REVIEW

Direct nodal sampling by echoendoscopy in lung cancer: the clinician's expectations

Direct nodal sampling by echoendoscopy in lung cancer

Maren Schuhmann · Ralf Eberhardt · Felix J. F. Herth

Abstract

Background Mediastinal lymph node staging for lung cancer remains one of the most important factors to determine patient outcome.
Methods Noninvasive imaging techniques such as CT, MRI, PET and PET-CT provide some answers but no tissue diagnosis.
Results The development of endo-oesophageal (EUS) and endobronchial ultrasound (EBUS) with fine-needle aspiration has provided the clinician with a tool to investigate the mediastinum and the adrenal gland with a safe, minimally invasive procedure that can be performed on an outpatient basis.
Conclusion The aim of this article was to give radiologists an overview of the techniques of EUS and EBUS and their role in the staging of lung cancer patients.

Keywords Endo-oesophageal ultrasound · Endobronchial ultrasound · Lung cancer

Introduction

Lung cancer is still the leading cause of cancer mortality worldwide with a poor overall survival rate. In the diagnosis of lung cancer mediastinal lymph node sampling is important for adequate staging in order to determine appropriate treatment as well as predicting outcome [1]. Apart from that,

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adequate staging of lung cancer is also important in order to improve research into lung cancer, for accurate comparison of data and for quality control. Noninvasive radiological staging can aid in the initial assessment of metastatic spread but lymph node sampling will still need to be performed to determine nodal infiltration. Mediastinoscopy used to be the gold standard for nodal sampling, but other techniques such as endobronchial ultrasound and endo-oesophageal ultrasound are playing a bigger role in obtaining tissue samples from mediastinal lymph nodes.

The TNM staging for lung cancer has recently been revised (Table 1), with the downstaging of a number of nodal stations. N0 describes no nodal spread; N1 represents spread to the ipsilateral intrapulmonary, hilar or peribronchial lymph nodes; N2 staging involves ipsilateral or subcarinal mediastinal nodes; N3 status describes contralateral mediastinal or supraclavicular nodes.

For an overview of mediastinal lymph nodes, see Fig. 1 [2]. Lymph node stations 3a and b are not demonstrated here as they are visualised only on a lateral view.

Imaging of the mediastinum

Computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and PET-CT are useful noninvasive imaging techniques for the staging of lung cancer; however, they are not sufficiently sensitive or specific to determine mediastinal lymph node involvement [3–7]. CT is usually the initial method for staging of the mediastinal nodes. According to national and international guidelines, however, only lymph nodes with a short axis diameter over a size of 1 cm (± positivity in PET if performed as a PET-CT for example) are usually considered to have suspected malignant involvement judged by radiological criteria.

Table 1 TNM staging table; the new changes are highlighted in grey, adjusted from Detterbeck et al. [2]

T and M		N0	N1	N2	N3
UICC6 and Descriptor	New T/M	Stage	Stage	Stage	Stage
T1 (<=2cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2 – 3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (<5cm)	T2a	IB	IIA	IIIA	IIIB
T2 (>5-7cm)	T2b	IIA	IIB	IIIA	IIIB
T2 (>7cm)	T3	IIB	IIIA	IIIA	IIIB
T3 invasion		IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		IIB	IIIA	IIIA	IIIB
T4 (extension)	T4	IIIA	IIIA	IIIB	IIIB
M1 (ipsilateral lung)		IIIA	IIIA	IIIB	IIIB
T4 (pleural effusion)	M1a	IV	IV	IV	IV
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV
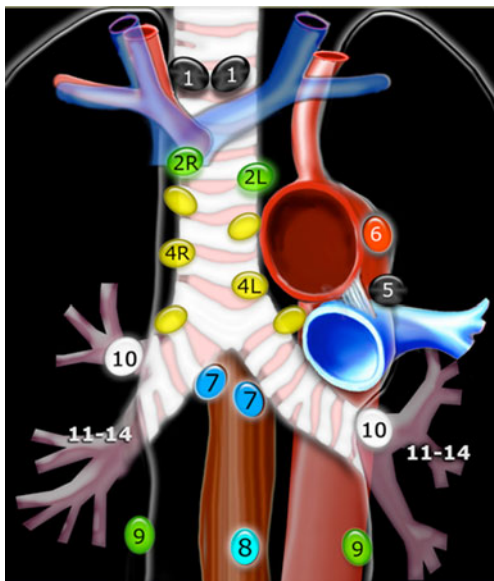
Fig. 1 Lymph node stations in the mediastinum. Lymph node stations 3a and b are only visible on side views and not accessible by endobronchial ultrasound (EBUS) or endoscopic ultrasound (EUS)

Integrated PET/CT has been reported to be more accurate than PET alone [8]. Given the high false-positive rate in CT and PET-CT [3], however, and the fact that these tests do not provide a tissue diagnosis, it is important to obtain lymph node tissue to determine operability.

Guidelines suggest that positive PET findings within the mediastinum should be confirmed with invasive techniques before any operative procedure [4, 9, 10]. Even when PET is negative, invasive staging ought to be considered if the tumour is central, positive N1 nodes on CT or PET are seen, positive mediastinal nodes on CT are seen or if there is low FDG uptake in the primary tumour [9, 10].

One study comparing PET/CT and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in lymph node staging showed the diagnostic accuracy of PET/CT to be 62.4% and that of EBUS-TBNA to be 97.4% [3, 5].

Tissue sampling techniques in the mediastinum

Cervical mediastinoscopy has been the gold standard for mediastinal staging for many years and has shown a pooled

sensitivity in two systematic reviews of 78–81% [9, 11]. Only certain lymph node stations are accessible (1, 2, 3, 4 and anterior 7), while access to the posterior and inferior mediastinum is limited and requires extended cervical mediastinoscopy or thoracoscopy. Even with these procedures, it is not possible to evaluate the hilar lymph nodes.

Since mediastinoscopy is an invasive and expensive procedure, requiring general anaesthesia and an operating theatre, less invasive techniques such as endobronchial ultrasound and endo-oesophageal ultrasound have been developed over the last few years.
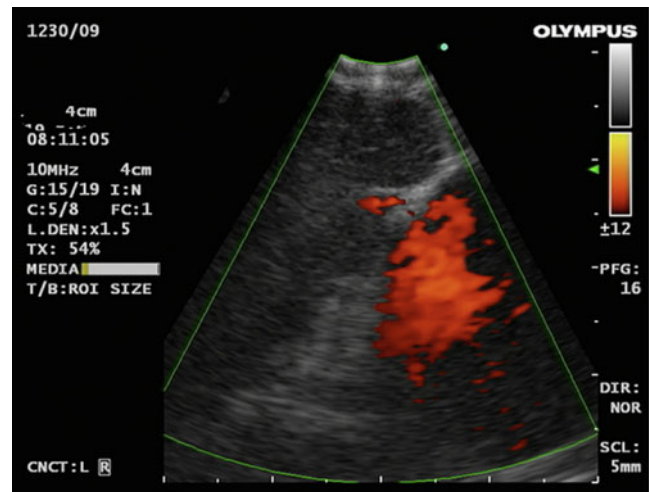
Endobronchial ultrasound

Developed in 2002, the EBUS bronchoscope (models Olympus BF-UC160F-OL8 or BF-UC260F-OL8 and Pentax EB-1970 UK) looks similar to a normal bronchovideoscope, and the smallest available diameter is currently 6.3 mm wide with a 2.2-mm working or instrument channel and a 30-degree side viewing optic. Furthermore, a curved linear array ultrasonic transducer sits on the distal end (Fig. 2) and can be used either with direct contact to the mucosal surface or via an inflatable balloon, which can be attached at the tip. This allows a conventional endoscopic picture side-by-side with the ultrasound view. Ultrasound is performed at a frequency of 7.5–12 MHz with tissue penetration of 20–50 mm. A dedicated ultrasound processor creates the ultrasound image.

Endobronchial ultrasound allows the bronchoscopist to visualise airway structures as well as surrounding tissue. It is very valuable for staging of advanced cancer with regard

Fig. 3 EBUS image with lymph node and adjacent pulmonary artery in power Doppler mode

to intramural or nodal spread. EBUS can identify N2 and N3 nodes without the need for surgical intervention. An additional advantage is the high resolution of mediastinal structures to show tumour invasion and to diagnose intrapleural tumours. At the same time colour Doppler as well as power Doppler can be used to identify surrounding vascular structures. The images obtained are generally easier to interpret than those of radial endobronchial ultrasound probes (Fig. 3).

Different needles of 21- and 22-gauge are available and can be advanced through the working channel of the EBUS scope (Fig. 4) in order to puncture lymph nodes under real-time ultrasound visualisation. The needle has an internal stylet to avoid contamination with bronchial wall mucosa

Fig. 2 Distal end of the EBUS Scope. With permission from Olympus, Tokyo, Japan

Fig. 4 Olympus EBUS Scope with TBNA (NA-201SX-4022) needle attached

during biopsy. Biopsies under real-time endosonography control allow for a better yield in comparison to 'blind' needle aspiration (Fig. 5). Ideally three punctures [12] of each lymph node should be performed to achieve an optimal yield.

Lymph node stations that can be reached via EBUS are the highest mediastinal (station 1), upper paratracheal (2L and 2R), lower paratracheal (4R and 4L), subcarinal (station 7), hilar (station 10) as well as interlobar (station 11) and lobar nodes (station 12). It is important to remember that lymph node stations 5, 6, 8 and 9 are not routinely accessible by this method. The highest staging lymph node should be biopsied first; otherwise, the needle requires changing each time to avoid contamination and false-positive results [13].
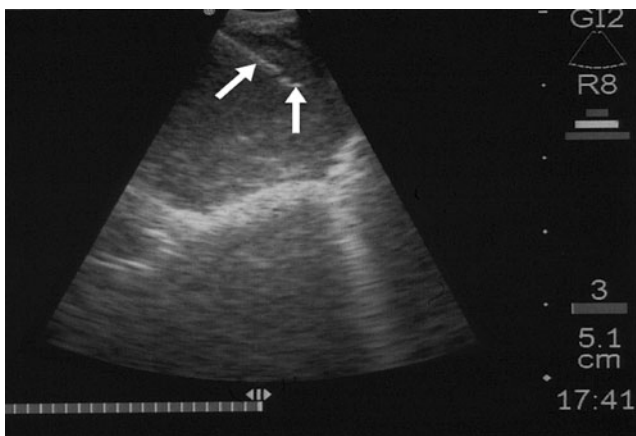
Lymph nodes at a size of 5 mm and upwards can be successfully sampled and have to date been proven to have excellent diagnostic yield. The learning curve for EBUS-TBNA has been evaluated and recorded at ten supervised procedures in order to achieve excellent sensitivity and diagnostic accuracy [14].

In a recent meta-analysis EBUS-TBNA has been shown to have a high pooled sensitivity of 93% and specificity of 100% [15]. Multiple publications provide evidence that even in patients with lymph nodes under 1 cm (which had been termed N0 by CT criteria), with the use of EBUS-TBNA a large percentage could still be shown to have N2/N3 disease (some despite also being negative on PET-CT) [16–18].

Complications such as bleeding or infection are very rare and have only been reported as case reports [19–21].

Endo-oesophageal ultrasound

Gastroenterologists have been using this technique for many years in the investigation of oesophageal and pancreatic malignancies. The linear EUS Scope (Olympus


Fig. 6 Distal end of the EUS Scope, with permission from Olympus, Tokyo, Japan

GF-UC160P-OL5/GF-UCT160-OL5 or Pentax EG-3830UT) has the same basic architecture as the EBUS scope and uses a device with between 5 and 10 MHz (Fig. 6). The tissue penetration of the ultrasound can be up to 8 cm (Fig. 7). Endo-oesophageal ultrasound (EUS) is especially useful in the staging of the posterior mediastinum, lymph node station 4L, 7, lower para-oesophageal (station 8), inferior pulmonary ligament lymph nodes (station 9) and coeliac lymph nodes. Lymph node stations 1L and 2L can also be reached. The left adrenal can be identified in up to 97% [22] and has a so-called 'seagull' shape on ultrasound. It is particularly well visualised in cases of metastatic enlargement (Fig. 8). Furthermore, the left lobe of the liver can also be accessed. The hilar and precarinal lymph nodes however cannot be reached, with lymph node stations 2R, 3 and 4R only poorly accessible by EUS.

Fig. 5 EBUS needle being advanced into lymph node
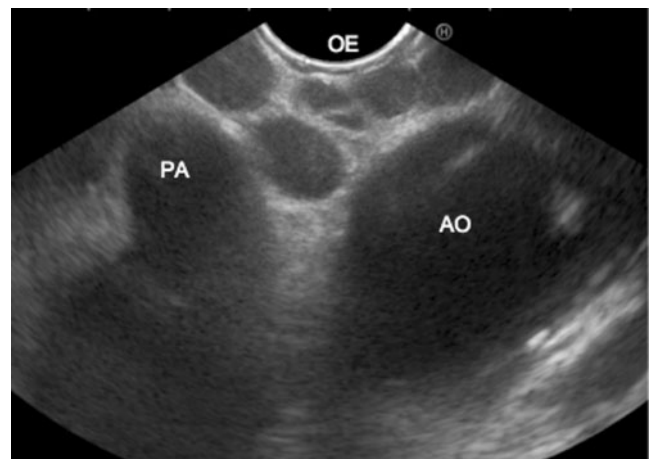
Fig. 7 EUS image. With kind permission from J. Annema. Multiple subcentimeter nodes between oesophagus (OE), aorta (AO) and pulmonary artery (PA). This represents lymph node station 4 left
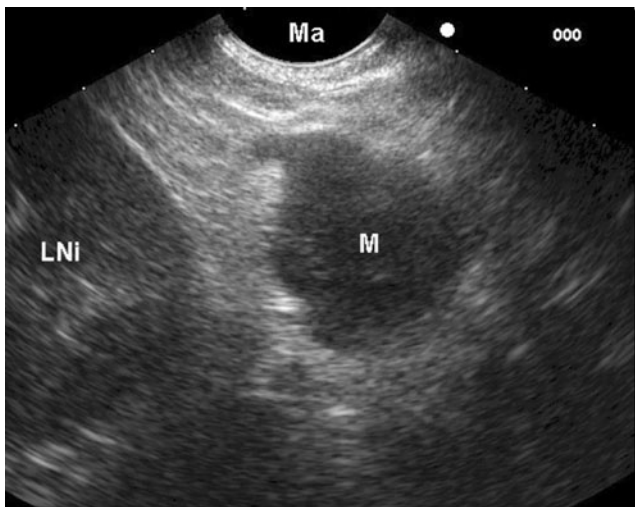
Fig. 8 EUS picture of enlarged left adrenal gland. With kind permission from J. Annema. Ma=stomach, M=left adrenal gland, LNi=left kidney

Table 2 Comparison of the range of tissue sampling sites between endo-oesophageal ultrasound fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)

	EUS	EBUS
Mediastinal staging (N2/N3)	++	++
Mediastinal restaging (N2/N3)	+	+
Hilar staging (N1/N3)	-	++
Intrapulmonary tumours (T)	+	+
Tumour invasion (T4) (central vessels)	+	-/+
Left adrenal gland (M1)	+	-

Needles used for biopsy are 19- or 21-gauge, again equipped with a stylet. Different types of needles are available for EUS, such as Medi-Globe, Olympus and Cook needles. The procedure is usually performed on an outpatient basis and takes approximately 30 min.

As with EBUS, the puncture of lymph nodes is performed under real-time ultrasound guidance.

Endo-oesophageal ultrasound is more accurate and has a higher predictive value than either PET or CT for posterior mediastinal lymph nodes [23], and multiple publications as well as a meta-analysis on endo-oesophageal ultrasound fine-needle aspiration (EUS-FNA) have shown a high sensitivity and specificity [23–25]. Even in patients without mediastinal lymph node enlargement on CT, EUS-FNA has been able to demonstrate metastases in 25% of lung cancer patients [16, 26].

The procedure carries only a very small risk of mediastinitis or bleeding. Unless cysts are punctured, antibiotics do not need to be administered routinely [27, 28].

Combining EBUS and EUS

A comparison of the range of sampling sites between EUS-FNA with EBUS-TBNA as shown in Table 2 highlights the fact that EUS and EBUS provide access to different areas of the mediastinum and also differing approaches to nodal stations, and are thought of as complementary procedures. In combining both techniques, most lymph node stations as well as the left adrenal gland can be reached (apart from stations 3, 5 and 6). In six recent series the accuracy of EUS-FNA and EBUS-TBNA used in combination for the diagnosis of mediastinal cancer was 95% [29–34]. Using

the EBUS scope for both endobronchial as well as endo-oesophageal sampling, the sensitivity for cancer detection was shown to be as high as 96% (EUS 89%, EBUS 91), with a specificity of 100% and negative predictive value of 96% (EUS 82%, EBUS 92%) [33].

Rapid on-site evaluation (ROSE) of the material obtained further increases the yield and has been shown to be cost-effective [35]. A cytopathologist screens the needle aspirates in the endoscopy suite for the presence of diagnostic material, ensuring adequate samples are obtained before ending the procedure. When a positive sample is collected, the procedure can be abandoned, thus avoiding unnecessary multiple punctures of lymph nodes.

It is important to remember however that with EBUS and EUS the negative predictive value is under discussion. The guidelines available [9, 10] currently recommend that samples that do not contain tumour cells require follow-up with a more definitive procedure such as mediastinoscopy or video-assisted thoracoscopy (VATS). Recent publications however [33, 34] suggest that the negative predictive value has improved significantly and therefore may no longer be an issue.

Application of endoscopic ultrasound in routine practice

The main barrier to the routine use of EBUS and EUS in staging lung cancer is the variable procedure reimbursement seen in different countries as well as inconsistent introduction into national or local guidelines.

To date most of these procedures have been performed at centres of excellence, and results on sensitivity and specificity are only available from these centres rather than from routine use at smaller hospitals. Competency in these techniques is becoming more common however, and with this wider practice more consistent utilisation should be possible. The guidelines with regard to how to achieve and maintain competency are currently under discussion.
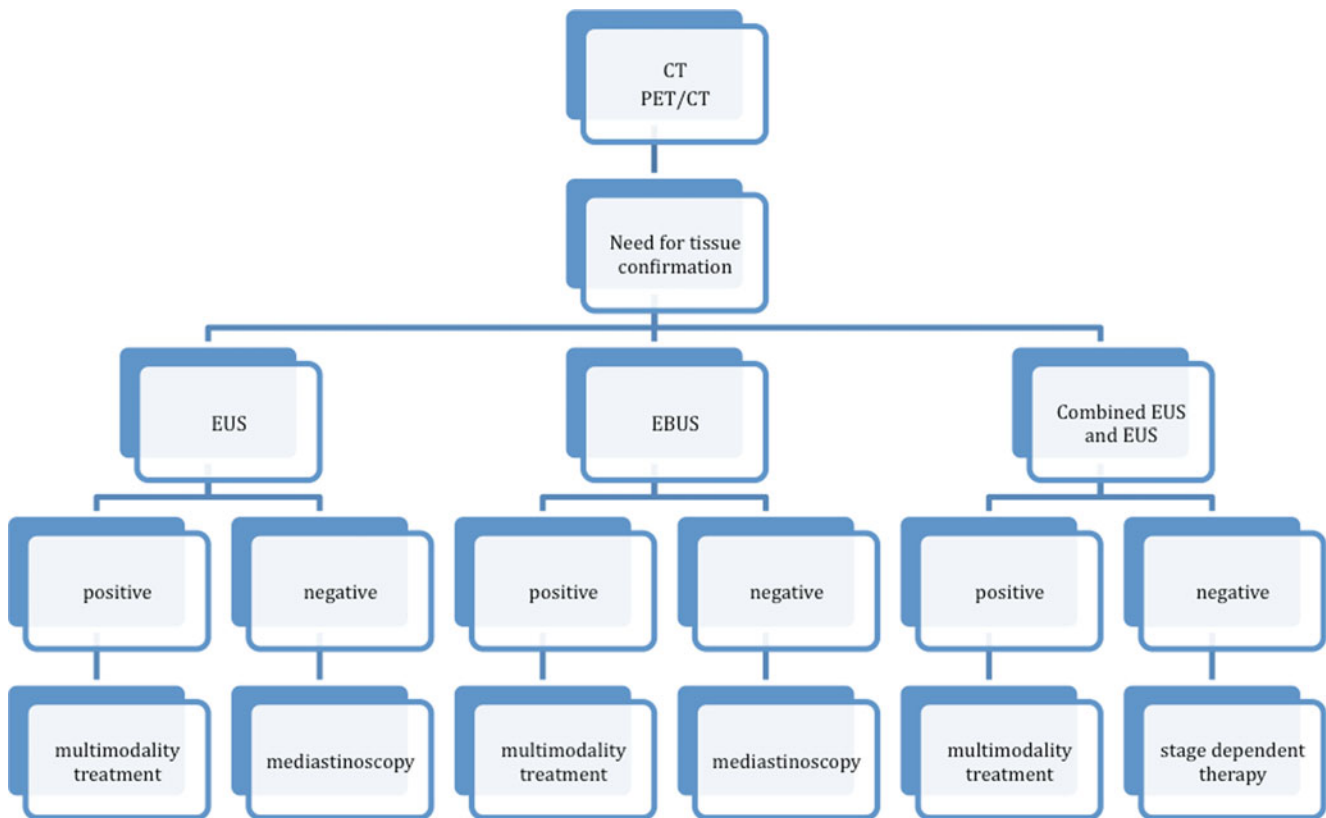
Fig. 9 Proposed decision tree

With the expansion in the use of the technique, it is important to note that the results of the biopsies depend largely on the availability of a trained cytopathologist, which might impede development in some institutions.

As previously mentioned, even though with the combination of both techniques most lymph node stations within the mediastinum can be reached, stations 3, 5 and 6 are not accessible to either technique and may require more invasive staging.

Decision tree for staging the mediastinum

With different staging techniques in lung cancer available to the physician, we propose a decision tree as shown in Fig. 9. The initial staging procedure should be a CT or PET-CT as both are easily available and noninvasive. If then there is a need for tissue confirmation the procedure should be EUS, EBUS or a combination of both depending on which lymph node stations need to be reached. As per the guidelines the next step should be mediastinoscopy in cases of negative cytology from the lymph node sampling.

Restaging of the mediastinum

Accurate restaging of the mediastinum is important in patients with stage III disease following induction chemo-radiotherapy to consider whether these patients would benefit from surgery. The discussion continues as to which technique ought to be applied to achieve the best sensitivity and specificity [36, 37].

Response evaluation of the mediastinum by serial CT after induction therapy can be difficult as gross residual tumour may be present at surgery despite stable disease on CT [38]. The sensitivity and specificity for PET-CT in the

Table 3 Comparison of sensitivity, specificity and accuracy of PET, mediastino-scopy (MES), EUS and EBUS for restaging the mediastinum in lung cancer

		n	Sensitivity (%)	Specificity (%)	Accuracy (%)
PET [44]	8 trials	380	59	85	
MES	3 trials	204	71	100	81
EUS [45, 46]	2 trials	58	70–75	96–100	86–92
EBUS [47, 48]	2 trials	185	67–76	86–100	77–80

evaluation of persistent mediastinal disease are less than in the initial mediastinal lymph node staging [39–41]. However, researchers have recently looked at the percentage change in SUVmax rather than the size of the lymph nodes or lesion, and found that if this decreases by more than 80% a complete response can be predicted with 96% accuracy [42]. Repeat mediastinoscopy for restaging is also a valuable tool despite the fact that sensitivity and accuracy are lower than for the first procedure [43].

The value of EBUS-TBNA and EUS-FNA in restaging of the mediastinum was evaluated in four different publications, demonstrating a high sensitivity, specificity and accuracy for these techniques (Table 3).

As mentioned before, the adequate restaging technique remains a matter of debate, as the comparison of the different techniques is still problematic. Endoscopic techniques are safe, minimally invasive and produce accurate results in comparison to surgical data from re-mediastinoscopy. Nevertheless, if needle aspiration is negative, surgical restaging is required to adequately assess the mediastinum before any decision is made to carry out surgery.

Conclusion

Overall, EBUS and EUS are both safe and effective techniques for the staging of the mediastinum, allowing a reduction in the number of invasive staging procedures.

Previously the main limitations to EBUS and EUS were that they used to be predominantly performed at centres of excellence and hence only on selected patients. Nowadays, though, more and more physicians and surgeons are trained in these techniques. Training remains an issue, and performance of an adequate amount of procedures per year is required in order to maintain competency. Reimbursement for these procedures can pose a further problem in some countries as well as the actual introduction into cancer guidelines within the hospitals.

Increasingly, however, both techniques are being used in hospitals across the world, improving the diagnostic yield. EBUS and EUS ought to be regarded as the first-line techniques for investigating the mediastinum.

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