Lung Cancer Staging: Clinical and Radiologic Perspectives

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Abstract

Keywords

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- TNM classification
- imaging

Published in 2009, the 7th edition of the American Joint Committee on Cancer TNM staging system is the culmination of an extensive worldwide initiative to standardize and validate lung cancer staging. Unlike prior editions, the new staging system is now inclusive of small cell carcinoma and carcinoid tumors. In addition, significant changes were made to the T and M descriptors, resulting in improved prognostic stratification of disease. This review article highlights these changes, the rationale for their inclusion in the new staging manual, and the role of the radiologist in determining stage.

Objectives: Upon completion of this article, the reader will be able to discuss the historical perspective leading up to the 7th edition of the AJCC TNM staging manual, highlight the changes made to the 7th edition, provide a radiologic perspective regarding the changes, and discuss the current limitations and future directions of the TNM staging guidelines.

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Lung Cancer Classification and Natural History

Lung cancer is the most common cause of cancer-related deaths in both men and women in the United States, and it accounts for more deaths than breast, prostate, colon, rectal, and pancreatic cancers combined. The 5-year survival rate for primary lung cancer is 16%, compared with 65%, 90%, and 99%

for colon, breast, and prostate cancer, respectively. Although the incidence of lung cancer in men is beginning to decline, the incidence in women is rising, such that since 1987, lung cancer has caused more cancer-related deaths in women than breast cancer. More than half of all people with lung cancer will die within 1 year of diagnosis; however, if diagnosed at an early stage, 5-year survival reaches ~50%.¹

Smoking is the major risk factor for lung cancer, with less common factors including radon and asbestos exposure. Smoking contributes to 80% and 90% of lung cancer deaths in men and women, respectively.² The benefits of smoking cessation have been established and should be included in all treatment regimens. This is particularly important in the era of improved cancer treatment and potentially leads to prolonged overall survival. Benefits include improved quality-of-life measures, such as decreased shortness of breath and fatigue, and increased energy, self-esteem, and performance status.^{3,4} Perhaps not as clearly intuitive is the improvement in clinical parameters, such as improved response to chemotherapy, decreased radiation therapy complications, decreased risk of secondary tumor development, and increased survival. The latter likely relates to the prolongation of cancer progression.^{3,5} Because the prevalence of smoking has declined in the United States, lung cancer is now more frequent among former smokers than current smokers.^{6,7}

Primary lung cancers are classified broadly as non-small cell lung carcinoma (NSCLC) or small cell lung carcinoma

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(SCLC). The former makes up ~85% of cases and the latter 15%. SCLC is distinguished by rapid growth rate, early regional lymph node dissemination, and spread to distant sites.^{8,9} Survival percentages for lung cancer drop significantly when only SCLC is considered. Without treatment, median survival from the time of diagnosis ranges between 2 and 4 months. Despite improvements in early diagnosis, advancements in treatment, and dramatic initial response to chemotherapy and radiation, 5-year survival rates for SCLC remain an abysmal 5 to 10%.

In patients with lung cancer who are surgical candidates, complete surgical resection remains the best option for cure. Approximately half of NSCLC cases are localized or locally advanced at the time of diagnosis and are treated by surgical resection alone or by combination therapy with or without resection. In contrast, ~80% of patients with SCLC have metastatic disease at the time of diagnosis.

Because the stage of disease at presentation is directly correlated to survival and is a key determinant of treatment, having a standardized and validated approach to stage the disease accurately is imperative. This is the primary focus of this review article, with an emphasis on the role of imaging in achieving this goal.

Historical Perspective

The TNM staging system was originally introduced in the 1940s, and the first edition of the International Union Against Cancer (UICC) handbook was published in 1968. Established at that time and still applicable today, objectives of the TNM staging system are fivefold: to aid the clinician in treatment planning, to give some indication of prognosis, to assist in evaluating the results of treatment, to facilitate the exchange of information between treatment centers, and to contribute to continuing investigations of human malignancies.¹⁰ In 1987 the UICC and American Joint Committee on Cancer (AJCC) joined forces to provide a uniform worldwide reference standard.

From 1975 to 1988, Dr. Clifton Mountain at the MD Anderson Cancer Center studied 5319 patients, of whom 83% were treated at his institution and 17% were within the National Cancer Institute Cooperative Lung Cancer Study Group.^{11,12} Data from this cohort eventually led to the publication of the 5th edition of the AJCC cancer staging manual in 1997.¹³ In 2002 the 6th edition of the AJCC cancer staging manual was published; there were no changes made to the prior edition with regard to lung cancer.

The 5th and 6th editions were limited by several factors. Patients were from no more than two institutional databases and were primarily treated with surgery. The group was therefore fairly homogeneous in terms of geography, gender, and treatment. Because the number of patients was limited, many of the subgroups were small. There was no external and little internal validation. In addition, since the publication of the 6th edition, there have been significant advances in imaging and diagnostic techniques including computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), and endobronchial ultrasound. In spite of these limitations, this early staging

system worked well and provided a strong foundation for the 7th staging system published in 2009.

Recognizing the limitations of earlier editions, the International Association for the Study of Lung Cancer (IASLC) established the International Staging Project on Lung Cancer in 1998. This initiative benefited from the cooperation of the UICC, AJCC, and the corresponding Japanese cancer societies. Jointly funded by unrestricted educational grants by Eli Lilly and Company and the AJCC, the lung cancer staging project sought to challenge the prior staging system with new recommendations that would be vigorously validated both internally and externally. An International Staging Committee was designated to oversee the project.¹⁴

Several features of the staging project are worth mentioning. Unlike the database that ultimately led to the 5th edition of the AJCC staging manual, the IASLC initiative incorporated data sets from >19 countries over a period of 10 years (1990–2000).^{15,16} Multiple treatment modalities (surgery, chemotherapy, radiation, or combined) were included, a significant departure from the prior edition. Included cases had a known cell type and adequate information on stage, treatment, or follow-up. Of the 100,869 cases that were initially included, 81,015 cases remained once exclusion criteria were imposed; of these, 67,725 represented NSCLC and 13,290 were SCLC cases. Only cases of NSCLC were included in analyses of the T, N, and M descriptors and analysis of the TNM subsets and stage groupings.¹⁷ Separate analyses of the subset of SCLC cases based on the 6th edition and the newly proposed TNM stage groupings was performed and demonstrated the applicability of the 7th edition TNM classification.^{18–20}

In 2007 proposals from the staging project were submitted to the UICC and AJCC, and subsequently accepted and incorporated into the 7th edition of the TNM staging manual.^{15–18,21,22} Effective January 1, 2010, new cases of lung cancer were staged using the revised 7th edition. ►**Table 1** summarizes the key changes of the 7th edition.

TNM Old and New

Overall survival based on stage was the major determinant of subgroups of TNM descriptors in the 7th edition. Staging revisions were validated across geographic regions and database type, and externally validated against the Surveillance, Epidemiology and End Results database. Given the retrospective nature of the data, data were used that had been collected for other purposes, and therefore some of the data were incomplete.

Between 10% and 15% of patients with NSCLC will change stage between the 6th and 7th editions.^{23,24} Changes to the descriptors and stage groupings in some cases may result in a change in therapy.¹⁷ In one series, change in management was calculated to occur in up to 17% of patients secondary to stage migration,²⁵ although another small series suggested only a 3% change in clinical management.²³

The TNM staging system has historically been applied only to NSCLC. Traditionally, SCLC was staged as a “limited” disease (LD) or “extensive” disease (ED). This staging system was originally introduced in the 1950s by the Veterans’

Table 1 Summary of key changes to the 7th edition of the TNM staging guideline*

New subdivisions	
	T1 is divided into T1a (≤ 2 cm) and T1b (> 2 cm to ≤ 3 cm)
	T2 is divided into T2a (> 3 cm to ≤ 5 cm) and T2b (> 5 cm to ≤ 7 cm)
	M1 is divided into M1a (contralateral nodules, pleural or pericardial dissemination) and M1b (distant metastases)
Upstaging	
	Tumors > 7 cm now T3; previously T2
	Pleural dissemination is now M1a; previously T4
Downstaging	
	Ipsilateral same lobe nodules now T3; previously T4
	Ipsilateral different lobe nodules now T4; previously M1

*The 7th edition staging system is now recommended for the classification of non-small cell and small cell carcinomas, and carcinoid tumors of the lung.

Administration Lung Study Group for use in their clinical trials. LD referred to carcinomas confined to one hemithorax; local extension and ipsilateral supraclavicular nodes were included, so long as they could be contained within the same radiation portal. ED represented all other cases. The new TNM staging system now incorporates SCLC and carcinoid tumors, both typical and atypical.^{18–20,26} Reviews of the 7th edition changes were elegantly made by UyBico et al and Marshall et al,^{9,27} and they are briefly summarized here.

T Descriptor

The T descriptor is defined by the size and extent of the primary tumor. The 7th edition placed greater emphasis on the role of the T descriptor, particularly tumor size, as a prognosticator of disease, and therefore more subdivisions were created to directly reflect the effect of primary tumor size on staging. Significant differences in overall survival were noted when the primary tumors were compared at the following size cut-offs: 2 cm, 3 cm, 5 cm, and 7 cm. These differences were maintained in patients with any type of resection (complete or incomplete) and with any level of nodal involvement. Reflecting these differences, T1 was subdivided into T1a (≤ 2 cm) and T1b (> 2 cm to ≤ 3 cm), and T2 was subdivided into T2a (> 3 cm to ≤ 5 cm) and T2b (> 5 cm to ≤ 7 cm) (►Table 2) (►Fig. 1).

Tumors > 7 cm were previously classified as T2 in the prior editions of the TNM staging manual. However, the larger database afforded by the IASLC showed that overall survival rates for these patients were actually similar to or paradoxically worse than those of T3 tumors.¹⁶ This led to the upstaging of tumors > 7 cm from T2 to T3 (►Fig. 1).

The anatomical extent of disease is also impacted by visceral pleural invasion, which is better defined in the 7th edition.²⁸ Although visceral pleural invasion does not affect resectability, invasion of the visceral pleura may determine whether adjuvant chemotherapy is offered. Invasion of the elastic layer of the visceral pleura has been proposed as the definition of visceral pleural invasion. PL0 indicates tumor that does not completely traverse the visceral pleura, PL1 indicates tumor that invades beyond the elastic layer, PL2

indicates tumor that invades to the pleural surface, and PL3 indicates tumor that invades into any component of the parietal pleura. PL1 and PL2 indicate visceral pleural invasion and therefore are a T2 descriptor, and PL3 indicates parietal pleural invasion and is a T3 descriptor. Direct tumor invasion across a fissure into the adjacent ipsilateral lobe is currently classified as T2a.²⁹

Previously classified as T4 disease, pleural dissemination was shown to have a significantly worse 5-year survival (11%) as compared with T4 tumors defined by additional nodules in the same lobe as the primary tumor (28%), T4 tumors defined by other factors (22%), and M1 tumors defined by additional nodules in a different, but ipsilateral lobe (22%).¹⁶ As such, the presence of pleural dissemination (“wet IIIB” disease in the 6th edition) would upstage a patient from T4 to M1a (stage IV) in the 7th edition^{16,21,30} (►Fig. 2).

Because the 5-year survival rate for T3 tumors was 31%,¹⁶ comparable with 28% of T4 tumors by additional nodules in the same lobe, the presence of the latter now results in a downstaging of the patient’s disease status (►Fig. 3). Likewise, the comparable survival characteristics of M1 tumors by additional nodules in a different ipsilateral lobe and T4 by other factors have resulted in a downstaging of the former to T4 (►Fig. 4).

In the 7th edition, the term “satellite nodules” has been replaced with “additional tumor nodules,” which represent grossly recognizable tumors in the same lobe.²⁹ This is contrasted to the concept of synchronous primary tumors, which the 7th edition describes as multiple tumors of different histologic cell types. In situations where the tumors are of the same cell type, tumors should only be considered synchronous primaries if the different tumors are of different subtypes, have no mediastinal metastases, and do not share a common nodal drainage pathway (►Fig. 5). Multiple synchronous primaries are more common with adenocarcinomas, and each tumor should be separately staged.

Substratified analysis of the retrospective database regarding tumor size, additional tumor nodules in the same lobe or in another lobe, and pleural dissemination was possible. However, other T2, T3 and T4 descriptors, including partial or total atelectasis, visceral pleural invasion, and endobronchial

Table 2 Definitions for TNM descriptors

T (Primary tumor)
TX Primary tumor cannot be assessed, or tumor proven by the 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 Tumor ≤ 2 cm in greatest dimension
T1b Tumor > 2 cm but ≤ 3 cm in greatest dimension
T2 Tumor > 3 cm but ≤ 7 cm, or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤ 5 cm): Involves main bronchus, ≥ 2 cm distal to the carina; invades visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a Tumor > 3 cm but ≤ 5 cm in greatest dimension
T2b Tumor > 5 cm but ≤ 7 cm in greatest dimension
T3 Tumor > 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina ^a but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe
N (Regional lymph nodes)
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)
M (Distant metastasis)
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
M1a Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion ^b
M1b Distant metastasis

Source: Adapted from Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumors. *J Thorac Oncol* 2007;2:706–714, with permission.

^aThe uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1.

^bMost pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3, or T4.

location could not be evaluated due to small subgroups, inconsistent clinical and pathology results, or lack of validation.¹⁶ The presence of localized or diffuse lymphangitic carcinomatosis has not been addressed in the 7th edition.

N Descriptor

The extent of nodal involvement is a critical component of the staging of lung cancer and often determines whether surgical resection is feasible. The N descriptor is defined by the extent of regional nodal involvement. Although lymph node maps

have been used for decades to facilitate a precise identification of metastases, discordance in the designation of nodal stations has resulted in inconsistencies in the reporting of nodal involvement in different regions of the world.³¹ Discrepancies in nodal mapping limited analysis of the IASLC nodal database, and in the 7th edition, no changes to the nodal classification were made.²² However, the IASLC proposed a new lymph node station map that is now widely adopted³² (→ **Figs. 6 and 7**). The new IASLC map reconciles the discrepancies between the Naruke nodal map, used in Japan,

Figure 1 (A–F) 7th edition size thresholds now at 2, 3, 5 and 7 cm. Computed tomography images of different patients. (A) A 75-year-old woman: A 1.1-cm nodule in the right middle lobe would be classified as T1a. (B) A 68-year-old woman: A 2.2-cm nodule in the left upper lobe would be classified as T1b. Note is made of mild centrilobular emphysema. (C) A 76-year-old woman: A 4.2-cm mass in the left lower lobe is a T2a lesion. Visceral pleural invasion was demonstrated pathologically at resection. (D) A 54-year-old woman: A 4.5-cm biopsy-proven typical carcinoid tumor would now be classified as T2a in the 7th edition. Subsegmental atelectasis is seen distal to the mass. (E) A 66-year-old woman: A 5.6-cm right upper lobe mass is a T2b lesion. (F) A 58-year-old woman: A 7.3-cm right upper lobe mass is now considered T3.

and the Mountain-Dresler map, previously endorsed by the American Thoracic Society.^{33,34} In addition, nodal zones were established that may better delineate bulky nodal disease that may extend beyond individual nodal station.^{22,32} ► **Table 3** summarizes the nodal stations, their groupings into “zones,” and the anatomical boundaries delineating each station (► **Table 3**).

M (Metastasis) Descriptor

The M descriptor denotes the extent of metastases to the thorax or distant sites. The 5-year survival rates significantly

differed between patients with additional nodules in a different ipsilateral lobe, pleural dissemination, contralateral lung nodules, and extrathoracic metastasis (16%, 6%, 3%, and 1%, respectively). Therefore, patients with additional tumor nodules in a different ipsilateral lobe have been downstaged to T4, and the M classification has been subdivided into M1a (contralateral nodules, pleural or pericardial dissemination) and M1b (distant metastases)²¹ (► **Figs. 8** and **9**). The MX category has been deleted from the 7th edition because the clinical assessment of metastasis can be based on physical examination alone.³⁵

Figure 2 (A, B) Pleural and pericardial dissemination. (A) A 66-year-old man with primary adenocarcinoma demonstrates pleural dissemination, a finding now considered M1a disease, reclassified from T4. (B) Computed tomography of a 56-year-old woman shows both pericardial dissemination and malignant pleural effusion, conferring classification of M1a disease, previously T4.

Stage Groupings

In addition to changes in T and M descriptors, changes to stage groupings occurred as a consequence of the project.¹⁷ ▶ **Table 4** presents a comparison of the stage groupings of the 6th edition versus 7th edition descriptors, T and M categories, and stage

Figure 3 A 76-year-old woman. Computed tomography images demonstrate two nodules in the right upper lobe that now carry a T descriptor of T3, reclassified from T4.

groupings. No new subdivisions were added. However, additional T and M descriptor subgroups have clearly increased the complexity of the stage groupings.

Clinical versus Pathologic Staging

Clinical staging (cTNM) is based on parameters acquired prior to treatment including the physical examination, imaging, laboratory data, and procedures performed for staging. The latter include bronchoscopy, esophagoscopy, mediastinoscopy, mediastinotomy, thoracentesis, thorascopy, and exploratory thoracotomy, all of which could include directed biopsies.

Pathologic staging (pTNM) not only incorporates information acquired for clinical staging but also includes information obtained during and after surgical resection, particularly following pathologic review. Not surprisingly, pathologic staging can more precisely estimate prognosis than clinical staging. Of note, pathologic staging can still be determined if the primary tumor is not resected, so long as the highest T, N, and M1 categories can be confirmed histologically.²⁹ Radiology can play a substantial role in the staging of lung cancer patients who are either not surgical candidates or whose clinical staging could obviate the need for resection.

Imaging Perspective

Computed Tomography and Magnetic Resonance Imaging

Tumor Histology, CT Appearance, and Size

Adenocarcinoma is the most common histologic subtype of lung cancer in most countries, both in men and women. Adenocarcinoma is also the most common cell type detected by low-dose CT screening. A revised classification of lung adenocarcinoma was published in 2011, sponsored by the IASLC, American Thoracic Society, and the European Respiratory Society, based on a multidisciplinary approach and incorporating advances in medical oncology, molecular biology, pathology, radiology, and surgery.³⁶ The reclassification of lung adenocarcinomas includes minimally invasive adenocarcinoma (MIA) and adenocarcinoma in situ to describe small solitary adenocarcinomas with either pure lepidic growth (AIS) or predominant lepidic growth with ≤ 5 -mm invasion (MIA).³⁶ These subsets demonstrate improved survival in comparison with stage IA tumors with invasive features, with 100% or near 100% disease-specific survival following complete surgical resection for AIS and MIA, respectively.³⁶ Invasive adenocarcinomas are classified using histologic subtyping by predominant pattern into lepidic, acinar, papillary, micropapillary, and solid patterns, with variants including invasive mucinous adenocarcinoma, colloid, fetal, and enteric adenocarcinomas.³⁶ The term “bronchioloalveolar cell carcinoma (BAC)” is no longer recommended.

Although not reflected in the current staging system, description of morphologic appearance of nodules on CT as pure ground glass (nonsolid), solid, or part solid (mixed solid-

Figure 4 (A, B) A 77-year-old man. Computed tomography images show tumor nodules in (A) the right upper and (B) right lower lobes. Multiple nodules in different lobes of the ipsilateral lung are now considered T4, previously M1.

ground glass, semisolid) may be useful in the assessment of the invasiveness of the tumor.^{36,37} The ground-glass component typically corresponds to a lepidic and the solid component to invasive patterns.³⁶ Multiple investigators have studied the CT appearance of adenocarcinoma and described features that may correlate with predictors of prognosis,

suggesting that cystic or bubble-like lucencies and intratumoral air bronchograms in stage IA adenocarcinoma correlate with well-differentiated tumors, whereas poor differentiation has been associated with notches or concave regions.^{38–43} Further research is needed to better understand the CT appearance of various histologic subtypes.

Figure 5 (A–D) Synchronous primary tumors in two different patients. (A, B) A 70-year-old man. Computed tomography (CT) images demonstrate (A) a right lower lobe typical carcinoid and (B) a left lower lobe adenocarcinoma in situ. (C, D) A 77-year-old woman. CT images demonstrate (C) a right upper lobe invasive adenocarcinoma, acinar predominance, and (D) a right lower lobe minimally invasive adenocarcinoma, lepidic predominance.

Figure 6 The International Association for the Study of Lung Cancer (IASLC) lymph node map including the proposed grouping of lymph node stations into “zones” for the purposes of prognostic analyses. (Used with permission from Rusch VW, Asamura H, Watanabe H, et al. The IASLC lung cancer staging project. A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009;4:568–577.)

CT has been shown to overestimate tumor size for NSCLC upon pathologic review. In a study of early stage lung adenocarcinoma, there was a relative difference of 18.3% between the tumor as measured on CT and that following resection⁴⁴ (29.5 mm and 24 mm, respectively). Overestimation of size on imaging could lead to erroneous upstaging of tumors. Factors contributing to this overestimation include measurement within maximally inflated lung on CT compared with measurement within deflated lung following resection. Perilesional edema, inflammation, or infiltration could also be

included on the CT measurement but could resolve following resection and therefore would be less likely to be measured on pathologic specimens.^{44,45} Given the subdivision of tumor size as independent prognosticators in the new staging system, clinicians should be aware of the possible overestimation seen on CT, which remains the imaging modality most commonly used in clinical staging (→Fig. 10).

Differences in CT scanners, window settings, slice thickness, and inter- and intraobserver variability may further impact measurement of nodules. Measurement of the total

Figure 7 (A–F) Illustrations of how the International Association for the Study of Lung Cancer (IASLC) lymph node map can be applied to clinical staging by computed tomography scan in (A–C) axial, (D) coronal, and (E, F) sagittal views. The border between the right and left paratracheal region is shown in (A) and (B). Ao, aorta; AV, azygos vein; Br, bronchus; IA, innominate artery; IV, innominate vein; LA, ligamentum arteriosum; LIV, left innominate vein; LSA, left subclavian artery; PA, pulmonary artery; PV, pulmonary vein; RIV, right innominate vein; SVC, superior vena cava. (Used with permission of Rusch VW, Asamura H, Watanabe H, et al. The IASLC lung cancer staging project. A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009;4:568–577.)

and solid components of the tumor is recommended until further research demonstrates whether invasive size is a better predictor of prognosis than total size.⁴⁶ Thin-section CT should be used for the measurement of part-solid lesions.

Chest Wall or Mediastinal Invasion

Chest wall invasion may be difficult to determine on CT. Although bone destruction provides direct evidence of chest wall invasion, other findings such as the extent of contact of mass with the chest wall, angle of the mass with the pleural surface, and the presence of a fat plane between the tumor and chest wall are useful but not definitive findings.⁴⁷ Prior reports have demonstrated no significant difference in sensitivity and specificity of CT and MRI in the diagnosis of chest

wall invasion, although several of these studies were performed over a decade ago.^{48,49} This equality may change with thin-section CT. Direct mediastinal invasion may be suggested on CT by infiltration into the mediastinal fat and extension around the great vessels or mainstem bronchi.⁵⁰ MRI is generally accepted as more accurate than CT in diagnosing mediastinal invasion.^{48,51}

Diaphragmatic Invasion, Pleural Involvement, Superior Sulcus Tumors

Motion artifact limits the ability of MRI to discern diaphragmatic invasion, and this therefore remains within the realm of thin-section CT. Although currently designated as T3, diaphragmatic invasion appears to have a poor prognosis even

Figure 8 M1a disease in a 71-year-old woman. Right upper lobe mass with direct mediastinal invasion narrowing the right mainstem bronchus, with ipsilateral and contralateral lung metastases and right pleural dissemination with malignant pleural effusion and nodularity of the right oblique fissure.

after complete resection and without N2 disease, and therefore this T descriptor may change as more survival data become available.

Although MRI has been suggested as superior to CT in determining pleural involvement,⁵² neither imaging modality can reliably differentiate between visceral (T2) or parietal (T3) pleural involvement, and special histologic staining is often required.²⁸

MRI has been shown to be superior to CT in differentiating T3 versus T4 disease in superior sulcus (Pancoast) tumors.⁵³ T3 tumors involve the inferior branches of the brachial plexus (C8 and/or T1) or the stellate ganglion; T4 tumors demonstrate vertebral body or spinal canal invasion, encasement of subclavian vessels, or involvement of the superior branches of the brachial plexus.

Nodal Metastases

Nodal size on CT alone is an unreliable measure of tumor involvement in lymph nodes. McLoud et al demonstrated only 7 of 19 lymph nodes measuring 2 to 4 cm in short axis were pathologically proven to be involved by tumor in patients with known bronchogenic carcinoma.⁵⁴ The sensitivity and specificity of CT in the detection of mediastinal nodal metastases has been reported to be on the order of 52 to 64% and 62 to 69% for NSCLC, respectively.^{48,54}

Data are available in the literature on the accuracy of MRI for evaluation of mediastinal nodal involvement. In one study, T2-weighted fat-suppressed echo imaging performed on a 3.0-T MR reported comparable sensitivity of 53%, but the specificity and accuracy levels for nodal metastases were higher, at 91% and 85%, respectively.⁵⁵ The high accuracy of MRI is comparable with that seen with dual-modality PET/CT, and in cases where MRI is performed to better assess mediastinal invasion, knowledge of its ability to detect nodal metastases is valuable.

American College of Chest Physician (ACCP) guidelines recommend that CT of the chest with contrast should be

Figure 9 (A–C) A 61-year-old woman. (A) A right upper lobe 2.8-cm peripheral adenocarcinoma is associated with right paratracheal and (B) bilateral supraclavicular nodes, consistent with N3 nodal disease. (C) The presence of brain metastases confers an M descriptor of M1b.

performed for patients with a known or suspected lung cancer who are eligible for treatment. In patients with enlarged discrete mediastinal nodes on CT (>1 cm) and no evidence of metastatic disease, further evaluation of the mediastinum should be performed prior to definitive treatment of the primary tumor.⁵⁶ In these guidelines, MRI of the chest is not recommended for routine staging of the mediastinum.

Distant Metastatic Disease

The utility of extrathoracic scanning for evaluation of metastatic disease is addressed in the AACP guidelines.⁵⁶ In the absence of clinical signs, symptoms, or abnormal laboratory

Table 3 International Association for the Study of Lung Cancer nodal map stations

Nodal station number	Nodal station name	Anatomical boundaries	Zone
1	Low cervical, supraclavicular, sternal notch	Upper border: lower margin of cricoid cartilage Lower border: clavicles, manubrium Laterality: midline trachea designates left and right	Supraclavicular zone
2R	Upper paratracheal (right)	Upper border: lung apex and pleural space Lower border: intersection of innominate vein and trachea Laterality: includes nodes extending to the left lateral border of the trachea	Upper zone
2L	Upper paratracheal (left)	Upper border: lung apex and pleural space Lower border: superior margin of aortic arch	
3a	Prevascular	Upper border: apex of chest Lower border: carina Anterior border: sternum Posterior border: SVC (right side) or left carotid artery (left side)	
3p	Retrotracheal	Upper border: apex of chest Lower border: carina	
4R	Lower paratracheal (right)	Upper border: intersection of innominate vein with trachea Lower border: lower margin of azygos vein Laterality: includes nodes extending to the left lateral border of the trachea	
4L	Lower paratracheal (left)	Upper border: upper margin of aortic arch Lower border: upper margin of left main pulmonary artery Lateral border: ligamentum arteriosum	
5	Subaortic (Aortopulmonary Window)	Upper border: lower margin of aortic arch Lower border: upper margin of left main pulmonary artery Medial border: ligamentum arteriosum	AP zone
6	Para-aortic (ascending aorta or phrenic)	Upper border: line tangential to the upper margin of the aortic arch Lower border: the lower margin of the aortic arch	
7	Subcarinal	Upper border: carina Lower border: upper margin of left lower lobe bronchus (left side) and lower margin of bronchus intermedius (right side)	Subcarinal zone
8	Paraesophageal (below carina)	Upper border: upper margin of left lower lobe bronchus (left side) and lower margin of bronchus intermedius (right side) Lower border: diaphragm	Lower zone
9	Pulmonary ligament	Upper border: inferior pulmonary vein Lower border: diaphragm	
10	Hilar	Upper border: lower margin of azygous vein (right side) and upper margin of pulmonary artery (left side) Lower border: interlobar region	Hilar/interlobar zone
11	Interlobar	11s: between upper lobe bronchus and bronchus intermedius on the right 11i: between middle and lower lobe bronchi on the right	
12	Lobar	Adjacent to lobar bronchi	Peripheral zone
13	Segmental	Adjacent to segmental bronchi	
14	Subsegmental	Adjacent to subsegmental bronchi	

Abbreviation: SVC, superior vena cava.

Source: Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P; Members of IASLC Staging Committee The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009;4(5):568–577.

Table 4 Stage grouping comparisons: 6th edition versus 7th edition descriptors, T and M categories, and stage groupings

Sixth edition T/M descriptor	7th edition T/M	N0	N1	N2	N3
T1 (≤ 2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (> 2 –3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤ 5 cm)	T2a	IB	IIA	IIIA	IIIB
T2 (> 5 –7 cm)	T2b	IIA	IIB	IIIA	IIIB
T2 (> 7 cm)	T3	IIB	IIIA	IIIA	IIIB
T3 invasion	T3	IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)	T3	IIB	IIIA	IIIA	IIIB
T4 (extension)	T4	IIIA	IIIA	IIB	IIIB
M1 (ipsilateral lung)	T4	IIIA	IIIA	IIB	IIIB
T4 (pleural effusion)	M1a	IV	IV	IV	IV
M1 (contralateral lung)	M1a	IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Source: Adapted from Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage grouping in the forthcoming (seventh) edition of the TNM classification of malignant tumors. *J Thorac Oncol* 2007;2:706–714, with permission.

Note: Cells in boldface indicate a change from the 6th edition for a particular TNM category.

tests, the yield of imaging for extrathoracic metastases is low, and hence routine scanning is not recommended. This recommendation is controversial, however. Site-specific symptoms require a directed imaging evaluation with the appropriate examination as indicated clinically, including head CT or MRI, whole-body PET scanning or bone scanning, and abdominal CT scanning.⁵⁶ In patients with clinical stage IIIA or IIIB disease with a negative clinical evaluation, imaging for occult extrathoracic metastases is recommended because asymptomatic metastases are found at a higher rate than anticipated. Biopsy confirmation of abnormal imaging findings is advised.

PET Imaging

From an imaging standpoint, the 7th edition of the TNM staging manual relies on anatomical data because anatomical data were

Figure 10 A 53-year-old man. This left upper lobe nodule measured 2.4 cm on computed tomography (CT) but was shown pathologically to be 1.7 cm, reclassifying the initial CT finding from cT1b to pT1a.

the type of information consistently available in such a massive retrospective database. In addition, functional imaging with PET to evaluate lung cancer was just beginning to be performed after the accumulation of the data set. The limitations of utilizing anatomical data only, however, are clear.

PET imaging is an invaluable tool in the armamentarium of lung cancer staging. PET scanning has been shown to be more accurate than CT in the identification of mediastinal adenopathy secondary to tumor involvement, with an accuracy range of 85 to 94% for PET and 58 to 69% for CT.^{57–60} In addition, with pathology as the gold standard, PET/CT dual modality imaging is more accurate in determining tumor stage for NSCLC than either PET or CT alone.^{60–62}

Roberts et al demonstrated a negative predictive value of 95.8% in their study evaluating the utility of PET in detecting mediastinal involvement in lung cancer patients. The authors of that study concluded that enlarged nodes seen on CT that do not demonstrate fluorodeoxyglucose uptake are effectively nonmetastatic in etiology. However, because the positive predictive value was only 75%, the authors recommended mediastinoscopy and biopsy in these cases.⁶³

Given the utility and now widespread use of PET scanning in lung cancer evaluation, PET is likely to play a larger role in subsequent iterations of the TNM staging system.

Future Considerations

Limitations of the 7th edition are primarily related to the retrospective collection of data, resulting in extensive information of some descriptors, particularly tumor size, but lack of information regarding other details, such as specific anatomical sites of tumor extension.⁶⁴ Thus descriptors that define T3 and T4, potential subdivisions of N1 and N2 nodal spread based on number of involved lymph nodes and nodal

stations, and differences in forms of M1 disease could not be validated. Data on nodal involvement were also compromised by differences in nodal maps. Also new since the data for the 7th edition were collected, PET imaging is now widely used. The IASLC has initiated the Prospective Project to address the limitations of the 7th edition with a large international prospective database.⁶⁴

Other factors that impact prognosis not currently integrated into TNM staging including sex, age, comorbidities, biological parameters, and molecular and genetic factors may also be assessed in the future. The feasibility of evaluating molecular and genomic data such as epidermal growth factor receptor (EGFR) status may be evaluated.⁶⁴ Clinical factors (age, gender, performance status), laboratory data (hypercalcemia, carcinoembryonic antigen levels), and molecular markers (EGFR mutation or bcl-2 expression) may play a larger role in the next staging manual. Although still within the realm of research, molecular imaging to target lung cancer cells more specifically could potentially obviate the need for pathologic examination and may significantly overhaul the process of cancer staging.^{65,66}

The histologic reclassification of adenocarcinomas has future research and clinical implications. In the next TNM revision, and in keeping with general rules of the TNM system, AIS may belong to the "pTis" category and MIA may be classified as "pTmi."⁶⁷ Potential areas for radiologic research include the natural history of single and multiple ground-glass nodules, CT attenuation characteristics of the different adenocarcinoma histologic subtypes, and possible CT differentiation of synchronous versus metachronous primary tumors from metastases.³⁶ The correlation of imaging findings and molecular features of adenocarcinoma is an intriguing area of multidisciplinary research.

With the advent and adoption of percutaneous thermal ablation for nonresectable lung malignancies, the potential achievement of locoregional control may very well confer additional survival benefit.⁶⁸ This treatment modality was not included in the 7th edition, and studies to assess its impact on survival are clearly indicated and may play a significant role in future iterations of the staging manual.

Conclusion

The 7th edition of the TNM staging system meets the five objectives originally set forth by the UICC, and it represents an impressive worldwide initiative to standardize and validate cancer staging. In addition to NSCLC, the new staging system is now inclusive of small cell carcinoma and carcinoid tumors. The 7th edition allows for improved prognostic stratification of disease, with significant changes in the T and M descriptors. The impact of the new staging system on established treatment algorithms is yet to be fully determined. The staging of lung cancer continues to evolve, and imaging will continue to play a vital role in accurate staging and optimization of patient care. The 8th edition (to be published in 2016) is expected to result in even greater advances in lung cancer staging.

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