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Impact of the Ninth International Association for the Study of Lung Cancer TNM Classification on Endobronchial Ultrasound for Lung Cancer Staging

To the Editor:

The forthcoming ninth edition of the International Association for the Study of Lung Cancer Lung Cancer (IASLC) TNM classification for lung cancer introduces a significant change for lymph node staging of lung cancer compared with the eighth edition. This ninth edition has a key refinement in the N category, namely the subdivision of N2 into N2a (single N2 station involvement) and N2b (multiple N2 station involvement). This subdivision allows for a more precise description of the extent of lymph node involvement, which can be critical for determining the appropriate treatment strategy and prognosis.[1]

Endobronchial ultrasound (EBUS) is currently the most frequently used method for lung cancer staging and has been recommended over mediastinoscopy for initial pathologic mediastinal staging due to its high accuracy and better safety profile. It is also preferred for patients with a positron emission tomography–computed tomography (PET-CT) normal mediastinum and primary tumor larger than 3 cm, central tumors, or cN1 disease to detect occult N2/N3 disease.[2]

These refinements in the N category bring new challenges for the clinical practice of those who perform EBUS. Previously, after puncturing station N3, it would be expected to puncture the N2 lymph node that is most suspicious of malignancy, according to PET-CT and ultrasound features. It would also be reasonable to puncture only one N2 lymph node if it presented highly suggestive features of malignancy.[3] Considering the ninth IASLC TNM classification and the major impact of the N2a and N2b subdivision on the final staging of T1-3 tumors, it becomes imperative to puncture all the ipsilateral mediastinal and subcarinal stations. This is also expected to increase the number of punctures at mediastinal stations that were less frequently sampled, such as the upper paratracheal nodes (2R/L). A detailed description by nuclear medicine consultants regarding PET-CT uptake of each mediastinum-hilar lymph node also becomes increasingly relevant. For example, inferior mediastinal nodes as the paraesophageal (station 8) and the pulmonary ligament (station 9) nodes may require puncture if they have significant uptake on PET-CT, in which case EBUS with bronchoscopy (EUS-b) should be performed after EBUS.[4] It is anticipated that staging EBUS will need to be an even more precise, comprehensive, and time-consuming examination with an anticipated increase in the number of punctured lymph node stations.

Mastering the N2 lymph node stations according to the IASLC guidelines becomes imperative during staging EBUS (Fig. 1). In addition, a thorough understanding of ultrasound references is crucial to reliably differentiate, for instance, between an ipsilateral station 1 (N3) and an ipsilateral station 2 (N2).

Regarding the Rapid On-site Evaluation (ROSE) technique, the need to puncture more than one N2 lymph node implies that ROSE plays a less active role in the EBUS staging process. Nevertheless, ROSE remains highly relevant for identifying representative samples and malignant cells during EBUS and may save a few punctures to the usual three that are recommended for EBUS lung cancer staging when ROSE is not available.[3]

According to previous literature, lymph nodes with short axis size less than 5 mm could be exempt from puncture. Furthermore, lymph nodes that present SUV_{max} less than 1.85 and short axis size less than 4.28 mm are

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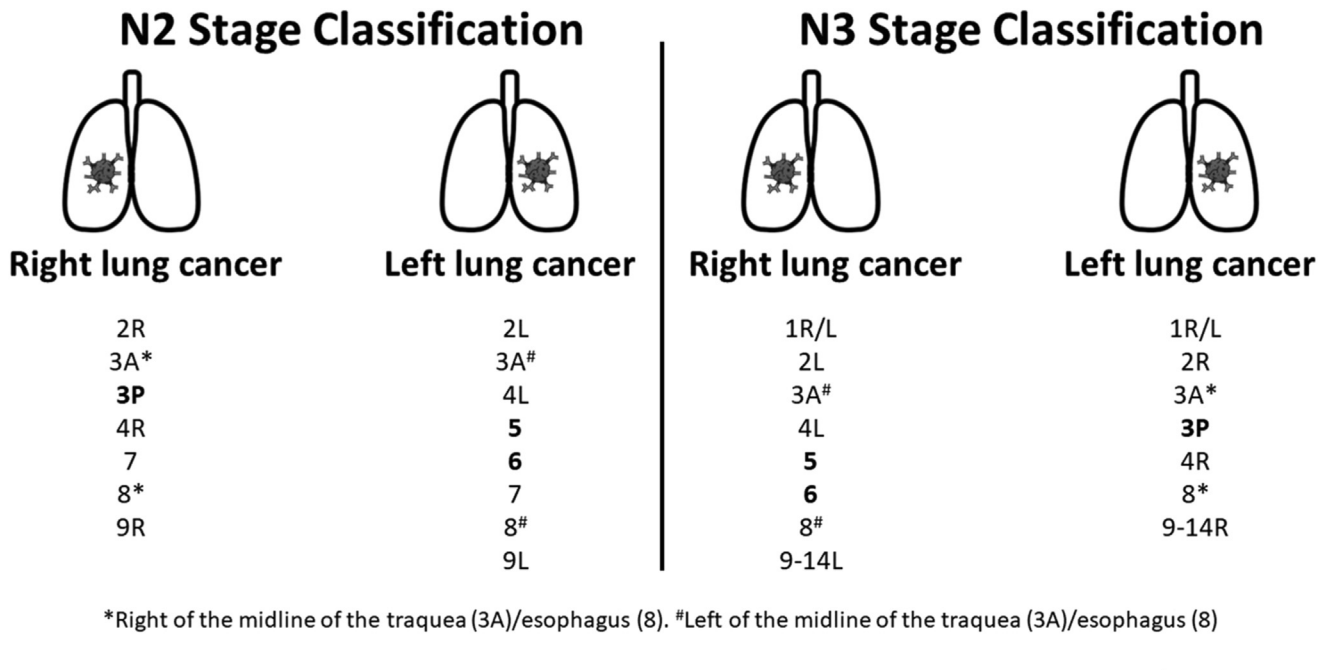

Figure 1. N2 and N3 stage classifications for right and left lung cancers according to IASLC. IASLC, International Association for the Study of Lung Cancer Lung Cancer.

considered benign and may not require fine-needle aspiration puncture.[3,5] Considering the forthcoming ninth IASLC TNM classification and its updates, the authors would like to highlight the future need for prospective cohorts to validate PET-CT and ultrasound features of malignancy that could exempt the puncture of benign N2 lymph nodes.

CRediT Authorship Contribution Statement

Nuno Faria: Conceptualization (Equal), Formal analysis (Lead), Investigation (Lead), Methodology (Lead), Project administration (Equal), Software (Equal), Visualization (Equal), Writing - original draft (Lead), Writing - review and editing (Equal).

Maria Inês Costa: Conceptualization (Equal), Formal analysis (Equal), Validation (Supporting), Writing - review and editing (Supporting).

Catarina Lacerda: Conceptualization (Equal), Formal analysis (Equal), Validation (Supporting), Writing - review and editing (Supporting).

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Reply to "Impact of the Ninth IASLC TNM Classification on Endobronchial Ultrasound for Lung Cancer Staging" by Faria et al

To the Editor:

In their letter to the editor, Faria et al.[1] have proved full understanding of the clinical implications of the subdivision of category N2 into N2a (involvement of a single N2 nodal station) and N2b (involvement of multiple N2 stations) that will be introduced in the forthcoming ninth edition of the TNM classification of lung cancer. They highlight the importance of a thorough endobronchial ultrasound (EBUS) transbronchial needle aspiration (TBNA) and endoscopic ultrasound-fine-needle aspiration in the staging of lung cancer, the adherence to the clinical guidelines when performing the procedure, and the changing relevance of rapid on-site examination, if available.

In addition to the thoughtful comments by Faria et al.,[1] we emphasize that during invasive mediastinal staging, systematic sampling is preferred than targeted random sampling. A study comparing targeted with systematic EBUS-TBNA reported that, among 107 patients with clinical N2 by positron emission tomography-computed tomography (PET-CT), targeted EBUS-TBNA misclassified 14 of 47 (30%) tumors classified as N2a. Systematic EBUS-TBNA revealed that 11 were N2b and three were N3.[2] Moreover, with the new changes in the subdivision of N2, the role of rapid on-site examination will even be more relevant. It has been reported that, after sampling a malignant lymph node, the EBUS-TBNA needle can be contaminated by malignant cells and, therefore, can be a source of false-positive results. The on-site cytopathologist is essential to determine whether a mediastinal node is malignant and, accordingly, to change the needle before exploring the rest of nodal stations.[3]

Faria et al.[1] do not elaborate on the indications of surgical invasive staging. The European Society of Thoracic Surgeons guidelines on preoperative nodal mediastinal staging recommend the confirmation of a negative EBUS-TBNA and endoscopic ultrasound-fine-needle aspiration result when the mediastinal lymph nodes are abnormal by PET-CT and when the mediastinum is normal but tumors are more than 3 cm in largest dimension, are centrally located, there is suspicion of N1 involvement, or the tumor is known to be adenocarcinoma with low uptake on PET. In these circumstances, confirmation with a minimally invasive surgical procedure (usually mediastinoscopy) is indicated.[4] The results of a clinical trial comparing EBUS-TBNA with mediastinoscopy for staging clinical N1 NSCLCs revealed that sensitivity and negative predictive values of mediastinoscopy were higher than those of EBUS-TBNA: sensitivity of 0.73 and 0.38 and negative predictive value of 0.91 and 0.81, respectively.[5] These results imply that, when the mediastinum is normal on PET-CT, mediastinoscopy enhances nodal staging and could be the initial staging test instead of ultrasound-guided endoscopies.

The ninth edition TNM for lung cancer increases our understanding of the prognostic impact of the anatomical tumor extent on the condition that the tumor is staged with the highest certainty. To this respect, the comments by Faria et al.[1] are highly appreciated and welcome.

CRediT Authorship Contribution Statement

Ramón Rami-Porta: Conceptualization, Methodology, Investigation, Writing—original draft.

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