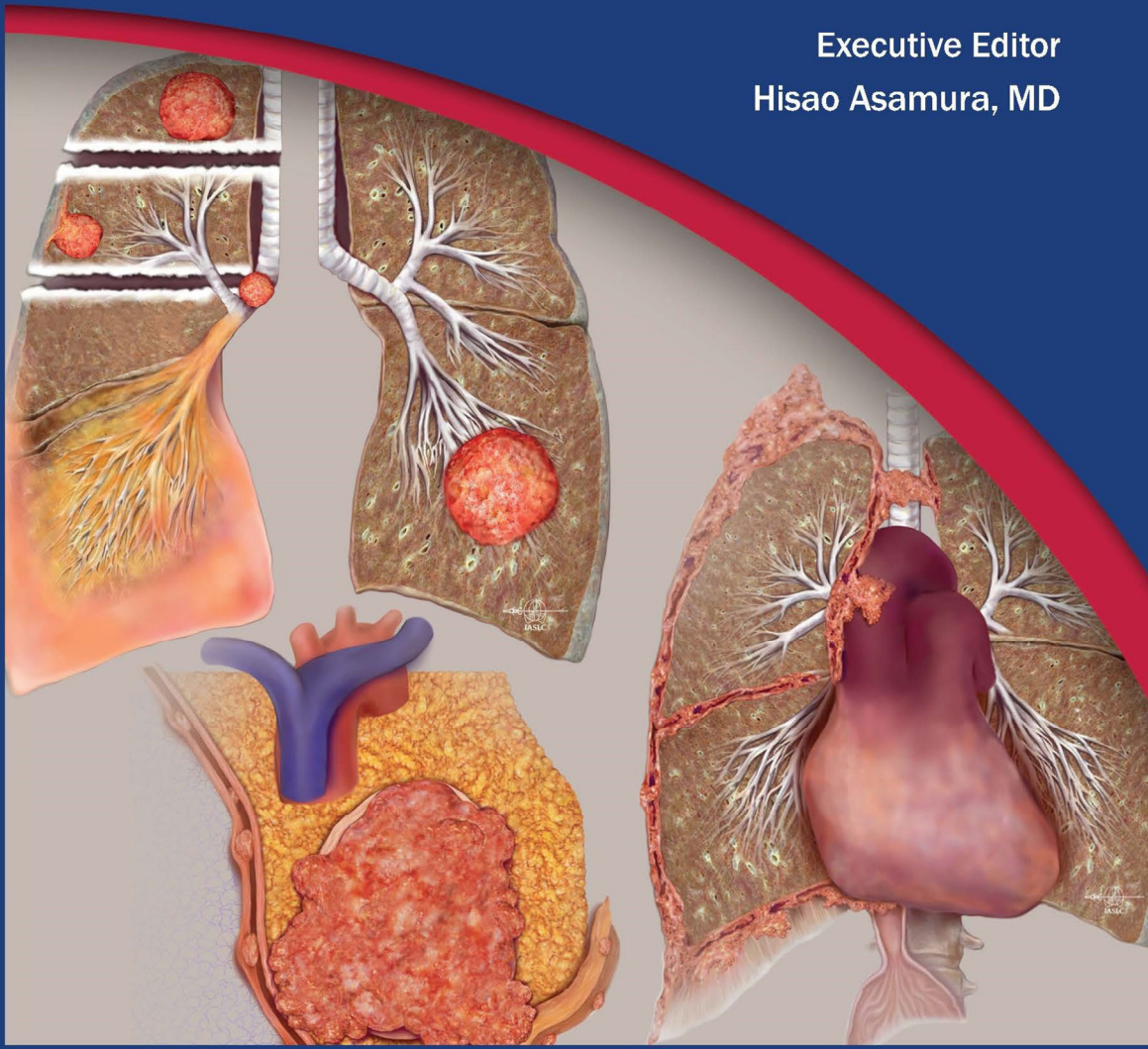
IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
Conquering Lung & Thoracic Cancers Worldwide in the 21st Century

THIRD EDITION

Staging Manual in Thoracic Oncology

Executive Editor
Hisao Asamura, MD



LUNG CANCER | THYMIC TUMORS | MESOTHELIOMA | ESOPHAGEAL CANCER

STAGING MANUAL IN THORACIC ONCOLOGY
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Hisao Asamura, MD, Executive Editor

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Dedication

To Ramón Rami-Porta, MD, PhD

Hospital Universitari Mútua Terrassa, University of Barcelona, and
Centros de Investigación Biomédica en Red de Enfermedades Respiratorias
(CIBERES) Lung Cancer Group, Terrassa, Barcelona, Spain

With gratitude, esteem, and respect

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Preface to the Third Edition

By Paul E. Van Schil, MD, PhD, IASLC President 2023-2025, and
Karen Kelly, MD, Chief Executive Officer, IASLC

The Staging and Prognostic Factors Committee (SPFC) of the IASLC is extremely proud to present the innovations proposed for the 9th edition of the TNM classification of malignant thoracic tumors, described here in the Third Edition of the Staging Manual in Thoracic Oncology.

An impressive database was created with the largest number of cases ever submitted, from 25 countries. Robust statistical analysis by our partners at Cancer Research And Biostatistics (CRAB) provided a solid basis for implementation of the 9th edition with several changes to improve the anatomic staging system and make it more clinically relevant. These recommendations have been forwarded to the Union for International Cancer Control and the American Joint Committee on Cancer for their approval, which we anticipate in 2025.

Under the excellent leadership of Hisao Asamura, Chair of the SPFC, Ramón Rami-Porta, Past-Chair, and Valerie Rusch, Chair-Elect, the SPFC produced updated core papers on the Tumor, Node, Metastasis (TNM) components, and global staging of lung cancer. Additonal analyses and publications addressed thymic epithelial tumors, neuroendocrine tumors, and pleural mesothelioma.

A special thanks goes to all members of the SPFC for their dedication and hard work, the participating institutions for sharing their data, CRAB for detailed statistical analysis, and all patients for their confidence and willingness to participate in large registries. The SPFC also thanks AstraZeneca for its generous support of this staging endeavor.

With the introduction of immunotherapy and additional targeted therapies, diagnostic and therapeutic algorithms have substantially changed. For this reason, the role of staging and restaging has become increasingly important. We hope that this 9th edition will provide a step forward in the overall management of patients with thoracic malignancies.

Preparations are being made for the 10th edition database which will incorporate new features beyond anatomical staging such as molecular biomarkers and delineation of screen-detected lung cancer. To allow for the inclusion of data from countries with limited resources, submission of cases containing only "essential" data elements will continue to be accepted to the 10th edition database. In this way, the staging systems will reflect the IASLC's commitment to providing high-level data that are clinically relevant worldwide.

Preface to the Second Edition

By David P. Carbone, MD, PhD, IASLC President, 2015-2017, and
Fred R. Hirsch, MD, PhD, Chief Executive Officer

The staging of patients with lung cancer and other thoracic malignancies is important for the treatment decisions. The UICC/IASLC Staging Classification is used all over the world and the IASLC is proud of launching the 8th Edition of the International Staging of Thoracic Malignancies. While the previous 7th Edition of the staging system was focusing on lung cancer, the new 8th Edition also include staging of thymus cancers and mesotheliomas. The new staging system is based on about 100.000 cases collected by international multidisciplinary investigators from all geographical regions of the world.

For the second consecutive time, the IASLC has been in charge to provide the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) with data-based recommendations to revise the TNM classification of thoracic malignancies. Both institutions have accepted the IASLC recommendations and incorporated them in their respective 8th edition staging manuals published in 2016.

The IASLC staging project has been performed by the IASLC Staging Committee under the leadership of Dr. Ramón Rami-Porta, MD, Spain. This project could not be performed without the generous unrestricted support from Lilly Oncology, USA.

The IASLC is proud to serve the international oncological community and thanks the UICC and the AJCC for entrusting it with such challenging and intellectually rewarding responsibility. It is our hope that the 8th Edition of the Staging Classification will be a useful tool for further research and will serve in the daily lung cancer clinic to the benefit for the many patients with lung cancer around the world.

Preface to the First Edition

By Nagahiro Saijo, MD, IASLC President, 2007-2009

The International Association for the Study of Lung Cancer (IASLC) is proud to present the details of the IASLC/International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) Revised Staging Classification for Lung Cancer in this Manual. The IASLC is the largest world-wide professional organization solely dedicated to reducing the worldwide burden of lung cancer. The International Staging Classification for Lung Cancer provides the basis for assigning prognosis and treatment selection for patients with lung cancer. Thus, its importance cannot be overemphasized, especially as we develop new methods of staging. These new methods include clinical procedures such as computed tomographic (CT) scans and CT/positron emission tomographic (PET) scans and new pathologic procedures such as endobronchial ultrasound (EBUS)-guided biopsies and video-assisted thoracic surgeon (VATS) biopsies. The IASLC recognizes that the staging classification will be most valuable and accurate if it is based on large numbers of cases carefully collected and analyzed. We are indebted to the diligent efforts of the IASLC Staging Committees chaired by Dr. Peter Goldstraw and whose members are listed in the Manual; the diligent efforts of the Cancer Research And Biostatistics (CRAB) office headed by Dr. John Crowley; the support of the IASLC Board of Directors whose members are also listed in the Manual; the financial support of Eli Lilly and Company and the support of the UICC and the AJCC to create a staging classification supported worldwide. We thank these individuals and organizations for their support and trust the revised staging classification will improve the outcome for lung cancer patients and their families.

Introduction: Brief Description of the IASLC Staging and Prognostic Factors Committee

Hisao Asamura, MD
Chair, IASLC Staging and Prognostic Factors Committee

The IASLC Staging Project is an international effort to study and improve the current staging system for thoracic cancers. Over the past two decades, the IASLC Staging Project, conducted by the IASLC Staging and Prognostic Factors Committee (SPFC), has been a steady source of evidence-based recommendations for the tumor, node, metastasis (TNM) classification for thoracic malignancies published by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC). The first phase of the IASLC Staging Project was led by Peter Goldstraw, MD, and collected the data of 100,869 lung cancer cases. The results of the analyses were published as the recommendations for the revision of the TNM classification and were adopted by the UICC and AJCC in 2010 as their 7th edition of the TNM classification of lung cancer.

The second phase of the IASLC Staging Project was chaired by Ramón Rami-Porta, MD, PhD. A new database of thoracic malignancies, namely lung cancer, thymic epithelial tumors, and malignant pleural mesothelioma, was established from around the world, and a revision of the TNM classification was developed based on the prognostic analyses. The new recommendations were accepted by UICC and AJCC as their 8th edition of the TNM classification for thoracic cancers, which has been in use since 2017. The summaries of the TNM classifications were published as the first and second editions of the *IASLC Staging Manual in Thoracic Oncology and the IASLC Staging Handbook in Thoracic Oncology*. It is important to recognize that lung cancer, thymic epithelial tumors, and malignant pleural mesothelioma are the only tumors whose TNM classification is based upon a global database and proposed by an organization outside of the UICC and the AJCC, such as the IASLC.

As the third phase of the IASLC Staging Project, the IASLC SPFC is in charge of the process of proposing revisions for new TNM classifications. The SPFC is composed of four domains: lung cancer (chaired by Paul Van Schil, MD, PhD), thymic tumors (chaired by Enrico Ruffini, MD), pleural mesothelioma (chaired by Valerie Rusch, MD), and carcinoma of the esophagus and of the esophagogastric junction (chaired by Wentao Fang, MD), with an international multidisciplinary expert panel of more than 120 members (including advisory board members).

The association between the anatomic extent of the tumor and prognosis was analyzed based on a large database collected from all over the world. This resulted in several improvements to the TNM classification, recommended as revisions for the 9th edition of the TNM classification to the UICC and the AJCC. This book, the third edition of the *IASLC Staging Manual in Thoracic Oncology*, describes the IASLC recommendations for changes and the rationale behind them. While conducting detailed evaluations of TNM factors, our challenge was to balance high specificity in prognostic characterization with simplicity, user-friendliness, and clinical relevance.

I hope that this updated TNM classification helps people involved in thoracic malignancies to deepen their understanding of these tumors. Also, I would like to thank all the researchers around the world who have contributed to the creation of these databases.

Methods for the Development of the 9th Edition Tumor, Node, Metastasis (TNM) Classification

Frank Detterbeck, MD

The purpose of TNM classification is to have a consistent nomenclature for the anatomic extent of a tumor – this allows communication about outcomes of patients with such tumors, and assessment of the applicability of data to an individual patient. A nomenclature must be clearly defined and stable in order to consistently carry the same meaning. However, periodically, a revision is undertaken to allow the system to adapt to advances in the field. An extensive process is in place regarding revisions of TNM classification of thoracic malignancies.[1] This involves an international multidisciplinary committee of experts, a large global database, a multi-tiered sophisticated statistical analysis, and careful consideration of additional factors (e.g. clinical relevance, implementability, backward compatibility).

The underlying concept is to organize a spectrum of tumors into biologically homogeneous groups – such tumors are likely to track together as treatments evolve and prognosis changes. Overall survival is used as a crude and indirect tool to define such homogeneity. Furthermore, consistent ordering and discrimination between categories and stage groups is required across multiple analyses (e.g. within subsets involving clinical or pathologic stage, R-status, T, N category cohorts) and adjusted multivariate Cox regression. The process used to develop and validate the classification system involved multiple phases, including planning, exploratory analysis, selection and confirmation, validation of generalizability, and extensive internal and external review, refinement, and vetting.[1]

A critical component for a consistent, universal system is ensuring generalizability;[2] domains of testing used are shown in Table 1. Sample size and other limitations hampered the assessment of some domains in some categories.

Caveats and Limitations

A categorization inherently involves establishing boundaries across what is fundamentally a continuum. Although the underlying analysis was extensive, questions remain to what degree observed outcomes reflect an inherent effect of the anatomic extent of the tumor vs confounding factors. The analysis involved a large international database, but this was not population-based or granular enough to allow a complete exploration of all settings and confounders. It is hard to assess

implementability until the system takes effect. As with previous editions, such assessments by others are welcomed. Isolated inconsistencies in an analysis of a particular cohort in a specific dataset are likely to appear. More concerning would be if the same issue was found again and again in external analyses of independent datasets. Considering the past performance of TNM classification and the extensive analysis done for the 9th edition, this is deemed very unlikely.

Finally, anatomic tumor extent is only one factor that must be taken into account to select the optimal treatment or predict the prognosis for an individual patient. Anatomic tumor extent applies primarily to local treatment modalities; selection of systemic modalities is increasingly based on molecular tumor characteristics. Developing a system to classify these is increasingly needed in partnership with TNM classification as both local and systemic therapies are increasingly used across the entire spectrum of lung cancer.

Table 1: Generalizability Assessments in the 9th Edition Lung Cancer TNM Classification System

	T	N	M	Stage Groups
Follow-up interval[a]	Yes	Yes	Yes	Yes
Geographic	Yes	Yes	Yes	Yes
Time Period[b]	Yes	Yes	Yes	Yes
Spectrum				
T, N, M categories	Yes	Yes	NA	NA
Histologic type	Yes	Yes	Yes	Yes
Methodologic				
c- vs pStage	Yes	Yes	NA	Yes
Treatment and/or R-status	Yes	Yes	Yes	Yes
Data source (EDC, batch)	Yes	–	Yes	Yes
Other	Yes[c]	–	Yes[d,e]	Yes[e]

Assessments of generalizability performed in the development of the 9th edition TNM classification system for lung cancer, according to recommended domains.[2]

[a] survival curves do not cross over time; [b] 9th edition classification applied to the 8th edition database, or splitting 9th edition data into early and late cohorts; [c] by high-, middle-, and low-income countries according to gross domestic product; [d] performance status; [e] comorbidities, specific organ system

EDC, electronic data capture; NA, not applicable

References

1. Detterbeck FC, Nishimura KK, Cilento VJ, et al. The International Association for the Study of Lung Cancer staging project: Methods and guiding principles for the development of the ninth edition TNM classification. *J Thorac Oncol*. 2022;17(6):806-815. doi:10.1016/j.jtho.2022.02.008
2. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. *Ann Intern Med*. 1999;130(6):515-524. Glossary of Terms. doi:10.7326/0003-4819-130-6-199903160-00016

Glossary of Terms

Frank Detterbeck, MD, Ramón Rami-Porta, MD, PhD, and Patricia Vigués

Tumor (T), node (N), and metastasis (M) are **components.**
These are made up of **categories** (e.g. T1, T2 …) and **subcategories** (e.g. T1a, T1b, T1c…).
Descriptors are the characteristics of the tumor included within a category/subcategory.

TNM classification **applies to tumors** (not patients).
Overall survival pertains to patients (it is not the tumors that survive).
Patients have **tumor**s that **are resected** (patients are not resected).
Patients have cancer. Cancer is not a characteristic of the patient. Expressions like 'cancer patients' should be avoided not to stigmatize the person; **'patients with cancer'** should be used, instead.[1]

It is best to speak of a **TNM classification** (not a TNM stage). The Union for International Cancer Control (UICC) avoids the term stage classification; the argument is that stage is already a classification, so it is redundant.
It is best to speak of **T, N, or M components or categories** (avoid T stage, N stage, M stage).
TNM categories are combined into **stage groups** (not groupings). Groupings would be appropriate if we are referring collectively to several different ways of assembling TNM categories into groups – but most of the time we are talking about only one way (e.g. 8th edition stage groups or 9th edition stage groups).

The term **stage (a noun)** is defined by the anatomic extent of disease (as defined by the UICC).
The term **staging** can be a verb, a noun, or an adjective (and other forms). The grammatical rules when and how "-ing" words can appropriately be used as a verb, noun or adjective etc. are complex. The meaning depends on the context, and using it correctly depends on how it is used together with other words. A loose use of the term "staging" often leads to a discrepancy between what the sentence means linguistically and what the actual intended meaning is. In spoken

language, a degree of looseness is tolerable, but in the written 9th edition papers it is important to be careful to be as clear as possible.

- The verb to stage (as defined by the UICC) refers to 1) the process of evaluation of a patient to identify the anatomic extent of the tumor, or 2) the process of assigning a TNM classification to an individual patient's tumor. Note that both these meanings involve application of TNM classification to an individual patient's tumor. Examples: "I am staging this lung cancer with endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA)" or "The most appropriate staging of this tumor is unclear."
- Staging can be an adjective that clarifies a noun; e.g. the staging committee, the staging manual, the staging rules.
- Staging can be a noun that is the subject or object of a sentence. For example, "Clinical staging includes computed tomography, positron emission tomography, and EBUS. The goal of this evaluation is accurate clinical staging." Note that in the first sentence "staging" means the process of evaluation, while in the second it means assignment of a TNM classification or a stage group. Note also that both of these sentences apply to individual patients.

In the Staging and Prognostic Factors Committee (SPFC) papers, using the word 'staging' as a verb is generally not consistent with the intended meaning – one is generally not referring to the process of evaluating the extent of a tumor or of assigning the stage group to an individual patient's tumor (applying the TNM rules); instead one is generally referring to a cohort of tumors identified by having applied the TNM classification rules. Hence, **clinical stage tumors** or **pathologic stage tumors** would be the most straightforward options. However, **clinically staged tumors** or **pathologically staged tumors** are also acceptable terms.

When using the term "staging" outside of a sentence that clarifies what type of word it is, some ambiguity results. For example, "Atlas of Lung Cancer Staging" could be interpreted as an atlas of TNM categories and groups, or a map to guide the use of EBUS to define a patient's tumor extent. "Atlas of Lung Cancer TNM Classification" would be more specific.

Examples of use of *staging* that is problematic:

"The survival curves for clinical and pathologic staging are shown in Fig X." What is meant is the survival of patients with tumors identified by either their clinical or pathological stage. The process of either tumor evaluation or assignment of TNM classification to a tumor (what "staging" denotes) does not fit the intended meaning. It is better to say "The survival curves of patients with clinical stage and pathologic stage tumors are shown in Fig X."

"This cancer is not properly staged." It is unclear whether this means the stage evaluation was limited (not using tests recommended by guidelines) or whether stage assignment (according to TNM rules) was not done. Using the terms **stage evaluation** and **stage assignment,** respectively, avoids such ambiguity.

While both American Joint Committee on Cancer (AJCC) and UICC use the terms **pT, pN, and pM**, the actual rule is that it is *inappropriate to define pT or pN unless a resection has been done.* Particularly when applied to T, N, or M components in clinical conversation about individual patients, the p-prefix is often used (incorrectly) to mean that tissue is available outside of a resection. AJCC and UICC describe exceptions when p- can be used without resection, but these are rare scenarios that are basically not clinically relevant. Furthermore, the rules for these exceptions differ between AJCC and UICC, do not quite make sense, and leave a number of aspects ambiguous or undefined. The simplest way to avoid this morass is to restrict the use of the p-prefix to a post-resection setting and ignore the exceptions (i.e. use clinical stage in those situations, which is acceptable).

To summarize, the **p-prefix should be used to mean a post-resection stage or TNM category**. Additionally, to avoid confusion (given the frequent misuse of p- for components to mean tissue was obtained), it is best to minimize the use of p for individual components (pT, pN, and pM) as much as possible.

Both 'anatomic' and 'anatomical' are acceptable per Webster's dictionary. 'Anatomic' is more commonly used in the medical field. 'Anatomical' is a more general term, and can apply to the structure of any living organism, including bacteria, plants etc. In the interest of consistency, '**anatomic'** is suggested in the context of SPFC publications.

Both 'pathologic' and 'pathological' are grammatically acceptable. 'Pathologic' more specifically means related to a disease, whereas 'pathological' in medicine means pertaining to the field of pathology, but 'pathological' is also a more general term that has definitions e.g. in mathematics and computer science. In the interest of consistency, '**pathologic'** is suggested in the context of SPFC publications.

Both 'node involvement' and 'nodal involvement' are acceptable; there does not appear to be a defined difference.

The expressions 'positive N1 or N2 or N3 nodes' should be avoided because they are redundant: N1, N2, and N3 already define that the nodes are involved by tumor, that is, they are positive for tumor.

The terms ‘metastatic nodes’ or ‘metastatic sites’ should be avoided. The nodes and the sites do not metastasize. It is better to say ’node involvement‘ or ’metastasis in extrathoracic sites.’

An organ system denotes all sites of an organ that is distributed in the body (e.g. the skeletal system, skin, extrathoracic lymphatic system) or of a paired organ (e.g. adrenal, kidney). The concept of an organ system is relevant in the classification of the extent of distant (M) metastases.

References

1. IASLC Language Guide, 2021. https://www.iaslc.org/IASLCLanguageGuide

PART I

LUNG CANCER

1

General and Lung Cancer Specific Rules of Tumor, Node, Metastasis (TNM) Classification

Frank Detterbeck, MD

General Structure of TNM

The description of the anatomic extent of a tumor consists of 3 components: T for the extent of the primary tumor, N for the involvement of lymph nodes, and M for distant metastases. Each T, N, and M component is divided into several categories (e.g. T1, T2…) and subcategories (e.g. T1a, T1b, T1c). Various characteristics, known as descriptors, define what is included within a T, N, or M category. Specific combinations of T, N, and M categories are clustered together in stage groups.

A prefix specifies the context of the TNM classification (Table 1). Clinical stage (c) is determined by all information available prior to a surgical resection, including symptoms, physical signs, imaging, procedures, and biopsies. Pathologic stage (p) is defined by the results of a surgical resection together with all clinical staging information.

Table 1. Context of TNM Classification

Prefix	Name	Definition
c	Clinical	Prior to initiation of any treatment, using any and all information available (i.e. physical examination, imaging, biopsies)
p	Pathologic	After resection, based on pathologic assessment
y	Restaging	After part or all of the treatment has been given, and can be applied in the absence of resection (ycTNM) or after resection (ypTNM)
r	Recurrence	Stage at time of a recurrence
a	Autopsy	Stage as determined by autopsy (cancer not suspected prior to death)

Confusion is created when the p-prefix is used differently, namely, to mean only that tissue is available (in the absence of a resection). This has become a common practice, especially when the p-prefix is applied to individual TNM

components. Although the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) 8th edition books readily use the notations pT and pN, AJCC and UICC limit this use to the setting of a surgical resection (with rare exceptions).[1,2] The AJCC explicitly defines the microscopic assessment of T and N during the diagnostic work-up as cT and cN. The rules for the rare exceptions differ between the AJCC and UICC and leave a number of aspects undefined or ambiguous. The AJCC and UICC also define exceptions when an overall pathologic stage can be assigned without resection.[1,2] The value of designating a pathologic stage in these instances is questionable, as these exceptions involve extensive (unresected) tumors – for the AJCC: tissue confirmation of 1) T4 AND N3 (M unspecified), or 2) T-any, N-any AND sufficient M1 biopsies to confirm the M subcategory (i.e. pM1b or pM1c);[1] for the UICC: biopsy confirmation of 1) T-any AND N1-3, or 2) the highest N (N3) or 3) a metastasis in extrathoracic sites (M1, not further characterized by M subcategories).[2]

Therefore, the IASLC does not recommend the application of the p-prefix to T and N components outside of the context of a surgical resection. Limiting the use of p- to post-resection TNM is the simplest way to achieve clarity (i.e. avoiding the rare exceptions allowed by the AJCC/UICC and recording only the cTNM of these tumors). In the absence of this policy, clarification should be sought whenever it is unclear whether the p-prefix is being used to mean "post-resection" or merely "tissue confirmation without resection." This is easily done when discussing an individual patient; when analyzing cases from a database it can be problematic unless further details (e.g. treatment modalities used) have been captured.

Type of Stage Evaluation Used

It is useful to have a notation of the type of evaluation used to identify the tumor stage of an individual patient. The Staging and Prognostic Factors Committee recommends an evaluation ("E") categorization (Table 2). This is not part of the general AJCC or UICC classification. However, it could serve to identify tissue confirmation and avoid resorting to the use of the p-prefix outside of a resection. The E category can be applied to either the stage as a whole or to individual components. When applied to the stage as a whole, the highest level of assessment used is applied to the entire stage (e.g. cT2b N2a M0, E3a if endobronchial ultrasound and transbronchial needle aspiration was used to define the N status, and imaging for the T and M status). The implied assumption is that managing clinicians applied the highest level of evaluation to the component that was the most critical question in establishing the correct stage. Thus, this approach is deemed to be based on a reasonable assumption and a practical balance of noting some detail of the evaluation used without too much complexity (e.g. defining an E-type for each component based on test[s] used).

The type of evaluation should not be viewed as a hierarchy of accuracy. The need for additional tests varies, as do the performance characteristics of the tests in individual patients.

Table 2. Type of Evaluation Used to Identify the Stage of a Tumor in a Patient

Label	Name	Definition
E1	Physical	Evidence from symptoms and physical exam
E2	Imaging	Evidence from special diagnostic means (CT, MRI, PET, ultrasound or direct visualization [endoscopy] without biopsy)
E3	Tissue	Invasive tests providing tissue for microscopy a) Cytology (e.g., EBUS-TBNA, thoracentesis) b) Histology (e.g., mediastinoscopy, core biopsy)
E4	Resection	Evidence of the extent of disease after definitive surgical resection and pathologic examination

CT, computed tomography; EBUS-TBNA, endobronchial ultrasound and transbronchial needle aspiration; MRI, magnetic resonance imaging; PET, positron emission tomography.

Details Regarding the Application of TNM Categories in Lung Cancer

General Application of TNM Categories

The TNM classification system for lung cancer applies to small cell and non-small cell lung carcinomas and bronchopulmonary carcinoid tumors. It does not apply to pulmonary sarcomas, lymphomas, and other rare tumors.

The TNM classification for lung cancer should be applied to tumors for which there is no doubt that they are lung cancers, i.e. (eventually) microscopically proven. It should not be applied when the diagnosis remains uncertain.

TX or NX should be used only if no information about T or N categories is available (including no clinical stage information). MX is not allowed, because symptoms and physical exam information are always available.

If there is doubt concerning the correct T, N, or M category to which a particular tumor should be allocated, the lower (i.e. less advanced) category (or stage) should be chosen.

When several T descriptors apply, the highest T category is used – e.g. a 6 cm tumor with visceral pleural invasion is classified as T3 due to size, and a 3 cm tumor invading the carina is classified as T4 due to the invasion.

Rules to classify tumors with multiple pulmonary sites of lung cancer are addressed in a different chapter of this manual.

Tissue Invasion

Invasion by the primary tumor into other structures (e.g. phrenic nerve, aorta) counts to determine the T category. Similarly, direct invasion of the primary tumor into lymph nodes is classified as lymph node involvement. In contrast, invasion

of T structures by involved nodes does not count to determine the T category. However, it can sometimes be impossible to determine if a tumor mass invading hilar/mediastinal structures represents the primary tumor or replaced involved lymph nodes; in such cases it is reasonable to count the invasion in determining the T category (together with an appropriate N designation). In rare instances the primary tumor may directly invade an extrathoracic organ (e.g. liver); this is not counted as M1 involvement.[1,2]

Primary Tumor Size

Tumor size is determined by the greatest dimension of: A) pathologically, the invasive component – i.e. not counting a noninvasive/lepidic component in non-mucinous adenocarcinomas, and B) clinically, the solid component (by thin-slice [≤1.5 mm] computed tomography, lung window parameters) – i.e. not counting a ground glass component.[3] Generally, axial images are sufficient, but multiplanar images can be used if deemed to better represent the largest tumor dimension.[4]

When an invasive tumor consists of multiple foci or is present on multiple histologic slides, making measurement of invasive tumor size difficult (e.g. part lepidic nonmucinous adenocarcinomas or foci of residual tumor after induction therapy), the tumor size is defined by multiplying the percent of invasive (or viable) tumor by the total size of the lesion.[3,5]

Details and Specific Additional Descriptors

Visceral pleural invasion is designated as T2a if invasion is present either beyond the elastic layer (PL1) or extending to the pleural surface (PL2).[6,7] The use of elastic stains is recommended if the invasion of the elastic layer is not clear on hematoxylin-eosin staining. Invasion of the parietal pleura (PL3) is classified as T3 (Figure 1).[8] A subdivision of chest wall invasion was suggested in the 8th edition of TNM but not yet formally adopted[2,7] In this schema tumors are designated as pT3a if invading only the parietal pleura, pT3b if invading the endothoracic fascia, and pT3c if invading the rib or soft tissue.

Lymphangitic carcinomatosis does not impact the TNM classification but is usually of major consequence in clinical management. Therefore, an "Ly" descriptor has been proposed.[7,9] A tumor would be designated clinically as cLy0 if lymphangitis is absent, cLy1 if present in the area around the primary tumor, cLy2 if present more broadly but confined to the lobe with the primary tumor, cLy3 if present in other ipsilateral lobes, and cLy4 if present in the contralateral lung.

Manifestations of Minimal Disease

Micrometastases are counted toward the N or M designation, identified by a notation of (mi) - e.g. N2(mi). These are defined as small clumps of tumor cells,

0.2-2 mm in greatest dimension, usually detected by routine histological staining and exhibiting mitoses and invasion.[1]

Isolated tumor cells are not counted toward the T, N, or M designation. These are defined as single tumor cells or isolated clusters of cells, <0.2 mm in greatest dimension, either detected by routine histological stains, immunohistochemistry, or molecular methods, usually without mitoses or invasion. However, a notation of (i+) or (mol+) can be added if isolated tumor cells are detected morphologically or by non-morphologic techniques, respectively - e.g., N0(mol+).[1]

Circulating tumor cells or disseminated tumor cells (e.g. in bone marrow) are defined as isolated tumor cells typically detected by special staining techniques. The presence of these is denoted as cM0(i+); they do not affect the TNM classification.[1] Other blood-based assessments, such as cell-free tumor DNA, are not included in the TNM classification system.

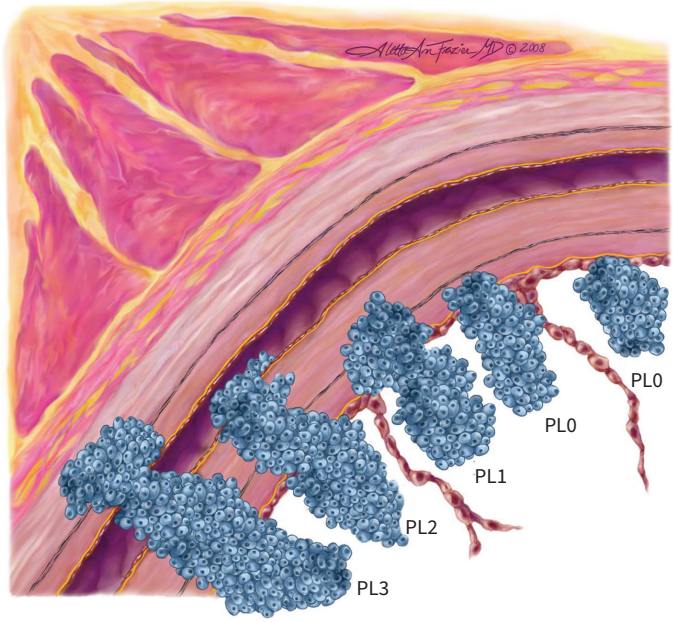


Figure 1. **Representation of visceral pleura invasion (VPI) for lung cancer. The different clusters of blue cells represent tumors with varying levels of VPI. PL0: Tumor within the subpleural lung parenchyma or invading superficially into the pleural connective tissue beneath the elastic layer. PL1: Tumor invades the elastic layer. PL2: Tumor invades the pleural surface. PL3: Tumor invades any component of the parietal pleura. PL0 is not a T descriptor. PL1 and PL2 are classified as T2. PL3 is classified as T3. Reprint with permission from Aletta Ann Frazier, MD. Reference: Travis et al. *J Thorac Oncol* 2008.[9]**

References

1. Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017..
2. Wittekind C, Brierley J, Lee A, et al. *UICC TNM Supplement, A Commentary on Uniform Use.* 5th ed. Oxford UK: Wiley Blackwell; 2019.
3. Travis D, Asamura H, Bankier AA, 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(8):1204-1223. doi:10.1016/j.jtho.2016.03.025
4. Bankier AA, MacMahon H, Goo JM, et al. Recommendations for measuring pulmonary nodules at CT: A statement from the Fleischner Society. *Radiology.* 2017;285(2):584-600. doi:10.1148/radiol.2017162894
5. Travis WD, Dacic S, et al. IASLC multidisciplinary recommendations for pathologic assessment of lung cancer resection specimens after neoadjuvant therapy. *J Thorac Oncol.* 2020;15(5):709-740. doi:10.1016/j.jtho.2020.01.00
6. Hammar S. Common Tumors. In: Dail D, Hammar S, eds. *Pulmonary Pathology*. New York: Springer-Verlag; 1994:1138.
7. Rami-Porta R. *IASLC Staging Manual in Thoracic Oncology, 2nd Edition.* North Fort Meyers: Editorial Rx Press; 2016.
8. Travis W, Brambilla E, Rami-Porta R, et al. Visceral pleural invasion: Pathologic criteria and use of elastic stains: Proposal for the 7th edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2008;3(12):1384-1390. doi:10.1097/JTO.0b013e31818e0d9f
9. Wittekind C, Compton C, Brierley J, Sobin L. *TNM Supplement: A Commentary on Uniform Use.* 4th ed. John Wiley & Sons, Ltd; 2012.

2

Overview of the Database

Hisao Asamura, MD

Since 1996, the IASLC, with its global, multidisciplinary reach, has been engaged in revising the tumor, node, and metastasis (TNM) classification of lung cancer and completed two phases of the Staging Project. Following the publication of the 8th edition of the TNM classification as the product of the second phase of the international Staging Project, the IASLC launched the third phase of its Staging Project in 2017. For this latest phase, a new database of lung cancer cases diagnosed between January 2011 and December 2019 was established.[1]

The newly established database is composed of 124,581 cases, of which 101,033 (81.1%) were submitted as batch datasets and 23,548 (18.9%) were submitted via the electronic data capture system. The data came from 25 countries and 75 unique sites. Cases were submitted from Asia/Australia (69,749 cases, 56.0%), Europe (30,827 cases, 24.7%), North America (19,608 cases, 15.7%), South/Central America (4,225 cases, 3.4%), and Africa and the Middle East (172 cases, 0.1%) (Figure 1).

After excluding cases with incomplete data, 87,043 cases were eligible for analysis (Figure 2). The dominant source of data was the Japanese Joint Lung Cancer Registry (Japan, 23,663 cases), followed by the University Hospital Heidelberg (Germany, 8,840 cases), West China Hospital, Sichuan University (China, 7,345 cases), Korean Association for Lung Cancer (Republic of Korea, 4,022 cases), and Samsung Medical Center (Republic of Korea, 3,645 cases). Of the 87,043 eligible cases, there were 52,069 (59.8%) invasive adenocarcinoma, 15,872 (18.2%) squamous cell carcinoma, 1,142 (1.3%) were adenocarcinoma *in situ*, 1,100 (1.3%) adenosquamous cell carcinoma, 1,057 (1.2%) were large cell carcinoma, 5,530 (6.4%) small cell lung cancer, and 689 (0.8%) large cell neuroendocrine carcinoma.

Approximately 67% of the cases underwent surgical treatment, with or without chemotherapy or radiotherapy. Of the 77,811 cases in which the clinical stage was available, the most frequent clinical stage according to the 8th edition of the TNM classification was stage IA2 (10,402 cases, 13.4%), followed by stage IVB (9,236 cases, 11.9%), and stage IA3 (7,357 cases, 9.4%). Of the 54,248 cases in which pathologic

stage was available, 22,206 cases (40.9%) were stage IA, 9,021 cases (16.6%) were stage IB, 8,246 (15.2%) were stage IIIA, and 7,625 (14.1%) were stage IIB, according to the 8th edition of the TNM classification. Of the 47,933 surgical cases in which margin status was available, R0 resection was achieved in 42,623 (88.9%). Information on molecular biomarkers was collected as well. Multifaceted analyses of the database were performed based on the strategic method designed by the Validation and Methodology Subcommittee of the Staging and Prognostic Factors Committee,[2] to provide findings that are reflected in the proposals to refine the TNM classification system.

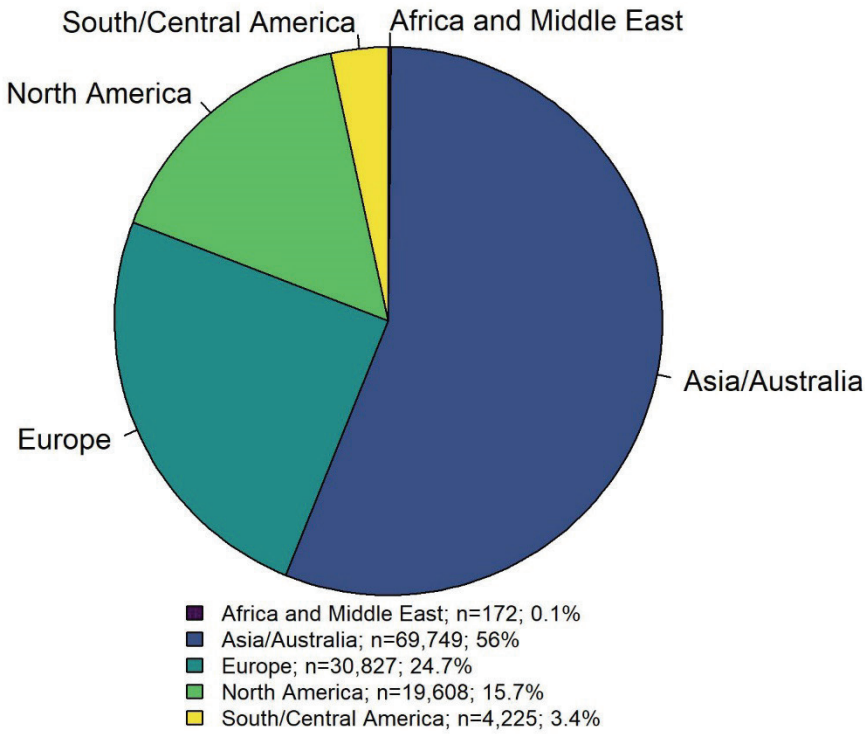


Figure 1. **Number of cases submitted, classified by region.**

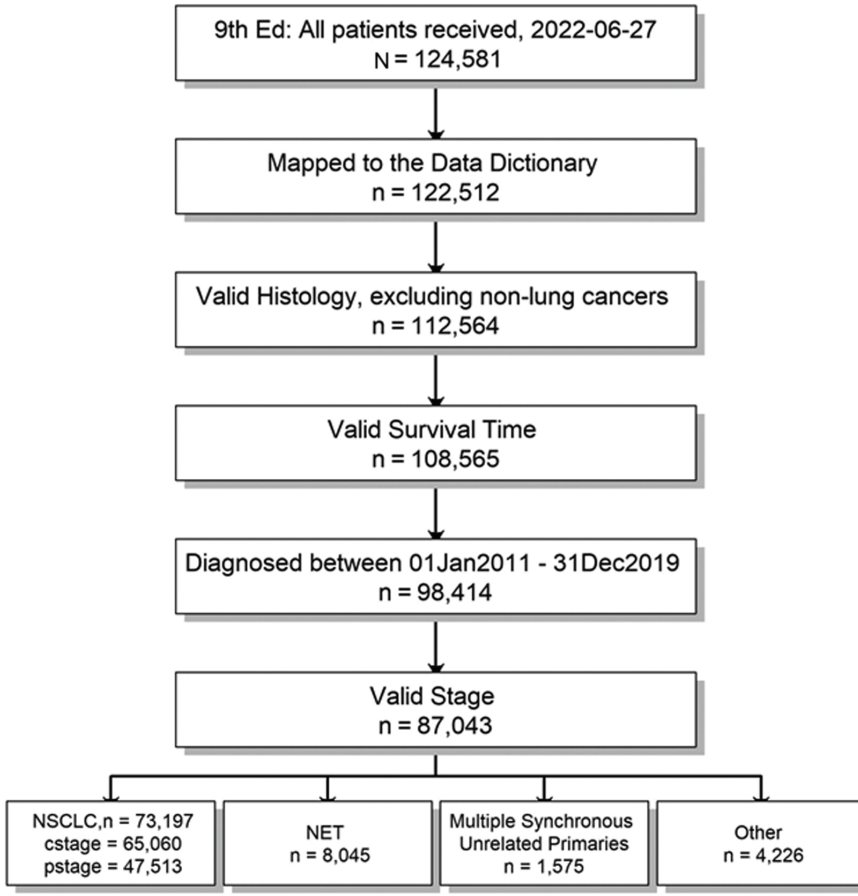


Figure 2. Case selection. The submitted data were mapped to a data dictionary and checked to verify if they included a valid histology, survival time, date of diagnosis window, and clinical and pathologic stages.

References

1. Asamura H, Nishimura KK, Giroux DJ, et al. IASLC lung cancer staging project: The new database to inform revisions in the ninth edition of the TNM classification of lung cancer. *J Thorac Oncol.* 2023 May;18(5):564-575. doi: 10.1016/j.jtho.2023.01.088
2. Detterbeck FC, Nishimura KK, Cilento VJ, et al. The International Association for the Study of Lung Cancer staging project: Methods and guiding principles for the development of the ninth edition TNM classification. *J Thorac Oncol.* 2022;17:806-815. doi:10.1016/j.jtho.2022.02.008

3

Tumor (T) Component

Paul E. Van Schil, MD, PhD

Table 1. **Primary Tumor Definitions**

T: Primary tumor	
Tx	Primary tumor cannot be assessed[a]
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*[b]
T1	Tumor surrounded by lung or visceral pleura, or in a lobar or more peripheral bronchus[c]
T1mi	Minimally invasive adenocarcinoma[d]
T1a	Tumor ≤1 cm in greatest dimension
T1b	Tumor >1 cm but ≤2 cm in greatest dimension
T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2	Tumor with any of the following features:
T2a	• tumor >3 cm but ≤4 cm in greatest dimension; • invades visceral pleura; • invades an adjacent lobe; • involves main bronchus (up to but not including the carina) or is associated with atelectasis or obstructive pneumonitis extending to the hilar region, involving either part of or the entire lung
T2b	Tumor >4 cm but ≤5 cm in greatest dimension
T3	Tumor with any of the following features: • tumor >5 cm but ≤7 cm in greatest dimension; • invades parietal pleura or chest wall; • invades pericardium, phrenic nerve, or azygos vein;[e] • invades thoracic nerve roots (i.e. T1, T2) or stellate ganglion; • separate tumor nodule(s) in the same lobe as the primary

continued on next page

T4	Tumor with any of the following features: • tumor >7 cm in greatest dimension; • invades mediastinum, thymus, trachea, carina, recurrent laryngeal nerve, vagus nerve, esophagus or diaphragm; • invades heart, great vessels (aorta, superior/inferior vena cava, intrapericardial pulmonary arteries/veins), supra-aortic arteries, or brachiocephalic veins; • invades subclavian vessels, vertebral body, lamina, spinal canal, cervical nerve roots, or brachial plexus (i.e. trunks, divisions, cords, or terminal nerves); • separate tumor nodule(s) in a different ipsilateral lobe than that of the primary

[a] This includes tumors proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

[b] This includes adenocarcinoma *in situ* – Tis (AIS) – and squamous cell carcinoma *in situ* – Tis (SCIS).

[c] 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.

[d] Solitary adenocarcinoma (not more than 3 cm in greatest dimension), with a predominantly lepidic pattern and not more than 5 mm invasion in greatest dimension.

[e] Although these structures lie within the mediastinum, the degree of mediastinal penetration by the tumor needed to invade these structures is not counted as T4.

Explanatory Notes

1. Invasion of visceral pleura (T2) is defined as "invasion beyond the elastic layer including invasion to the visceral pleural surface" (Table 1). The use of elastic stains is recommended when this feature is not clear on routine histology.
2. Tumor with direct invasion of an adjacent lobe, across the fissure or by direct extension at a point where the fissure is deficient, should be classified as T2a unless other criteria assign a higher T category.
3. Invasion of azygos vein is classified as T3.
4. Invasion of thoracic nerve roots (e.g. T1, T2) or stellate ganglion is classified as T3.
5. Invasion of thymus is classified as T4.
6. Invasion of subclavian vessels, vertebral body, lamina, spinal canal, cervical nerve roots, or brachial plexus (e.g. trunks, divisions, cords or terminal nerves) is classified as T4.
7. Invasion of the brachiocephalic veins is classified as T4.
8. Invasion of the vagus nerve is classified as T4.
9. Invasion into hilar fat, unless other criteria assign a higher T, is classified as T2a.

What is new for the 9th Edition?

The survival curves for patients with clinical and pathologic stage tumors separate nicely (Figure 1). As demonstrated in Figure 1, significant and clinically relevant differences were observed with the exception of cT2b versus cT3 in univariable analysis, but not in multivariable analysis (Table 2). For this reason, no changes were implemented for the T-component in the 9th edition compared to the 8th edition.[1]

T3 with chest wall invasion was evaluated as a separate descriptor compared to the other T3 descriptors.[2] However, survival differences were only significant for

patients with pathologic stage but not with clinical stage tumors (Figure 2). As our clinical decision-making depends on clinical stage, no changes were implemented.

Table 2. **Multivariable Survival Analyses of T-component Stratified by Data Source**

	Clinical T-component N=33,545; R^2=36.3536		
	n/N (%)	HR (95% CI)	P-value
T1b (vs T1a)	8,937/33,545 (26.64%)	1.81 (1.59-2.07)	<.0001
T1c (vs T1b)	6,664/33,545 (19.87%)	1.54 (1.43-1.65)	<.0001
T2a (vs T1c)	6,290/33,545 (18.75%)	1.36 (1.27-1.45)	<.0001
T2b (vs T2a)	2,512/33,545 (7.49%)	1.35 (1.25-1.45)	<.0001
T3 (vs T2b)	3,598/33,545 (10.73%)	1.10 (1.01-1.19)	0.0239
T4 (vs T3)	2,475/33,545 (7.38%)	1.52 (1.41-1.63)	<.0001
Age 65 or Older (vs younger than 65)	18,962/33,545 (56.53%)	1.43 (1.37-1.50)	<.0001
Female (vs Male)	17,603/33,545 (52.48%)	0.96 (0.92-1.00)	0.0392
Europe (vs Asia)	4,002/33,545 (11.93%)	1.55 (1.45-1.65)	<.0001
North America (vs Asia)	6,256/33,545 (18.65%)	1.33 (1.26-1.41)	<.0001
Rest of World (vs Asia)	927/33,545 (2.76%)	1.80 (1.59-2.04)	<.0001
Squamous (vs Non-squamous)	8,133/33,545 (24.25%)	1.40 (1.34-1.47)	<.0001
	Pathologic T-component N=28,771; R^2=34.5095		
	n/N (%)	HR (95% CI)	P-value
T1b (vs T1a)	5,105/28,771 (22.09%)	1.97 (1.62-2.40)	<.0001
T1c (vs T1b)	3,604/28,771 (15.57%)	1.64 (1.47-1.82)	<.0001
T2a (vs T1c)	9,648/28,771 (24.96%)	1.36 (1.25-1.48)	<.0001
T2b (vs T2a)	2,707/28,771 (8.07%)	1.32 (1.23-1.42)	<.0001
T3 (vs T2b)	3,706/28,771 (13.36%)	1.11 (1.02-1.20)	0.0115
T4 (vs T3)	2,046/28,771 (7.54%)	1.40 (1.29-1.52)	<.0001
Age 65 or Older (vs younger than 65)	15,377/28,771 (49.29%)	1.45 (1.38-1.52)	<.0001
Female (vs Male)	14,677/28,771 (46.91%)	0.85 (0.81-0.89)	<.0001
Europe (vs Asia)	3,310/28,771 (15.61%)	1.41 (1.31-1.52)	<.0001
North America (vs Asia)	5,741/28,771 (23.85%)	1.34 (1.26-1.43)	<.0001
Rest of World (vs Asia)	1,424/28,771 (6.12%)	1.38 (1.25-1.52)	<.0001
Squamous (vs Non-squamous)	6,848/28,771 (23.09%)	1.31 (1.24-1.38)	<.0001

Clinical T-component (upper panel), pathologic T-component (lower panel). Hazard Ratios reflect the risk associated among those with the trait, versus the reference category in parentheses. P-value from Wald $\chi 2$ test in adjusted Cox regression.

HR, Hazard Ratio; 95% CI, 95% confidence interval; n, number of patients with the trait; N, total number of patients evaluated; %, percent with the trait; vs, versus

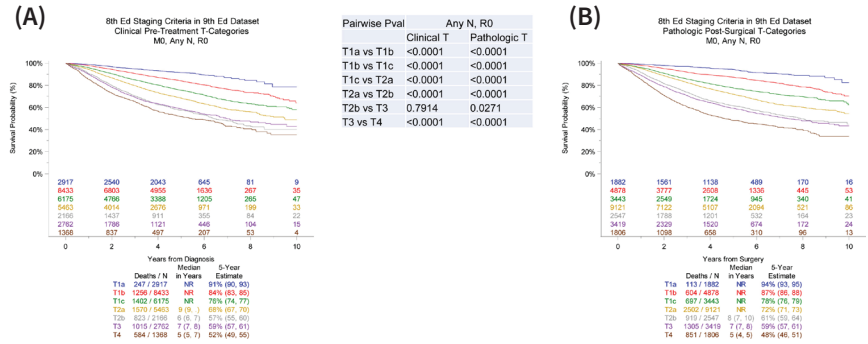


Figure 1. Validation of the 8th edition T-categories in the 9th edition database. Overall survival of patients with (A) clinical stage and (B) pathologic stage N0 M0 R0 tumors.

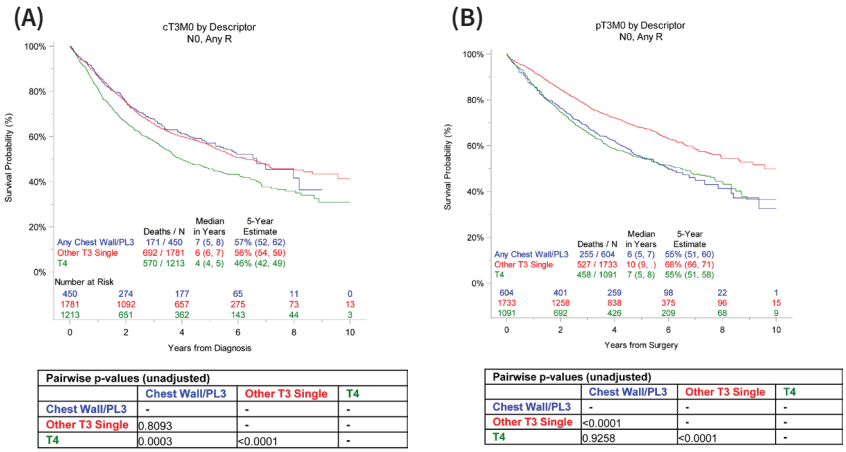


Figure 2. Validation of the 8th edition T3 descriptors in the 9th edition database. Overall survival of patients with (A) clinical stage and (B) pathologic stage T3 N0 M0 R-any tumors.

References

1. Van Schil PE, Asamura H, Nishimura KK, et al. The IASLC lung cancer staging project: Proposals for the revisions of the T descriptors in the forthcoming ninth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2024; 19(5):749-765. doi:10.1016/j.jtho.2023.12.006
2. Ugalde Figueroa PA, Marques E, Cilento VJ, et al. Completeness of resection and long-term survival of patients undergoing resection for T3 non-small-cell lung cancer: An International Association for the Study of Lung Cancer analysis. *J Thorac* Oncol. 2024; 19(1):141-152. doi: 10.1016/j.jtho.2023.09.277.

4

Node (N) Component

James Huang, MD

Table 1. **Regional Lymph Nodes Definitions**

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar and/or intrapulmonary lymph nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
	N2a – Single N2 station involvement
	N2b – Multiple N2 station involvement
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)

Explanatory Notes

1. Recommendations for the 9th edition are based upon recommendations from the IASLC Lung Cancer Staging Project (Table 1).[1,2]
2. The regional lymph nodes are the intrathoracic, scalene, and supraclavicular nodes.
3. The IASLC lymph node classification is the recommended means of describing regional lymph node involvement for lung cancers (see Chapter on Lymph Node Chart).[3] Ipsilateral or contralateral node involvement in station #1 is classified as N3. Involvement of mediastinal nodes, if limited to the midline stations or ipsilateral stations (#2-9), is classified as N2. Involvement of ipsilateral stations #10-14 is classified as N1. Contralateral involvement of # 2, 4, 5, 6, 8, 9, 10-14 is classified as N3.
4. Direct extension of the primary tumor into lymph nodes is counted as lymph node involvement.
5. The IASLC nodal chart[3] has been adopted as the international chart that defines nodal stations used in clinical or pathologic TNM classification where detailed assessment of nodes has been made (see Chapter on Lymph Node Chart).

6. Clinical N classification may be based on radiographic findings with or without pathologic confirmation via invasive staging procedures (i.e. endobronchial ultrasound, mediastinoscopy, etc.). Pathologic N stage is based upon microscopic confirmation of metastasis on pathologic examination of the resected lung cancer.

What is new for the 9th Edition?

For the 9th edition, two additional subcategories have been added to the N2 category to allow for the quantification of nodal involvement in the mediastinum based on the number of N2 nodal stations involved.[1] The subcategory N2a denotes metastasis limited to a single ipsilateral mediastinal or subcarinal station. The subcategory N2b denotes metastases in multiple (more than one) mediastinal or subcarinal stations. Survival analyses demonstrated a clear and consistent prognostic difference between single and multiple N2 station involvement in both clinical and pathologic stages (Figure 1, Table 2). (Clear differences in single versus multiple station involvement at the N1 level were not seen consistently in both clinical and pathologic stages, so no subdivision of the N1 category was recommended for the 9th edition).

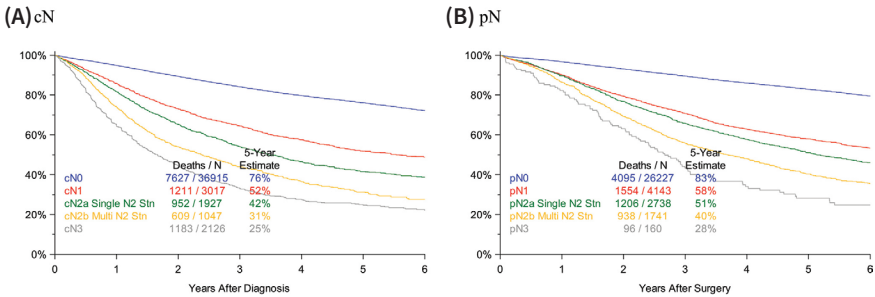


Figure 1. Overall survival of patients by clinical N categories (A), and pathologic N categories (B).[1]

Table 2. Adjusted Hazard Ratios for Overall Survival of Patients Between 9th Edition N Categories

	cN (44,309 patients)		pN (34,342 patients)	
	HR (95% CI)	P-value	HR (95% CI)	P-value
N1 vs N0	1.96 (1.84-2.08)	<0.0001	2.40 (2.26-2.55)	<0.0001
N2a vs N1	1.42 (1.28-1.56)	<0.0001	1.45 (1.31-1.60)	<0.0001
N2b vs N2a	1.27 (1.13-1.43)	<0.0001	1.46 (1.32-1.62)	<0.0001
N3 vs N2b	1.51 (1.35-1.70)	<0.0001	1.62 (1.29-2.03)	<0.0001

Note: Overall survival was compared between 9th edition N categories based on a Cox proportional hazards model with covariates of 9th edition N category, sex, age, histologic type, history of prior malignancy, geographical region, and completeness of resection (for pathologic stage tumors).[1]

HR, Hazard Ratio; 95% CI, 95% Confidence Interval; P-value from chi-square test score in Cox regression model

References

1. Huang J, Osarogiagbon RU, Giroux DJ, et al. The International Association for the Study of Lung Cancer staging project for lung cancer: Proposals for the revision of the N descriptors in the forthcoming ninth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2024; 19(5):766-785. doi: 10.1016/j.jtho.2023.10.012
2. Osarogiagbon RU, Van Schil P, Giroux DJ, et al. The International Association for the Study of Lung Cancer lung cancer staging project: Overview of challenges and opportunities in revising the nodal classification of lung cancer. *J Thorac Oncol.* 2023;18:410-418. doi:10.1016/j.jtho.2022.12.009
3. Rusch VW, Asamura H, Watanabe H, et al. 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;4:568-577. doi:10.1097/JTO.0b013e3181a0d82e

5

Metastasis (M) Component

Kwun M. Fong, MD, PhD

Table 1. Distant Metastasis Definitions

M0	No distant metastasis
M1	Distant metastasis
M1a	Tumor with pleural or pericardial nodules or malignant pleural or pericardial effusions[1], separate tumor nodule(s) in a contralateral lobe
M1b	Single extrathoracic metastasis in a single organ system[2]
M1c	Multiple extrathoracic metastases
M1c1	Multiple extrathoracic metastases in a single organ system[3]
M1c2	Multiple extrathoracic metastases in multiple organ systems

Explanatory Notes

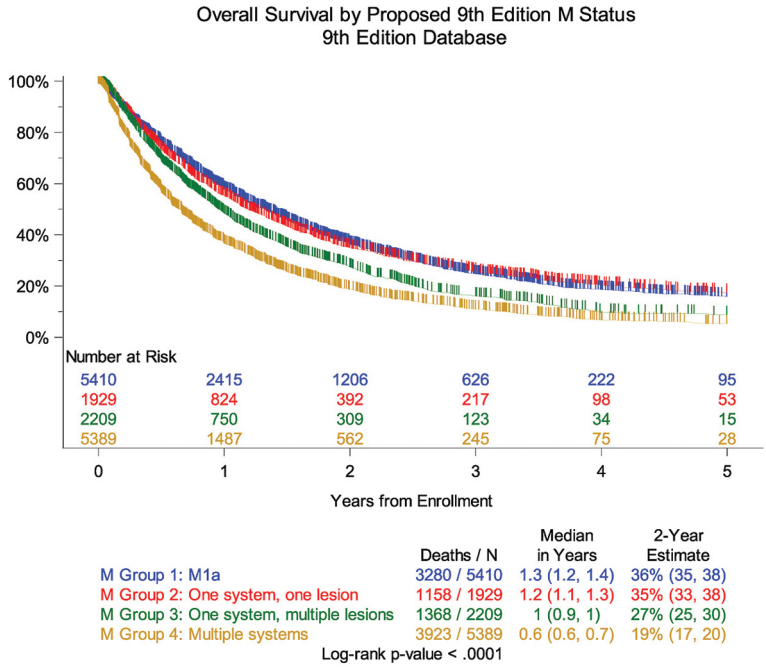
1. Most pleural (or pericardial) effusions in patients with lung cancer are due to the tumor. In a few patients, however, multiple microscopic examinations of pleural (or pericardial) fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a stage descriptor. An effusion thought to be malignant is thus counted as M1a (Table 1), whether it is microscopically proven or not.
2. This includes involvement of a single non-regional node.
3. For example, the skeleton is considered one organ system. Multiple metastases in several bones are classified as M1c1. Multiple metastases in the liver are classified as M1c1. Metastasis involving liver and bone would be considered M1c2.

What is new for the 9th Edition?

M1c (multiple extrathoracic metastases in a single or multiple organ system[s]) is now divided into M1c1 (multiple extrathoracic metastases in a single organ system) and M1c2 (multiple extrathoracic metastases in several organ systems) (Figure 1, Table 2).[1]

For example, the skeleton is considered one organ system. Multiple metastases in several bones are classified as M1c1. Multiple metastases in the liver are classified as M1c1.

Metastases involving more than one organ system, e.g. both liver and bone, would be considered M1c2.



Pairwise p-values (unadjusted)			
	1 System, 1 Lesion	1 System, M Lesions	M Systems, M Lesions
M1a	0.5217	<0.0001	<0.0001
1 System, 1 Lesion		<0.0001	<0.0001
1 System, M Lesions			<0.0001

Figure 1. **Overall survival of patients by 9th edition M status in the 9th edition database.**

Table 2. Cox Regression for Overall Survival by Number of Lesions and Sites, Stratified by Datasource; Analysis of M Categories

Category	Variable	n/N (%)	HR (95% CI)	P-value
M1 categories: M1a, M1b, M1c1 (single organ system), and M1c2 (multiple organ systems)				
M1a	M1a	5406/14926 (36%)	(reference level)	N/A
M1b	M1b; single organ system, single lesion (vs. M1a)	1927/14926 (13%)	1.18 (1.10-1.27)	<.001
M1c1 single organ system	M1c1; single organ system, multiple lesions (vs. M1b)	2207/14926 (15%)	1.17 (1.08-1.27)	<.001
M1c2 multiple organ systems	M1c2; multiple organ systems, multiple lesions (vs. M1c1 single organ system)	5386/14926 (36%)	1.33 (1.25-1.41)	<.001
Adjustment Factors				
	Age ≥ 65	8577/14926 (57%)	1.35 (1.30-1.41)	<.001
	Male	8838/14926 (59%)	1.32 (1.27-1.38)	<.001
	Squamous	2529/14926 (17%)	1.34 (1.27-1.41)	<.001
	Region: Asia (vs. other)	6872/14926 (46%)	0.93 (0.89-0.97)	<.001

References

1. Fong KM, Rosenthal A, Giroux DJ, et al. The International Association for the Study of Lung Cancer staging project for lung cancer: Proposals for the revision of the M descriptors in the forthcoming ninth edition of the TNM classification of lung cancer. *J Thorac Oncol.* 2024; 19(5):786-802. doi: https://doi.org/10.1016/j.jtho.2024.01.019

6

Stage Groups

Ramón Rami-Porta, MD, PhD

Table 1. **Stage Groups of the 9th Edition of the Tumor, Node, Metastasis (TNM) Classification of Lung Cancer[2]**

9th Edition TNM Descriptors and Stages						
				N2		
T/M	Categories and Descriptors	N0	N1	N2a	N2b	N3
T1	T1a ≤1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a Visceral pleura / central invasion	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe separate tumor nodules	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 >7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral separate tumor nodules	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Contralateral tumor nodules	IVA	IVA	IVA	IVA	IVA
	M1a Pleural / pericardial effusion, nodules	IVA	IVA	IVA	IVA	IVA
	M1b Single extrathoracic metastasis	IVA	IVA	IVA	IVA	IVA
	M1c1 Multiple metastases in 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Multiple metastases in >1 organ systems	IVB	IVB	IVB	IVB	IVB

Explanatory Notes

In the tumor, node, and metastasis (TNM) classification, tumors with similar prognosis are clustered together in stage groups. In each revision of the classification,

changes in the descriptors or categories of the T, the N, and the M components of the classification imply changes in the stage group assignment; sometimes new T, N, or M categories require re-definition of stage groups, or a more refined and contemporary understanding of prognosis requires a reshuffling of TNM combinations that comprise a stage group (Table 1).

In the IASLC 9th edition database, from a total of 124,581 registered patients,[1] 75,636 were evaluable: 58,108 patients with clinical stage non-small cell lung cancer (NSCLC), 39,135 with pathologic stage NSCLC, and 62,542 with best stage NSCLC were available for the analyses of the stage groups.[2]

The changes in the categories of the 9th edition of TNM classification of lung cancer are summarized in Table 2.[3-5]

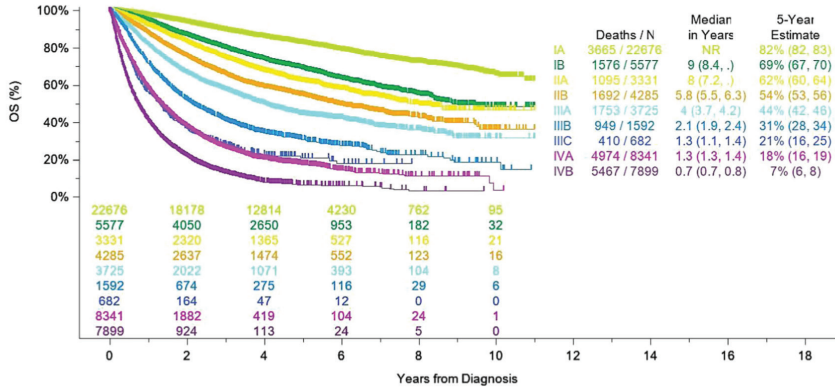
The 9th edition of the TNM classification system has several implications. The stage groups more closely reflect the prognostic impact of anatomic tumor extent and align with features affecting management (Figures 1 and 2). The changes in the N and in the M categories will require a detailed clinical and pathologic evaluation process to properly quantify the amount of nodal disease, and the number of distant metastases and organ systems involved. However, the fundamental principle remains that a change in nomenclature (i.e. the stage group designation according to the 9th versus the 8th edition) does not alter the evidence we have that guides treatment (i.e. the results of existing clinical trials). Therefore, the clinical judgment of the responsible medical team must be exercised cautiously when planning treatment for patients whose tumors have moved to a different stage.[6,7]

What is new for the 9th Edition Stages?

1. T1N2a is assigned to stage IIB
2. T1N1 is downstaged from stage IIB to stage IIA
3. T2N2b is assigned to stage IIIB
4. T3N2a is assigned to stage IIIA

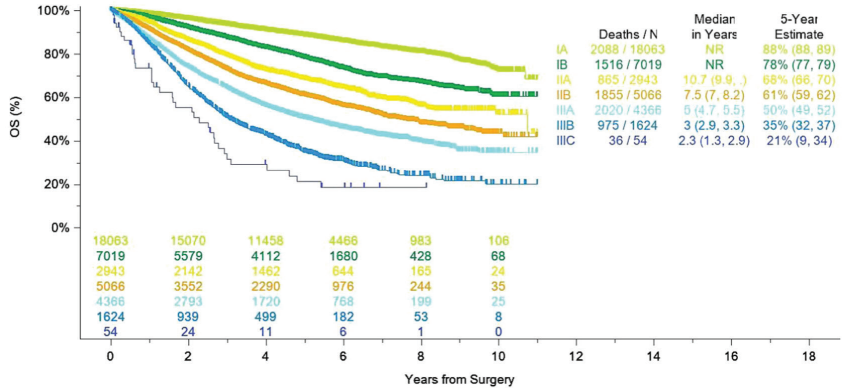
Table 2. Changes in the T, the N and the M Categories of the 9th Edition of the TNM Classification of Lung Cancer[3,4,5]

Categories	Changes
T	There are no changes
N	N2 is divided into: N2a: involvement of a single N2 nodal station N2b: involvement of several N2 nodal stations
M	M1c is divided into: M1c1: multiple extrathoracic metastases in a single organ system M1c2: multiple extrathoracic metastases in multiple organ systems



Multivariable Cox Model	9th Edition Clinical TNM Stage Groups N=55,986; R^2=65.0371		
	n/N (%)	HR (95% CI)	P-value
IB (vs IA)	5,513/55,986 (9.85%)	1.77 (1.67-1.88)	<.0001
IIA (vs IB)	3,280/55,986 (5.86%)	1.18 (1.09-1.28)	<.0001
IIB (vs IIA)	3,701/55,986 (6.61%)	1.25 (1.16-1.35)	<.0001
IIIA (vs IIB)	3,590/55,986 (6.41%)	1.33 (1.24-1.43)	<.0001
IIIB (vs IIIA)	1,489/55,986 (2.66%)	1.53 (1.41-1.66)	<.0001
IIIC (vs IIIB)	632/55,986 (1.13%)	1.62 (1.44-1.83)	<.0001
IVA (vs IIIC)	7,931/55,986 (14.17%)	1.10 (0.99-1.23)	0.0643
IVB (vs IVA)	7,309/55,986 (13.06%)	1.68 (1.61-1.75)	<.0001
Age ≥65 (vs <65)	31,754/55,986 (56.72%)	0.70 (0.68-0.72)	<.0001
Female (vs Male)	27,370/55,986 (48.89%)	1.20 (1.17-1.24)	<.0001
Europe (vs Asia)	11,875/55,986 (21.21%)	1.30 (1.26-1.35)	<.0001
North America (vs Asia)	9,811/55,986 (17.52%)	1.10 (1.05-1.14)	<.0001
Rest of World (vs Asia)	1,294/55,986 (2.31%)	1.78 (1.62-1.95)	<.0001
Squamous (vs non-squamous)	12,304/55,986 (21.98%)	0.70 (0.68-0.72)	<.0001

Figure 1. **Survival of patients with clinical stage tumors by 9th edition tumor, node, metastasis (TNM) classification.**[2]



Multivariable Cox Model	9th Edition Pathologic TNM Stage Groups N=38,280; R^2=46.0529		
	n/N (%)	HR (95% CI)	P-value
IB (vs IA)	6,990/38,280 (18.26%)	1.84 (1.72-1.97)	<.0001
IIA (vs IB)	2,928/38,280 (7.65%)	1.40 (1.29-1.52)	<.0001
IIB (vs IIA)	4,375/38,280 (11.43%)	1.25 (1.15-1.36)	<.0001
IIIA (vs IIB)	4,329/38,280 (11.31%)	1.49 (1.40-1.59)	<.0001
IIIB (vs IIIA)	1,618/38,280 (4.23%)	1.70 (1.57-1.83)	<.0001
IIIC (vs IIIB)	52/38,280 (0.14%)	1.60 (1.13-2.25)	0.0074
Age ≥65 (vs <65)	21,478/38,280 (56.11%)	0.61 (0.58-0.64)	<.0001
Female (vs Male)	19,824/38,280 (51.79%)	1.03 (0.99-1.07)	0.1725
Europe (vs Asia)	4,227/38,280 (11.04%)	1.51 (1.42-1.61)	<.0001
North America (vs Asia)	6,351/38,280 (16.59%)	1.55 (1.46-1.65)	<.0001
Rest of World (vs Asia)	1,393/38,280 (3.64%)	1.58 (1.43-1.75)	<.0001
Squamous (vs Non-squamous)	8,431/38,280 (22.02%)	0.68 (0.65-0.72)	<.0001

Figure 2. Survival of patients by pathologic stage tumors by 9th edition tumor, node, metastasis (TNM) classification.[2]

References

1. Asamura H, Nishimura KK, Giroux DJ, et al. IASLC lung cancer staging project: The new database to inform revisions in the ninth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2023 May;18(5):564-575. doi: 10.1016/j.jtho.2023.01.088.
2. Rami-Porta R, Nishimura KK, Giroux DJ, et al. The International Association for the Study of Lung Cancer lung cancer staging project: Proposals for revision of the TNM stage groups in the forthcoming ninth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2024;19(7):1007-1027. doi:10.1016/j.jtho.2024.02.011

3. Van Schil PE, Asamura H, Nishimura K, et al. The IASLC lung cancer staging project: Proposals for the revisions of the T-descriptors in the forthcoming ninth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2024;19(5):749-765. doi.org/10.1016/j.jtho.2023.12.006
4. Huang J, Osarogiagbon RU, Giroux DJ, et al. The IASLC lung cancer staging project: Proposals for the revision of the N descriptors in the forthcoming ninth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2024;19(5):766-785. doi.org/10.1016/j.jtho.2023.10.012
5. Fong KM, Rosenthat A, Giroux DJ, et al. The IASLC lung cancer staging project: Proposals for the revisions of the M descriptors in the forthcoming ninth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2024;19(5):786-802. doi.org/10.1016/j.jtho.2024.01.019
6. Boffa D, Detterbeck F, Smith EJ et al. Should the 7th edition of the lung cancer stage classification system change treatment algorithms in non-small cell lung cancer? *J Thorac Oncol*. 2010;5(11):1779-83. doi:10.1097/JTO.0b013e3181ee80c7
7. Boffa DJ, Greene FL. Reacting to changes in staging designations in the 7th edition of the AJCC Staging Manual. *Ann Surg Oncol*. 2011;18(1):1-3. doi:10.1245/s10434-010-1427-z

7

Residual Tumor (R) Classification

Frank Detterbeck, MD, and Marcin Ostrowski, MD, PhD

Residual Tumor (R) Classification

The R-classification is a description of the residual tumor left after a resection. The tumor, node, metastasis (TNM) classification describes the anatomic extent of cancer in general, without considering treatment. This is supplemented by the R-classification, which categorizes the presence or absence of residual tumor after surgical resection. In addition to the traditional R categories of complete resection (R0), a microscopically positive margin (R1) and gross tumor remaining (R2), the IASLC recommends an 'uncertain' category R(un) for lung cancer, in which the presence of residual tumor or the prognostic implication is uncertain (Table 1, Figure 1).[1,2]

Table 1. Residual Tumor After Surgical Resection

Symbol	Name	Descriptor
R0	No residual	No identifiable tumor remaining, negative surgical margins, adequate node assessment,[a] and highest node station assessed is negative
R0(un)	Uncertain residual	Limited node assessment[a]
		Highest station assessed is positive
R1(un)		R1(is) carcinoma *in situ* at the bronchial margin
		R1(cy+) pleural lavage performed with malignant cytology
R1	Microscopic residual	Microscopically positive surgical margins but no visible tumor remaining[b]
		Extranodal extension of an involved hilar or mediastinal node[c]
		Malignant pleural or pericardial nodules or effusion[d]
R2	Gross residual	Gross (visible or palpable) tumor remaining[b]
		Lack of resection of involved nodes
RX	Unknown	Margin cannot be assessed

[a] recommended assessment is ≥6 node stations (including subcarinal and two other mediastinal stations);

[b] applies to any site of tumor resection (i.e. primary tumor, involved nodes, resected pleural implants, resected extrathoracic metastasis);

[c] applies when identified microscopically, regardless of how the nodes are resected (individually, in fragments, en-bloc packet of an entire node station) – provided there is no gross tumor remaining;

[d] this classification (R1) applies if a resection has been accomplished that meets criteria for R0 in a patient with a malignant pleural (or pericardial) effusion or resected nodules

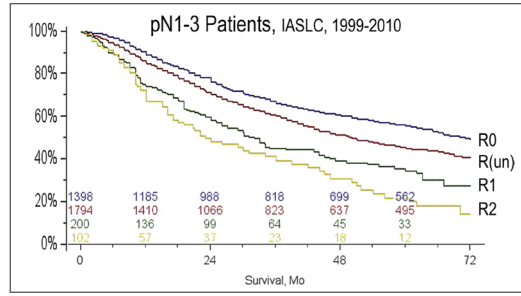


Figure 1. Prognostic impact of R-classification categories. Overall survival of patients by R-Classification. 3,494 patients, 1999-2010, IASLC 8th edition database.[2]

Site-Specific Explanatory Notes

General

When multiple R descriptors apply, the highest applicable R category is used. The R0(un) descriptors only apply if the resection otherwise meets criteria for an R0 resection.

The IASLC recommends using the R-classification after surgical resection; other measures of response are recommended after other treatment modalities. The IASLC recommends applying the R-classification to all sites involved in a resection (e.g. the primary tumor, intrathoracic lymph nodes, pleural nodules, or distant metastases). Specifically, if resection of oligometastatic distant metastases is undertaken (e.g. adrenal, brain metastases) the R-classification should be applied to describe the completeness of the procedure. In all cases, it is recommended that the site of resection is recorded, e.g. R0 (thorax) or R0 (adrenal).

The R-classification should apply to a specific surgical procedure and not count tumor at another site that is to be addressed at another time, and perhaps with another treatment modality. It is important to clearly communicate the completeness of the resection, even if it is only one part of the treatment plan. It is also critical to acknowledge that another site of the tumor remains to be addressed; this is essential for accurate recording in databases. Recording the site of resection, e.g. R0 (thorax), and the M1 category accomplishes this.

Specific Descriptors

R0(un) limited node assessment

The IASLC recommends that a full node evaluation should include ≥6 node stations, including at least the subcarinal station and two other mediastinal stations. Less than this is designated as a limited node assessment.

Both preoperative invasive node assessment and intraoperative assessment count. The surgeon should accurately identify nodes for the pathologist (e.g. station 10 and 11) and the pathologist should dissect and identify intraparenchymal node stations. Actual exploration of a node station that is documented as containing no nodes counts as an assessment of that node station. If the tissue submitted from a node station reveals no nodal tissue, or there is insufficient tissue (e.g. aspiration cytology) to allow a definitive diagnosis, it counts as an assessment of that station.

If a limited node assessment reveals no involved nodes, the tumor is classified as N0 by the IASLC, American Joint Committee on Cancer and Union for International Cancer Control; if no nodes at all are assessed it is classified as NX. The resection in both of these scenarios is classified as R0(un) (provided the resection meets other criteria for R0).

R0(un) highest station assessed is positive

This refers to the highest lymph node station assessed (not an individual highest node). The term 'highest' means most cephalad (i.e. lowest station number).

R1(is) carcinoma *in situ* at the bronchial margin

This refers specifically to carcinoma *in situ* at the bronchial margin (i.e. not an invasive cancer, which would be classified as R1).

R1(cy+) pleural lavage performed with malignant cytology

This applies only to a pleural lavage that is done in the absence of a pleural effusion. If no lavage was performed the R1(cy) descriptor does not apply. The technique of performing lavage has not been standardized.

R1 extranodal extension

Extranodal extension is defined as a finding on pathologic evaluation of hilar and mediastinal nodes. This applies (provided there is no gross tumor remaining) regardless of how the nodes were resected (as intact individual nodes, in fragments, or as a node packet involving an entire node station). Extranodal extension is not contingent on identification of a resection margin around the nodes (or whether there is extension to a resection margin). It does not apply to intraparenchymal nodes, which presumably are surrounded by a margin of the resected lung. The definition of extranodal extension includes a tumor that is directly extending beyond the node capsule into perinodal tissue, as well as discontinuous tumor deposits in lymphatics or perinodal fatty tissue. Perinodal isolated tumor cells do not count, but perinodal micrometastases do count toward this descriptor.

What is new for the 9th Edition?

Highest node assessment applies to a node station rather than an individual node. A complete node evaluation should involve ≥6 node stations rather than ≥6 individual nodes. All procedures done to assess nodes are counted together to determine this, including preoperative and intraoperative assessments; a documented actual exploration that demonstrates the absence of nodes in that station is counted as an assessment.

The uncertain descriptors of positive pleural lavage cytology or carcinoma *in situ* at a bronchial margin are more explicitly identified as R1(un) descriptors.

Extranodal extension is more clearly defined as a pathologic finding of hilar and mediastinal nodes, irrespective of whether nodes are removed in pieces or as an intact node station specimen, and regardless of whether the tumor is identified at a resection margin of resected hilar/mediastinal nodes.

The IASLC recommends using the R-classification for lung cancer only in the context of a surgical resection, and not consider expansion to describe response to nonsurgical treatment modalities.

References

1. Detterbeck FC, Ostrowski M, Hoffmann H, et al. The International Association for the Study of Lung Cancer lung cancer staging project: Proposals for revision of the classification of residual tumor after resection for the forthcoming ninth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2024; 19(7):1052-72. doi:10.1016/j.jtho.2024.03.021
2. Edwards JG, Chansky K, Van Schil P, et al. The IASLC lung cancer staging project: Analysis of resection margin status and proposals for residual tumor descriptors for non-small cell lung cancer. *J Thorac Oncol.* 2020;15(3):344-359. doi:10.1016/j.jtho.2019.10.019

8

Multiple Pulmonary Sites of Lung Cancer

Frank Detterbeck, MD

Patterns of Disease Leading to Multiple Pulmonary Sites of Lung Cancer

The first step in approaching a patient suspected of having multiple pulmonary sites of lung cancer is to exclude likely benign lesions, e.g. small nodules <6 mm are common and rarely malignant (~1%).[1,2] The next step is to establish which of four disease patterns is involved, namely synchronous primary lung cancer, separate tumor nodules, multifocal ground glass/lepidic (GG/L) adenocarcinoma, or pneumonic-type adenocarcinoma (Figure 1, Table 1).[3] These are distinguished because they exhibit different biological behaviors; hence different rules of TNM classification apply.

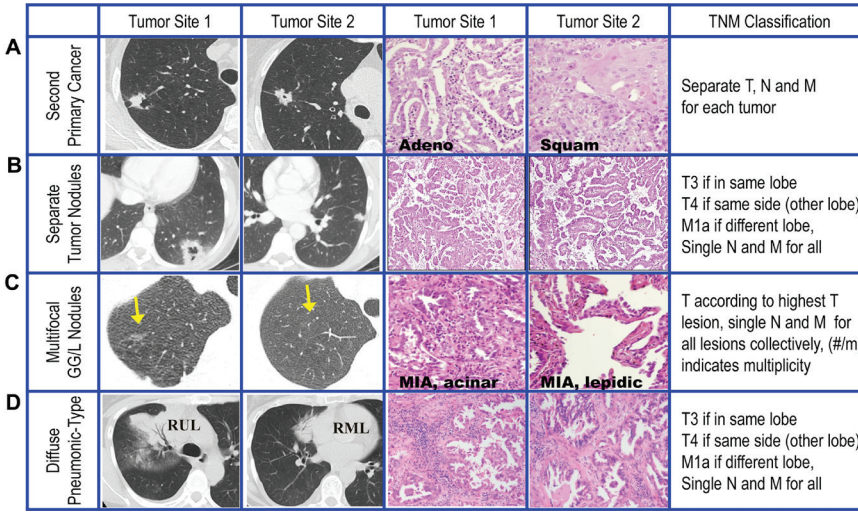


Figure 1. Representative examples of four patterns of disease which manifest multiple pulmonary sites of lung cancer. (A) Second primary cancers. A patient with two primary lung cancers in the RUL. CT images of each in the left two panels, corresponding microscopic images showing an adenocarcinoma and a squamous carcinoma in the next two panels. Note that most second primary cancers are of the same (not a different) histologic type. (B) Separate tumor nodules. A patient with a separate tumor nodule of the same histotype as the index tumor. The left panels show CT images of each lesion; the right panels show the corresponding microscopic images. (C) Multifocal GG/L lung cancer. A patient with

multifocal GG/L tumors in the right upper lobe (who had other GG/L tumors in other lobes). Arrows point to two GG/L tumors on CT in the left two panels; the next two panels show corresponding microscopic images (both were adenocarcinoma with a prominent lepidic component, although with different other adenocarcinoma subtypes). These tumors are classified together as GG/L tumors regardless of such secondary differences. (D) Pneumonic-type of lung cancer. A patient with pneumonic-type of lung cancer (this patient also had focal sites of disease in the RLL). The left panels show CT images of the RUL and RML with the typical regional areas with a ground glass and consolidative appearance; the next panels show the corresponding microscopic images.

Adeno, adenocarcinoma; CT, computed tomography; GG/L tumors, tumors with prominent ground glass (imaging) or lepidic (histologic) features; MIA, minimally invasive adenocarcinoma; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; Squam, squamous cell carcinoma.

Table 1. Schematic Summary of Patterns of Disease and TNM Classification in Patients With Lung Cancer With Multiple Pulmonary Sites of Involvement

	Second Primary Lung Cancer	Separate Tumor Nodule	Multifocal GG/L Nodules	Pneumonic-Type of Adenocarcinoma
Imaging Features	Two or more distinct tumors with imaging characteristic of lung cancer (e.g. spiculated)	Typical lung cancer (e.g. 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 morphology by comprehensive histologic assessment	Adenocarcinomas with prominent lepidic component (typically varying degrees of AIS, MIA, LPA)	Same histology 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 ipsi- or contralateral lobes; single N and M
Conceptual View	Unrelated tumors	Single tumor, with intrapulmonary metastasis	Field cancerization leading to development of separate tumors	Single tumor, diffuse pulmonary involvement

AIS, adenocarcinoma *in situ*; GG/L, ground glass/lepidic; LPA, lepidic predominant adenocarcinoma; MIA, minimally invasive adenocarcinoma

Formal clinical and pathologic criteria to distinguish the four disease patterns have been defined (included in Union for International Cancer Control [UICC] and American Joint Committee on Cancer [AJCC] TNM classification books and not repeated here).[3] Briefly, synchronous primary cancers have the appearance of traditional lung cancers (i.e. solid, spiculated). The histologic type is more often the

same (i.e. two adenocarcinomas or two squamous carcinomas) but they are judged to be second primary cancers either on clinical grounds or by a more detailed histologic analysis.[4] Separate tumor nodules are also solid. Typically, there is one dominant lesion; the separate nodules are histologically identical. Multifocal GG/L adenocarcinoma is typically readily identifiable by imaging – multiple GG lesions with varying degrees of a solid component. A detailed histological assessment of each lesion is unnecessary. The biological behavior is generally indolent with a distinctly low propensity for nodal and distant metastases. Pneumonic adenocarcinoma also has a typical radiographic appearance; histologically these are often mucinous adenocarcinomas.

Distinguishing synchronous primary cancers and separate tumor nodules can sometimes be difficult. Synchronous primary cancers are often the same histologic type and may exhibit mutational similarities; a definitive assessment generally requires a resection specimen. However, a multidisciplinary assessment using all available information (imaging characteristics, kinetics of progression, histologic features) generally yields a reliable distinction. Furthermore, when separate tumor nodules are treated with resection, patient survival is similar to that of synchronous primary cancers treated surgically.[4,5]

Application of Tumor, Node, Metastasis (TNM)

- *Synchronous and metachronous primary lung cancers.* Regardless of tumor location, a separate TNM is defined for each tumor.[4]
- *Separate tumor nodules of the same histopathologic type (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 of the primary tumor; T4, if located in a different ipsilateral lobe; M1a, if located in the contralateral lung. A single N category and the appropriate M category depending on the number of extrathoracic metastases applies collectively to all the tumor nodules.[5]
- *Multifocal pulmonary adenocarcinoma with GG/L features.* Regardless of the location of the tumors, T is determined by the highest T lesion with the number (#) or (m) for multiple in parentheses, and a single N and M applies collectively to all the tumors.[6]
- *Diffuse pneumonic-type lung adenocarcinoma*. A) Single focus of disease. The general TNM classification is applied, with the T category defined by tumor size. B) Multiple foci of disease. Tumor classification is based on the location of the involved areas (including miliary involvement): T3, if located in one lobe; T4, if located in other ipsilateral lobes; M1a, if the contralateral lung is involved, with the T category defined by the largest tumor. C) If tumor size is difficult to deter-

mine: T3 applies if confined to one lobe, T4 if there is evidence of involvement of another ipsilateral lobe, M1a if involvement of the contralateral lung. In all circumstances, the N category and the appropriate M category, depending on the number and location of metastases, applies collectively to all pulmonary sites.[6]

Additional Points

The recommendations apply to grossly identified tumors and to those identified at microscopic examination (a lung cancer specific recommendation).

The prognosis of T3, T4, and M1a separate tumor nodules is equivalent when adjusted for confounding by treatment received. Prognosis is equally good for patients with T3, T4, and M1a separate tumor nodules treated surgically, and equally limited when treated non-surgically.[5]

Specifically for lung cancer, the designation of separate tumor nodules applies to both grossly recognized nodules (e.g. by imaging) as well as when identified only microscopically.

Comparative molecular testing is playing an increasing role in determining if there is a clonal relationship between multiple nodules of lung cancer.

What is new for the 9th Edition?

No changes have been made to the 8th edition definitions and criteria for the four patterns of disease, or the application of TNM to these entities.

References

1. MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: From the Fleischner Society 2017. *Radiology.* 2017;284(1):228-243. doi:10.1148/radiol.2017161659
2. Kazerooni E, Aberle DR, Black WC, et al. "Lung-RADS® 2022" 2022; https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/Lung-RADS-2022.pdf. Accessed November 2023.
3. Detterbeck F, Nicholson F, Franklin W, et al. The IASLC lung cancer staging project: Summary of proposal 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(5):639-650. doi:10.1016/j.jtho.2016.01.024
4. Detterbeck F, 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(5):651-665. doi:10.1016/j.jtho.2016.01.025
5. Detterbeck F, Bolejack V, Arenberg D, 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(5):681-692. doi:10.1016/j.jtho.2015.12.114
6. Detterbeck F, Marom E, Arenberg D, 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 eight edition of the TNM classification. *J Thorac Oncol*. 2016;11(5):666-680. doi:10.1016/j.jtho.2015.12.113

9

Ground-Glass Opacities, Adenocarcinoma *In Situ*, and Minimally Invasive Adenocarcinoma

William D. Travis, MD

Classification of Ground Glass Nodules and Adenocarcinomas with Lepidic Patterns

The concept of using invasive rather than total size as the size T descriptor for nonmucinous lung adenocarcinomas with a part lepidic pattern was introduced for the first time in the 8th edition tumor, node, metastasis (TNM) classification.[1-4] While invasive size is the primary method of determining the size T descriptor for all lung cancers, the existence of a lepidic (noninvasive) pattern that can be distinguished from invasive patterns and demonstration of consistent correlations with patient outcomes according to invasive rather than total size is not as clearly established in histologic types other than nonmucinous lung adenocarcinomas.

Adenocarcinoma *in situ* (AIS) is a localized small (≤3 cm) adenocarcinoma with pure lepidic growth. No stromal, vascular, or visceral pleural invasion or spread through air spaces (STAS) are seen. Invasive patterns (papillary, acinar, micropapillary, or solid) are absent.[5] It is categorized as Tis (AIS).[2-4]

Minimally invasive adenocarcinoma (MIA) is defined as a small, solitary adenocarcinoma, (≤3 cm), with a predominantly lepidic pattern with a small ≤5 mm invasive component. Invasive components consist of tumor cells invading myofibroblastic stroma or histologic patterns other than lepidic including acinar, papillary, micropapillary, solid, colloid, fetal, or invasive mucinous adenocarcinoma. The diagnosis of MIA is excluded if there is vascular, lymphatic, or visceral pleural invasion, necrosis, or if STAS is present.[5] It is categorized as T1mi.[2-4]

Pathologically, if the invasive area is solitary and can be measured with a ruler either grossly or microscopically, this is the preferred approach. In cases which are difficult to measure, such as cases with multiple foci of invasion or if the invasive area is on more than one slide, another way to estimate the invasive size is to sum the percentages of the invasive components and multiply this by the overall

tumor diameter (i.e. a 3.0 cm tumor with 10% invasive component would have an estimated invasive size of 0.3 cm).[1,5]

Clinical T classification of ground-glass or part-solid nodules that are regarded to be lung cancers should follow the same framework of tumor size parameters as used for pathologic T classification of nonmucinous lung adenocarcinomas (AIS, MIA and part lepidic invasive adenocarcinomas).[1] For clinical tumor, node, metastasis (TNM) classification by computed tomography (CT), the single largest dimension should be recorded using contiguous thin (≤1.5 mm) sections and multiplanar reconstructions with lung windows.[1,6]

The CT findings of ground-glass versus solid nodules in nonmucinous lung adenocarcinomas tend to correspond respectively to lepidic versus invasive patterns seen pathologically (Figure 1).[1] However, this correlation is not absolute; so when CT features suggest nonmucinous AIS, MIA and LPA, the suspected diagnosis and clinical stage may be refined after pathologic evaluation of resected specimens. The correlation of ground-glass/solid patterns by CT with lepidic/invasive patterns by histology, respectively, is not as clear with mucinous AIS, MIA, or invasive mucinous adenocarcinomas. This is because in mucinous adenocarcinomas, part solid nodules are less common than the patterns of solid nodules or consolidation on CT. This correlation is also not well studied in the uncommon cases of combined adenocarcinomas and squamous cell carcinoma (adenosquamous carcinomas) or mixed invasive mucinous and nonmucinous adenocarcinomas.

For nonmucinous lung adenocarcinomas with a lepidic component that do not meet criteria for AIS or MIA the invasive size should be used for TNM classification.[1,5] For nonmucinous lung adenocarcinomas, the total tumor size in greatest dimension in addition to the invasive size should be reported both in CT and pathology reports. This principle is not applicable to other histologic types of lung cancer.

The CT images on HRCT can be suggestive of pathologic diagnoses, but they are not specific as ground-glass 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 ground glass on CT and lepidic pattern microscopically as well as solid on CT and invasive patterns histologically. A pathologic differential diagnosis is listed for each of the proposed possibilities on CT (Figure 1). Final pT classification of these tumors requires complete pathologic examination in resected specimens.

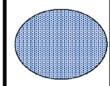
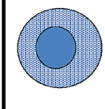
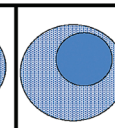
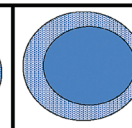
cT*	CT image on HRCT						
	Solid part	0 cm	0 cm	≤0.5 cm†	0.6-1.0 cm†	1.1-2.0 cm†	2.1-3.0 cm†
	Total tumor size including GG	≤0.5 cm	0.6-3.0 cm†‡	≤3.0 cm†‡	0..6-3.0 cm††	1.1-3.0 cm††	2.1-3.0 cm††
	Pathologic Differential Diagnosis	AAH‡, AIS, MIA	AIS, MIA, LPA	MIA, LPA, AIS	LPA, Invasive AD, MIA	LPA, Invasive AD	Invasive AD
	Clinical Stage*		cTis‡‡	cT1mi‡‡	cT1a	cT1b	cT1c
pT	Invasive part	0 cm	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 compnent	Invasive AD with a lepidic component or lepidic predominant AD	Invasive AD with lepidic component
	Pathologic Stage		pTis‡‡	pT1mi‡‡	pT1a	pT1b	pT1c

Figure 1. Clinical and pathologic T descriptor classification of small (≤3 cm) lung adenocarcinomas with a ground-glass and lepidic component by CT and pathology.*

AAH, atypical, adenomatous hyperplasia; AD, adenocarcinoma; AIS, adenocarcinoma *in situ*; CT, computer tomography; GG, ground glass; HRCT, high resolution CT; LPA, lepidic adenocarcinoma; MIA, minimally invasive adenocarcinoma

* (See Footnotes to Figure 1 and following classification description on next page)

Tis (AIS)

cT: These lesions typically show pure ground-glass nodules (GGN) measuring ≤3 cm. However, pure GGN can also be MIA or invasive adenocarcinoma.[‡‡]

pT: These tumors show pure lepidic growth without invasion, measuring ≤3cm.[‡‡] If the pure GGN or lepidic predominant nodule measures >3.0 cm, it is classified as lepidic predominant adenocarcinoma and should be designated as T1a. The invasive size in both cTis and pTis for AIS is 0 cm.

T1mi

cT: MIA usually shows a ground glass predominant nodule ≤3 cm with a solid component that should appear ≤ 0.5 cm.[†,‡‡] Although some MIAs have a larger solid component on CT due to 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.[†,‡‡]

T1a

cT: Ground glass predominant nodules measuring ≤3.0 cm with a solid component measuring 0.6-1.0 cm.[†]

pT: When a lepidic predominant adenocarcinoma measuring ≤3.0 cm has an invasive component measuring 0.6-1.0 cm, it is classified as pT1a.[†]

T1b

cT: Ground-glass predominant nodules measuring ≤3.0 cm with a solid component measuring 1.1-2.0 cm.[†]

pT: When a lepidic predominant adenocarcinoma measuring ≤3.0 cm has an invasive component measuring 1.1-2.0 cm, it is classified as pT1b.[†]

T1c

cT: Ground-glass predominant nodules measuring ≤3.0 cm with a solid component measuring 2.1-3.0 cm are classified as T1c.

pT: When an invasive adenocarcinoma with a lepidic component measuring ≤3.0 cm has an invasive component measuring 2.1-3.0 cm, it is classified as T1c.[†]

Footnotes:

*** The ground glass versus solid components seen on CT, generally correspond to lepidic versus invasive components, respectively, on pathologic examination of a resected specimen. cT category applying rule number four of the TNM classification (when in doubt, opt for the lesser category)**

[†] In cases where there are multiple foci of solid or invasive components, see text for estimation of invasive size.

[‡] Size is not the only distinguishing feature between AAH and AIS.

[‡‡] If a pure GGN by CT or pure lepidic adenocarcinoma by pathology (therefore with an invasive size of 0 cm) is >3 cm in total size, it should be classified as T1a. Similarly, if a ground glass 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, it should be classified as cT1a or pT1a, respectively.

[††] If the total tumor size is >3.0 cm, depending on the invasive size, these categories can be classified as T1a, T1b, or T1c.

References

1. Travis WD, Asamura H, Bankier AA, 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;11:1204-23. doi:10.1016/j.jtho.2016.03.025
2. Rami-Porta R. IASLC Staging Manual in Thoracic Oncology. 2nd ed. North Fort Meyers: Editorial Rx Press; 2016.
3. Brierley JD, Gospodarowicz M, Wittekind C. Lung, Pleural and Thymic Tumors. In: O'Sullivan B, Mason M, Asamura H, et al., eds. UICC TNM Classification of Malignant Tumors. 8th ed. Oxford: Wiley Blackwell; 2017:105-17.
4. Rami-Porta R, Asamura H, Travis WD, et al. Lung. In: Amin MB, ed. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017:431-56.
5. WHO Classification of Tumours Editorial Board. WHO Classification of Tumours: Thoracic Tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2021.
6. Bankier AA, MacMahon H, Goo JM, et al. Recommendations for measuring pulmonary nodules at CT: A statement from the Fleischner Society. *Radiology*. 2017;285:584-600. doi:10.1148/radiol.2017162894

10

Bronchopulmonary Neuroendocrine Neoplasms

Ming Sound Tsao, MD, and Andrew Nicholson, DM

Tumor, Node, Metastasis (TNM) Classification for bronchopulmonary neuroendocrine neoplasms (NENs)

The 5th edition of the World Health Organization (WHO) Classification of Thoracic Tumours defined NEN as including the precursor lesion diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH), neuroendocrine tumors (NETs), and neuroendocrine carcinomas (NECs).[1] NETs show less aggressive biology and include typical carcinoid (TC) and atypical carcinoid (AC), as defined by mitotic count cut-off and the presence or absence of necrosis.[2] In contrast, NECs are subclassified into large cell neuroendocrine carcinomas (LCNEC) and small cell carcinoma (SCLC) based on their cell size and cytoplasmic/nuclear features. Combined SCLC are SCLC with mixed non-small cell lung cancer (NSCLC) or LCNEC components.[2]

The 9th edition TNM classification and stage group should be applied to all NENs (TCs, AC, LCNECs, SCLCs and combined SCLC cases). Stratification by TNM stage should be used in clinical trials involving stage I-III SCLC patients.[1,3-7] Compared to the prior Veteran Administration Lung Study Group system that categorized SCLC into "limited" and "extensive" groups, the TNM system demonstrated a better prognostic discrimination for SCLC patients.[8]

Multiple carcinoids with a background of DIPNECH should be regarded as independent primaries[2]. DIPNECH is considered a pre-invasive lesion and is not currently classified by stage.[2]

References

1. Nicholson AG, Tsao MS, Beasley MB, et al. The 2021 WHO Classification of Lung Tumors: Impact of advances since 2015. *J Thorac Oncol*. 2022;17(3):362-387. doi:10.1016/j.jtho.2021.11.003
2. WHO Classification of Tumours Editorial Board. Thoracic tumours. WHO Classification of Tumours series, 5th ed. Lyon: International Agency for Research on Cancer; 2021:127-149

3. Nicholson AG, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer lung cancer staging project: Proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2016;11(3):300-11. doi:10.1016/j.jtho.2015.10.008
4. Shepherd FA, Crowley J, Van Houtte P, et al. The International Association for the Study of Lung Cancer lung cancer staging project: Proposals regarding the clinical staging of small cell lung cancer in the forthcoming seventh edition of the tumor, node, metastasis classification for lung cancer. *J Thorac Oncol*. 2007;2(12):1067-77. doi:10.1097/JTO.0b013e31815bdc0d
5. Travis WD, Giroux DJ, Chansky K, et al. The IASLC lung cancer staging project: Proposals for the inclusion of broncho-pulmonary carcinoid tumors in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2008;3(11):1213-23. doi:10.1097/JTO.0b013e31818b06e3
6. Vallieres E, Shepherd FA, Crowley J, et al. The IASLC lung cancer staging project: Proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2009;4(9):1049-59. doi:10.1097/JTO.0b013e3181b27799
7. Yoon JY, Sigel K, Martin J, et al. Evaluation of the prognostic significance of TNM staging guidelines in lung carcinoid tumors. *J Thorac Oncol*. 2019;14(2):184-192. doi:10.1016/j.jtho.2018.10.166
8. Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer—what limits limited disease? *Lung Cancer*. 2002;37(3):271-6. doi:10.1016/s0169-5002(02)00072-7

11

Lymph Node Map

Shun-ichi Watanabe, MD

Table 1. IASLC Nodal Definitions

Nodal station	Description	Definition
#1 (Left/Right)	Low cervical, supraclavicular and sternal notch nodes	Upper border: Lower margin of cricoid cartilage Lower border: Clavicles bilaterally and, in the midline, the upper border of the manubrium **#L1 and #R1 limited by the midline of the trachea.**
#2 (Left/Right)	Upper paratracheal nodes	**2R:** Upper border: Apex of 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 **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 **As for #4, in #2 the oncologic midline is along the left lateral border of the trachea.**
#3	Pre-vascular and retrotracheal nodes	**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

continued on next page

Nodal station	Description	Definition
#4 (Left/Right)	Lower paratracheal nodes	**4R:** Includes right paratracheal nodes, and pretracheal nodes extending to the left lateral border of trachea Upper border: Intersection of caudal margin of innominate vein with the trachea Lower border: Lower border of 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
#5	Subaortic (aorto-pulmonary window)	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)	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
#7	Subcarinal nodes	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
#8 (Left/Right)	Para-esophageal nodes (below carina)	Nodes lying adjacent to the wall of the esophagus and to the right or 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 (Left/Right)	Pulmonary ligament nodes	Nodes lying within the pulmonary ligament Upper border: The inferior pulmonary vein Lower border: The diaphragm
#10 (Left/Right)	Hilar nodes	Includes nodes immediately adjacent to the main-stem 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 on the right; upper rim of the pulmonary artery on the left Lower border: Interlobar region bilaterally

continued on next page

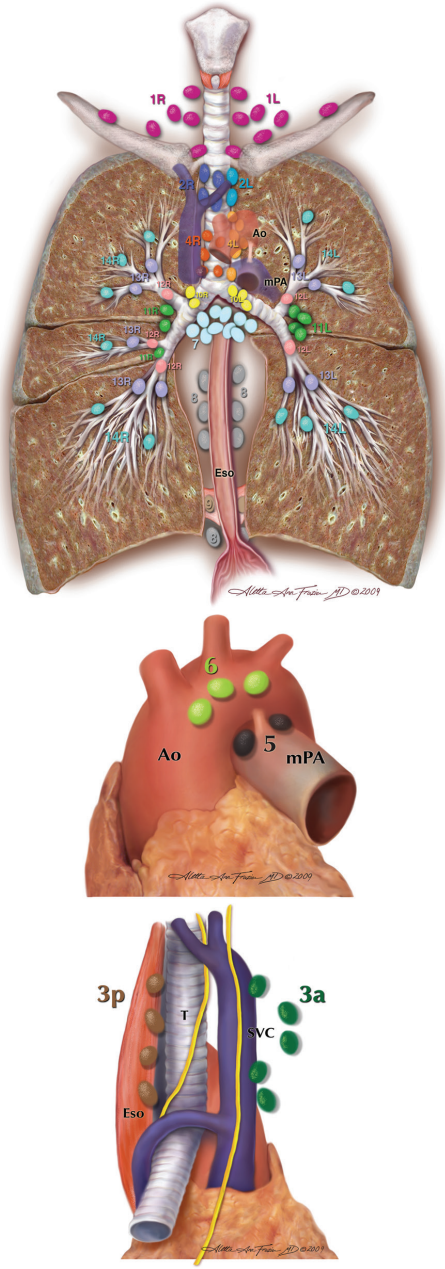
Nodal station	Description	Definition
#11	Interlobar nodes	Between the origin of the lobar bronchi ***#11s:** Between the upper lobe bronchus and bronchus intermedius on the right ***#11i:** Between the middle and lower lobe bronchi on the right *optional sub-categories
#12	Lobar nodes	Adjacent to the lobar bronchi
#13	Segmental nodes	Adjacent to the segmental bronchi
#14	Sub-segmental nodes	Adjacent to the subsegmental bronchi

Explanatory Notes

The IASLC lymph node classification continues to be the recommended means of describing regional lymph node involvement for lung cancer (Table 1).[1] This IASLC nodal chart has been adopted since 2009 as the international chart for the documentation of nodal stations at clinical or pathologic staging where detailed assessment of nodes has been made, usually by invasive techniques or at surgery. The concept of nodal zones was introduced in the 7th edition of the tumor, node, metastasis (TNM) classification of lung cancer as a simpler system for clinical staging.[1]

The IASLC nodal chart has clear anatomic landmarks to define each nodal station. However, on using this map, some controversial areas have been identified that pose problems at the time of labeling the correct nodal station. These controversial areas are: the right paratracheal and hilar lymph nodes, the left inferior paratracheal and aortopulmonary lymph nodes, the subcarinal lymph nodes, and the right hilar lymph nodes.

In the third phase of the IASLC Staging Project, leading to the 9th edition of the TNM classification of lung cancer, the nodal chart remains unchanged but realistic drawings and intraoperative pictures have been added to clarify the anatomic location of the lymph nodes and to reduce interobserver variability and stage migration (Figures 1 and 2). The four intraoperative views on the right paratracheal and hilar lymph nodes, the left inferior paratracheal and aortopulmonary lymph nodes, the subcarinal lymph nodes, and the right hilar lymph nodes are meant to better explain the location of the different nodal stations (Figures 3-6).



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

SUPERIOR MEDIASTINAL NODES

Upper zone
- 2R Upper Paratracheal (right)
- 2L Upper Paratracheal (left)
- 3a Prevascular
- 3p Retrotracheal
- 4R Lower Paratracheal (right)
- 4L Lower Paratracheal (left)

AORTIC NODES

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

INFERIOR MEDIASTINAL NODES

Subcarinal zone
- 7 Subcarinal

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

N1 NODES

Hilar/Interlobar zone
- 10 Hilar
- 11 Interlobar

Peripheral zone
- 12 Lobar
- 13 Segmental
- 14 Subsegmental

Figure 1. IASLC nodal chart with stations and zones.

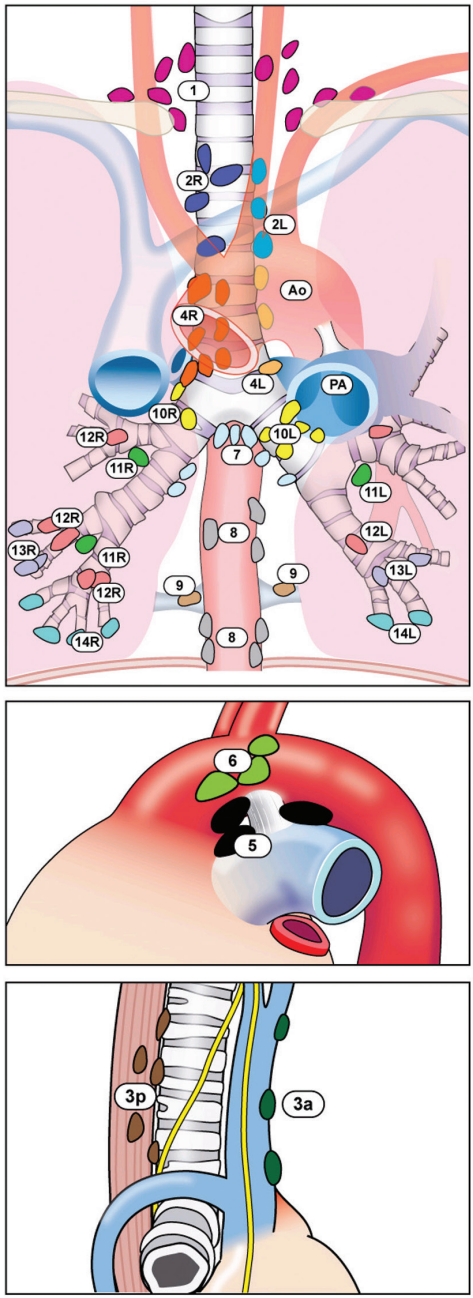


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Figure 2. IASLC nodal chart with stations and zones.

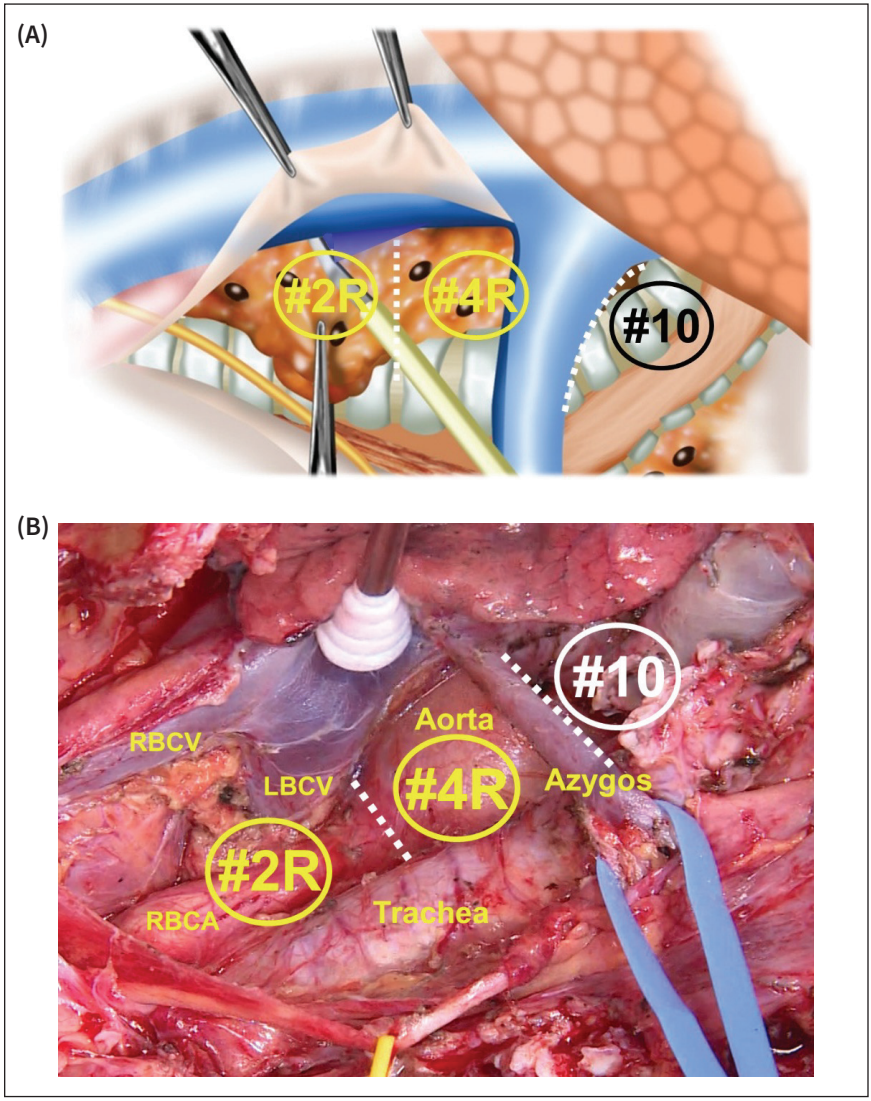


Figure 3. **Intraoperative view of right superior mediastinal and hilar nodes by (A) schematic representation and (B) photo. The drawing and the intraoperative photograph show the anatomic structures that separate three nodal stations. The point where the inferior border of the left brachiocephalic vein crosses the anterior aspect of the trachea separates the right superior paratracheal lymph nodes (#2R) from the right inferior paratracheal lymph nodes (#4R); and the inferior border of the azygos vein separates the right inferior paratracheal lymph nodes (#4R) from the right hilar lymph nodes (#10R).**

LBCV, left brachiocephalic vein; RBCA, right brachiocephalic artery; RBCV, right brachiocephalic vein.

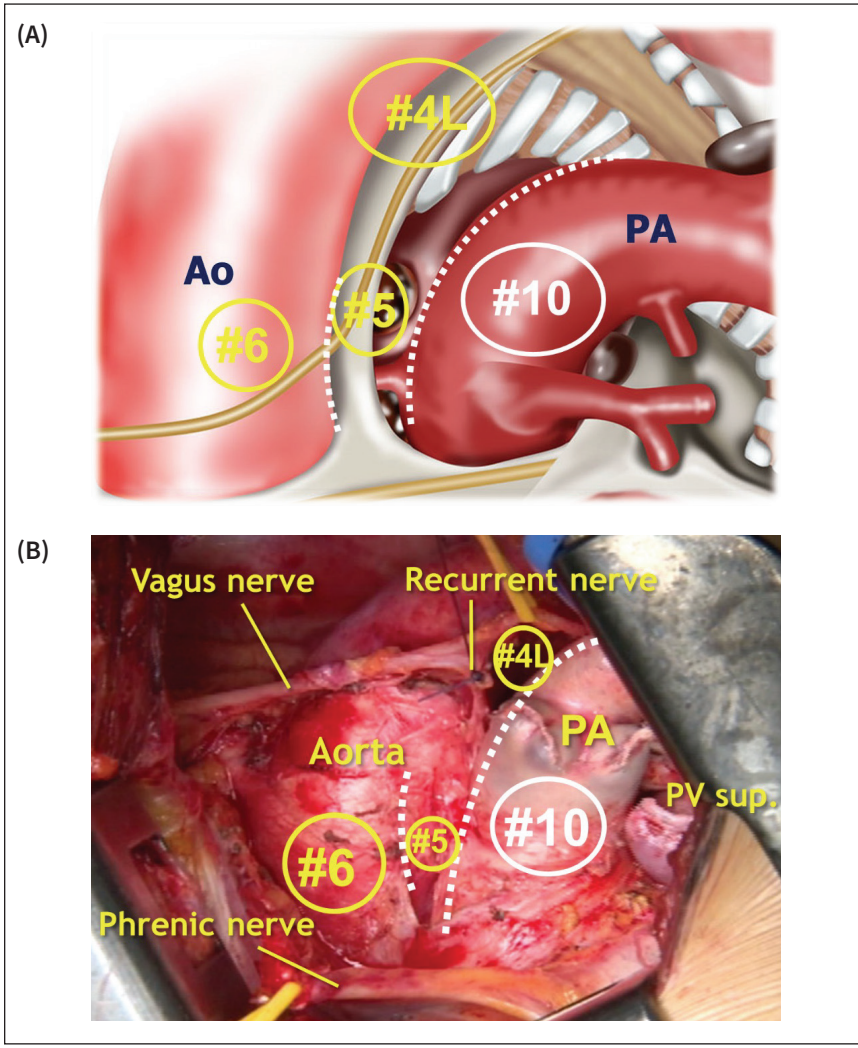


Figure 4. **Intraoperative view of left superior mediastinal, aortopulmonary, and hilar nodes by (A) schematic representation and (B) photo. The drawing and the intraoperative photograph show the limits of four left-sided nodal stations. It is important to note that the borders of the aortic arch and of the pulmonary artery are not straight but curved. This fact is not always considered when identifying the location of the lymph nodes on computed tomography. The drawing and the photograph highlight this anatomic detail. Subaortic (aorto-pulmonary) lymph nodes (#5) are located lateral to the ligamentum arteriosum between the lower border of the aortic arch and the upper rim of the pulmonary artery. The left inferior paratracheal lymph nodes (#4L) are located medial to the ligamentum arteriosum and in the irregular triangular space formed by the lower margin of the aortic arch, the upper rim of the pulmonary artery and the left wall of the distal trachea. Lymph nodes caudal to the upper rim of the pulmonary artery and extending to the interlobar region are the left hilar lymph nodes (#10L). The para-aortic (phrenic nerve) lymph nodes (#6) are located anteriorly and laterally to the ascending aorta between the upper and lower borders of the aortic arch.**

Ao, aorta; PA, pulmonary artery; PV, pulmonary vein

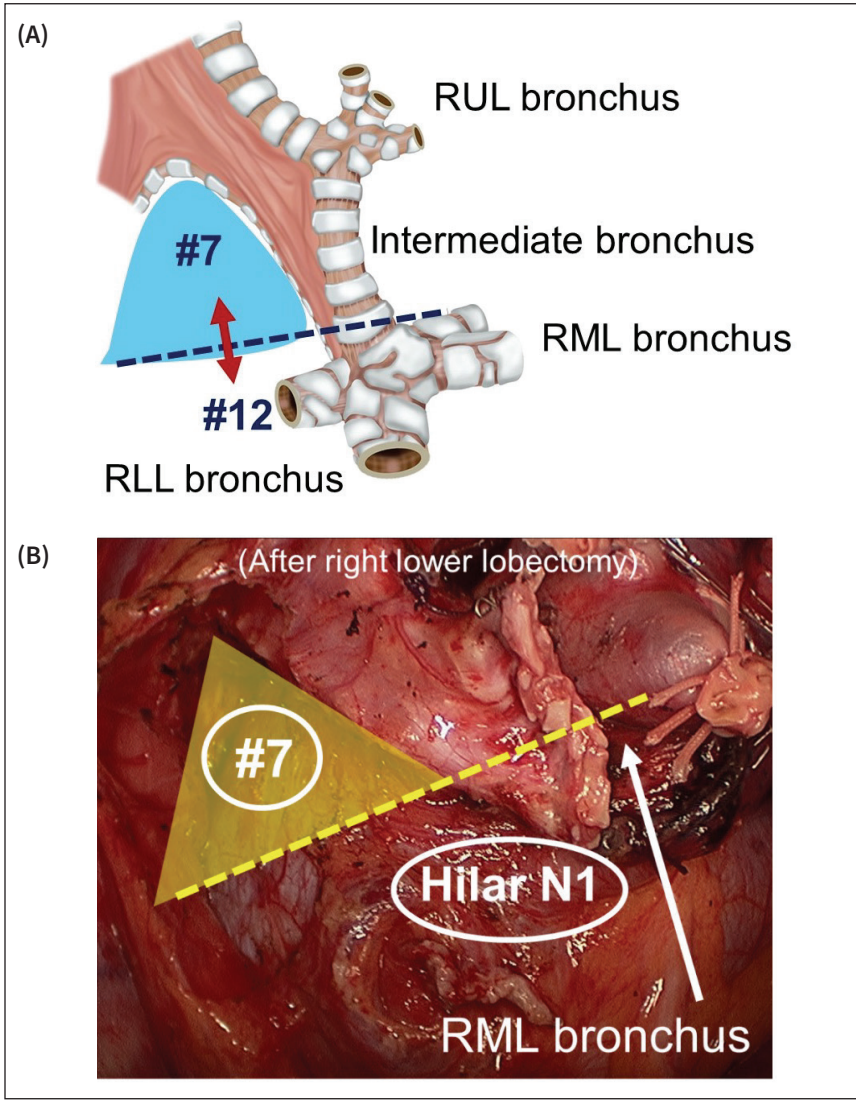


Figure 5. **Intraoperative view of right subcarinal area by (A) schematic representation and (B) photo after right lower lobectomy. The subcarinal nodal station is an irregular pyramid limited cranially by the carina, caudally by the lower border of the bronchus intermedius on the right and the upper border of the lower bronchus on the left, anteriorly by the right pulmonary artery and the pericardium, laterally by the bronchi are hilar, and those associated with the esophagus are para-esophageal.**

RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe

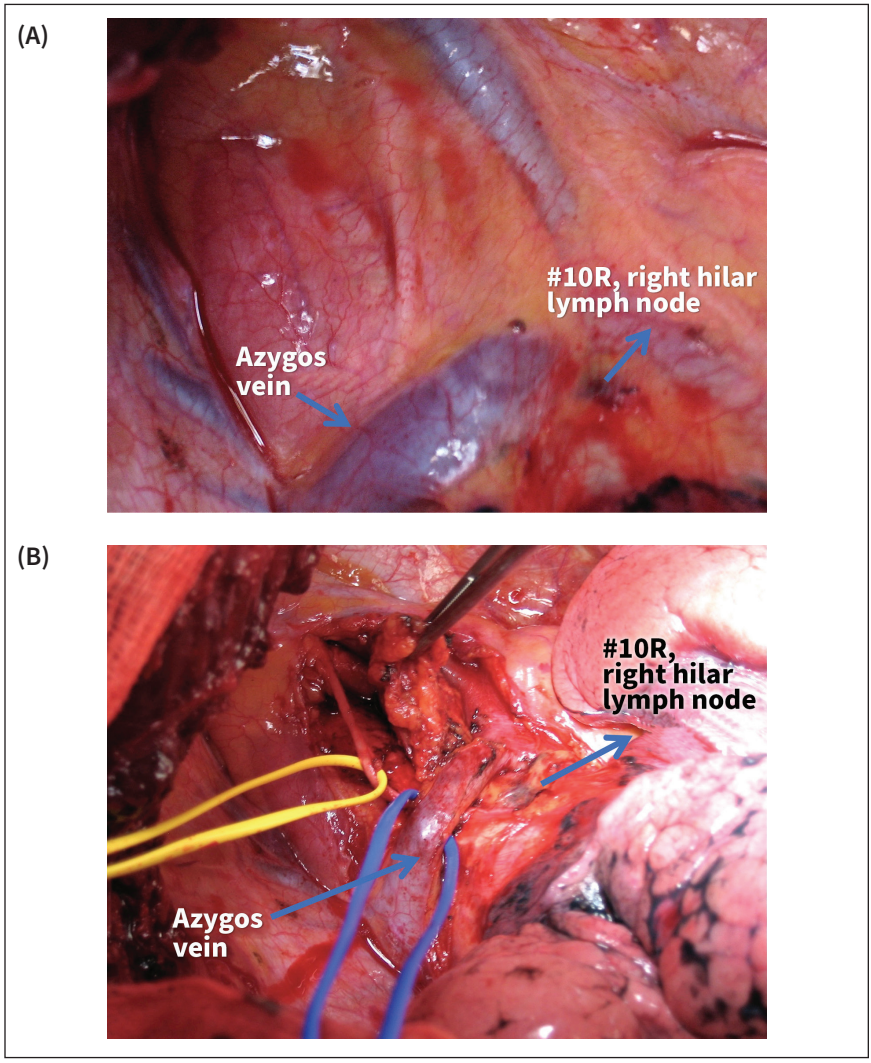


Figure 6. **Intraoperative view of a right hilar lymph node. (A) Right hilar lymph node before opening of the mediastinal pleura. The intraoperative photograph shows the right upper mediastinum. The dark structure caudal to the lower rim of the azygos vein is a right hilar lymph node (#10R). However, from the anatomic point of view, it is located in the mediastinum. (B) Right hilar lymph node after opening of the mediastinal pleura. This intraoperative photograph shows that to reach the lymph node that is caudal to the lower rim of the azygos vein it is necessary to open the mediastinal pleural. This means that this node, called right hilar lymph node (#10R) in the IASLC lymph node chart, is anatomically located in the mediastinum.**

Reference

1. Rusch VW, Asamura H, Watanabe H, et al. 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(5):568-577. doi:10.1097/JTO.0b013e3181a0d82e

12

Histologic Descriptors

William D. Travis, MD

The histologic descriptors of lymphatic and blood vessel invasion as well as perineural invasion are established prognostic markers in cancer, including lung cancer.[1,2] Spread through air spaces (STAS) is a new histologic descriptor specific for lung cancer. These histologic tumor characteristics are not incorporated into pT categories or stage groups and they are not able to be identified in a clinical (non-resection) setting.[3] Nevertheless, the prognostic implications make it important to note their presence.

Lymphatic, Vascular, and Lymphovascular Invasion Classifications

While the vascular (V) classification in general refers only to venous invasion according to the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC),[4] specifically in lung cancer, the V classification applies to arterial as well as venous invasion.[1,2]

Lymphatic (L) (Table 1) and V (Table 2) invasion can be reported separately or combined into a category of lymphovascular invasion (LVI) (Table 3), depending on the local custom.[5] If V and/or L invasion is identified in a lung cancer specimen, it can be classified as either V1, L1, or as LVI-1 in a combined category. Invasion into the wall of a blood vessel can be diagnosed even if the tumor is not present in the vascular lumen.[2] The use of elastic stains to assess vascular invasion is optional (Figure 1).

Table 1. L- Lymphatic Invasion

LX	Lymphatic invasion cannot be assessed
L0	No lymphatic invasion
L1	Lymphatic invasion present

Table 2. V - Vascular Invasion (Includes Invasion of Veins and/or Arteries or Arterioles)

VX	Vascular invasion cannot be assessed
V0	No vascular invasion
V1	Vascular invasion present
Vascular invasion (V1) includes either microscopic and/or macroscopic vascular invasion.	

Table 3. LVI - Lymphovascular Invasion (Lymphatic and/or Vascular Invasion)

LVI-X	Lymphovascular invasion cannot be assessed
LVI-0	Lymphovascular invasion not present
LVI-1	Lymphovascular (lymphatic and/or vascular invasion) invasion present
Vascular invasion in the LVI classification includes either microscopic and/or macroscopic vascular invasion.	

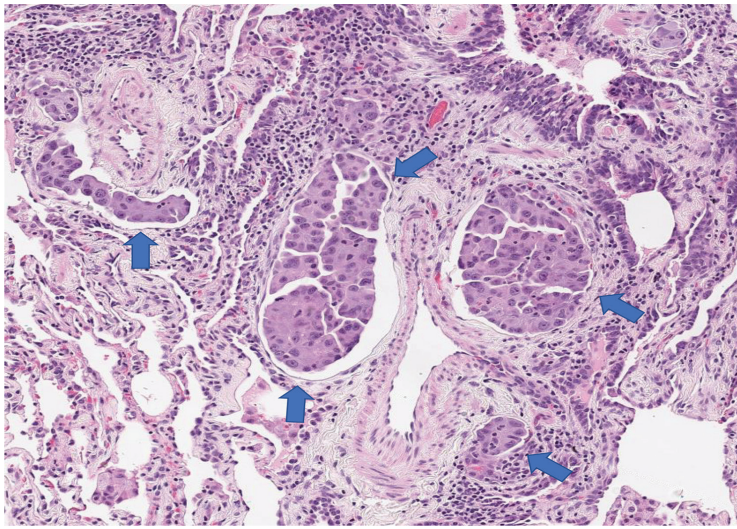


Figure 1. Lung adenocarcinoma with lymphatic invasion. The lymphatics (blue arrows) surrounding a bronchiole are filled with tumor cells of an adenocarcinoma.

Perineural Invasion

Perineural invasion can be recorded as Pn1 (Table 4). Perineural invasion is an uncommon finding in lung cancer. There are few studies in lung cancer that report conflicting data regarding the prognostic significance of this finding.[6-8]

Table 4. Pn – Perineural Invasion

PnX	Perineural invasion cannot be assessed
Pn0	No perineural invasion
Pn1	Perineural invasion present

Spread Through Air Spaces

The presence of STAS is associated with lower overall and recurrence-free survival in lung cancer and is recommended as a new histologic descriptor (Table 5).[3,9] STAS is defined as the presence of tumor cells within the first alveolar spaces in the lung parenchyma beyond the edge of the main tumor. At least two STAS clusters should be present.[9] In order to diagnose STAS, it is important to exclude artifacts by the following criteria: 1) Mechanically induced tumor floaters that are randomly situated often at the edge of the tissue section or out of the plane of section; 2) Jagged edges of tumor cell clusters suggesting fragmentation or edges of a knife cut during specimen processing; 3) Isolated tumor clusters at a distance from the tumor rather than spreading in a continuous manner from the tumor edge and 4) Linear strips of cells lifted off alveolar walls (Figure 2).[3, 10-12] Like LVI, STAS is not incorporated into T categories.

Table 5. STAS - Spread Through Air Spaces

STAS-X	STAS cannot be assessed
STAS-0	No STAS
STAS-1	STAS present

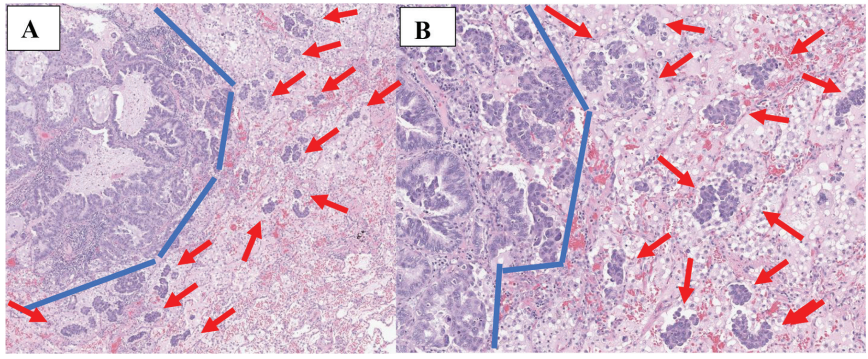


Figure 2. Lung adenocarcinoma with spread through air spaces. (A) Adenocarcinoma with acinar and micropapillary patterns showing many tumor cell clusters (red arrows) within airspaces beyond the edge of the tumor (highlighted by the blue line). (B) Higher power of the tumor clusters (red arrows) within alveolar spaces beyond the edge of the tumor (highlighted by the blue line) show a micropapillary pattern similar to areas within the tumor.

Histologic Grading

Histologic grading of lung cancers is a way to indicate the aggressiveness of the tumor.[2] The general system involves four grades: well differentiated (grade 1), moderately differentiated (grade 2), poorly differentiated (grade 3) and undifferentiated (grade 4) .[2, 11] However, it is acceptable to combine grade 3 and grade 4 into a single poorly differentiated grade 3 category. In general, grade is determined by a

combination of histologic and cytologic features, including similarity to the tissue of origin, pattern or architecture of the tumor cell growth, pleomorphism, mitoses and necrosis.[2] Although similarities exist among different organ systems, grade is defined specific to the histologic type and site of origin (i.e. lung cancer).

For nonmucinous lung adenocarcinoma, the IASLC grading system is recommended.[11, 13]

Grade	Histologic Patterns
1	Lepidic predominant with no or <20% high grade patterns
2	Acinar or papillary predominant with no or <20% high grade patterns
3	Any tumor with ≥20% high grade patterns (solid, micropapillary, cribriform, or complex glandular patterns)

There is no established grading system for squamous cell carcinoma.

For neuroendocrine neoplasms, the following grades are recognized: typical carcinoid (grade 1), atypical carcinoid (grade 2), and small cell carcinoma and large cell neuroendocrine carcinoma (grade 3).[11]

Some lung cancers are categorized as grade 3 by definition, such as large cell carcinoma, pleomorphic carcinoma, carcinosarcoma, pulmonary blastoma, NUT carcinoma and thoracic SMARCA4-deficient undifferentiated tumor.[11]

References

1. Wittekind C, Compton CC, Brierley J, et al. Additional descriptors. In: UICC TNM Supplement, A Commentary on Uniform Use. 4th ed. Oxford: Wiley Blackwell; 2012:18-22 and 77.
2. Wittekind C, Brierley JD, Lee A, et al. TNM Supplement; A Commentary on Uniform Use: 5th Edition. 5th ed. Oxford: Wiley Blackwell; 2019.
3. Travis WD, Eisele M, Nishimura KK, et al. The International Association for the Study of Lung Cancer (IASLC) staging project for lung cancer: Recommendation to introduce spread through air spaces as a histologic descriptor in the ninth edition of the TNM classification of lung cancer. Analysis of 4061 pathologic stage I NSCLC. *J Thorac Oncol*. 2024; 19(7):1028-1051. doi:10.1016/j.jtho.2024.03.015
4. Brierley JD, Gospodarowicz M, Wittekind C. UICC TNM Classification of Malignant Tumors. 8th ed. Oxford: Wiley Blackwell; 2017.
5. Gress DM, Edge SB, Greene FL, et al. Histologic and Specimen Descriptors. In: Amin MB, Edge, SB, Greene FL, eds. AJCC Cancer Staging Manual, 8th ed. New York: Springer; 2017:28-9.
6. Sayar A, Turna A, Solak O, et al. Nonanatomic prognostic factors in resected nonsmall cell lung carcinoma: The importance of perineural invasion as a new prognostic marker. *Ann Thorac Surg.* 2004;77:421-5. doi:10.1016/S0003-4975(03)01645-X
7. Kilicgun A, Turna A, Sayar A, et al. Very important histopathological factors in patients with resected non-small cell lung cancer: Necrosis and perineural invasion. *Thorac Cardiovasc Surg.* 2010;58:93-7. doi:10.1055/s-0029-1186240
8. Yilmaz A, Duyar SS, Cakir E, et al. Clinical impact of visceral pleural, lymphovascular and perineural invasion in completely resected non-small cell lung cancer. *Eur J Cardiothorac Surg.* 2011;40:664-70. doi:10.1016/j.ejcts.2010.12.059

9. Aly RG, Rekhtman N, Li X, et al. Spread through air spaces (STAS) is prognostic in atypical carcinoid, large cell neuroendocrine carcinoma, and small cell carcinoma of the lung. *J Thorac Oncol.* 2019;14:1583-93. doi:10.1016/j.jtho.2019.05.009
10. Kadota K, Nitadori J, Sima CS, et al. Tumor spread through air spaces is an important pattern of invasion and impacts the frequency and location of recurrences after limited resection for small stage I lung adenocarcinomas. *J Thorac Oncol.* 2015;10:806-14. doi:10.1097/JTO.0000000000000486
11. WHO Classification of Tumours Editorial Board. WHO Classification of Tumours: Thoracic Tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2021.
12. Travis WD, Brambilla E, Burke AP, et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. 4th ed. Lyon: International Agency for Research on Cancer; 2015.
13. Moreira AL, Ocampo PSS, Xia Y, et al. A grading system for invasive pulmonary adenocarcinoma: A proposal from the International Association for the Study of Lung Cancer Pathology Committee. *J Thorac Oncol.* 2020;15:1599-610. doi:10.1016/j.jtho.2020.06.001

13

Molecular Database

Fred R. Hirsch, MD, PhD, Ray U. Osarogiagbon, MD, and
David P. Carbone, MD, PhD

The emerging discovery of biologically distinct subsets of non small-cell lung cancer (NSCLC) indicates the need to study whether including molecular biomarkers will add value to the current the strictly anatomy-based tumor, node, metastasis (TNM) staging system within the context of biomarker delineation of prognosis. For this reason, the IASLC's Staging and Prognostic Factors Committee accumulated biomarker data concurrently with the conventional variables for developing the 9th edition of the NSCLC staging system. The structure of the IASLC Molecular Database has been previously published.[1] The purpose of establishing an international molecular database in conjunction with the international staging system is to correlate the TNM classification with molecular features to determine how a future classification might include key molecular features, and whether such a hybrid approach would provide a practical and more clinically meaningful classification. The necessary analysis has not been performed at this point; therefore molecular features are not included in the 9th edition of the Union for International Cancer Control/American Joint Committee on Cancer/IASLC staging. One of the key goals for the 10th edition will be to include robustly validated recommendations for incorporating prognostic molecular associations with the lung cancer staging system. We will use the 9th edition molecular database to formulate ideas on how to achieve this complex task, given geographic, racial, and ethnic differences in the molecular features of lung cancer, and wide global variation in the capture of such data.

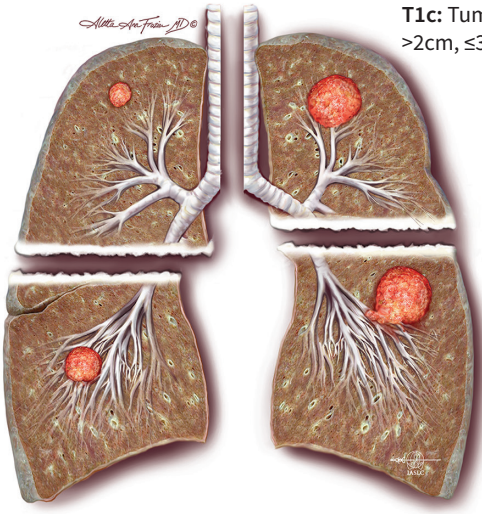
Reference

1. Osarogiagbon RU, Rami-Porta R, Tsao MS, et al. International Association for the Study of Lung Cancer molecular database project: Objectives, challenges and opportunities. *J Thorac Oncol.* 2021;16(6):897-901. doi:10.1016/j.jtho.2021.03.003

14

Atlas of Lung Cancer Tumor, Node, Metastasis (TNM) Classification

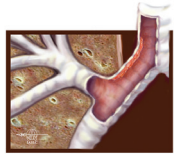
T1a, T1b T1c



T1a: Tumor ≤1cm

T1b: Tumor >1cm, ≤2cm

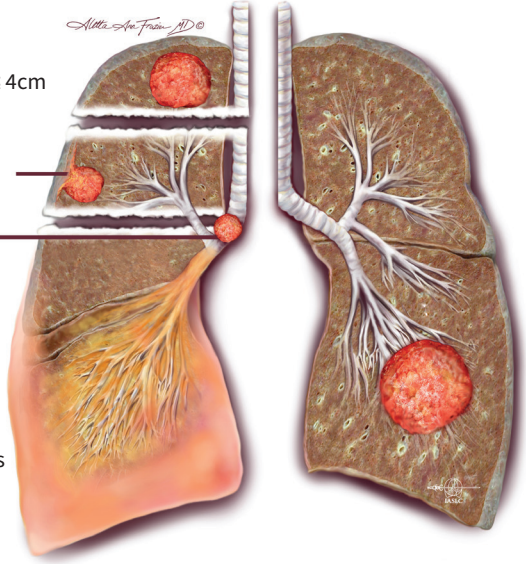
T1c: Tumor >2cm, ≤3cm



Superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is T1

Tumor ≤3cm; without endobronchial extension proximal to the lobar bronchus

T2a T2b



Tumor > 3cm, ≤ 4cm

Tumor ≤ 4cm, invasion of the visceral pleura

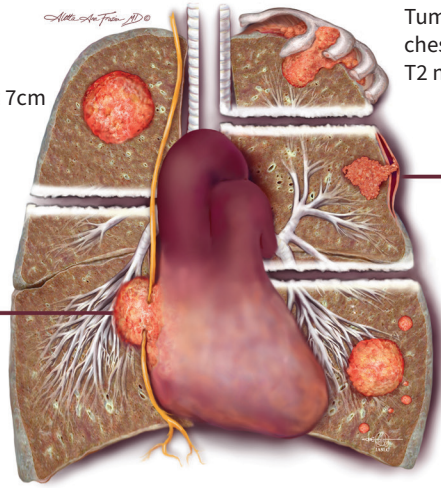
Tumor involves main bronchus, regardless of distance from carina but without carinal involvement

Associated atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the entire lung

Tumor > 4cm, ≤ 5cm (with or without other T2 descriptors)

Note: if the tumor is associated with atelectasis or pneumonitis, it is T2a if lesion ≤ 4cm or if tumor size cannot be measured; it is T2b if lesion > 4cm, ≤ 5cm.

T3

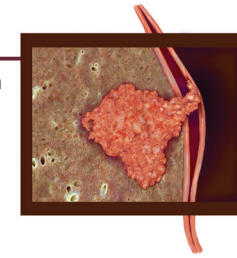


Tumor
> 5cm, ≤ 7cm

Tumor invades parietal pleura or chest wall or invades thoracic T1, T2 nerve roots, or stellate ganglion

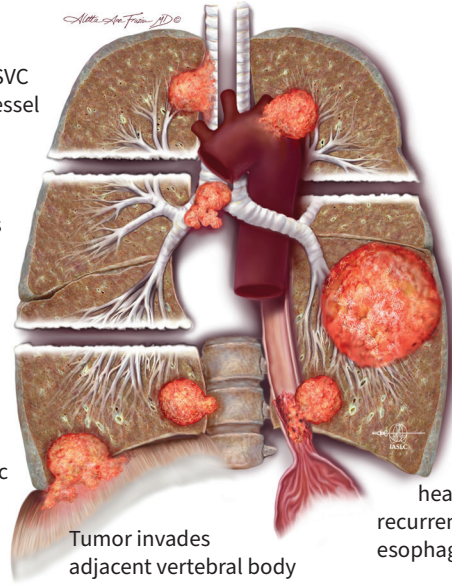
Invasion of the azygos vein, phrenic nerve, or pericardium

Invasion of parietal pleura



Separate tumor nodule(s) in the lobe of the primary

T4



Tumor invades trachea and/or SVC or other great vessel

Tumor involves carina

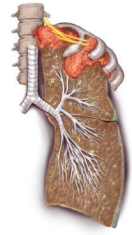
Tumor > 7cm

Diaphragmatic invasion

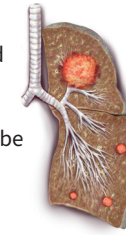
Tumour invades mediastinum, thymus, heart, vagus nerve, recurrent laryngeal nerve, esophagus or diaphragm

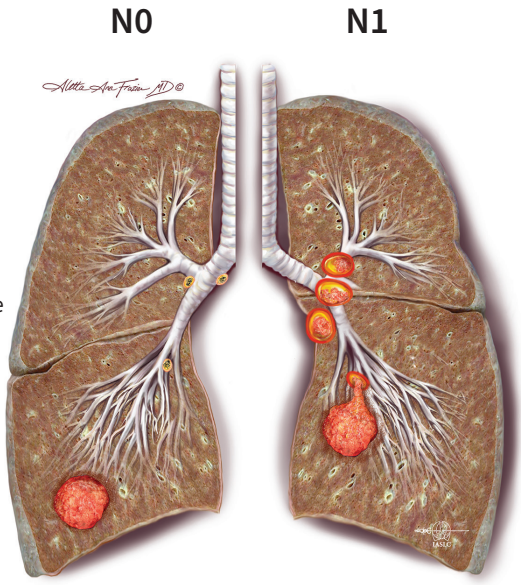
Tumor invades adjacent vertebral body

Tumor that invades subclavian vessels, vertebral body, lamina, spinal canal, cervical nerve roots, or brachial plexus

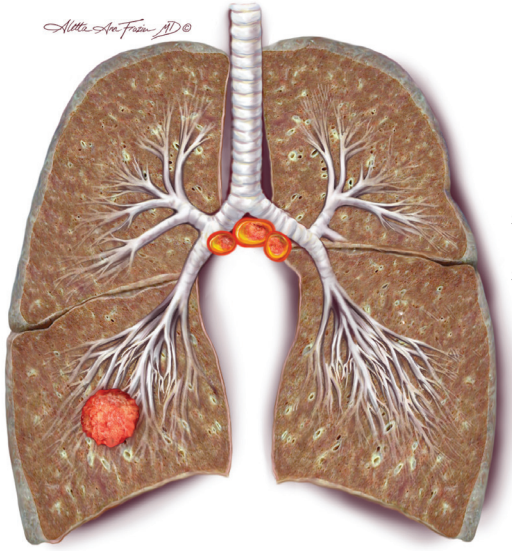


Tumor accompanied by ipsilateral, separate tumor nodules, different lobe



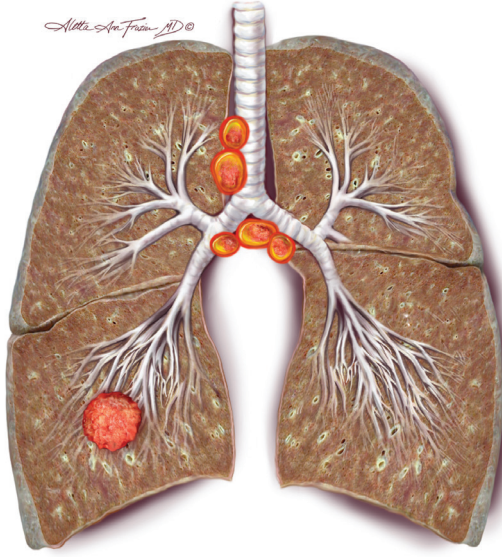


N2a



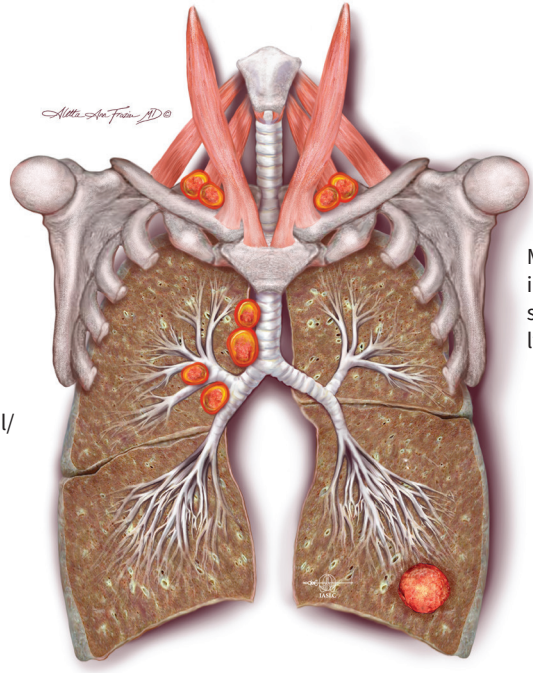
Metastasis to single ipsilateral mediastinal or subcarinal lymph node station

N2b



Metastasis to multiple ipsilateral mediastinal and/or subcarinal lymph node stations

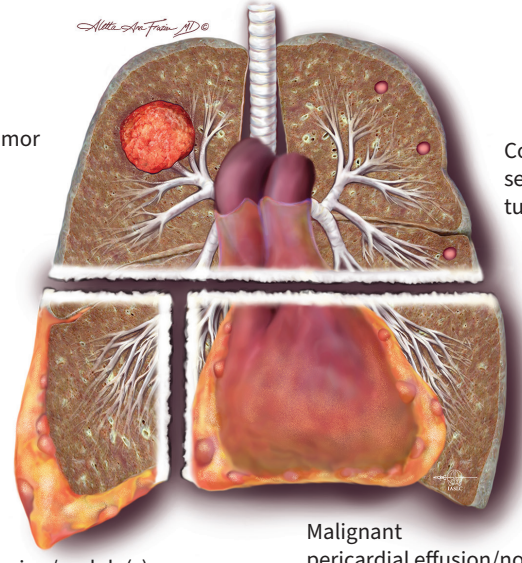
N3



Metastasis in ipsilateral scalene/ supraclavicular lymph node(s)

Metastasis in contralateral hilar/mediastinal/ scalene/ supraclavicular lymph node(s)

M1a



Primary tumor

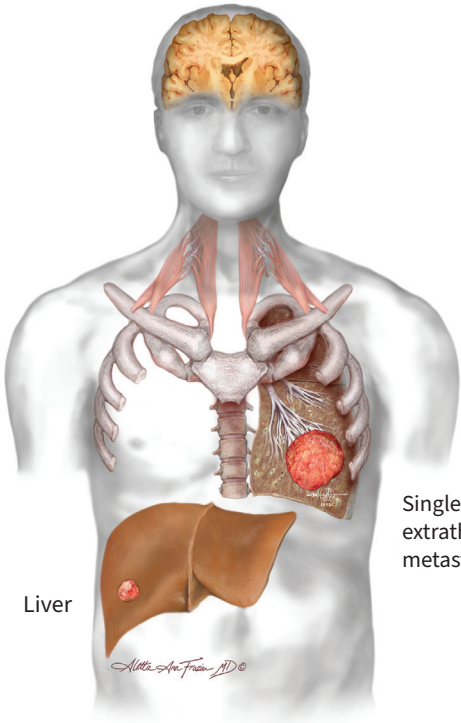
Contralateral, separate tumor nodule(s)

Malignant pleural effusion/nodule(s)

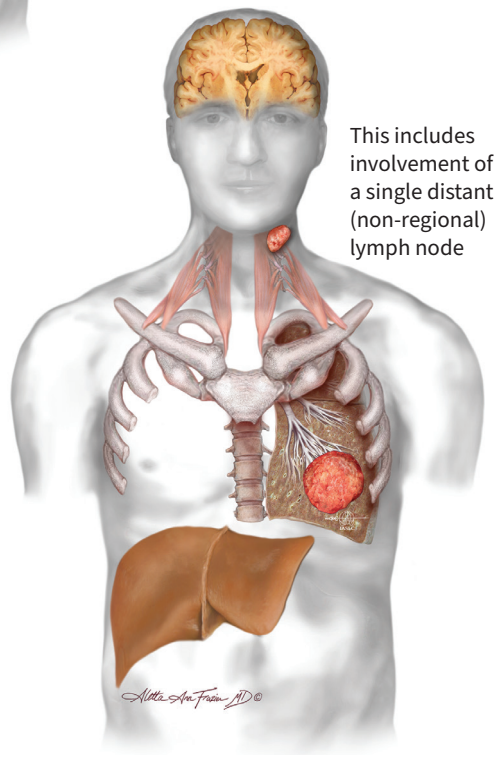
Malignant pericardial effusion/nodule(s)

Note: when the pleural (pericardial) effusions are negative after multiple microscopic examinations, and the fluid is non-bloody and not an exudate, they should be excluded as a staging descriptor.

M1b

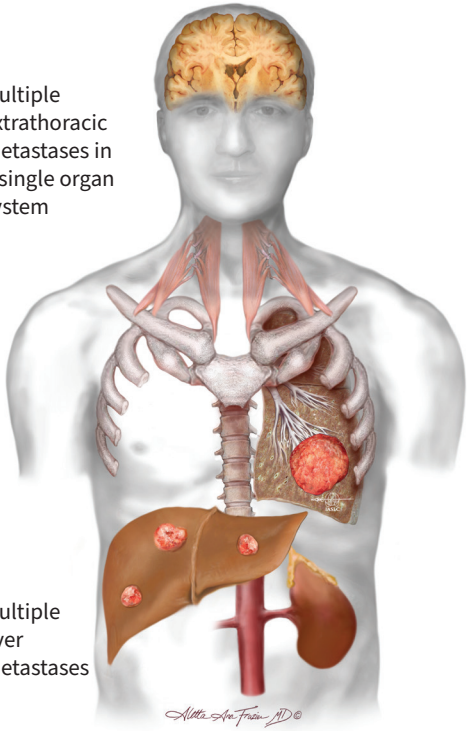


M1b



M1c1

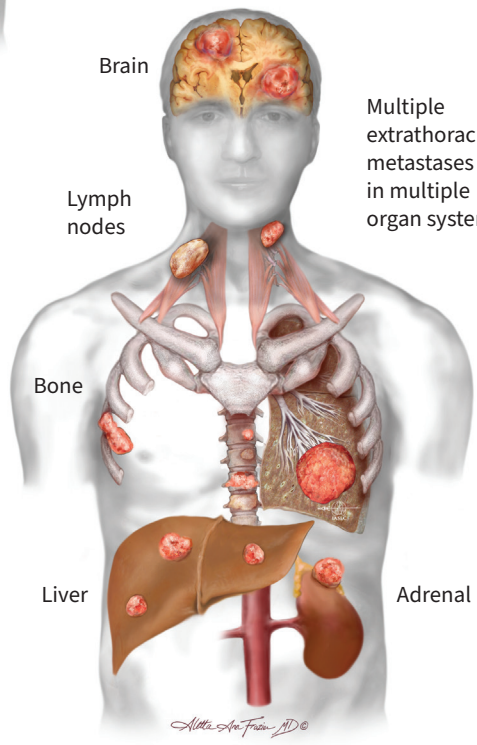
Multiple extrathoracic metastases in a single organ system



An organ system denotes all sites of an organ that is distributed in the body (e.g. the skeletal system, skin, extrathoracic lymphatic system) or of a paired organ (e.g. adrenal, kidney)

Multiple liver metastases

M1c2



PART II

THYMIC EPITHELIAL TUMORS

15

Introduction

Enrico Ruffini, MD

The first tumor, node, metastasis (TNM)-based classification of thymic epithelial tumors (TETs) recognized by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) was proposed by the International Thymic Malignancies Interest Group (ITMIG) and the IASLC Staging and Prognostic Factors Committee (SPFC) – Thymic Domain (TD) in 2014 and became effective in 2017 (2018 in the United States) as part of the 8th edition TNM UICC/AJCC classification of malignant tumors.[1] The TNM classification replaced the Masaoka-Koga stage system which was used by most Institutions since 1994 with minor refinements. A survey from the IASLC SPFC-TD concluded that the TNM classification for thymic tumors was well-received and was deemed useful by the majority of the responders.[2] However, some unresolved issues emerged which were worth considering for revision.

A newly formed IASLC SPFC-TD was constituted in 2017 to provide recommendations for the 9th revision of the TNM, expected to become effective in 2024.

The present section of the *IASLC Staging Manual* summarizes the recommendations for the T, N, and M components and the stage groups for the 9th edition of TNM classification of thymic epithelial tumors. A brief description of the collaborative thymic database which was used for the analysis is also provided. A chapter about the ITMIG/IASLC nodal map and its re-assessment for the 9th TNM has been included, which might be of practical interest to the users in a clinical setting.

Explanatory Notes

Thymic epithelial tumors

ICD code: ICD-0-3 C37.9

Application of the present TNM classification. The present TNM classification applies to all epithelial thymic tumors, including thymomas, thymic carcinomas, and neuroendocrine tumors of the thymus. Sarcomas, lymphomas and other rare nonepithelial tumors are excluded. The 2021 World Health Organization (WHO)

Classification of Tumors of the Thymus and Mediastinum should be used for the histologic types.[3]

Regional lymph nodes. The regional lymph nodes are classified according to the ITMIG/IASLC Lymph Node Map for Thymic Epithelial Tumors[4] into 1) Anterior region (N1): prevascular mediastinal and anterior cervical lymph nodes; 2) Deep region (N2): visceral mediastinal and deep cervical lymph nodes. All lymph nodes within these regions are categorized in the N component.

All lymph nodes outside these regions are considered non-regional lymph nodes and should be classified as distant metastases (M1b category).

Clinical TNM classification. The clinical TNM is determined by the imaging assessment based on chest computed tomography scan with intravenous contrast, and magnetic resonance imaging or positron emission tomography (PET), when applicable. Enlarged lymph nodes (>1 cm in short axis dimension) or FDG avid nodes on PET scan should be considered as nodal metastases for the clinical assessment. Pre-treatment histologic examination of the mass is indicated when imaging is unclear, in case of induction therapy before surgical resection, or when nonsurgical therapy is indicated in advanced stages.

Pathologic TNM classification. Pathologic TNM is defined after surgical resection. For pathologic classification, invasion of the T and N structures should be microscopically confirmed.

T component. The T component is classified based on the level of involvement from level 1 (T1) to level 4 (T4). The T category is assigned to the highest level of invasion irrespective of the invasion of any lower level. The T category remains the same whether there is involvement of one or more structure of that level. Direct extension of the tumor to the pleura or pericardium are included in the T component and should be distinguished from pleural or pericardial metastases which are best classified in the M component.

N component. Direct extension of the primary tumor into lymph nodes is classified as lymph node metastasis. The extent of lymph node dissection is determined by the clinical stage at presentation and by the histologic type if available (thymomas versus thymic carcinomas/neuroendocrine thymic tumor) and should follow ITMIG recommendations.[5]

Handling of the surgical specimen. Policies and procedures for the surgeons and pathologists regarding the handling of the surgical specimen after resection of thymic tumors should be followed according to the ITMIG's recommendations.[5] Among others, the following policies should be followed: 1) An immediate intra-operative marking of the specimen for any area of surgical concern; 2) A correct orientation of the specimen also with the aid of a "mediastinal board"; and 3) A reporting by the surgeon of any margin ≤3 mm.

References

1. Detterbeck FC, Stratton K, Giroux D, et al. The IASLC/ITMIG thymic epithelial tumors staging project: Proposal for an evidence-based stage classification system for the forthcoming eighth edition of the TNM classification of malignant tumors.. *J Thorac Oncol*. 2014;9: S65–S72. doi:10.1097/JTO.0000000000000290
2. Ruffini E, Fang W, Guerrera F, et al. The International Association for the Study of Lung Cancer thymic tumors staging project: The impact of the eighth edition of the Union for International Cancer Control and American Joint Committee on Cancer TNM Stage Classification of Thymic Tumors. *J Thorac Oncol*. 2020; 15(3):436-447. doi:10.1016/j.jtho.2019.11.013
3. Marx A, Chan JKC, Calabrese L, et al. The 2021 WHO Classification of Tumors of the Thymus and Mediastinum: What is new in thymic epithelial, germ cell, and mesenchymal tumors? *J Thorac Oncol.* 2022;17(2):200-213. doi: 10.1016/j.jtho.2021.10.010
4. Marom E, Fang W, Ruffini E, et al. The International Association for the Study of Lung Cancer thymic epithelial tumor staging project: A re-assessment of the International Thymic Malignancy Interest Group/International Association for the Study of Lung Cancer lymph node map for thymic epithelial tumors for the forthcoming ninth edition of the TNM classification of malignant tumors. *J Thorac Oncol.* 2023;18(12):1672-1688. doi: 10.1016/j.jtho.2023.09.001
5. Detterbeck F, Moran C, Huang J. Which way is up? Policies and procedures for surgeons and pathologists regarding resection specimens of thymic malignancy. *J Thorac Oncol.* 2011;6(7 Suppl 3):S1730-1738. doi: 10.1097/JTO.0b013e31821ea567

16

Overview of the Database

Enrico Ruffini, MD, and Andreas Rimner, MD

For the 9th edition of the tumor, node, metastasis (TNM) classification of thymic epithelial tumors (TETs), the IASLC Thymic Domain of the Staging and Prognostic Factors Committee collated a central database of patients with TETs, including thymoma, thymic epithelial tumors, and neuroendocrine thymic tumors, managed by the Cancer Research And Biostatistics (CRAB) organization.[1]

Major thymic consortia and individual institutions across the world contributed. The data were submitted as batch data sets starting in 2019 with the final accrual up to December 2021.

The contributors of the collaborative thymic database for the 9th edition are listed in Table 1 along with the number of cases submitted.

Overall, 11,347 patients with a TET diagnosed between 1965 and 2021 were collected. Of these, after cleaning of the data and evaluation of the available information, 9,147 cases were used for the analysis. Figure 1 illustrates the dataflow after filtering and classification among the different histologic types.

Asia was the region providing most of the cases (n=5,628, 61.5%), followed by Europe (n=3,113, 34.0%). Most patients received surgical treatment (n=8,830, 96.5%). Information about the clinical Stage (cStage) was provided in 810 cases (8.9%), while information about pathologic Stage (pStage) was available in 5,233 cases (57.2%). Information about both pStage and cStage was available in 1,506 cases (16.5%).

Thymoma was the most frequent TET (n=7,662, 83.7%), followed by thymic carcinoma (n=1,345, 14.7%). Information on resection status was available in 8,768 patients (95.8%). A complete resection was achieved in 7,647 patients (84%).

As compared to the database that was used for the 8th edition, an increased number of cases available for analysis (n=9,147 versus 8,145), an increased number of nonsurgical cases (n=251 versus 127), and a decreased number of patients with missing information on resection status (n=379 versus n=419) was observed.

The engagement and the dedication of people from different disciplines across the world constituting the thymic community needs to be recognized and acknowledged.

What is new for the 9th Edition?

1. The database used for the 9th edition included prospective and updated retrospective data. Prospective data has the theoretical advantage to provide more granular information on crucial elements for the staging. Updated retrospective data has the advantage to provide longer follow-up, which is important due to the usually slow-growing behavior of TETs.
2. All major thymic consortia across the world contributed to the data collection, resulting in a broader range of data sources as compared to the 8th edition of TNM classification.

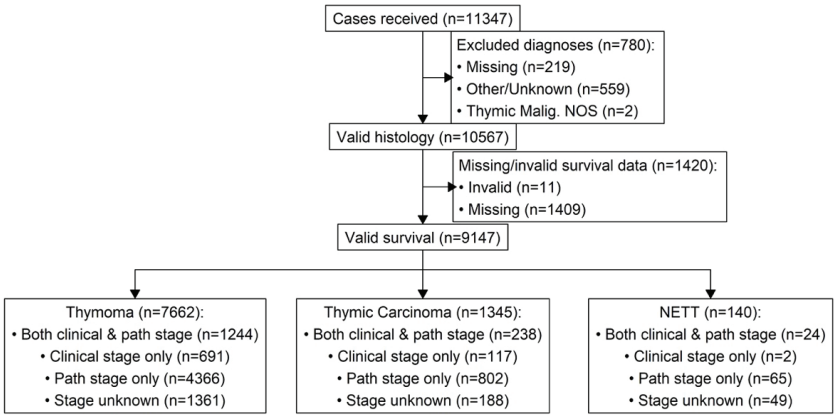


Figure 1. Flowchart of the thymic database used for the 9th edition of TNM classification after filtering of non-usable data.

NETT, neuroendocrine thymic tumors; NOS, not otherwise specified

Table 1. Data Sources for the Thymic Database and Submitted Cases

Contributing Source	Cases Submitted	Cases Eligible for Analysis
JART	2,711 (24%)	2,659 (29%)
ESTS	2,305 (20%)	1,411 (15%)
KART	1,363 (12%)	1,357 (15%)
ChART (Retrospective)	1,532 (14%)	1,172 (13%)
ITMIG	1,233 (11%)	813 (9%)
RYTHMIC	395 (3%)	383 (4%)
ChART (Prospective)	625 (6%)	343 (4%)
MSKCC	322 (3%)	288 (3%)
Guy's, United Kingdom	285 (3%)	262 (3%)
Turkey-Ankara	197 (2%)	166 (2%)
Australia-Sydney	114 (1%)	97 (1%)
Spanish Thymic Group	124 (1%)	86 (1%)
Italy-Rome	64 (1%)	63 (1%)
Turkey-Istanbul	77 (1%)	47 (1%)
Total	11,347	9,147

* Note: Cases of thymoma, thymic carcinoma, and neuroendocrine tumors of the thymus with valid survival data were eligible for analysis.

ChART, Chinese Alliance for Research in Thymoma; ESTS, European Society of Thoracic Surgeons; ITMIG, International Thymic Malignancy Interest Group; JART, Japanese Association for Research in the Thymus; KART, Korean Association for Research in the Thymus; MSKCC, Memorial Sloan Kettering Cancer Center; RYTHMIC, Réseau Tumeurs THYMiques et Cancer

References

1. Rimner A, Ruffini E, Cilento V, et al. The International Association for the Study of Lung Cancer thymic epithelial tumors staging project: An overview of the central database informing revision of the forthcoming ninth edition of the TNM classification of malignant tumors. *J Thorac Oncol.* 2023;18(10):1386-1398. doi:10.1016/j.jtho.2023.07.008

17

Tumor (T) Component

Mirella Marino, MD, and Meinoshin Okumura, MD, PhD

Table 1. Tumor (T) Categories for the 9th Edition of the TNM Classification of Thymic Epithelial Tumors

T category	Descriptor*
T1	A tumor that is limited to the thymus with or without encapsulation, directly invades into the mediastinal fat only or directly invades the mediastinal pleura but does not involve any other mediastinal structure. T1 is subdivided into 1. T1a (5 cm or less in its greatest dimension) 2. T1b (larger than 5 cm in its greatest dimension) irrespective of mediastinal pleura (MP) invasion. *Level 1 structures—thymus, anterior mediastinal fat, mediastinal pleura*
T2	Tumor directly invades the pericardium (either partial or full-thickness), or the lung or the phrenic nerve. *Level 2 structures—pericardium, lung, phrenic nerve*
T3	Tumor directly invades any of the following: 1) Brachiocephalic vein, 2) Superior vena cava, 3) Chest wall or 4) Extrapericardial pulmonary arteries or veins. *Level 3 structures—brachiocephalic vein, SVC, chest wall, hilar pulmonary vessels*
T4	Tumor directly invades any of the following: 1) Aorta (ascending, arch, or descending), 2) Arch vessels, 3) Intrapericardial pulmonary artery or veins, 4) Myocardium, 5) Trachea, or 6) Esophagus. *Level 4 structures—aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery or veins, myocardium, trachea, esophagus*

*T categories are defined by "levels" of invasion; they reflect the highest degree of invasion regardless of how many other (lower level) structures are invaded.

Explanatory Notes

1. **T1 category:** a) *Tumor size*: In the T1 category, the T size cut point of ≤ 5 cm (T1a) and > 5 cm (T1b) was established as relevant to outcome both in a training set and a validation set for thymoma and thymic carcinoma (TC). The optimal T size cut point identified was examined in multiple different subsets using overall

survival (OS) or freedom from recurrence (FFR) with respect to clinical tumor size (c-Tsize) and pathologic tumor size (p-Tsize) measurement in thymomas and TC. Tumor size did not remain significant as independent factor after validation analysis for T2/T3/T4 categories. b) ***Mediastinal pleura (MP)***: Considering the difficulty in recognizing and reporting invasion of the MP both by imaging and by pathologic diagnosis, MP was dropped from the TNM classification (Table 1). However, MP was retained as "additional histologic descriptor" to be recorded when available.

2. **T2 category:** Thymoma with involvement of the phrenic nerve or lung had longer FFR as compared to T3 categories involving other organs. In R0 patients with TC, FFR and cumulative incidence of recurrence (CIR) with T3N0M0 tumors due to involvement of the lung or phrenic nerve were similar to that of T2N0M0 R0 cases. Therefore, T3-lung and T3-phrenic nerve were downstaged to T2. The pericardium is the other structure included in the T2 category.
3. **T3 category:** After exclusion of phrenic nerve and lung, the T3 category remained unchanged in the 9th edition.
4. **T4 category:** The T4 category remained unchanged in the 9th edition.

What is new for the 9th Edition?

1. The T1 category is subclassified into T1a (≤ 5 cm) and T1b (> 5 cm). Mediastinal pleura invasion is dropped from the TNM classification and should be listed as "additional histologic descriptor".[1]
2. Lung and phrenic nerve involvement are downstaged from T3 to T2.[1]

Figure 1 shows overall survival of patients by pathologic T categories of thymomas, thymic carcinomas and neuroendocrine thymic tumors. Figure 2 shows the cumulative incidence of recurrence of tumors by pathologic T categories for the three tumor types.

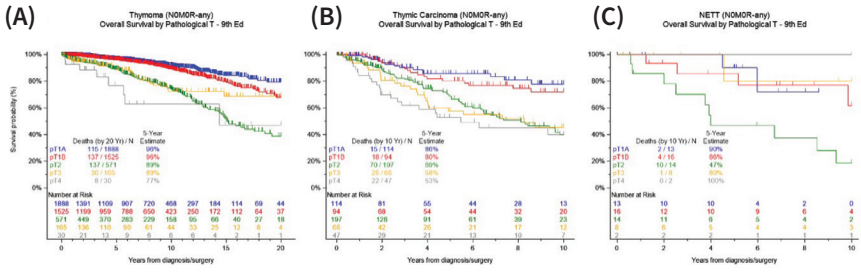


Figure 1. Overall survival of patients by pathologic T category (9th edition) in N0M0R-any for thymoma (A), thymic carcinoma (B), and neuroendocrine thymic tumors (C).

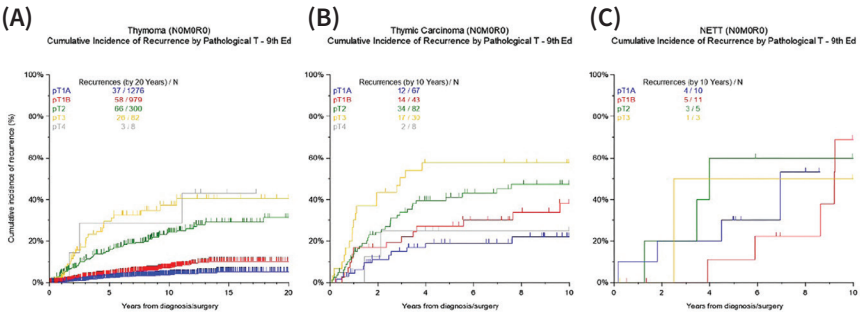


Figure 2. **Cumulative incidence of recurrence of tumors by pathologic T category (9th edition) in N0M0R0 cases for thymoma (A), thymic carcinoma (B), and neuroendocrine thymic tumors (C).**

References

1. Okumura M, Marino M, Cilento V, et al. The International Association for the Study of Lung Cancer thymic epithelial tumor staging project: Proposal for the T component for the forthcoming ninth edition of the TNM classification of malignant tumors. *J Thorac Oncol.* 2023;18(12):1638-1654. doi:10.1016/j.jtho.2023.08.024

18

Node (N) Component

Wentao Fang, MD

Table 1. **N Categories for the 9th Edition of the TNM Classification of Thymic Epithelial Tumors**

N category	Descriptor*
N0	No nodal involvement
N1	Anterior (perithymic) nodes
N2	Deep intrathoracic or cervical nodes

* Involvement must be pathologically proven in pathologic staging.

TNM, tumor, node, metastasis.

Explanatory Notes

1. **Incidence of nodal disease.** Lymph node involvement used to be considered uncommon in thymic malignancies. Recent evidence shows that lymph node metastasis might have been underestimated, especially in high grade histologic types and in locally invasive tumors. In the 9th TNM database, overall lymph node involvement rates are 1.5% in thymomas, 17.6% in thymic carcinomas and 27.7% in neuroendocrine tumors, respectively. There is a close association of higher tumor (T) categories with a greater likelihood of nodal involvement, including in thymoma.
2. **Prognostic impact.** Lymph node status is now recognized as an important prognostic factor for thymic tumors. The International Thymic Malignancy Interest Group/IASLC lymph node map for thymic epithelial tumors, recently re-assessed,[1] is recommended for the determination of the N component. The 9th edition of tumor, node, metastasis (TNM) classification (Table 1) provides a good definition of the prognostic impact of lymph node involvement. Patients with nodal involvement, especially N2 disease, have much worse survival than those without. Especially in patients with thymic carcinomas, there is significant discrimination in survival among each pN category.

3. **Clinical assessment of N component.** Procedures for assessing the N status before treatment include physical examination, imaging (computed tomography, magnetic resonance imaging, ultrasound, and positron emission tomography [PET] scan), endoscopy, and/or surgical biopsy. In the 9th edition database, there is a high concordance between the pN0 and cN0 categories. There is a low concordance between the pN+ and the cN+ tumors, as data are limited on patients with both cN+ and pN+ status and few patients with cN+ without resection had their suspected lymph nodes sampled for pathologic examination. Clinically, lymph nodes ≥ 1 cm in short axis on imaging and those with increased standardized uptake value uptake on PET scan should be suspected of disease involvement. Biopsy of suspected nodes (if accessible) is recommended for the purpose of accurate stage assignment, due to some evidence in the literature showing that many enlarged nodes with thymoma are not involved.
4. **Pathologic assessment of N component.** It is recommended that at least anterior mediastinal nodes should be removed routinely along with the thymus during resection. For tumors with invasion of mediastinal structures (T2 and above) or those with known high-grade histology (thymic carcinomas and neuroendocrine tumors), a systematic sampling of deep nodes (paratracheal nodes on the right side and aortopulmonary window nodes on the left side) is recommended. Removal and careful notation of any suspicious nodes (either by imaging or intraoperative assessment) is important so that pathological examination and reporting on nodal status can be carried out.[2]

What is new for the 9th Edition?

Through analyses of the robust data for the 9th edition, the survival differences in different N categories in the 8th edition were verified by a data-driven process. In particular, a statistically significant survival difference was found in thymic carcinoma between pN0, pN1, and pN2 ($p<0.05$, Figure 1). Therefore, no changes from the 8th edition were made for the N classifications in the 9th edition.[3]

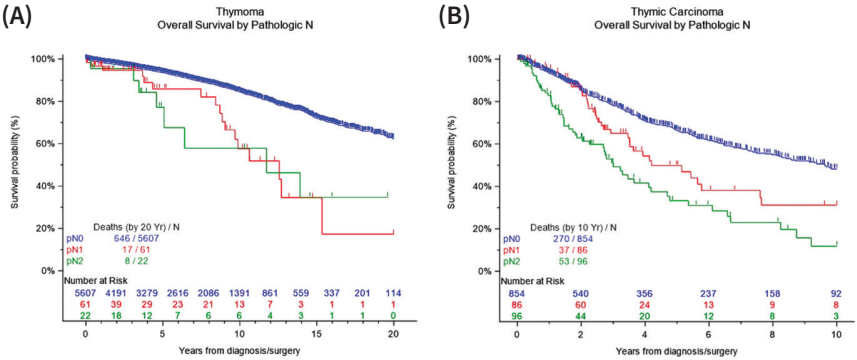


Figure 1. Overall survival of patients by pathologic N in thymoma (A), thymic carcinoma (B). Neuroendocrine thymic tumors (NETT) not shown due to insufficient sample size.

References

1. Marom EM, Fang V, Ruffini E. The International Association for the Study of Lung Cancer thymic epithelial tumor staging project: A re-assessment of the International Thymic Malignancy Interest Group/International Association for the Study of Lung Cancer lymph node map for thymic epithelial tumors for the forthcoming ninth edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2023;18(12):1672-1688. doi:10.1016/j.jtho.2023.09.001
2. Detterbeck FC, Moran C, Huang J, et al. Which way is up? Policies and procedures for surgeons and pathologists regarding resection specimens of thymic malignancy. *J Thorac Oncol.* 2011;6(7 Suppl 3):S1730-S1738. doi:10.1097/JTO.0b013e31821ea567
3. Fang W, Girard N, Cilento V, et al. The International Association for the Study of Lung Cancer thymic epithelial tumors staging project: Proposals for the N and the M components for the forthcoming ninth edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2023;19(1):52-70. doi: 10.1016/j.jtho.2023.09.1447

19

Metastasis (M) Component

Nicolas Girard, MD, PhD

Table 1. Metastasis (M) Categories for the 9th Edition of the TNM Classification of Thymic Epithelial Tumors

M category	Descriptor
M0	No metastatic pleural, pericardial, or distant sites
M1	Distant metastasis
M1a	Separate pleural or pericardial nodule(s)
M1b	Pulmonary intraparenchymal nodule or distant organ metastasis*

*Involvement of non-regional lymph nodes is staged as M1b.

TNM, tumor, node, metastasis

Explanatory Notes

1. **Descriptors:** Metastases from thymic tumors are historically separated into three categories: M0 if there are no metastases in extrathoracic sites, M1a if there are pleural or pericardial nodules separate from the primary tumor mass, and M1b if there are pulmonary intraparenchymal nodules and/or distant (extra-thoracic) metastases (Table 1). The M1a category includes pleural or pericardial tumor nodules that may be located on the visceral or parietal pleura or the pericardial or epicardial surfaces. This differs from direct extension of a tumor to the pericardium or pleura without separate nodules which is classified as T3 disease. The M1b category includes: 1) Pulmonary nodules which are in the lung, with a rim of normal lung between the nodule and the pleural surface; 2) Any extrathoracic metastatic lesion; and 3) Any non-regional lymph nodes (e.g. high neck, retro-crural, axillary, or extrathoracic lymph nodes).
2. **Patients available for the analysis from the database for the 9th Edition.** Most patients had pathologic stage information; data on cM0, cM1a and cM1b categories were available for 24.7% of thymoma and 25.9% thymic carcinoma cases, respectively. The limited number of resected M1 cases, together with the high proportion of M0 cases, led to a low correlation between pM categories

and cM categories. Pathologic M1a was correctly identified clinically in 76% of thymomas and 53% of thymic carcinoma; pM1b was correctly identified in 14% of thymoma and 33% of thymic carcinomas.[1]

What is new for the 9th Edition?

Survival analysis in the 9th edition database validated the differences in the pM categories in the 8th edition staging system, with good discrimination in patients with thymoma and thymic carcinoma (Figure 1). No changes were made from the 8th edition for the M component.[1]

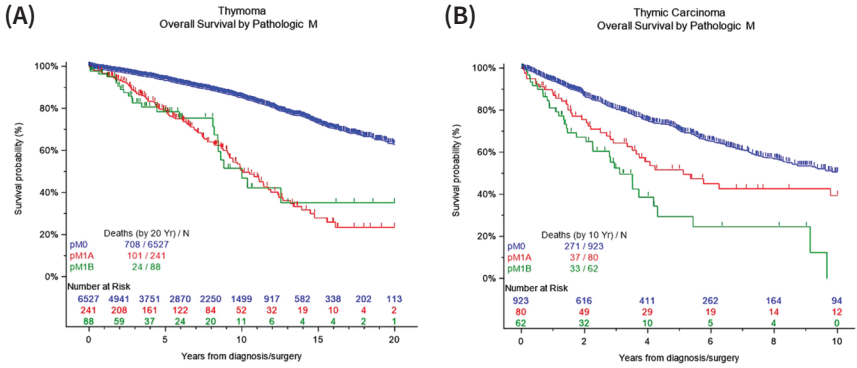


Figure 1. Overall survival of patients by pathologic M in (A) thymoma and (B) thymic carcinoma. Neuroendocrine thymic tumors (NETT) are not shown due to insufficient sample size.

References

1. Fang W, Girard N, Cilento V, et al. The International Association for the Study of Lung Cancer thymic epithelial tumors staging project: Proposals for the N and the M components for the forthcoming ninth edition of the TNM classification of malignant tumors. *J Thorac Oncol.* 2023;19(1):52-70. doi: 10.1016/j.jtho.2023.09.1447

20

Stage Groups

Enrico Ruffini, MD, and James Huang, MD

Table 1. Stage Groups for the 9th Edition of the TNM Classification of Thymic Epithelial Tumors

Stage	T category	N category	M category
I	T1a-b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	T any T any	N1 N0,N1	M0 M1a
IVB	T any T any	N2 N any	M0, M1a M1b

Note: any invasion must be histologically confirmed for pathologic stage

TNM, tumor, node, metastasis

Explanatory Notes

1. **T category and stage groups:** The stage groups I to IIIB are determined primarily by the T category (T1 to T4), in patients with N0 and M0 disease.
2. **N category and stage groups:** Tumors with anyTM0 and N1 disease are staged as stage IVA. Tumors with anyTM0 and N2 disease are staged as stage IVB.
3. **M category and Stage groups:** Tumors with anyTN01 and M1a disease are staged as stage IVA. Tumors with anyT-anyN and M1b disease are staged as stage IVB.

Figure 1 shows the cumulative incidence of recurrence for thymomas and thymic carcinomas.

What is new for the 9th Edition?

The stage group remains the same as in the 8th edition of TNM classification (Table 1).[1]

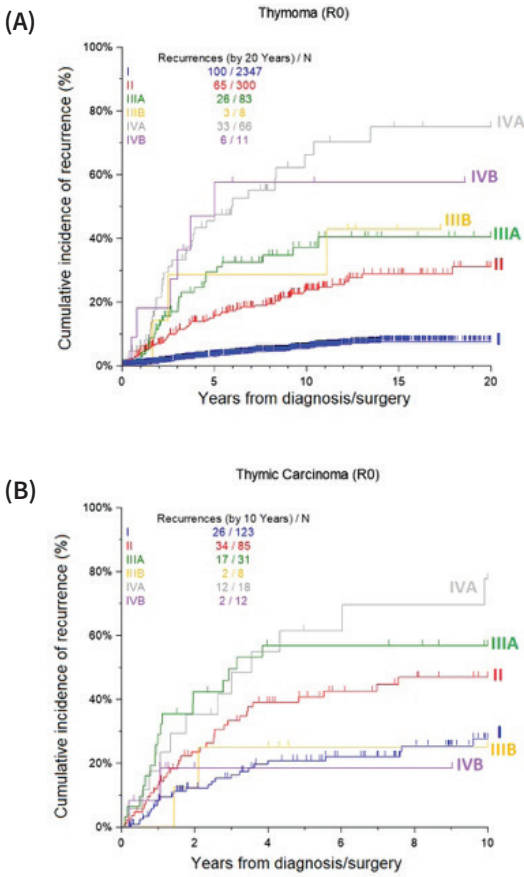


Figure 1. **Cumulative incidence of recurrence in patients with thymoma (A) and thymic carcinoma (B) by stage as defined by the 9th edition of TNM classification.**

References

1. Ruffini E, Huang J, Cilento V. The International Association for the Study of Lung Cancer thymic epithelial tumors staging project: Proposal for a stage classification for the forthcoming ninth edition of the TNM classification of malignant tumors. *J Thorac Oncol.* 2023;18(12):1655-1671. doi:10.1016/j.jtho.2023.09.002

21

Lymph Node Map

Edith M. Marom, MD

The International Thymic Malignancy Interest Group (ITMIG) created the first map for thymic epithelial malignancies in conjunction with the 8th edition of the tumor, node, metastasis (TNM) classification, representing the first official TNM classification of thymic epithelial malignancies.[1] The map was based on clinical experience and published studies, but it was largely intuitive because of limited available data.

The 9th edition of the TNM classification for thymic epithelial malignancy database was the first to collect data with a lymph node map to serve as guidance. With more than double the number of pathologically-proven assessable node positive data compared with that of the 8th edition database, this lymph node map was validated and remains the same for the 9th edition of TNM classification of thymic epithelial malignancies.

The unchanged node boundaries of the N1 and N2 categories (Table 1 and 2) have been stressed and visual clarifications have been added to the nomenclature of nodal stations within these regions for better documentation with the 9th edition of TNM classification.

Lymph nodes not defined by this regional lymph node map are considered distant metastatic (M) disease.

Explanatory Notes

1. The ITMIG/IASLC lymph node map should be used to correctly determine the N component for staging thymic epithelial tumors.
2. The node map should be employed for the clinical as well as for the pathologic N classification.

What is new for the 9th Edition?

The ITMIG/IASLC lymph node map remains the same as in the 8th edition of TNM classification.[2]

Table 1. **Anterior Region (N1) – Prevascular Mediastinum and Anterior Cervical Lymph Nodes**

Region Boundaries	Node Groups*	Node Group Boundaries
Superior: Lower border of cricoid cartilage **Lateral (Neck):** Medial border of the carotid sheath/jugular vein **Lateral (Chest):** Mediastinal pleura **Anterior:** Sternum **Posterior (medially):** Great vessels, pericardium **Posterior (laterally):** Phrenic nerve **Inferior:** Xiphoid, diaphragm	Low anterior cervical: Peritracheal, peri-thyroid, (AAO-HNS/ASHNS level 6/IASLC level 1)	Superior: Lower border of the cricoid cartilage Lateral: Common carotid arteries Inferior: Superior border of the manubrium
	Peri-thymic	Proximity to the thymus
	Prevascular (IASLC level 3a)	Superior: Apex of chest Anterior: Posterior sternum Posterior: Anterior SVC Inferior: Carina
	Para-aortic, ascending aorta, superior phrenic (IASLC level 6)	Superior: Line tangential to sup border of aortic arch Inferior: Inferior border of aortic arch
	Supradiaphragmatic/inferior phrenic/pericardial (along inferior poles of thymus)	Superior: Inferior border of aortic arch Anterior: Post sternum Posterior: Phrenic nerve (laterally) or pericardium (medially) Inferior: Diaphragm

Note: Region and node group boundaries adapted directly from definitions established by IASLC,[3] and AAO-HNS, ASHNS.[4]

AAO-HNS, American Academy of Otolaryngology-Head and Neck Surgery; ASHNS, American Society for Head and Neck Surgery; SVC, superior vena cava.

Table 2. Deep Region (N2) – Visceral Mediastinum and Deep Cervical Nodes

Region Boundaries	Node Groups*	Node Group Boundaries
Superior: Level of lower border of cricoid cartilage **Anteromedial (Neck):** Lateral border of sternohyoid, medial border of carotid sheath/jugular vein **Posterolateral (Neck):** Anterior border of trapezius **Anterior (chest):** Aortic arch, aortopulmonary window-anterior border of the SVC **Posterior (chest):** Esophagus **Lateral (chest):** Pulmonary hila **Inferior:** Diaphragm	Peri-jugular (AAO-HNS/ASHNS level 4)	Superior: Level of lower border of cricoid cartilage Anteromedial: Medial border of the jugular vein and carotid artery Posterolateral: lateral border of sternocleidomastoid Inferior: Clavicle
	Supraclavicular (AAO-HNS/ASHNS level 5b)	Superior: Level of lower border of cricoid cartilage Anteromedial: Posterior border of sternocleidomastoid Posterolateral: Anterior border of trapezius Inferior: Clavicle
	Internal mammary arteries	Proximity to internal mammary arteries
	Upper paratracheal (IASLC level 2)	Superior: Superior border of manubrium, apices of lungs Inferior: Intersection of lower border of innominate vein with trachea; superior border of aortic arch
	Lower paratracheal (IASLC level 4)	Superior: Intersection of lower border of innominate vein with trachea; superior border of aortic arch Inferior: Lower border of azygos vein, superior border of left main pulmonary artery
	Subaortic/aorto-pulmonary window (IASLC level 5)	Superior: Inferior border of aortic arch Inferior: Superior border of left main pulmonary artery
	Subcarinal (IASLC level 7)	Superior: Carina Inferior: Upper border of lower lobe bronchus on the left; lower border of bronchus intermedium on the right
	Hilar (IASLC level 10)	Superior: Lower rim of azygos vein on right, upper rim of pulmonary artery on left Inferior: Interlobar region bilaterally

Note: Region and node group boundaries adapted directly from definitions established by IASLC,[3] and AAO-HNS, ASHNS.[4]

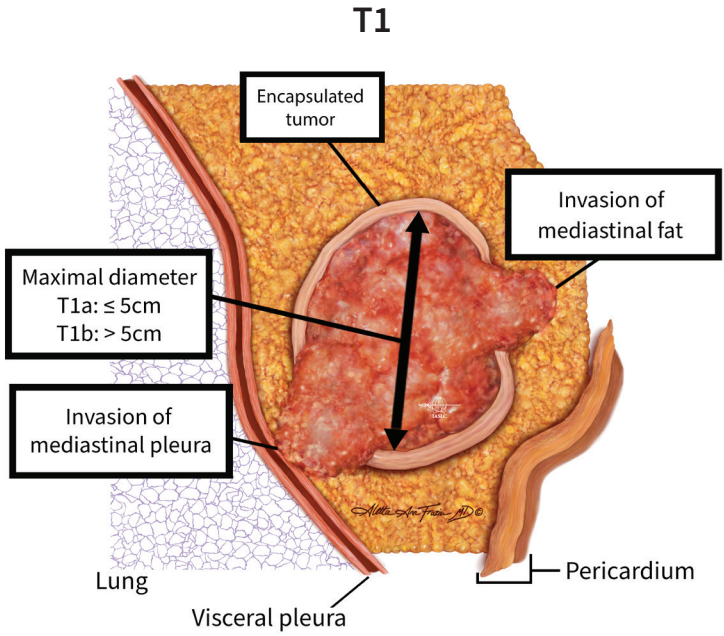
AAO-HNS, American Academy of Otolaryngology-Head and Neck Surgery; ASHNS, American Society for Head and Neck Surgery; SVC, superior vena cava.

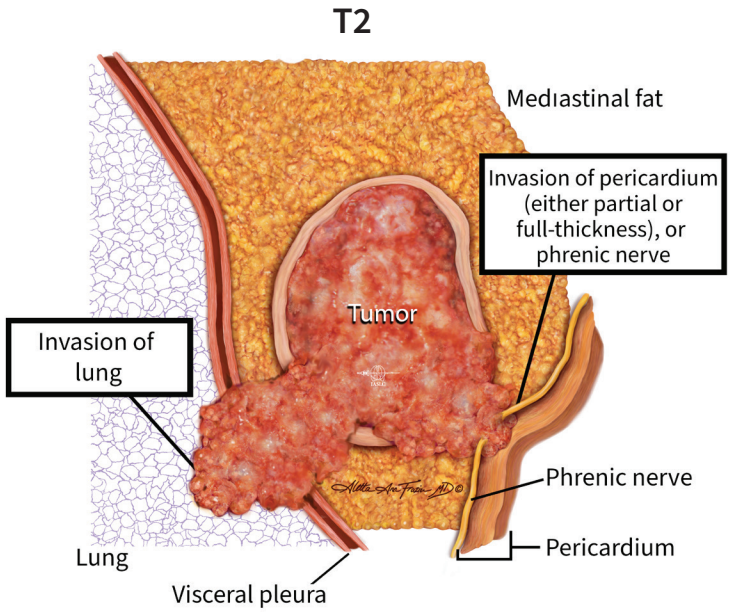
References

1. Bhora FY, Chen DJ, Detterbeck FC. The ITMIG/IASLC thymic epithelial tumors staging project: A proposed lymph node map for thymic epithelial tumors in the forthcoming eighth edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2014;9(9Suppl 2): S88-S96. doi:10.1097/JTO.0000000000000293
2. Marom EM, Fang V, Ruffini E. The International Association for the Study of Lung Cancer thymic epithelial tumor staging project: A re-assessment of the International Thymic Malignancy Interest Group/International Association for the Study of Lung Cancer lymph node map for thymic epithelial tumors for the forthcoming ninth edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2023;18(12):1672-1688. doi: 10.1016/j.jtho.2023.09.001
3. Rusch V, Asamura H, Watanabe H. 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(5):568-577. doi:10.1097/JTO.0b013e3181a0d82e
4. Robbins KT, Clayman G, Levine PA. Neck dissection classification update: Revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. *Arch Otolaryngol Head Neck Surg*. 2002;128(7):751-758. doi:10.1001/archotol.128.7.751

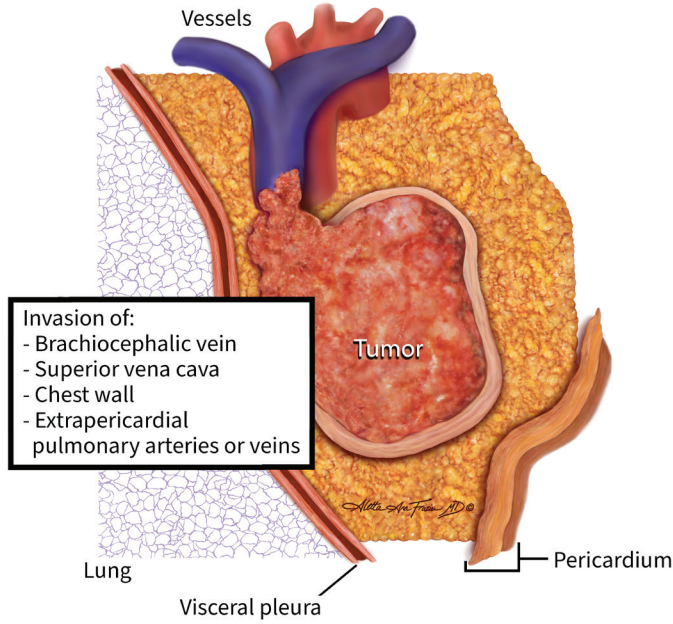
22

Atlas of Thymic Epithelial Tumors Tumor, Node, Metastasis (TNM) Classification

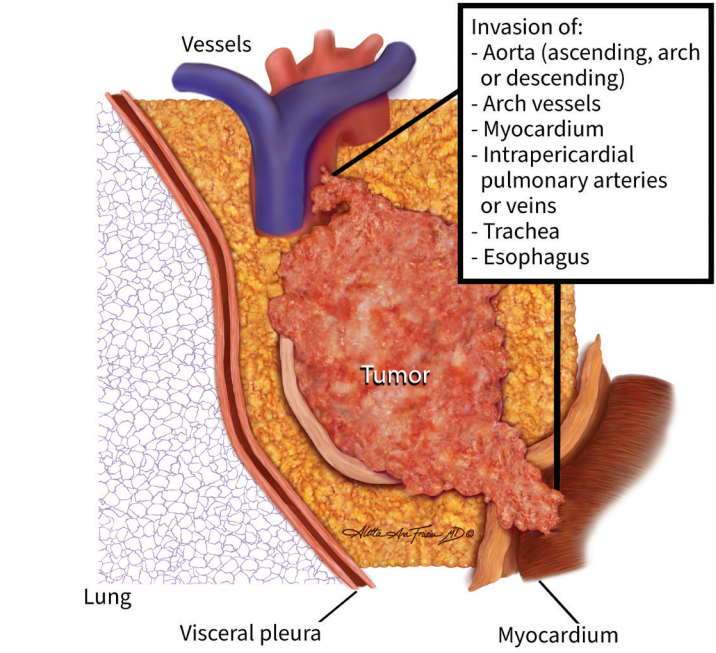

T1
Encapsulated tumor
Invasion of mediastinal fat
Maximal diameter
T1a: ≤ 5cm
T1b: > 5cm
Invasion of mediastinal pleura
Lung
Visceral pleura
Pericardium


T2
Mediastinal fat
Invasion of pericardium (either partial or full-thickness), or phrenic nerve
Tumor
Invasion of lung
Phrenic nerve
Pericardium
Lung
Visceral pleura

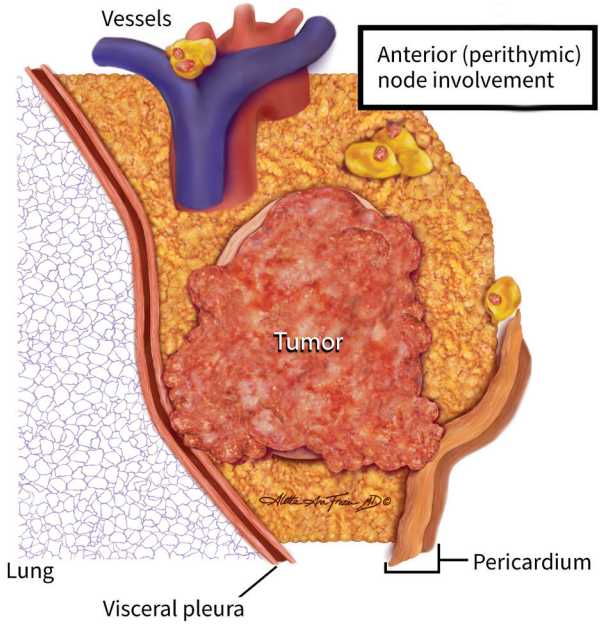
T3


Vessels
Invasion of:
- Brachiocephalic vein
- Superior vena cava
- Chest wall
- Extrapericardial pulmonary arteries or veins
Tumor
Pericardium
Lung
Visceral pleura

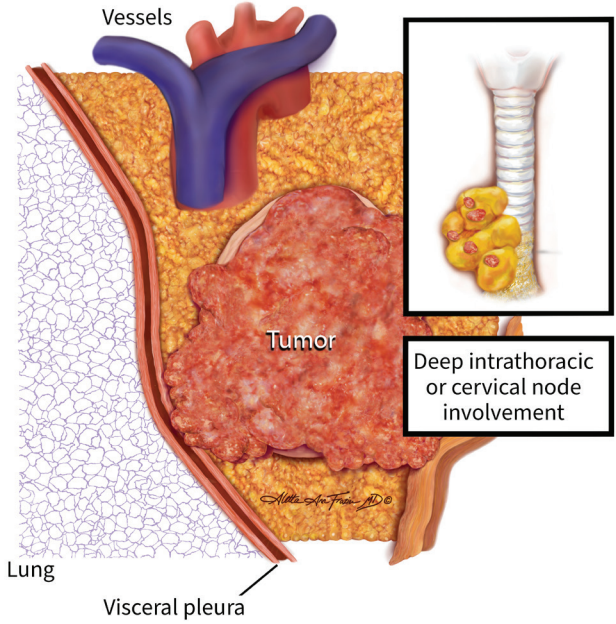
T4


Vessels
Invasion of:
- Aorta (ascending, arch or descending)
- Arch vessels
- Myocardium
- Intrapericardial pulmonary arteries or veins
- Trachea
- Esophagus
Tumor
Lung
Visceral pleura
Myocardium

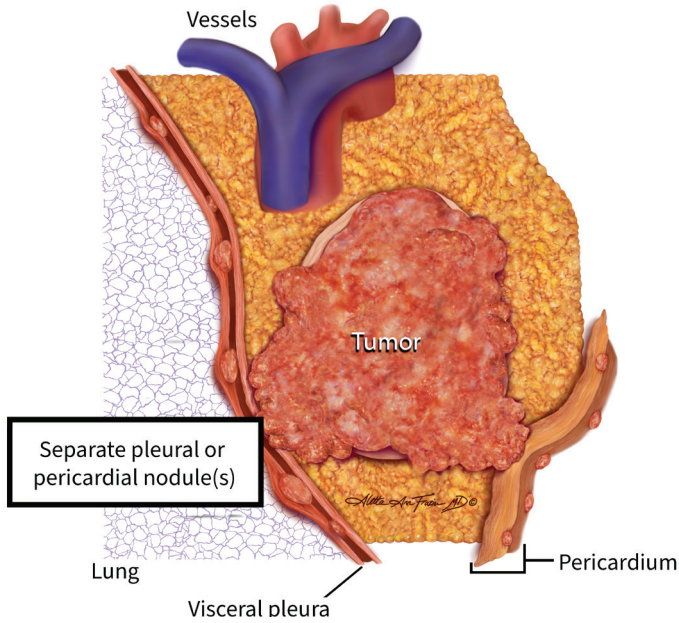
N1


Vessels
Anterior (perithymic) node involvement
Tumor
Lung
Visceral pleura
Pericardium

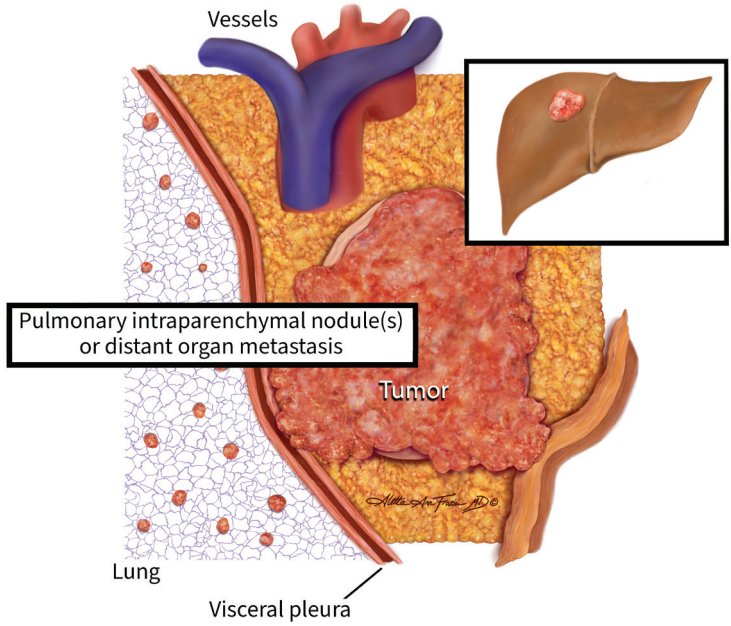
N2


Vessels
Tumor
Deep intrathoracic or cervical node involvement
Lung
Visceral pleura

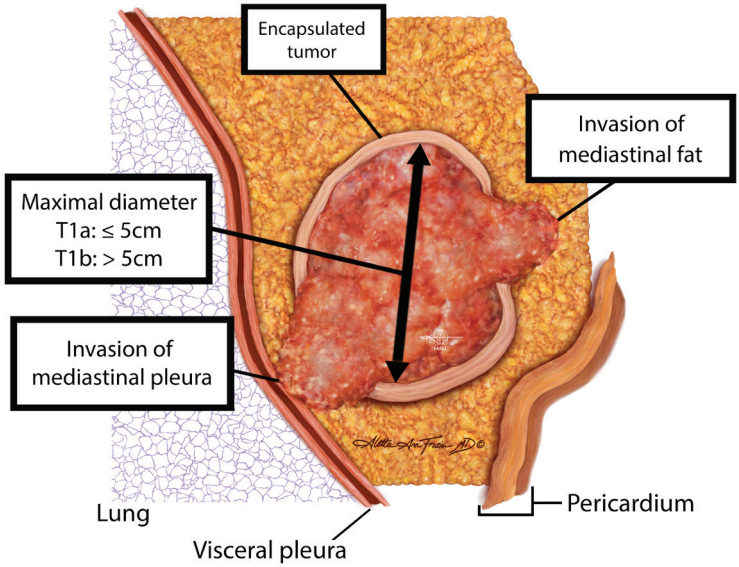
M1a


Vessels
Tumor
Separate pleural or pericardial nodule(s)
Lung
Visceral pleura
Pericardium

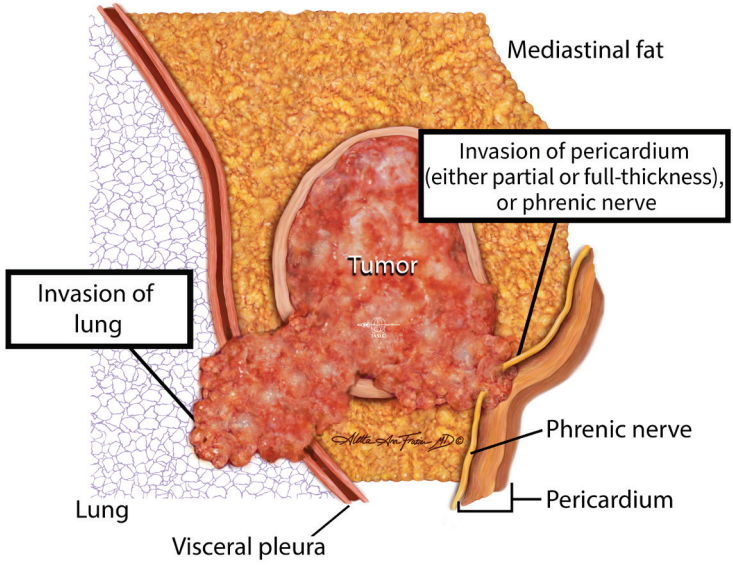
M1b


Vessels
Pulmonary intraparenchymal nodule(s) or distant organ metastasis
Tumor
Lung
Visceral pleura

Stage I
T1N0M0

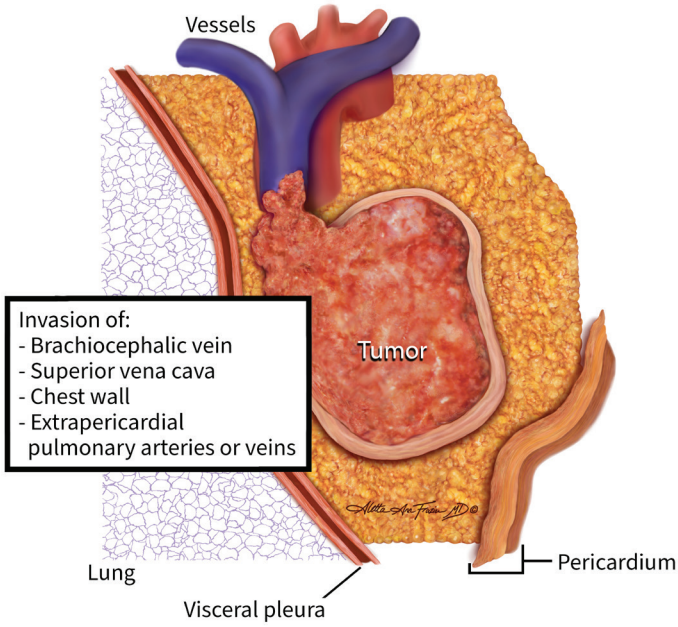


Stage II
T2N0M0



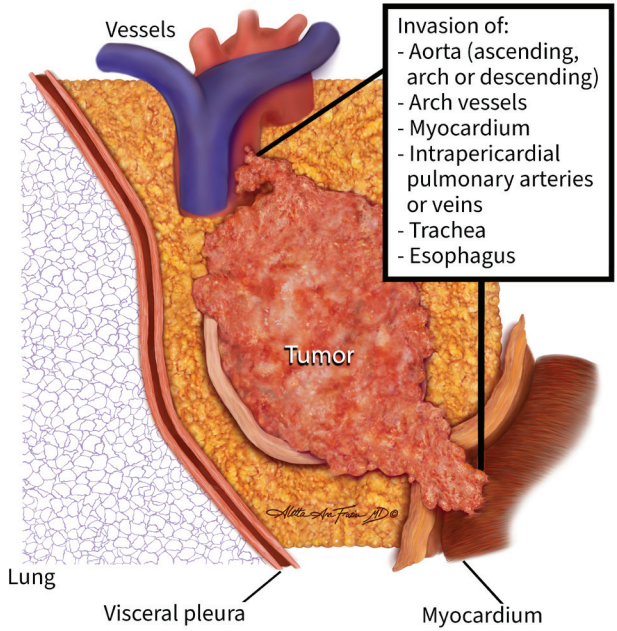
Stage IIIA

T3N0M0



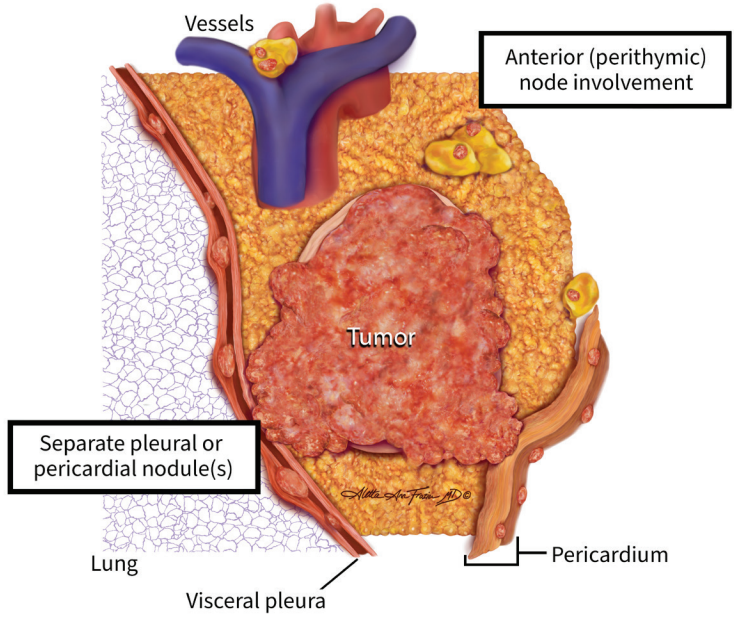
Stage IIIB

T4N0M0



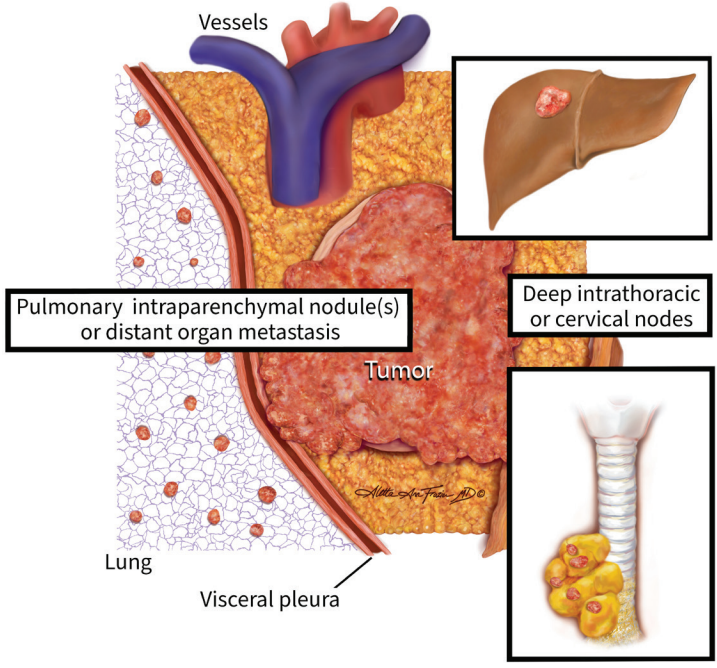
Stage IVA

Any T, N1M0; any T, N0-1, M1a



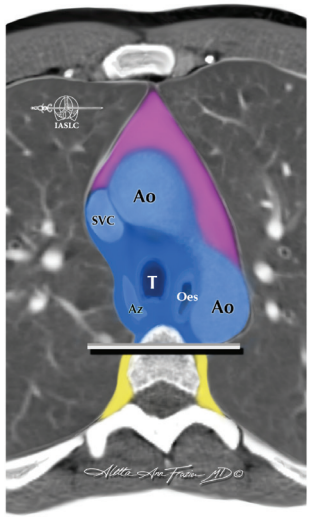
Stage IVB

Any T, N2, M0-1a; any T, any N, M1b

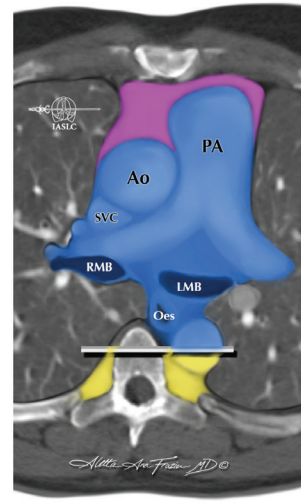


ITMIG Mediastinal Compartments

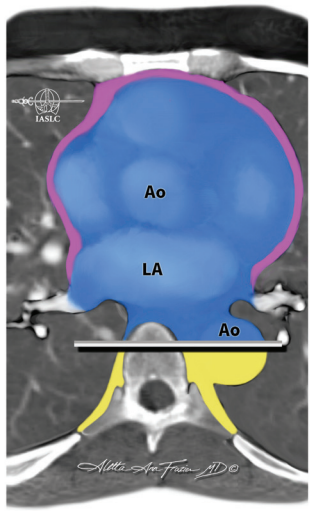
Axial #1[1]



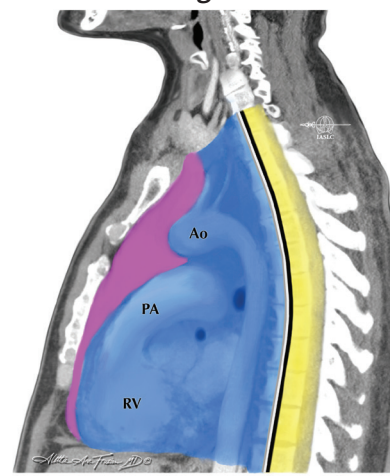
Axial #2



Axial #3



Sagittal



Prevascular compartment
Visceral compartment
Paravertebral compartment
Visceral-paravertebral boundary

Ao: aorta
PA: pulmonary artery
SVC: superior vena cava
T: trachea
Az: azygos vein
Oes: esophagus
RMB: right main bronchus
LMB: left main bronchus
LA: left atrium
RV: right ventricle

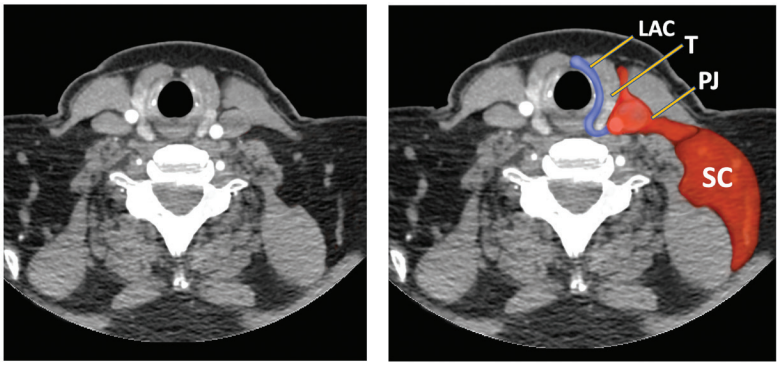
ITMIG: International Thymic Malignancy Interest Group.

Reference:

1. Carter B, Tomiyama N, Bhora F et al. A Modern Definition of Mediastinal Compartments. *J Thorac Oncol*. 2014; 9(9): S97-S101.

ITMIG/IASLC Lymph Node Map for Thymic Epithelial Tumors

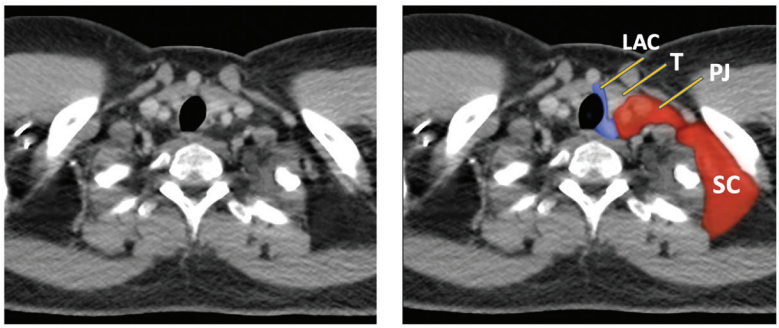
Lower Neck/Cricoid Cartilage Level



N1 region N2 region

Lymph node levels at the lower neck, below the level of the cricoid cartilage.
LAC, low anterior cervical region; PJ, peri-jugular region; SC, supraclavicular region; T, thyroid

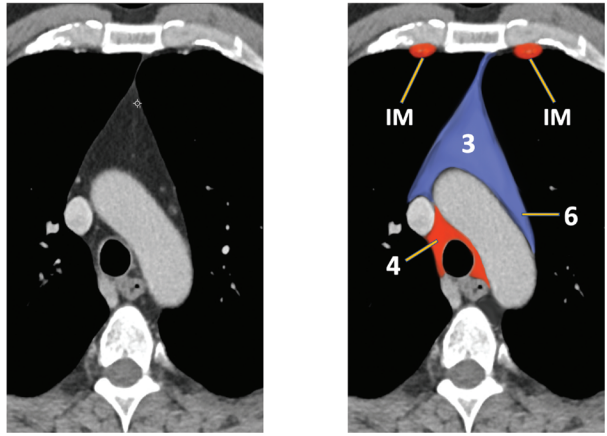
Lower Neck/Mid Trachea Level



N1 region N2 region

Lymph node levels at the lower neck, mid trachea level.
LAC, low anterior cervical region; PJ, peri-jugular region; SC, supraclavicular region; T, thyroid

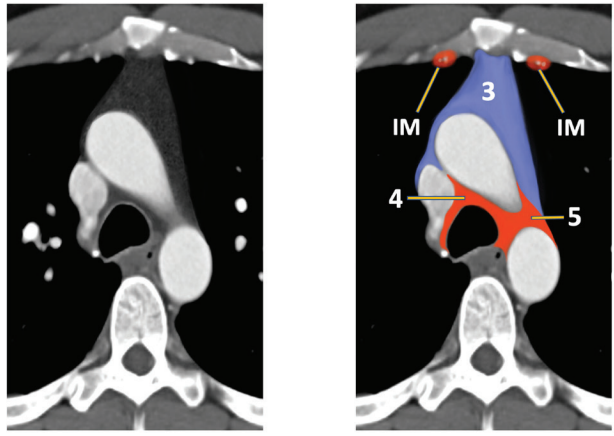
Aortic Arch Level



N1 region N2 region

Shaded lymph node groups at the level of the aortic arch.
IM, internal mammary node group. Numbers 3, 4, 6 refer to IASLC node map used for lung cancer.

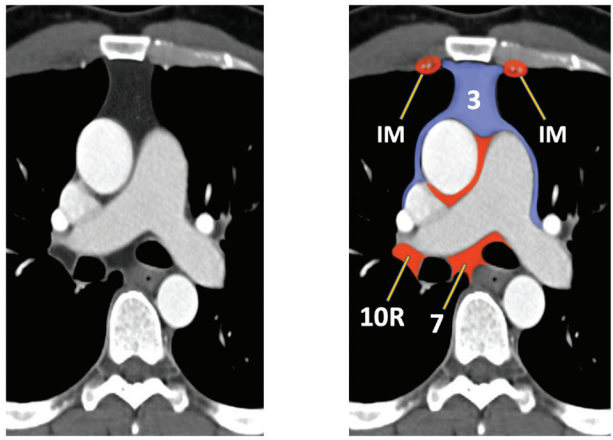
Aorto-Pulmonary Window Level



N1 region N2 region

Shaded lymph node groups at the level of the aorto-pulmonary window.
IM, internal mammary node group. Numbers 3, 4, 5 refer to IASLC node map used for lung cancer.

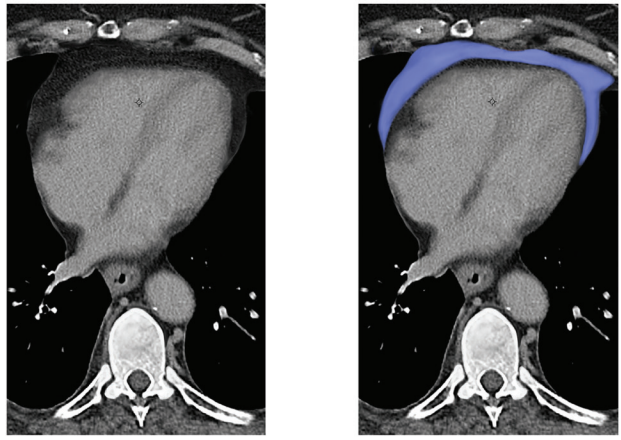
Main Pulmonary Artery Level



N1 region N2 region

Shaded lymph node groups at the level of the main pulmonary artery.
IM, internal mammary node group. Numbers 3, 7, 10R refer to IASLC node map used for lung cancer.

Lower Chest (base of the heart) Level



N1 region

Native and shaded CT in the lower chest demonstrating the anterior (perithymic) region (N1).

PART III

PLEURAL MESOTHELIOMA

23

Overview of the Database

Andrea S. Wolf, MD, and Valerie W. Rusch, MD, FACS

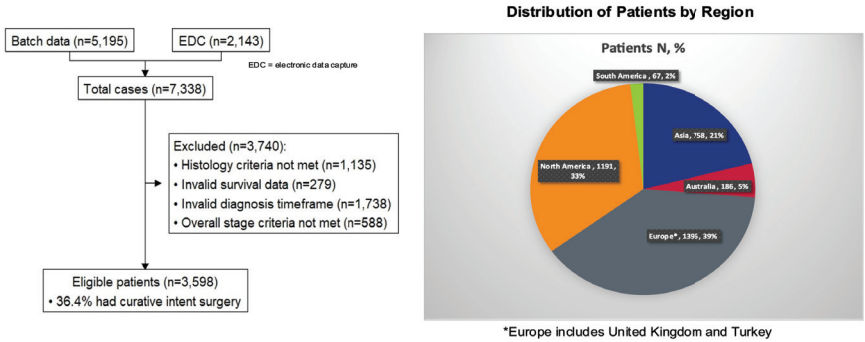


Figure 1. **The IASLC database used to inform the 9th edition of the tumor, node, metastasis (TNM) classification for pleural mesothelioma.**

*International Association for the Study of Lung Cancer

Table 1. **Overview of Iterations of the IASLC Pleural Mesothelioma Databases used to Inform the 7th, 8th, and 9th Editions of the AJCC and UICC Pleural Mesothelioma Staging Systems**

	Edition of the AJCC and UICC Pleural Mesothelioma Staging System		
Feature	**7th**	**8th**	**9th**
Total available cohort	3101	3519	7338
Total eligible cases	2316	2450	3598
Period of Diagnosis	1995-2009	2000-2013	2013-2022
Geographic Origin			
Europe*	1049 (45.3%)	1173 (47.9%)	1396 (38.8%)
North America	1048 (45.3%)	817 (33.3%)	1191 (33.1%)
Asia	150 (6.5%)	233 (9.5%)	758 (21.0%)
Australia	69 (3.0%)	227 (9.3%)	186 (5.2%)
South America			67 (1.9%)

* Europe includes United Kingdom and Turkey

continued on next page

Feature	7th	8th	9th
Histology of included patients			
Epithelioid	1596 (68.9%)	1784 (72.8%)	2799 (77.8%)
Non-epithelioid	685 (29.6%)	666 (27.2%)	799 (22.2%)
No data	35 (1.5%)	0 (0.0%)	0 (0.0%)
Surgical Procedures Performed			
Surgery-palliative	729 (31.5%)	692 (28.2%)	1146 (31.9%)
Surgery-curative	1494 (64.5%)	1291 (52.7%)	1310 (36.4%)
No surgery	70 (3.0%)	458 (18.7%)	821(22.8%)
No data	23 (1.0%)	9 (0.4%)	321 (8.9%)

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control

Explanatory Notes

The IASLC collaborated with the International Mesothelioma Interest Group to propose the first tumor, node, and metastasis (TNM) classification system for diffuse pleural mesothelioma (PM) in 1995.[1] This was subsequently accepted by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) for the 6th edition of the TNM classifications.[2] For the 7th edition, the IASLC Staging and Prognostic Factors Committee Mesothelioma Domain developed and analyzed a multicenter dataset of patients with PM (predominantly managed surgically) which validated the TNM classification used in the 6th edition.[3] For the 8th edition, a new international and considerably expanded database was developed that included patients managed both surgically and non-surgically. Analyses of this database led to major revisions in the N component descriptors and stage groups, and provided exploratory data on the use of quantitative pleural thickness measurements that might be used for future revision of the T component descriptors.[4]

To inform revisions in the 9th edition of the TNM classification system, data submission was solicited for patients diagnosed between 2013 and 2022 with expanded data elements based on the analyses in the 8th edition, including pleural thickness measurements, updated surgical nomenclature, and molecular markers. The resulting database consisted of a total of 3,598 analyzable cases from Europe, Australia, Asia, North America, and South America (Figure 1). With only 1,310 (36.4%) patients undergoing curative intent operations, this iteration of the database includes far more patients treated non-surgically than previously (Table 1). Four separate manuscripts describe the revisions in the T, N, and M components as well as the stage groups, which are also outlined in the subsequent staging manual chapters.[1-4]

What is new for the 9th Edition?

1. Increased number of patients with better geographic distribution.
2. Improved balance of the patient population in the database with a larger proportion of patients treated non-surgically.
3. Inclusion of quantitative pleural thickness measurements to support revision of T component descriptors.
4. Larger number of patients with M1 disease at diagnosis to support analysis of M component descriptors.
5. Submission of molecular data from selected institutions.

References

1. Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma. *Chest*. 1995;108:1122-8. doi:10.1378/chest.108.4.1122
2. Rusch VW, Giroux D, Kennedy C, et al. Initial analysis of the International Association for the Study of Lung Cancer mesothelioma database. *J Thorac Oncol*. 2012;7:1631-9. doi:10.1097/JTO.0b013e31826915f1
3. Pass HI, Giroux D, Kennedy C, et al. The IASLC mesothelioma database: Improving staging of a rare disease through international participation. *J Thorac Oncol*. 2016;11(12):2082-8. doi:10.1016/j.jtho.2016.09.123
4. Wolf AS, Eisele M, Giroux DJ, et al. The International Association for the Study of Lung Cancer pleural mesothelioma staging project: Expanded database to inform revisions in the ninth edition of the TNM classification of pleural mesothelioma. *J Thorac Oncol*. 2024;doi:10.1016/j.jtho.2024.01.018

24

Tumor (T) Component

Ritu R. Gill, MBBS, MPH, Anna K. Nowak, PhD, MBBS,
and Valerie W. Rusch, MD, FACS

Table 1. Tumor (T) Descriptors

Primary Tumor (T)		
Category	**Clinical T (cT)**	**Pathologic T (pT)**
Tx	Tumor cannot be assessed	
T0	No tumor is present	
T1	Tumor limited to the ipsilateral pleura with Psum[a] ≤12 mm with no involvement of the fissure (Fmax[b] ≤5 mm)	Tumor limited to the ipsilateral pleura with no involvement of the fissure
T2	Tumor involving the ipsilateral pleura with Psum[a] ≤12 mm and with any of the following: • Involvement of the fissure (Fmax[b] >5 mm) • Mediastinal fat invasion • Solitary area of chest wall soft tissue invasion or Tumor involving the ipsilateral pleura with Psum[a] >12 mm but ≤30 mm, with or without: • Involvement of the fissure (Fmax[b] >5 mm) • Mediastinal fat invasion • Solitary area of chest wall soft tissue invasion	Tumor involving the ipsilateral pleura and with any of the following: • Involvement of the fissure • Ipsilateral lung parenchyma invasion • Diaphragm (non-transmural) invasion
T3	Tumor involving the ipsilateral pleura with Psum[a] >30 mm; with or without: • Involvement of the fissure (Fmax[b] >5mm) • Mediastinal fat invasion • Solitary area of chest wall soft tissue invasion	Tumor limited to the ipsilateral pleura (with or without fissure involvement) and with invasion of any of the following: • Mediastinal fat • Surface of pericardium • Endothoracic fascia • Solitary area of chest wall soft tissue

continued on next page

Category	Clinical T (cT)	Pathologic T (pT)
T4	Tumor with invasion of any of the following (any Psum[a]): • Chest wall bony invasion (rib) • Mediastinal organs (heart, spine, esophagus, trachea, great vessels) • Diffuse chest wall invasion • Direct tumor extension through the diaphragm or pericardium • Direct extension to the contralateral pleura • Presence of malignant pericardial effusion	Tumor with invasion of any of the following: • Chest wall bony invasion (rib) • Mediastinal organs (heart, spine esophagus, trachea, great vessels) • Diffuse chest wall invasion • Transmural invasion of the diaphragm or pericardium • Direct extension to the contralateral pleura • Presence of malignant pericardial effusion

[a] Psum = pmax1 + pmax2 + pmax3 (sum of 3 measurements of maximal pleural thickness measured on axial images along the chest wall or mediastinum in each of the three divisions of the chest – upper, middle and lower divided by two lines; one at the top of the aortic arch and the second drawn at the top of the left atrium)

[b] Fmax = maximal thickness of pleural tumor along the fissures measured on sagittal images

Explanatory Notes

In the 9th edition of the pleural mesothelioma (PM) staging system, the clinical T1-3 (cT1-3) categories have been extensively revised to include a size criterion based on measurements of pleural thickness, in addition to retaining most of the descriptors of invasion of adjacent structures used in the 8th edition.[1] The cT descriptors of invasion of adjacent structures that cannot be reliably assessed on computed tomography (CT) imaging (e.g. invasion of endothoracic fascia or diaphragm) have been eliminated.[2] To measure pleural thickness on axial CT imaging, the involved hemithorax is divided into three approximately equally sized regions using a virtual demarcation at the level of the top of the aortic arch, and at the top of the left atrium (Figure 1). The maximum pleural thickness is assessed on axial CT images perpendicular to the chest wall or mediastinum in each third of the hemithorax (pmax1, pmax2, and pmax3) and the three measurements are combined to estimate the *sum of the maximal pleural thickness* (Psum = pmax1 + pmax2 + pmax3). The presence of visceral pleural involvement within the fissure is defined as a maximal pleural thickness measurement (Fmax) on *sagittal* CT images measuring >5 mm and upstages T1 tumors to T2.[2] However, cT4 is defined by invasion of tumor through the diaphragm, or pericardium, or diffuse chest wall invasion, or invasion of bones or mediastinal structures irrespective of any *Psum* measurements, which do not add any prognostic information for these very locally advanced primary tumors (Table 1).

The pathologic T (pT) descriptors remain unchanged from the 8th edition.[3] Because pleural tumor resection usually results in specimens removed piecemeal, pleural tumor thickness cannot be reliably measured by surgeons or pathologists. Therefore, most of the pT descriptors used in the 8th edition have been retained.

Overall survival analyses of multicenter data submitted to the IASLC PM database support the use of this different approach to cT versus pT categories and descriptors and show statistically better separation of T categories relative to those used in the 8th edition (Figure 2 and Table 2).

Mesothelioma *in situ* and localized mesothelioma are rare manifestations of mesothelioma for which there is limited clinical data.[4,5] Because of their rarity and the only recent refinement of their diagnostic criteria, data was not collected for these tumors in the IASLC-PM mesothelioma database.[6] Therefore, they could not be included in the analysis of this database, and they are not listed in the main table of T descriptors.

What is new for the 9th Edition?

1. The major change is the addition of size criteria assessed by *Psum* for cT1-3 categories.
2. Fissure involvement (defined as pleural thickness >5 mm on sagittal CT imaging) is now upstaged to cT2 category.
3. cT descriptors from the 8th edition of the staging system that cannot be reliably identified on CT imaging have been eliminated.
4. Fissure involvement by pathologic findings is now upstaged to pT2.

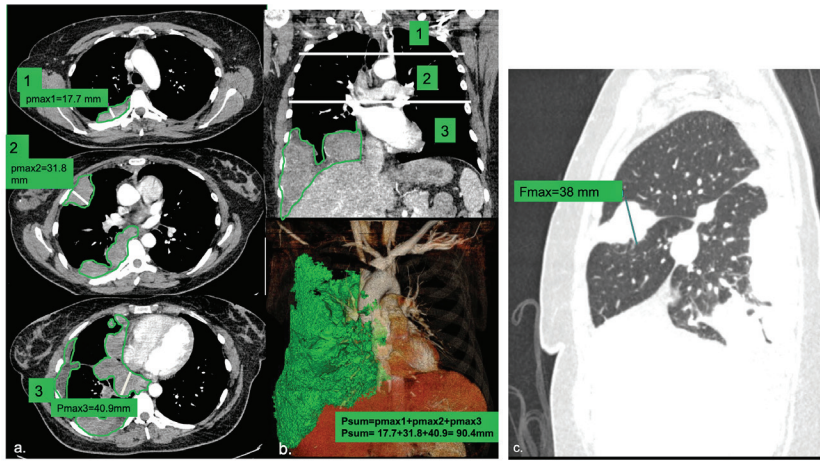


Figure 1. **(A) Axial images with maximal pleural thickness measurement at each of the three levels; p1max = 17.7 mm; p2max = 31.8 mm and p3max = 40.9 mm and Psum = 17.7 = 31.8 + 40.9 = 90.4 mm (-cT3 category). (B) Coronal images of a patient with right-sided pleural mesothelioma showing the division of the chest into approximate thirds by a line drawn at the level of the aortic arch and a second line at the top of the left atrium, dividing the chest into three relatively equal parts (upper, middle, and lower levels). The maximum pleural thickness on each of these levels (pmax1, pmax2, and pmax3) is measured and combined to derive a sum of maximum pleural thickness (Psum = pmax1 + pmax2 + pmax3); (C) Sagittal image showing fissure involvement by tumor; maximal fissure thickness Fmax = 38 mm.**

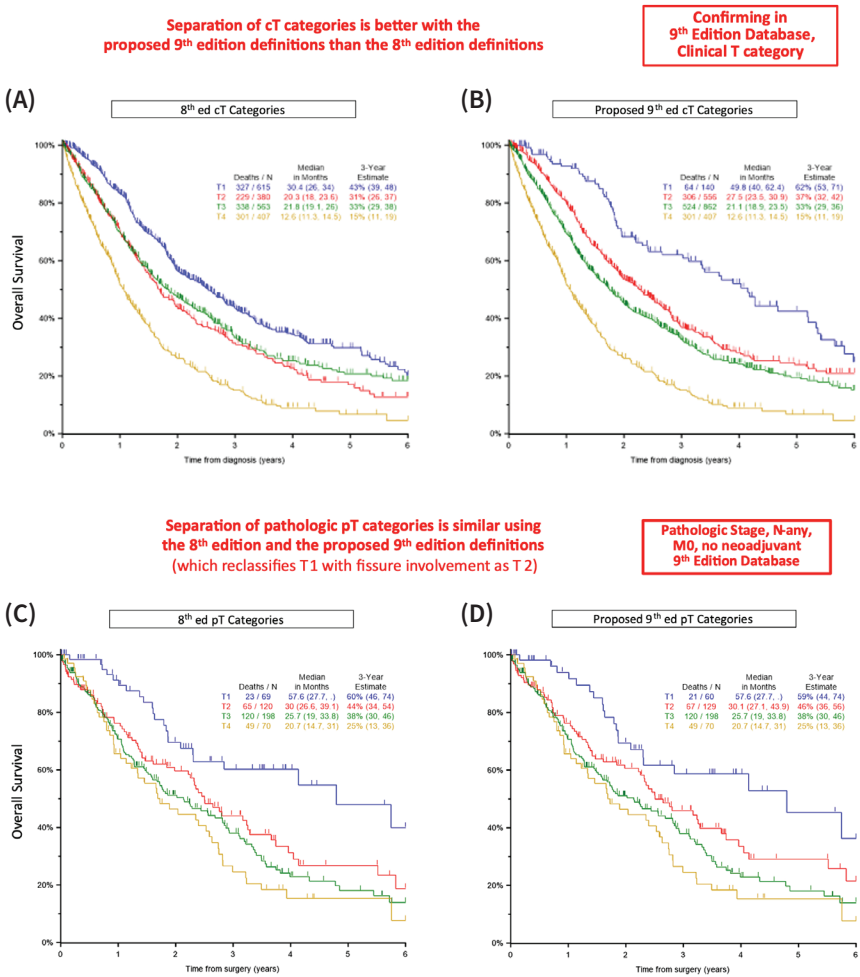


Figure 2. Overall survival of patients by (A) 8th edition clinical T applied to the 9th edition data, (B) 9th edition clinical T applied to the 9th edition data, (C) 8th edition pathologic T applied to the 9th edition data, and (D) 9th edition pathologic T applied to the 9th edition data.

Table 2. Statistical Assessment of Differences Between Adjacent T Categories

Comparison	8th edition P-value	9th edition P-value
Clinical T, 9th Edition Data, n=1,965		
T1 vs T2	<0.0001	<0.0001
T2 vs T3	0.3841	0.0007
T3 vs T4	<0.0001	<0.0001
Pathologic T, 9th Edition Data, n=457		
T1 vs T2	0.0056	0.0277
T2 vs T3	0.2335	0.1153
T3 vs T4	0.2880	0.2880
Clinical T, 8th Edition Data, n=567		
T1 vs T2	0.1056	0.0240
T2 vs T3	0.9460	0.1068
T3 vs T4	0.0032	0.0077

Table depicts p-values for log-rank comparisons of overall survival of adjacent T categories by 8th edition and 9th edition definitions in the 8th edition and the 9th edition databases.

vs, versus

References

1. Gill RR, Nowak AK, Giroux DJ, et al. The International Association for the Study of Lung Cancer mesothelioma staging project: Proposals for revisions of the "T" descriptors in the forthcoming ninth edition of the TNM classification for pleural mesothelioma. *J Thorac Oncol*. 2024;doi:10.1016/j.jtho.2024.03.007
2. Gill RR, Yeap BY, Bueno R, et al. Quantitative clinical staging for patients with malignant pleural mesothelioma. *J Natl Cancer Inst.* 2018;3:258-264. doi:10.1093/jnci/djx175
3. Nowak AK, Chansky K, Rice DC, et al. The IASLC mesothelioma staging project: Proposals for revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for pleural mesothelioma. *J Thorac Oncol*. 2016; 11(12):2089-2099. doi: 10.1016/j.jtho.2016.08.147
4. WHO Classification of Tumours Editorial Board. WHO Classification of Tumours: Thoracic Tumours. Lyon: International Agency for Research on Cancer; 2021.
5. Sauter JL, Dacic S, Galateau-Salle F, et al. The 2021 WHO Classification of Tumours of the Pleura: Advances since the 2015 classification. *J Thorac Oncol*. 2022;17(5):608-622. doi:10.1016/j.jtho.2021.12.014
6. Wolf AS, Eisele M, Giroux DJ, et al. The International Association for the Study of Lung Cancer pleural mesothelioma staging project: Expanded database to inform revisions in the ninth edition of the TNM classification of pleural mesothelioma. *J Thorac Oncol*. 2024;doi:10.1016/j.jtho.2024.01.018

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Node (N) Component

Andrea R. Billè, MD, PhD, R. Taylor Ripley, MD, David C. Rice, MBBS, and Valerie W. Rusch, MD, FACS

Table 1. Node (N) Component

Category	Clinical (cN) and pathologic (pN) N descriptors
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to ipsilateral intrathoracic lymph nodes (includes ipsilateral bronchopulmonary, hilar, subcarinal, paratracheal, aortopulmonary, para-esophageal, peridiaphragmatic, pericardial fat pad, intercostal, and internal mammary nodes)
N2	Metastases to contralateral lymph nodes. Metastases to ipsilateral or contralateral supraclavicular lymph nodes

Explanatory Notes

In the 7th edition of the pleural mesothelioma (PM) staging system, the N component definitions were directly adopted from those used in the lung cancer staging system.[1,2] Subsequently, several retrospective series as well as analyses of the IASLC PM database done to inform recommendations for the 8th edition of the staging system, showed that the patterns of lymph node involvement in PM differed from those seen in lung cancer. In PM, metastases to mediastinal lymph nodes, including those in unusual locations (e.g. internal mammary, peridiaphragmatic, intercostal) occur frequently, often in the absence of involvement of bronchopulmonary or hilar lymph nodes.[3,4] Thus, analyses of the IASLC PM database for the 8th edition led to substantial revisions of the N component, with N1 indicating metastases in any ipsilateral intrathoracic lymph nodes, and N2 indicating metastases in contralateral intrathoracic or any supraclavicular lymph nodes. The N3 descriptor was eliminated. The nomenclature for lymph node stations utilized the IASLC lung cancer lymph node map, but also added mediastinal lymph node stations frequently involved in PM (Figure 1).[5]

The IASLC PM database developed to inform the 9th edition of the staging system was analyzed to determine whether revisions of the 8th edition N descriptors were

needed.[5] In 2,688 cases eligible for cN and 880 cases eligible for pN analyses, there were significant differences in overall survival (OS) between N0 and N1 (Figure 2). Additional analyses showed no statistically significant differences in OS in patients with single versus multiple station pN1 disease; or between patients who had 1-3 versus 4-10 lymph node stations removed at surgery. Therefore, the N component in the 9th edition of the PM staging system is unchanged from that in the 8th edition (Table 1).[6]

What is new for the 9th Edition?

There are no changes relative to the N component in the 8th edition.

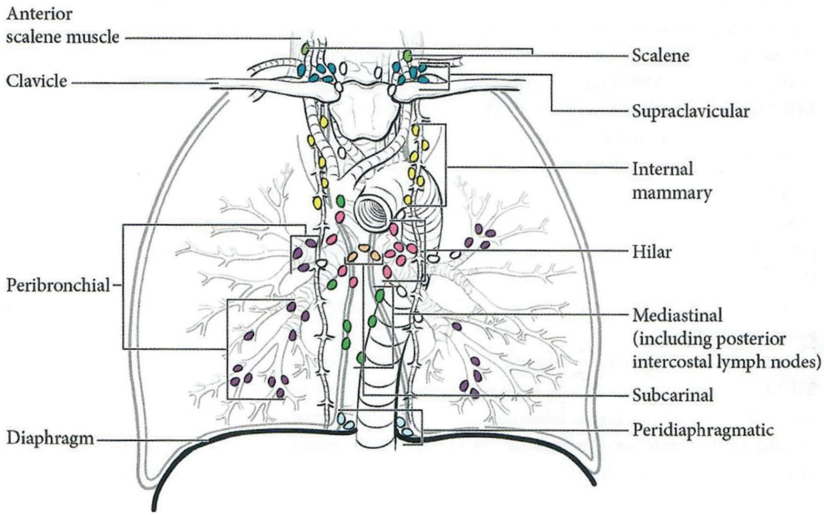

Figure 1. **The regional lymph node map for PM. The nomenclature and the numbering system used to designate lymph node stations in lung cancer are also used in PM but several mediastinal lymph node stations (not designated by numbers) have been added, including the internal mammary, peridiaphragmatic, pericardial fat pad, and posterior intercostal lymph nodes. Reference: *AJCC Cancer Staging Manual* 8th edition. New York: Springer; 2017.[5]**

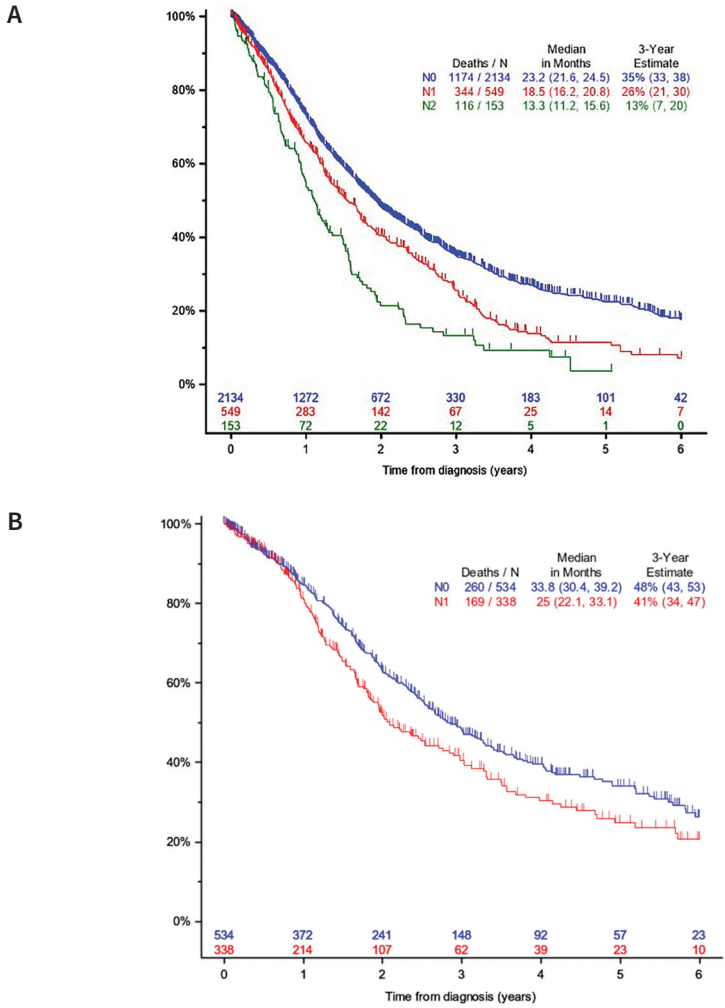

Figure 2. **Kaplan Meier curves showing differences in overall survival of patients by cN category (A); and pN category in patients who had extrapleural pneumonectomy, extended pleurectomy/decortication or pleurectomy/decortication for surgical resection with curative intent (B).**

References

1. Rusch VW, Asamura H, Watanabe H, et al. 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(5):568-77. doi:10.1097/JTO.0b013e3181a0d82e
2. Rusch VW, Giroux D, Kennedy C, et al. Initial analysis of the International Association for the Study of Lung Cancer mesothelioma database. *J Thorac Oncol.* 2012;7:1631-9. doi:10.1097/JTO.0b013e31826915f1

3. Flores RM, Routledge T, Seshan VE, et al. The impact of lymph node station on survival in 348 patients with surgically resected malignant pleural mesothelioma: Implications for revision of the American Joint Committee on Cancer staging system. *J Thorac Cardiovasc Surg*. 2008;136(3):605-10. doi:10.1016/j.jtcvs.2008.02.069
4. Rice DC, Chansky K, Nowak AK, et al. The IASLC mesothelioma staging project: Proposals for revisions of the N descriptors in the forthcoming eighth edition of the TNM classification for malignant pleural mesothelioma. *J Thorac Oncol.* 2016;11(12):2100-11. doi:10.1016/j.jtho.2016.09.121
5. Rusch VW, Nowak AK, Rice D, et al. Malignant pleural mesothelioma. In: Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017:463.
6. Billè AR, Ripley RT, Giroux DJ, Gill RR, et al. Proposals for the N descriptors in the forthcoming ninth edition of the TNM classification for pleural mesothelioma. *J Thorac Oncol.* in press 2024. doi.org/10.1016/j.jtho.2024.05.003

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Metastasis (M) Component

Hedy Lee Kindler, MD, and Valerie W. Rusch, MD, FACS

Table 1. Metastasis (M) Component

Category	Clinical M descriptor (cM)
M0	No distant metastasis
M1	Distant metastasis present

Explanatory Notes

The M component of the pleural mesothelioma (PM) staging system describes the presence or absence of distant metastases at diagnosis (Table 1). By convention, the M component is based on clinical staging alone. Historically, the 7th edition of the PM staging system was derived from information on patients in the IASLC PM database who were treated surgically, and thus did not allow analysis of overall survival (OS) in patients presenting with metastatic disease.[1] Data submitted to the IASLC database for the 8th edition of the PM staging system included patients managed non-surgically, among which were 84 patients who had M1 disease at diagnosis.[2] A statistically significant difference in median OS for M0 versus M1 (13.4 versus 9.7 months, $P = .0013$, hazard ratio, 1.64) supported the distinction between these two categories and the recommendation that M1 disease be classified as stage IV disease. Data collected for the M component of the 9th edition of the PM staging system were drawn from 3,221 patients of whom 228 (7%) had M1 disease at diagnosis.[3] Median OS was inferior for patients with M1 compared with M0 tumors: 10.5 versus 21.5 months ($P < .0001$), with an estimated 1-year OS of 46% versus 71%, respectively (Figure 1). Among 158 patients with organ-specific documentation of M1 disease, there was no statistically significant difference in OS between those with metastatic disease in a single organ versus multiple organ systems (median OS 12.6 versus 8.8 months, $P = .45$) (Figure 2), or in those with intrathoracic versus more distant metastatic disease (median OS of 14.4 versus 10.9 months, $P = .64$) (Figure 3). To date, this represents the largest reported number of patients with PM with well-described M1 disease at diagnosis, analyzed for survival outcomes. Therefore, the available data corroborate the

categories of M0 and M1 identified in the 8th edition, and currently do not support the development of M1 subcategories (Figures 2 and 3).

What is new for the 9th Edition?

There are no changes relative to the M component in the 8th edition.

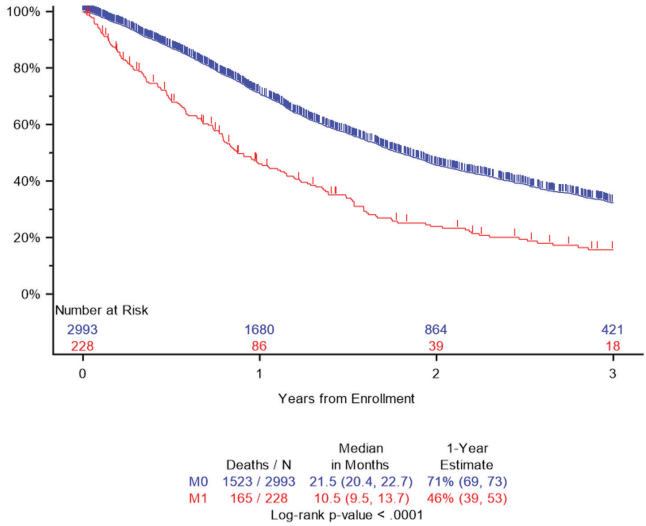

Figure 1. **Overall survival of patients by M category (M0 versus M1).**

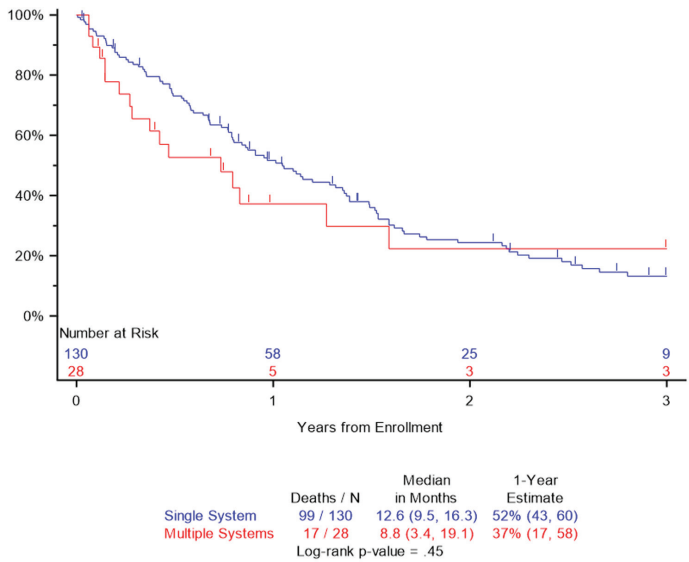

Figure 2. **Overall survival by number of involved organ systems (single versus multiple) in patients with M1 disease.**

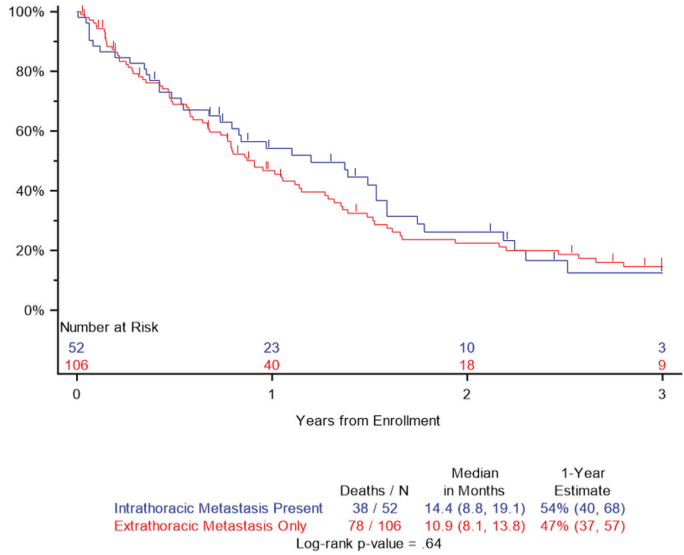

Figure 3. Overall survival of patients by the presence of intrathoracic versus extrathoracic metastases in patients with M1 disease.

References

1. Rusch VW, Giroux D, Kennedy C, et al. Initial analysis of the International Association for the Study of Lung Cancer mesothelioma database. *J Thorac Oncol.* 2012;7:1631-9. doi:10.1097/JTO.0b013e31826915f1
2. Rusch VW, Chansky K, Kindler HL, et al. The IASLC mesothelioma staging project: Proposals for the M descriptors and for revision of the TNM stage groupings in the forthcoming eighth edition of the TNM classification for mesothelioma. *J Thorac Oncol.* 2016;11(12):2112-9. doi:10.1016/j.jtho.2016.09.124
3. Kindler HL, Rosenthal A, Giroux DJ, et al. The IASLC mesothelioma staging project: Proposals for the M descriptors in the forthcoming ninth edition the TNM Classification for Pleural Mesothelioma. *J Thorac Oncol.*, in press 2024.

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Stage Groups

Anna K. Nowak, PhD, MBBS, and Valerie W. Rusch, MD, FACS

Table 1. Tumor, Node, Metastasis (TNM) Stage Groups in the 9th Edition of the Pleural Mesothelioma Staging Classification

	N0	N1	N2
T1	I	II	IIIA
T2	II	IIIA	IIIA
T3	IIIA	IIIA	IIIA
T4	IIIB	IIIB	IIIB
M1	IV	IV	IV

Explanatory Notes

In the 8th edition of the pleural mesothelioma (PM) staging system, the stage groups were extensively revised because of changes in the node (N) component.[1] Relative to the 7th edition,[2] these revisions also reflected the contribution to the IASLC PM database of data from patients presenting with advanced disease and patients managed non-surgically. By contrast with the 8th edition, data submitted to the IASLC PM database for the 9th edition of the staging system included information on a larger number of patients managed non-surgically, and more patients presenting with metastatic disease (M1) at diagnosis.[3] Analyses of the clinical tumor (cT) component added systematic pleural thickness measurements on computed tomography (CT) to qualitative T descriptors used in the 7th and 8th editions but eliminated some qualitative cT descriptors that cannot be accurately assessed on CT (e.g. invasion of the endothoracic fascia). Because pleural thickness measurements cannot be reliably assessed on surgical specimens, especially piecemeal specimens obtained at pleurectomy/decortication, only existing qualitative descriptors were used to describe the pathologic T (pT) component. Descriptors for the N and M components in the 9th edition are unchanged from those in the 8th edition. Recursive partitioning analyses of overall survivals (OS) indicated that further revision of the stage groups was appropriate in the 9th edition. As shown above (Table 1), stages IA and IB have

now been merged into Stage I, applicable only to T1N0M0 tumors. Stage II includes T1N1 and T2N0 tumors.[3] These changes lead to a clear separation of the Kaplan Meier curves for OS (Figures 1 and 2), especially among clinically staged (c stage) tumors (Figure 1). A comparison with the 8th edition stage groups is shown in Table 2. Although the difference in OS between c stages IIIB and IV does not meet statistical significance, a decision was made to limit c stage IV to patients presenting with M1 disease, thereby maintaining the convention for cTNM classification.

What is new for the 9th edition?

1. The stage IA and stage IB categories have been merged into stage I.
2. Only T1N0M0 tumors are now classified as stage I.
3. T2N0M0 tumors are now classified as stage II.
4. All T3 (N0-2) M0 tumors are now classified as stage IIIA.
5. All T4 (N0-2) M0 tumors are still classified as stage IIIB, and T-any N-any M1 tumors are still classified as stage IV.

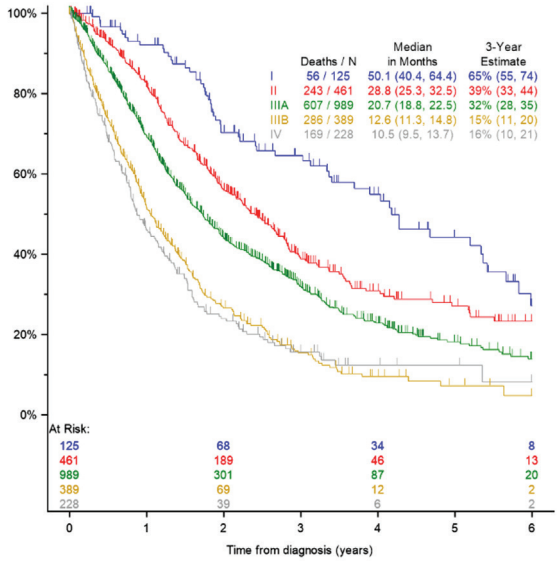

Figure 1. Overall survival of patients by 9th edition clinical stage groups in the 9th edition data set (n=2,192).

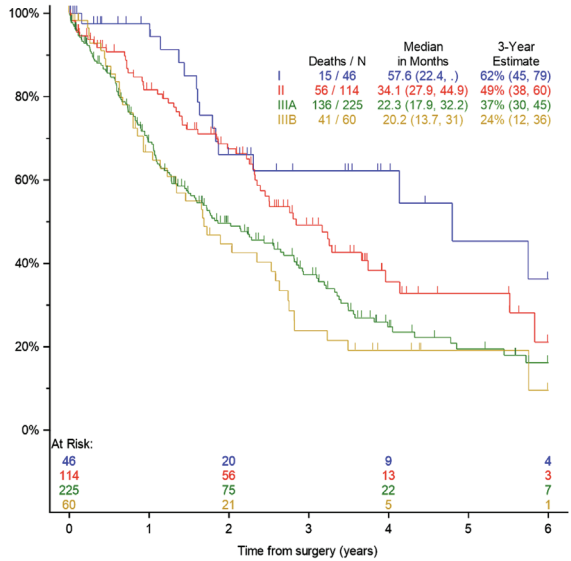

Figure 2. **Overall survival of patients by 9th edition pathologic stage groups in the 9th edition data set (n=445).**

Table 2. **Tumor, Node, Metastasis (TNM) Stage Groups in the 9th Edition of the Pleural Mesothelioma Staging Classification Relative to Those Used in the 8th Edition**

	N0		N1		N2	
	v8	v9	v8	v9	v8	v9
T1	IA	I	II	II	IIIB	IIIA
T2	IB	II	II	IIIA	IIIB	IIIA
T3	IB	IIIA	IIIA	IIIA	IIIB	IIIA
T4	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB
M1	IV	IV	IV	IV	IV	IV

References

1. Rusch VW, Chansky K, Kindler HL, et al. The IASLC mesothelioma staging Project: Proposals for the M descriptors and for revision of the TNM stage groupings in the forthcoming eighth edition of the TNM classification for mesothelioma. *J Thorac Oncol.* 2016;11(12):2112-9. doi:10.1016/j.jtho.2016.09.124
2. Rusch VW, Giroux D, Kennedy C, et al. Initial analysis of the International Association for the Study of Lung Cancer mesothelioma database. *J Thorac Oncol*. 2012;7:1631-9. doi:10.1097/JTO.0b013e31826915f1
3. Nowak AK, Giroux DJ, Eisele M, et al. The IASLC Pleural Mesothelioma Staging Project: Proposal for revision of the TNM stage groupings in the forthcoming ninth edition of the TNM classification for pleural mesothelioma. *J Thorac Oncol,* in press 2024. doi.org/10.1016/j.jtho.2024.05.002

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Prognostic Factors

Andrea S. Wolf, MD, and Harvey I. Pass, MD

Table 1. Multivariable Bidirectional Stepwise Model Featuring the 2014 Prognostic Factors, Including Pathologic Stage and Anemia (Normalized for Patient sex)

Validation cohort with sufficient data for all candidate model features (n=496)			
		Overall Survival	
Variable	n/N (%)	HR (95% CI)	P-value
No adjuvant treatment	67/496 (14%)	1.63 (1.21-2.21)	0.0014
Platelets > 400*10^9/L	87/496 (18%)	1.71 (1.30-2.26)	0.0001
Anemia	291/496 (59%)	1.62 (1.28-2.05)	<.0001
Histology: Non-epithelioid (vs. epithelioid)	75/496 (15%)	1.70 (1.27-2.29)	0.0004
Pathologic stage III/IV (vs. I/II)	260/496 (52%)	1.52 (1.20-1.91)	0.0004

HR, hazard ratio; 95% CI, 95% confidence interval; *P* value from score Chi-square test in Cox regression.

Table 2. Multivariable Bidirectional Stepwise Model Featuring Variables From 2014 Prognostic Factors Validation Dataset With AJCC/UICC 8th Edition Clinical Stage With Anemia and Mesothelin

Validation cohort with clinical stage, sufficient data for all candidate model features (n=747)			
		Overall Survival	
Variable	n/N (%)	HR (95% CI)	P-value
Histology: other (vs. epithelioid)	161/747 (22%)	2.01 (1.63-2.48)	<.0001
Anemia	377/747 (50%)	1.57 (1.30-1.88)	<.0001
Mesothelin > 6.7 nmol/L	481/747 (64%)	1.43 (1.17-1.75)	0.0006
Clinical stage III/IV (vs. I/II)	214/747 (29%)	1.31 (1.07-1.60)	0.0089
Platelets > 400*10^9/L	148/747 (20%)	1.37 (1.09-1.74)	0.0077
Age ≥ 50	687/747 (92%)	1.49 (1.04-2.15)	0.0304

American Joint Committee on Cancer, AJCC; HR, hazard ratio; 95% CI, 95% confidence interval, Union for International Cancer Control, UICC; *P* value from score Chi-square test in Cox regression.

Explanatory Notes

In 2009, the IASLC initiated an international pleural mesothelioma (PM) database to improve TNM classification.[1] Sequential iterations of the IASLC database have informed the development of the 7th, 8th, and 9th editions of the PM staging system.[1-3] Data entered from 1995-2009 to inform the 7th edition of the PM staging system were analyzed previously to evaluate supplemental prognostic variables.[4] These variables were studied in three scenarios: a) all data available including *pathologic stage* in addition to the core variables of tumor histology, patient sex and age, and type of surgical procedure, b) only *clinical stage* along with the core variables, and c) minimal variables available upon patient presentation including patient age and sex, tumor histology, and laboratory parameters. Recently, these variables were further evaluated with new data submitted for the 8th edition of the PM staging system to determine if the previous models could be improved.[5]

For this second analysis of prognostic factors, the patients entered into the database from 1995-2009 were considered as the training set and the patients entered from 2009-2019 as the validation cohort. Patients were assessed for association between prior prognostic variables and overall survival using Cox proportional hazards regression with bidirectional stepwise selection. Additional variables were analyzed, and models were compared using Harrell's C-index.

The training dataset included 3,101 patients, and the validation cohort 1,733 patients. Again, the models considered different scenarios including one where pathologic stage was available in addition to the core variables (Table 1) and one that included information at the time of initial patient evaluation in the absence of pathologic stage (Table 2). For the multivariable pathologic stage model applied to the training cohort, C-index was 0.68; 95% CI, 0.656-0.705. For the validation dataset (n = 497), C-index was 0.650; 95% CI, 0.614-0.685, and pathologic stage, histology, sex, adjuvant therapy, and platelet count were independently associated with survival. Adding anemia (adjusted to norms for patient sex) to the model increased the C-index to 0.652; 95% CI, 0.618-0.686. A basic presentation model including all parameters without stage yielded a C-index of 0.668; 95% CI, 0.641-0.695. Serum mesothelin level was a significant predictor in the model where only clinical stage information was available but not in the one where pathologic stage was available. It is hypothesized that elevated serum mesothelin level may represent a marker for increased tumor volume and may therefore be a variable colinear with pathologic tumor stage. By comparison, the European Organization for Research and Treatment of Cancer (EORTC) model yielded C-indices of 0.550; 95% CI, 0.511-0.589 and 0.577; 95% CI, 0.550-0.604 for pathologic stage and presentation models, respectively.[6] The IASLC training model performed well in the validation set and better than previously reported models including the EORTC model. Because the 9th edition of the PM

staging system incorporates extensive changes in the T component and in the stage groups resulting in much improved association of clinical stage with prognosis, a future re-analysis of prognostic factors including clinical stage is planned.

What is new for the 9th Edition?

1. The validity of the model of prognostic factors developed from the data available for the 7th edition of the PM staging system is corroborated in an analysis of updated data used to inform the 8th and 9th edition staging systems.
2. The addition of anemia, adjusted to norms for patient gender, improves the initial IASLC model which remains superior to other models including the EORTC model.

References

1. Rusch VW, Giroux D, Kennedy C, et al. Initial analysis of the International Association for the Study of Lung Cancer mesothelioma database. *J Thorac Oncol* 2012;7:1631-9. doi:10.1016/j.jtho.2016.09.123
2. Pass HI, Giroux D, Kennedy C, et al. The IASLC Mesothelioma Database: Improving staging of a rare disease through international participation. *J Thorac Onco*l 2016;11(12):2082-8. doi: 10.1016/j.jtho.2016.09.123
3. Wolf AS, Eisele M, Giroux DJ, et al. The International Association for the Study of Lung Cancer pleural mesothelioma staging project: Expanded database to inform revisions in the ninth edition of the TNM classification of pleural mesothelioma. *J Thorac Oncol*. 2024;doi:10.1016/j.jtho.2024.01.018
4. Pass HI, Giroux D, Kennedy C, et al. Supplementary prognostic variables for pleural mesothelioma: A report from the IASLC Staging Committee. *J Thorac Oncol* 2014;9(6):856-64. doi:10.1097/JTO.0000000000000181
5. Wolf AS, Rosenthal A, Giroux DJ, et al. The International Association for the Study of Lung Cancer pleural mesothelioma staging project: Updated modeling of prognostic factors in pleural mesothelioma. *J Thorac Oncol.* 2023;18(12):1689-1702. doi:10.1016/j.jtho.2023.08.005
6. Curran D, Sahmoud T, Therasse P, et al. Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience. *J Clin Oncol.* 1998;16(1):145-52. doi:10.1200/JCO.1998.16.1.145

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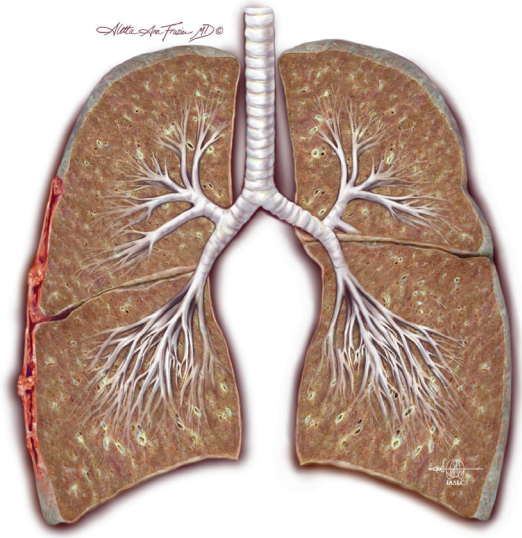
Atlas of Pleural Mesothelioma Tumor, Node, Metastasis (TNM) Classification

T1

CLINICAL T (cT)
cT1: Tumor limited to the ipsilateral pleura with **Psum[a] ≤12mm** with no involvement of the fissure (**Fmax[b] ≤5mm**)

PATHOLOGICAL T (pT)
pT1: Tumor limited to the ipsilateral pleura with no involvement of the fissure



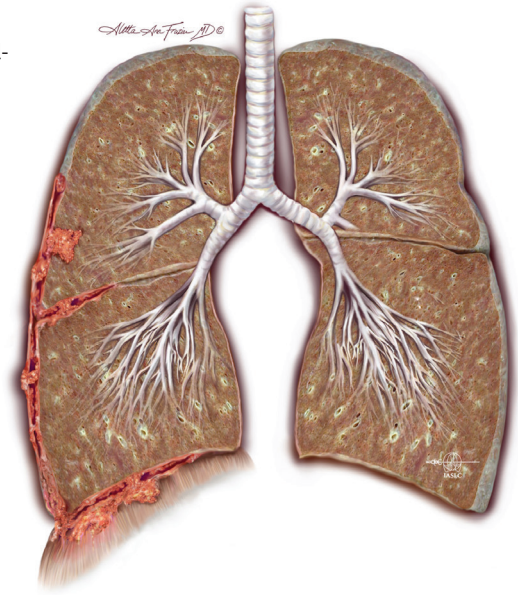
T2

cT2: Tumor involving the ipsilateral pleura with **Psum[a] ≤12mm** and with any of the following:
- involvement of the fissure (**Fmax[b] >5mm**)
- mediastinal fat invasion
- solitary area of chest wall soft tissue invasion;

or

Tumor involving the ipsilateral pleura with **Psum[a] >12mm but ≤30mm**, with or without:
- involvement of the fissure (**Fmax[b] >5mm**)
- mediastinal fat invasion
- solitary area of chest wall soft tissue invasion

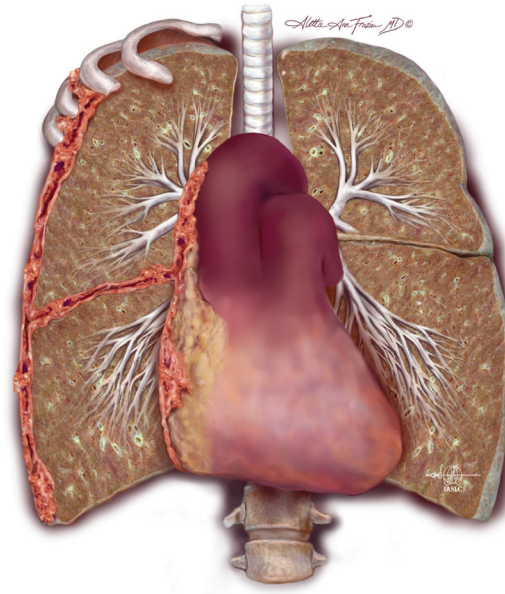
pT2: Tumor involving the ipsilateral pleura and with any of the following:
- involvement of the fissure
- ipsilateral lung parenchyma invasion
- diaphragm (non-transmural) invasion



T3

cT3: Tumor involving the ipsilateral pleura with **Psum[a] > 30 mm**; with or without:
- involvement of the fissure (**Fmax[b] >5mm**)
- mediastinal fat invasion
- solitary area of chest wall soft tissue invasion

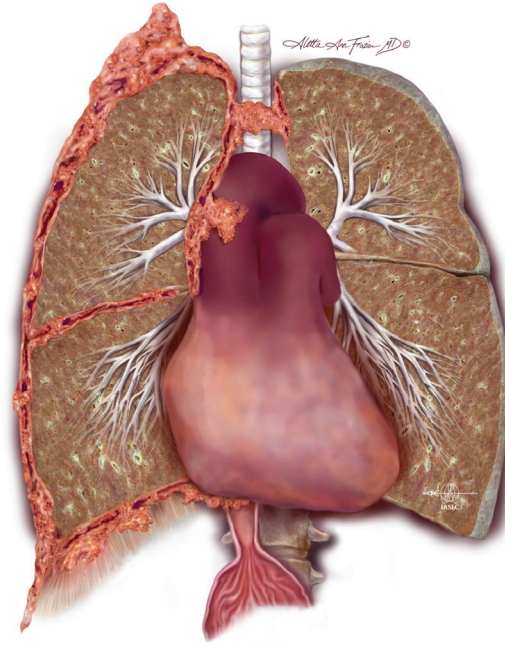
pT3: Tumor limited to the ipsilateral pleura (with or without fissure involvement) and with invasion of any of the following:
- mediastinal fat
- surface of pericardium
- endothoracic fascia
- solitary area of chest wall soft tissue



T4

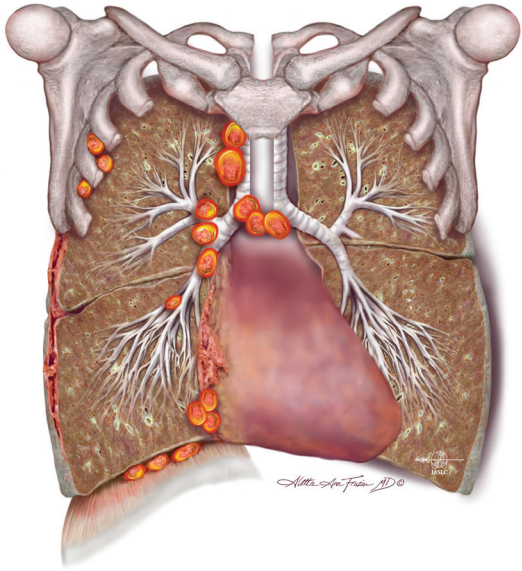
cT4: Tumor with invasion of any of the following (**any Psum[a]**):
- chest wall bony invasion (rib)
- mediastinal organs (heart, spine, esophagus, trachea, great vessels)
- diffuse chest wall invasion
- direct tumor extension through the diaphragm or pericardium
- direct extension to the contralateral pleura
- presence of malignant pericardial effusion

pT4: Tumor with invasion of any of the following:
- chest wall bony invasion (rib)
- mediastinal organs (heart, spine esophagus, trachea, great vessels)
- diffuse chest wall invasion
- transmural invasion of the diaphragm or pericardium
- direct extension to the contralateral pleura
- presence of malignant pericardial effusion



N1

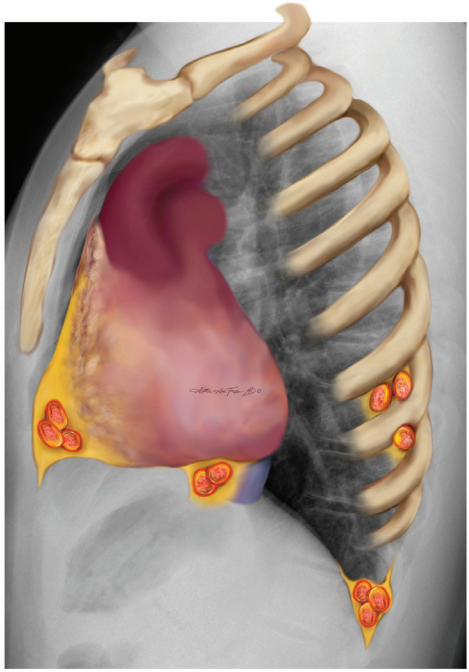
Metastases to ipsilateral intrathoracic lymph nodes (includes ipsilateral bronchopulmonary, hilar, subcarinal, paratracheal, aortopulmonary, para-esophageal, peridiaphragmatic, pericardial fat pad, intercostal, and internal mammary nodes)



Lateral N1

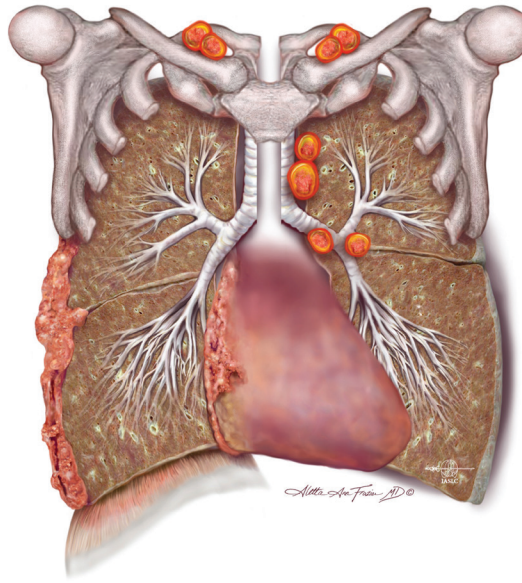
Nodal groups

- Anterior pericardial fat pad
- Fat pad adjacent to IVC
- Posterior intercostal nodes
- Posterior costophrenic angle



N2

Metastases in the contralateral mediastinal, ipsilateral or contralateral supraclavicular lymph nodes



PART IV

CANCER OF THE ESOPHAGUS AND OF THE ESOPHAGOGASTRIC JUNCTION

30

T, N, M Components and Stage Groups

Wentao Fang, MD

Tumor, node, and metastasis (TNM) classification is a means of recording extent of a disease observed by the clinician, whereas staging implies interpretation of these findings regarding prognosis. For carcinomas of the esophagus and the esophagogastric junction, T category (Table 1) is decided by depth of tumor invasion, N category (Table 2) is determined by number of regional lymph node involved, and M category (Table 3) is determined by presence or absence of distant metastasis. Stage and prognostic groups include clinical (cStage, before treatment decision), pathologic (pStage, after esophagectomy alone), and post-neoadjuvant pathologic therapy (ypStage) classification. Separate groupings for different cell types are required for clinically staged tumors (cTNM, Table 4 and 5). Pathological stage is similar for both squamous cell carcinoma and adenocarcinoma (pTNM, Table 6). The American Joint Committee on Cancer also has a pathological prognostic group, with non-anatomical factors including tumor grade and location. Post-neoadjuvant therapy pathological stage (ypTNM) is also identical for both histopathologic cell types (Table 7).

New analysis of the T, N, M, and overall stage groupings for carcinomas of the esophagus and the esophagogastric junction was not undertaken, as there has been no data collected for the 9th edition. The categories and descriptors provided in this chapter remain unchanged and are consistent with the 8th edition Union for International Cancer Control (UICC) TNM classifications.[1]

Table 1. T Component – Primary Tumor

Category	Descriptor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*/high-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosa, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosa
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades pleura, pericardium, azygos vein, diaphragm, or peritoneum (resectable)
T4b	Tumor invades other adjacent structures such as aorta, vertebral body, or trachea (non-resectable)

Table 2. N Component – Regional Lymph Nodes

Category	Descriptor
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 - 2 regional lymph nodes
N2	Metastasis in 3 - 6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes

Table 3. M Component – Distant Metastasis

Category	Descriptor
M0	No distant metastasis
M1	Distant metastasis

Table 4. Clinical Stage for Squamous Cell Carcinoma of the Esophagus and the Esophagogastric Junction (cTNM)

Stage 0	Tis	N0	M0
Stage I	T1	N0, N1	M0
Stage II	T2	N0, N1	M0
	T3	N0	M0
Stage III	T1, T2	N2	M0
	T3	N1, N2	M0
Stage IVA	T4a, T4b	N0, N1, N2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Table 5. Clinical Stage for Adenocarcinoma of the Esophagus and the Esophagogastric Junction (cTNM)

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N0	M0
Stage III	T2	N1	M0
	T3, T4a	N0, N1	M0
Stage IVA	T1-T4a	N2	M0
	T4b	N0, N1, N2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Table 6. Pathologic Stage for Cancers of the Esophagus and the Esophagogastric Junction (pTNM)

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T1	N1	M0
	T3	N0	M0
Stage IIIA	T1	N2	M0
	T2	N1	M0
Stage IIIB	T2	N2	M0
	T3	N1, N2	M0
	T4a	N0, N1	M0
Stage IVA	T4a	N2	M0
	T4b	Any N	M0
	AnyT	T3	M0
Stage IVB	AnyT	Any N	M1

Pathologic stage is similar for both squamous cell carcinoma and adenocarcinoma.

Table 7. Pathologic Stage After Neoadjuvant Therapy for Cancers of the Esophagus and the Esophagogastric Junction (ypTNM)

Stage	T	N	M
Stage I	T0-2	N0	M0
Stage II	T3	N0	M0
Stage IIIA	T0-2	N1	M0
Stage IIIB	T3	N1	M0
	T0-3	N2	M0
	T4a	N0	M0
Stage IVA	T4a	N1-2	M0
	T4a	NX	M0
	T4b	N0-2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

ypStage is also identical for both histopathologic cell types.

Explanatory Notes

1. Anatomic locations: The esophagus traverses three anatomic compartments: cervical, thoracic, and abdominal. The thoracic esophagus is divided into equal thirds: upper, middle, and lower. The abdominal esophagus is included in the lower thoracic section (Table 8). Cancers located in the cervical esophagus are staged as upper thoracic esophageal cancers, not as head and neck cancers. Cancers involving the esophagogastric junction with their epicenters within the proximal 2 cm of the gastric cardia (Siewert types I/II) are to be staged as esophageal cancers.
2. Rules for classification: Cancers staged using this staging system are epithelial cancers, including squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, undifferentiated carcinoma, neuroendocrine cancers, and adenocarcinoma with neuroendocrine features. Other malignancies, such as sarcomas, nonepithelial cancers, and gastrointestinal stromal tumors, are not staged using this system.
3. The T category is defined according to the depth of primary tumor invasion of the esophagus and the adjacent structures. Although size (length) of the tumor is also relevant, the depth of tumor invasion is of more important prognostic impact for esophageal cancers (Table 1).
4. The N category in the 9th edition TNM classification is decided by number of lymph nodes containing metastases (positive nodes), which is an important prognostic factor for esophageal cancer. Therefore, the minimum requirement for regional lymphadenectomy should include at least seven or more lymph nodes harvested for histological examination. If the lymph nodes are negative, but the minimal number of nodes examined is not met, classify as pN0 (Table 2).
5. Regional lymph nodes: Lymph nodes in continuity with the esophagus are considered regional nodes for esophageal cancers. These are irrespective of the site of the primary tumor, and refer to those lymph nodes in the esophageal drainage area including the celiac axis nodes and para-esophageal nodes in the neck but not the supraclavicular nodes (Table 9).
6. The M category in the 9th edition TNM classification is decided by whether there is distant organ metastasis or not (Table 3).
7. Unique TNM categories after neoadjuvant therapies (ypTisN1-3M0 and ypT0N0-3M0) were first introduced in the 8th edition staging system (Table 7). Upon analysis of the Worldwide Esophageal Cancer Collaboration data, marked difference in survival profiles were seen between patients who had received neoadjuvant therapy and those patients with clinically and pathologically staged cancers.

What is new for the 9th Edition?

The 9th edition TNM classification and stage groups for carcinoma of the esophagus and the esophagogastric junction are similar to the 8th edition classification, without any modification.

Table 8. Anatomical Divisions of the Esophagus

Cervical	From lower border of the cricoid cartilage to the thoracic inlet (suprasternal notch)
Upper thoracic	From the thoracic inlet to the level of the tracheal bifurcation
Mid-thoracic	The proximal half of the esophagus between the tracheal bifurcation and the esophagogastric junction
Lower thoracic	The distal half of the esophagus between the tracheal bifurcation and the esophagogastric junction

Table 9. Regional Lymph Node Stations for Cancers of the Esophagus and Esophagogastric Junction

Lymph Node Station	Name	Location
1R	Right lower cervical paratracheal nodes	Between supraclavicular paratracheal space and apex of lung
1L	Left lower cervical paratracheal nodes	Between supraclavicular paratracheal space and apex of lung
2R	Right upper paratracheal nodes	Between intersection of caudal margin of brachiocephalic artery with trachea and apex of lung
2L	Left upper paratracheal nodes	Between top of aortic arch and apex of lung
4R	Right lower paratracheal nodes	Between intersection of caudal margin of brachiocephalic artery with trachea and apex of lung
4L	Left lower paratracheal nodes	Between top of aortic arch and carina
7	Subcarinal nodes	Caudal to carina of trachea
8U	Upper thoracic paraesophageal lymph nodes	From apex of lung to tracheal bifurcation
8M	Middle thoracic paraesophageal lymph nodes	From tracheal bifurcation to caudal margin of inferior pulmonary vein
8Lo	Lower thoracic paraesophageal lymph nodes	From caudal margin of inferior pulmonary vein to esophagogastric junction
9R	Pulmonary ligament nodes	Within right inferior pulmonary ligament
9L	Pulmonary ligament nodes	Within left inferior pulmonary ligament
15	Diaphragmatic nodes	On dome of diaphragm and adjacent to or behind its crura
16	Paracardial nodes	Immediately adjacent to gastroesophageal junction
17	Left gastric nodes	Along course of left gastric artery
18	Common hepatic nodes	Immediately on proximal common hepatic artery
19	Splenic nodes	Immediately on proximal splenic artery
20	Celia nodes	At base of celiac artery

References

1. Oesophagus including oesophagogastric junction. In: Brierley JD, Gospodarowicz MK, Wittekind C, eds. TNM classification of malignant tumors. Lyon: International Union Against Cancer. 8th ed. Wiley; 2017:57-62.
2. Rice TW, Ishwaran H, Blackstone EH, et al.Recommendations for clinical staging (cTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. *Dis Esophagus.* 2016;7:913-19. doi: 10.1111/dote.12540
3. Rice TW, Apperson-Hansen C, Drice TW, et al. Recommendations for pathologic staging (pTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. *Dis Esophagus.* 2016;7:897-905. doi: 10.1111/dote.12533
4. Rice TW, Ishwaran H, Kelsen DP, et al.. Recommendations for neoadjuvant pathologic staging (ypTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. *Dis Esophagus.* 2016;7:906-12. doi: 10.1111/dote.12538
5. Rice TW, Apperson-Hansen C, DiPaola LM, et al. Worldwide Esophageal Cancer Collaboration: Clinical staging data. *Dis Esophagus*. 2016;7:707-14. doi: 10.1111/dote.12538
6. Rice TW, Chen L-Q, Hofstetter WL, et al. Worldwide Esophageal Cancer Collaboration: Pathologic staging data. *Dis Esophagus.* 2016;7:724-33. doi: 10.1111/dote.12520
7. Rice TW, Lerut TEMR, Orringer MB, et al. Worldwide Esophageal Cancer Collaboration: Neoadjuvant pathologic staging data. *Dis Esophagus.* 2016;7:715-23. doi: 10.1111/dote.12513

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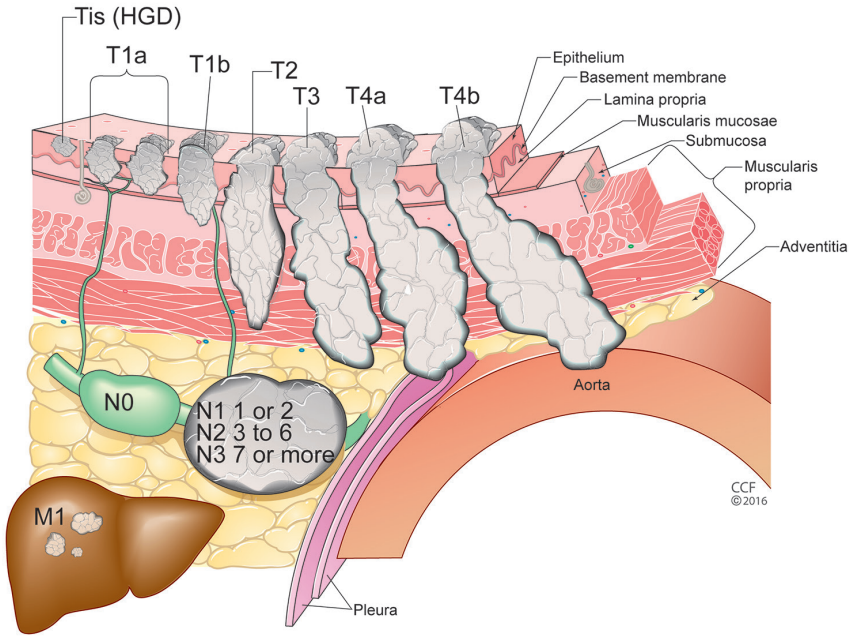
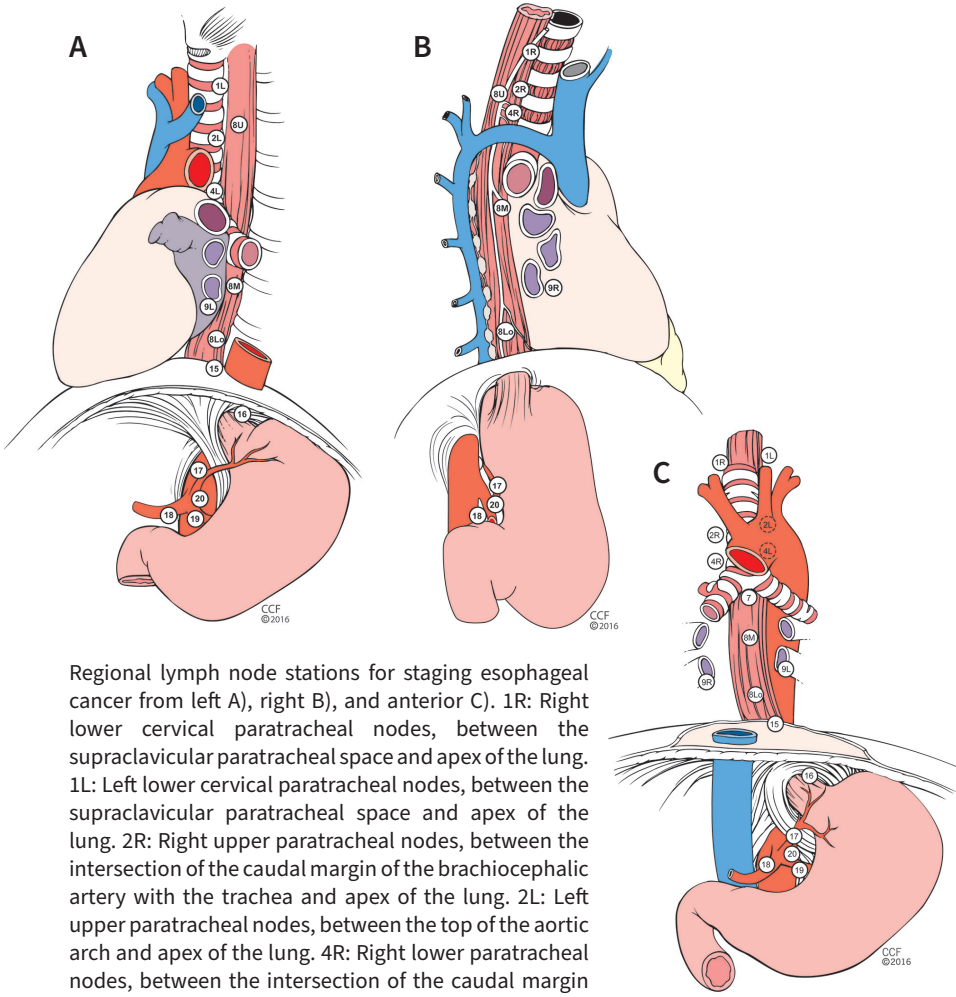
Atlas of Cancer of the Esophagus and of the Esophagogastric Junction Tumor, Node, Metastasis (TNM) Classification

Figure 1. **Ninth Edition TNM categories.**



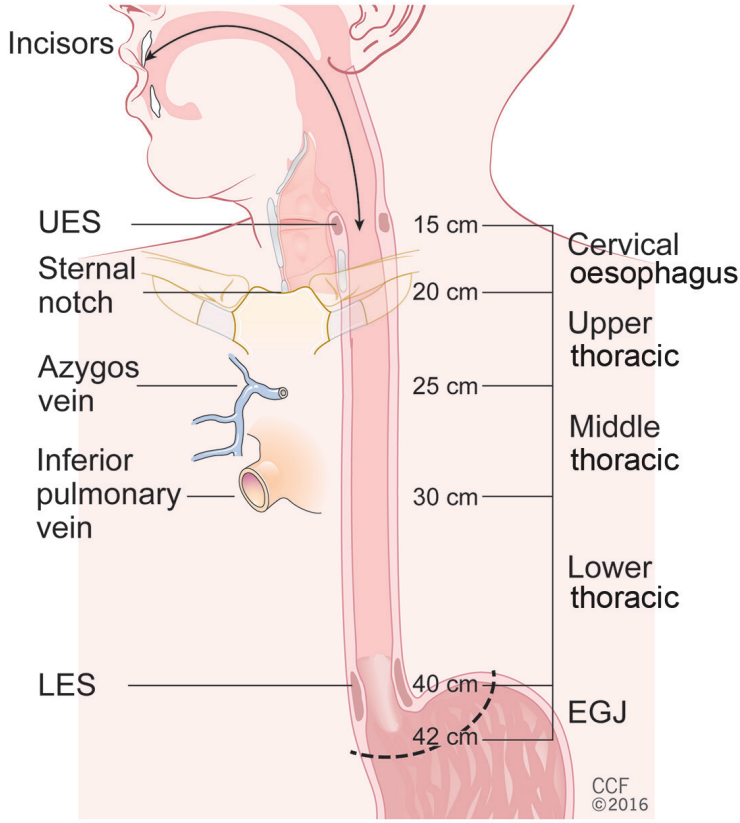
T is categorized as Tis: high-grade dysplasia; T1: cancer invades lamina propria, muscularis mucosae, or submucosa and is subcategorized into T1a (cancer invades lamina propria or muscularis mucosae) and T1b (cancer invades submucosa); T2: cancer invades muscularis propria; T3: cancer invades adventitia; T4, cancer invades local structures and is subcategorized as T4a: cancer invades adjacent structures such as pleura, pericardium, azygos vein, diaphragm, or peritoneum and T4b: cancer invades major adjacent structures such as aorta, vertebral body, or trachea. N is categorized as N0: no regional lymph node metastasis; N1, regional lymph node metastases involving 1 to 2 nodes; N2, regional lymph node metastases involving 3 to 6 nodes; and N3, regional lymph node metastases involving 7 or more nodes. M is categorized as M0: no distant metastasis; and M1: distant metastasis.

Figure 2. **Lymph node maps for esophageal cancer.**



Regional lymph node stations for staging esophageal cancer from left A), right B), and anterior C). 1R: Right lower cervical paratracheal nodes, between the supraclavicular paratracheal space and apex of the lung. 1L: Left lower cervical paratracheal nodes, between the supraclavicular paratracheal space and apex of the lung. 2R: Right upper paratracheal nodes, between the intersection of the caudal margin of the brachiocephalic artery with the trachea and apex of the lung. 2L: Left upper paratracheal nodes, between the top of the aortic arch and apex of the lung. 4R: Right lower paratracheal nodes, between the intersection of the caudal margin of the brachio cephalic artery with the trachea and cephalic border of the azygos vein. 4L: Left lower paratracheal nodes, between the top of the aortic arch and the carina. 7: Subcarinal nodes, caudal to the carina of the trachea. 8U: Upper thoracic paraesophageal lymph nodes, from the apex of the lung to the tracheal bifurcation. 8M: Middle thoracic paraesophageal lymph nodes, from the tracheal bifurcation to the caudal margin of the inferior pulmonary vein. 8Lo: Lower thoracic paraesophageal lymph nodes, from the caudal margin of the inferior pulmonary vein esophagogastric junction. 9R: Pulmonary ligament nodes, within the right inferior pulmonary ligament. 9L: Pulmonary ligament nodes, within the left inferior pulmonary ligament. 15: Diaphragmatic nodes, lying on the dome of the diaphragm and adjacent to or behind its crura. 16: Paracardial nodes, immediately adjacent to the gastroesophageal junction. 17: Left gastric nodes, along the course of the left gastric artery. 18: Common hepatic nodes, immediately on the proximal common hepatic artery. 19: Splenic nodes, immediately on the proximal splenic artery. 20: Celiac nodes, at the base of the celiac artery. Cervical periesophageal level VI and level VII lymph nodes are named as per the head and neck map.

Figure 3. Location of esophageal cancer primary site, including typical endoscopic measurements of each region measured from the incisors.



Exact measurements depend on body size and height. Location of cancer primary site is defined by cancer epicenter. Cancers involving the esophagogastric junction (EGJ) that have their epicenter within the proximal 2 cm of the cardia (Siewert types I/II) are to be staged as esophageal cancers. Cancers whose epicenter is more than 2 cm distal from the EGJ, even if the EGJ is involved, will be staged using the stomach cancer TNM and stage groups.

Key: LES, lower esophageal sphincter; UES, upper esophageal sphincter.

The third phase of the International Association for the Study of Lung Cancer (IASLC) Staging Project culminates with the publication of the third edition of the *IASLC Staging Manual in Thoracic Oncology*.

Since publication of the previous edition, an impressive database was created with the largest number of cases ever submitted, from 25 countries. The IASLC Staging and Prognostic Factors Committee (SPFC) has produced updated core papers on the Tumor, Node, Metastasis (TNM) components, and global staging of lung cancer. Additionally, the analyses and publications resulting from the third phase of the IASLC Staging Project address thymic epithelial tumors, neuroendocrine tumors, and pleural mesothelioma.

This *Manual* truly represents a collaborative endeavor. Special thanks go to all members of the SPFC for their dedication and hard work, to the participating institutions for sharing their data, to Cancer Research And Biostatistics (CRAB) for detailed statistical analysis, and to all patients for willingness to participate in large registries. The SPFC also thanks AstraZeneca for its generous support of this staging project, which will advance the overall management of patients with thoracic malignancies.

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