The TNM System Is Adequate for Making Treatment Decisions and Prognostication in Lung Cancer

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The Union for International Cancer Control (UICC) published the first brochure with the TNM classification of lung cancer in 1966, two decades after the French surgical oncologist, Pierre Denoix, initially developed this system to determine the anatomical extent of malignant tumors, which the UICC accepted in 1960. After the American Joint Committee on Cancer adopted it more than a decade later, both institutions have been in charge of updating the TNM staging system.1 The second to the sixth editions of the TNM classification of lung cancer were based on a relatively small North American database managed by Clifton F. Mountain.

For the seventh and the eighth editions, revision of the lung cancer TNM staging system was based on analyses of databases collected by the International Association for the Study of Lung Cancer (IASLC). The IASLC Staging and Prognostic Factors Committee (SPFC) managing the IASLC Staging Project has been active for more than 25 years; since 2017, the SPFC has been working toward the ninth edition of the TNM classification of lung cancer, malignant pleural mesothelioma, and epithelial thymic tumors.2 The resulting proposals for revision of the TNM system are due for ratification in 2024.

More than half a century since its conception, the TNM classification of lung cancer continues to serve as a lingua franca for communicating details about the extent, severity, and likely prognosis of lung cancer across time and space. It connects the present to the past and, probably still, the future. The classification is an international code that allows us to understand each other when we talk about lung cancer. Treatment algorithms are based on the anatomical extent of the tumor defined by stages that group carcinomas with similar prognosis. Before and after treatment, each stage is associated to different prognosis. Tumor stage is almost always a major selection criterion in clinical trials, including contemporary trials in the age of personalized oncology with targeted therapies and immunotherapy, thus serving as a key component of advances in the understanding and treatment of lung cancer. Because optimal treatment is heavily stage dependent, the TNM staging system assists us in the evaluation, and comparison, of the results of treatment. Finally, the classification supports all types of cancer control activities, from early diagnosis and screening to staging and treatment.3

With greater understanding of cancer biology and the emergence of highly effective molecular targeted therapies that yield significantly improved survival in appropriately treated patients, there is an emerging agitation to incorporate genome-based and protein-based information in the prognostication of lung cancer. This nascent effort comes despite the fact that the clinical and pathologic stages derived from the analyses of the databases used to inform the seventh and eighth editions of the TNM classification of lung cancer are very good prognosticators4 (Fig. 1A and B).

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Nevertheless, when we compare the additive prognostic capacity gained in the eighth edition stages over the seventh edition staging system by means of the $R^2$ statistic, the gain was incremental. For clinical stages, the $R^2$ was 67.5 for the seventh edition and 68.3 for the eighth edition. For pathologic stages, the $R^2$ was 45.7 and 46.9 for the seventh and the eighth editions, respectively. This should not surprise us. The anatomical extent of tumor determined by the TNM classification is but one prognostic factor. Prognosis is dynamic, potentially changing from initial diagnosis, with the thoroughness of staging, in response to therapy, and at recurrence. It is multifactorial, influenced by a myriad of known and unknown tumor-, patient-, care-delivery-, and environment-related factors. The relatively low $R^2$ means that there is a lot of room for improvement, but developing prognostic prediction models is a complex process.

Improvements in prognosis can be achieved by using the TNM classification at its maximum capacity. The classification requires histopathologic diagnosis of cancer, specification of cell type and differentiation grade (G), the anatomical location of the tumor, and its anatomical extent determined by the T, the N, and the M components of the classification. In addition to this fundamental content, there are “optional descriptors”—vascular invasion (V), lymphatic permeation (L), and perineural invasion (Pn)—and, for patients who undergo surgical resection, the completeness of resection indicated by the residual tumor (R) classification. Although all have prognostic relevance and refine the prognosis given by the TNM classification of the tumor, the adjective “optional” condemned them to near death: they rarely accompany the TNM classification.

The presence of V, L, and Pn, even in early stage lung carcinomas, significantly worsens prognosis. For example, evidence suggests that stage IA NSCLC with L and V may be upstaged to stage IB. After surgical resection, the absence of residual tumor (R0) or its microscopic (R1) or macroscopic (R2) presence also modifies the prognosis given by the pathologic (p) TNM. The type of resection specifically defined for lung cancer—complete, incomplete, and uncertain—is prognostic and should accompany all pTNM classifications. Although for the pretreatment clinical (c) classification the cTNM may be enough, the postresection pathologic classification should include L, V, Pn, and R, in addition to the pTNM. The information provided by the descriptors of tumor invasiveness and the completeness of resection refine postoperative prognosis and may be used to indicate adjuvant therapy or more intensive follow-up on an individualized basis.

Prognostication may also be improved by combining independent, validated, survival-impactful variables (“prognostic factors”) to create different prognostic groups. Recognizing the importance of prognostic factors...
related to the tumor (besides the TNM classification), the patient, and the environment, the UICC has added prognostic factor grids for resected and advanced NSCLC and SCLC to its staging manual.\(^3\) With construction of the international database for analysis of variables proposed for the ninth edition of TNM, the IASLC SPFC initiated a project to collect information on biomarkers. This database contains detailed information on more than 80,000 patients with lung cancer, approximately 10,000 of which include molecular data (gene mutations, copy number alterations, and protein expression), which will be useful to explore the possibility of augmenting prognostication beyond that provided by the anatomical extent of the tumor.

Despite the clamor to transition from a purely anatomy-based staging system for lung cancer to one that incorporates biological information, it seems unlikely that molecular classification will supplant the venerable TNM system, given all its advantages as a pragmatic lingua franca. Unlike molecular data, the TNM classification is universally available. It can be determined to certain degrees in almost any clinical setting, whether a poorly resourced clinic or a university hospital with the most advanced technology. Although it requires, at a minimum, radiologic imaging of the chest, its thoroughness of application can be qualified by the “certainty factor”—the intensity with which the extent of the tumor has been studied. Of great significance for global health, TNM can also be simplified as the “essential TNM,” a simplified set of variables used to provide a pragmatic, yet standardized, approach to staging in care-delivery environments where resources are scarce and when information may be incomplete.\(^3\)

Molecular data are not readily available even in relatively wealthy countries and are not available in most countries in the world, significantly limiting their utility in a universally applicable global staging system. Although the TNM classification can be applied to and can guide therapy in all lung cancers, molecular markers are identified in approximately 50% of adenocarcinomas and 5% of squamous cell carcinomas, thus limiting its use in the remaining lung cancers with unidentified molecular markers.\(^5,6\)

The TNM classification remains relevant in clinical practice because it guides therapy, including the indications for targeted therapies and immunotherapy. It remains the primary means of communicating prognosis across time and space. It connects the present to the past, and the future. Nevertheless, desirous we are for a day when knowledge of cancer biology advances to the point of robust, clear, independent delineation of prognosis, and implementation barriers such as cost and accessibility are eliminated, and biomarker-based treatment becomes so effective that lung cancer becomes routinely eradicable by simple, easily administered nonsurgical treatment, the reality of our time is that the time-honored anatomical TNM staging system will remain with us for the foreseeable future. We should optimize it and, just as important, use it to its maximal potential for the benefit of our patients.

CRediT Authorship Contribution

**Statement**

Ramón Rami-Porta: Conceptualization, Original draft preparation, Writing—review and editing.

Raymond U. Osarogiagbon, Hisao Asamura: Conceptualization, Writing—review and editing.

**References**


