Original Paper

Comments on the Eighth Edition of the TNM Classification for Lung Cancer

Radical changes and limitations: Does size matter?

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ABSTRACT

AIM-BACKGROUND: Staging of cancer at the time of diagnosis is the most important predictor of survival, and treatments options should be based on the stage. The aim of this overview is to discuss the changes in the 8th classification of lung cancer and its impact on predicting patients' prognosis. Potential limitations of the classification and future directions are discussed. **METHODS:** A systematic literature search was performed to identify relevant reports. Studies and articles were identified using online searches of The U.S. National Library of Medicine via www.pubmed.com. The whole article is based on the IASLC Staging and Prognostic Factors Committee report. An international lung cancer database was developed from 35 sources in 16 countries around the globe with staging and outcome data on 94708 lung cancer cases. **RESULTS:** This new edition of lung cancer TNM staging placed additional emphasis on tumor size and size cut points have further added. The node classification remained unchanged in the new edition. It also emphasizes on the different prognostic value of single o multiple metastatic foci. **CONCLUSIONS:** New staging is based on analyzing survival in large databases based on tumor size and disease proliferation and therefore is expected to assess an individual patient's prognosis more accurately. It is evident that an improved survival may eflects improvements in diagnosis and treatment. This eighth edition of the TNM classification for lung cancer placed additional emphasis on tumor size.
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INTRODUCTION - AIM

Cancer is a major public health problem worldwide and is the second leading cause of death following heart disease in the United States. Lung cancer incidence rates began declining in the mid1980s in men and in the

mid-2000s in women as a result of reductions in smoking prevalence that began decades earlier.[1] Contemporary differences in lung cancer incidence patterns between men and women reflect historical differences in tobacco use. Women took up smoking in large numbers later than men, first initiated smoking at older ages, and were slower to quit, including recent upturns in smoking prevalence in some birth cohorts. Declines in lung cancer incidence and death rates continue to be larger in men than in women.[2,3]

In contrast to the steady increase in survival for most cancers, advances have been slow for lung cancer, for which the 5-year relative survival is currently 18%. This low rate is partly because more than one-half of cases are diagnosed at an advanced stage, for which 5-year survival is 4%. There is promise for improving lung cancer survival rates because of earlier detection through screening with spiral computed tomography. However, it is important to realize that screening, as well as other changes in detection practices, introduces lead time bias in survival rates, thereby reducing their usefulness in measuring progress against cancer.[4,5]

In USA lung cancer death rates declined 38% between 1990 and 2012 among males and 13% between 2002 and 2012 among females due to reduced tobacco use as a result of increased awareness of the health hazards of smoking and the implementation of comprehensive tobacco control. Male lung cancer death rates are also decreasing in the western world and increasing in China and several other countries in Asia and Africa. Female lung cancer death rates are increasing worldwide, with the exception of United States, Canada and Australia. Researchers recently estimated that tobacco control efforts adopted in the wake of the First Surgeon General's report on smoking and health in 1964 have resulted in 8 million fewer premature smoking related deaths, one-third of which are due to cancer. Despite this progress, 80% of deaths from lung cancer are caused by smoking.[6-10]

Breast cancer is still the leading cause of cancer death in women aged 20 to 59 years, but is replaced by lung cancer in women aged 60 years or older. Among men, lung cancer is the leading cause of cancer death for those aged 40 years or older.[1]

Complete resection of lung cancer is associated with significantly longer survival remission but only about 25% of patients are candidates for surgical treatment at the time of diagnosis.[11] Staging of cancer at the time of diagnosis is the most important predictor of survival, and treatments options should be based on the stage. Since the first introduction of TNM staging for lung cancer, there have been significant changes. Like other tumors, lung cancer classification and staging assess the anatomical extension of the tumor which is critical to choosing a therapy and provides information on prognosis.[12]

The aim of this overview is to discuss the basis for the changes in the 8th classification of lung cancer and its impact on predicting patients' prognosis. Potential limitations of the classification and future directions are discussed.

METHODS

A systematic literature search was performed to identify relevant reports. Studies and articles were identified using online searches of The U.S. National Library of Medicine via www.pubmed.com. Several searches were conducted to retrieve all potentially relevant articles, mostly randomized control trials and meta-analysis; the searches were performed between November 2016 and January 2017. The whole article is based on the IASLC Staging and Prognostic Factors Committee report. The following keywords were analyzed to identify relevant case series, guidelines, and reviews: NSCLC, TNM, staging, IASLC.[6]

Approach to development of the 8th TNM Classification

An international lung cancer database was developed from 35 sources in 16 countries around the globe with staging and outcome data on 94708 lung cancer cases. In conjunction with a new Electronic Data Capture (EDC) system which has provided a total of 4667 cases that were used in this latest revision, another 90,041 cases have been contributed by individual sites in retrospective fashion.

The database contains cases that were treated using all modalities of care, including multi modality treatment, and diagnosed between 1999 and 2010. For the analyses of TNM categories only cases with a histologic diagnosis of NSCLC and complete staging information were included. For cases in which chemotherapy was received before surgery, only clinical stage was considered. Candidate proposals for overall TNM stage groups were developed in conjunction with proposed changes to the T and M categories. The existing N descriptors were validated, and no changes were proposed for the eighth edition.[13,14]

The analysis was applied using the statistical package R, Version 3.1.0 (R Project for Statistical Computing, Vienna, Austria). The algorithm generates a tree-based model for the survival data using log-rank test statistics for recursive partitioning and, for selection of the impor-

tant groupings, bootstrap resampling to correct for the adaptive nature of the splitting algorithm. The analysis grouped cases on the basis of the best stage (pathologic if available, otherwise clinical) after determination of best split points on the basis of overall survival using an ordered variable for the newly proposed T categories and the current N categories (excluding N_X cases). Candidate TNM stage grouping schemes were evaluated in part by assessing overall survival by clinical, pathologic, and best stage. Survival was measured from the date of diagnosis for clinically staged tumors and from the date of surgery for pathologically staged tumors and calculated by the Kaplan-Meier method. Contrasts between adjacent stage groups were evaluated by Cox regression analysis, adjusted for baseline factors (age, performance status, and cell type) and type of database submission by using the SAS System for Windows Version 9.4 PHREG procedure (SAS, Cary, NC).

RESULTS

A. New Tumor Staging

The T staging is determined by the size of primary tumor in long axis, or direct extent of the tumor into adjacent structures such as mediastinum or chest wall. Main changes in staging classification are reflected in the T staging. These changes are largely related to the re-classification of the size and location of the primary tumor (Table 1). The former staging system had 5 size-based categories with cut-off points at 2, 3, 5 and 7 cm. Tumors measuring <2 cm were classified as T1a, whereas

TABLE 1. T descriptors for the eighth edition of TNM classification for lung cancer.

Tx	Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a]
T1a(mi)	Minimally invasi ve adenocarcinoma[b]
T1a	Tumor ≤1 cm in greatest dimension[a]
T1b	Tumor >1 cm but ≤2 cm in greatest dimension[a]
T1c	Tumor >2 cm but ≤3 cm in greatest dimension[a]
T2	Tumor >3 cm but ≤5 cm or tumor with any of the following features:[c] - Involves main bronchus regardless of distance from the carina but without involvement of the carina - Invades visceral pleura - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
T2a	Tumor >3 cm but ≤4 cm in greatest dimension
T2b	Tumor >4 cm but ≤5 cm in greatest dimension
T3	Tumor >5 cm but ≤7 cm in greatest dimension or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
T4	Tumor >7 cm in greatest dimension or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina

Note: Changes to the seventh edition are in bold.

[a] 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.

[b] Solitary adenocarcinoma, ≤3cm with a predominately lepidic pattern and ≤5mm invasion in any one focus.

[c] T2 tumors with these features are classified as T2a if ≤4 cm in greatest dimension or if size cannot be determined, and T2b if >4 cm but ≤5 cm in greatest dimension.

those measuring 2-3 cm were classified as T1b. T2 disease was also subdivided into T2a (>3 - 5 cm) and T2b (>5 cm - 7cm). The tumors larger than 7 cm were classified as T3. The eighth edition of the TNM classification for lung cancer placed additional emphasis on tumor size and size cut points have further proliferated, such that size will now be a descriptor in all T categories. The division of the category T1 into T1a, T1b, and T1c on the basis of new size cut points of 1 cm and 2 cm has resulted in these cases (when associated with the categories N0 and M0) being assigned to stage IA1, IA2, and IA3, respectively, and thus reflecting the statistically different prognosis of such cases. These new cut points and the stage groupings should be used in any trials of novel therapies, such as sublobar resection and non-surgical treatment options. We also have to keep in mind that 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,dis classified as T1a. For the first time a new term was introduced, defined as *Minimally invasive adenocarcinoma* and marked as T1a(mi): it refers to a solitary adenocarcinoma, ≤ 3cm with a predominately lepidic pattern and ≤5mm invasion in any one focus. The T2 stage includes tumor >3 cm but ≤5 cm or tumor that involves main bronchus regardless of distance from the carina but without involvement of the carina, or invades visceral pleura, or associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung. T2 tumors with these features are classified as T2a if ≤4 cm in greatest dimension or if size cannot be determined, and T2b if >4 cm but ≤5 cm in greatest dimension.

Tumors >5 cm but ≤7 cm in greatest dimension or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium are classified as T3.

The T4 stage presents tumors >7 cm in greatest dimension or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina.

The additional cut-off points changes will definitely alter treatment recommendations in the future.

B. New Node staging

The N classification describes the degree of spread to regional lymph nodes. This remained unchanged in the 8th edition as the new data showed no change in node staging related survival (Table 2). The regional nodal classification for lung cancer was described by Mountain and Dresler[15].

Various techniques are used to identify nodal spread. Previous studies showed that the sensitivity and specificity of CT and PET for predicting malignant involvement of mediastinal lymph nodes were 60% and 81%, and 84% and 89%, [respectively [16]. Lymph node sampling is regarded as the most accurate predictor of nodal status. Mediastinoscopy has been regarded as the "gold standard" for staging of the mediastinum, but it is invasive and has limitations in accessing to the posterior and inferior mediastinal nodes. Furthermore, the sensitivity for mediastinoscopy is still only 80%-90%, and, in 10%-15% of cases, the technique returns a false-negative diagnosis[17,18]. Endobronchial ultrasound-guided transbronchial needle biopsy (EBUS-TBNA) is reported to have a sensitivity of 85% and a negative predictive value of 90%[19]. Maybe a combined EBUS and esophageal endoscopic ultrasound (EUS) allows better access to the mediastinal and hilar lymph nodes than is usually accessible by mediastinoscopy[20]. A further study of 150 consecutive lung cancer patients reported that combination of EUS fine needle aspiration (EUS-FNA) and EBUS-TBNA had higher sensitivity (93%) and higher negative predictive value (97%), when compared to that of each[technique[21]. However, it needs to be highlighted that not all lymph node stations are accessible by EUS [techniques.[22]

C. New Metastasis staging

The M staging defines the presence of metastases beyond regional lymph nodes. In the 8th edition of the lung

TABLE 2. N descriptors for the eighth edition of TNM classification for lung cancer

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

cancer classification, cases with intrathoracic metastatic disease to the contralateral lung or with pleural/pericardial dissemination remains classified as M1a disease. It is true that most pleural or pericardial effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging descriptor. The category M1b is now assigned to cases with is a single metastatic deposit (in one organ). This includes involvement of a single distant (non-regional) lymph node. The more common situation involving multiple metastatic deposits, usually in more than one organ, is now classified as M1c (Table 3).

DISCUSSION

A. Impact of new staging system on patient management

The revised lung cancer staging based on the new TNM classification is shown in Table 4. [23] New staging is based on analyzing survival in large databases based on tumor size and disease proliferation and therefore, is expected to assess an individual patient's prognosis more accurately. Many patients will receive a different staging category based on the 8th edition of the TNM staging system (Table 5). Only patients with tumor >3 cm but ≤5 cm in greatest dimension which involves main bronchus regardless of distance from the carina but without involvement of the, carina, or invades visceral, pleura, or being associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung with absence of regional lymph node metastasis or presenting metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension are down-

TABLE 3. M descriptors for the eighth edition of TNM classification for lung cancer

M0	No distant metastasis	
M1	Distant metastasis present	
	M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion[a]
	M1b	Single extrathoracic metastasis[b]
	M1c	Multiple extrathoracic metastases in one or more organs

Note: Changes to the seventh edition are in bold.

[a] Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor and the fluid is non-bloody and 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 staging descriptor.

[b] This includes involvement of a single distant (non-regional) lymph node.

TABLE 4. Current eighth TNM classification for lung cancer

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

Note: Changes to the seventh edition are highlighted in bold

TABLE 5. Differences between the seventh and the eight edition of lung cancer staging. Where there is a change, the resultant stage groupings proposed for the eighth edition are in bold, and the stage in the seventh edition is given in parenthesis.

Descriptors in 7th edition	Descriptors in 8th edition	Stages			
		N categories			
		N0	N1	N2	N3
T1 ≤1cm	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	T3	IIB	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 >7 cm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3[a]	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3[b]	T2a	**IB** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T3 [c]	T2b	**IIA** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T4	T4	IIIA	IIIA	IIIB	**IIIC** (IIIB)
M1a	M1a	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b single lesion	M1b	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1c multiple lesions	M1c	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)

[a] Tumor that invades diaphragm

[b] Tumor >3 cm but ≤4 cm in greatest dimension which involves main bronchus regardless of distance from the carina but without involvement of the carina, or invades visceral pleura, or being associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung

[c] Tumor >4 cm but ≤5 cm in greatest dimension which involves main bronchus regardless of distance from the carina but without involvement of the carina, or invades visceral pleura , or being associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung

staged. These cases are still considered candidates for adjunctive chemotherapy along with surgery. It doesn't seem that this new lung cancer staging offers a greater role to surgery, e.g, sthese patients who previously would have been assigned a stagerIIB or asIIIA diagnosis, are now respectively stage IBBand IIB.

We always must considersthat patients who undergo biopsy or surgical resection of the tumor and/or lymph nodes may have their TNM classification revised based on histological findings. The clinical staging of the patient thus changes into pathological staging and is described by adding prefix "p" based on pathological measurements and findings, and these would influence treatment strategies and estimated prognosis.

The IASLC Staging and Prognostic Factors Committee have attempted to resolve some issues in which data is limited by review of the literature and by consensus. These include how one should assess tumor size in case of small tumors of mixed density accidentally detectedhduring n CT screening s. The committee's recommendation is that it should be the solid element on imaging, or the invasive component on pathological examination which should be measured to determine T size.

B. Limitations of new classification

There are glaring deficiencies in the global distribution of the data, with no data at all being included from Africa, South America or the Indian subcontinent. Other vast countries such as Russia, China, and Indonesia are not represented or only poorly represented. Only Japan is over-represented which contributed 41% of the total cases.[23]

Oncenagain, the new classification does not take into account a single tumor which involves two lobes across a fissure.

Currently, PET is routinely used in many centers as an additional diagnostic tool which may change the clinical stage of the disease in a given patient. PET often upstages the disease (in comparison to conventional CT scan) by identifying newer, metabolically active sites of disease). However, it must be noted that the data based analyzed for the 8th TNM classification did not include much data from PET studies.

Lymphangitis carcinomatosis is believed to be associated with worse prognosis in lung cancer patients. However, still there is no evidence to support this. The new TNM classification does not specifically take account of lymphangitis.

It is evident an improved survival that may reflects improvements in diagnosis, such as the increasing vogue for computed tomography (CT) screening; improvements in the staging algorithm with the widespread use of positron emission tomography scanning and less invasive mediastinal staging by endobronchial ultrasound and endoscopic ultrasound; and improvements in treatment, including the following: the use of adjuvant therapy after complete resection, the availability of radical options for treating less fit individuals with stereotactic body radiation therapy and minimally invasive surgical options, and targeted agents providing improved results in stage IV disease because their toxicity profile allows consideration of such treatment in patients with worse performance levels.

The net effect of all these diagnostic and therapeutic improvements was that stage-for-stage survival increased in all stages (Table 6).

A new stage grouping has also been created for the most advanced local disease categories, T3 and T4 associated with N3 disease but category M0. Such cases are now classified as stage IIIC, reflecting their worse outcome than that of cases involving tumors that remain in stage IIIB. The prognosis for stage IIIC cases is similar to that for stage IVA cases, but the separation is justified by the different treatment approaches used in such cases.

TABLE 6. Five year survival by clinical stage according to the current TNM staging compared to the previous 7th edition

Eight lung cancer staging (2016)		Seventh lung cancer staging (2009)	
Stage IA1	92%	**Stage IA**	82%
Stage IA2	83%		
Stage IA3	77%		
Stage IB	68%	**Stage IB**	66%
Stage IIA	60%	**Stage IIA**	52%
Stage IIB	53%	**Stage IIB**	47%
Stage IIIA	36%	**Stage IIIA**	36%
Stage IIIB	26%	**Stage IIIB**	19%
Stage IIIC	13%		
Stage IVA	10%	**Stage IV**	6%
Stage IVB	0%		

CONCLUSIONS

A. What's next?

The process by which TNM classification in lung cancer evolves has been changed irrevocably. The IASLC should improve on the above described limitations in time for the 9th edition of TNM classification. A larger prospective data set should be applied for the 7-year cycle leading up to the 9th edition. A web-based data collection system is being developed and tested to make data submission easier for those who collaborate. Furthermore, data collection must be expanded to incorporate more cases of neuro-endocrine tumors and mesothelioma.

B. And don't forget

It is important to remind ourselves that stage does not dictate treatment. Stage is one, and perhaps the single most important, of several prognostic factors that guide the appropriate treatment option(s) to offer the patient. Any change to established treatment algorithms should be based on clinical judgment.

Informed by prospective trials. The eighth edition of the TNM classification for lung cancer placed additional emphasis on tumor size. After all, size matters!

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