VIII LUNG CANCER

JEFFREY CRAWFORD, M.D.

Definition and Classifications

Bronchogenic carcinoma of the lung—lung cancer—comprises a group of malignant neoplasms that arise from bronchial epithelium. The four major pathologic cell types of lung cancer are small cell carcinoma, adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Because they have overlapping clinical behavior and response to treatment, adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are generally grouped together in the category of non–small cell lung cancer (NSCLC). NSCLC represents 75% to 80% of all cases of lung cancer. Classification systems for the four major types of lung cancer have been formulated by the World Health Organization, the Armed Forces Institute of Pathology, and the Working Party for Lung Cancer [see Table 1].

Epidemiology and Etiology

In the United States, lung cancer is the second most common cancer in both men and women, surpassed only by prostate cancer in men and breast cancer in women. For 2003, a total of 169,400 new cases were predicted [cancer in men and breast cancer in women. For 2003, a total of 169,400 new cases were predicted [cancer in both men and women, surpassed only by prostate cancer. By 2003, 12% of those in women. However, lung cancer is the leading cause of cancer deaths, accounting for 31% and 25% of all cancer-related deaths in men and women, respectively. For 2003, expected deaths from lung cancer were 154,900 [see Table 2].

The epidemiology of lung cancer in the United States directly reflects patterns in cigarette smoking, albeit with a 10- to 15-year lag time. Over recent decades, the prevalence of cigarette smoking in men has decreased from nearly 50% to approximately 25%, and the incidence of lung cancer in men has declined somewhat. During that same period, the prevalence of cigarette smoking in women has declined only 11%, to approximately 25%, and the incidence of lung cancer in men has now leveled off.

In men, the incidence of lung cancer peaked in 1984, at 86.5 per 100,000 population, and by 1996 had declined to 70 per 100,000 population. For women, the incidence in 1996 was 42.3 per 100,000 population. Since 1987, more women have died each year from lung cancer than from breast cancer, and the margin between the two diseases continues to widen. Estimates suggest that in 2003, over 50% more women died of lung cancer than of breast cancer.

Unfortunately, cigarette smoking became increasingly popular in teenagers in the 1990s. In the United States, the prevalence of cigarette smoking in high-school students increased during the 1990s, peaking during 1996 to 1997, then began a gradual decline. The popularity of smoking varied by ethnicity and race. In a 1999 survey of high-school students, smoking rates were 15.8% in blacks, 25.8% in Hispanics, and 32.8% in whites.

SMOKING CESSATION AND LUNG CANCER

Cigarette smoking continues to contribute to the risk of lung cancer long after a person has stopped smoking. The American Cancer Society evaluated this relationship in a 6-year prospective study involving more than 900,000 persons. This study included persons who had never smoked, current smokers, and former smokers. As expected, the risk of dying of lung cancer was lower in patients who had quit smoking early in life than in those who quit later on, and the risk was significantly lower in those who quit than in those who did not. In a person who smoked 26 cigarettes a day starting at 17 years of age and stopped smoking between the ages of 30 and 49, the risk of death from lung cancer is slightly greater than that for persons who never smoked. For a person quitting smoking between the ages of 50 and 64, the risk of death from lung cancer plateaus at the risk level at the time of quitting and remains level until about the age of 75, when the risk appears to increase further. In this model, the annual lung cancer mortality for current smokers at age 75 is 1% for men and 0.5% for women, which is approximately 20 times higher than that of nonsmokers. Nonsmokers (i.e., persons with a lifetime exposure of less than 100 cigarettes) have a rela-

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Table 1 Major Classifications of Lung Cancer

<table>
<thead>
<tr>
<th>System</th>
<th>Non–Small Cell Lung Cancer</th>
<th>Small Cell Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Squamous Cell* Carcinoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>World Health Organization, No. 2 (WHO–No. 2)</td>
<td>Spindle cell variant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acinar</td>
<td>Papillary</td>
</tr>
<tr>
<td></td>
<td>Bronchioalveolar</td>
<td>Solid carcinoma with mucin</td>
</tr>
<tr>
<td>Armed Forces Institute of Pathology (AFIP)</td>
<td>Well differentiated</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td></td>
<td>Poorly differentiated</td>
<td>Bronchioalveolar</td>
</tr>
<tr>
<td></td>
<td>Lymphocyte-like (oat cell)</td>
<td>Polygonal (intermediate)</td>
</tr>
<tr>
<td>Working Party for Lung Cancer (WPLC)</td>
<td>Well differentiated</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td></td>
<td>Poorly differentiated</td>
<td>Bronchioalveolar/papillary</td>
</tr>
</tbody>
</table>

Note: both the WHO–No. 2 and AFIP systems have a fifth category, adenosquamous cell carcinoma; benign lesions, dysplasia, carcinoma in situ, carcinoid tumors, soft tissue sarcomas, and other respiratory tract lesions, which account for only a few percent of all lung cancers, are not included in this table.

*For the WPLC system, the classification is epidermoid.

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February 2004 Update
tive risk of lung cancer of 0.05 or less as compared with current smokers. For former smokers, the relative risk of lung cancer death depends on the age of smoking cessation. The risk was 0.45 for smokers who quit in their early 60s, 0.2 for those who stopped smoking in their early 50s, and 0.1 for those who stopped smoking in their 50s. All available data indicate that the lung cancer risk for former smokers is still consistently greater than for those who never smoked. Stopping smoking at any age can reduce lung cancer mortality, but the risk reduction is much greater for smokers who quit at a younger age.

In addition to age effects, there is a dose-response relationship for smoking and lung cancer. The risk for lung cancer increases with the duration of smoking and the number of cigarettes smoked. Earlier age of starting to smoke, deeper inhalation, and use of cigarettes that are unfiltered or have a high tar and nicotine content also increase the risk of lung cancer. In the current United States population over the age of 50, 23% are current smokers and 35% are former smokers. Because both groups remain at elevated risk for lung cancer for their lifetimes, clinicians should take an accurate quantitative smoking history in all patients.

**GENETIC SUSCEPTIBILITY AND MOLECULAR MECHANISMS**

The risk of lung cancer is affected by genetic susceptibility. Women smokers may be at higher risk for the development of lung cancer than men with a similar smoking history. Furthermore, lung cancer mortality appears to be higher in African Americans.

Mechanisms for genetic susceptibility to lung cancer include genes that govern smoking behavior, which affect dopamine reward mechanisms related to nicotine and nicotine metabolism, as well as gender; individual capacity for carcinogen metabolism; germline mutations coding for dysfunctional genes; and capacity to repair DNA damage from carcinogens. Several genetic abnormalities have been associated with lung cancers [see Table 3].

**LUNG CANCER IN NONSMOokers**

Given the dominant role of cigarette smoking in the etiology of lung cancer, determining the risk posed by other substances is difficult. As many as 25% of cases of lung cancer in nonsmokers may result from second-hand tobacco smoke. A small percentage of lung cancers result from occupational exposure to carcinogens, including asbestos, arsenic, cadmium, chromium, radiation, radon, and chemicals such as chromoethyl ether. Heavy residential exposure to radon may be synergistic with cigarette smoking in promoting lung cancer, but the risk from residential radon for nonsmokers remains unclear.

**Pathophysiology and Pathogenesis**

The prevalences of histologic subtypes of lung cancer in men and women have changed in ways that mirror the changes in smoking habits. In the early studies that established the association between smoking and lung cancer, cigarettes were unfiltered, most of the participants were men, and squamous cell carcinoma was the most common cell type. Now, with filtered cigarettes widely popular and larger numbers of women smoking, adenocarcinoma is the most common type of lung cancer in both young men and women. This changing pattern of histology correlates temporally with the change from unfiltered to filtered cigarettes and with reductions in the tar and nicotine content of cigarettes. Those changes in cigarette manufacturing have led to deeper inhalation of smoke into the lungs, which exposes the distal airways more heavily to the carcinogenic influences of tobacco smoke. Other factors likely play a part as well. In nonsmokers, adenocarcinomas are the most common histologic type of lung cancer.

The initiation of carcinogenesis from cigarette smoke is related to a complex mixture of carcinogens and tumor promoters combined with the delivery vehicle of inhalation. Serial studies of bronchial epithelium in smokers demonstrate an evolution from dysplasia to metaplasia to neoplastic changes. Each stage has been associated with a number of genetic alterations, and the pivotal mechanisms are a topic of intense investigation. Factors associated with genetic susceptibility have yet to be identified and may emerge from studies of lung cancer in nonsmokers. Thus, the main clinical criterion for susceptibility remains a history of current or former smoking.

**Table 3** Selected Molecular Genetic Abnormalities Associated with Lung Cancer

<table>
<thead>
<tr>
<th>Abnormal Genes</th>
<th>Mutation</th>
<th>Frequency of Abnormal Expression (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>NSCLC</td>
</tr>
<tr>
<td>Oncogenes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K-ras</td>
<td>Point mutation (codon 12)</td>
<td>30</td>
</tr>
<tr>
<td>myc family</td>
<td>DNA amplification/overexpression</td>
<td>10</td>
</tr>
<tr>
<td>HER-2/neu</td>
<td>Increased expression of p185neu</td>
<td>25</td>
</tr>
<tr>
<td>Tumor suppressor genes</td>
<td>Deletion</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Point mutation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overexpression</td>
<td></td>
</tr>
<tr>
<td>p53</td>
<td>Deletion</td>
<td>15</td>
</tr>
<tr>
<td>Rb</td>
<td>Deletion</td>
<td>50</td>
</tr>
<tr>
<td>3p</td>
<td>Deletion</td>
<td></td>
</tr>
</tbody>
</table>

NSCLC—non–small cell lung cancer   SCLC—small cell lung cancer

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February 2004 Update
ACP Medicine
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Prevention

PRIMARY PREVENTION

Given that 87% of cases of lung cancer occur in smokers and that the risk of lung cancer is lower by at least 20-fold in persons who have never smoked, the obvious strategy for primary prevention is to keep young persons from starting to smoke and to promote smoking cessation in smokers of all ages [see CE:III Reducing Risk of Injury and Disease]. Although public health measures that discourage smoking in public places and in the workplace, as well as the development of negative societal attitudes toward smoking, are helpful in reducing the prevalence of smoking in adults, progress against smoking has been slow and teenage smoking rates remain unacceptably high.

SECONDARY PREVENTION

The use of nutritional supplements by smokers as a strategy to reduce lung cancer was suggested by an epidemiologic association of lower serum levels of β-carotene, vitamin E, and retinoids with a higher risk of lung cancer. Unfortunately, in clinical trials, these agents did not reduce lung cancer risk. One of the best known trials, the CARET (β-Carotene and Retinol Efficacy Trial), comprised over 18,000 smokers of both sexes randomized to receive a retinoid drug, retinol palmitate, in combination with β-carotene or placebo. In this trial, patients who received β-carotene and retinol palmitate had a higher rate of development of lung cancer (relative risk = 1.36) and higher lung cancer mortality (relative risk = 1.59). In another placebo-controlled trial, from Finland, that studied the effects of vitamin E and β-carotene, smokers who received β-carotene were more likely to develop lung cancer (relative risk = 1.16). Vitamin E produced no effect. The risk of harm from β-carotene or placebo. In this trial, patients who received β-carotene and retinol palmitate had a higher rate of development of lung cancer (relative risk = 1.36) and higher lung cancer mortality (relative risk = 1.59).

Diagnosis

SCREENING

Most patients with lung cancer present with advanced inoperable disease. Screening for detection of lung cancer at an earlier stage is therefore an attractive idea, especially because persons at high risk for lung cancer can be readily identified by a smoking history.

Early randomized trials of screening, conducted in the United States and in the former Czechoslovakia, suggested that chest x-ray alone was not a satisfactory screening tool to detect early lung cancer tumors. Curable tumors are often too small or indistinct to be detected on a standard chest x-ray.

Spiral CT scanning may be a more sensitive technique for lung cancer screening. With this technique, radiologists obtain a low-resolution image of the entire thorax in a single breath-hold, with low radiation exposure and relatively rapid throughput compared with standard CT scans. A number of studies have demonstrated the feasibility of spiral CT scanning in screening for lung cancer. In the Early Lung Cancer Action Project (ELCAP), 1,000 asymptomatic persons older than 60 years with a smoking history of 10 or more pack-years underwent both spiral CT and chest x-ray. CT detected malignant nodules in 2.7% of the patients, compared with 0.6% by chest x-ray. Benign nodules were detected at a rate of 20.6% by CT versus 6.1% by chest x-ray, so careful follow-up is critical for avoiding unnecessary biopsy. A Mayo Clinic study of spiral CT also demonstrated enhanced detection of malignant nodules, most of which were early-stage lung cancer, but an even higher yield of benign nodules (60%), which emphasizes the potential drawback of this technique.

At present, no data from randomized trials exist to allow an evidence-based recommendation either for or against lung cancer screening. Despite encouraging results from nonrandomized trials, several issues remain to be addressed, including lead-time bias, generalization to a broader population, application to younger patients at lower risk of lung cancer, and long-term benefit in terms of lower lung cancer mortality. Furthermore, a decision and cost-effectiveness analysis has suggested that the cost of implementing such a strategy would be substantial. Currently, spiral CT screening cannot be recommended except in the context of a clinical trial. Other new technologies that deserve consideration as potential screening methods include analysis of sputum cytology by molecular markers and localization of tumors by fluorescence bronchoscopy.

The National Cancer Institute is currently enrolling patients in the National Lung Screening Trial (NLST), a randomized, controlled trial that will compare standard chest x-rays with spiral CT as a screening method for lung cancer. The NLST will enroll 50,000 current or former smokers between the ages of 55 and 74 years at clinical trial sites throughout the United States. Study participants will receive either a chest x-ray or a spiral CT once a year for 5 years and will then undergo monitoring until 2009. The researchers will be looking for a reduction in mortality of 20% or more with either modality. In addition to the screenings, some NLST centers will test for biologic markers that may have potential for screening.

CLINICAL MANIFESTATIONS AND LABORATORY STUDIES

The signs and symptoms of lung cancer vary with the anatomic location of the tumor, its extension into surrounding structures, metastatic spread, and the systemic effects of paraneoplastic syndromes. Unfortunately, only 6% of patients with lung cancer are asymptomatic at the time of diagnosis. The remainder of the patients present with symptoms resulting from regional spread of the tumor, mediastinal lymph node involvement, or distant metastases.

Pulmonary Manifestations

The most common manifestation of the primary tumor is cough, which results from endobronchial erosion and irritation. Others are, in decreasing order of frequency, dyspnea, chest pain, hemoptysis, and postobstructive pneumonia or pneumonitis [see Table 4]. Centrally located tumors also typically cause stridor, wheezing, hemoptysis, dyspnea, or chest pain, often central in location. Occlusion of the airway by a tumor can lead to a postobstructive infiltrate or pneumonia. Large tumors may cavitate and present as a lung abscess.

Manifestations of Intrathoracic Disease

Intrathoracic extension of the tumor or spread to mediastinal
lymph nodes may produce a variety of symptoms. Although individually these symptoms occur in fewer than 10% of patients with lung cancer, collectively they represent significant complications of locally advanced NSCLC, either at diagnosis or during the subsequent disease course. Hoarseness may result from invasion of the recurrent laryngeal nerve and resultant vocal cord paralysis. Dysphagia may be a sign of compression of the esophagus. Extensive tumor involvement of the right mediastinal lymph nodes often results in the superior vena cava syndrome, which is characterized by plethoric appearance; distention of the venous drainage of the arm and neck; and edema of the face, neck, and arms. Vena cava obstruction usually progresses gradually, allowing the development of collateral venous drainage that may be detected on physical examination.

Shoulder and arm pain from superior sulcus (Pancoast) tumor syndrome is a commonly misdiagnosed sign of lung cancer. The pain results from local extension of a tumor in the apex of the lung, with involvement of the eighth cervical and first thoracic nerves. Unfortunately, this condition is often mistaken for arthritis. In many cases, careful physical examination will identify ipsilateral Horner syndrome, which is characterized by ptosis, miosis, and anhydrosis. The Horner syndrome is related to paravertebral extension and sympathetic nerve involvement of the tumors.

Pleuritic pain and chest wall pain occur most commonly in patients with primary tumors in the lung periphery that spread to the pleura and, in some cases, extend directly to the chest wall. Associated pleural effusion may occur in such cases; large effusions may cause dyspnea. Malignant pericardial effusions may also develop and can cause cardiac tamponade.

Paraneoplastic syndromes

A minority of lung cancer patients present with paraneoplastic manifestations. The biology of these syndromes remains poorly characterized, but the syndromes appear to be cytokine-mediated responses to antigens from the intrathoracic lung tumor, rather than the result of distant spread of cancer.

The most common paraneoplastic feature associated with lung cancer is clubbing of the fingers from periosteal swelling of the distal phalanges, which may occur in 5% to 15% of patients. In a small percentage of patients, clubbing may be part of a symptomatic hypertrophic osteoarthropathy. These patients often complain of a distal symmetrical arthritis that most commonly involves the ankles or knees but can also involve the wrists, elbows, and other joints. Misdiagnosis of this condition as a strictly rheumatologic phenomenon often results in delayed recognition of the underlying neoplasm.

Although weight loss and fatigue are commonly an indication of distant metastasis, they can also represent a paraneoplastic phenomenon that occasionally occurs even with early-stage tumors. Especially in patients with small cell lung cancer (SCLC), paraneoplastic manifestations can also take the form of specific neurologic syndromes, such as the Lambert-Eaton syndrome. These patients present with muscle weakness, a variety of peripheral neuropathies, and central nervous system involvement such as subacute cerebellar degeneration or limbic encephalitis.

Another category of neoplastic syndromes relates to aberrant hormone or peptide production by lung cancer tumor cells. The most common of these is hyponatremia secondary to production of antidiuretic hormone (SIADH). Hypercalcemia can result from tumors that secrete parathyroid hormone; and Cushing syndrome, from tumors that secrete adrenocorticotropic hormone. In general, these hormonal syndromes are more common in SCLC than in NSCLC, because of the neuroendocrine nature of SCLC. However, hypercalcemia can have a range of causes—including both remote effects and direct interactions between tumor and bone—and is much more common in NSCLC than in SCLC.

Table 4

<table>
<thead>
<tr>
<th>Site of Tumor Involvement</th>
<th>Signs or Symptoms</th>
<th>Percentage of Patients Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Cough</td>
<td>50–75</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>30–40</td>
</tr>
<tr>
<td></td>
<td>Chest pain</td>
<td>25–40</td>
</tr>
<tr>
<td></td>
<td>Hemoptysis</td>
<td>15–30</td>
</tr>
<tr>
<td></td>
<td>Pneumonia/pneumonitis</td>
<td>10–25</td>
</tr>
<tr>
<td>Intrathoracic</td>
<td>Hoarseness</td>
<td>&lt; 10</td>
</tr>
<tr>
<td></td>
<td>Dysphagia</td>
<td>&lt; 10</td>
</tr>
<tr>
<td></td>
<td>Facial/arm swelling</td>
<td>&lt; 10</td>
</tr>
<tr>
<td></td>
<td>Shoulder/arm pain</td>
<td>&lt; 10</td>
</tr>
<tr>
<td></td>
<td>Pleural/chest wall pain</td>
<td>&lt; 10</td>
</tr>
<tr>
<td></td>
<td>Pleural/pericardial effusion</td>
<td>&lt; 10</td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic syndromes</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Extrathoracic</td>
<td>Anorexia/weight loss</td>
<td>30–50</td>
</tr>
<tr>
<td></td>
<td>Generalized weakness</td>
<td>20–40</td>
</tr>
<tr>
<td></td>
<td>Bone pain</td>
<td>20–30</td>
</tr>
<tr>
<td></td>
<td>Liver abnormalities</td>
<td>10–20</td>
</tr>
<tr>
<td></td>
<td>Headache/CNS abnormalities</td>
<td>5–15</td>
</tr>
<tr>
<td></td>
<td>Flank pain</td>
<td>&lt; 10</td>
</tr>
<tr>
<td></td>
<td>Other (e.g., subcutaneous nodule, distant lymph nodes)</td>
<td>&lt; 10</td>
</tr>
</tbody>
</table>

Extrathoracic manifestations of lung cancer relate to the extent and site of distant spread. The most common of these are anorexia, weight loss, and fatigue. Bone pain commonly accompanies metastasis to bone, but with the increased use of imaging, asymptomatic bony metastases are commonly found. Liver abnormalities may be detected on clinical examination or on laboratory or imaging studies, but they are generally asymptomatic. The frequency of CNS involvement varies with the extent of other known disease, with a low incidence in patients who have no nodal spread of cancer. However, in patients with other signs of mediastinal or distant involvement, the incidence of occult brain metastases is in the range of 5% to 15%, even in NSCLC.

Occasionally, flank pain will be a presenting feature of adrenal metastases. Although flank pain occurs in fewer than 10% of patients, the adrenal gland is the most frequent site of distant metastatic spread of lung cancer, as detected by CT imaging. Adrenal insufficiency is an unusual but potentially fatal complication of adrenal metastasis from lung cancer, and it is often overlooked because the weight loss and fatigue it causes are common features in lung cancer patients. In selected cases, an adrenal stimulation test may identify patients with limited reserve who may benefit from steroid-replacement therapy.

Patients who have bronchial carcinoid tumors metastatic to liver or other sites may experience the carcinoid syndrome. This dramatic but rare syndrome is characterized by episodic
CT and PET image analysis are currently being developed.

Although PET scanning can detect lesions between 0.5 and 1.0 cm. In addition, techniques that incorporate simultaneous PET and CT—particularly in the adrenal gland and bone—likely represent metastatic disease. The sensitivity and specificity for mediastinal lymph node involvement, as well as to determine resectability. For patients with more peripheral lung masses or solitary pulmonary nodules, the procedure of choice for confirming the presence of cancer and the prospects for definitive surgery is an initial needle biopsy performed under radiologic guidance or resection by video-assisted thoracoscopic surgery (VATS). In patients with solitary pulmonary nodules, biopsy may show that the cause is not cancer but rather a benign tumor or an inflammatory, infectious, or congenital disorder.

For patients who have evidence of bulky intrathoracic disease but who are not likely to be surgical candidates, the preferred method of evaluation is bronchoscopy. During the bronchoscopy, the surgeon may perform brushings, washings, or transbronchial biopsies of the primary lesion or any associated central mediastinal lymph nodes. Patients presenting with pleural effusions can be evaluated by diagnostic thoracentesis. In some cases, VATS can provide both definitive diagnosis and management of pleural effusions.

In addition to the clinical stage, the so-called physiologic stage of the patient is also important for determining which diagnostic strategy is best. In patients who are not candidates for surgery because of constraints such as severe comorbid disease or limited pulmonary reserve, transthoracic needle biopsy or bronchoscopy alone may suffice. Improvements in needle-biopsy techniques have reduced the complications of these procedures, and improvements in cytology have enhanced its diagnostic power. Although these cytologic exams often cannot differentiate subtypes of NSCLC, they are 95% accurate in distinguishing SCLC from NSCLC. Definitive staging is particularly important in patients with NSCLC because of the evolution in treatment strategies for both operable (stage I to IIIA) and inoperable (stage IIIB) cases. Definitive surgical staging with bronchoscopy and mediastinoscopy remains the preferred approach for most patients with apparent early-stage lung cancer who would be candidates for surgery. For patients who have evidence of bulky intrathoracic disease but who are not likely to be surgical candidates, the preferred method of evaluation is bronchoscopy. During the bronchoscopy, the surgeon may perform brushings, washings, or transbronchial biopsies of the primary lesion or any associated central mediastinal lymph nodes. Patients presenting with pleural effusions can be evaluated by diagnostic thoracentesis. In some cases, VATS can provide both definitive diagnosis and management of pleural effusions.

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Table 5: Common Causes of a Solitary Pulmonary Nodule

<table>
<thead>
<tr>
<th>Malignant</th>
<th>Benign</th>
<th>Congenital</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchogenic carcinoma</td>
<td>Noninfectious granuloma</td>
<td>Arteriovenous malformation</td>
<td>Rheumatoid nodule</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Sarcoïdosis</td>
<td>Bronchogenic cyst</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>Wegener granulomatosis</td>
<td></td>
<td>Pulmonary infarction</td>
</tr>
<tr>
<td>Large cell</td>
<td>Infectious granuloma</td>
<td></td>
<td></td>
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<tr>
<td>Metastatic cancers</td>
<td>Tuberculosis</td>
<td></td>
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<tr>
<td></td>
<td>Histoplasmosis</td>
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</tr>
<tr>
<td></td>
<td>Coccidioidomycosis</td>
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<td></td>
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<tr>
<td></td>
<td>Nontuberculac mycobacteria</td>
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<td></td>
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<tr>
<td></td>
<td>Benign tumors</td>
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<tr>
<td></td>
<td>Hamartoma</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Lipoma</td>
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<tr>
<td></td>
<td>Fibroma</td>
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flushing that may be associated with abdominal pain, diarrhea, and wheezing.

CLINICAL STAGING

When the results of the clinical examination and chest x-ray indicate early-stage lung cancer, imaging studies may be limited to a chest CT. However, in patients who have clinical, laboratory, or radiologic signs of regional tumor spread, a search for occult bone and CNS metastases is warranted. For patients with suspected metastatic disease, the standard imaging evaluation should include a chest CT with images through the adrenal glands, a bone scan, and a CT or MRI scan of the brain.

The role of PET scanning in the evaluation of lung cancer patients is currently under study. F-18 fluorodeoxyglucose (FDG) uptake is greater in malignant cells than in normal, benign cells. Several series have suggested that FDG-PET imaging can be very useful in determining whether abnormalities seen on CT—particularly in the adrenal gland and bone—likely represent metastatic disease. The sensitivity and specificity for mediastinal lymph node metastases is still being clarified. PET scans are also useful for evaluation of solitary pulmonary nodules, with a sensitivity of 90% to 95% and specificity of 80% to 100% for the detection of cancer. Because PET imaging can detect unsuspected metastatic disease in 11% to 14% of patients and thus help avoid futile surgery in these cases, Medicare in the United States provides coverage for FDG-PET imaging.

Definitive surgical staging with bronchoscopy and mediastinoscopy by the thoracic surgeon, to determine the type and stage of cancer with respect to mediastinal lymph node involvement, as well as to determine resectability.

For patients with more peripheral lung masses or solitary pulmonary nodules, the procedure of choice for confirming the presence of cancer and the prospects for definitive surgery is an initial needle biopsy performed under radiologic guidance or resection by video-assisted thoracoscopic surgery (VATS). In patients with solitary pulmonary nodules, biopsy may show that the cause is not cancer but rather a benign tumor or an inflammatory, infectious, or congenital disorder [see Table 5].

For patients who have evidence of bulky intrathoracic disease but who are not likely to be surgical candidates, the preferred method of evaluation is bronchoscopy. During the bronchoscopy, the surgeon may perform brushings, washings, or transbronchial biopsies of the primary lesion or any associated central mediastinal lymph nodes. Patients presenting with pleural effusions can be evaluated by diagnostic thoracentesis. In some cases, VATS can provide both definitive diagnosis and management of pleural effusions.

In addition to the clinical stage, the so-called physiologic stage of the patient is also important for determining which diagnostic strategy is best. In patients who are not candidates for surgery because of constraints such as severe comorbid disease or limited pulmonary reserve, transthoracic needle biopsy or bronchoscopy alone may suffice.

Improvements in needle-biopsy techniques have reduced the complications of these procedures, and improvements in cytology have enhanced its diagnostic power. Although these cytologic exams often cannot differentiate subtypes of NSCLC, they are 95% accurate in distinguishing SCLC from NSCLC. Definitive staging is particularly important in patients with NSCLC because of the evolution in treatment strategies for both operable (stage I to IIIA) and inoperable (stage IIIB) cases. Definitive surgical staging with bronchoscopy and mediastinoscopy remains the preferred approach for most patients with apparent early-stage lung cancer who would be candidates for surgery. For the surgical population, the primary diagnostic procedure in most patients should be a bronchoscopy and mediastinoscopy by the thoracic surgeon, to determine the type and stage of cancer with respect to mediastinal lymph node involvement, as well as to determine resectability.

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Surgical Staging

Cancer stage is by far the most important prognostic factor in lung cancer. Histology (i.e., SCLC versus NSCLC) may influence choice of treatment options. Survival rates for patients with the same stage of lung cancer are quite similar, regardless of whether they have SCLC or NSCLC. Other characteristics that can affect outcome are patient characteristics such as performance status, recent weight loss, and significant comorbid conditions. In addition, studies suggest that stage for stage, outcome with both SCLC and NSCLC is better for women than men.
for men. As with other cancers, advanced age may have an adverse effect on outcome, but age per se seems to be less important than the comorbid conditions that are more common in the elderly.

Staging of lung cancer is by the TNM (tumor, node, metastases) classification [see Figure 1]. It is based on the size, location, and regional extension of the primary tumor; on the location of regional malignant lymph nodes that drain the region; and on the absence or presence of distant metastases. T1 and T2 tumors are operable tumors differentiated predominantly by size. T1 tumors are 3 cm or less in their greatest dimension, surrounded by lung or visceral pleura, and without bronchoscopic evidence of invasion more proximal than the lobar bronchus. T2 tumors have any one of the following characteristics: size greater than 3 cm, main bronchus involvement, location 2 cm or more distal to the carina, invasion of the visceral pleura, or association with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.

T3 tumors are tumors of any size that directly invade the chest wall, diaphragm, mediastinal pleura, parietal pleura, or pericardium; are located in the main bronchus less than 2 cm distal to the carina but do not involve the carina; or are associated with atelectasis or obstructive pneumonitis of the entire lung. T3 tumors can be considered marginally operable but require a more extensive operation that may involve removal of the chest wall or pericardium or, for more proximal tumors, a sleeve resection.

T4 tumors are grossly inoperable because they invade the mediastinum, heart, great vessels, trachea, esophagus, a vertebral body, or the carina. Tumors are also classified as T4 if they are associated with a malignant pleural or pericardial effusion or with satellite tumor nodules within the same lobe as the primary tumor.

Lymph node status is determined as N0 (no lymph node involvement), N1 (metastases to the lymph nodes within the confines of the lung), and N2 or N3 (extrapulmonary metastases). N2 represents involvement of ipsilateral mediastinal lymph nodes, whereas N3 represents involvement of contralateral lymph nodes or more distant nodes, including hilar or supraclavicular nodes.

N1 and N2 nodes are further denoted by specific location (station) [see Figure 2]. Other than level-10 hilar nodes, which may be enlarged on CT, N1 nodal involvement is generally not suspected until it is discovered at the time of surgery. Although N2 and N3 nodes can be suspiciously enlarged on CT, 40% of nodes greater than 2 cm are enlarged because of inflammation, and 10% of normal-sized nodes contain malignancy. Thus, mediastinoscopy is essential for providing pathologic definition of nodal involvement so that treatment options can be finalized.

**International System for Staging Lung Cancer**

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Clinical Staging</th>
<th>Surgical Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median Survival (Months)</td>
<td>Five-Year Survival (%)</td>
</tr>
<tr>
<td>I</td>
<td>T1 N0 M0</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>T2 N0 M0</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>II</td>
<td>T1 N1 M0</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>T2 N1 M0</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>T3 N0 M0</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>IIA</td>
<td>T1–3 N2 M0</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>T3 N1 M0</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>IIIB</td>
<td>N3 (any T) M0</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>T4 (any N) M0</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>IV</td>
<td>M1 (any T or N)</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

**Figure 1** An international TNM four-stage system is used in the clinical and surgical evaluation of lung cancer. Definitions of TNM categories are simplified.

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Surgical resection. Stage IV disease is treated with chemotherapy, palliative radiation, and supportive care [see Table 6].

**Surgery** Before a patient with stage I or II lung cancer undergoes surgery, the physician must undertake a determination of operability, which includes assessment of the medical risk of thoracotomy, as well as the risk of removal of the requisite pulmonary parenchyma. Cardiopulmonary disease, which is usually a consequence of tobacco use, is the major cause of postoperative morbidity and mortality in patients with stage I or II disease and, consequently, is the most significant medical factor in determining operability.

Pulmonary function testing and arterial blood gas analysis are used to determine the feasibility of pulmonary resection. Postoperative pulmonary function is estimated on the basis of the patient’s preoperative function and the projected resection of pulmonary parenchyma. Resection is generally contraindicated when the predicted postoperative forced expiratory volume at 1 second (FEV1) and forced vital capacity are less than 30% of predicted values. In patients with marginal results on preoperative pulmonary function studies, ventilation-perfusion scanning may be required to determine resectability. Postoperative FEV1 may be predicted after assessing the contribution to overall pulmonary function made by each lung and by specific pulmonary segments.

In patients who have a history of angina or whose preoperative electrocardiogram shows ischemia or arrhythmia, radionuclide evaluation of myocardial perfusion or function is indicated. Normal results with these studies reliably exclude significant coronary artery disease; patients with positive results should undergo coronary arteriography. Recent myocardial infarction, uncontrolled heart failure, or uncontrollable arrhythmia precludes thoracotomy for pulmonary resection.

The final determination of resectability is made at thoracotomy. Contraindications to pulmonary resection at the time of thoracotomy include pleural metastases, extensive mediastinal lymph node involvement (N3 disease), or direct extension of the tumor to critical structures (T4 disease). In addition, pulmonary resection is aborted if the extent of resection required would leave the patient with inadequate pulmonary reserve, as determined by preoperative pulmonary function studies.

Four main oncologic principles guide resection for lung cancer: (1) removal of the entire tumor with an anatomically complete portion of lung (lobectomy or pneumonectomy), to ensure removal of all intraparenchymal lymphatic drainage; (2) en bloc resection of adjacent structures, if technically possible, including the chest wall, diaphragm, and pericardium, without transgressing the tumor; (3) assessment of questionable resection margins by frozen-section analysis to optimize the potential for complete resection; and (4) sampling or complete dissection of all accessible mediastinal lymph nodes to improve staging.

In patients with small (< 3 cm) peripheral nodules and no mediastinal lymphadenopathy by CT criteria (i.e., no lymph nodes > 1 cm in diameter), the procedure of choice is lobectomy and mediastinal lymph node dissection. Less extensive resection, such as wedge resection or segmentectomy, has been shown to be associated with significantly greater risk of local recurrence and cancer-specific death. In patients with T2 or T3 tumors or with mediastinal adenopathy on chest CT, cervical mediastinoscopy should be performed before exploration for pulmonary resection.

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**N2 Nodes**
- **Superior Mediastinal Nodes**
  1. Highest mediastinal
  2. Upper paratracheal (2r, 2l)
  3. Pretracheal and retrotracheal (3a, 3p)
  4. Lower paratracheal (including azygos nodes) (4r, 4l)
- **Anterior Mediastinal Aortic Nodes**
  5. Subaortic (aortopulmonary window)
  6. Para-aortic (ascending aorta or phrenic)
- **Inferior Mediastinal Nodes**
  7. Subcarinal
  8. Paraesophageal (below carina)
  9. Pulmonary ligament

**N1 Nodes**
- 10. Hilal, peribronchial (10r, 10l)
- 11. Interlobar
- 12. Lobar
- 13. Segmental

Figure 2 Draining lymph node sites (nodal stations) in the chest that can be involved by lung cancer are noted. Clinical staging of cancer of the mediastinum is carried out by CT scanning; surgical staging is performed by mediastinoscopy, mediastinotomy, thoracoscopy, or, sometimes, thoracotomy. A lymph node larger than 1 cm on CT scan is considered abnormal, but cancer involvement must be proved by biopsy. The upper paratracheal nodal stations are designated as 2r (right) and 2l (left); the lower paratracheal nodal stations are designated as 4r and 4l. Stations 8r, 8l, 9r, and 9l are contiguous with the mediastinum, but positive nodes in these sites are not common. Station 10 nodes, when confirmed as positive by mediastinoscopy, are classified as tracheobronchial angle nodes (10r and 10l) and signify mediastinal involvement. In the drawing, r is right; l, left; a, anterior; and p, posterior.
**Table 6  Therapy and Prognosis for Non–Small Cell Lung Cancer**

<table>
<thead>
<tr>
<th>Stage (%)</th>
<th>Surgery</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>Five-Year Survival (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (10)</td>
<td>T1N0 (coin lesion): lobectomy (poor pulmonary function, segmental resection) T2N0: lobectomy</td>
<td>None</td>
<td>Research</td>
<td>T1N0: 45–80 T2N0: 35–65</td>
</tr>
<tr>
<td>II (10)</td>
<td>T1N1 or T2N1: lobectomy; pneumonectomy usually required when hilar nodes are grossly involved</td>
<td>May reduce local recurrence but does not affect survival</td>
<td>Research</td>
<td>T1N1: 20–52 T2N1: 20–40</td>
</tr>
<tr>
<td>IIIA (20)</td>
<td>T3 (potentially resectable): radical resection of chest wall lesions; used after RT of Pancoast tumors</td>
<td>Used after surgery; may reduce local recurrence; used preoperatively for Pancoast tumors</td>
<td>Combined with RT and surgery†</td>
<td>T3 (chest wall): 30–55 T3 (Pancoast tumors): 20–40</td>
</tr>
<tr>
<td></td>
<td>N2 (potentially resectable): radical resection of early intranodal disease; not indicated for extranodal or fixed, matted nodes</td>
<td>Used after surgery; may reduce local recurrence; used preoperatively in some patients with early intranodal disease</td>
<td>Combined with RT and surgery†</td>
<td>N2: 10–50</td>
</tr>
<tr>
<td>IIIB (20)</td>
<td>T4, N3, or both (unresectable)</td>
<td>Standard treatment for palliation of pain, hemoptysis, atelectasis, hoarseness, SVC syndrome</td>
<td>Combined with RT†</td>
<td>Median, 30 wk</td>
</tr>
<tr>
<td>IV (40)</td>
<td>Used rarely for isolated metastases</td>
<td>Useful for palliation of pain or other local problems‡</td>
<td>Response rates of 30%–40%; prolongation of survival</td>
<td>Median, 13–18 wk</td>
</tr>
</tbody>
</table>

*Survival is higher in patients staged by surgery than in patients staged clinically.
†Randomized trials show prolonged survival when chemotherapy is added to radiotherapy, surgery, or both.
RT—radiotherapy  SVC—superior vena cava

**Chemotherapy**  The benefit of chemotherapy for patients with stage I or II NSCLC is controversial. In clinical practice, treatment recommendations for such cases do not routinely include chemotherapy. Nevertheless, in reviewing treatment options with these patients, it is important to discuss the evolving data from clinical trials of chemotherapy.

A meta-analysis found that adjuvant treatment with alkylating agents in this setting resulted in a 5% decrease in survival, compared with surgery alone (P = 0.005).28 Cisplatin-based regimens were associated with a 5% improvement in 5-year survival, but this effect did not reach statistical significance (P = 0.08). On the other hand, the clinical trials included in this meta-analysis were performed between 1965 and 1991, and both chemotherapy and supportive care have improved significantly since that time. Therefore, randomized trials of adjuvant chemotherapy versus supportive care alone in stage I and II NSCLC are currently under way. An intergroup trial sponsored by the Cancer and Leukemia Group B (CALGB) is comparing carboplatin and paclitaxel with supportive care in patients with stage IB disease. An intergroup trial sponsored by the National Cancer Institute of Canada (NCI-C) has compared cisplatin and vinorelbine with supportive care alone in patients with stage IB, IIA, and IIB disease; results of this trial are pending. The International Adjuvant Lung Cancer Trial (IALT), in which patients with stages I through IIIA resected NSCLC were randomized to cisplatin-based chemotherapy versus observation, found a 4% absolute improvement in survival with chemotherapy.29 It is hoped that ongoing studies will confirm this benefit. In the meantime, the option of adjuvant chemotherapy should be discussed with patients after definitive surgical resection.

Another treatment strategy for stage I and II disease is the use of induction (preoperative) chemotherapy. Because of encouraging results from a phase II trial in patients with completely resected stage IB, IIA, or IIB NSCLC,27 the Southwest Oncology Group is leading a prospective, randomized trial of induction chemotherapy with three cycles of paclitaxel and carboplatin followed by surgery, compared with surgery alone. Other randomized clinical trials of both induction and adjuvant chemotherapy are currently being conducted for patients with stage IB, IIA, or IIB NSCLC. Eligible patients should be encouraged to enroll in these clinical trials, so that oncologists can determine whether chemotherapy is beneficial in this setting.

**Radiation therapy**  Surgery is the treatment of choice for stage I NSCLC, but patients with medical contraindications to surgery can be treated with radiation therapy alone. Retrospective studies of such cases have shown 5-year survival rates ranging from 10% to 30%.31 Better local control was found in patients with smaller tumors (<3 cm) and in those treated with higher doses of radiation (>65 Gy). Consequently, recommended radiation doses range from 65 to 70 Gy; the total dose is typically given in 2-Gy fractions. Omission of nodal areas from the treatment fields has been found to reduce morbidity and has resulted in a nodal failure rate of only 4% to 9%. Therefore, in most cases, the primary tumor is treated with a standard margin of 1.5 to 2 cm. It is important to take into account any movement of the tumor from respiration, and this is best done under fluoroscopy. Unfortunately, most patients treated with radiation therapy succumb to recurrent lung cancer, and at least 60% experience local failure.

**Stage III–Operable Patients**

Patients with stage IIIA disease who appear to be candidates for surgical resection but in whom mediastinoscopy shows ipsilateral mediastinal lymph node involvement are evaluated for induction therapy (chemotherapy alone or chemotherapy and radiation therapy). Induction therapy with systemic chemotherapy has the potential to treat occult metastatic disease, which is common in patients with stage IIIA disease, even when organ-specific scans are negative. Three randomized, prospective trials that compared induction chemotherapy before surgery with surgery alone in patients with operable stage IIIA NSCLC were small in sample size, but all demonstrated...
benefit from induction chemotherapy, with at least a doubling in 3-year survival.\textsuperscript{3,36}

The addition of radiation therapy to induction therapy may improve local control in conjunction with surgical resection and may also decrease distant metastatic spread during therapy.\textsuperscript{27} A prospective study has suggested that chemoradiation before surgery is beneficial in patients with stage IIIA NSCLC.\textsuperscript{37} A randomized intergroup comparison of chemoradiation alone with chemoradiation followed by surgery has been conducted;\textsuperscript{38} preliminary results suggest longer disease-free survival in the surgical arm but higher initial mortality, which complicates the analysis. Important questions remain about induction therapy, including the following: What are the optimum agents for chemotherapy? Should chemotherapy be used alone or in combination with radiation treatment? Does radiation therapy or surgery provide better local control? Should all three modalities of therapy be utilized? To answer these questions, enrollment of patients with stage IIIA NSCLC in clinical trials is critical.

After induction therapy, staging studies are repeated. Repeat mediastinoscopy is useful for reassessing the mediastinal lymph nodes, although this is more difficult than the primary procedure. Alternatively, the ipsilateral mediastinal lymph nodes may be assessed at exploratory thoracotomy. Pulmonary resection is not recommended if the involved lymph nodes have not responded to induction therapy or if there is evidence of disease progression, because the prognosis for extended survival is dismal in such patients.

Patients with involvement of the chest wall, diaphragm, or pericardium may be surgical candidates but only if the tumor can be completely resected. Incomplete resection of NSCLC provides no curative or palliative benefit.

**Postoperative radiation therapy** The treatment of patients found to be in stage II or III after resection is somewhat controversial. These patients are at a high risk for local and regional recurrences after surgery alone; however, they also have a very high likelihood of distant disease.\textsuperscript{39} In a study of patients with stage II or III disease who had undergone a complete resection and were randomized to receive radiation therapy or no further treatment, the patients who received radiation therapy were found to have a significantly lower rate of local failure (3\% versus 21\% for patients who did not receive postoperative radiation).\textsuperscript{40} However, there was no evidence of a survival benefit for the patients receiving postoperative radiation. Two caveats regarding this study are that it included only patients with squamous cell carcinoma and that most of the patients in the study had N1 nodal disease, precluding a valid subgroup analysis of the relationship between nodal status and survival.

A meta-analysis of nine published and unpublished randomized trials of postoperative radiation therapy—which included 2,128 patients with stage I, II, or III lung cancer treated from 1966 to 1994, largely with cobalt radiation techniques—found that overall, mortality was approximately 7\% higher for patients who received postoperative radiation therapy.\textsuperscript{41} On subgroup analysis, the adverse effect was most apparent in patients with N0 and N1 disease; survival of patients with N2 disease was the same in the two groups. The results of this study indicate that radiation therapy is detrimental to patients with early stage (I and II) lung cancer that has been completely resected; the question of whether postoperative radiation therapy benefits patients with N2 disease remains unanswered. This meta-analysis has been critiqued for its inclusion of patients treated with a wide variety of radiation doses and techniques, many of them now outdated, which may have skewed the data from showing a survival benefit with postoperative radiation therapy.

In summary, the use of postoperative radiation therapy in patients with stage II or III NSCLC yields a significant increase in local control, which may be particularly important in patients with positive surgical margins. However, because of the high frequency of metastatic disease in these patients, postoperative radiation therapy appears to provide no survival benefit. Patients offered postoperative radiation therapy should clearly understand that its goal is improved local control. Meanwhile, the possible role of combination radiation therapy and chemotherapy as an adjuvant to surgery is the subject of ongoing clinical trials.

**Adjuvant chemotherapy** As in stage I and II NSCLC, the role of adjuvant chemotherapy in resected stage III disease is not well supported by the results of randomized clinical trials, although the IALT results (see above) may provide such support.\textsuperscript{23,24} On the other hand, a trial comparing adjuvant cisplatin and etoposide plus radiation with radiation alone in resected stage II and IIIA disease found no survival advantage for the group receiving adjuvant chemotherapy.\textsuperscript{37}

**Stage III B disease** A small subgroup of patients with stage IIIB NSCLC may be candidates for surgical resection. In general, T4 tumors are considered unresectable; however, there are two exceptions to this generalization. First, patients with a single satellite nodule within the same pulmonary lobe as the primary tumor are offered resection if the disease is apparently resectable by lobectomy and the results of both mediastinoscopy and organ-specific staging studies are negative. Second, in rare cases of very limited involvement of the vena cava, main pulmonary artery, or aorta by the primary tumor, en bloc resection and vascular reconstruction may be offered to selected patients; long-term survival in such cases ranges from 10\% to 20\%.

Some patients with contralateral mediastinal lymph node involvement (N3) are treated with induction therapy followed by surgical resection. However, the standard of care for these cases is chemotherapy and radiation therapy.

**Stage III C–Inoperable Patients**

**Radiation therapy** Without treatment, most patients with stage IIIB NSCLC will succumb to their disease within 1 year. Radiation therapy does result in an improved outcome, with up to 20\% of patients surviving 2 years and up to 5\% surviving 5 years, but there is a high likelihood of local recurrence, ranging from 25\% to 50\% in some studies.\textsuperscript{42} Distant recurrence is also common. An analysis of several studies reveals that patients with weight loss greater than 5\%, performance status of less than 10\%, to 20\%.

In an attempt to increase the efficacy of radiation therapy, fractionation schemes have been tested, including treatments given two or three times daily. A randomized trial, performed in Europe, is comparing the effectiveness of continuous hyperfractionated accelerated radiation therapy (HART), given three times a day, with conventional radiation treatment. Results of this protocol reveals a statistically significant survival benefit of 9\% at 3 years for patients treated in the continuous HART arm.\textsuperscript{43} There is also a significant increase in local control, with 7\% fewer failures at 3 years in the CHART arm. These benefits
are most prominent in patients with squamous cell carcinoma. The results of several trials indicate that the addition of chemotherapy to radiation therapy leads to an improved survival. A multigroup, randomized study found that patients with unresectable cancer who received chemotherapy and radiation therapy in combination had a statistically improved overall survival compared with those who received only radiation either once or twice daily. For chemoradiation, standard radiation, and hyperfractionation, 3-year survival rates were 17%, 11%, and 9%, respectively, and median survival rates were 13.2 months, 11.4 months, and 12 months. In a comparison of HART with once-daily radiation therapy after induction chemotherapy, the 2-year survival was 40% for the HART arm, compared with 33% for the standard radiation therapy group; toxicities, particularly esophagitis, were also increased.

Clinical trials are currently evaluating the use of three-dimensional treatment planning systems to increase the dose of radiation therapy delivered to the primary tumor. Preliminary results show that dose escalation is feasible and does not lead to increased toxicity and that outcomes are comparable to or better than historical controls.

Chemoradiotherapy. The standard treatment for inoperable stage III NSCLC is a combination of chemotherapy and radiation therapy. The chemotherapy should be a platinum-based combination regimen; the radiation should be given at conventional doses, generally 66 Gy. The use of chemoradiotherapy in these cases is supported by level I-A evidence. For unresectable stage III disease, chemotherapy plus radiation therapy is appropriate for patients with a good performance status (an Eastern Cooperative Oncology Group [ECOG] score of 0 to 1 or, possibly, 2).

The optimal strategy for coordinating chemotherapy with radiation therapy is evolving. Possibilities include chemotherapy before, during, or after radiation treatment. Promising results have been reported from a recent randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and radiation treatments. Median survival in this trial was approximately 18 months, which compares favorably with the 13 to 14 months reported in previous trials. This trial utilized cisplatin-based chemotherapy along with vinorelbine, paclitaxel, or gemcitabine, which are all agents with documented benefit in stage IV NSCLC (see below). A randomized phase III trial is needed to determine whether the apparent improvement in median survival stems from the sequencing of chemotherapy and radiation treatment, the use of the new agents, or both.

Concurrent administration of chemotherapy and radiation therapy has also been found to be beneficial. In a randomized trial of chemotherapy with mitomycin, vinblastine, and cisplatin given either before or along with thoracic radiation, the 2-year survival rates with sequential and concurrent treatment were 27% and 35%, respectively. Subsequent trials point to a survival benefit from concurrent chemotherapy and radiation treatment compared with sequential therapy, as well as an increase in toxicity, particularly esophagitis and pneumonitis.

Treatment Strategies in Stage III Disease

The optimal approach to management of stage III NSCLC remains undefined. At present, it is clear that chemotherapy, when used in combination with surgery or radiation treatment, can improve patient survival in both operable and inoperable disease. In patients with inoperable stage III NSCLC, long-term survival is better with platinum-based combination chemotherapy and radiation therapy than with either modality alone. Every attempt should be made to enroll patients in clinical trials to further clarify the optimal strategy.

Because the benefits of combination therapy have been largely demonstrated in only younger patients with higher performance status, physicians should use caution in applying these approaches to elderly patients or those with poor performance status. In the absence of data from elderly and poor-performance patient populations, low-dose chemotherapy and concurrent radiation can be considered. An alternative strategy that may result in less toxicity from esophagitis would be the use of combination chemotherapy followed by radiation treatment. This strategy allows individualization of treatment based on the patient's tolerance of induction chemotherapy. However, older patients with good performance status should not be denied the potential benefit of combined-modality therapy. In this setting, it would appear that the most appropriate choice for chemotherapy is a cisplatin-based or carboplatin-based regimen with one of the newer agents used in the management of stage IV disease.

Stage IV Disease

For patients with stage IV NSCLC, chemotherapy plus supportive care improves both survival and quality of life, compared with supportive care alone. Because 5-year survival in stage IV disease is 1% or less, discussions of outcomes in the literature often describe median survival, which can be measured in months. For a physician who is speaking with an individual patient, however, it is more meaningful to discuss the probability of living 1 or 2 years. A statement based on median survival in a large population of patients, such as “You have 6 months to live,” does not help that patient understand the range of survival that occurs even in stage IV NSCLC. It gives the patient a better idea of the probabilities if the physician instead specifies the percentage of patients with advanced NSCLC who are alive at 1 year after diagnosis. According to a National Cancer Center database, untreated patients with stage IV disease had a 1-year survival of 9% to 11%, whereas patients receiving chemotherapy had a 1-year survival of 20% to 25%. These data are robust, because the population includes more than 700,000 patients with lung cancer, diagnosed between 1985 and 1995, and includes all stages and treatment categories for lung cancer. However, because this represents a database rather than a randomized comparison of groups, the survival data do not reflect the clinical factors that would guide the decision to forgo treatment in some patients. Such factors might include low performance status, comorbid disease, and advanced age, all of which may adversely affect survival.

Which chemotherapeutic agents are best for stage IV disease? A meta-analysis of trials of supportive care alone versus supportive care with chemotherapy for advanced-stage disease demonstrated a 6% decrease in 1-year survival with the use of alkylating agents alone and a 4% improvement in 1-year survival with the use of vinca alkaloids or etoposide. Neither of these results reached statistical significance, however. By contrast, randomized trials of cisplatin-based combination chemotherapy versus supportive care showed an absolute increase of 10% in 1-year survival (P < 0.0001). These studies generally restricted eligibility to patients with higher performance status and enrolled a disproportionate number of younger patients.

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with less comorbid disease than commonly seen in the community. Nevertheless, it is of interest that the magnitude of benefit in this trial is similar to that documented in the National Cancer Center database.

On the basis of this meta-analysis and additional data, an expert panel for the American Society of Clinical Oncology has concluded that in stage IV disease, platinum-based combination chemotherapy prolongs survival and is most appropriate for patients with good performance status, including an ECOG score of 0 or 1 or, possibly, 2. Although randomized trials of platinum-based chemotherapy have almost all involved cisplatin, carboplatin has a more favorable safety profile and lower toxicity. Furthermore, randomized trials comparing cisplatin and carboplatin with etoposide in NSCLC have shown comparable efficacy. Although a European study has suggested a small survival benefit for cisplatin therapy, compared with carboplatin-based therapy, in the United States carboplatin continues to be the most widely used agent in the palliative management of patients with advanced lung cancer.

The 1990s brought the advent of newer agents in the treatment of NSCLC, including vinorelbine, paclitaxel, and gemcitabine, all three of which have received Food and Drug Administration approval for use (in combination with cisplatin) in the treatment of advanced disease. The approval of these newer agents was based on the results of randomized clinical trials that compared them, in combination with cisplatin, with either cisplatin alone or cisplatin in combination with older agents. In these trials, vinorelbine and cisplatin were associated with 1-year survival of 40% and 36%. These differences were statistically superior to vinorelbine alone, cisplatin and vindesine, or cisplatin alone; 1-year survival with cisplatin as a single agent was only 20%. Similarly, the combination of cisplatin and gemcitabine provided a 1-year survival of 39%, compared with 26% for cisplatin alone. In the study that led to the approval of paclitaxel for NSCLC, 1-year survival was 32% in the control groups that received cisplatin and etoposide, compared with 37% to 40% for patients receiving paclitaxel. Survival with paclitaxel depended on the dose used; patients receiving a higher dose required supportive therapy with granulocyte colony-stimulating factor. A randomized trial has demonstrated a better survival rate with cisplatin and docetaxel than with cisplatin and vinorelbine. In this study, survival for a carboplatin and docetaxel group was similar to that for a cisplatin and vinorelbine group, but the former had a more favorable side-effect profile.

Overall, comparative trials have suggested that several different combination regimens may be equally effective in advanced disease, although toxicities vary. The optimal regimen should comprise two chemotherapy drugs, including a platinum agent and one of the newer chemotherapeutic agents. Of the newer agents, paclitaxel, vinorelbine, gemcitabine, or docetaxel would all be reasonable choices.

**Palliative radiation therapy** Radiation therapy is used for palliation of symptoms caused by metastatic NSCLC. These include obstructive symptoms, bone pain, and neurologic compromise from spinal cord compression or brain metastasis. In randomized trials, palliative radiation has been shown to produce some pain relief in 75% to 90% of patients and complete pain relief in at least 50%. Several fractionation schemes seem equally effective, but there is some evidence that prolonged treatment provides longer-lasting pain relief.

Superior vena cava syndrome responds to radiation treatment in approximately 50% of cases, but a substantial number of patients do not respond. Approximately 75% of patients have resolution of hemoptysis, and 50% will have cessation of cough after palliative radiation therapy. About 50% to 75% of patients with brain metastasis have a symptomatic response.

Spinal cord compression can also be treated with radiation therapy. Of patients who have only pain, 75% remain ambulatory, but only 30% to 35% of patients with muscle weakness improve.

**Quality-of-life considerations** Studies of chemotherapy for advanced NSCLC have largely focused on length of survival. In view of the modest benefits of treatment, however, the impact of chemotherapy on quality of life is a critical consideration. Although earlier trials often did not assess quality of life, virtually all of the current randomized clinical trials have quality-of-life measures as a significant component. These studies suggest that combination chemotherapy often results in the improvement of symptoms such as cough, dyspnea, chest pain, and hemoptysis, often even when there is minimal evidence of tumor response. In general, these studies have shown that chemotherapy produces symptomatic improvement in more than 50% of patients. This figure is significantly higher than the objective response rate, which generally varies between 20% and 40% for combination regimens. The seeming discrepancy between these figures likely reflects the fact that even minor responses, or simply stabilizing the growth of the cancer, may bring at least short-term improvement in symptoms. With the improved toxicity profiles of the newer agents, improvements in quality-of-life differences may be easier to demonstrate.

**The elderly and other special populations** Now that the benefits of chemotherapy have been established in younger patients with good performance status, researchers are evaluating its benefits in older patients and those with lower performance status. The first randomized trial of chemotherapy versus supportive care in the elderly (≥70 years), the Elderly Lung Cancer Vinorelbine Italian Study group (ELVIS) trial, assessed the effects of vinorelbine, as compared with supportive care alone, on both quality of life and survival of patients with advanced NSCLC. In this study, 1-year survival was 32% for the vinorelbine-treated group, compared with 14% for best supportive care alone. On the basis of this trial, the FDA has approved vinorelbine for single-agent use in NSCLC. Because of the superior outcome with the combination of cisplatin and vinorelbine, single-agent treatment has not been widely used in high-performance-status populations. However, the ELVIS trial suggests that single-agent chemotherapy is beneficial in elderly patients, many of whom may not be eligible for combination chemotherapy. However, for the fit elderly, a subset analysis of a randomized trial of carboplatin and paclitaxel compared with paclitaxel alone demonstrated a survival advantage for the combination regimen in patients older than 70 years; this result was comparable to that in younger patients.

**Relapse of disease** For patients in whom initial chemotherapy has failed, two randomized trials have now demonstrated the benefit of salvage chemotherapy. A trial comparing docetaxel with either ifosfamide or vinorelbine showed a survival advantage for patients receiving docetaxel, particularly at the dose of 75 mg/m². A trial comparing docetaxel with best
supportive care showed that docetaxel produced improvement in both survival and quality of life.66 On the basis of these trials, the FDA has approved docetaxel for salvage chemotherapy in this setting.

Gefinitib, a tyrosine kinase inhibitor, has received FDA approval as monotherapy for patients with locally advanced or metastatic NSCLC that has failed to respond to both platinum-based therapy and docetaxel. Approval was granted under accelerated-approval regulations; although no controlled trials have shown an improvement in symptoms or survival with the agent, gefinitib has produced objective responses and symptomatic improvement in this heavily pretreated population. Toxocities include a skin rash, which is common, and interstitial lung disease, which is a rare but potentially fatal complication of gefinitib.67 There is reason to hope that this agent, which targets epidermal growth factor receptors, will usher in an era of more precise therapy for lung cancer.

SMALL CELL CARCINOMA OF THE LUNG

Whereas the management of NSCLC changed substantially during the past decade, the management of SCLC has evolved more slowly. Important refinements in therapy have occurred, however. Currently, new directions in therapy are being developed, on the basis of better understanding of the biology of this disease.

As in NSCLC, the outcome in patients with SCLC is determined largely by stage at presentation [see Table 7]. The difference between the two diseases lies in the stage distribution. In NSCLC, 25% to 30% of patients present with stage I or II disease; in SCLC, that figure is well below 5%. Several factors may contribute to this difference, but a principal one appears to be that small cell carcinoma arises from neuroendocrine cells, which normally reside below the bronchial epithelium in the mucosa and submucosa. This region is much more heavily supplied with lymphatics, which would facilitate the earlier spread of these cancer cells to regional and distant lymph nodes, as well as hematogenous spread. In addition, in the 1960s it was learned that SCLC was more sensitive to chemotherapy than NSCLC. Because of the advanced stage at presentation and this chemosensitivity, SCLC fell largely into the domain of medical oncologists and radiation therapists rather than that of thoracic surgeons.

### Table 7 Therapy and Prognosis for Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Surgery</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>Median Survival (months)</th>
<th>Two-Year Disease-Free Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited I</td>
<td>T1N0 T2N0</td>
<td>Lobectomy</td>
<td>None</td>
<td>T1N0 T2N0 Research</td>
<td>&gt; 48</td>
</tr>
<tr>
<td>Limited II</td>
<td>T1N1 T2N1</td>
<td>Lobectomy; pneumonectomy rarely used</td>
<td>Rarely used</td>
<td>Several regimens available</td>
<td>&gt; 14</td>
</tr>
<tr>
<td>Limited IIIA, IIIB</td>
<td>T3, N2, or both: research T4 or N3: not indicated</td>
<td>Decreases local recurrences; used prophylactically for CNS</td>
<td>Several regimens available; high-dose programs with autologous marrow rescue are being researched</td>
<td>Complete response: 50%–80%</td>
<td>&gt; 12</td>
</tr>
<tr>
<td>Extensive IV</td>
<td>Not indicated</td>
<td>Useful for palliation of pain, atelectasis, SVC syndrome</td>
<td>Several regimens available</td>
<td>Complete response: 30%–50%</td>
<td>&gt; 8</td>
</tr>
</tbody>
</table>

SVC = superior vena cava

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**Early-Stage Disease**

Early-stage solitary pulmonary nodules have been referred to as peripheral small cell carcinoma. In patients without mediastinal nodal involvement, this disease is associated with a 5-year survival in the 30% to 60% range, depending on the series. Long-term follow-up of these patients suggests a high tendency for distant relapse, both systemically and in the CNS. Surgery should be the therapy of choice for patients with no evidence of distant disease or of mediastinal nodal involvement. Because the number of patients presenting at this stage is small, no definitive randomized trials of adjuvant therapy have been performed and there is no consensus on adjuvant therapy. In the United States, it has been standard to recommend adjuvant chemotherapy, either alone or in combination with prophylactic cranial radiation or chest radiation.

Surgery with mediastinal lymph node dissection, followed by four cycles of adjuvant platinum and etoposide, was the subject of a phase II trial in patients with stage I to IIIA SCLC conducted by the Japanese Collaborative Oncology Group.68 In patients with stage I disease, who constituted the bulk of the study population, 5-year survival was 69%. In the limited number of patients with stage II or IIIA disease, survival was 38% to 40%. No prophylactic cranial irradiation was done, and the rate of CNS relapse was 17%, even in the stage I population, which suggests that prophylactic cranial radiation should have a role in this population.

**Limited-Stage or Extensive-Stage Disease**

At least 95% of patients with SCLC present with either limited-stage or extensive-stage disease. Limited-stage SCLC corresponds to stage IIIA or IIIB NSCLC without malignant pleural effusion but, generally, with supravacular lymph node involvement. Simplistically, limited-stage SCLC patients include those in whom the primary tumor and involved nodes, including supravacular nodes, can be encompassed in a standard radiation port. By contrast, patients with extensive disease have a malignant pleural effusion, contralateral lung involvement, or metastases at more distant sites. This staging separation has been important for selecting treatment and determining prognosis. Patients with limited-stage disease have a 5-year survival of 15% to 20% when treated with the combination of...
chemotherapy and radiation. In contrast, patients with extensive-stage disease generally have a 5-year survival of 1% to 2% and have been treated primarily with chemotherapy, plus adjuvant radiation as needed. The distinction between limited- and extensive-stage disease has largely been based on clinical examination, as well as on the standard imaging studies of chest CT through the adrenal glands, bone scan, and brain CT or MRI. Of patients with no evidence of distant metastases on these studies, an additional 5% will be found to have distant disease by bone marrow evaluation. Currently, approximately 25% to 30% of patients with SCLC present with limited-stage disease, and the remainder present with extensive-stage disease; however, with the development of more sophisticated imaging techniques and the increased use of PET imaging, some degree of stage migration is likely to occur.

**Limited-stage disease**  Chemotherapy has been the mainstay of treatment for limited-stage disease for the past 30 years. For at least the past 10 years, the standard treatment has been based on etoposide, either as a single agent or combined with either cisplatin or carboplatin, generally for four to six cycles. Most of the advances in the understanding of treatment of limited-stage SCLC have come from trials evaluating the role of radiation therapy. These trials have shown that cure in limited-stage SCLC is associated with the use of full-dose combination chemotherapy, along with thoracic and cranial radiation therapy. Thoracic radiation appears to be more beneficial if it is done concurrently with chemotherapy, rather than sequentially. Secondly, starting radiation therapy during the first few cycles of chemotherapy appears to provide a survival advantage over beginning radiation therapy at the end of chemotherapy. The explanation for this is that drug resistance may evolve rapidly in small cell carcinoma, so in some patients, delaying thoracic radiation even for a few months may result in escape of drug-resistant cells from the lung and mediastinum to distant sites. Early intervention with radiation may result in the destruction of these cells and an increase in the rate of cure. However, as with NSCLC, the benefit of concurrent chemotherapy and radiation must be balanced against its higher toxicity (e.g., esophagitis).

Although clinical practice varies, most oncologists initiate radiation therapy with chemotherapy cycle one or with cycles two or three. The choice of timing depends on the clinical situation. The advantage of delaying radiation for one or two cycles is that during this time the tumor mass may be significantly reduced, therefore easing the patient’s symptoms and often improving performance status, so that the patient is better able to cope with combination treatment. Most initial trials of concurrent therapy have used pretreatment tumor volumes to determine radiation fields. However, newer strategies of radiation therapy will take advantage of chemotherapy-induced tumor reduction and use higher doses of radiation delivered to a smaller tumor volume. In one major trial, twice-daily radiation, compared with once-daily treatment, has been associated with improved surgical outcome, but twice-daily treatment is also associated with significantly higher toxicity rates. The use of twice-daily radiation can be considered in some patients with high performance status. The standard dose of daily radiation therapy that is given concurrently with chemotherapy has increased from 45 Gy to 60 Gy.

Another significant advance in the understanding of SCLC involves the role of prophylactic cranial irradiation. Early trials that used prophylactic cranial irradiation along with chemotherapy reported a high incidence of both immediate and delayed neurologic toxicity. Studies have used prophylactic cranial irradiation at lower dose fractions and have delayed its initiation until chemotherapy has been completed. These adjustments seem to be associated with substantially diminished immediate and delayed neurotoxicity. Moreover, a meta-analysis of the use of prophylactic cranial irradiation from randomized clinical trials (largely composed of patients with limited-stage disease) has demonstrated not only a reduction in CNS relapse but also an increase in long-term survival by approximately 5%.

Several issues involving prophylactic cranial irradiation remain to be settled. One is its role in elderly patients, who appear to be at higher risk for neurotoxicity. Also, although trials of SCLC have often included patients in complete remission from either limited or extensive disease, most of the patients have had limited disease. Therefore, the strength of the recommendation for prophylactic cranial irradiation in patients in complete remission from extensive-stage SCLC is less certain.

A number of trials have evaluated maintenance chemotherapy or the addition of other treatments after chemoradiotherapy for SCLC. Phase II studies of high-dose chemotherapy for patients in remission have suggested an encouraging long-term survival rate, and a potential long-term benefit has also been reported in a small number of patients who received a vaccine against a tumor ganglioside (BEC-2); the latter approach is currently the subject of a randomized phase III trial. No benefit for these approaches has yet been proved, however, so maintenance therapy after completion of standard therapy cannot be recommended for SCLC patients, except in the context of a clinical trial.

**Extensive-stage disease**  Progress in the treatment of extensive-stage SCLC over the past 10 years has been slower than that of limited-stage SCLC. As with limited-stage disease, treatment centers on chemotherapy. Although several different chemotherapy combinations have been demonstrated to have equivalent survival outcomes, etoposide-based regimens have been shown to be superior to older regimens such as cyclophosphamide, doxorubicin, and vincristine. Secondly, most clinical trials in SCLC have used cisplatin, but as noted above, carboplatin has a better therapeutic ratio, is equally effective, and causes significantly less nausea, vomiting, and neurotoxicity. Currently, however, cisplatin and carboplatin are used with roughly equal frequency for SCLC in community practice in the United States. Both agents are generally administered every 3 to 4 weeks, depending on hematologic recovery. Although the combination of platinum and etoposide remains the most commonly used regimen in the United States, cisplatin and irinotecan has been approved for treatment of SCLC in Japan, and randomized trials of this combination are ongoing in the United States.

**Special populations**  Adaptation of treatment to special populations is another very important principle in the management of SCLC. Standard combination chemotherapy regimens, which were developed for younger, healthier patients, pose a greater risk of severe myelosuppression and life-threatening complications in elderly patients with significant comorbid disease and in patients with poor performance status. Modified regimens should be considered in such patients. If combination therapy is employed, the use of carboplatin (dosed according
to renal function) rather than cisplatin may produce less toxicity in this population. Although monotherapy with low-dose etoposide is certainly a consideration, most elderly patients should be considered for combination carboplatin and etoposide therapy if permitted by their level of functional illness and degree of comorbid illness. Whether these patients should receive significantly reduced doses or near-standard doses plus hematopoietic growth factor has not been well studied.

**Relapse of disease** Although SCLC typically responds to therapy, the majority of patients with limited-stage disease and nearly all patients with extensive-stage disease will experience relapses. For limited-stage patients, the duration of remission may range from months to years. For most patients with extensive-stage disease, remission generally lasts only weeks to months after completion of chemotherapy. In both groups of patients, a major issue is the emergence of drug resistance, which has severely hampered the benefit of second-line or so-called salvage chemotherapy.

In this setting, a critical factor in choosing therapy is the time to relapse. For patients who have had a prolonged remission (longer than 1 year), retreatment with the same regimen will often produce a response. On the other hand, in patients who fail to respond to initial therapy (primary drug resistance), no therapy has been convincingly shown to be beneficial, so these patients are best enrolled in experimental trials.

For patients who have had a remission of at least 2 months after initial therapy, topotecan has been shown to produce a significant improvement in disease-related symptoms—particularly dyspnea, but also anorexia, hoarseness, and fatigue—and has been approved for second-line therapy for patients with SCLC. The other commonly used approach in relapses of SCLC has been prolonged courses of oral etoposide for 10 to 21 days per cycle. Other agents that have shown promise for salvage therapy include paclitaxel, irinotecan, vinorelbine, and gemcitabine. These agents, as well as more novel approaches, warrant further investigation.

**Supportive Care**

Supportive care is important across all stages of both NSCLC and SCLC. In patients with advanced or refractory disease, it often becomes the principal form of therapy. As the ability of oncologists to deliver both chemotherapy and radiation safely has improved, it is clear that one of the best supportive care approaches is to palliate disease-related symptoms with chemotherapy, radiation, or both.

Over the past 10 years, management of pain, depression, nausea, weight loss, and constipation in cancer patients has been improved by the development of pharmacologic agents with better efficacy and less toxicity [see CX Symptom Management in Palliative Medicine]. In patients who are receiving myelosuppressive chemotherapy and so are at high risk for neutropenic complications, the use of colony-stimulating factors has been demonstrated to substantially reduce the risk of fever, neutropenia, and infection. How to identify the populations who are at highest risk and are thus candidates for primary prophylaxis with colony-stimulating factors is an area that needs further investigation.

Anemia and fatigue are now appreciated as especially important concerns in patients with lung cancer. Analysis of the 1,748 lung cancer patients enrolled in the prospective trials of recombinant human erythropoietin for cancer patients with anemia has shown that amelioration of anemia led to significant improvements in quality of life; these improvements applied to patients with SCLC or NSCLC receiving a variety of chemotherapy regimens. Although all anemic cancer patients may benefit from higher hemoglobin levels, those with lung cancer may reap particular benefits because of dyspnea and fatigue related to the cancer itself, as well as comorbid diseases and the treatments used. In addition to substantially enhancing quality of life, normalization of hemoglobin levels may also improve therapeutic outcome, perhaps by improving tolerance to treatment or by reducing tumor hypoxia. Studies evaluating the role of hemoglobin maintenance in reducing cognitive dysfunction during treatment are ongoing.

**TREATMENT UPDATES**

The National Cancer Center Network (NCCN) provides evidence-based, expert-panel guidelines for the management of cancer, as well as supportive care guidelines. Clinicians are encouraged to review the NCCN Web site (http://www.nccn.org) for annual updates of lung cancer management guidelines.

**Prognosis**

At present, the 5-year survival rate for lung cancer is approximately 14%. The chance of survival is heavily dependent on stage at presentation, however. For example, 5-year survival in patients with stage I NSCLC is approximately 63%. Unfortunately, more than 40% of all patients with NSCLC have stage IV disease at diagnosis, and in this population the survival at 5 years is 1% or less. In patients with SCLC, 5-year survival ranges from 30% to 60% for peripheral disease (stage I/II) to 1% to 3% for patients with extensive disease (stage III/IV). Unfortunately, approximately 65% to 70% of patients with small cell lung cancer present with extensive disease.

The author has received grants or research support or has been a consultant or a member of the speakers’ bureau of Abgenix, Inc.; Amgen, Inc.; AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Co; GlaxoSmithKline; ImClone Systems Incorporated; Immunex Corporation; Eli Lilly and Company; Ortho Biotech Products, LP; QLT Inc.; and Schering-Plough Corporation during the past 12 months.

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February 2004 Update

ACP Medicine

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Acknowledgment

The author would like to acknowledge the Ruth and Herman Albert Thoracic Oncology Program at Duke Comprehensive Cancer Center for support of this work and, in particular, Thomas A. D’Amico, M.D., Joseph A. Govert, M.D., Michael J. Kelly, M.D., and Timothy Shafman, M.D., for their participation in the multidisciplinary development of this chapter.