S

Stage classification is an essential part of the approach to patients with cancer, and there are many things we would like to get from a stage classification. The primary purpose of the classification is to consistently describe the anatomic extent of disease, thus providing a common, consistent language. The anatomic extent of the tumor has a major impact on which treatment we choose and what the outcome will be. However, it is important to recognize that the stage classification does not by itself completely define the prognosis (which depends on multiple factors, eg, comorbidities, performance status, treatment given) or serve as a treatment algorithm (which is driven by data from clinical trials and treatment selection criteria). Efforts to develop a comprehensive prognostic index system are under way.

Stage classification is founded on the TNM system, which dates back to 1944. Furthermore, the method of staging is classified as clinical stage (denoted by the prefix c) and pathologic stage (denoted by the prefix p). Clinical stage is determined using all information available prior to any treatment, and pathologic stage is determined after a resection. The extent of clinical staging can vary from a clinical evaluation alone (history and physical examination) to extensive imaging (CT and PET scans) or invasive staging techniques. It must be emphasized that a surgical staging procedure (eg, mediastinoscopy) is still part of clinical staging because surgical resection as a treatment has not taken place.

The current Lung Cancer Stage Classification system is the seventh edition, which took effect in January 2010. This article reviews the definitions for the TNM descriptors and the stage grouping in this system.

**Abbreviations:** AAH = atypical adenomatous hyperplasia; ACCP = American College of Chest Physicians; AJCC = American Joint Committee on Cancer; BAC = bronchioloalveolar carcinoma; GGO = ground glass opacity; IASLC = International Association for the Study of Lung Cancer; ITC = isolated tumor cell; UICC = Union Internationale Contre le Cancer
The Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) are the official bodies that define, review periodically, and refine the stage classification systems. The current seventh edition of the lung cancer staging system was based on a major initiative undertaken by the International Association for the Study of Lung Cancer (IASLC). This 12-year project increased the patient base from 5,319 (collected over several decades predominantly at one institution) to >100,000 (from around the world, all cases diagnosed between 1990 and 2000).

In validating where to make a distinction between one stage descriptor or group and another, the IASLC required that consistent differences in prognosis had to be seen in data sets from different continents, database types, clinical and pathologic staging, and histologic subtypes. Furthermore, external validation against large databases was done. The statistical analysis was quite sophisticated; in all, the current classification is a quantum leap forward that is unequaled by any other cancer site. However, although the database was large and involved many institutions from 20 countries, the distribution of cases was not uniform. Certain patient subgroups came predominantly from one region or one type of database and were treated in many different ways, and the IASLC database did not report treatment-specific outcomes.

1.0 METHODS

This article addresses the official Lung Cancer Stage Classification system. Therefore, the primary sources of information were the AJCC and UICC staging manuals. These sources were supplemented by the publications of the IASLC International Staging Committee, which provided the basis for the AJCC/UICC classification, as well as American College of Chest Physicians (ACCP) publications that reviewed and discussed details of the classification.

2.0 T DESCRIPTOR

2.1 Size

A detailed analysis of tumor size by the IASLC staging committee confirmed that 3 cm was significant as a cut point; thus, the definition of T1 vs T2 was retained. In addition, significant cut points were identified at 2.5, and 7 cm. Therefore, subgroups were defined for T1 (T1a and T1b) and T2 (T2a and T2b) as shown in Figure 1. The survival differences between each size subgroup were highly statistically significant in pathologically staged patients; among clinically staged patients, the trends were consistent but not always significant (probably because of a more limited data set). Tumors >7 cm led to survival that tracked with other definitions of T3 (ie, invasion, central location) and were, therefore, placed within this group.

The size of a tumor is defined as the greatest dimension, but how this is determined is not addressed by AJCC, UICC, or IASLC. The ACCP panel suggests that for consistency, this measurement be done on an axial CT image using lung windows during inspiration whenever possible (c stage); for p stage, we suggest the greatest dimension (in any direction) of the specimen fixed after inflation or of the unfixed specimen (fixation causes about 20% shrinkage). Further issues arise with semisolid or ground glass opacities (GGOs), which have not been addressed by the AJCC or UICC. One can measure the solid or the ground glass component with either mediastinal or lung windows on a CT image. Emerging data suggest that the size of the solid (invasive) component is of greater prognostic value than the ground glass (lepidic) component. The ACCP panel suggests recording the size of both the GGO and the solid component on lung windows (or the percent solid by area) for c stage and both the entire tumor (including lepidic portions) and the invasive component for p stage. This suggestion is consistent with a recent UICC supplement handbook.

2.2 Invasion

There were insufficient numbers of patients for whom reliable data were available to investigate the validity of other traditional T2, T3, or T4 descriptors (visceral pleural invasion, central location within a lobar or mainstem bronchus, partial or complete atelectasis, direct invasion of particular structures, etc). These traditional definitions were retained even though they could not be confirmed because there were no data to suggest that they are not valid.

Invasion beyond the elastic layer of the pleura is defined as T2, including invasion into an adjacent lobe. Elastin stains should be used whenever there is ambiguity. T3 includes invasion into the parietal or mediastinal pleura or the parietal pericardium. T4 includes invasion of the visceral (inner) pericardial surface and the intrapericardial pulmonary artery and pulmonary veins. Involvement of either the intrapericardial or extrapericardial vena cava or aorta is considered T4. We suggest that involvement of the azygous vein be classified as T3 because it is not counted among the great vessels (but this is not addressed by IASLC, AJCC, or UICC).

A Pancoast tumor is classified as T4 if there is unequivocal involvement of C8 or higher nerve roots, cords of the brachial plexus, subclavian vessels, vertebral bodies, lamina, or spinal canal. The tumor is classified as T3 if it involves only thoracic nerve roots (eg, T1 or T2 nerve roots).
suggests that only unambiguous mediastinal fat involvement be used as a criterion for T4 status (eg, extensive replacement by tumor on CT scan); otherwise, the lower T3 classification should be chosen.  

3.0 N Descriptor

Analysis of the prognostic influence of the N descriptor resoundingly supported the traditional categorization of N0, N1, N2, and N3; therefore, these definitions were carried forward (Fig 1). Direct extension of a primary tumor into a node is classified as nodal involvement. Station 1 nodes are classified as supraclavicular nodes, which include the low cervical nodes, caudal to the lower margin of the cricoid (N3).
Extrathoracic node involvement is designated as M1b (eg, a positive axillary node).

Further analyses were done to explore whether particular node stations within an N category had any particular impact. No such relationship could be identified (Fig 2).\(^8\) Specifically, there was no difference in survival among patients with involvement of only peripheral N1 nodes or hilar N1 nodes, and no difference based on which N2 nodal stations were involved. This was true globally as well as within geographic regions. Survival among patients with pN2 right upper lobe tumors with and without N1 involvement (skip metastases) was not different, although there was a slight difference among such patients with a left upper lobe tumor.\(^8\)

The IASLC staging committee developed a new node map\(^24\) to overcome ambiguities arising from discrepancies between previous node maps in use in different geographic regions. Furthermore, the committee defined several nodal zones as follows: a supraclavicular zone (station 1), an upper zone (stations 2-4), an aortopulmonary zone (stations 5 and 6), a subcarinal zone (station 7), a lower zone (stations 8 and 9), a hilar zone (stations 10 and 11), and a peripheral zone (stations 12-14). There were no differences in prognosis among involvement of different nodal zones within the N1 or N2 category. Specifically, there was no difference between patients with a left upper lobe tumor and involvement of nodes only in station 5 and 6 and patients with a tumor in a different lobe and involvement of another single N2 nodal zone.\(^8\)

The number of involved nodal zones appeared to have a prognostic impact. Patients with pathologic single-zone N1 involvement had better survival than those with pathologic multizone N1 involvement (5-year survival, 45% vs 35%; \(P < .09\)). Similarly, patients with pathologic single-zone N2 involvement had better survival than those with pathologic multizone N2 involvement (5-year survival, 34% vs 20%; \(P < .001\)). In fact, the survival curves of patients with pathologic multizone N1 and single-zone N2 involvement were almost superimposed.\(^3\) However, the prognostic impact of the number of pathologic nodal zones involved could not be validated within T-stage categories and by geographical region, type of databases, or clinical staging because the number of patients in the subsets was too small.\(^3\) Therefore, the IASLC staging committee decided against subdivision of N categories. The prognostic impact of nodal involvement by direct extension of a primary tumor also could not be validated through the IASLC database because of insufficient sample sizes but was retained because it is consistent with general UICC and AJCC rules.

3.1 Node Map

The IASLC node map is shown in Figures 3 and 4. Important features include better definition of the subcarinal zone as extending down to the level of origin of the left lower lobe and right middle lobe bronchus.\(^24\) The border between left- and right-side paratracheal nodes is the left lateral border of the trachea (not the midline). The 4R nodal area extends from the lower border of the left innominate vein to the lower border of the azygous vein; the 4L nodal region extends from the level of the top of the aortic arch to the upper border of the left-side pulmonary artery medial to the ligamentum. The level 2 regions extend from the border of level 4 to the upper border of the manubrium in the midline. The supraclavicular nodes extend from the lower border of the clavicles to the lower border of the cricoid. Further details and definitions of all the node stations can be found in Rusch et al.\(^24\)

3.2 Criteria for Pathologic N Assessment

The following comments apply to nodal staging at the time of resection. Issues regarding clinical (pretreatment) staging are discussed in section 7.0 of this article, “Type of Stage Classification.”

A general AJCC/UICC recommendation is that at least six lymph nodes/stations be sampled for pathologic node staging. The IASLC manual recommends that three mediastinal (including level 7) and three N1 nodes/stations be sampled. Whether the number is supposed to apply to node stations or individual nodes is undefined. Moreover, the pathologist cannot distinguish six nodal fragments from six separate nodes (unless the surgeon is meticulous in how nodes and fragments are labeled and submitted). However, the IASLC staging committee encourages systematic intraoperative node assessment as recommended by clinical guidelines.\(^25,26\)
Furthermore, the definition of number of nodes/stations needed for pathologic staging by IASLC and AJCC is confusing. If all nodes are negative, the tumor is defined as pN0, regardless of the number sampled, yet if some are positive, it is implied that only cN status be used if fewer than six nodes/stations were sampled. To avoid this awkward inconsistency, the ACCP panel endorses the suggestion that whenever fewer than six nodes/stations are sampled at resection, the tumor is classified as pN0, pN1, or pN2 with the uncertainty descriptor [eg, pN0(un)], as is described in section 8.0 of this article, “Additional Descriptors.” This descriptor has been suggested by IASLC for further testing relative to the completeness of resection (R) classification; however, extrapolation to address an inconsistency in the formal rules.

Figure 3. [Section 3.1] The International Association for the Study of Lung Cancer lymph node map, including the proposed grouping of lymph node stations into zones for the purposes of prognostic analyses. Ao = aorta; Eso = esophagus; L = left side; mPA = main pulmonary artery; R = right side; SVC = superior vena cava; T = trachea. Reproduced with permission from Rusch et al.24

Supraclavicular zone
1. Low cervical, supraclavicular, and sternal notch nodes

Superior mediastinal nodes
Upper zone
2R. Upper Paratracheal (right)
2L. Upper Paratracheal (left)
3a. Prevascular
3p. Retrotracheal
4R. Lower Paratracheal (right)
4L. Lower Paratracheal (left)

Aortic nodes
AP zone
5. Subaortic
6. Para-aortic (ascending aorta or phrenic)

Inferior mediastinal nodes
Subcarinal zone
7. Subcarinal

Lower zone
8. Paraesophageal (below carina)
9. Pulmonary ligament

N1 nodes
Hilar/Interlobar zone
10. Hilar
11. Interlobar

Peripheral zone
12. Lobar
13. Segmental
14. Subsegmental
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regarding the definition of pN status seems reasonable to the panel.

Biopsy of only one sentinel node is considered adequate and is denoted as pN0(sn) if findings are negative and pN1-3(sn) if positive, reflecting the level of the sentinel node. However, sentinel node identification in lung cancer is variable and not widely practiced.  

4.0 M Descriptor

The new stage classification system no longer recognizes the term MX because clinical staging information is always available. A history and physical examination are critical parts of clinical staging and often are very reliable without further imaging or biopsy.

The presence of distant metastases is classified as M1b. Slightly worse survival was seen in patients with multiple vs a solitary distant metastasis (median survival, 5 months vs 6 months; 1 year survival, 20% vs 23%; \( P = 0.006 \)). No differences were noted by the site of a solitary distant metastasis except slightly shorter survival for a solitary brain metastasis. However, the data set was too limited for adequate validation, and further subdivision of the M1b category was not undertaken.

Pleural (or pericardial) involvement (either multiple implants or a malignant effusion) is classified as M1a because of slightly better survival than for distant metastatic sites and worse survival than for other categories of T4. These prognostic differences were highly statistically significant and held up to internal validation (across database types and geographic
regions) as well as external validation (ie, the Surveillance Epidemiology and End Results [SEER] database). The IASLC, AJCC, and UICC manuals are confusing about whether M1a applies to only the ipsilateral pleura or also to the contralateral pleura; the ACCP panel suggests that it apply to both.

5.0 Stage Grouping

The IASLC staging committee defined stage groupings (Figs 5, 6). Despite the recognition of many new subdivisions of the T and M descriptors, the stage grouping has no new subdivisions. However, the definition of the stage groups has become more complex because of the additional T and M descriptor subgroups. An online tool to manage the complexity and to assist in on-the-spot definition of a tumor’s stage is available at http://staginglungcancer.org. Illustrations of the TNM categories and subcategories included within each stage group are shown in Figures 7 to 9.

6.0 Additional Tumor Nodules and Multiple Primary Lung Cancers

The classification of patients with additional tumor nodules has created confusion largely related to a lack of appreciation of distinctly different categories of such nodules. Applying a classification system intended for one category to a different group has the potential to lead to suboptimal treatment and outcomes.

The first category involves patients with a newly found lung cancer who have another (small) nodule detected by imaging. The majority (about 75%) of additional pulmonary nodules seen on CT imaging in patients with potentially operable cI to cIIIa primary lung cancer are benign (see “Evaluation of Individuals With Pulmonary Nodules: When Is It Lung Cancer?” by Gould et al in the ACCP Lung Cancer Guidelines). An expert panel (ie, a multidisciplinary tumor board that includes chest radiology, thoracic surgery, and pulmonary medicine) usually can arrive at a strong consensus about most of these lesions. Although firm data are lacking, experience suggests that the judgment is seldom wrong when such an informed review deems an additional nodule to most likely be benign.

A second category involves patients with an advanced primary cancer (most often also with nodal involvement) who have several pulmonary nodules or a single pulmonary nodule and other sites that appear typical for distant metastases. Again, the judgment of a tumor board that the additional nodules in such a presentation represent metastatic disease is rarely called into question by the subsequent course of the disease (although specific data documenting this are lacking).

6.1 Second Primary Lung Cancers

Occasionally, patients with a typical clinical presentation of a lung cancer (ie, a solid, spiculated mass in a patient with lung cancer risk factors) also exhibit a second lesion with such a typical appearance (either synchronously or metachronously). In fact, the incidence of a second primary lung cancer has been consistently found to be approximately 1.5% to 2% per patient per year. Traditionally, this group has been defined by a clinical team guided by criteria developed empirically by Martini and Melamed in 1975.
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and more recently refined by the ACCP using indirect data (Fig 10). The majority of tumors classified in this way have been of the same histologic type, which is logical because the etiology of both cancers is likely the same (ie, genetic predisposition, environmental exposures). Furthermore, similar survival results have consistently been found whether the histologic type is the same or different, suggesting that the traditional definition of second primary lung cancers based on clinical features (as opposed to one based only on different histology) is generally correct.

The IASLC staging committee puts the responsibility of identifying second primary lung cancers squarely on the pathologist. However, defining second primary lung cancers primarily by histologic features is problematic for several reasons. First, this deviates from the definition that has been in use, thereby defining patients differently moving forward than what was done in the IASLC database. Second, this creates tremendous pressure to use genetic and morphologic characteristics that are not yet standardized or validated. Finally, pathologic assessment has primarily involved resected specimens, yet clinical
Differentiation of adenocarcinomas (in resected specimens) by the percentage of morphologic patterns (e.g., acinar, papillary) has been proposed.\textsuperscript{16,19,22,66-70} Definition of second primary lung cancers by genetic characteristics has produced conflicting results so far.\textsuperscript{71-77} How valid these measures are in differentiating a second primary lung cancer from a metastasis requires further study, and whether these techniques can be applied to small biopsy specimens is unclear.

The AJCC, UICC, and IASLC rules are confusing with regard to stage classification. The IASLC stated that “multiple synchronous primary tumors should be staged separately.”\textsuperscript{6} However, the next sentence states, “The highest T category and stage of disease should be assigned and the multiplicity of the number of tumors should be indicated in parenthesis, e.g. T2(m) or T2(5).”\textsuperscript{7} It seems contradictory that separate staging can be achieved by combining all tumors under one TNM designation. The AJCC specified that this multiple tumor classification T(m) applies to tumors of the same histology,\textsuperscript{4} but the IASLC implied that the T(m) NM classification be used even with different histologic types.\textsuperscript{8} The UICC 2010 manual did not comment on this,\textsuperscript{3} but the 2012 supplement manual stated, “A tumor in the same organ with a different histologic type is counted as a new tumor.”\textsuperscript{9} Finally, the AJCC manual stated that in “simultaneous bilateral cancers in paired organs, the tumors are classified separately as independent tumors in different organs,”\textsuperscript{4} with essentially the same wording used by UICC and IASLC.\textsuperscript{3} Whether this means a TNM designation for each one or for both together is not explained. Furthermore, there is confusion about whether the lungs are considered together as one organ or two paired organs (unclear in AJCC but clearly listed as a paired single organ by UICC).\textsuperscript{3,4}

Therefore, the ACCP panel endorses the suggestion that second primary lung cancers be defined by an experienced multidisciplinary team,\textsuperscript{14} using collective judgment and considering all information (including the imaging, risk factors, suspicion of distant dissemination, and the pathologist’s confidence given the available specimens). A careful evaluation for distant and mediastinal metastases is strongly recommended (see the articles “Methods for Staging Non-small Cell
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In addition, with the hope that this will reduce confusion, the ACCP panel recommends that when two lung cancers with a typical appearance (solid, spiculated, or lobulated) are deemed to be synchronous primary cancers, they be classified with a TNM descriptor for each tumor. The combined T(m) classification should be reserved for multifocal tumors (usually more than two) that typically have a GGO appearance (as discussed in section 6.3).

6.2 Additional Pulmonary Tumor Nodules

The IASLC database contains cases of lung cancer with additional pulmonary tumor nodules of cancer, accounting for a small portion (2.5%) of the database. Second primary lung cancers and metastatic disease (M1) were specifically excluded from this category; however, there is no information regarding how the contributing centers defined such additional nodule cases beyond this.

Because of similar relative survival differences, these nodules were classified within the T3, T4, and M1a descriptor cohorts if they were located in the same lobe, an ipsilaterally different lobe, or the contralateral lung, respectively (ie, T3Satell, T4IpsiNod, and M1aContrNod in Fig 1). Because of conflicting definitions in the IASLC and AJCC manuals, it is unclear whether the additional tumor nodule designation is meant to apply only to lesions that can be recognized grossly or also to lesions detected solely by the pathologist.

It has been suggested that the IASLC stage classification of additional pulmonary tumor nodules T(m) be used for patients with a dominant classic lung cancer (ie, solid, spiculated) who have an additional nodule with similar radiographic and histologic features. The ACCP panel endorses this definition and suggests...
that the additional nodule classification also applies to lesions that are not clinically apparent. It is not clear that this definition matches the cases included in the IASLC database. The database may have included some multifocal, predominantly GGO lesions because this cohort included mostly cases from Asia (where such tumors appear to becoming more common). Although the fact that the IASLC database includes only cases from 1990 to 2000 probably diminishes this effect because the detection of GGO lesions appears to have been less common during this period.

It is important to note that the IASLC database does not clearly define the prognosis of patients with additional nodules that are encountered clinically today. First, the definitions used in the IASLC database for this cohort are unclear. Second, the prognosis varies significantly among geographic regions and types of databases. Finally, treatment was not accounted for in the analysis yet varied markedly (96% and 88% of T3 Satellite and T4 Ipsilateral Nodule, respectively, were managed surgically vs 2% of M1a Contralateral Nodule). In fact, patients with additional tumor nodules who underwent resection exhibited good 5-year survival (45% for T3 Satellite N0 M0 R0, 48% for pT4 Ipsilateral N0 M0 R0).

6.3 Multiple (Multifocal) Lung Cancers

Multifocal disease is well recognized for bronchioloalveolar carcinoma (BAC) however, because the term BAC was used in different ways, its use has been abandoned. Although the term BAC has been retired, patients are still seen with multiple foci of such tumors. The spectrum of lesions that were included under the rubric of BAC included newly defined histologic entities (ie, adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma); the nature and relationship of these lesions to one another is not yet well understood.

These factors have led to confusion about how to classify multifocal disease, which is exacerbated by wording in the stage classification manuals that can be interpreted in different ways. Such multifocal tumors (ie, what would formerly have been called multifocal BAC) currently are variably classified as multiple distant metastases, synchronous second primary cancers, and additional nodules. A more uniform classification is needed, or the data collected will be uninterpretable.

The ACCP panel endorses the suggestion that the T(m) designation be used for patients with multifocal lung cancer, meaning patients with several GGO lesions that are malignant or contain numerous small foci. The AJCC and UICC rules suggest that multiple simultaneous tumors be classified by the highest T stage of one focus with the number of tumors in parentheses. For example, a patient with four GGO lesions all measuring <2 cm would be classified as having T1a(4) disease. In this classification category, the N and M designations apply to all the multiple tumor foci. The T(m) designation should only be applied to lesions that are either proven or strongly suspected to be malignant, that is, not atypical adenomatous hyperplasia (AAH) lesions. This appears to be consistent with the intent of the T(m) designation according to the IASLC manual, which specifically mentions the common occurrence of multiple foci of BAC tumors.

The ACCP panel defines multifocal lung cancers as multiple GGO lesions, which may, however, develop a solid component. There may be a few or many lesions. We include patients with such a malignant GGO lesion (either suspected or proven) and other small GGO lesions that are likely AAH because data suggest that AAH is a precursor to such tumors. Including such patients also satisfies the need for a clinically applicable definition. At the other end of the spectrum are patients with an infiltrative pattern of disease confined to a particular area (segment or lobe) or appearing diffusely in the lung parenchyma (also called pneumonic type of adenocarcinoma). These lesions should also be included among multifocal cancers.

Multifocal cancers appear to have a decreased propensity for nodal or systemic spread and an increased propensity to develop additional pulmonary foci. This feature seems to fit with what was intended by the T(m) nomenclature, which designates multiple tumors in the T descriptor but maintains a composite N and M designation that applies to all the multiple tumors in aggregate. Further study of this form of lung cancer is needed. Nevertheless, adoption of a classification nomenclature, even if imperfect, will facilitate such research by more precisely identifying a specific and homogeneous population.

7.0 Type of Stage Classification

The main stage classification types are clinical and pathologic (Fig 11). According to the AJCC manual, clinical stage (pretreatment classification) encompasses “any information obtained...before initiation of definitive treatment,” incorporating symptoms and...
physical examination; imaging; endoscopy; biopsy; and surgical staging procedures, including exploration. The pathologic stage (postsurgical classification) includes information from the clinical stage supplemented by “information obtained...through completion of definitive surgery.” Other stage classification types (Fig 11) include restaging after induction treatment (designated yc or yp), staging when recurrence develops (designated by r), or staging at autopsy (designated by a). Although pathologic stage is more accurate, clinical stage is what is available when treatment decisions are made.

Complexity arises because the AJCC allows clinical and pathologic classification to be applied to individual T, N, and M descriptors and allows use of individual pT and pN descriptors outside the setting of (intended) surgical resection. This creates confusion because procedures explicitly classified as clinical staging nevertheless yield results that can define a pT or pN descriptor, and the overall classification can be a mixture of clinical or pathologic individual T, N, and M descriptors. Note that the UICC and IASLC do not recognize this individual p designation outside the setting of a surgical resection (or attempted resection).

Definition of pT status outside the setting of attempted resection requires biopsy specimen proof of invasion to confirm the highest T category. Practically speaking, such a clinical determination of pT is rare but might include biopsy specimen proof of carinal involvement (or potentially an excisional wedge resection specimen that defines the largest tumor dimension yet was not intended as a therapeutic procedure). The designation of pM can be used when there is biopsy specimen proof of a distant (or pleural/pericardial) metastasis; however, a pM0 designation does not exist, even if a biopsy is done (only cM0).

AJCC definition of pN outside the setting of attempted resection is particularly problematic. This requires one of the following: (1) biopsy specimen proof of N3; (2) all nodes with negative biopsy specimen findings, regardless of number sampled (presumably at least 1); (3) any microscopic evaluation of nodes if pT status is defined; or (4) a sentinel node biopsy specimen and definition of pT status. Thus, although endobronchial ultrasound or mediastinoscopy explicitly comprise clinical staging, the result can be viewed as defining a pN status.

Complex rules govern assignment of an overall clinical or pathologic designation to a mixture of individual descriptors (eg, cT1pN3cM1, pT2cN0cM1, cT2cN0pM1). In the absence of resection, the overall classification is pathologic if (1) an M1 biopsy specimen finding is positive (ie, cTcNpM1), (2) an N3 biopsy specimen finding (the highest N category) is positive (ie, cTpN3cM0), or (3) the T stage is confirmed by biopsy specimen and nodal involvement at any level is confirmed (ie, pT1-4pN1-3cM0). All other combinations of cT, pT, cN, pN, and cM define an overall clinical stage. The definition is awkward in a non-resectional setting because pN0 is unacceptable for defining overall pathologic stage (eg, pT1-4pN1-3cM0 is classified as pathologic, whereas pT1-4pN0cM0 is clinical). Presumably, these rules pertain only to patients with unresected lesions; otherwise, clinical staging would apply to all with N0, even if resected, including a complete lymphadenectomy.

The AJCC staging rules are ambiguous and appear to allow for several approaches. The approach that avoids the confusion and ambiguity arising from the others is to restrict pathologic staging to the postresection stage (or rarely an aborted resection with extensive biopsy specimens). Pretreatment staging remains clinical; if such staging involves biopsy specimens, the UICC rules allow for the use of cT, cN, or cM along with a certainty factor classification (eg, cN2C3) rather than pT or pN. The C designation is described in the next section and summarized in Figure 12. This approach is suggested by the ACCP panel.

8.0 Additional Descriptors

8.1 Certainty Factor

The UICC has defined an optional C factor (Fig 12) to denote the extent of investigation performed to establish the stage designation (ie, clinical evaluation, imaging and needle aspiration, surgical staging, resection). This factor can be applied to the entire stage or to individual T, N, and M descriptors. This factor carries the misleading name of certainty, implying that certainty is related primarily to the specific technique, whereas in reality, the clinical setting is most important (eg, a normal mediastinum on PET scan has a false-negative rate of <5% for peripheral cI tumors vs about 25% for central tumors). Furthermore, the thoroughness of staging procedures varies greatly.

8.2 Completeness of Resection

The completeness of resection (radicality) is more clearly defined in the new system (Fig 12). A positive margin includes nodal margins and positive pleural or pericardial fluid cytology. According to suggestive individual studies, several new classifications will be tested, including pleural or pericardial lavage cytology, highest mediastinal node involvement, or nodal classification based on a limited assessment. Additional descriptors have been developed for the depth of visceral pleural invasion, chest wall invasion, lymphatic and vascular invasion, and the number of nodal zones involved.
**Certainty Factor**

| C1   | Evidence from standard diagnostic means (inspection, palpation and standard radiography [eg. CXR]) |
| C2   | Evidence from special diagnostic means (CT scan, MRI, PET, endoscopy, biopsy specimen, cytology) |
| C3   | Evidence from surgical exploration and biopsy specimen or cytology |
| C4   | Evidence of the extent of disease after definitive surgical resection and pathological examination |
| C5   | Evidence from autopsy specimen |

**Residual Tumor Classification**

| R0   | No residual tumor |
| R1   | Microscopically positive margin because of: |
|      | Positive margin |
|      | Extracapsular extension at margins of resected nodes |
|      | Positive pleural or pericardial cytology |
| R2   | Macroscopic residual tumor at: |
|      | Resection margin |
|      | Resected or unresected nodes |
|      | Pleural or pericardial nodules |

**Proposed New Classifications for Testing**

| R0(un) | R0, but uncertain because of: |
|        | Inadequate number of nodes/stations sampled |
|        | Highest mediastinal node removed/sampled is positive |
| R1(is) | R0, but carcinoma in situ at bronchial margin |
| R1(cy+) | R0, but positive pleural lavage cytology |

**Micrometastases (0.2-2 mm)**

| N0   | No nodal involvement (of any type) |
| N1,2,3(mi) | N1, N2, or N3 involvement by a micrometastasis |

**Isolated Tumor Cells (<0.2 mm)**

| N0   | No nodal involvement and ITCs not investigated |
| N0(i+) | No nodal involvement histologically; negative morphologic findings for ITCs |
| N0(i+) | No nodal involvement histologically; positive morphologic findings for ITCs |
| N0(mol-) | No nodal involvement histologically; negative non-morphologic findings for ITCs |
| N0(mol+) | No nodal involvement histologically; positive non-morphologic findings for ITCs |

The classification can also be applied to distant metastatic sites (M0). Nonmorphologic techniques include DNA or RNA analysis or flow cytometry. CXR = chest radiograph; ITC = isolated tumor cell.

*In greatest dimension.

### 8.3 Minimal Disease

Sophisticated immunohistochemical and genetic techniques permit detection of very small tumor deposits (Fig 12). A micrometastasis as defined by the UICC and AJCC is 0.2 to 2 mm in size and usually is detected by routine hematoxylin and eosin staining; typically, mitoses and invasion are seen. Such micrometastases in nodes or distant sites are counted as positive and denoted by the symbol (mi) [eg cN1(mi), pN2(mi)]. However, the prognostic impact was not evaluated in the IASLC staging analysis.

Isolated tumor cells (ITCs) are small clumps of tumor cells (<0.2 mm), typically without mitoses or vascular or lymphatic invasion. ITCs within nodes (or distant sites) are not counted in the stage classification and should be coded as N0 (or M0), regardless of node level harboring the ITCs [eg. pN0(i+), pN0(mol+)]. The prognostic value of ITCs has been inconsistent.

### 9.0 Applicability to Different Lung Cancer Types

The seventh edition of the Lung Cancer Stage Classification is applicable to all major types of primary lung cancer. The system was developed based on non-small cell lung cancer; however, validation studies in patients with small cell lung cancer11 and carcinoid tumors12 have demonstrated that the definitions are also of value in these cohorts. Therefore,
the stage classification should be applied to patients with these tumors as well.

10.0 Discussion

The purpose of the stage classification system is to provide a nomenclature to describe the anatomic extent of disease. In the past, the descriptors and groupings have been based largely on what seemed to be logical; in the current seventh edition, this is based on extensive statistical analysis. The basis for deciding that a particular cut point or definition was a good criterion to distinguish one group from another was a difference in prognosis between the groups that was consistent in multiple subset analyses (geographic, histologic, database type, time period, clinical or pathologic) as well as in external validation (ie, Surveillance Epidemiology and End Results database). Thus, prognosis was used as a tool in the analysis, and differences in prognosis were the end points of analysis.

How do we use the staging nomenclature? A clinical need is to select the optimal treatment of patients, and the anatomic extent of disease is certainly a major factor in the treatment selection. However, we cannot expect the stage classification to serve as a treatment algorithm. First, many other factors affect the treatment selection, including functional status, comorbidities, histology, and personal factors. Second, the criterion used to separate or group patients was not whether current guidelines recommended treatment that was the same or different. Finally, progress in defining optimal treatment should be continuous and informed by the results of clinical trials. Stage classification is relatively static, updated every 7 or 8 years when a new edition is produced. Thus, the stage classification is useful in describing one factor related to choosing a treatment strategy and in assessing whether the results of a clinical trial may be applicable to a particular patient, but it does not by itself define a treatment approach.

Another clinical need is to define prognosis. Again, the anatomic extent of disease is an important factor that contributes to prognosis. However, there are

FIGURE 13. [Section 10.0] Median survival (mo) of the clinical T descriptor cohort (cN0, cM0) in the International Association for the Study of Lung Cancer database according to the geographic region and database type. Aus = Australia; Clin = clinical.2

FIGURE 14. [Section 10.0] Median survival (mo) of the clinical N descriptor cohort (cTany, cM0) in the International Association for the Study of Lung Cancer database according to the geographic region and database type. See Figure 13 legend for expansion of abbreviations.2

FIGURE 15. [Section 10.0] Treatment given (as percentage of total) in NCDB (2004-2007) to patients with non-small cell lung cancer (n = 22,044) whose stage grouping shifted from the designation in the sixth to the seventh edition of the Lung Cancer Stage Classification system. Ch = chemotherapy; ChRT = chemoradiotherapy; ChRT-S = chemoradiotherapy then surgery; Ch-S = chemotherapy then surgery; NCDB = National Cancer Database; No Tmt = no treatment; RT = radiotherapy; S = surgery alone; S-Ch = surgery then chemotherapy; S-ChRT = surgery then chemoradiotherapy; S-RT = surgery then radiotherapy. See Figure 4 legend for expansion of other abbreviations. Reproduced with permission from Boffa et al.110

FIGURE 16. [Section 10.0] Median survival (mo) of the clinical N descriptor cohort (cTany, cM0) in the International Association for the Study of Lung Cancer database according to the geographic region and database type. See Figure 13 legend for expansion of abbreviations.2
many other prognostic factors, including those related to the tumor, patient, treatment, and clinical and social setting. There is a need for a prognostication tool that takes these factors into account, and it is often suggested that the stage classification be modified to include other factors (e.g., shifting stage grouping up or down depending on patient age or other factors). However, prognostication is extremely complex, and such an approach is overly simplistic. For example, certain factors may be highly significant if a particular treatment is given but have little relevance in other settings. Therefore, acknowledging only a few prognostic factors and adjusting the TNM stage would be insufficient to define prognosis yet could tremendously complicate use of the TNM system; it is best to separate prognostication from anatomic disease description and allow time for development of a sophisticated prognostication tool.

We need to be careful in applying prognostic data from the IASLC database. It is true that this database is the largest available and defines prognosis for patients with a certain anatomic extent of disease from around the world, but there were marked differences in prognosis in different geographic regions and by database type (Figs 13, 14), and which region or database type was better varied between T and N categories. It is not clear why prognosis varied so much; no consistent factor has been identified, although many have

**Figure 16.** [Section 11.0] ACCP suggestions to avoid ambiguities in the IASLC, UICC, and AJCC stage classification systems.

**T stage**
- Measure clinical size by largest dimension on an axial CT image during inspiration and lung windows, whenever possible.
- Measure pathologic size as the largest dimension in an inflated, fixed specimen.
- Record both dimensions for a solid and ground glass component and for an invasive and lepidic component (if applicable).
- Mediastinal invasion should be classified as T4 only if there is extensive involvement (e.g., extensive replacement by tumor on CT image).

**N stage**
- Designation of pN status requires that six or more nodes or stations have been sampled; otherwise, the uncertainty suffix should be added [e.g., pN0(un)].

**M stage**
- Mx is not an allowable designation.a
- Contralateral pleural involvement is designated M1a.b

**Additional tumor nodules and multiple primary lung cancers**
- Patients should not be classified under this rubric if judged by an expert panel (including a pulmonologist, thoracic radiologist, surgeon, and pathologist) to have either (1) additional imaged lesions likely to be benign or (2) compelling clinical and imaging evidence of multiple sites of distant dissemination.
- Classification of lesions as second primary lung cancers should be based on the judgment of an experienced multidisciplinary team, taking into account all factors (e.g., clinical, imaging) not just histologic factors.
- Second primary lung cancers should be staged separately, each with a TNM descriptor.b
- Classification of lesions as additional tumor nodules should be used for solid, typical dominant lung cancers and a limited number of solid additional nodules of the same histologic type (but not for second primary lung cancers, suspected metastases or benign nodules, or GGO lesions).
- Multifocal lung cancers (involving or arising from GGO lesions) should be classified by the highest T stage of the lesions, a suffix for the number of lesions, and N and M descriptors that apply to all of the multiple tumor foci collectively [e.g., T1a(4) N0 M0].

**Type of stage classification**
- Clinical stage includes any and all information available prior to definitive treatment (e.g., symptoms, physical examination, imaging, endoscopy, biopsy specimen, and surgical staging procedures).a
- Pathologic stage applies when this is supplemented by information available after surgical resection (or attempted resection with extensive exploration and biopsy).a
- Individual T, N, and M descriptors should be designated as p only if a surgical resection has taken place (or attempted resection with extensive exploration and biopsy).
- The C descriptor (C1-5) should be added, if desired, to clinical T, N, and M descriptors to indicate whether the stage is based on clinical evaluation, imaging, biopsy specimen, etc.

**Minimal disease classification**
- Micrometastases (0.2-2 mm in size and usually recognized by standard microscopy) are counted in the TNM classification.a
- Isolated tumor cells (sometimes clumped but < 0.2 mm, usually identified by immunohistochemistry or molecular techniques) do not change the TNM classification.a

ACCP = American College of Chest Physicians; AJCC = American Joint Committee on Cancer; GGO = ground glass opacity; IASLC = International Association for the Study of Lung Cancer; UICC = Union Internationale Contre le Cancer.

aExplicitly defined by AJCC or UICC, listed here nevertheless because of common lack of awareness of this.
bImplied by AJCC or UICC.
been suggested (eg, genetic variation, such as the frequency of epidermal growth factor receptor mutations or differences in the proportion of nonsmokers in different regions). Furthermore, the treatment given was not accounted for or validated in the IASLC database. A comparison of what treatment was given in the US National Cancer Database (which does have validated treatment data) for those cohorts whose stage grouping changed from the sixth to the seventh edition shows marked variation (Fig 15). Therefore, we must acknowledge that the IASLC database does not precisely define the prognosis for a particular patient, and we certainly cannot assume that it has defined the prognosis for a particular treatment approach.

We must be particularly careful in the use of prognosis to guide decisions about treatment. The fact that survival is poor does not necessarily imply that it is worth adding further therapy (eg, adjuvant chemotherapy); what we really need is data demonstrating that additional treatment actually improves survival. At the same time, we should not rule out a particular approach just because (our perception of) prognosis is poor. In the IASLC database, patients with pleural involvement or with ipsilaterally different lobe nodules who underwent resection actually had good survival (5-year survival, 31% if pT4 N0 M0 and 48% for pT4 N0 M0). The patients who underwent resection, of course, represent a selected subgroup. However, these observations illustrate how the interplay among clinical and pathologic staging, treatment approach, and patient selection can influence our perception of similar outcomes.

Although the stage groupings are a reasonable way to group patients and are based on a sound statistical analysis, this does not prove that the tumor biology is homogeneous. For example, the survival curves of patients with T4 tumors and T4 tumors do not necessarily track together, suggesting that there may be biologic differences. Certainly, there are groups that have a similar prognosis but markedly different clinical characteristics (eg, stage IIIA includes patients with N2 disease, those with extensive local invasion only, and those with ipsilateral additional tumor nodules). We must view stage classification as a useful tool that may well change over time as our understanding and treatment outcomes evolve.

### 11.0 CONCLUSION

There is no question that the IASLC staging classification is a major advance. The size of the database, the broad international spectrum, the careful and detailed analysis, and the internal and external validation are tremendous achievements and relatively unique among types of cancer. Inevitably, it is also more complex, and with more refined data comes a greater ability to discern granular details. As with any complex system, rules that seem clear in one context can seem awkward or conflicting in another. This article reviews the fundamental definitions as well as suggested approaches that minimize the conflicts in those cases where ambiguous rules create confusion (Fig 16). A thorough understanding of the stage classification is essential because it is fundamental to our ability to converse clearly about patients with cancer.

### ACKNOWLEDGMENTS

**Author contributions:** Dr Detterbeck had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Detterbeck contributed to the conceptual approach, review of staging manuals, and writing of the manuscript. Dr Postmus contributed to the review and revisions of the manuscript. Dr Tanoue contributed to the review and revisions of the manuscript.

**Financial/nonfinancial disclosures:** The authors have reported CHEST the following conflicts of interest: Dr Detterbeck is a member of the International Association for the Study of Lung Cancer International Staging Committee and a speaker in an educational program regarding lung cancer stage classification; both activities are funded by Lilly Oncology (Lilly USA, LLC). He has participated on a scientific advisory panel for Oncimmune (USA) LLC; an external grant administration board for Pfizer, Inc; a multicenter study of a device for Medela; and formerly a multicenter study of a device for DeepBreeze. Compensation for these activities is paid directly to Yale University. Drs Postmus and Tanoue have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

**Role of Sponsors:** The American College of Chest Physicians was solely responsible for the development of these guidelines. The remaining supporters played no role in the development process. External supporting organizations cannot recommend panelists or topics, nor are they allowed prepublication access to the manuscripts and recommendations. Further details on the Conflict of Interest Policy are available online at http://chestnet.org.

**Endorsements:** This guideline is endorsed by the European Society of Thoracic Surgeons, Oncology Nursing Society, American Association for Bronchology and Interventional Pulmonology, and the Society of Thoracic Surgeons.

**Other contributions:** The authors thank Ramon Rami-Porta, MD, for his thoughtful critique during the development of this article and review of the final manuscript.

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