CHEST

The Proposed Ninth Edition TNM Classification of Lung Cancer

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A universal nomenclature of the anatomic extent of lung cancer has been critical for individual patient care as well as research advances. As progress occurs, new details emerge that need to be included in a refined system that aligns with contemporary clinical management issues. The ninth edition TNM classification of lung cancer, which is scheduled to take effect in January 2025, addresses this need. It is based on a large international database, multidisciplinary input, and extensive statistical analyses. Key features of the ninth edition include validation of the significant changes in the T component introduced in the eighth edition, subdivision of N2 after exploration of fundamentally different ways of categorizing the N component, and further subdivision of the M component. This has led to reordering of the TNM combinations included in stage groups, primarily involving stage groups IIA, IIB, IIIA, and IIIB. This article summarizes the analyses and revisions for the TNM classification of lung cancer to familiarize the broader medical community and facilitate implementation of the ninth edition system.

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Stage classification is a cornerstone of managing patients with cancer by providing a universal, consistent nomenclature about the anatomic extent of disease. This enables reliable communication and promotes assessment of the applicability of clinical trial results to an individual patient's tumor. TNM classification applies to a tumor (ie, the anatomic extent). The patient has many other characteristics that are explicitly not part of stage classification. TNM classification is not a prognostic model, as many patient-, setting-, and treatment-related factors also affect prognosis. Finally, treatment is not determined by the nomenclature of stage; this merely enables communication. Clinical studies define the role of treatment strategies; these are constantly evolving and include many factors besides anatomic tumor extent.

A nomenclature must remain consistent and stable over time. Nevertheless, advances in imaging and treatment reveal new aspects to be clinically relevant. An organized, formal process is used to

ABBREVIATIONS: AJCC = American Joint Committee on Cancer; GG = ground-glass; GG/L = ground- glass/lepidic; IASLC = International Association for the Study of Lung Cancer; LCAL = lung cancer with air lucency; SPFC = Staging and Prognostic Factors Committee; STAS = spread though air spaces; UICC = Union for International Cancer Control; VPI = visceral pleural invasion

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Take-home Points

Study Question: How is the ninth edition TNM classification of lung cancer different from the eighth edition system?

Results: N2 is subdivided into single- and multistation N2, and M1c is subdivided into single- and multiorgan system M1c, resulting in a rearrangement of T and N categories included in the stage groups IIA, IIB, IIIA, and IIIB.

Interpretation: A consistent nomenclature about anatomic extent of disease is fundamental to clear communication about clinical trial results and applicability to individual patients.

periodically refine the classification. The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) periodically review, coordinate, and define new editions of TNM to maintain relevance and global consistency.

Since 1996, in collaboration with AJCC and UICC, the International Association for the Study of Lung Cancer (IASLC) has developed infrastructure to refine successive editions of TNM. This involves an international multidisciplinary committee (the Staging and Prognostic Factors Committee [SPFC]), a large global database, and extensive statistical analysis (e-Fig 1).[1] The SPFC encompasses domains of thoracic malignancies (lung, thymic, mesothelioma, and esophageal), with multiple subcommittees focused on specific aspects of TNM. The current article describes the SPFC proposals for the ninth edition TNM classification of lung cancer; these have been formally adopted by the AJCC and UICC and are slated to take effect on January 1, 2025.

Methods

TNM Structure

The TNM system consists of three components: T for primary tumor extent, N for lymph node involvement, and M for distant metastases. Each T, N, and M component is divided into several categories (eg, T1, T2) and subcategories (eg, T1a, T1b). Various characteristics, known as descriptors, define what is included within a T, N, or M category. Combinations of T, N, and M categories are clustered together into stage groups.

A prefix specifies the context of TNM classification (Table 1). Clinical stage (c) refers to the final pretreatment stage (based on symptoms, physical signs, imaging, and biopsy results gathered within 4 months of diagnosis).[2] Pathologic stage (p) is defined according to the results of a surgical resection together with all clinical staging information (and, per AJCC, imaging deemed necessary following resection). Once established, the TNM classification is definitive for the specific context and must remain unchanged. The term presumptive or preliminary stage describes stage as it iteratively evolves during the process of patient evaluation.

Unfortunately, the p-prefix is often loosely applied to T and N components with a different meaning, namely that biopsy material is available (without resection). AJCC/UICC restrict use of pT and pN to a surgical resection (with rare exceptions).[2,3] AJCC explicitly defines microscopic assessment of T and N during diagnostic workup as cT and cN.[2] Rare exceptions when a pathologic designation is permitted without resection involve extensive tumors, are described differently by AJCC and UICC, and leave aspects undefined or ambiguous (e-Appendix 1).[2,3] Therefore, IASLC recommends that the p-prefix not be applied to individual components outside the context of surgical resection.[4]

TABLE 1] Context of TNM Classification

Prefix	Name	Definition
c	Clinical	Prior to initiation of any treatment, using any and all information available (eg, physical examination, imaging, biopsy results)
p	Pathologic	Following resection, based on pathologic assessment and all clinical information
y	Restaging	After part or all of the treatment has been given, and can be used in a nonsurgical setting (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)

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 examination
E2	Imaging	Evidence from special diagnostic means (CT scan, MRI, PET scan, ultrasound or direct visualization [endoscopy] without biopsy)
E3	Tissue	Invasive tests providing tissue for microscopy (a) Cytology (eg, EBUS-TBNA, thoracentesis) (b) Histology (eg, mediastinoscopy, core biopsy)
E4	Resection	Evidence of the extent of disease following definitive surgical resection and pathologic examination

EBUS-TBNA = endobronchial ultrasound-transbronchial needle aspiration.

To communicate the type of testing involved in defining the stage, the SPFC suggests an evaluation ("E") categorization (Table 2),[4] applicable to either individual components or the overall stage. For the latter, the highest level of assessment used is applied to the entire stage (eg, T2bN2aM0 E3a if endobronchial ultrasound-transbronchial aspiration was used to define the N status). This assumes that managing clinicians used the highest level of evaluation for the component that was most critical in establishing the correct stage. The type of evaluation does not automatically define accuracy; the need for additional tests varies, as do the performance characteristics of the tests in individual patients.

Database

A database of 124,581 patients diagnosed with lung cancer from 2011 to 2019 was assembled, with follow-up through December 2021.[1] Following exclusions due to missing information and quality checks, 87,329 patients were available for analysis, with a focus on 73,421 with non-small cell lung cancer. Geographically, 56% came from Asia/Australia, 25% from Europe, 16% from North America, 3.4% from South/Central America, and 0.1% from Africa/Middle East. Individual analyses imposed specific criteria; overall, for c- and p-stages, 58,193 and 39,192 cases were available for stage group analyses, 33,982 and 30,715 for T component analyses, 45,032 and 35,009 for N component analyses, and 14,937 (c-stage only) for M component analyses, respectively.[5-8] Separate confirmatory analyses of the proposed revisions were performed for small cell and carcinoid tumors of the lung.

When the T category and stage group were determined by the primary tumor size, the eighth edition definitions were used whenever available (ie, solid [c-stage] or invasive [p-stage] component size). The method on how size was measured was missing in approximately 50% of cases, however, reflecting that the eighth edition size measurement recommendations were published in 2016.[9] Cases with specific solid/invasive size and those with an unspecified method of the size measurement were combined; separate analyses according to type of size measurement were deemed inappropriate due to confounding by time period. However, secondary analyses comparing the overall cohort vs a cohort with solid/invasive size measurements found similar ordering and discrimination.

Analysis

A formal methodology was followed to divide what is essentially a continuum into categories and groups.[10] Overall survival was used to reflect inherent biological behavior, together with practical considerations and relevance in a contemporary clinical context. Because prognosis varies (eg, over time, according to region, setting, histotype), the SPFC required consistent ordering and discrimination across multiple tiers of subset analyses. Additional tests for within-group homogeneity, broad generalizability, and assessment of potential confounders were included as appropriate.

To promote stability over time, changes were required to be based on strong evidence and to permit backward compatibility. Analyses involving < 50 patients and survival differences $< 5\%$ were considered questionable due to poor ability to assess potential confounders or consistency among subgroup analyses. Although differences were generally required to be statistically significant, sample size and potential confounding were taken into account. Furthermore, the widespread acceptance alone of certain anatomic characteristics sometimes justified retention.

Results

The TNM classification applies to primary lung carcinomas, including non-small cell lung cancer, small cell lung cancer, and bronchopulmonary carcinoid tumors. It does not apply to pulmonary sarcomas or lymphomas.

TNM Categories and Descriptors

Potential revisions of the T, N, and M categories were explored by assessing consistency and generalizability of discrimination, as well as usefulness in the context of current clinical care strategies. Following discussions within each subcommittee and the entire SPFC, the definitions shown in Table 3[7] were selected. This involved no changes to the T component, subdivision of N2 (into N2a with metastasis to a single station and N2b to multiple N2 stations), and subdivision of M1c (into M1c1 with multiple metastases in a single organ system and M1c2 involving multiple organ systems).

T Categories: The T descriptors primarily involve increasing size, or increasing invasion peripherally (eg, visceral pleura, chest wall) or centrally (eg, main bronchus, carina).[6] When multiple T descriptors are applicable to a tumor, the highest T category is chosen. The size measurement is defined by the largest dimension of the solid component (on imaging, c-stage) or the invasive component (on microscopy, p-stage).[9] The size of a ground-glass (GG) or lepidic component is not counted.

The solid component size is measured on thin CT scan images ($\leq$ 1.5 mm) using lung windows, although mediastinal windows can be useful to evaluate changes in density over time.[11] Generally, axial images are sufficient, but multiplanar images can be used if deemed to better represent the largest tumor dimension.[11] If there are several solid components, the size of the largest solid portion is used.[9] Microscopically, the largest dimension of the invasive component is used; any adjacent spread through air spaces (STAS) is not counted.[9,12] Rarely, when pathologic measurement is problematic and deemed inaccurate, using the clinical measurement as the pT size is recommended.[3,9,13]

A Pancoast tumor is classified as T3 if it involves thoracic (ie, T1 or T2) nerve roots, the stellate ganglion, or the chest wall (ribs or soft tissue). It is classified as T4 if it involves vertebral bodies, the spinal canal, subclavian vessels, cervical nerve roots, or components of the brachial plexus.[7]

N Categories: Various potential revisions were considered, including a shift to the number of node stations, zones, and hybrid approaches.[5] The analyses supported maintaining the traditional categories by anatomic location but subdividing N2 into single vs multiple station involvement (Table 3). Specifically, consistent ordering and discrimination were shown in multiple cohorts: R0, R-any, T1, T2, T3, and T4, and in pairwise comparisons of adjacent (sub)categories and by multivariable regression. Generalizability was verified across time periods, histotypes, geographic regions, source data types, and treatment approaches.[5] Consistent ordering and discrimination were seen in both c- and p-stage analyses (not previously feasible for p-stage).

The ninth edition classification highlights the need for thorough clinical assessment and reporting, as well as thorough preoperative and intra-operative node evaluation. If no nodes are assessed, the NX designation applies. The data granularity was insufficient to assess which imaging modalities or biopsy techniques were used or the thoroughness thereof. Nevertheless, the consistent survival differences observed in a large global database provide evidence of real-life applicability (although the analysis excluded cases without sufficient information about the number and sites of node involvement).

The ninth edition N classification underscores the value of consistent definitions of node stations. No changes are recommended to the lung cancer node map (Fig 1).

M Categories: The M subcommittee explored several issues, including assessments of metastatic burden (size, number of lesions, and/or sites), impact of specific metastatic sites, and a definition of oligometastatic disease.[8] The distinction of M1a, M1b, and M1c remained consistent in the ninth edition database. The prognostic impact of a pleural effusion deemed to be malignant was similar regardless of whether it was cytologically proven (this does not include effusions believed to be benign). A size threshold for the largest metastasis could not be defined with sufficient consistency. The impact of specific metastatic sites (eg, brain, adrenal, bone) was also inconsistent. Investigation of permutations of the number of lesions and metastatic organ sites suggested that the most robust categorization involved four categories (Table 3): M1a (intrathoracic metastases), M1b (single extrathoracic metastasis), M1c1 (multiple metastases in a single organ system), and M1c2 (multiple metastases in multiple organ systems).[8]

TABLE 3] Definitions for the T, N, and M Descriptors

T: Primary tumor	
T0	No evidence of primary tumor
Tis	Carcinoma in situ (squamous cell carcinoma or adenocarcinoma)
T1	Tumor surrounded by lung or visceral pleura, or in a lobar or more peripheral bronchus
T1mi	Minimally invasive adenocarcinoma[a]
T1a	Tumor ≤ 1 cm in greatest dimension[b]
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 or invades an adjacent lobe - Involves main bronchus (not carina) or atelectasis/obstructive pneumonitis extending to the hilum[c]
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, thoracic nerve roots (eg, T1, T2), or stellate ganglion - Invades pericardium, phrenic nerve, or azygous vein - Separate tumor nodule(s) in the same lobe as the primary
T4	Tumor with any of the following features: - Tumor > 7 cm in greatest dimension - Invades vertebra, lamina, spinal canal, subclavian vessels, brachial plexus, or cervical nerve roots - Invades thymus, trachea, carina, recurrent laryngeal nerve, esophagus, or diaphragm - Invades heart or great vessels (aorta, superior/inferior vena cava, intrapericardial vessels) - Separate tumor nodule(s) in a different ipsilateral lobe than that of the primary
N: Regional lymph node involvement	
N0	No regional lymph node metastasis
N1	Metastasis(es) in ipsilateral pulmonary or hilar lymph nodes
N2	Metastasis(es) in ipsilateral mediastinal and/or subcarinal lymph node(s)
N2a	…involving a single ipsilateral mediastinal/subcarinal nodal station
N2b	…involving multiple ipsilateral/subcarinal mediastinal nodal stations
N3	Metastasis in supraclavicular or scalene node(s) or contralateral mediastinal/hilar node(s)
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Malignant pleural or pericardial effusion[d] or pleural/pericardial nodules Separate tumor nodule(s) in a contralateral lobe
M1b	Single extrathoracic metastasis[e]
M1c	Multiple extrathoracic metastases
M1c1	…involving a single organ system[f]
M1c2	…involving multiple organ systems

TX, NX = T or N status unable to be assessed. TX includes tumors proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy. (Reprinted with permission from Rami-Porta et al.[7])

[a]Solitary adenocarcinoma (≤ 3 cm), predominantly lepidic, and ≤ 5 mm invasion in any one focus.

[b]A superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is classified as T1a.

[c]Atelectasis/obstructive pneumonitis may involve part of or the entire lung.

[d]Pleural effusions are excluded that are cytologically negative and clinically judged not to be due to cancer (eg, transudative, nonbloody).

[e]This includes involvement of a single nonregional node.

[f]A diffuse organ system, such as the skeleton, is considered one organ (ie, metastases limited to several bones are classified as M1c1).[7]

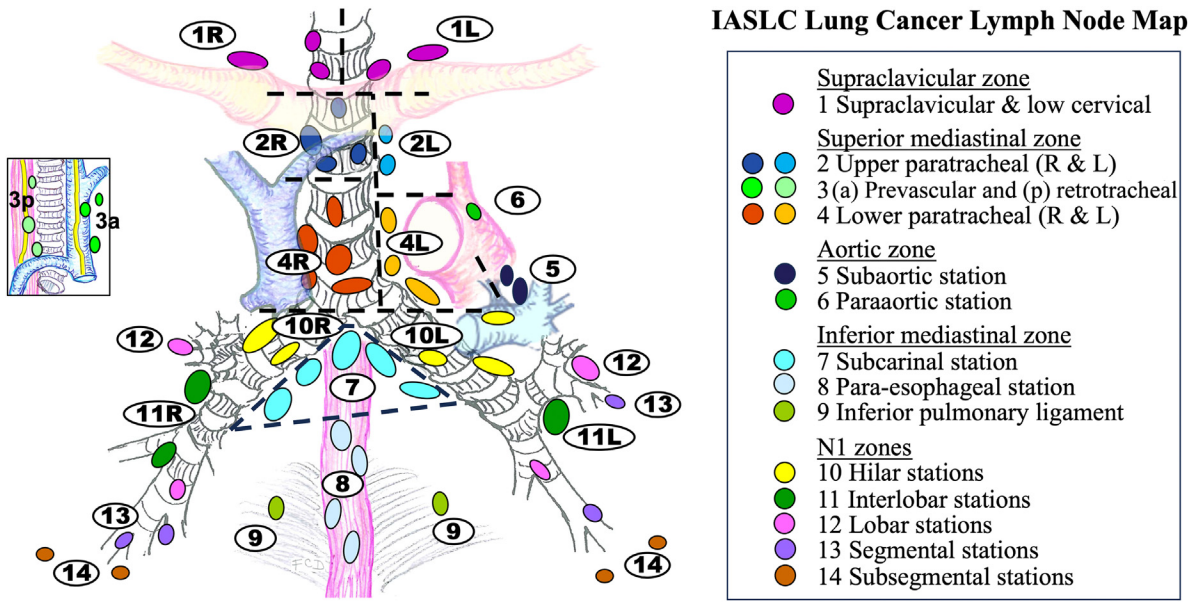

Figure 1 – *The International Association for the Study of Lung Cancer (IASLC) Node Map. L indicates left and R indicates right in the map. Key boundaries include: The apex of the lung or top of the manubrium distinguishes supraclavicular (#1) from #2R/L nodes, the left border of the trachea to distinguish right from left mediastinal nodes, the lower border of the left innominate vein to distinguish #2R from #4R nodes, the upper border of the aortic arch to distinguish #2L from #4L nodes, the lower border of the azygous vein to distinguish #4R from #10R nodes, and the upper border of the left pulmonary artery to distinguish #4L from #10L. The ligamentum arteriosum (in a sagittal plane) is the boundary between #4L (medial) and #5 (lateral to this). The subcarinal station (#7) extends inferiorly to the upper edge of the lower lobe bronchus on the left and the upper edge of the middle lobe/superior segment bronchus on the right.*

This was consistent in multivariable analysis and multiple subset analyses (eg, region, time period, performance status, surgical/nonsurgical management, histotype).

An increasing number of metastases correlated with incrementally decreasing survival.[8] Multiple thresholds of dichotomization were statistically significant, but no inflection point emerged to define oligometastatic disease. Although some potential confounders were shown to have little impact (eg, metastatic site), others could not be adequately assessed (eg, comorbidities, treatment details). It was deemed better to view the number of metastases as a clinical consideration together with the feasibility of local treatment; arbitrary selection of a dichotomization threshold for stage categorization seems unjustified.[8]

The M1c1 definition should be applied to an organ system, regardless of whether the organ is solitary, paired, or diffuse throughout the body (eg, skeleton). The analysis performed of the available data reflects this definition.

It was not possible to define whether the M1c1 descriptor should include a limit to the number of metastases in one organ system. It is likely that this represents a continuum that is best left to clinical judgment in individual patients, rather than arbitrarily choosing a threshold.

Separation of M1b and M1c1 was not fully investigated. These groups were not consistently distinct in all analyses; detailed investigation of potential reasons or confounders was not performed. It was deemed that distinguishing M1b and M1c1 should be maintained, based on lack of clear evidence to the contrary, the historical precedent, and a clinical consensus that views a solitary metastasis differently than multiple metastases. Similarly, in some subgroups, the separation of M1a and M1b was minimal. However, distinguishing these categories is maintained in the ninth edition for the same reasons.

Stage Groups

The new N and M subcategories mandated a new definition of stage groups. Several candidate proposals were examined in a training data set (two-thirds of the data, balanced according to year of diagnosis and type of data source) using several approaches (ie, recursive portioning, multivariable regression), and assessments of within-group homogeneity and between-group discrimination in overall survival. Additional

8th Edition TNM Categories

T/M	Label	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a Inv	IB	IIB	IIIA	IIIB
	T2a >3-4	IB	IIB	IIIA	IIIB
	T2b >4-5	IIA	IIB	IIIA	IIIB
T3	T3 >5-7	IIB	IIIA	IIIB	IIIC
	T3 Inv	IIB	IIIA	IIIB	IIIC
	T3 Same Lobe Nod	IIB	IIIA	IIIB	IIIC
T4	T4 >7	IIIA	IIIA	IIIB	IIIC
	T4 Inv	IIIA	IIIA	IIIB	IIIC
	T4 Ipsi Nod	IIIA	IIIA	IIIB	IIIC
M1	M1a Pl Dissem	IVA	IVA	IVA	IVA
	M1a Contr Nod	IVA	IVA	IVA	IVA
	M1b Single Les	IVA	IVA	IVA	IVA
	M1c Mult Les	IVB	IVB	IVB	IVB

9th Edition TNM Categories

T/M	Description	N0	N1	N2		N3
				N2a	**N2b**	
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 tumor nodule	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 >7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral tumor nodule	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pleural/pericardial dissemination	IVA	IVA	IVA	IVA	IVA
	M1a Contralateral tumor nodule	IVA	IVA	IVA	IVA	IVA
	M1b Single extrathoracic lesion	IVA	IVA	IVA	IVA	IVA
	M1c1 Multiple lesions, 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Multiple lesions, >1 organ system	IVB	IVB	IVB	IVB	IVB

Figure 2 – *Comparison of eighth and ninth edition stage groups for lung cancer. New N and M categories are indicated in bold font; red outlines highlight the TNM combinations that are reassigned. Contr Nod = contralateral separate tumor nodule; Inv = invasion; Ipsi Nod = ipsilateral separate tumor nodule; Les = lesion (extrathoracic metastatic lesion); Mult = multiple; Pl Dissem = pleural or pericardial involvement; Same Lobe Nod = same lobe separate tumor nodule. (Reprinted with permission from Rami-Porta et al.[7])*

considerations included alignment with evolving treatment strategies and ease of adoption of potential changes.

Figure 2 compares the eighth edition stage groups vs the ninth edition schema that emerged as the best.[7] The new stage groups exhibit robust homogeneity in both the c- stage and the p-stage.[7] Multivariable regression revealed consistent ordering and discrimination, confirmed in the validation cohort and multiple subset analyses of generalizability (e-Figs 2-4).[7] The unadjusted pairwise comparisons of cIIIC vs cIVA were mostly not statistically significant; distinguishing these groups is nonetheless deemed appropriate because of the fundamental difference between M0 and M1. Other sporadic nonsignificant unadjusted comparisons are attributable to limited sample sizes and potential confounders.

Figure 3 shows that M0 tumors are coalesced into groups that largely lie along diagonals; higher stage groups consist of tumors with progressively higher T or higher N categories. Figure 4 schematically depicts the specific TNM combinations included in the stage groups. The 5-year survival according to stage group is summarized in e-Tables 1 and 2; outcomes vary according to time period, region, and multiple other characteristics.[7,14,15]

Conceptually, the biological behavior of a locally invasive tumor (higher T/low N) seems different than that of a lower T tumor that has greater nodal dissemination (higher N).[16] However, the analysis exhibited general homogeneity in overall survival. Furthermore, it is unclear that the optimal therapy is fundamentally different for higher T/lower N tumors vs lower T/higher N tumors that are included in the same stage group.

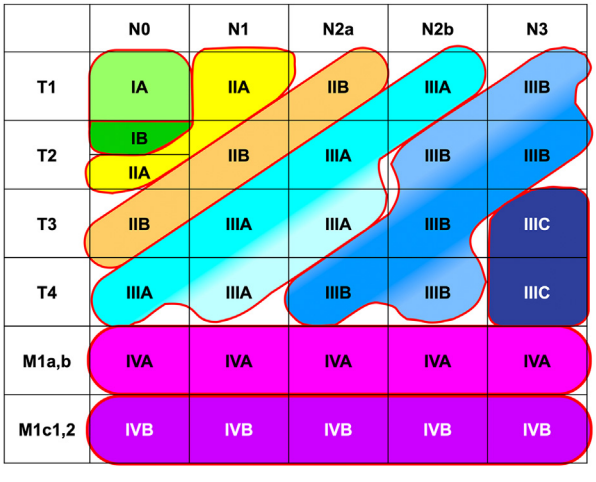

Figure 3 – *Grid of TNM categories included in stage groups in the ninth edition TNM classification of lung cancer.*

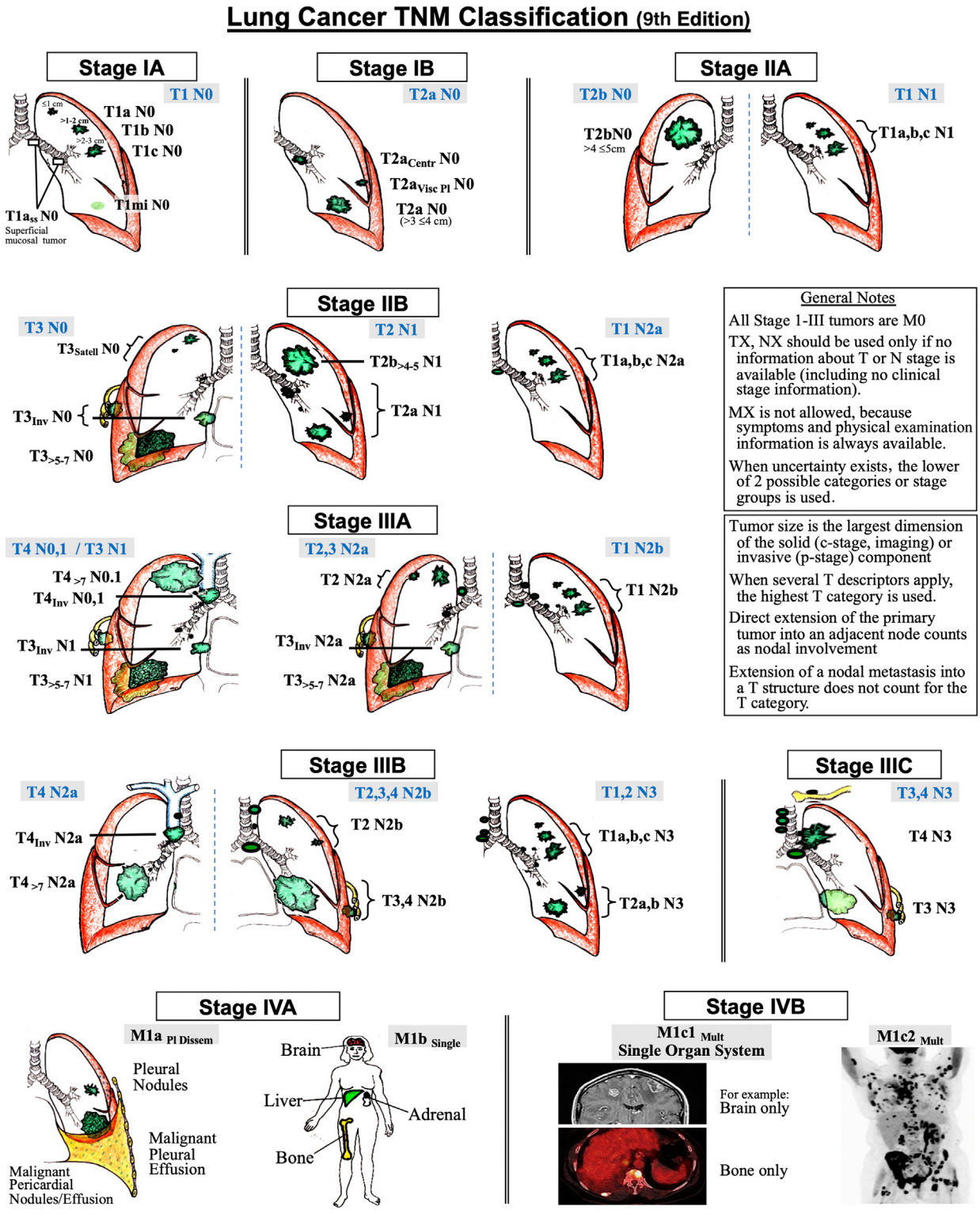

Figure 4 – *Specific TNM categories included in the ninth edition stage groups. Centr = central; Inv = invasion; Mult = multiple; Pl Dissem = pleural or pericardial involvement; Satell = same lobe separate tumor nodule; Visc Pl = visceral pleural invasion.*

General Rules Regarding TNM Classification

Primary tumor invasion into other structures (eg, phrenic nerve, aorta) counts to determine the T category. Similarly, extension of a primary tumor into a lymph node counts as nodal involvement. However, extension of nodal involvement into a T structure (eg, nodal extension into the recurrent laryngeal nerve) does not count as T involvement.[2,3] If it is impossible to determine if invasion of hilar/mediastinal structures emanates from the primary tumor or involved lymph nodes, the invasion is counted in determining the T category.[7] Finally, in rare instances, the primary tumor may directly invade an extrathoracic organ (eg, liver); this is not classified as M1.[2,3]

A general AJCC/UICC rule is that when uncertainty exists regarding which designation is appropriate, the lower of the categories or stage groups in question should be used.[2,3]

Multiple Pulmonary Sites

The SPFC did not undertake any changes to the classification of multiple pulmonary sites of lung cancer. This topic encompasses four entities that represent different disease processes with different biological behavior (e-Fig 5, Table 4[17]). It is crucial to distinguish these; criteria that define this are provided in e-Tables 3 to 6.[17-20]

Synchronous second primary lung cancers are not rare. The clinical characteristics (ie, presentation, imaging) and biological behavior (ie, outcomes, recurrence patterns) for each tumor are similar to that of single "typical" lung cancers (ie, solid, spiculated).[19] Most second primary lung cancers have the same histotype and may have similar biomarker patterns. This means histotype and biomarker patterns alone are not entirely reliable to classify two tumors as separate primary or related tumors; clinical information and imaging appearance are crucial components. Subsequent outcomes generally confirm a clinical assessment that two tumors are synchronous primary lung cancers.[19] Second primary lung cancers should be designated with a T, N, and M category for each tumor.

Some patients with a solid primary lung cancer have one or more solid separate tumor nodule(s) of the same histotype. The mechanism by which they arise is unclear. These tumors are classified according to the location of the separate nodule relative to the index tumor (T3 for same-lobe, T4 for ipsilateral different lobe, and M1a for contralateral lobe) with a single N and M category.[18] However, when resected, outcomes are equally good for T3, T4, and M1a separate tumor nodules, only slightly lower than those of similar tumors without a separate tumor nodule.[18] Although distinguishing synchronous primary cancers and a separate tumor nodule can be difficult, the same management is generally warranted (aggressive treatment of each lesion), and subsequent outcomes are also similar.

The most common disease pattern involving multiple pulmonary sites is that of multiple GG nodules. This group has different demographic characteristics, excellent outcomes, and infrequent nodal or extrathoracic recurrences.[20] Most of these lesions do not progress over 5 to 10 years.[21,22] The T category of these GG/L tumors is the solid/invasive size of the highest T lesion with multiplicity indicated by the number or "m" in parentheses and a collective N and M category for all [eg, T1a(m)N0M0]. This multifocal adenocarcinoma entity is readily recognized by imaging; a detailed histologic assessment of each GG/L tumor nodule is unecessary.[20]

A less common pattern of lung cancer appears radiologically similar to pneumonia (so-called "pneumonic-type" lung cancer). Extrathoracic involvement is infrequent, but prognosis is distinctly worse than for the other entities exhibiting multiple pulmonary sites of lung cancer.[20] Diffuse pneumonic-type lung cancers are designated by size, or, when size measurement is difficult, T3 if in one lobe, T4 if involving multiple ipsilateral lobes, and M1a if involving both lungs with a single N and M category for all areas of involvement.

Recently, lung cancer with air lucency (LCAL) has emerged as another pattern of disease with frequent multiple pulmonary sites of involvement.[23] Progression of LCAL is often indolent, but sometimes rapid acceleration occurs, especially when a solid component develops. Progression is associated with frequent nodal involvement and a poor prognosis. TNM classification of LCAL has not been officially addressed. We suggest that TNM classification be done similar to multifocal GG/L adenocarcinoma, with T defined by the solid component of the largest lesion and (#/m) to indicate multiplicity, and a single N and M.

Other Staging-Related Definitions

R Status: The classification of resection completeness as R0 (complete), R1 (microscopically positive resection margin), and R2 (gross unresected tumor) is firmly embedded in the AJCC/UICC classification. Lung cancer

TABLE 4] Patterns of Disease of Patients With Multiple Pulmonary Sites of Lung Cancer

	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 (eg, spiculated)	Typical lung cancer (eg, solid, spiculated) with separate solid nodule	Multiple ground-glass or part-solid nodules	Patchy areas of ground glass and consolidation
Pathologic features	Different histotype or different morphology by comprehensive histologic assessment	Distinct lesions with the same morphology by comprehensive histologic assessment	Adenocarcinomas with prominent lepidic component (typically varying degrees of adenocarcinoma in situ, MIA, LPA)	Same histology throughout (most often invasive mucinous adenocarcinoma)
TNM classifica-tion	Separate cTNM and pTNM for each cancer	Location of separate nodule relative to primary site determines if T3, T4, or M1a; single N and M	T based on highest T lesion with (#/m) indicating multiplicity; single N and M	T based on size, or T3 if in single lobe, T4 or M1a if in different ipsilateral or contralateral lobes; single N and M
Conceptual view	Unrelated tumors	Single tumor, with intrapulmonary metastasis	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. (Reprinted with permission from Detterbeck et al.[17])

also includes an uncertain category [R(un)], in which the presence of residual tumor or the prognostic implication is uncertain (e-Fig 6, Table 5).[4,24] Validation studies have confirmed progressively lower survival for R0 vs R(un) vs R1 vs R2 (R1 and R2 are sometimes less clearly distinct, perhaps due to R2 sample size).[24]

Two uncertain category descriptors are labeled R0(un), involving negative margins but a limited lymph node evaluation or the highest node station assessed was positive. Multiple studies have shown that limited node assessment is associated with lower survival.[24] IASLC defines a full assessment as six or more node stations,

TABLE 5] Residual Tumor Following 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

(Reprinted with permission from Detterbeck et al.[24])
[a]Recommended assessment is ≥ 6 node stations (including subcarinal and two other mediastinal stations).
[b]Applies to any site of tumor resection (ie, 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.

including the subcarinal and two or more other mediastinal stations and hilar/lobar stations. IASLC counts stations invasively assessed either preoperatively or intra-operatively, as well as a documented absence of nodes in a station.[4,24] Subdivision of the N2 category and the shift to sublobar resection highlight the importance of careful node assessment. The American Cancer Society 2020 Operative Standard calls for sampling of three or more mediastinal stations and one hilar station.[25] However, some data suggest that the benefit associated with more thorough node evaluation is not seen in small GG tumors.[26]

The R(un) category also includes carcinoma in situ at the bronchial margin and when a pleural lavage was performed and its findings were cytologically positive.[4,24] These are designated as R1 (as defined by the UICC)[13] with the addition of (is+) and (cy+), respectively, to distinguish them from a standard positive margin or malignant pleural effusion. Pleural lavage has been studied extensively (a meta-analysis included 28 studies and > 20,000 patients),[27] but it is seldom practiced outside of Japan. Pleural lavage cytology is positive in approximately 5% of patients, which correlates consistently with lower survival and higher recurrence rates following adjustment for confounders.[24] However, pleural recurrence accounts for only approximately 30% of recurrences.

A macroscopically complete resection in the face of a malignant pleural effusion or nodules is designated as an R1 resection. Although such patients generally do not undergo resection, in those who do, 5-year survival rates of approximately 20% are reported consistently.[24]

When a resection involves several R descriptors, the highest applicable R category is used. IASLC recommends using the R classification only in the context of a surgical resection and not consider expansion to describe response to nonsurgical treatment modalities.[4,24]

IASLC recommends applying the R classification to any site of resection (primary tumor, nodes, pleural nodules, or an extrathoracic metastasis).[4,24] The site of resection should be recorded (eg, R0 [thorax] or R0 [adrenal]). In addition, the R classification applies to a specific surgical procedure, and it does not count tumor in another site that is to be addressed separately (perhaps with another treatment modality). Recording the site of resection (eg, R0 [thorax]) and the M category communicates the completeness of a specific resection and acknowledges remaining tumor at another site. This approach can accommodate separate management steps, as well as a combination of treatment modalities, and can communicate the completeness of a specific step, all of which are important aspects with the increasing use of definitive local therapy for oligometastatic disease.

Additional Histologic Descriptors: The TNM system includes several additional histologic descriptors; however, only visceral pleural invasion (VPI) affects stage classification. Both invasion through the pleural elastic layer (PL1) and extension to the visceral pleural surface (PL2) are counted as VPI. In the eighth and ninth edition analyses, VPI had prognostic impact in small tumors, justifying the T2 designation.[6,28] The eighth edition analysis also suggested a prognostic impact for VPI in each larger tumor category and a gradation between PL1 and PL2, but these observations do not affect the T category.

The term STAS refers to a microscopic observation of tumor cells adjacent to a lung cancer (median, 1-1.5 mm).[29-31] A detailed ninth edition analysis confirms that STAS is a consistent independent negative prognostic factor, regardless of histotype or resection extent.[12] Nevertheless, STAS does not affect tumor size measurement or the T category.

Other histologic features include lymphatic invasion (L), vascular invasion (V), and lymphangitic carcinomatosis (Ly, which may be adjacent to the tumor, lobar, or more diffuse).[3,4] These features do not affect the T category; their association with worse prognosis is not entirely consistent.[12]

Minimal Disease Manifestations: The AJCC/UICC define micrometastases in nodes or distant sites as small deposits of tumor cells (> 0.2-2 mm) detected by routine hematoxylin-eosin staining. Micrometastases are counted toward N and M categories with the additional symbol (mi) [eg, N2(mi)].[2,4,32] Isolated tumor cells are isolated cells or small clumps of tumor cells ≤ 0.2 mm, mostly only detected using special techniques. Isolated tumor cells do not count toward the N or M categories,[2,4] and their prognostic significance is unclear. Circulating tumor cells (isolated tumor cells in blood, typically detected by special staining techniques) are denoted as cM0(i+); they do not affect the TNM designation. Other blood-based assessments, such as cell-free tumor DNA, are not included in the TNM system.

Discussion

The seventh edition TNM classification of lung cancer was dramatically different by involving a database 20

times larger than ever before, an international multidisciplinary team, and extensive statistical analyses.[33] Nevertheless, changes were relatively minor, consisting primarily of adding three size thresholds to the T component. The eighth edition involved a similarly large database, team, and analysis, this time resulting in a major overhaul of the T component, subdividing in 1-cm increments and reallocating many descriptors.[34] The N component remained unchanged in both of these revisions.

In the ninth edition, the T component is minimally refined, but the N component is significantly altered. The general evolution of awareness and detailed node assessment has allowed relevant subcategories to emerge that affect clinical management. Increased data granularity permitted exploration of fundamentally different approaches to the N component, including the final proposal to subdivide N2 into N2a and N2b. In addition, this led to classification of T1N2aM0 as stage IIB (instead of IIIA as in the eighth edition).

The M component was divided into M1a and M1b in the seventh edition; M1a, M1b, and M1c in the eighth edition; and now M1a, M1b, M1c1, and M1c2 in the ninth edition. A larger cohort of M1 tumors in the ninth edition allowed exploration of several aspects, including a definition of oligometastatic disease appropriate for aggressive local therapy. The analysis shows that oligometastatic burden is a continuum without a clear inflection threshold, best left as a matter of clinical trials and judgment.

The field of lung cancer has evolved significantly. Effective treatment was once largely limited to surgical resection and early-stage tumors. All treatment modalities have advanced, and multimodality treatment is increasingly used across the spectrum of tumor extent: systemic therapy in early stage and local therapy in advanced stages. This creates an increased focus on anatomic tumor extent in advanced stages (ie, higher N and M categories).

Although anatomic characteristics are instrumental for local therapies, nonanatomic tumor-related factors are important for systemic therapies (eg, presence/absence of driver mutations, PD-L1 expression). Such factors are already used in individual patient care. However, a system is needed that organizes nonanatomic factors, thereby providing a structure for databases, analysis, and communication, similar to what TNM has provided for anatomic factors. Challenges in developing this include the rapidity of advances, the mixture of prognostic and predictive factors, and multiplicity of lines of treatment.

A classification system for nonanatomic tumor-related factors that complements TNM would be a component of a prognostic model. An accurate prognostic model would need to account for the impact of many additional patient-, setting-, and treatment-related factors. We need to clarify what would be most useful: a model for a large group or individualized patient-specific prediction (as well as determining which outcome to address). Inherent challenges in developing a model include: predictions based on past data do not include present-day advances, revalidation is needed whenever new factors are added, and uncertainty (eg, random events) cannot be eliminated (furthermore, the more individualized the prediction, the greater the uncertainty).

The TNM classification cannot be expected to appropriately address the complexity of nonanatomic tumor-related factors or to be a comprehensive prognostic model. Efforts to meet these needs are ongoing. TNM is purely a classification of anatomic tumor extent; this does not diminish the tremendous impact it has had over decades in facilitating care delivery and clinical research.

What implications will the new TNM classification have on daily practice? It is important to recognize that changing nomenclature (eg, IIB in the ninth vs IIIA in the eighth edition for T1N2aM0) does not change the data we have from clinical studies of outcomes and the effectiveness of specific treatments. Furthermore, although the increased granularity of the ninth edition highlights the impact of details of tumor extent, the observations were observed fairly consistently in a global real-life collective of patients managed as deemed appropriate during the past decade. Further nuances of how to optimally manage patients will undoubtedly emerge from ongoing research, enhanced and stimulated by the granularity of the ninth edition TNM classification.

Conclusions

The process of refining the ninth edition of the TNM classification of lung cancer is nearly complete; only formal adoption and implementation remain. The changes include clarifying details but most prominently involve subdivision of the N2 and M1c categories and reorganization of the TNM combinations included in stage groups IIA, IIB, IIIA, and IIIB. The current article also summarizes the extensive, multitiered analyses underlying these changes, which provide confidence in the consistency of discrimination and generalizability of the ninth edition classification.

Changes in what is meant by the redefined stage groups mostly affects analyses of databases and large patient populations. At a TNM level (what is needed in individual care delivery), implementation should be straightforward because the changes are readily backwards compatible. Changes in stage group nomenclature do not change the data we have about outcomes for patients with tumors of a particular T, N, and M extent. The universal language that TNM provides regarding anatomic extent has been made more granular, hopefully facilitating patient care.

By circulating this summary of the analyses and definitions of the ninth edition TNM classification of lung cancer, we hope to promote familiarity and ease the transition to implementation of the system in 2025.

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Additional information: The e-Appendix, e-Figures, and e-Tables are available online under "Supplementary Data."

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