Accurate staging of non-small cell lung cancer—tissue is the issue

Neal Navani[1,2]

[1]Thoracic Medicine, University College London Hospital, London, UK; [2]Lungs for Living Research Centre, University College London, London, UK

Correspondence to: Neal Navani, MD PhD. Lungs for Living Research Centre, UCL Respiratory, Rayne Building, University College London, 5 University Street, London, WC1E 6JF, UK. Email: n.navani@ucl.ac.uk.

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I thank the journal for the interest in our article (1) and Dr. Jantz for his thoughtful comments. I agree with Dr. Jantz's stance on the importance of mediastinal staging for non-small cell lung cancer (NSCLC) and agree that data from investigations for lung cancer staging are established. However, it is less well understood in the literature how these tests interact in clinical practice and their impact on the patient. While our study certainly included older trials, it is not clear that modern lung cancer staging techniques offer better performance in routine clinical practice outside of expert centres. The most recent study comparing clinical to pathological staging included Dutch registry data from 38 hospitals and was published in 2016 (2). Patients were routinely able to undergo PET-CT and endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) and yet concordant cTNM and pTNM occurred in only 54.6% of the patients. The impact on patient outcomes from this study is also unknown. It is established that PET-CT should be carried out prior to treatment with curative intent [such as surgery or stereotactic ablative radiotherapy (SABR)] as it may detect previously unknown metastatic disease and therefore change the treatment algorithm. However, uptake of PET-CT for this indication in routine clinical practice is not well known and randomised trials of PET prior to surgery have failed to show a survival benefit (3).

Modern lung cancer management, prognosis and eligibility for clinical trials is often entirely dependent upon accurate clinical staging. A worrying aspect of the data from our paper and other studies is that a significant proportion of patients are overstaged by clinical staging. Comprehensive data on overstaging is lacking as patients with clinically staged inoperable disease are excluded from analyses that compare cTNM to pTNM as they are not offered surgery. However, overstaging may have the catastrophic effect of denying patients treatment with curative intent. Therefore, biopsy proven inoperability should be the principle that multi-disciplinary teams apply to staging. This is reflected in lung cancer quality standards published by the American College of Chest Physicians which mandates that patients with one to three distant metastases should have an attempt at biopsy confirmation of a site of metastasis, or documentation of a reason that this was not possible or necessary (4).

Tissue is also the issue for accurate nodal staging of NSCLC. International guidelines agree that EBUS and/or endoscopic ultrasound (EUS) should be employed after PET-CT for optimal staging of intra-thoracic lymph nodes. It is recommended that lymph nodes greater than 10mm in short axis should be invasively sampled, regardless of fluorodeoxyglucose (FDG) uptake, if that lymph node affects patient management. This is reflected most recently in the UK National Institute of Clinical Excellence lung cancer update (5). Patients with central tumours (as defined by concentric lines) should also be offered invasive nodal staging as the location of these tumours is associated with substantial risk of having occult nodal disease in any station (6).

However, simply carrying out an EBUS procedure for nodal staging is inadequate if the quality of EBUS that is carried out does not adhere to international standards. A systematic approach to the mediastinum should be applied with N3 nodes sampled prior to N2 and then N1 lymph nodes. All lymph nodes ≥5 mm in short axis should be sampled. This has been underlined in the SCORE study which showed a superior sensitivity for detecting N2/N3 disease was achieved with systematic nodal sampling [with EBUS and EUS using a EBUS scope (EUS-B)] compared to sampling based on PET-CT appearances (7). In a randomised trial of EBUS-TBNA, a systematic approach to staging by EBUS-TBNA improved staging inaccuracy and was associated with improved survival (8). Accurate nodal staging therefore depends upon the quality of EBUS that takes place and should be the subject of quality assurance.

Our paper highlights discrepancies in accurate staging and the editorial by Jantz rightly emphasizes the importance of adhering to current guidelines for staging of NSCLC. However, how can staging of NSCLC be improved? First, novel imaging techniques, contrast and PET tracers may have a role to play. Whole-body MRI may have advantages over current techniques for detecting metastases in the adrenals, liver and brain and was the subject of a large prospective trial that showed it could streamline imaging for NSCLC (9). Second, we require further real-world data on current staging accuracy and the degree of concordance between cTNM and pTNM could be considered an important quality indicator for the diagnostic process and be a trigger for quality improvement. Finally, we require more patient experience data on the diagnostic and staging pathway. Patients report that speed of the process may be more important to them than accuracy (10) and future studies in the area should endeavor to collect patient reported outcomes as well as including follow-up to demonstrate outcome on clinically relevant endpoints beyond staging sensitivities.

Lung cancer management is becoming increasingly complex as progress is made in understanding tumour heterogeneity and many novel treatments becoming available. However, accurate staging for patients with NSCLC remains integral to high quality care.

Acknowledgments

Footnote

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