CHAPTER 7

Non–small-cell lung cancer, mesothelioma, and thymoma

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In the United States, lung cancer has been the leading cause of cancer death in men for years, and since 1988, it has become the number-one cause of cancer death in women. It is estimated that 171,900 new cases of lung cancer will be diagnosed in 2003, and 157,200 deaths due to this disease will occur. This exceeds the combined number of deaths from the second, third, and fourth leading causes of cancer (breast, prostate, and colon cancer, respectively).

Lung cancer appears to develop from a stem cell that can differentiate along multiple lines. Although multiple cell types are often found within a single lung tumor, one type usually predominates. Based on therapeutic approach, there are two major subdivisions of lung cancer: 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.

This chapter will focus on the diagnosis, staging, pathology, and treatment of NSCLC, including carcinoid tumors of the lungs, as well as the pulmonary evaluation of lung cancer patients and the follow-up of long-term survivors. This chapter will conclude with a brief discussion of mesothelioma.

Chapter 6 will provide information on the staging, pathology and pathophysiology, and treatment of the far less common SCLC. In addition, this chapter will also provide basic information on the epidemiology, etiology, screening and prevention, and signs and symptoms of lung cancer in general.

NON–SMALL-CELL LUNG CANCER

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

Staging and prognosis

Staging

The staging of lung cancer must be conducted in a methodical and detailed manner in order to permit appropriate therapeutic recommendations to be made and to allow treatment results from different institutions to be compared. The TNM staging system, recently updated by Mountain (Table 1), applies equally well to all histologies. However, TNM staging is generally not utilized in SCLC, as it does not predict well for survival. Rather, SCLC is generally staged as limited (M0) or extensive (M1) disease.

Stage is commonly reported as either clinical or pathologic. The former is based on noninvasive (or minimally invasive) tests, whereas the latter 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 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). In short, patients who are ambulatory have a significantly longer survival than those who are nonambulatory. Similarly, patients who have lost > 5% of body weight during the preceding 3-6 months have a worse prognosis than patients who have not lost a significant amount of weight.

Molecular prognostic factors Several studies published over the 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 obtained.

TABLE 1: TNM staging of lung cancer

Primary tumor (T)

Tx	Tumor proven by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically or any tumor that cannot be assessed, as in pretreatment staging
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3.0 cm in greatest dimension, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy
T2	Tumor > 3.0 cm in greatest dimension, or tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region (but involving less than the entire lung). At bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina
T3	Tumor of any size with direct extension into the chest wall (including superior sulcus tumors), diaphragm, or mediastinal pleura or pericardium without involving the heart, great vessels, trachea, esophagus, or vertebral body; or tumor in the main bronchus within 2 cm of, but not involving, the carina
T4	Tumor of any size with invasion of the mediastinum or involving the heart, great vessels, trachea, esophagus, vertebral body, or carina; or presence of malignant pleural effusion

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed
N0	No demonstrable metastasis to regional lymph nodes
N1	Metastasis to lymph nodes in the peribronchial and/or ipsilateral hilar region, including direct extension
N2	Metastasis to ipsilateral mediastinal and subcarinal lymph nodes
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes

Distant metastasis (M)

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

Stage grouping

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

From Mountain CF: Revisions in the international system for staging lung cancer. Chest 111:171–1717, 1997.

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. Also, auscultation of the chest may show evidence of large airway obstruction and pulmonary consolidation. An enlarged liver may indicate hepatic metastases.

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

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

Imaging studies

Chest x-rays should always be done in a high-risk patient with new respiratory symptoms. Not only are PA and lateral chest x-rays of fundamental importance in assessing the local extent of the primary tumor, they 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 frequently helpful and well worth the effort expended in their retrieval.

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

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

difficult to detect on a chest radiograph but are usually readily apparent on a CT scan.

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

PET scanning may prove a valuable tool for evaluation of NSCLC patients treated with chemoradiotherapy or radiation therapy. In a recent study, the PET response was a powerful predictor of survival ($P = .0001$) *(MacManus RJ, Hicks RJ, Matthews JP, et al: Proc Am Soc Clin Oncol [abstract] 21:338a, 2002).*

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

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

Obtaining a tissue diagnosis

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

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

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

A CT-guided needle biopsy may diagnose up to 90% of peripheral lung cancers. However, needle biopsy is usually reserved for patients who are not candi-

TABLE 2: Selective indications for mediastinoscopy

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

dates for an operation due to distant metastatic disease or poor performance status. If the patient is a candidate for surgery, resection is generally recommended for any suspicious mass whether the needle biopsy is positive or nondiagnostic. Therefore, for patients with a suspicious peripheral lesion that is not associated with pleural effusion or mediastinal adenopathy, it is reasonable to proceed directly to surgery.

Mediastinoscopy provides not only a histologic diagnosis but also yields important staging information (Table 2). Median radiologic techniques of CT and PET scanning have largely replaced mediastinoscopy. If multiple lymph node levels contain tumor, most thoracic surgeons would not proceed directly to operation, but would offer these patients neoadjuvant therapy as part of a clinical trial. Alternatively, such patients could receive nonoperative primary therapy. However, if only one ipsilateral nodal level is positive for metastatic tumor, many surgeons will perform a pulmonary resection and lymph node dissection and advise participation in an adjuvant therapy trial. Surprisingly, the survival for patients with ipsilateral mediastinal nodal disease (IIIA) was the same as the survival for patients with contralateral mediastinal nodal disease (IIIB) in the neoadjuvant study by SWOG.

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

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

Evaluation for distant metastases

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

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

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

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

Diagnosis and evaluation of suspected carcinoid tumor

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

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

Intraoperative staging

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

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

Pulmonary evaluation

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

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

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

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

Pathology

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

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

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

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

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

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

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

Treatment

All investigators agree that patients with clinically staged IA, IB, IIA, and IIB NSCLC should undergo resection of their tumors. There is a similar consensus that, except for the rare individual with a solitary brain metastasis, patients with stage IV disease should be treated nonoperatively. While multimodality therapy is routinely recommended for stage IIIA and IIIB disease, its exact nature and sequence remain controversial.

SURGICAL APPROACH

The appropriate treatment of NSCLC is resection of the lobe containing the tumor. Occasionally, a bilobectomy or pneumonectomy is required. Mortality following lobectomy and pneumonectomy approximates 3% and 7%, respectively. A wedge or segmental resection has a 3-5 times higher incidence of local recurrence and a lower 5-year survival than a lobectomy. Therefore, if the patient can tolerate the procedure, the standard operation should be a lobectomy, rather than a wedge resection or segmentectomy.

Video-assissted thoracoscopic surgery (VATS) Traditionally, lung cancers have been resected through a posterolateral thoracotomy incision. Many surgeons have switched to a muscle-sparing incision, because studies have shown that this approach reduces pain. Currently, the trend is toward an even less invasive approach: lobectomy and lymph node dissection with VATS. It appears that this approach offers the same cancer operation and survival with perhaps lower morbidity and mortality.

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

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

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

Preoperative histologic assessment of the mediastinal lymph nodes is essential if multilevel metastases are suspected, as there have been few long-term survivors among patients with metastatic disease at more than one level. Such patients should be treated nonsurgically or offered participation in a trial designed to assess the benefits of neoadjuvant therapy. Although patients with stage IIIB tumors are usually treated with radiation and chemotherapy (see 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 a significant percentage of patients. The surgical approach, therefore, should be similar to that used in NSCLC; namely, resection. If a small tumor in a proximal airway is identified and there is no histologic evidence of lymph node disease, a bronchoplastic procedure with preservation of lung tissue can sometimes be performed. Rates of survival at 10 years are $>$ 90% for patients with stage I disease and 60% for patients with stage II disease.

ADJUVANT THERAPY

Radiation therapy

A trial conducted by the Lung Cancer Study Group (LCSG) clearly showed that, in patients with squamous cell carcinoma of the lung and resected N1/N2 disease, administration of postoperative radiation reduced the risk of recurrence in the chest from 20% to 1%. While there was no improvement in overall survival, postoperative radiation 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.

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. This complicated subject has recently been extensively reviewed using an evidence-based approach.

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

At present, therefore, the appropriate role of postoperative radiation therapy remains controversial. However, it should be seriously considered in patients at high risk for locoregional relapse (ie, those with N2 disease, squamous his-

tology, multiple positive lymph nodes, extracapsular extension, or close or microscopically positive margins).

Chemotherapy

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

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

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

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

A recent randomized trial of observation vs postoperative adjuvant chemotherapy (3 cycles of cisplatin 80 mg/m^2 on day 1 and vindesine 3 mg/m^2 on days 1 and 8 every 4 weeks) in patients with completely resected pathologic stage IIIA (N2) NCSLC showed no improvement with adjuvant chemotherapy *(Ichinose Y, Tada H, Koike T, et al: Proc Am Soc Clin Oncol [abstract] 20:331a, 2001).*

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

Similarly, a recent randomized trial comparing adjuvant radiotherapy (50 Gy/5 wk) vs adjuvant chemotherapy (cisplatin, 75 mg/m^2 on day 1, plus ifosfamide (Ifex), 1.5 g/m^2 on days 1-4, for 3 cycles every 4 weeks) followed by the same radiation in patients with resected N2 disease showed no improvement in outcome with the addition of chemotherapy to radiotherapy (Wolf M, Muller, H, Seifart U, at al: Proc Am Soc Clin Oncol 20:311a [abstract], 2001).

NEOADJUVANT CHEMOTHERAPY OR CHEMORADIATION

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

Stage IIIA/IIIB disease The greater effectiveness of current chemotherapeutic regimens in settings of reduced disease bulk suggested that their use prior to

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

Recently, an intergroup trial demonstrated an impressive 50% *pathologic* complete response rate and a 50% 3-year survival rate with preoperative chemotherapy (cisplatin/etoposide) administered concurrently with irradiation (45 Gy) to patients with T3-T4 N0 M0 Pancoast tumors.

Surgeons have a wide variety of opinions regarding the use of preoperative irradiation. A few surgeons believe that irradiation should never be given preoperatively, but most of them believe that the preoperative dose should be limited to 45-50 Gy. The current trend is toward the use of > 60 Gy preoperatively.

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

In a recent analysis of 686 patients who underwent surgical resection of N2 NSCLC, preoperative chemotherapy was associated with better survival outcome in a subgroup of patients with clinically evident N2 disease ($P < .0001$). Five-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 III 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. However, the results of a randomized trial (recently closed) comparing preoperative chemoradiation to definitive chemoradiation (in pathologic N2 disease) are not yet availabe.

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

A phase III trial comparing neoadjuvant chemotherapy with paclitaxel/carboplatin (Paraplatin) vs surgery alone in early-stage NSCLC (the Bimodality Lung Oncology Team [BLOT] vs NOT study) is now ongoing in the United States, based on promising phase II results (3-year survival rates of 64%) with this strategy (Pisters K, Ginsberg R, Giroux D, et al: Proc Am Soc Clin Oncol 20:323a [abstract], 2001)

TREATMENT OF MEDICALLY INOPERABLE PATIENTS WITH STAGE I/II DISEASE

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

Radiation therapy

Several institutions have reported their experience with definitive radiation therapy for such patients. 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), medically inoperable patients with early-stage NSCLC clearly should be offered radiation therapy, with reasonable expectation of cure. Recently, 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.

Radio-frequency ablation

Patients who are not operative candidates can also be treated with radio-frequency 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 radiological 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%-10%, 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 an accelerated regimen that delivered 54 Gy over 2½ weeks (CHART). The altered fractionation schedule resulted in improved 2-year survival.

Various efforts are currently under way to look at combining altered fractionation schema with chemotherapy. Although the preliminary results of RTOG 9410 do not favor altered fractionation (see "Concurrent vs sequential chemoradiation"), 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 they found no benefit to 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% (Proc Am Soc Clin Oncol 19:504a [abstract], 2000).

Conformal radiation therapy

Hayman et al reported updated results of the Michigan phase I dose-escalation trial of 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 (31/32) of the patients completed therapy to 74 Gy, as planned. The grade 3/4 esophagitis rate overall was relatively low at only11%. Moreover, the results found a promising median survival of 26 months and 3-year survival of 47% (Proc Am Soc Clin Oncol 19:496a [abstract], 2000).

Interestingly, investigators at M. D. Anderson Cancer Center found that the maximum tolerated dose (MTD) of gemcitabine (Gemzar) administered weekly concurrent with conventional (2D) thoracic radiation was only 125 mg/m^2/wk × 7 weeks vs 190 mg/m^2/wk × 7 weeks utilizing 3D conformal radiotherapy (Proc Am Soc Clin Oncol 20:312a [abstract], 2001). 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 to chemoradiation in patients with stage III NSCLC. Several meta-analyses have demonstrated a small, but statistically significant, improvement in survival with the combined-modality regimens. Indeed, six randomized trials have demonstrated a statistically significant survival advantage favoring chemoradiation: three of these trials employed sequential chemoradiation and three, concurrent chemoradiation.

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

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

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

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

Analyses of these positive randomized trials favoring chemoradiation over radiation alone suggest a difference in the patterns of failure that relates to the method of combining chemotherapy with thoracic radiotherapy. In the three trials employing sequential chemoradiation, the improvement in survival rates over radiation alone appeared to be linked to a decrease in the development of distant metastases. In contrast, in the three positive trials employing concurrent chemoradiation, the survival advantage appeared to be associated with an improvement in locoregional control.

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

Few studies in lung cancer report 5-year survival results. The median survival generally reported for stage IV disease is about 8 months even with novel therapeutic approaches, which is similar to the median survival reported for stage IIIB NSCLC with malignant pleural effusion. As the preceding and other trials in the literature show, 5-year survival rates are rarely reported for stage IIIA/IIIB lung cancers. Most studies report a median survival and 3-year survival rates. The Furuse trial of chemoradiation is one of the few lung cancer trials reporting 5-year survival results. Furuse et al evaluated mitomycin, vindesine, and Platinol (MVP), administered either concurrently with 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%; $P = .04$).

Concurrent vs sequential chemoradiation A phase III trial has previously reported an advantage for concurrent over sequential chemoradiation. Furuse et al recently 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 ($P = .6$) (Proc Am Soc Clin Oncol 19:484a [abstract]), 2000).

Curran et al presented the preliminary results of a larger randomized trial (>600 patients) comparing sequential vs concurrent chemoradiotherapy (RTOG [Radiation Therapy Oncology Group] 9410). The median survival with concurrent cisplatin/vinblastine and once-daily radiation was 17.0 months vs 14.6 months with sequential treatment ($P = .03$). The third treatment arm (concurrent cisplatin/oral etoposide and hyperfractionated radiation) was intermediate with a median survival of 15.6 months. Even elderly (≥ 70 years) patients on RTOG 94-10 benefited from concurrent chemotherapy and once-daily radiation therapy.

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 as a new treatment paradigm.

Recently, two randomized phase II trials also appear to support the use of concurrent chemoradiation for locally advanced NSCLC. Choy et al performed a randomized phase II study in 276 patients of three chemoradiation regimens with paclitaxel, carboplatin, and thoracic irradiation in their locally advanced multimodality protocol (LAMP). They found that concurrent chemoradiation 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 (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 and sequential chemotherapy followed by irradiation. The chemotherapy consisted of four cycles of cisplatin and vinorelbine. They reported a median survival in the concurrent arm of ~20 months, vs ~13 months in the other arm ($P = .02$).

As supported by clinical trials, the PCS-Lung Study demonstrated that patients with clinical stage (CS) III NSCLC received chemotherapy plus radiation therapy (RT) more than RT alone ($P < .0001$). In clinical stage I NSCLC, though, RT 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 CS ($P < .0001$), increasing KPS ($P < .0001$), 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 RT. Only 3% of all patients were treated on IRB-approved trials, demonstrating the need for improved accrual to clinical trials *(Movsas V, Moughan J, Komaki R, et al: Int J Radiat Oncol Biol Phys 54:101, 2002).*

TABLE 3: Active new 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)

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 in 1998-1999 (see box on previous page).

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

A strategy under investigation to reduce the toxicity of intensive combined-modality strategies is the use of the radioprotector amifostine (Ethyol). A small randomized trial (n = 62) suggests that twice-weekly amifostine (500 mg/m^2 IV) administered before chemotherapy and twice-daily radiation therapy for locally advanced NSCLC can reduce the incidence of acute esophagitis and pneumonitis, with no suggestion of tumor protection (*Komaki R, Lee JS, Milas L, et al: Proc ASTRO [abstract] 54:105, 2002*). This radioprotective agent has been further tested as a strategy to reduce chemo-radiation-induced esophagitis in a larger phase III study (RTOG 98-01), which has also prospectively collected critical quality-of-life data.

In addition to paclitaxel and carboplatin, many other chemotherapeutic agents with activity in NSCLC have emerged in the 1990s, including docetaxel (Taxotere), vinorelbine, gemcitabine, UFT (uracil and tegafur), 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 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 (cisplatin/etoposide) followed by consolidation docetaxel (75-100 mg/m^2 q21d × 3). In this group of pathologically documented stage IIIB NSCLC patients (pleural effusion excluded), a promising median survival of 27 months was found. Toxicity during consolidation consisted primarily of neutropenia (56% grade 4).

TABLE 4: 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]
Gatzemier (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

Current treatment recommendations

At present, it is reasonable to consider concurrent chemoradiation 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 new chemotherapeutic agents have produced response rates in excess of 20% in NSCLC (Table 3). The potentially useful new agents include the taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine, and irinotecan. Several of these new drugs have unique mechanisms of action compared to the mechanisms of agents that have previously shown some effectiveness against NSCLC. For instance, paclitaxel and docetaxel cause increased polymerization of tubulin, gemcitabine is an antimetabolite, and irinotecan is a topoisomerase I inhibitor.

Furthermore, randomized trials demonstrated that a new agent plus cisplatin combination significantly improves the response rate over cisplatin monotherapy (historically considered the most active agent for NSCLC). This increase in response rates translates into significant, although modest, improvement in survival outcome for patients receiving vinorelbine, gemcitabine and also tirapazamine, which is a hypoxic cell cytotoxin. Although tirapazamine is not a chemotherapy agent in a classical sense, it will be a very useful addition to the chemotherapy armamentarium because it does not cause myelosuppression (Table 4).

These studies suggest that combination chemotherapy with newer agents will significantly improve the outcome of NSCLC patients, as discussed below. It seems clear that conducting randomized trials comparing newer chemotherapy regimens with best supportive care is no longer acceptable.

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 very difficult task because there is no survival advantage documented for one regimen over another or standard regimen vs regimens containing newer agents.

Table 5 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 results between the trials. Nevertheless, there is a trend indicating that regimens containing newer agents show higher response rates and also better survival outcome in some series when compared with 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 Le Chevalier 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, the 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 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).

TABLE 5: 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 (%)
LeChavalier (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	560	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

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, 550 eligible patients with chemotherapy-naive stage IIIB to IV NSCLC were randomly assigned to 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 paclitaxel (250 mg/m^2 over 24 hours with growth factor) 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, 9.9 months; 1-year survival rate, 38.9%) compared with etoposide plus cisplatin (median survival time, 7.6 months; 1-year survival rate, 31.8%; $P = .048$). Comparing survival rates for the two dose levels of paclitaxel revealed no significant differences.

In a European trial of similar design reported by Giaconne et al, cisplatin/paclitaxel improved the response rate and the 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 an out-patient 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 5).

Second-line chemotherapy

A randomized phase III study conducted by the Cancer and Leukemia Group B (CALGB) further supported the superiority of combination chemotherapy over 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 performance status 2 patients. This randomized CALGB trial showed a median survival advantage for the combination of ~6 weeks in 582 patients.

Gemcitabine plus cisplatin

Gemcitabine is also FDA-approved 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 4). 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 the gemcitabine combined with vinorelbine regimen is associated with significantly better survival than single-agent vinorelbine in elderly NSCLC patients.

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 5).

Major randomized trials comparing new regimens

To identify a better chemotherapy regimen for 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 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). While both regimens provided effective palliation in 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, 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 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 com-

pared with the control arm, paclitaxel and cisplatin. Gemcitabine plus cisplatin was associated with 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 recently received FDA approval for this indication based on two randomized phase III trials confirming the promising phase II results of docetaxel monotherapy in advanced NSCLC patients previously treated with platinum-based chemotherapy.

In a multicenter US trial reported by Fossella et al, 373 patients were randomized to receive either docetaxel, 100 mg/m^2 (D100) or 75 mg/m^2 (D75) vs a control regimen of vinorelbine (30 mg/m^2/wk) or ifosfamide (2 g/m^2 × 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 between the three groups, the 1-year survival was significantly greater 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 8 cycles of chemotherapy should be administered to patients with stage IV NSCLC (Clinical Practice Guidelines. J Clin Oncol: 2996-3018, 1997). However, therapy should be individualized depending on the quality of tumor response and the patient's tolerance.

Promising novel agents

Several novel agents are being developed for the treatment of solid tumors, including lung cancer. For example, farnesyl transferase inhibitors target

prenylation of the *ras* family of proto-oncogenes. Farnesylation causes the *ras* oncogene to be constitutively active.

Other novel agents include signal transduction inhibitors, such as tyrosine kinase inhibitors (eg, ZD1839 [Iressa]), antiangiogenic agents, and monoclonal antibodies (C225 [anti-EGF receptor antibody], trastuzumab [Herceptin]). Many of these novel agents are being tested in combination with chemotherapeutic agents, as their mechanisms of action suggest that these agents may be far more effective as chronic inhibitors of cancer progression than as classic cytotoxics.

To date, most phase I studies of these various compounds have suffered from a difficulty in developing pharmacologically or molecularly driven end points that will serve as reasonable intermediate biomarkers of efficacy or even surrogates for toxicity. Further research has focused on the novel small molecule tyrosine kinase inhibitors erlotinib (Tarceva) and gefitinib (Iressa). 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 vs 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.

In general, there apears to be little to favor triplet cytotoxic drug combinations vs doublet combinations in NSCLC (Kelly K, Mikhaeel-Kamel N, Pan Z, et al: Clin Cancer Res 6:3474-3479, 2000). However, an area of great excitement 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, tirapazamine, and UFT.

The mechanisms of action of these new small molecules is 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 (a retinoid-X-receptor [RXR]-specific novel retinoid), resulted in substantial median and 2-year survival rates in stage IIIB NSCLC patients with malignant pleural effusion or stage IV NSCLC patients. Median survival on 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 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 survivals. 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 ZD1839 or the farnesyl transferase inhibitor SCH66336 have shown promising efficacy in small trials that have included NSCLC patients; ZD1839 alone resulted in an 18% response rate in second- or third-line therapy of NSCLC in a study population recruited across several continents.

However, there have been some provocative phase I and II data with both the rexinoid bexarotene and the farnesyl transferase inhibitor lonafarnib (Sarasar) in combination with chemotherapy leading 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. They will test the principle of 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 stage IV NSCLC patients who have good performance status (ECOG performance status, 0/1) and have not lost a significant amount of weight ($< 5\%$ of usual weight) would be to encourage them to participate in a clinical trial.

However, it would also be appropriate to treat this group of patients with etoposide plus cisplatin or with one of the newer combination regimens, such as gemcitabine/cisplatin, vinorelbine/cisplatin, paclitaxel/cisplatin, paclitaxel/carboplatin, or docetaxel/cisplatin (Tables 6, 7).

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

TABLE 6: Single-agent chemotherapy regimens for NSCLC

Drug	Dose and schedule
Vinorelbine	30 mg/m^2 IV weekly
Le Chevalier T, Brisgand D, Douillard J-Y, et al: J Clin Oncol 12:360–367, 1994.	
Vinorelbine	For patients 70 years old or older: 30 mg/m^2 IV on days 1and 8, every 21 days
Gridelli C, Perrone F, Cigolari S, et al: Proc Am Soc Clin Oncol 20:308a [abstract], 2001.	
Docetaxel	75 mg/m^2 IV on day 1 every 3 weeks
Shephaerd FA, Dancey J, RamlauR, et al: J Clin Oncol 18:2095–2103, 2000.	
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 19:1910a [abstract], 2000.	

Table prepared by Ishmael Jaiyesimi, DO

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

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

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

Results in advanced-stage NSCLC Two prospective, randomized trials (European; US/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.

TABLE 7: Chemotherapy regimens recommended for NSCLC

Regimen	Agents	Dose and schedule	Treatment interval
PE	Cisplatin 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	Cisplatin Paclitaxel	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	Cisplatin Gemcitabine	100 mg/m^2 IV on day 1 1,000 mg/m^2 IV on days 1, 8, and 15	4 weeks
PD	Cisplatin Docetaxel	75 mg/m^2 IV on day 1 75 mg/m^2 IV on day 1	3 weeks
PV	Cisplatin 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

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).

PALLIATION OF LOCAL AND DISTANT SYMPTOMS

Radiation therapy

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

Recent studies have demonstrated varying degrees of benefit for strategies beyond palliative whole-brain irradiation in the management of brain metastases.

TABLE 8: Percentage of patients with NSCLC symptoms 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.

Sperduto et al reported the results of RTOG 95-08, a randomized trial comparing whole brain irradiation (3,750 cGy in 250 cGy fractions) vs WBRT + stereotactic radiosurgery boost in 333 patients with 1-3 brain metastases. They found a statistically significant survival advantage with WBRT + 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, among others. All subsets of patients in the WBRT + SRS group were more likely to have stable or improved performance status than those in the WBRT alone group.

In another randomized trial, 401 patients with unresected brain metastases (KPS ≥ 70) were randomized to receive WBRT (30 Gy) ± the redox mediator motexafin gadolinium (MGd). Overall, there was no improvement in survival, but time to neurologic 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). In a final randomized trial, Antonadou et al compared WBRT± 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 × 6 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 + 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, most radiation oncologists use doses of ~30 Gy in 10 fractions for palliative treatment. Data from the United Kingdom suggest that similar efficacy without greater toxicity may be achieved with more ab-

breviated schedules, such as 17 Gy in 2 fractions 1 week apart or single fractions of 10 Gy (see Table 8). Such schedules may facilitate the coordination of radiation 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 QLQ C-30 questionnaire 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.

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

Chemotherapy

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

A randomized phase II study suggests that rhuMAb 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 (CP) chemotherapy alone. CP alone patients with progressive disease 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 CP alone. Although sudden and life-threatening hemoptysis occurred in 6 rhuMAb VEGF-treated subjects and was fatal in 4, survival data are encouraging, and a phase III trial is in progress without crossover to rhuMAb VEGF.

Thus, while radiation therapy remains the most appropriate modality for the treatment of such problems as superior vena cava obstruction, spinal cord compression, brain metastases, or localized bone pain, patients who have

TABLE 9: Staging of mesothelioma according to Butchart

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

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

Follow-up of long-term survivors

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

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

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

MESOTHELIOMA

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

Epidemiology

Gender Males are affected five times more commonly than females.

Age The median age at diagnosis is 60 years.

Etiology and risk factors

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

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

Diagnosis

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

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

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

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

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

Pathology

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

Staging and prognosis

The most commonly utilized staging system for mesothelioma, that of Butchart, is based on inexact descriptions of the extent of local tumor growth or distant metastases (Table 9). Other, more detailed staging systems based on TNM criteria have been proposed.

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

Treatment

Treatment rarely results in cure and should be considered palliative.

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

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

Although the median survival of patients treated with aggressive multimodality regimens that include surgery appears to be superior to survival of patients treated with chemotherapy and radiotherapy alone, the apparent improvement may be the result of selection bias.

Innovative treatments There are many new agents being tested for malignant mesothelioma, including ranpirnase (Onconase [p30 protein]), gemcitabine, paclitaxel, docetaxel, pemetrexed (Alimta), liposomal N-DDP, and gene therapy. In particular, pemetrexed, a novel multitargeted antifolate inhibited thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT), showed a promising activity in malignant pleural mesothelioma in the recently conducted phase II trial. The overall response rate was 16% in the vitamin-supplemented group. The responders also had marked improvement in quality of life. In parallel, the largest phase III randomized trial was recently reported at the 2002 meeting of the American Society of Clinical Oncology (ASCO).

In this phase III single-blind study for malignant pleural mesothelioma, pemetrexed plus cisplatin was compared with cisplatin alone in chemotherapy-naive patients with malignant pleural mesothelioma. The largest phase III trial to date enrolled 456 patients, of whom 280 patients also received folic acid and vitamin B supplementation to reduce toxicity. The group of patients who were treated with pemetrexed plus cisplatin showed a better survival benefit than those who were treated with cisplatin alone. Therefore, pemetrexed plus cisplatin with folic acid/vitamin B supplementation should be considered standard front-line therapy for patients with malignant pleural mesothelioma.

THYMOMA

Thymoma is a rare mediastinal tumor that occurs mainly in the anterosuperior mediastinum.

Epidemiology

Gender The tumor affects both sexes equally.

Age Thymoma is most often seen in people in the fourth and fifth decades of life.

Etiology and associated syndromes

The etiology of thymomas is unknown, and the risk factors have not been identified. Thymoma is a tumor originating within the epithelial cells of the thymus. One-third to one-half of patients present with an asymptomatic anterior mediastinal mass, one-third present with local symptoms (eg, cough, chest pain, superior vena cava syndrome, and/or dysphagia), and one-third of cases are detected during the evaluation of myasthenia gravis. Distant metastases are distinctly uncommon at initial presentation of this tumor.

In addition to myasthenia gravis, which occurs in approximately 30% of patients with thymoma, a host of paraneoplastic syndromes have been seen in association with thymoma. These other syndromes, which occur in less than 5% of patients, include pure red cell aplasia, hypogammaglobulinemia, and a variety of other autoimmune disorders.

Diagnosis

The most commonly described symptoms are pleuritic chest pain or discomfort, dry cough, and dyspnea. Physical examination may reveal adenopathy, wheezing, fever, superior vena cava syndrome, vocal cord paralysis, and other paraneoplastic syndromes.

Chest x-ray and CT scan A chest x-ray provides an initial basis for diagnosis. The location, size, density, and presence of calcification within the mass can all be determined. Comparison of the film to previously obtained films is usually

TABLE 10: Clinicopathologic correlates of thymoma

Authors	Number of patients	Subgroups (percentage)
Verley and Hollman (Cancer 55:1074, 1985)	200	Type I: Spindle and oval cells (30) Type II: Lymphocyte rich (30) Type III: Differentiated epithelial rich (33) Type IV: Undifferentiated epithelial rich (equivalent to thymic carcinoma) (7)
Bernatz, et al (Surg Clin North Am 53:885, 1973)	283	Predominantly lymphocytic (25) Mixed lymphoepithelial (43) Predominantly epithelial (25) Spindle cell (6)
Muller-Hermelink, et al (Curr Top Pathol 75:207, 1986)	58	Cortical (43) Mixed: Predominantly cortical (8) Mixed: Common (36) Medullary (5) Mixed: Predominantly medullary (8)

helpful. Following identification of a mediastinal mass on conventional radiography, contrast-enhanced CT scanning should be performed. CT scanning can differentiate the cystic form from solid lesions as well as the presence of fat, calcium, or fluid within the lesion. MRI is increasingly available for use in the evaluation of mediastinal pathology, but it is less frequently utilized than CT. MRI is superior to CT scanning in defining the relationship between mediastinal masses and vasular structures and is useful in the assessment of vascular invasion by the tumor.

TABLE 11: Thymoma staging systems of Masaoka et al

Stage	Description
Stage I	Macroscopically completely encapsulated Microscopically no capsular invasion
Stage II	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura Microscopic invasion into capsule
Stage III	Macroscopic invasion into neighboring organs (pericardium, great vessels, lungs)
Stage IVA	Pleural or pericardial dissemination
Stage IVB	Lymphogenous or hematogenous metastasis

Masaoka A, Monden Y, Nakahara K, et al: Follow-up study of thymomas with special reference to their clinical stages. Cancer 48:2485, 1981.

TABLE 12: Common chemotherapy regimens for thymoma

Drug	Dose and schedule
Cyclophosphamide, doxorubicin, cisplatin, and prednisone	
Cyclophosphamide	500 mg/m^2 IV on day 1
Doxorubicin	20 mg/m^2/d infused continuously on days 1-3
Cisplatin	30 mg/m^2/d IV on days 1-3
Prednisone	100 mg/d PO on days 1-5
Repeat cycle every 3-4 weeks	

Adapted from Shin DM, Walsh GL, Komaki R, et al: Ann Intern Med 129:100–104, 1998.

Table prepared by Ishmael Jaiyesimi, DO

Invasive diagnostic tests CT-guided percutaneous needle biopsy specimens are obtained using fine-needle aspiration techniques and cytologic evaluation or with larger-core needle biopsy and histologic evaluation. Fine-needle specimens are usually adequate to distinguish carcinomatosis lesions, but core biopsies may be necessary to distinguish most mediastinal neoplasms. Immunohistochemical techniques and electron microscopy have greatly improved the ability to differentiate the cell of origin in mediastinal neoplsms. Most series reported diagnostic yields for percutaneous needle biopsy of 70%-100%.

Mediastinoscopy is a relatively simple surgical procedure accomplished under general anesthesia. It is an adequate approach to the superior, middle, and upper posterior mediastinum, and most series report a diagnostic accuracy of 80%-90%. Anterior mediastinotomy (Chamberlain approach) provides for direct biopsy of tissue and has a diagnostic yield of 95%-100%. Thoracotomy is occasionally necessary to diagnose mediastinal neoplasms, but its indications have been largely supplanted by video-assisted thoracoscopic techniques, which yield 100% accuracy.

The most common tumors one must include in the differential diagnosis of an anterior mediastinal tumor are lymphomas and germ-cell tumors. Immunohistochemical markers are helpful to differentiate thymoma from tumors originating from other cell types.

Pathology

Three of the most common classification schemes for thymoma are listed in Table 10. Verley and Hollman propose a classification system based on tumor architecture, cellular differentiation, and predominant cell type. Bernatz et al describe a simpler classification by presenting thymoma based on the percentage of epithelial cells and lymphocytes. In both of these systems, thymoma with a predominance of epithelial cells was associated with a greater increased incidence of invasion and a subsequently worse prognosis.

Staging and prognosis

The staging system prognosed by Masaoka et al has been widely adopted (Table 11). Stage is an independent predictor of recurrence and long-term survival, as the 5-year survival rate for stage I thymoma was 96%; stage II, 86%; stage III, 69%; and stage IV, 50%.

Treatment

SURGICAL TREATMENT

All patients whose tumors are potentially resectable should undergo surgery. If the patients have evidence of myasthenia gravis, a preoperative consultation with a clinical neurologist should be considered. The incision of choice is almost always a median sternotomy, which is quick and easy to make, and provides excellent exposure to the anterior mediastinum and neck. Although the surgeon is considered the best judge of the tumor's invasiveness, it is often difficult to grossly separate invasion from adherence to surrounding tissue.

Complete resection of thymoma has been found to be the most significant predictor of long-term survival. Several studies have examined the extent of surgical resection on survival and disease-free survival rates. In 241 operative cases, Maggi and colleagues found an 82% overall survival rate in those whose tumors underwent complete resection, and a 26% survival rate at 7 years in those undergoing biopsy alone. Other investigators reported similar results in surgical patients. Therefore, regardless of stage, tumor resectability is one of the important predictors of treatment outcome.

RADIATION TREATMENT

Thymomas are generally radiosensitive tumors, and the use of radiation therapy in their treatments is well established. It has been used to treat all stages of thymoma, either before or after surgical resection. General agreements exist regarding the postoperative treatment of invasive thymoma (stage II and III), while the role of radiation in the treatment of encapsulated (stage I) thymomas is less clear. The value of adjuvant radiation therapy for invasive thymomas is well documented and should be included in the treatment regimen regardless of the completeness of tumor resection.

CHEMOTHERAPY

Chemotherapy has been used in the treatment of invasive thymomas with increasing frequency during the past decade (Table 12). The most active agents appear to be cisplatin, doxorubicin, ifosfamide, and corticosteroids. Combination chemotherapy has generally shown higher response rates and has been used in both neoadjuvant and adjuvant settings and in the treatment of metastatic or recurrent thymomas. CAP (cyclophosphamide, doxorubicin [Adriamycin], and Platinol) or CAPPr (cyclophosphamide, Adriamycin, Platinol, and prednisone) regimens have been used in neoadjuvant and/or adjuvant settings. These regimens have also been used in recurrent thymoma.

Unresectable thymoma

Advanced-stage (III/IVA) thymomas are usually difficult to remove completely. Multidisciplinary approaches, including induction chemotherapy followed by surgical resection, postoperative radiation therapy, and consolidation chemotherapy have recently been reported.

Induction chemotherapy consists of cyclophosphamide (500 mg/m^2 IV on day 1), doxorubicin (20 mg/m^2/d, continuous infusion, days 1-3), cisplatin (30 mg/m^2/d IV on days 1-3), and prednisone (100 mg PO on days 1-5), repeated every 3-4 weeks for 3 courses. Twenty-two evaluable patients were consecutively treated from 1990 to 2000 in a prospective phase II study at M. D. Anderson Cancer Center. After induction chemotherapy, 17 of 22 patients (77%) had major responses, including three complete responses.

Twenty-one patients underwent surgical resection. All patients received postoperative radiation therapy and consolidation chemotherapy. With median follow-up time of 50.3 months, overall survival rates at 5 years and 7 years were 95% and 79%, respectively. Progression-free survival rates were 77% at 5 years and 7 years. The multidisciplinary approaches to unresectable thymoma appear to be promising.

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