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# Editorial Comment: Validation Study for the N Descriptor of the Newly Proposed 9th Edition of the TNM Staging System Proposed by the International Association for the Study of Lung Cancer



Merve A. Türk, MD*

The cancer staging is a triple component of tumor size (T), lymph node involvement (N), and the presence of metastases (M). The TNM system has undergone several revisions in lung cancer staging, and the latest TNM 8th edition has been in use worldwide since 2017. The N stage of 8th staging is based on the anatomical location of nodal metastases rather than the number of metastasized lymph nodes. The location-based classification does not reflect tumor burden in regional lymph nodes. To demonstrate prognostic heterogeneity, it has been emphasized that factors other than anatomical elements of lymph nodes are also effective and that lymph nodes should be reclassified into subgroups.[1–3] The objectives were to eliminate heterogeneity in the planned classification, to be applicable in clinical practice, and to have a clinical presentation of the new classification.[4]

The recent publication by Kim et al.[5] in a large series, not only focused on overall survival (OS) and recurrence-free survival (RFS) at the clinical and pathological N stage of the N descriptor but also analyzed other survival factors that affect OS and RFS in lung cancer. According to age, gender, histology, comorbid diseases, and year of surgery, models were created, and 5-year survival differences were demonstrated in the N classification, except for the T4 group. However, it is known that EGFR mutations are the most common oncogenic factor in lung adenocarcinoma in never-smokers in East Asia. The detection of mutation analysis in NSCLC and appropriate treatments in this patient group have shown significant differences in survival. The study by Janjigian et al[6] demonstrated the disease-free survival effect of adjuvant erlotinib in resected stage IA–IIIA patients. The use of mutation analyses was not widespread at the time the database was created in the study by Kim et al.[5] Therefore, a confounder in OS and RFS was known but could not be used in the analyses. Mutation analyses may be added to the database developed for the TNM staging system in future studies. The impact of genetic mutation analysis, which is an important determinant of NSCLC prognosis, on the N factor in staging remains important.

The differentiation of the N descriptor into single N (N2a) and multiple N (N2b) was shown in the study to balance the heterogeneity in staging and to provide a clearer distinction in all categories.[5] A comparison was also made with the staging proposed by Asamura et al.[1] where, due to the small sample size, an overlap between the survival curves was observed. In the study by Kim et al,[5] a specific group of patients who underwent surgical resection and did not receive neoadjuvant therapy was included, to show how the results would be in the heterogeneity of the whole world. However, Huang et al.[4] obtained similar results to the present study with data from a larger population in a study to validate the current N classification for the ninth edition of the staging system and revision of the categories to include nodal metastasis burden. In the clinical implications of these results, the importance of distinguishing between N2a and N2b is emphasized, as it could potentially allow for different therapeutic approaches. As the use of immunotherapy has become widespread, favorable

*Corresponding author.

Department of Pulmonology, İzmir Bozyaka Training and Research Hospital, Izmir, Turkey

Address for correspondence: Merve Ayik Türk, MD, Department of Pulmonology, İzmir Bozyaka Training and Research Hospital, 286/3 St. No:17 İzmir 35353, Turkey. E-mail: merve.ayik@hotmail.com

Cite this article as: Türk MA. Editorial comment: validation study for the N descriptor of the newly proposed 9th edition of the TNM staging system proposed by the International Association for the Study of Lung Cancer. *J Thorac Oncol* 2024;19:1133-1134



ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2024.06.003

postoperative survival data have been obtained in N2 disease with neoadjuvant treatments.[7] The definition of N2a or N2b disease will have a clinical contribution in order to determine the definition of operability in N2 disease and to provide clear evidence in which patient group surgery may be a treatment option. In this sense, the fact that the study population includes a special group is considered to be in line with the clinical presentation of staging.

Unlike N1 stations, which are difficult to distinguish in clinical staging, the division of N2 lymph nodes into single and multiple stations will be easier to implement with radiologic developments and the widespread use of positron emission tomography/computed tomography. However, it is thought that there may be difficulties in N2a or N2b differentiation in suspicious lymph nodes that are more difficult to access in patients who need invasive clinical staging. The classification of lymph nodes at the boundary of anatomical location, even in the anatomical N descriptor, has weaknesses as it may involve the subjective decisions of surgeons or pathologists.[8,9] Despite the widespread use of positron emission tomography/computed tomography and endobronchial ultrasound or transesophageal ultrasound providing convenience in terms of mediastinal staging, it is thought that there may be difficulties in N2a/N2b differentiation, especially in invasive mediastinal staging after treatments such as chemoimmunotherapy, especially in interventional procedures. It will also need a systematic approach to the evaluation of lymph nodes with experience in invasive mediastinal staging and N2a or N2b differentiation.

The method used to evaluate the lymph nodes collected in invasive mediastinal staging also needs to be standardized. In the study,[5] there was a standardized lymph node assessment from a single center. However, it is known that incomplete removal of lymph nodes seriously affects nodal categorization.[9] Since this may change the pathological N results, the importance of standardized methods should be emphasized.[10] Furthermore, the differences in survival outcomes are clearly emphasized in the numerical distinction of lymph nodes in the pathological N stage, but the effect of factors such as lymph node ratio, size, and extracapsular distribution on the stage is not known.

In the study by Kim et al.[5] which emphasized the important results of the single/multiple N2 distinction and included the effective variables on OS/RFS in the analysis, it was shown that the distinction between N2a or N2b provides a more homogeneous distribution in staging. Demonstrating the difference in N involvement in staging is thought to provide new treatment approaches with the developments in treatment options in NSCLC. However, it still arouses curiosity to what extent this staging will have a clear clinical contribution and how applicable it will be to clinicians.

## CRediT Authorship Contribution Statement

**Merve A. Türk:** Conceptualization, Investigation, Methodology, Project administration, Resources, Software, Writing - original draft, Writing - review and editing.

## Disclosure

The author declares no conflict of interest.

## References


1. Asamura H, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer lung cancer staging project: proposals for the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2015;10:1675–1684.
2. Yun JK, Lee GD, Choi S, et al. Comparison between lymph node station- and zone-based classification for the future revision of node descriptors proposed by the International Association for the Study of Lung Cancer in surgically resected patients with non-small-cell lung cancer. *Eur J Cardiothorac Surg*. 2019;56:849–857.
3. Park BJ, Kim TH, Shin S, et al. Recommended change in the N descriptor proposed by the International Association for the Study of Lung Cancer: a validation study. *J Thorac Oncol*. 2019;14:1962–1969.
4. Huang J, Osarogiagbon RU, Giroux DJ, et al. The International Association for the Study of Lung Cancer staging project for lung cancer: proposals for the revision of the N descriptors in the forthcoming ninth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2024;19:766–785.
5. Kim IH, Lee GD, Choi S, et al. Validation study for the N descriptor of the newly proposed ninth edition of the TNM staging system proposed by the International Association for the study of lung cancer. *J Thorac Oncol*. 2024;19:1218–1227.
6. Janjigian YY, Park BJ, Zakowski MF, et al. Impact on disease-free survival of adjuvant erlotinib or gefitinib in patients with resected lung adenocarcinomas that harbor EGFR mutations. *J Thorac Oncol*. 2011;6:569–575.
7. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386:1973–1985.
8. Osarogiagbon RU, Allen JW, Farooq A, Wu JT. Objective review of mediastinal lymph node examination in a lung cancer resection cohort. *J Thorac Oncol*. 2012;7:390–396.
9. Ramirez RA, Wang CG, Miller LE, et al. Incomplete intrapulmonary lymph node retrieval after routine pathologic examination of resected lung cancer. *J Clin Oncol*. 2012;30:2823–2828.
10. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2006;30:787–792.