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A M E R I C A N C O L L E G E O F



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The New Lung Cancer Staging System

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The International Association for the Study of Lung Cancer (IASLC) has conducted an extensive initiative to inform the revision of the lung cancer staging system. This involved development of an international database along with extensive analysis of a large population of patients and their prognoses. This article reviews the recommendations of the IASLC International Staging Committee for the definitions for the TNM descriptors and the stage grouping in the new non-small cell lung cancer staging system. (CHEST 2009; 136:260–271)

Abbreviations: AJCC = American Joint Committee on Cancer; IASLC = International Association for the Study of Lung Cancer; NSCLC = non-small cell lung cancer; SEER = Surveillance, Epidemiology, and End Results; UICC = Union Internationale Contre le Cancer

Definition of the stage is an essential part of the approach to patients with cancer, and it has led to the development of a universally accepted stage classification systems for most tumors. The Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) serve as the official bodies that define, periodically review, and refine the stage classification systems. The 6th edition of the staging system was published in 2002,¹ and the 7th edition will be published in 2009. In preparation for this, much work has been done by the International Association for the Study of Lung Cancer (IASLC) to recommend changes that are based on a large international database and are backed by careful validation and statistical analysis. This article reviews the development and final recommendations of the IASLC International Staging Committee for non-small cell lung cancer (NSCLC),

which have been accepted by the UICC and AJCC for the new edition.

For editorial comment see page 6

The TNM staging system for lung cancer dates back to an initial proposal by Dr. Clifton Mountain that was adopted by the AJCC in 1973 and by the UICC in 1974. The original system was based heavily on intuition with limited corroboration from a database of 2,155 patients from the MD Anderson Cancer Center in Houston, TX. Subsequent revisions of the TNM staging system continued to be based on this database, which grew to include 5,319 cases at the time the lung cancer staging system was last revised in 1997. The limitations of this system are that it was based on what was essentially a single institution series, included a limited number of patients (so that many subgroups were quite small), spanned a long time frame, and was weighted somewhat toward surgically treated patients by the nature of the database. Nevertheless, this early work laid a significant foundation and defined a staging system that has held up very well even in comparison with the new IASLC staging system.

FUNDAMENTALS OF THE UICC/AJCC STAGING SYSTEM

The NSCLC stage classification is based on the TNM system, which is used for most cancers. The T descriptor defines the extent of the primary tumor,

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Table 1—Types of Staging Assessments

Prefix	Name	Definition
c	Clinical	Prior to initiation of any treatment, using any and all information available (eg, including mediastinoscopy)
p	Pathologic	After resection, based on pathologic assessment
y	Restaging	After part or all of the treatment has been given
r	Recurrence	Stage at time of a recurrence
a	Autopsy	Stage as determined by autopsy

the N descriptor the extent of involvement of regional lymph nodes, and the M descriptor the extent of spread to distant sites. The staging system is based solely on the anatomic extent of disease. Other factors, such as clinical symptoms or molecular biological characterization of the tumor, have not been included. Increasing T status reflects tumors that are larger or invasive into more peripheral (ie, visceral pleura, chest wall) or more central structures (ie, lobar or mainstem bronchus, mediastinum). In lung cancer, nodal staging depends on the location of involved nodes (as opposed to the number of nodes). The M descriptor defines the presence or absence of more distant metastatic disease.

The method of staging has a major impact on the prognostic implications of the stage classification, a fact that is well recognized by the UICC and AJCC as shown in Table 1. The two most commonly encountered types of stage assessment are *clinical staging* (the stage determined using all information available prior to any treatment) and *pathologic staging* (determined after a resection has been carried out). The extent of clinical staging can vary from a clinical evaluation alone (history and physical examination) to extensive imaging (CT/PET scans) or invasive staging techniques. It must be emphasized that a surgical staging procedure (such as mediastinoscopy) is still part of clinical staging because surgical resection as a treatment has not taken place. Clinical stage is denoted by the prefix “c” and pathologic stage by the prefix “p.” The UICC also defines a classification system for the presence or absence of residual tumor after treatment, as shown in Table 2. Typically this is applied to describe the completeness of a surgical resection.

DEVELOPMENT AND METHODOLOGY OF THE IASLC STAGING SYSTEM

A proposal to develop an international effort to inform a future revision of the TNM staging classification for lung cancer originated in 1996 at a

Table 2—Residual Tumor After Treatment

Symbol	Name	Definition
R0	No residual	No identifiable tumor remaining; negative surgical margins
R1	Microscopic residual	Microscopically positive margins but no visible tumor remaining
R2	Gross residual	Gross (visible or palpable) tumor remaining

workshop sponsored by IASLC. An international committee was established and work began in 1999. An unrestricted grant from Eli Lilly and Company enabled the establishment of a database (Eli Lilly and Company played no role in the data collection, analysis, or recommendation development process). The database was developed in cooperation with Cancer Research and Biostatistics (Seattle, WA), which is an independent scientific foundation and the statistical center for the Southwest Oncology Group. Data elements and definitions were finalized in October 2002. Data were collected from multiple sources and sites around the globe. Committees were formed to analyze the data and develop recommendations (including validation and methodology, T, N, M descriptors, nodal chart, prognostic factors, and small cell lung cancer). The initial recommendations were revised and approved by the full IASLC International Staging Committee. These proposals were published in a series of detailed articles in the *Journal of Thoracic Oncology* in 2007.^{2–6} The proposed staging recommendations were presented to the AJCC and UICC in 2007, were approved by these bodies, and are slated to be published in the 7th edition of the *UICC Staging Manual* in 2009.

At the time the database was closed to additional entries, 100,869 cases had been submitted from 45 sources in 20 countries.⁷ The final data set involved 81,015 cases after exclusion of ineligible cases (due to incomplete information in 42%, outside the 1990 to 2000 time frame in 28%, unknown histology in 13%, incomplete survival data in 6%, recurrent cases in 6%, and ineligible histologic types in 6% [carcinoid, sarcoma, and others]).^{5,7} Small cell lung cancer accounted for 16% and NSCLC for 84% of cases. Only the NSCLC cases were used to derive the T, N, M descriptors and stage groupings reviewed in this article. SCLC and carcinoid tumor staging are addressed in separate publications.^{8,9} The database included cases from four continents (the proportion of NSCLC cases is as follows: Europe, 58%; North America, 21%; Asia, 14%; and Australia, 7%). Submitted cases came from series (40%), registries (30%), and clinical trials (30%). Treatment involved

surgery only in 41%, radiotherapy only in 11%, chemotherapy only in 23%, and combined modalities in the rest. Clinical staging included patients subsequently treated with neoadjuvant (preoperative) therapy, whereas preoperatively treated patients were excluded from analyses of pathologic staging.

Subsets of the NSCLC patients were defined that met the analytic requirements for each T, N, M analysis. These subsets were substantially smaller than the entire group of NSCLC patients within the IASLC database. For example, clinical and pathologic T stage involved 5,760 and 15,234 cases, respectively, that were M0 and included a complete set of cTNM or pTNM as well as sufficient T descriptor details.² For clinical and pathologic N stage, 38,265 and 28,371 cases, respectively, were selected that were cM0

with sufficient N status assessment (any T).³ For M stage, 6,596 cases were included that were cM1 or had an additional nodule in a separate ipsilateral lobe.⁴ The definition of stage grouping involved 13,267 clinical stage and 16,937 pathologic stage patients.⁵

The major determinant chosen for development of subgroups of T, N, and M descriptors as well as the stage groupings was the overall survival, based on the best stage (pathologic, if available; otherwise clinical). Regrouping of stage descriptors was allowed, sacrificing backward compatibility with the previous TNM system in favor of greater simplicity. Stage grouping schemes were developed using a recursive partitioning and amalgamation algorithm, and validated as described later. Care was taken to prevent a deviant subset involving unstable curves or small

Table 3—Definitions for T, N, M Descriptors

Descriptors	Definitions	Subgroups*
T	Primary tumor	
T0	No primary tumor	
T1	Tumor ≤ 3 cm, † surrounded by lung or visceral pleura, not more proximal than the lobar bronchus	
T1a	Tumor ≤ 2 cm †	T1a
T1b	Tumor > 2 but ≤ 3 cm †	T1b
T2	Tumor > 3 but ≤ 7 cm † or tumor with any of the following ‡: <ul style="list-style-type: none"> Invades visceral pleura, involves main bronchus ≥ 2 cm distal to the carina, atelectasis/obstructive pneumonia extending to hilum but not involving the entire lung 	
T2a	Tumor > 3 but ≤ 5 cm †	T2a
T2b	Tumor > 5 but ≤ 7 cm †	T2b
T3	Tumor > 7 cm; <ul style="list-style-type: none"> or directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina §; or atelectasis/obstructive pneumonitis of entire lung; or separate tumor nodules in the same lobe 	T3 _{>7} T3 _{Inv}
T4	Tumor of any size with invasion of heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; <ul style="list-style-type: none"> or separate tumor nodules in a different ipsilateral lobe 	T3 _{Centr} T3 _{Centr} T3 _{Satell} T4 _{Inv} T4 _{Ipsi Nod}
N	Regional lymph nodes	
N0	No regional node metastasis	
N1	Metastasis in ipsilateral peribronchial and/or perihilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes	
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes	
M	Distant metastasis	
M0	No distant metastasis	
M1a	Separate tumor nodules in a contralateral lobe; <ul style="list-style-type: none"> or tumor with pleural nodules or malignant pleural dissemination 	M1a _{Contr Nod} M1a _{Ipsi Dissem}
M1b	Distant metastasis	M1b
Special situations		
TX, NX, MX	T, N, or M status not able to be assessed	
Tis	Focus of <i>in situ</i> cancer	Tis
T1§	Superficial spreading tumor of any size but confined to the wall of the trachea or mainstem bronchus	T1 _{SS}

*These subgroup labels are not defined in the IASLC publications²⁻⁵ but are added here to facilitate a clear discussion.

†In the greatest dimension.

‡T2 tumors with these features are classified as T2a if ≤ 5 cm.

§The uncommon superficial spreading tumor in central airways is classified as T1.

||Pleural effusions are excluded that are cytologically negative, nonbloody, transudative, and clinically judged not to be due to cancer.

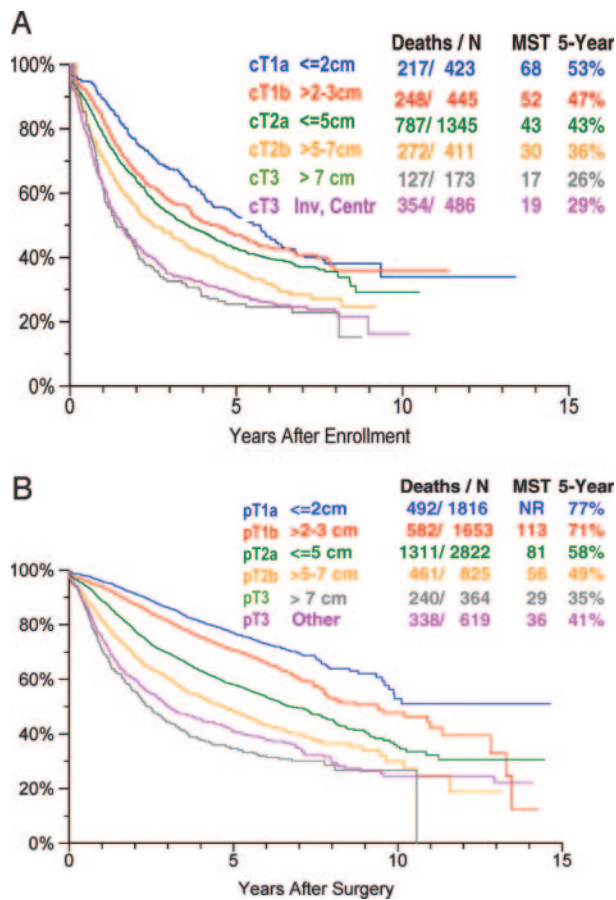


FIGURE 1. Prognosis according to size category. A: overall survival by tumor size for patients with cT1-3N0M0 tumors using the IASLC classification. Modified from Rami-Porta et al.² B: overall survival by tumor size for patients with pT1-3N0M0 R0 tumors using the IASLC classification. Modified from Rami-Porta et al.² Centr = central; Inv = invasion; MST = median survival time (months); 5-year = 5-year overall survival.

numbers of patients from driving a recommendation, unless the effect was consistent and externally validated in a population-based series.

The proposed staging revisions were both internally and externally validated.⁶ Internal validation required that differences in outcomes among the proposed subgroups were consistently observed within each type of database and geographic region, as well as the time period (from 1990 to 1995 vs from 1995 to 2000) for stage groupings.^{2,5} Furthermore, for the T descriptor size categories and the stage groupings, the cases used were separated into a randomly selected training set involving approximately two thirds of the cases and a validation set involving the rest.^{2,5,6} In each analysis this validation confirmed the training set results. Finally, the proposed descriptors were externally validated against the Surveillance, Epidemiology and End Results (SEER) database from the same time period, controlling for cell type, gender, age, and region.

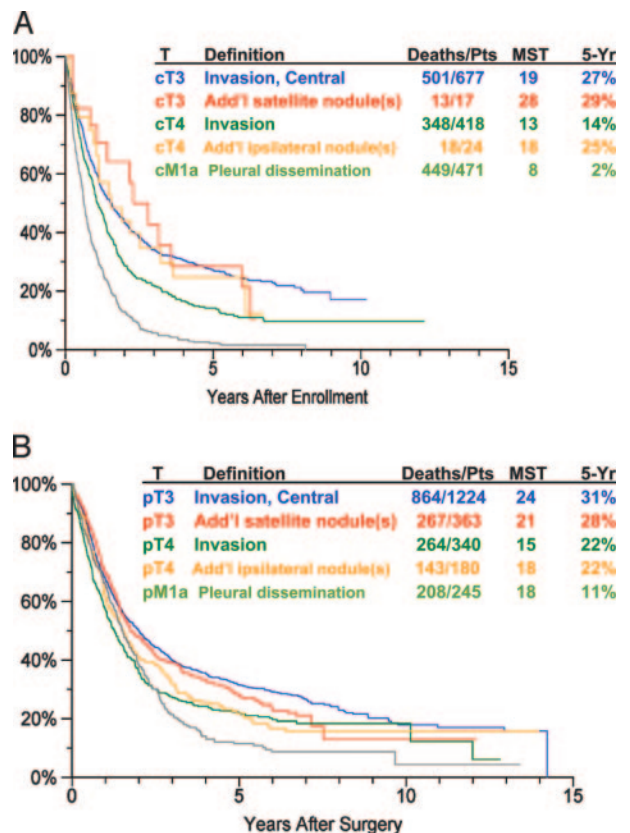


FIGURE 2. Prognosis according to additional nodules, T4 invasion, and pleural dissemination. A: overall survival for patients with cT3,4/cM1a status due to additional tumor nodules using the IASLC classification (any cN), compared with other categories of T3 and T4. Modified from Rami-Porta et al.² B: overall survival for patients with pT3,4/pM1a status due to additional tumor nodules using the IASLC classification (any pN, any R), compared with other categories of T3 and T4. Modified from Rami-Porta et al.² Add'l = additional; Pts = patients. See the legend of Figure 1 for abbreviations not used in the text.

Some details of the analyses are worth noting. The size criteria for the T descriptor are quite robust and broadly applicable, having been extensively validated. The optimal size cutpoints were initially determined using a pN0 R0 learning set (rounded to the nearest whole centimeter).² This was then tested in a pN0 R0 validation set as well as in other node stage groups and in incompletely resected patients. The analysis was also confirmed within different histologic types of NSCLC, among different types of databases and geographic regions. In contrast, the analysis of the impact of additional nodules in the primary tumor lobe or in a different ipsilateral lobe is derived from a potentially skewed population, namely primarily resected patients from Asia and Australia. Nevertheless, the results were supported by data from other geographic regions and by SEER data.² The N status analysis involved a large number of patients and was consistently a major prognostic

factor in all regions and database types. However, survival was consistently better in each N category in Asian/Australian patients, intermediate in North American, and worse in European patients.⁶ The M descriptor analysis was almost exclusively based on clinically staged patients for distant metastases and contralateral lung nodules, but 34% of patients with pleural dissemination and 53% of patients with additional nodules in a different ipsilateral lobe were pathologically staged (*ie*, resected) patients.⁴

T DESCRIPTOR

The IASLC International Staging Committee analyzed the effect of tumor size in detail, in part because there were many patients in whom reliable information was available. The size threshold of 3 cm was confirmed as a significant cutpoint and retained as a definition of a T1 vs a T2 tumor. In addition, significant cutpoints were identified at 2, 5, and 7 cm. Tumors > 7 cm had survival that tracked with other definitions of T3 (*ie*, invasion or central location) and are therefore placed within this group. The 2-cm and 5-cm additional cutpoints were addressed by the definition of subgroups of T1 (T1a and T1b) and T2 (T2a and T2b). The survival differences between each of these size subgroups were highly statistically significant in pathologically staged patients, regardless of pN status or R status. Among clinically staged patients, survival differences between cT1a, cT1b, and cT2a were not consistently statistically significant, probably due to the smaller numbers of patients for whom these data were available. Table 3 summarizes the definitions of the T descriptor subgroups. The survival curves for the size categories of the T descriptor for clinically and pathologically staged patients are shown in Figure 1.

The prognostic value of additional tumor nodules was also investigated. (Nodules were counted as synchronous primary cancers only if they were of different histologic types or were explicitly defined as synchronous primary cancers in the source database.) Patients with additional satellite nodules in the same lobe as the primary tumor had relatively good survival, similar to T3 patients, and therefore are now classified as T3 (previously classified as T4). The survival of these patients (T3_{Satell}) was statistically significantly better than patients with T4 tumors because of invasion of major mediastinal structures (T4_{Inv}). However, the prognosis of these patients (T4_{Inv}) is not statistically different than that of patients with an additional tumor nodule in a different ipsilateral lobe (T4_{Ipsi Nod}). Therefore, an ipsilateral nodule in a different lobe is now classified as T4 (previously classified as M1). In contrast, clinically

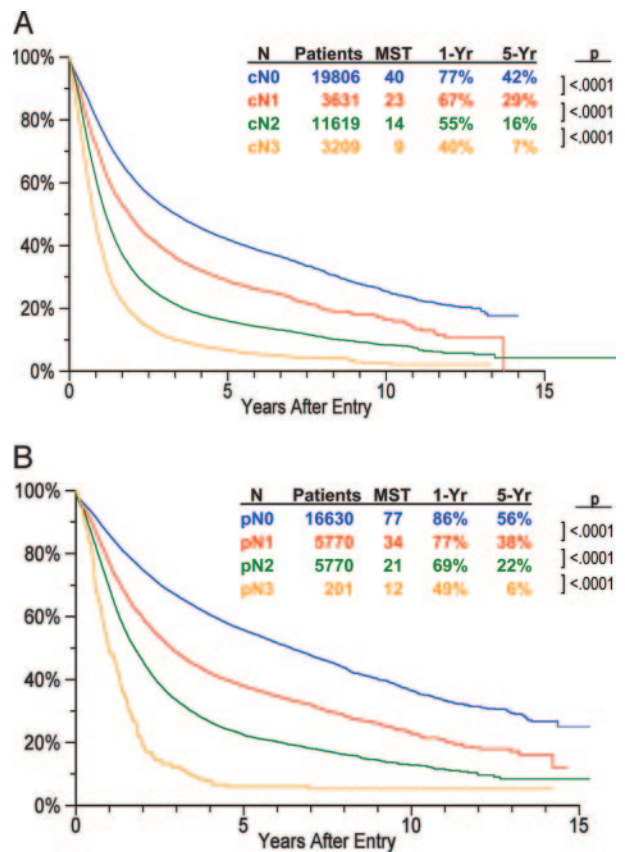


FIGURE 3. Prognosis according to the N category. A: overall survival by cN category (any cT, cM0) using the IASLC classification. Reproduced from Rusch et al.³ B: overall survival by pN category (any pT, pM0) using the IASLC classification. Reproduced from Rusch et al.³ 1-yr = 1-year overall survival. See the legend of Figure 1 for abbreviations not used in the text.

staged patients with pleural dissemination clearly have statistically significant worse survival than T4 by invasion (T4_{Inv}) or than patients with an additional nodule in a different ipsilateral lobe (T4_{Ipsi Nod}). Therefore, patients with pleural dissemination are classified as M1a. The survival curves for clinically and pathologically staged patients in these subgroups are shown in Figure 2, A and B, respectively.

Although the survival is generally similar for the subsets of patients included by the revised definitions of T3 and T4, some findings in the IASLC analysis suggest that there are instances where differences between the subsets of T3 and T4 patients may be important. For example, the survival curves of T4_{Inv} and T4_{Ipsi Nod} patients do not necessarily track together closely, suggesting there may be different factors at work leading to the observed outcomes in each of these subsets. In addition, it should be noted that resected patients with an additional tumor nodule in a different ipsilateral lobe exhibit good 5-year survival rate (48% for pT4_{Ipsi Nod} N0 M0 R0;

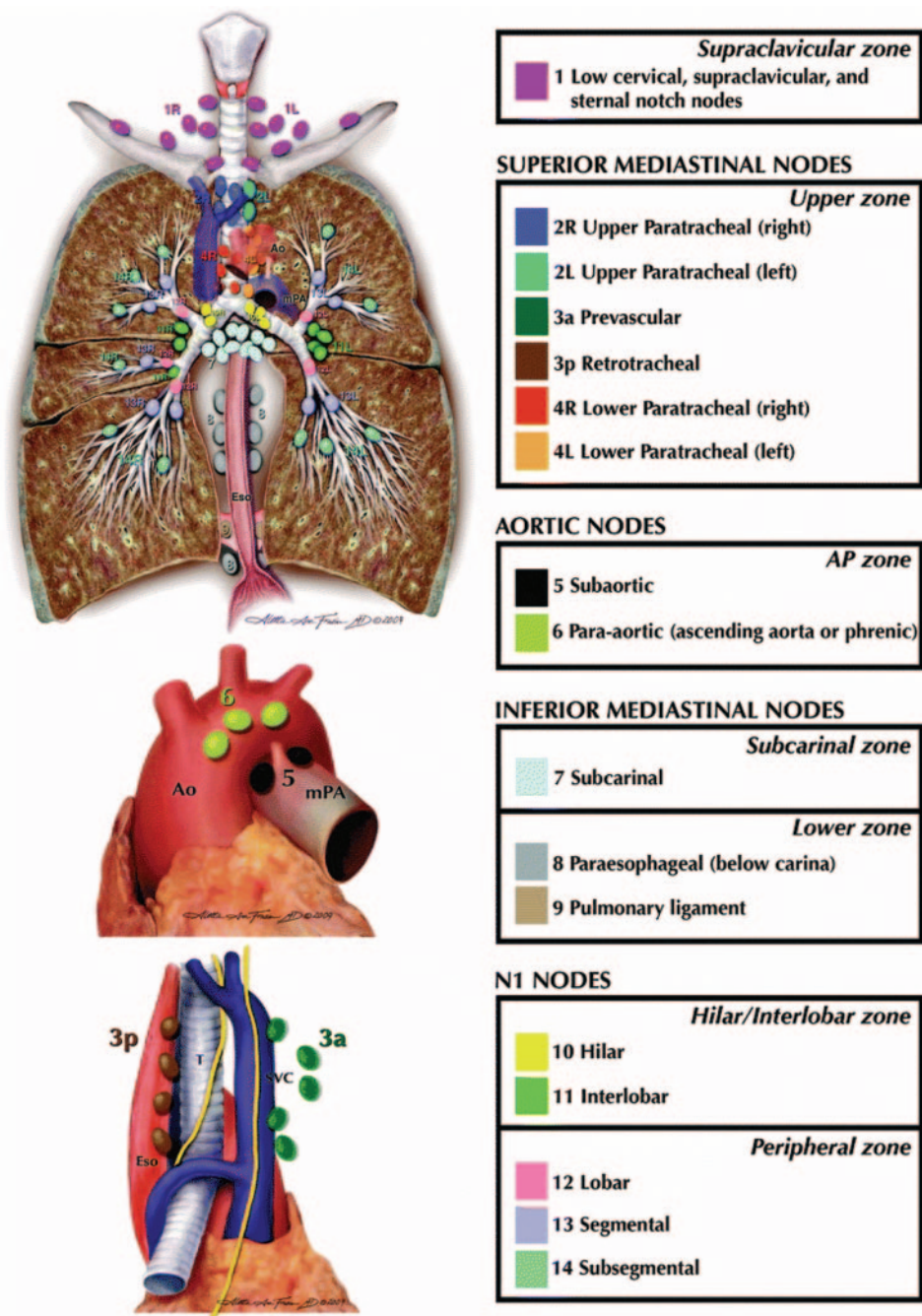


FIGURE 4. The IASLC lymph node map, including the proposed grouping of lymph node stations into “zones” for the purposes of prognostic analyses. Reproduced from Rusch.¹¹

42% for pT₄_{Ipsi Nod} N0 M0, any R), when compared with resected patients with T4 tumors by invasion (5-year survival rate: 35% for pT₄_{Inv} N0M0 R0; 30% for pT₄_{Inv} N0M0, any R) Furthermore, resected patients who were found to have pleural dissemination do not have statistically different survival than patients with T4 invasion or with an additional tumor nodule in a different ipsilateral lobe, and they exhibit fairly good 5-year survival rate (31% if pT_{Any} N0 M1a_{Pl} Disse_m, R0;

24% if pT_{Any} N0 M1a_{Pl} Disse_m, any R).² The resected patients, of course, represent a selected subgroup. However, these observations illustrate how the interplay between clinical and pathologic staging, treatment approach, and patient selection can influence our perception of similar outcomes. The T descriptor groupings do not necessarily reflect fundamental biological similarities, and we must continue to reevaluate results going forward.

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

N DESCRIPTOR

Analysis of the prognostic influence of the N descriptor resoundingly supported the traditional categorization of N0, N1, N2, and N3, as shown for clinically and pathologically staged patients in Figure 3.³ Therefore, no changes were made in the N descriptor as defined in the 6th edition of the staging manual. Further analyses were done to explore whether particular node stations within an N category had any particular impact. No such relationship could be identified.³ Specifically, there was no difference in survival between 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. The effect of skip metastases was also investigated (involvement of an N2 node station without involvement of any N1 nodes). Survival among pN2 patients with right upper lobe tumors with and without N1 involvement was not different, although there was a slight difference among such patients with a left upper lobe tumor.³

Analysis of details of nodal involvement is hampered by the fact that there are some discrepancies between the nodal map used in Asia and that used in other geographic regions. Furthermore, there are questions about how reproducibly some of the boundaries between different nodal stations can be determined during mediastinoscopy or thoracotomy.¹⁰ To address this issue prospectively, the IASLC International Staging Committee has developed a new node map (Fig 4).¹¹ To address the issue retrospectively in the database, the committee defined several nodal zones: an upper zone (stations 1 to 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 to 14). There were no differences in prognoses between the 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

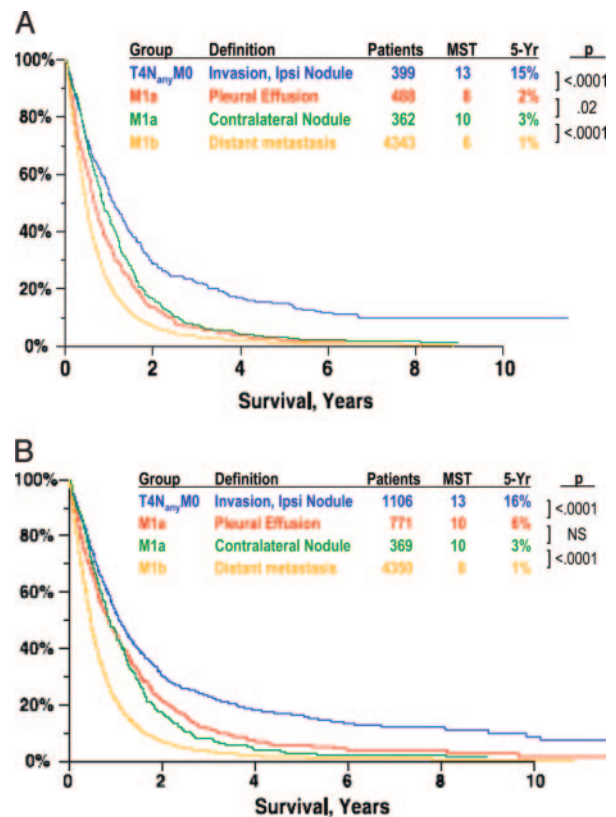


FIGURE 5. Prognosis according to the M category. A: overall survival by T4 and M category by clinical stage. B: overall survival by T4 and M category using the best stage (pathologic stage if available, otherwise clinical stage). Modified from Postmus et al.⁴ Ipsi = ipsilateral; NS = not significant. See the legend of Figure 1 for abbreviations not used in the text.

of nodes only in stations 5 and 6 vs patients with a tumor in a different lobe and involvement of another single N2 node zone.³

The number of involved nodal zones did appear to have a prognostic impact. Patients with single-zone N1 involvement had better survival than those with multizone N1 involvement (5-year survival rate, 48% vs 35%, respectively; $p < 0.09$). Similarly, patients with single-zone N2 involvement had better survival than those with multizone N2 involvement (5-year survival rate, 34% vs 20%, respectively; $p < 0.001$). In fact, the survival curves of patients with multizone N1 and single-zone N2 involvement were almost superimposed.³ However, the prognostic impact of the number of nodal zones involved could not be confirmed within T stage categories because the numbers of patients in the subsets were too small.³ Therefore, the IASLC International Staging Committee decided against the subdivision of N categories. Definitions of the N descriptor subgroups are shown in Table 3.

M DESCRIPTOR

The committee on the M descriptor considered patients traditionally classified as M0 or M1 (distant

Table 4—TNM Elements Included in Stage Groups

Stage Groups	Descriptors, % of all			Patients, %*
	T	N	M	
Ia	T1a,b	N0	M0	15
Ib	T2a	N0	M0	13
IIa	T1a,b	N1	M0	2
	T2a	N1	M0	4
	T2b	N0	M0	4
IIb	T2b	N1	M0	2
	T3	N0	M0	14
IIIa	T1–3	N2	M0	20
	T3	N1	M0	6
	T4	N0,1	M0	2
IIIb	T4	N2	M0	1
	T1–4	N3	M0	3
IV	T _{Any}	N _{Any}	M1a,b	14

*Percentage of patients in IASLC database according to best stage (rounded to nearest integer).⁵

metastases), but it also considered patients with a malignant pleural effusion or with additional tumor nodules in the lung.⁴ After analysis and discussion, patients with an additional tumor nodule in the primary tumor lobe or a different ipsilateral lobe were redefined along with other aspects of the T descriptor (see “T Descriptor” section). The remaining cohorts categorized by the M descriptor were each markedly different than patients with T4 tumors. Their survival separated into two distinct prognostic groups, which led to the definition of an M1a subgroup that includes patients with either pleural dissemination or contralateral pulmonary nodules and an M1b subgroup with distant metastases.⁴ The survival curves of these patients defined by

T/M	Subgroup	N0	N1	N2	N3
T1	T1a	Ia	IIa	IIIa	IIIb
	T1b	Ia	IIa	IIIa	IIIb
T2	T2a	Ib	IIa	IIIa	IIIb
	T2b	IIa	IIb	IIIa	IIIb
T3	T3 _{>7}	IIb	IIIa	IIIa	IIIb
	T3 _{Inv}	IIb	IIIa	IIIa	IIIb
	T3 _{Satell}	IIb	IIIa	IIIa	IIIb
T4	T4 _{Inv}	IIIa	IIIa	IIIb	IIIb
	T4 _{Ipsi Nod}	IIIa	IIIa	IIIb	IIIb
M1	M1a _{Contra Nod}	IV	IV	IV	IV
	M1a _{pl Disem}	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

FIGURE 6. Stage groups according to TNM descriptor and subgroups.

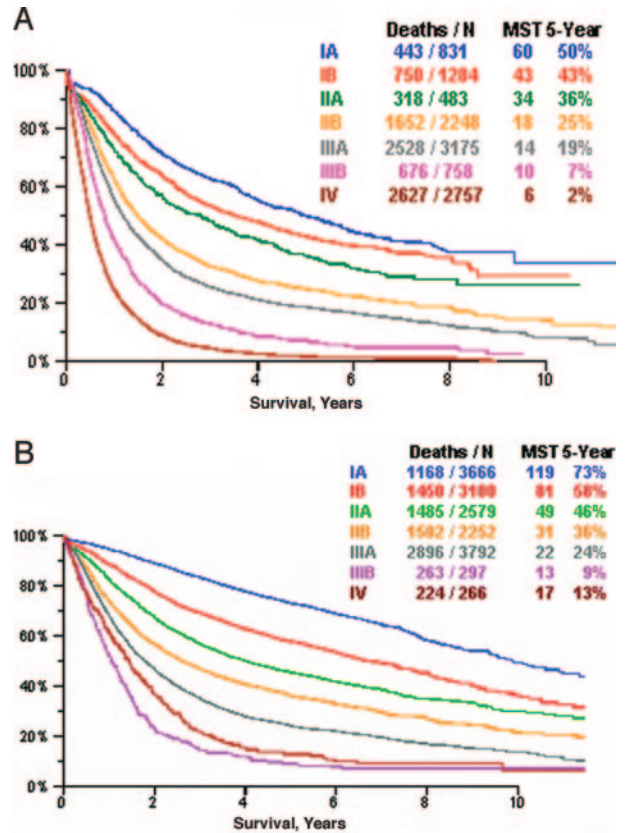


FIGURE 7. Stage grouping. A: overall survival by clinical stage for the proposed IASLC stage grouping. Reproduced from Goldstraw et al.⁵ B: overall survival by pathologic stage for the proposed IASLC stage grouping. Reproduced from Goldstraw et al.⁵ See the legend of Figure 1 for abbreviations not used in the text.

clinical stage and by best stage (pathologic if available, otherwise clinical) are shown in Figure 5, A and B, respectively. The differences in prognosis between these groups were highly statistically significant and held up to internal validation (comparisons across types of databases and geographic regions), as well as external validation (comparison with the SEER database).⁴

The prognostic impact of one vs more than one contralateral pulmonary nodule could not be assessed. Slightly worse survival was seen in patients with multiple vs a solitary distant metastasis (median survival time, 5 vs 6 months, respectively; 1-year survival rate, 20% vs 23%, respectively; $p = 0.006$).⁴ However, further subdivision of the M1b category was not undertaken.

STAGE GROUPING

The IASLC International Staging Committee has defined stage groupings. Despite the recognition of many new subdivisions of the T and M descriptor,

the stage grouping has not added any new subdivisions. However the definition of the stage groups has become more complex due to the additional T and M descriptor subgroups. Two different representations of the stage grouping scheme are shown in Table 4 and Figure 6. Survival curves for the stage groupings based on clinical and pathologic staging are shown in Figure 7, A and B, respectively. Illustrations providing a graphic representation of the TNM categories and subcategories included within each stage group are shown in Figures 8, 9, and 10.

DISCUSSION

The development of the new NSCLC staging system represents an astounding amount of work. This extends from the careful detailed analysis as summarized in this article, back through the establishment of a database (with the necessary definitions, quality controls, and data cleansing), to the individuals and institutions that collected data in the first place with sufficient detail and rigor. An effort of this magnitude as a basis for a staging system is quite

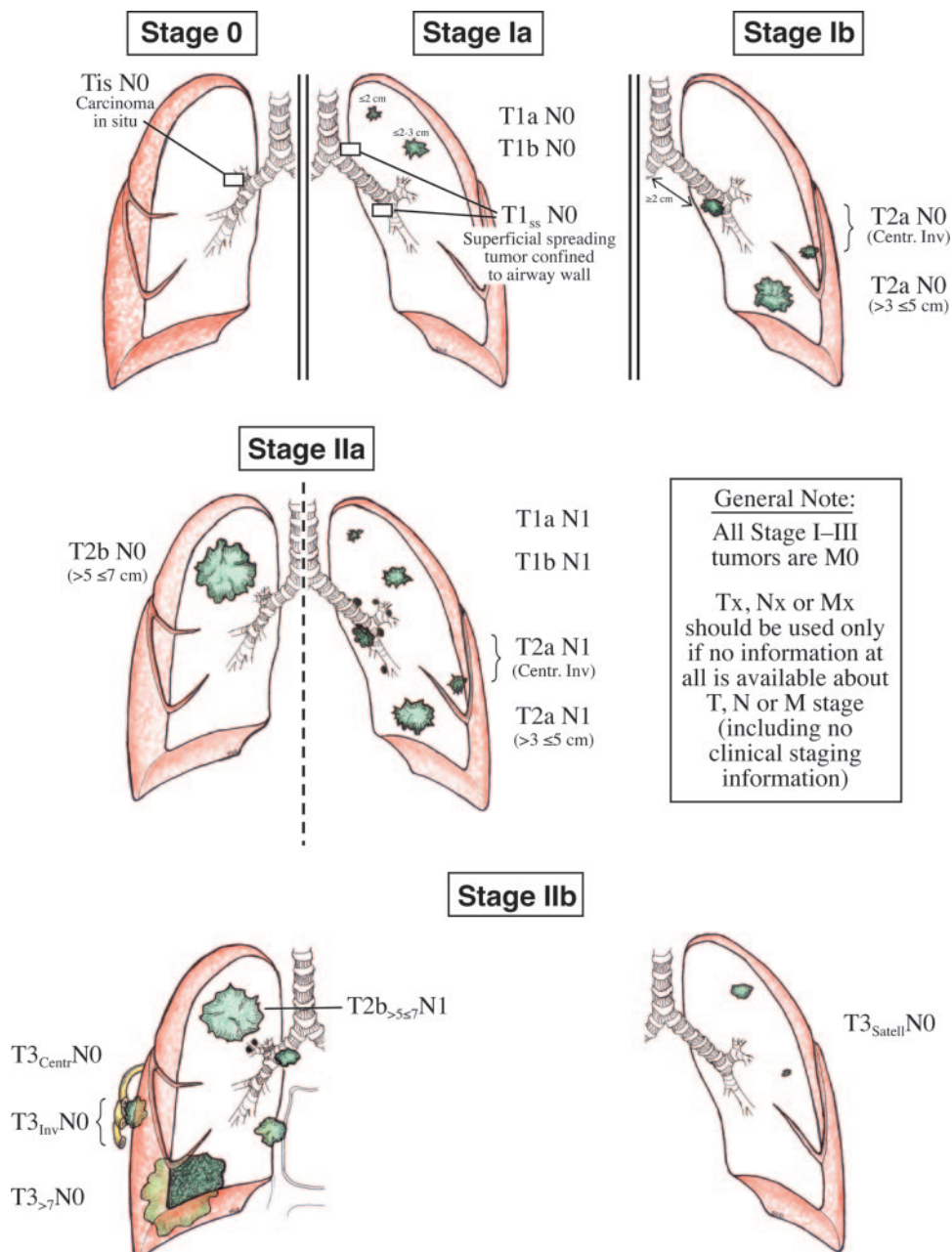


FIGURE 8. Graphic illustration of stages 0, I, and II.

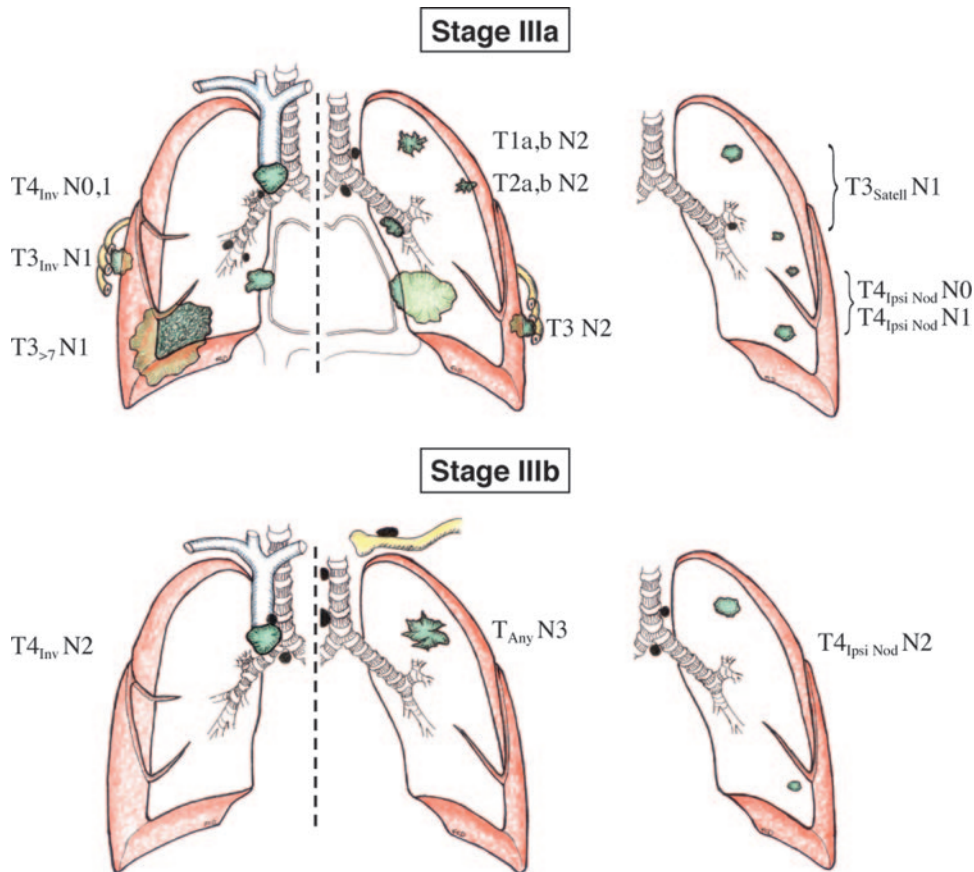


FIGURE 9. Graphic illustration of stages IIIa and IIIb.

unique among types of cancer. The IASLC International Staging Committee made every effort to go as far as the available data allowed, and issues that were not fully addressed are in areas in which insufficient data were available. Much work of the committee has not yet been published, and much work is still ongoing.

It is inevitable that the new NSCLC staging system is more complex. An increasing amount of data allows one to be able to discern an increasing number of details and differences, leading to the definition of an increasing number of subgroups. This in turn makes the organization of stage groups inherently more complex. In addition to the complexity, however, the new system is also somewhat less intuitive regarding which T, N, and M categories belong together in a stage group. This reflects the fact that the older systems involved less data and relied at least to some extent on what seemed intuitively logical, whereas the new system is based quite strictly on an extensive analysis of a large database.

The definitions of the TNM descriptors and the stage groups and subgroups were determined primarily by the outcome measure of overall survival.

This was chosen because prognosis for anatomic categories of disease was the only outcome measure and method of patient characterization for which data exists for a large number of patients. The IASLC International Staging Committee was careful to limit the analysis to a recent time period (from 1990 to 2000), and it conducted extensive internal validation across continents, time periods, and database types. The committee was also careful to only adopt definitions that were consistently shown to be statistically distinct (in analyses of smaller subgroups, only a consistent trend was required because the size of the subgroups was insufficient to show statistical significance).

Although definition of prognosis is clearly one of the major purposes of a staging system, there are many other goals and uses. The most prominent are provision of a common nomenclature about patients and the definition of homogeneous groups of patients. In addition, many people expect a staging system to define an algorithm of treatment, meaning they expect a staging system to group patients into cohorts for which particular treatment approaches are appropriate. No classification system will meet all

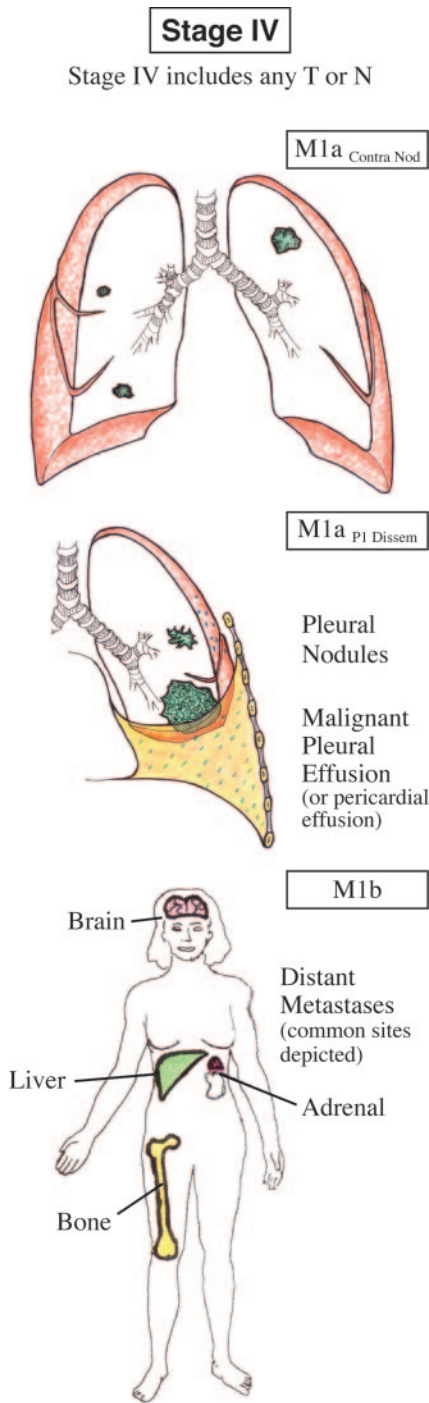


FIGURE 10. Graphic illustration of stage IV.

needs equally. Furthermore, the desired goals are interrelated, and the factors that influence them change over time. New treatment approaches are defined that affect prognosis. Advances in imaging alter the stage assignment of a patient (stage migration), which affects the prognosis of all stage groups.^{12,13} Finally, changing methods of detection (eg, CT screening) can alter the spectrum of disease

that is encountered.¹⁴ As we consider how the new staging system fulfills our needs, we must keep these factors in mind.

The IASLC system clearly meets the need for a common nomenclature. A balance must be struck between a system that is simple and one that is detailed enough to distinguish subgroups that are distinct. However, increasing data and knowledge require us to collect an increasing amount of detail. At a minimum we should track not just the TNM descriptors but also the subgroup of the T, N, or M category (ie, T3_{Satell} or T3_{Inv} instead of just T3). A set of data elements to collect prospectively for the next revision of the staging system is being developed by the IASLC International Staging Committee.¹⁵

The IASLC staging system clearly addresses the goal of defining prognosis. A strict focus on prognosis leads to an emphasis on pathologic staging because it is most accurate. However, pathologic staging is inherently somewhat academic because it is not available until after major decisions about treatment have been made (ie, surgical resection). Clinical staging is more practical because it can guide decisions at the outset. Finally, we must remember that prognosis changes as treatment advances and can be very dependent on our attitudes and beliefs. For example, we typically view patients with pleural dissemination as having such a poor prognosis that only palliative care is appropriate, but the relatively good prognosis of resected patients with pleural dissemination suggests there may be a subgroup in whom such a pessimistic attitude is not appropriate.

We should not be tempted to use the stage grouping as a simple algorithm that defines treatment. The optimal treatment is defined by clinical trials, and eligibility for a particular treatment depends on multiple factors, including modality-related factors, patient-related factors (eg, performance status or comorbidities), and tumor-related factors (eg, histology, stage, or proximity to other organs). Furthermore, ongoing clinical research should refine our treatment at a faster pace than revisions in the staging system. Therefore, although a staging system provides a nomenclature to facilitate discussion of one aspect of the applicability of clinical trial results to newly diagnosed patients, it is an oversimplification to use stage group as a treatment algorithm.

Definition of homogeneous cohorts of patients requires agreement on which measures best demonstrate homogeneity. Identification of homogeneous cohorts will require attention to details beyond stage grouping or prognosis alone. Certainly there are groups that have similar prognosis but have markedly different clinical characteristics (eg, stage IIIa includes patients with N2 disease [T1-3 N2 M0], those

with extensive local invasion only [T_{4Inv} N0 M0], and those with ipsilateral additional tumor nodules [T_{4Ipsi Nod} N0 M0].

The ideal system would reflect the biological behavior of the tumor because patients grouped by tumor behavior characteristics will probably continue to have similarities with one another (*eg*, similar prognosis and treatment approach), even as new treatments are developed and outcomes change. This suggests that classification by molecular biological characteristics may be more useful. Unfortunately, however, the ability to predict tumor biology is rudimentary, and only a limited number of patients have data available on nonanatomic characteristics.¹⁶

An attempt to introduce an element of biological behavior into an anatomically based staging system is inherently speculative, given our current understanding. Clinical observation suggests that there may be four different types of biological behavior: tumors that are characterized primarily by a propensity to spread to regional lymph nodes, those characterized primarily by direct local invasion, those characterized by a propensity to develop additional foci of cancer within the lung, and those with a propensity for systemic dissemination.¹⁷ One can argue that in some instances the observed anatomic characteristics may be more reflective of the location of the tumor or the point in time at which it is discovered, rather than the biological behavior. However, it may, in fact, be the tumor biology that determines the location and stage at which a tumor is likely to be found. We believe it is important to explore potential ways to characterize tumor behavior as we implement the IASLC staging system and continue to study the course of disease in patients with lung cancer.

In conclusion, the IASLC staging classification is unquestionably a major advance. The size of the database, the broad international spectrum, the careful and detailed analysis, as well as the internal and external validation, are tremendous achievements and relatively unique among types of cancer. This extensive effort has allowed the worldwide experience with lung cancer to be brought together to create a sound and evidence-based staging classification. To improve on this will require not only prospective collection of more data according to the data elements defined by our experience so far, but also thoughtful investigation of novel factors and views that may enhance our understanding in the future.

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