Staging of Lung Cancer

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The morphology of the tumor and the anatomic extent of the disease are important factors influencing treatment selection and ultimately survival for patients with lung cancer. The American Joint Committee TNM system provides a method for consistent reproducible description of the primary tumor (T), the status of the regional lymph nodes (N), and the presence or absence of distant metastasis (M). The TNM subsets thus classified can be grouped into three "stages" of disease such that the survival expectations for patients in each stage and cell type are similar. This classification of patients with respect to estimates of their prognosis is essential for valid comparisons of treatment modalities and meaningful communication of end results information.

Clinical characteristics which influence survival are reflected in the staging recommendations. The size of the lesion, the proximal margination, and the presence or absence of other pulmonary complications are features which distinguish the T classification as T1, T2, or T3. The presence or absence of lymph node involvement has an important bearing on survival expectations. Advancing from no nodal involvement, N0, to involvement of the peribronchial and hilar nodes, N1, and then to the mediastinal nodes, N2, causes progressive erosion in survival expectations. The tumor morphology and specific nodes that are involved are important components of this relationship. The presence of distant metastasis, M1, is synonymous with an extremely poor prognosis. Using these prognostic elements, the TNM subsets are combined into three stages of disease so that patients in each group will have a generally similar life expectancy, the survival for patients with stage I disease being significantly greater than that for patients with stage II disease which is significantly greater than survival for patients with stage III disease.

Improvements in the outcome for lung cancer patients depend upon the depth and scope of our scientific understandings and our ability to communicate our observations to one another. Measures of response to treatment can be translated into therapeutic practice only if uniform evaluators are used. Accordingly, a reproducible valid system for staging of lung cancer is recommended.

Advances in the diagnosis and therapy of lung cancer have related largely to application of a multimodality treatment concept and to refinements in the treatment selection process. Accurate, reproducible classification of histology and anatomic extent of disease is fundamental to the rational application of these elements of management.

By means of these classifications, we determine the nature of the tumor, describe its biologic behavior, and assess the therapeutic options. The results of different modalities of treatment can only be meaningful if they are based on a system of uniform evaluators. For many years pathologists have directed their efforts toward providing consistent criteria for histologic classification of lung cancer that mini-

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mized interobserver variability. Classification of disease extent using the TNM system makes possible a common language for describing the total tumor burden in a given patient at any specific point in the course of the disease. Accordingly, a clinical stage, surgical evaluative stage, a postsurgical treatment-pathologic stage, retreatment stage, and autopsy stage may all be applicable. Using this scheme and the histologic information, a quantitative estimate of a patient's prognosis can be made. Furthermore, the anatomic extent of disease expressed in terms of the primary tumor, the regional lymph nodes, and distant metastasis serves as a valuable aid in treatment planning.

The definitions for the TNM factors and stage grouping rules shown in Tables 1 and 2 were developed by the Task Force on the Lung of the American Joint Committee for Cancer Staging and End Results Reporting [1]. These recommendations were based on the analysis of survival patterns in a large series of patients with primary lung cancer treated according to conventional or standard modalities.

The survival studies showed that a specific survival pattern for each major histologic grouping, regardless of any other tumor, host, or therapeutic influence, exists, and three significantly different survival patterns were evident according to

| TABLE 1 |
| TNM Classification |

| Primary Tumor (T) | |
| TX | Tumor proven by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically, or any tumor that cannot be assessed as in a retreatment staging. |
| T0 | No evidence of primary tumor. |
| TIS | Carcinoma in situ. |
| T1 | A tumor that is 3.0 cm or less in greatest diameter, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy. |
| T2 | A tumor more than 3.0 cm in greatest diameter, or a tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region. At bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung, and there must be no pleural effusion. |
| T3 | A tumor of any size with direct extension into an adjacent structure such as the parietal pleura or chest wall, the diaphragm, or the mediastinum and its contents; or a tumor demonstrable bronchoscopically to involve a main bronchus less than 2.0 cm distal to the carina; or any tumor associated with atelectasis or obstructive pneumonitis of an entire lung or pleural effusion. |

| Nodal Involvement (N) | |
| N0 | No demonstrable metastasis to regional lymph nodes. |
| N1 | Metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region, or both, including direct extension. |
| N2 | Metastasis to lymph nodes in the mediastinum. |

| Distant Metastasis (M) | |
| MX | Not assessed. |
| M0 | No (known) distant metastasis. |
| M1 | Distant metastasis present. Specify ____________________________ |
STAGING OF LUNG CANCER

TABLE 2
Stage Grouping

| Occult Carcinoma |
|------------------|
| TX N0 M0         |
| An occult carcinoma with bronchopulmonary secretions containing malignant cells but without other evidence of the primary tumor or evidence of metastasis to the regional lymph nodes or distant metastasis. |

Stage I

TIS N0 M0
Carcinoma in Situ
T1 N0 M0
T1 N1 M0
T2 N0 M0
A tumor that can be classified T1 without any metastasis or with metastasis to the lymph nodes in the peribronchial and/or ipsilateral hilar region only, or a tumor that can be classified T2 without any metastasis to nodes or distant metastasis.

NOTE: TX N1 M0 and T0 N1 M0 are also theoretically possible, but such a clinical diagnosis would be difficult if not impossible to make. If such a diagnosis is made, it would be included in stage I.

Stage II

T2 N1 M0
A tumor classified as T2 with metastasis to the lymph nodes in the peribronchial and/or ipsilateral hilar region only.

Stage III

T3 with any N or M
N2 with any T or M
M1 with any T or N
Any tumor more extensive than T2, or any tumor with metastasis to the lymph nodes in the mediastinum, or any tumor with distant metastasis.

measures of disease extent for patients with squamous cell, large cell, and adenocarcinoma [2]. The necessity of reporting end results by cell type was clearly shown. No parameters could be identified that affected the survival in patients with undifferentiated small cell carcinoma and it was originally thought not to be worthwhile to apply the staging system to them. Recent improvements in the treatment of patients with small cell carcinoma with multiradical chemotherapy and multimodality treatment have resulted in an increase of survival rate, especially in those with limited extent of disease, and, therefore, it is now advisable to apply the TNM classification and stage grouping to patients with this cell type. End results should be reported separately for the major histologic groupings or at least according to small cell and non-small cell subsets.

STAGE GROUPING IN CARCINOMA OF THE LUNG

The "T" component describes the primary tumor and numerical descriptors, T1, T2, and T3, reflect the survival dynamics, which are related to tumor size and location, extent of proximal margination, and complications such as atelectasis, obstructive pneumonitis, and pleural effusion. The "N" component describes the regional lymph nodes and the survival dynamics, reflected by numeric descriptors, N0, N1, and N2, are related to the absence of or to the presence and extent of such
involvement. The "M" component describes distant metastasis and survival is related to the presence or absence of such metastasis, M0 or M1. The TNM subsets thus classified are combined into three stages of disease, the patients in each stage having relatively similar expectations for survival.

STAGE I DISEASE

The different common presentations of Stage I disease are shown in Fig. 1. In patients with this classification all of the tumor and its manifestations are confined to the lung of origin and all of the disease is considered completely resectable. Stage I disease includes tumors that are less than 3 cm in greatest diameter with or without peribronchial or hilar lymph node extension or metastasis. In the figure, a typical "coin" lesion is shown in the periphery of the left upper lobe. The anticipated survival for T1 N0 M0 patients is now sufficiently high that they are currently being excluded from some national clinical trials of adjuvant treatment, since the value of any adjuvant modality would be extremely hard to evaluate unless the treatment were nearly 100 percent effective. Shown in the middle drawing, in the left upper lobe is a similarly small lesion with metastasis to the peribronchial and hilar lymph nodes, T1 N1 disease. Stage I disease includes larger tumors or those of any size that invade the visceral pleura, involve the main stem bronchus, or have associated atelectasis or obstructive pneumonitis extending to the hilar region, but which have no evidence of metastasis or direct extension to any lymph nodes, T2 N0 disease, as illustrated in the lower figure.

T1 N0 M0 DISEASE

Figure 2 illustrates the typical roentgenographic appearance of T1 N0 M0 disease in a 60-year-old female patient who was a non-smoker. This lesion was found on routine follow-up X-ray 14 years postdefinitive treatment for squamous cell carcinoma of the cervix. The lesion was, however, considered to be a primary bronchogenic carcinoma. Sputum cytology was negative, as was the distal metastatic screen. Bronchoscopy revealed no endobronchial lesions and the findings at surgery confirmed the clinical stage assignment. Pathological report of the wedge resection of the right upper lobe of the lung was reported as bronchogenic squamous carcinoma and direct transition from bronchiolar respiratory mucosa with tumor was identified, substantiating lung origin. Hilar and mediastinal lymph node biopsies were negative.

STAGE II DISEASE

Stage II disease consists of just one subset, illustrated in Fig. 3, that is, T2 lesions having involvement of the peribronchial and/or hilar nodes either through direct extension or metastasis. The disease is technically completely resectable, but survival expectations for non-small cell patients with Stage II disease vary according to histologic classification. In squamous cell carcinoma, involvement of the regional lymphatic structures does not carry as heavy a burden of mortality as in the other cell types. Involvement of the hilar nodes in the presence of a tumor larger than 3 cm causes a marked drop in survival expectations in patients with adenocarcinoma. Shown in Fig. 3 are two examples of Stage II disease. In the left upper lobe, a tumor invading the visceral pleura with metastasis to the hilar nodes only is shown. In the right upper lobe, a tumor of the right upper lobe bronchus with obstructive pneumonitis and metastasis to the hilar lymph nodes is shown.
FIG. 1. Stage I Disease. From: American Joint Committee for Cancer Staging and End Results Reporting: Staging of Lung Cancer 1979. Chicago, IL.
T2 N1 DISEASE

This patient, whose X-ray is shown in Fig. 4, is a 71-year-old male whose disease was discovered when he sought emergency medical attention for trauma to the chest from a fall. A routine chest X-ray revealed a left ninth rib fracture and a left upper lung mass. Figure 4 is our initial examination, showing a mass lesion in the posterior segment of the left upper lobe with questionable hilar adenopathy. A calcified granuloma was noted in the left lower lobe. At bronchoscopy, no abnormalities were visualized within the tracheobronchial tree. Bronchial washings as well as cytological examination of multiple sputum samples were negative. Screen for distal metastasis was negative and no disease was found in the mediastinal lymph nodes at mediastinoscopy. A clinical state assignment of T2 N1 M0—Stage II disease was made. The patient underwent left upper lobectomy and pathological examination of the resected specimen confirmed the extent of disease which was reported as poorly differentiated adenocarcinoma of the left upper lobe with metastasis to hilar and intrapulmonary lymph nodes. No disease was found in the mediastinal lymph nodes removed at the time of surgery. Our earlier studies of end results according to postsurgical treatment-pathologic stage showed that 18 percent of patients with this level of disease with adenocarcinoma may be expected to achieve long-term survival following resection. Accordingly, this patient was considered a candidate for surgical adjuvant treatment, and was subsequently randomized to a regimen involving multidrug chemotherapy, designed for patients with this level of disease extent.

STAGE III DISEASE—OPERABLE

Patients with Stage III disease include those with tumors more extensive than T2 or any tumor with metastasis to the lymph nodes in the mediastinum or any tumor with distant metastasis. Survival expectations for these Stage III patients overall are very dismal. However, they can be dichotomized into inoperable and operable groups. A less discouraging outcome may be anticipated for selected subsets of Stage III—M0 patients having limited disease in which complete resection of all known
tumor is technically feasible and is biologically rational. This latter admonition is derived from observations of our own experience, and the work of others, that patients with adenocarcinoma that has metastasized to the mediastinal lymph nodes have an extremely poor prognosis [3]. Therefore, in terms of conventional single modality treatment, patients of this histologic classification with N2 disease would not be considered in the operable Stage III group. In contrast, a survival better than what might be achieved with any other single modality may be anticipated for Stage III—N2 M0 patients with squamous cell or undifferentiated large cell carcinoma [3]. Two examples of this level of disease extent are shown in Fig. 5. In the upper drawing, T2 tumor involving the hilar and tracheobronchial lymph nodes is shown. One subset of Stage III—N2 disease that can be mistaken clinically for Stage I or Stage II disease is shown in the lower figure, T1 N2 disease, a small tumor with metastasis to the hilum and mediastinal lymph nodes. An additional group of operable Stage III patients are patients with T3 N0 M0 disease in which there is direct extension of a peripheral primary tumor to the intercostal muscle and ribs. These are
locally invasive lung tumors without evidence of regional or disseminated disease. Pulmonary resection, usually lobectomy with en bloc resection, is undertaken with marlex prosthetic repair or omental or musculocutaneous graft if necessary (Fig. 6).

Figure 7 is our initial examination of a patient determined clinically to have Stage III—T2 N2 operable disease. He consulted his own physician for treatment of an upper respiratory infection accompanied by low-grade fever and cough.

Our examination showed a large mass, in the left lower lobe with some associated atelectasis or pneumonitis. The mass was judged clinically to be about 5 × 7 cm and tomograms were confirmatory. Distal metastasis screen was negative. Bronchoscopic examination showed tumor in the left lower lobe. At mediastinoscopy, right paratracheal, left paratracheal, and tracheobronchial nodes were negative; however, ipsilateral subcarinal lymph node biopsy was reported as containing metastatic squamous cell carcinoma. The findings at surgery confirmed the clinical stage assignment of T2 N2 Stage I disease. Two of 15 hilar and two of 13 mediastinal nodes were positive in the resected specimen.

STAGE III—INOPERABLE DISEASE

Unfortunately, the largest proportion of patients fall into this category at the time of diagnosis. T2 N2 disease in which the high or proximal paratracheal or contralateral paratracheal lymph nodes are involved are clinically excluded as surgical candidates at mediastinoscopy. Tumors demonstrated at bronchoscopy to be less than 2 cm from the carina, even if no positive lymph nodes are identified, are classified as T3 and are generally unresectable. Those patients with T3 tumors directly invading the aorta, main pulmonary artery or veins, recurrent or phrenic nerves are likewise not surgical candidates. Another condition contributing to a Stage III—T3 disease classification and placing patients in the inoperable group is the presence of pleural effusion, which is clinically determined to relate to the malignant process. In this regard, we noted that there was very little difference in survival in those patients with pleural effusion that contained malignant cells and those in whom no positive cells were identified.
Distant Metastatic Sites

The presence of distant metastasis outside the ipsilateral hemithorax and the mediastinum, regardless of the T or N value, is indicative of Stage III disease and is classified M1. Except in anecdotal cases, this usually is synonymous with a fatal outcome.

The TNM system can be applied to most patients with lung cancer with certainty and the appropriate stage designated with consistency. One group of 15 patients was staged independently by 26 physicians and research assistants with more than 90 percent consistency in the TNM designations and stage assignment [4].

A system of classification which takes into account all variables influencing survival would be hopelessly complex and unmanageable. The number of combinations and permutations of all known or suspected variables is almost infinite. Even large series of cases would be stratified to such an extent that very few patients would
be classified in any one described subset of the total population. Furthermore, it must be remembered that no two patients are completely similar nor can their characteristics be completely described. In practice, we can only group together patients who are generally alike. This is done by abstracting certain common features and disregarding or omitting other aspects that are dissimilar.

The following suggestions are made as conventions which may be followed in the interest of consistency.

SUGGESTIONS FOR APPLICATION OF THE LUNG CANCER STAGING SYSTEM

The following suggestions for application of the Lung Cancer Staging System have been published by the American Joint Committee, Task Force on the Lung, in the recent fascicle, Staging of Lung Cancer, 1979.

T0 is to be used when there is no demonstrable evidence of the primary tumor in the lung but there is evidence of metastatic cancer in a lymph node or elsewhere justifying a N1 or N2 or M1 designation, and it is concluded clinically that the primary is in the lung. T0 may also be used in the Retreatment Staging of a patient who had resection of his cancer and has proof of recurrence in the regional lymph nodes or a distant metastasis without evidence of recurrence in the lung.

TX is used when a patient has a positive sputum for malignant cells but a negative roentgenogram of the chest and a negative bronchoscopic examination. Such a designation is usually temporary as in most cases the source of the positive sputum can be localized and an appropriate T designation can be assigned. A clinical stage assignment of TX N0 M0 could be made. TX may also be used in the Retreatment Staging when it is impossible to evaluate the extent of residual primary tumor after radiotherapy and the development of radiation pneumonitis and fibrosis in the field of radiotherapy.

T2 is used when there is direct extension into the visceral pleura, but T3 is used if the lesion directly invades the parietal pleura. Any ipsilateral discontinuous lesion or lesions in or on the visceral or parietal pleura should be designated T3. However, a discontinuous lesion outside the parietal pleura in the chest wall or diaphragm should be designated M1. In contrast, a similar lesion in the mediastinum is most likely a
lymph node that has been completely replaced by cancer cells and should be designated N2.

Ipsilateral multiple primary tumors of the same cell type or unknown cell type should be classified T2 unless there is other evidence of T3 disease.

Clinical classification of hilar masses may be difficult. If the hilar mass can be separated from the mediastinum, hilar tomograms or computerized axial tomography (CAT) may indicate whether the mass is the primary tumor or metastatic disease in the hilar lymph nodes and the appropriate T and N designation assigned to the patient. If the hilar mass cannot be separated from the mediastinum, especially if there is a broad base of the lesion against the mediastinum, direct extension into the mediastinum is probable and the lesion should be designated T3. Vocal cord paralysis, superior vena caval obstruction, and compression of the trachea or the esophagus are usually related to metastases to the mediastinal lymph nodes and, if not proven otherwise, should be classified N2.

The M1 designation should be used only when there is reasonable proof of metastatic cancer, not when it is only possible. For example, elevated serum alkaline phosphatase without other evidence of metastatic cancer in liver or bone would not justify the designation M1.

In all cases, the designation of the greatest extent of disease that is applicable for a given patient should be used, but only when there is reasonable evidence of that extent of disease. It is recognized that a number of other factors beyond morphology and anatomic extent of disease are important in the classification of lung cancer and these are recognized and accounted for in the AJC recommendations, as follows:

First, the host performance status, (H), which is correlated with activity of disease and prognosis, should be recorded before first treatment and at each subsequent examination of the patient. Over a decade ago, Feinstein described the importance of comorbidity as an index of tumor aggressiveness and growth rate [5]. The physical state or performance status is designated H and takes into consideration all co-factors. The values, which are equivalent to the Zubrod and Karnofsky scales, are as
follows: H0 is equivalent to normal activity; H1 represents symptomatic and ambulatory status—patient is able to care for himself; H2 includes patients ambulatory more than 50 percent of the time, occasionally needing assistance; H3 includes those patients ambulatory 50 percent or less of the time, nursing care needed, and H4 indicates a bedridden condition—the patient may need hospitalization.

Second, when the cancer is treated by definitive surgical procedures, residual cancer, designated R, is recorded if any such disease is present. R0 signifies no residual tumor, R1, microscopic residual tumor, and R2, macroscopic residual tumor.

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