Editorial

# Improving accuracy of hilar and lobar nodal staging in non-small cell lung cancer

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Lung cancer is the leading cause of cancer deaths and its 5-year survival rates vary from 4–17% depending on stage (1,2). Selection of optimal therapy is based on preoperative TNM stage. The status of mediastinal or hilar lymph nodes (LN) is the most important factor to determine the stage (3). Modern staging is based on the use of computed tomography (CT) with intravenous contrast that can quickly and effectively rule out distant metastatic disease and direct patients to correct therapy. The use of CT in staging is limited by the fact that LN size is not reliable parameter to presence of metastatic nodes (4). 18F-FDG-positron emission tomography (PET/CT) combined with CT significantly improves the accuracy of LN staging over CT only, but is also limited by dissatisfactory sensitivity i.e., false negative rate (5). Current guidelines recommend endobronchial ultrasound (EBUS) or endoscopic ultrasound (EUS) with transbronchial fine-needle aspiration (TBNA) over mediastinoscopy if non-invasive staging suggests mediastinal or hilar LN involvement (6). Main reasons for low sensitivity of PET/CT are partial volume effect causing false negatives in small nodes and tumours, presence of micrometastases undetectable by PET and hilar symmetric uptake due to chronic granulomatous inflammation masking malignant nodes, especially in countries endemic with tuberculosis (5).

In clinical practice main goal of staging is to rule out distant metastases and mediastinal LN involvement as those patients do not benefit of surgical therapy. Hilar and lobar (N1) staging of LNs has received less attention in clinical staging historically but is gaining more interest as new treatment options such as sublobar resections, stereotactic body radiation therapy (SBRT) and radiofrequency ablation (RFA) are emerging, and are associated with higher local failure rates possibly related to undetected lobar LN metastases (7). Also, patients with single N1 level LN metastasis have improved prognosis compared to multiple N1 LN metastases (8), and neoadjuvant therapy to improve survival has been suggested for this subgroup.

Only a few studies report accuracy of PET/CT for detecting N1 LN metastases. Carrillo *et al.* (9) reported sensitivity of 48.5%, specificity of 80%, negative predictive value (NPV) of 48.5% and positive predictive value (PPV) of 83.3% in resected stage II non-small cell lung cancer (NSCLC). Pepek *et al.* (10) reported sensitivity of 44%, specificity of 83%, PPV of 37% and NPV of 86% in all resected stages of NSCLS. Akthar *et al.* (11) have reported 92.4% NPV for resected stage I NSCLC.

In experienced hands, EBUS can reach N-stations 10–11 unreachable to mediastinoscopy, but stations N12 (segmental nodes) can be difficult (7). In a study by Yasufuku *et al.* (12) the sensitivity, specificity, diagnostic accuracy, and NPV of EBUS-TBNA between N0 and N1 disease was 76.2%, 100%, 96.6%, and 96.2%, respectively. The accuracy of mediastinal staging was 95.7%. They also sampled R12 nodes but stated that the rigid part on the tip as well as the outer diameter of the convex probe EBUS prevents visualization of lobar LN (station 12) in the upper lobes and the middle lobe. EUS in addition to EBUS is known to improve accuracy of mediastinal staging (7), but no reports could be found regarding staging of hilar or lobar LNs. In their interesting article, Dejima *et al.* (13)

have shown that combining high resolution CT (HRCT) with PET/CT to evaluate nodal total lesion glycolysis (TLG) can improve accuracy of intrapulmonary nodal staging, likely by minimising the partial volume effect. Modifying TLG (mTLG) with HRCT showed the sensitivity, specificity, PPV, and NPV for diagnosis of lobar LN metastasis of 71%, 88%, 44%, and 96%, respectively. These results are clearly improved as compared to previously published and comparable to results of EBUS-TBNA. In the study by Dejima *et al.* (13), false negatives were caused by micrometastases and false positives by chronic inflammation. No radiologic modality to date is able to distinguish malignancy from inflammation or detect micrometastases. However, their study shows that with technological progress improving staging is possible. Future technological advances suggested to improve quality of radiologic nodal staging could be diffusion-weighted imaging of magnetic resonance imaging (MRI) that has shown promise in assessment of tumour heterogeneity (14) and decreasing the false positive rate compared to PET. Dual time point PET/CT (15) and time-of-flight (TOF) PET (16) and PET/MRI (17) have been suggested to improve quality of PET imaging and could possibly improve accuracy of staging in future. Also, development of EBUS technology is likely to improve N1 level staging, as Yasufuku *et al.* (12) suggest that smaller and convex probes could assist in reaching N12 stations. EBUS and PET/CT are likely to complement each other in this important issue.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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