STAGING CLASSIFICATION OF LUNG CANCER

A Critical Evaluation

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In patients with lung cancer, the relationship between the anatomic extent of the disease at diagnosis and survival duration is well known. This relationship is the basis for the staging concept. Many host and tumor characteristics have been investigated for their influence on prognosis in this disease[5, 9, 13, 19, 20, 42, 44]; however, end results studies according to components of the International System for Staging Lung Cancer, the TNM factors (T-primary tumor, N-regional lymph nodes, M-distant metastasis), and the stage group remain benchmarks for estimating prognosis, entering patients into clinical trials, comparing differing treatments, and evaluating new prognostic factors. The consistent, reproducible definitions provide the means for universal communication about the status of treatment for specific groups of patients. These tenets are confirmed in the most recent texts on the diagnosis and treatment of lung cancer; their organization of content according to staging components describes clinical evaluations and recommendations for therapy in these terms.[15, 46] The staging system as an effective vehicle for communicating new knowledge about lung cancer also is revealed in the national and international medical literature.[6, 7, 16, 26, 29, 53]

THE INTERNATIONAL SYSTEM FOR STAGING LUNG CANCER

The International System for Staging Lung Cancer[38] has had widespread application since its adoption by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) in 1997.[2, 23, 25] Box 1 and Table 1 document the definitions and the stage grouping of the TNM subsets. The system is applicable for the four major cell types of lung cancer: adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and small cell carcinoma. Clinical staging, cTNM-cStage, is based on all diagnostic and evaluative information obtained before the

Table 1. TNM (TUMOR, REGIONAL LYMPH NODES, METASTASIS) BY STAGE*

Stage	TNM Subset
0	Carcinoma in situ
IA	T1 N0 M0
IB	T2 N0 M0
IIA	T1 N1 M0
IIB	T2 N1 M0
	T3 N0 M0
IIIA	T3 N1 M0
	T1 N2 M0
	T2 N2 M0
	T3 N2 M0
IIIB	T4 N0 M0 T4 N1 M0
	T4 N2 M0
	T1 N3 M0 T2 N3 M0
	T3 N3 M0 T4 N3 M0
IV	Any T Any N M1

*Staging is not relevant for occult carcinoma, designated TX N0 M0. *From* Mountain CF: Revisions in the International Staging System for Lung Cancer. Chest III 1712, 1997; with permission.

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Box 1. TNM (Tumor, Regional Lymph Nodes, Metastasis) Descriptors

Primary Tumor (T)

TX Primary tumor cannot be assessed or tumor proved by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0 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 the lobar bronchus* (i.e., not in the 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
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 parietal pericardium; or 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 or pericardial effusion†; or with satellite tumor nodule(s) within the ipsilateral primary tumor lobe of the lung

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes involved by direct extension of the primary tumor
N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3 Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis present‡. Specify sites

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*T1: The uncommon superficial tumor of any size with its invasive component limited to the main bronchus is classified as T1.
†T4: Most pleural effusions associated with lung cancer are caused by tumor. There are, however, a few patients in whom cytopathologic examination of pleural fluid (on more than one specimen) is negative for tumor, the fluid is nonbloody, and is not an exudate. In such cases in which these elements and clinical judgment dictate that the effusion is not related to the tumor, the patients should be staged T1, T2, or T3, excluding effusion as a staging element.
‡M1: Separate metastatic tumor nodule(s) in the ipsilateral nonprimary tumor lobe(s) of the lung also are classified M1.
From Mountain CF: Revisions in the International System For Staging Lung Cancer. Chest 111:1711, 1997; with permission.

start of treatment, including the results of invasive procedures, such as bronchoscopy, needle biopsy, mediastinoscopy, and diagnostic thoracoscopy. The clinical stage is assigned to each patient and is not changed throughout the course of the disease. The importance of the clinical classification cannot be overemphasized because this information is correlated with end results studies to serve as a guide for treatment planning. The survival data in Figures 1 and 2 demonstrate that clinical staging groups patients according to measurable anatomic features of their disease that are relevant to treatment options and prognosis.

The classification schema also is useful for surgical–pathologic staging, pTNM-pStage, based on pathologic examination of resected specimens. In Figure 3, survival data according to pStage reflect the more accurate evaluation of disease extent that is available from surgical–pathologic data. The options for definitive treatment and survival patterns are related to pStage factors. A retreatment classification, rTNM-rStage, is useful for assessing the efficacy of the first step in multistep treatment plans. For example, protocols of induction therapy may use the rTNM-rStage as criteria for assigning or randomizing patients to subsequent treatments. The use of identical definitions for each type of classification is essential; elements that can be determined only from surgical specimens are not included in the schema.

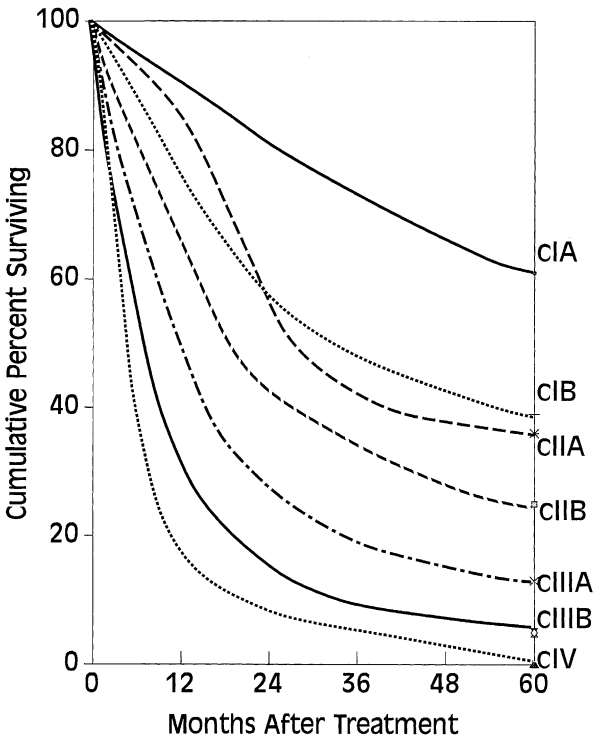

Figure 1. Cumulative proportion of patients with non–small cell lung carcinoma expected to survive 5 years according to clinical stage. Number of patients: cIA, n = 675; cIB, n = 1130; cIIA, n = 26; cIIB, n = 329; cIIIA, n = 445; cIIIB, n = 836; cIV, n = 1166. Overall comparison: $P < .05$. Pairwise comparison: cIA versus cIB, $P < .05$; cIB versus cIIA, $P > .05$; cIIA versus cIIB, $P < .05$; cIIB versus cIIIA, $P < .05$; cIIIA versus cIIIB, $P < .05$; cIIIB versus cIV, $P < .05$. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification. Houston, Mountain and Libshitz, 1999, p 65; with permission.)

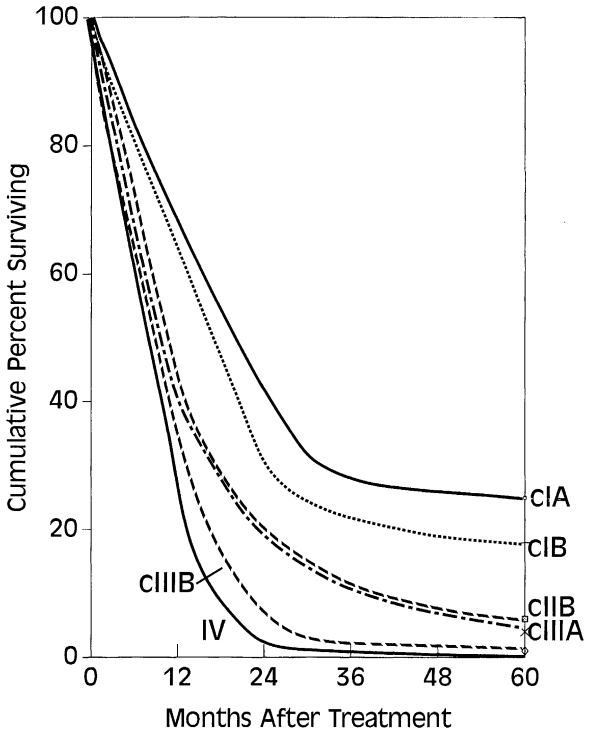

Figure 2. Cumulative proportion of patients with small cell lung carcinoma expected to survive 5 years according to clinical stage. Number of patients: cIA, n = 12; cIB, n = 59; cIIA, n = 3; cIIB, n = 28; cIIIA, n = 66; cIIIB, n = 194; cIV, n = 261. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification, Houston, Mountain and Libshitz, 1999, p 67; with permission.)

Disease Extent by Stage

Stage 1A is reserved for the best prognostic group (i.e., patients with T1 N0 M0 tumors). An example is the small tumor in the left lower lobe shown in Figures 4 and 5. No evidence of metastasis or invasion proximal to a lobar bronchus was demonstrated (cStage 1A disease). The influence of tumor size, location, and invasion on survival time is reflected in the survival pattern for these patients, whose prognosis is significantly better than that of any other stage category, according to clinical and surgical pathologic criteria (see Figs. 1 and 3). Patients with cStage IA non–small cell lung cancer usually are referred for consideration of definitive surgical treatment, and those with small cell tumors may be assigned to investigational adjuvant surgical protocols (see Fig. 2).[31]

Stage 1B classifies tumors with increasing size and invasion (Fig. 6). One example of T2 N0 M0 disease is shown in Figure 7, a CT scan of the chest that confirmed a 4-cm tumor in the left upper lobe. No pleural involvement or metastasis was present (cStage 1B). Although patients with non–small cell cStage 1B tumors are candidates for definitive surgical treatment, prognosis can be eroded because of the size, location, and invasive characteristics of the group—reflected in the survival data from clinical and surgical–pathologic criteria (See Figs. 1 and 3). Patients with small cell tumors may be assigned to studies of investigational adjuvant surgical treatment programs (see Fig. 2).[22] The difference in survival between the stage 1A and 1B groups is statistically significant by clinical and surgical–pathologic criteria.

Stage IIA is reserved for patients with T1 tumors that have intrapulmonary or hilar lymph node metastasis (T1 N1 M0 disease). Although this clinical presentation is infrequent and the outcome is similar to that for the stage IB group, the classification is important to identify and study the implications of the early spread of lung cancer and its most appropriate staging (Figs. 8 and 9). Figure 8 is a CT scan (lung windows) through a lesion, seen on chest roentgenogram in the right lower lobe, that confirmed a T1 tumor. The CT scan (soft tissue windows) in Figure 9 reveals a right hilar node that later was proved to contain metastasis (cStage IIA). Patients with cStage IIA tumors are candidates for surgical treatment, and their prognosis is

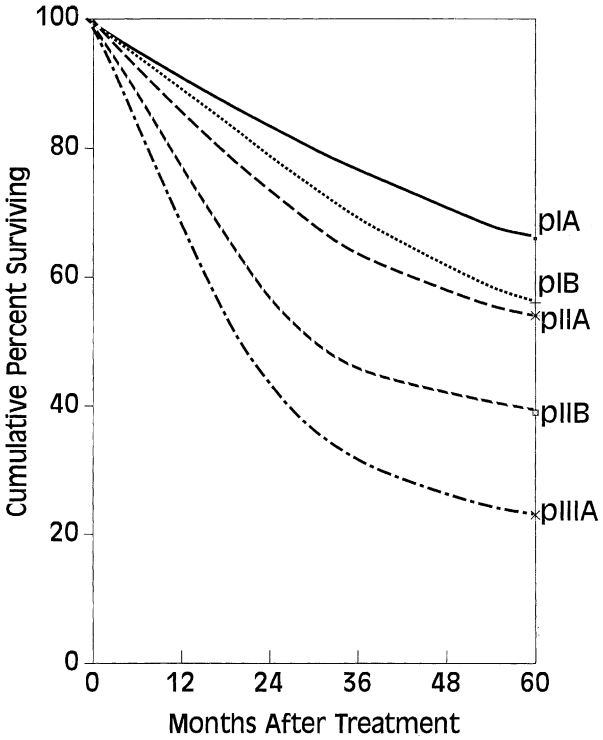

Figure 3. Cumulative proportion of patients with non–small cell lung cancer expected to survive 5 years according to surgical-pathologic stage. pStage IA, n = 511; pIB, n = 549; pIIA, n = 76; pIIB, n = 375; pIIIA, n = 399. Overvall comparison: $P < .05$. Pairwise comparisons: pIA versus pIB, $P < .05$; pIB versus pIIA, $P > .05$; pIIA versus pIIB, $P < .05$; pIIB versus pIIIA, $P < .05$. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification. Houston, Mountain and Libshitz, 1999, p 66; with permission.)

similar to that for patients with cStage IB disease (see Figs. 1 and 3).

Stage IIB includes two anatomic subsets: T2 N1 M0 and T3 N0 M0 tumors. Earlier versions of the staging system included patients with T3 N0 M0 tumors in stage IIIA; however, the 1997 revisions took into account that the survival for this group was nearly identical to that for patients with T2 N1 M0 tumors; the two subsets now are designated stage IIB. The two subsets are shown diagrammatically in Figure 10:

- Tumors larger than 3 cm in greatest dimension or those of any size that invade the visceral pleura or the main bronchus more than 2 cm distal to the carina, all with metastasis involving the intrapulmonary, including hilar lymph nodes.
- Tumors with limited, circumscribed extrapulmonary extension and no evidence of metastasis.

One example of cStage IIB is shown in Figure 11, which illustrates chest wall invasion by a tumor in the right upper lobe. No evidence of lymph node involvement was present. A significant difference in survival, according to clinical and surgical–pathologic criteria, is shown for the stage IIB groups compared with the outcome for stage IIA patients (see Figs. 1 and 3).

The survival patterns shown in Figures 1 and 3 for patients with stage IA, IB, IIA, and IIB non–small cell lung cancer reflect the potential for cure of the treatment options for these groups of patients. The implications of stage migration and more accurate evaluation of disease extent are reflected in the differences in survival patterns between the clinically staged and surgical–pathologic–staged patients. The outcome for patients with small cell cancer according to clinical stage shows that the classification identifies those groups with a potential for achieving the complete response required for long-term survival. As noted earlier, investigational protocols involving adjuvant surgery are designed for specific TNM groups.

Stage IIIA includes four anatomic subsets that are shown diagrammatically in Figure 12: T3 tu-

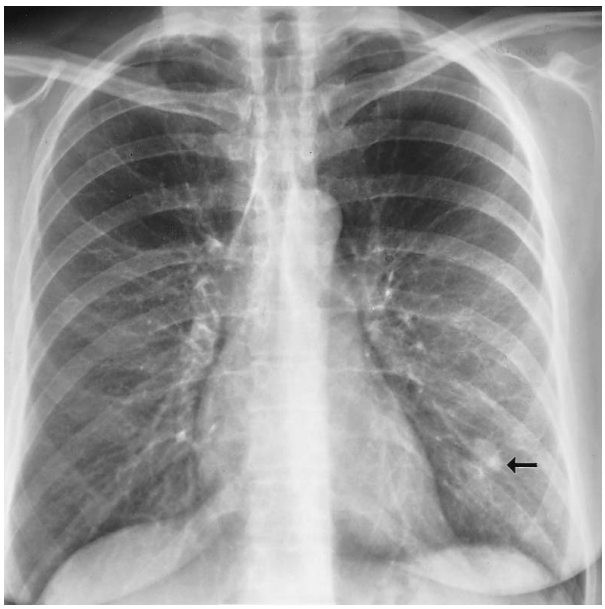

Figure 4. PA chest radiograph showing a <2-cm left lower lobe bronchogenic carcinoma *(arrow)*, stage IA. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification. Houston, Mountain and Libshitz, 1999, p 28; with permission.)

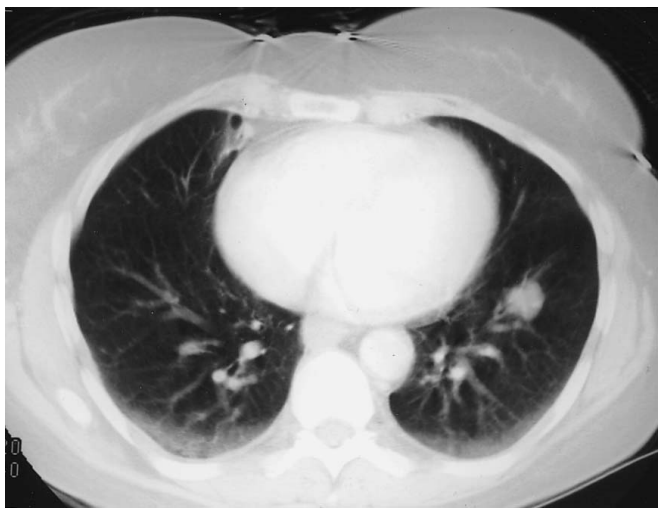

Figure 5. CT scan of the lesion in Figure 4, T1 N0 M0. The lymph nodes were not involved. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification. Houston, Mountain and Libshitz, 1999, p 29; with permission.)

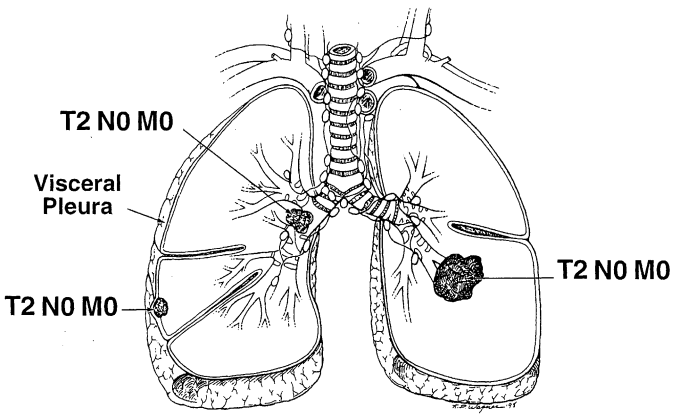

Figure 6. Stage 1B. Patients with T2 primary tumors and no evidence of lymph node metastasis, the T2 N0 M0 subset, are assigned to stage IB. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification. Houston, Mountain and Libshitz, 1999, p 29; with permission.)

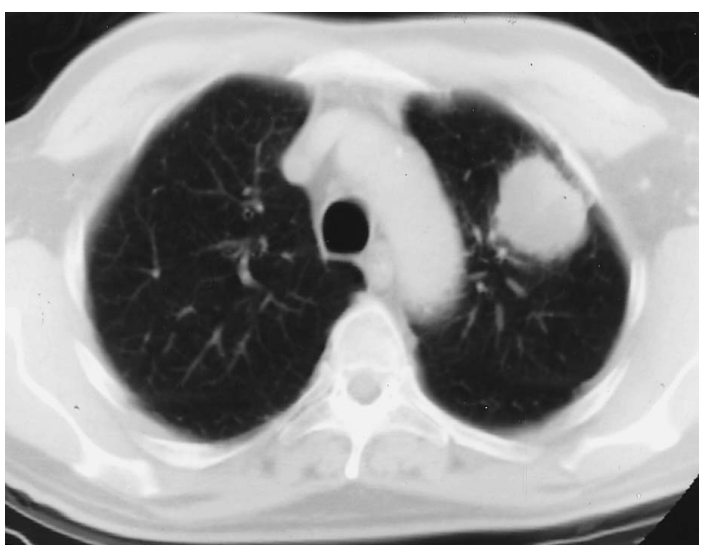

Figure 7. CT scan of a 4-cm left upper lobe bronchogenic carcinoma. The lymph nodes and visceral pleura were not involved. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification. Houston, Mountain and Libshitz, 1999, p 30; with permission.)

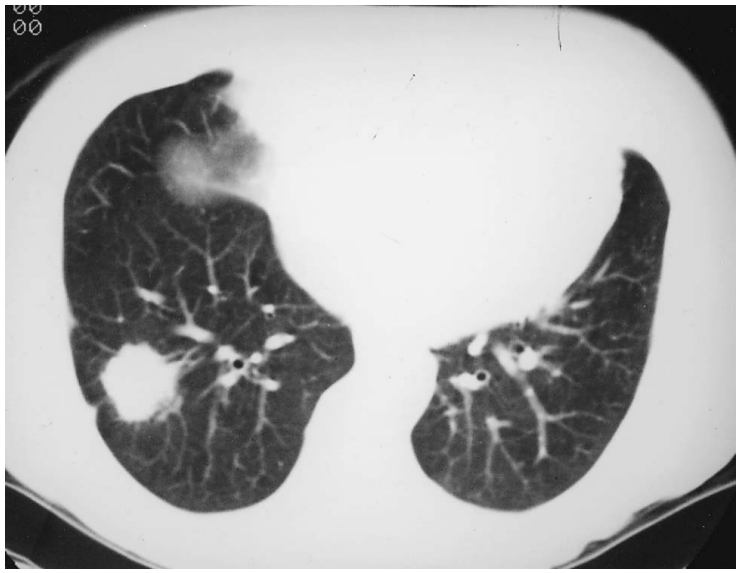

Figure 8. CT scan (lung windows) through a 3-cm spiculated bronchogenic carcinoma in the right lower lobe. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification. Houston, Mountain and Libshitz, 1999, p 32; with permission.)

mors with metastasis limited to the ipsilateral intrapulmonary, including hilar, lymph nodes, T3 N1 M0 disease, and T1, T2, and T3 tumors with metastasis to ipsilateral mediastinal and subcarinal lymph nodes and T1–2–3 N2 M0 disease. The CT scan in Figure 13 shows a stage cIIIA-T2 N2 M0 tumor, a right hilar mass, and right paratracheal adenopathy. Selected patients with cStage IIIA tumors may be referred for surgical treatment, depending on the potential for complete resection of all known disease. This group accounts for the difference in survival patterns between the patients with cStage IIIA and pStage IIIA disease. Patients who are not surgical candidates usually

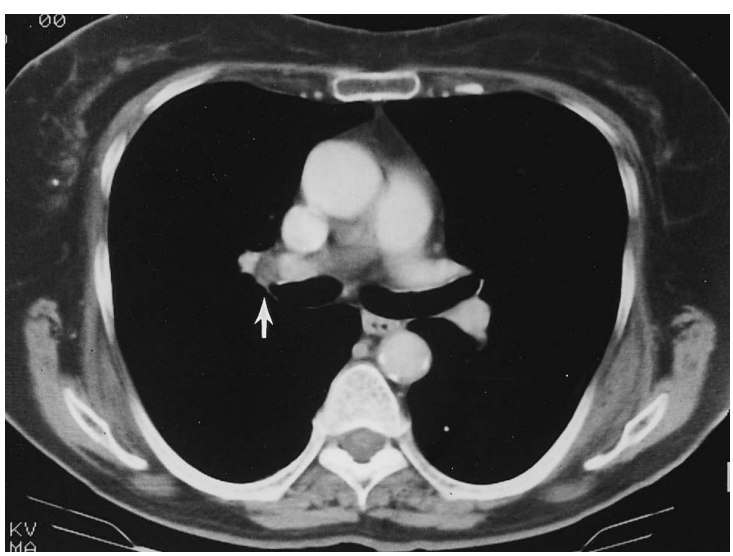

Figure 9. CT scan (soft tissue windows) shows a right hilar node *(arrow)* that was proved to contain metastatic disease, T1 N1 M0, stage IIA. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification. Houston, Mountain and Libshitz, 1999, p 32; with permission.)

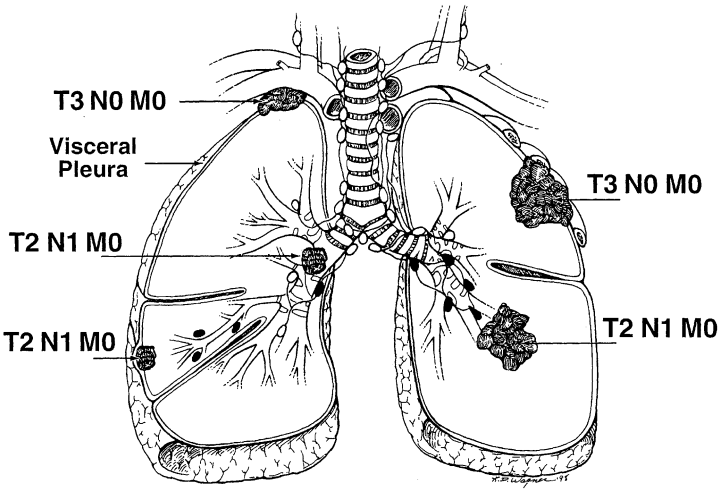

Figure 10. Stage IIB. Two anatomic subsets, T2 N1 M0 and T3 N0 M0 tumors, are designated stage IIB. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification. Houston, Mountain and Libshitz, 1999, p 33; with permission.)

are referred for radiotherapy, chemotherapy, or combined programs.

Stage IIIB classifies tumors with extensive extrapulmonary tumor invasion of structures, such as the trachea, esophagus, heart, and major vessels, and metastasis to the contralateral mediastinal and hilar lymph nodes and ipsilateral, and contralateral supraclavicular lymph nodes. No distant metastasis is present. T4 and any T N3 M0 are the anatomic subsets. An example of a cStage IIIB tumor is shown in the CT scan in Figure 14. Marked compression of the superior vena cava is shown from a right upper lobe tumor; extensive mediastinal adenopathy is present, and a right pleural effusion is seen (T4 N2 and M0 disease). The survival expectations for patients with cStage IIIB disease are shown in Figures 2 and 3.

Stage IV designates the presence of distant metastasis (M1 disease). Ipsilateral metastasis in non–primary tumor lobes also is designated M1. The survival for all patients, with metastasis to distant organ and lymph node sites, cStage IV, is poor, and palliative treatment usually is planned (see Fig. 1).

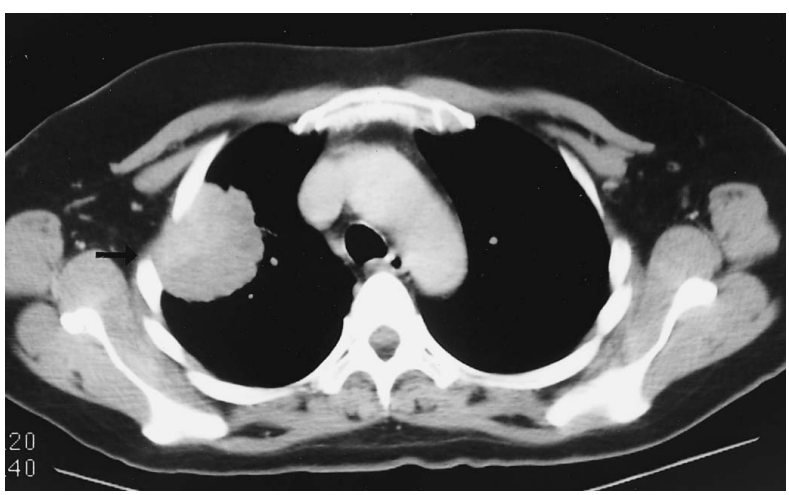

Figure 11. CT scan of a right upper lobe bronchogenic carcinoma showing chest wall invasion *(arrow)*. The lymph nodes were free of disease, T3 N0 M0, stage IIB. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification. Houston, Mountain and Libshitz, 1999, p 34; with permission.)

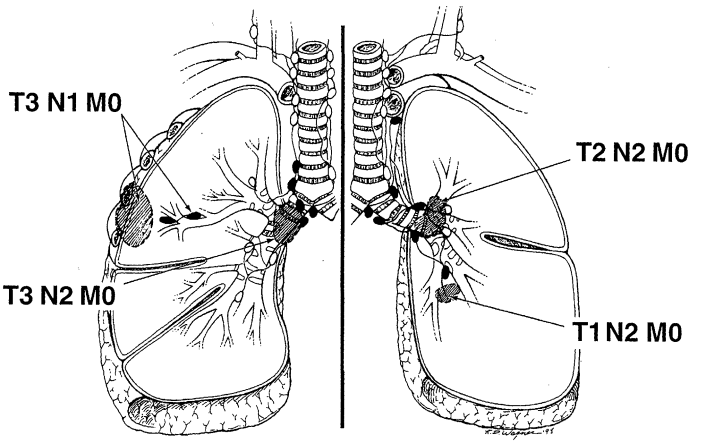

Figure 12. Stage IIIA. Included are four anatomic subsets: T3 N1 M0 and T1, T2, and T3 N2 M0 tumors. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification. Houston, Mountain and Libshitz, 1999, p 35; with permission.)

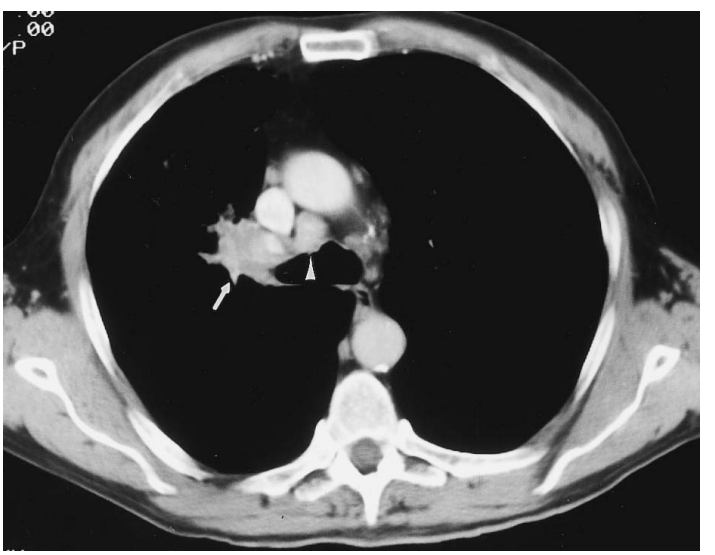

Figure 13. CT scan of the chest shows a right hilar mass *(arrow)* and right paratracheal adenopathy *(arrowhead)*. There is a suggestion of compression of the right mainstem bronchus anteriorly, T2 N2 M0, stage IIIA disease. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification. Houston, Mountain and Libshitz, 1999, p 36; with permission.)

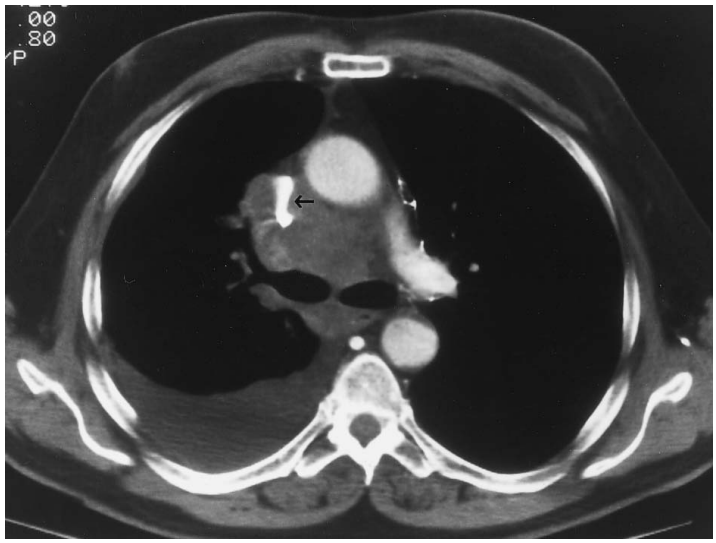

Figure 14. CT scan of the chest shows marked compression of the superior vena cava *(arrow)* from right upper lobe bronchogenic carcinoma; extensive mediastinal adenopathy is present and a right pleural effusion is seen, T4 N2 M0, stage IIIB. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification. Houston, Mountain and Libshitz, 1999, p 39; with permission.)

REGIONAL LYMPH NODE CLASSIFICATION

The classification for regional lymph nodes was developed in response to a recognized need for a single system of nomenclature that could be used internationally. The following recommendations are derived from the best features of several lymph node mapping schema used over the past decade[3, 40, 43] and a study of the literature dealing with the anatomy of the mediastinal pleura and patterns of lymph node drainage. The current system is illustrated diagrammatically in Figures 15 and 16.[41] It is important to relate the drawings to the definitions of the lymph node stations described in Box 2; anatomic landmarks delineating each nodal compartment are documented in the table.

Defining and Classifying *Mediastinal* and *Intrapulmonary* Including *Hilar Nodes*

Anatomic landmarks identify all lymph node stations within the mediastinal pleural reflection as N2 and all lymph node stations distal to the mediastinal pleural reflection and within the visceral pleura as N1. The point of fusion of the two pleural reflections cannot be determined clinically; the definable upper lobe bronchi are used as the most appropriate landmarks for this point (see Fig. 15). The most proximal nodes in the N1 compartment, numbers 10L and 10R, are designated hilar nodes, and 11 R/L through 14 R/L are intrapulmonary nodes with specific designations related to the location on or between the bronchi. Figure 16 illustrates anatomic landmarks for defining N2 nodes in the lower tracheobronchial tree. In the past, this area was one of controversy and confusion that has been resolved with the present recommendations.[10] In the absence of proof of metastasis in the mediastinal nodes, an N2 classification is assigned to ipsilateral nodes larger than 1 cm in short diameter on imaging. Pretracheal and retrotracheal nodes that would be accessible to the surgeon at thoracotomy also are classified N2. Objective confirmation of the status of the mediastinal lymph nodes is important in patients who meet all other criteria of operability because all enlarged nodes are not metastasis and the positive predictive value of CT scanning is low.

CRITICAL EVALUATION OF THE STAGING SYSTEM

A critical assessment of staging classification for lung cancer proceeds from the philosophy that a useful staging system could not take into account all of the innumerable factors that may exert an influence on the outcome in patients with this disease. It generally is recognized that, in a given patient, the total tumor burden cannot be quantitated and the balance between host defenses and the heterogeneity of the malignancy cannot be measured. The influence of newly acquired data that may challenge earlier accepted dogma, the impact of new technology and research discover-

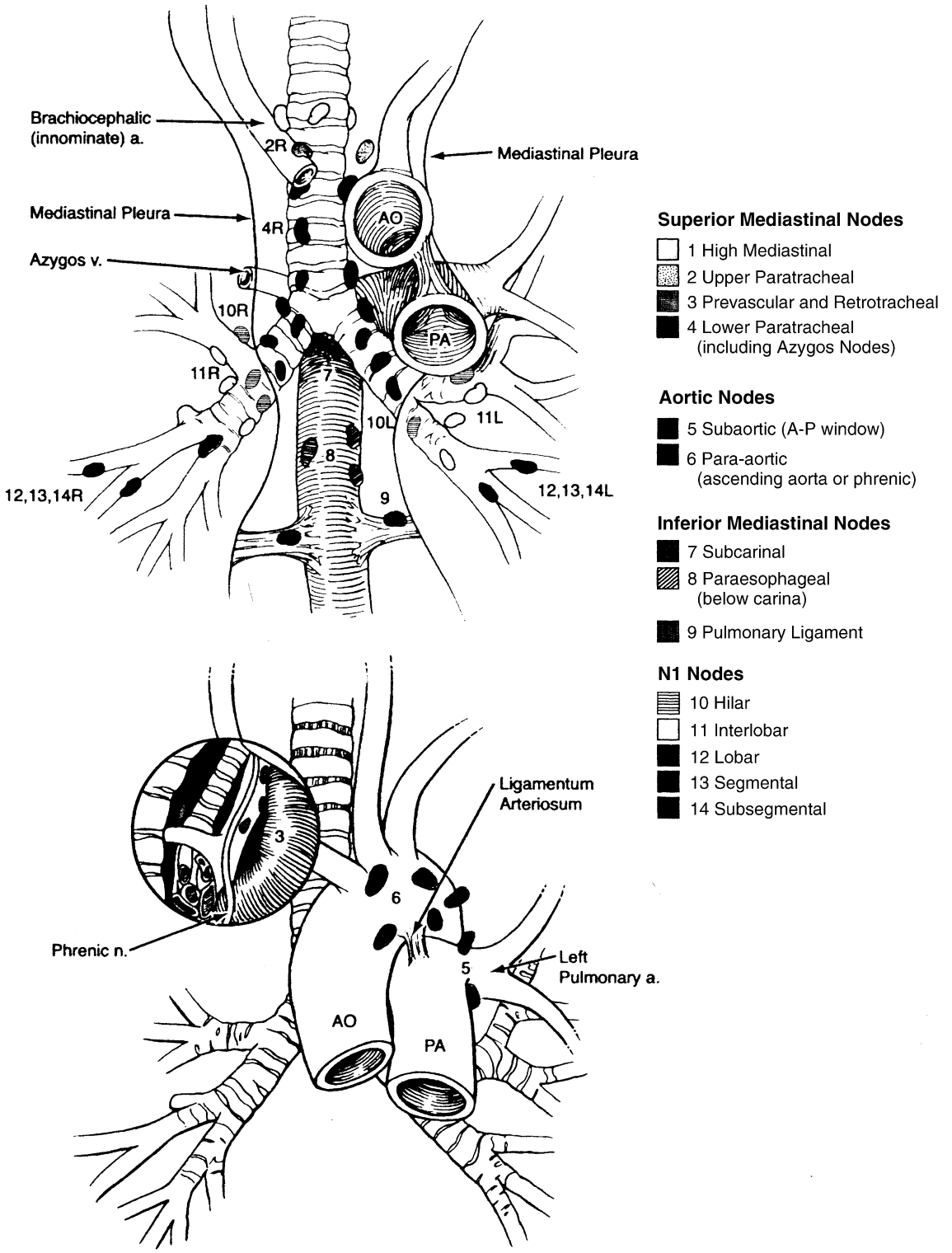

Figure 15. Regional lymph node stations for lung cancer staging. (*From* Mountain CF, Dresler CM: Regional lymph node classification for lung cancer staging. Chest 111:1718–1723, 1997 [Modifications from Naruke/American Thoracic Society/Lung Cancer Study Group maps]; with permission.)

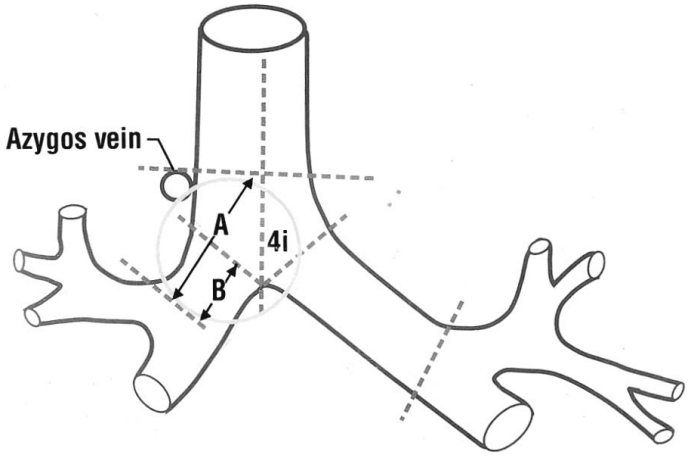

Figure 16. Anatomic landmarks for defining N2 nodes in the lower tracheobronchial tree. The mediastinal nodes that lie along the right main bronchus and distal to the cephalic border of the azygos vein are classified N2. The area is depicted by *(A)* and the length of the right main bronchus is represented by *(B)*. These distances are variable with the length of the main bronchus observed between 0 cm, with one or more segments of the upper lobe arising from the most distal trachea, to 2.5 cm. The length of the left main bronchus is less variable and the nodes along its length are classified N2. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging, Imaging and Lymph Node Classification. Houston, Mountain and Libshitz, 1999, p 48; with permission.)

ies, and problems encountered in the application of a widely used system must be taken into account. Staging of lung cancer is an anatomic system based on the TNM concept originated in 1946 by Denoix[12] as a consistent method for describing and communicating the facts in a given case of cancer. Later, the TNM anatomic subsets with similar prognostic implications were combined in stage groups. We now come full circle in this regard: The usefulness of the TNM anatomic subsets for designing investigational protocols has emerged, and heterogeneity of end results for TNM anatomic subsets in stage groups has presented problems in interpretation of survival data.

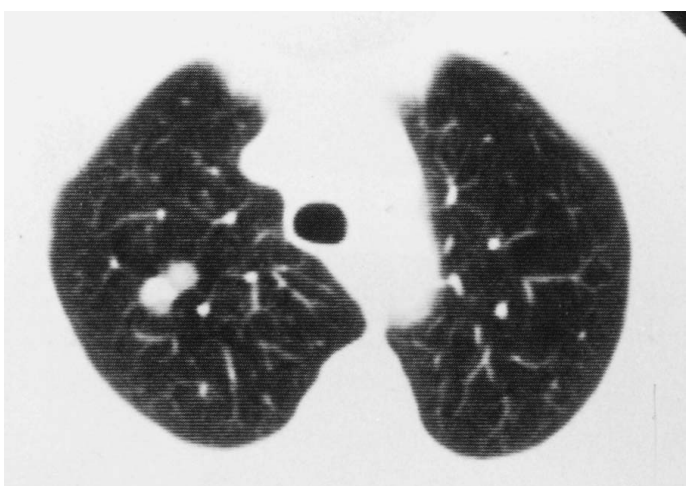

Figure 17. CT scan of the chest (lung windows) shows a primary and satellite (non–lymph node) nodules. Both are less than 3 cm with no main bronchus or pleural involvement. (*From* Mountain CF, Libshitz HI, Hermes KE: Lung Cancer. A Handbook for Staging and Imaging. Houston, Mountain and Libshitz, 1992, p 43; with permission.)

Box 2. Lymph Node Map: Nodal Stations by Anatomic Landmarks

Nodal Station: Anatomic Landmarks

N2 Nodes: all N2 nodes lie within the mediastinal pleural envelope.

1. Highest mediastinal nodes: Nodes lying above a horizontal line at the upper rim of the brachiocephalic vein where it ascends to the left, crossing in front of the trachea at its midline
2. Upper paratracheal nodes: Nodes lying above a horizontal line drawn tangential to the upper margin of the aortic arch and below the inferior boundary of #1 nodes
3. Prevascular and retrotracheal nodes: Prevascular and retrotracheal nodes may be designated 3A and 3P. Midline nodes are considered to be ipsilateral.
4. Lower paratracheal nodes: The lower paratracheal nodes on the right lie to the right of the midline of the trachea between a horizontal line drawn tangential to the upper margin of the aortic arch and a line extending across the right main bronchus at the upper margin of the upper lobe bronchus, and contained within the mediastinal pleural envelope. The lower paratracheal nodes on the left lie to the left of the midline of the trachea between a horizontal line drawn tangential to the upper margin of the aortic arch and a line extending across the left main bronchus at the level of the upper margin of the left upper lobe bronchus, medial to the ligamentum arteriosum and contained within the mediastinal pleural envelope. The lower paratracheal nodes may be classified into #4s (superior) and #4i (inferior) subsets. The #4s nodes may be defined by a horizontal line extending across the trachea and drawn tangential to the cephalic border of the azygos vein. The #4i nodes may be defined by the lower boundary of #4s and the lower boundary of #4, as previously described.
5. Subaortic (A-P window): Subaortic nodes are lateral to the ligamentum arteriosum or the aorta or left pulmonary artery and proximal to the first branch of the left pulmonary artery and lie within the mediastinal pleural envelope
6. Para-aortic nodes (ascending aorta or phrenic): Nodes lying anterior and lateral to the ascending aorta and the aortic arch or the innominate artery, beneath a line tangential to the upper margin of the aortic arch
7. Subcarinal nodes: Nodes lying caudal to the carina of the trachea but not associated with the lower lobe bronchi or arteries within the lung
8. Paraesophageal nodes (below carina): Nodes lying adjacent to the wall of the esophagus and to the right or left of the midline, excluding subcarinal nodes
9. Pulmonary ligament nodes: Nodes lying within the pulmonary ligament, including those in the posterior wall and lower part of the inferior pulmonary vein

N1 Nodes: all N1 nodes lie distal to the mediastinal pleural reflection and within the visceral pleura

10. Hilar nodes: The proximal lobar nodes, distal to the mediastinal pleural reflection and the nodes adjacent to the bronchus intermedius on the right. Radiographically, the hilar shadow may be created by enlargement of hilar and interlobar nodes
11. Interlobar nodes: Nodes lying between the lobar bronchi
12. Lobar nodes: Nodes adjacent to the distal lobar bronchi
13. Segmental nodes: Nodes adjacent to the segmental bronchi
14. Subsegmental nodes: Nodes around the subsegmental bronchi

From Mountain CF, Dresler CM: Regional lymph node classification for lung cancer. Chest 111:1720, 1997; with permission.

The International Staging System for Lung Cancer was developed in 1985 from a large database of information on patients with lung cancer and the input of international committees.[1, 24, 37] This modification of earlier staging recommendations resolved differences in international recommendations for classifying lung cancer, such as designating distant metastasis, M1, as stage IV, including only patients with no lymph node metastasis in stage I, and revising the definitions for the N category to be more responsive to the needs of radiation oncologists. The 1997 revised recommendations for staging lung cancer addressed problems that had emerged with wide application of the International System by subdividing stages I and II into four groups: stages 1A, 1B, IIA, and IIB. The stage IIIA category was modified to account for the superior survival of patients with T3 N0 M0 tumors, which is similar to that of patients with stage IIB disease. A new recommendation for classifying clinical presentations of multiple (i.e., non–lymph node) intrapulmonary nodules was adopted.[2, 23, 25, 38]

Major Challenges for the Future

The concept of the extent of disease, in terms of anatomic factors, as the primary indicator for

prognosis and treatment planning is a major challenge to the staging classification of lung cancer. Biologic prognostic factors remain to be confirmed as feasible and reproducible for most patients; however, the scientific literature and studies in progress attest to their importance as determinants of survival for specific patients. The role of performance status in structuring treatment plans also has been acknowledged for many years, and scales for recording this element are an accepted component of patient evaluation. Whether this element should or could be integrated in staging classification continues to be questioned.

Classification of Satellite Nodules and Ipsilateral Nodules in Non–Primary Tumor Lobes

The most controversial element in the 1997 Revised System for the Staging of Lung Cancer may be the classification of ipsilateral, non–lymph node, intrapulmonary metastasis or clinical presentations of multiple nodules in the ipsilateral lung (Fig. 17). A staging rule covering such presentations must be based on clinical (not surgical–pathologic) estimates of disease extent. Difficulties are encountered because of the small number of patients available for end results studies, clinical difficulty of separating intrapulmonary lymph node metastasis from true satellite nodules, and a significant number of clinically apparent secondary nodules proved to be benign at surgery.

Some discussion of the events that led to the current rules for classifying patients with this extent of disease may provide insight into the complexity of developing internationally acceptable rules for classification. Deslauriers et al[14] first published a study of the influence of satellite nodules on prognosis. They demonstrated that satellite nodules, which they considered a manifestation of local disease, had a deleterious effect on prognosis and recommended that such cases be classified as T3, stage IIA disease. They concluded that the finding of satellite nodules should not be considered a deterrent to curative resection, including tumors located in a different lobe.

In the same time frame, the present author addressed this issue with similar findings. Recommendations were developed for classifying ipsilateral multiple nodules that were consistent with the existing definition of M1 disease (i.e., metastasis outside of the hemithorax of origin, as opposed to metastasis involving the regional lymph nodes, N1, N2, N3; and malignant pleural effusion, considered a local or regional manifestation of disease). These recommendations were also consistent with the general clinical practice in which a patient, who was otherwise operable and resectable, still would be considered for surgical resection by a physician's medical colleagues. The AJCC and the UICC adopted these recommendations, which were published in 1992 editions of their staging manuals.[1, 24] The 1992 classification recommended that multiple tumor masses in the same lobe meeting the criteria for T1 should be designated as T2; a T2 tumor with another mass (not a lymph node) in the same lobe should be designated T3, and all other ipsilateral intrapulmonary masses should be designated T4 (intrapulmonary ipsilateral metastasis in the non–primary tumor lobe should be classified as T4). Contralateral intrapulmonary masses (non–lymph node) should be designated as M1. Studies for the 1997 revisions of the staging system supported the validity of this classification of ipsilateral multiple nodules. When the 1996 recommendations for staging revisions were under discussion at the UICC-TNM Prognostic Factors Project Committee Meeting in Geneva (May 1996), however, data were submitted from Japan that supported the following recommendation: satellite tumors in the primary tumor lobes of the lung should be classified T4 (stage IIIB), and intrapulmonary ipsilateral metastasis in distant (i.e., non–primary tumor) lobes of the lung should be classified as M1 (stage IV).[41] It is not known if the data were derived from clinical or surgical–pathologic information. This rule was adopted by the UICC and AJCC.

The issue is important because the current staging rules that place patients with intrapulmonary metastasis into stages IIIB and IV, which (with few exceptions) generally are considered inoperable, mean that such patients may never be referred for a surgical opinion by their primary care providers, internists, and pulmonary specialists. The question of overstaging some patients with satellite lesions in the same lobe and excluding them from consideration for definitive surgery has been noted by others.[21] The results of studies by Deslauriers et al,[14] Yoshino et al,[64] and Okada et al[45] support the earlier 1992 definitions. Most of these studies, however, used surgical–pathologic criteria. The studies of Kamiyoshihara et al,[27] also based on information from lobectomy, pneumonectomy, and mediastinal lymph node dissection, proposed that the revised staging of ipsilateral intrapulmonary metastasis was appropriate. Further study and documentation of the implications of ipsilateral intrapulmonary metastasis, according to clinical presentation, are essential. Presently, it can be said with some certainty that satellite or multiple ipsilateral pulmonary metastasis adversely affects survival; clinical classification by current technology is not highly reliable; and, regardless of classification, patients with ipsilateral multiple pulmonary nodules should be considered for resection if surgery otherwise is not contraindicated.

Other Questions

The survival expectations for patients with tumors classified T3 N2 M0 require further study. It has been suggested that the outcome achieved for these patients is poorer than that achieved for patients with T1-T2 N2 M0 tumors. Increased tumor

size and invasiveness in the presence of mediastinal lymph node metastasis may limit the options for definitive treatment for this group. Malignant pleural effusion also portends a poor prognosis, whether or not malignant cells are identified, and it has been suggested that this element could place a patient in the stage IV prognostic group.[33] Pleural effusion, however, is a regional manifestation of disease, and data have not shown its presence to be consistent with stage IV.[37] The question of the role of malignant pleural effusion in patients who are otherwise operable also needs further investigation.

An improved prognosis for patients with T4 N0 M0 tumors compared with the outcome for patients in other stage IIIB anatomic subsets has been suggested and warrants further study. In recent years, the refinement of surgical techniques has enabled this treatment option for several patients with T4 N0 M0 tumors, which may influence the end results for the group.[52]

Synchronous multiple primary tumors should be staged independently, with the tumor having the highest stage of disease or more serious prognostic implications used for data entry of a single patient. A specific field may be assigned for identifying multiple primary cancers. A recent report confirms the implications of synchronous multiple primary tumors on survival and verifies the upstaging rule.[61]

Most of the challenge relating to staging definitions and rules derives from the fact that patients within a stage group represent a heterogeneous population in terms of the biology of their tumors. The effect of this phenomenon on prognosis remains under investigation.

The Implications of New Technology on Refinements in Staging

Advances in methods for detecting the true extent of disease in patients with lung cancer, such as positron emission tomography (PET), eventually result in less stage migration and end results, according to clinical stage, that are similar to the surgical–pathologic survival patterns. Positron emission tomography differentiates malignant from benign processes based on metabolism rather than on anatomy.[34] Recent advances in CT scanning, such as improved image acquisition times, have improved image quality by decreasing respiratory motion and enhancing patient compliance and throughput. This technique has matured into an efficient and accurate diagnostic tool for evaluating primary lung cancer.[59] As the technique becomes validated as cost-effective for screening selected populations, helical CT scanning holds promise for increasing the proportion of patients diagnosed with early stage, resectable disease.[16]

Positron Emission Tomography

Evaluation of the Primary Tumor-The T Compartment

In the evaluation of the primary tumor, the clinician is concerned with size because of the correlation between size and the probability of lymph node involvement and between size, as an independent variable, and overall survival. It is not size alone, but rather size and location of the primary, that is important. Computed tomography scanning remains the best imaging technique to evaluate these parameters in view of the poor spatial resolution of PET.

Evaluation of Regional Lymph Nodes: The N Compartment

The influence of mediastinal lymph node metastasis on prognosis is related to the number of nodes containing metastasis, the levels of involvement, and the presence of microscopic or macroscopic disease.[39, 47, 57] A definite problem is the low sensitivity, specificity, and overall accuracy rates of CT scan examination. Although the rates vary, a meta-analysis of 42 studies examining the accuracy of CT scanning in detecting mediastinal nodes found a sensitivity of 79% and a specificity of 78%.[4] Large nodes may be negative for metastasis and small nodes may contain metastatic disease. In a recent study of patients with clinical N0-1 disease by CT scan evaluation, 18% (68 out of 379) of patients were found to have pathologic N2 tumors at surgery.[56] Invasive techniques, such as mediastinoscopy and mediastinotomy, may have an accuracy of less than 80%. In a series of 859 patients undergoing CT scan examination and cervical mediastinoscopy or anterior mediastinotomy, 14.5% (103 out of 859) had unsuspected N2 disease at thoracotomy.[11] Positron emission tomography is reportedly more accurate than these evaluations. The results of PET mediastinal node evaluation in 10 studies, recently summarized by Coleman,[8] indicate that the ranges of sensitivity, specificity, and accuracy for mediastinal node evaluation are as follows: sensitivity, 66% to 100%; specificity, 81% to 100%, and accuracy, 80% to 100%. The accuracy of PET was better than that of CT scanning in every study reviewed. Other reports note that 93% to 95% of negative PET scans are correct, which are high negative predictive values.[48, 50] Nodes smaller than 1 cm may be assessed incorrectly by PET scan, but this would not alter a decision for resection; such nodes, if positive, may be solitary and contain only microscopic disease. More caution is advised in interpreting the results of positive PET scans. The specificity of PET for mediastinal metastasis is lower than the sensitivity; one study shows that the positive predictivevalue of the method is 74%.[48] Inflammatory processes can affect radiotracer uptake.[50] Obstructive pneumonitis is often present in association with lung cancer; false-positive studies might prevent surgery in patients who

are otherwise operable. The author recommends that positive scans require biopsy confirmation. Recent studies have shown that patients are upstaged or downstaged, from the stage determined by standard methods in 21% of scanned patients.[32] It seems that PET markedly will decrease the need for invasive mediastinal staging techniques.

Evaluation of Distant Metastasis: The M Compartment

The investigation of failure after curative surgery revealed that the first site of failure was distant metastatic disease in approximately 75% of patients who developed recurrence or metastasis—true regardless of the pStage, histologic cell type, or any other factor that could be examined.[39] Many useless resections also take place because of unrecognized asymptomatic gross metastases. Imaging cannot solve the first problem of failure; however, PET is proving helpful in avoiding the second problem of unrecognized distant metastasis that was not appreciated before surgical treatment. Recent studies report that whole-body PET altered management in up to 40% of patients and that occult metastases were detected in 11% to 16.5% of patients selected for curative surgery.[35, 36, 45, 63] Approximately 75% of detectable abdominal metastases may be found by CT scanning if it includes the upper abdomen; however, the high incidence of benign lesions in the adrenal glands presents a problem. Adrenal metastases reportedly are present at diagnosis in 20% of patients, and PET is advocated because the sensitivity and specificity of the technique are 100% and 80% to 100%, respectively.[17, 18, 35] Accordingly, if such a PET scan is negative, no further evaluation is required; however, a biopsy should be taken of a positive lesion if the findings would deny an otherwise operable patient consideration for surgical treatment. Bone metastasis has been detected in 13% of a PET-scanned series, with 75% being asymptomatic.[32] There are fewer false-positive reports with PET than with radionuclide scans using technetium. Positron emission tomography detects occult brain metastasis; however, it has a low sensitivity (68%), probably because of the high glucose uptake in normal brain tissue, and it reportedly is least accurate in this area.[54] The role of PET for retreatment staging and for assessing local recurrent disease must be developed. Conventional radiologic imaging of patients having stable disease or a partial response to preoperative adjuvant therapy cannot be relied on as criteria for subsequent resection.

Complementarity of Computed Tomography and Positron Emission Tomography Scanning

With respect to staging, the complementarity of CT and PET scanning comes close to giving *one-stop shopping*, which improves the accuracy of staging, decreases the number of inappropriate or unnecessary invasive procedures, improves the prediction of survival, and scientifically refines clinical trials of new treatment strategies. These advantages should be considered when the cost-effectiveness of the tests is evaluated.

The author recommends PET to enhance lung cancer staging in those clinical situations in which it has been shown to provide more precise information than may be obtained from conventional imaging.

The Challenge of Biologic Prognostic Factors

Examination of survival data for patients who have had curative surgery shows a spectrum of curability for each stage group, indicating that failure does occur for some patients with all favorable characteristics and success is achieved for some not expected to do well (see Fig. 3). The pattern of first-observed failure in these patients was distant metastatic disease, which is not a surprising observation; however, it was surprising to find that distal metastasis was the first site of failure in 75% of patients who failed treatment regardless of the stage or cell type or any other factor examined.[39] The technical limits of detecting occult and sometimes gross disease probably account for some mistaging and a portion of the failure; however, research on the origin and development of lung tumors reveals biologic components that seem to influence their malignant potential. Many tumor-cell components and some host factors have been reported to predict a good or bad outcome after curative treatment; however, few have been validated for clinical use. For example, the prognostic significance of angiogenesis[9, 44]; polysialic acid expression[19]; proliferation markers, such as nucleolar protein p120[60] and AgNor cell proliferation index[13]; overexpression of dihydrodiol dehydrogenase,[20] tumor necrosis factor–α, and transforming growth factor–β[5]; *HER2/neu* overexpression[30]; preoperative neopterin concentration[49]; *p53* and *K-ras* mutations[55]; the *c-mos* proto-oncogene[19]; and many other studies has provided a body of literature suggesting the implications of biologic prognostic factors. Some of the findings have been used to develop preclinical and clinical studies of gene therapy.[51] Authors of most studies suggest that the presence or absence of the factor might be used to select patients for specific treatment programs. Most authors also suggest that additional study is warranted.

There is little doubt that biologic prognostic factors will be identified and confirmed that will add to the accuracy of anatomic staging factors. The challenge for the future is to integrate this knowledge into a prognostic index.

SUMMARY

The International System for Staging Lung Cancer has been validated as a prognostic index and

questioned regarding the implications of factors that require further study. As technology for evaluating the anatomic extent of disease is increasingly refined, the accuracy of clinical staging is greatly improved and provides a major benefit for individualized treatment selection. Advancing knowledge of the origin and development of lung tumors presents the challenge of appropriate integration of this body of science into clinical practice.

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