NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of endobronchial ultrasound-guided transbronchial biopsy for peripheral lung lesions

Lung lumps are commonly investigated using a thin flexible telescope (bronchoscope) inserted into the airways of the lung via the patient's mouth or nose. Ultrasound-guided transbronchial biopsy is intended for diagnosing patients with a lung lump that cannot be reached by conventional bronchoscopy because the lump does not protrude into the airways. With the patient under local or general anaesthetic, a bronchoscope including an ultrasound probe is used instead of a conventional bronchoscope. Ultrasound images of the lung are obtained through the bronchoscope and these help to guide the doctor to the location of the lump, to obtain samples for further tests.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make 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 August 2009.

Procedure name

- Endobronchial ultrasound-guided transbronchial biopsy for peripheral lung lesions.

Specialty societies

- British Thoracic Society (BTS)
- British Society of Interventional Radiology
- The Royal College of Radiologists (RCR)

- Society for Cardiothoracic Surgery in Great Britain and Ireland (SCTS)
- Association of Cancer Physicians

Description

Indications and current treatment

In this overview 'peripheral lung lesions' describes lung lesions that cannot be visualised using conventional bronchoscopy because they do not protrude into the bronchial tree.

Patients with peripheral lung lesions are often asymptomatic and the abnormality is detected incidentally on chest X-ray or computed tomography (CT) scanning. Symptoms of cough, haemoptysis and breathlessness may be present, but are more often associated with endobronchial tumours that are accessible to standard bronchoscopic biopsy.

This overview is concerned only with the diagnosis of peripheral lung lesions and not with their treatment.

Current biopsy techniques include blind transbronchial lung biopsy via a bronchoscope, image-guided percutaneous lung biopsy, or (thoracoscopic or open) surgical biopsy.

What the procedure involves

The procedure can be undertaken with the patient under general anaesthesia or local anaesthesia with or without conscious sedation. The lesion is identified by prior CT, positron emission tomography (PET) or conventional chest X-ray investigations. A flexible fibre-optic bronchoscope with a radial mini-probe or catheter located in the working channel is inserted through the nose or mouth, into the airways of the lungs and towards the target peripheral lesion using endobronchial ultrasound (EBUS) guidance. Once the bronchoscope is in the appropriate location the ultrasound mini-probe or catheter is withdrawn and biopsy forceps are introduced into the working channel. Use of a guide sheath can help to keep the bronchoscope location fixed during the removal of the probe and insertion of biopsy instruments. Fluoroscopic assistance may also be used. Biopsy forceps are normally used to obtain a histological sample of the target lesion; however, biopsy needles can also be used.

List of studies included in the overview

This overview is based on 1484 patients from 3 randomised controlled trials (RCTs)[1,2,3], 3 non-randomised comparative studies[4,5,6], two crossover studies[7,9] and a case series[8].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Efficacy

Studies described below present data on diagnostic yield and diagnostic accuracy (sensitivity and specificity) which conceptually require comparison of the evaluated test with a 'gold standard' comparator. However, in the context of these studies no unique 'gold standard' test was available. Most studies appear to have treated all definitively positive cancer diagnoses obtained by EBUS-guided transbronchial biopsy (TBB) testing as true positives, without reference to a 'gold standard'. For those EBUS–TBB investigations that were negative, different confirmatory tests appear to have been employed for different patients, including other types of bronchoscopic lung biopsy, CT-guided percutanoues biopsy, surgical biopsy or natural course of illness.

Several of the studies summarised below also report efficacy outcomes for different lesion size subgroups. Sensitivity and specificity of the method does depend on lesion size (significantly lower for smaller lesions), but for brevity of the presentation and consistency, only overall results (for lesions of any size) are presented below. In those studies that such subgroup analysis is reported, the findings have been presented in the 2nd column of the relevant sections of Table 2.

An RCT of 293 patients compared 144 patients investigated with EBUS-guided TBB against 149 patients investigated with non-EBUS guided TBB. The study reported a diagnostic yield of 79% (48/61) for malignant lesions and 69% (18/26) for benign lesions in the EBUS–TBB group compared to 55% (46/83) and 44% (16/36) in the non-EBUS–TBB group[1].

An RCT of 202 patients comparing 103 patients investigated with EBUS transbronchial needle aspiration (TBNA) + TBB + bronchial washing (BW) against 99 patients investigated with EBUS–TBB + BW reported a diagnostic yield of 78% (69/88) in the EBUS–TBNA + TBB + BW group compared to 61% (57/94) in the EBUS–TBB + BW group ($p = 0.015$). For each procedure separately, the diagnostic yield was 63% (55/88) for TBNA, 49% (89/182) for TBB ($p = 0.049$ compared to TBNA) and 20% (36/182) for BW ($p < 0.001$ compared to TBNA)[2].

An RCT of 120 patients compared 39 patients investigated with EBUS–TBB against 39 patients investigated with electromagnetic navigation bronchoscopy (ENB)–TBB against 40 patients who were investigated with a combination of EBUS/ENB–TBB. This study reported a diagnostic yield of 69% (27/39) in the EBUS–TBB group, 59% (23/39) in the ENB–TBB group and 88% (35/40) in the EBUS/ENB–TBB group ($p = 0.02$)[3].

A non-randomised comparative study of 261 procedures compared 140 procedures using EBUS–TBB (using a guide sheath [GS]) with 121 procedures using percutaneous CT-guided fine needle aspiration (CT–FNA).

This study reported a sensitivity of 66% (93/140) in the EBUS–TBB group compared to 64% (77/121) in the CT–FNA group[4].

Two non-randomised comparative studies compared EBUS–TBB with non-EBUS–TBB: 218 patients (122 vs 96) and 92 patients (50 vs 42) reported overall accuracy of 66% (80/122)[5] and 84% (42/50)[6] respectively for EBUS–TBB compared to 43% (41/96) (p = 0.0007)[5] and 83% (35/42)[6] respectively for non-EBUS–TBB. The smaller of the two studies also used fluoroscopy to assist both procedures.

A crossover study of 107 patients compared EBUS-TBB with positron emission tomography (PET), and a combination of both. Overall diagnostic yield was significantly higher when both the tests were combined (91% 97/107), than in either the EBUS-TBB group (69% 74/107), or the PET group 79% (84/107) (p < 0.01)[9].

A crossover study of 50 patients compared EBUS–TBB with fluoroscopy TBB and reported diagnostic accuracy of 80% (40/50) in the EBUS group compared to 76% (38/50) in the fluoroscopy group[7].

A case series of 150 patients using EBUS (using a guide sheath)–TBB reported a diagnostic yield of 77% (116/150)[8].

Safety

Pneumothorax

An RCT of 293 patients reported pneumothorax in 3% (3/119) of patients undergoing TBB without EBUS guidance compared with 0% in patients undergoing EBUS-guided biopsy [1].

An RCT of 202 patients reported pneumothorax determined by chest radiograph taken 1 to 2 hours after the procedure in 2% (2/88) of patients in the EBUS–TBNA + TBB + BW group and 2% (2/94) of patients in the EBUS–TBB + BW group[2].

An RCT of 120 patients reported pneumothorax in 5% (2/39) of the EBUS–TBB group, 5% (2/39) in the ENB TBB group and 8% (3/40) in the combined EBUS/ENB–TBB group[3]. All patients with pneumothorax were admitted for observation. 4 were treated with chest drain insertion (3 with chest tubes and1 with a small bore catheter) and 1 was managed with manual aspiration and observation. The other 2 cases required observation and supplemental oxygen.

A non-randomised comparative study of 261 procedures reported pneumothorax in 1% (2/140) of patients in the EBUS–GS TBLB group compared with 22% (27/121) of patients in the percutaneous CT–FNA group (p < 0.01)[4].

A crossover study of 50 patients reported one case of pneumothorax treated by thoracostomy[7].

Bleeding

An RCT of 293 patients reported bleeding in 6% (7/119) of patients in the group where a TBB was taken without EBUS guidance in comparison to 0% in the EBUS-guided group[1].

An RCT of 202 patients reported bleeding in 5% (4/88) of patients in the EBUS–TBNA + TBB + BW group compared to 2% (2/94) of patients in the EBUS–TBB + BW group[2].

A non-randomised comparative study of 261 procedures reported bleeding in 1% (1/140) of patients in the EBUS–GS TBLB group compared with 3% (4/121) of patients in the percutaneous CT–FNA group[4].

A crossover study of 50 patients reported self-limited bleeding in 4% (2/50) of patients[7].

A case series of 150 patients reported moderate bleeding (≤ 30 ml) in 1% (2/150) of patients[8].

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to endobronchial ultrasound-guided transbronchial biopsy for peripheral lung lesions. Searches were conducted of the following databases, covering the period from their commencement to 12 August 2009 and updated to 24 November 2009: 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, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with peripheral lung lesions.
Intervention/test	Endobronchial ultrasound-guided transbronchial biopsy (EBUS–TBB)
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.

Existing reviews on this procedure

There were no published reviews identified at the time of the literature search.

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

- Endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal masses. NICE interventional procedures guidance 254 (2008). Available from www.nice.org.uk/IPG254

Clinical guidelines

- Lung cancer diagnosis and treatment. NICE clinical guideline 24 (2005). Available from www.nice.org.uk/CG24 [Review in progress. Expected publication date: March 2011]

Table 2 Summary of key efficacy and safety findings on endobronchial ultrasound-guided transbronchial biopsy for peripheral lung lesions

Abbreviations used: BW, bronchial washing; CT-FNA, computed tomography-guided fine needle aspiration; EBUS–GS TBLB, endobronchial ultrasound guide-sheath transbronchial lung biopsy; EBUS–TBB, endobronchial ultrasound-driven transbronchial biopsy; EBUS–TBNA, endobronchial ultrasound-driven transbronchial needle aspiration; ENB–TBB, electromagnetic navigation bronchoscopy transbronchial biopsy; NPV, negative predictive value; NS, not significant; PPV, positive predictive value; RCT, randomised controlled trial; TBB/TBBX, transbronchial biopsy

Study details	Key efficacy findings	Key safety findings	Comments
Paone G (2005)[1] **RCT** Italy Study recruitment period: 2001-–2003 Study population: patients with peripheral lung lesions n = **293 (144 vs 149)** Age: EBUS–TBB: 65 years (mean) TBB: 68 years (mean) Sex: EBUS–TBB: 71% (62/87) male TBB: 68% (81/119) male Patient selection criteria: patients must be aged 18+ years; inpatients; give informed consent; accept the randomisation protocol. Technique: EBUS–TBB (after localisation of the target lesion, the EBUS probe was removed and 5 biopsy samples were taken in the same place indicated by the probe using flexible TBB forceps) vs TBB (same number of samples removed in the same way as the EBUS–TBB group. The bronchoscope used for this procedure did not have ultrasound guidance and the location of the lesion was identified from a chest CT scan taken prior to the procedure). Both procedures were performed under local anaesthesia. Follow-up: **not reported** Conflict of interest/source of funding: not reported	Number of patients analysed: **206 (87 vs 119)** <u>Definite diagnosis obtained</u> EBUS–TBB: 75.8% (66/87) TBB: 52.1% (62/119) <u>Diagnostic yield</u> **Malignant lesions**: EBUS–TBBB 78.7% (48/61); TBB 55.4% (46/83) **Benign lesions**: EBUS–TBBB 69.2% (18/26); TBB 44.4% (16/36) <u>Diagnostics (all peripheral lung lesions)</u> **EBUS–TBB (n = 87)** / **TBB (n = 119)** / p value: Sensitivity (%): 78.7 (68.4 – 89) / 55.4 (44.7 – 66.1) / 0.004 Specificity (%): 100 / 100 / NS NPV (%): 66.7 (53.3 – 80) / 49.3 (34.9 – 63.8) / NS PPV (%): 100 / 100 / NS Accuracy (%): 85 (77.9 – 92.5) / 69 (60.6 – 77.2) / 0.007 <u>Diagnostics (lung lesion > 3 cm diameter)</u> **EBUS–TBB (n = 40)** / **TBB (n = 61)** / p value: Sensitivity (%): 82.8 (69 – 96.5) / 77.3 (64.9 – 89.7) / NS Specificity (%): 100 / 100 / NS NPV (%): 68.8 (50.2 – 87.3) / 63 (46.7 – 79.2) / NS PPV (%): 100 / 100 / NS Accuracy (%): 88 (77.3 – 97.7) / 84 (74.3 – 92.9) / NS	TBB group: Bleeding: 5.9% (7/119) Pneumothorax: 2.5% (3/119) No complication in the EBUS–TBB group	**Follow-up issues:** • 293 were randomised but only 221 (97 vs 124) received the interventions. This was because 28 decided to undergo lung surgery, 23 did not accept the randomisation procedure, 12 patients had a primary lesion diagnosed in another site and in 9 patients the peripheral lung lesion disappeared. A further 15 patients were unavailable for follow-up and are not included in the analysis. **Total dropout rate = 30%** (87/293) **Study design issues:** • Single centre • Randomisation satisfactory (used random numbers with a 1:1 allocation ratio) • All patients received a CT scan to determine the location and size of the peripheral lung lesion prior to the intervention. • Two study-blinded pathologists analysed the samples for histology. Unclear whether patients were blinded. Not possible to blind the study investigator. • Patients in whom the procedures did not provide a diagnosis underwent additional procedures (not described) to obtain a definitive diagnosis.

Abbreviations used: BW, bronchial washing; CT-FNA, computed tomography-guided fine needle aspiration; EBUS–GS TBLB, endobronchial ultrasound guide-sheath transbronchial lung biopsy; EBUS–TBB, endobronchial ultrasound-driven transbronchial biopsy; EBUS–TBNA, endobronchial ultrasound-driven transbronchial needle aspiration; ENB–TBB, electromagnetic navigation bronchoscopy transbronchial biopsy; NPV, negative predictive value; NS, not significant; PPV, positive predictive value; RCT, randomised controlled trial; TBB/TBBX, transbronchial biopsy

Study details	Key efficacy findings	Key safety findings	Comments

Diagnostics (lung lesion <3 cm diameter)

	EBUS–TBB (n = 47)	TBB (n = 58)	p value
Sensitivity	75 (60 – 90)	30.7 (16.3 – 45.3)	0.0002
Specificity	100	100	NS
NPV	65.2 (46.2 – 84.3)	41.3 (1.4 – 69.2)	NS
PPV	100	100	NS
Accuracy	83 (72.2 – 93.7)	53 (40.6 – 66.3)	0.001

Diagnostics (lung lesion ≤2 cm diameter)

	EBUS–TBB (n = 25)	TBB n = 31)	p value
Sensitivity	71 (47 – 95)	23 (3 – 43)	< 0.001
Specificity	100	100	NS
NPV	73 (46 – 100)	52 (3 – 100)	0.18
PPV	100	100	NS
Accuracy	84 (12 – 65)	58 (40 – 75)	0.07

Abbreviations used: BW, bronchial washing; CT-FNA, computed tomography-guided fine needle aspiration; EBUS–GS TBLB, endobronchial ultrasound guide-sheath transbronchial lung biopsy; EBUS–TBB, endobronchial ultrasound-driven transbronchial biopsy; EBUS–TBNA, endobronchial ultrasound-driven transbronchial needle aspiration; ENB–TBB, electromagnetic navigation bronchoscopy transbronchial biopsy; NPV, negative predictive value; NS, not significant; PPV, positive predictive value; RCT, randomised controlled trial; TBB/TBBX, transbronchial biopsy

Study details	Key efficacy findings	Key safety findings	Comments
Chao TY (2009)[2] **RCT** Taiwan Study recruitment period: 2005–2006 Study population: patients with peripheral pulmonary lesions (lesions that were not visible by standard bronchoscopy) n = **202 (103 vs 99)** Age: 62.3 years (mean) Sex: 61% (111/182) male Patient selection criteria: patients with findings of endobronchial lesions, extrinsic compression, submucosal infiltration or orifice narrowing on standard bronchoscopy were excluded. Patients who received repeat bronchoscopy, refused sampling procedures or refused the randomisation protocol were also excluded. Technique: EBUS–TBB and bronchial washing vs EBUS–TBNA, TBB and bronchial washing (procedure performed under local anaesthesia [lidocaine]). No guide sheath or fluoroscopic assistance used in either procedure. Once the location of the target lesion was diagnosed precisely by EBUS in both groups, the probe was marked with coloured tape against the orifice of the working channel. This assisted the investigator to be able to measure the distance to the lesion before inserting equipment to obtain the biopsy. Follow-up: **not reported** Conflict of interest/source of funding: none ('the authors have no conflict of interest to disclose')	Number of patients analysed: **182 (88 vs 94)** Definite diagnosis obtained EBUS–TBB: 75.8% (66/87) TBB: 52.1% (62/119) <u>Diagnostic yield</u> Overall: 69.2% (126/182) **Diagnostic yield of 3 different procedures** **Diagnostic yield of 3 different procedures** All p values are comparison with TBNA	EBUS–TBNA, TBB + BW group Bleeding: 4.5% (4/88) Pneumothorax (determined by chest radiograph 1–2 hours after procedures): 2.3% (2/88) EBUS–TBB + BW group Bleeding: 2.1% (2/94) Pneumothorax (determined by chest radiograph 1–2 hours after procedures): 2.1% (2/94) No difference in complication rates between groups. All complications were self limiting and none required tube thoracostomy or endotracheal intubation.	**Follow-up issues:** • 202 were randomised but only 182 (94 vs 88) were analysed. **Dropout rate = 9.9%** (20/202). In the EBUS–TBNA, TBB + BW group 11 did not complete the study (3 described as lost, 1 failed TBNA, 2 could not tolerate the procedure and 5 had bacterial pneumonia). In the EBUS–TBB + BW group 9 did not complete the study (4 described as lost, 3 could not tolerate the procedure and 2 had bacterial pneumonia). **Study design issues:** • Single centre • Method of randomisation was not stated. • TBNA and TBB: 3 aspirates/ specimens per lesion were obtained. • All specimens were analysed by 2 study-blinded cytopathologists. • If diagnosis could not be made by bronchoscopy, further workup included chest ultrasonography-guided trans-thoracic biopsy, CT-guided biopsy or operation. When no histological diagnosis could be made, the final diagnosis was obtained by clinical follow-up and therapeutic response.

	EBUS–TBNA, TBB + BW	EBUS–TBB + BW	p value
Overall	78.4% (69/88)	60.6% (57/94)	0.015
Malignant	79.2% (57/72)	56.5% (39/69)	0.006
Benign	75% (12/16)	72% (18/25)	NS

	TBNA (n = 88)	TBB (n = 182)	BW (n = 182)
No. positive samples	55	89	36
Diagnostic rates	62.5%	48.9% (p = 0.049)	19.8% (p < 0.001)
Diagnostic sensitivity for malignancy	72.2% (52/72)	50.4% (71/141) p = 0.004	13.5% (19/141) p < 0.001
Diagnostic sensitivity for benign	18.8% (3/16)	43.9% (18/41) p = NS	41.5% (17/41) p= NS

Abbreviations used: BW, bronchial washing; CT-FNA, computed tomography-guided fine needle aspiration; EBUS–GS TBLB, endobronchial ultrasound guide-sheath transbronchial lung biopsy; EBUS–TBB, endobronchial ultrasound-driven transbronchial biopsy; EBUS–TBNA, endobronchial ultrasound-driven transbronchial needle aspiration; ENB–TBB, electromagnetic navigation bronchoscopy transbronchial biopsy; NPV, negative predictive value; NS, not significant; PPV, positive predictive value; RCT, randomised controlled trial; TBB/TBBX, transbronchial biopsy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**

Abbreviations used: BW, bronchial washing; CT-FNA, computed tomography-guided fine needle aspiration; EBUS–GS TBLB, endobronchial ultrasound guide-sheath transbronchial lung biopsy; EBUS–TBB, endobronchial ultrasound-driven transbronchial biopsy; EBUS–TBNA, endobronchial ultrasound-driven transbronchial needle aspiration; ENB-TBB, electromagnetic navigation bronchoscopy transbronchial biopsy; NPV, negative predictive value; NS, not significant; PPV, positive predictive value; RCT, randomised controlled trial; TBB/TBBX, transbronchial biopsy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**

Abbreviations used: BW, bronchial washing; CT-FNA, computed tomography-guided fine needle aspiration; EBUS–GS TBLB, endobronchial ultrasound guide-sheath transbronchial lung biopsy; EBUS–TBB, endobronchial ultrasound-driven transbronchial biopsy; EBUS–TBNA, endobronchial ultrasound-driven transbronchial needle aspiration; ENB–TBB, electromagnetic navigation bronchoscopy transbronchial biopsy; NPV, negative predictive value; NS, not significant; PPV, positive predictive value; RCT, randomised controlled trial; TBB/TBBX, transbronchial biopsy

Study details	Key efficacy findings	Key safety findings	Comments

Eberhardt R (2007)[3]

RCT
Germany, Israel and USA
Study recruitment period: 2003–2006

Study population: patients with evidence of peripheral lung lesions (lesions surrounded by normal lung parenchyma without any CT evidence of endobronchial abnormalities) or solitary nodules on CT scan

n = **120**
Age: 53 years (mean) (range: 19–81 years)
Sex: 58% (68/118) male

Patient selection criteria: patients aged 18+ years, had signed consent form and were candidates for bronchoscopy or surgery were included. Patients who were pregnant or had implantable pacemakers or defibrillators were excluded.

Technique: EBUS–TBB (guide sheath or extended working channel used) vs ENB-TBB (patients placed in electromagnetic location board and probe guided to site of lesions by multi-planar CT images) vs combination EBUS/ENB TBB (ENB used to navigate to lesion and then EBUS probe inserted through extended working channel to confirm location before taking biopsy with forceps). Moderate sedation or general anaesthesia was used at the discretion of the investigator to perform the procedures. All procedures performed on outpatient basis and no fluoroscopy was used.

Follow-up: **not reported**
Conflict of interest/source of funding: none (none of the authors who participated in the consent or randomisation of patients had a financial relationship with the commercial entity)

Number of patients analysed: **118 (39 vs 39 vs 40)**

Definite diagnosis obtained: 72% (85/118). The remaining 33 patients required a subsequent surgical biopsy (gold standard) to establish histological diagnosis.

Diagnostic yield

	EBUS–TBB (n = 39)	ENB-TBB (n = 39)	ENB/EBUS–TBB (n = 40)	p value
Size of lesions (mm)	25 ± 5	28 ± 8	24 ± 5	0.03
Overall diagnostic yield	69.2% (27/39)	58.9% (23/39)	87.5% (35/40)	0.02

Diagnostic yield by lesion size

	≤20 mm	20–30 mm	>30 mm	p value
EBUS–TBB	77.8% (7/9)	69.6% (16/23)	57.1% (4/7)	0.8
ENB-TBB	75% (3/4)	50% (11/22)	69.2% (9/13)	0.5
ENB/EBUS–TBB	90% (9/10)	87.5% (21/24)	83.3% (5/6)	0.99

Diagnosis

	EBUS–TBB (n = 39)	ENB-TBB (n = 39)	ENB/EBUS–TBB (n = 40)	p value
Malignant lesions	82.1% (32/39)	74.4% (29/39)	77.5% (31/40)	0.71
Benign lesions	17.9% (7/39)	25.6% (10/39)	22.5% (9/40)	0.71

EBUS–TBB group:
pneumothorax: 5.1% (2/39)

ENB-TBB group:
pneumothorax: 5.1% (2/39)

ENB/EBUS–TBB group:
pneumothorax: 7.5% (3/40)

No statistically significant difference in pneumothorax rates between groups

All patients with pneumothorax were admitted for observation. 4 were treated with chest drains (3 with chest tubes and 1 with a small-bore catheter) and 1 was managed with manual aspiration and observation. The other 2 cases required observation and supplemental oxygen.

No cases of bleeding that required therapeutic interventions were recorded.

Follow-up issues:

- 120 were randomised but only 118 (39 vs 39 vs 40) were analysed. **Dropout rate = 1.7%.** All patients with failed bronchoscopic diagnosis and who were unwilling or unable to have surgical biopsy were excluded from final analysis.

Study design issues:

- Multicentre
- Method of randomisation is satisfactory (computer-generated random number list used).

Study population issues:

- No clinically significant differences in baseline characteristics (age, sex and type of anaesthesia used) between groups except size of lesions.

Abbreviations used: BW, bronchial washing; CT-FNA, computed tomography-guided fine needle aspiration; EBUS–GS TBLB, endobronchial ultrasound guide-sheath transbronchial lung biopsy; EBUS–TBB, endobronchial ultrasound-driven transbronchial biopsy; EBUS–TBNA, endobronchial ultrasound-driven transbronchial needle aspiration; ENB-TBB, electromagnetic navigation bronchoscopy transbronchial biopsy; NPV, negative predictive value; NS, not significant; PPV, positive predictive value; RCT, randomised controlled trial; TBB/TBBX, transbronchial biopsy

Study details	Key efficacy findings	Key safety findings	Comments

Malignant disease

	EBUS–TBB	ENB-TBB	ENB/EBUS–TBB	p value
Sensitivity	71.9% (23/32)	55.2% (16/29)	90.3% (28/31)	0.009
Specificity	100% (7/7)	100% (10/10)	100% (9/9)	–
PPV	100% (23/23)	100% (16/16)	100% (28/28)	–
NPV	43.7% (7/16)	43.5% (10/23)	75% (9/12)	0.16

Benign disease

	EBUS–TBB	ENB-TBB	ENB/EBUS–TBB	p value
Sensitivity	57.1% (4/7)	70% (7/10)	77.8% (7/9)	0.79
Specificity	100% (32/32)	100% (29/29)	100% (31/31)	–
PPV	100% (4/4)	100% (7/7)	100% (7/7)	–
NPV	91.4% (32/35)	90.6% (29/32)	93.9% (31/33)	0.9

Abbreviations used: BW, bronchial washing; CT-FNA, computed tomography-guided fine needle aspiration; EBUS–GS TBLB, endobronchial ultrasound guide-sheath transbronchial lung biopsy; EBUS–TBB, endobronchial ultrasound-driven transbronchial biopsy; EBUS–TBNA, endobronchial ultrasound-driven transbronchial needle aspiration; ENB-TBB, electromagnetic navigation bronchoscopy transbronchial biopsy; NPV, negative predictive value; NS, not significant; PET, positron emission tomography; PPV, positive predictive value; RCT, randomised controlled trial; TBB/TBBX, transbronchial biopsy

Study details	Key efficacy findings	Key safety findings	Comments
Mizugaki H, (2009)[9] **Non-randomised comparative study** Japan Study recruitment period: 2003 to 2006 Study population: patients with small peripheral pulmonary lesions ≤30mm. n = **107 (107 crossover design)** Age: not stated Sex: not stated Patient selection criteria: patients with endobronchial disease were excluded. Technique: EBUS–GS TBB under local anaestheic and biopsy with fluoroscopic guidance vs PET scan vs combination of both techniques. Follow-up: **not reported** Conflict of interest/source of funding: none	Number of patients analysed: **107** Diagnostic yield EBUS–TBB (n = 107) / PET (n = 107) / Both (n=107) / p= Size of lesions (mm): 21.7 ± 6.1 mm / N/A / N/A Overall diagnostic yield: 69.2% (74/107) / 78.5% (84/107) / 90.7 (97/107) / <0.01* Lesions <20mm: 54.5% (24/44) / 70.5% (31/44) / 81.8% (36/44) Lesions 20mm to 30mm: 76.2% (48/63) / 84.1% (53/63) / 96.8 (61/63) / <0.05* p= size: < 0.05 / < 0.01 / Not reported Benign lesions: 50.0% / 56.3% / 68.8% / Not significant Malignent lesions: 72.5% / 82.4% / 94.5% / <0.01* P = status: < 0.05 / < 0.01 / Not reported *p value for both Vs EBUS-TBB and PET Final diagnosis of peripheral lung lesion achieved by Video assisted thoracoscopic surgery , percutaneous needle biopsy, or clinical/radiographic follow up In the combined EBUS TBB and PET group diagnostic sensitivity was 94.5% and specificity was 68.8% In the combined group 10 lesions were not identified, n = 3 adenocarcinoma, n = 1 large cell carcinoma, n = 1 metastasis of renal cell carcinoma, n = 5 benign lesions.	Safety outcomes were not reported on	**Follow-up issues:** • Retrospective analysis. **Study design issues:** • Not all outcomes/analysis were reported for all groups • Not clear whether sensitivity and specificity relates to identification of lesions or prediction of malignancy. **Study population issues:** • Patient accrual method not described.

Fielding DI (2008)[4]

Non-randomised comparative study
Australia
Study recruitment period:
EBUS–GS TBLB: 2003–2006; CT FNA: 2005–2006

Study population: patients with peripheral lung lesions (solitary pulmonary nodules or persistent small subsegmental infiltrates affecting one or two subsegments)

n = **252 (138 vs 114) (261 [140 vs 121] procedures)**
Age: EBUS–GS TBLB: 63 years (mean); CT-FNA: 64 years (mean)
Sex: EBUS–GS TBLB: 52% (73/140) male; CT-FNA: 58% (70/121) male

Patient selection criteria: patients with endobronchial disease were excluded.

Technique: EBUS–GS TBLB (under conscious sedation and fluoroscopy used to ensure that the ultrasound probe did not reach the visceral pleura and allow observation of biopsy forceps opening) vs percutaneous CT-guided fine needle aspiration (CT-FNA). All patients had a chest X-ray following the procedures.

Follow-up: **not reported**

Conflict of interest/source of funding: none (no funding received for the study and the authors reported no potential conflicts of interest)

Number analysed: **261 (140 vs 121) procedures**

	EBUS–GS TBLB (n = 140)	CT-FNA (n = 121)
Size of lesions (mm)	29 ± 12 (range: 8–80)	37 ± 22.5 (range: 6–120)
Lesion touching visceral pleura	16.4% (23/140)	31% (38/121)
Specimen positive (sensitivity)	66.4% (93/140)	63.6% (77/121)
Malignant sensitivity	63% (46/73)	75% (64/85)
Benign sensitivity	70% (46/65)	32% (9/29)

No p values reported for the above outcomes

In the EBUS group, there was a significantly lower sensitivity for lesions touching the visceral pleura (35%, 8/23) compared to those not touching (74%, 86/117) (p<0.001). No difference noted in the CT-FNA group.

	EBUS–GS TBLB (n = 140)	CT-FNA (n = 121)	p value
Pneumothorax	1.4% (2/140)	22.3% (27/121)	<0.01
Intercostal catheter	0	7% (8/121)	<0.01
Unplanned admissions	1.4% (2/140) (average length of stay 1 day)	7.4% (9/121) (average length of stay 1.8 days)	<0.01
Bleeding	0.7% (1/140)*	3.3% (4/121)	NR
Haemoptysis	0	9.1% (11/121)	NR

* <50 ml in an elderly patient due to inflamed proximal bronchial wall caused by minor abrasion from the bronchoscope

In the CT-FNA group the rate of pneumothorax was significantly lower in cases where the lesion touched the visceral pleura in comparison with lesions surrounded by lung tissue (2.6% vs 31.7%, p = 0.0001).

Perilesional emphysema was seen in 22% of pneumothorax

cases but this was not significant (p = 0.07) compared with the pneumothorax

Follow-up issues:

- Only patients who underwent biopsy were reported. Unclear how many patients were excluded by this criteria.

Study design issues:

- EBUS–GS TBLB is a prospective case series. CT-FNA is a retrospective case series.
- Final diagnosis obtained from biopsy (EBUS–GS TBLB or CT-FNA), subsequent lesion resection or radiological resolution.

Study population issues:

- The authors do not comment on how comparable the 2 groups are in terms of baseline characteristics. No statistical analysis performed.

Abbreviations used: BW, bronchial washing; CT-FNA, computed tomography-guided fine needle aspiration; EBUS–GS TBLB, endobronchial ultrasound guide-sheath transbronchial lung biopsy; EBUS–TBB, endobronchial ultrasound-driven transbronchial biopsy; EBUS–TBNA, endobronchial ultrasound-driven transbronchial needle aspiration; ENB-TBB, electromagnetic navigation bronchoscopy transbronchial biopsy; NPV, negative predictive value; NS, not significant; PET, positron emission tomography; PPV, positive predictive value; RCT, randomised controlled trial; TBB/TBBX, transbronchial biopsy

Study details	Key efficacy findings	Key safety findings	Comments
		rate in the CT-FNA group where there was no emphysema.	

Abbreviations used: BW, bronchial washing; CT-FNA, computed tomography-guided fine needle aspiration; EBUS–GS TBLB, endobronchial ultrasound guide-sheath transbronchial lung biopsy; EBUS–TBB, endobronchial ultrasound-driven transbronchial biopsy; EBUS–TBNA, endobronchial ultrasound-driven transbronchial needle aspiration; ENB-TBB, electromagnetic navigation bronchoscopy transbronchial biopsy; NPV, negative predictive value; NS, not significant; PET, positron emission tomography; PPV, positive predictive value; RCT, randomised controlled trial; TBB/TBBX, transbronchial biopsy			
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Abbreviations used: BW, bronchial washing; CT-FNA, computed tomography-guided fine needle aspiration; EBUS–GS TBLB, endobronchial ultrasound guide-sheath transbronchial lung biopsy; EBUS–TBB, endobronchial ultrasound-driven transbronchial biopsy; EBUS–TBNA, endobronchial ultrasound-driven transbronchial needle aspiration; ENB-TBB, electromagnetic navigation bronchoscopy transbronchial biopsy; NPV, negative predictive value; NS, not significant; PET, positron emission tomography; PPV, positive predictive value; RCT, randomised controlled trial; TBB/TBBX, transbronchial biopsy

Study details	Key efficacy findings	Key safety findings	Comments

Yang MC (2004)[5]

Non-randomised comparative study
Taiwan
Study recruitment period: 2001–2002

Study population: patients with bronchoscopically invisible peripheral malignant lung tumours (confirmed by biopsy or surgical resection histological examination, cytological diagnosis or clinical course)

n = **218 (122 vs 96)**

Age: EBUS: 66 years (mean), non-EBUS: 64.3 years (mean)

Sex: EBUS: 66% (80/122) male, non-EBUS: 65% (62/96) male

Patient selection criteria: patients diagnosed with benign lesions

Technique: EBUS–TBLB (no guide sheath or fluoroscopy used) vs non-EBUS–TBLB (performed using conventional flexible fibre-optic bronchoscopy). All procedures performed under local anaesthesia and all patients had a chest X-ray or CT scan before the procedure.

Follow-up: **not reported**

Conflict of interest/source of funding: not reported

Number of patients analysed: **218 (122 vs 96)**

Diagnostic accuracy

	EBUS–TBLB (n = 122)	Non-EBUS–TBLB (n = 96)	p value
Overall	65.6% (80/122)	42.7% (41/96)	0.0007
Small cell carcinoma	88.9% (8/9)	22.2% (2/9)	0.0044
Non-small-cell carcinoma	67.7% (67/99)	50.0% (35/70)	0.0207
Metastatic carcinoma	35.7% (5/14)	23.5% (4/17)	0.457
Lesions <2 cm	54.5% (6/11)	0.0% (0/5)	<0.04
Lesions >2 cm	66.0% (68/103)	42.3% (33/78)	<0.002
Lesions with a well defined margin (mass type)	64.9% (74/114)	39.8% (33/83)	<0.001
Lesions without definite margin (infiltrate type)	75.0% (6/8)	61.5% (8/13)	<0.53

Multivariate analysis (see below) indicates factors that are significantly associated with predicting diagnostic accuracy of transbronchial lung biopsy. The findings show that tumours located in the left upper lobe are harder to diagnose using TBLB and that use of EBUS and presence of primary lung cancer significantly increase diagnostic yield.

	Regression coefficient	OR (95% CI)	p value
Left upper lobe	–1.518	0.219 (0.065 – 0.735)	0.014
Tumour origin	1.74	5.697 (1.974 – 16.445)	0.001
EBUS guidance	1.018	2.768 (1.523 – 5.031)	0.001

No bleeding, pneumothorax or respiratory distress reported in either group during or after the procedures. There were no significant differences in cough or chest pain between the two groups during or after the procedure (figures not reported).

Study design issues:

- Retrospective study
- Included cases were chosen after a diagnosis of malignant lung tumour was made. The 122 EBUS patients are a subset of 408 patients who had EBUS–TBLB for suspected peripheral lung lesion.
- Independent pathologist made histological examination and interpretation of the biopsy specimens. A second independent pathologist reviewed any cases the first pathologist was unsure of.
- If bronchoscopic examination did not produce a diagnosis, other methods were used including repeat procedure, chest echo, CT-guided mass aspiration/biopsy, pleural effusion study, pleural biopsy or operation.

Study population issues:

- No significant difference in cell type of pattern of lung lesions between the two groups.

Abbreviations used: BW, bronchial washing; CT-FNA, computed tomography-guided fine needle aspiration; EBUS–GS TBLB, endobronchial ultrasound guide-sheath transbronchial lung biopsy; EBUS–TBB, endobronchial ultrasound-driven transbronchial biopsy; EBUS–TBNA, endobronchial ultrasound-driven transbronchial needle aspiration; ENB-TBB, electromagnetic navigation bronchoscopy transbronchial biopsy; NPV, negative predictive value; NS, not significant; PET, positron emission tomography; PPV, positive predictive value; RCT, randomised controlled trial; TBB/TBBX, transbronchial biopsy			
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Study details	Key efficacy findings	Key safety findings	Comments

Shirakawa T (2004)[6]

Non-randomised comparative study
Japan
Study recruitment period: EBUS + fluoroscopy: 2001; fluoroscopy only: 1999–2000

Study population: patients with normal visible airways with peripheral lung lesions

n = **92 (50 vs 42)**

Age: EBUS + fluoroscopy: 68.4 years (mean); fluoroscopy: 65.3 years (mean)

Sex: EBUS + fluoroscopy: 54% (27/50) male; fluoroscopy: 52% (22/42) male

Patient selection criteria: patients had to give informed consent.

Technique: EBUS–TBB assisted by fluoroscopy (catheter sheath used in 21 patients) vs TBB assisted by fluoroscopy only.

Follow-up: **not reported**

Conflict of interest/source of funding: supported by a grant from the Japanese Foundation for Research and Promotion of Endoscopy.

Number of patients analysed: **92 (50 vs 42)**

	EBUS + fluoroscopy (n = 50)	Fluoroscopy only (n = 42)
Lung cancer	48% (24/50)	54.8% (23/42)
Benign disease	50% (25/50)	45.2% (19/42)
No diagnosis	2% (1/50)	0
Biopsy tools inserted into lesion	66% (33/50)	76.2% (32/42)
Overall accuracy (distinguishing between lung cancer and benign disease)	84% (42/50)	83.3% (35/42)
Accuracy when biopsy tools inserted into lesion	100% (33/33)*	87.5% (28/32)

*p=0.02

Patients diagnosed with lung cancer

	EBUS + fluoroscopy	Fluoroscopy only	p value
Sensitivity	70.8% (17/24)	69.6% (16/23)	NR
Specificity	75.8% (25/33)	73.1% (19/26)	NR
Sensitivity where biopsy tools reach the lesion	100.0% (15/15)	75.0% (12/16)	0.06
Sensitivity where unclear if biopsy tool reached lesion	33.3% (1/3)	66.7% (4/6)	NR
Sensitivity where biopsy tools did not reach lesion	16.7% (1/6)	0% (0/1)	NR
Specificity when clear image obtained	100.0% (18/18)	80.0% (16/20)	0.02

	Biopsy tools able to reach the lesion	Unclear if biopsy tool reached lesion	Biopsy tools did not reach lesion
Patients in EBUS group who had to change position (n = 45)	16.7% (5/30)	60.0% (3/5)	90.0% (9/10)*

*repeated position changes required

Not reported

Study design issues:

- Prospective study
- Patients in EBUS group had been randomly allocated; however, the control group used in this study does not appear to be the patients who were not allocated to EBUS as they are from a different time period before EBUS was introduced in the hospital.
- Diagnosis based on results of bronchoscopy, symptoms, signs, clinical course, X-ray and CT images. 7 patients in the EBUS group and 7 patients in the fluoroscopy group who tested negative for lung cancer after TBB were found later to have lung cancer by another method (CT-guided needle aspiration cytology, ultrasound-guided needle aspiration cytology, cytology of sputum or surgical procedures). It is unclear if all patients who were negative after TBB were tested using another method.
- Authors note that they sometimes failed to introduce the forceps to the same place as the US probe and so they used a catheter sheath in 21 cases which proved efficient in 76.2% (16/21).

Study population issues:

- Authors report that the patient groups were comparable. No statistical tests performed.

Abbreviations used: BW, bronchial washing; CT-FNA, computed tomography-guided fine needle aspiration; EBUS–GS TBLB, endobronchial ultrasound guide-sheath transbronchial lung biopsy; EBUS–TBB, endobronchial ultrasound-driven transbronchial biopsy; EBUS–TBNA, endobronchial ultrasound-driven transbronchial needle aspiration; ENB-TBB, electromagnetic navigation bronchoscopy transbronchial biopsy; NPV, negative predictive value; NS, not significant; PPV, positive predictive value; RCT, randomised controlled trial; TBB/TBBX, transbronchial biopsy

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Herth FJF (2002)[7]

Crossover study
Germany, Israel, USA
Study recruitment period: 2000–2001

Study population: patients with peripheral lung lesions

n = 50

Age: 62.5 years (mean)

Sex: 74% (37/50) male

Patient selection criteria: see above.

Technique: all patients had EBUS–TBBX and fluoroscopic TBBX in random order. A minimum of 4 specimens were taken for each procedure. General anaesthesia or conscious sedation were used. All patients had a chest CT prior to the procedure and the size of lesions recorded by their longest diameter.

Follow-up: not reported

Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: 50

Mean diameter of lesion: 3.31 ± 0.92 cm
Mean number of specimens taken:
EBUS: 4.34 ± 0.55
Fluoroscopy: 4.56 ± 0.61

<table>
<tr><th></th><th>EBUS–TBBX (n = 50)</th><th>Fluoroscopy TBBX (n = 50)</th></tr>
<tr><td>Overall diagnostic accuracy</td><td>80% (40/50)</td><td>76% (38/50)*</td></tr>
<tr><td>Accuracy for malignant disease</td><td>80% (36/45)</td><td>78% (35/45)</td></tr>
<tr><td>Accuracy for benign disease</td><td>80% (4/5)</td><td>60% (3/5)</td></tr>
<tr><td>Accuracy for lesions in upper lobes</td><td>84% (32/38)</td><td>87% (33/38)</td></tr>
<tr><td>Accuracy for lesions in lower/middle lobes</td><td>67% (8/12)</td><td>42% (5/12)</td></tr>
<tr><td>Accuracy for lesions <3cm</td><td>81% (17/21)</td><td>57% (12/21)</td></tr>
<tr><td>Accuracy for lesions >3cm</td><td>79% (23/29)</td><td>90% (26/29)</td></tr>
</table>
*no significant difference between groups

In the EBUS group, 4 lesions could not be localised (all in right upper lobe).

In 18% (9/50) of patients the diagnosis obtained by bronchoscopy saved a surgical procedure (2 sarcoidosis, 2 tuberculosis, 1 infection, 1 metastatic disease and 3 small-cell lung cancer)</td>
<td>Self-limited bleeding: 4% (2/50)

Pneumothorax treated by thoracostomy: 2% (1/50)

Unclear which of the procedures caused the complications above.

No severe bleeding or deaths occurred with the diagnostic procedures.</td>
<td>Study design issues:
Prospective study
Patients had procedures in random order.
Forceps were changed between EBUS and fluoroscopic examinations to avoid cellular cross-contamination.
The histological results were compared for the two methods.
All patients for whom a definite diagnosis could not be made from EBUS or fluoroscopy TBBX had a surgical procedure.
Patient population issues:
86% (43/50) were smokers.
No difference in diagnostic yield when analysing patient subgroups by age, sex or smoking habit.
Other issues:
Percentages for accuracy of lesion <3 cm in the EBUS group and accuracy of lesion >3 cm in the fluoroscopy group are inaccurate in the paper based on the figures given (80% and 89% respectively) and were recalculated by IP analyst.</td>
</tr>
</table>

Abbreviations used: BW, bronchial washing; CT-FNA, computed tomography-guided fine needle aspiration; EBUS–GS TBLB, endobronchial ultrasound guide-sheath transbronchial lung biopsy; EBUS–TBB, endobronchial ultrasound-driven transbronchial biopsy; EBUS–TBNA, endobronchial ultrasound-driven transbronchial needle aspiration; ENB-TBB, electromagnetic navigation bronchoscopy transbronchial biopsy; NPV, negative predictive value; NS, not significant; PPV, positive predictive value; RCT, randomised controlled trial; TBB/TBBX, transbronchial biopsy

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Kurimoto N (2004)[8]

Case series
Japan
Study recruitment period: 2001–2002

Study population: patients with solitary peripheral pulmonary lesions detected by CT and chest X-ray

n = 150

Age: not reported

Sex: not reported

Patient selection criteria: see above

Technique: all patients had EBUS–GS TBB where either biopsy forceps and/or a bronchial brush were used to obtain a sample. Fluoroscopy was also used during this procedure.

Follow-up: not reported

Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: 150

<table>
<tr><th></th><th>Brushing</th><th>Forceps</th><th>p value</th><th>Combined</th></tr>
<tr><td>% of procedures where diagnosis could be made (diagnostic yield)</td><td>60% (90/150)</td><td>80.9% (89/110)</td><td>NR</td><td>77.3% (116/150)</td></tr>
<tr><td>Diagnostic yield for malignant disease</td><td>71% (71/100)</td><td>86.7% (65/75)</td><td>0.01</td><td>81.2% (82/101)</td></tr>
<tr><td>Diagnostic yield for benign disease</td><td>38% (19/50)</td><td>68.6% (24/35)</td><td>0.002</td><td>69.3% (34/49)</td></tr>
</table>
In the remaining 34 patients in whom a diagnosis could not be made from EBUS–GS TBB, 5.9% (2/34) were diagnosed using transthoracic needle aspiration, 70.6% (24/34) by thoracotomy, 5.9% (2/34) by post-bronchoscopic sputum and in 17.6% (6/34) tissue diagnosis could not be made. The last 6 patients were considered to have inflammatory lesions when the roentgenographic shadows disappeared during follow-up.

<table>
<tr><th></th><th>Brushing</th><th>Forceps</th><th>Combined</th></tr>
<tr><td>Probe located within lesion</td><td>66.9% (81/121)</td><td>82.3% (79/96)</td><td>86.8% (105/121)</td></tr>
<tr><td>Probe located adjacent to lesion</td><td>36.8% (7/19)</td><td>7.1% (1/14)</td><td>42.1% (8/19)</td></tr>
<tr><td>P value</td><td>NR</td><td><0.0001</td><td><0.0001</td></tr>
</table>

<table>
<tr><th>Lesion size</th><th>Diagnostic yield</th></tr>
<tr><td>≤10 mm</td><td>76.2% (16/21)</td></tr>
<tr><td>>10 to ≤15 mm</td><td>76% (19/25)</td></tr>
<tr><td>>15 to ≤20 mm</td><td>68.6% (24/35)</td></tr>
<tr><td>>20 to ≤30 mm</td><td>76.7% (33/43)</td></tr>
<tr><td>≤30 mm</td><td>74.2% (92/124)</td></tr>
<tr><td>>30 mm</td><td>92.3% (24/26)*</td></tr>
</table>
*p = 0.04 compared to diagnostic yield for lesions ≤30 mm

10 lesions could not be imaged by EBUS – in these cases a curette was inserted and then the EBUS probe reinserted when lesion located. Diagnostic yield: 30% (3/10) using this method.</td>
<td>Moderate bleeding (≤30 ml): 1.3% (2/150)

No severe bleeding pneumothorax, death or other significant clinical morbidity occurred.</td>
<td>Study design issues:
• Prospective study

Patient population issues:
• No demographic data reported for this study.</td>
</tr>
</table>

Validity and generalisability of the studies

- The length of follow-up is not reported in any of the studies.
- None of the studies test all patients with the same 'gold standard' (for example, surgical biopsy) in addition to the procedure of interest; therefore it is uncertain whether the sensitivity and specificity results are accurate.
- Only one of the studies[4] included in table 2 compares EBUS-guided TBB to percutaneous CT-guided FNA which is the diagnostic method most widely used to investigate peripheral lung lesions that are not visible at conventional bronchoscopy in the UK.
- Efficacy data chiefly relate to diagnostic accuracy – no studies examined other potential efficacy outcomes, such as impact on timeliness of treatment (post-diagnosis), avoidance of repeat appointments/procedures, patient preference for this procedure compared to percutaneous biopsy testing, and so on.
- Safety data relate to pneumothorax development and bleeding, not consideration of the safety aspects of potential false negatives (or false positives).

Specialist Advisers' opinions

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

Mr Mohammed Munavvar, Mr Robert C Rintoul, Mr Pallav Shah and Dr Kristopher M Skwarski (British Thoracic Society [BTS]) and Mr Jagan Rao (Society for Cardiothoracic Surgery in Great Britain and Ireland [SCTS]).

- One of the Specialist Advisers has performed this procedure at least once and the other four Specialist Advisers have never performed this procedure. Three of the Advisers stated that this procedure is not practiced in the UK.
- One Specialist Adviser stated that this procedure is established practice, two others considered this to be a minor variation on an existing procedure that is unlikely to alter the procedure's safety and efficacy, and one Adviser stated that this is a novel procedure in the UK but established elsewhere.

- Comparators suggested by the Specialist Advisers were CT-guided transthoracic lung biopsy (standard practice) and transbronchial lung biopsy (with or without fluoroscopic guidance).
- Theoretical adverse events were pneumothorax, bleeding and false negative results.
- Adverse events reported in the literature: one Adviser stated that the risk should be less than current standard blind transbronchial lung biopsy (pneumothorax: 2%, haemorrhage: 2–5% and failed procedure: 5% in the literature). The other Adviser reported that the levels of pneumothorax in the literature are low (1–5%) compared to 25% for CT-guided biopsy. One of the Advisers stated that the procedure seems quite safe.
- Efficacy outcome: diagnostic yield, sensitivity, specificity, positive and negative predictive values, avoidance of CT-guided procedures (that is, reducing radiation exposure for the patient), patient acceptability and time taken to perform procedure were all suggested. One Specialist Adviser stated that the literature indicates that sensitivity is dependent on size of lesion and ability to localise the lesion with the ultrasound probe. He stated that the literature shows sensitivity of 65–84%.
- One Specialist Adviser stated that the potential benefits are shorter hospital stay, reduced need for repeat fibre-optic bronchoscopy and biopsy, reduced need for open surgical biopsy or radiation exposure from CT-guided biopsy techniques.
- Training and facilities: the procedure should be performed by a competent, fully trained bronchoscopist with access to radial ultrasound miniprobes in a bronchoscopy unit with standard safety equipment. Visiting overseas centres where this procedure is performed would be sensible and input from radiology to help with localisation and pathology for optimising biopsies is also important.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme was unable to obtain patient commentary for this procedure.

Issues for consideration by IPAC

- Future studies: RCT completed in Taiwan in March 2009 (yet to be published) looking at EBUS–TBB with vs without a guide sheath. Target enrollment: 180.

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Appendix A: Additional papers on endobronchial ultrasound-guided transbronchial biopsy for peripheral lung lesions

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

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Lie CH, Chao TY, Chung YH et al. (2009) New image characteristics in endobronchial ultrasonography for differentiating peripheral pulmonary lesions. Ultrasound in Medicine & Biology 35:376-381.	Case series n = 193 Follow-up: not reported (NR)	Active bleeding: 14.3% No pneumothorax	Larger/comparative studies included in table 2 No useful efficacy data – patients had either TBB, TBNA, BAL, CT-guided biopsy or surgery to establish diagnosis.
Yamada N, Yamazaki K, Kurimoto N et al. (2007) Factors related to diagnostic yield of transbronchial biopsy using endobronchial ultrasonography with a guide sheath in small peripheral pulmonary lesions. Chest 132:603-608.	Case series n = 155 Follow-up: NR	Definite diagnosis: 67% Diagnostic yield: Probe inserted in lesion: 83% Probe adjacent to lesion: 61% Probe outside lesion: 4% ($p < 0.001$) lesions ≤15 mm: 40% lesions >15 mm: 76% ($p < 0.001$)	Larger/comparative studies included in table 2 Contains so safety data.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Yoshikawa M, Sukoh N, Yamazaki K et al. (2007) Diagnostic value of endobronchial ultrasonography with a guide sheath for peripheral pulmonary lesions without X-ray fluoroscopy. Chest 131:1788–93.	Case series n = 121 Follow-up: NR	Diagnosis possible from biopsy: 61.8% Diagnostic yield Lesions >20 mm: 75.6% Lesions ≤20 mm: 29.7% (p < 0.01) Pneumothorax in one patient.	Larger/comparative studies included in table 2
Chung YH, Lie CH, Chao TY et al. (2007) Endobronchial ultrasonography with distance for peripheral pulmonary lesions. Respiratory Medicine 101:738–45.	Case series n = 113 Follow-up: NR	Diagnostic yield when measuring distance from bronchial orifice to lesion: 78.9% Diagnostic yield when not measuring distance: 57.1% (p = 0.013) Mild bleeding in 5 patients and one pneumothorax.	Larger/comparative studies included in table 2
Herth FJ, Eberhardt R, Becker HD et al. (2006) Endobronchial ultrasound-guided transbronchial lung biopsy in fluoroscopically invisible solitary pulmonary nodules: a prospective trial.[see comment]. Chest 129:147–50.	Case series n = 54 Follow-up: NR	Biopsy able to establish diagnosis: 70% One pneumothorax	Larger/comparative studies included in table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Dooms CA, Verbeken EK, Becker HD et al. (2007) Endobronchial ultrasonography in bronchoscopic occult pulmonary lesions.[see comment]. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 2:121–4.	Case series n = 50 Follow-up: NR	Histologic diagnosis possible: 84% Moderate bleeding in one patient.	Larger/comparative studies included in table 2
Asano F, Matsuno Y, Tsuzuku A et al. (2008) Diagnosis of peripheral pulmonary lesions using a bronchoscope insertion guidance system combined with endobronchial ultrasonography with a guide sheath. Lung Cancer 60:366–73.	Case series n = 31 Follow-up: NR	Pathological diagnosis possible from lesion: 84.4% No complications observed.	Larger/comparative studies included in table 2
Asahina H, Yamazaki K, Onodera Y et al. (2005) transbronchial biopsy using endobronchial ultrasonography with a guide sheath and virtual bronchoscopic navigation. Chest 128:1761–5.	Case series n = 29 Follow-up: NR	Diagnosis possible from biopsy: 63.3%	Larger/comparative studies included in table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Huang C-T, Ho C-C, Tsai Y-J et al. (2009) Factors influencing visibility and diagnostic yield of transbronchial biopsy using endobronchial ultrasound in peripheral pulmonary lesions. Respirology 14:859–864.	Case series n = 83 Follow-up: NR	EBUS images could not be obtained in 28% (23/83). Visualisation of lesion < 20mm significantly lower than lesions ≥ 20mm ($p < 0.001$). Definitive diagnosis possible in 73% patients. Multivariate analysis shows that location of lesion on CT scan and position of probe in the lesion were independent predictors of diagnostic yield ($p < 0.001$ and $p = 0.001$ respectively)	Larger/comparative studies included in table 2
Kikuchi E, Yamazaki K, Sukoh N et al. (2004) Endobronchial ultrasonography with guide-sheath for peripheral pulmonary lesions. European Respiratory Journal 24:533–7.	Case series n = 24 Follow-up: NR	Diagnosis possible: 58.3% One pneumothorax. No major bleeding.	Larger/comparative studies included in table 2
Okimasa S, Yoshioka S, Shibata S et al. (2007) Endobronchial ultrasonography with a guide-sheath and virtual bronchoscopy navigation aids management of peripheral pulmonary nodules. Hiroshima Journal of Medical Sciences 56:19–22.	Case report n = 1 Follow-up: NR	Biopsy possible – diagnosis of pneumonia.	Larger/comparative studies included in table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Oki M, Saka H, Kitagawa C et al. (2009) Endobronchial ultrasound-guided transbronchial biopsy using novel thin bronchoscope for diagnosis of peripheral pulmonary lesions. Journal of Thoracic Oncology 4:1274-1277.	Case series n = 71 Follow-up: NR	Diagnostic histologic specimens obtained in 69% (49/71) patients. No significant complications.	Larger/comparative studies included in table 2
Inoue T, Miyazawa T, Kurimoto N et al. (2006) Gefitinib therapy for pulmonary adenocarcinoma with EGFR mutation diagnosed by transbronchial lung biopsy using endobronchial ultrasonography with guide sheath. Journal of Bronchology 13:201–3.	Case report n = 1 Follow-up: 15 days after treatment started	Biopsy possible – diagnosis adenocarcinoma. Details of treatment (radiation therapy and gefitinib).	Larger/comparative studies included in table 2

Appendix B: Related NICE guidance for endobronchial ultrasound-guided Trans-Bronchial Biopsy for peripheral lung lesions

Guidance	Recommendation
Interventional procedures	**Endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal masses. NICE interventional procedures guidance 254 (2008).** **1 Guidance** 1.1 Current evidence on the safety and efficacy of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS–TBNA) for mediastinal masses appears adequate to support the use of this procedure provided that normal arrangements are in place for consent, audit and clinical governance. 1.2 This procedure requires a combination of skills, and clinicians planning to undertake it should receive specific training.

Clinical guidelines	**Lung cancer diagnosis and treatment. NICE clinical guideline 24 (2005).** **Key recommendations:** **Access to services** • All patients diagnosed with lung cancer should be offered information, both verbal and written, on all aspects of their diagnosis, treatment and care. This information should be tailored to the individual requirements of the patient, and audio and videotaped formats should also be considered. • Urgent referral for a chest X-ray should be offered when a patient presents with: – haemoptysis, or – any of the following unexplained or **persistent** (that is, lasting more than 3 weeks) symptoms or signs: • cough • chest/shoulder pain • dyspnoea • weight loss • chest signs • hoarseness • finger clubbing • features suggestive of metastasis from a lung cancer (for example, in brain, bone, liver or skin) • cervical/supraclavicular lymphadenopathy. • If a chest X-ray or chest computed tomography (CT) scan suggests lung cancer (including pleural effusion and slowly resolving consolidation), patients should be offered an urgent referral to a member of the lung cancer multidisciplinary team (MDT), usually a chest physician. **Staging** • Every cancer network should have a system of rapid access to 18F-deoxyglucose positron emission tomography (FDG-PET) scanning for eligible patients. **Radical radiotherapy alone for treatment of non-small-cell lung cancer** • Patients with stage I or II non-small-cell lung cancer (NSCLC) who are medically inoperable but suitable for radical radiotherapy should be offered the continuous hyperfractionated accelerated radiotherapy (CHART) regimen. **Chemotherapy for non-small-cell lung cancer** • Chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100) to improve survival, disease control and quality of life.

	Palliative interventions and supportive and palliative care • Non-drug interventions for breathlessness should be delivered by a multidisciplinary group, coordinated by a professional with an interest in breathlessness and expertise in the techniques (for example, a nurse, physiotherapist or occupational therapist). Although this support may be provided in a breathlessness clinic, patients should have access to it in all care settings. **Service organisation** • The care of all patients with a working diagnosis of lung cancer should be discussed at a lung cancer MDT meeting. • Early diagnosis clinics should be provided where possible for the investigation of patients with suspected lung cancer, because they are associated with faster diagnosis and less patient anxiety. • All cancer units/centres should have one or more trained lung cancer nurse specialists to see patients before and after diagnosis, to provide continuing support, and to facilitate communication between the secondary care team (including the MDT), the patient's GP, the community team and the patient. Their role includes helping patients to access advice and support whenever they need it.

Appendix C: Literature search for endobronchial ultrasound-guided transbronchial biopsy for peripheral lung lesions

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	12 August 2009	Issue 3, 2009
Database of Abstracts of Reviews of Effects – DARE (CRD website)	12 August 2009	N/A
HTA database (CRD website)	12 August 2009	N/A
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	12 August 2009	Issue 3, 2009
MEDLINE (Ovid)	12 August 2009	1950 to July Week 5 2009
MEDLINE In-Process (Ovid)	12 August 2009	August 11, 2009
EMBASE (Ovid)	12 August 2009	1980 to 2009 Week 32
CINAHL (NLH Search 2.0)	12 August 2009	1981 to Present
BLIC (Dialog DataStar)	12 August 2009	1995 to date

Trial sources searched on 12 August 2009

- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database
- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov

Websites searched on 12 August 2009

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

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

MEDLINE search strategy

The MEDLINE search strategy was adapted for use in the other sources.

1 Ultrasonography/
2 (Ultrasonograph* or Sonograph* or Echograph*).tw.
3 (Ultrasound-guide* or Ultrasound guide*).tw.

4 or/1-3
5 Bronchoscopy/
6 Bronchoscopes/
7 (Bronchoscop* adj3 biops*).tw.
8 (Endobronchial* adj3 biops*).tw.
9 (Flexible* adj3 telescop*).tw.
10 (Transbronchial* adj3 biops*).tw.
11 (Trans-bronchial* adj3 biops*).tw.
12 (Trans* bronchial* adj3 biops*).tw.
13 (Transbronchial* adj3 needle* adj3 aspirat*).tw.
14 (Trans-bronchial* adj3 needle* adj3 aspirat*).tw.
15 (Trans bronchial* adj3 needle* adj3 aspirat*).tw.
16 (EBUS-TBB or EBUS-TBBX or TBNA).tw.
17 (Radial* adj3 ultrasound* adj3 mini-probe*).tw.
18 Olympus.tw.
19 or/5-18
20 4 and 19
21 Lung Neoplasms/
22 ((Lung* or Pulmonar*) adj3 (Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or Mass* or Lesion*)).tw.
23 (Mediastinal* adj3 mass*).tw.
24 Solitary Pulmonary Nodule/
25 (Solitar* adj3 (Pulmonar* or Lung*) adj3 Nodule*).tw.
26 ((Lung* or Pulmonar*) adj3 coin* adj3 lesion*).tw.
27 or/21-26
28 20 and 27
29 Animals/ not Humans/
30 28 not 29