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REVIEW ARTICLE

Non-small cell lung cancer staging: proposed revisions to the TNM system

Bryan J. Schneider

University of Michigan Medical Center, Ann Arbor, MI, USA

Corresponding address: Bryan J. Schneider, MD, C350 Med Inn; Box 5848, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-0934, USA.
Email: bryansch@umich.edu

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Abstract

Patients with non-small cell lung cancer (NSCLC) require careful staging at the time of diagnosis to determine prognosis and guide treatment recommendations. The seventh edition of the *TNM Classification of Malignant Tumors* is scheduled to be published in 2009 and the International Association for the Study of Lung Cancer (IASLC) created the Lung Cancer Staging Project (LCSP) to guide revisions to the current lung cancer staging system. These recommendations will be submitted to the American Joint Committee on Cancer (AJCC) and to the Union Internationale Contre le Cancer (UICC) for consideration in the upcoming edition of the staging manual. Data from over 100,000 patients with lung cancer were submitted for analysis and several modifications were suggested for the T descriptors and the M descriptors although the current N descriptors remain unchanged. These recommendations will further define homogeneous patient subsets with similar survival rates. More importantly, these revisions will help guide clinicians in making optimal, stage-specific, treatment recommendations.

Keywords: *Non-small cell lung cancer; neoplasm staging; Lung Cancer Staging Project; staging revisions.*

Introduction

Lung cancer is the leading cause of cancer-related death in the world. Approximately 85% of patients present with non-small cell lung cancer (NSCLC) and treatment may consist of surgery, radiation therapy, chemotherapy or a combination of these modalities depending on tumor stage and the goals of therapy. Accurate staging of the disease is essential for several reasons. First, staging helps to identify patients with similar prognoses and can give rough estimates of survival. Staging also identifies patients who may benefit from similar treatment options. More importantly for researchers, staging helps to standardize a 'common language for investigators to conduct trials on similar patient populations. This also helps to guide new treatment strategies based on the tumor behavior at a particular stage. Patients with suspected NSCLC typically undergo initial clinical staging, which includes a physical exam and imaging studies such as computed tomography (CT). The pathologic stage is then determined with either a biopsy of suspected metastatic disease or after surgical resection and lymph node sampling of earlier stage disease.

The current tumor node metastasis (TNM) system for staging NSCLC was last revised in 1997 with the goal of refining the definitions of patient groups with similar prognoses and treatment options[1]. These revisions were based on 5319 patients, predominantly from the M.D. Anderson Cancer Center in the United States. Major changes that were introduced with this revision included the division of stage I into IA and IB, and stage II into IIA and IIB based on subclassifications of tumor size. Other changes included a T4 classification for satellite nodules in the same lobe, an M1 classification for malignant nodules in other lobes, and the reclassification of T3N0M0 to stage IIB from stage IIIA.

Over the past decade, questions have been raised regarding the ability to generalize the recommendations from this single-institution study with minimal external validation to populations around the world. At the same

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time, new technologies and approaches to define tumor stage have certainly beckoned a re-look at our current TNM staging system.

The seventh edition of the *TNM Classification of Malignant Tumors* is due to be published in 2009. In anticipation of this, the International Association for the Study of Lung Cancer (IASLC) created the Lung Cancer Staging Project (LCSP) in 1998 to help make revisions of the present stage groupings in an attempt to more accurately reflect the survival of patient subsets and guide appropriate treatment recommendations[2]. This task force is comprised of representatives from 45 institutions in 20 countries around the world. Data from 100,869 lung cancer cases from 1990 to 2000 were submitted to create a retrospective database for this project and 67,725 of these cases were deemed adequate for analysis[3]. Of these cases, 53,646 were clinically staged, 33,933 were pathologically staged and 20,006 were staged both clinically and pathologically. The remaining cases were mainly excluded based on the diagnosis outside the study period or inadequate information on the stage, treatment and follow up. This 10-year time period was chosen based on relatively consistent staging practices with CT and allowed for a 5-year period to assess survival endpoints. Unfortunately, positron emission tomography (PET) was not routinely used during this period and therefore was not part of the clinical staging evaluation.

The data base for this project was created in cooperation with the Cancer Research and Biostatistics (CRAB) data center, a Seattle-based center with expertise in data collection from multicenter studies. Subcommittees were created to analyze the data germane to each T, N, or M descriptor and recommendations were made where reclassification of a descriptor would better describe the prognosis of that particular patient subset. Several modifications regarding T and M descriptors were proposed, although the N descriptors remain unchanged. These proposals will be submitted to the American Joint Committee on Cancer (AJCC) and to the Union Internationale Contre le Cancer (UICC) for consideration during the revision of the staging manual.

Table 1 AJCC TNM staging system for lung cancer (6th edition, 2002)

Primary tumor (T)	
T1	Tumor ≤ 3 cm diameter without invasion more proximal than lobar bronchus
T2	Tumor >3 cm diameter; tumor with pleural invasion; partial lung atelectasis; proximal extent ≥ 2 cm from the carina
T3	Tumor of any size with: chest wall invasion; diaphragm, pericardium, or diaphragm involvement; complete lung atelectasis; proximal extent <2 cm from the carina
T4	Tumor of any size with: mediastinal, great vessel, trachea, esophageal, carinal or vertebral body invasion; malignant pleural or pericardial effusion; same lobe satellite nodule(s)
Nodal involvement (N)	
N0	No regional lymph node involvement
N1	Ipsilateral hilar and/or ipsilateral peribronchial nodal involvement
N2	Ipsilateral mediastinal and/or subcarinal nodal involvement
N3	Contralateral mediastinal or hilar nodal involvement; supraclavicular nodal involvement
Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis; metastatic tumor nodules in different lobes from the primary tumor

Adapted from: AJCC Cancer Staging Manual, 6th edition, New York, 2002.

Table 2 Proposed definitions for the T descriptors

	Primary tumor (T)
T1	Tumor ≤ 3 cm diameter without invasion more proximal than lobar bronchus
T1a	Tumor ≤ 2 cm diameter
T1b	Tumor >2 cm but ≤ 3 cm diameter
T2	Tumor >3 cm but ≤ 7 cm diameter; tumor with pleural invasion; partial lung atelectasis; proximal extent ≥ 2 cm from the carina
T2a	Tumor >3 cm but ≤ 5 cm diameter
T2b	Tumor >5 cm but ≤ 7 cm diameter
T3	Tumor >7 cm or tumor with invasion of chest wall, diaphragm, pericardium, or diaphragm; complete lung atelectasis; proximal extent <2 cm from the carina; satellite tumor nodules in the same lobe
T4	Tumor of any size with: mediastinal, great vessel, trachea, esophageal, carinal or vertebral body invasion; different lobe satellite nodule(s) in the same lung

Adapted from: Goldstraw *et al.*[3].

Proposed revisions of the T descriptors

Table 1 summarizes the current TNM staging system used in clinical practice. Several revisions have been proposed regarding the T descriptors after analysis of 18,198 any T, any N, M0 patients with sufficient clinical or pathologic T and N staging (Table 2)[4]. The proposed modifications in T staging were then internally validated using 20,994 patients from a larger data set and externally validated using NSCLC cases from the 1990–2000 Surveillance, Epidemiology and End Results (SEER) registry database.

Recommendations were made for tumor 'cutpoints' at 2, 3, 5 and 7 cm. By clinical assessment, patients with no lymph node involvement and tumors ≤ 2 cm, >2 to ≤ 3 cm, >3 to ≤ 5 cm, >5 to ≤ 7 cm and >7 cm demonstrated median survival times of 68, 52, 43, 30 and 17 months, respectively. Although the survival difference for the two smallest cutpoints did not reach statistical significance, the survival differences among the 3–7 cm cutpoints did reach statistical significance and, interestingly, patients with tumors larger than 7 cm had nearly identical survival as those with clinical T3 tumors (17 vs. 19 months, $p = 0.61$).

Patients with a satellite nodule in the same lobe (currently classified as T4) were found to have a prognosis that is comparable to patients with T3 lesions ($p = 0.28$)

and not with T4 lesions involving invasion of mediastinal structures. Because of this, recommendations were made to reclassify same-lobe satellite nodules as T3 disease. Similarly, patients currently staged M1 by 'same lung, different lobe' pulmonary nodules had survival rates comparable to patients with T4 lesions ($p = 0.41$) and not to patients with extrathoracic metastases who consistently fare worse. Therefore, nodules in the ipsilateral lung, but in different lobes were re-classified as T4 disease.

Finally, patients demonstrating clinical evidence of pleural dissemination of disease (currently staged as T4) have a significantly worse median survival than patients with T4 lesions involving invasion of mediastinal structures (8 vs. 13 months, $p < 0.0001$). In addition, pleural/pericardial dissemination is not curable by current treatment modalities and was therefore upstaged to M1a. In summary, recommendations have been made to subclassify T1 lesions into T1a (≤ 2 cm) and T1b (>2 to ≤ 3 cm) and T2 lesions into T2a (>3 to ≤ 5 cm) and T2b (>5 to ≤ 7 cm) based on tumor size cutpoints that demonstrated significant survival differences. Further recommendations include upstaging tumors >7 cm from T2 to T3, downstaging same lobe satellite nodules from T4 to T3, downstaging same lung, different lobe nodules from M1 to T4 and upstaging pleural/pericardial dissemination from T4 to M1a. All of these proposals were supported by heavily validated data.

Analysis of the N descriptors

For over three decades the N descriptors for NSCLC have remained constant as detailed in Table 1[5]. The LCSP investigators evaluated clinical N staging data on 38,265 patients with clinical M0 NSCLC and the pathologic N staging data on 28,371 patients treated surgically[6]. The analysis was confounded by the fact that 60% of the data came from Japan where a different nodal mapping system (Naruke map) is used that classifies lymph nodes along the inferior border of the subcarinal space as N1 rather than N2.

For the 38,265 patients with clinical 'any T, M0' NSCLC, 5-year survival was strongly associated with clinical N stage: N0, 42%; N1, 29%; N2, 16%; and N3, 7%. The survival differences between adjacent groups were all statistically significant ($p < 0.0001$). For patients managed surgically with no evidence of M1 disease, these 5-year survival trends remained relatively constant after pathologic staging: N0, 56%; N1, 38%; N2, 22%; and N3, 6% ($p < 0.0001$).

Investigators also evaluated patient survival based on the anatomic location of pathologically involved lymph nodes and the presence or absence of 'skip metastases' (N2 involvement without N1 involvement), but no meaningful differences in survival were identified. In contrast, classification of the lymph node stations into 6 separate 'zones' identified survival differences based on the degree and location of zone involvement (Table 3). Patients who had N1 single-zone disease demonstrated a 5-year survival of 48% compared to patients with N1 multiple-zone disease who had a 5-year survival of 35% ($p < 0.009$). Patients with N2 single-zone disease had a 5-year survival of 34% similar to patients with N1 multiple-zone disease. However, patients with N2 multiple-zone disease had a 5-year survival of only 20% ($p < 0.0001$). These results suggested that nodal disease involvement could be subdivided into N1a (single N1 zone), N1b (multiple N1 zones), N2a (single N2 zone) and N2b (multiple N2 zones) based on the survival differences. However, when the small group of T1, any N, M0 patients was analyzed based on this nodal paradigm, the sample size was not large enough to draw valid conclusions. Only a prospective study would be able to determine if this nodal zone paradigm would improve upon the current N descriptors. Therefore, the final conclusion of the Lung Cancer Staging Project was that the N descriptors should remain unchanged for the upcoming revision of the lung cancer staging system.

Table 3 Definition of nodal zones

Nodal zone	Lymph node stations
Upper zone (R)	1, 2, 3, 4 (superior mediastinal nodes)
AP zone (L)	5, 6 (aortic nodes)
Subcarinal zone	7 (subcarinal nodes)
Lower zone	8, 9 (inferior mediastinal nodes)
Hilar zone	10, 11 (N1 nodes)
Peripheral zone	12, 13, 14 (N1 nodes)

Adapted from: Rusch *et al.*[6].

Proposed revisions of the M descriptors

Accurate staging with regard to the M descriptor is probably the most important component of the NSCLC patient evaluation. It will determine if the patient is treated aggressively with intent to cure or is treated palliatively for symptoms from incurable disease. From the retrospective LCSP database, 6596 cases were analyzed for M stage, the majority of which came from Europe (52%) and the rest from North America, Asia and Australia[7]. As for the T stage analysis, results of interest were internally validated among geographic regions and between various submitted databases and then externally validated in 27,393 patients from the United States SEER registry.

The current staging system classifies pleural or pericardial dissemination as T4 disease. However, in the LCSP analysis, patients with clinical 'other T4 disease, any N, M0' have a longer median survival than those with T4 pleural dissemination, any N, M0 (13 vs. 8 months; $p < 0.0001$). This translates into a 1-year survival of 53% versus 36%, respectively.

Patients with additional malignant nodules in the contralateral lung are also almost uniformly deemed incurable by current treatment modalities and are

presently classified as M1 disease. Despite this, patients with intrathoracic metastases have a better survival rate than those with extrathoracic disease with a median and 1-year survival of 10 vs. 6 months and 45% vs. 22%, respectively ($p < 0.0001$). However, no significant survival difference was identified between patients with pleural dissemination and patients with contralateral lung nodules. Based on these findings, recommendations were made to upstage/subclassify pleural and pericardial dissemination as M1a based on a worse prognosis than patients with 'other T4 disease', but a better prognosis than patients with extrathoracic metastases (Table 4). Similarly, patients with contralateral lung nodules would also be subclassified as stage M1a due to the comparable survival rate. Distant metastatic disease outside of the lung, pleura, or pericardium would then be subclassified as M1b.

A controversial area among treating clinicians is the management of patients with NSCLC and a single metastatic site, especially in the brain. From the retrospective LCSP analysis, median and 1-year survivals were not substantially different for patients with multiple extrathoracic metastases compared to patients with a single metastatic site despite a statistically significant survival difference (5 vs. 6 months; 20 vs. 23%, $p = 0.006$). In addition, investigators could not identify prognostic differences based on location of single-site disease and therefore, no revisions were made based on these parameters. In summary, recommendations regarding M descriptors included the reclassification of pleural/pericardial dissemination to M1a, the subclassification of contralateral lung nodules to M1a and extrathoracic (distant) metastases to M1b.

Small cell lung cancer

Using the proposed revisions to the TNM system for NSCLC, 12,620 small cell lung cancer (SCLC) cases were evaluated and a survival analysis was performed on clinically staged patients[8]. The vast majority of patients were not staged pathologically as surgery is rarely offered to this population. In addition, TNM data were difficult to obtain as one-third of the patients were staged with the Veterans' Administration Lung Study Group (VALSG) staging system only. This system is commonly used in clinical practice where limited-stage SCLC is defined as disease confined to one side of the chest and can be encompassed in a 'feasible radiation field'[9]. Patients who demonstrate SCLC on both sides of the chest or outside the thorax (brain, bones, liver, adrenal glands, etc.) are classified as having extensive-stage SCLC.

Not surprisingly, there was an inverse correlation between the T and N classifications and survival. However, patients with 'otherwise limited-stage' SCLC and a pleural effusion (cytology positive or negative) had an intermediate prognosis between limited-stage patients without an effusion and extensive-stage patients. This questions whether the M1a designation would be appropriate for SCLC with a pleural effusion. Although the subcommittee recommended the adaptation of the TNM staging system for SCLC, it is unlikely to alter the treatment recommendations for patients with either limited- or extensive-stage disease. Unfortunately, too few patients were evaluable to shed light on controversial areas in the treatment of SCLC such as the role of radiation therapy in patients with either supraclavicular nodal involvement or a pleural effusion. Ultimately, data need to be prospectively collected in clinical trials, especially in limited-stage studies where survival differences can be identified among the stage I–III subsets.

Table 4 Proposed definitions for the M descriptors

	Metastasis (M)
M0	No metastasis
M1	Metastasis
M1a	Metastatic tumor nodules in different lobes from the primary tumor; malignant pleural or pericardial effusion
M1b	Distant metastasis

Adapted from: Goldstraw *et al.*[3].

Conclusion

A comparison between the proposed revisions and the current NSCLC TNM staging system is presented in Table 5. From a patient care standpoint, these revisions clearly refine patient subsets that now have very similar prognoses. More importantly, many of these new groupings allow for more homogeneous, stage-specific treatment. This is in contrast to the present TNM system where patients with incurable stage IIIB NSCLC due to a malignant effusion are managed with palliative chemotherapy and patients with IIIB disease due to contralateral mediastinal lymph node involvement may receive potentially curative chemoradiation. If malignant

Table 5 Comparison of current vs. proposed stage groupings of TNM subsets

Stage	Current TNM	Proposed TNM
Stage IA	T1, N0, M0	T1a–T1b, N0, M0
Stage IB	T2, N0, M0	T2a, N0, M0
Stage IIA	T1, N1, M0	T2b, N0, M0
		T1a–T2a, N1, M0
Stage IIB	T2, N1, M0	T2b, N1, M0
		T3, N0, M0
Stage IIIA	T3, N1, M0	T1a–T3, N2, M0
	T1–3, N2, M0	T3, N1, M0
		T4, N0–1, M0
Stage IIIB	Any T, N3, M0	T4, N2, M0
	T4, any N, M0	Any T, N3, M0
Stage IV	Any T, any N, M1	Any T, any N, M1a–M1b

Adapted from: AJCC Cancer Staging Manual, 6th edition, New York, 2002 and Goldstraw *et al.*[3].

effusions are reclassified as M1a, then all stage IIIB patients could be considered for potentially curative therapy with chemoradiation. In addition, the new, more homogeneous, stage IIIA classification would allow consideration of neoadjuvant chemotherapy or chemoradiation prior to definitive surgical resection. Since T4, N0–1, M0 patients were moved to IIIA from IIIB, patients with revised IIIB disease should not be candidates for neoadjuvant therapy and should be treated with definitive chemoradiation. Patients with T3, N0, M0 disease based on satellite metastases in the same lobe (now classified as stage IIB) should undergo evaluation for resection similar to patients with other T3 lesions. Prior to these recommendations, the T4 designation of this subgroup made clinicians hesitant to recommend surgery given the poor prognosis of other stage IIIB patients with surgical resection.

Although the data utilized to make these recommendations are retrospective, this project represents a monumental achievement in multinational collaboration to improve and standardize the present staging system in an effort to optimize patient care and clinical research. From the initial 100,869 patients, 81,495 were diagnosed during the study period from 1990 to 2000 and 81,015 were deemed adequate for analysis. Of these, 67,725 were non-small cell cases and 13,290 were small cell cases that were analyzed separately. In contrast to the M.D. Anderson database used in the 1997 revision that mostly consisted of surgical patients, this database consisted of patients receiving a wide breadth of treatments: 41% were treated with surgery alone, 11% with radiation alone, 23% with chemotherapy alone and 25% with multimodality therapy.

As with all retrospective studies, there are some limitations to this approach. In spite of this huge data set, some subsets were still too small to make solid conclusions. For example, survival analyses could only be performed in 2876 patients with pathologic N1 and N2 disease. Patients with a resectable primary tumor and a single metastatic site in the brain or adrenal gland may achieve long-term survival with an aggressive multimodality approach even though this practice could not be supported by the present study[10–12]. Positron emission tomography has also been incorporated into the standard evaluation of patients with NSCLC since 2000. Clearly, the ever-evolving workup for patients with NSCLC will affect the accuracy of the staging system and efforts are underway to collect patient staging data prospectively in anticipation for future revisions of the NSCLC staging system. These limitations should not overshadow the efforts by the LCSP investigators, who have made solid recommendations to the AJCC and UICC based on extensive data from across the globe. The proposed revisions for the T and M descriptors will indeed help clinicians provide more accurate prognoses and guide rationale treatment recommendations for patients with NSCLC.

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