

## How should performance in EBUS mediastinal staging in lung cancer be measured?

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Sir,

There has been a paradigm shift in mediastinal staging algorithms in non-small cell lung cancer over the last decade in the United Kingdom (UK). This has seen endoscopic nodal staging (predominantly endobronchial ultrasound, EBUS) almost replace surgical staging (predominantly mediastinoscopy) as the pathological staging procedure of first choice. An explosion of EBUS services has facilitated this, with 45% of National Health Service Trusts currently delivering EBUS procedures almost exclusively by chest physicians (Cusworth *et al*, 2015). However, performance measures for this pivotal procedure in lung cancer management are not widely agreed or published. We believe that there is an urgent need for systematic data collection by all EBUS services to standardise practice and assess outcomes; a view also held by members of a UK expert round table discussion for improving lung cancer outcomes and an EBUS review article (Sethi *et al*, 2013; Rintoul *et al*, 2015). The performance measures for EBUS in lung cancer depend on whether the procedure is done purely for pathological diagnosis (diagnostic EBUS) or for mediastinal nodal staging (systematic staging EBUS). The drive for systematic nodal staging, in patients with potentially early stage disease, is to improve the accuracy of staging (and not be reliant on radiological staging), thereby improving patient selection for the most appropriate treatment and hopefully improve survival. In line with this, systematic staging EBUS has been shown to improve survival in lung cancer patients *vs* non-endoscopic staging in *post hoc* analysis (Navani *et al*, 2015). When considering the performance measures for systematic staging EBUS, there are some important discussion points as follows:

### HOW IS SYSTEMATIC STAGING EBUS PERFORMED?

There is a clear need for standardisation of EBUS practice across all centres to ensure optimal outcomes. For staging EBUS, a systematic examination of the mediastinum is recommended beginning with an examination of the contralateral N3 nodal stations followed by N2 stations and finally N1 lymph nodes when required. Any lymph node measuring  $\geq 5$  mm is sampled aiming for a minimum of three N2/3 lymph node stations sampled per procedure. This technique has demonstrated excellent sensitivity and negative predictive values (NPV) from expert centres (Herth *et al*, 2008; Yasufuku *et al*, 2011; Navani *et al*, 2015). This technique needs to be distinguished from a 'targeted' procedure whereby only abnormal lymph nodes on pre-procedure radiology are imaged and sampled. This technique is more allied to diagnostic EBUS although it is acknowledged that this often yields staging information sufficient to determine treatment. In the majority of cases, a systematic staging EBUS will require a longer procedure time compared with standard flexible bronchoscopy. The optimal sedation practice for systematic staging EBUS is debated. In the UK, the standard practice remains physician-led conscious sedation with a combination of midazolam and an opiate such as fentanyl or alfentanil. Some expert centres use anaesthetist-led deep sedation, for example, using propofol. The use of propofol and anaesthetic-led administration in flexible bronchoscopy has been shown to improve patient satisfaction and tolerance through reduction in cough, pain and discomfort without affecting complications such as hypoxia. This evidence is summarised in a recent review article (Jose *et al*, 2013). Anaesthetic-led sedation in staging EBUS, where there may be additional benefits of allowing more extensive sonographic assessment and a higher volume of nodal sampling, has not been studied. Ultimately, the effectiveness of a sedation strategy will be reflected in the performance measures of that

service. Failure to achieve the benchmarks set out in this document may prompt reconsideration of the sedation practice and could provide an area for potential adjustment to drive improvements.

### HOW SHOULD PERFORMANCE BE MEASURED FOR SYSTEMATIC STAGING EBUS?

The most important performance measures of staging EBUS are sensitivity and NPV, both influenced by the false-negative rate. Specificity and positive predictive value are not discriminatory and widely reported as 100% in meta-analysis and systematic reviews totalling several thousand patients (Adams *et al*, 2009; Gu *et al*, 2009; Varela-Lema *et al*, 2009). Although it is not common place for positive N2/3 disease identified by staging EBUS to undergo surgical verification, false positives are considered extremely rare and confined to case reports such as carcinoma-*in situ* at the bronchial puncture site (Sanz-Santos *et al*, 2012). For sensitivity and NPV calculations, the identification of patients with N2/3 metastases missed by systematic staging EBUS is pivotal. This requires a thorough review of any subsequent pathological nodal sampling (e.g., mediastinoscopy or intra-operative lymph node sampling) and a minimum of 6 months clinical-radiological follow up. The denominator for sensitivity calculations should be the overall number of patients with N2/3 nodal metastases (even in those lymph node stations inaccessible with EBUS). This provides a far more accurate assessment of the ability of EBUS to stage the mediastinum than a per lymph node denominator. The British Thoracic Society quality standard for systematic staging EBUS sensitivity is  $> 88\%$  but both sensitivity and NPV have been shown to be dependent upon the overall prevalence of N2/3 metastases in the population undergoing EBUS. For example, although the American College of Chest Physicians (ACCP) report a sensitivity of 89% and NPV of 91% for staging EBUS in a large meta-analysis, they also demonstrate that sensitivity is positively correlated with the prevalence of N2/3 disease within the patients undergoing EBUS, whereas NPV is negatively correlated (Silvestri *et al*, 2013) (Table 1). This could reflect a biological difference in the nodes in higher

**Table 1. Sensitivity and negative predictive value of endobronchial ultrasound (EBUS) for nodal staging in lung cancer (Results from ACCP meta-analysis and recommended minimum standards) based on the prevalence of N2/3 disease**

N2/3 prevalence (%)	Sensitivity		Negative predictive value	
	ACCP meta-analysis (%)	Minimum standard (%)	ACCP meta-analysis (%)	Minimum standard (%)
> 80	96	> 90	83	> 80
60–80	91	> 88	83	> 80
40–60	87	> 85	89	> 85
20–40	87	> 80	95	> 90
< 20	78	> 75	96	> 92

Abbreviation: ACCP = American College of Chest Physicians. Adapted from the ACCP Lung Cancer Staging Guidelines meta-analysis of EBUS (Silvestri *et al*, 2013).

**Table 2. Indications for pathological nodal staging in lung cancer based on index CT Staging of the thorax (assuming a lack of distant metastatic disease)**

Group	Description	N2/3 prevalence (%)	Pathological nodal staging required?
A	Invasive, conglomerate nodal disease	100	No. Diagnostic procedure only <sup>a</sup>
B	Discrete mediastinal lymph node enlargement	60	Yes
C	Central tumour or enlarged hilar (N1) nodes. Normal mediastinum.	20–25	Yes
D	Peripheral tumour. Normal hilum and mediastinum.	5–10	No. Proceed straight to treatment assuming PET negative as well <sup>b</sup>

Abbreviations: ACCP = American College of Chest Physicians; CT = computed tomography. Adapted from the ACCP Lung Cancer Staging Guidelines (Silvestri *et al*, 2013).

<sup>a</sup>May sometimes need systematic sampling to define radiotherapy field.

<sup>b</sup>If positron emission tomography positive mediastinal nodes will need staging endobronchial ultrasound (EBUS).

prevalence populations *vs* lower prevalence populations (macroscopic nodal involvement in larger FDG-avid nodes *vs* microscopic metastases in small non-avid nodes). It is therefore crucial that the prevalence of N2/3 metastases is presented alongside the sensitivity and NPV for all systematic staging EBUS centres. Furthermore, the ACCP staging guidelines also describe appropriate patient selection for pathological nodal staging by separating patients into four groups (groups A–D, excluding those with distant disease) based on the index staging computed tomography (CT) scan of the thorax. These groups are also based on the differing prevalence of N2/3 disease (Table 2) and can therefore help to define standards for staging EBUS within these groups, thereby not using a single standard for all staging EBUS.

Taking all these considerations into account, we propose the following data fields should be recorded for all staging EBUS centres:

- EBUS procedure indication.
- Sedation strategy (physician-led *vs* anaesthetic-led; conscious sedation *vs* deep sedation).
- Type of EBUS procedure (diagnostic or systematic staging).
- ACCP group based on index staging CT of the thorax.
- Nodal stations sampled.
- Nodal staging based on EBUS pathology (N0–N3).
- Final nodal staging (N0–N3).
- Method of confirmation of final nodal staging (subsequent pathological sampling or 6 months clinical–radiological follow up).
- Complications; in line with definitions provided by the British Thoracic Society Guidelines for Bronchoscopy (Du Rand *et al*, 2013).

We propose these data are used to report:

- Number of N2/3 lymph node stations sampled per procedure.
- Prevalence of N2/3 disease in patients undergoing systematic staging EBUS.
- Sensitivity of systematic staging EBUS to detect N2/3 disease, stratified by ACCP group.
- NPV for exclusion of N2/3 disease by systematic staging EBUS, stratified by ACCP group.

This detailed breakdown of EBUS performance may identify specific patient groups where improvements may be needed that may otherwise not have been apparent, and provides information on patient selection as well as performance. Furthermore, we propose a set of minimum standards for sensitivity and negative predictive value based on N2/3 prevalence that we believe is an achievable benchmark for staging EBUS centres to be working (Table 1).

This statement has focused on EBUS as the endoscopic technique of choice for mediastinal staging, as this technique is widely available across the UK. However, we also acknowledge that combining endoscopic ultrasound from the oesophagus with EBUS (EBUS–EUS) has a number of potential benefits (Annema *et al*, 2010). In addition to sampling mediastinal nodes by EBUS, EUS provides a different approach to some lymph node groups (2L, 4L and 7) as well as access to the inferior mediastinal stations (8 and 9) that are inaccessible to EBUS. Furthermore EUS can allow access to the left adrenal gland, left lobe of the liver and coeliac lymph nodes providing extra thoracic staging in the same sitting for selected cases. While there are implications in terms of resources to implement this on a wider scale in the UK, EBUS–EUS is advocated as the endoscopic staging tool of choice in the European guidelines

(De Leyn *et al*, 2014). Chest physicians using the EBUS scope in the oesophagus (EUS-B) could address some of these resource issues and should be subjected to the same rigorous assessment of performance described here.

In conclusion, we advocate all services collect and publish standardised outcome data with the ultimate goal of agreed national standards for evaluation and commissioning. Furthermore, we advocate that accreditation is considered for centres performing staging EBUS-TBNA using standards defined by a relevant professional group such as the British Thoracic Society or the Royal College of Physicians. This will help to ensure that standards are maintained for this important staging investigation.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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