement of a clip during the course of percutaneous biopsy prior to beginning adjuvant therapy. There can sometimes be a complete clinical and/or radiographic response after neoadjuvant chemotherapy or hormonal therapy, and this may facilitate a wide local incision.

The role of sentinel node biopsy in the treatment of breast cancer after neoadjuvant chemotherapy has yet to be defined. Studies have shown that pathologically positive axillary lymph nodes can be sterilized when neoadjuvant che-

```
                    FAC × 4 courses

    ┌──────────────────────┐        ┌──────────────────────┐
    │ Adequate response    │        │ Inadequate response  │
    │ for negative         │        │ for negative         │
    │ margin surgery       │        │ margin surgery       │
    └──────────────────────┘        └──────────────────────┘

         Surgeryᵃ                     Switch to
                                      taxane-based
                                      chemotherapy
```

FAC × 4 courses

Adequate response for negative margin surgery → **Surgery**ᵃ → **Additional systemic therapy (4–6 cycles of FAC)** → **Radiation therapy**

Inadequate response for negative margin surgery → **Switch to taxane-based chemotherapy** →

- **Adequate response for negative margin surgery** → **Surgery** → **Radiation therapy**
- **Inadequate response for negative margin surgery** → **Radiation therapy** → **Surgery if operable**

For women with hormone-receptor–positive tumors (ER and/or PR positive): endocrine therapy

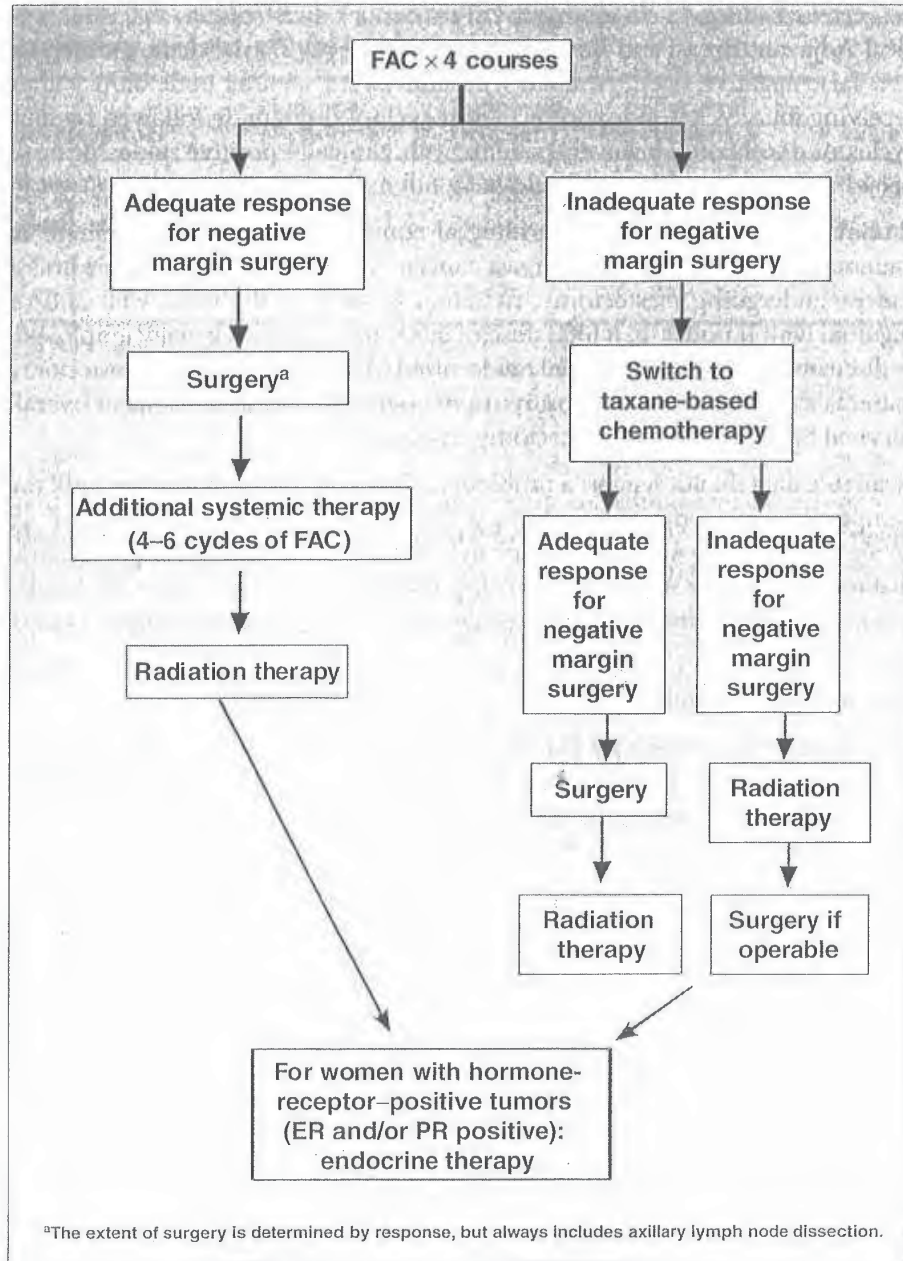ᵃThe extent of surgery is determined by response, but always includes axillary lymph node dissection.

FIGURE 1: Multimodality approach to locally advanced breast cancer

motherapy is utilized. There are other biologic concerns with sentinel node biopsy after neoadjuvant chemotherapy. The lymphatics may undergo fibrosis or may become obstructed by cellular debris, making the mapping procedure unreliable, with false-negative rates of up to 25%. The rate of conversion from positive to negative nodes can be enhanced when four cycles of a doxorubicin-based regimen are followed by four cycles of docetaxel. Sentinel node biopsy will only be accurate then if all the metastatic deposits within the axilla respond

in a similar fashion to chemotherapy. Preliminary data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial demonstrated an 11% false-negative rate in women who underwent sentinel node biopsy after receiving four cycles of doxorubicin and cyclophosphamide followed by four cycles of docetaxel. However, patients with clinically positive nodes prior to neoadjuvant chemotherapy should have full node dissection.

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 postmastectomy patients with any number of positive nodes derive a disease-free and/or overall survival benefit from postmastectomy irradiation.

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, irradiation is generally indicated following mastectomy for patients with locally advanced disease (primary tumors $\geq$ 5 cm and/or $\geq$ four 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.

In the largest trial yet reported, investigators from all of the bone marrow transplant centers in the Netherlands randomly assigned 885 women with stages II and III breast cancer with four or more tumor-positive nodes to a standard therapy arm of five courses of FEC (5-FU, epirubicin [Ellence], and cyclophosphamide) followed by radiation therapy and tamoxifen or an investigational treatment arm of four cycles of FEC followed by high-dose chemotherapy with cyclophosphamide, thiotepa, and carboplatin with peripheral blood stem-cell support followed by radiation therapy and tamoxifen. After a median follow-up of 57 months, there was a trend for improved 5-year relapse-free survival rates in the high-dose group, but it was not statistically significant (hazard ratio [HR] = 0.83; $P = .09$). In the subgroup of patients with 10 or more positive nodes, however, the relapse-free survival rate reached statistical significance (HR = 0.71; $P = .05$). There was also a suggestion that the benefit seen in the high-dose group may be confined to patients with HER-2/*neu*-negative tumors.

The second-largest trial evaluating 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,

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

Investigators	Number of patients	Follow-up (median)	Survival benefit?	P value
Rodenhuis et al	885	36 mo	Yes	$P < .05$
Peters et al	783	36 mo	No	NS
Scandinavian Breast Cancer Study Group	525	20 mo	No	NS

NS = not significant

and carmustine (BiCNU) with autologous stem-cell support following adjuvant therapy with cyclophosphamide, doxorubicin, and 5-FU. Preliminary results of this study, with 783 participants, showed a reduction in relapse frequency of over 30% in patients receiving high-dose chemotherapy; a 3-year survival rate of 68% was observed 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 historic data showing a 30% 5-year disease-free survival rate with conventional-dose chemotherapy.

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 the context of a clinical trial, high-dose chemotherapy cannot be recommended for patients with primary or metastatic breast cancer.

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%-2.0% 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%-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 local recurrence had synchronous distant metastatic disease.
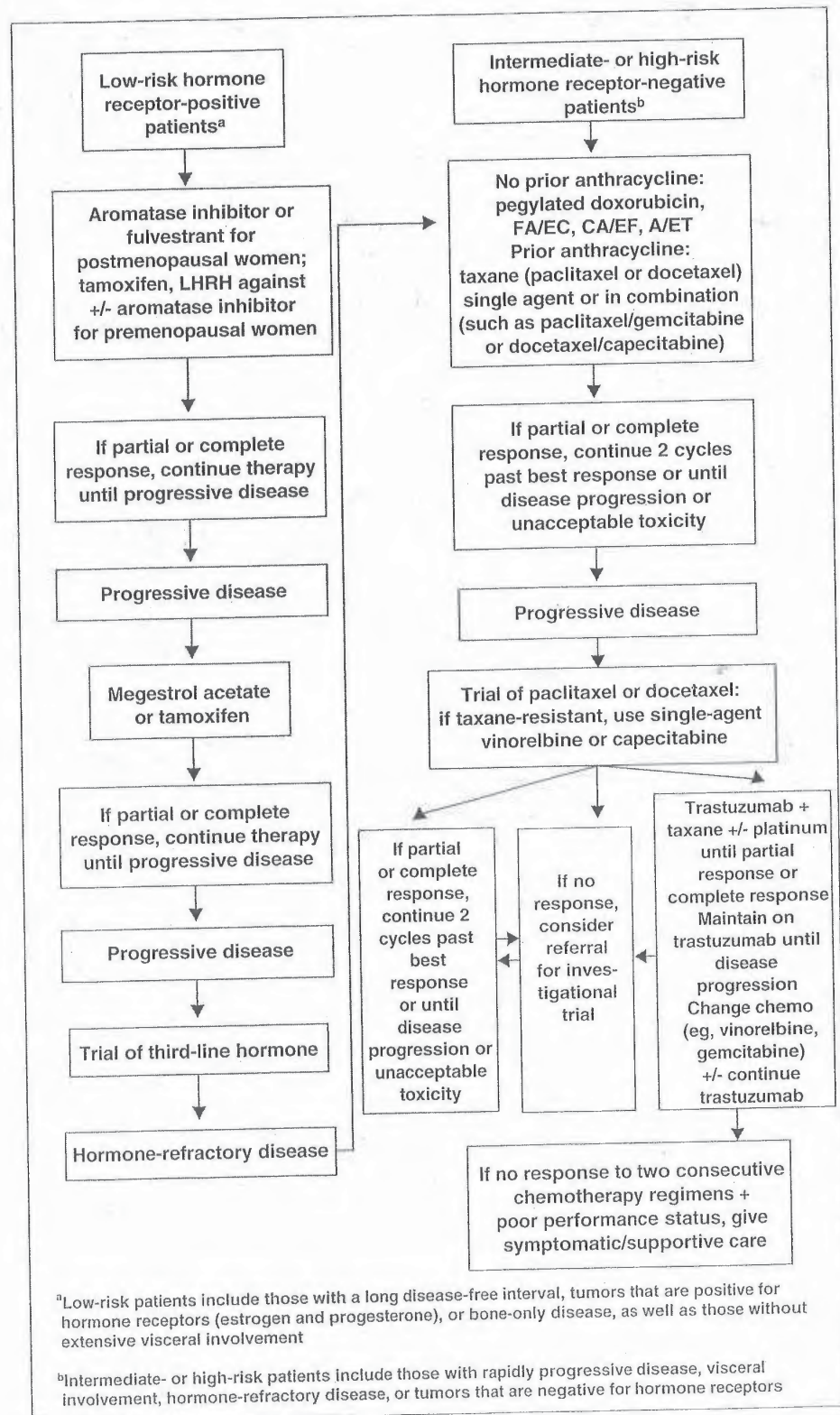
Low-risk hormone receptor-positive patients[a]

↓

Aromatase inhibitor or fulvestrant for postmenopausal women; tamoxifen, LHRH against +/- aromatase inhibitor for premenopausal women

↓

If partial or complete response, continue therapy until progressive disease

↓

Progressive disease

↓

Megestrol acetate or tamoxifen

↓

If partial or complete response, continue therapy until progressive disease

↓

Progressive disease

↓

Trial of third-line hormone

↓

Hormone-refractory disease

Intermediate- or high-risk hormone receptor-negative patients[b]

↓

No prior anthracycline: pegylated doxorubicin, FA/EC, CA/EF, A/ET Prior anthracycline: taxane (paclitaxel or docetaxel) single agent or in combination (such as paclitaxel/gemcitabine or docetaxel/capecitabine)

↓

If partial or complete response, continue 2 cycles past best response or until disease progression or unacceptable toxicity

↓

Progressive disease

↓

Trial of paclitaxel or docetaxel: if taxane-resistant, use single-agent vinorelbine or capecitabine

↓

If partial or complete response, continue 2 cycles past best response or until disease progression or unacceptable toxicity

If no response, consider referral for investigational trial

Trastuzumab + taxane +/- platinum until partial response or complete response Maintain on trastuzumab until disease progression Change chemo (eg, vinorelbine, gemcitabine) +/- continue trastuzumab

↓

If no response to two consecutive chemotherapy regimens + poor performance status, give symptomatic/supportive care

[a]Low-risk patients include those with a long disease-free interval, tumors that are positive for hormone receptors (estrogen and progesterone), or bone-only disease, as well as those without extensive visceral involvement

[b]Intermediate- or high-risk patients include those with rapidly progressive disease, visceral involvement, hormone-refractory disease, or tumors that are negative for hormone receptors

FIGURE 2: Treatment approach to metastatic breast cancer.

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 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 irradiation 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 repeated 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.

Recurrent disease in the chest wall 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 postmastectomy irradiation 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.

A double-blind, placebo-controlled study of exemestane (Aromasin) demonstrated that it had a modest effect on bone loss in women with early-stage postmenopausal breast cancer who had already undergone surgery and irradiation. The investigators evaluated its effects on bone loss in 147 women with bone mineral density (BMD) levels that fell within 2 SDs of the mean level for women aged 65. Patients were randomized to receive exemestane orally for 2 years or placebo. Exemestane was well tolerated, and no patient who had a normal BMD level at baseline developed osteoporosis. Of the 19 patients with osteopenia at baseline, 6 in the exemestane arm and 5 in the placebo arm developed osteoporosis in the spine, and 3 in the exemestane arm and 5 in the placebo arm developed osteoporosis in the femoral neck. A total of nine patients had bone fractures. The authors concluded that exemestane had no effect on the spine and little effect on the femoral neck (Lonning PE, Geisler J, Krag LE,s et al: Proc Am Soc Clin Oncol [abstract] 23:6, 2004).

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 study conducted at Yale University 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 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 postmastectomy recurrence of disease in the chest wall

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 fol-

lowing radiation therapy at the time of postmastectomy recurrence of disease in the chest wall in patients with estrogen-receptor–positive tumors. 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 the 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 or high risk, based on the biologic aggressiveness of the disease. As shown schematically in Figure 2, the management approach to these two groups differs.

To determine whether weekly infusion of paclitaxel improves response rates vs the standard 3-hour infusion, 577 patients with metastatic breast cancer who had received one or two prior regimens were randomized to receive standard (175 mg/m^2) or weekly (80 mg/m^2) paclitaxel. Weekly paclitaxel was shown to be superior with respect to response rate (40% vs 28%, P = .017), time to disease progression (9 vs 5 mo, P = .0008), and overall survival (24 vs 16 mo). When trastuzumab became standard therapy for HER-2–positive tumors, all patients with HER-2–positive disease received trastuzumab, whereas patients with HER-2–negative disease were randomized to receive either addition of trastuzumab or not. The addition of trastuzumab did not improve any of these end points. Weekly paclitaxel caused more grade 3 sensory/motor neuropathy and less grade ≥ 3 granulocytopenia. The authors concluded that weekly is superior to standard paclitaxel in the management of metastatic breast cancer. (*Seidman A, Berry D, Cirrincione C, et al: Proc Am Soc Clin Oncol [late-breaking abstract 512] 23, 2004*).

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, whose tumor is hormone receptor-positive (ie, estrogen receptor-positive and/or progesterone receptor-positive, may be treated with a trial of hormone therapy.

First-line hormonal therapy consists of an aromatase inhibitor, with careful serial assessment of clinical and disease responses.

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.

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 every day
or	
Toremifene	60 mg PO every day
Anastrozole	1 mg PO every day
or	
Letrozole	2.5 mg PO every day
or	
Exemestane	25 mg PO every day
Fulvestrant	250 mg IM every month
Megestrol	40 mg PO 4 times a day
Fluoxymesterone	10 mg PO 3 times a day
Aminoglutethimide	250 mg PO 4 times a day
Premenopausal	
Tamoxifen	20 mg PO every day
Luteinizing hormone-releasing hormone analogues	
Leuprolide	7.5 mg IM depot every 28 days 22.5 mg IM every 3 months 30 mg IM every 4 months
Goserelin	3.6 mg SC depot every 28 days 10.8 mg SC every 3 months
Megestrol	40 mg PO 4 times a day
Fluoxymesterone	10 mg PO 3 times a day

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). They may be used sequentially and may provide disease palliation for prolonged periods in some patients.

Second-line hormonal agents The choice of second-line endocrine therapy depends on the front-line endocrine agent used. Typically, if tamoxifen was used, the second-line agent includes an aromatase inhibitor or fulvestrant (Faslodex) for postmenopausal women. For premenopausal women, the choice may be megestrol acetate or induction of menopause with an LHRH agonist with or without an aromatase inhibitor. If aromatase inhibitors were used as front-line agents for postmenopausal women, second-line options can be to change to another class of aromatase inhibitor, fulvestrant, or tamoxifen.

The most commonly used second-line hormonal agents had been progestational drugs, such as megestrol. Recent randomized trials have indicated that the aromatase inhibitors, such as anastrozole (Arimidex), letrozole (Femara),

fulvestrant, and exemestane (Aromasin), are equally effective for palliation of metastatic disease, have less toxicity, and may provide a survival advantage compared with megestrol. Therefore, they are the drugs of choice for second-line therapy following tamoxifen administration. Tamoxifen may also be considered as second-line therapy for patients initially treated with an aromatase inhibitor.

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

Cytotoxic agents Hormone-refractory disease can be treated with systemic cytotoxic therapy. FAC, paclitaxel, TAC (Taxotere [docetaxel], Adriamycin [doxorubicin], cyclophosphamide), or docetaxel may be used in this situation. (For a more detailed discussion of these agents, see section on "Intermediate- or high-risk patients." For doses, see Table 1.)

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 FAC (see Table 1), 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 1). They include vinblastine, mitomycin (Mutamycin), thiotepa, capecitabine, vinorelbine (Navelbine), and gemcitabine.

Paclitaxel One of the most active 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.

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 hematologic and neurologic toxicities.

Docetaxel, approved by the US Food and Drug Administration (FDA) for anthracycline-resistant locally advanced or metastatic breast cancer, has demonstrated overall response rates of 41% in patients with doxorubicin-resistant disease. It has been shown to be superior to mitomycin/vinblastine in patients whose disease progressed after an anthracycline-based chemotherapy regimen.

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Abraxane, an albumin-bound form of paclitaxel is indicated for the second-line treatment of metastatic breast cancer. In a phase III multicenter trial comparing Abraxane with paclitaxel, 460 patients with metastatic breast cancer were randomized to receive either 260 mg/m² of Abraxane over 30 minutes or 175 mg/m² of paclitaxel over 3 hours. Patients treated with Abraxane had a significantly higher response rate of 21.5% than did patients treated with paclitaxel (11.1%). The toxicity profile of Abraxane was comparable to that of paclitaxel, although grade 3 sensory neuropathy occurred in 10% of patients treated with Abraxane (vs 2%). However, rapid improvement of neuropathy was documented in 58% of these patients after a median of 22 days. (O'Shaughnessy JA, Tjulandin S, et al: Breast Ca Res Treat 82(supp 1) (abstract 44), 2003).

The recommended starting dose of docetaxel—100 mg/m² 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/m² 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/m² may achieve equivalent therapeutic benefit with improved safety. As with paclitaxel, the 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 or 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 schedules of 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, as have combinations of capecitabine and docetaxel, carboplatin and paclitaxel, and gemcitabine and cisplatin. These newer combinations need to be compared with standard AC or FAC (CAF) regimens in phase III trials. Recent studies also suggest that sequential weekly chemotherapy may be as effective as more intensive combinations with respect to overall survival in patients with metastatic breast cancer.

Monoclonal antibody therapy

Trastuzumab, 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 consisting of 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

TABLE 4: 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	32.0	38.0	NS
Lotz et al	61	5	29.8	18.5	NS

NS = not significant

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 with 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 cancer expresses 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 out-

patient 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 4), it appears that most of the benefit occurs in women with low-bulk disease, especially those in complete clinical remission. A recent meta-analysis with longer follow-up also demonstrated a benefit for the addition of high-dose therapy to standard, anthracycline-containing chemotherapy for advanced disease in the setting of patients 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 as an adjunct to treatment of patients with bone metastasis. Use of these agents results in a significant reduction in skeleton-related events, including pathologic fracture, bone pain, and the need for radiation therapy to bone. Pamidronate (Aredia) and zoledronic acid (Zometa), both in IV formulations, are available in the United States. Oral bisphosphonates used for this indication, such ibandronate and clodronate, are not in the US market.

Patients with breast carcinoma who had all types of bone metastases (osteolytic, mixed, or osteoblastic) were randomized to receive treatment with either 4 mg or 8 mg of of zoledronic acid as a 15-minute infusion or 90 mg of pamidronate as a 2-hour infusion every 3-4 weeks for 12 months. The proportion of patients who had a skeleton-related event (defined as a pathologic fracture, spinal cord compression, radiotherapy, or surgery to bone) was comparable between treatment groups (approximately 45%). However, among patients who had breast carcinoma with at least one osteolytic lesion, treatment with 4 mg of zoledronic acid was more effective than 90 mg of pamidronate in reducing skeletal complications.

The most commonly reported adverse events for either zoledronic acid or pamidronate were bone pain, nausea, fatigue, emesis, and fever. The 4-mg dose of zoledronic acid results in elevated serum creatinine levels in about 7.7% of patients, vs 6.0% with pamidronate. A larger proportion of patients had elevated serum creatinine levels with 8-mg of zoledronic acid; therefore, this

dose is not recommended. Symptomatic hypocalcemia, although relatively rare, requires frequent monitoring of calcium and phosphate levels during treatment.

ROLE OF RADIATION THERAPY IN METASTATIC DISEASE

Irradiation 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 irradiation.

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 irradiation (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 chloride (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 progressive disease 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 lungs or liver is not proven, but, in highly selected cases, surgery may be beneficial.

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

Solitary brain metastasis Patients with a long disease-free interval and 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.

Gamma- and cyber-knife radiosurgery is increasingly used to manage brain metastases. In some instances, these modalities have been used in patients who have multiple metastatic brain lesions or in patients who had previously received conventional treatment modalities for brain metastases, including whole-brain irradiation. No radiation-induced dementia and a remarkably low incidence of local failure were reported with these treatments. Although in the past, local control of brain metastasis was an issue, these treatment modalities are shifting the question of survival to that of systemic control.

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

Follow-up of long-term survivors

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

SUGGESTED READING

Berry DA, Broadwater G, Klein JP, et al: High-dose versus standard chemotherapy in metastatic breast cancer: Comparison of Cancer and Leukemia Group B Trials with data from the Autologous Blood and Marrow Transplant Registry. J Clin Oncol 20:743–750, 2002.

Green MC, Buzdar AU, Smith T, et al: Weekly paclitaxel followed by FAC as primary systemic chemotherapy of operable breast cancer improves pathologic complete remission rates when compared to every 3-week paclitaxel therapy followed by FAC–Final results of a prospective phase II randomized trial (abstract). Proc Am Soc Clin Oncol 21:35a, 2002.

Howell A, Robertson JF, Quaresma AJ, et al: Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol 20:3396–3403, 2002.

Kuerer HM, Hunt K: The rationale for integration of lymphatic mapping and sentinel node biopsy in the management of breast cancer after neoadjuvant chemotherapy. Semin Breast Dis 5:80–87, 2002.

Loesch D, Robert N, Asmar L, et al: Phase II multicenter trial of a weekly paclitaxel and carboplatin regimen in patients with advanced breast cancer. J Clin Oncol 20:3857–3864, 2002.

Mackey JR, Paterson A, Dirix LY, et al: Final results of the phase III randomized trial comparing docetaxel, doxorubicin, and cyclophosphamide to FAC as first-line chemotherapy for patients with metastatic breast cancer (abstract). Proc Am Soc Clin Oncol 21:35a, 2002.

Martincich L, Montemurro F, De Rosa G, et al: Monitoring response to primary chemotherapy in breast cancer using dynamic contrast-enhanced magnetic resonance imaging. Breast Cancer Res Treat 83:67–76, 2004.

O'Shaughnessy J, Miles D, Vukelja S, et al: Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results. J Clin Oncol 20:2812–2823, 2002.

Robertson JF, Osborne CK, Howell A, et al: Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: A prospective combined analysis of two multicenter trials. Cancer 98:229–238, 2003.

Rodenhuis S, Bontenbal M, Beex LV, et al: High-dose chemotherapy with hematopoietic stem-cell rescue for high-risk breast cancer. N Engl J Med 349:7–16, 2003.

Rosen LS, Gordon DH, Dugan W Jr, et al: Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer 100:36–43, 2004.

Sledge GW, Neuberg D, Bernardo P, et al: Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An intergroup trial (E1193). J Clin Oncol 21:588–592, 2003.

van der Hoeven JJ, Krak NC, Hoekstra OS, et al: 18F-2-fluoro-2-deoxy-d-glucose positron emission tomography in staging of locally advanced breast cancer. J Clin Oncol 22:1253–1259, 2004.

Wahl RL, Siegel BA, Coleman RE, et al: Prospective multicenter study of axillary nodal staging by positron emission tomography in breast cancer: A report of the staging breast cancer with PET study group. J Clin Oncol 22:277–285, 2004.

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CHAPTER 14

Pancreatic, neuroendocrine GI, and adrenal cancers

Al B. Benson III, MD, Robert J. Myerson, MD, PhD, and John Hoffman, MD

PANCREATIC CANCER

Pancreatic cancer is the fifth leading cause of cancer death in the United States. In the year 2005, an estimated 32,180 new cases will be diagnosed, and 31,800 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 The incidence is higher in the black population, with an excess risk of 40%-50% over whites. Perhaps more importantly, black males probably have 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 clear surgical margins, negative lymph nodes, and reduced perioperative mortality.

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 50% of patients with pancreatic adenocarcinoma have clinically apparent metastatic disease. Among patients whose disease is considered to be resectable, 50% will die of recurrent tumor within 2 years.

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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, however, appear to be a significant relationship between pancreatic cancer and environmental carcinogens.

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 smoking 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-controlled study showed a correlation between caffeine consumption and pancreatic cancer. However, other studies have been unable to confirm this relationship.

Alcohol A clear-cut relationship between alcohol use and pancreatic carcinoma has not been 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.

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 of developing pancreatic cancer than those without these mutations.

Signs and symptoms

The initial clinical features of pancreatic carcinoma include anorexia, weight loss, abdominal discomfort or pain, and new-onset diabetes mellitus or thrombophlebitis. The 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 symptom is back pain, which stems from tumor invasion of the splanchnic plexus and retroperitoneum or pancreatitis. This pain is described as severe, gnawing, and radiating to the middle of the back. Pain can also be epigastric or in the right upper quadrant if bile duct obstruction is present.

Jaundice In a majority of cases, patients with pancreatic cancer present with epigastric or back pain and/or jaundice. Painless or sometimes painless jaundice occurs with early lesions near the intrapancreatic bile duct.

GI symptoms Tumor invasion of the duodenum or gastric outlet may give rise to nausea or vomiting as a presenting symptom. This symptom 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 physicians 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 include Trousseau's syndrome (migratory superficial phlebitis), ascites, Virchow's node (left supraclavicular lymph node), or a periumbilical mass (Sister Mary Joseph's node).

Screening and diagnosis

Early diagnosis of pancreatic carcinoma is difficult but essential if surgical resection and cure are to be improved. Defining early lesions at a resectable stage remains a diagnostic challenge. To date, leading medical organizations have not recommended routine screening of asymptomatic individuals for pancreatic cancer.

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. Also, the sensitivity of CA19-9 is not high (20%) in stage I cancers. Nevertheless, CA19-9 may be a useful marker for diagnosing patients at high risk with the appropriate symptoms, such as smokers, recent-onset diabetics, those with familial pancreatic cancer, or those with unexplained weight loss or diarrhea. This marker also is useful in following disease and in assessing the adequacy of resection or therapy.

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 10%-15% of patients thought to have resectable disease are found to have distant metastases at laparoscopy. The false-negative rate of laparoscopy is < 10%. The strongest indications for laparoscopy are locally advanced disease and tumors of the body and tail of the pancreas.

Peritoneal cytology also is being explored for the diagnosis of pancreatic carcinoma. Cytology is positive in 5%-10% of patients who are thought to have localized disease. There are anecdotal cases of long-term survival after resection where positive cytology of peritoneal washings was noted. However, the clinical/prognostic value of this test is not yet known.

Imaging techniques

Imaging for pancreatic carcinoma is best performed with conventional ultrasonography and CT.

Ultrasonography The limit of sonographic resolution for early pancreatic carcinoma is a diameter on the order of 1.0-1.5 cm. A mass located in the pancreatic head will produce dilatation of the common bile duct and pancreatic 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 distant lymphadenopathy, encasement or occlusion of the superior mesenteric artery (SMA) or celiac artery, occlusion of the portal vein or superior mesenteric vein (SMV), and distant metastases.

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 contrast medium than angiography.

PET The use of positron emission tomography with [18]fluorodeoxyglucose (FDG-PET) in the evaluation of patients with pancreatic cancer is expanding. A recent study of 126 patients with focal, malignant, or benign pancreatic lesions showed high sensitivity of FDG-PET for detection of small pancreatic neoplasms. Lack of focal glucose uptake excludes pancreatic neoplasms (sensitivity 85.4%, specificity 60.9%).

MRI At present, MRI is not as accurate as CT in diagnosing and staging pancreatic carcinoma. MRI may be as useful as CT in staging and can provide magnetic resonance angiography and magnetic resonance cholangio-pancreatography (MRC) images if needed. As yet, MRC is not a standard test for the diagnosis of pancreatic carcinoma, but it may become helpful in the future.

Endoscopic ultrasonography (EUS) is a newer modality for the diagnosis of pancreatic carcinoma, with an overall diagnostic accuracy rate of approximately 85%-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/SMV 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 and may be less risky in spreading cells by needle tracking than percutaneous biopsies.

In a comparison of EUS and spiral CT, both techniques showed comparable efficacy in detecting tumor involvement of lymph nodes and the SMVs and portal veins. However, EUS is less helpful in the evaluation of the SMA.

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 or tapered cutoff of either or both the main pancreatic and common bile ducts.

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 cancers arising from mucinous cystic neoplasms 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, SMA, and para-aortic lymph node groups also may be involved.

Staging and prognosis

Pancreatic adenocarcinoma is staged according to local spread of disease, 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 of disease to the duodenum, bile duct, or peripancreatic tissues. A T4 advanced cancer may extend directly to the SMA or celiac axis, meaning that the cancer is unresectable.

Independent prognostic factors Lymph node metastases and tumor size and differentiation have independent prognostic value in patients with pancreatic carcinoma. Significantly improved survival is seen in patients with smaller lesions, lymph node-negative tumors, and tumors in which the surgical margins are not involved.

TABLE 1: TNM staging of pancreatic tumors

Primary tumor (T)

Tx	Primary tumor cannot be assessed
T0	No evidence of a primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the pancreas, ≤ 2 cm in diameter
T2	Tumor limited to the pancreas, > 2 cm in diameter
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional lymph nodes (N)

N0	No involved regional lymph nodes
N1	Any involved regional lymph nodes

Distant metastases (M)

Mx	Presence of distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases

Stage grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1-3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

From Fleming ID, Cooper JS, Henson DE, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Lymph node and margin status Prior to the age of adjuvant therapy, lymph node status was the most dominant prognostic factor (Figure 1). It is now rivaled by surgical margin status in series where surgical margins have been meticulously examined.

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 16 operable cases per year).

Extended resections may include portal or superior mesenteric vessels, colon, adrenal, or stomach. If resection of adjacent organs or tissues results in the conversion of a positive to a negative resection margin, it is of great potential benefit to the patient.

Determination of resectability

The initial approach to surgery for pancreatic carcinoma includes a determination of resectability. This determination should be first made preoperatively with high-quality CT or MRI and perhaps EUS. Operative determination of resectability includes careful examination of the liver, porta hepatis, and portal and superior mesenteric vessels. The head of the pancreas and uncinate process are mobilized by an extensive Kocher maneuver to evaluate the head of the pancreas. The SMA is palpated, and its relationship to the tumor is assessed. The hepatic artery and celiac trunk are examined to make certain there is no vascular encasement.

Criteria for unresectability include distant metastases and involvement of the SMA and celiac axis.

An analysis of 200 patients who underwent resection of pancreatic adenocarcinoma in the era prior to adjuvant therapy 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 rate 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-preserving vs standard Whipple procedure) did not influence survival.

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, but this finding has not been shown to alter long-term nutritional status. If there is any doubt about cancer proximity or blood supply to the pylorus, an antrectomy should be performed. If the tumor approaches the pylorus or involves the subpyloric nodes, classic antrectomy is preferred.

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 peritumoral pancreatitis. Most large series of pancreaticoduodenectomy for carcinoma include resections of benign pathology based on clinical judgment. A
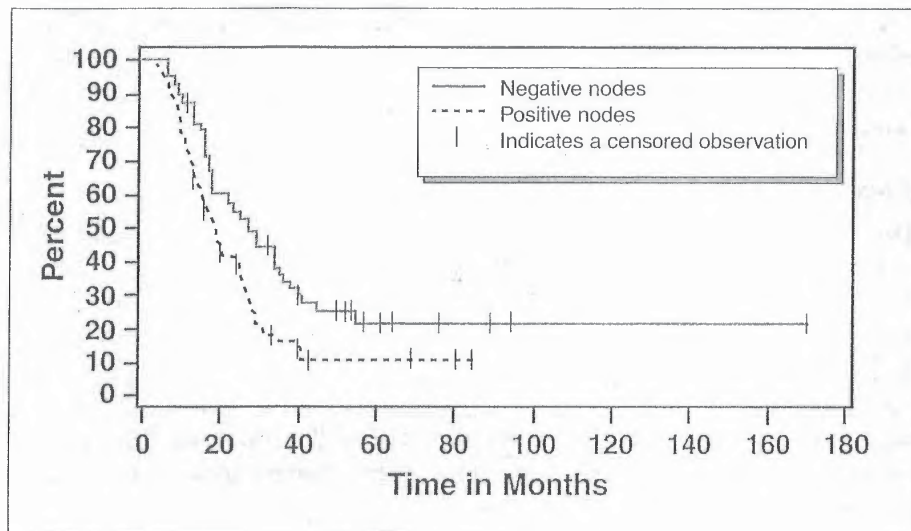
FIGURE 1: Actuarial survival as a function of regional lymph node status in patients with pancreatic cancer.

negative fine-needle cytology should not deter an experienced surgeon from proceeding with resection. However, medicolegal considerations may prompt a biopsy.

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 cholangiojejunostomy and gastrojejunostomy. A duct-mucosal anastomosis is preferred to the pancreatico-jejunostomy. Pancreaticogastrostomy is also an effective and safe means of creating the anastomosis.

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. Most of the septic complications arise from pancreaticojejunostomy leaks.

In many series, early delayed gastric emptying is the leading cause of morbidity for pylorus-preserving procedures. 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 and adequate drainage. Pancreatic fistulas heal with conservative measures in more than 95% 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.

CANCER MANAGEMENT: A MULTIDISCIPLINARY APPROACH

Biliary tract obstruction Either a choledochojejunostomy or cholecysto-jejunostomy 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 believe that prophylactic bypasses are safe and should be performed in all patients. One phase III trial supports prophylactic bypass, but another does not.

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 37 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 therapy may help render locally advanced lesions resectable with negative margins (RO resection). Postoperative (adjuvant) radiation therapy may help eliminate suspected residual microscopic disease in the tumor bed and/or regional lymphatics. Alternative radiation techniques, including intensity-modulated radiotherapy (IMRT) and 3D conformal radiation therapy, are being explored.

A 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 with gemcitabine, both agents given before and after chemoradiation therapy, in patients with resected pancreatic cancer. Radiation therapy 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. This study has recently completed its accrual goal, and analysis is pending.

With an effective chemotherapeutic agent, there is greater potential for adequate locoregional cytotoxicity—as well as control of subclinical distant disease—than could be obtained with limited doses of adjuvant radiation therapy alone.

Preoperative chemoradiation therapy Several single-institution studies have evaluated the role of preoperative irradiation in conjunction with fluorouracil (5-FU)- and gemcitabine (Gemzar)-based chemotherapy. In these studies, 60%-80% of the lesions were completely resected 1.0-1.5 months after the completion of chemoradiotherapy. Median survival has ranged from 16 to 36 months, but

no phase III trials have been conducted to evaluate preoperative therapy vs postoperative sequencing.

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. There are research initiatives to further address the role of neoadjuvant chemotherapy. For example, a new Eastern Cooperative Oncology Group (ECOG) study will evaluate gemcitabine plus radiotherapy vs gemcitabine, 5-FU, and cisplatin followed by radiotherapy and 5-FU for patients with locally advanced disease. Other phase II studies involved high-dose gemcitabine and high-dose gemcitabine and cisplatin with short-term radiation therapy to locally advanced cancer.

Postoperative chemoradiation therapy A small Gastrointestinal Tumor Study Group (GITSG) trial demonstrated a significant prolongation of survival (median survival increase, from 11 to 20 months) among patients with pancreatic adenocarcinoma who received irradiation plus bolus 5-FU chemotherapy after curative resection, as compared with those given no adjuvant treatment. An improvement in the long-term cure rate was also observed among those given chemoradiation therapy.

The European Organization for Research and Treatment of Cancer (EORTC) completed a trial of 218 patients similar to that of the GITSG trial but without maintenance chemotherapy. Reported data suggest no significant difference between split-course radiation therapy with bolus 5-FU and observation only after curative resection (two-tailed P value = .099); however, there was a trend toward benefit in median survival favoring those who received treatment. The European trial is difficult to interpret because 20% of patients randomized to receive postoperative treatment were not treated, and the study was inadequately powered for survival.

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 5.0-5.5 weeks without a treatment break.

Careful attention to field size is important. The GITSG trial 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.

A total of 541 patients were enrolled in a trial conducted by the European Study Group for Pancreatic Cancer (ESPAC). This study evaluated the benefits of adjuvant therapy. The design was complex, attempting to assess several options. It included no further therapy after surgery, chemoradiation therapy (bolus 5-FU with split-course radiotherapy), chemotherapy (5-FU with leucovorin), and chemoradiation therapy followed by chemotherapy.

Interpretation of the results is confounded by the fact that some institutions opted for a full 2×2 randomization (all four options), whereas others allowed

only two options (no further therapy vs chemotherapy or no further therapy vs chemoradiation therapy). Patients receiving these two options could also have therapy other than that prescribed in the randomization. Furthermore, no data were collected regarding time to recurrence or whether treatment was given after recurrence. Curiously, the median survival of those in the control group was more than 17 months, much longer than those of the control groups from the GITSG and EORTC trials.

Only the 5-FU with leucovorin arm would be considered a state-of-the-art approach, and it was demonstrated to improve survival significantly ($P= .0005$). This finding would suggest a strong benefit to postoperative chemotherapy. If radiation therapy is included, it would probably best be given after 1-2 months of full-dose chemotherapy. Most practitioners would recommend continuous-course radiation therapy rather than split-course treatment.

The ESPAC is now conducting a postoperative trial comparing various chemotherapy regimens with a control group. In the United States, the findings of several phase II trials of postoperative regimens as well as a phase III trial will be available soon. In addition, the GI Intergroup is considering a randomized phase II trial to explore new combinations incorporating the monoclonal antibodies bevacizumab (Avastin) and cetuximab (Erbitux), each given with gemcitabine; irradiation will be given with oral capecitabine (Xeloda).

Locally advanced but potentially resectable lesions

These lesions comprise 10%-15% of the cases presenting to physicians. Data from preoperative chemoradiation series indicate that trimodality therapy is essential for long-term survival in these patients. There is now a randomized phase II ECOG trial (E1200) evaluating gemcitabine with radiation therapy (500 mg/m^2/50 min/wk during radiation therapy of 5,040 cGy with tightened fields) plus postresectional gemcitabine or preoperative chemotherapy, with a dose of two cycles of gemcitabine, 5-FU, and cisplatin, followed by 5-FU/radiation therapy, then surgery, and then postoperative gemcitabine. End points are margin-free resectability and survival.

TREATMENT OF UNRESECTABLE DISEASE

Irradiation can prolong and/or improve quality of life in some patients with unresectable adenocarcinoma of the pancreas. It is better combined with chemotherapy. Long-term survival is, unfortunately, highly unusual.

Chemoradiation therapy 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 irradiation with chemotherapy alone and demonstrated a significant improvement with combined-modality therapy (median survival, 42 vs 32 weeks).

TABLE 2: Chemotherapy regimens for pancreatic cancer

Drug/combination	Dose and schedule
Fluorouracil/radiation therapy (GITSG regimen)	
Fluorouracil	500 mg/m^2/d IV bolus for 3 consecutive days once every 4 weeks during radiation therapy
Radiation therapy	Two courses of 2,000 cGy each, separated by 2 weeks (total dose, 4,000 cGy)
Gastrointestinal Tumor Study Group: Cancer 59:2006–2010, 1987.	
Infusional 5-FU with radiation therapy	
Concurrent radiation therapy and chemotherapy phase:	
Fluorouracil	150-250 mg/m^2/d, 24 hours/day during radiation therapy
Radiation therapy	Median dose of 4,500 cGy/25 fractions (range 4,000 cGy/ 20 fractions to 5,040 cGy/28 fractions)
Fisher B, Perera F, Kocha W, et al: Int J Radiat Oncol Biol Phys 45:291–295, 1999.	
Single-agent regimen	
Gemcitabine	1,000 mg/m^2 IV infused over 30 minutes once a week for 7 weeks, followed by a 1-week rest period
Subsequent cycles once a week for 3 consecutive weeks out of every 4 weeks	
Burris HA, Moore MJ, Andersen J, et al: J Clin Oncol 15:2403–2413, 1997.	

Table prepared by Ishmael Jaiyesimi, DO

Based on these data, except in a protocol setting, the palliative management of a patient with unresectable pancreatic adenocarcinoma who has significant local symptoms 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 should be used.

Approaches under investigation At present, numerous trials are exploring a variety of chemoradiation therapy approaches, including single-agent or combination therapy with oral or infusional 5-FU, paclitaxel, cisplatin, gemcitabine, docetaxel (Taxotere), and oxaliplatin (Eloxatin). Trials with combined gemcitabine and irradiation are of particular interest due to the activity of this drug in pancreatic cancer and the fact that it is a potent radiosensitizer. The benefit of irradiation for patients with locally advanced disease, however, remains a research question because of toxicity concerns and the relatively brief survival rates. Therefore, a new ECOG trial will evaluate gemcitabine alone vs gemcitabine and irradiation for this group of patients.

If gemcitabine is given either before or after a course of radiation therapy, full doses of 1,000 mg/m^2 are possible. If irradiation and gemcitabine are given concurrently, doses of either modality must be sharply reduced. A current phase II trial is combining "full-dose" gemcitabine (1,000 mg/m^2) with radiation therapy

directed at the primary tumor alone (36 Gy). In addition, a Radiation Therapy Oncology Group (RTOG) randomized trial evaluated radiation therapy (50.4 Gy) and weekly gemcitabine and paclitaxel with or without the farnesyl transferase inhibitor R11577 for locally advanced pancreatic cancer. In that trial, the gemcitabine dose was 75 mg/m^2/wk and the paclitaxel dose was 40 mg/m^2/wk. Radiation was conventionally fractionated to a dose of 50.4 Gy. Both these trials are now completed and being analyzed.

The dose of gemcitabine that can be given concurrently with irradiation depends on the volume and dose of radiation. If full doses of gemcitabine (1,000 mg/m^2/wk) are given concurrently with irradiation, the dose of radiation must be makedly reduced to avoid unacceptable GI toxicity.

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, they 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 (Table 2) 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 [Mutamycin]) 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 with 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 important, 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/m^2/min) suggested an improved 1-year survival with the fixed-dose rate.

Three Intergroup metastatic pancreatic trials are currently accruing patients. The ECOG is about to complete a trial of gemcitabine (Gemzar) vs fixed-rate infusion gemcitabine vs fixed-rate gemcitabine plus oxaliplatin (Eloxatin, nearly 800 patients). The CALGB is comparing bevacizumab (Avastin) plus gemcitabine with gemcitabine alone, and the SWOG is accruing patients for a trial of gemcitabine with and without cetuximab (Erbitux).

Combination therapy There have been a number of recent attempts to improve the therapeutic outcome for patients with metastatic pancreatic cancer by comparing promising combinations of agents in randomized clinical trials. Unfortunately, the results have been disappointing. The ECOG compared gemcitabine with or without 5-FU, demonstrating a median survival of 5.4 months for gemcitabine vs 6.7 months for the combination; however, this difference was not statistically significant. Another trial explored the addition of irinotecan to gemcitabine. There was no survival benefit when this regimen was compared with gemcitabine alone, although the combination did increase tumor response rate (16.1% vs 4.4%, $P < .001$),

Combination trials were presented during ASCO 2004. A European study of the topoisomerase inhibitor exatecan (DX-89511) vs gemcitabine included 339 patients, showing no significant difference in survival. Furthermore, pain, quality of life, and time to tumor progression were worse in the exatecan arm. Another trial evaluated exatecan and gemcitabine vs gemcitabine alone in 349 patients. Efficacy parameters were similar for both arms of the trial.

A phase III study of 565 patients compared gemcitabine with the combination of gemcitabine plus the multitargeted antifolate pemetrexed (Alimta) and demonstrated a significant response benefit with the combination (14.8% vs 7.1%, $P = .004$). However, survival and disease progression-free survival were comparable. There was increased hematologic toxicity with the combination.

A fourth trial evaluated standard-dose gemcitabine vs a fixed-rate infusion of gemcitabine plus oxaliplatin. The trial accrued 326 patients and showed a superior response rate for the combination (26.8% vs 11.3%) and superior disease progression-free survival (5.8 vs 3.7 months). Although these results were not statistically significant, a trend toward increased survival was shown with the gemcitabine/oxaliplatin combination. Furthermore, during ASCO 2003, a trial exploring the combination of cisplatin plus gemcitabine showed no survival advantage for the combination.

Agents with marginal activity include mitomycin, doxorubicin, ifosfamide (Ifex), streptozocin (Zanosar), and docetaxel. To date, monoclonal antibody therapy and hormonal manipulation have been ineffective. A phase II study of anti–epidermal growth factor receptor (EGFR)–antibody IMC-C225 (cetuximab) combined with gemcitabine has shown a 12% partial response rate and 39% stable disease in advanced pancreatic cancer. Side effects included rash/folliculitis and fatigue. A phase III trial of the combination is accruing patients (see boxed item).

The ECOG is also exploring EGFR-directed therapy in pancreatic cancer with a new randomized phase II trial comparing docetaxel and irinotecan (CPT-11,

Camptosar) with or without cetuximab. The trial will correlate EGFR expression with outcome after therapy. Other "targeted" therapies are under investigation.

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 K-*ras* protein function.

Many patients seek "complementary" or "alternative" treatment strategies. The NCI (National Cancer Institute) has activated a phase III study of gemcitabine vs intensive pancreatic proteolytic enzyme therapy with ancillary nutritional support for pancreatic cancer patients based on phase II data.

PANCREATIC ENDOCRINE TUMORS

Pancreatic endocrine tumors (PETs) cover a spectrum of neoplasms. Many, although not all, originate from the pancreatic islets of Langerhans.

PETs 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, γ cells and enterochromaffin cells, which primarily secrete glucagon, insulin, somatostatin, and serotonin, respectively. All of these hormones may be secreted in excess by PETs. Other hormones that may be secreted by these tumors include vasoactive intestinal peptide (VIP), gastrin, pancreatic polypeptide (PP), and calcitonin. The aggressiveness of a PET in terms of its metastatic potential appears to be due to the cell of origin.

> Approximately 20% of patients with ZES develop the syndrome in the setting of the MEN-1 syndrome. MEN-1 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-1, which has been localized to the long arm of chromosome 11, was recently identified and named *MENIN*.

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.

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 MEN-1 syndrome. Patients with the sporadic form of ZES may have single or multiple gastrinomas. This finding contrasts with patients with hereditary MEN-1 PETs, 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 portions 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 disease 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 PETs cause considerable morbidity due to the inappropriately elevated levels of the hormones that they secrete, even "nonfunctional" PETs, ie, those without an associated demonstrable hormone-related syndrome (such as PPomas, neurotensinomas, and nonsecretory PETs), may be aggressive. Nonfunctional tumors account for up to 30% of all PETs. 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 and an elevated insulin-glucose ratio (> 0.3).

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 ulcerative disease.

VIPomas VIP excess causes a profuse, watery diarrhea, hypokalemia, hypophosphatemia, and hypochlorhydria (WDHA syndrome).

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 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.

Because the success of preoperative localization tests is disappointing and 90% of these tumors will be found and successfully resected by an experienced endocrine surgeon, there is a general trend toward performing fewer tests. 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 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, EUS, and intraoperative endoscopy have all been reported to be useful in localizing gastrinomas. More recently, somatostatin receptor scintigraphy (SRS) has become a valuable tool for PET localization; several studies have suggested greater sensitivity and specificity when compared with other diagnostic tests.

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-cell 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 approach 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 widespread metastatic disease can be identified and spared surgical exploration. In addition, some series report that patients with nonmetastatic sporadic gastrinoma may have a higher 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 approach 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 of metastatic gastrinoma at a young age, a surgical approach may be warranted. Surgery 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 During surgery, the entire pancreas should be mobilized and scanned ultrasonographically to permit a thorough examination of the pancreatic head, duodenum, stomach, mesentery, liver, and splenic hilum. Intraoperative endoscopy with transillumination of the bowel wall may also be useful in identifying duodenal lesions. 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.

Surgical resection of liver metastases is controversial. However, several authors have demonstrated meaningful survival in patients with small, isolated lesions. The use of ablative procedures, with open, laparoscopic, or percutaneous techniques, can reduce the neurohormonal tumor burden.

Radiation therapy for PETs

Adjuvant therapy The role of adjuvant radiation therapy for PETs 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 irradiation 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 PETs may respond to palliative doses of irradiation. Long-term control of unresectable disease has been reported.

Chemotherapy for PETs

PETs are more sensitive to chemotherapy than are carcinoid tumors.

Single agents Agents that have demonstrated antitumor activity include recombinant human interferon alfa-2a and alfa-2b (Roferon-A, Intron A, respectively), 5-FU, doxorubicin, dacarbazine (DTIC-Dome), and streptozocin.

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 PETs, as well as a better complete response rate (33% vs 12%) and median survival duration (26.0 vs 16.5 months). Therapy with doxorubicin plus streptozocin was superior to therapy with 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 PETs, although this success 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 PETs 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 insulinomas include diazoxide (Hyperstat), 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 (chemo-embolization), is an alternative palliative therapy for patients with either carcinoid tumors or a PET who have predominant liver metastases or who are symptomatic. Embolization is best reserved for patients with < 75% tumor involvement of the liver, bilirubin level < 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, lungs, 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, although 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 problem 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 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 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). 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 bulky disease, in common with other solid malignancies, but also on treating the complications of hormonal excess.

TREATMENT OF BULKY 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. Duodenal lesions should be locally excised if small (< 2 cm), with radical resection reserved for larger tumors.

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 cancer progresses after other therapeutic interventions.

Radiation therapy

Carcinoid tumors are responsive to radiation therapy 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 treatment 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 alfa-2b. However, the response rate with these agents is in the range of 10%-20%, the response duration is < 6 months, and complete remission is 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. 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. Other somatostatin analogs, including lanreotide and vapreotide, are under investigation.

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.

Patients who demonstrate disease resistance with somatostatin analog treatment alone may benefit from combination therapy with interferon-α and this somatostatin analog.

Radiolabeled somatostatin analogs A promising experimental treatment approach involves the use of octreotide or other somatostatin analogs conjugated to radioisotopes (eg, indium-111 or yttrium-90) in patients whose tumors express somatostatin receptors (eg, those with a positive OctreoScan result). This approach allows targeted in situ radiotherapy by taking advantage of internalization of the radioligand into the cell to produce DNA damage and cell death, with little effect on normal tissue. Initial reports have shown favorable results with this technique.

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 (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 (Metaret), 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%-1.0% 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 than other adrenal lesions. 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 the 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% of cases 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, all 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 useful diagnostic tool that is more convenient than urine collection. Dynamic provocative tests are 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 methyliodobenzyl guanidine (MIBG) and SRS 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 may require 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 arrhythmia. 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- 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.

Except for in tumors < 6 cm, the laparoscopic approach to pheochromocytoma is probably the technique of choice. In the absence of obvious local tumor 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.

SUGGESTED READING

ON PANCREATIC CANCER

Berlin JD, Catalano P, Thomas JP, et al: Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinomas. Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol 1:3270–3275, 2002.

Buchsbaum DJ, Bonner JA, Grizzle WE, et al: Treatment of pancreatic cancer xenografts with erbitux (IMC-C225) anti-EGFR antibody, gemcitabine, and radiation. Int J Radiat Oncol Biol Phys 15:1180–1193, 2002.

Crane CH, Wolff RA, Abruzzese JL, et al: Combining gemcitabine with radiation in pancreatic cancer: Understanding important variables influencing the therapeutic index. Semin Oncol 28(suppl 10):25–33, 2001.

Huang JJ, Yeo CJ, Sohn TA, et al: Quality of life and outcomes after pancreaticoduodenectomy. Ann Surg 231:890–898, 2000.

Maisey N, Chau I, Cunningham D, et al: Multicenter randomized phase III trial comparing protracted venous infusion (PVI) fluorouracil (5-FU) with PVI 5-FU plus mitomycin in inoperable pancreatic cancer. J Clin Oncol 15:3130–3136, 2002.

Milano MT, Chmura SJ, Garofalo MC, et al: Intensity-modulated radiotherapy in treatment of pancreatic and bile duct malignancies: Toxicity and clinical outcome. Int J Radiat Oncol Biol Phys 1:445–453, 2004.

Neoptolemos JP, Stocken DD, Friess H, et al: A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 18:1200–1210, 2004. Erratum in: N Engl J Med Aug 12:726, 2004.

Rocha Lima CM, Green MR, Rotche R, et al: Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 15:3776–3783, 2004.

Rose DM, Delbeke D, Beauchamp RD, et al: 1-Fluorodeoxyglucose-positron emission tomography in the management of patients with suspected pancreatic cancer. Ann Surg 229:729–737, 1999.

Tempero M, Plunkett W, Ruiz Van Haperen V, et al: Randomized phase II comparison of dose-intense gemcitabine: Thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 15:3402–3408, 2003.

Willett CG, Clark JW: Update on combined-modality treatment options for pancreatic cancer. Oncology (Huntingt) 17:29–36, 2003.

Wong GY, Schroeder DR, Carns PE, et al: Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: A randomized controlled trial. JAMA 3:1092–1099, 2004.

Yeo CJ: The Johns Hopkins experience with pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary carcinoma. J Gastrointest Surg 4:231–232, 2000.

ON NEUROENDOCRINE GI TUMORS

Ducreux M, Ruszniewski P, Chayvialle JA, et al: The antitumoral effect of the long-acting somatostatin analog lanreotide in neuroendocrine tumors. Am J Gastroenterol 95:3276–3281, 2000.

Faiss S, Pape UF, Bohmig M, et al: Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors. The International Lanreotide and Interferon Alfa Study Group. J Clin Oncol 15:2689–2696, 2003.

Fazio N, Oberg K: Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors. J Clin Oncol 1:573–574, 2004.

Kulke MH, Mayer RJ: Carcinoid tumors. N Engl J Med 340:858–868, 1999.

Kvols LK, Krenning EP, Pauwels S, et al: Phase I study of 90Y-SMT487 (Octreother) in patients with somatostatin receptor (SS-R) positive neuroendocrine (NE) tumors (abstract). Proc Am Soc Clin Oncol 19:207, 2000.

Moertel CG, Lefkopoulo M, Lipsitz S, et al: Streptozocin-doxorubicin, streptozocin-fluorouracil, or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med 326:519–523, 1992.

Nilsson O, Kolby L, Wangberg B, et al: Comparative studies on the expression of somatostatin receptor subtypes, outcome of octreotide scintigraphy and response to octreotide treatment in patients with carcinoid tumours. Br J Cancer 77:632–637, 1998.

Norton JA, Alexander HR, Fraker DL, et al: Comparison of surgical results in patients with advanced and limited disease with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. Ann Surg 234:495–506, 2001.

Raderer M, Kurtaran A, Leimer M, et al: Value of peptide receptor scintigraphy using (123)I-vasoactive intestinal peptide and (111)In-DTPA-D-Phel-octreotide in 194 carcinoid patients: Vienna University Experience, 1993 to 1998. J Clin Oncol 18:1331–1336, 2000.

Ramanathan RK, Cnaan A, Hahn RG, et al: Phase II trial of dacarbazine (DTIC) in advanced pancreatic islet cell carcinoma. Study of the Eastern Cooperative Oncology Group-E6282. Ann Oncol 12:1139–1143, 2001.

Rubin J, Ajani J, Schirmer W, et al: Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. J Clin Oncol 17:600–606, 1999.

Sarmiento JM, Que FG: Hepatic surgery for metastases from neuroendocrine tumors. Surg Oncol Clin N Am 12:231–242, 2003.

Solorzano CC, Lee JE, Pisters PW, et al: Nonfunctioning islet cell carcinoma of the pancreas: Survival results in a contemporary series of 163 patients. Surgery 130:1078–1085, 2001.

Virgolini I, Patri P, Novotny C, et al: Comparative somatostatin receptor scintigraphy using in-111-DOTA-lanreotide and in-111-DOTA-Tyr3-octreotide versus F-18-FDG-PET for evaluation of somatostatin receptor-mediated radionuclide therapy. Ann Oncol 12(suppl 2):S41–S45, 2001.

Waldherr C, Pless M, Maecke HR, et al: The clinical value of [90Y-DOTA]-D-Phel-Tyr3-octreotide (90Y-DOTATOC) in the treatment of neuroendocrine tumours: A clinical phase II study. Ann Oncol 12:941–945, 2001.

Yao KA, Talamonti MS, Nemcek A, et al: Indications and results of liver resection and hepatic chemoembolization for metastatic gastrointestinal neuroendocrine tumors. Surgery 130:677–682, 2001.

ON ADRENAL NEOPLASMS

Jossart GH, Burpee SE, Gagner M: Surgery of the adrenal glands. Endocrinol Metab Clin North Am 29:57–68, 2000.

Kendrick ML, Lloyd R, Erickson L, et al: Adrenocortical carcinoma: Surgical progress or status quo? Arch Surg 136:543–549, 2001.

Sosa JA, Udelsman R: Imaging of the adrenal gland. Surg Oncol Clin N Am 8:109–127, 1999.

Vassilopoulou-Sellin R, Schultz PN: Adrenocortical carcinoma: Clinical outcome at the end of the 20th century. Cancer 92:1113–1121, 2001.

Wajchenberg BL, Albergaria Pereira MA, Medonca BB, et al: Adrenocortical carcinoma: Clinical and laboratory observations. Cancer 88:711–736, 2000.

ON CARCINOIDS

Goede AC, Winslet MC: Surgery for carcinoid tumours of the lower gastrointestinal tract. Colorectal Dis 5:123–128, 2003.

Kolby L, Persson G, Franzen S, et al: Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours. Br J Surg 90:687–693, 2003.

Krenning EP, de Jong M: Therapeutic use of radiolabelled peptides. Ann Oncol 11(suppl 3):267–271, 2000.

Oberg K: Carcinoid tumors: Molecular genetics, tumor biology, and update of diagnosis and treatment. Curr Opin Oncol 14:38–45, 2002.

Schell SR, Camp ER, Caridi JG, et al: Hepatic artery embolization for control of symptoms, octreotide requirements, and tumor progression in metastatic carcinoid tumors. J Gastrointest Surg 6:664–670, 2002.

Soreide JA, van Heerden JA, Thompson GB, et al: Gastrointestinal carcinoid tumors: Long-term prognosis for surgically treated patients. World J Surg 24:1431–1436, 2000.

van der Horst-Schrivers AN, Wymenga AN, de Vries EG: Carcinoid heart disease. N Engl J Med 348:2359–2361, 2003.

ON PHEOCHROMOCYTOMAS

Baghai M, Thompson GB, Young WF Jr, et al: Pheochromocytomas and paragangliomas in von Hippel-Lindau disease: A role for laparoscopic and cortical-sparing surgery. Arch Surg 137:682–689, 2002.

Eisenhofer G, Lenders JW, Linehan WM, et al: Plasma normetanephrine and metanephrine for detecting pheochromocytoma in von Hippel-Lindau disease and multiple endocrine neoplasia type 2. N Engl J Med 340:1872–1880, 1999.

Goldstein RE, O'Neill JA Jr, Holcomb GW III, et al: Clinical experience over 48 years with pheochromocytoma. Ann Surg 229:755–764, 1999.

Vaughan ED Jr: Diseases of the adrenal gland. Med Clin North Am 88:443–466, 2004.

Zendron L, Fehrenbach J, Taverna C, et al: Pitfalls in the diagnosis of phaeochromocytoma. BMJ 13:629–630, 2004.

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 5:1 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, whereas in the Far East and sub-Saharan Africa, this neoplasm occurs at an incidence of 150 per 100,000 population and comprises almost 50% of all diagnosed tumors. A study analyzing SEER (Surveillance, Epidemiology, and End Results) data has shown that the incidence of hepatocellular carcinoma is rising in both white and black populations in the United States, with a current incidence of about 3.4 cases per 100,000 in whites and 5.6 per 100,000 in blacks. Modeling of the spread of hepatitis C virus (HCV) suggests that this number may continue to increase dramatically.

Age The incidence of hepatocellular cancer increases with age. The mean age at diagnosis is 53 years in Asia and 67 years in the United States.

Race The incidence of hepatocellular tumors is higher in Asian immigrants and blacks than in whites.

Survival In patients who undergo curative resection, the 5-year survival rate is approximately 20%. Recurrence is common, with metastases arising in the remaining liver, lungs, bone, kidneys, and heart. Most patients present with unresectable disease. Patients with unimpaired liver function who can undergo resection may experience significantly longer survival than those whose disease is not resected.

HEPATOBILIARY

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). The presence of the hepatitis B "e" antigen has been found to increase risk ninefold. The most compelling epidemiologic 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. The hepatitis B "x" gene, which can interact with $p53$, has been a focus of recent study on the pathogenesis of hepatocellular carcinoma.

Hepatitis C has also been implicated in hepatocellular carcinoma development. The molecular mechanisms of HCV infection and carcinogenesis are poorly understood. Unlike patients with hepatitis B infection, hepatocellular carcinoma patients infected with hepatitis C usually have cirrhotic livers at diagnosis; this finding suggests an extended period of infection (or hepatic damage) before malignancy develops.

Alcohol Patients with alcoholic cirrhosis are at risk for hepatocellular carcinoma, but the addition of HCV infection increases that risk dramatically.

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, fever, chills, 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, abdominal 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

Presently, no organization recommends routine screening of average-risk, asymptomatic adults for liver, gallbladder, and biliary tract cancers.

α-Fetoprotein is produced by 70% of hepatocellular carcinomas. The normal range for this serum marker is 0-20 ng/mL, and a level > 200 ng/mL is essentially diagnostic for hepatocellular cancer in the absence of chronic, active hepatitis B infection. In the presence of active hepatitis B infection, the diagnostic cutoff is considered to be at least 1,000 ng/mL. In the setting of hepatitis C infection, the cutoff for diagnosis of hepatocellular carcinoma has

not been well studied, but the specificity of values > 200 ng/mL appears to be high. 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.

Imaging The initial diagnostic test in the symptomatic patient may be ultrasonography, as it is noninvasive and can detect lesions as small as 1 cm. Ultrasound findings should be followed up with more specific imaging.

Triple-phase, high-resolution CT and contrast-enhanced MRI are the primary imaging modalities used to diagnose and stage hepatocellular carcinoma. Recent reports have documented a high number of false-positive results with CT angioportography (CTAP) and CT hepatic angiography (CTHA). CT scan predicts resectability in only 40%-50% of cases and does not accurately determine the functional extent of cirrhosis. Major difficulties arise when the liver parenchyma is not homogeneous and the lesions are smaller than 1 cm.

Laparoscopy is useful 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 ultrasonography should be used to confirm preoperative imaging tests. The laparoscopic results may change surgical management in up to one-third of selected patients.

High-risk patients should be screened for hepatocellular carcinoma using ultrasonography and serum α-fetoprotein levels. At present, however, there is no standard screening interval, and screening has not been shown to affect survival. Data suggest that, for screened patients, there is an increase in the proportion of cancers that are resectable. A study comparing 6-month and 12-month survival intervals in a cohort of HIV-infected patients with hemophilia showed no substantial benefit to more frequent screening.

Pathology

Three morphologic 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 relatively 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). The Okuda staging system accounts for the degree of liver dysfunction and may

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PPROACH

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 without vascular invasion
T2	Solitary tumor with vascular invasion or multiple tumors none > 5 cm
T3	Multiple tumors > 5 cm or tumor involving a major branch of the portal or hepatic vein(s)
T4	Tumor(s) with direct 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	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	T4	N0	M0
Stage IIIC	Any T	N1	M0
Stage IV	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

better predict prognosis than the TNM stage. However, the Okuda staging system does not adequately predict resectability. Because of the limited value of standard staging, the most important factors determining survival are technical resectability of lesions and degree of dysfunction of the normal liver. Groups in Italy and China have created prognostic indices that may prove useful for making treatment decisions.

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, vascular invasion, and a high serum α-fetoprotein level.

Treatment

SURGERY

Surgery is the form of treatment that offers the greatest 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 preoperatively.

Only stage I or II tumors have a significant likelihood of being resectable for cure. However, a large tumor may still be potentially resectable for cure. 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.

Bilobar disease may be addressed 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, main portal vein involvement, 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. Cirrhosis has been a major deterrent to resection in western nations. Resectability rates vary from 0%-43% for cirrhotic patients, whereas up to 60% of patients without cirrhosis undergo resection. Use of the modified Child-Pugh classification of liver reserve may guide the surgeon in preoperative assessment of liver function status and may aid in the selection of operable patients.

When resection is performed in the presence of cirrhosis, Child class A patients fare better than Child class B or C patients. Survival rates at 5 years following resection range from 4%-36%, with noncirrhotic patients living longer than cirrhotic patients.

Transplantation Owing 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 stages 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 single tumors < 5 cm or multiple tumors (up to 3 with none > 3 cm) can be considered for transplantation. Larger tumors may be treated with resection when feasible. Chemoembolization followed by transplantation may be considered in selected patients. The use of transplantation is significantly limited by the scarcity and lack of immediate availability of donor organs. Recently, changes in the organ allocation system have decreased waiting times for patients with documented hepatocellular cancer.

ADJUVANT AND PALLIATIVE 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. A number of prognostic factors have been identified for patients with unresectable hepatocellular carcinoma. These factors, taken alone, can have a great effect on survival rates, making cross-treatment comparisons more difficult because considerable selection bias may be present in any nonrandomized trial.

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 irradiation has been combined with chemotherapy and transcatheter arterial chemoembolization, with objective response rates of approximately 40%-50% and median survival rates of about 18 months. Patients with tumor regrowth after chemoembolization may respond to radiotherapy.

Radiation therapy has also been delivered using yttrium-90 microspheres infused via the hepatic artery. This approach has encouraging response rates, and a low toxicity profile and may be complementary with other forms of therapy.

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, with doses up to 90 Gy given safely to selected patients.

Multiple institutions have reported response rates as high as 90% with acceptable toxicity when conformal radiation therapy was combined with transcatheter arterial chemoembolization (TACE). Good response and local control rates have also been reported for proton, carbon ion, and stereotactic radiotherapy.

Hepatic TACE

Normal hepatocytes receive most of their blood supply from the portal vein, whereas tumors create new blood vessels from branches of the hepatic arterial system. This target is exploited by embolization of the hepatic artery with any number of substances, resulting in radiographic response rates in about 50% of patients and evidence of tumor liquefaction in over two-thirds of patients. Embolization is accomplished by advancing a catheter within the tumor-feeding branch of the hepatic artery. Materials injected have included Gelfoam powder, polyvinyl alcohol, iodized oil (Lipiodol), collagen, and autologous blood clot. Chemoembolization should be reserved for symptomatic tumors, reducing tumor size for resection or ablation, or as a bridge while awaiting transplant.

A randomized study tested radiofrequency ablation (RFA) vs percutaneous ethanol injection as the sole first-line anticancer treatment in 102 people with cirrhosis and either a single hepatocellular carcinoma ≤ 5 cm in diameter or up to 3 tumors each ≤ 3 cm. Local recurrence-free survival rates were significantly higher ($P = .002$) for RFA (96%) than for percutaneous ethanol injection (62%) at 2 years, with a nonsignificant difference in overall survival (98% for RFA vs 88% for ethanol; *Lencioni RA, Allgaier H-P, Cioni D, et al: Radiology 228:235-240, 2003*).

The effect of TACE on survival remains controversial, with randomized studies returning mixed results. A randomized, controlled trial in Spain was stopped early due to a survival benefit, but the number of analyses of data performed represents a potential problem for interpreting these data.

Intratumoral ethanol injection

The direct injection of 95% ethanol into a neoplastic lesion causes cellular dehydration and coagulation necrosis. Intratumoral ethanol ablation is employed via a percutaneous route under ultrasonographic guidance. 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.

Although intratumoral ethanol injection appears to be an effective palliative modality in certain patients, its effect on patient survival is unclear.

CRYOTHERAPY AND RADIOFREQUENCY ABLATION

Similar to ethanol ablation, cryotherapy and radiofrequency ablation (RFA) techniques are suitable for treatment of localized disease. Cryotherapy has been used intraoperatively to ablate small solitary tumors outside a planned resection (ie, in patients with bilobar disease). Cryotherapy must be performed using laparotomy, which limits its use in the palliative setting. RFA can be performed either via laparotomy or percutaneously and has limitations similar to those of ethanol ablation. As with ethanol ablation, there are no data about a survival advantage with these therapies, which may prove to be most useful for temporary tumor control in patients awaiting liver transplants.

Based on promising response rates and occasional complete pathologic response rates, the PIAF regimen was tested against single-agent doxorubicin in a multicenter study performed in China. Not surprisingly, the phase III response rate with PIAF was lower than that in a phase II study, at 20.4% The response rate to doxorubicin was 10%. Despite this difference, there was no improvement in overall survival for the patients receiving the combination therapy. Use of combination therapy outside a clinical trial should be done with caution, given the comorbidities of patients with hepatocellular cancer (Yeo W, Zee B, Leung WT, et al: Proc Am Soc Clin Oncol [abstract] 23:319, 2004).

A cautionary note regarding percutaneous RFA has been raised by publication of a report from Barcelona, citing 4 of 32 patients in a series who developed needle-track tumor seeding relating to subcapsular tumor location and poorly differentiated tumors.

Chemotherapy

Systemically administered chemotherapy has, for the most part, been disappointing in hepatocellular carcinoma patients. This fact relates to both low rates of response to available agents and to difficulty with toxicity for modestly active agents because of liver dysfunction. Agents with partial response rates near or above 10% include doxorubicin, fluorouracil (5-FU), and cisplatin. Two newer agents, oxaliplatin (Eloxatin) and gemcitabine (Gemzar), which do not require liver metabolism or excretion, have garnered some interest. Both agents appear to be more active when partnered with a second agent. At present, there is no apparent role for adjuvant systemic chemotherapy.

Intra-arterial chemotherapy (HAI) Use of HAI, principally floxuridine (fluorodeoxyuridine [FUDR]), has good biologic rationale but is hampered by high rates of biliary complications and the requirement for surgical pump placement in patients who are generally poor surgical candidates. A meta-analysis concluded that HAI after curative liver resection improved survival significantly at both 2 (23% benefit) and 3 (28% benefit) years.

An Italian cooperative group has studied a regimen of oxaliplatin with infused 5-FU (similar to those used in colorectal cancer) in patients with advanced hepatocellular cancer. The majority of patients in this trial of 31 patients were unexposed to previous systemic chemotherapy. Patients were treated with oxaliplatin (100 mg/m²) on day 1 and 5-FU (200 mg/m²/day) continuously every 2 weeks. Grade 3 toxicities were few, and partial response was noted in nine patients (29%), making this regimen worthy of further study (Frustaci S, Bearz A, Basso B, et al: Proc Am Soc Clin Oncol [abstract] 22:1346, 2003).

Biologic therapy Interferon-alfa (IFN-α) has been shown to have potential beneficial effects in prevention of hepatocellular carcinoma; however, recent randomized studies have failed to show a benefit in patients with preexisting cirrhosis and advanced cancers. Adjuvant interferon, however, was associated with a reduction in recurrence in two small randomized trials. This finding needs to be confirmed in a much larger trial. Moderate-to-high doses of interferon are poorly tolerated by patients with frankly cirrhotic livers.

Retinoid therapy In one Japanese randomized trial, polyprenoic acid has been shown to significantly decrease the rate of recurrence of hepatocellular carcinoma after cura-

CANCER MANAGEMENT: A MULTIDISCIPLINARY APPROACH

tive resection. A survival advantage was also demonstrated with long-term follow-up. Unfortunately, this compound has been unavailable for further study.

Hormone therapy A small trial reported a survival benefit at 1 year for patients treated with medroxyprogesterone acetate. This result needs to be validated. In one randomized study, people with variant estrogen receptors had a significant improvement in median survival from 7 to 18 months when megestrol acetate was given.

Biochemotherapy Recent results of combination biochemotherapy in a study of 154 patients by Leung et al have been encouraging. Using a combination of cisplatin, interferon-α-2a (Roferon-A), doxorubicin, and 5-FU for 4 days out of 28 days, they have shown a response rate of around 20%. Moreover, 10% of patients whose tumors were initially thought to be unresectable subsequently underwent complete resection. Eight of these patients had documented pathologic complete remissions. The question of whether this regimen can be used routinely in the neoadjuvant setting will be the subject of further study. Of note, all patients in this series had hepatitis B-associated hepatocellular carcinoma. More recently, Patt et al studied a less-toxic regimen of continuous 5-FU with interferon-α-2b (Intron A), demonstrating a median survival of 15.5 months.

Targeted Therapies

Novel agents are now being studied in hepatocellular carcinoma (see boxed items), and some show promise for improving the outlook of this difficult disease.

BILIARY TRACT CANCERS

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.

An exciting and innovative therapy for hepatocellular cancer (HCC) was recently reported. Based on the observation that HCC lacks the enzyme capable of synthesizing the nonessential amino acid arginine, an arginine-depleting therapy was tested in patients with HCC. The treatment (arginine deaminase conjugated to pegylated polyethylene glycol) has few side effects, and in patients treated at a dose that completely suppressed serum arginine levels, the response rate was astounding (9 of 19 patients). Formal phase II testing of this compound is under way (Izzo F, Marra P, Beneduce G, et al: J Clin Oncol 22:1815-1822, 2004).

Testing of modern targeted therapies in hepatocellular cancer (HCC) has begun. A group led by Philip at Karmanos Cancer Institute has reported results of a phase II trial of the epidermal growth factor receptor (EGFR)-targeting agent erlotinib (Tarceva) in HCC and biliary tumors. Erlotinib was administered orally, 150 mg daily, to 35 patients with HCC. As of this report, 20 patients were evaluable, with an end point of disease progression-free survival at 6 months. Seven patients met the end point, and 3 of 20 patients had partial radiographic response, signaling interesting activity (Philip PA, Mahoney M, Thomas J, et al: Proc Am Soc Clin Oncol [abstract] 23:318, 2004).

Epidemiology

GALLBLADDER CANCER

Gender Women are more commonly afflicted with gallbladder cancer than are men, with a female-to-male ratio of 1.7:1.

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, 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. This risk does not decline after total colectomy for ulcerative colitis.

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; they 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.

CANCER MANAGEMENT: A MULTIDISCIPLINARY APPROACH

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 level.

Ultrasonography is useful for defining a thickened gallbladder wall and may show tumor extension into the liver.

CT is more helpful than ultrasonography in assessing adenopathy and spread of disease into the liver, porta hepatis, or adjacent structures. MRI may be used to evaluate intrahepatic spread.

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. Tissue confirmation of suspected bile duct cancer can be difficult. The goals of the diagnostic evaluation include the determination of the level and extent of obstruction, the extent of local invasion of disease, 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.

Ultrasonography 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% of patients.

Cholangiography is essential to determine the location and nature of the obstruction. Percutaneous THC is used for proximal lesions and ERCP

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
TI		Tumor invades the lamina propria or muscle layer
	TIa	Tumor invades the lamina propria
	TIb	Tumor invades the muscle layer
T2		Tumor invades perimuscular connective tissue; no extension beyond the serosa or into the liver
T3		Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4		Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
NI	Regional lymph node metastasis

Distant metastasis (M)

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
MI	Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage IA	TI	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	TI	NI	M0
	T2	NI	M0
	T3	NI	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	MI

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

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.

CANCER MANAGEMENT: A MULTIDISCIPLINARY APPROACH

TABLE 3: Staging of bile duct tumors

Primary tumor (T)

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
TI	Tumor confined to the bile duct histologically
T2	Tumor invades beyond the wall of the bile duct
T3	Tumor invades the liver, gallbladder, pancreas, and/or ipsilateral branches of the portal vein (right or left) or hepatic artery (right or left)
T4	Tumor invades any of the following sites: main portal vein or its branches bilaterally; common hepatic artery; or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
NI	Regional lymph node metastasis

Distant metastasis (M)

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
MI	Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage IA	TI	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	TI	NI	M0
	T2	NI	M0
	T3	NI	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	MI

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

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 initial route of spread of gallbladder cancer is locoregional rather than distant. For patients undergoing resection for presumed high-risk gallbladder masses or preoperatively defined disease limited to the gallbladder, 25% of patients will have lymphatic involvement and 70% will have direct extension of disease into the liver defined at operation.

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. Patients with 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 of disease 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 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%-15%.

Type of therapy Median survival is also improved in patients who have undergone 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 of disease. The AJCC (American Joint Committee on Cancer) 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 12-20 months for patients with disease limited to the bile ducts and ≤ 8 months when the disease has spread.

Tumor location Survival is also related to tumor location, with patients with distal lesions doing better than those with mid or proximal tumors.

Success of therapy Curative resection and negative margins result in improved survival.

Treatment

In the absence of polyps identified ultrasonographically and confirmed by CT during the work-up of suspected cholelithiasas, relatively few patients with gallbladder cancer are diagnosed prior to surgery. 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. Laparoscopic cholecystectomy may be adequate for T1 tumors. If there is direct extension of disease to or through the serosa, the resection should include the gallbladder bed (segments IVb and V) and a porta hepatis lymphadenectomy. Disease that involves the gallbladder node is 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 Higher resolution CT or MRI with biliary reconstruction may be supplemented with hepatic arteriography, portal venography, or duplex imaging 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 procedure 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 resection of the bile duct with associated portal lymphadenectomy. 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 to the hilum for high lesions and in a standard drainage pattern following pancreaticoduodenectomy.

Oxaliplatin (Eloxatin), a newer platinum agent, appears to have activity in the biliary neoplasms. In a study presented at the ASCO 2003 meeting, a German group treated 29 patients with advanced biliary adenocarcinomas with oxaliplatin (130 mg/m²/q21d) and capecitabine (1,000 mg/m² bid) on days 1-14 of 21 days. Of 22 evaluable patients, 5 patients (29%) had responded. It was not clear from the abstract, however, whether responding patients had gallbladder cancer or cholangiocarcinomas (Nehls O, Oettle H, Hartmann J, et al: Proc Am Soc Clin Oncol [abstract] 22:1126, 2003).

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

A review of the patterns of initial disese recurrence after resection of gallbladder cancer (80 patients, in whom disease recurred in 53) and hilar cholangiocarcinoma (76 patients, in whom disease recurred in 52) found a distinct difference with regard to total locoregional failure vs total distant failure. Hilar cholangiocarcinomas were much more likely to include locoregional failure alone or as a component (65% of all failures), compared with gallbladder cancer (28% of all failures). Distant failure was found alone or as a component in 72% of all recurrences of gallbladder cancer but only in 36% of hilar cholangiocarcinomas.

Despite these observations, there are no good prospective data to define the role of adjuvant radiation or chemoradiation treatment. For bile duct tumors, a review of 192 patients found that a benefit from adjuvant chemoradiation therapy was more evident in distal tumors than in intrahepatic or perihilar tumors. Another retrospective review, however, found that on multivariate analysis, only lymph node status was prognostically significant.

ADJUVANT CHEMOTHERAPY

A recently published randomized trial performed in Japan showed that treatment with 5-FU and mitomycin (Mutamycin) produced a survival benefit in patients with resected gallbladder cancers. The data came from a planned subset of a larger trial in which 112 patients with gallbladder cancer were randomized. At 5 years, 26% of chemotherapy-treated patients were alive, compared with 14% of those treated with surgery and observation alone. These data warrant consideration of chemotherapy for these patients, but definitive conclusions would require a larger randomized trial.

TREATMENT OF UNRESECTABLE DISEASE

Like pancreatic adenocarcinoma, unresectable biliary tract carcinoma has a poor prognosis.

Stenting

Many patients with unresectable disease, particularly those with pain, nausea, or pruritus, will benefit from nonsurgical percutaneous or endoscopic stenting.

Radiation therapy

There are few 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 therapy for unresectable bile duct tumors. Median survival ranges from 10-24 months, and 5-year survival rates are approximately 10% with these approaches. Cholangitis, however, may occur more frequently in people treated with brachytherapy.

A randomized study of stenting alone vs stenting with photodynamic therapy (PDT) in 39 people with histologically confirmed nonresectable proxmial cholangiocarcinoma found a significantly longer survival rate in the PDT group (median 493 days vs 98 days, $P < .0001$) with a corresponding significant improvement in quality of life. Given that inclusion in the study required a tumor > 3 cm and that PDT treats a radius of about 7 mm around the light source, it is unlikely that the entire tumor was treated, and by approximately 3 years, only 2 of the 20 PDT patients were alive. Nevertheless, this study demonstrated the importance of local control in people with nonmetastatic cholangiocarcinoma and its association with quality of life (Ortner ME, Caca K, Berr F, et al: Gastroenterology 125:1355-1363, 2003).

Chemotherapy

Because biliary tract malignancies are uncommon cancers, the number of clinical trials and the number of patients in those trials are limited. Generally speaking, responses to chemotherapy are infrequent and brief. However, newer drugs and drug combinations are better tolerated and stand to improve on past results.

5-FU has historically been the most active single agent, with single-agent response rates in the 10%-20% range.

Capecitabine (Xeloda), a prodrug of 5-FU (see chapter 16), produced responses in 4 of 8 gallbladder cancers but in only 1 of 18 cholangiocarcinomas in a phase II study presented by Hassan et al from M. D. Anderson Cancer Center.

Gemcitabine Multiple studies have documented gemcitabine as an active agent, particularly in gallbladder cancer. Cisplatin and gemcitabine may be a synergistic doublet, with reported response for gallbladder cancer in the range of 30%-50%.

Other agents with reported activity in biliary tract malignancies include oxaliplatin,

A phase II study conducted in Italy provides the best estimate yet of the response rate of gallbladder cancer to the combination of gemcitabine (Gemzar) and cisplatin in a Western population. A total of 44 patients were enrolled in a multicenter study and received gemcitabine (1,200 mg/m²) with cisplatin (35 mg/m²) on days 1 and 8 of 21 days for six courses. Of 42 evaluable patients, there were 4 complete responses and 16 partial responses. This rate of response is in line with other reports. Despite this response rate, however, median survival was only 7 months, reflecting the often explosive growth of this malignancy (Reyes-Vidal J, Gallardo J, Yanez E, et al: Proc Am Soc Clin Oncol [abstract] 22:1095, 2003).

cisplatin, docetaxel (Taxotere), mitomycin, doxorubicin, and the nitrosureas. Combination regimens do not clearly improve on the results of single-agent chemotherapy and as such remain investigational.

Hepatic arterial chemotherapy There is limited experience with hepatic arterial chemotherapy for biliary tract neoplasms, but there are case reports of responses to floxuridine in the literature.

Treatment recommendations In the absence of a clinical trial, patients should be offered gemcitabine or 5-FU (or capecitabine), with or without leucovorin. Other agents, such as doxorubicin or cisplatin, may be added, but, as noted, there is no unequivocal evidence that combination chemotherapy produces any substantial benefits in improving quality of life or survival.

SUGGESTED READING

ON HEPATOCELLULAR CARCINOMA

Camma C, Schepis F, Orlando A, et al: Transarterial chemoembolization for unresectable hepatocellular carcinoma: Meta-analysis of randomized controlled trials. Radiology 224:47–54, 2002.

Gupta S, Bent S, Kohlwes J: Test characteristics of alpha-fetoprotein for detecting hepatocellular carcinoma in patients with hepatitis C: A systematic review and critical analysis. Ann Intern Med 1394:46–50, 2003.

Lencioni RA, Allgaier H-P, Cioni D, et al: Small hepatocellular carcinoma in cirrhosis: Randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology 228:235–240, 2003.

Levy I, Sherman M, The Liver Cancer Study Group of the University of Toronto: Staging of hepatocellular carcinoma: Assessment of the CLIP, Okuda, and Child-Pugh staging systems in a cohort of 257 patients in Toronto. Gut 50:881–885, 2002.

Llovet J, Bruix J: Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 37:429–442, 2003.

Llovet JM, Real MI, Montana X, et al: Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. Lancet 359:1734–1739, 2002.

Mathurin P, Raynard B, Dharancy S, et al: Meta-analysis: Evaluation of adjuvant therapy after curative liver resection for hepatocellular carcinoma. Aliment Pharmacol Ther 17:1247–1261, 2003.

Patt YZ, Hassan MM, Lozano RD, et al: Phase II trial of systemic continuous fluorouracil and subcutaneous recombinant interferon alfa-2b for treatment of hepatocellular carcinoma. J Clin Oncol 21:421–427, 2003.

Tanaka Y, Hanada K, Mizokami M, et al: Inaugural Article: A comparison of the molecular clock of hepatitis C virus in the United States and Japan predicts that hepatocellular carcinoma incidence in the United States will increase over the next two decades. Proc Natl Acad Sci U S A 99:15584–15589, 2002.

Yang HI, Lu SN, Liaw YF, et al: Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 347:168–174, 2002.

Yao FY, Bass NM, Ascher NL, et al: Liver transplantation for hepatocellular carcinoma: Lessons from the first year under the Model of End-Stage Liver Disease (MELD) organ allocation policy. Liver Transpl 10:621–630, 2004.

ON GALLBLADDER TUMORS

Doval DC, Sekhon JS, Gupta SK, et al: A phase II study of gemcitabine and cisplatin in chemotherapy-naive, unresectable gall bladder cancer. Br J Cancer 90:1516–1520, 2004.

Jarnagin WR, Ruo L, Little SA, et al: Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: Implications of adjuvant therapeutic strategies. Cancer 98:1689–1700, 2003.

Kresl JJ, Schild SE, Henning GT, et al: Adjuvant external beam radiation therapy with concurrent chemotherapy in the management of gallbladder carcinoma. Int J Radiat Oncol Biol Phys 52:167–175, 2002.

Patt YZ, Hassan MM, Aguayo A, et al: Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. Cancer 101:578–586, 2004.

Takada T, Amano H, Yasuda H, et al: Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer 95:1685–1695, 2002.

ON BILE DUCT TUMORS

Jung GS, Huh JD, Lee SU, et al: Bile duct: Analysis of percutaneous transluminal forceps biopsy in 130 patients suspected of having malignant biliary obstruction. Radiology 224:725–730, 2002.

Kim S, Kim SW, Bang YJ, et al: Role of postoperative radiotherapy in the management of extrahepatic bile duct cancer. Int J Radiat Oncol Biol Phys 54:414–419, 2002.

Ortner MEJ, Caca K, Berr F, et al: Successful photodynamic therapy for nonresectable cholangiocarcinoma: A randomized prospective study. Gastroenterology 125:1355–1363, 2003.

Siqueira E, Schoen RE, Silverman W, et al: Detecting cholangiocarcinoma in patients with primary sclerosing cholangitis. Gastrointest Endosc 56:40–47, 2002.

Taieb J, Mitry E, Boige V, et al: Optimization of 5-fluorouracil (5-FU)/cisplatin combination chemotherapy with a new schedule of leucovorin, 5-FU, and cisplatin (LV5FU2-P regimen) in patients with biliary tract carcinoma. Ann Oncol 13:1192–1196, 2002.

Colon, rectal, and anal cancers

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COLORECTAL CANCER

Despite the existence of excellent screening and preventive strategies, colorectal carcinoma remains a major public health problem in Western countries. An estimated 104,950 new cases of colon cancer and 40,340 cases of rectal cancer are expected to occur in the United States in 2005, with an estimated 56,290 deaths, accounting for approximately 10% of cancer deaths.

Colorectal carcinoma is the third leading cause of death from cancer in both males and females, comprising 11% of all cancers diagnosed in men and women. 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 2.4 times as common as rectal cancer. Rectal cancer is defined as cancer arising below the peritoneal reflection, up to approximately 12-15 cm from the anal verge.

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 (1.2:1), whereas rectal carcinomas are more common in men than in women (1.7:1).

Age The risk of developing colorectal tumors begins to increase at age 40 years and rises with age. In the United States, the median age at presentation is 72 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

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TABLE 1: Five-year survival in colorectal cancer[a]

Time of detection	5-year survival rate (%)
In early, localized stage	90
After spread to adjacent organs or lymph nodes	67
After spread to distant sites	9

[a] Source: Cancer Facts & Figures—2005. Atlanta, American Cancer Society, 2005.

the large bowel, with occurrence in the proximal colon becoming more common.

Survival Five-year survival rates (Table 1) for patients with stages I, II, and III colorectal carcinomas have improved in recent years. This fact 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 therapy 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 for their adopted country, suggesting the importance of environmental factors in colorectal cancer. Smoking and alcohol intake (more than one drink per day) increase the risk of 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. Historically, diets rich in cereal fiber or bran and yellow and green vegetables are said to have protective effects, although recent studies have failed to prove a risk reduction with increasing dietary fiber intake. 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.

Inflammatory bowel disease Patients with inflammatory bowel disease (ulcerative colitis, Crohn's disease) have a higher 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.

COLORECTAL

TABLE 2: Hereditary polyposis syndromes

Adenomatous polyposis

Familial adenomatous polyposis (FAP)

Characterized by hundreds or thousands of sessile or pedunculated polyps 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.
An attenuated form of FAP that is clinically characterized by the presence of tens or hundreds of polyps exists

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 (occurring in 8%-13% of patients)

Turcot's syndrome

This rare syndrome is characterized by malignant colon and brain tumors. Two different types of Turcot's have been identified: one characterized by an adenomatous polyposis coli (APC) mutation resulting in colon cancer and malignant glioblastoma; the second characterized by a mismatch repair gene mutation resulting in colon cancer and astrocytoma

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 develop 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

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A study designed to determine the usefulness of immunohistochemical analysis for the diagnosis of mismatch repair (MMR) gene defective colorectal tumors in 172 cases of colorectal cancer detected microsatellite instability (MSI) in 13 (1.6%) tumors. All showed loss of protein expression of hMLHI (11 of 13) or hMSH2 (2 of 13; $P < .000$). Patients with MMR-defective tumors more frequently had poorly differentiated tumors (5 of 13 [38%] vs 18 of 159 [11%]; $P = .02$) located in the ascending colon (8 of 13 [62%] vs 30 of 159 [19%]; $P = .0001$) and a personal history of other neoplasms (4 of 13 [31%] vs 18 of 159 [11%]; $P = .05$). There were no differences in age, family history of cancer, or TNM stage (Jover R, Paya A, Alenda C, et al: Am J Clin Pathol 122:389-394, 2004).

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 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.

Genetic factors The risk of developing colorectal cancer is significantly increased in several forms of inherited susceptibility (Table 2). The risks of developing colorectal cancer in the subgroups of familial or hereditary colorectal cancer vary from 15% in relatives of patients with colorectal cancer diagnosed before 45 years of age, through 20% for family members with two first-degree relatives with colorectal cancer, to approximately 70%-95% in patients with familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer (HNPCC).

Familial adenomatous polyposis (FAP) is inherited as an autosomal-dominant trait with variable penetrance. Patients characteristically develop pancolonic and rectal adenomatous polyps. Approximately 50% of FAP patients will develop adenomas by 15 years of age and 95% by age 35. Left untreated, 100% of patients with FAP will develop colorectal cancer, with an average age at diagnosis ranging from 34 to 43 years. Total colectomy, usually performed on patients in their mid-to-late teens, is the preventive treatment of choice in this group of patients. The familial adenomatous polyposis coli *(APC)* gene has been localized to chromosome 5q21. Currently, it is possible to detect mutations in the

APC gene in up to 82% of families with FAP. Mutations in the *APC* gene combined with mutational activation of proto-oncogenes, especially K-*ras*, occur sequentially in the neoplastic transformation of bowel epithelium in patients with FAP. Use of cyclo-oxygenase-2 (COX-2) inhibitors such as celecoxib has been shown to reduce the number of polyps in patients with FAP.

HNPCC is transmitted as an autosomal-dominant trait. It is associated with germline mutations in one of five DNA mismatch repair genes (*MSH2, MLH1, PMS1, PMS2,* and *MSH6*). The incidence a mutated mismatch repair gene is approximately 1 in 1,000 people. The Amsterdam criteria were proposed in 1991 as a way to help identify patients at risk of HNPCC. In 1999, they were revised (Amsterdam II) to recognize extracolonic manifestations as part of the family history. The criteria include the following factors:

- three or more relatives with a histologically verified HNPCC-associated cancer (colorectal, endometrial, small bowel, ureter, or renal pelvis), one of whom is a first-degree relative of the other two (FAP should be excluded)
- colorectal cancer involving at least two generations
- one or more colorectal cancers diagnosed before the age of 50.

The Bethesda criteria were developed based upon an analysis of high-risk patients who did not meet the Amsterdam criteria but still demonstrated germline mutations in either *MSH2* or *MLH1* gene. These criteria are much less restrictive than the Amsterdam criteria and serve to help identify those individual patients at risk of HNPCC who might benefit from further evaluation, such as the following:

- individuals with cancer in families who meet the Amsterdam criteria
- individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers; endometrial, ovarian, gastric, hepatobiliary, small bowel, or transitional cell carcinoma of the renal pelvis or ureter
- individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma; one of the cancers diagnosed at age younger than 45 years; and the adenoma diagnosed at age younger than 40 years
- individuals with colorectal cancer or endometrial cancer diagnosed at age < 45 years
- individuals with right-sided colorectal cancer with an undifferentiated pattern (solid/cribriform) on histology diagnosed at age < 45 years
- individuals with signet ring-cell–type colorectal cancer diagnosed at age < 45 years
- individuals with colorectal adenomas diagnosed at age < 40 years.

Poynter and colleagues investigated the association between 3-hydroxy-2-methylglutaryl coenzyme A (HMG CoA)-reductase inhibitors and colorectal cancer in a population-based case-control study of incident colorectal cancer. Of 3,342 participants, 267 reported using HMG CoA-reductase inhibitors for at least 5 years. Investigators found that use of these agents was associated with a 51% reduction in the risk of colorectal cancer, and the protective effect seems to be specific to the class of lipid-lowering agents (Poynter JN, Rennert G, Bonner JD, et al: Proc Am Soc Clin Oncol. [abstract] 23:1, 2004).

Mutations in the DNA mismatch repair genes *MLH1* or *MSH2* can be found in approximately 40% of individuals who meet these criteria. Genetic evaluation for HNPCC should be considered in families that meet the Amsterdam criteria, in affected individuals who meet the Bethesda criteria, and in first-degree relatives of those individuals with known mutations. For situations in which HNPCC is suspected but the first three Bethesda criteria are not met, microsatellite instability (MSI) testing may be considered. Over 90% of HNPCC colorectal cancers will demonstrate MSI, compared with 15%-20% of sporadic colorectal cancers, and thus a normal result in the absence of compelling clinical criteria usually excludes the diagnosis of HNPCC. Alternatively, *MSH6* may be involved in a substantial proportion of patients in whom HNPCC is suspected and should be considered in those with tumors that are low in MSI.

Chemoprevention

Chemoprevention aims to block the action of carcinogens on cells before the development of cancer.

Antioxidants and calcium Controlled trials of vitamins C and E and calcium have produced mixed results. Clinical trials have shown that calcium supplementation modestly decreases the risk of colorectal adenomas.

Nonsteroidal anti-inflammatory drugs inhibit colorectal carcinogenesis, possibly by reducing endogenous prostaglandin production through COX inhibition. Sulindac has induced regression of large bowel polyps in patients with FAP. Controlled studies have shown a reduction in the incidence of colorectal polyps with regular, long-term use of aspirin.

COX-2 inhibitors Expression of COX-2 mRNA is enhanced in tissue obtained from human colorectal adenomas and adenocarcinomas. In December 1998, the US Food and Drug Administration (FDA) approved celecoxib (Celebrex), a COX-2 inhibitor, for the chemoprevention of polyps in FAP. In December 2004, NCI stopped drug administration in an ongoing clinical trial investigating a new use of Celebrex to prevent colon polyps because of an increased risk of cardiovascular (CV) events in patients taking Celebrex versus those taking a placebo (see sidebar).

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; they 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/or an abdominal mass may also accompany carcinoma of the right side of the colon.

TABLE 3: American Cancer Society guidelines on screening and surveillance for the early detection of colorectal adenomas and cancer—Average risk

Test	Interval (beginning at age 50)	Comment
FOBT and flexible sigmoidoscopy	FOBT annually and flexible sigmoidoscopy every 5 years	Flexible sigmoidoscopy together with FOBT is preferred over FOBT or flexible sigmoidoscopy alone. All positive tests should be followed up with colonoscopy[a]
Flexible sigmoidoscopy	Every 5 years	All positive tests should be followed up with colonoscopy[a]
FOBT	Annually	The recommended take-home multiple sample method should be used. All positive tests should be followed up with colonoscopy[a,b]
Colonoscopy	Every 10 years	Colonoscopy provides an opportunity to visualize, sample, and/or remove significant lesions
Double-contrast barium enema	Every 5 years	All positive tests should be followed up with colonoscopy

[a] If colonoscopy is unavailable, not feasible, or not desired by the patient, double-contrast barium enema (DCBE) alone or the combination of flexible sigmoidoscopy and DCBE is an acceptable alternative. Adding flexible sigmoidoscopy to DCBE may provide a more comprehensive diagnostic evaluation than DCBE alone in finding significant lesions. A supplementary DCBE may be needed if a colonoscopic exam fails to reach the cecum, and a supplementary colonoscopy may be needed if a DCBE identifies a possible lesion or does not adequately visualize the entire colorectum.

[b] There is no justification for repeating FOBT in response to an initial positive finding.

FOBT = Fecal occult blood test

Adapted with permission from Smith RA, von Eschenbach AC, Wender R, et al: CA Cancer J Clin 53:27-43, 2003.

TABLE 4: American Cancer Society guidelines on screening and surveillance for the early detection of colorectal adenomas and cancer—Increased or high risk

Risk category	Age to begin	Practice
Increased risk		
A single, small (< 1 cm) adenoma	3-6 years after initial polypectomy	Colonoscopy[a]
If the exam is normal, the patient can thereafter be screened as per average-risk guidelines.		
A large (> 1 cm) adenoma, multiple adenomas, or adenomas with high-grade dysplasia or villous change	Within 3 years after the initial polypectomy	Colonoscopy[a]
If the exam is normal, repeat examination in 3 years; if the exam is normal then, the patients can thereafter be screened as per average-risk guidelines.		
Personal history of curative-intent resection of colorectal cancer	Within 1 year after cancer resection	Colonoscopy[a]
If the exam is normal, repeat examination in 3 years; if the exam is normal then, repeat examination every 5 years.		
Either colorectal cancer or adenomatous polyps in any first-degree relative before age 60 or in two or more first-degree relatives at any age (if not a hereditary syndrome)	Age 40, or 5-10 years before the youngest case in the immediate family	Colonoscopy[a]
Every 5-10 years. Colorectal cancer in relatives more distant than first-degree relatives does not increase risk substantially above the average-risk group.		
High risk		
Family history of familial adenomatous polyposis (FAP)	12 years	Early surveillance with endoscopy and counseling to consider genetic testing
If the genetic test is positive, colectomy is indicated. These patients are best referred to a center with experience in the management of FAP.		
Family history of hereditary nonpolyposis colorectal cancer (HNPCC)	Age 21	Colonoscopy and counseling to consider genetic testing
If the genetic test is positive or if the patient has not had genetic testing, every 1-2 years until age 40, then annually. These patients are best referred to a center with experience in the management of HNPCC.		
Inflammatory bowel disease, chronic ulcerative colitis, Crohn's disease	Cancer risk begins to be significant 8 years after the onset of pancolitis or 12-15 years after the onset of left-sided colitis	Colonoscopy with biopsies for dysplasia
Every 1-2 years. These patients are best referred to a center with experience in the surveillance and management of inflammatory bowel disease.		

[a] If colonoscopy is unavailable, not feasible, or not desired by the patient, double-contrast barium enema (DCBE) alone or the combination of flexible sigmoidoscopy and DCBE is an acceptable alternative. Adding flexible sigmoidoscopy to DCBE may provide a more comprehensive diagnostic evaluation than DCBE alone in finding significant lesions. A supplementary DCBE may be needed if a colonoscopic exam fails to reach the cecum, and a supplementary colonoscopy may be needed if a DCBE identifies a possible lesion or does not adequately visualize the entire colorectum.

Adapted with permission from Smith RA, von Eschenbach AC, Wender R, et al: CA Cancer J Clin 53:27-43, 2003.

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 (FOBT) 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 FOBTs, 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 FOBT. Recently, results from a large trial also showed a decreased incidence of colorectal cancer associated with FOBT, largely because of increased use of polypectomy resulting from diagnostic endoscopy following positive tests.

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. Even though flexible sigmoidoscopy visualizes only the distal portion of the colorectum, the identification of adenomas can lead to colonoscopy. When we add the percentage of colorectal neoplasms in the distal 60 cm of the colorectum to the percentage of patients with distal polyps leading to complete colonoscopy, 80% of those individuals with a significant neoplasm anywhere in the colorectum can be identified.

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. Colonoscopy is the best follow-up strategy for evaluating patients with positive guaiac-based FOBTs and the best screening modality for high-risk patients.

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

> Pickhardt et al evaluated the performance characteristics of CT virtual colonoscopy for screening in 1,233 average-risk asymptomatic adults. The sensitivity of virtual colonoscopy for adenomatous polyps was 93.8% for polyps at least 10 mm in diameter, 93.9% for polyps at least 8 mm in diameter, and 88.7% for polyps at least 6 mm in diameter. The sensitivity of optical colonoscopy for adenomatous polyps was 87.5%, 91.5%, and 92.3% for the three sizes of polyps, respectively (*Pickhardt AJ, Choi JR, Hwang I, et al: N Engl J Med* 349:2191-2200, 2003).

the cecum cannot be reached. A supplementary double-contrast barium enema may be needed if a colonoscopic exam fails to reach the cecum.

Some recent studies have suggested that CT virtual colonoscopy may have a sensitivity and specificity for detecting neoplastic polyps which approaches that of optical colonoscopy. Unfortunately, other studies have demonstrated clear superiority of optical colonoscopy. Until additional confirmatory studies are available, virtual CT colonoscopy should not replace routine optical colonoscopic screening.

Barium enemas can accurately detect colorectal carcinoma; however, the false-negative rate associated with double-contrast barium enemas ranges from 2% to 61% because of misinterpretation, poor preparation, and difficulties in detecting smaller lesions. A supplementary colonoscopy may be needed if double-contrast barium enema does not adequately visualize the entire colon or to obtain histopathology or perform polypectomy in the event of abnormal findings.

Recommendations for average-risk individuals Adults at average risk should begin colorectal cancer screening at age 50. The American Cancer Society (ACS) guidelines on screening and surveillance for the early detection of colorectal adenomatous polyps and cancer provide five options for screening average-risk individuals (Table 3).

For those individuals who elect FOBT alone, or in combination with flexible sigmoidoscopy, a single test of a stool sample in the clinical setting (as, for instance, is often performed with the stool sample collected on the fingertip during a digital rectal examination) is not an adequate substitute for a full set of samples using the take-home card system. Because combining flexible sigmoidoscopy with FOBT can substantially increase the benefits of either test alone, the ACS regards annual FOBT accompanied by flexible sigmoidoscopy every 5 years as a better choice than either FOBT or flexible sigmoidoscopy alone. In a recent review of the current status of emerging technologies for colorectal cancer screening, the ACS modified its guidelines for FOBT to include immunochemical tests. The ACS concluded that in comparison with guaiac-based tests for the detection of occult blood, immunochemical tests are more patient-friendly and are likely to produce equal or better sensitivity and specificity.

The choice of colonoscopy or double-contrast barium enema for screening may depend on factors such as personal preference, cost, and the local availability of trained clinicians to perform a high-quality examination. For those who elect either colonoscopy or double-contrast barium enema for screening, there is no need for annual FOBT. Digital rectal examination should be performed at the time of the sigmoidoscopy or colonoscopy.

Recommendations for screening increased-risk and high-risk individuals Risk of colorectal cancer is even higher among individuals with hereditary syndromes. Individuals with a history of inflammatory bowel disease of significant duration are also at increased risk.

Those individuals who have been diagnosed as having adenomatous polyps or a personal history of curative-intent resection of colorectal cancer should undergo a colonoscopy to remove all polyps from the colorectum, after which a colonoscopic

exam should be repeated at an interval to be determined on the basis of the size, multiplicity, and histologic appearance of the adenoma(s) (Table 4). If colonoscopy is not available, or not feasible, flexible sigmoidoscopy followed by double-contrast barium enema may be used for surveillance.

A family history of either colorectal cancer or colorectal adenomas increases the risk of developing colorectal cancer. Risk is higher for individuals with a family history involving first-degree relatives, those family members with younger age of onset, and those with multiple affected family members. Individuals with a single first-degree relative diagnosed with colorectal cancer or an adenomatous polyp after age 60, or with affected relatives who are more distant than first-degree relatives, can be considered to be at "average risk." In general, colonoscopy is recommended 5-10 years prior to the earliest diagnosis in the family or age 40, whichever is earlier. Subsequent colonoscopy should be repeated at intervals to be determined on the basis of the initial examination. If a colonoscopy is not available or not feasible, flexible sigmoidoscopy followed by a double-contrast barium enema can be used.

Individuals at elevated risk due to the known or likely presence of FAP or HNPCC should begin surveillance at an early age with endoscopic examinations (Table 4). There is ample evidence to support endoscopic surveillance as a method of early detection. A program of biennial colonoscopy starting at age 20 to 25 years is recommended for HNPCC carriers. For those with FAP, it is recommended that regular sigmoidoscopy start at the age of 12 years and continue at 2-year intervals. DNA testing of at-risk individuals provides the opportunity to identify those who should undergo intensive surveillance.

Individuals with a history of extensive inflammatory bowel disease affecting the colon should begin colonoscopic surveillance with biopsy for dysplasia every 1-2 years after 8 years of symptoms. Prophylactic colectomy should be considered in the presence of persistent dysplasia.

Diagnosis

Initial work-up An initial diagnostic work-up for patients suspected of having colorectal tumors should include:

- digital rectal examination and FOBT
- 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.

TABLE 5: 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 IIA	T3	N0	M0	B2
IIB	T4	N0	M0	B3
Stage IIIA	T1-2	N1	M0	C1[d]
IIIB	T3-4	N1	M0	C2-3[d]
IIIC	Any T	N2	M0	C1-3[d]
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

[c] M0 = no distant metastasis; M1 = distant metastasis

[d] C1 = T2 N1, T2 N2   C2 = T3 N1, T3 N2   C3 = T4 N1, T4 N2

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th Ed. New York, Springer-Verlag, 2002.

FDG-PET scanning FDG([18]fluorodeoxyglucose)-PET scanning has emerged as a highly sensitive study for the evaluation of patients who may be candidates for resection of isolated metastases from colorectal cancer. Although not usually recommended in the evaluation of primary disease, this modality can aid in the staging of recurrence.

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 and the tendency to spread within the peritoneum. Approximately 10% of colorectal adenocarcinomas are mucinous. It is more commonly seen in younger patients.

Signet-ring–cell carcinoma is an uncommon variant, comprising 1% of colorectal adenocarcinomas. These tumors contain large quantities of intracellular mucinous elements (causing the cytoplasm to displace the nucleus) and tend to in-

volve the submucosa, making their detection difficult with conventional imaging techniques.

Other tumor types Squamous cell carcinomas, small-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.

There has been a considerable amount of debate in the literature regarding the therapeutic role of extended lymphadenectomy in the treatment of colon cancer. A recent retrospective review analyzed the number of lymph nodes removed from patients entered into an intergroup colon cancer trial. The survival rates for both lymph node-positive and lymph node-negative patients were significantly higher when higher numbers of lymph nodes were removed and examined. This study suggests that a therapeutic benefit may exist to extended lymphadenectomy for colon cancer (Le Voyer TE, Sigurdson ER, Hanlon AL, et al: J Clin Oncol 21:2912-2919, 2003).

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 bowel 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 lungs the most frequently affected extra-abdominal organ. Other sites of hematogenous spread include the bones, kidneys, adrenal glands, and brain.

Staging and prognosis

The TNM staging classification, which is based on the depth of tumor invasion in the intestinal wall, the number of regional lymph nodes involved, and the presence or absence of distant metastases, has largely replaced the older Dukes' classification scheme (Table 5).

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). However, there appears to be a superior survival for patients with stage III disease whose disease is confined to the bowel wall (ie, $\leq$ T2, N+).

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 lesion

has had no influence on survival. Elevated expression of thymidylate synthase and allelic loss of chromosome 18 have been correlated with a poor prognosis.

Treatment

PRIMARY TREATMENT OF LOCALIZED DISEASE

Management of colorectal carcinoma relies primarily on resection of the bowel with the adjacent draining lymph nodes. The need for adjuvant systemic or local chemotherapy or immunotherapy, with or without concurrent irradiation, 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. Surgical resection can be performed by open or laparoscopic approach. The type of resection depends on the anatomic location 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.

Rectum For rectal carcinoma, the distal surgical margin should be at least 2 cm, although some investigators have suggested that a smaller but still negative margin may be adequate. The resection should include the node-bearing mesorectum surrounding the rectum. This procedure, which is termed total mesorectal excision (TME), is accomplished using a sharp dissection technique (see Figure 1). The use of TME has been associated with a significant reduction in local recurrence rates for patients with rectal cancer.

Posteriorly, the mesorectal dissection is carried out along the presacral fascia. Anteriorly, the dissection follows the posterior vaginal wall in females or Denonvilliers' fascia in males, both of which may be resected in the presence of an anterior wall rectal cancer. Reported rates of local recurrence following TME for rectal cancer have generally been < 10%, com-
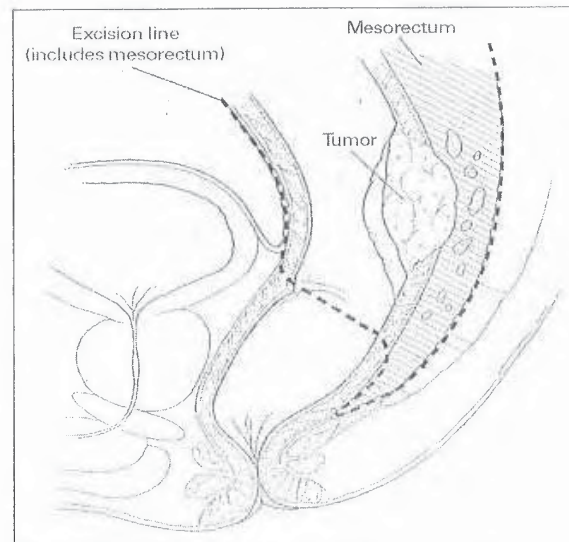

FIGURE 1: Mesorectal excision
Adapted with permission from N Engl J Med 345(9):690-692, 2001.

pared with rates of recurrence up to 30% prior to the advent of TME. Selective use of radiation therapy can improve upon the results of TME alone.

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 for tumors in the lower one-third of the rectum. 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.

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.

Two prospective randomized trials involving laparoscopic colorectal resection have recently been published. A multicenter group in the United States randomized 872 patients with right, left, or sigmoid colon cancers to receive laparoscopic vs open colectomy. At 3 years of follow-up, there were no differences in recurrence rates or survival (The Clinical Outcomes of Surgical Therapy Study Group: N Engl J Med 350:2050-2059, 2004). A similar study randomized 403 patients with rectosigmoid carcinoma to receive laparoscopic vs open colectomy. At 5 years of follow-up, there were no differences in recurrence rates or survival (Leung KL, Kwok SP, Lam SC, et al: Lancet 363:1187-1192, 2004). Although the operative time for laparoscopy was longer, both studies demonstrated a reduction in postoperative hospitalization and narcotic use.

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. In most series, transanal excision for these good histology T1 lesions results in excellent long-term control. However, some studies with long-term follow-up demonstrated significant local recurrence rates, even with T1 lesions. For T2 or T3 tumors, the standard therapy remains a transabdominal resection because of the risk of mesorectal nodal spread. Preoperative transrectal ultrasonography is useful in defining lesions that can be resected by local excision alone. A trial sponsored by the CALGB (Cancer and Leukemia Group B) demonstrated reasonable results for patients with T2 rectal cancer undergoing negative margin local excision followed by fluorouracil (5-FU) and external-beam radiation therapy. The locoregional recurrence rate at 6 years was only 14%. Good results with local excision alone following chemoradiotherapy for rectal cancer, have been reported. The role of local excision alone in this clinical scenario awaits confirmatory studies.

Neoadjuvant therapy For rectal cancers approaching the anal sphincter, preoperative (neoadjuvant) irradiation or the combination of chemotherapy and irradiation will significantly reduce the size of the majority of tumors. This

TABLE 6: Chemotherapy regimens for colorectal adenocarcinoma

Drug/combination	Dose and schedule

Adjuvant low-dose leucovorin/fluorouracil

Leucovorin	20 mg/m^2 IV bolus on days 1-5 immediately before fluorouracil
Fluorouracil	425 mg/m^2/d IV bolus on days 1-5

Repeat cycle at 4 weeks, 8 weeks, and then every 5 weeks for 6 cycles.

Poon MA, O'Connell MJ, Moertel CG, et al: J Clin Oncol 7:1407–1418, 1989.

Adjuvant high-dose leucovorin/fluorouracil

Leucovorin	500 mg/m^2 IV infused over 2 hours every week for 6 weeks
Fluorouracil	500 mg/m^2 IV infused over 1 hour after the start of leucovorin every week for 6 weeks

Repeat cycle every 8 weeks for 6 cycles.

Wolmark N, Rockette H, Fisher B, et al: J Clin Oncol 11:1879–1887, 1993.

Single-agent irinotecan

Irinotecan	125 mg/m^2 IV infused over 90 minutes weekly for 4 weeks, followed by a 2-week rest

Pitot HC, Wender DB, O'Connell MJ, et al: J Clin Oncol 15:2910–2919, 1997.

Irinotecan	350 mg/m^2 IV infused over 90 minutes repeated every 3 weeks

NOTE: Patients with performance status of 2 or age $\geq$ 70 years should receive 300 mg/m^2 IV infused over 90 minutes.

Cunningham D, Pyrhonen S, James RD, et al: Lancet 352:1413–1418, 1998.

Irinotecan/fluorouracil/leucovorin (IFL)

Irinotecan	125 mg/m^2 IV infused over 90 minutes once a week for 4 weeks
Fluorouracil	500 mg/m^2 IV bolus once a week for 4 weeks
Leucovorin	20 mg/m^2 IV bolus once a week for 4 weeks

Repeat cycle every 6 weeks: ie, give all of the drugs once a week for 4 weeks, followed by 2 weeks rest, and then start the cycle again.

Saltz LB, Cox JV, Blanke C, et al: N Engl J Med 343:905–914, 2000.

Irinotecan/fluorouracil/leucovorin (FOLFIRI)

Leucovorin	400 mg/m^2 IV infused over 2 hours on day 1
Irinotecan	180 mg/m^2 IV infused over 90 minutes on day 1
Fluorouracil	400 mg/m^2 IV bolus on day 1
Fluorouracil	2,400 mg/m^2 46-hour IV infusion

Andre T, Louvet C, Maindrault-Goebel F, et al: Eur J Cancer 35:1343–1347, 1999.

Drug/combination	Dose and schedule
Oxaliplatin/fluorouracil/leucovorin (FOLFOX4)	
Oxaliplatin	85 mg/m^2 IVPB over 2 hours on day 1 only
Leucovorin	200 mg/m^2/d over 2 hours on day 1 given simultaneously with oxaliplatin
Fluorouracil	400 mg/m^2 IV bolus over 2 to 4 minutes
Fluorouracil	600 mg/m^2 continuous infusion over 22 hours on days 1 and 2 every 14 days for 12 cycles
Andre T, Boni C, Mounedji-Boudiaf L, et al: N Engl J Med 350:2343–2351, 2004.	
Oxaliplatin/fluorouracil/leucovorin (FOLFOX6)	
Leucovorin	400 mg/m^2 IV infused over 2 hours on day 1
Oxaliplatin	100 mg/m^2 IV infused over 90 minutes on day 1
Fluorouracil	400 mg/m^2 IV bolus on day 1
Fluorouracil	2,400 mg/m^2 46-hour IV infusion
Maindrault-Goebel F, Louvet C, Andre T, et al: Eur J Cancer 35:1338–1342, 1999.	
Capecitabine/oxaliplatin (CapeOx)	
Oxaliplatin	130 mg/m^2 IV infused on day 1 only followed by
Capecitabine	1,000 mg/m^2 IV orally twice daily in the evening on day 1 to the morning of day 15
Cycle repeated every 3 weeks.	
Cassidy J, Tabernero J, Twelves C, et al: J Clin Oncol 22:2084-2091, 2004.	
Fluorouracil as an irradiation enhancer—bolus	
Leucovorin	20 mg/m^2 IV bolus on days 1-5, 29-33 immediately before fluorouracil
Fluorouracil	325 mg/m^2/d IV bolus on days 1-5, 29-33
Hyams DM, Mamounas EP, Petrelli N, et al: Dis Colon Rectum 40:131–139, 1997.	
Fluorouracil as an irradiation enhancer— continuous infusion	
Fluorouracil	225 mg/m^2/d IV continuous infusion during irradiation
O'Connell MJ, Martenson JA, Wieand HS, et al: N Engl J Med 331:502–507, 1994.	
Irinotecan/fluorouracil/leucovorin (IFL) with bevacizumab	
Irinotecan	125 mg/m^2 IV once a week for 4 weeks, cycle repeated every 6 weeks
Fluorouracil	500 mg/m^2 IV once a week for 4 weeks, cycle repeated every 6 weeks
Leucovorin	20 mg/m^2 IV once a week for 4 weeks, cycle repeated every 6 weeks
Bevacizumab	5 mg/kg IV every 2 weeks
Hurwitz H, Fehrenbacher L, Novotny W, et al: N Engl J Med 350:2335–2342, 2004.	

Drug/combination	Dose and schedule
Fluorouracil and leucovorin plus bevacizumab	
Leucovorin	500 mg/m^2 IV infused over 2 hours once a week for 6 weeks, then a 2-week rest period
Fluorouracil	500 mg/m^2 IV bolus slow push 1 hour after leucovorin infusion once a week for 6 weeks, then a 2-week rest period
Bevacizumab	5 mg/kg IV continuous infusion over 90 minutes every 2 weeks

Kabbinavar F, Hurwitz H, Fehrenbacher I, et al: J Clin Oncol 21:60–65, 2003.

Cetuximab with or without irinotecan	
Cetuximab	400 mg/m^2 initial dose followed by 250 mg/m^2 weekly
OR	
Irinotecan	350 mg/m^2 every 3 weeks, 180 mg/m^2 every 2 weeks, or 125 mg/m^2 weekly for 4 weeks
Cetuximab	400 mg/m^2 initial dose followed by 250 mg/m^2 weekly
Repeat cycle every 6 weeks.	

Cunningham D, Humblet Y, Siena S, et al: Proc Am Soc Clin Oncol 22:252 (abstract 1012), 2003.

> Compared with 5-FU and leucovorin, capecitabine (Xeloda) provides an equivalent or superior benefit in the adjuvant treatment of resected stage III colon cancer. Patients in the capecitabine arm also experienced fewer severe toxicities, including less stomatitis and neutropenic fever/sepsis (*Cassidy J, Scheithauer W, McKendrick H, et al: Proc Am Soc Clin Oncol [abstract] 23:247S, 2004*).

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 disease of the majority will be rendered resectable following neoadjuvant therapy. One additional role of neoadjuvant therapy may be in facilitating transanal excision of T2 and T3 rectal cancers in poor surgical risk patients. A number of investigators have reported good results with transanal excision of T2 and T3 tumors following a complete response to neoadjuvant therapy. However, this approach cannot be considered the current standard of care.

Laparoscopic colonic resection The use of laparoscopic colonic resection is becoming an oncologically acceptable method of treating cancers of the colon. The potential advantages include a shorter hospital stay, reduced postoperative ileus, decreased time away from work, fewer adhesive complications, and a lower risk of hernia formation. The potential disadvantages compared with open transabdominal resection include longer operative time, higher operative costs, and technical considerations related to operative skill.

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, local therapy, such as irradiation, 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 of 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 combined chemotherapy is the principal adjuvant therapy for colon cancer (Table 6). The administration of single-agent 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 postoperative observation.

5-FU plus levamisole (Ergamisol) 5-FU combined with levamisole, an antihelminthic agent with nonspecific immunostimulating properties, was the first adjuvant regimen to demonstrate a decrease in the recurrence rate and an increase in disease-free and overall survival in patients with stage III colon cancer. This combination is given over 1 year. It has largely been replaced by 5-FU and leucovorin, a combination with equivalent activity that can be given over 6 months.

5-FU plus leucovorin Studies have demonstrated the benefits of 5-FU plus leucovorin (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 (Mayo Clinic) 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 6 cycles. More recently, completed randomized trials by the National Surgical Adjuvant Breast and Bowel Project (NSABP) have used three rather than six cycles of therapy

An analysis of survival data from patients with stage II or III disease treated in four consecutive NSABP adjuvant chemotherapy trials showed similar relative

reductions in disease recurrence and mortality as well as similar improvements in overall survival in patients with stage II and III disease.

5-FU and leucovorin plus other agents The addition of other agents to 5-FU and leucovorin is currently being assessed.

Monoclonal antibody 17 1A (edrecolomab) A randomized study of 17 1A antibody in patients with stage III colon cancer showed it to be inferior to 5-FU and leucovorin. Its addition to 5-FU and leucovorin did not improve disease-free or overall survival. A trial of the antibody in stage II colon cancer recently completed accrual. No results are yet available from this trial.

Irinotecan (CPT-11, Camptosar) The addition of irinotecan to 5-FU and leucovorin is being assessed in a phase III trial. (See discussion of irinotecan under treatment of advanced colon cancer.) A recent letter to investigators involved in the phase III trial of bolus 5-FU and leucovorin with or without irinotecan reported no benefit to the addition of irinotecan. Until further details are provided, irinotecan should not be used in the adjuvant setting outside a clinical trial.

Oxaliplatin (Eloxatin) has been approved by the FDA for first-line therapy of advanced colorectal cancer and has been evaluated for resected stage II and III colon cancer in a phase III trial from Europe (MOSAIC). The use of FOLFOX compared with the same infusional regimen without oxaliplatin led to a higher 3-year disease-free survival rate in those receiving FOLFOX. This clinical trial led to the recent approval of oxaliplatin for adjuvant therapy in Europe. (See further discussion about oxaliplatin in the first-line setting under treatment of advanced colon cancer.)

Radiation therapy

Postoperative irradiation to the tumor bed should be considered in patients with T3 node-positive and T4 (B3 or C3) tumors located in retroperitoneal portions of the colon because more than 30% of these patients develop a local recurrence. Retrospective studies suggest improved local control with irradiation, particularly in patients with positive resection margins. However, an underpowered intergroup trial failed to show a benefit to adjuvant chemotherapy and irradiation compared with adjuvant chemotherapy alone in selected patients with T3 node-positive and T4 disease. The 5-year disease-free survival in both groups was 51%.

ADJUVANT THERAPY FOR RECTAL CANCER

Local recurrence alone or in combination with distant metastases occurs in up to 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 15%-30% for stage II tumors. In stage III disease, the incidence of pelvic failure increases to 50% or more. The use of TME significantly reduces this risk of local recurrence; however, local recurrence remains a concern in patients with stages II and III disease.

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.

The recent findings of the NSABP R-02 trial indicated postoperative adjuvant chemotherapy resulted in similar survival rates to those of postoperative chemoradiation therapy but was associated with a significantly higher rate of locoregional failure.

Radiation therapy alone

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, even in patients undergoing TME surgery. However, with the exception of one recent study, preoperative therapy 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 therapy

Postoperative chemoradiation therapy Clinical trials of surgical adjuvant treatment indicate that postoperative radiation therapy with concurrent chemotherapy (chemoradiation therapy) is superior to postoperative radiation therapy alone or surgery alone. Postoperative chemoradiation therapy is a standard of care for patients with stage II or III rectal cancer based largely on the findings of the North Central Cancer Treatment Group (NCCTG) and Gastrointestinal Tumor Study Group (GITSG) trials. A summary of the 5-year survival results of the Patterns of Care Study (PCS) of the American College of Radiology and the results of the National Cancer Data Base (NCDB), both of which are representative of American national averages, is shown in Table 7.

The most effective combination of drugs, optimal mode of administration, and sequence of irradiation 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 irradiation 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,

TABLE 7: Five-year overall survival in Patterns of Care Study (PCS) vs the National Cancer Data Base (NCDB), Gastrointestinal Tumor Study Group (GITSG), and Mayo/North Central Cancer Treatment Group (Mayo/NCCTG) studies

Study	5-year survival	
Bimodality vs trimodality	**S + RT**	**S + RT + CT**
Stage II		
PCS	61%	81%
NCDB	55%	62%
Stage III		
PCS	33%	65%
NCDB	39%	42%
Postop CRT vs postop RT	**Postop RT**	**Postop CRT**
GITSG (7175)	52%	59%
Mayo/NCCTG (7945)	48%	57%
PCS	50%	69%

S = surgery; RT = radiation therapy; CT = chemotherapy; CRT = concurrent irradiation therapy and chemotherapy

Adapted from Coia LR, Gunderson LL, Haller D, et al: Cancer 86:1952–1958, 1999.

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 therapy Preoperative chemoradiation therapy may be preferred to postoperative adjuvant treatment, particularly in patients with T3 or T4 lesions. Such treatment may enhance resectability and may be associated with a lower frequency of complications compared with postoperative treatment. In a recent report of a randomized trial conducted by the German Rectal Cancer Study, Sauer et al found that compared with postoperative chemoradiotherapy, preoperative chemoradiotherapy significantly decreased local failure (7% vs 11%, $P = .02$) and sphincter preservation in low-lying tumors (39% vs 19%, $P < .004$). In addition, the incidence of chronic anastomotic recurrence was also lowest in the preoperative chemoradiotherapy group (2.7% vs 8.5%, $P = .001$).

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, para-

caval) lymph nodes. Anastomotic recurrences heralded by symptoms are the most curable, followed by local soft-tissue recurrences. Regional and retro-peritoneal lymph node recurrences portend a poor prognosis and systemic disease.

Metastasectomy Metastases to the liver and lungs account for most cases of non-nodal 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%-60%, depending on the number of metastases and stage of disease. Resection of solitary metastases in patients with stage I or II disease results in a 5-year survival rate of ~40%.

Adjuvant therapy after resection of hepatic metastases has been assessed in several randomized trials. Intra-arterial administration of floxuridine, using a hepatic artery catheter, alternating with systemic 5-FU and leucovorin, improves overall survival and reduces the risk of recurrence within the liver.

Chemotherapy The development of chemotherapy for colorectal cancer has become a very active field (Table 6). After decades of 5-FU–based treatment, and of little clinical gains, the arrival of new, effective agents has significantly changed the way this cancer is treated. Although 5-FU remains the backbone of most regimens, the new agents irinotecan and oxaliplatin are rapidly becoming an important part of front-line treatment of this disease in the United States and abroad. The rapid development of newer agents, such as the molecular-targeted agents, holds the promise that progress will continue in chemotherapy for colorectal cancer.

5-FU, synthesized by Heidelberger in 1957, remains an important agent 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 than by other methods. 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.

Overall, the incidence of side effects is significantly lower when 5-FU is delivered by continuous infusion. A meta-analysis of more than 1,200 patients treated with either continuous infusion or bolus regimens of 5-FU demonstrated superior response rates and a small survival advantage for the continuous infusion regimens.

> A randomized phase III trial of the anti-VEGF antibody bevacizumab, combined with IFL, resulted in a significantly higher median survival, disease progression-free survival, and overall response rate compared with bevacizumab plus placebo (Hurwitz H, Fehrenbacher L, Novotny W, et al: N Engl J Med 350:2335-2342, 2004).

TABLE 8: NCCN recommendations for post-treatment surveillance/monitoring*

- History and physical examination every 3 months for 2 years, then every 6 months for a total of 5 years

- CEA level evaluation every 3 months for 2 years, then every 6 months or years 2-5 for T2 or greater lesions

- Colonoscopy in 1 year, repeat in 1 year if results are abnormal or at least every 2-3 years if results are negative for polyps. If no preoperative colonoscopy has been performed due to an obstructing lesion, colonoscopy in 3-6 months

- Abdominal/pelvic CT scan in addition to chest x-ray or chest CT for patients with resected stage IV disease only:

  Every 6 months for 2 years, then every 6-12 months for a total of 5 years

* http://www.nccn.org

CEA = carcinoembryonic antigen; NCCN = National Comprehensive Cancer Network

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Two large randomized trials demonstrated improved response rates and overall survival for the combination of 5-FU plus leucovorin and irinotecan (discussed later in this chapter).

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.

Although there is no agreement as to the optimal dose of leucovorin, two dosing schedules have been approved by the FDA:

■ "low-dose" leucovorin regimen, consisting of leucovorin, 20 mg/m²/d, immediately followed by 5-FU, 425 mg/m²/d

■ "high-dose" leucovorin regimen, consisting of leucovorin, 200 mg/m²/d, immediately followed by 5-FU, 370 mg/m²/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, 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 FDA approval was based on two phase III trials showing that irinotecan (350 mg/m² once every 3 weeks) significantly increased survival, compared with best supportive care and infusional 5-FU, respectively, in patients with recurrent or progressive cancer following first-line 5-FU therapy.

CANCER MANAGEMENT: A MULTIDISCIPLINARY APPROACH

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TABLE 9: 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, bladder)[a]

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

[a] Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4.

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th Ed. New York, Springer-Verlag, 2002.

Irinotecan increased the median survival by 27% and 41%, respectively, in the two trials.

Irinotecan is active in patients whose disease progressed while 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/m² weekly for 4 weeks, followed by a 2-week rest period (United States), and 350 mg/m² every 3 weeks (Europe).

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.

5-FU plus leucovorin and irinotecan The results of two large randomized trials comparing the combination of 5-FU plus leucovorin and irinotecan vs 5-FU plus leucovorin in the first-line treatment of metastatic colorectal cancer have been reported. Both trials demonstrated improved response rates and overall survival for the three-drug combination. The two trials used different schedules and were conducted in different locations, yet their results were remarkably consistent. The response rates for the three-drug combination ranged from 35%-40%, and the median time to disease progression was approximately 7 months.

This combination of irinotecan, 5-FU, and leucovorin is one option for patients with metastatic colorectal cancer. Based on its superior activity, compared with 5-FU and leucovorin, the FDA approved this combination as first-line treatment for patients with metastatic colorectal cancer in 2000.

A portion of patients receiving bolus infusions of irinotecan, 5-FU, and leucovorin will develop severe and life-threatening diarrhea and neutropenia shortly after the initiation of therapy. Careful monitoring and prompt intervention are essential with the initiation of this combination.

Capecitabine (Xeloda) is an oral fluorinated pyrimidine FDA approved for use in advanced colon cancer. It is converted to 5-FU through a three-step process after ingestion. In a phase III trial of previously untreated patients with metastatic colon cancer, capecitabine produced higher response rates than 5-FU and leucovorin. Overall survival and time to disease progression were similar (noninferior) to those with 5-FU and leucovorin. The recommended dose of capecitabine is 2,500 mg/m² each day, given as a twice-daily dose, for 14 days followed by a 1-week rest period. The side effects of capecitabine tend to be similar to those seen with prolonged infusion of 5-FU, with hand-foot syndrome being the most common.

Oxaliplatin is a new diaminocyclohexane platinum that has undergone 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 cancer, response rates of 27% have been reported with oxaliplatin alone, and rates as high as 57% have been noted

when the drug is combined with 5-FU. Patients receiving oxaliplatin, infusional 5-FU, and leucovorin have achieved overall survivals of > 20 months in several reported trials. However, many of these patients have received second- and even third-line therapies at the time of disease progression. Oxaliplatin's toxicity profile includes nausea/vomiting and cumulative, reversible peripheral neuropathy. Patients may also develop a reversible, cold-induced, acute pharyngolaryngeal neuropathy.

Oxaliplatin combined with infusional 5-FU and leucovorin was approved by the FDA in 2002 as second-line therapy for patients with disease progression after treatment with irinotecan, 5-FU, and leucovorin. This approval was based on an improved time to disease progression compared with that of either oxaliplatin alone or infusional 5-FU and leucovorin.

A multicenter, randomized phase III study (ASCO 2002, 2003) showed improved outcome with regard to response rate, time to disease progression, and overall survival for patients receiving first-line therapy for metastatic colorectal cancer with oxaliplatin, infusional 5-FU, and leucovorin, compared with irinotecan, 5-FU, and leucovorin. At the time of the 2003 presentation, the time to disease progression for the oxaliplatin combination was 8.7 months, compared with 6.9 months for the irinotecan combination. The oxaliplatin regimen also had a significantly better overall survival (19.5 vs 14.8 months) and response rate (45% vs 31%). Based on the results of this trial, in January 2004, the FDA approved oxaliplatin with infusional 5-FU and leucovorin as first-line therapy.

Molecular-targeted agents A variety of monoclonal antibodies and small molecules are being evaluated in clinical trials and preclinical studies. Two of these agents (cetuximab [Erbitux] and bevacizumab [Avastin]) have been FDA approved for use.

Cetuximab is a human/mouse chimeric antibody directed against the epithelial growth factor receptor (EGFR). In a randomized trial of patients with colorectal cancer refractory to irinotecan, patients were randomized to receive either cetuximab and irinotecan or cetuximab alone. The addition of cetuximab to irinotecan led to a significantly higher response rate compared with cetuximab alone. The median survival for those receiving cetuximab and irinotecan was also longer. Based on the results of this study, cetuximab has been approved by the FDA for use in patients whose disease is refractory to irinotecan with tumors expressing EGFR.

Bevacizumab is a humanized monoclonal antibody that binds circulating vascular endothelial growth factor (VEGF). When given with either 5-FU and leucovorin or irinotecan, 5-FU, and leucovorin (IFL) as first-line therapy in patients with metastatic colorectal cancer, bevacizumab led to improved outcome. The addition of bevacizumab to 5-FU and leucovorin resulted in significant improvement in disease progression-free survival. Even better results were seen with IFL. The addition of bevacizumab to IFL resulted in significant improvement in overall survival and response rate. These studies led to the FDA approval of bevacizumab. It is indicated for use in first-line therapy for metastatic colorectal cancer when combined with 5-FU–based chemotherapy.

Intrahepatic floxuridine administration Renewed interest in regional delivery of floxuridine 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 (IA) of floxuridine than with systemic therapy. A 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 floxuridine infusions appears to decrease biliary sclerosis.

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 more than 70% of patients. Obstruction cannot be reliably relieved by irradiation, and diverting colostomy is recommended. Only 15% of patients with recurrent rectal cancers achieve local disease control with irradiation, and median survival is < 2 years.

Chemoradiation therapy 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 irradiation 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 controversial. Guidelines for post-treatment surveillance/monitoring adopted by the National Comprehensive Cancer Network (NCCN), a consortium of 19 American cancer centers, are shown in Table 8.

ANAL CANAL CARCINOMA

Epidemiology, etiology, and risk factors

In the United States, about 3,990 new cases of anal canal carcinoma are diagnosed each year. Overall, it is slightly more common 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 of disease into adjacent organs (vagina, urethra, or bladder). Reexamination under general anesthesia may be necessary. A diagnostic incisional biopsy is required.

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 if results of aspiration are inconclusive.

Pathology

Squamous cell carcinomas Most anal canal malignancies are squamous cell carcinomas. They 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 adenocarcinomas.

Small-cell carcinomas of the anal canal are aggressive neoplasms similar in natural history to bronchogenic small-cell carcinomas. If such a histology is 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 the depth of disease penetration. Early anal melanomas < 2.0 mm in depth can be cured with wide excision. More advanced disease can be treated with local excision and external-beam irradiation with excellent local control. Abdominoperineal resection is indicated only rarely in the management of anal melanoma.

Adenocarcinomas are uncommon cancers associated with a poor prognosis. Treatment should be aggressive and based on a multimodality approach. The rarity of this tumor precludes the development of specific clinical trials.

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 9). The TNM classification distinguishes between anal canal carcinoma and anal margin tumors, since the latter exhibit biologic behavior similar to that of other skin cancers and are staged as skin cancers.

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 later in this chapter), 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.

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TABLE 10: Chemotherapy regimens for anal canal cancer

Drug/combination	Dose and schedule
Fluorouracil/mitomycin/radiation therapy	
Fluorouracil	1 g/m^2/d IV infused continuously on days 1-4 and 29-32
Mitomycin	15 mg/m^2 IV on day 1
Irradiation	200 cGy/d for 5 days per week (total dose, 3,000 cGy)

Give chemotherapy concurrently with irradiation; start both modalities on the same day.

Leichman L, Nigro ND, Vaitkevicius VK, et al: Am J Med 78:211–215, 1985.

Fluorouracil/cisplatin/radiation therapy	
Fluorouracil	1 g/m^2/d IV infused continuously for 4 days
Cisplatin	25 mg/m^2/d IV on days 2-5 following standard hydration

Give chemotherapy concurrently with irradiation, except in elderly or frail patients.

Wagner JP, Mahe MA, Romestaing P, et al: Int J Radiat Oncol Biol Phys 29:17–23, 1994.

Table prepared by Ishmael Jaiyesimi, DO

This modality carries a high potential for radiation necrosis and fails to incorporate treatment of the inguinal nodes.

Combined-modality treatment

Chemotherapy given concurrently with irradiation is the preferred therapy for most patients with anal canal cancer (Table 10). Investigators from Wayne State University pioneered the use of simultaneous pelvic irradiation and chemotherapy in the treatment of patients with anal canal carcinomas. They 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 days 29-32. Mitomycin (Mutamycin), 15 mg/m^2, was administered as an IV bolus on day 1. A total of 4 to 6 weeks after the completion of therapy, patients had a deep muscle biopsy of the anal canal scar.

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An updated analysis of this experience demonstrated that 38 of 45 patients (84%) were rendered disease free after chemotherapy and irradiation. Individuals who had positive biopsies underwent an abdominoperineal resection.

Because of the success of this experience, other investigators have attempted to implement infusional 5-FU and mitomycin with irradiation 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.

A randomized trial from the Radiation Therapy Oncology Group (RTOG) showed that the use of mitomycin with irradiation and 5-FU increased complete tumor regression and improved colostomy-free survival over irradiation

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%).

Several investigators have compared the results of irradiation alone vs irradiation plus chemotherapy. Cummings et al found that with identical irradiation doses and techniques, the local control rate for cancers > 2 cm rose from 49% with radiation therapy alone to 85% when 5-FU and mitomycin were combined with irradiation. 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 therapy over irradiation.

A complete response to combined chemotherapy and radiation therapy is expected in 80%-90% of patients with anal cancer. It is important to evaluate the response of therapy with a careful examination and biopsy of the anal canal after treatment. Anal canal cancers can continue to regress for up to 3 or more months after completion of treatment. For this reason, it is recommended that a biopsy be performed no sooner than 3 months after the completion of treatment. If localized persistent disease is identified after initial treatment, or if subsequent recurrence is diagnosed, abdominoperineal resection is expected to yield long-term disease control and survival in 40%-60% of patients.

Chemotherapy

Reports of other chemotherapeutic agents in anal cancer have been relatively anecdotal, with limited phase II studies. Because of the activity of cisplatin 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

Andre T, Boni C, Mounedji-Boudiaf L, et al: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350:2343–2351, 2004.

Benson AB III, Goldberg RM: Optimal use of the combination of irinotecan and 5-fluorouracil. Semin Oncol 30(3 suppl 6):68–77, 2003.

Clinical Outcomes of Surgical Therapy Study Group: A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 350:2050–2059, 2004.

Fuchs CS, Moore MR, Harker G, et al: Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. J Clin Oncol 21:807–814, 2003.

Goldberg RM, Sargent DJ, Morton RF, et al: A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 22:23–30, 2004.

Lacy AM, Garcia-Valdecasas JC, Delgado S, et al: Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: A randomised trial. Lancet 359:2224–2229, 2002.

Leung KL, Kwok SP, Lam SC, et al: Laparoscopic resection of rectosigmoid carcinoma: Prospective randomised trial. Lancet 363:1187–1192, 2004.

Le Voyer TE, Sigurdson ER, Hanlon AL, et al: Colon cancer survival is associated with increasing number of lymph nodes analyzed: A secondary survey of intergroup trial INT-0089. J Clin Oncol 21:2912–2919, 2003.

Paty PB, Nash GM, Baron P, et al: Long-term results of local excision for rectal cancer. Ann Surg 236:522–529, 2002.

Rothenberg ML: Current status of capecitabine in the treatment of colorectal cancer. Oncology 16(12 suppl 14):16–22, 2002.

Rothenberg ML, Oza AM, Bigelow RH, et al: Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: Interim results of a phase III trial. J Clin Oncol 21:2059–2069, 2003.

Sauer R, German Rectal Cancer Group: Adjuvant versus neoadjuvant combined modality treatment for locally advanced rectal cancer: First results of the German Rectal Cancer Study (CAO/ARO/AIO-94) [abstract]. Int J Radiat Oncol Biol Phys 57(suppl):S124–S125, 2003.

Swanson RS, Compton CC, Stewart AK, et al: The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol 10:65–71, 2003.

Tepper JE, O'Connell M, Niedzwiecki D, et al: Adjuvant therapy in rectal cancer: Analysis of stage, sex, and local control–Final report of intergroup 0114. J Clin Oncol 20:1744–1750, 2002.

Tournigand C, Andre T, Achille E, et al: FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. J Clin Oncol 22:229–237, 2004.

Weeks JC, Nelson H, Gelber S, et al: Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: A randomized trial. JAMA 287:321–328, 2002.

ON ANAL CANAL CARCINOMA

Ballo MT, Gershenwald JE, Zagars GK, et al: Sphincter-sparing local excision and adjuvant radiation for anal-rectal melanoma. J Clin Oncol 20:4555–4558, 2002.

Nilsson PJ, Svensson C, Goldman S, et al: Salvage abdominoperineal resection in anal epidermoid cancer. Br J Surg 89:1425–1429, 2002.

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A color atlas
of colorectal lesions

Compiled by Lawrence B. Cohen, MD
Department of Gastroenterology
Mount Sinai School of Medicine
New York, New York

COLOR ATLAS

Normal rectal mucosa
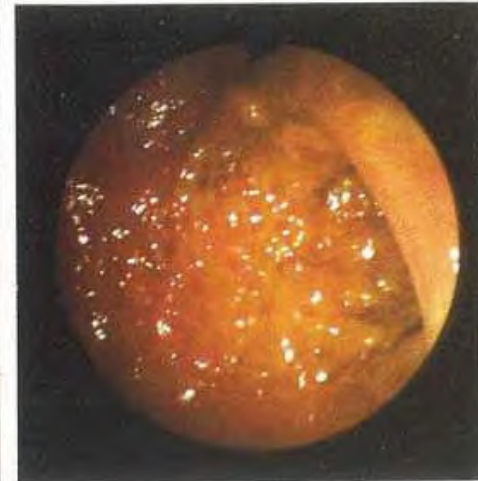

Normal sigmoid colon
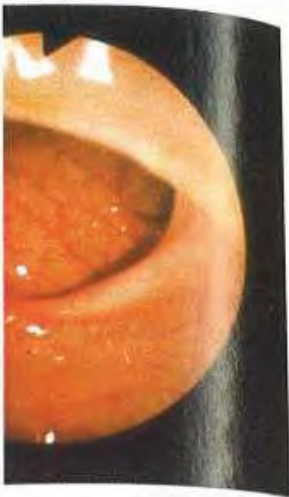

Adenomatous polyp with long pedicle
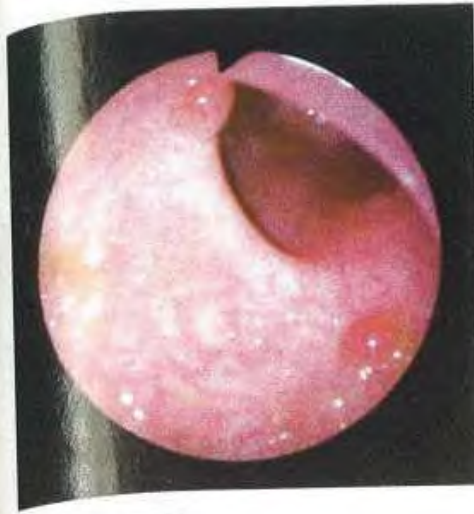

Another polyp

Another adenomatous sessile polyp

"Carpet"-like polyps

colon

Small adenomas

Nonadenomatous hyperplastic polyp

Lipoma

Pneumatosis cystoides

polyps
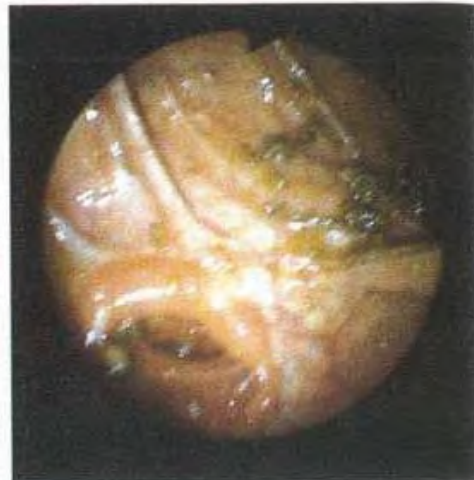
Bulky, polypoid adenocarcinomas

Flat, ulcerated adenocarcinoma

Diverticula
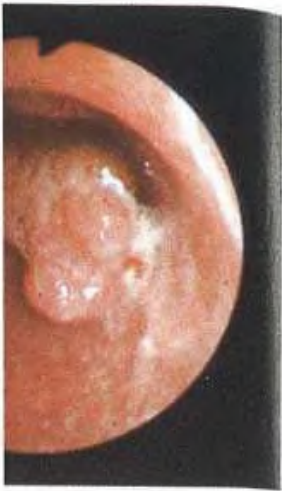
Scattered pseudopolyps

Clustered pseudopolyps
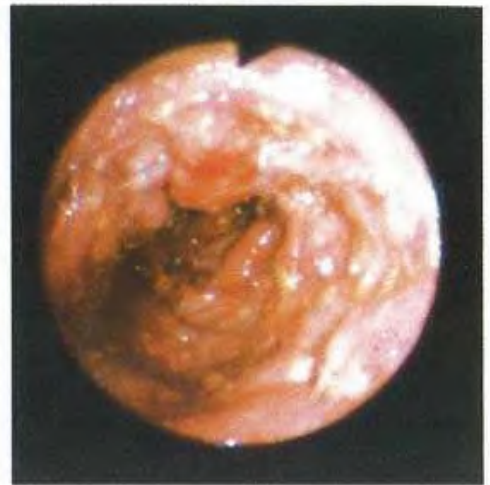
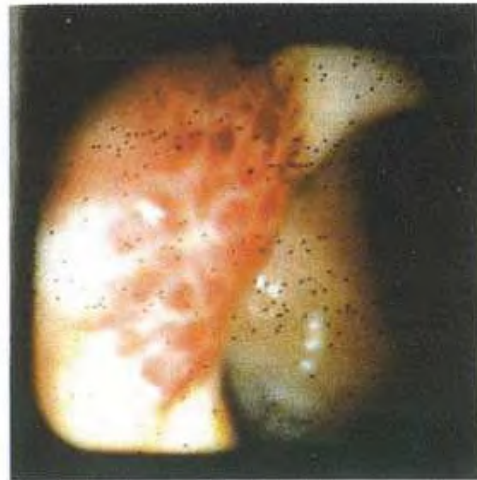Surgical anastomosis

Antibiotic-associated colitis

polyps

Colonic manifestations of
AIDS-cytomegalovirus colitis

Excavating ulcers of CMV infection

sis

Submucosal Kaposi's sarcoma

Endoscopic photography courtesy
of Lawrence B. Cohen, MD,
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CHAPTER 19

Urothelial and kidney cancers

Bruce G. Redman, DO, Mark Kawachi, MD, and Mark Hurwitz, MD

UROTHELIAL CANCER

In the year 2005, an estimated 63,210 new cases of bladder cancer will be diagnosed in the United States, and approximately 13,180 patients will die of this disease.

Urothelial cancers encompass carcinomas of the bladder, ureters, and renal pelvis; these cancers occur at a ratio of 50:3:1, respectively. Cancer of the urothelium is a multifocal process. Patients with cancer of the upper urinary tract have a 30%-50% chance of developing cancer of the bladder at some time in their lives. On the other hand, patients with bladder cancer have a 2%-3% chance of developing cancer of the upper urinary tract. The incidence of renal pelvis tumors is decreasing.

Epidemiology

Gender Urothelial cancers occur more commonly in men than in women (3:1) and have a peak incidence in the seventh decade of life.

Race Cancers of the urothelial tract are also more common in whites than in blacks (2:1).

Etiology and risk factors

Cigarette smoking The major cause of urothelial cancer is cigarette smoking. A strong correlation exists between the duration and amount of cigarette smoking and cancers at all levels of the urothelial tract. This association holds for both transitional cell and squamous cell carcinomas.

Analgesic abuse Abuse of compound analgesics, especially those containing phenacetin, has been associated with an increased risk of cancers of the urothelial tract. This risk appears to be greatest for the renal pelvis, and cancer at this site is usually preceded by renal papillary necrosis. The risk associated with analgesic abuse is seen after the consumption of excessive amounts (5 kg).

Chronic urinary tract inflammation also has been associated with urothelial cancers. Upper urinary tract stones are associated with renal pelvis cancers.

Chronic bladder infections can predispose patients to cancer of the bladder, usually squamous cell cancer.

Occupational exposures have been associated with an increased risk of urothelial cancers. Workers exposed to arylamines in the organic chemical, rubber, and paint and dye industries have an increased risk of urothelial cancer similar to that originally reported for aniline dye workers.

Balkan nephropathy An increased risk of cancer of the renal pelvis and ureters occurs in patients with Balkan nephropathy. This disorder is a familial nephropathy of unknown cause that results in progressive inflammation of the renal parenchyma, leading to renal failure and multifocal, superficial, low-grade cancers of the renal pelvis and ureters.

Genetic factors There are reports of families with a higher risk of transitional cell cancers of the urothelium, but the genetic basis for this familial clustering remains undefined.

Signs and symptoms

Hematuria is the most common symptom in patients presenting with urothelial tract cancer. It is most often painless, unless obstruction due to a clot or tumor and/or deeper levels of tumor invasion have already occurred.

Urinary voiding symptoms of urgency, frequency, and/or dysuria are also seen in patients with cancers of the bladder or ureters but are uncommon in patients with cancers of the renal pelvis.

Vesical irritation without hematuria can be seen, especially in patients with carcinoma in situ of the urinary bladder.

Symptoms of advanced disease Pain is usually a symptom of more advanced disease, as is edema of the lower extremities secondary to lymphatic obstruction.

Diagnosis

Initial work-up The initial evaluation of a patient suspected of having urothelial cancer consists of excretory urography, followed by cystoscopy. In patients with upper tract lesions, retrograde pyelography can better define the exact location of lesions. Definitive urethroscopic examination and biopsy can be accomplished utilizing rigid or flexible instrumentation.

At the time of cystoscopy, urine is obtained from both ureters for cytology, and brush biopsy is obtained from suspicious lesions of the ureter. Brush biopsies significantly increase the diagnostic yield over urine cytology alone. Also, at the time of cystoscopy, a bimanual examination is performed to determine whether a palpable mass is present and whether the bladder is mobile or fixed.

Evaluation of a primary bladder tumor In addition to biopsy of suspicious lesions, evaluation of a bladder primary tumor includes biopsy of selected mucosal sites to detect possible concomitant carcinoma in situ. Biopsies of the

primary lesion must include bladder wall muscle to determine whether there is invasion of muscle by the overlying carcinoma.

CT For urothelial cancers of the upper tract or muscle invasive bladder cancers, a CT scan of the abdomen/pelvis is performed to detect local extension of the cancer and involvement of the abdominal lymph nodes.

Bone scan For patients with bone pain or an elevated alkaline phosphatase level, a radioisotope bone scan is performed.

A chest x-ray completes the staging evaluation.

Pathology

Transitional cell carcinomas constitute 90%-95% of urothelial tract cancers.

Squamous cell cancers account for 3%-7% of urothelial carcinomas and are more common in the renal pelvis and ureters.

Adenocarcinomas account for a small percentage (< 3%) of bladder malignancies and are predominantly located in the trigone region. Adenocarcinomas of the bladder that arise from the dome are thought to be urachal in origin.

Carcinoma in situ In approximately 30% of newly diagnosed bladder cancers, there are multiple sites of bladder involvement, most commonly with carcinoma in situ. Although carcinoma in situ can occur without macroscopic cancer, it most commonly accompanies higher disease stages.

When carcinoma in situ is associated with superficial tumors, rates of recurrence and disease progression (development of muscle invasion) are higher (50%-80%) than when no such association is present (10%). Carcinoma in situ involving the bladder diffusely without an associated superficial tumor is also considered an aggressive disease. Most patients with this type of cancer will develop invasive cancers of the bladder.

Staging and prognosis

Staging system Urothelial tract cancers are staged according to the American Joint Committee on Cancer (AJCC) TNM classification system (Table 1). Superficial bladder cancer includes papillary tumors that involve only the mucosa (Ta) or submucosa (T1) and flat carcinoma in situ (Tis). The natural history of superficial bladder cancer is unpredictable, and recurrences are common. Most tumors recur within 6-12 months and are of the same stage and grade, but 10%-15% of patients with superficial cancer will develop invasive or metastatic disease.

Prognostic factors For carcinomas confined to the bladder, ureters, or renal pelvis, the most important prognostic factors are T stage and differentiation pattern. The impact of associated carcinoma in situ on Ta and T1 lesions is discussed above (see section on "Pathology"). Less-differentiated Ta-T1 lesions also are associated with higher recurrence and progression rates. Patients with well-differentiated Ta lesions without carcinoma in situ have a 95%

TABLE 1: TNM staging of urothelial tract cancers

Primary tumor (T)

Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Ta		Noninvasive papillary tumor
Tis		Carcinoma in situ: "flat tumor"
T1		Tumor invades subepithelial connective tissue
T2		Tumor invades muscle
	pT2a	Tumor invades superficial muscle (inner half)
	pT2b	Tumor invades deep muscle (outer half)
T3		Tumor invades perivesical tissue
	pT3a	Microscopically
	pT3b	Macroscopically (extravesical mass)
T4		Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
	T4a	Tumor invades prostate, uterus, vagina
	T4b	Tumor invades pelvic wall, abdominal wall

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed
N0	No regional node involvement
N1	Metastasis in a single node, ≤ 2 cm in greatest dimension
N2	Metastasis in a single node, > 2 cm but ≤ 5 cm in greatest dimension; or multiple lymph nodes, none > 5 cm in greatest dimension
N3	Metastasis in a lymph node, > 5 cm in greatest dimension

Distant metastasis (M)

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-N3	M0
	Any T	Any N	M1

survival rate, whereas those with high-grade T1 lesions have a 10-year survival rate of 50%.

Muscle invasive carcinoma carries a 5-year survival rate of 20%-50%. When regional lymph nodes are involved, the 5-year survival rate is 0%-20%.

Treatment

TREATMENT OF LOCALIZED DISEASE

Surgical approaches to superficial bladder cancer

Transurethral resection Most patients with superficial bladder cancer can be treated adequately with transurethral resection (TUR). Such procedures preserve bladder function, entail minimal morbidity, and can be performed repeatedly. Survival rates > 70% at 5 years are expected. Although TUR removes existing tumors, it does not prevent the development of new lesions. Patients should be followed closely.

Laser The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser has achieved good local control when used in the treatment of superficial bladder tumors. However, it has not been adopted for general use because of its limitations in obtaining material for staging and grading of tumors.

Partial cystectomy is an infrequently utilized treatment option for patients whose tumors are not accessible or amenable to TUR.

Radical cystectomy is generally not used for the treatment of superficial bladder tumors. The indications for radical cystectomy include:

- Unusually large tumors that are not amenable to complete TUR, even on repeated occasions
- Some high-grade tumors
- Multiple tumors or frequent recurrences that make TUR impractical
- Symptomatic diffuse carcinoma in situ (Tis) that proves unresponsive to intravesical therapy
- Prostatic stromal involvement.

Intravesical therapy The indications for intravesical therapy include:

- Stage T1 tumors, especially if multiple
- Multifocal papillary Ta lesions, especially grade 2 or 3
- Diffuse carcinoma in situ (Tis)
- Rapidly recurring Ta, T1, or Tis disease.

In the United States, four intravesical agents are commonly used: thiotepa, an alkylating agent; bacillus Calmette-Guérin (BCG), an immune modulator/stimulator; and mitomycin (Mutamycin) and doxorubicin, both antibiotic chemotherapeutic agents. The dose of BCG varies with the strain (50 mg [Tice] or 60 mg [Connaught]). Mitomycin doses range from 20 to 40 mg.

Although all four agents reduce the tumor recurrence rate, BCG is the most effective. For the treatment of papillary Ta and T1 lesions, BCG and mitomycin have the greatest efficacy (complete response rate, approximately 50%). For the treatment of carcinoma in situ (Tis), BCG is extremely effective.

Surgical approaches to invasive bladder cancer

Radical cystectomy Invasive bladder cancer (stage II or higher) is best treated by radical cystectomy. Candidates for radical cystectomy include:

- Patients with muscle-invasive tumor (depth of invasion is not important, merely its presence), regardless of grade

- Patients with high-grade, invasive, lamina propria tumors with evidence of lymphovascular invasion, with or without carcinoma in situ (Tis)

- Patients with diffuse carcinoma in situ or recurrent superficial cancer who do not respond to intravesical therapy.

In men, radical cystectomy includes en bloc pelvic lymph node dissection and removal of the bladder, seminal vesicles, and prostate. In women, radical cystectomy entails en bloc pelvic lymph node dissection and anterior exenteration, including both ovaries, fallopian tubes, uterus, cervix, anterior vaginal wall, bladder, and urethra.

Partial cystectomy is an infrequently utilized treatment option and should only be considered when there is a solitary lesion in the dome of the bladder and when random biopsy results from remote areas of the bladder and prostatic urethra are negative.

Urethrectomy is routinely included in the anterior exenteration performed in female patients. Urethrectomy in male patients is performed if the tumor grossly involves the prostatic urethra or if prior TUR biopsy results of the prostatic stroma are positive. Delayed urethrectomy for positive urethral cytology or biopsy is required in about 10% of male patients.

Urinary reconstruction may involve any one of the following: intestinal conduits (eg, ileal, jejunal, or colonic), continent cutaneous diversion (eg, Indiana pouch, Kock pouch), or orthotopic reconstruction (in both male and female patients).

Surgical approaches to ureteral and renal pelvic tumors

Optimal surgical management of urothelial malignancies of the ureter and renal pelvis consists of nephroureterectomy with excision of a bladder cuff. Some tumors may respond well to local resection, and tumor specifics may allow for a more conservative intervention.

Upper ureteral and renal pelvic tumors (because of similar tumor behavior and anatomic aspects) may be considered as a group, whereas lower ureteral tumors may be considered as a separate group.

Upper ureteral and renal pelvic tumors are best treated with nephroureterectomy. Solitary, low-grade upper tract tumors may be considered for seg-

mental excision or ureteroscopic surgery if close surveillance is feasible. Care should be exercised, however, as multicentricity is more probable and the risk of recurrence is greater than for lower ureteral lesions.

Lower ureteral lesions may be managed by nephroureterectomy, segmental resection, and neovesical reimplantation or by endoscopic resection. A 15% recurrence rate is seen after segmental resection or endoscopic excision. Careful follow-up is mandatory. Disease progression, the development of a ureteral stricture precluding periodic surveillance, and poor patient compliance are indications to abandon conservative management and perform nephroureterectomy.

ROLE OF RADIATION THERAPY

Radiation therapy for bladder cancer

Primary radiation or chemoradiation therapy Radiation therapy, either alone or in conjunction with chemotherapy, is the modality of choice for patients whose clinical condition precludes surgery, either because of extensive disease or poor overall status. Trials have shown that patients treated with irradiation and cisplatin with or without fluorouracil (5-FU) have improved local control, as compared with patients treated with irradiation alone.

Other studies suggest that TUR followed by radiation therapy combined with cisplatin or 5-FU chemotherapy, with cystectomy reserved for salvage, provides a survival equivalent to that achieved with initial radical cystectomy while allowing for bladder preservation in many patients. The extent of TUR and the absence of hydronephrosis are important prognostic factors in studies of bladder-conserving treatment. Updates from institutions in Europe and the United States on over 600 patients with long-term follow-up support the durability of outcomes previously reported.

A randomized phase III study of bladder preservation with or without neoadjuvant chemotherapy following TUR, conducted by the Radiation Treatment Oncology Group (RTOG), revealed no advantage to the use of MCV (methotrexate, cisplatin, and vinblastine) before radiation therapy and concurrent cisplatin. The favorable outcome without neoadjuvant chemotherapy may make bladder preservation a more acceptable option for a wider range of patients.

Preoperative irradiation may improve survival in patients undergoing radical cystectomy. Its use is limited due to concern over complications occurring with the urinary diversions currently utilized.

Radiation dose and technique Initially, a pelvic field is treated to 4,500 cGy utilizing a four-field box technique, with 180 cGy delivered daily. The bladder tumor is then boosted to a total dose of 6,480 cGy utilizing multifield techniques, with 180 cGy delivered daily.

TABLE 2: Chemotherapy regimens for bladder carcinoma

Drug/combination	Dose and schedule
M-VAC	
Methotrexate	30 mg/m^2 IV on days 1, 15, and 22
Vinblastine	3 mg/m^2 IV on days 2, 15, and 22
Adriamycin (doxorubicin)	30 mg/m^2 IV on day 2
Cisplatin	70 mg/m^2 IV on day 2

NOTE: Reduce doxorubicin dose to 15 mg/m^2 in patients who have received prior pelvic irradiation. On days 15 and 22, methotrexate (30 mg/m^2) and vinblastine (3 mg/m^2) are given only if the WBC count is > 2,500 cells/mL and the platelet count is > 100,000 cells/mL.

Repeat cycles every 28-32 days even if the interim dose is withheld due to myelosuppression or mucositis.

Loehrer PJ Sr, Einhorn LH, Elson PJ, et al: J Clin Oncol 10:1066–1073, 1992.

Paclitaxel/carboplatin	
Paclitaxel	200 mg/m^2 IV infused over 3 hours
Carboplatin	Dose calculated by the Calvert formula to an area under the curve (AUC) of 5 mg/mL/min IV infused over 15 minutes after paclitaxel

Repeat cycle every 21 days.

PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; as well as ranitidine, 50 mg IV, and diphenhydramine, 50 mg IV, both 30-60 minutes prior to paclitaxel.

Redman B, Smith D, Flaherty L, et al: J Clin Oncol 16:1844–1848, 1998.

Gemcitabine/cisplatin	
Gemcitabine	1 g/m^2 IV on days 1, 8, and 15
Cisplatin	75 mg/m^2 IV on day 1

Repeat cycle every 28 days.

Kaufman D, Stadler W, Carducci M, et al: Proc Am Soc Clin Oncol 17:320a, 1998.

Radiation therapy for renal pelvic and ureteral cancers

In patients with renal pelvic and ureteral lesions who have undergone nephroureterectomy, postoperative local-field irradiation is offered if there is periureteral, perirenal, or peripelvic extension or lymph node involvement. A dose of approximately 4,500-5,040 cGy is delivered utilizing multifield techniques.

Palliative irradiation

Palliative radiation therapy is effective in controlling pain from local and metastatic disease and in providing hemostatic control. A randomized study comparing 3,500 cGy in 10 fractions vs 2,100 cGy in 3 hypofractionated treatments revealed high rates of relief of hematuria, frequency, dysuria, and nocturia with either regimen. In selected cases of bladder cancer, aggressive palliation to approximately 6,000 cGy may be warranted to provide long-term local control. Concurrent chemotherapy, such as cisplatin, should be considered.

Drug/combination	Dose and schedule
PCG	
Paclitaxel	200 mg/m^2 IV infused over 3 hours on day 1
Carboplatin	Dose calculated on AUC of 5, 15-minute IV infusion on day 1
Gemcitabine	800 mg/m^2 30-minute IV on days 1 and 8

Repeat cycle every 21 days.

PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; diphenhydramine, 50 mg IV, 30 minutes prior to paclitaxel; and either cimetidine, 300 mg IV, or ranitidine, 50 mg IV, 30 minutes prior to paclitaxel.

Hussain M, Vaishampayan U, Du W, et al: J Clin Oncol 19:2527–2533, 2001.

Paclitaxel/cisplatin	
Paclitaxel	135 mg/m^2 IV infused over 3 hours
Cisplatin	70 mg/m^2 IV infused over 2 hours

Repeat cycle every 3 weeks until disease progression or for a maximum of 6 cycles.

PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; as well as ranitidine, 50 mg IV, or cimetidine, 300 mg IV, prior to paclitaxel, and diphenhydramine, 50 mg IV, 30 minutes prior to paclitaxel.

Burch PA, Richardson RI, Cha SS, et al: Proc Am Soc Clin Oncol 18:1266a, 1999.

TCG	
Taxol (paclitaxel)	80 mg/m^2 IV infused over 1 hour on days 1 and 8
Cisplatin	70 mg/m^2 on day 1
Gemcitabine	1 g/m^2 IV on days 1 and 8

Repeat cycle every 21 days.

PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; as well as diphenhydramine, 50 mg IV, 30 minutes prior to paclitaxel, and either cimetidine, 300 mg IV, or ranitidine, 50 mg IV, 30 minutes prior to paclitaxel.

Vaishampayan U, Smith D, Redman B, et al: Proc Am Soc Clin Oncol 18:333a (abstract 1282), 1999.

Table prepared by Ishmael Jaiyesimi, DO

CHEMOTHERAPY FOR ADVANCED DISEASE

Treatment of advanced metastatic urothelial cancer is palliative. Cisplatin, paclitaxel, and gemcitabine (Gemzar) have all demonstrated single-agent activity for the systemic treatment of this disease. A randomized trial showed an advantage for a regimen of M-VAC (methotrexate, vinblastine, Adriamycin [doxorubicin], and cisplatin) over cisplatin alone with regard to disease progression-free and overall survival. Combination regimens with cisplatin or carboplatin (Paraplatin), usually with paclitaxel or gemcitabine or in combination with methotrexate and vinblastine with or without doxorubicin, produce

response rates of 40%-60% in patients with advanced disease, with a median survival of 12-14 months (Table 2). In another randomized trial, the combination of gemcitabine and cisplatin exhibited equivalent survival to M-VAC in metastatic bladder cancer but was clinically better tolerated. The role of combination chemotherapy in the adjuvant treatment of resected urothelial cancer remains undetermined and an area of clinical research. A randomized trial of neoadjuvant M-VAC in locally advanced resectable bladder cancer showed a trend in survival favoring M-VAC over surgery alone, but it was not statistically significant.

KIDNEY CANCER

Approximately 36,160 new cases of renal cell carcinoma will be diagnosed in the year 2005 in the United States, with an associated 12,660 deaths. There has been a steady increase in the incidence of renal cell carcinoma that is not explained by the increased use of diagnostic imaging procedures. Mortality rates have also shown a steady increase over the past 2 decades.

Epidemiology

Gender and age This malignancy is twice as common in men as in women. Most cases of renal cell carcinoma are diagnosed in the fourth to sixth decades of life, but the disease has been reported in all age groups.

Ethnicity Renal cell carcinoma is more common in persons of northern European ancestry than in those of African or Asian descent.

Etiology and risk factors

Renal cell carcinoma occurs most commonly as a sporadic form and rarely as a familial form. The exact etiology of sporadic renal cell carcinoma has not been determined. However, smoking, obesity, and renal dialysis have been associated with an increased incidence of the disease.

Genetic factors More recently, a genetic basis has been sought for this disease.

von Hippel-Lindau disease, an autosomal-dominant disease, is associated with retinal angiomas, CNS hemangioblastomas, and renal cell carcinoma.

Chromosomal abnormalities Deletions of the short arm of chromosome 3 (3p) occur commonly in renal cell carcinoma associated with von Hippel-Lindau disease. In the rare familial forms of renal cell carcinoma, translocations affecting chromosome 3p are uniformly present. Sporadic renal cell carcinoma of the nonpapillary type is also associated with 3p deletions.

Associated malignancy Two studies from large patient databases have reported a higher-than-expected incidence of both renal cell cancer and lymphoma. No explanation for this association has been found.

Signs and symptoms

Renal cell carcinoma has been associated with a wide array of signs and symptoms. The classic triad of hematuria, flank mass, and flank pain occurs in only 10% of patients and is usually associated with a poor prognosis. With the routine use of CT scanning for various diagnostic reasons, renal cell carcinoma is being diagnosed more frequently as an incidental finding.

Hematuria More than half of patients with renal cell carcinoma present with hematuria.

Other common signs/symptoms Other commonly associated signs and symptoms of renal cell carcinoma include normocytic/normochromic anemia, fever, and weight loss.

Less common signs/symptoms Less frequently occurring, but often described, signs and symptoms include polycythemia, hepatic dysfunction not associated with hepatic metastasis, and hypercalcemia. Although not a common finding at the time of diagnosis of renal cell carcinoma, hypercalcemia ultimately occurs in up to 25% of patients with metastatic disease.

Diagnosis

Contrast-enhanced CT scanning has virtually replaced excretory urography and renal ultrasonography in the evaluation of suspected renal cell carcinoma. In most cases, CT imaging can differentiate cystic from solid masses and also supplies information about lymph nodes and renal vein/inferior vena cava (IVC) involvement.

Ultrasonography is useful in evaluating questionable cystic renal lesions if CT imaging is inconclusive.

Venography and MRI When IVC involvement by tumor is suspected, either IVC venography or MRI is needed to evaluate its extent. MRI is currently the preferred imaging technique for assessing IVC involvement at most centers.

Renal arteriography is not used as frequently now as it was in the past in the evaluation of suspected renal cell carcinoma. In patients with small, indeterminate lesions, arteriography may be helpful. It is also used by the surgeon as part of the preoperative evaluation of a large renal neoplasm.

Percutaneous cyst puncture is used in the evaluation of cystic renal lesions that are thought to be potentially malignant on the basis of ultrasonography or CT imaging. Percutaneous cyst puncture permits the collection of cyst fluid for analysis, as well as the evaluation of cyst structure via instillation of contrast medium after fluid removal. Benign cyst fluid is usually clear to straw-colored and low in protein, fat, and lactic dehydrogenase (LDH) content, whereas malignant fluid is usually bloody with high protein, fat, and LDH content.

Evaluation of extra-abdominal disease sites includes a chest x-ray. In the face of a normal chest x-ray, CT imaging of the chest adds no further helpful

information. A bone scan is required if a patient has symptoms suggestive of bone metastasis and/or an elevated alkaline phosphatase level.

Pathology

Renal cell carcinoma arises from the proximal renal tubular epithelium. Histologically, renal cell carcinoma can be of various cellular types: clear cell, granular cell, and sarcomatoid (spindle) variant. The majority of these tumors are mixtures of clear and granular cell types. Approximately 1%-6% of renal cell carcinomas are of the sarcomatoid variant, which is a more aggressive malignancy with a worse prognosis.

Staging and prognosis

Staging system The preferred staging system for renal cell carcinoma is the TNM classification (Table 3).

Prognostic factors The natural history of renal cell carcinoma is highly variable. However, approximately 30% of patients present with metastatic disease at diagnosis, and one-third of the remainder will develop metastasis during follow-up.

Five-year survival rates after nephrectomy for tumors confined to the renal parenchyma (T1/2) are > 80%. Renal vein involvement without nodal involvement does not affect survival. Lymph node involvement and/or extracapsular spread is associated with a 5-year survival of 10%-25%. Patients with metastatic disease have a median survival of 1 year and a 5-year survival of 0%-20%.

Treatment

Surgery

Radical nephrectomy is the established therapy for localized renal cell carcinoma. At surgery, the kidneys, adrenal gland, and perirenal fat (structures bound by Gerota's fascia) are removed. Also, limited regional lymph node dissection is often performed for staging purposes. Partial nephrectomy is considered in patients for whom a radical nephrectomy would result in permanent dialysis.

Since complete resection is the only known cure for renal cell carcinoma, even in locally advanced disease, surgery is considered if the involved structures can be safely removed. In the presence of metastatic disease, surgery is generally considered for palliation only. However, in patients with metastatic disease who are candidates for cytokine therapy and have a good performance status, a debulking nephrectomy may benefit survival by several months.

Radiation therapy for renal cell carcinoma

Primary radiation therapy Radiation therapy may be considered for palliation as the primary therapy for renal cell carcinoma in patients whose clinical

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TABLE 3: TNM staging of renal cell carcinoma

Primary tumor (T)

Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1		Tumor ≤ 7 cm in greatest dimension, limited to the kidneys
	T1a	Tumor ≤ 4 cm in greatest dimension, limited to the kidneys
	T1b	Tumor > 4 cm but not > 7 cm in greatest dimension, limited to the kidneys
T2		Tumor > 7 cm in greatest dimension, limited to the kidneys
T3		Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
	T3a	Tumor directly invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota's fascia
	T3b	Tumor grossly extends into renal vein or its segmental (muscle-containing) branches or vena cava below the diaphragm
	T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4		Tumor invades beyond Gerota's fascia

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node
N2	Metastasis in more than one regional lymph node

Distant metastasis (M)

Mx	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 III	T1	N1	M0
	T2	N1	M0
	T3a	N0-N1	M0
	T3b	N0-N1	M0
	T3c	N0-N1	M0
Stage IV	T4	N0-N1	M0
	Any T	N2	M0
	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

TABLE 4: Biologic therapy regimens for renal cell carcinoma

Dose and schedule

High-dose IL-2

IL-2: 600,000 or 720,000 IU/kg IV infused over 15 minutes every 8 hours until toxicity develops; or 14 consecutive doses for 5 days

After a 5- to 9-day rest period, an additional 14 doses of IL-2 are administered over a 5-day period. If patients show evidence of tumor regression or stable disease, 1-2 more courses of treatment may be given.

Fyfe G, Fisher RI, Rosenberg SA, et al: J Clin Oncol 13:688–696, 1995.

Low-dose IL-2

IL-2: 72,000 IU/kg by IV bolus every 8 hours to a maximum of 15 doses every 7-10 days for 2 cycles

NOTE: The cycles represent one course of therapy. Patients who are stable or responding after one course of therapy receive a second course. Third and fourth courses are given only if patients demonstrate further tumor regression.

Yang JC, Topalian SL, Parkinson D, et al: J Clin Oncol 12:1572–1576, 1998.

Table prepared by Ishmael Jaiyesimi, DO

condition precludes surgery, either because of extensive disease or poor overall condition. A dose of 4,500 cGy is delivered, with consideration of a boost up to 5,500 cGy.

Postoperative radiation therapy is controversial. However, it may be considered in patients with perinephric fat extension, adrenal invasion, or involved margins. A dose of 4,500 cGy is delivered, with consideration of a boost.

Palliation Radiation therapy is commonly used for palliation for metastatic and local disease.

Systemic therapy for advanced disease

Metastatic renal cell carcinoma is resistant to chemotherapeutic agents. An extensive review of currently available agents concluded that the overall response rate to chemotherapy is 6%.

Interleukin-2 The only FDA-approved treatment for metastatic renal cell carcinoma is high-dose interleukin-2 (IL-2, aldesleukin [Proleukin]; Table 4).

High-dose regimen High-dose IL-2 (720,000 IU/kg IV piggyback every 8 hours for 14 doses, repeated once after a 9-day rest) results in a 15% remission rate (7% complete responses, 8% partial responses). The majority of responses to IL-2 are durable, with a median response duration of 54 months.

The major toxicity of high-dose IL-2 is a sepsis-like syndrome, which includes a progressive decrease in systemic vascular resistance and an associated decrease in intravascular volume due to a "capillary leak." Management includes judicious use of fluids and vasopressor support to maintain blood pressure and intravascular volume and at the same time to avoid pulmonary toxicity due to noncardiogenic

pulmonary edema from the capillary leak. This syndrome is totally reversible.

Other doses and schedules Because of the toxicity of high-dose IL-2, other doses and schedules have been and are being evaluated. Several trials of low-dose IL-2 ($3\text{-}18 \times 10^6$ IU/d), either alone or combined with interferon alfa (Intron A, Roferon-A), have reported response rates similar to those achieved with high-dose IL-2. Patients should be encouraged to participate in ongoing clinical trials of metastatic renal cell carcinoma.

Immunotherapy New immunotherapeutic approaches under investigation for the treatment of advanced renal cell cancer include the use of peripheral blood stem cell transplantations, dendritic cell-based vaccines, and monoclonal antibodies. Early reports on the use of allogeneic stem cell transplantation from HLA-matched donors to invoke a graft-vs-tumor reaction have shown encouraging preliminary results that warrant further investigation. A humanized monoclonal antibody against the G250 antigen found on all clear cell, and the majority of non-clear cell, renal carcinomas is also in clinical trials.

Another area of promising therapeutic clinical research in advanced renal cell cancer is the evaluation of antiangiogenic factors. Most renal cell carcinomas are highly vascular tumors, and inhibition of tumor neovascularity holds new promise for better treatments.

> SU011248 and BAY 43-9006 are novel agents under development, with early reports showing activity in advanced kidney cancer. These agents block angiogenic pathways as well as pathways important in cell proliferation. Initial reports have shown partial response and prolonged disease stabilization (*Motzer RJ, Rini BI, Michaelson MD, et al: Proc Am Soc Clin Oncol [abstract] 23:381, 2004; Ratain MJ, Flaherty KT, Stadler WM, et al: Proc Am Soc Clin Oncol [abstract] 23:381, 2004*).

SUGGESTED READING

ON UROTHELIAL CANCER

Barton Grossman H, Natale RB, Tangen CM, et al: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 349:859–866, 2003.

Duchesne GM, Bolger JJ, Griffiths GD, et al: A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: Results of Medical Research Council Trial BA09. Int J Radiat Oncol Biol Phys 47:379–388, 2000.

Hudson MA, Herr HW: Carcinoma in situ of the bladder. J Urol 153:564–572, 1995.

Hussain MH, Glass TR, Forman J, et al: Combination cisplatin, 5-fluorouracil, and radiation therapy for locally advanced unresectable or medically unfit bladder cancer cases: A Southwest Oncology Group study. J Urol 165:56–60, 2001.

Rodel C, Grabenbauer GG, Kuhn R, et al: Combined-modality treatment and selective organ preservation in invasive bladder cancer: Long-term results. J Clin Oncol 20:3048–3050, 2002.

Shipley WU, Kaufman DS, Zehr E, et al: Selective bladder preservation by combined modality protocol treatment: Long-term outcomes of 190 patients with invasive bladder cancer. Urology 60:62–67, 2002.

Von der Maase H, Hansen SW, Roberts JT, et al: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: Results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 17:3068–3077, 2000.

ON KIDNEY CANCER

Flanigan RC, Salmon SE, Blumenstein BA, et al: Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal cell cancer. N Engl J Med 345:1655–1659, 2001.

Motzer RJ, Mazumder M, Bacik J, et al: Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 17:2530–2540, 1999.

Parkinson DR, Sznol M: High-dose interleukin-2 in the therapy of metastatic renal cell carcinoma. Semin Oncol 22:61–66, 1995.

Rabinovitch RA, Zelefsky MJ, Gaynor JJ, et al: Patterns of failure following surgical resection of renal cell carcinoma: Implications for adjuvant local and systemic therapy. J Clin Oncol 12:206–212, 1994.

Stodlen WM, Vogelzang NJ: Low-dose interleukin-2 in the treatment of metastatic renal cell carcinoma. Semin Oncol 22:67–73, 1995.

CHAPTER 25

Soft-tissue sarcomas

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The soft-tissue sarcomas are a group of rare but anatomically and histologically diverse neoplasms. This is due to the ubiquitous location of the soft tissues and the nearly three dozen recognized histologic subtypes of soft-tissue sarcomas. In the United States, approximately 9,400 new cases of soft-tissue sarcoma are identified annually, and about 3,490 patients die of the disease each year. The age-adjusted incidence is 2 cases per 100,000 persons.

Epidemiology

Unlike the more common malignancies, such as colon cancer, little is known about the epidemiology of soft-tissue sarcomas. This, again, reflects the uncommon nature of these lesions.

Gender There is a slight male predominance, with a male-to-female ratio of 1.1:1.0.

Age The age distribution in adult soft-tissue sarcoma studies is < 40 years, 20.7% of patients; 40-60 years, 27.6% of patients; and > 60 years, 51.7% of patients.

Race Studies in large cohorts of patients demonstrate that the race distribution of soft-tissue sarcomas mirrors that of the American population (86% Caucasian, 10% African-American, 1% Asian-American, and 3% other).

Geography Studies have suggested that the incidence and mortality of soft-tissue sarcomas may be increasing in New Zealand. There are no currently available data addressing this possibility in the United States.

Etiology and risk factors

In the majority of cases of patients with soft-tissue sarcoma, no specific etiologic agent is identifiable. However, a number of predisposing factors have been recognized.

Radiation therapy Soft-tissue sarcomas have been reported to originate in radiation fields following therapeutic irradiation for a variety of solid tumors. Frequently, they are seen in the lower-dose regions at the edge of the radiation target volume. By definition, radiation-induced sarcomas arise no sooner than 3 years after radiation therapy and often develop decades later. The majority of these sarcomas are high-grade lesions (90%), and osteosarcoma is a predomi-

nant histology. Malignant fibrous histiocytoma (MFH), angiosarcoma, and other histologic subtypes have also been reported.

Chemical exposure Exposure to various chemicals in specific occupations or situations has been linked with the development of soft-tissue sarcoma. These chemicals include the phenoxy acetic acids (forestry and agriculture workers), chlorophenols (sawmill workers), Thorotrast (diagnostic x-ray technicians), vinyl chloride (individuals working with this gas, used in making plastics and as a refrigerant), and arsenic (vineyard workers).

Chemotherapy Soft-tissue sarcomas have been reported after previous exposure to alkylating chemotherapeutic agents, most commonly after treatment of pediatric acute lymphocytic leukemia. The drugs implicated include cyclophosphamide (Cytoxan, Neosar), melphalan (Alkeran), procarbazine (Matulane), nitrosoureas, and chlorambucil (Leukeran). The relative risk of sarcoma appears to increase with cumulative drug exposure.

Chronic lymphedema Soft-tissue sarcomas have been noted to arise in the chronically lymphedematous arms of women treated with radical mastectomy for breast cancer (Stewart-Treves syndrome). Lower-extremity lymphangiosarcomas have also been observed in patients with congenital lymphedema or filariasis complicated by chronic lymphedema.

Trauma and foreign bodies Although a recent history of trauma is often elicited from patients presenting with soft-tissue sarcoma, the interval between the traumatic event and diagnosis is often short; thus, a causal relationship is unlikely. Chronic inflammatory processes, however, may be a risk factor for sarcoma. Foreign bodies, such as shrapnel, bullets, and implants, have also been implicated.

Signs and symptoms

Signs and symptoms of soft-tissue sarcoma depend, in large part, on the anatomic site of origin. Due to the ubiquitous location of the soft tissues, these malignancies may arise at any site in the body where soft tissues are located. Since 50% of soft-tissue sarcomas arise in an extremity, the majority of patients present with a palpable soft-tissue mass. Pain at presentation is noted in only one-third of cases.

Extremity and superficial trunk Extremity and superficial trunk sarcomas account for 60% of all soft-tissue sarcomas. The majority of patients present with a painless primary soft-tissue mass.

Retroperitoneum Retroperitoneal sarcomas account for 15% of all soft-tissue sarcomas. Most patients (80%) present with an abdominal mass, with 50% of patients reporting pain at presentation. Due to the considerable size of the retroperitoneum and the relative mobility of the anterior intra-abdominal organs, these tumors often grow to substantial size before the patient's nonspecific complaints are evaluated or even before an abdominal mass is noted on physical examination.

Viscera Visceral soft-tissue sarcomas, which comprise 15% of all soft-tissue sarcomas, present with signs and symptoms unique to their viscus of origin. For example, GI leiomyosarcomas or gastrointestinal stromal tumors (GISTs) present with GI symptoms that are usually indistinguishable from those of the more common adenocarcinomas. Similarly, uterine leiomyosarcomas frequently present with painless vaginal bleeding, such as that often noted in patients with more common uterine malignancies.

Head and neck Head and neck sarcomas comprise 10% of all soft-tissue sarcomas. Although generally smaller than sarcomas in other sites, they may present with important mechanical problems related to compression or invasion of adjacent anatomy (eg, orbital contents, airway, or pharynx). In addition, their proximity to critical anatomy can pose management difficulties due to compromise in the delivery of both surgery and radiotherapy.

Pathology

Histopathologic classification As a consequence of the wide spectrum of soft tissues, a variety of histologically distinct neoplasms have been characterized. The current histopathologic classification is based on the putative cell of origin of each lesion. Such classification based on histogenesis is reproducible for the more differentiated tumors. However, as the degree of histologic differentiation declines, it becomes increasingly difficult to determine cellular origin.

In addition, many of these tumors dedifferentiate. This process results in a variety of overlapping patterns, making uniform classification difficult. Experienced soft-tissue pathologists frequently disagree as to the cell of origin of an individual tumor. Comparative studies have demonstrated concordance in histopathologic diagnosis in only two-thirds of cases. MFH used to be the most common histologic subtype of soft-tissue sarcoma. However, in one study, reanalysis histologically, immunohistochemically, and ultrastructurally allowed reclassification in 84% of tumors to a specific line of differentiation.

Assignment of a specific histologic subtype is of secondary importance. This is because, with the possible exceptions of certain small-cell sarcomas, rhabdomyosarcoma, fibrosarcoma, and some forms of angiosarcoma, histogenesis is not directly related to biologic behavior. The propensity for distant metastases and disease-related mortality are best predicted on the basis of histologic grade and tumor size.

Staging and prognosis

AJCC/UICC staging system

The relative rarity of soft-tissue sarcomas, the anatomic heterogeneity of these lesions, and the presence of more than 30 recognized histologic subtypes of variable grade have made it difficult to establish a functional system that can accurately stage all forms of this disease. The revised staging system (6th edition) of the American Joint Committee on Cancer (AJCC) and the Interna-

TABLE 1: AJCC/UICC staging system for soft-tissue sarcomas

Primary tumor (T)

Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1		Tumor ≤ 5 cm in greatest dimension
	T1a	Superficial tumor[a]
	T1b	Deep tumor[a]
T2		Tumor > 5 cm in greatest dimension
	T2a	Superficial tumor[a]
	T2b	Deep tumor[a]

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Grade (G)

Gx	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Poorly differentiated or undifferentiated (four-tiered systems only)

Stage grouping

Stage I	T1a-T2b	N0	M0	G1,2	G1	Low
Stage II	T1a-T2a	N0	M0	G3,4	G2,3	High
Stage III	T2b	N0	M0	G3,4	G2,3	High
Stage IV	Any T	N1	M0	Any G	Any G	High or low
	Any T	N0	M1	Any G	Any G	High or low

[a] Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.

AJCC = American Joint Committee on Cancer; UICC = International Union Against Cancer

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

tional Union Against Cancer (UICC) is the most widely employed staging classification for soft-tissue sarcomas (Table 1). All soft-tissue sarcoma subtypes are included, except dermatofibrosarcoma protuberans. Four distinct histologic grades are recognized, ranging from well differentiated to undifferentiated.

Histologic grade and tumor size are the primary determinants of clinical stage. Tumor size is further substaged as "a" (a superficial tumor that arises outside the investing fascia) or "b" (a deep tumor that arises beneath the fascia or invades the fascia).

The AJCC/UICC system is designed to optimally stage extremity tumors but is also applicable to torso, head and neck, and retroperitoneal lesions. It should not be used for sarcomas of the GI tract.

CANCER MANAGEMENT: A MULTIDISCIPLINARY APPROACH

A major limitation of the current staging system is that it does not take into account the anatomic site of soft-tissue sarcomas. Anatomic site, however, is an important determinant of outcome. Patients with retroperitoneal, head and neck, and visceral sarcomas have a worse overall prognosis than do patients with extremity tumors. Although the anatomic site is not incorporated as a specific component of any current staging system, outcome data should be reported on a site-specific basis.

Prognostic factors

Understanding relevant clinicopathologic prognostic factors is important in treatment planning for patients with soft-tissue sarcoma. Several reports document the adverse prognostic significance of tumor grade, anatomic site, tumor size, and depth relative to the investing fascia (for extremity and body wall tumors). Patients with high-grade lesions, large (T2) sarcomas, nonextremity subsite, or deep tumor location are at increased risk for disease relapse and sarcoma-specific death.

Sarcoma-specific nomogram Kattan and colleagues from Memorial Sloan-Kettering Cancer Center have developed a sarcoma-specific nomogram for estimation of sarcoma-specific 12-year survival. The nomogram takes into account pretreatment clinicopathologic factors, including anatomic site, histologic subtype, tumor size, histologic grade, tumor depth, and patient age. The nomogram is based on prospectively collected data and has been validated in a population of 2,136 patients with sarcoma. The nomogram can be found on www.nomograms.org and is available in a handheld personal digital assistant version. The sarcoma nomogram may be useful for patient stratification for clinical trials and for risk assessment and treatment planning for individual patients.

Prognostic factors for local vs distant recurrence Unlike other solid tumors, the adverse prognostic factors for local recurrence of a soft-tissue sarcoma differ from those that predict distant metastasis and tumor-related mortality. In other words, patients with a constellation of adverse prognostic factors for local recurrence are not necessarily at increased risk for distant metastasis or tumor-related death. This concept has been recently validated by an analysis of the Scandinavian Sarcoma Group prospective database. In 559 patients with soft-tissue sarcomas of the extremities and trunk treated with surgery alone, inadequate surgical margin was found to be a risk factor for local recurrence but not for distant metastasis. Therefore, staging systems that are designed to stratify patients for risk of distant metastasis and tumor-related mortality using these prognostic factors (such as the AJCC/UICC system) do not stratify patients for risk of local recurrence.

Screening and diagnosis

Currently, there are no screening tests for soft-tissue sarcomas. Since the majority of patients with soft-tissue sarcoma have lesions arising in the extremities or superficial trunk, most of the comments here apply to soft-tissue lesions in

those sites. A separate algorithm is usually employed for the evaluation of a primary retroperitoneal mass or visceral sarcoma.

Physical examination should include an assessment of the size of the mass and its mobility relative to the underlying soft tissues. The relationship of the mass to the investing fascia of the extremity (superficial vs deep) and nearby neurovascular and bony structures should be noted. Site-specific neurovascular examination and assessment of regional lymph nodes should also be performed.

Biopsy Any soft-tissue mass in an adult extremity should be biopsied if it is symptomatic or enlarging, is > 5 cm, or has persisted beyond 4-6 weeks.

Percutaneous approaches Percutaneous tissue diagnosis can usually be obtained with fine-needle aspiration (FNA) for cytology or by percutaneous core biopsy for histology. The needle track should be placed in an area to be excised or that can be encompassed in adjuvant radiotherapy fields if they are to be used. In most instances, when an experienced cytopathologist and/or histopathologist examines the specimen, a diagnosis of malignant soft-tissue sarcoma can be made. FNA is often viewed as a suboptimal method of establishing an initial diagnosis of soft-tissue sarcoma. Histology is usually preferred to cytology because more tissue is obtained, which allows for a more accurate delineation of tumor type and grade. Percutaneous tissue diagnosis is preferred to facilitate subsequent treatment planning and to permit surgical resection to be performed as a one-stage procedure.

Open biopsy In some cases, an adequate histologic diagnosis cannot be secured by percutaneous means. Open biopsy is indicated in these instances, with the exception of relatively small superficial masses, which can be easily removed by excisional biopsy with clear margins.

Biopsies should be incisional and performed with a longitudinal incision parallel to the long axis of the extremity. This approach facilitates subsequent wide local excision of the tumor and the incisional scar and results in minimal difficulties in wound closure. It also facilitates inclusion of any scars within the area of the tumor in adjuvant radiation fields without the excessive morbidity of large-field radiotherapy planning. The incision should be centered over the mass at its most superficial location. It is important to note that care should be taken not to raise tissue flaps. Meticulous hemostasis should be ensured after the biopsy to prevent dissemination of tumor cells into adjacent tissue planes by hematoma.

Retroperitoneal or intra-abdominal mass Biopsy of primary retroperitoneal soft-tissue masses is generally not required for radiographically resectable masses, nor is biopsy recommended for suspected GISTs. The circumstances under which percutaneous or preoperative biopsy of retroperitoneal masses should be strongly considered include:

- tissue diagnosis for radiographically unresectable disease
- clinical suspicion of lymphoma or germ-cell tumor
- tissue diagnosis for neoadjuvant treatment, including radiotherapy and/ or chemotherapy
- suspected metastases from another primary tumor.

Primary tumor imaging Optimal imaging of the primary tumor depends on the anatomic site. For soft-tissue masses of the extremities, MRI has been regarded as the imaging modality of choice because it enhances the contrast between tumor and muscle and between tumor and adjacent blood vessels and also provides multiplanar definition of the lesion. However, a recent study by the Radiation Diagnostic Oncology Group that compared MRI and CT in 183 patients with malignant bone and 133 patients with soft-tissue tumors showed no specific advantage of MRI over CT from a diagnostic standpoint.

For pelvic lesions, the multiplanar capability of MRI may provide superior single-modality imaging. In the retroperitoneum and abdomen, CT usually provides satisfactory anatomic definition of the lesion. Occasionally, MRI with gradient sequence imaging can better delineate the relationship of the tumor to midline vascular structures, particularly the inferior vena cava and aorta. In the future, MRI-CT fusion techniques may facilitate treatment planning using conformal radiotherapy techniques.

More invasive studies, such as angiography and cavography, are almost never required for the evaluation of soft-tissue sarcomas.

Imaging for metastatic disease Cost-effective imaging to exclude the possibility of distant metastatic disease depends on the size, grade, and anatomic location of the primary tumor. In general, patients with low-grade or intermediate-/high-grade tumors < 5 cm in diameter require only a chest x-ray for satisfactory staging of the chest. This reflects the fact that these patients are at comparatively low risk of presenting with pulmonary metastases. In contrast, patients with high-grade tumors ≥ 5 cm should undergo more thorough staging of the chest by CT.

Patients with retroperitoneal and intra-abdominal visceral sarcomas should undergo single-modality imaging of the liver to exclude the possibility of synchronous hepatic metastases. The liver is a common site for a first metastasis from these lesions.

Treatment

TREATMENT OF LOCALIZED DISEASE
Surgical resection is the cornerstone of therapy for patients with localized disease. Over the past 20 years, there has been a gradual shift in the surgical management of soft-tissue sarcoma of the extremities away from radical ablative surgery, such as amputation or compartment resection, and toward limb-sparing approaches combining wide local resection with preoperative or postoperative radiotherapy. The development of advanced surgical techniques (eg, microvascular tissue transfer, bone and joint replacement, and vascular reconstruction) and the application of multimodality approaches have allowed most patients to retain a functional extremity without any compromise in survival.

Surgery

The surgical approach to soft-tissue sarcomas depends on careful preoperative staging with MRI or CT for lesions of the extremities and a percutaneous histologic diagnosis and assessment of grade. In most instances, preoperative imaging studies allow for accurate prediction of resectability.

The surgical approach to soft-tissue sarcomas is based on an awareness that these lesions tend to expand and compress tissue planes, producing a pseudocapsule comprising normal host tissue interlaced with tumor fimbriae. Conservative surgical approaches in which the plane of dissection is immediately adjacent to this pseudocapsule, such as intracapsular or marginal excision, are associated with prohibitive local recurrence rates of 33%-63%.

Wide local resection encompassing a rim of normal tissue around the lesion has led to improvements in local control, with local recurrence rates of approximately 30% in the absence of adjuvant therapies. However, studies indicate that carefully selected patients with localized, small (T1), low-grade soft-tissue sarcomas of the extremity can be treated by wide resection alone, with local recurrence rates of < 10%. For example, in a cohort of 56 patients with primarily subcutaneous or intramuscular lesions treated with wide local excision without adjuvant irradiation, 4 local recurrences were noted.

The need for adjuvant irradiation in small (< 5 cm), high-grade lesions has been studied. A retrospective review of 204 patients with stage IIB soft-tissue sarcoma of the extremity treated at Memorial Sloan-Kettering Cancer Center has been completed. A total of 57% of patients did not receive adjuvant radiation therapy, whereas 43% received either brachytherapy or external-beam radiation therapy. With a median follow-up of 67 months, there was no significant difference in 5-year local control, distant replase-free survival, or disease-specific survival when adjuvant irradiation was delivered.

Further studies will be required to define which subsets of patients with primary extremity sarcoma can be treated by wide excision surgery alone. Preoperative or postoperative radiotherapy should be employed for patients with primary T1 sarcomas in whom a satisfactory gross surgical margin cannot be attained without compromise of functionally important neurovascular structures.

Limb-sparing surgery plus irradiation Limb-sparing surgery employing adjuvant irradiation to facilitate maximal local control has become the standard approach for large (T2) soft-tissue sarcomas of the extremities. In most centers, upward of 90% of patients are treated with limb-sparing approaches. Amputation is reserved as a last-resort option for local control and is used with the knowledge that it does not affect survival. This approach was validated in a prospective National Cancer Institute (NCI) study, in which patients with a limb-sparing surgical option were randomized to receive limb-sparing surgery with postoperative radiation therapy or amputation. Both arms of the study included postoperative therapy with doxorubicin, cyclophosphamide, and methotrexate.

Surgical procedure The planned resection should encompass the skin, subcutaneous tissues, and soft tissues adjacent to the tumor, including the previous

biopsy site and any associated drain sites. The tumor should be excised with a 2- to 3-cm margin of normal surrounding tissue whenever possible. Since good adjuvant approaches are available to facilitate local control, this ideal margin is sometimes compromised rather than attempting resection of adjacent, possibly involved bone or neurovascular structures that would result in significant functional loss. In the rare circumstance of gross involvement of neurovascular structures or bone, they can be resected en bloc and reconstructed.

Metal clips should be placed at the margins of resection to facilitate radiation field planning, when and if external irradiation is indicated. Drain sites should be positioned close to the wound to allow inclusion in radiation therapy fields. As noted earlier, avoidance of transverse incisions greatly facilitates the ability to include the tissues at risk in radiation target volume without unduly large fields.

> The Netherlands Cancer Institute published its results in patients with unresectable soft-tissue sarcoma of the extremities who were perfused with melphalan and TNF-alpha. A total of 49 patients were treated and followed for a median of 26 months. One patient died shortly after perfusion, but 31 patients (63%) were able to undergo resection of the tumor. Based on clinical and pathologic grounds, an overall response was seen in 31 patients (63%), and a complete response was seen in 4 patients (8%). A total of 28 patients (57%) had local control with limb preservation. Toxicity was frequent but usually mild (Noorda EM, Vrouenraets BC, Nieweg OE, et al: Cancer 98:1483-1490, 2003).

Regional lymphadenectomy Given the low, 2%-3%, prevalence of lymph node metastasis in adult sarcomas, there is no role for routine regional lymphadenectomy. Patients with angiosarcoma, embryonal rhabdomyosarcoma, synovial sarcoma, and epithelioid histologies have an increased incidence of lymph node metastasis and should be carefully examined and radiographically imaged for lymphadenopathy. Clinically apparent lymphadenopathy should be treated with therapeutic lymphadenectomy. A recent analysis suggested that select patients undergoing lymphadenectomy, particularly in the absence of systemic metastases, may have a 5-year survival rate of 57%.

Radiotherapy

Scheduling Radiation therapy is usually combined with surgical resection in the management of patients with soft-tissue sarcomas of the extremities. The decision of whether to use preoperative (neoadjuvant) or postoperative (adjuvant) irradiation remains controversial and has been addressed in a phase III randomized trial.

Preoperative irradiation has a number of theoretic and practical advantages: (1) Smaller radiation portals can be utilized, as the scar, hematomas, and ecchymoses do not need to be covered. (2) Preoperative irradiation may produce tumor encapsulation, facilitating surgical resection from vital structures. (3) It is easier to spare a strip of skin and thereby reduce the risk of lymphedema. (4) The size of the tumor may be reduced, thus decreasing the extent of surgical resection. (5) Lower radiation doses can be utilized, as there are fewer relatively radioresistant hypoxic cells.

Preoperative irradiation also has several drawbacks, however. They include (1) the inability to precisely stage patients based on pathology due to downstaging and (2) increased problems with wound healing.

Studies of preoperative irradiation from the University of Florida, M. D. Anderson Cancer Center, and Massachusetts General Hospital demonstrated local control rates of 90% using doses of approximately 50 Gy. Survival depended on the size and grade of the primary tumor. Distant metastases were the primary pattern of failure.

Postoperative irradiation A number of retrospective reports, as well as a randomized trial from the NCI, have demonstrated that limb-sparing surgery plus postoperative irradiation produces local control rates comparable to those achieved with amputation. Five-year local control rates of 70%-90%, survival rates of 70%, and limb-preservation rates of 85% can be expected.

Equivocal or positive histologic margins are associated with higher local recurrence rates, and, therefore, adjuvant external-beam irradiation should be considered in all patients with sarcoma of the extremities with positive or close microscopic margins in whom reexcision is impractical. Postoperative doses of 60-65 Gy should be used.

Interstitial therapy with iridium-192 is used at some institutions as a radiation boost to the tumor bed following adjuvant external-beam irradiation. At Memorial Sloan-Kettering Cancer Center, adjuvant brachytherapy is often used in place of external irradiation. In a randomized trial, the 5-year local control rate was 82% in patients who received adjuvant brachytherapy, vs 69% in those treated with surgery alone. On subset analysis, the local control rate was found to be 89%, vs 66% in those patients with high-grade lesions. This study and further studies have indicated that brachytherapy has no impact on local control for low-grade lesions.

If an implant alone is used, the dose is 40-45 Gy to a volume that includes all margins; when a boost is combined with additional external-beam irradiation, a dose of 20-25 Gy is utilized. Some data suggest a higher rate of wound complications and a delay in healing when implants are afterloaded prior to the third postoperative day. Although some centers load implants sooner, this step must be performed with caution and strict attention to the incision site.

Over a 15-year period, 202 patients with high-grade sarcoma of the extremities underwent complete gross resection and adjuvant brachytherapy to a median dose of 45 Gy, delivered over 5 days. With a median follow-up of 61 months, the 5-year local control, distant relapse-free survival, and overall survival rates were 84%, 63%, and 70%, respectively. These rates compared favorably with data on external-beam irradiation. Morbidity of brachytherapy was considered acceptable, with reoperation rates of 12%, bone fractures in 3%, and nerve damage in 5%.

Comparison of irradiation techniques Comparable local control results (90%) are obtained with preoperative, postoperative, and interstitial techniques, although rates of wound complications are higher with preoperative techniques.

Brachytherapy can offer a number of advantages. When brachytherapy is employed as the sole adjuvant, the entire treatment (surgery and irradiation) is completed in a 10- to 12-day period, compared with the 10-12 weeks required for typical external-beam irradiation (6-7 weeks) and surgery (4- to 6-week break before or after irradiation). Generally, smaller volumes can be irradiated with brachytherapy, which could improve functional results. However, smaller volumes may not be appropriate, depending on the tumor size, grade, and margin status.

The National Cancer Institute of Canada Clinical Trials Group published 3-year median follow-up results of a randomized phase III trial comparing preoperative with postoperative radiotherapy for limb soft-tissue sarcoma (Figures 1A-1D). Wound complications were observed in 31 of 88 patients (35%) in the preoperative group and 16 of 94 patients (17%) in the postoperative group (difference, 18% [95% CI: 5-30]; $P = .01$). Tumor size and anatomical site were also significant risk factors in multivariate analysis. Local control was identical in both arms of the trial. Five-year outcomes have recently been reported, and no difference in metastases, cause-specific survival, or overall survival was noted. Because preoperative radiotherapy is associated with a greater risk of wound complications than postoperative radiotherapy, but less late fibrosis and edema, the choice of regimen for patients with soft-tissue sarcoma should take into account the timing of surgery and radiotherapy and the size and anatomic site of the tumor.

Regardless of the technique employed, local control is a highly achievable and worthwhile end point, as demonstrated in a study of 911 patients treated by various techniques at Memorial Sloan-Kettering Cancer Center. Of the 116 patients who developed a local recurrence, 38 patients subsequently developed metastases and 34 patients died. Metastases after local recurrence were predicted in patients with high-grade or large (> 5 cm) tumors.

Treatment recommendations Adjuvant radiotherapy should be employed for virtually all high-grade sarcomas of the extremities and larger (≥ 5 cm) low-grade lesions. If small (T1) lesions can be resected with clear margins, radiotherapy can be omitted. Postoperative therapy with either external-beam irradiation (with or without an interstitial implant boost) or an implant alone will achieve a high likelihood of local control and, therefore, limb preservation. Preoperative irradiation, although equally efficacious, does carry a higher wound complication rate than the postoperative approach.

The 5-year results of the NCI of Canada Clinical Trials Group phase III randomized trial of preoperative vs postoperative radiotherapy in extremity soft-tissue sarcomas were reported at the ASCO 2004 meeting. A total of 190 patients were randomized to receive treatment (94 preoperative and 96 postoperative irradiation). The updated results continue to show no difference in local control, metastatic relapse-free survival, and recurrence-free survival. The previously reported difference in overall survival has not been seen with longer follow-up. The 5-year overall survival rate was 73% vs 67% ($P = .48$). Tumor size and grade were the only significant predictors for metastatic relapse, overall survival, and cause-specific survival (O'Sulllivan B, Davis A, Turcotte R, et al: J Clin Oncol [abstract] 22:14S, 2004).
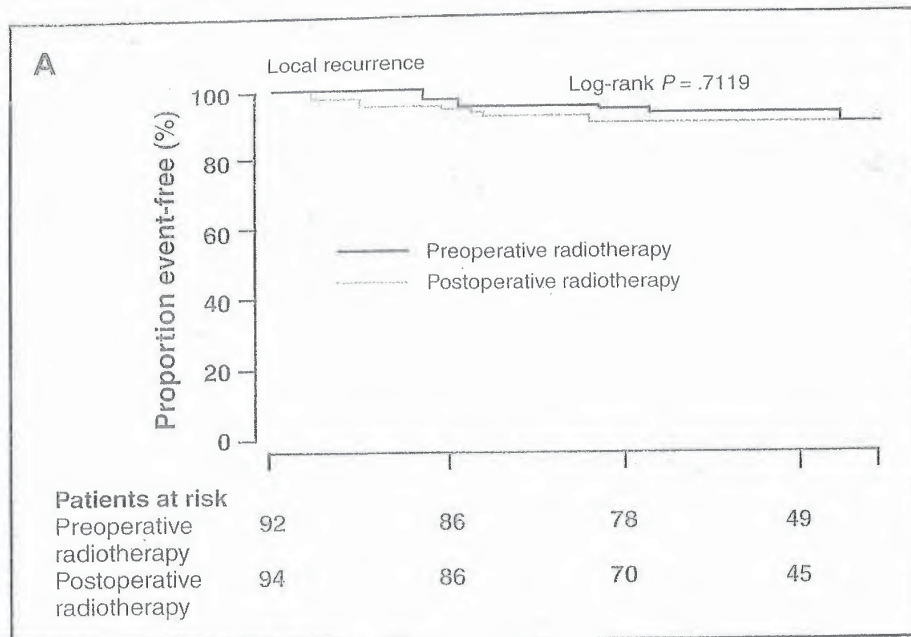
FIGURE 1A: Kaplan-Meier plots for probability of local recurrence in the National Cancer Institute of Canada Clinical Trials Group phase III trial.
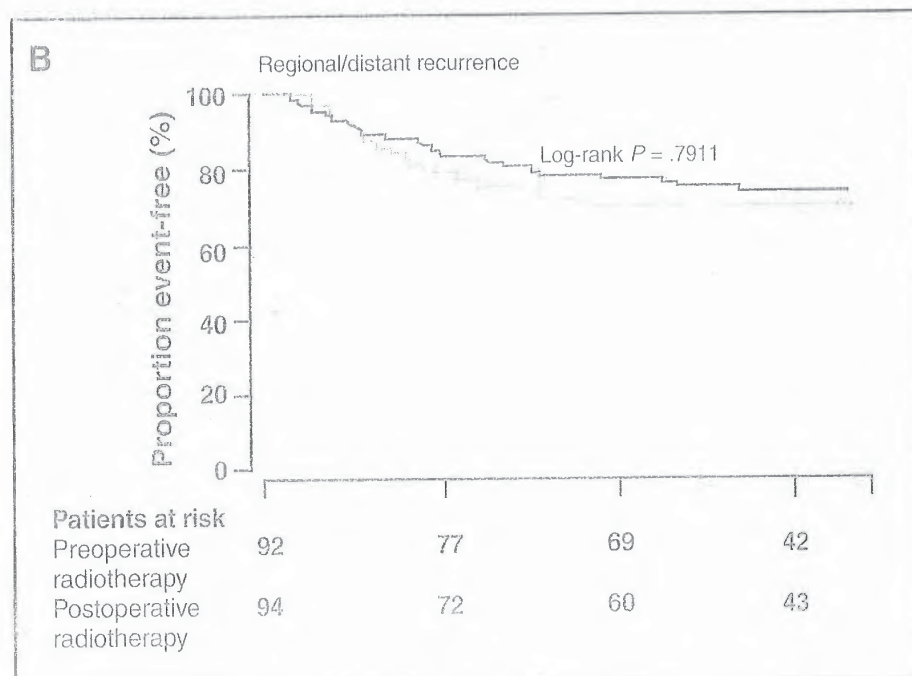

FIGURE 1B: Kaplan-Meier plots for probability of metastatic (regional and distant) recurrence in the National Cancer Institute of Canada Clinical Trials Group phase III trial.
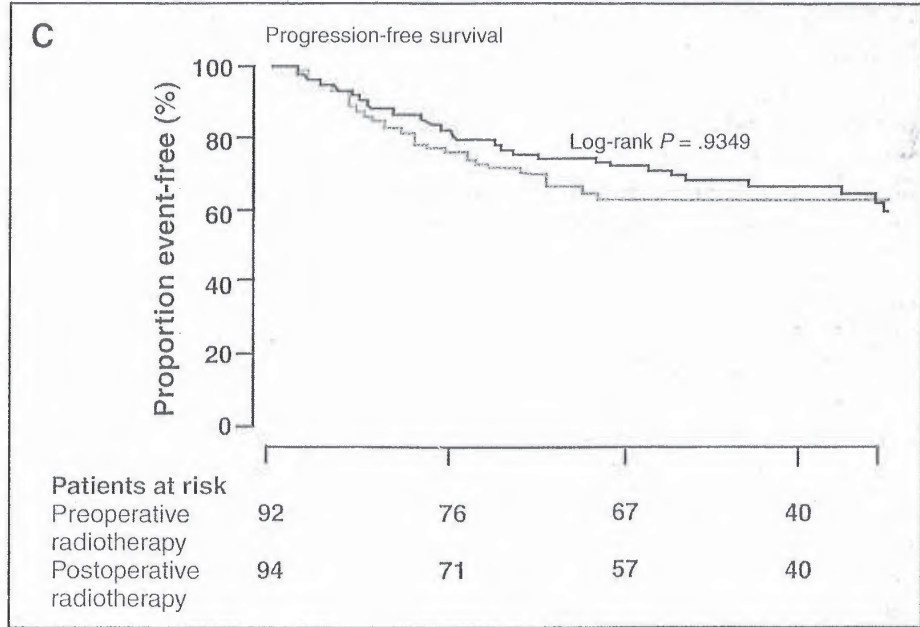
Progression-free survival

Log-rank *P* = .9349

Patients at risk

Preoperative radiotherapy	92	76	67	40
Postoperative radiotherapy	94	71	57	40

FIGURE IC: Kaplan-Meier plots for probability of progression-free survival in the National Cancer Institute of Canada Clinical Trials Group phase III trial.
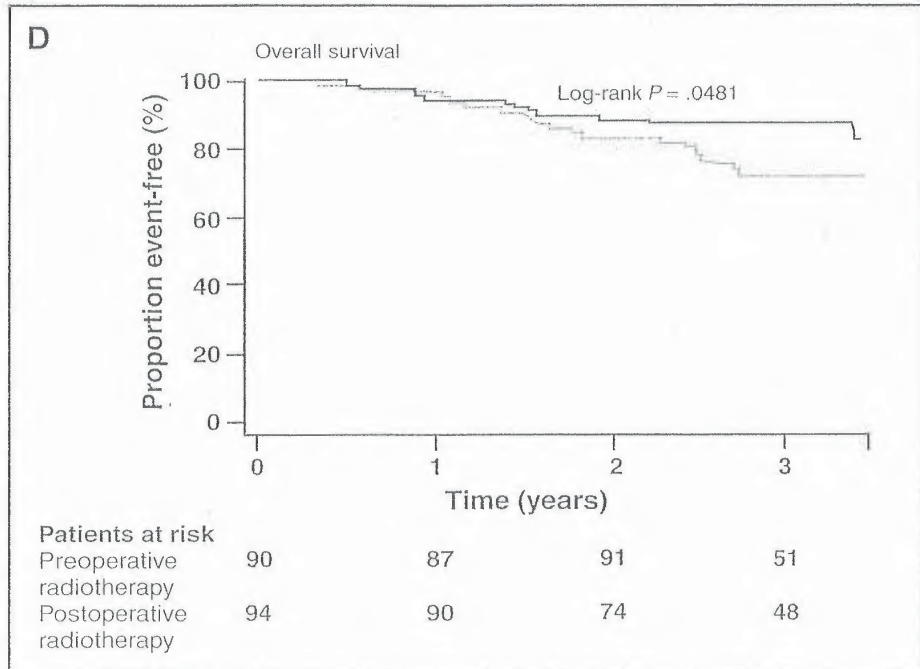
D

Overall survival

Log-rank *P* = .0481

Time (years)

Patients at risk

Preoperative radiotherapy	90	87	91	51
Postoperative radiotherapy	94	90	74	48

FIGURE ID: Kaplan-Meier plots for probability of overall survival in the National Cancer Institute of Canada Clinical Trials Group phase III trial.

From O'Sullivan R, Davis AM, Turcotte R, et al: Lancet 359:2235–2241, 2002.

Primary radiation therapy

Several studies on radiation therapy alone in the treatment of unresectable or medically inoperable soft-tissue sarcomas have reported 5-year survival rates of 25%-40% and local control rates of 30%. Local control depends largely on the size of the primary tumor. Radiation doses should be at least 65-70 Gy, if delivery of such doses is feasible. The tumor's location may be particularly important in determining this dose because of the potential for damage to critical structures (eg, the spinal cord) by the higher doses normally used.

Radiation therapy in retroperitoneal sarcomas

Only 50% of patients with retroperitoneal sarcomas are able to undergo complete surgical resection. Of patients undergoing complete resection, one-half develop local recurrence. This significant local failure rate suggests a potentially important role for adjuvant treatment in all patients with retroperitoneal sarcomas. However, the role of radiation therapy in the treatment of retroperitoneal sarcomas remains controversial due to the rarity of the tumor, the paucity of data, the retrospective nature of available studies, the low doses of radiation used in many studies, and the lack of consistent policies in determining the indications for radiation therapy.

Postoperative irradiation Two-year local control rates of 70% have been reported with the addition of postoperative irradiation. However, irradiation of the retroperitoneum/abdomen in doses that have effected local control in soft-tissue sarcoma of the extremities (50-65 Gy) is usually associated with significant GI toxicity. Obviously, the incidence of GI toxicity depends on the exact fields and technique used. However, as most retroperitoneal sarcomas are > 10-15 cm, the radiation fields employed are generally also quite large, and bowel is often located and/or tethered in the high-risk area. Three-dimensional treatment planning and conformal techniques can now be utilized to maximize the radiation dose to the tumor bed while minimizing the dose to the surrounding normal tissues.

Preoperative irradiation The advantages of preoperative radiotherapy have already been discussed for soft-tissue sarcomas of the extremities. In the retroperitoneum, an additional advantage is that bowel is frequently displaced significantly by the tumor. In contrast to the postoperative setting, the bowel being treated is also unlikely to be tethered by adhesions from prior surgery. These features significantly offset acute toxicity of large-field intra-abdominal radiotherapy (eg, nausea, vomiting, and diarrhea) as well as the potential for late-onset bowel toxicity. Conformal techniques capable of sparing normal tissues are also more easily applied in the preoperative setting, when the tumor can be visualized and the target area more readily defined. The American College of Surgeons Oncology group (ACSOG) has recently opened a prospective, randomized trial (ACSOG 2 9031) investigating this very issue. In this phase III study, patients will be randomized to undergo surgical resection of the retroperitoneal tumor alone vs preoperative irradiation followed by surgical resection.

Intraoperative irradiation In a prospective trial from the NCI, 35 patients with completely resected retroperitoneal sarcomas were randomized to receive either intraoperative electron-beam irradiation (IORT) followed by low-dose (30-40 Gy) postoperative external-beam irradiation or high-dose postoperative external-beam irradiation (35-40 Gy plus a 20-Gy boost). Absolute local recurrence rates were significantly lower in the IORT group ($P < .05$), but disease-specific and overall survival rates did not differ between the two groups.

Similarly, a nonrandomized series from the Massachusetts General Hospital has suggested improved local control with IORT for patients with retroperitoneal sarcoma. In 16 patients who underwent irradiation, complete gross resection, and IORT, overall survival and local control rates were 74% and 83%, respectively. These numbers diminished to 30% and 61%, respectively, in the 13 patients treated with irradiation and complete gross resection without IORT. Although these local control results are encouraging, IORT remains investigational and cannot be advocated on a routine basis at this time.

Isolated limb perfusion

Recent studies have evaluated the role of isolated limb perfusion (ILP) in the management of sarcomas of the extremities. These studies have generally been extrapolations from protocols initially designed to treat locally advanced melanoma.

The agents most commonly employed for ILP have been melphalan and tumor necrosis factor-alpha (TNF-α), with or without interferon-gamma (IFN-γ-1b [Actimmune]). The results of the largest series of ILP in patients with locally advanced soft-tissue sarcoma of the extremities were reported by Eggermont and colleagues. TNF has now been approved in Europe for ILP in patients with locally advanced, grade 2/3 soft-tissue sarcomas of the extremities.

ROLE OF ADJUVANT CHEMOTHERAPY

The striking success of combined-modality therapy in children with osteogenic sarcoma, embryonal rhabdomyosarcoma, and the Ewing's sarcoma family of tumors has provided the stimulus for the use of aggressive combined-modality approaches in adults. The literature is replete with reports of the apparent benefit of combined-modality therapy in patients with resectable soft-tissue sarcoma. Yet most series are either retrospective or small nonrandomized trials.

Postoperative chemotherapy

A number of published trials have compared postoperative chemotherapy with observation alone in adults who had undergone resection of a primary or recurrent soft-tissue sarcoma. Most of these trials included fewer than 100 patients, and even the largest trial had inadequate statistical power to detect a 15% difference in survival. Other flaws confound the interpretation of many of the studies. Some trials included low-risk patients with small and/or low-grade sarcomas. In some trials, patient ineligibility rates were as high as 20%, and in none of the trials published before 2000 was ifosfamide (Ifex) part of the combination evaluated.

In five of the six trials in which doxorubicin monotherapy was studied, including one study limited to patients with uterine sarcoma, a significant improvement in survival could not be demonstrated. Among the trials of combination chemotherapy, most used the combination known as CyVADIC (cyclophosphamide, vincristine, Adriamycin [doxorubicin], and dacarbazine [DTIC-Dome]). A significant survival advantage was seen only in one combination chemotherapy trial.

Nonetheless, some of the trials showed a trend or a statistically significant improvement in disease-free survival among patients who were administered adjuvant chemotherapy, especially among those with high-grade sarcomas of the extremities. Analyses of the pooled results of the published literature are consistent with this observation.

SMAC meta-analysis A formal meta-analysis of individual data from 1,568 patients who participated in randomized trials of postoperative adjuvant chemotherapy vs no chemotherapy control patients was performed by the Sarcoma Meta-Analysis Collaboration (SMAC). Although not all data were available for all patients, the analysis demonstrated a significant reduction in the risk of local or distant recurrence in patients who received adjuvant chemotherapy.

The overall hazard ratio for distant relapse-free survival was 0.70; ie, the risk of distant relapse (metastasis) was reduced by 30% in treated patients. The absolute benefit at 10 years was 10%, so the recurrence-free survival rate at 10 years was improved from 60% to 70%. Also, the hazard ratio for local recurrence-free survival was 0.73 (27% reduction in the risk of local recurrence), and the absolute benefit was 6%.

The hazard ratio for overall survival, however, was 0.89, which did not meet the criteria for statistical significance. The observed survival at 10 years was 54% for patients who received chemotherapy and 50% for those who did not. Subset analysis failed to show that the effects of chemotherapy differed by primary site, although the best evidence for an effect of adjuvant chemotherapy was seen in patients with sarcoma of the extremities.

Ifosfamide-containing trials Only one trial included in the meta-analysis used an ifosfamide-containing regimen; that trial involved only 29 patients. An attempt to conduct a large prospective trial of postoperative chemotherapy with the MAID (mesna [Mesnex], Adriamycin [doxorubicin], ifosfamide, and dacarbazine) regimen in the United States failed because of insufficient patient accrual.

An Italian cooperative group conducted a trial in which patients 18-65 years old with high-grade (≥ 5 cm) or any recurrent sarcoma of the extremities were randomized to receive postoperative chemotherapy or observation alone. The treatment consisted of five cycles of epirubicin (Ellence), 60 mg/m^2 on days 1 and 2, plus ifosfamide, 1.8 gm/m^2 on days 1-5. Granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) was used to support the granulocyte counts during therapy.

The trial had been planned for 200 patients but was interrupted after accrual of 104 patients, when an interim analysis showed a significant survival advantage for the chemotherapy-treated group. At 36 months after the last randiza-

tion, with a median follow-up of 59 months, median overall survival among the patients who received adjuvant chemotherapy was 75 months, vs 46 months in control patients $(P = .03)$.

Preoperative chemotherapy

Preoperative chemotherapy has been adopted at many centers for patients with large high-grade sarcoma. The specific regimens employed have evolved over the years but generally contain both an anthracycline and ifosfamide. Some investigators have added concurrent, sandwiched or sequential preoperative radiation therapy in nonrandomized trials. European investigators have also explored combination chemotherapy with regional hyperthermia.

> The updated results of the Italian Cooperative Group trial were recently published. With a median follow-up of 89.6 months, the difference in overall survival in the two groups is no longer statistically significant. However, the 5-year overall survival was 66% in those who received adjuvant chemotherapy (epirubicin [60 mg/m²] and ifosfamide [1.8 g/m²]), vs 46% in the control group ($P = .04$; *Frustaci S, De Paoli A, Bidoli E, et al: Oncology 65[suppl 2]:80-84, 2003*).

Aside from theoretic considerations, there are several pragmatic reasons to favor preoperative over postoperative treatment. First, a reduction in the size of a large lesion may permit surgical resection with less morbidity. Second, compliance may be better with preoperative therapy. One observation that supports the neoadjuvant approach is that response to preoperative chemotherapy, whether pathologic or radiographic, predicts improved tumor control and survival.

Neoadjuvant chemotherapy has been explored in a prospective randomized trial initiated by the EORTC (European Organization for Research on the Treatment of Cancer). The trial was open to patients who had a sarcoma measuring at least 8 cm (of any grade), a primary or recurrent intermediate- to high-grade (grade 2/3) sarcoma of any size, or a locally recurrent or inadequately excised grade 2/3 sarcoma. In spite of these broad eligibility criteria, accrual was slow, and the trial was closed after only 150 patients entered.

Patients were randomized to receive either immediate surgery, followed by radiation therapy for close or positive margins, or three cycles of chemotherapy with doxorubicin (50 mg/m² by IV bolus) plus ifosfamide (5 g/m² by 24-hour continuous infusion) with mesna. Among the 134 eligible patients, over 80% had primaries of the extremities, but only 4% had grade 2/3 lesions > 8 cm. Among 49 patients assessable for response, 29% had major objective responses, including 4 complete responses. Only 18% had progression of disease before surgery. Chemotherapy was generally well tolerated and never prevented surgery. With a median follow-up of 7.3 years, the estimated 5-year survival rate among the 67 surgery-alone patients was 64% and among the neoadjuvant chemotherapy patients was 65% $(P = .22)$.

More recently, there have been trials exploring the role of neoadjuvant chemotherapy and radiation therapy to decrease the rate of distant failure and possibly impact survival. A study reported from Massachusetts General Hospital enrolled patients with high-grade soft-tissue sarcomas (8 cm or larger). Patients were treated with three cycles of preoperative chemotherapy consisting of mesna, Adriamycin (doxorubicin), ifosfamide, and dacarbazine (MAID) interdigitated

with 44 Gy of radiation therapy. This reigmen was followed by surgical resection and three cycles of postoperative MAID chemotherapy. In cases with positive surgical margins, an additional 16 Gy of radiation therapy was delivered.

This regimen resulted in a significant improvement in 5-year freedom from distant metastasis (75% vs 44%, $P = .0016$) when compared with historic control patients. Additionally, 5-year disease free and overall survival rates were 70% vs 42% ($P = .0002$) and 87% vs 58% ($P = .0003$) for the MAID and control groups, respectively. There was a 29% rate of wound healing complications in the MAID group.

The M. D. Anderson Cancer Center conducted a phase I trial to define the maximum tolerated dose of continuous infusion doxorubicin administered with preoperative radiation therapy to a dose of 50 Gy. A total of 27 patients with intermediate- or high-grade sarcomas were enrolled in the trial. The maximum tolerated dose of doxorubicin was 17.5 mg/m^2/wk. Twenty-six patients underwent surgery, and all had a macroscopic complete resection (R0 or R1). Two patients had a pathologic complete response. These studies suggest that further investigation of a preoperative approach combining chemotherapy and radiation therapy is warranted.

Treatment recommendations

- Multidisciplinary treatment planning should precede the initiation of any therapy. An experienced multidisciplinary team should evaluate pathologic material and imaging studies and coordinate the integration of surgical resection, irradiation, and systemic therapy.

- Ideally, patients should be offered participation in clinical trials. Unfortunately, there are no active trials in the United States that will definitively answer the most important questions. Thus, a decision to treat must be made on an individual basis.

- Preoperative chemotherapy should be considered for fit, high-risk patients after a discussion of the risks and potential benefits. Older patients, especially those with cardiac or renal disease, are not optimal candidates for such treatment.

- Patients who do not receive preoperative chemotherapy may still be offered postoperative treatment. Adjuvant doxorubicin/ifosfamide combinations may improve relapse-free survival in carefully selected patients and can be considered for the treatment of those with tumor size > 5 cm, deep tumor location, and high histologic grade.

- For patients who opt for preoperative or postoperative chemotherapy, a regimen that includes doxorubicin (60-75 mg/m^2) or epirubicin (120 mg/m^2) plus ifosfamide (9-10 g/m^2) or the MAID regimen (see the section on "Combination chemotherapy"), given for a total of five cycles, would be a reasonable choice.

- Outside the context of a clinical trial, concurrent chemotherapy and irradiation should be avoided.

TREATMENT OF LOCAL RECURRENCE

Despite optimal multimodality therapy, local recurrence develops in 10%-50% of patients, with a median local recurrence-free interval of ~24 months. Local recurrence rates are a function of the primary site and are highest for retroperitoneal and head and neck sarcomas, for which adequate surgical margins are difficult to attain. In addition, high-dose adjuvant irradiation of these sites is often limited by the relative radiosensitivity of surrounding structures. These factors result in local recurrence rates of 40% for retroperitoneal sarcomas and up to 50% for head and neck sarcomas, which are substantially higher than the 10% proximity typically seen for extremity sarcomas.

A recent large retrospective analysis of patients with high-grade sarcoma of the extremities was reported from UCLA. Local recurrence required amputation in 38% of cases and was associated with a threefold decrement in survival. This finding accentuates the necessity for adequate local therapy for sarcomas presenting primarily as well as for multidisciplinary management of local recurrence.

Reoperation Following staging evaluation, patients with isolated local recurrence should undergo reoperation. The results of reoperation in this setting are good, with two-thirds of patients experiencing long-term survival.

Adjuvant radiation therapy If no prior radiation therapy was employed, adjuvant irradiation (50-65 Gy) should be used before or after surgery for locally recurrent disease. Radiation therapy (external-beam irradiation or brachytherapy) should be considered in patients for whom previous radiation doses were subtherapeutic or the previous radiation field design permitted additional treatment.

Reports from Memorial Sloan-Kettering Cancer Center, M. D. Anderson Cancer Center, and Princess Margaret Hospital suggest that patients who develop local recurrence following previous full-dose irradiation represent a difficult local control challenge. A report from Memorial Sloan-Kettering Cancer Center suggests that limb-sparing surgery combined with adjuvant brachytherapy may produce excellent local control and function in this group.

ILP Ongoing clinical investigations are defining the role of ILP in the management of patients with locally recurrent sarcoma.

TREATMENT OF LIMITED PULMONARY METASTASIS

Thoracotomy and metastasectomy The most common site of metastatic disease involvement of soft-tissue sarcoma is the lungs. Rates of 3-year survival following thoracotomy for pulmonary metastasectomy range from 23%-42%. This fact, combined with the limited efficacy of systemic therapy, is the basis for the recommendation that patients with limited pulmonary metastases and no extrapulmonary disease should undergo thoracotomy and metastasectomy.

Appropriate patient selection for this aggressive therapeutic approach to metastatic disease is essential. The following are generally agreed upon criteria: (1) the primary tumor is controlled or controllable; (2) there is no extrathoracic meta-

static disease; (3) the patient is a medical candidate for thoracotomy; and (4) complete resection of all disease appears to be possible.

Preresection chemotherapy Chemotherapy is often recommended before resection of pulmonary metastases. However, there are no convincing data to support this approach.

CHEMOTHERAPY FOR UNRESECTABLE LOCALLY ADVANCED OR METASTATIC DISEASE

Single agents

Doxorubicin Early trials of doxorubicin reported major responses in approximately 30% of patients with advanced soft-tissue sarcoma. In more recent randomized series, however, the rate of response has been closer to 17%.

Subset analysis of patients with soft-tissue sarcoma from a broad phase II trial in which patients were randomized to receive various doses of doxorubicin demonstrated a steep dose-response relationship; patients treated with doses < 60 mg/m^2 rarely responded. Whether dose intensification of doxorubicin is associated with improved survival remains an open question (see section on "Intensifying chemotherapy").

Pegylated liposomal doxorubicin (Doxil in the United States, Caelyx in Europe) has demontrated limited activity in phase II trials, especially in patients whose disease is refractory to standard doxorubicin. In a randomized comparison among 95 previously untreated patients, however, the response rates to pegylated liposomal doxorubicin (50 mg/m^2 every 4 weeks; 10%) and to standard doxorubicin (75 mg/m^2 every 3 weeks; 9%) were similar, with no significant difference in time to disease progression or survival. Response rates improved to 14% and 12%, respectively, when GIST cases were excluded.

Ifosfamide In a randomized phase II trial conducted by the EORTC, 18% of patients treated with ifosfamide (5 g/m^2) experienced major responses, in contrast to 12% of patients treated with cyclophosphamide (1.5 g/m^2), despite the greater myelosuppression with the latter agent. In a large American phase II trial, 17 of 99 patients with soft-tissue sarcoma responded to ifosfamide (8 g/m^2). All of the patients had been treated previously with doxorubicin-based therapy, suggesting a degree of non–cross-resistance.

Increasing ifosfamide dose Responses to ifosfamide ($\geq$ 12 g/m^2) have been observed in patients whose disease progressed while receiving lower doses, supporting the concept of a dose-response relationship.

In a randomized trial, the response to 9 g/m^2 of ifosfamide (17.5%) was superior to the 3% response observed among patients treated with 5 g/m^2. The reason for the low response to the lower dose was unclear. In a subsequent trial by the same investigators, the response to 12 g/m^2 was only 14%, however.

Among 45 "assessable" patients enrolled in a Spanish phase II trial of ifosfamide (14 g/m^2 given by continuous infusion over 6 days), the response rate was 38%, but 47% of patients developed febrile neutropenia and 32%, grade 3 neurotoxicity.

At M. D. Anderson Cancer Center, ifosfamide (14 g/m^2 given by continuous infusion over 3 days) yielded responses in 29% of 37 patients with soft-tissue sarcoma and 40% of patients with bone sarcoma. Also within that report was a small cohort of patients in whom the response to the same total dose of ifosfamide was higher when the drug was given by an intermittent bolus rather than a continuous infusion; this finding led the authors to suggest that bolus therapy is more efficacious than continuous infusion. Pharmacokinetic studies, however, have shown no difference between a 1-hour infusion or bolus injection of ifosfamide with respect to the area under the curve for serum ifosfamide or its metabolites or the levels of ifosfamide metabolites in urine.

In an EORTC phase II trial, ifosfamide (12 g/m^2 given as a 3-day continuous infusion every 4 weeks) yielded a response rate of 17% among 89 chemotherapy-naive patients and 16% among 25 previously treated patients.

Ifosfamide doses as high as 14-20 g/m^2 have been given with hematopoietic growth factor support; reported response rates are high, but neurologic and renal toxicities often are dose-limiting. The available data suggest that synovial sarcoma is particularly sensitive to ifosfamide.

An ongoing randomized phase II study is evaluating the efficacy of trabectedin (Yondelis) in the treatment of patients with soft-tissue sarcoma refratory to conventional chemotherapy. The study has accrued 60 patients with leiomyosarcoma or liposarcoma to date who have been assigned to one of two treatment arms: trabectedin as a 3-h infusion every week for 3 consecutive weeks of a 4-week cycle (arm A) or as a 24-h IV infusion every 3 weeks (arm B). All patients were pretreated with dexamethasone. Of these 60 patients, 29 are evaluable. Activity has been noted in both arms, with three patients in arm B demonstrating a partial response. Tolerability appears to be consistent with prior experience with this agent (*Samuels BL, Rushing D, Chawla SP, et al: Proc Am Soc Clin Oncol [abstract] 23:814, 2004*).

Dacarbazine The activity of dacarbazine in soft-tissue sarcoma has been recognized since the 1970s and was confirmed in a formal phase II trial. This marginally active agent has been used mostly in doxorubicin-based combinations.

Ecteinascidin (ET-743, trabectedin [Yondelis]), a novel compound derived from a marine organism, has demonstrated promising activity as well. In phase I trials, ET-743 demonstrated activity in heavily pretreated patients with advanced sarcoma. Two phase II trials of ET-743 (1,500 mg/m^2 over 24 hours every 3 weeks) in refractory non-GIST soft-tissue sarcoma have been reported. In one trial, 2 partial responses and 4 minor responses were seen among 52 patients; 9 additional patients had stable disease for at least 6 months. Twenty-four percent of patients were disease progression free at 6 months. Median survival was 12.8 months, with 30% of patients alive at 2 years. In the other trial, responses were observed in 3 of 36 patients, with 1 complete response and 2 partial responses, for an overall response rate of 8% (95% CI: 2-23). Responses, however, were durable, lasting up to 20 months. The predominant toxicities were neutropenia and elevation of transaminase levels. Two phase II trials of ET-743 in patients with GIST showed no therapeutic activity.

TABLE 2: Chemotherapy regimens for soft-tissue sarcoma

Drug/combination	Dose and schedule
AD (96-hour infusional)	
Adriamycin (doxorubicin)	15 mg/m^2/d for 4 days (96-hour continuous infusion), total dose of 60 mg IV over 4 days
Dacarbazine	250 mg/m^2/d for 4 days (96-hour continuous infusion), total dose of 1,000 mg/m^2 IV over 4 days

Repeat cycle every 21 days.

Antman K, Crowley J, Balcerzak SP, et al: J Clin Oncol 11:1276–1285, 1993.

AD (bolus)	
Adriamycin (doxorubicin)	60 mg/m^2 on day 1 by rapid IV infusion
Dacarbazine	750 mg/m^2 on day 1 by rapid IV infusion.

Repeat cycle every 21 days.

NOTE: Bolus dosage was compared with Adriamycin (doxorubicin) at 60 mg/m^2 and dacarbazine at 750 mg/m^2 delivered by continuous IV infusion for 96 hours on days 1-4. The median survival times between the two treatment arms were equivalent, with the toxic effects being milder in the infusional dosage.

Zalupski M, Metch B, Balcerzak S, et al: J Natl Cancer Inst 83:926–932, 1991.

AIM	
Adriamycin (doxorubicin)	30 mg/m^2 IV on days 1 and 2 by rapid IV infusion
Ifosfamide	3,750 mg/m^2 on days 1 and 2 by IV infusion over 4 hours
Mesna	750 mg/m^2 IV infused immediately preceding and 4 and 8 hours after ifosfamide administration on days 1 and 2

Repeat cycle every 21 days.

NOTE: IV hydration at 300 mL/h beginning 3 hours before each treatment cycle and for 3 days at 100 mL/h after each day-1 ifosfamide infusion. Granulocyte colony-stimulating factor, 5 μg/kg subcutaneously, may be given starting 24-48 hours daily for 10 days or until a granulocyte count of 1,500/μL is reached. Appropriate supportive measures should be given.

Edmonson JH, Ryan LM, Blum RH, et al: J Clin Oncol 11:1269–1275, 1993.

Other agents Gemcitabine (Gemzar) has demonstrated modest activity in several phase II trials, although results of a recent Southwest Oncology Group (SWOG) trial were disappointing. Taxanes, vinca alkaloids, and platinum compounds have demonstrated only marginal activity, however. It should be noted that the taxanes, gemcitabine, and vinorelbine have been observed to be active in angiosarcoma, especially angiosarcoma involving the scalp and face.

Combination chemotherapy

Combination chemotherapy regimens have been used widely in the management of patients with soft-tissue sarcoma. High response rates have been reported in a number of single-arm phase II trials. Most combination regimens include an anthracycline (either doxorubicin or epirubicin) plus an

Drug/combination	Dose and schedule
EIM	
Epirubicin	60 mg/m^2 IV infused on days 1 and 2, total dose of 120 mg/m^2 per cycle
Ifosfamide	1.8 g/m^2/d on days 1-5, total dose of 9 g/m^2 per cycle
Mesna	360 mg/m^2 IV infused immediately before and 4 and 8 hours after ifosfamide infusion

Repeat cycle every 3 weeks for a total of 5 cycles.

Granulocyte colony-stimulating factor, 300 μg subcutaneously given on days 8 through 15.

Hydration (1,500-2,000 mL) of fluids IV given after ifosfamide.

Frustaci S, Gherlinzoni F, De Paoli A, et al: J Clin Oncol 19:1238–1247, 2001.

Drug/combination	Dose and schedule
MAID	
Mesna	2.5 mg/m^2/d IV infused continuously over 24 hours on days 1-4
Adriamycin (doxorubicin)	20 mg/m^2/d IV infused continuously over 24 hours on days 1-3
Ifosfamide	2.5 g/m^2/d IV infused continuously over 24 hours on days 1-3
Dacarbazine	300 mg/m^2/d IV infused continuously over 24 hours on days 1-3

Repeat cycle every 21 days.

Elias A, Ryan L, Sulkes A, et al: J Clin Oncol 7:1208–1216, 1989.

Drug/combination	Dose and schedule
Gemcitabine and docetaxel[*]	
Gemcitabine	900 mg/m^2 IV on days 1 and 8
Docetaxel	100 mg/m^2 on day 8

Repeat cycle every 21 days.

NOTE: Granulocyte colony-stimulating factor is given subcutaneously on days 9 and 15. Patients who have undergone prior pelvic radiation therapy receive 25% dose reduction of both agents. Gemcitabine is delivered over 30 to 90 minutes in cycles 1 and 2 and by 90-minute infusion in all subsequent cycles.

[*] This regimen is still under study.

Hensley ML, Maki R, Venkatraman E, et al: J Clin Oncol 20:2824–2831, 2002.

Table prepared by Ishmael Jaiyesimi, DO

alkylating agent, dacarbazine, or both agents. Overall, response rates are higher in these single-arm trials than when the same regimens are tested in larger, randomized studies.

AD and CyVADIC regimens The combination of Adriamycin (doxorubicin) plus dacarbazine (AD regimen) has been studied extensively (Table 2). Also, for over a decade, the CyVADIC regimen was widely accepted as the standard of care. In a prospective, randomized trial, however, CyVADIC did not prove to be superior to doxorubicin alone.

Doxorubicin (or epirubicin) plus ifosfamide Combinations of doxorubicin (or epirubicin) plus ifosfamide have consistently yielded responses in over 25% of patients in single-arm trials. In sequential trials conducted by the EORTC, doxorubicin at 75 mg/m^2 plus ifosfamide (5 g/m^2) was superior to doxorubicin at 50 mg/m^2 plus ifosfamide (5 g/m^2). A prospective randomized EORTC trial with 314 patients compared the two regimens. There was no difference in response rate or overall survival, but disease progression-free survival favored the more intensive regimen.

The strategy of intensifying the dosing of ifosfamide within the context of combination chemotherapy was explored in a randomized phase II trial. This study included both patients with localized disease treated with four cycles of preoperative chemotherapy as well as patients with metastatic disease. Overall, there was no survival benefit for patients treated with doxorubicin (60 mg/m^2) plus 12 g/m^2 of ifosfamide over those treated with doxorubicin (60 mg/m^2) plus 6 g/m^2 of ifosfamide. Also, there was no advantage to the patients with localized disease in terms of disease-free survival.

MAID regimen The MAID regimen (mesna, Adriamycin [doxorubicin; 60 mg/m^2], ifosfamide [7.5 g/m^2], and dacarbazine [900 mg/m^2], all given over 3 days; Table 2) yielded an overall response rate in 47% of patients in a large phase II trial. In a randomized comparison of AD vs MAID regimens, the response to MAID was 32%, vs 17% with the two-drug regimen ($P < .002$). However, the price paid for the higher response was toxicity; of 8 toxic deaths reported in this trial, 7 occurred among the 170 patients treated with MAID. All treatment-related deaths occurred in patients > 50 years old. During the study, the doses of MAID were reduced to lessen toxicity. Median survival did not differ significantly between the two regimens, although a trend favoring the AD regimen was noted.

Combination chemotherapy vs single-agent doxorubicin Combination chemotherapy has been compared with single-agent doxorubicin in eight randomized phase III trials. Two trials were limited to patients with uterine sarcoma. Some of these studies showed superior response rates with combination chemotherapy, but none of the trials found a significant survival advantage. Kaplan-Meier plots of survival are virtually superimposable within each trial and from trial to trial.

It should be emphasized that approximately 20%-25% of patients entered into such trials are alive 2 years after therapy was initiated. Complete responses are uncommon and do not appear to translate into prolonged survival.

Gemcitabine plus docetaxel In a phase II study of 34 patients with unresectable leiomyosarcoma, mostly uterine in origin, 53% responded to a combination of gemcitabine (given by 90-minute infusion) plus docetaxel (Taxotere), with filgrastim support. An additional 20% had stable disease. Almost half of the patients had disease progression after anthracycline-based therapy. The median time to disease progression was 5.6 months, and grade 3-4 toxicity was uncommon. A prospective, randomized trial comparing this regimen with gemcitabine alone in a spectrum of histologic types of sarcoma is ongoing.

Intensifying chemotherapy Hematopoietic growth factors have facilitated the evaluation of dose-intensive chemotherapy in patients with sarcoma. The nonhematologic toxicities (cardiac, neurologic, and renal) of the agents most active in soft-tissue sarcoma prevent dramatic dose escalation.

Phase I and II trials of dose-intense anthracycline/ifosfamide regimens with hematopoietic growth factor support have shown that doxorubicin (70-90 mg/m^2) can be used in combination with ifosfamide (10-12 g/m^2) in selected patients. Response rates as high as 69% have been reported. Although toxicity increases, often dramatically, with these relatively modest dose escalations, the clinical benefit in terms of survival or palliation in patients with metastatic disease remains uncertain.

No randomized trial has demonstrated a survival advantage for patients treated with these more aggressive regimens. In one randomized trial, however, the French Federation of Cancer Centers Sarcoma Group demonstrated that, in comparison with standard doses, a 25% escalation in doses of MAID with G-CSF support did not improve outcome.

High-dose therapy with autologous stem-cell transplantation. Most trials are small and presumably involve highly selected patients. In one recent trial involving 30 patients with metastatic or locally advanced sarcoma accrued over a period of 6 years, more than 20% were free of disease progression at 5 years after high-dose therapy with stem-cell rescue. Complete response to standard induction chemotherapy predicted superior 5-year survival. Based on these favorable results, the investigators suggested a prospective randomized trial examining this approach. Although some groups are still exploring this approach, the appropriateness of generalizing these results to most patients with soft-tissue sarcoma remains speculative.

Prognostic factors for response to therapy Over the past 20 years, the EORTC has collected data on more than 2,000 patients with metastatic disease who participated in first-line anthracycline-based chemotherapy trials. Multivariate analysis of these data indicated that the patients most likely to respond to chemotherapy are patients without liver metastases ($P < .0001$), younger patients, individuals with high histologic grade, and those with liposarcoma. In this Cox model, the factors associated with superior survival were good performance status, absence of liver metastases, low histologic grade, a long time to metastasis after treatment of the primary tumor, and young age.

More recently, these same investigators have reported that the observed response rate is superior in patients who have pulmonary metastases only, as compared with those who have metastases to the lungs and other sites or to other sites only. These findings highlight the danger of reaching broad conclusions based on extrapolations from small trials that include highly selected patients. The EORTC data are also consistent with the observation that patients with metastatic GI sarcoma rarely respond to standard chemotherapy regimens. This increasingly recognized observation has been used to explain the low response rates seen in some trials.

> The French Sarcoma Group has initiated a phase III randomized trial looking at intermittent vs continuous imatinib therapy after completion of 1 year of continuous imatinib therapy. A total of 159 patients have enrolled in the trial. A partial or complete response was achieved in 52% of patients. Twenty-three patients were randomized to join the intermittent arm and 23, the continuous arm. After 3 months, 5 patients (21%) in the intermittent arm had evidence of disease progression, vs no patients in the continuous arm. Reintroduction of imatinib resulted in tumor control in all patients (Blay JY, Berthaud D, Perol D, et al: J Clin Oncol [abstract] 22:14S, 2004).

Targeted therapy for GISTs

Advances in our understanding of the biology of GIST, and the availability of an effective therapy for patients with advanced disease, have resulted in intense interest in this entity and rapid expansion of this disease. Because this entity had not been recognized, the incidence of GIST was underappreciated. GIST is the most common nonepithelial tumor of the gastrointestinal tract, with an estimated annual incidence of several thousand cases in the United States. Approximately 50%-60% of GISTS arise in the stomach and 25% in the small bowel. Other sites include the rest of the gastrointestinal tract, the omentum, mesentery, and retroperitoneum. These tumors may range in size from millimeters to huge masses.

Histologically, most are spindle cell lesions, but 20% may be predominantly epithelioid, and some have mixed features. Mitotic activity may range from very low to quite high. More than 95% stain positive for CD117, a marker of *KIT*, a transmembrane receptor with tyrosine kinase activity. In addition, 80% of GISTs are positive for BCL-2; 70%, for CD34; 50%, for muscle-specific actin; and 35%, for smooth muscle actin. Staining for desmin is uncommon (< 5%). It is thought that GISTs are related to the *KIT*-positive interstitial cells of Cajal, the pacemaker cells of the myenteric plexus. Prognosis for patients whose primary tumor is resected is related to size and mitotic activity.

The demonstration of the efficacy of imatinib (Gleevec) in GIST has been among the most dramatic and exciting observations in solid-tumor oncology. A randomized multicenter trial evaluated two doses of oral imatinib (400 vs 600 mg) in 147 patients with advanced GISTs. With median follow-up of 288 days, 54% had a partial response, and 28% had stable disease, but there were no complete responses. Response was sustained, with a median duration over 6 months. Most patients had mild grade 1 or 2 toxicity, but only 21% had severe grade 3 or 4 toxicity. GI or intra-abdominal hemorrhage occurred in 5% of patients. There was no difference in response or toxicity between the two doses.

These observations were expanded in two parallel, multi-institution trials in which patients with GISTs were randomized to receive imatinib (400 or 800 mg daily). The results were remarkably similar. In the American trial, among 746 registered patients, the overall response rate was 43% for patients treated with 400 mg and 41% for those treated with 800 mg. There were no differences in survival between the two arms. At 2 years, disease progression-free and overall survival rates in the 400-mg arm were 50% and 78%, respectively, In the 800-mg arm, the rate of disease progression-free survival at 2 years was 53%, and the rate of overall survival was 73%.

In a large European trial, 946 patients were randomized to receive imatinib (400 mg daily or bid). Among the 615 patients whose response could be evaluated, there was no difference in response frequency (43%) or survival between the two arms. Complete responses were seen in 3% and 2% of the lower-dose and higher-dose patients, respectively. Sixty-nine percent of patients progressing on 400 mg of imatinib were allowed to cross over to the higher dose (800 mg). Further therapeutic activity was seen, with 26% of these patients free of disease progression at 1 year.

In an analysis of prognostic factors for toxicity and response, the investigators found that the toxicity profile was related to initial levels of hemoglobin and albumin. Furthermore, toxicity was dose-dependent. Favorable disease progression-free survival was associated with good performance status, high hemoglobin level, gastric origin, and hepatic lesions.

Among a group of 127 patients with advanced GISTs, activating mutations of KIT or PDGFRA (platelet-derived growth factor receptor-alpha) were identified in 87.4% and 3.9% of patients, respectively. In patients harboring an exon 11 mutation of KIT, the partial remission rate was 83.5%, whereas in patients without a discernible mutation in KIT or PDGFRA, the partial remission rate was 9.1%. The presence of an exon 11 mutation in KIT correlated with clinical response, decreased risk of treatment failure, and improved overall survival.

The National Comprehensive Cancer Network (NCCN) recently established a GIST Task Force to develop guidelines for the evaluation and treatment of patients with GIST. This group recommended 400 mg daily as the initial starting dose of imatinib. Dose escalation should be considered in patients who do not respond initially or who demonstrate unequivocal disease progression. Surgery remains the primary modality for treatment of primary GIST, but adjuvant and neoadjuvant trials are ongoing. The efficacy, dose, and duration of imatinib therapy in these settings have not been established, so participation of patients in such trials should be encouraged.

Assessment of response and treatment after disease progression on imatinib The use of standard (RECIST) response criteria in patients with GIST may be misleading. On CT or MR imaging, large tumor masses may become completely necrotic without a reduction in size for months in spite of dramatic clinical improvement. Indeed, such masses may actually increase in size. [18]FDG ([18]fluorodeoxyglucose) PET imaging may be extremely useful in selected patients, since response may be seen as early as 24 hours after a dose of imatinib. It should be noted that the survival of patients with stable disease parallels the survival of patients with major objective responses using RECIST criteria.

Surgery does not cure GIST that recurs after resection of primary disease and should be managed as metastatic disease. However, multimodality therapy should be considered in patients with limited sites of disease. It has also been recognized that patients with disease progression in limited sites of disease, occasionally with a growing nodule within a previously necrotic metastasis, may experience rapid disease progression of previously controlled areas. Thus, imatinib should be continued indefinitely in such patients, who should be referred for investigational therapy.

Studies of the genomic and biochemical profiles of GISTs suggest that essential downstream kinases may remain activated in patients with GISTs resistant to imatinib mesylate. Thus, it is notable that SU11248, a small molecule kinase inhibitor that targets multiple tyrosine kinases, has demonstrated promising clinical activity in patients with GISTs.

Recommendations for the treatment of metastatic sarcoma

- For patients with rapidly progressive disease or with symptoms, combination chemotherapy with an anthracycline/ifosfamide combination is indicated. For most patients, however, sequential single-agent therapy is less toxic and not inferior in terms of survival.

- The importance of histology relevant to selection of therapy is increasingly being appreciated. It is especially important to distinguish GISTs from GI leiomyosarcomas. Patients with suspected GIST should be referred to subspecialty centers experienced in the multimodality management of this disease.

- Periods of watchful waiting may be appropriate for many patients with metastatic sarcoma who have no or only minimal symptoms.

SUGGESTED READING

Alektiar KM, Leung D, Zelefsky MJ, et al: Adjuvant brachytherapy for primary high-grade soft-tissue sarcoma of the extremity. Ann Surg Oncol 9:48–56, 2002.

Burton GV, Rankin C, Flaherty LE, et al: Phase II trial of gemcitabine as first line chemotherapy in patients with metastatic or unresectable soft tissue sarcomas (STS) (abstract). Proc Am Soc Clin Oncol 22:820, 2003.

Coindre JM, Terrier P, Guillou L, et al: Predictive value of grade for metastasis development in the main histologic types of adult soft-tissue sarcomas: A study of 1,240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer 91:1914–1926, 2001.

Corless CL, Fletcher JA, Heinrich MC, et al: Biology of gastrointestinal stromal tumors. J Clin Oncol 22:3813–3825, 2004.

DeLaney TF, Spiro IJ, Suit HD, et al: Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. Int J Radiat Oncol Biol Phys 56:1117–1127, 2003.

Eilber FC, Rosen G, Nelson SD, et al: High-grade extremity soft-tissue sarcomas: Factors predictive of local recurrence and its effect on morbidity and mortality. Ann Surg 237:218–226, 2003.

Fletcher JA, Corless CL, Dimitrijevic S, et al: Mechanisms of resistance to imatinib mesylate (IM) in advanced gastrointestinal stromal tumor (GIST) (abstract). Proc Am Soc Clin Oncol 22:815, 2003.

Fletcher CD, Gustafson P, Rydholm A, et al: Clinicopathologic re-evaluation of 100 malignant fibrous histiocytomas: Prognostic relevance of subclassification. J Clin Oncol 19:3045–3050, 2001.

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Frustaci S, Gherlinzoni F, De Paoli A, et al: Adjuvant chemotherapy for adult soft-tissue sarcomas of the extremities and girdles: Results of the Italian randomized cooperative trial. J Clin Oncol 19:1238–1247, 2001.

Gieschen HL, Spiro IJ, Suit HD, et al: Long-term results of intraoperative electron-beam radiotherapy for primary and recurrent retroperitoneal soft-tissue sarcoma. Int J Radiat Oncol Biol Phys 50:127–131, 2001.

Hensley ML, Maki R, Venkatraman E, et al: Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: Results of a phase II trial. J Clin Oncol 20:2824–2831, 2002.

Kasper B, Meissner J, Harter C, et al: High-dose chemotherapy (HDCT) with autologous peripheral blood stem cell transplantation (PBSCT) for bone and soft tissue sarcomas (abstract). Proc Am Soc Clin Oncol 22:817, 2003.

Kattan MW, Leung DH, Brennan MF: Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol 20:791–796, 2002.

Kraybill WG, Spiro I, Harris J, et al: Radiation Therapy Oncology Group (RTOG) 95-14: A phase II study of neoadjuvant chemotherapy (CT) and radiation therapy (RT) in high-risk (HR), high grade, soft-tissue sarcomas (STS) of the extremities and body wall: A preliminary report (abstract). Proc Am Soc Clin Oncol 20:348, 2001.

Le Cesne A, Blay J, Judson I, et al: ET-743 is an active drug in adult soft-tissue sarcoma (STS): A STBSG-EORTC phase II trial (abstract). Proc Am Soc Clin Oncol 20:353, 2001.

Le Cesne A, Judson I, Crowther D, et al: Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide vs high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft-tissue sarcomas: A trial of the European Organization for Research on the Treatment of Cancer/Soft-Tissue and Bone Sarcoma Group. J Clin Oncol 18:2676–2684, 2000.

Noorda EM, Vrouenraets BC, Nieweg OE, et al: Isolated limb perfusion with tumor necrosis factor-alpha and melphalan for patients with unresectable soft tissue sarcoma of the extremities. Cancer 98:1483–1490, 2003.

O'Sullivan B, Bell RS, Bramwell VHC: Sarcomas of the soft tissues, in Souhami RL, Tannock I, Hohenberger P, et al (eds): Oxford Textbook of Oncology, 2nd ed, pp 2495–2523. Oxford, Oxford University Press, 2002.

O'Sullivan B, Davis A, Turcotte R, et al: Five-year results of a randomized phase III trial of preoperative vs post-operative radiotherapy in extremity soft tissue sarcoma (abstract). Proc Am Soc Clin Oncol 22:14S, 2004.

O'Sullivan B, Davis AM, Turcotte R, et al: Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: A randomized trial. Lancet 359:2235–2241, 2002.

Pisters PW, Patel SR, Prieto VG, et al: Phase I trial of preoperative doxorubicin-based concurrent chemoradiation and surgical resection for localized extremity and body wall soft tissue sarcomas. J Clin Oncol 22:3375–3380, 2004.

Riad S, Griffin AM, Liberman B, et al: Lymph node metastasis in soft tissue sarcoma in an extremity. Clin Orthop Sep:129–134, 2004.

Rubin BP, Singer S, Tsao C, et al: KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. Cancer Res 61:8118–8121, 2001.

Trovik CS, Bauer HC, Alvegard TA, et al: Surgical margins, local recurrence, and metastasis in soft-tissue sarcomas: Five hundred fifty-nine surgically treated patients from the Scandinavian Sarcoma Group Register. Eur J Cancer 36:710–716, 2000.

Van den Abbeele AD, Badawi RD Cliche J-P, et al: ^{18}F-FDG-PET predicts response to imatinib mesylate (Gleevec) in patients with advanced gastrointestinal stromal tumors (GIST) (abstract). Proc Am Soc Clin Oncol 21:403, 2002.

Van Glabbeke MM, Verweij J, Casali PG, et al: Prognostic factors of toxicity and efficacy in patients with gastro-intestinal stromal tumors (GIST) treated with imatinib: A study of the EORTC-STBSG, ISG, and AGITG (abstract). Proc Am Soc Clin Oncol 22:818, 2003.

Wendtner C-M, Abdel-Rahman S, Krych M, et al: Response to neoadjuvant chemotherapy combined with regional hyperthermia predicts long-term survival for adult patients with retroperitoneal and visceral high-risk soft-tissue sarcomas. J Clin Oncol 20:3156–3164, 2002.

Worden FP, Taylor JMG, Bierman JS, et al: A randomized phase II evaluation of standard dose ifosfamide (IFOS) plus doxorubicin (DOX) versus high dose ifosfamide plus DOX in patients with high-grade soft tissue sarcomas (abstract). Proc Am Soc Clin Oncol 22:817, 2003.

Zalcberg JR, Verweij J, Casali PG, et al: Outcome of patients with advanced gastrointestinal stromal tumors (GIST) crossing over to a daily imatinib dose of 800 mg (HD) after progression on 400 mg (LD)–An international, intergroup study of the EORTC, ISG, and AGITG (abstract). Proc Am Soc Clin Oncol 22:819, 2004.