NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal masses

This procedure can be used for patients who are being tested for various diseases, including lung cancer. Under local or general anaesthesia, a thin flexible telescope (bronchoscope) is inserted via the patient's mouth into the lungs. Images of the region between the two lungs (the mediastinum) are obtained using an ultrasound probe attached to the bronchoscope. The operator uses these images as a guide when taking samples of cells from masses suspected of disease. The aim of the procedure is to help reach a diagnosis and establish whether the disease has spread.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2007.

Procedure name

- Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for mediastinal masses

Specialty societies

Societies to approach for Specialist Advice:

- British Society of Interventional Radiology
- Royal College of Radiologists
- British Thoracic Society
- Association of Cancer Physicians

Societies/organisations to approach for consultation:

- British Association of Surgical Oncology
- The Society of Cardiothoracic Surgeons of Great Britain and Ireland

Description

Indications

EBUS-TBNA is performed to investigate mediastinal masses, predominantly to help diagnose mediastinal lymphadenopathy of unknown origin, and in the staging of non-small cell lung cancer to assess the potential for curative treatment by surgery. Conditions commonly associated with mediastinal lymphadenopathy include neoplastic disease of the lung or other organs, atypical infections and sarcoidosis.

Current treatment and alternatives

Following chest radiograph and computed tomography (CT) scanning of the chest, a variety of imaging and biopsy techniques may be used to help establish a diagnosis, or help stage non-small cell lung cancer. Mediastinal lesions or lymph nodes can be sampled during bronchoscopy by conventional (non-ultrasound guided) transbronchial needle aspiration (TBNA). Magnetic resonance imaging and ^{18}F-deoxyglucose positron emission tomography (FDG-PET) scanning can also be used. More invasive biopsy procedures (mediastinoscopy, thoracoscopy, mediastinotomy or thoracotomy) may be used, where bronchoscopic methods are not possible or have been unsuccessful, to help biopsy mediastinal lymph nodes. Transthoracic needle aspiration, and endoscopic (transoesophageal) ultrasound-guided fine-needle aspiration (EUS-FNA) are less invasive techniques that have also been used. In EUS-FNA, an endoscope is inserted into the oesophagus and a needle is extended through the oesophageal wall into the lymph node or lesion. Real-time guidance is provided during the procedure by an ultrasound probe also introduced through the endoscope.

What the procedure involves

The aim of EBUS-TBNA is to obtain samples of tissue from mediastinal masses for cytopathological examination. EBUS-TBNA is intended to enable access to all the lymph nodes that are accessible by conventional bronchoscopy or by mediastinoscopy. It is unable to image or access subaortic and para-oesophageal lymph nodes (levels 5, 6, 8 and 9) because of their position in relation to the bronchi and structures of the mediastinum.

EBUS-TBNA may be performed under local anaesthesia with sedation, or under general anaesthesia. A flexible bronchoscope containing an ultrasound probe (usually linear scanning, meaning that it scans parallel to the insertion direction of the bronchoscope) is inserted via the trachea and guided through the bronchial tree towards the appropriate area of the mediastinum. A balloon sheath attached to the tip of the probe may be inflated with water to improve

contact with the bronchial wall. The targeted lymph node or mass is identified using normal bronchoscopic visualisation and real-time ultrasound imaging. Doppler-flow ultrasound imaging may be used to help locate major blood vessels and minimise the risk of their puncture. A needle is extended from the bronchoscope through the bronchial wall and punctures the mass. Suction is applied to draw tissue material into the needle. Usually, real-time ultrasound guidance continues to be available during this aspiration step. Once the bronchoscope has been withdrawn, the material is sent for cytopathological examination. Sometimes the sample may be examined immediately after the procedure to assess whether adequate material has been obtained. A mass may be punctured several times, and several masses can be biopsied during the same session.

Efficacy

Six of the seven studies included in this overview were of patients with a suspected or established diagnosis of lung cancer,[1–5,7] One study was of patients with suspected sarcoidosis.[6] In six of these studies, lymph nodes were punctured under real-time ultrasound guidance,[1–6]and in one study real-time ultrasound was used to target the nodes but not during their puncture.[7]

Studies reported sensitivity (the proportion of patients finally diagnosed with the condition who were identified by EBUS-TBNA), specificity (the proportion of patients without the condition who were correctly identified by EBUS-TBNA), and accuracy (the proportion of all EBUS-TBNA results which agreed with the final diagnosis).

The studies of patients with suspected or known lung cancer compared the results of EBUS-TBNA with a final diagnosis established later, but the means by which this diagnosis was reached varied between studies.[1–5,7]

A study of 100 patients employed surgery to reach the final diagnosis, comparing EBUS-TBNA against the surgical results in all patients. Sensitivity and specificity of EBUS-TBNA for the detection of lymph node malignancy were 92% and 100% respectively.[5]

Five of the remaining studies each performed surgery in some patients, but in other patients the final diagnosis was reached by observing their clinical course. [1–5] Consequently, the ‘gold standard’ diagnostic technique, against which EBUS-TBNA was compared, differed between patients within each study. A study of 502 patients reported that sensitivity, specificity and accuracy of EBUS-TBNA for detection of lymph node malignancy were 94%, 100% and 94%, respectively.[3] A case series of 108 patients reported that sensitivity, specificity and accuracy of EBUS-TBNA for the detection of the correct lymph node stage (i.e. only recording an EBUS-TBNA result as ‘true’ if it was identical to the final staging) were 95%, 100% and 96%, respectively.[4]

Two studies compared the results of several diagnostic techniques against the final diagnosis (as above, established through surgical staging in some patients and by observation of clinical course in others). The first study, of 33 patients, reported that the sensitivity, specificity and accuracy of EBUS-TBNA to detect the correct lymph node stage were 85% (95% confidence interval

[CI]: 62 to 97%), 100% (95% CI: 63 to 100%) and 89% (95% CI: 72 to 98%), respectively.[2] In the same patients, sensitivity, specificity and accuracy of EUS-FNA (again compared with the final diagnosis obtained by surgical staging or observation of the clinical course) were 80% (95% CI: 56 to 94%), 100% (95% CI: 63 to 100%) and 86% (95% CI 67 to 96%), respectively.[2]

The second study, of 102 patients, reported that sensitivity, specificity and accuracy of EBUS-TBNA for detection of malignancy were 92%, 100% and 98%, respectively.[1] In the same patients, sensitivity, specificity and accuracy of CT scanning (compared with the final diagnosis obtained by surgical staging or observation of the clinical course) were 77%, 55% and 61%.[1] The results for FDG-PET scanning were 80%, 70% and 73%, respectively.

A randomised controlled trial of 100 patients who had EBUS-TBNA and 100 patients who had conventional TBNA found that EBUS-TBNA was successful in obtaining a mediastinal lymph node aspirate (either positive or negative for malignancy) in 80 patients, whilst TBNA was successful in 71 ($p < 0.05$). [7] (The proportions of positive and negative diagnoses were not reported).

One study, of 65 patients with suspected sarcoidosis, reported that sensitivity, specificity and accuracy of EBUS-TBNA for detection of the disease were 88%, 100% and 88%, respectively.[6] In this study a final diagnosis of sarcoidosis was based upon clinical and radiological findings, evidence of the disease from pathology and a negative culture result.

Five of the six studies included in this overview that used real-time ultrasound guidance throughout the procedure reported the proportion of aspiration attempts that were successful in providing adequate material for evaluation.[1–3, 5,6] This ranged from 94% in a study of 502 patients[3] to 100% in two studies, of 102 and 100 patients.[1,5] The randomised controlled trial of 200 patients reported that 85% of samples obtained by EBUS-TBNA contained lymphocytes compared with 66% of samples obtained by conventional TBNA (significant, p value not stated). [7]

Safety

One case series of 108 patients reported minor oozing of blood at the puncture site in some patients (number not stated), but no other complications.[4] The remaining six studies reported that no complications occurred.[1–3, 5–7]

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to EBUS-TBNA for mediastinal masses. Searches were conducted via the following databases, covering the period from their commencement to 23 July 2007: Medline, PreMedline, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. (See Appendix C for details of search strategy.)

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with mediastinal masses
Intervention/test	Endobronchial ultrasound-guided transbronchial needle aspiration
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on two studies that compare the outcomes (in a single group of patients) of two or more diagnostic techniques against the final diagnosis,[1,2] and four studies that compare EBUS-TBNA only against the final diagnosis.[3–6] One randomised controlled trial compared the diagnostic yield between who underwent EBUS-TBNA with patients who underwent conventional TBNA.[7]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (Table 2) are listed in Appendix A.

Existing reviews on this procedure

The European Society of Thoracic Surgeons published guidelines on preoperative lymph node staging for non-small cell lung cancer in 2007.[8] The guidelines state, “For primary staging, mediastinoscopy remains the gold standard for the superior mediastinal lymph nodes…Transbronchial needle aspiration, ultrasound-guided bronchoscopy (EBUS-FNA, esophagoscopy (EUS-FNA) and transthoracic needle aspiration (TTNA) are new techniques that provide cyto-histological diagnosis and are minimally invasive techniques. They can be complementary to surgical invasive staging techniques. Their specificity is high but their negative predictive value is low. For this reason an invasive surgical technique is indicated if they yield negative results. However, if fine needle aspiration is positive, this result may be valid as proof of N2 or N3 disease.”

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Interventional procedures

None

Technology appraisals

None

Clinical guidelines

'Lung cancer: diagnosis and treatment'. NICE Clinical Guideline 24 (2005). Available from http://guidance.nice.org.uk/CG24

Public health

None

Table 2 Summary of key efficacy and safety findings on endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal masses

Abbreviations used: CI: confidence intervals; CT: computed tomography; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ^{18}F-deoxyglucose positron emission tomography; MHz: mega Hertz (unit of frequency); MRI, magnetic resonance imaging.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Yasufuku et al 2006[1]

Case series [see comment*]

Japan

Study period: 2003–2005

n = 102

Population: Before EBUS-TBNA, all patients were assessed by CT scan, FDG-PET, brain MRI and bone scan and FDG-PET. Patients regarded as candidates for curative thoracic surgery by a multidisciplinary team were included in this study.

Indications: Evaluation of mediastinal lymph nodes in patients with suspected or pathologically established lung cancer.

Technique:
EBUS-TBNA: Real-time EBUS-TBNA with ultrasound biopsy bronchoscope device (Olympus XBF-UC260F-OL8, linear-scanning, 7.5 MHz frequency) with a 22-gauge needle. Patients were under conscious sedation. Lymph nodes with short diameter > 5 mm were sampled by TBNA. Cytopathology was performed on-site to confirm adequate sampling. Up to</td>
<td>All lymph nodes were successfully sampled.

Comparison of results from each technique to the final diagnosis for detection of accurate lymph node stage
For each diagnostic test (CT, FDG-PET and EBUS-TBNA), the result was compared with the ‘gold standard’, the patient’s final diagnosis (obtained by thoracotomy in some patients and by observation of clinical course in others)
<table>
<tr><td></td><td colspan="4">Number of patients</td></tr>
<tr><td>Test</td><td>True positive</td><td>True negative</td><td>False positive</td><td>False negative</td></tr>
<tr><td>CT</td><td>20</td><td>42</td><td>34</td><td>6</td></tr>
<tr><td>FDG-PET</td><td>20</td><td>54</td><td>23</td><td>5</td></tr>
<tr><td>EBUS-TBNA</td><td>24</td><td>76</td><td>0</td><td>2*</td></tr>
</table>
[‘True positive’ or ‘true negative’ = staging from the test (CT, FDG-PET or EBUS-TBNA was identical to the stage given in the final diagnosis; ‘false positive’ = the test indicated a lower stage than the final diagnosis; ‘false negative’ = the test indicated a higherstage than final diagnosis.]
*These 2 patients with false negative results on EBUS-TBNA were shown to have N2 disease following complete lymphadenectomy.

Data from the table above was used to calculate the following statistics, comparing each diagnostic technique against the ‘gold standard’ final diagnosis
<table>
<tr><td></td><td colspan="5">Percentages</td></tr>
<tr><td></td><td>Sensitivity</td><td>Specificity</td><td>PPV</td><td>NPV</td><td>Accuracy</td></tr>
<tr><td>CT</td><td>76.9</td><td>55.3</td><td>37.0</td><td>87.5</td><td>60.8</td></tr>
<tr><td>FDG-PET</td><td>80.0</td><td>70.1</td><td>46.5</td><td>91.5</td><td>72.5</td></tr>
<tr><td>EBUS-TBNA</td><td>92.3</td><td>100.0</td><td>100.0</td><td>97.4</td><td>98.0</td></tr>
</table>
PPV = positive predictive value</td>
<td>”The EBUS-TBNA procedure was uneventful, and there were no complications. All patients tolerated the procedure very well.”</td>
<td>*The study reports results from three different diagnostic techniques (each performed on all 102 patients) and compares them all with the final diagnosis.

The cytopathologist was blinded to patient details.

CT and FDG-PET scans were read by operators blinded to results of the other tests.

All EBUS-TBNA procedures were performed by the same operator.</td>
</tr>
</table>

Abbreviations used: CI: confidence intervals; CT: computed tomography; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ^{18}F-deoxyglucose positron emission tomography; MHz: mega Hertz (unit of frequency); MRI, magnetic resonance imaging.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
four more attempts were made to obtain adequate tissue . CT scanning: Chest and upper-abdominal CT with contrast single injection and multidetector-row CT. Lymph nodes with short axis > 1 cm were considered positive for malignancy. FDG-PET: Whole-body imaging. FDG-PET was considered positive for N1, N2 or N3 lymph node if the PET report stated that there was hypermetabolic activity consistent with metabolic disease (defined as standardised uptake value > 2.5). Diagnoses were confirmed by thoracotomy with complete lymph node dissection, or by clinical course only if the EBUS-TBNA result showed N3 or extensive N2 disease. **Follow-up: Not stated** Conflict of interest: No conflicts to declare. The study was supported by a grant from the Japanese Foundation for Research and Promotion of Endoscopy.	NPV = negative predictive value Difference in accuracy between the three techniques was highly significant ($p < 0.00001$).		

Abbreviations used: CI: confidence intervals; CT: computed tomography; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ^{18}F-deoxyglucose positron emission tomography; MHz: mega Hertz (unit of frequency); MRI, magnetic resonance imaging.

Study details	Key efficacy findings	Key safety findings	Comments
Vilmann et al 2005[2] **Case series** [*see comment] Denmark Study period: not stated **n = 33** Indications: Staging for patients with an established diagnosis of non-small-cell lung cancer (n = 20), or diagnosis of a suspicious mediastinal lesion in patients with suspected lung cancer (n = 13). These diagnoses were based on CT scan in 31 patients and FDG-PET scan in 1 patient. All patients had previously undergone conventional (not ultrasound-guided) TBNA and sometimes thransthoracic needle aspiration, but with inconclusive results. Technique: Patients underwent both EBUS-TBNA and EUS-FNA in the same session while under general anaesthesia. EBUS-TBNA: Real-time EBUS-TBNA was performed using a prototype ultrasound biopsy bronchoscope device (Olympus XBF-UC40P, linear-array, 7.5 MHz, penetration depth 4–5 cm) with a 22-gauge needle. The scope was introduced through an	Some regions that were accessed by EBUS-TBNA could not be accessed by EUS-FNA and vice versa. **Mean number of needle passes:** 2.3 (range 1–3). There was no difference between the two methods. **EBUS-TBNA** EBUS-TBNA was unsuccessful in 1 patient because of difficulty penetrating a cartilage ring of the trachea. 60 lesions were sampled, with 28 malignant results. Suspicious cells were found in 4 lesions. 11 additional cancer diagnoses and 3 samples with suspicious cells were obtained by EBUS-TBNA that were not obtained by EUS-FNA. Comparison of results from EBUS-TBNA for detection of mediastinal cancer with final diagnosis (excluding the 1 patient in whom biopsy was unsuccessful): Sensitivity: 85% (95% CI: 62 to 97%) Specificity: 100% (95% CI: 63 to 100%) Negative predictive value: 72% (95% CI: 39 to 94%) Accuracy: 89% (95% CI: 72 to 98%) EBUS-TBNA up-staged 4 patients from N0 to N2. **EUS-FNA** EUS-FNA was unsuccessful in 1 patient because of stenosis of the proximal oesophagus. 59 lesions were sampled, with 26 malignant results. Suspicious cells were found in 4 lesions. 12 additional cancer diagnoses, 1 sample with suspicious cells and 1 benign diagnosis (sarcoidosis) were obtained by EUS-FNA that were not obtained by	”There were no complications.”	*The study reports results from two different diagnostic techniques (both performed on all 33 patients) and compares them with the final diagnosis. The final diagnosis, against which EBUS-TBNA was judged, was obtained by lymphadenectomy through thoracotomy in some patients and by observing the clinical course in others. However, it is not clear how many patients underwent thoracotomy.

Abbreviations used: CI: confidence intervals; CT: computed tomography; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ^{18}F-deoxyglucose positron emission tomography; MHz: mega Hertz (unit of frequency); MRI, magnetic resonance imaging.

Study details	Key efficacy findings	Key safety findings	Comments
endotracheal tube. EUS-FNA: A conventional linear-array echo endoscope was inserted into the oesophagus. A 22-gauge needle was used for transoesophageal aspiration. No on-site cytopathology was available. The number of samples needed was judged according to the macroscopic appearance of the aspirate on the slide. The EBUS-TBNA and EUS-FNA diagnoses were confirmed by thoracotomy or clinical course. **Follow-up: not stated** Conflict of interest: none stated	EBUS-TBNA **Comparison of results from EUS-FNA for detection of mediastinal cancer with final diagnosis (excluding the 1 patient in whom biopsy was unsuccessful):** Sensitivity: 80% (95% CI: 56 to 94%) Specificity: 100% (95% CI: 63 to 100%) Negative predictive value: 66% (95% CI: 35 to 90%) Accuracy: 86% (95% CI: 67 to 96%) EUS-FNA up-staged 3 patients from N0 to N2, and 1 patient from N2 to N3. **EBUS-TBNA and EUS-FNA results combined** Of the 31 patients in whom successful biopsies were achieved by both methods, 20 patients were found to have mediastinal involvement by at least one method. All positive diagnoses of lymph node metastases were confirmed either by lymphadenectomy (through thoracotomy) or during clinical follow-up. Of the 11 patients with a benign diagnosis, the diagnosis was confirmed either by lymphadenectomy (through thoracotomy) or during clinical follow-up in 8 patients (all benign). No confirmation could be made in 3 patients because they did not undergo surgery, or were treated because of other metastases.		

Abbreviations used: CI: confidence intervals; CT: computed tomography; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ^{18}F-deoxyglucose positron emission tomography; MHz: mega Hertz (unit of frequency); MRI, magnetic resonance imaging.

Study details	Key efficacy findings	Key safety findings	Comments
Herth et al 2006[3] **Case series** Germany Study period: 2002–2004 **n = 502 patients** Population: Patients with mediastinal or hilar lymphadenopathy who had been referred for TBNA Indications: Sampling and diagnosis of enlarged lymph nodes of unknown origin or lung cancer staging, especially exclusion of N3 nodes Technique: Chest radiograph, CT scan and conventional flexible bronchoscopy were performed for all patients before EBUS-TBNA. Real-time EBUS-TBNA with ultrasound biopsy bronchoscope device (Olympus BF-7160, 7.5 MHz frequency, 50 mm penetration) with a 22-gauge needle. 38% of patients had the procedure under local anaesthesia with moderate sedation and 63% under general anaesthesia. The needle could be visualised directly and via ultrasound during the needle puncture. Doppler ultrasound was used to visualise vessels. Two	In the 502 patients, 572 lymph nodes were identified as enlarged more than 1 cm by CT scanning, and were punctured. **Proportion of biopsies that were successful (i.e. contained evaluable lymphocytes)** 94% (470/502) of patients, 94% (535/572) of lymph nodes In the 37 nodes that were not successfully diagnosed by EBUS-TBNA, diagnoses were made by mediastinoscopy: 35 nodes had malignancy, 2 had sarcoidosis. **Comparison of EBUS-TBNA results for detection of malignancy with final diagnosis (obtained either by thoracotomy, thoracoscopy, mediastinoscopy or clinical follow-up)** Sensitivity: 94% Specificity: 100% Accuracy: 94% Positive predictive value: 100% Negative predictive value: 11%	”No complications were associated with EBUS-TBNA.”	The final diagnosis, against which EBUS-TBNA was judged, was obtained either through thoracotomy, thoracoscopy, mediastinoscopy or by observing the clinical course. It is not clear how many patients were finally diagnosed by each of these approaches. Both the conventional bronchoscopy and EBUS-TBNA procedures were performed by the same operator. The cytopathologist was blinded to patient details. Consecutive patients were enrolled prospectively into the study. The results did not appear to differ between patients who had general anaesthesia and those who had local anaesthesia. The authors note that the procedure can be used repeatedly for the same patient.

Abbreviations used: CI: confidence intervals; CT: computed tomography; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ^{18}F-deoxyglucose positron emission tomography; MHz: mega Hertz (unit of frequency); MRI, magnetic resonance imaging.

Study details	Key efficacy findings	Key safety findings	Comments
aspirates per node were taken, and placed on at least four slides. There was no rapid on-site cytology. Diagnoses based on EBUS-TBNA were confirmed by lymphadenectomy through thoracotomy, or thoracoscopy or clinical follow-up. A positive EBUS-TBNA result was accepted as evidence of cancer. If a specific diagnosis was not obtained by EBUS-TBNA, the patient underwent mediastinoscopy. **Follow-up: Not stated** Conflict of interest: The EBUS-TBNA device was a prototype loaned for the study by the manufacturer. None of the authors had any financial stake in the manufacturer.			

Abbreviations used: CI: confidence intervals; CT: computed tomography; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ^{18}F-deoxyglucose positron emission tomography; MHz: mega Hertz (unit of frequency); MRI, magnetic resonance imaging.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Yasufuku et al 2005[4]

Case series

Japan

Study period: 2002–2004

n = 108

Population: Patients with suspected or pathologically suspected lung cancer

Indications: Staging of non-small-cell lung cancer where CT scan has shown enlargement of lymph node/s (short axis diameter ≥ 1 cm) or a mediastinal lesion suspected of malignancy. Patients with a final diagnosis of other malignancies or benign disease, or N3 or extensive N2 disease evident on chest CT scan were excluded.

Technique: Procedures performed were under local anaesthesia with conscious sedation. Conventional bronchoscopy was performed before EBUS-TBNA. Real-time EBUS-TBNA was performed using an ultrasound biopsy bronchoscope device (Olympus XBF-UC260F-OL8). Cytopathology was performed on-site to confirm adequate sampling. Up to four more attempts were made to obtain adequate tissue. Final</td>
<td>The median number of bronchoscope passes needed to obtain adequate samples was 2 (range 1–5).

Comparison of EBUS-TBNA results for detection of the correct lymph node stage with the final diagnosis (Malignant final diagnosis made on basis of malignant EBUS-TBNA result plus clinical course, or surgical pathological confirmation. Benign final diagnosis made on basis of complete thoracic lymphadenectomy or clinical course.)
<table>
<tr><td>EBUS-TBNA result</td><td colspan="3">Final diagnosis (number of patients)</td></tr>
<tr><td></td><td>Malignant</td><td>Benign</td><td>Total</td></tr>
<tr><td>Malignant</td><td>70</td><td>0</td><td>70</td></tr>
<tr><td>Benign</td><td>4</td><td>34</td><td>38</td></tr>
<tr><td>Total</td><td>74</td><td>34</td><td>108</td></tr>
</table>
Sensitivity: 94.6%
Specificity: 100%
Accuracy: 96.3%</td>
<td>”We did not experience technical difficulties with the balloon, and all procedures were performed safely.”

Minor oozing of blood was observed at the puncture site in some patients.

No patients experienced significant bleeding, pneumothorax or pneumomediastinum.</td>
<td>Consecutive patients, prospectively enrolled

35 of the patients in this study were included in the paper by Yasufuku et al, 2004 (Table 2).

The cytopathologist was blinded to patient details.</td>
</tr>
</table>

Abbreviations used: CI: confidence intervals; CT: computed tomography; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ^{18}F-deoxyglucose positron emission tomography; MHz: mega Hertz (unit of frequency); MRI, magnetic resonance imaging.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
diagnosis of malignancy made on basis of malignant EBUS-TBNA result plus clinical course, or surgical pathological confirmation. Benign final diagnosis made on basis of complete thoracic lymphadenectomy or clinical course. **Follow-up: at least 12 months for some patients** Conflict of interest: not stated			

Abbreviations used: CI: confidence intervals; CT: computed tomography; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ^{18}F-deoxyglucose positron emission tomography; MHz: mega Hertz (unit of frequency); MRI, magnetic resonance imaging.

Study details	Key efficacy findings	Key safety findings	Comments
Herth et al 2006[5] **Case series** Germany Study period: 2003–2005 **n = 100** Indications: Patients indicated for bronchoscopy, who had CT evidence suggesting a lung tumour (T1–T4), and known (n = 87) or suspected (n = 13) diagnosis of non-small-cell lung cancer, but *without* CT evidence of enlarged mediastinal lymph nodes. Technique: Chest radiograph, CT scan and conventional bronchoscopy were performed for all patients before EBUS-TBNA. Local anaesthesia with sedation (n = 22) or general anaesthesia (n = 78) was used. Real-time EBUS-TBNA was performed using an ultrasound biopsy bronchoscope device (Olympus XBF-UC160F-OL8; linear scanning, 7.5 MHz) and a 22-gauge needle. All visualised nodes sized 5–10 mm were punctured. Each node was punctured twice. Rapid on-site cytology was performed. All patients underwent surgical staging by thoracotomy, thoracoscopy or mediastinoscopy fewer than 10 days after EBUS-TBNA.	119 lymph nodes were punctured by EBUS-TBNA (at least 1 per patient). All punctures were adequate. There were lymphocytes in every smear. EBUS-TBNA was positive for metastases in 19% (19/100) of patients, all of whom had previously had negative CT scans. All patients underwent mediastinoscopy (n = 15) or thoracotomy (n = 85) after EBUS-TBNA. Malignant lymph nodes were detected in 2 patients who had negative EBUS-TBNA findings. In these patients, EBUS-TBNA samples had been taken of the lymph node in these regions. Smears had shown lymphocytes but no malignancy. **Statistics for detection of malignancy by EBUS-TBNA** Sensitivity: 92% Specificity: 100% Negative predictive value: 96%	”No complications occurred”.	Consecutive patients, prospectively enrolled. The cytopathologist was blinded to patient details. The authors commented that EBUS-TBNA can routinely access posterior mediastinal (level 7) and hilar lymph nodes (levels 10 and 11) whereas mediastinoscopy cannot.

Abbreviations used: CI: confidence intervals; CT: computed tomography; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ^{18}F-deoxyglucose positron emission tomography; MHz: mega Hertz (unit of frequency); MRI, magnetic resonance imaging.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Follow-up: 10 days Conflict of interest: Not stated			

Abbreviations used: CI: confidence intervals; CT: computed tomography; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ^{18}F-deoxyglucose positron emission tomography; MHz: mega Hertz (unit of frequency); MRI, magnetic resonance imaging.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Wong et al 2007[6]

Case series

Japan and Germany

Study period: 2003–2005

n = 65

Population: details not given

Indications: Clinical and radiological features suggestive of sarcoidosis (74% stage I disease: 26% stage II), with hilar or mediastinal lymph node enlargement > 1 cm shown on CT scan.

Technique: Conventional bronchoscopy was performed for all patients before EBUS-TBNA. Local anaesthesia with sedation was used. Real-time EBUS-TBNA of lymph nodes was performed using an ultrasound biopsy bronchoscope device (Olympus XBF-UC260F-OL8). Cytopathology was performed on-site to confirm adequate sampling. Up to four more attempts were made to obtain adequate tissue. Diagnosis of sarcoidosis was made if clinico-radiological findings were supported by pathological tissue demonstrating non-caseating granulomas without necrosis, and a negative culture result from EBUS-TBNA or surgical</td>
<td>Adequate samples were obtained in 95% (62/65) of patients.

Comparison of EBUS-TBNA results with final diagnosis (made on the basis of clinico-radiological findings plus pathology and culture results from EBUS-TBNA or from surgical biopsy)
<table>
<tr><td>EBUS-TBNA result</td><td colspan="4">Final diagnosis (number of patients)</td></tr>
<tr><td></td><td>Sarcoidosis</td><td>Not sarcoidosis</td><td>Undefined</td><td>Total</td></tr>
<tr><td>Sarcoidosis</td><td>56</td><td>0</td><td>0</td><td>56</td></tr>
<tr><td>No sarcoidosis*</td><td>5</td><td>1</td><td>3</td><td>9</td></tr>
<tr><td>Total</td><td>61</td><td>1</td><td>3</td><td>65</td></tr>
</table>
*including 3 patients with inadequate samples.

Of the 3 patients without a defined final diagnosis, adequate samples had been taken from 2 patients, which showed only non-specific reactive changes. The third patient did not undergo further diagnostic tests because their condition was improving.

Statistics for detection of sarcoidosis by EBUS-TBNA
[Calculated by the IP analyst from numbers given in the article]
Sensitivity: 87.5% (conservative estimate, assuming the patients without a diagnosis had sarcoidosis)
Specificity: 100%
Accuracy: 87.7% (conservative estimate, assuming the patients without a diagnosis had sarcoidosis)</td>
<td>”There were no complications due to pneumothorax, pneumomediastinum or excessive bleeding.”</td>
<td></td>
</tr>
</table>

Abbreviations used: CI: confidence intervals; CT: computed tomography; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ^{18}F-deoxyglucose positron emission tomography; MHz: mega Hertz (unit of frequency); MRI, magnetic resonance imaging.

Study details	Key efficacy findings	Key safety findings	Comments
biopsy. Patients were followed up clinically and radiologically after the procedure. **Follow-up: 18 months** Conflict of interest: None			

Abbreviations used: CI: confidence intervals; CT: computed tomography; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ^{18}F-deoxyglucose positron emission tomography; MHz: mega Hertz (unit of frequency); MRI, magnetic resonance imaging.

Study details	Key efficacy findings	Key safety findings	Comments
Herth et al 2004 [7] **Randomised controlled trial** USA and Israel Study period: 2001–2002 **n = 200** (EBUS-TBNA: n = 100 Conventional TBNA: n = 100) Population: Patients with enlarged lymph nodes referred for TBNA Indications: Main indications were diagnosis of enlarged lymph nodes of unknown origin and cancer staging, especially the exclusion of N3 nodes. Technique: Patients were under general anaesthesia or conscious sedation. Conventional bronchoscopy was performed for all patients initially. Patients were randomised to EBUS-TBNA or conventional (non-ultrasound guided) TBNA. No onsite cytopathology was used. Patients underwent surgical biopsy following EUS-TBNA or TBNA only if the procedure had not produced a specific diagnosis. EBUS-TBNA technique: An ultrasound probe (20 MHz) was inserted through the working channel	**Patients with enlarged subcarinal lymph nodes (n = 100)** Proportion of samples obtained that were lymphocyte-positive: EBUS-TBNA: 86% (43/50) TBNA: 74% (37/50) p< 0.05 **Patients with enlarged lymph nodes in other locations (n = 100)** Proportion of samples obtained that were lymphocyte-positive: EBUS-TBNA: 84% (42/50) TBNA: 58% (29/50) p< 0.001 Proportion of samples obtained that enabled a specific diagnosis: EBUS-TBNA: 74% (37/50) TBNA: 54% (27/50) p< 0.001 **All patients combined (n = 200)** Proportion of samples obtained that enabled a specific diagnosis: EBUS-TBNA: 80% (80/100) TBNA: 71% (71/100) p< 0.05 "No patients with lymphocytes only on TBNA had a more specific diagnosis after surgery."	No complications occurred.	Unlike the other studies included in Table 2, real-time ultrasound guidance was available for identifying lymph nodes but not during the puncture of the nodes. The devices used were not purpose made for EBUS-TBNA. Patients with were divided into those with and without enlarged subcarinal lymph nodes (because these nodes are more easily accessed). Randomisation into each intervention arm was performed separately for each group, as was analysis. The cytopathologist was blinded to the patient's intervention arm.

Abbreviations used: CI: confidence intervals; CT: computed tomography; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; FDG-PET: ^{18}F-deoxyglucose positron emission tomography; MHz: mega Hertz (unit of frequency); MRI, magnetic resonance imaging.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
of a bronchoscope. When the exact location of the target lymph nodes had been noted, the probe was withdrawn from the bronchoscope and a 22-gauge needle was inserted through the bronchoscope to perform TBNA. **Follow-up: not stated** Conflict of interest: Not stated			

Validity and generalisability of the studies

- Three studies (total n = 275) used on-site cytopathology to assess whether samples contained adequate material, potentially helping the operator to decide whether additional aspiration attempts were required.[1,4,6] Four studies did not have this facility (total n = 835).[2,3,5]

- Five of the studies included in Table 2 compared the EBUS-TBNA result with a 'final diagnosis'. Only one of the seven studies (Herth et al 2006)[5] performed surgical investigations to reach this final diagnosis in *all* patients. In four studies the EBUS-TBNA result contributed to decisions about further diagnostic investigations and treatment, and thus to the final diagnosis.[1,3,4,6] In most patients, it appears that surgical confirmation of the EBUS-TBNA result was obtained only if the EBUS-TBNA was negative. For most patients with a positive EBUS-TBNA result, the result appears to have been accepted and the final diagnosis would be altered only if this was suggested by the patient's clinical condition during further care. (One study stated that diagnoses were verified either at thoracotomy or during clinical follow-up, but did not explicitly state the role of the EBUS-TBNA result in decision-making.[2]) If these studies had produced some false-positive results as a result of not confirming positive EBUS-TBNA results surgically, the specificity of EBUS-TBNA (reported as 100% in all studies) may have been artificially high.

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

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- Two Specialist Advisers stated that they performed EBUS-TBNA regularly, and one said he had performed the procedure for more than 400 patients since 2005. One Specialist Adviser said he had performed this procedure more than once, but not regularly and the other has never performed this procedure.
- Two Specialist Advisers commented that the procedure was established practice, but that its use was restricted by the few EBUS-TBNA devices in the UK. One Specialist Adviser regarded this procedure as a minor variation on conventional TBNA and another regarded it as novel.
- One Specialist Adviser commented that the primary indication for this procedure should be diagnosis and staging of lung cancer rather than all 'mediastinal masses', although it may sometimes may be used for other indications.
- Specialist Advisers listed theoretical adverse events as hoarse voice, sore throat, cough, coughing up a small amount of blood, fever, significant bleeding, pneumothorax, pneumomediastinum, mediastinitis and respiratory failure. One Specialist Adviser reported that asymptomatic pneumomediastinum had occurred in one patient in his practice.

- Key efficacy outcomes were considered to be the ability to stage the mediastinum, quality and adequacy of pathological specimens, diagnostic accuracy of EBUS-TBNA in comparison with CT scans, PET, mediastinoscopy or lung resection.
- One Specialist Adviser commented that sensitivity of the procedure should be maintained above 90%.
- One Specialist Adviser commented that there is some uncertainty about the ability to obtain sufficient material for accurate diagnosis compared to mediastinoscopy which obtains a much larger biopsy.
- Most Specialist Advisers expressed no concerns about safety or efficacy of the procedure.
- Regarding training and experience of operators, the Specialist Advisers stated that operators should have good skills in routine bronchoscopy (oral approach), have attended a course about the procedure and visited existing practitioners before performing it, and should perform several procedures under supervision. They should be able to interpret the ultrasound images produced during the procedure.
- Two Specialist Advisers hoped that EBUS-TBNA would be performed in only a limited number of centres in future, in order to ensure that operators have sufficient experience and recent practice in the technique, and that cytopathologists are experienced in analysing specimens.

Issues for consideration by IPAC

- The title of this overview refers to the broad category of ‘mediastinal masses’. However, all literature included in Table 2 relates to EBUS-TBNA for sampling of lymph nodes only. IPAC may wish to consider altering the title to reflect this.
- Five of the six studies included in Table 2 were of patients with known or suspected lung cancer. Only one study was of patients with benign disease (65 patients with sarcoidosis).
- All studies in Table 2 used real-time ultrasound guidance throughout the procedure. Studies that used a single-channel bronchoscope (such that the ultrasound probe has to be withdrawn before the needle can be inserted so that the aspiration step of the procedure is not under real-time ultrasound guidance) have been included in Appendix A.
- All studies with real-time guidance used an ultrasound puncture bronchoscope device manufactured by Olympus, either the XBF-UC160F-OL8 or XBF-UC260F-OL8 model, or a prototype version.
- The British Thoracic Society is in the process of updating its Guideline on bronchoscopy, which it expects to publish in late 2008/early 2009.
- The NICE Clinical Guideline on Lung Cancer states that FDG-PET scanning has a central role in staging non-small cell lung cancer. When FDG-PET scanning is available, histological/cytological confirmation may not be required. The relevant sections of the Clinical Guideline are reproduced in Appendix B.

References

1. Yasufuku K, Nakajima T, Motoori K et al. (2006) Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. *Chest* 130 (3): 710–718.
2. Vilmann P, Krasnik M, Larsen SS et al. (2005) Transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy: a combined approach in the evaluation of mediastinal lesions. *Endoscopy* 37 (9): 833–839.
3. Herth FJ, Eberhardt R, Vilmann P et al. (2006) Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. *Thorax* 61 (9): 795–798.
4. Yasufuku K, Chiyo M, Koh E et al. (2005) Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. *Lung Cancer* 50 (3): 347–354.
5. Herth FJ, Ernst A, Eberhardt R et al. (2006) Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically normal mediastinum. *European Respiratory Journal* 28 (5): 910–914.
6. Wong M, Yasufuku K, Nakajima T et al. (2007) Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. *European Respiratory Journal* 29 (6): 1182–1186.
7. Herth F, Becker HD, Ernst A (2004) Conventional vs endobronchial ultrasound-guided transbronchial needle aspiration: a randomized trial. *Chest* 125 (1): 322–325.
8. De Leyn P, Lardinois D, Van Schil PE et al. (2007) ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. *European Journal of Cardio-Thoracic Surgery* 32 (1): 1–8.

Appendix A: Additional papers on endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal masses not included in summary Table 2

The following table outlines studies considered potentially relevant to the overview not included in the main data extraction table (Table 2). It is by no means an exhaustive list of potentially relevant studies.

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Herth FJ, Becker HD, Ernst A (2003) Ultrasound-guided transbronchial needle aspiration: an experience in 242 patients. *Chest* 123 (2): 604–607.	n = 242 Follow-up: not stated in abstract	Non-real-time EBUS-TBNA Aspiration was successful in 86% of patients, and a firm diagnosis or cancer stage was obtained in 72% of patients. No complications	Ultrasound guidance was not in real time during puncture of the lesion. More recent studies that used real-time guidance have been included in Table 2.
Herth FJ, Lunn W, Eberhardt R et al. (2005) Transbronchial versus transesophageal ultrasound-guided aspiration of enlarged mediastinal lymph nodes. *American Journal of Respiratory and Critical Care Medicine* 171 (10): 1164–1167.	n = 160 Follow-up: not stated	All patients underwent non-real-time EBUS-TBNA and EUS-FNA. EBUS-TBNA Successful aspiration (containing lymphocytes) in 89% (142/160) of patients Diagnosis made: 86% (137/160) EUS-FNA Successful aspiration: 79% (126/160) Diagnosis made: 76% (121/160) Complications None	Ultrasound guidance was not in real time during puncture of the lesion. More recent studies that used real-time guidance have been included in Table 2.

Kanoh K, Kurimoto N, Miyazawa T et al. (2002) A case of real-time endobronchial ultrasonography-guided bronchial needle aspiration using a double-channel flexible bronchoscope. *Journal of Bronchology* 9 (2): 112–114.	n= 1 Follow-up: not stated in abstract	Real-time EBUS-TBNA Performed successfully with one aspiration attempt. Patient was diagnosed with malignancy.	Larger case series of real-time EBUS-TBNA are included in Table 2.
Kanoh K, Miyazawa T, Kurimoto N et al. (2005) Endobronchial ultrasonography guidance for transbronchial needle aspiration using a double-channel bronchoscope. *Chest* 128 (1): 388–393.	n = 55	Randomised controlled trial of EBUS-TBNA using a double- or single-channel bronchoscope. With the single-channel scope, the ultrasound probe had to be withdrawn before the needle could be inserted. With the double-channel scope, the probe was retracted into the tip of the scope before the needle was inserted into the second working channel. *Firm diagnosis* Double: 97% Single: 76% *Mean no. penetrations required to establish diagnosis* Double: 1.2 Single: 1.4 No complications occurred in the double-channel group but a self-limiting haemorrhage of < 30 mL occurred in 1 patient in the single-channel group.	A radial type ultrasound transducer was used in this study, unlike the studies in Table 2, which all used linear-array ultrasound. The double-channel method used in this study did offer real-time ultrasound guidance during penetration of the lesion, but differed from the techniques in Table 2 by not allowing guidance during penetration of the bronchial wall. The authors mentioned that they were going on to use a linear-array device. We considered that inclusion of this study in Table 2 would not help with interpretation of the evidence on real-time EBUS-TBNA.
Krasnik M, Vilmann P, Larsen SS et al. (2003) Preliminary experience with a new method of endoscopic transbronchial real time ultrasound guided biopsy for diagnosis of	n = 11 Follow-up: not stated	Real-time EBUS-TBNA Successful aspiration of 15 lesions. Malignant	Larger case series of real-time EBUS-TBNA are included in Table 2.

mediastinal and hilar lesions. *Thorax* 58 (12): 1083–1086.		diagnosis made by EBUS-TBNA in 9 patients. The 2 benign diagnoses were confirmed by mediastinoscopy. No complications	
Nakajima T, Yasufuku K, Suzuki M et al. (2007) Histological diagnosis of spinal chondrosarcoma by endobronchial ultrasound-guided transbronchial needle aspiration. *Respirology* 12 (2): 308-310.	n = 1 Follow-up: not stated in abstract	A rare case of spinal chondrosarcoma which was successfully diagnosed by real-time EBUS-TBNA.	Larger case series of real-time EBUS-TBNA are included in Table 2.
Nakajima T, Yasufuku K, Wong M et al. (2007) Histological diagnosis of mediastinal lymph node metastases from renal cell carcinoma by endobronchial ultrasound-guided transbronchial needle aspiration. *Respirology* 12 (2): 302–303.	n = 1 Follow-up: not stated in abstract	Mediastinal lymph node metastasis successfully diagnosed by real-time EBUS-TBNA.	Larger case series of real-time EBUS-TBNA are included in Table 2.
Plat G, Pierard P, Haller A et al. (2006) Endobronchial ultrasound and positron emission tomography positive mediastinal lymph nodes. *European Respiratory Journal* 27 (2): 276–281.	n = 33 Follow-up: not stated in abstract.	All patients had positive findings from FDG-PET for mediastinal malignancy. Non-real-time EBUS-TBNA was attempted in all patients but not all lesions could be identified by EBUS. Average number of TBNA samples per patient was 4.2 (standard deviation 1.5). Diagnoses were obtained in 82%, 78% of which were obtained by EBUS-TBNA and the rest by conventional TBNA. In 76% surgical staging procedures were suppressed.	Ultrasound guidance was not in real time during puncture of the lesion. More recent studies that used real-time guidance have been included in Table 2.
Rintoul RC, Skwarski KM, Murchison J et al. (2004) Endoscopic and endobronchial ultrasound real-time fine-needle aspiration for staging of the mediastinum in lung cancer. *Chest* 126 (6): 2020–2022.	n = 2 Follow-up: not stated	EBUS-TBNA result was positive for malignancy in 1 patient, confirmed by EUS-FNA. In 1 patient, EBUS-TBNA result was negative, confirmed by EUS-FNA and surgery.	Larger case series of real-time EBUS-TBNA are included in Table 2.

		No complications in 1 patient, not reported for other patient.	
Rintoul RC, Skwarski KM, Murchison JT et al. (2005) Endobronchial and endoscopic ultrasound-guided real-time fine-needle aspiration for mediastinal staging. *European Respiratory Journal* 25 (3): 416–421.	n = 18 Follow-up: not stated in abstract	Real-time EBUS-TBNA was undertaken in 18 out of 20 cases, showing disease in 11 out of 18 patients and provided a primary diagnosis for 8 patients. EBUS-TBNA was negative in 6 patients, confirmed by mediastinoscopy or clinical follow-up in 4. Results for EBUS-TBNA: Sensitivity 85% Specificity 100% Accuracy 89% No complications.	Larger case series of real-time EBUS-TBNA are included in Table 2.
Shannon JJ, Bude RO, Orens JB et al. (1996) Endobronchial ultrasound-guided needle aspiration of mediastinal adenopathy. *American Journal of Respiratory & Critical Care Medicine* 153 (4 Pt 1): 1424–1430.	n = 82 Follow-up: not stated	Patients randomised to non-real-time EBUS-TBNA (n = 40) or to conventional TBNA (n = 42). Sampling successful in 84% of patients. Statistics for the 54 patients with cancer involving mediastinum or lung cancer with a negative surgical mediastinal exploration showed no advantage to ultrasound guidance. *EBUS-TBNA* Sensitivity 83% Specificity 100% Accuracy 87% TBNA	Ultrasound guidance was not in real time during puncture of the lesion. More recent studies that used real-time guidance have been included in Table 2.

		Sensitivity 91% Specificity 100% Accuracy 92% No complications	
Vincent B, Huggins JT, Doelken P et al. (2006) Successful real-time endobronchial ultrasound-guided transbronchial needle aspiration of a hilar lung mass obtained by traversing the pulmonary artery. *Journal of Thoracic Oncology* 1 (4): 362–364.	n = 1 Follow-up: not stated in abstract	Patient with a left hilar mass who underwent biopsy by means of intentional traverse of the pulmonary artery.	Larger case series of real-time EBUS-TBNA are included in Table 2.
Yasufuku K, Chiyo M, Sekine Y et al. (2004) Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. Chest 126 (1): 122–128.	n = 70 Follow-up: not stated	Real-time EBUS-TBNA Median number of bronchoscope passes to obtain an adequate sample was 2 (range 1–5). Adequate samples were obtained in 97% (68/70) of patients. For detection of malignancy Sensitivity: 95.7% Specificity: 100% Accuracy: 97.1% No complications	35 of the patients in this study were subsequently included in the study published by Yasufuku et al (2005)[4], which is included in Table 2.

Appendix B: Related published NICE guidance for endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal masses

Guidance programme	Recommendation
Interventional procedures	None applicable
Technology appraisals	None applicable
Clinical guidelines	Clinical Guideline 24: Lung cancer: diagnosis and staging *1.2 Diagnosis* 1.2.1 Where a chest X-ray has been requested in primary or secondary care and is incidentally suggestive of lung cancer, a second copy of the radiologist's report should be sent to a designated member of the lung cancer MDT, usually the chest physician. The MDT should have a mechanism in place to follow up these reports to enable the patient's GP to have a management plan in place. 1.2.2 Patients with known or suspected lung cancer should be offered a contrast-enhanced chest CT scan to further the diagnosis and stage the disease. The scan should also include the liver and adrenals. 1.2.3 Chest CT should be performed before: • an intended fibreoptic bronchoscopy; • any other biopsy procedure. 1.2.4 Bronchoscopy should be performed on patients with central lesions who are able and willing to undergo the procedure. 1.2.5 Sputum cytology is rarely indicated and should be reserved for the investigation of patients who have centrally placed nodules or masses and are unable to tolerate, or unwilling to undergo, bronchoscopy or other invasive tests. 1.2.6 Percutaneous transthoracic needle biopsy is recommended for diagnosis of lung cancer in patients with peripheral lesions. 1.2.7 Surgical biopsy should be performed for diagnosis where other less invasive methods of biopsy have not been successful or are not possible.

	1.2.8 Where there is evidence of distant metastases, biopsies should be taken from the metastatic site if this can be achieved more easily than from the primary site. 1.2.9 An 18F-deoxyglucose positron emission tomography (FDG-PET) scan should be performed to investigate solitary pulmonary nodules in cases where a biopsy is not possible or has failed, depending on nodule size, position and CT characterisation. *1.3 Staging* 1.3.1 Non-small-cell lung cancer 1.3.1.1 In the assessment of mediastinal and chest wall invasion: • CT alone may not be reliable • other techniques such as ultrasound should be considered where there is doubt • surgical assessment may be necessary if there are no contraindications to resection. 1.3.1.2 Magnetic resonance imaging (MRI) should not routinely be performed to assess the stage of the primary tumour (T-stage; see Appendix E) in NSCLC. 1.3.1.3 MRI should be performed, where necessary to assess the extent of disease, for patients with superior sulcus tumours. 1.3.1.4 Every cancer network should have a system of rapid access to FDG-PET scanning for eligible patients. 1.3.1.5 Patients who are staged as candidates for surgery on CT should have an FDG-PET scan to look for involved intrathoracic lymph nodes and distant metastases. 1.3.1.6 Patients who are otherwise surgical candidates and have, on CT, limited (1–2 stations) N2/3 disease of uncertain pathological significance should have an FDG-PET scan. 1.3.1.7 Patients who are candidates for radical radiotherapy on CT should have an FDG-PET scan. 1.3.1.8 Patients who are staged as N0 or N1 and M0 (stages I and II) by CT and FDG-PET and are suitable for surgery should not have cytological/histological confirmation of lymph nodes before surgical resection.

	1.3.1.9 Histological/cytological investigation should be performed to confirm N2/3 disease where FDG-PET is positive. This should be achieved by the most appropriate method. Histological/cytological confirmation is not required: • where there is definite distant metastatic disease • where there is a high probability that the N2/N3 disease is metastatic (for example, if there is a chain of high FDG uptake in lymph nodes). 1.3.1.10 When an FDG-PET scan for N2/N3 disease is negative, biopsy is not required even if the patient's nodes are enlarged on CT. 1.3.1.11 If FDG-PET is not available, suspected N2/3 disease, as shown by CT scan (nodes with a short axis > 1 cm), should be histologically sampled in patients being considered for surgery or radical radiotherapy. 1.3.1.12 An MRI or CT scan should be performed for patients with clinical signs or symptoms of brain metastasis. 1.3.1.13 An X-ray should be performed in the first instance for patients with localised signs or symptoms of bone metastasis. If the results are negative or inconclusive, either a bone scan or an MRI scan should be offered. 1.3.2 Small-cell lung cancer (SCLC) 1.3.2.1 SCLC should be staged by a contrast-enhanced CT scan of the patient's chest, liver and adrenals and by selected imaging of any symptomatic area.
Public health	None applicable

Appendix C: Literature search for endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal masses

IP: 413 Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for mediastinal masses		
Database	**Date searched**	**Version searched**
Cochrane Library	17/07/2007	Issue 3, 2007
CRD databases (DARE & HTA)	24/07/2007	Issue 3, 2007
Embase	23/07/2007	1980 to 2007 Week 29
Medline	23/07/2007	1950 to July Week 2 2007
PreMedline	23/07/2007	July 20, 2007
CINAHL	23/07/2007	1982 to July Week 2 2007
British Library Inside Conferences	24/07/2007	-
NRR	24/07/2007	2007, Issue 3
Controlled Trials Registry	24/07/2007	-

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases.

1	(endobronch$ adj3 ultraso$).tw.
2	EBUS.tw.
3	1 or 2
4	exp Biopsy, Needle/
5	needl$.tw.
6	4 or 5
7	EBUS TBNA.tw.
8	3 and 6
9	7 or 8
10	Animals/
11	Humans/
12	10 not (10 and 11)
13	9 not 12