Introduction  Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive mediastinal lung cancer staging and diagnostic procedure. Current surgical staging with mediastinoscopy is more invasive and expensive. EBUS-TBNA performs as well as mediastinoscopy in many respects and better than conventional transbronchial needle aspiration (TBNA). EBUS-TBNA can be useful in the diagnosis of unexplained mediastinal lymphadenopathy or masses. This review covers when EBUS-TBNA is considered, comparative mediastinal staging studies, procedural and training issues, as well as other applications.

Staging  Quick diagnosis and accurate lung cancer staging are essential to allay patient anxiety, give the best chance of selection for radical treatment, and otherwise allow prompt palliative treatment. Mediastinal lymph node metastases determine prognosis, resectability, and survival (because mediastinal metastases in nonsmall cell lung cancer [NSCLC] correlate with extrathoracic metastases), and staging algorithms have therefore taken this into account. Noninvasive staging by computed tomography (CT) and positron emission tomography (PET) has its problems, although it can give useful staging and guide where to obtain tissue for confirmation. Mediastinal sampling techniques include mediastinoscopy (and associated surgical staging techniques), EBUS-TBNA, and conventional TBNA. Mediastinoscopy is traditionally performed when radical treatment is considered, but it only accesses stations 2R, 2L, 4R, 4L, and 7 (see FIGURE 1). It performs well (78%–81% sensitivity, 91% negative predictive value in studies with mean prevalence of 39%) and yields a large tissue core but is not without its problems. It takes a long time, is invasive with a small risk of important serious complications, and is expensive and rationed, requiring a thoracic surgical team, general anesthesia, and often overnight admission. Conventional TBNA at flexible bronchoscopy samples the mediastinal nodes, is a less invasive technique, but its performance is inferior to mediastinoscopy (76–78% sensitivity, 71%–72% negative predictive value in studies with mean prevalence of 75%) because the tissue size is smaller (although tissue cores from a 19-gauge needle can still be obtained) and sampling is not done under direct vision, although higher sensitivities of up to 82% have been reported in expert centers and also in newly developed services in higher prevalence cohorts (above 75%).
EBUS-TBNA is a logical development from TBNA allowing real-time sampling (with image capture for audit purposes), better safety, and improved performance comparable to mediastinoscopy in sensitivity (considering the higher disease prevalence in the studies) although its negative predictive value is inferior (88%-93% sensitivity, 76% negative predictive value in studies with mean prevalence of 68%),\(^4\)\(^\text{,}^{4-9}\) so that mediastinoscopy should be performed in EBUS-TBNA-negative cases if there is a high clinical suspicion of malignancy. EBUS-TBNA is much quicker, performed as a day case out of theatre, and is less invasive than mediastinoscopy. The sonographic appearances at EBUS-TBNA can also help predict malignancy and additional pathology in the proximal pulmonary vasculature.\(^14\)\(^\text{,}^{15}\) The closely related endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) can be performed at the same time as EBUS-TBNA and gives access to stations 4L, 5-9, as well as the left adrenal gland and left lobe of the liver. EBUS-TBNA does have its drawbacks compared to conventional TBNA: it costs much more, takes longer, and requires longer training. Occasionally, the EBUS-TBNA sample gets contaminated with bronchial epithelial cells, which affects the utility of some tumor markers.\(^16\)

**Changes to treatment** The arrival of EBUS-TBNA with a superior negative predictive value to conventional TBNA offers potential changes to treatment approaches in N2 NSCLC. Its use in staging solitary or multiple discrete or bulky N2 disease in lung cancer staging offers the potential to stratify patients who may benefit from combination chemoradiotherapy and in whom surgery may not be the most appropriate treatment.

**Endobronchial ultrasound-guided transbronchial needle aspiration vs. computed tomography and positron emission tomography** Comparative studies are summarized in Table 1. Two studies have compared EBUS-TBNA with preoperative radiological staging in patients with a radiologically "normal" mediastinum.\(^17\)\(^\text{,}^{18}\) EBUS-TBNA was superior to radiological staging in both studies (Table 1),\(^17\)\(^\text{,}^{18}\) although nodal diameters were down to levels that would limit the utility of PET. EBUS-TBNA was also superior to radiological staging for nodes of between 5 and 20 mm (Table 1),\(^19\) especially for adenocarcinoma, which is known to have a higher rate of mediastinal metastases\(^20\) and lower PET activity.\(^21\) Combined EBUS-TBNA/EUS-FNA was superior to either EBUS-TBNA or EUS-FNA alone for subcentimeter nodes on CT.\(^22\) EBUS-TBNA may therefore have a role in preoperative staging and is superior to radiological staging but may be more effective when combined with EUS-FNA.

**Endobronchial ultrasound-guided transbronchial needle aspiration vs. conventional transbronchial needle aspiration** EBUS-TBNA is superior to conventional TBNA although there are few comparative studies. On the basis of a recent systematic review, conventional TBNA had a 76% sensitivity\(^4\) compared with 88% to 93% for EBUS-TBNA.\(^4\)\(^\text{,}^{4-9}\) However, expert centers can achieve sensitivities of up to 82% in higher prevalence cohorts, although with a lower negative predictive value of 67%.\(^12\) The impressive performance in this study reflects the expertise in TBNA but also the higher prevalence of disease. Conventional TBNA continues to have a role in centers where EBUS-TBNA is not available (because of the cost and training requirements) with the limitation of its lower negative predictive value.

**Endobronchial ultrasound-guided transbronchial needle aspiration vs. mediastinoscopy** There are only 3 comparative studies to date yielding differing results (Table 2), although the data from one of these studies are preliminary.\(^21\)\(^\text{,}^{24}\) One study favored mediastinoscopy and 3 patients were upstaged by mediastinoscopy indicating that EBUS-TBNA may not completely replace it, although the prevalence of disease was lower.\(^24\) More recent data from a randomized multicenter controlled trial (ASTER) of combined endosonography (EBUS-TBNA/EUS-FNA) followed by surgical staging (for negative findings) vs. surgical staging in potentially resectable NSCLC has revealed a higher detection of nodal metastases (50% vs. 35%) and a reduction in futile thoracotomies with no increase in complications.\(^25\)

Noncomparative studies (Table 2) have not performed surgical staging in EBUS-TBNA-positive tumors. Therefore, the role of EBUS-TBNA in these patients is less clear, and EBUS-TBNA should perhaps be considered as a good alternative to mediastinoscopy.
Unexplained mediastinal lymphadenopathy In addition to staging, another important application of EBUS-TBNA is to diagnose unexplained mediastinal lymphadenopathy due to malignant or benign disease. Many lung tumors are extraluminal and not always accessible via conventional bronchoscopic techniques; EBUS-TBNA is commonly the sole diagnostic method in lung cancer patients (22% in a typical real-world cohort of patients). EBUS-TBNA can therefore reduce the need for other diagnostic procedures (CT-guided biopsy or diagnostic mediastinoscopy) in such situations and can be diagnostic in 45% of cases following a negative bronchoscopy and CT-guided biopsy. EBUS-TBNA has applications in the diagnosis of sarcoidosis although studies are limited largely to cohort studies with sensitivities from 71% to 93% depending on patient selection criteria (Table 3). The lowest sensitivities were obtained in a selected cohort after a negative bronchoscopy and then using real-life criteria without a CT scan for all stages. Higher sensitivities were achieved in patients with enlarged nodes on CT and stage 1–2 disease. The one randomized trial did show superiority for EBUS-TBNA cases. Transcervical bilateral extended surgical mediastinal lymphadenectomy was performed in all negative cases in a large prospective cohort study, and false-negative EBUS-TBNA results were attributed to proven small metastatic deposits. A lower negative predictive value was noted in another larger prospective study (although sensitivity was comparable, see Table 2), indicating the need to surgically stage EBUS-TBNA-negative nodes when clinical suspicion is high. Current guidelines recommend EBUS-TBNA for staging bulky mediastinal disease or discrete N2 or N3 disease. Mediastinoscopy is still the preferred tool for radical treatment staging but given the findings from the recent ASTER trial, this position may need to be re-evaluated and the role for EBUS-TBNA/EUS-FNA is likely to extend into staging early-stage disease. Recommendations for restaging are less clear but mediastinoscopy leads to adhesions, which reduces the utility of re-mediastinoscopy, whereas initial staging with EBUS-TBNA/EUS-FNA may reduce adhesions. Alternatively, EBUS-TBNA can restage with a 68% sensitivity and 78% negative predictive value with false negative results only in sub-5 mm nodes with small deposits. EBUS-TBNA has applications in the diagnosis of sarcoidosis although studies are limited largely to cohort studies with sensitivities from 71% to 93% depending on patient selection criteria. The lowest sensitivities were obtained in a selected cohort after a negative bronchoscopy and then using real-life criteria without a CT scan for all stages. Higher sensitivities were achieved in patients with enlarged nodes on CT and stage 1–2 disease. The one randomized trial did show superiority for EBUS-TBNA
TABLE 3  Studies (cohort unless specified) evaluating endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of sarcoidosis

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Criteria</th>
<th>Technique</th>
<th>Sensitivity, %</th>
<th>Node size, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakajima et al.32</td>
<td>31</td>
<td>stage 1</td>
<td>EBUS-TBNA</td>
<td>90.3</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Tournoy et al.33</td>
<td>80</td>
<td>initial negative FB</td>
<td>EBUS-TBNA</td>
<td>71</td>
<td>NA</td>
</tr>
<tr>
<td>Garwood et al.34</td>
<td>48</td>
<td>all stages</td>
<td>EBUS-TBNA</td>
<td>85</td>
<td>4–40 (mean 16)</td>
</tr>
<tr>
<td>Wong et al.35</td>
<td>65</td>
<td>stage 1–2</td>
<td>EBUS-TBNA</td>
<td>87.5</td>
<td>7–37 (mean 20.5)</td>
</tr>
<tr>
<td>Oki et al.36</td>
<td>15</td>
<td>stage 1–2</td>
<td>EBUS-TBNA</td>
<td>93</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Tremblay et al.37</td>
<td>50a</td>
<td>stage 1</td>
<td>EBUS-TBNA</td>
<td>83.3</td>
<td>&gt;10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBNA</td>
<td>60.9</td>
<td></td>
</tr>
</tbody>
</table>

a randomized controlled trial

Abbreviations: FB – flexible bronchoscopy, TBNA – conventional transbronchial needle aspiration, others – see TABLES 1 and 2

over conventional TBNA with a histology-gauge needle.37

EBUS-TBNA has other applications in benign disease. It can increase the diagnostic yield of smear-negative tuberculosis beyond bronchoalveolar lavage by use of molecular techniques on the EBUS-TBNA sample.39 Similar application of limited esophageal EUS-FNA with an EBUS scope (even without molecular techniques) has been reported to have a high yield for tuberculosis in a recent case series of smear-negative cases.40 EBUS-TBNA can enable diagnosis of hamartoma from the sonographic and histological appearances, avoiding more invasive procedures.41

In suspected mediastinal lymphoma, EBUS-TBNA is not the first-choice diagnostic tool (usually a larger tissue core is required by mediastinoscopy), but it can be diagnostic with the use of flow cytometry, which may be of particular help when the patient is unfit for a mediastinoscopy. In a small retrospective study, mediastinal lymphoma was diagnosed by EBUS-TBNA obtaining a 91% sensitivity.42

Procedural issues  Radial probe endobronchial ultrasound gives a 360º view using high frequencies (range 20–30 MHz) giving high resolution of less than 1 mm but lower depth penetration of 5 cm.43,44 They are ideal for visualizing the airway wall and surrounding small paracardial lesions in detail and are used for assessment of airway tumor infiltration to guide endobronchial therapy and peripheral pulmonary nodule sampling. Sampling is done sequentially and not in real time. The probes are smaller and can fit down a 2.8 mm working channel (or even 2 mm). The remainder if this discussion focuses on the linear probe.

The linear probe visualizes mediastinal lymph nodes, masses, and proximal vasculature in particular and allows real-time sampling, giving a larger tissue core than conventional TBNA (FIGURE 2A and 2b). In clinical practice, a separate flexible bronchoscopy is sometimes done because the white light endoscopic image is inferior on the EBUS-TBNA scope, and the scope is also larger in external diameter limiting full examination of the distal tracheobronchial tree. The supine patient is normally intubated orally from behind under either conscious sedation or general anesthesia with a laryngeal mask. The probe can be sheathed with an inflatable balloon to improve ultrasonic image quality but in clinical practice, this is often unnecessary. It uses a lower frequency range of about 7.5 MHz, giving good depth penetration of about 9 cm at the expense of some loss in resolution, although newer linear probes have a frequency range of 5 to 20 MHz.

The endoscopic image is not the same as encountered at conventional bronchoscopy and is at an obliquely angled view of 30º forward with the ultrasonic image (FIGURE 3, M-mode with optional power Doppler to avoid vascular puncture) at an angled forward view of 90º parallel to the EBUS bronchoscope shaft. The EBUS-TBNA needle is a sheathed 22-gauge needle (although 21-gauge has been used too, but not 19-gauge as sometimes used for conventional TBNA) (FIGURE 4) with an internal removable stylet (FIGURE 5), and the technique is similar to conventional TBNA with some modifications: firstly, the length of needle expulsion is determined using the calibrator at the side of the sonographic image and set on the needle operating system (FIGURES 3 and 4); secondly, it is important to agitate the stylet when in the node to remove debris before sampling. Serpiginous tissue cores are deemed “optimal” and 2 samples alone if “optimal” are sufficient,45 but many centers perform up to 4 passes if samples are not “optimal” subject to patient tolerance as studies suggest additional benefit here.46 The higher stage nodes are sampled first (N3, then N2) to prevent upstaging by contamination.

Many centers use liquid cytology bottles for samples, supported by a recent study.47 Conventional TBNA studies suggest that the smear technique (smearing the sample onto glass slides and fixing in alcohol) is superior, resulting in less cellular distortion (FIGURE 28), which may potentially be of value in sarcoidosis and tuberculosis for example.46–50 Rapid on-site evaluation for cytopathology improves the diagnostic yield of TBNA but is not routinely available in many centers.51,52 For histology tissue cores, formalin and saline (for microbial culture) pots are used.
EBUS-TBNA has a similar safety profile to conventional flexible bronchoscopy and is well tolerated.53,54 A postprocedure chest radiograph (CXR) is not usually performed as pneumomediastinum, pneumothorax, and hemomediastinum (avoided by real-time sampling usually) are very rare, although some centers do perform a CXR after hilar node sampling.55,56 Infectious complications can occur including mediastinal abscess57 and bacteremia, but the latter are usually asymptomatic.58,59 More recent data suggest that metal particles can be released into lymph nodes when using EBUS-TBNA needles, but not from conventional TBNA. This may result from friction between the stylet and needle; the significance of this is currently unknown but requires further study.60

Training
Conventional TBNA should be performed for proximal enlarged mediastinal adenopathy at the same time as bronchoscopy (even if there is an endobronchial lesion) because it is cheap compared with EBUS-TBNA, easier to learn,61 well tolerated,62 and available, providing diagnostic and staging information.

Conventional TBNA can also avoid mediastinoscopy in 35% of cases63,64 and save costs (£550 per patient when used as a new service in a real-world United Kingdom cohort).13 EBUS-TBNA differs from conventional bronchoscopy and TBNA. There are 2 different (often simultaneous) views. The ultrasonic image needs to be acquired, interpreted correctly, and maintained. The endoscopic white light view has less resolution than at conventional bronchoscopy and the distal tracheobronchial tree cannot be accessed (due to the higher external diameter of the scope). The scope itself is more fragile, heavier, and thicker at its end with an altered angle of endoscopic view. Training bodies recommend between 40 to 50 supervised procedures with a minimum 5 to 25 procedures annually to maintain level of skill but this refers to radial probe EBUS. The British Thoracic Society is in the process of issuing new guidance.

Although the learning curve has traditionally been thought to be short, backed up by good results from newly developed EBUS-TBNA services (although performance is influenced by node size, disease prevalence, and tumor histology),65-67 more recent data suggest learning can take much longer even among experienced bronchoscopists,
Sampling substernal thyroid nodules where standard EUS-FNA is not possible.

Summary
EBUS-TBNA is a minimally invasive staging technique for NSCLC but also allows diagnosis of unexplained mediastinal lymphadenopathy. When radical treatment is contemplated, mediastinoscopy is still mostly used for staging but this may be replaced in the future by EBUS-TBNA given more recent trial data. Currently, mediastinoscopy is still advisable for EBUS-TBNA-negative nodes when the pretest probability of lung cancer is high.

EBUS-TBNA requires training and has a definite learning curve even for experienced bronchoscopists. EBUS-TBNA can avoid unnecessary mediastinoscopies or other diagnostic procedures. A combined EBUS-TBNA/EUS-FNA service accessing all nodal stations is feasible with sufficient expertise and patient throughput. For centers without EBUS-TBNA, conventional TBNA should be performed because it is cheap, well tolerated, learnable, and performs no worse than EBUS-TBNA for large proximal nodes.

Summary for internists and primary care practitioners
From the perspective of the internist or primary care practitioner, mediastinoscopy is the most invasive technique used by the thoracic surgeon under general anesthetic for staging the mediastinum when radical treatment is contemplated. It gives the largest amount of tissue but cannot access all the mediastinal stations, can have complications, and is most expensive but has remained the gold standard. Conventional TBNA offers a local anesthetic minimally
invasive procedure done by the pulmonologist, allowing access to the hilar stations as well with good results (slightly inferior to mediastinoscopy), especially in specialist centers with experienced operators, although a negative result is not as reliable. Similarly, EBUS-TBNA offers a local anesthetic minimally invasive procedure done by pulmonologists, but allowing more reliable access to smaller, more distant nodes in the mediastinum and real-time sampling to reduce bleeding. It performs as well as mediastinoscopy in many respects but further studies are needed to clarify how reliable a negative result is, and its development is limited by cost and training requirements.

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Ultrasonografia wewnątrzoskrzelowa z przezoskrzelową biopsją igłową

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STRESZCZENIE
Przezoskrzelowa biopsja igłowa wykonywana pod kontrolą ultrasonografii wewnątrzoskrzelowej (endobronchial ultrasound-guided transbronchial needle aspiration – EBUS-TBNA) to najnowsze osiągnięcie w bronchoskopii. Jest narzędziem służącym do oceny stopnia zaawansowania niedrobnokomórkowego raka płuc (nonsmall cell lung carcinoma – NSCLC), ale pozwala także na diagnozowanie powiększonych węzłów chłonnych śródpiersia o nieznanej etiologii w przebiegu choroby nowotworowej lub nienowotworowej. Jest procedurą minimalnie inwazyjną, stosowaną do oceny stopnia zaawansowania przy podejrzeniu NSCLC z zajęciem węzłów chłonnych węzki, cechą N2 lub N3, bądź obecnością masywnego guza w śródpiersiu. Jeżeli istnieje duże prawdopodobieństwo raka płuc, a wynik EBUS-TBNA jest ujemny, nadal zaleca się wykonanie mediastinoskopii, jednak w świetle ostatnich wyników badań wytyczne te mogą się zmienić. EBUS-TBNA jest drogą procedurą, co może ograniczyć jej zastosowanie w systemie opieki zdrowotnej, który ma ograniczone nakłady finansowe. Klasyczna (bez użycia ultrasonografii) przezoskrzelowa biopsja igłowa nadal odgrywa istotną rolę w ocenie stopnia zaawansowania raka płuc, szczególnie tam, gdzie EBUS-TBNA jest niedostępna. Pozwala ona uniknąć wykonywania zbędnych mediastinoskopii.

SŁOWA KLUCZOWE
mediastinoskopia, przezoskrzelowa biopsja igłowa, rak płuc, stopnie zaawansowania raka, ultrasonografia wewnątrzoskrzelowa