The Newly Proposed Lung Cancer TNM Classification: Review and Clinical Implications

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Lung cancer remains the number one cause of cancer-related mortality in the Western world, with more than 1,000,000 deaths each year [1]. Staging is vital in the approach to lung cancer since it offers both prognostic information and a guide for treatment decisions. A unified and universally accepted staging system is also essential to standardize nomenclature for international comparisons of clinical trials. The TNM system provides a detailed description of cancers based on the extent of the anatomic involvement, by defining the primary tumor (T), the regional lymph node involvement (N), and the presence of distant metastases (M) [2]. In this chapter we will review the proposed changes for the eighth edition of the International Association for the Study of Lung Cancer (IASLC) TNM staging system, and we will discuss its clinical implications, strengths, and limitations.

History

The tumor-node-metastases (TNM) staging system currently applied to almost all solid malignancies was coined by Dr. Pierre Denoix in the 1940s [3]. As chair of the Union Internationale Contre le Cancer (UICC) staging committee, he coordinated the standardization of TNM staging for 23 solid organ cancers [4]. The first proposal for lung cancer TNM staging was developed by Dr. Clifton Mountain and adopted by the American Joint Committee on Cancer (AJCC) and the UICC in 1973 and 1974, respectively [5]. This original system was based on outcome data from a single institution (MD Anderson Cancer Center, Houston, TX, USA) and a limited number of patients (2155, 1712 with non-small cell lung cancer (NSCLC)). Three subsequent revisions occurred in the following 25 years, all based on Dr. Mountain's database which continued to grow up to 5319 cases by the time of the last revision in 1997 [6]. Some of the limitations of this system such as the small number of patients—particularly for subgroup analysis—the single institution origin, and the lack of external validation prompted the IASLC to create the IASLC staging committee. This group composed of international members of all disciplines involved in lung cancer was set to develop and analyze a more powerful, current, and universal database of patients with lung cancer in order to review its staging. An unrestricted grant from Eli Lilly helped establish the database (the company had no role in data collection or analysis), which was created in collaboration with the CRAB (Cancer Research and Biostatistics Office, Seattle, Washington). Subcommittees were formed to retrieve and analyze data on T, N, and M descriptors,

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prognostic factors, nodal mapping, bronchopulmonary carcinoid tumor, and small-cell lung cancer (SCLC) [7]. The IASLC recommendations for the seventh TNM staging system were published in a series of articles in the *Journal of Thoracic Oncology* in 2007–2009 [8–18]. While the sixth edition of the AJCC and UICC lung cancer TNM staging system published in 2002 was mainly a review of Dr. Mountain's work, the seventh edition, adopted in January 2010, was based on a truly international database of patients treated by all modalities, with rigorous analysis and validation [13]. Despite the vastness of this database, not all T, N, and M descriptors could be thoroughly analyzed, and this prompted the IASLC Staging and Prognostic Factors Committee to launch a second phase of its Lung Cancer Staging Project with the objective to overcome the limitations of the initial project [19].

Data Source and Methodology

A new database was utilized to inform the eighth edition of the TNM classification of lung cancer [19]. This new database consists of 94,708 patients diagnosed from 1999 to 2010. Their data originated from established databases (90,041 patients) or were submitted via the electronic data capture (EDC) system set by Cancer Research and Biostatistics (4667 patients). The inclusion criteria were new lung cancer diagnosis (not recurrent cancer), adequate follow-up for survival analysis, histological subtyping, and complete clinical (c) TNM and/or pathological (p) TNM staging. Europe contributed 46,560 patients; Asia, 41,705; North America, 4660; Australia, 1593; and South America, 190. These new data came from 35 sources in 16 countries. After excluding 17,552 patients, mainly because of unknown or different histology and incomplete stage information, 77,156 patients (70,967 with NSCLC and 6189 with SCLC) remained for analyses. The majority of these patients (99%) had been collected by consortia or registries, with no patients coming from clinical trials. Nearly 85% of the patients underwent surgical treatment either alone or in combination with chemotherapy or radiotherapy.

In this new database, the TNM descriptors were collected according to the seventh edition. In addition, a total of 23 non-anatomical elements was collected to aid with prognostic calculations. These included, among others, patient-related elements (i.e., demographics, lung function tests, performance status, smoking history), tumor related (i.e., T and N SUV max, histology and degree of differentiation, vascular invasion), and environment related (i.e., method of detection, treatment, geographic of origin). This was done with the idea of combining anatomical and non-anatomical elements for a more accurate prognosis. Although this database includes a smaller number of patients, it is richer than the prior one in details allowing for refinement in the analysis of the different descriptors.

Proposal for the Revision of T Descriptors

In the NSCLC group, 33,115 patients met the T descriptors subcommittee's initial analytic requirements of M0 NSCLC, a complete set of either clinical (c) TNM or pathological (p) TNM, known tumor size, and sufficiently detailed T descriptors to support the assigned T category [20]. Survival was measured from the date of diagnosis for clinically staged patients to the date of surgery for pathologically staged patients, and overall survival was assessed with Kaplan-Meier method. Log-rank statistics were derived from hypothetical size cut points, and the highest log-rank statistic was used to select the optimum cut point.

Tumor Size

The size cut point of 3 cm was confirmed and retained to differentiate T1 from T2 tumors, and it continues to be the best cut point for all sizes over all T categories. Five-year survival was analyzed at 1-cm increment in tumor size: ≤1 cm (92%), >1–2 cm (83%), >2–3 cm (76%), >3–4 cm (67%), >4–5 cm (60%), >5–6 cm (56%), >6–7 cm (46%), and >7 cm (38%). This analysis showing a progressive decrease in survival for each 1-cm

cut point led to a new proposal for the T status according to tumor size (see summary of proposed changes in Table 22.1).

Involvement of the Main Bronchus

Involvement of the main bronchus less than 2 cm from the main carina, without invasion of the carina (currently a T3 descriptor), was found to have better prognosis than other T3 descriptors. The distance from the carina (up to 2 cm or >2 cm) does not seem to increase risk of death after adjusting for tumor size. Hence, it was proposed to group all tumors invading the main bronchi regardless of the distance to the carina—as long as the carina is not invaded—as T2.

Involvement of the Diaphragm

Involvement of the diaphragm, a current T3 descriptor, was found to confer a worse prognosis than other T3 descriptors both in clinical and pathological settings. Hence, it is proposed to reclassify involvement of the diaphragm as T4.

Table 22.1 Proposed descriptors for the eighth TNM classification of lung cancer

Descriptor	Subgroup	Definition
T (tumor)		
T0		No evidence of primary tumor
T1		Tumor ≤3 cm, surrounded by the lung or visceral pleura, not more central than the lobar bronchus
	T1a (mi)	**Minimally invasive adenocarcinoma** (solitary adenocarcinoma <3 cm, with predominant lepidic pattern and <5 mm invasion)
	T1a	≤1 cm
	T1b	>1 cm and ≤2 cm
	T1c	>2 cm and ≤3 cm
T2		Tumors >3 cm and ≤5 cm or with any of the following features: – **Involves main bronchus without invading main carina, regardless distance to main carina** – Involves visceral pleura – **Associated atelectasis or pneumonitis of part or all the lung**
	T2a	>3 cm and ≤4 cm
	T2b	>4 cm and ≤5 cm
T3		**Tumors >5 cm and ≤7 cm** (prior T2b) or with separate nodule(s) in same lobe, invading chest wall, phrenic nerve, or parietal pericardium
T4		**Tumors >7 cm** (prior T3) or with separate nodule(s) in a different ipsilateral lobe, **invading diaphragm** (prior T3), mediastinum, heart, great vessels, trachea, carina, recurrent laryngeal nerve, esophagus, or vertebral body
N (regional LN)		
N0		No regional metastases
N1		Metastases to ipsilateral peribronchial, perihilar, or intrapulmonary LN
N2		Metastases to subcarinal or ipsilateral mediastinal LN
N3		Metastases to contralateral hilar or mediastinal LN or involvement of any scalene or supraclavicular LN
M (metastasis)		
M0		No metastasis
M1		Metastasis present
	M1a	Separate nodule(s) in contralateral lung, malignant pleural/pericardial effusion, or pleural/pericardial nodule
	M1b	**Single extrathoracic metastasis**
	M1c	**Multiple extrathoracic metastases in one or more organs**

Note: Changes to the seventh edition of TNM are in bold. *LN* lymph node. Adapted from Goldstraw et al. [25]

Atelectasis/Pneumonitis

This new analysis showed that complete atelectasis/pneumonitis may have a better prognosis than other T3 descriptors, and besides the small number of patients with this characteristics, it is proposed to reclassify these patients from T3 to T2. The new proposal is to include in T2 category patients with any degree of atelectasis or pneumonitis.

Ground Glass/Lepidic Features and Pneumonic-Type Tumors

Tumors presenting with ground glass/lepidic pattern (GG/L) and "pneumonic" type infiltrates are typically multifocal and have different biologic behavior, and they are difficult to classify with our current TNM. A subcommittee of the IASLC was created to provide a consistent nomenclature for these particular presentations of lung cancer [21]. Since the IASLC database did not capture information on GG/L and pneumonic-type tumors, an evidence-based approach was taken, systematically reviewing the literature from 1995 to 2015. Multifocal GG/L lung adenocarcinoma should be classified by the T category of the lesion with the highest T, with the number (#) of lesions or simply (m) for multiple indicated in parentheses. The size is determined by the largest diameter of the solid component (by CT) or the invasive component under the microscope. The designation of T should be used for adenocarcinomas in situ (AIS) and T1a (mi) for minimally invasive adenocarcinomas (MIA) (e.g., T1a (mi) (m) N0 M0). The (#) or (m) is applied regardless of location (e.g., same lobe, different lobe of the lung). The T component should include all tumors whether resected or not that are thought to be malignant (either suspected or proved), as well as to those that are only discovered on pathological examination [20]. A single N and M category is applied to all GG/L tumors. Pneumonic-type lung cancer has a worse prognosis than GG/L type, yet nodal or extrathoracic metastases are rare. In cases of pneumonic-type cancers with a single area of tumor, the current TNM is easily applied. Unlike with GG/L tumors, in cases of multiple areas of involvement, the T or M category will be applied: T3 within same lobe, T4 within different lobe of same lung, and M1a in contralateral lung. This classification applies to both grossly and microscopically found tumors. If a tumor crosses a boundary between two lobes, a T4 classification should be applied. If a tumor is confined to one lobe but hard to measure, a T3 classification is given.

Summary of "Proposed" T Changes for the Eighth Edition of the TNM Classification of Lung Cancer

- The subclassification of T1 into:
  T1a: tumor 1 cm or less in greatest dimension
  T1b: tumor more than 1 cm but not more than 2 cm in greatest dimension
  T1c: tumor more than 2 cm but not more than 3 cm in greatest dimension
- The subclassification of T2 into:
  T2a: tumor more than 3 cm but not more than 4 cm in greatest dimension
  T2b: tumor more than 4 cm but not more than 5 cm in greatest dimension
- The reclassification of tumors more than 5 cm but not more than 7 cm in greatest dimension as T3.
- The reclassification of tumors more than 7 cm in greatest dimension as T4.
- The grouping of the involvement of the main bronchus as a T2 descriptor, regardless of distance from the carina, but without invasion of the carina.
- The grouping of partial and total atelectasis or pneumonitis as a T2 descriptor.
- The reclassification of diaphragm invasion as T4.
- Multiple GG/L tumors should be given the T category of the largest lesion with the number of lesions between parenthesis or simply (m) next to the T category, with bilateral lesions not considered as M1a.

- Both clinical and pathological information (when available) should be applied to GG/L tumors when describing the TNM.
- Pneumonic-type tumors are classified according to the size of the involved area, and they follow the standard definitions of T3, T4, and M1a for lesions in different lobes.

Proposal for the Revision of N Descriptors

Nodal status continues to be one of the most reliable indicators of prognosis in lung cancer, and it is a major determinant of the optimal therapeutic option. The seventh edition of the TNM staging categorized the N status based on the location of the involved lymph nodes (LN) as N0 (no LN involved), N1 (ipsilateral hilar LN involvement), N2 (ipsilateral mediastinal LN involvement), and N3 (contralateral hilar or mediastinal or ipsilateral/contralateral supraclavicular LN involvement), regardless the number of LN involved. This seventh edition of the TNM also accepted the IASLC nodal map as the standard of care to describe LN involvement in lung cancer [11, 13]. The new database was analyzed to corroborate the prognostic ability of the current N categorization and to explore if there is a more sophisticated method for describing LN involvement [22]. Among 70,976 patients with NSCLC, data on the "N component" were available in 38,910 (54.8%) patients for "clinical" nodal (cN) status and in 31,426 (44.3%) patients for pathological nodal (pN) status. Of note, Japan submitted the most data, which consisted of 23,012 (59.1%) patients for cN status and 23,463 (74.7%) patients for pN status, in which the "Naruke-Japanese map" was exclusively used to designate the location of metastatic lymph nodes and to determine the nodal status [23]. Despite the fact that in 2009 the new international lymph node map (IASLC map) was promulgated by the IASLC and recommended by the seventh edition of the TNM, this map was rarely utilized. With the collected data, it was not possible to reconcile the discrepancies between the two maps.

Nodal Staging

Clear differences in overall survival were evidenced again in the new database for both clinically and pathologically staged cases, supporting the traditional classification of N0, N1, N2, and N3, without changes from the seventh TNM (new 5-year survival rates were 60%/75% for cN0/pN0, 37%/49% for cN1/pN1, 23%/36% for cN2/pN2, and 9%/20% for cN3/pN3). For T1 and T2 tumors, cN status continued to show a difference in prognosis for each category. For T3 and T4 tumors, there was no statistically significant difference between cN0 and cN1, but there was a difference between cN1 and cN2 and cN2 and cN3. Further analyses were performed to explore the prognostic impact of combining the number of involved LN stations with the current nodal categories in T—any M0 patients. Unfortunately this specific data on the number of involved stations was only available on pathological data and not clinical. Pathological N categories were further subdivided: pN1 was divided into pN1 single (pN1a) and pN1 multiple (pN1b), and pN2 was divided into pN2 single (pN2a) and pN2 multiple (pN2b). The survival curves for pN1b and pN2a overlapped, with 5-year survival rates of 50% and 49% for R0 resections, respectively (Fig. 22.1). The presence of skip metastasis was further taken into consideration: pN2a was divided into pN2 single with skip (no pN1 involvement, pN2a1), pN2 single without skip (pN1 involvement as well, pN2a2), and pN2b. There was a statistically significant difference in 5-year survival between pN2a1 (skip) and pN2a2 (no skip) (54% vs. 43%, respectively). However, there was no significant difference in prognosis between pN1b and pN2a1 (50% vs. 52%, respectively). These results indicated that the prognosis of pN2a1 (skip metastasis) was close to that of pN1b (multiple N1 stations). Since these interesting findings derived from pathological data and could not be corroborated in clinical staging, they could not be utilized to propose modifications in the N descriptors. Moreover, the analysis on the N descriptor was thought to be partly hampered by differences between the Naruke and the MD-ATS nodal maps.

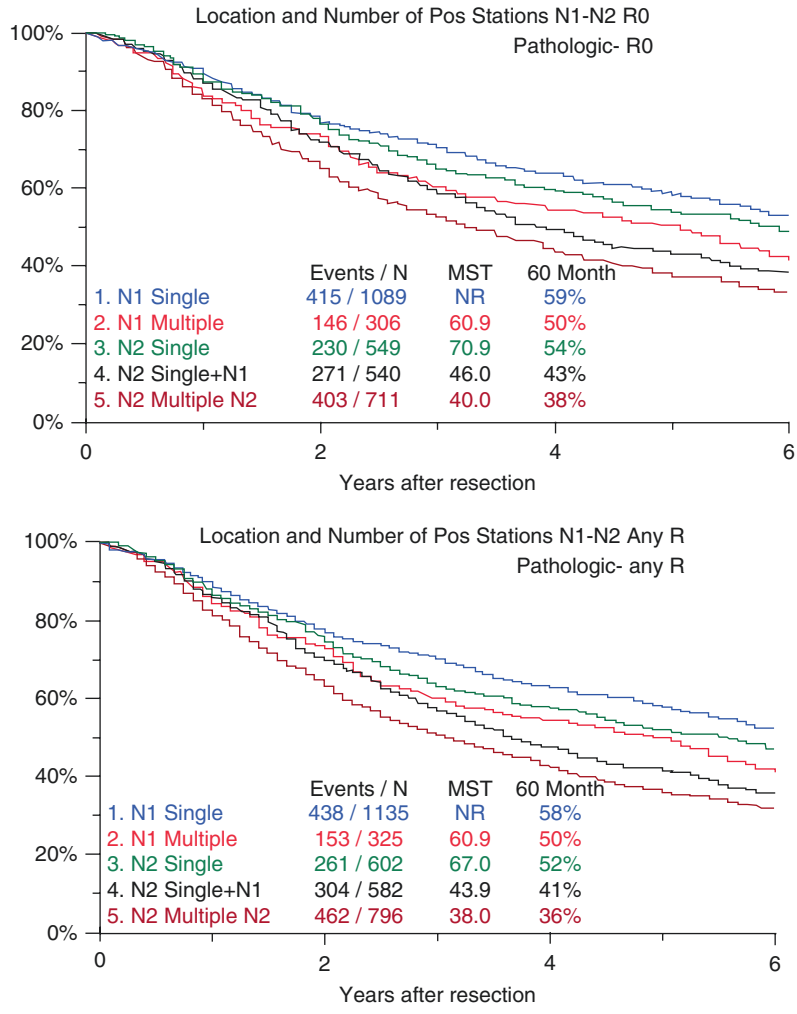

Fig. 22.1 Analysis of survival in patients with pN1 and pN2 disease with single and multiple station involvement, both for R0 and any R resections. R0 = complete resection. Any R = complete and incomplete resections. Copyright IASCL 2015

Summary of "Proposed" N Changes for the Eighth Edition of the TNM Classification of Lung Cancer

- No changes were made in N descriptors, retaining the traditional N0, N1, N2, and N3.
- Further N category classification based on single versus multiple involved stations and presence or absence of skip metastases needs further prospective evaluation before it can be applied to our TNM system.
- The IASLC nodal map recommended by the seventh edition of TNM continues to be recommended to provide precise anatomic definitions for all LN stations.

Proposal for the Revision of M Descriptors

Since the database generated for the seventh edition of the TNM, there have been multiple advances in diagnosis, staging, and management of lung cancer. The widespread use of PET-CT and MRI, the more precise local radiation therapies, the advent of minimally invasive surgery, and the individualized molecular-targeted oncologic treatments have

changed our approach to patients with advanced disease. With the new and prospectively collected database being much richer than the prior one, the IASLC Staging and Prognostic Factors Committee has revised the M descriptors focusing on the burden of metastatic disease [24]. While data from 2411 non-resected M1 patients was available for analysis, only 1059 patients submitted through EDC had the specific data required to assess the objectives set out by IASLC, and the analysis was restricted to this group of patients. Median follow-up for M1a and M1b cases in the EDC was 29.3 months. Overall survival was measured since the day of diagnosis for clinically staged patients, and survival was estimated with Kaplan-Meier method. The analysis corroborated the difference in prognosis between the seventh edition TNM M1a (pleural/pericardial effusions, contralateral/bilateral tumor nodules, pleural/pericardial nodules) and M1b patients (extrathoracic metastases). The former category is showing a median survival of 11.5 months and the latter 7.5 months. In addition, the new database showed that patients with a single extrathoracic metastatic site had a similar survival to patients with M1a disease (median survival of 11.4 months) and much better survival than those patients with multiple extrathoracic metastases (median of 6.3 months). This prompted the reclassification of extrathoracic disease into M1b (single metastasis) and M1c (multiple metastatic disease in one organ or metastasis in multiple organs).

Summary of "Proposed" M Changes for the Eighth Edition of the TNM Classification of Lung Cancer

- Maintain M1a category (pleural/pericardial effusions, contralateral/bilateral tumor nodules, pleural/pericardial nodules).
- Reclassify current M1b category for patients with a single extrathoracic metastatic lesion.
- Introduce the new category M1c for patients with extrathoracic metastatic disease characterized by either multiple lesions in a single organ or lesions in multiple organs.

Proposal for the Revision of Stage Groupings

Based on the previously described proposed changes to T and M descriptors (Table 22.1), new subsets of group stages were also developed [25]. Proposed TNM stage groupings were evaluated for survival based on clinical, pathologic, and best stage. Survival was calculated with Kaplan-Meier method, and it was measured from the date of diagnosis for clinically staged tumors to the date of surgery for pathologically staged tumors. The newly proposed stage groupings are summarized in Table 22.2. The proposed changes in T or M categories are translated into multiple migrations between stage groups. These migrations are highlighted with up or down arrows in Table 22.2. The overall survival for clinical and pathologically stage in the proposed stage grouping of the eighth edition of TNM is summarized in Table 22.3.

Small Cell Lung Cancer (SCLC)

SCLC represents approximately 15% of all lung cancers. Since SCLC is rarely amenable for surgery, the use of TNM staging for SCLC is seldom utilized, and for simplicity, disease is either referred to as "limited" (LD) or "extensive" (ED). The former corresponds to disease confined to one hemithorax with or without ipsilateral LN or pleural effusion, and the latter to all other cases. This broad classification can potentially hide patients who would benefit from more aggressive therapies [7, 10]. The results of the analyses performed by this IASLC subcommittee confirmed that TNM staging closely correlates with survival of SCLC by stage, identifies patients with different prognosis, and can be applied to surgically managed patients [7, 10]. Hence, the seventh edition of TNM recommended applying the TNM criteria, particularly to early SCLC. The proposed revision for the eighth edition of TNM classification discussed above was applied to SCLC [26]. A total of 5002 patients, of which 4848 were clinically staged, 582 pathologically staged, and 428 both clinically and pathologically

Table 22.2 Proposed stage groupings for the eighth TNM classification of lung cancer

Seventh TNM descriptor	Proposed eighth TNM descriptor	N0	N1	N2	N3
T1 ≤1 cm	T1a	**IA1** (IA)	**IIB** (IIA) ▲	IIIA	IIIB
T1 >1–2 cm	T1b	**IA2** (IA)	**IIB** (IIA) ▲	IIIA	IIIB
T1 >2–3 cm	T1c	**IA3** (IA)	**IIB** (IIA) ▲	IIIA	IIIB
T2 >3–4 cm	T2a	IB	**IIB** (IIA) ▲	IIIA	IIIB
T2 >4–5 cm	T2b	**IIA** (IB) ▲	**IIB** (IIA) ▲	IIIA	IIIB
T2 >5–7 cm	T3	**IIB** (IIA) ▲	**IIIA** (IIB) ▲	**IIIB** (IIIA) ▲	**IIIC** (IIIB) ▲
T3 >7 cm	T4	**IIIA** (IIB) ▲	IIIA	**IIIB** (IIIA) ▲	**IIIC** (IIIB) ▲
T3 endobronchial 3–4 cm (location/atelectasis)	T2a	**IB** (IIB) ▼	**IIB** (IIIA) ▼	IIIA	IIIB
T3 endobronchial 4–5 cm (location/atelectasis)	T2b	**IIA** (IIB) ▼	**IIB** (IIIA) ▼	IIIA	IIIB
T3 invasion	T3	IIB	IIIA	**IIIB** (IIIA) ▲	**IIIC** (IIIB) ▲
T3 diaphragm invasion	T4	**IIIA** (IIB) ▲	IIIA	**IIIB** (IIIA) ▲	**IIIC** (IIIB) ▲
T4	T4	IIIA	IIIA	IIIB	**IIIC** (IIIB) ▲
M1a	M1a	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b single metastasis	M1b	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b multiple metastases	M1c	**IVB** (IV) ▲	**IVB** (IV) ▲	**IVB** (IV) ▲	**IVB** (IV) ▲

Note: Stage migrations are bolded, prior stage is within parenthesis, and arrows indicate up- or downstaging. Adapted from Goldstraw et al. [25]

Table 22.3 Overall survival by clinical and pathological stage according to the proposed eighth TNM stage groupings

Proposed stage	MST (months) (clinical/pathological)	Twenty-four-month survival rate (%) (clinical/pathological)	Sixty-month survival rate (%) (clinical/pathological)
IA1	NA/NA	97/97	92/90
IA2	NA/NA	94/94	83/85
IA3	NA/NA	90/92	77/80
IB	NA/NA	87/89	68/73
IIA	NA/NA	79/82	60/65
IIB	66/NA	72/76	53/56
IIIA	29.3/41.9	55/65	36/41
IIIB	19/22	44/47	26/24
IIIC	12.6/11	24/30	13/12
IVA	11.5/NA	23/NA	10/NA
IVB	6/NA	10/NA	0/NA

MST median survival time, *NA* not available

staged, were included. The proposed changes to T and M descriptors were able to discriminate as well as the prior ones (seventh edition). The revision of the TNM stages was also evaluated in this new database; however, some stage categories were underrepresented. Statistically significant differences in prognosis were only seen between stages IIB and IIIA and between stages IIIC and IV. The IASLC committee continues to recommend the use of TNM classification for patients with SCLC who have limited disease.

Discussion

The seventh TNM staging system represented a major step forward in lung cancer care with a clear progression from previous versions of the staging

system. Despite its large size, the database utilized for this seventh edition of TNM was purely retrospective and not all descriptors could be validated. This prompted the creation of a new database that gathered both prospective and retrospective data and that were utilized to inform the eighth revision of the TNM. Multiple changes in T descriptors, M descriptors, and group stages are being proposed for the eighth edition, and, of course, with these changes the new TNM system has inevitably gained higher complexity. We will briefly discuss some limitations and clinical implications of the methodology and different descriptors.

Methodology

Though the IASLC Staging and Prognostic Factors Committee is devoted to prospectively collect data that is specifically designed to revise the TNM, the added complexity of such data has led to the continuous utilization of retrospective sources of data that was collected for other purposes. Of note, although the new database continues to be international in nature, it has a higher proportion of patients from Asia (mostly from Japan, contributing to 41%), which has increased the proportion of patients receiving surgery as part of their treatment from 53 to 85%. In addition, there was an increase in the number of cases coming from registries and a lack of cases from clinical trials. These variations resulted in an increased stage-for-stage survival in all stages and a decrease in survival for advanced stages. The migration of descriptors and stages has sacrificed the backwards compatibility with previous TNM staging. This backward incompatibility makes it difficult to extrapolate established treatment algorithms to the new stage groupings. However, it is important to remember that stage alone does not dictate treatment. Changes to treatment algorithms based on new stages should be assessed in clinical trials [13]. Although many people might expect a staging system to be able to allocate patients to different treatment strategies, this would only be an oversimplification of lung cancer management. The TNM staging system has a limited capacity to define prognosis with a particular treatment, and it was not intended to do so. Optimal treatment can only be defined with clinical trials. Suitability for a particular therapy is based on the interaction of different factors: patient related (i.e., performance status), tumor related, and therapy related.

T Descriptors

The proposal for the eighth TNM has clearly reinforced the crucial impact that tumor size has on prognosis, with well-defined and validated new cut points. The survival analyses according to 1-cm cut points showed that from 1 to 5 cm, every cm counts, and the larger the tumor, the worse the prognosis. In lung cancer screening programs, where 60–70% of lung cancers are detected in stage I, recognizing the difference in prognosis of these smaller tumors is highly relevant [27]. While data regarding the involvement of the main bronchus that informed the seventh edition of TNM was not reliable, a distinction was made based on the distance to the carina (T3 if <2 cm, T2 if 2 cm or more). The new database has proven that the prognosis is the same, regardless the distance from the carina (as long as the carina is not involved), hence simplifying this descriptor to a single T2. Though invasion of the diaphragm has been grouped in T3 invasion by the seventh TNM, it has been shown to confer worse prognosis, and it has been upstaged to T4 in the proposed revision. Complete atelectasis was now showed to have a similar prognosis as partial atelectasis, and they were grouped together as T2. It is important to notice that there is a paucity of patients in this new database that underwent chemotherapy or radiation therapy as the sole treatment modality. Since the prognostic implications of these different T descriptors may differ when different therapies are applied, the generalizability of the new database findings is reduced.

N Descriptors

No major changes resulted from the analyses of the N descriptors, and it was proposed that the current

N0, N1, N2, and N3 definitions were carried to the eighth edition of TNM without modifications [22]. While the number of involved LN (tumor burden) is relevant in the nodal categorization of most tumors, for lung cancer the N category is solely based on the location of the involved LN. Unfortunately this new database did not have information regarding the exact number of LN involved. However, data on the number of LN "stations" was available from a few institutions, and further analysis was performed, evaluating the prognosis of single versus multiple LN stations at N1 and N2 levels and the prognosis of skip metastasis (N2 without N1). Patients with multiple N1 stations were found to have a similar prognosis as those with a single N2 stations, and patients with skip N2 metastases were found to have a better prognosis than those without skip metastases (who had N1 in addition to N2 disease). A major limitation of the new database with regard to the N descriptors is that roughly two thirds of the cases originated in Japan, where, despite the recommendations of the seventh TNM of adopting the IASLC lymph node map, the Naruke map was utilized [23]. One of the major discrepancies between the Naruke map and the IASLC map is that the Naruke map considers LN in the subcarinal space along the inferior border of the main stem bronchus to be station 10 (hence, N1), whereas these are considered as station 7 (and, therefore, N2) in the well-established IASLC nodal map. Thus, the above findings based on single versus multiple stations or skip metastases were not proposed as changes for the eighth edition TNM. The IASLC staging manual requires that three mediastinal and three N1 lymph nodes or stations be sampled. What remains unclear is whether they refer to the number of individual nodes or stations, which can create a significant difference in staging. Unfortunately, to date, there is no validated data to support a specific number of LN or stations to be sampled, and systematic intraoperative node assessment is recommended by clinical guidelines [11, 13].

M Descriptors

The new database was able to specifically analyze the prognostic impact of the burden of metastatic disease [24]. Single metastatic disease (M1b) was found to have a prognosis similar to that of M1a (pleural/pericardial effusion or nodules or contralateral lung nodule). Though metastatic disease to the adrenals seemed to confer a worse prognosis (in comparison to other organs), this could not be confirmed in all patient groups. Multiple metastases in one or multiple organs (M1c) were found to confer a worse survival in comparison to single metastatic disease. While retrospective data had already suggested this difference in prognosis between single and multiple metastases in lung cancer, this is the first time the concept is validated prospectively [28–30]. Future collection of the exact number of metastatic sites, size of metastatic lesions, pathological confirmation of lesions, and number of involved organs may help us discriminate subsets of patients with more favorable prognosis that may benefit from potentially curative therapies within clinical trials [24].

Summary

The UICC seventh edition of the TNM classification system was undoubtedly a major improvement in our scientific basis for the staging of lung cancer, supported by a large international database, and subjected to thorough internal and external validation process. The much richer and prospectively collected database that supports the recommendations for the eighth edition TNM has allowed the IASLC committees to propose multiple key modifications to the T and M descriptors as well as to the stage groupings. As these proposals are accepted and placed in practice, more ambiguities will come up to light, and it is paramount to gather, scrutinize, and share this data to better comprehend the limitations of this TNM system and to rise above them.

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