The IASLC Lung Cancer Staging Project: Overview of Challenges and Opportunities in Revising the Nodal Classification of Lung Cancer.

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Abstract

The status of lymph node involvement is a major component of the tumor, node, metastasis (TNM) staging system. The N categories for lung cancer have remained unchanged since the 4th edition of the TNM staging system, partly because of differences in nodal mapping nomenclature, partly because of insufficient details to verify possible alternative approaches for staging. In preparation for the rigorous analysis of the International Association for the Study of Lung Cancer (IASLC) database necessary for the 9th edition TNM staging system, members of the N-Descriptors Subcommittee of the IASLC Staging and Prognostic Factors Committee reviewed the evidence for alternative approaches to categorizing the extent of lymph node involvement with lung cancer which is currently based solely on the anatomic location of lymph node metastasis. We reviewed the literature focusing on non-small cell lung cancer (NSCLC) to stimulate dialogue and mutual understanding among subcommittee members engaged in developing the 9th edition TNM staging system for lung cancer, which has been proposed for adoption by the American Joint Committee on Cancer and Union for International Cancer Control in 2024. The discussion of the range of possible revision options for the N categories, including the pros and cons of counting lymph nodes, lymph node stations or lymph node zones also provides transparency to the process, explaining why certain options may be discarded, others deferred for future consideration. Finally, we provide a preliminary discussion of the future directions that the N-Descriptors Subcommittee might consider for the 10th edition and beyond.

Evolution of the nodal staging component. The status of nodal involvement (the N categories) is a major lung cancer prognostic factor, which also guides treatment, especially for patients considered candidates for curative-intent therapy. In the first edition of the Union for International Cancer Control (UICC) lung cancer TNM staging system published in 1968, the N component of TNM was stratified in three categories: N0, N1 (any intrathoracic nodal involvement) and NX (unknown). Mediastinal nodal involvement was delineated as N2 in the second edition in 1973, and the N3 category was created with the 4th edition in 1987 to separately identify metastasis to contralateral mediastinal, hilar and the supraclavicular and scalene nodes.[1] There has been no change in the N categories since then.[2-5] Leading up to the revisions for the 9th edition of the lung cancer staging system, which is proposed for adoption in 2024, we reviewed alternative approaches to refining the N categories. In this whitepaper, we overview the N-Descriptors Subcommittee's process for adopting, deferring for future re-consideration or rejecting the various options.

Despite great interest in improving the stratification of prognosis on the basis of nodal involvement, for the 6th edition TNM, Dr. Clifton Mountain once again deferred further revision of the N categories until construction of a robust international dataset and resolution of differences between the American Thoracic Society and the Japanese (Naruke) lymph node maps.[6,7] The 7th edition, based on analysis of the retrospectively collected International Association for the Study of Lung Cancer (IASLC) database, was complicated by unresolved differences in the nodal staging maps and data limitations.[8,9] For example, although analyses suggested that N1 and N2 could be subdivided into N1a, N1b, N2a, N2b, the recommendation

was ultimately deferred because the number of available cases did not allow validation of each N category across each T category. However, the IASLC lymph node map was adopted as a new global standard; Dr. Peter Goldstraw proposed the lymph node zones concept as a pragmatic solution to ambiguities of lymph node mapping as well as a potentially simpler, more practical approach to nodal staging in resource-challenged care-delivery environments; and Electronic Data Capture (EDC) was introduced to facilitate more structured, accurate and complete data collection for the 8th edition database.[4,10]

With the 8th edition, there remained overwhelming reliance on the less formally structured datasets submitted outside the EDC format and most of the lymph node information did not reflect the new IASLC lymph node map. Explored, but again deferred, was the possibility of adopting prognostic N1 and N2 subsets N1a, N1b, N2a1, N2a2, and N2b, based on the location and number of positive lymph node stations.[5] The nodal zone concept was not further explored. With a larger dataset, including a much larger component collected through the EDC, and uniform adoption of the IASLC lymph node map, the 9th edition database now provides the opportunity to robustly examine alternative ways to define the N categories.

Overview of approach to the 9th edition N component. The incumbent system, which advances solely on the anatomic centrifugality of sites of lymph node metastasis from the primary tumor location - N0 (no), N1 (hilar/intrapulmonary), N2 (ipsilateral mediastinal) and N3 (contralateral mediastinal or supraclavicular) lymph node involvement- has stood the test of time. Nevertheless, concerns persist that it inadequately quantifies the burden of nodal metastasis.

For consideration, alternative approaches must achieve greater prognosis discriminatory ability, be clinically coherent, and backwards-compatible with the incumbent staging system.[11] A fundamental rule of the UICC is that clinical staging descriptors (derived from information obtained from procedures short of an attempted resection) and pathologic staging descriptors (obtained at the time of attempted surgical resection) should match.[12] While not an absolute requirement – clinical and pathologic N descriptors differ in cancers of the lip, breast, penis, testes and urinary tract– the advantage of simplicity inherent in using similar descriptors for clinical and pathologic categories means that candidate approaches that deviate from this simple rule must provide a high level of additional clinical utility and prognosis discriminatory ability.

The threshold for considering alternative approaches. Candidate changes should be associated with clinically meaningful and consistently ordered prognosis discrimination between patient clusters based on the descriptors and across multiple population subgroups. However, there is no *a priori* statistically defined threshold for adopting alternative approaches.[11] Our efforts are primarily focused on patients and their care and therefore clinical relevance is paramount. The statistical power to detect a meaningful result is related to both the sample size and magnitude of effect. Therefore, as the sample size increases, it becomes more likely to find a statistically significant result at smaller levels of separation between adjacent N categories. In a survey of members of the N-Descriptors Sub-committee, the minimum-required difference between adjacent groups at the 5-year time-point ranged between 2.5% and 10%. A difference of 5% in the 5-year survival was selected as a rough benchmark, with extra scrutiny to be given to

proposals that are statistically significant but below this clinical discrimination threshold, and vice versa.

Ideally, the ordering of prognostic differences should be maintained in clinically and pathologically staged tumors. By definition, pathologic staging is obtained at the time of attempted surgical resection, clinical staging encompasses all other staging activities, including invasive mediastinal nodal staging procedures. Although pathologic nodal staging is more accurate than clinical staging, in theory all tumors undergo clinical staging, but only a minority (typically, the fittest patients and those with early clinical stage) undergo pathologic staging. Therefore, it is important for clinical descriptors to be attainable and reasonably discriminatory of prognosis, irrespective of surgical or non-surgical treatment, even if the magnitude of difference between survival curves might differ between clinically and pathologically staged cohorts. Furthermore, because of the relative infrequency of surgery in patients with advanced nodal stage (especially pN3), attainment of statistical significance is less important in accepting the discriminatory potential of variables demarcating advanced pathologic nodal stage subsets.

Changes should minimally disrupt criteria used to define treatment options. Although staging criteria do not determine treatment (prior experience and evidence from clinical trials should guide treatment decisions), the TNM staging system facilitates communication and helps standardize understanding of clinical practice. It is important that the descriptors used to define the stage categories should be clinically relevant. The purpose of revising the clinical descriptors and the assignments within the staging criteria is not to change clinical practice. Indeed, the stage

classification process itself reflects a spectrum of clinical practice within any cohort. Nevertheless, clinical practice tends to respond to stage as efforts are made to aggregate homogeneous groups of patients for specific types of treatments and to compare outcomes of ostensibly similar-risk patients in clinical trials.[11,13] It is therefore important that revisions of the clinical and pathologic staging system minimally disrupt aggregate groups of patients for whom evidence has evolved to direct treatment in certain ways.

Candidate approaches to stratifying the extent of nodal metastasis. Across cancers, various factors can influence N classification. For example, in head and neck cancer, lymph node size, ipsilateral versus bilateral or contralateral location as well as extra-nodal extension are N descriptors. In esophageal cancer, the N categories solely depend on the overall number of regional lymph nodes involved, with 1-2 nodes classified as N1, 3-6 as N2 and ≥7 as N3. Esophageal cancer provides an example of drastic N-staging system change in that in previous versions of the staging system, the location of the primary tumor and lymph node metastases were critical in differentiating N and M categories. In vulvar cancer a fixed or ulcerated lymph node qualifies as N3, while in penile cancer, palpability of lymph nodes is a differentiator.[12]

Since the last revision of the lung cancer N categories with the 4th edition TNM system, multiple investigators have reported on the discriminatory value of the number of lymph nodes examined (in discriminating pN0 survival),[14-18] the number of positive lymph nodes,[19-22] the ratio of positive lymph nodes to total examined lymph nodes;[23,24] the number of involved lymph node stations;[5,25,26] the number of involved lymph node zones;[4,25,26] and the implications of extra-

capsular extension of lymph node metastasis.[27,28] Although the 9th edition database dictionary includes the variables required for these analyses, the completeness of the data entry will determine the feasibility of examining these candidate descriptors. Furthermore, the practical utility of lymph node counts for staging is questionable, given the well-known problems with poor standardization of the counts, variable specimen labelling and variable handling of fragmented lymph node specimens.[29] Furthermore, detecting extra-capsular extension and counting individual lymph nodes on radiologic studies may be too challenging. Preliminary evaluation of the dataset suggests the feasibility of robust analysis of lymph nodes by stations and zones, which may therefore be the primary focus of the 9th edition revision.

Number and location of involved lymph node stations as N-category descriptors. The number and location of positive lymph node stations discriminates prognosis between groups of patients. Multi-station N1 disease connotes worse prognosis than single station N1 disease. The more proximal the involved N1 station, the worse the prognosis, thus station 10 involvement is associated with worse survival than station 11 and 12.[31-35] Similarly, single ipsilateral mediastinal nodal station involvement has better prognosis than multi-station ipsilateral nodal involvement.[36] For the 8th edition, Asamura et al explored the possibility of sub-setting N1 and N2 according to involvement of single or multiple stations, but ultimately deferred this approach mainly because the results, derived from pathologically staged tumors, could not be validated at clinical staging.[5] Staging based on the number of stations is particularly susceptible to confounding by the thoroughness of examination.[30]

The nodal zones concept. The idea of grouping thoracic lymph node stations into anatomical zones was first introduced in the lymph node map for the 7th edition of the TNM atlas in 2009 to overcome the conflict between the American Thoracic Society and Naruke lymph node maps.[6,9,10] It also had the theoretical advantage of simplifying the staging process by reducing from 14 stations to seven zones, potentially providing a more feasible staging system for resource-constrained programs. Analysis of the 7th edition database indicated that the number of involved zones (single-zone N1, multiple-zone N1 or single-zone N2, and multiple-zone N2) could separate patients into groups with distinct prognosis.[4] Data limitations, including the inability to validate the results at clinical staging, precluded the incorporation of new N categories based on the number of involved nodal zones into the 7th edition TNM. In a study involving 3,971 patients, a multivariate analysis showed that pathologic lymph node zones, as well as lymph node stations, independently predicted overall survival and freedom from recurrence.[25] The number of involved lymph nodes and nodal zones were also demonstrated to be useful prognosis discriminators.[26]

Challenges and major conceptual questions. Notwithstanding the international provenance, size and robustness of the 9th edition database, it will only be as useful as the completeness and accuracy of its contents. Any pragmatically collected dataset has the dual challenges of heterogeneity in quality and missingness. The precision of the methods used to detect nodal involvement, the thoroughness of retrieval and reporting of staging information impact the assignment of stage and can confound its prognosis discriminatory ability.[30,37] In terms of imaging for nodal staging in NSCLC, PET-CT has been proven superior to CT scan.[38] A change in

system to require the counting of lymph nodes, stations or zones will require more uniform radiology reporting, with greater anatomic lymph node station details using the IASLC lymph node map nomenclature, than might be typical in current practice. It will also require more standard application of recommended sampling of nodal stations during invasive clinical nodal staging procedures than is currently the case.[39] Radiologists, pulmonologists and surgeons and their various organizations will need to integrate the nodal map nomenclature deeper into their training, practice and communication processes.

Guidelines exist to encourage more thorough clinical nodal staging practices, which, depending on the clinical context, may require the combination of both radiologic (CT and PET-CT scanning) and invasive (endobronchial ultrasound, mediastinoscopy, etc.) tests.[40,41] However, the prognosis discriminatory ability of a robust staging system should hold up, irrespective of the thoroughness of application. Therefore, the variables should not depend on the use of specific staging modalities. The same applies to pathologic nodal staging, which also varies significantly, ranging from non-examination of lymph nodes and poor examination of hilar or intrapulmonary and mediastinal lymph nodes to guideline-concordant staging.[30,37,42,43]

The IASLC's proposal to include the R-uncertain category in the description of the completeness of resection raises the issue of the quality of pathologic nodal evaluation, given that most resections that fall into this category have had suboptimal nodal assessment.[44-46] Suboptimal nodal evaluation reduces the accuracy of any N-staging system, but it should not preclude the

possibility of staging. Nevertheless, it may render a system based on counting lymph nodes, stations or zones more difficult to apply than the incumbent system. In particular, count-based staging systems might be particularly difficult to apply in resource-poor care delivery environments where modern radiologic diagnostics and invasive staging are less readily available.

Radiologic versus histologically confirmed clinical nodal stage. The accuracy of solely imaging-based versus histological nodal staging relates to the 'certainty factor'. The term 'imaging TNM' or iTNM was introduced in 1997, to refer to solely radiological staging of lung cancer. The agreement between iTNM and pTNM was only 35%. The N descriptor was correctly determined by chest CT in 35%, over-estimated in 45%, and under-estimated in 20% of cases.[47] With the introduction of integrated PET-CT scanning, accuracy significantly increased. In a retrospective analysis evaluating 1,001 nodal stations, overall sensitivity, specificity, positive and negative predictive values, and accuracy of PET-CT scanning for detecting lymph node metastasis were 58%, 99%, 75%, 97% and 96% on per-nodal- station basis.[48] A Cochrane systematic review including 45 studies, revealed a high degree of heterogeneity between the different studies, with large confidence intervals, leading to the conclusion that the accuracy of PET-CT scanning was insufficient to allow management based on PET-CT alone.[49] A new PET-CT criterion for predicting lymph node metastases in resectable lung cancer was recently proposed.[50] An ipsilateral hilar node standardized uptake value (SUV)/ contralateral hilar node SUV or I/C-SUV ratio > 1.34 with a tumor SUVmax ≥ 2.5 had the highest accuracy for predicting nodal involvement. Sensitivity, specificity, positive and negative predictive values, and accuracy of

nodal staging were 61%, 85%, 84%, 63% and 71%, respectively.[50] For this reason, the European Society of Thoracic Surgeons revised guidelines recommending minimally invasive or invasive techniques, still hold true.[41] These matters will take on greater significance in a count-based staging system.

Improving station labelling to improve nodal staging. Any shift to a count-based staging system will also have to confront the great variability in the thoroughness of pathologic nodal evaluation, ranging from simple visual inspection of the unopened mediastinum to systematic lymphadenectomy.[37,42,43,51] There has traditionally been considerable discrepancy in the designation of nodal station between Japanese and European Surgeons,[6,52] and a lot of variability even within countries and institutions.[51,53] To reduce inconsistency, the anatomical landmarks are crucial to define zones and lymph node stations.[10] Strategies to improve lymph node retrieval, labelling and examination include use of lymph node collection kits, which reduce the proportion of R uncertain resections.[54,55] Using an intraoperative lymph node map with anatomical landmarks may help to provide more consistent data on lymph node dissection and prevent labelling inconsistency during surgery.[52] The use of photographs or videos may be helpful, especially for delineating poorly demarcated adjacent stations, such as station 10 versus station 4. Implementation of processes to standardize staging practice may enhance future data collection and analysis efforts.

The impact of neoadjuvant therapy. The “y” prefix for TNM is applied to cases in which classification is performed following multimodality therapy and the “p” prefix is applied after

post-resection histopathologic examination. Currently this is a generic classification without regard to the type or efficacy of multi-modality therapy. Past iterations of the staging system have been based on groups of patients who had primary surgical resection and excluded recipients of neoadjuvant therapy.[4,5] Neoadjuvant therapy has become more readily accepted and, driven by the exciting results of recent neoadjuvant immunotherapy trials, is now primed for sharp increase in routine clinical practice.[56,57]

Given this development, it seems problematic to exclude such patients in developing the staging system. This is particularly relevant for the N categories because clinical nodal involvement is a major reason for the looming sea-change in adoption of neoadjuvant immunotherapy. The prognosis discriminatory ability of the ypN descriptors needs rigorous evaluation in light of new targeted treatments and immunotherapies, each with significant impact on the survival of biomarker-delineated subsets of lung cancer patients. The discriminatory capacity of a robust staging system should be maintained irrespective of treatment exposure. Therefore, we will evaluate how the clinical and pathologic staging systems function in the neoadjuvant setting.

Prognostic impact of the N3 nodal location. The relationship between N3 and M1 continues to be debated. For example, patients with N3 disease are often eligible to participate in clinical trials of palliative systemic therapy. The N3 designation includes lymph nodes in the contralateral hilum and mediastinum, and ipsilateral or contralateral supraclavicular fossa. It is an uncommonly studied group of patients with poor prognosis, and there has not been enough

evidence to compare supraclavicular with contralateral mediastinal and hilar involvement. In a retrospective analysis of 204 patients with N3 NSCLC, 5-year overall survival was 36% in recipients of definitive chemo-radiotherapy who did not have, versus 27% in those who had, supraclavicular lymph node metastasis, although the difference was not statistically significant.[58] A recent analysis of 40 patients with N3 NSCLC who also received definitive radiotherapy reported 11 months median OS. There were no significant factors affecting OS, but supraclavicular lymph node involvement negatively influenced PFS (HR 2.08 [1.03-4-17], p 0.039) in multivariate analysis.[59] Cohorts with cTxN3M0 had 9 months median survival in the 7th TNM edition and 10 months in the 8th.[4,5] Interestingly, the cohorts with cTxNxM1a had median survival of 8 months (pleural dissemination) and 10 months (contralateral lung nodules) in the 7th TNM edition and 9 months in the 8th.[60,61]

Hierarchical priority of sensitivity analyses for candidate approaches to the 9th edition N categories. In addition to discriminatory capacity in the full analytic dataset, candidate approaches to N-category stratification must be sufficiently robust, yet applicable across different care delivery environments. The primary analysis will be conducted in the largest dataset that meets data quality requirements, but limited to M0 cases. Because clinical staging is available to all patients, but pathologic staging only to the minority who undergo attempted surgical resection, the primary analysis will be based on the clinical staging information. Approaches that meet the pre-specified discriminatory capacity will be selected for further exploration, including the discriminatory potential for pathologic staging. Additional analyses will be performed according to geography (China, Europe, Japan/South Korea, North America, Rest

of the World), T-category, histology (squamous versus non-squamous), surgical resection versus non-surgical resection cohorts (clinical staging only), complete (R0) versus all resections (pathologic staging only).

Updates for the 10th edition database. The emerging widespread adoption, diversity and effectiveness of neoadjuvant therapy options may profoundly impact on the discriminatory implications of N-category descriptors. For example, it would be valuable to closely examine proposed definitions of major pathologic response as it pertains to lymph nodes and their association with prognosis. It will become increasingly important to explore the concepts of "complete pathological response" and "major pathologic response" which are known prognostic factors for disease-free survival, to determine how to integrate them into ypTNM. For the yT descriptors the percentage of remaining viable tumor cells is currently used to define 'major pathologic response', the possibility of a similar relationship to the yN descriptors needs to be explored. The current database structure will not have sufficient details to support such analyses. However, for the 10th edition database, especially with the growing proportion of cases that are submitted via the EDC, it should be possible to enrich for the relevant variables. The consistency of prognosis discrimination across biomarker-delineated subsets of NSCLC cannot be examined in the current dataset, but should be possible in the near-future, with greater experience in contributing comprehensive biomarker data in the 10th edition.[62]

Recommendations for overcoming data constraints. The IASLC database has shown sequential improvement from the 7th to the current (9th) edition datasets. For example, the 9th edition

database has a larger component of data entered through the EDC, is larger in size, with more granular details to permit robust analysis of lymph nodes by station and zone. In addition it represents an era of full implementation of the IASLC lymph node map. However, opportunity remains to improve the quality of contributed data and the diversity of data sources. Although data entry through the EDC, by itself, guarantees neither accurate nor complete data, it represents an improvement over unstructured data submission, a large volume of which occurred late in the data collection process.

Emerging practice changes, especially the use of biomarker-directed treatment selection, neoadjuvant immunotherapy and targeted therapies, raise the need for greater details on treatment and response, especially in neoadjuvantly treated patients (ypN), and collection of additional variables to quantify pathologic response and their impact on the prognosis discriminatory ability and clinical utility of the staging system. More information on biomarkers and adjuvant treatments is also needed.[62]

Summary. We sought to stimulate the N-Descriptors Subcommittee to think critically about the work involved in revising for the 9th edition TNM, with close attention to the existing literature; carefully examine the range of potential approaches to optimize the N categories for greater prognosis discriminatory and clinical value whilst also providing transparency on the Committee's process for exploring alternative approaches; examine how data limitations constrain the current effort and how they might be overcome in future iterations of the database. We provide a brief summary of the strengths and limitations of the 9th edition database, and the candidate

approaches we think can be rigorously explored to modify the strictly anatomy-based incumbent classification system which has had an exceptionally long run. For the pragmatic reasons discussed, in revising for the 9th edition, we will focus attention on the number and location of lymph node stations and lymph node zones as new variables with which to categorize the extent of nodal involvement. It will be interesting to see how the alternative candidates measure up to the incumbent system, especially when combined with the T and M categories.

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CRediT Statement.

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