American Thoracic Society/European Respiratory Society

Pretreatment Evaluation of Non-Small-cell Lung Cancer

THIS OFFICAL STATEMENT OF THE AMERICAN THORACIC SOCIETY AND THE EUROPEAN RESPIRATORY SOCIETY WAS ADOPTED BY THE ATS BOARD OF DIRECTORS. MARCH 1997 AND BY THE ERS EXECUTIVE COMMITTEE, APRIL 1997 AND ENDORSED BY THE AMERICAN COLLEGE OF CHEST PHYSICIANS BOARD OF REGENTS

At the beginning of the 20th century lung cancer was a rare malignancy. It is now occurring in epidemic proportions worldwide. It is the most common cause of death from malignancy in the United States, the United Kingdom, and a number of other countries. The rate of lung cancer in women in the United States is increasing, while the rate in males is beginning to decline, especially in those less than 50 yr of age. Women account for 40% of all lung cancer cases, and lung cancer has surpassed breast cancer as the most common cause of death from malignancy. Smoking is the predominant risk factor associated with lung cancer. The risk is related to the number of cigarettes smoked, age at starting smoking, and the duration of smoking (see ATS statement on cigarette smoking and health. 1996. *Am. J. Respir. Crit. Care* Med. 153:861–865). It is estimated that smoking accounts for 80–90% of all cases of lung cancer. The vast majority of cases could be prevented by never smoking, and the risk of developing lung cancer could be lessened by smoking cessation. Lung cancer is easier to prevent than cure.

SCREENING

When lung cancer is diagnosed as an incidental finding in an asymptomatic patient, survival is better than when the diagnosis is based on symptoms. It has been hypothesized that screening for lung cancer would lead to a reduction in disease-specific mortality. Several studies of radiographic screening conducted in the 1960s showed no reduction in lung cancer mortality. In the early 1970s the National Cancer Institute conducted three large lung cancer screening studies, all with a prospective randomized design; two evaluated the benefit of adding sputum cytologic evaluations every 4 mo to yearly chest radiographs and the third evaluated the effect of cytologic and radiographic screening every 4 mo compared with a recommendation of yearly chest radiograph and sputum cytology (l-5). None of these trials evaluated screening compared with a no-screening control. Radiographic screening detected significantly more lung cancers than did cytology alone; the two tests together had the greatest sensitivity. Neither the addition of cytology to chest radiograph nor intensive screening with both modalities improved lung cancer mortality. A more recent prospective randomized study conducted in Czechoslovakia also failed to demonstrate an improvement in lung cancer mortality in a population screened by both cytology and chest radiograph compared with no screening (6). These studies have led to the current American Cancer Society recommendation that screening for lung cancer is not recommended.

The populations examined in these studies were all males over the age of 40 with approximately a 20 pack/yr smoking history. Since the design of these studies, our understanding of risk for lung cancer has advanced. Features that identify individuals with significantly increased risk for lung cancer have been identified. These include airflow obstruction (7), family history of lung cancer, exposure to other respiratory carcinogens, particularly asbestos and radon gas, and a previous history of lung or other aerodigestive cancer. Recent reports suggest that smoking females are more susceptible than males (8). Screening studies focused on high-risk populations have not been conducted. Furthermore, the understanding of the biology of premalignant airway epithelium is advancing rapidly. It is likely that early preneoplastic lesions may be amenable to interventions, including smoking cessation, chemoprevention, and local therapies. At the present time, no prophylactic intervention other than smoking cessation has been shown to be efficacious. Currently, ongoing trials are readdressing the issue of screening for lung cancer.

SYMPTOMS AND SIGNS

Clinical abnormalities associated with lung cancer are myriad. In a small percentage, the initial presentation is an abnormal chest radiograph that was obtained for other reasons.

The majority of patients present with symptoms and have advanced disease. Symptoms may result from the primary tumor, metastases, or systemic manifestations caused by non-metastatic (paraneoplastic) syndromes (9).

Local Symptoms and Intrathoracic Spread

The frequency of symptoms, local and systemic, in lung cancers is summarized in Table 1. Cough is the most common presenting symptom of lung cancer. Patients who have a persistent cough or a change in cough should have a chest radiograph, especially if they are smokers and aged over 40 yr. Many lung cancers occur in central airways and may lead to postobstructive pneumonia. Failure of acute exacerbation of chronic bronchitis to clear within a few weeks should raise the suspicion of a neoplasm. Hemoptysis is a common presenting symptom. It is rarely severe and is usually only streaking of blood in the sputum. The most common description is that of coughing up blood for several days in succession. The chest radiograph is usually abnormal, but if normal in a heavy smoker aged over 40 yr, the yield of endobronchial tumors at fiberoptic bronchoscopy is less than 5% (10). Dyspnea develops early in up to 60% of patients. It is usually associated with increasing cough and sputum. If the tumor is occluding a major airway, it can cause breathlessness, which may be associated with a unilateral wheeze. Chest discomfort is common and occurs in up to 60% of patients at diagnosis. This is often of an ill-defined nature, intermittent and aching in quality. Definite pleuritic pain may occur as a result of infection or direct spread of tumor to the pleural surface, although this can also be painless. Invasion of ribs or vertebrae will cause continuous localized aching pain. Shoulder pain, often radiating down the upper inner arm, can be caused by a tumor in the apex of the lung or superior sulcus (Pancoast's tumor). Involvement of the last cervical and first thoracic segment of the sympathetic trunk produces Horner's syndrome. Hoarseness secondary to entrapment of

TABLE 1

CLINICAL FEATURES ON PRESENTATION

	Frequency Depending on Cell Type (%)
Cough	8-61
Dyspnea	7–40
Chest pain	20-33
Hemoptysis	6-31
Anorexia/malaise	55-88
Hoarseness	3-I 3
Dysphagia	1-5
Bone pain	6-I 3
Clubbing	O-20
Supraclavicular nodes	26–42
Pleural effusion	12-33
Hepatomegaly	3-20
Neurological manifestations	4-21

Modified from reference 9.

the left recurrent laryngeal nerve is a frequent presenting symptom. Superior vena caval (SVC) obstruction is due to either occlusion of the vena cava by tumor or thrombosis from tumor breaching and damaging the luminal surface. It is commonly associated with metastatic spread from right-sided tumors into the paratracheal lymph node chain. Dysphagia results from esophageal compression by enlarged metastatic mediastinal lymph nodes and less commonly from direct tumor invasion. Cardiac metastases are rare and occur late because the pericardium appears to be an efficient natural barrier. However, pericarditis does occur and occasionally an effusion may cause classic symptoms of tamponade.

Extrathoracic Manifestations

About one third of patients present with symptoms as a result of distant metastases. Supraclavicular and anterior cervical nodes are enlarged in 15-30% patients during the course of their illness. Bone pain is present in up to 20% of all patients at presentation. Liver metastases occur with lung cancer; however, liver function tests are seldom abnormal until the metastases are numerous and large. Adrenal lesions and para-aortic lymph node metastases may occur and are most commonly seen with small-cell cancers. Intracranial metastases occur in 10% of patients at presentation. Spinal cord metastases are less common but tend to occur in patients with cerebral metastases.

Paraneoplastic Syndromes

Paraneoplastic syndromes occur in approximately 10–20% patients with lung carcinoma. A variety of remote effects of lung cancer may occur that are unrelated to direct invasion, obstruction, or metastatic effects (Table 2). This topic has been reviewed elsewhere (11).

Laboratory Tests

All patients should have a complete blood count and a chemistry group that includes electrolytes, calcium, alkaline phosphatase, albumin, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and creatinine. The electrolytes, urea, and creatinine may show the changes associated with the syndrome of inappropriate antidiuretic hormone secretion, most commonly seen in small-cell lung cancer. Liver enzymes are rarely disturbed unless there are extensive metastases. The serum albumin remains a prognostic factor with reduction in levels suggesting advanced disease. Serum calcium should also

TABLE 2

PARANEOPLASTIC SYNDROMES ASSOCIATED WITH LUNG CANCER

Systemic	Endocrine or metabolic	Hematologic
Anorexia, cachexia, weight loss*	Cushing's syndrome	Anemia*/polcythemia
Fever	Hypercalcemia*	Hypercoagulability
Orthostatic hypotension	Hyponatremia*	Thrombocytopenic purpura
Nonbacterial thrombotic endocarditis	Hyperglycemia	Dysproteinemia (including amyloidosis)
Dermatomyositis/polymyositis	Hypertension	Leukocytosis/leukoerythroblastic reaction
Systemic lupus erythematosus	Acromegaly	Eosinophilia
Cutaneous	Hyperthyroidism	Neurologic
Acquired hypertrichosis langinosa	Hypercalcitoninemia	Peripheral neuropathy*
Barex's syndrome (acrokeratosis)	Cynecomastia	Lambert-Eaton myasthenic syndrome*
Clubbing*	Galactorrhea	Necrotizing myelopathy
Dermatomyositis	Carcinoid syndrome	Cerebral encephalopathy
Erythema gyratum repens	Hypoglycemia	Visual loss
Exfoliative dermatis (erythroderma)	Hypoposphatemia	Visceral neuropathy
Hypertrophic pulmonary osteoarthropathy	Lactic acidosis	Renal
Superficial thrombophlebitis*	Hypouricemia	Glomerulopathies
Tripe palms	Hyperamlasemia	Tubulointerstitial disorders
Acanthosis nigricans		
Acquired ichthyosis		
Acquired palmoplantar keratoderma		
Erythema annulare centrifugum		
Dermatitis herpetiformis		
Extramammary Paget's disease		
Florid cutaneous papillomatosis		
Pemphigus vulgaris		
Pityriasis rotunda		
Pruritus		
Sign of Leser-Trelat		
Sweet's syndrome		
Vaculitis		

• Indicates the more common pareneoplastic syndromes,
From reference 11.

be measured, particularly if the subject has non-specific symptoms, such as weight loss, anorexia, and confusion. No other laboratory tests are routinely recommended.

Serum Tumor Markers

Several molecular and biological substances manufactured by, or associated with, the different cell types of lung cancer have been studied to assess whether they provide more sensitive detectors of disease presence or progression (12). Unfortunately, none appears sufficiently sensitive or has a high enough specificity to add to our ability to reliably detect occult disease or influence disease management. The routine measurement of any of these substances in the screening, staging, or evaluation of disease progression is not recommended.

PATHOLOGIC DIAGNOSIS

The pathologic diagnosis of lung cancer can be established either on cytologic or surgical biopsy specimens (13-15). The certainty of the diagnosis may depend on the quantity and quality of viable tumor cells in the specimen. One of the most important issues in the approach to lung cancer diagnosis is close communication between pathologist and clinician, especially if the case is unusual or the pathologic diagnosis does not seem to fit with the clinical situation. Some bronchoscopic biopsies are damaged by crush artifact, making the separation of small-cell lung cancer (SCLC) from non small-cell lung cancer (NSCLC) difficult. There are six types of cytologic specimens that can be obtained for diagnosis: sputum, bronchial washings, bronchial brushings, transbronchial needle aspirates, bronchoalveolar lavage, and transthoracic fine needle aspiration biopsy (14). Histologic biopsy specimens can be obtained from endobronchial, transbronchial, transthoracic, or open biopsy procedures, such as excisional wedge biopsy, thoracoscopic biopsy, lobectomy, or pneumonectomy. Small tissue cores can be obtained for histologic material with transbronchial or transthoracic needle biopsy. Among the available diagnostic techniques is sputum cytology. The diagnostic yield increases with induced versus spontaneously expectorated samples and examination of multiple (usually at least three) specimens rather than a single sample (14).

Histologic Classification of Lung Cancer

The major histologic subtypes of lung cancer include squamous cell carcinoma, adenocarcinoma, SCLC, and large-cell carcinoma (Table 3) (16). In the past decade, adenocarcinoma has surpassed squamous cell carcinoma as the most common histologic subtype of lung cancer in the United States (17). Squamous cell carcinoma is recognized by the histologic features of intercellular bridging, squamous pearl formation, and individual cell keratinization. Adenocarcinomas may take the form of several histologic subtypes, including acinar (gland forming), papillary, bronchioloalveolar, and solid with mucus formation. Cases with mixed adeno- and squamous differentiation are called adenosquamous carcinoma. Large-cell carcinoma is a poorly differentiated NSCLC. It is a diagnosis of exclusion made after ruling out the presence of adenocarcinomatous or squamous differentiation. Large-cell carcinoma can be difficult to separate from poorly differentiated squamous cell carcinomas, adenocarcinomas, or small-cell carcinomas. Histochemical stains such as mucicarmine or Periodic-acid Schiff after diastase digestion may be necessary to separate solid adenocarcinomas with mucus formation from some large-cell carcinomas. Bronchioloalveolar carcinoma (BAC) is an adenocarcinoma of the lung that grows in a lepidic fashion along the alveolar septa (16). This histologic pattern is most often found in association with other patterns of adenocarcinoma; histologically pure BAC is less common. The diagnosis should be restricted to cases where this histologic pattern is exhibited throughout the tumor (18).

TABLE 3

WORLD HEALTH ORGANIZATION HISTOLOGIC CLASSIFICATION*

Dysplasia/carcinoma in situ	
Squamous cell carcinoma (30%)†	
SCLC (18.2%)	SCLC (IASLC 1988)‡
Oat cell carcinoma	Pure SCLC
Intermediate cell type	Mixed small-cell/large-cell carcinoma
Combined oat cell carcinoma	Combined SCLC
Adenocarcinoma (30.7%)	
Acinar adenocarcinoma	
Papillary adenocarcinoma	
Bronchioloalveolar carcinoma	
Solid carcinoma with mucus formation	
Large-cell carcinoma (9.4%)	
Variants:	
Giant cell carcinoma (0.3%)	
Clear cell carcinoma	
Adenosquamous carcinoma (1.5%)	
Carcinoid tumor (1 .0%)	
Bronchial gland carcinomas	
Mucoepidermoid carcinoma (0.05%)	
Adenoid cystic carcinoma (0.04%)	
Others	

* Data adapted from reference 16.

† Percentages (in parentheses) of subtypes of cancer from the Surveillance, Epidemiology, and End Results (SEER) Program for the 5-yr period between 1983 and 1987. Remaining categories from the SEER data include: undifferentiated carcinoma NOS (1.7%), and other unspecified carcinoma (7.1%) (17).

‡ Modified classification SCLC proposed by the International Association for the Study of Lung Cancer (IASLC) (19).

Since there are major differences in the therapeutic approach to patients with SCLC and NSCLC, pathologic differentiation between the two types is critical. The distinction of NSCLC from SCLC should not rest on a single criterion such as cell size or nucleoli, but on multiple additional features including nuclear-to-cytoplasmic ratio, nuclear chromatin, nuclear molding, cell shape (fusiform versus polygonal), and hematoxylin vascular staining (19). Disagreement among expert lung cancer pathologists between SCLC and NSCLC may occur in up to 5–7% of cases.

In small, poorly preserved biopsy specimens, SCLC can be difficult to distinguish from carcinoid tumors, lymphocytic infiltrates, or poorly differentiated NSCLC, especially in the presence of crush artifact, ischemic changes, artifacts introduced by frozen section, poor fixation, and poor histologic sections (19). In some cases, comparison with cytology specimens taken at the time of bronchoscopy will provide the definitive diagnosis. Lymphoid infiltrates, whether due to small lymphocytic lymphoma or chronic inflammation, can be distinguished from SCLC by their dyscohesive pattern of growth, contrasting with the epithelial clustering and nuclear molding of SCLC. Immunohistochemistry may be helpful since SCLC virtually always stains with keratin but not with common leukocyte antigen, while the staining pattern is the opposite with lymphoid cells. SCLC may stain with neuroendocrine markers such as chromogranin, synaptophysin, and LEU-7; however, 20–25% of cases will be negative for all of these markers. Neuronspecific enolase is not a reliable marker for SCLC since it stains up to two thirds of NSCLC. If the biologic be-

havior of a tumor raises doubts about the diagnosis of SCLC, additional tissue, such as bone marrow and other biopsies, may be needed to establish the diagnosis.

Subtyping of NSCLC (adeno-, squamous, or large cell) can be very difficult in bronchoscopic biopsy specimens. Approximately 40% of surgically removed specimens differ in cell type from their corresponding bronchoscopic specimens (18). If clear-cut morphologic criteria cannot be satisfied for subclassification as squamous cell or adenocarcinoma, the general diagnosis of "lung cancer, non small-cell type" should be made.

Preneoplastic Lesions

The concept of a progressive sequence of dysplasia, carcinoma *in situ*, and invasive carcinoma is generally accepted for squamous cell carcinoma but not for other histologic types of lung carcinoma (13).

Neuroendocrine Lung Tumors

Neuroendocrine tumors of the lung can be classified as typical carcinoid, atypical carcinoid, large-cell neuroendocrine carcinoma, small-cell carcinoma, and non small-cell carcinoma with neuroendocrine differentiation (NSCLC-NE) (13, 20). This classification is currently in evolution, and to date there has not been uniformity in the application of these terms. Neuroendocrine differentiation can be demonstrated by immunohistochemistry or electron microscopy in 10–20% of histologically ordinary NSCLC without neuroendocrine features by light microscopic morphology (NSCLC-NE) (20).

Primary versus Metastatic Lesions

The problem of differentiating between a primary versus a metastatic carcinoma of the lung may arise. There are a variety of pathologic criteria and immunohistochemical tests that can be useful in this differential diagnosis (13, 14). In addition, the distinction of malignant mesothelioma from adenocarcinoma of the lung is an occasional problem. A panel of histochemical and immunohistochemical tests as well as electron micoscopy may be necessary to make this separation (13, 14).

IMAGING MODALITIES FOR INTRATHORACIC STAGING

Computed tomography (CT) of the chest is an accepted tool for staging non small-cell carcinoma of the lung. The vast majority of primary lung cancers are initially detected on chest radiography, and there may be certain instances in which the chest radiograph alone is a sufficient imaging procedure; for example, when an obvious metastatic bone lesion is detected or when large bulky contralateral mediastinal lymph nodes are present. However, numerous studies have shown that chest radiography lacks sensitivity in the detection of mediastinal lymph node metastases and chest wall and mediastinal invasion.

Technical Standards for Computed Tomography of the Chest

The following are technical criteria that should be met for adequate CT evaluation in lung cancer: (I) third or fourth generation CT equipment with slice scanning times of 2 s or less; (2) maximum slice thickness and slice interval of 10 mm; (3) scan area to include from above the apices of the lungs through the adrenal glands; (4) the field of view should include the contiguous chest wall; (5) printed hard copies should have appropriate lung and mediastinal windows. The administration of intravenous contrast is not essential. However, it is recommended in central tumors with probable mediastinal invasion and when there is difficulty differentiating mediastinal vessels from enlarged lymph nodes.

Evaluation of the Primary Tumor (the T Factor)

CT has limited usefulness in the detection of chest wall and parietal pleural invasion. Such lesions are classified as T3 lesions and are potentially resectable. Surgical resection, however, involves *en bloc* resection of the pulmonary malignancy and the contiguous chest wall. CT is neither sensitive nor specific in detecting chest wall invasion. Webb and colleagues (21) demonstrated a sensitivity of only 62% for CT in distinguishing T3/T4 tumors from T1/T2 tumors. Only the presence of a mass in the chest wall or definite rib destruction are helpful indicators of chest wall invasion. Similarly, the resectability of central tumors that invade the mediastinum can often be made only at the time of surgery. The sensitivity of CT in the detection of invasion of vital mediastinal structures is similarly low, with reports of sensitivity in the ranges of 60–75%. Adequate evaluation of mediastinal invasion requires contrast-enhanced images, which preferably should be performed with thin sections (5 mm or less) (Figure 1).

Magnetic resonance imaging (MRI) has been shown to be slightly but not significantly better in the detection of both mediastinal and chest wall invasion. MRI is particularly useful and is recommended in the evaluation of superior sulcus tumors. Multiplanar imaging capability permits accurate evaluation of involvement of the brachial plexus, spinal canal, chest wall, and subclavian artery by such tumors (21).

Evaluation of Nodal Metastases (the N Factor)

A meta-analysis of 42 studies examining the accuracy of CT in detecting mediastinal nodes found a sensitivity of 79% and a specificity of 78%, although subsequent investigations have suggested somewhat lower sensitivities and specificities. McLoud and coworkers (22) reported that the sensitivity and specificity of CT was 64% and 62%, respectively, using a short-axis diameter greater than 1 cm. However, despite the somewhat limited sensitivity of CT, N2 disease not apparent on CT scan has been shown to be resectable with up to a 30% 5 yr survival. In addition, CT may help serve as a guide to the selection of nodes for transbronchial needle aspiration, and it may also help identify enlarged nodes that are technically beyond the reach of mediastinoscopy. A study by the Canadian Lung Oncology Group evaluated the use of CT as a methodology to decide on the necessity for mediastinoscopy in all cases. Two diagnostic strategies were used: (I) mediastinoscopy in all eligible patients; and (2) mediastinoscopy only in patients whose CT showed evidence of enlarged nodes greater than 1 cm in short axis. Their study showed that use of CT in comparison with mediastinoscopy in all patients was likely to produce the same or fewer unnecessary thoracotomies, and it was also likely to be less expensive (23) (Figure 1).

It should be emphasized that because of the low specificity of CT, enlarged lymph nodes must be biopsied for accurate staging. Benign hyperplastic nodes as large as 4 cm have been described in association with bronchogenic carcinoma. This is particularly true when there is associated obstructive pneumonitis.

The use of CT in staging T1 lesions is also controversial. The prevalence of mediastinal nodal metastases associated with T1 lesions is low but has been variably reported to be between 5–15%. Because of such a low prevalence, it has been suggested that CT may not be necessary in such patients and that the preoperative staging should be limited to plain chest radiographs. However, Seely and coworkers (24) found a 21% prevalence of nodal metastases among 104 patients with T1 lesions. The sensitivity of CT in this study was 77% for the detection of these metastases. However, the question of per-

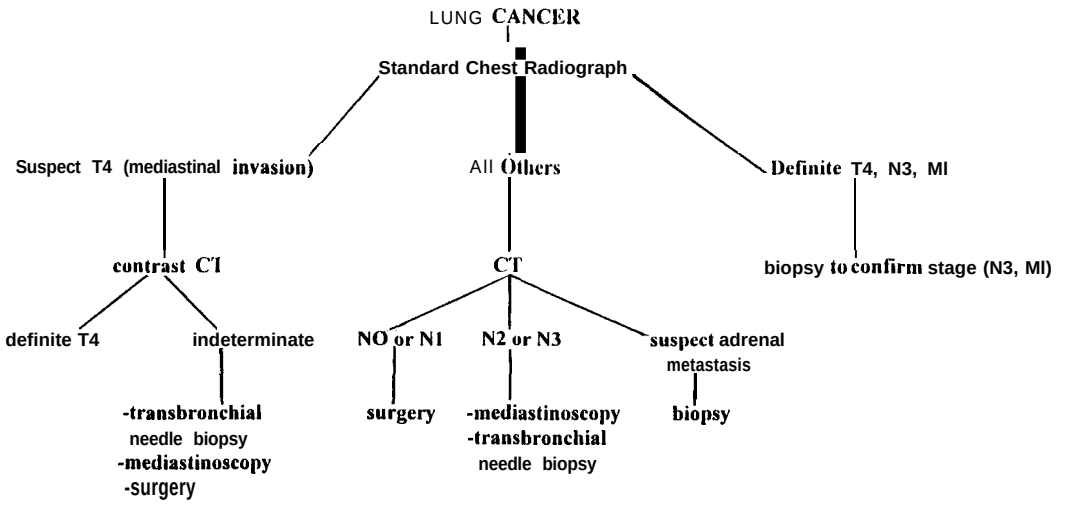

Figure 1.

forming CT in T1 peripheral nodules may be moot. CT is often indicated for other reasons apart from staging, including evaluation of the lesion with CT densitometry, which may detect benign patterns of calcification or fat, suggesting a benign lesion such as a hamartoma.

In summary, CT for evaluation of mediastinal adenopathy is recommended in all patients with suspected bronchogenic carcinoma, including those with T1 lesions.

Other Imaging Procedures

Studies of position emmision tomography (PET) scanning in relatively small numbers of patients suggest that this technique is more sensitive and more specific than CT for staging the mediastinum in lung cancer. Chin and colleagues (25) reported a sensitivity of 78%, a specificity of 81%, and a negative predictive value of 89%. However, this technique is still in the early stages of development and is not readily available except in academic centers.

THE SEARCH FOR EXTHORACIC METASTASES: CLINICAL AND IMAGING EVALUATION

The search for metastatic disease requires a thorough history and physical examination, accompanied by appropriate laboratory testing (Table 4). Specific abnormalities may guide the clinician in the decision to pursue further testing. Similarly, nonspecific findings such as weight loss should also raise suspicion that metastatic disease is present. Two recent meta-analyses compared the results of clinical evaluation with those of routine head CT, abdominal CT, and radionuclide bone scan in patients with newly diagnosed lung cancer (26, 27). There was great variation in the methodology of individual studies, particularly in the performance and reporting of the clinical evaluation, leading the authors to make only cautious recommendations about the need for routine head or abdominal CT or radionuclide bone scan. Both meta-analyses indicated that in studies where a comprehensive clinical evaluation was negative, the likelihood of finding metastatic disease on subsequent staging tests was low. Positive findings in the clinical evaluation should prompt further testing.

Evaluation of Distant Metastases on Chest CT (the M Factor)

Adrenal metastases. There appears to be general agreement among radiologists that CT of the thorax should include the adrenals because they are a frequent site of metastases from NSCLC. Adrenal adenomas occur in 2-10% of the general population. They are typically homogeneous, well circumscribed, and less than 3 cm in diameter. They can often be recognized on CT by their low attenuation, which is due to fatty content ($\leq$ -10 Hounsfield units [HU]). New advances in chemical shift imaging with MRI and PET may also allow distinction of adrenal adenomas from metastases without the need for percutaneous biopsy. However, biopsy of the adrenal gland should be performed in any indeterminate adrenal mass that is not shown to contain fat by either CT or MRI (Figure 1). Oliver and coworkers (28) showed that an enlarged adrenal gland was more likely to be an adenoma than metastatic disease in preoperative patients with NSCLC. A meta-analysis that combined data from greater than 1,000 patients with all stages and cell types of lung cancer found the prevalence of metastases (6.9%) at presentation was greater than adenomas (2.1%) (26). Although there are definite limitations in the evaluation of adrenal metastatic disease, inclusion of the adrenals on CT requires a minimum of extra time, CT slices, and radiation dose, and does not require the administration of contrast.

TABLE 4

STANDARDIZED CLINICAL EVALUATION FOR METASTATIC DISEASE IN PATIENTS PRESENTING WITH PRIMARY LUNG CANCER

Symptoms elicited in history
Constitutional: weight loss
Musculoskeletal: focal skeletal pain, chest pain
Neurological: headaches, syncope, seizures, extremity weakness, recent change in mental status
Signs found on physical examination
Lymphadenopathy (> 1 cm)
Hoarseness
Superior *vena cava* syndrome
Bone tenderness
Hepatomegaly
Focal neurologic signs: papilledema
Soft tissue mass
Routine laboratory tests
Hematocrit < 40% in males
Hematocrit < 35% in females
Elevated alkaline phosphatase, GGT, SCOT, calcium

Adapted from reference 26.

Liver metastases. The role of liver imaging as part of the initial staging chest CT for the detection of liver metastases is controversial. Most liver lesions are benign, and contrast is required to discriminate benign lesions, such as cysts and hemangiomas, from metastatic tumor. Standard contrast-enhanced CT (nonhelical or spiral) requires extra scanning time and increased radiation dosage and is therefore not recommended if the clinical evaluation is negative (26, 27). However, helical or spiral CT permits evaluation of both the thorax and the entire liver with a single bolus of contrast in a much reduced scan time. Percutaneous biopsy, if clinically indicated, is recommended for liver lesions suspicious for metastatic disease.

Cranial metastases. Cranial metastases are uncommon in patients with lung cancer but increase during the course of disease. The recommendations for routine head CT in asymptomatic patients vary among studies because the types of clinical evaluation performed differed (26). Pooled data from studies that used a comprehensive clinical evaluation (Table 4) indicate that metastases to the brain are found in no more than 3% of patients who have a negative clinical evaluation. Nevertheless, some investigators still advocate routine head CT in the staging of lung cancer, because the finding of a positive scan in an asymptomatic patient would prevent an unnecessary thoracotomy. This recommendation is not without risk, since false-positive results with head CT have been reported in as many as 11% of patients (29). A solitary lesion discovered on head CT may warrant biopsy before excluding the patient from a potentially curative thoracotomy. The recommendation is to perform head CT only in patients with newly diagnosed NSCLC who have positive findings on clinical evaluation (e.g., headaches, seizures) or in patients with nonspecific findings that suggest widespread disease (e.g., marked weight loss, severe anemia), if metastatic disease has not been documented elsewhere. This approach is supported by a recent analysis of the cost-effectiveness of head CT in patients without clinical evidence of metastatic disease (30). The use of routine MRI of the head has not been adequately studied and is not recommended at this time.

Bone metastases. Bone metastases are a frequent complication of lung cancer and may be demonstrated by a radionuclide bone scan. However, caution must be taken in interpreting bone scan findings because false-positive scans are common. The clinical evaluation is useful in deciding whether to obtain a radionuclide bone scan (Table 4) (26, 27). Common clinical findings of bone metastases include bone pain, pathologic fractures, and/or an elevated alkaline phosphatase or serum calcium level. The presence of any one of these in patients with NSCLC should prompt a radionuclide bone scan. Additionally, a bone scan should be obtained in patients with nonspecific findings indicative of metastatic disease, unless metastases have been documented elsewhere. If a radionuclide scan is performed and shows multiple areas of uptake consistent with metastases, no further evaluation is necessary. However, an isolated area of uptake may require further evaluation. A biopsy of the bone is seldom necessary for definitive diagnosis. If the clinical evaluation is negative, a radionuclide bone scan should not be performed.

In summary, the search for metastatic disease requires a careful clinical evaluation in the assessment of patients with newly diagnosed NSCLC. A negative clinical evaluation should reassure the clinician that the likelihood of metastatic disease is low and that no further diagnostic testing is warranted. When the clinical evaluation reveals abnormal findings, further evaluation is indicated, because approximately 50% of these patients will have metastatic disease (26). Any abnormality discovered by CT or radionuclide studies must be carefully considered, because false-positive test results do occur. In cases where there is any doubt, histologic confirmation should be obtained so that patients will be accurately staged and appropriately treated. The Summary Table outlines the tests recommended by the committee for all patients.

SUMMARY TABLE

Part A: Recommended tests for all patients

- Complete blood count
- Electrolytes, calcium, alkaline phosphatase albumin, AST, ALT, T, bili, creatinine
- Chest roentgenogram
- CT of chest through the adrenals*
- Pathologic confirmation of malignancy?

Part B: Recommended tests for selected but not all patients

Test	Indication
CT of liver with contrast or liver ultrasound	Elevated liver function tests; abnormal non contrast-enhanced CT of liver or abnormal clinical evaluation (see Table 4)
CT of brain with contrast or MRI brain	CNS symptoms or abnormal clinical evaluation
Radionuclide bone scan	Elevated alkaline phosphatase (bony fraction), elevated calcium, bone pain, or abnormal clinical evaluation
Pulmonary function tests	If lung resection or thoracic radiotherapy planned
Arterial blood gases	Patients with borderline resectability due to limited cardiopulmonary status
Quantitative radionuclide perfusion lung scan or exercise testing to evaluate maximum oxygen consumption	Patients with borderline resectability due to limited cardiopulmonary status

* May not be necessary if patient has obvious MI disease on chest X-ray or physical exam.

† While optimal in most cases, tissue diagnosis may not be necessary in some cases where the lesion is enlarging and/or the patient will undergo surgical resection regardless of the outcome of a biopsy.

THE ROLE OF BRONCHOSCOPY IN DIAGNOSING LUNG CANCER

Flexible fiberoptic bronchoscopy (FFB) is used to diagnose both central and peripheral lung lesions, but, in patients who present with a solitary pulmonary nodule where the suspicion of malignancy is high, surgical resection without prior invasive testing may be reasonable. FFB has a twofold role in the management of patients with suspected lung cancer: diagnosis and local staging.

Central Lesions

The overall diagnostic yield for NSCLC and SCLC, presenting as central lesions using bronchial forceps biopsy and brushing, is about 70% (31) but increases to $> 90\%$ when the lesion is visible bronchoscopically. Although the combination of bronchial biopsy and brushing is additive, the addition of bronchial washings does not further increase the yield. Three or four biopsies are usually adequate for diagnosis. The incidence of false-positive results with bronchial biopsies and brushings is low (for further details concerning bronchoscopic technique, see reference 32).

The major complication associated with forceps biopsy and/or bronchial brushing of central lesions is bleeding. Minor bleeding occurs frequently and is usually of no consequence. Major bleeding (> 50 cc) happens infrequently (2%).

The most important application of transbronchial needle aspiration (TBNA) is in staging malignant disease by aspirating mediastinal lymph nodes, which, if positive, can preclude the need for further surgical staging (33) (Figure 1). The overall sensitivity of TBNA staging of the mediastinum is 50%, with a specificity of 96%. Results are improved with proper attention to technique (33). Since the larger the lymph node, the greater the likelihood of a positive aspirate, a CT scan should be done before this procedure to help in selecting the best area to be sampled. The onsite presence of a cytologist further optimizes the yield. To avoid contamination, TBNA should be done before other samples are taken, and the needle should never be passed through an area with obvious endobronchial tumor. The major complications associated with TBNA are pneumathorax and bleeding, which are extremely uncommon even if pulmonary or systematic vessels are inadvertently entered and aspirated.

Peripheral Lesions

The procedure of choice for the diagnosis of a peripheral lesion is controversial. The combined diagnostic yield from transbronchial biopsies, transbronchial brushings, and washings with biplane fluoroscopy varies from 40–80% (31). The best determinant of diagnostic yield is the size of the lesion. Lesions that are < 2 cm in diameter have a bronchoscopic yield of about 30% or less, while those > 2 cm have a yield of 60-70% and those > 4 cm have a yield of approximately 80% (31).

Some authors emphasize the advantage of using TBNA and/or bronchoalveolar lavage (BAL) in addition to routine bronchoscopic techniques to enhance the diagnostic yield of peripheral lesions. Shure and Fedullo (34) reported that the addition of TBNA increased the diagnostic yield from 48% to 69%. The diagnostic yield increases with increasing size of the lesion.

BAL has also been used as a diagnostic tool for detecting peripheral lung neoplasms. In all studies, the yield is significantly affected by the type of cancer and the size of the lesion. The highest yields are reported in patients with bronchioloalveolar carcinoma and those whose tumors are > 3 cm. The addition of BAL to the evaluation of peripheral lesions has not convincingly improved the diagnostic yield of other sampling techniques and is not recommended for routine use (35, 36).

The complication rate from FFB in the diagnosis of peripheral carcinomas is extremely low and includes pneumothorax and significant hemorrhage, both of which occur in < 2% of patients undergoing these procedures.

THE ROLE OF TRANSTHORACIC NEEDLE ASPIRATION IN DIAGNOSING LUNG CANCER

Because the diagnostic accuracy of fluoroscopically or CT-guided transthoracic needle aspiration (TTNA) for diagnosing malignancy is in the range of 80–95%, it is the procedure of choice for sampling peripheral nodules (i.e., lesions < 3 cm) (37). The presence of a cytopathologist increases the diagnostic yield. Proof of a benign diagnosis is infrequent but can be improved by use of core samples. Only the conclusive evidence of a specific benign diagnosis can exclude malignancy. Although the specificity and positive predictive value of TTNA for cancer are extremely high, 20–30% of patients with negative (nondiagnostic) TTNA may have malignant lesions (37). If the clinical suspicion for malignancy is high, surgical removal of the lesion is indicated despite a negative TTNA. Since this is the case, many would proceed directly to surgical resection without TTNA or bronchoscopy. A repeat TTNA is diagnostic in 35–65% of cases. Patients with a nondiagnostic TTNA who do not undergo surgical removal of the lesion must be followed serially for at least 2 yr to assure a benign diagnosis. Other indications for TTNA include the diagnosis of mediastinal masses, the staging of patients with suspected local extension of cancer to the hilum, mediastinum, chest wall, or pleura, and the diagnosis of a chest abnormality after a nondiagnostic bronchoscopy.

The most frequent complication of TTNA is pneumothorax and occurs in 25–30% of patients, with 5–10% requiring some type of chest tube insertion. Other complications include self-limited intraparenchymal bleeding and, rarely, severe hemorrhage, air embolism, and tumor seeding of the needle tract. Rare deaths have also been reported.

Solitary Pulmonary Nodule

A widely accepted standard management plan for the solitary pulmonary nodule (SPN) (that is, a single-well circumscribed lesion < 3 cm within the lung) of unknown etiology is exploratory thoracotomy or video-assisted thoracoscopic surgery, unless benignity is established by clinical criteria or there are absolute contraindications to surgery. Criteria for a benign diagnosis include detection of fat or a benign pattern of calcification on computed tomogram (such as popcorn, laminated or diffuse) within the nodule, stability of the nodule (usually manifest as no growth over a 2-yr period determined from review of previous radiographs), and/or a very low probability of malignancy based on age (usually under 35 yr), and no exposure to tobacco smoke or other lung carcinogens. Besides the history of smoking, other risk factors for malignant disease include the size of the nodule, (lesions > 2 cm are more likely to be malignant), age over 50, and a prior history of a malignant lesion (38). If a diagnostic procedure is needed and the patient cannot undergo surgery, TTNA is the procedure of choice.

Most studies show that FFB is of little benefit in patients with SPN. Torrington and Kern (39) evaluated 91 patients with SPNs with FFB and found a low diagnostic yield. It did not obviate the need for surgery in those who did have lung cancer, and it did not alter the surgical staging. Additionally, it did not affect operative time or the operative procedure (39).

The use of the CT phantom nodule to determine density of an indeterminate SPN has generally been abandoned due to an unacceptably high misdiagnosis rate of 10–15% (40). PET has been used to evaluate SPN for malignancy with sensitivity rates of 85–95% and specificity of 80–90%. The exact role of PET scanning for evaluation of SPN is currently being defined. It is an expensive test that is not readily available except in academic centers (41, 42).

Occult Lung Cancer

In patients with no chest radiographic abnormalities, in whom cancer cells are found on cytologic analysis of sputum, direct visualization of the upper respiratory tract by an otolaryngologist and careful FFB of the tracheobronchial tree are indicated. When a lesion is found, direct forceps biopsies and brushings are obtained. If no lesion is identified at initial bronchoscopy and CT scanning of the chest, then FFB under general anesthesia should be performed with brushing sampling of all subsegments. If positive cytology results are obtained, the procedure should be repeated in the segment or lobe involved. If results are positive on two different occasions, surgical intervention is recommended.

A novel bronchoscopic autofluorescent imaging system has been developed to detect lung cancer and dysplasia (41). In a clinical trial, the sensitivity of the autofluorescent system (73%) was 50% greater than that of white light bronchoscopy (48%) in detecting both dysplasia and carcinoma *in situ.* Autofluorescent bronchoscopy may improve the ability of FFB to diagnose lung cancer in its early and occult stages. However, at this time the utility of autoflourescent bronchoscopy is unproven.

THE EVALUATION OF PLEURAL EFFUSIONS IN NON SMALL-CELL LUNG CANCER

Up to one-third of patients with NSCLC have a pleural effusion at the time of presentation (Table 1). The presence of a pleural effusion when a patient has lung cancer frequently indicates pleural metastases, but may be due to a sympathetic or parapneumonic process. Therefore, proof of malignancy is mandatory if it will alter management.

Thoracentesis alone (without closed needle biopsy) is usually satisfactory as the initial method to assess the presence of malignant involvement of the pleura. Cytologic examination of 50-100 ml of fluid will be positive for malignant cells in approximately 65% of all patients who have malignant pleural effusions. Most studies that have compared the diagnostic yield of cytologic examination of pleural fluid versus the yield from closed needle pleural biopsy have included patients with cancers from other primary sites as well as lung cancers. A retrospective analysis by Prakash and Reiman (44) included 81 patients with lung cancer who had malignant pleural involvement. The overall yield for cytology and pleural biopsy was 49181 (60%). Of the 49 cases, 47 were diagnosed by pleural fluid cytology, whereas only two additional cases were diagnosed with closed needle biopsy of the pleura. Since repeat thoracentesis may provide a positive specimen in as many as 30% more patients with malignant effusions (45), a second thoracentesis is preferred over routine closed needle pleural biopsy.

If thoracentesis does not prove that the pleural effusion is malignant, then the next step should be thoracoscopy. The diaphragmatic, visceral, and/or mediastinal pleura are easily accessible to a thoracoscope. Thoracoscopy will confirm the diagnosis of pleural involvement with cancer in $> 95\%$ of patients (46, 47). Additional merits of thoracoscopy include the potential to stage lymph node involvement or invasion of other mediastinal structures that would preclude successful resection with curative treatment. If there are no other contraindications to surgical resection, then thoracoscopy should be performed at the time of the planned surgical resection. A diagnosis of pleural metastases would preclude any attempt at surgical resection.

ASSESSMENT OF LUNG FUNCTION

Objective assessment of lung function is important for patients with lung cancer who are thought to be resectable. Whereas lobectomy or bilobectomy will spare more functioning lung tissue, it may be necessary to perform a pneumonectomy to completely resect a tumor. It is crucial to identify individuals who cannot tolerate resection, so that other forms of treatment that minimize loss of lung function can be offered as alternatives to surgery.

All non small-cell lung cancer patients without metastaticle disease should undergo spirometry before a treatment plan is chosen. Spirometry alone may provide sufficient information to determine whether a lung cancer patient can undergo resection of lung tissue. If the FEV_1 is > 2.0 L or $> 60\%$ of the predicted normal value, a pneumonectomy is likely to be tolerated (48). Additional simple measurements that predict a patient's ability to tolerate a pneumonectomy include a maximal voluntary ventilation $> 50\%$ of the predicted normal value, and a ratio of residual volume to total lung capacity that is $< 50\%$ (48, 49) or a diffusing capacity ($D_{L_{CO}}$) $> 60\%$ of the predicted normal value. Arterial blood gas analysis is another important and simple preoperative study. Hypoxemia ($Pa_{O_2} < 60$ mm Hg on room air at sea level) is a relative contraindication to lung resection, but right-to-left intrapulmonary shunting of blood flow because of lung atelectasis caused by bronchial obstruction may be an exception. Hypercapnia (> 45 mm Hg) that cannot be corrected is also a strong relative contraindication to lung resection.

If these data do not suggest a potentially safe resection, regional lung function assessment by quantitative radionuclide scanning and exercise testing helps to discriminate those at high risk of death with surgery. Perfusion lung scanning has been shown to be reliable (50). The product of preoperative FEV_1 and the percentage perfusion to the lung that will remain after surgery reliably predicts the postoperative FEV_1. If the predicted postoperative FEV, is $\geq 40\%$ of the predicted normal value, the likelihood of survival after pneumonectomy is high (0–15% operative mortality) (51). Similar criteria with estimates of loss of lung tissue after lobectomy have also proved accurate (46).

Exercise testing can provide additional information to assess operative risk (52). If progressive exercise testing reveals that maximal oxygen consumption is > 20 ml/kg/min, perioperative complications or death rates are not increased. Conversely, a maximal oxygen consumption < 10 ml/kg/min is strongly associated with increased morbidity and death when lung resection is performed. Patients with maximum oxygen consumption between IO-20 ml/kg/min will have higher complication rates after resection.

PREOPERATIVE EVALUATION OF NON SMALL-CELL LUNG CANCER: MEDIASTINOSCOPY, MEDIASTINOTOMY, AND THORACOSCOPY

Cure rates for non small-cell lung cancer are highly dependent on stage of disease and particularly the presence or absence of mediastinal lymph node metastasis (ipsilateral, N2, or contralateral, N3). Surgical curability is significantly less when mediastinal lymph node metastasis has occurred to multiple stations or when extracapsular nodal spread exists (53). CT evaluation of mediastinal lymph node metastasis has a sensitivity and specificity of only 60–70% when l-cm size is used as criteria for abnormality. In addition, as many as 37% of nodes 2-4 cm in diameter will not be found to have metastatic involvement at thoracotomy (22). Histological evaluation of mediastinal lymph nodes is essential for proper staging and treatment. A specific schema for mediastinal lymph nodes has been agreed upon (Figure 2). Mediastinoscopy, mediastinotomy, thoracoscopy, and TBNA each have a role to play in determining mediastinal lymph node status. A positive TBNA may preclude the need for additional surgical staging of the mediastinum (Figure 1).

Cervical Mediastinoscopy

Cervical mediastinoscopy is currently the best procedure to assess right paratracheal lymph nodes (area 4R) and, most times, subcarinal nodes (area 7). Left paratracheal (area 4L), supraaortic (area 6), and aortopulmonary window nodes (area 5) are not usually accessible due to the aortic arch. Pathologic evaluation is indicated for any patient believed to be a surgical candidate prior to thoracotomy if the CT scan has identified

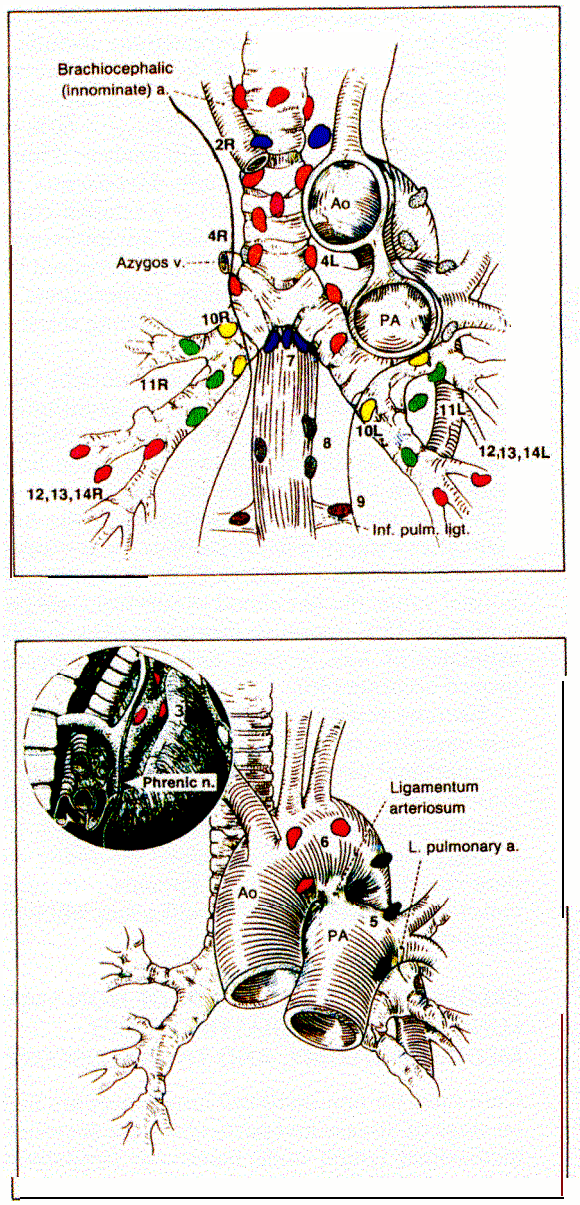

Figure 2. Regional nodal stations for lung cancer staging.

accessible lymph nodes > 1 cm in diameter. At mediastinoscopy, sampling of lymph nodes from multiple lymph node stations is optimal since patients with multilevel nodal disease are not usually operable for cure. This is also the case for extracapsular lymph node metastasis (54). For patients with suspected aortopulmonary window lymph node metastasis on the left side, either anterior mediastinotomy or left thoracoscopy is the procedure of choice.

The following guidelines are generally accepted for staging patients with NSCLC with regard to the mediastinal lymph node status. Patients with NSCLC should have a CT scan of the chest. If there are no lymph nodes in the mediastinum greater than 1 cm in diameter, the likelihood of there being N2 disease is small, and neither mediastinoscopy nor anterior mediastinotomy are essential prior to attempted curative surgical resection. If lymph nodes greater than 1 cm are identified, mediastinoscopy is indicated for right-sided nodes, and either anterior mediastinotomy or thoracoscopy is indicated for left-sided nodes (23). Mediastinoscopy with biopsy of the right paratracheal nodes (4R) is also indicated if left-sided nodes are enlarged to exclude contralateral lymph node metastasis (N3) (Figure 2).

STAGING SYSTEM FOR NON SMALL-CELL LUNG CANCER

In general, the purpose of the staging system is to group patients into anatomic subsets that can be used to assist in predicting prognosis and determining therapeutic options. The accuracy of staging is critical to the comparison of therapeutic results. Table 5 includes the TNM classification of the international staging system that has been approved by the AJCC and UICC in 1996. Table 6 identifies the stage grouping (55).

Several aspects of the new system should be stressed. There is a category for noninvasive tumors. These are defined as tumor *in situ* (TIS) and are stage 0. T3 tumors are defined

as those tumors that invade structures but are surgically resectable by conventional criteria. As an example, superior sulcus tumors that do not invade the vertebral body are T3. The presence of cytologically malignant pleural effusion (T4) represents unresectable disease.

Stage I has now been subdivided into stage IA (T1NOMO) and IB (T2NOMO). It should be noted that those patients with T1N1MO disease are now stage IIA, and stage IIB includes T2N1MO and T3NOMO. T3NOMO was moved from stage IIIA to IIB due to its relatively better survival. Stage IIIB groupings remain the same. Stage IV includes any patient with distant metastasis (Ml); however, the line of demarcation for supraclavicular (N3) versus cervical nodes (Ml) is inexact. If there is doubt, the patient should be assigned the better prognostic stage.

Pathological staging is more precise than clinical staging. Those patients who have definitive pathologic staging should be designated with the "p" prefix, while clinically staged patients are connoted by the prefix "c". Whenever possible, patients should be staged according to the TNM system, as an aid to evaluating the result of treatment.

Areas of Controversy and Confusion

The status of satellite nodule(s) has been clarified (see footnotes, Table 5). A satellite nodule(s) in the primary tumor-bearing lobe is classified as T4. Tumor nodule(s) in the ipsilateral lung but nonprimary tumor-bearing lobe are classified as Ml. The staging system classifies level 10 lymph nodes as intrapulmonary nodes (Figure 2). The term hilar nodes refers to intrapulmonary nodes (N1). If a lymph node can be biopsied at mediastinoscopy without creating a pneumothorax, then it is best classified as a mediastinal node (N2) with the appropriately numbered station (Figure 2).

The stage of disease does not categorically determine the optimal treatment approach. While it is generally agreed that those patients who are medically fit and have stage IA/B or IIA/B disease are best treated with surgical resection and patients with stage IV (Ml) disease are not surgical candidates, deviation from these parameters are noted in the literature. There is considerable disagreement on the optimal treatment approach to patients with IIIA and even subsets of IIIB disease.

MANAGEMENT OPTIONS

Following the completion of staging, patients can be appropriately referred. Ideally, patients are seen in a multidisciplinary thoracic oncology clinic with a pulmonary specialist, medical oncologist, radiation oncologist, and thoracic surgeon. This multispecialty approach is most advantageous when the optimal therapy is most controversial.

Operable Patients: Stages IA/B, IIA/B, Selected IIIA

Operable patients who are clinically stage IA/B or IIA/B are usually treated with surgery, since this is the treatment that has produced the vast majority of long-term survivors (56).

TABLE 5

TNM DEFINITIONS

Primary tumor(T):	
TX	Primary tumor cannot be assessed, or tumor proven by presence of malignant ceils in sputum or bronchial washings but not visualized by imaging or bronchoscopy.
TO	No evidence of primary tumor.
Tis	Carcinoma in situ.
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than lobar bronchus (i.e., not in main bronchus).*
T2	Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension; Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura; or Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.
T3	Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, or pericardium; tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, or carina; or tumor with a malignant pleural effusion+ or pericardial effusion, or satellite nodule(s) within the primary bearing lobe.
Lymph node (N):	
NX	Regional lymph nodes cannot be assessed.
NO	No regional lymph node metastasis.
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, including direct extension.
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s).
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).
Distant metastasis (M):	
MX	Presence of distant metastasis cannot be assessed.
MO	No distant metastasis.
MI	Distant metastasis.‡

• The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1

† Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytologic examinations of pleural fluid are negative for cancer. In these cases the fluid is nonbloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged T1, T2, or T3. Pericardial effusion is classified according to the same rules,

*Tumor nodule(s) in the ipsilateral lung non primary tumor-bearing lobe are classified as Ml.

TABLE 6

NEW INTERNATIONAL REVISED STAGE GROUPING

Stage 0	TIS
Stage IA	T1, NO, MO
Stage IB	T2, NO, MO
Stage IIA	T1, N1, MO
Stage IIB	T2, N1, MO
	T3, NO, MO
Stage IIIA	TI-3, N2, MO
	T3, N1, MO
Stage IIIB	T4, Any N, MO
	Any T, N3, MO
Stage IV	Any T, Any N, MI

Adapted from reference 55.

These patients are best served by referral to a thoracic surgeon with a special interest in lung cancer surgery. Typical 5-yr survival figures for resected patients with stage IA and IB are 70–80% and 50–60%, respectively. Stage IIA/B patients have a 35-50% 5-yr survival rate. Adequate surgery usually consists of either a lobectomy, bilobectomy, or a pneumonectomy with mediastinal node sampling for staging purposes. Lesser procedures are associated with higher rates of local recurrence and a trend toward decreased survival (57). Because of the high incidence of second malignancies of the lung, esophagus, or head and neck area, postoperative stage I patients may be offered participation in investigational chemoprevention protocols. Adjuvant therapy is not currently the standard of care but is being evaluated for postoperative stage IB, IIA and B, and IIIA patients.

The treatment of patients with N2 stage IIIA is more controversial, with wide variations in reported surgical series (58). A multi-modality approach with the input of pulmonary physician, thoracic surgeon, medical oncologist, and radiation oncologist is best for this group of patients, since they are generally treated with radiation therapy and chemotherapy. Four large randomized studies have now shown that chemotherapy and radiation therapy produced superior survival when compared with radiation therapy alone (59-62). The exact role of surgery as an adjunct to chemoradiotherapy has not been fully defined.

Patients who are considered borderline candidates for resection due to poor pulmonary function but who would otherwise be operative candidates should still be referred for thoracic surgery evaluation. Ideally, joint consultation among surgeon, pulmonologist, and radiation oncologist will result in the best treatment approach. Thoracoscopy or thoracotomy with limited resection is feasible in some patients who cannot tolerate a lobectomy.

Inoperable Patients: Stages IIIB and IV

Patients with IIIB NSCLC and good performance status (Zubrod, 0 or 1, Karnofsky > 70%) NSCLC are typically treated with combined chemoradiotherapy. Options for patients found to have stage IV disease are palliative care or chemotherapy with radiation therapy for the palliative treatment of bronchial obstruction, painful bone metastases, or central nervous system metastases. Those individuals with good performance status and weight loss of less than 5% in the last 6 mo are those most likely to respond to chemotherapy. These patients should be referred to a medical oncologist to review treatment options or for enrollment in controlled clinical trials. If palliative care is the best option, referral to a physician well versed in palliative care should be considered. At a minimum, this requires knowledge of pain control measures, a working relationship with an established hospice program, and attention to the psychosocial needs of the dying patient and his/her family. This is an area best covered, although not exclusively, under the aegis of medical oncology. The pulmonologist, thoracic surgeon, and radiation oncologist may contribute to the management of patients with endobronchial obstruction of the trachea or major bronchi or for those individuals with symptomatic malignant pleural effusion.

Medically Inoperable Patients

Stage I, II, and III patients who are inoperable for medical reasons may be considered for radiation therapy alone if they cannot tolerate combined modality therapy. Randomized trials have demonstated that combined chemotherapy and radiotherapy result in significantly better survival. Stage IV patients with significant comorbid illnesses may be candidates for palliative therapy only.

POSTSCRIPT

In the United States over 170,000 individuals,will be diagnosed with lung cancer in 1997. The 5-yr survival rate is currently 13%. We do not know the optimal treatment for the various histologies and stages. Our state-of-the-art knowledge about treatment has been derived predominantly from clinical trials. In spite of limited knowledge and sometimes marginally effective therapies, only 1–2% of all lung cancer patients are enrolled in clinical trials.

Primary care and subspecialty physicians are strongly urged to participate and/or support the enrollment of their lung cancer patients in prospective clinical trials. With the large number of cooperative oncology groups and the proliferation of community cancer oncology programs that are supported by the National Cancer Institute, clinical trials are available to the patient without a great deal of inconvenience and, at the same time, offer patients the best available treatments. Without clinical trials there will be no advance in the state of the art, and we will continue to settle for the dismal 5-yr survival of 13 %.

This Official Statement was prepared by an Ad-hoc Committee of the Assembly on Clinical Problems. Members of the Committee are: JAMES JETT, M.D. (Chairman), RICHARD FEINS, M.D., PAUL KVALE, M.D., THERESA MCCLOUD, M.D., YORK W. MILLER, M.D., MICHAEL PERRY, M.D., WILLIAM SAUSE, M.D., GERALD SILVESTRI, M.D., DIANE STOVER, M.D., STEPHEN SPIRO, M.D., and WILLIAM TRAVIS, M.D.

References

1. Frost, J. K., W. C. Ball, Jr., M. L. Levin, M. S. Tockman, R. R. Baker, D. Carter, et al. 1984. Early lung cancer detection: results of the initial prevalence radiologic and cytologic screening in the Johns Hopkins study. *Am. Rev. Respir. Dis.* 130:549–554.
2. Melamed, M. R.. B. J. Flehinaer, M. B. Zaman, R. T. Heelan, W. A. Perchick, and N. Martin. 1984. Screening for early lung cancer: results of the Memorial Sloan-Kettering study in New York. Chest 86:44–53.
3. Fontana, R. S., D. R. Sanderson, L. B. Woolner, W. F. Taylor, W. E. Miller, and J. R. Muhm. 1986. Lung cancer screening: the Mayo program. *J. Occup. Med.* 28:746–750.
4. Tockman, M. S. 1986. Survival and mortality from lung cancer in a screened population: the Johns Hopkins Study. Chest 89:324S–325S.
5. Flehinger, B. J., M. Kimmel, J. Polyak, and M. R. Melamed. 1993. Screening for lung cancer: the Mayo Lung Project revisited. Cancer 72:1573–1580.
6. Kubik, A., D. M. Parkin, M. Khlat, J. Erban, J. Polak, and M. Adamec. 1990. Lack of benefit from semi-annual screening for cancer of the lung: follow-up report of randomized controlled trial on a population of high-risk males in Czechoslovakia. *Int. J. Cancer* 45:26–33.
7. Tockman, M. S., N. R. Anthonisen, E. C. Wright, and M. G. Donithan. 1987. Airway obstruction and the risk for lung cancer. *Ann. Int. Med.*

106:512–518.
8. Zang, E. A., and E. L. Wynder. 1996. Differences in lung cancer risk between men and women: examination of the evidence. *J.* Nat. Cancer *Inst.* 88:183–192.
9. Spiro, S. G. 1995. Bronchial tumors, In R. A. L. Brewis, B. Corrin, D. M. Geddes, and G. J. Gibson, editors. Respiratory Medicine. W. B. Saunders. New York.
10. Poe, R. H.. R. H. Isreal, M. G. Marin, *et* al. 1988. Utility of fiberoptic bronchoscopy in patients with hemoptysis and a non localizing chest roentgenogram. *Chest* 93:70–75.
11. Patel, A. M., and J. R. Jett. 1996. Clinical presentation and staging of lung cancer. *In* J. Aisner, R. Arrigada, M. R. Green, N. Martini, and M. C. Perry. editors. Comprehensive Textbook of Thoracic Oncology. Williams and Wilkins. Baltimore. 293-318.
12. Ferrigno, D., and G. Buccheri. 1995. Clinical applications of serum markers for lung cancer. *Respir. Med.* 89:587–597.
13. Colby, T. V., M. N. Koss. and W. D. Travis. 1995. Tumors of the lower respiratory tract. *In* Armed Forces Institute of Pathology Fascicle, Third Series. Armed Forces Institute of Pathoiogy, Washington, DC.
14. Travis. W. D., J. Linder, and B. Mackay. 1996. Classification histology, cytology and electron microscopy. In H. I. Pass, J. B. Mitchell, D. H. Johnson. and A. T. Turrisi, editors. Lung Cancer, Principles and Practice. Lippincott-Raven, Philadelphia. 361-395.
15. Association of Directors of Anatomic and Surgical Pathology. 1995. Recommendations for the reporting of resected primary lung carcinomas. *Hum. Pathol.* 26:937–939.
16. World Health Organization. 1981. Histological Typing of Lung Tumors. 2nd ed. World Health Organization. Geneva.
17. Travis. W. D.. L. B. Travis. and S. S. Devesa. 1995. Lung cancer. *Cancer* 75:191–202.
18. Roggli, V. L.. R. T. Vollmer, S. D. Greenberg. M. H. McGavran. H. J. Spjut, and R. Yesner. 1985. Lung cancer heterogeneity: a blinded and randomized study of 100 consecutive cases. Hum. *Pathol.* 16:569–579.
19. Hirsch. F. R., M. J. Matthews, S. Aisner, 0. Campobasso. J. D. Elema, A. F. Gazdar, er al. 1988. Histopathologic classification of small cell lung cancer: changing concepts and terminology. *Cancer* 62:973–977.
20. Travis. W. D., R. I. Linnoila, M. G. Tsokos. C. L. Hitchcock, G. B. Cutler, Jr.. L. Nieman. *et* al. 1991. Neuroecdocnne tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma: an ultrastructural. immunohistochemica!. and flow cytometric study of 35 cases, *Am J. Surg. Pathol.* 15:529–553.
21. Webb, W. R., C. Gatsonis, E. A. Zerhouni. *et* al. 1991. CT and MR staging in non-small cell bronchogenic carcinoma: report of the Radiologic Diagnostic Oncology Group. *Radiology* 178:705–713.
22. McLoud, T. C., P. M. Bourgouin, R. W. Greenberg, et al. 1992. Bronchogenic carcinoma: analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling. *Radiology 182: 319-323.*
23. The Canadian Lung Oncology Group. 1995. Investigation for mediastinal disease in patients with apparently operable lung cancer. *Ann. Thorac. Surg.* 60:1382–1389.
24. Seely, J., J. R. Mayo, R. R. Miller, *et al.* 1993. T1 lung cancer: prevalence of mediastinal nodal metastases (diagnostic accuracy of CT). *Radiology* 186:129–132.
25. Chin, R.. Jr.. R. Ward. J. W. Keys. Jr., R. H. Choplm, J. C. Reed. S. Wallenhaupt. A. S. Hudspeth, and E. F. Haponik. 1995. Mediastmal staging of non-small cell lung cancer with positron emission tomography. *Am. J. Respir. Crit. Care Med.* 152:2090–2096.
26. Silvestri, G. A., B. Littenberg, and G. L. Colice. 1995. The clinical evaluation for detecting metastatic lung cancer: a meta-analysis. *Am. J. Respir. Crit. Core Med.* 152:225–230.
27 Hillers, T. K., M. D. Sauve, and G. H. Guyatt. 1994. Analysis of published studies on the detection of extrathoracic metastases in patients presumed to have operable non-small cell lung cancer. *Thorax* 49: 14–19.
28. Oliver, T. W.. Jr., M. E. Bernadino, J. I. Miller. *et al.* 1984. Isolated adrenal masses in non small cell bronchogenic carcinoma. *Radiology 153:* 217–218.
29. Patchell. P. A.. P. A. Tibbs, J. W. Walsh. *et al.* 1990. A randomized trial of surgery in the treatment of single brain metastases. N. *Engl. J. Med.* 322:494–500.
30. Colice, G. L., J. D. Birkmeyer. W. C. Black. B. Littenberg, and G. A. Silvestri. 1995. Cost-effectiveness of head CT in patients with lung cancer and no clinical evidence of metastases. *Chest* 108:1264–1271.
31. Arroliga. A. C.. and R. A. Matthay. 1993. The role of bronchoscopy in lung cancer. *Clin. Chest Med.* 14:87–98.
32. Borchers, S. D., and J. F. Beamis, Jr. 1996. Flexible bronchoscopy. *Chest Surg. Clin. North Am.* 6:169–192.
33. Harrrow, E. M., and K. P. Wang. 1996. The staging of **lung** cancer by bronchoscopic transbronchial needle aspiration. *Chest Surg. C/in. North Am.* 6:223–235.
34. Shure, D., and P. F. Fedullo. 1983. Transbronchial needle aspiration of peripheral masses. *Am. Rev. Respir. Dis.* 128:1090–1092.
35. Pirozynski, M. 1992. Bronchoalveolar lavage in the diagnosis of peripheral, primary lung cancer. *Chest* 102:372–374.
36. de Gracia, J.. C. Brave, M. Miravitles, N. Tallada, R. Orriols, J. Bellmunt, *et al.* 1993. Diagnostic value of bronchoalveolar lavage **in** peripheral lung cancer. *Am. Rev. Respir. Dis.* 147:649–652.
37. Salazar, A. M.. and J. L. Westcott. 1993. The role of transthoracic needle biopsy for the diagnosis and staging of lung cancer. *Clin. Chest Med.* 14:99–110.
38. Midthun, D. E., S. J. Swensen, and J. R. Jett. 1993. Approach to the solitary pulmonary nodule. *Mayo Clin. Proc.* 68:378–385.
39. Torrington, K. G., and J. D. Kern. 1993. The utility of fiberoptic bronchoscopy in the evaluation of the solitary pulmonary nodule. *Chest* 104:1021–1024.
40. Swenson. S. J., G. F. Harms, R. L. Morin, and J. L. Myers. 1991. CT evaluation of solitary pulmonary nodules: value of 185-H reference phantom. *AJR* Am. *J. Roentgenol.* 156:925–929.
41. Dewan, N. A., N. C. Gupta, L. S. Redepenning, *et al.* 1993. Diagnostic efficacy of PET-FDG imaging in solitary pulmonary nodules. *Chest* 104: 997-l 002.
42. Patz, E. F., V. J. Lowe: J. M. Hoffman, *et al.* 1993. Focal pulmonary abnormalities: evaluation with F-18 fluorodeoxyglucose PET scanning. *Radiology* 188:487–490.
43. Lam. S.. C. MacAulay, J. Hung. J. LeRiche. H. E. Profio, and B. Palcic. 1993. Detection of dysplasia and carcinoma in situ with a lung unaging fluorescence endoscope device. *J. Thorac. Cariovsc. Surg.* 105:1035–1040.
44. Prakash. U. B. S., and H. M. Reiman. 1985. Comparison of needle biopsy with cytologic analysis for the elevaluation of pleural effusion: analysis of 414 cases. *Mayo Clin. Proc.* 60:158–164.
45. Light, R. W., Y. S. Eozan. and W. C. Ball. 1973. Cells in pleural fluid: their value in differential diagnosis. *Arch. Intern Med.* 132:84–60.
46. Boutin. C., J. R. Viallat, P. Cargnino. *et al.* 1981. Thoracoscopy in malignant pleural effusions. *Am. Rev. Respir. Dis.* 124:588–592.
47. Menzies, R.. and M. Charbonneau. 1991. Thoracoscopp for the diagnosis of pleural disease. *Ann. Intern. Med.* 114:271–276.
48. Dunn. W. F.. and P. D. Scanlon. 1993. Preoperative pulmonary function testing for patients with lung cancer. *Mayo Clin. Proc.* 68:371–377.
49. Putnam. J. B.. Jr., D. E. Lammermeier, R. Colon. er al. 1990. Predicted pulmonary function and survival after pneumonectomy for primary lung carcinoma. *Ann. Thorac. Surg.* 49:909–914.
50. Wernly, J. A., T. R. DeMeester, P. T. Kirchner. *et* al. 1980. Clinical value of quantitative ventilation-perfusion lung scans in the surgical management of bronchogenic carcinoma. *J. Thorac. Cardio. Surg. 80: 535-543.*
51. Markos, J., B. P. Mullan, D. R. Hillman, *et al. 1989.* Preoperative assessment as a predictor of mortality and morbidity after lung resection. *Am. Rev. Respir. Dis.* 139:902–910.
52. Bechard. D., and L. Wetstein. 1987. Assessment of exercise oxygen consumption as preoperative criterion for lung resection. *Ann Thorac. Surg.* 44:344–349.
53. Luke, W. P.. F. G. Pearson. T. R. J. Todd. *et al.* 1986. Prospective evaluation of mediastinoscopy for assessment of carcinoma of the lung. *J. Thorac. Cardiovas. Surg.* 91:53–56.
54. Pearson. F. G., N. C. DeLarue, R. Ilves. *et al.* 1995. Significance of positive mediastinal lymph nodes identified at mediastinoscopy in patients with resectable cancer of the lung. *J. Thorac. Cardiovasc. Surg.* 83: 1.
55.' Mountain, C. F. 1997. The new lung cancer staging system. *Chest* (In **press)**
56. Martini, N., and R. J. Ginsberg. 1996. Treatment of stage I and II disease. In J. Aisner, R. Arrigada, R. Green. N. Martini, and M. C. Perry. editors. The Comprehensive Textbook of Thoracic Oncology. Williams and Wilkens, Baltimore.
57. Lung Cancer Study Group. 1995. Randomized trial of lobectomy versus limited resection for TINO nonsmall cell lung cancer. *Ann Thorac. Surg.* 60:615–623.
58. Rusch, V. W.. and Y. Gincherman. 1996. Surgical management of stage IIIA non-small cell lung cancer. *In* J. Aisner, R. Arrigada, M. R. Green, N. Martini, and M. C. Perry, editors. The Comprehensive Textbook of Thoracic Oncology. Williams and Wilkins, Baltimore.
59. Dillman, R. 0.. J. Herndon. S. J. Seagren, *et al.* 1996. Improved survival in stage III non-small cell lung cancer: seven year follow-up of cancer

and leukemia group B, (CALGB) 8433 Trial. *J. Natl.* Cancer *Inst.* 88: 1210–1216.

60. LeChevalier, T., R. Arriagada, E. Quoix, *et* al. 1991. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non small cell lung cancer: first analysis of a randomized trial in 353 patients. *J. Natl.* Cancer *Inst.* 83:417–423.

61. Schaake-Koning, C., W. VanDen Bogeart, 0. Dalesio, et al. 1992. Effects of concomitant cisplatin and radiotherapy on inoperable non-small cell lung cancer. N. *Engl. J. Med.* 326:524–530.

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