Dilemmas in Lung Cancer Staging

Ioannis Vlahos, BSc, MBBS, MRCP, FRCR

KEYWORDS

• TNM8 • Non–small cell lung cancer (NSCLC) • Staging • Limitations • Dilemmas
• Computed tomography (CT) • PET-CT • IASLC

KEY POINTS

- The 8th edition of the non–small cell lung cancer (NSCLC) TNM staging reflects an extremely well-validated evidence-based advance, better stratifying survival than prior staging systems.
- Despite revisions, and several white paper recommendations, the staging system demonstrates residual limitations and dilemmas that relate to the TNM database, the application of radiological staging as well as clinical management.
- Dilemmas arise as to the radiological assignment of T-descriptors in certain clinical scenarios.
- The unchanged imaging staging of nodal disease retains limitations in guiding management of N2 disease.
- Multiple factors impact stage migration and apparent survival differences that also affect backwards compatibility of the staging system with prior staging iterations and management guidance.

INTRODUCTION

The staging of non–small cell lung cancer (NSCLC) is at a juncture; the current 7th edition of the TNM staging system (TNM7) is about to be superseded by the widespread adoption of the 8th edition (TNM8). As with the introduction of TNM7, the TNM8 reclassification of the T, N, M descriptors as well as their associated stage groupings represents a substantial step change for multidisciplinary NSCLC teams and their supporting radiologists.[1–4]

The periodic adjustment of staging systems is a required process to respond to evolution in the natural incidence of disease subtypes, new understandings in the pathology, surgery, and treatment of lung cancer, and advances in staging methodologies. As with all staging systems, the principal purpose of the lung cancer staging system remains to categorize groups of patients with similar disease extent, to accurately prognosticate survival, and to guide best management. The process of staging should be easy to implement, logical, unambiguous, and reproducible, utilizing all current imaging methodologies.

The implementation of TNM7 addressed many limitations of the earlier staging iterations but left several issues unaddressed.[5–8] TNM8 attempts to address many of these, although remaining issues persist, and new issues are raised by staging system changes. This article reviews limitations of the current staging system and dilemmas facing imagers in their interactions with surgical, oncologic, pathologic, and other colleagues managing NSCLC. Unless otherwise specifically stated, the TNM and stage groupings in this article refer to TNM8 as described in the proposal publications of the International Association for the Study of Lung Cancer (IASLC).

STRENGTHS AND WEAKNESSES OF TNM8 PROCESS

The IASLC reclassification of NSCLC represents an unparalleled data-based advancement of the

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Department of Radiology, St. George's NHS Foundation Trust Hospitals and School of Medicine, St James' Wing, Blackshaw Road, London SW17 0QT, UK
E-mail address: ioannis.vlahos@stgeorges.nhs.uk

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accuracy of staging through TNM7 and TNM8. The historical 6th edition (2002) of the TNM classification system, itself unchanged from the 5th edition (1997), was based on only 5319 surgically staged cases, predominantly from a single site.[9] The TNM7 Lung Cancer Project accumulated a database of 68,463 validated NSCLC patients from 46 centers across 20 countries, staged clinically, principally by CT, during 1990 to 2000. A survival analysis of this database supported reclassification of the T, N, and M descriptors and their associated stage groupings in TNM7, adopted by the International Union against Cancer and the American Joint Committee on Cancer in December 2009.

The retrospective nature of the TNM7 database prohibited a detailed analysis of several clinical parameters as well as the validity of existing T parameters. To address these limitations, a prospective study was launched in 2009 in order to create a new database to inform TNM8.[10] This ambitious project incorporated an electronic data capture (EDC) form to record detailed staging information to assess the validity of each of the components of the TNM staging system. The EDC aim was to accumulate extensive clinical, surgical, pathologic, and outcome data that could influence survival. The EDC included demographic data, such as sex, age, and smoking history, and clinical data, such as comorbidities, performance status, serologic and pulmonary function values, and the presence of paraneoplastic syndromes. Pathologic data included histologic subtype, tumor grade, and extent of lymphovascular or visceral pleural invasion (VPI). Where available, biological, molecular, and genetic factors and surgical data relating to resection margins and outcome were recorded. If performed, maximum standardized uptake values from ^{18}F-fludeoxyglucose PET-computed tomography (CT) were solicited.

The finalized TNM8 database comprised new diagnoses of lung cancer between 1999 and 2010.[11] Although of a similar large size to the TNM7 database (70,967 NSCLC validated cases), it is important to recognize several differences between TNM7 and TNM8 databases that have implications for the applicability of the TNM8 staging system and may indicate areas that may change in later TNM versions. Although the TNM8 database was prospectively accrued, most cases were submitted from established databases, with less than 5% submitted by EDC with all the required elements. Hence, in large part the database is lacking in the detailed parameters desired from a prospective evaluation. Although the database remains international, it is now more geographically skewed. Asian cases increased from 11.5% to 44%, almost exclusively from Japan (93%). Correspondingly, the contribution from North America (5%) and Australia (1.7%) was markedly reduced (previously 21%, 9.3%, respectively). The European contribution to cases was mildly reduced (49% vs 58%), but notably these again were disproportionately from a single nation, Denmark (73%). South America contributed only 0.3% of cases.

The altered geographic distribution is important because overall the cases from Asia, and hence the entire database, were predominantly stage I, whereas European cases were most often stage IV. The Asian cases may have included earlier stage subsolid lesions; however, these data are not recorded. Critically, mutations of epidermal growth factor receptor (EGFR) are also known to be more common in Asian populations; however, these data were also not captured.

The early stage preponderance is reflected in management paradigms and ultimately patient survival profile. As a result, in TNM8, 85% of patients underwent surgery alone, or in combination with chemotherapy or radiotherapy (53% in TNM7). The reduction of advanced stages of disease in the database, and the absence of any chemotherapy trial patients, is reflected in only 9.3% of patients undergoing chemotherapy alone, radiotherapy alone (1.5%), or both (4.7%) compared with TNM7 (23%, 11%, 12%, respectively).

The different constituent characteristics of the current TNM8 database impact on the wider relevance of the new staging system. Arguably the modified staging system descriptors and stages may be more optimized to differentiating survival in early surgically treatable disease than in advanced nonsurgical disease.

IMAGING METHODOLOGIES

A robust staging system must reflect the prevalent imaging modalities available for accurate determination of patient stage. A deficiency of the retrospective TNM7 dataset was that many patients in the acquisition period did not undergo PET-CT. PET-CT functional imaging has proved an invaluable adjunct to CT staging, increasing the diagnostic accuracy of determination of malignancy within primary, nodal, and metastatic sites and providing prognostic information via standardized uptake values.[12–14] Considering the 2 largest contributors of cases, it is likely that a smaller proportion of the earlier stage Japanese cases (submitted earlier in 3 tranches in 1999, 2002, and 2004) underwent PET-CT than the later collected advanced stage Danish cases (submitted gradually over 2001–2010). However, none of the cases from