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1. Summarize significant modifications for staging of lung cancers in the recently released eighth edition of the American Joint Committee on Cancer (AJCC) Staging Manual.
2. Describe the clinical significance of modifications for staging of lung cancers in the recently released eighth edition of the AJCC Staging Manual.

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Lung Cancer—Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual

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Abstract: The revision for the eighth edition of the tumor, node, and metastasis (TNM) classification of lung cancer was based on analyses of the International Association for the Study of Lung Cancer database, which included 77,156 evaluable patients diagnosed with lung cancer from 1999 to 2010. Among tumor (T) descriptors, the following new tumor-size groups were created: T1a, ≤ 1 cm; T1b, >1 to 2 cm; T1c, >2 to 3 cm; T2a, >3 to 4 cm; T2b, >4 to 5 cm; T3, >5 to 7 cm; and T4, >7 cm. Tis and T1mi were introduced for adenocarcinoma in situ and minimally invasive adenocarcinoma, respectively. Endobronchial tumors located <2 cm from the carina have better prognosis than those with any other T3 descriptor and were classified as T2. Total atelectasis/pneumonitis was classified as a T2 descriptor, because it has a T2 prognosis. Diaphragmatic invasion is now T4. Visceral pleural invasion remains unchanged, and mediastinal pleura invasion, which is seldom used, disappears as a T descriptor. The lymph node (N) component descriptors are unchanged, but the number of involved nodal stations has prognostic impact. For the metastasis (M) component, M1a (intrathoracic metastases) remains unchanged, but extrathoracic metastases are divided into a single extrathoracic metastasis (new M1b) and multiple extrathoracic metastases in a single organ or multiple organs (M1c). Stage IA is now divided into IA1, IA2, and IA3 to accommodate T1a, T1b, and T1cN0M0 tumors, respectively; all N1 disease is stage IIB except for T3-T4N1M0 tumors, which are stage IIIA; a new stage IIIC is created for T3-T4N3M0 tumors; and stage IV is divided into IVA (M1a and M1b) and IVB (M1c). This revision enhances our capacity for prognostication and will have an important impact in the management of patients with lung cancer and in future research. *CA Cancer J Clin* 2017;67:138–155. © 2017 American Cancer Society.

Keywords: lung cancer, lung cancer staging, nonsmall cell lung cancer, regional lymph node map, small cell lung cancer, stage grouping, TNM classification, visceral pleural invasion

Practical Implications for Continuing Education

- > More subgroups are created based on tumor size.
- > Quantification of nodal disease has prognostic impact.
- > Different categories are created for single and multiple extrathoracic metastases.

Introduction

The revisions introduced in the eighth edition of the tumor, node, and metastasis (TNM) classification of lung cancer have emanated from analyses of the International Association for the Study of Lung Cancer (IASLC) database. This has meant the consolidation of a data-based process for the periodic revision of the classification, which started in the early 2000s with the revision of the sixth edition toward the seventh edition.^{1,2} The purpose of this article is to summarize the characteristics of the

TABLE 1. Innovations in the Descriptors Introduced in the Eighth Edition of the TNM Classification of Lung Cancer Compared With the Seventh Edition

DESCRIPTOR	SEVENTH EDITION	EIGHTH EDITION
T component		
0 cm (pure lepidic adenocarcinoma \leq 3 cm total size)	T1a if \leq 2 cm; T1b if >2-3 cm	Tis (AIS)
\leq 0.5 cm invasive size (lepidic predominant adenocarcinoma \leq 3 cm total size)	T1a if \leq 2 cm; T1b if >2-3 cm	T1mi
\leq 1 cm	T1a	T1a
>1-2 cm	T1a	T1b
>2-3 cm	T1b	T1c
>3-4 cm	T2a	T2a
>4-5 cm	T2a	T2b
>5-7 cm	T2b	T3
>7 cm	T3	T4
Bronchus <2 cm from carina	T3	T2
Total atelectasis/pneumonitis	T3	T2
Invasion of diaphragm	T3	T4
Invasion of mediastinal pleura	T3	-
N component		
No assessment, no involvement, or involvement of regional lymph nodes	NX, N0, N1, N2, N3	No change
M component		
Metastases within the thoracic cavity	M1a	M1a
Single extrathoracic metastasis	M1b	M1b
Multiple extrathoracic metastases	M1b	M1c

Abbreviations: AIS, adenocarcinoma in situ; mi, minimally invasive adenocarcinoma; Tis, tumor in situ.

database used for the latest revision; to describe the most important findings from the multiple analyses performed leading to the recommendations for changes introduced in the eighth edition; to comment on those situations beyond the official T, N, and M descriptors that need rules for homogeneous classification; and to point out the clinical and research implications of the new classification. The eighth edition of the TNM classification will be enacted on January 1, 2017.

The Database

The IASLC database used to inform the eighth edition of the TNM classification of lung cancer included data on a total of 94,708 patients diagnosed with lung cancer from 1999 to 2010, originating from 35 different databases in 16 countries on 5 continents. The database was stored, managed, and analyzed by Cancer Research And Biostatistics, a biostatistical agency appointed by the IASLC. After exclusions, 77,156 patients remained evaluable, including 70,967 with nonsmall cell lung cancer and 6189 with small cell lung cancer. Nearly 85% of the patients underwent surgical treatment, either alone (57.7%) or with chemotherapy (21.1%), radiotherapy (1.5%), or both (4.4%). Most of

these patients were from Europe and Asia, but there also were patients from North and South America and from Australia. Data on 73,251 patients had been retrospectively registered but contained the necessary information to study the T and the N descriptors. For the M descriptors, data on 3905 patients prospectively collected through the online electronic data capture (EDC) system provided detailed information on the number and location of metastatic sites to allow the recommendation of some changes in the M descriptors.³ The methods and validation used in the analyses of the database have been described in detail elsewhere.⁴

The Innovations

Table 1 summarizes the innovations introduced for the T, N, and M descriptors in the eighth edition of the classification.

The T Descriptors

The analysis of the T component is complex, because it has many descriptors: tumor size, endobronchial location, atelectasis/pneumonitis, and the invasion of the many anatomic structures around the lung. The prognosis of each

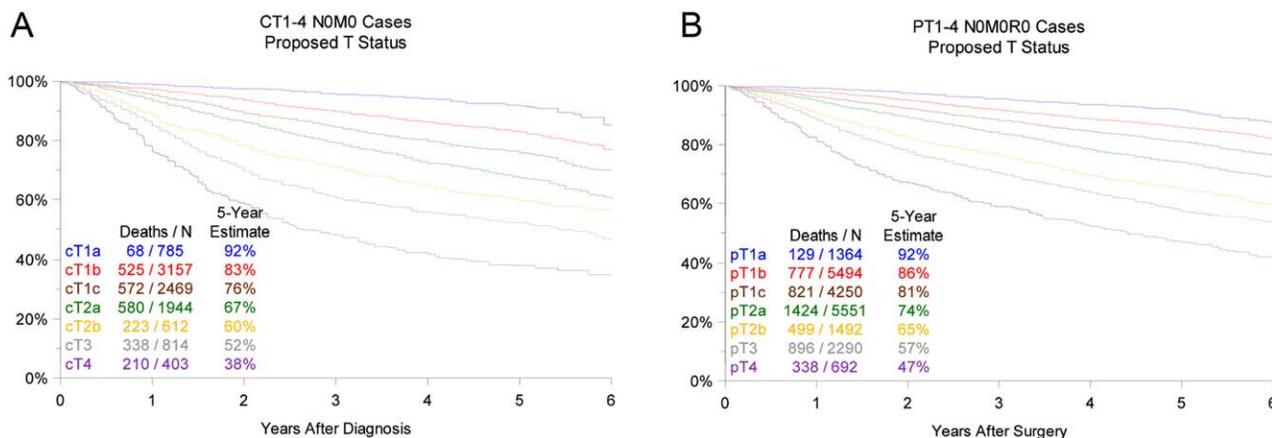


FIGURE 1. Survival According to the (A) Clinical and (B) Pathologic T Descriptors of the Eighth Edition of the TNM Classification of Lung Cancer. cT indicates clinical T classification; pT, pathologic T classification. Reprinted from: Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2015;10:990-1003⁵ with permission from Elsevier.

individual T descriptor was assessed in patients who had pathologically staged tumors with and without nodal involvement that were completely and incompletely resected. The same analyses were then performed in the population of patients who had clinically staged tumors, either with or without nodal involvement. All findings were consistent in all studied populations.⁵ These analyses showed that the 3-cm cutoff point still separates T1 from T2 tumors, but tumor size arises as a more important prognostic factor, because, from ≤ 1 cm to 5 cm, each centimeter separates tumors with a significantly different prognosis. Tumors measuring from >5 to ≤ 7 cm (now T3) were found to have a worse prognosis than was determined in the previous editions of the TNM classification, and those >7 cm (now T4) were associated with a prognosis similar to that of other descriptors in the T4 category. Another important finding was that, in the analyses of this series, endobronchial location <2 cm from the carina (a T3 descriptor in the seventh edition), but without involvement of the carina, had the same prognosis as endobronchial location >2 cm from the carina (a T2 descriptor in the seventh edition). The same occurred with total atelectasis/pneumonitis, ie, atelectasis or pneumonitis involving the whole lung (a T3 descriptor in the seventh edition): in the analyses of the new database, it had the same prognosis as partial atelectasis/pneumonitis, ie, atelectasis or pneumonitis involving part of the lung and extending to the hilar region (a T2 descriptor in the seventh edition). Conversely, invasion of the diaphragm (a T3 descriptor in the seventh edition, T4 in the eighth edition) had a worse prognosis than other T3 descriptors that was similar to the prognosis of T4 tumors. Finally, it was found that mediastinal pleural invasion was rarely used as a descriptor. In the light of these findings, the recommendations for the T descriptors in the eighth edition are shown in Table 1: New categories were introduced based on tumor size, endobronchial location <2

cm from carina and total atelectasis/pneumonitis were down staged (from T3 to T2), and invasion of the diaphragm was upstaged (from T3 to T4), while invasion of the mediastinal pleura was deleted as a descriptor. Figure 1 shows the survival curves according to clinical (cT) and pathologic (pT) T descriptors.⁵

Visceral pleural invasion, defined as the involvement of its elastic layer, was well assigned to its T2 category, but specific analyses of this descriptor showed that the 2 types of invasion (PL1, tumor invades beyond the elastic layer; and PL2, tumor invades to the pleural surface) had different prognoses, PL2 being associated with the worst outcome.⁶ Figure 2 shows a graphic representation of the different types of visceral pleural involvement and their definitions.⁶ The finding that visceral pleural invasion is not only a negative prognostic factor but that separation of PL1 and PL2 further stratifies prognostic subgroups indicates that its precise assessment for depth of invasion should be actively pursued. Elastic stains are recommended to clarify the status of visceral pleural invasion for cases in which initial hematoxylin-and-eosin-stained slides show that the tumor abuts the pleura and there is any question whether invasion is present.⁶

The N Descriptors

Analyses of the current N descriptors at clinical and pathological staging showed that they clearly separate tumors of significantly different prognosis (Fig. 3).⁷ Therefore, there was no need to suggest any modifications. On this occasion, quantification of nodal disease was also explored. For the seventh edition, quantification was based on the number of the newly defined nodal zones. The nodal zones group neighboring nodal stations. For example, the upper mediastinal nodal stations, including the right and left superior and inferior paratracheal, prevascular, and retrotracheal nodal stations are grouped in the upper zone; and the lobar, segmental, and subsegmental nodal stations are

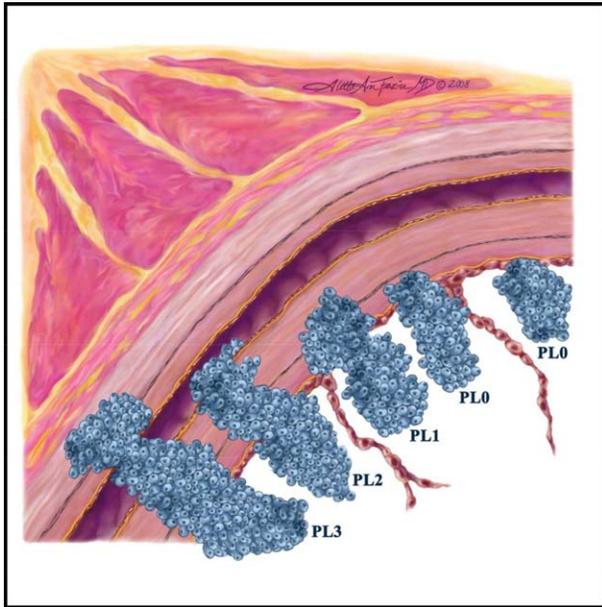


FIGURE 2. Visceral Pleura Invasion. PL0 indicates tumor within the subpleural lung parenchyma or invading superficially into the pleural connective tissue; PL1, tumor invades beyond the elastic layer; PL2, tumor invades the pleural surface; PL3, tumor invades any component of the parietal pleura. Copyright © 2008 Aletta Ann Frazier, MD. Reprinted from: Travis WD, Brambilla E, Rami-Porta R, et al. Visceral pleural invasion: pathologic criteria and use of elastic stains. Proposal for the seventh edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2008;3:1384-1390⁶ with permission from Elsevier.

grouped in the peripheral zone (Table 2) (Fig. 4).⁸ It was found that the number of involved nodal zones had prognostic impact.⁹ For the eighth edition, the number of involved nodal stations was considered. The nodal stations contain lymph nodes that are located within clearly defined anatomic landmarks in the lung, the hilum, the mediastinum, and the supraclavicular area (Table 2).⁸ Similar to the nodal zones, the more involved nodal stations, the worse the prognosis.⁷ These findings derived exclusively from pathologic staging after examination of the resected lymphadenectomy specimens and could not be reproduced at clinical staging. This is the main reason why they were

not used to modify the N descriptors. However, both the number of involved nodal zones and the number of involved nodal stations allow the refinement of postoperative prognosis and assist in making decisions on adjuvant therapy. The recommendation is to define nodal involvement in a quantitative way, especially at pathological staging, but also at clinical staging with the available means. Clinical quantification of nodal disease—based on anatomic and metabolic images; on transbronchial needle aspirations, either blind or assisted by ultrasound (endobronchial ultrasound transbronchial needle aspiration); on transesophageal fine-needle aspirations assisted by ultrasound; or on limited biopsies at surgical staging with mediastinoscopy or thoracoscopy—in general will be less accurate than pathologic quantification based on the study of the lymphadenectomy specimen.

Nodal quantification by the number of involved nodal stations is defined as follows:

- N1a: involvement of a single N1 nodal station;
- N1b: involvement of multiple N1 nodal stations;
- N2a1: involvement of a single N2 nodal station without N1 involvement (skip metastasis);
- N2a2: involvement of a single N2 nodal station with N1 involvement; and
- N2b: involvement of multiple N2 nodal stations.

Prognosis worsens as the number of involved nodal stations increases, but N1b and N2a1 have the same prognosis.⁷ This new analysis shows that discreet (one-station) mediastinal nodal disease without N1 disease has the same prognosis as multiple N1 stations. Five-year survival rates in the population of patients who underwent complete resection for the different N subcategories are: N1a, 59%; N1b, 50%; N2a1, 54%; N2a2, 43%; and N2b, 38%.⁷

Figure 4 shows the lymph node map with specification of nodal stations and zones, and Table 2 defines the anatomic limits of the nodal stations and their grouping into nodal zones.⁸

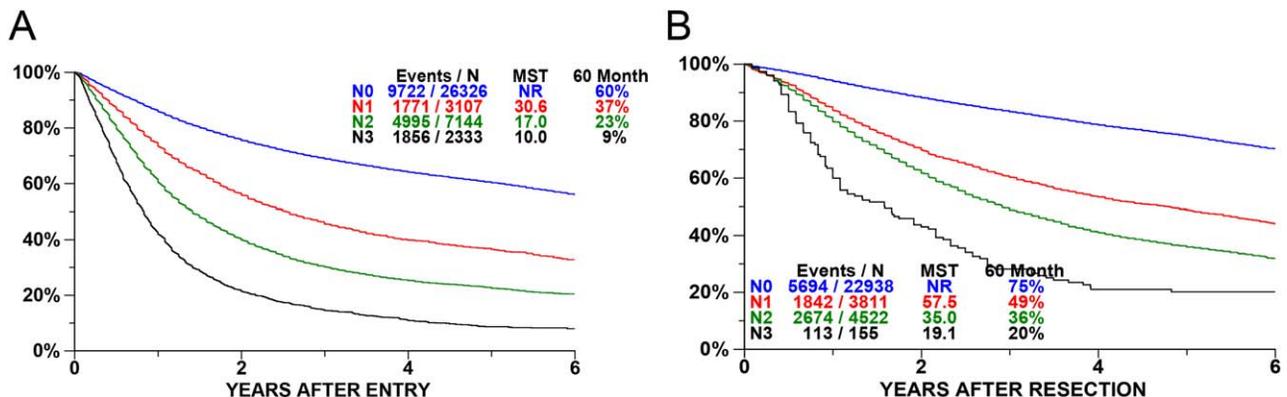


FIGURE 3. Survival According to (A) Clinical and (B) Pathologic N Categories. MST indicates median survival time (in months); NR, not reached. Reprinted from: Asamura H, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the N descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2015;10:1675-1684⁷ with permission from Elsevier.

TABLE 2. Anatomic Limits of the Nodal Stations of the International Association for the Study of Lung Cancer Lymph Node Map and Their Grouping in Nodal Zones

LYMPH NODE STATION NO.	ANATOMICAL LIMITS
Supraclavicular zone	
1: Low cervical, supraclavicular, and sternal notch nodes	<ul style="list-style-type: none"> • Upper border: Lower margin of cricoid cartilage • Lower border: Clavicles bilaterally and, in the midline, the upper border of the manubrium; 1R designates right-sided nodes, and 1L designates left-sided nodes in this region • For lymph node station 1, the midline of the trachea serves as the border between 1R and 1L
Upper zone	
2: Upper paratracheal nodes	<ul style="list-style-type: none"> • 2R: Upper border: Apex of the right lung and pleural space and, in the midline, the upper border of the manubrium • Lower border: Intersection of caudal margin of innominate vein with the trachea • Similar to lymph node station 4R, 2R includes nodes extending to the left lateral border of the trachea • 2L: Upper border: Apex of the lung and pleural space and, in the midline, the upper border of the manubrium • Lower border: Superior border of the aortic arch
3: Prevascular and retrotracheal nodes	<ul style="list-style-type: none"> • 3a: Prevascular • On the right: Upper border, apex of chest; lower border, level of carina; anterior border, posterior aspect of sternum; posterior border, anterior border of superior vena cava • On the left: Upper border, apex of chest; lower border, level of carina; anterior border, posterior aspect of sternum; posterior border, left carotid artery • 3p: Retrotracheal • Upper border, apex of chest; lower border, carina
4: Lower paratracheal nodes	<ul style="list-style-type: none"> • 4R: Includes right paratracheal nodes and pretracheal nodes extending to the left lateral border of the tracheal • Upper border: Intersection of caudal margin of innominate vein with the trachea • Lower border: Lower border of the azygos vein • 4L: Includes nodes to the left of the left lateral border of the trachea, medial to the ligamentum arteriosum • Upper border: Upper margin of the aortic arch • Lower border: Upper rim of the left main pulmonary artery
Aortopulmonary zone	
5: Subaortic (aortopulmonary window)	<ul style="list-style-type: none"> • Subaortic lymph nodes lateral to the ligamentum arteriosum • Upper border: The lower border of the aortic arch • Lower border: Upper rim of the left main pulmonary artery
6: Para-aortic nodes (ascending aorta or phrenic)	<ul style="list-style-type: none"> • Lymph nodes anterior and lateral to the ascending aorta and aortic arch • Upper border: A line tangential to the upper border of the aortic arch • Lower border: The lower border of the aortic arch
Subcarinal zone	
7: Subcarinal nodes	<ul style="list-style-type: none"> • Upper border: The carina of the trachea • Lower border: The upper border of the lower lobe bronchus on the left; the lower border of the bronchus intermedius on the right

TABLE 2. *Continued*

LYMPH NODE STATION NO.	ANATOMICAL LIMITS
Lower zone	
8: Paraesophageal nodes (below carina).	<ul style="list-style-type: none"> • Nodes lying adjacent to the wall of the esophagus and to the right or the left of the midline, excluding subcarinal nodes • Upper border: The upper border of the lower lobe bronchus on the left; the lower border of the bronchus intermedius on the right • Lower border: The diaphragm
9: Pulmonary ligament nodes	<ul style="list-style-type: none"> • Nodes lying within the pulmonary ligament • Upper border: The inferior pulmonary vein • Lower border: The diaphragm
Hilar/interlobar zone	
10: Hilar nodes	<ul style="list-style-type: none"> • Includes nodes immediately adjacent to the mainstem bronchus and hilar vessels, including the proximal portions of the pulmonary veins and main pulmonary artery • Upper border: The lower rim of the azygos vein in the right, upper rim of the pulmonary artery on the left • Lower border: Interlobar region bilaterally
11: Interlobar nodes	<ul style="list-style-type: none"> • Between the origins of the lobar bronchi • Optional notations for subcategories of station: <ul style="list-style-type: none"> • 11s: Between the upper lobe bronchus and bronchus intermedius on the right • 11i: Between the middle and lower bronchi on the right
Peripheral zone	
12: Lobar nodes	<ul style="list-style-type: none"> • Adjacent to the lobar bronchi
13: Segmental nodes	<ul style="list-style-type: none"> • Adjacent to the segmental bronchi
14: Subsegmental nodes	<ul style="list-style-type: none"> • Adjacent to the subsegmental bronchi

Reprinted and adapted from: Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P. The IASLC Lung Cancer Staging Project. A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2009;4: 568-577⁸ with permission from Elsevier.

The M Descriptors

The information from patients registered through the EDC system enabled specific analyses of the number and location of extrathoracic metastases and validation of the current M1a descriptors. Figure 5A shows the survival curves for the M1a descriptors. All have similar prognosis. These results validated the M1a descriptors proposed in the seventh edition; therefore, no modifications are needed.¹⁰

Specific analyses of the sites of metastases showed that most had similar prognosis, but adrenal metastases tended to have worse prognosis. However, when the number of metastases was studied, patients with a single metastasis had significantly better prognosis than those with several metastases either in one organ or in several organs. Therefore, there was reliable enough data to reclassify M1b as those tumors with a single extrathoracic metastasis and to create the new category M1c for those tumors with multiple extrathoracic metastases in one organ or several organs. Figure 5B shows the survival curves of patients

with endothoracic metastasis (M1a), with a single extrathoracic metastasis (M1b) and with multiple extrathoracic metastases (M1c).¹⁰ M1a and M1b tumors have similar prognosis, but it makes sense to keep them separate, because they represent different forms of metastatic involvement and require different diagnostic and therapeutic approaches.

The Stages

There are modifications in the stage grouping. Some stages accommodate tumors with TNMs that belonged to other stages in the previous edition of the classification, and others were created to separate groups of tumors with significantly different prognosis. Stage IA is now divided into stages IA1, IA2, and IA3 to include the new T1a, T1b, and T1c N0M0 tumors. Stages IB and IIA now group T2aN0M0 and T2bN0M0 tumors, respectively. All N1M0 tumors are now grouped into stage IIB, together with T3N0M0, except for T3-T4N1M0 tumors, which are grouped into stage IIIA. Similarly, all N2M0 tumors

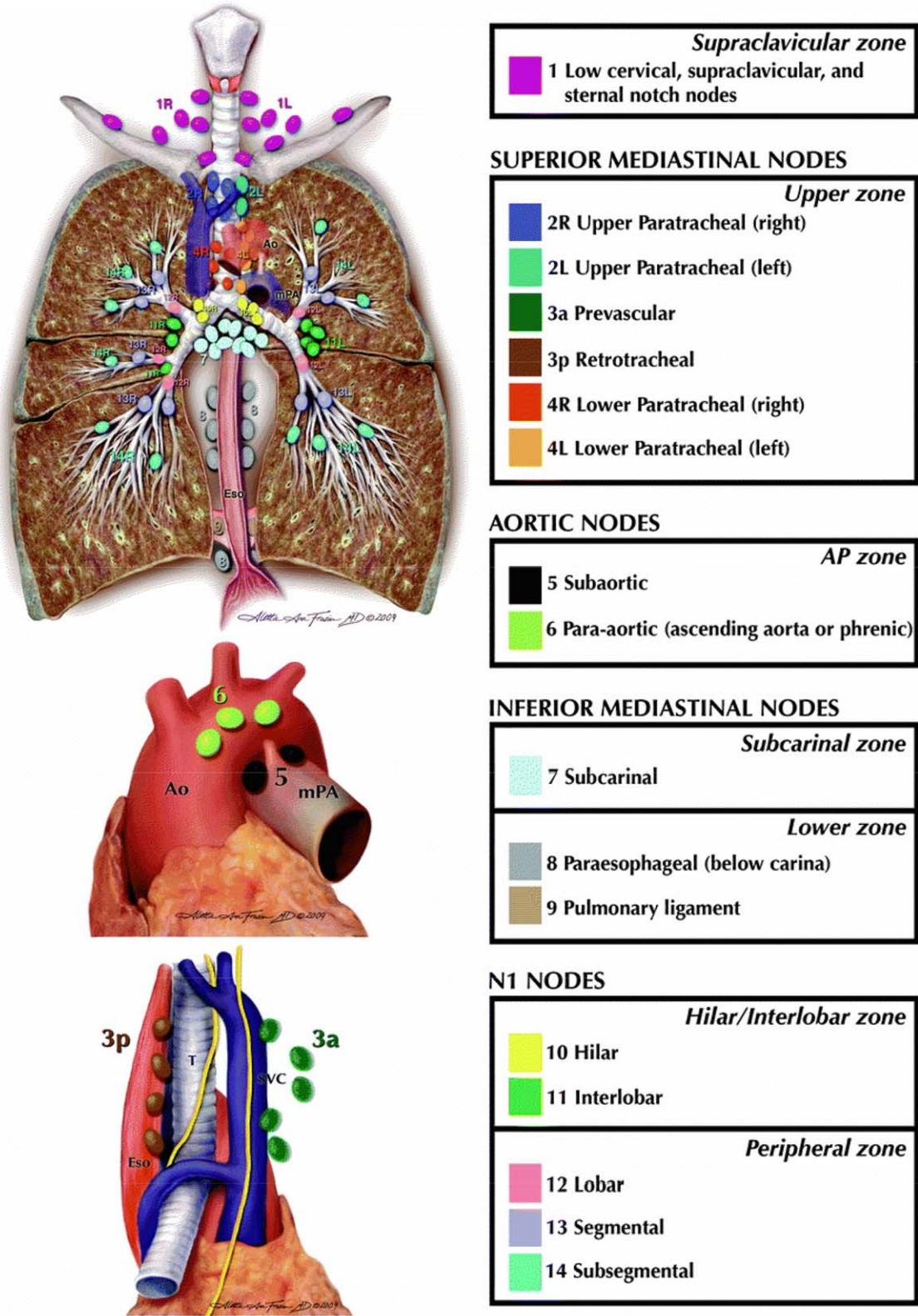


FIGURE 4. International Association for the Study of Lung Cancer (IASLC) Lymph Node Map. AP indicates aortopulmonary; Ao, aorta; Eso, esophagus; L, left; MPA, main pulmonary artery; R, right; SCV, superior vena cava; T, trachea. Copyright © 2009 Aletta Ann Frazier, MD. Reprinted from: Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P. The IASLC Lung Cancer Staging Project. A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2009;4:568-577⁸ with permission from Elsevier.

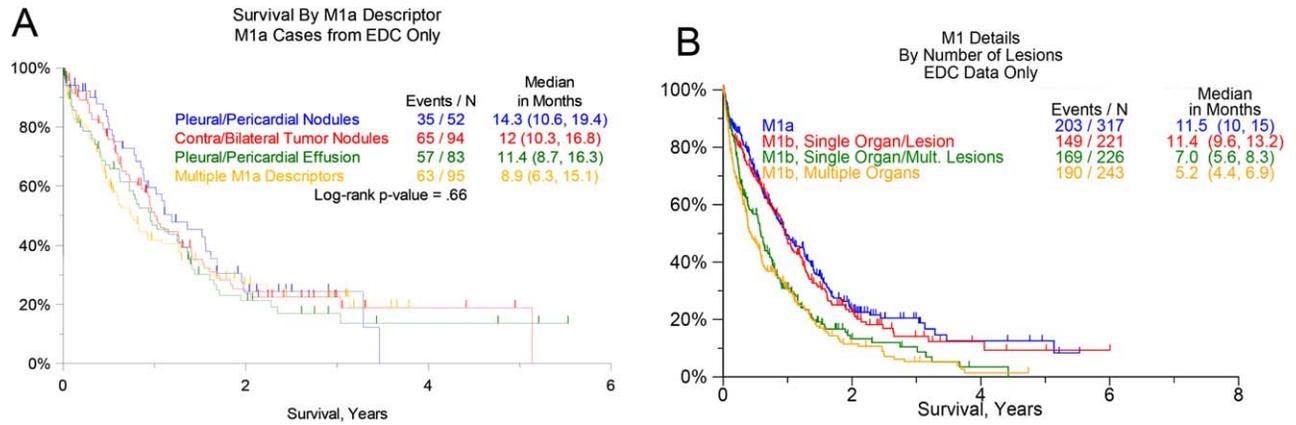


FIGURE 5. Survival According to (A) M1a and (B) M1b Descriptors and the Multiplicity of Extrathoracic Metastases. EDC indicates electronic data capture. Reprinted from: Eberhardt WE, Mitchell A, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the M descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2015;10:1515-1522¹⁰ with permission from Elsevier.

are now stage IIIA, except for T3-T4N2M0 tumors, which are in stage IIIB, together with all N3M0 tumors, except for T3-T4N3M0 tumors, for which a new stage IIIC was created. Finally, stage IV is now divided into stage IVA to group M1a and M1b tumors and stage IVB to include M1c tumors.¹¹ Figure 6 shows the survival graphs and survival rates of the clinical and pathologic stages from the eighth edition.¹¹ There is the expected

worsening in survival as tumor stage increases. All survival differences are significant except for those between stages IIIC and IVA. Despite the lack of survival differences, it makes sense to have these tumors in different stages, as they represent different forms of disease extent (locregional and metastatic, respectively).

Table 3 shows the definitions of the T, N, and M descriptors for the eighth edition of the TNM

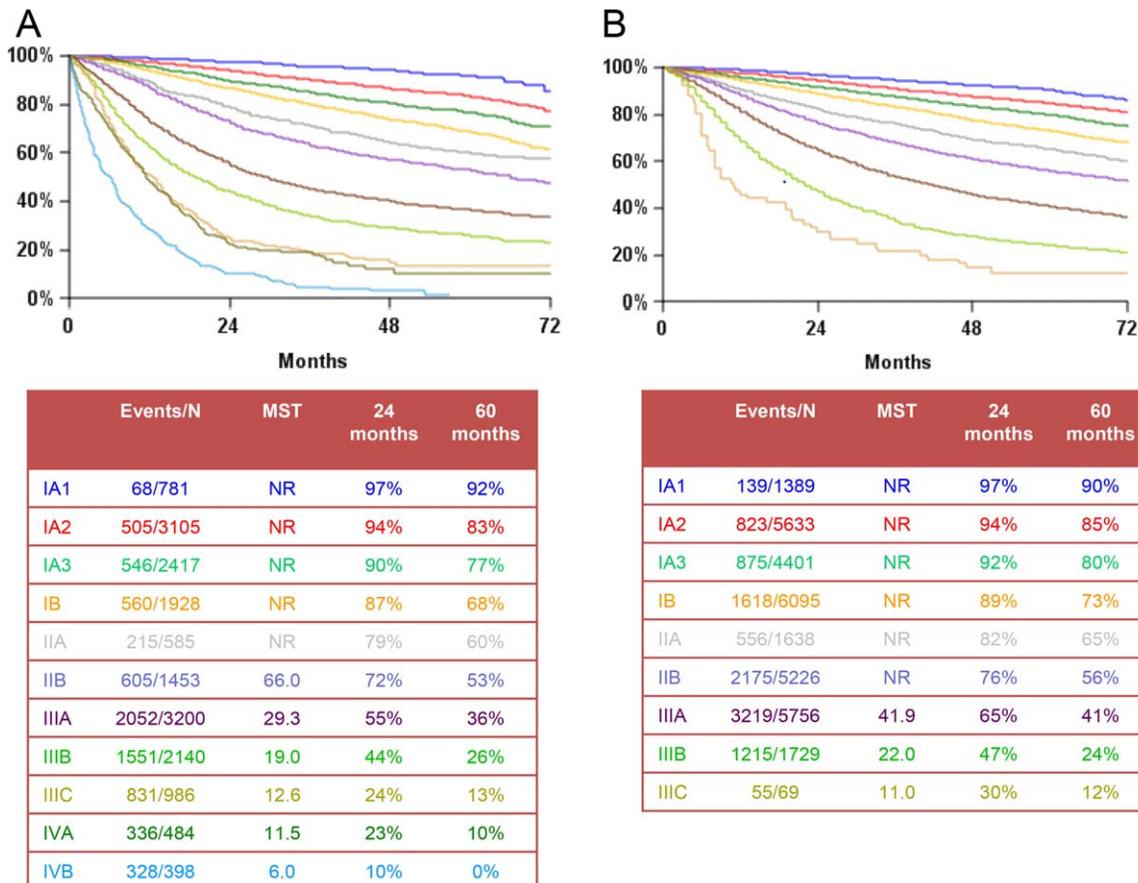


FIGURE 6. Survival by (A) Clinical and (B) Pathologic Stages. MST indicates median survival time (in months); NR, not reached. Reprinted from: Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung Cancer Staging Project: proposals for the revision of the stage grouping in the forthcoming (eighth) edition of the TNM classification of lung cancer. *J Thorac Oncol.* 2016;11:39-51¹¹ with permission from Elsevier.

TABLE 3. Categories, Subcategories, and Descriptors of the Eighth Edition of the TNM Classification of Lung Cancer

CATEGORY	SUBCATEGORY	DESCRIPTORS
T: Primary tumor		
TX		Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0		No evidence of primary tumor
Tis		Carcinoma in situ: <ul style="list-style-type: none"> • Tis (AIS): adenocarcinoma • Tis (SCIS): squamous cell carcinoma
T1		Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus); the uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a
	T1mi	Minimally invasive adenocarcinoma
	T1a	Tumor 1 cm or less in greatest dimension
	T1b	Tumor more than 1 cm but not more than 2 cm in greatest dimension
	T1c	Tumor more than 2 cm but not more than 3 cm in greatest dimension
T2		Tumor more than 3 cm but not more than 5 cm; or tumor with <i>any</i> of the following features (T2 tumors with these features are classified T2a if 4 cm or less or if size cannot be determined and as T2b if greater than 4 cm but not larger than 5 cm): <ul style="list-style-type: none"> • Involves main bronchus regardless of distance to the carina, but without involving the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the entire lung
	T2a	Tumor more than 3 cm but not more than 4 cm in greatest dimension
	T2b	Tumor more than 4 cm but not more than 5 cm in greatest dimension
T3		Tumor more than 5 cm but not more than 7 cm in greatest dimension or one that directly invades any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or associated separate tumor nodule(s) in the same lobe as the primary
T4		Tumors more than 7 cm or one that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe to that of the primary
N: Regional lymph nodes		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2		Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3		Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral, or contralateral scalene, or supraclavicular lymph node(s)
M: Distant metastasis		
M0		No distant metastasis
M1		Distant metastasis
	M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion; most pleural (pericardial) effusions with lung cancer are due to tumor; in a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate; where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor
	M1b	Single extrathoracic metastasis in a single organ and involvement of a single distant (nonregional) node
	M1c	Multiple extrathoracic metastases in one or several organs

Reprinted and adapted from: Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the stage grouping in the forthcoming (8th) edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2016;11:39-51¹¹ with permission from Elsevier.

TABLE 4. Stage Grouping of the Eighth Edition of the TNM Classification of Lung Cancer

STAGE	T	N	M
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA1	T1mi	N0	M0
	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a,b,c	N1	M0
	T2a,b	N1	M0
	T3	N0	M0
IIIA	T1a,b,c	N2	M0
	T2a, b	N2	M0
	T3	N1	M0
	T4	N0	M0
IIIB	T4	N1	M0
	T1a,b,c	N3	M0
	T2a,b	N3	M0
	T3	N2	M0
IIIC	T4	N2	M0
	T3	N3	M0
IVA	T4	N3	M0
	Any T	Any N	M1a
IVB	Any T	Any N	M1b
	Any T	Any N	M1c

Abbreviations: T1mi, minimally invasive adenocarcinoma; Tis, tumor in situ. Reprinted and adapted from: Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the stage grouping in the forthcoming (8th) edition of the TNM classification of lung cancer. *J Thorac Oncol.* 2016;11:39-51¹¹ with permission from Elsevier.

classification, and Table 4 shows the new stage groupings.¹¹ This classification applies to small cell¹²⁻¹⁴ and nonsmall cell lung cancers and to bronchopulmonary carcinoids,¹⁵ but it does not apply to sarcomas or other rare tumors of the lung.

Uniform Classification of Situations Not Covered in the T, N, and M Descriptors

Despite the periodic revisions of the TNM classification, there are situations that remain uncovered by the different descriptors. Over the years, these situations have been debated, and recommendations on how to classify them have been reached by consensus. The following

recommendations are provided to facilitate homogenous classification¹⁶:

- Paralysis of the recurrent laryngeal nerve, superior vena caval obstruction, and compression of the trachea or esophagus related to direct extension of the primary tumor are classified as T4 but would be classified as N2 if caused by ipsilateral mediastinal nodal disease.
- Pancoast (superior sulcus) tumors are classified as T4 if there is evidence of invasion of the vertebral body or spinal canal, encasement of the subclavian vessels, or unequivocal involvement of the superior branches of the brachial plexus (C8 or above) but as T3 if these situations are not present.
- Direct invasion of an adjacent lobe, across the fissure or directly if the fissure is incomplete, is classified as T2a, unless other criteria assign a higher T category.
- Invasion of the phrenic nerve is T3, but invasion of the recurrent laryngeal nerve is T4.
- Invasion into hilar fat is classified as T2a, unless other criteria assign a higher T category.
- Direct extension to visceral pericardium and invasion into the mediastinal fat are classified as T4.
- Involvement of great vessels, ie, aorta, superior vena cava, inferior vena cava, main pulmonary artery (pulmonary trunk), intrapericardial portions of the right and left pulmonary artery, and intrapericardial portions of the superior and inferior right and left pulmonary veins, is classified as T4.
- Discontinuous tumor nodules in the ipsilateral parietal or visceral pleura are classified as M1a; but, if the tumor nodules are outside the parietal pleura in the chest wall or in the diaphragm, they are classified as M1b, if single, or M1c, if multiple.

New Site-Specific Recommendations

The analyses of the IASLC database, the review of published articles, and a series of international and multidisciplinary consensus meetings generated the following new lung cancer-specific recommendations, which are implemented in the eighth edition of the TNM classification of lung cancer.

Introduction of Tis (Adenocarcinoma in Situ) and T1mi

Since publication of the seventh edition of the TNM classification, new entities of adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) have been introduced.^{17,18} Previously, Tis referred only to squamous cell carcinoma in situ; but now, criteria for the diagnosis of AIS and for its clinical staging by computed tomography (CT) and pathologic staging are defined.¹⁸ It also is recommended to designate the histologic type of

cT*	CT image on HRCT						
	Solid part	0	0 cm	≤0.5 cm†	0.6-1.0 cm†	1.1-2.0 cm †	2.1-3.0 cm †
	Total tumor size including GG	≤0.5 cm	0.6-3.0 cm	≤3.0 cm††	0.6-3.0 cm††	1.1-3.0 cm††	2.1-3.0 cm††
	Pathologic Differential Diagnosis	AAH‡, AIS, MIA	AIS, MIA, LPA	MIA, LPA, AIS	LPA, Invasive AD, MIA	LPA, Invasive AD	Invasive AD
Clinical Stage*		cTis	cT1mi	cT1a	cT1b	cT1c	
pT	Invasive part	0	0 cm	≤0.5 cm†	0.6-1.0 cm†	1.1-2.0 cm †	2.1-3.0 cm †
	Total tumor size including lepidic growth part	Usually ≤0.5 cm‡	≤3.0 cm	≤3.0 cm	0.6-3.0 cm††	1.1-3.0 cm††	2.1-3.0 cm††
	Pathology	AAH	AIS	MIA	Lepidic predominant AD or Invasive AD with lepidic component	Invasive AD with a lepidic component or lepidic predominant AD	Invasive AD with lepidic component
	Pathologic Stage		pTis	pT1mi	pT1a	pT1b	pT1c

FIGURE 7. Proposed Eighth Edition Clinical and Pathologic T Descriptor Classification of Small (≤3 cm) Lung Adenocarcinomas With Ground-Glass and Lepidic Components by Computed Tomography and Pathology. Clinical T (cT) categories: Computed tomography (CT) images on high-resolution CT (HRCT) can be suggestive of pathologic diagnoses, but they are not specific, because ground-glass (GG) opacities do not always correspond to lepidic patterns, and solid components do not always correlate with invasive components. However, there is a general correlation between GG observed on CT and lepidic patterns observed microscopically and between solid components observed on CT and histologically identified invasive patterns. A pathologic differential diagnosis is listed for each of the proposed possibilities on CT imaging. Final pathologic T (pT) categories of these tumors require complete pathologic examination in resected specimens. Tis (adenocarcinoma in situ [AIS]): (cT) These lesions typically show a pure GG nodule (GGN) measuring ≤3 cm. However, pure GGN can also be minimally invasive adenocarcinoma (MIA) or invasive adenocarcinoma (AD) (double daggers). (pT) These tumors show pure lepidic growth without invasion, measuring ≤3 cm (double daggers). If the pure GGN or lepidic-predominant nodule measures >3.0 cm, then it is classified as lepidic-predominant adenocarcinoma (LPA) and should be staged as T1a. T1mi: (cT) MIA usually has a GG-predominant nodule ≤3 cm with a solid component that should appear ≤0.5 cm (single and double daggers). Although some MIAs have a larger solid component on CT because of other benign components, such as scar or organizing pneumonia, these cases can only be diagnosed by pathologic examination. (pT) MIA histologically shows a lepidic-predominant adenocarcinoma nodule measuring ≤3 cm with an invasive component measuring ≤0.5 cm (single and double daggers). T1a: (cT) These have GG-predominant nodules measuring ≤3.0 cm with a solid component measuring 0.6 to 1.0 cm (single dagger). (pT) When an LPA measuring ≤3.0 cm has an invasive component measuring 0.6 to 1.0 cm, it is classified as pT1a (single dagger). T1b: (cT) These have GG-predominant nodules measuring ≤3.0 cm with a solid component measuring 1.1 to 2.0 cm (single dagger). (pT) When an LPA measuring ≤3.0 cm has an invasive component measuring 1.1 to 2.0 cm, it is classified as pT1b (single dagger). T1c: (cT) GG-predominant nodules measuring ≤3.0 cm with a solid component measuring 2.1 to 3.0 cm are classified as T1c. (pT) When an invasive adenocarcinoma with a lepidic component measuring ≤3.0 cm has an invasive component measuring 2.1 to 3.0 cm, it is classified as T1c (single dagger). An asterisk indicates that all of the cT categories are presumptive, assuming that the GG versus solid components correspond to lepidic versus invasive components, respectively, on pathologic examination of a resected specimen. For the cT category, rule number 4 of the TNM classification is applied (when in doubt, opt for the lesser category; single dagger). In cases where there are multiple foci of solid or invasive components, the suggested way to estimate the invasive size is to sum the percentage area of the invasive components and multiply this amount by the overall tumor diameter (double daggers). Size is not the only distinguishing feature between atypical adenomatous hyperplasia (AAH) and AIS (double daggers). If a pure GGN identified by CT or pure lepidic adenocarcinoma identified by pathology is larger than 3 cm, then it should be classified as T1a. Similarly, if a GG-predominant, part-solid nodule has a solid component ≤0.5 cm or if a tumor meets pathologic criteria for MIA, but the total size is >3 cm, then it should be staged as cT1a or pT1a, respectively (double daggers). If the total tumor size is larger than 3.0 cm, then, depending on the invasive size, these categories can be classified as T1a, T1b, or T1c. As shown in Table 4, Tis (AIS) is stage 0, and T1mi is stage IA1. Reprinted from: Travis WD, Asamura H, Bankier A, et al. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol.* 2016;11:1204-1223¹⁸ with permission from Elsevier.

carcinoma in situ: Tis (AIS) for AIS and Tis (SCIS) for squamous cell carcinoma in situ. In addition, it is recommended to use T1mi for lesions suspected to be MIA by CT or confirmed pathologically as MIA.¹⁸ Figure 7 shows how to classify small adenocarcinomas at both clinical and pathologic staging and provides definitions for each category.¹⁸

Measurement of Tumor Size in Part-Solid Nonmucinous Adenocarcinomas

Part-solid adenocarcinomas present with both solid and ground-glass components on CT. At pathological examination, the solid component usually corresponds to the invasive part, and the ground-glass component corresponds to the lepidic part (with growth restricted to

neoplastic cells along preexisting alveolar structures and lacking stromal, vascular, alveolar space, or pleural invasion). To define the T category by tumor size, only the size of the solid component on CT or the size of the invasive component at pathologic examination are considered, because it is the size of the solid/invasive component that determines prognosis. However, documentation of both the size of the solid component/invasive part and of the whole tumor, including the ground-glass and lepidic components in radiology and pathology reports, respectively, is recommended.¹⁸

Measurement of Tumor Size After Induction (Preoperative) Therapy

In cases where a single, discrete, measurable focus of viable tumor is not identifiable, it can be difficult to estimate tumor size after induction (preoperative) therapy. In such cases, the recommendation of the IASLC to determine tumor size at pathologic staging after induction (preoperative) therapy (ypT) is that tumor size can be measured by multiplying the percentage of viable tumor cells by the total size of the tumor.¹⁸

Classification of Lung Cancers With Multiple Sites of Involvement

To avoid ambiguity and to facilitate the homogeneous classification of lung cancer with multiple sites of disease, an ad hoc subcommittee of the IASLC Staging and Prognostic Factors Committee developed the following recommendations based on analyses of the IASLC database for which data were available, the review of published reports, and a wide multidisciplinary and international consensus. The following recommendations apply not only to grossly identified tumors but also to those identified at microscopic examination, and they differ depending on the pattern of disease.¹⁹

Synchronous and metachronous primary lung cancers

Regardless of tumor location, a separate TNM is defined for each primary tumor. The clinical and pathological criteria to differentiate second primary tumors from related tumors are defined in Table 5.²⁰

Separate tumor nodules with similar histopathologic features (intrapulmonary metastases)

Classification depends on the location of the separate tumor nodule(s): T3 if the separate tumor nodule(s) is(are) in the same lobe as the primary tumor, T4 if located in a different ipsilateral lobe, and M1a if located in the contralateral lung. If there are additional extrathoracic metastases, then the tumor will be classified as M1b or M1c, depending on the number of metastatic sites. The clinical and pathological criteria to categorize separate tumor nodules (intrathoracic metastasis) are defined in Table 6.²¹

Multifocal pulmonary adenocarcinoma with ground-glass/lepidic features

Regardless of the location of the tumors, the rule of the highest T with the number (#) or (m) (for multiple in parentheses) and an N and an M for all of the multiple tumors collectively applies for these tumors. For example, a patient has a part-solid tumor of 3 cm in greatest dimension consisting of a predominant ground-glass opacity and a 4-mm solid component in the right upper lobe; in addition, there are 3 pure ground-glass opacities in the right lung and 2 pure ground-glass opacities in the left lung measuring between 1 and 3 cm; and there is no suspicion of nodal involvement on CT. The clinical classification of this tumor would be: cT1mi(6) N0 M0. In the absence of a pathologic diagnosis, this classification shows that the most advanced tumor is likely to be a minimally invasive adenocarcinoma (the ground-glass component corresponding to the lepidic part and the solid component corresponding to the invasive part, being minimally invasive because it measures less than 5 mm) accompanied by 5 other lesions that are less invasive, that is, they have a lower T classification. If T1mi is the most advanced, then the other 5 lesions can only be adenocarcinomas in situ: Tis (AIS). Table 7 shows the clinical and pathologic criteria for defining these tumors.²²

Diffuse pneumonic-type lung adenocarcinoma

If the disease presents with a single focus, then the general TNM classification is applied, with the T category defined by tumor size. When multiple foci of disease are present, tumor classification is based on the location of the involved areas (including miliary involvement; ie, multiple small nodules in the lung parenchyma): T3 if located in one lobe, T4 if located in other ipsilateral lobes, and M1a if the contralateral lung is involved, with the T category defined by the largest tumor. When it is difficult to determine tumor size, T4 applies if there is evidence of involvement of another ipsilateral lobe. In all circumstances, the N category should apply to all pulmonary sites, and the appropriate M category should be applied, depending on the number and location of metastases. The clinical and pathological criteria to define these tumors are shown in Table 8.²²

Table 9 summarizes the basic radiographic and pathologic features, the recommended TNM classification, and the conceptual view of the 4 patterns of lung cancer with multiple sites of involvement.¹⁹

Implications for Clinical Practice and Research

All new editions of the TNM classification bring changes in clinical practice and prospects for further research. The specific implications for clinical practice and research brought by the eighth edition are summarized as follows:

TABLE 5. Criteria for Separate Versus Related Pulmonary Tumors

<p>Clinical criteria^a</p> <p>Tumors may be considered separate primary tumors if:</p> <ul style="list-style-type: none"> They are clearly of a different histologic type (eg, squamous carcinoma and adenocarcinoma) by biopsy <p>Tumors may be considered to be arising from a single tumor source if:</p> <ul style="list-style-type: none"> Exactly matching breakpoints are identified by comparative genomic hybridization <p>Relative arguments that favor separate tumors:</p> <ul style="list-style-type: none"> Different radiographic appearance or metabolic uptake Different biomarker pattern (driver gene mutations) Different rates of growth (if previous imaging is available) Absence of nodal or systemic metastases <p>Relative arguments that favor a single tumor source:</p> <ul style="list-style-type: none"> Same radiographic appearance Similar growth patterns (if previous imaging is available) Significant nodal or systemic metastases Same biomarker pattern (and same histotype) <p>Pathologic criteria (ie, after resection)^b</p> <p>Tumors may be considered separate primary tumors if:</p> <ul style="list-style-type: none"> They are clearly of a different histologic type (eg, squamous carcinoma and adenocarcinoma) They are clearly different by a comprehensive histologic assessment They are squamous carcinomas that have arisen from carcinoma in situ <p>Tumors may be considered to be arising from a single tumor source if:</p> <ul style="list-style-type: none"> Exactly matching breakpoints are identified by comparative genomic hybridization <p>Relative arguments that favor separate tumors (to be considered together with clinical factors):</p> <ul style="list-style-type: none"> Different pattern of biomarkers Absence of nodal or systemic metastases <p>Relative arguments that favor a single tumor source (to be considered together with clinical factors):</p> <ul style="list-style-type: none"> Matching appearance on comprehensive histologic assessment Same biomarker pattern Significant nodal or systemic metastases
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^aNote that a comprehensive histologic assessment is not included in clinical staging, as it requires that the entire specimen has been resected.

^bPathologic information should be supplemented with any clinical information that is available. Reprinted from: Detterbeck FC, Franklin WA, Nicholson AG, et al. The IASLC Lung Cancer Staging Project: background data and proposed criteria to distinguish separate primary lung cancers from metastatic foci in patients with two lung tumors in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2016;11:651-665²⁰ with permission from Elsevier.

Concerning the T Component

- Tumor size must be accurately measured, because small changes in size mean considerable differences in survival.
- Both physicians and patients must be aware of the prognostic relevance of tumor size when a decision to follow up lung nodules without pathologic diagnosis is made.
- Accurate tumor size measurement is also relevant in part-solid tumors; this implies measurement of the solid component on CT and of the invasive part on microscopic examination.
- Refinement of methods to measure tumor size with radiologic and pathologic correlation is a topic that needs further research.
- Visceral pleural invasion has been confirmed as an important prognostic factor and should be actively looked for by the pathologist; elastic stains should be used if visceral pleural invasion is not evident on hematoxylin-and-eosin staining.
- The smallest coded tumors, ≤ 1 cm in size (T1a), and Tis (AIS) and T1mi may constitute research opportunities to investigate tumor growth rate,

TABLE 6. Criteria to Categorize a Lesion as a Separate Tumor Nodule (Intrapulmonary Metastasis)^a

<p>Clinical criteria</p> <p>Tumors should be considered to have a separate tumor nodule(s) if:</p> <p>There is a solid lung cancer and a separate tumor nodule(s) with a similar solid appearance and with (presumed) matching histologic appearance</p> <ul style="list-style-type: none"> • This applies whether or not a biopsy has been performed on the lesions, provided that there is strong suspicion that the lesions are histologically identical • This applies whether or not there are sites of extrathoracic metastases <p>AND provided that:</p> <p>The lesions are NOT judged to be synchronous primary lung cancers</p> <p>The lesions are NOT multifocal GG/L lung cancer (multiple nodules with ground-glass/lepidic features) or a pneumonic type of lung cancer</p> <p>Pathologic criteria</p> <p>Tumors should be considered to have a separate tumor nodule(s) (intrapulmonary metastasis) if:</p> <p>There is a separate tumor nodule(s) of cancer in the lung with a similar histologic appearance to a primary lung cancer</p> <p>AND provided that:</p> <p>The lesions are NOT judged to be synchronous primary lung cancers</p> <p>The lesions are NOT multiple foci of LPA, MIA, or AIS</p>
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Abbreviations: AIS, adenocarcinoma in situ; GG/L, ground glass/lepidic; LPA, lepidic-predominant adenocarcinoma; MIA, minimally invasive adenocarcinoma. ^aNote: A radiographically solid appearance and the specific histologic subtype of solid adenocarcinoma denote different things. Reprinted from: Detterbeck FC, Bolejack V, Arenberg DA, et al. The IASLC Lung Cancer Staging Project: background data and proposals for the classification of lung cancer with separate tumor nodules in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2016;11:681-692²¹ with permission from Elsevier.

tumor density on CT and magnetic resonance imaging, intensity of standardized uptake values of positron emission tomography, types of resection (lobectomy vs segmentectomy and wedge resection), alternative nonsurgical therapies, molecular profiles, and genetic signatures.

- The diversity of tumor sizes found in all T categories may help stratify future clinical trials.

Concerning the N Component

- Quantification of nodal disease has prognostic relevance, and it should be determined according to the

TABLE 7. Criteria Identifying Multifocal Ground-Glass/Lepidic Lung Adenocarcinoma^a

<p>Clinical criteria</p> <p>Tumors should be considered multifocal GG/L lung adenocarcinoma if:</p> <p>There are multiple subsolid nodules (either pure ground glass or part-solid), with at least one suspected (or proven) to be cancer</p> <ul style="list-style-type: none"> • This applies whether or not a biopsy has been performed of the nodules • This applies if the other nodules(s) are found on biopsy to be AIS, MIA, or LPA • This applies if a nodule has become >50% solid but is judged to have arisen from a GGN, provided there are other subsolid nodules • GGN lesions <5 mm or lesions suspected to be AAH are not counted <p>Pathologic criteria</p> <p>Tumors should be considered multifocal GG/L lung adenocarcinoma if:</p> <p>There are multiple foci of LPA, MIA, or AIS</p> <ul style="list-style-type: none"> • This applies whether a detailed histologic assessment (ie, proportion of subtypes, etc) shows a matching or different appearance • This applies if one lesion(s) is LPA, MIA, or AIS and there are other subsolid nodules of which a biopsy has not been performed • This applies whether the nodule(s) is (are) identified preoperatively or only on pathologic examination • Foci of AAH are not counted

Abbreviations: AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; GGN, ground-glass nodule; LPA, lepidic predominant adenocarcinoma; MIA, minimally invasive adenocarcinoma. ^aNote: A radiographically solid appearance and the specific histologic subtype of solid adenocarcinoma denote different things. Reprinted from: Detterbeck FC, Marom EM, Arenberg DA, et al. The IASLC Lung Cancer Staging Project: background data and proposals for the application of TNM staging rules to lung cancer presenting as multiple nodules with ground glass or lepidic features or a pneumonic-type of involvement in the forthcoming eighth edition of the TNM classification. *J Thorac Oncol.* 2016;11:666-680²² with permission from Elsevier.

TABLE 8. Criteria Identifying the Pneumonic Type of Adenocarcinoma^a

<p>Clinical criteria</p> <p>Tumors should be considered a pneumonic type of adenocarcinoma if:</p> <p>The cancer manifests in a regional distribution, similar to a pneumonic infiltrate or consolidation</p> <ul style="list-style-type: none"> • This applies whether there is one confluent area or multiple regions of disease; the region(s) may be confined to one lobe, in multiple lobes, or bilateral, but should involve a regional pattern of distribution • The involved areas may appear to be ground glass, solid consolidation, or a combination thereof • This can be applied when there is compelling suspicion of malignancy whether or not a biopsy has been performed of the area(s) • This should not be applied to discrete nodules (ie, GG/L nodules) • This should not be applied to tumors causing bronchial obstruction with resultant obstructive pneumonia or atelectasis <p>Pathologic criteria</p> <p>Tumors should be considered pneumonic-type of adenocarcinoma if:</p> <p>There is diffuse distribution of adenocarcinoma throughout a region(s) of the lung, as opposed to a single well demarcated mass or multiple, discrete well demarcated nodules</p> <ul style="list-style-type: none"> • This typically involves an invasive mucinous adenocarcinoma, although a mixed mucinous and nonmucinous pattern may occur • The tumor may show a heterogeneous mixture of acinar, papillary, and micropapillary growth patterns, although it is usually lepidic-predominant
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Abbreviation: GG/L, ground glass/lepidic. ^aNote: A radiographically solid appearance and the specific histologic subtype of solid adenocarcinoma denote different things. Reprinted from: Detterbeck FC, Marom EM, Arenberg DA, et al. The IASLC Lung Cancer Staging Project: background data and proposals for the application of TNM staging rules to lung cancer presenting as multiple nodules with ground glass or lepidic features or a pneumonic-type of involvement in the forthcoming eighth edition of the TNM classification. *J Thorac Oncol*. 2016;11:666-680²² with permission from Elsevier.

number of involved nodal stations or the number of involved nodal zones, especially at pathological staging, to refine prognosis and make decisions on adjuvant therapy, but also at clinical staging, when the initial therapeutic decisions are made.

- Upfront surgery for single-station N2 disease without N1 disease will be discussed by surgeons, but its proponents will have to be aware that the results on quantification of nodal disease derive from pathologic staging and could not be reproduced at clinical staging, when therapeutic decisions are made. Therefore, this surgical approach can only be applied if a very thorough mediastinoscopy is performed at the time of clinical staging with the objective not only to biopsy lymph nodes but also to perform a lymphadenectomy of the upper mediastinum (transcervical mediastinoscopic lymphadenectomy). It is important to realize that even the smallest solid tumors can be associated to mediastinal nodal disease. In the IASLC database used to inform the eighth edition of the TNM classification, pN3 was found in less than 1% of the 3 pT1 subcategories. However, the rate of pN2 disease was 3.21% for pT1a, 6.27% for T1b, and 9.44% in T1c. The rates of pN1 disease were 3.08% for pT1a, 4.92% for pT1b, and 8.98% for pT1c. These results are important when making decisions on the use of imaging, metabolic, and invasive methods at clinical staging.
- The IASLC lymph node map (Fig. 4) should be used to classify nodal disease; otherwise, international data will never be homogeneous.

Concerning the M Component

- It is important to register the number of metastases and their location.
- The separate classification of a single extrathoracic metastasis (M1b) from multiple extrathoracic metastases (M1c) will help to clarify the future definitions of oligometastasis and oligoprogression and to facilitate the research on radical treatment of patients with these conditions.

Concerning the Stage Grouping:

- Although therapeutic protocols are based on tumor stage and histologic type, a taxonomic change in stage per se does not suggest an automatic change in therapy; therapeutic recommendations should derive from properly designed clinical trials and not from changes in tumor classification.
- The creation of new stages in the eighth edition will help the stratification of patients with lung cancer for future clinical trials and the refinement in predicting prognosis.

Conclusion

The eighth edition of the TNM classification of lung cancer defines new tumor-size groups, confirms the prognostic relevance of quantifying nodal disease, establishes a new category for single extrathoracic metastasis, and creates new stage groupings. In this way, it improves our understanding of the anatomic extent of the tumor, enhances our capacity to indicate prognosis at clinical and pathologic staging, and

TABLE 9. Schematic Summary of Patterns of Disease and TNM Classification in Patients Who Have Lung Cancer With Multiple Pulmonary Sites of Involvement

VARIABLE	SECOND PRIMARY LUNG CANCER	SEPARATE TUMOR NODULE (INTRAPULMONARY METASTASIS)	MULTIFOCAL GG/L NODULES	PNEUMONIC TYPE OF ADENOCARCINOMA
Imaging features	Two or more distinct masses with imaging characteristics of lung cancer (eg, spiculated)	Typical lung cancer (eg, solid, spiculated) with separate solid nodule	Multiple ground-glass or part-solid nodules	Patchy areas of ground glass and consolidation
Pathologic features	Different histotype or different morphology by comprehensive histologic assessment	Distinct masses with the same morphologic features by comprehensive histologic assessment	Adenocarcinomas with prominent lepidic component (typically varying degrees of AIS, MIA, LPA)	Same histologic features throughout (most often invasive mucinous adenocarcinoma)
TNM classification	Separate cTNM and pTNM for each cancer	Location of separate nodule relative to primary site determines if T3, T4 or M1a; single N and M	T based on highest T lesion with (#/m) indicating multiplicity; single N and M	T based on size or T3 if in single lobe, T4 or M1a if in different ipsilateral or contralateral lobes; single N and M
Conceptual view	Unrelated tumors	Single tumor, with intrapulmonary metastasis	Separate tumors, albeit with similarities	Single tumor, diffuse pulmonary involvement

Abbreviations: AIS, adenocarcinoma in situ; GG/L, ground glass/lepidic; LPA, lepidic-predominant adenocarcinoma; MIA, minimally invasive adenocarcinoma; p, pathologic; TNM, tumor, node, metastasis. ^aReprinted from: Detterbeck FC, Nicholson AG, Franklin WA, et al. The IASLC Lung Cancer Staging Project: summary of proposals for revisions of the classification of lung cancers with multiple pulmonary sites of involvement in the forthcoming eighth edition of the TNM classification. *J Thorac Oncol.* 2016;11:539-650¹⁹ with permission from Elsevier.

increases the possibilities of research by facilitating tumor stratification for future clinical trials. ■

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