EDITORIAL

The Only Constant Is Change: Introducing the International Association for the Study of Lung Cancer Proposals for the Ninth Edition of TNM Stage Classification of Thoracic Tumors

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A fundamental cornerstone to managing patients with cancer is stage classification. This provides a universal, well-defined nomenclature to describe the anatomic extent of the tumor. The ability to communicate clearly and consistently is essential in selecting a treatment strategy, for example, during multidisciplinary discussions, in assessing how well the individual patient fits clinical trial data, and thus in predicting outcomes after a treatment approach.

The language we use must be stable, well defined, and used consistently by all. Recognizing this, stage classification is formally defined by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC)—two separate agencies that agree on a classification of the anatomic extent of malignant tumors. This classification, published in the UICC and AJCC stage classification manuals that are used worldwide, follows a TNM structure.

Nevertheless, even when consistency is essential, change is inevitably needed. Thus, periodically, the UICC and AJCC refine the classification of anatomic extent of cancers. The next edition of TNM stage classification (the ninth edition) is planned to take effect in 2025. Change is needed to reflect advances in imaging, diagnostic techniques, and treatment. Particularly in lung cancer, the field has progressed tremendously—including changes in detection, minimally invasive surgical techniques, methods of targeting and fractionation of radiotherapy, and the emergence of targeted therapies and immunotherapy.

Thoracic malignancies are relatively unique with regard to stage classification, because the International Association for the Study of Lung Cancer (IASLC) has made it a priority since 1996 to ensure that the best possible scientific basis exists for stage classification revisions. The IASLC has developed large international databases and a robust analytical process. The Staging and Prognostic Factors Committee (SPFC) of the IASLC is a multidisciplinary group of worldwide experts tasked with using this to develop proposals for revision for thoracic malignancies for the UICC and AJCC to adopt. The Cancer Research And Biostatistics center provides expert statistical analysis. The SPFC proposals will be published in multiple papers in the next year in each issue of the *Journal of Thoracic Oncology* to introduce the proposals to the thoracic community.

Similar to the IASLC proposals for the UICC and AJCC seventh and eighth editions, databases of approximately 100,000 lung cancers, 10,000 thymic malignancies, and 5000 mesotheliomas were assembled for the ninth edition.[1,2] The SPFC is divided into domains (lung, thymic, mesothelioma, and esophageal); these are subdivided into subcommittees to address specific aspects (the main ones being T, N, M, and stage groups). Virtual meetings of the subcommittees have been ongoing for several years; with joint meetings of the entire SPFC at the IASLC annual meetings. The SPFC has been coordinating with the UICC and AJCC; although these are the official bodies to decide on the ninth edition

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classification, it is anticipated that the SPFC proposals will be adopted without change, consistent with previous editions.

An extensive process was used to develop the ninth edition proposals.[3] Guiding principles include that changes should be based on compelling data, should reflect the impact of the anatomic tumor extent (as opposed to a particular setting, treatment, or other confounders), preserve backward compatibility if possible, and the system should be practical (mesh with relevant tumor features in current clinical practice). The process involved a planning phase (identification of potential questions to be addressed on the basis of literature and clinical changes), database development to allow issues to be addressed, and exploratory analysis. Potential TNM descriptors and categories were required to reveal consistent discrimination by a multi-tiered statistical analysis and be deemed clinically relevant. Demonstration of generalizability was required across time periods, regions, tumor types, practice settings, and external validation. Feedback and approval of final proposals were obtained from the entire SPFC (all domains) and the IASLC board of directors.

Prognosis was used as a major tool in the analytical process. Nevertheless, prognosis is affected not only by anatomic tumor extent but also by many other tumor-related (e.g., histotype, genomic characteristics), patient-related (e.g., performance status, age, comorbidities), environment-related (e.g., resource availability, detection methods), and treatment-related factors. This is reflected in differences in prognosis depending on the region, setting, type of source data, and treatment. Statistical analyses accounted for such differences, in addition to the multi-tiered requirement for consistent discrimination across multiple subset analyses. Furthermore, potential confounders were evaluated whenever possible to ensure a robust process to refine stage classification.

Despite the extensive effort, inevitably some limitations were encountered. These include sample size in subset analyses and the ability to assess and account for particular confounders. These limitations were critically considered and potential changes were rejected unless there was strong confidence in the thoroughness of the analysis that was able to be conducted. The SPFC welcomes independent investigation of the ninth edition proposals by the thoracic community in the coming years.

The SPFC hopes to draw attention to the series of papers that are to be published in upcoming issues of the journal. The actual proposed refinements and the basis for them cannot be covered in this editorial. It is only possible in this introductory article to highlight a few key changes.

In the lung domain, key changes include subdivision of the N2 category into a single station (N2a) and multistation (N2b) involvement. Similarly, tumors with more than one extrathoracic metastases are subdivided into M1c1 (involving a single organ system) and M1c2 (involving multiple organ systems). These changes have implication on how T, N, and M categories are arranged into stage groups. This high-level description glosses over many details of factors that were analyzed and ways to refine the stage classification system that were considered.

In the thymic domain, tumor size was studied extensively. In early stage tumors, 5 cm emerged as a threshold for subdivision of T1 into T1a and T1b. Furthermore, the SPFC was able to evaluate in greater detail the impact of invasion into specific perithymic structures, leading to definition of T2 as invasion of the pericardium, lung, and phrenic nerve, and T3 as invasion of the brachiocephalic vein, superior vena cava, chest wall, or extrapericardial pulmonary arteries and veins. The full analysis includes many more details, including the evaluation of the N and M categories and the thymic node map.

No changes are proposed to the esophageal stage classification. For the eighth edition, the Worldwide Esophageal Cancer Collaboration organized the database and analysis as a parallel initiative to the IASLC SPFC activities in lung, thymic malignancies, and mesothelioma. For the ninth edition, an analysis involving the International Society for Disease of the Esophagus and the International Esodata Study Group database was planned. Nevertheless, this could not be sufficiently accomplished to develop proposals for the ninth edition of TNM.

The focus of potential changes in the mesothelioma domain arises from a greater ability to assess tumor burden in the current database through the addition of systematic pleural thickness measurements. Analyses are still ongoing, but final proposals for changes will be forthcoming soon.

Change is always associated with some effort. Just when one system becomes second nature, you have to learn a new one. Furthermore, with a large database, there is a trend to increased granularity that leads to increased complexity. As with previous editions of TNM, IASLC will develop tools (e.g., pocket cards, posters, a manual, and a handbook) to make the transition easier.

Reflecting on the evolution of lung cancer stage classification, it is apparent that the impact of anatomic disease extent has become broader as treatment has become more multidisciplinary across the spectrum of disease extent. With the advent of local therapy for oligometastatic disease, anatomic extent is increasingly important in stage IV. Similarly, the impact of

biomarkers predictive of response to systemic therapies is increasingly important in early stage tumors. This underscores the need to develop a useful way of classifying non-anatomic tumor characteristics in addition to the anatomic extent. The IASLC molecular database has been accruing data that will enable addressing this, but the initiative is not sufficiently mature for inclusion in the ninth edition proposals.

Stage classification remains a nomenclature for anatomic disease extent. It is important to remember that stage classification does not attempt to account for all factors that determine prognosis, nor does it encompass all the factors that affect treatment selection. Stage classification is not designed to be a prognostic model or a treatment guideline; it is merely a tool that helps estimate prognosis and select treatment together with other information.

The thoracic community should look forward to the ninth edition stage classification proposals that will be appearing in upcoming issues of the *Journal of Thoracic Oncology*. Despite the inherent challenges of adapting to change and some limitations of the development process, we also need to appreciate what this represents. Thoracic malignancies are unique regarding the amount of analysis that underpins the stage classification. It is a tribute to the strength of the community and organization that IASLC represents that made this possible.

CRediT Authorship Contribution Statement

Frank C. Detterbeck, Conceptualization, Writing—original draft, Writing—review and editing.

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