Endobronchial ultrasound-guided procedures

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Marc Bevan, Marianne Chau, Jun Feng and Koji Makino from IMS Health. The report was edited by Ann Jones.
The report was endorsed by the Minister for Health and Ageing on 20 May 2008.

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Medical Services Advisory Committee—role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from IMS Health was engaged to conduct a systematic review of literature on endobronchial ultrasound guided transbronchial sampling procedures for non-small cell lung cancer staging, diagnosis of mediastinal/hilar masses, depth diagnosis of endobronchial cancers and diagnosis of peripheral lung lesions. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of EBUS-guided procedures for investigation of non-small cell lung cancer, mediastinal/hilar masses, endobronchial cancer and peripheral lung lesions

Clinical need

Lung cancer is the leading cause of cancer death globally (AIHW 2006). In Australia, lung cancer was the fifth most common notifiable cancer in 2003, when it accounted for 8.9 per cent of all cancers (8249 diagnoses reported) (AIHW and AACR 2007). In the same year, lung cancer was responsible for 6988 deaths (4506 male; 2482 female), resulting in 43,325 person-years of life lost (before 75 years of age) due to premature cancer death. This was the highest number of person-years of life lost among all notifiable cancers in Australia (AIHW and AACR 2007).

Improvements in lung cancer staging and diagnosis may contribute to enhanced patient management by avoiding invasive diagnostic procedures, and offering more accurate curative and palliative treatment planning. Advances in these areas enhance survival and quality of life.

Safety

EBUS-guided procedures for non-small cell lung cancer (NSCLC) staging, diagnosis of mediastinal/hilar masses, depth diagnosis of endobronchial cancers and diagnosis of peripheral lung lesions appear to be as safe as other minimally-invasive diagnostic tests. The most frequently reported adverse events were bleeding and pneumothorax. These mainly occurred among patients who underwent either EBUS or fluoroscopy-guided transbronchial biopsy. There also appeared to be a trend toward a higher frequency of pneumothoraces using electromagnetic navigation bronchoscopy-transbronchial biopsy (ENB-TBBX).

Effectiveness

Evidence from the literature indicated that the diagnostic yield of EBUS-TBNA was greater than TBNA in NSCLC staging and diagnosis of mediastinal/hilar masses. It was also found that the sensitivity and diagnostic yield of EBUS-TBNA were at least equivalent to endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) in specific subgroups. There were insufficient data to assess the impact of EBUS-TBNA on patient management. Treatment effectiveness evidence was not examined because it was considered that EBUS-TBNA would not identify any unique patient groups that were substantially different from those currently seen in Australian clinical practice. Evidence was insufficient to address uncertainty regarding the clinical impact of EBUS-TBNA compared with its major comparators, TBNA and mediastinoscopy.

No trials were identified that compared the diagnostic performance of EBUS with or without EBBX to EBBX alone in diagnosing the depth of endobronchial cancers. In the absence of evidence supporting diagnostic accuracy, patient management and treatment effectiveness evidence was not sought.

The evidence suggested that the sensitivity of EBUS-TBBX is equivalent to fluoroscopy-TBBX in the diagnosis of peripheral lung lesions. The studies evaluated indicated that the diagnostic yield of EBUS-TBBX was greater than TBBX alone and at least equivalent to electromagnetic- and fluoroscopic-guided TBBX. It was also found that the diagnostic yield of EBUS-TBBX may be greater than other methods of guided-TBBX in diagnosing smaller peripheral lesions. No evidence was found to assess the impact of EBUS-TBBX on patient management. Treatment effectiveness evidence was not examined because it was considered that EBUS-TBBX would not identify unique patient groups that were substantially different from those presently seen in Australian clinical practice. There were insufficient data to address uncertainty surrounding the clinical impact of EBUS-TBBX compared with its major comparators, fluoroscopy-TBBX and TTNA.

Economics

The economic analysis presented in this assessment examined whether the introduction of EBUS-guided procedures under the proposed indications represented value for money for the Australian healthcare system. A full economic evaluation that comparatively assessed alternative strategies in terms of costs and health outcomes, such as life years and quality-adjusted life years, was not considered to be feasible due to a lack of relevant clinical data.

A decision analytic model was constructed to assess cost implications of EBUS-guided procedures when compared with current procedures. A cost analysis of EBUS-TBNA relative to TBNA alone was performed for NSCLC staging and diagnosis of mediastinal/hilar masses of unknown origin. A cost analysis of EBUS-TBBX relative to TBBX was also conducted for diagnosis of peripheral lung lesions less than 3 cm diameter. A lack of clinical data meant that a cost analysis was not conducted for depth diagnosis of endobronchial cancers.

The analysis indicated that use of EBUS-TBNA was associated with cost savings of $347 per patient when compared with TBNA for NSCLC staging or diagnosing mediastinal/hilar masses. The use of EBUS-TBBX for diagnosis of peripheral lung lesions less than 3 cm diameter was estimated to generate cost savings of $364 per patient. This reflected the economic benefits associated with improved yield offered by using EBUS-guided procedures.

The current analysis assumed that use of EBUS had no impact on the overall diagnostic accuracy of TBNA/TBBX procedures. Should use of EBUS influence diagnostic accuracy of either procedure, patients' prognoses would likely be affected, creating important health outcomes and economic implications. No relevant data were available to allow evaluation of these outcomes.

Sensitivity analyses indicated that the yield rate represents the most critical variable in the analysis. This was the anticipated result because the greatest clinical benefit is likely to result from avoiding expensive and invasive follow-up surgical procedures.

Epidemiological data indicated that the total costs of employing EBUS-TBNA were estimated at between $2.5 and $3.6 million annually for assessment of central, mediastinal and hilar tumours. The total annual cost of EBUS-TBBX for diagnosis of peripheral lung lesions less than 3 cm diameter was estimated at between $1.2 and $2.2 million.

Use of EBUS procedures generated cost savings compared with current procedures. The extent of the total cost saving for EBUS-TBNA for assessment of NSCLC and mediastinal/hilar masses was expected to be from $763,994 to $1.1 million. EBUS-TBBX for diagnosis of peripheral lung lesions less than 3 cm diameter was associated with cost savings of between $363,802 and $691,224. These cost savings represent important financial implications for considering public funding of EBUS-guided sampling procedures.

The cost savings associated with the implementation of EBUS as presented may represent conservative estimates. This is because EBUS guidance could replace more invasive biopsy modalities for some patients as a first line assessment for lung cancer, thereby generating further cost offsets.

Recommendation

MSAC has considered the safety, effectiveness and cost-effectiveness of endobronchial ultrasound (EBUS)-guided procedures for the investigation of non-small cell lung cancer, mediastinal/hilar masses, endobronchial cancer and peripheral lung lesions compared to mediastinoscopy and transbronchial needle aspiration.

The MSAC finds that the EBUS-guided procedures for the staging of non-small cell lung cancer, and the investigation of mediastinal/hilar masses and peripheral lung lesions is safer, more effective and likely to be cost saving when compared to mediastinoscopy and transbronchial needle aspiration.

MSAC finds that, though safe, there is insufficient evidence on the effectiveness and cost-effectiveness of the EBUS-guided procedure for the evaluation of endobronchial cancer.

MSAC recommends that public funding should be **supported** for EBUS-guided procedures for the staging of non-small cell lung cancer, and the investigation of mediastinal/hilar masses and peripheral lung lesions.

MSAC recommends that public funding should **not be supported** for the EBUS-guided procedure for the evaluation of endobronchial cancer.

— The Minister for Health and Ageing accepted this recommendation on 20 May 2008—

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of endobronchial ultrasound (EBUS)-guided transbronchial sampling procedures for non-small cell lung cancer (NSCLC) staging, diagnosis of mediastinal/hilar masses, depth diagnosis of endobronchial cancers and the diagnosis of peripheral lung lesions. The MSAC evaluates new and existing health technologies and procedures for which public funding is sought in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. The MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The MSAC's terms of reference and membership are at **Appendix A**. The MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, oncology, surgery, internal medicine, general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence of endobronchial ultrasound guided transbronchial sampling procedures for non-small cell lung cancer staging, diagnosis of mediastinal/hilar masses, depth diagnosis of endobronchial cancers and the diagnosis of peripheral lung lesions.

Background

The procedure

Endobronchial ultrasound (EBUS) is a minimally invasive procedure that involves an ultrasound probe being introduced into the thoracic region via the bronchial airway. The ultrasound probe can be used to generate images of pulmonary and mediastinal structures (Herth et al 2000). The lymph node stations that are accessible using EBUS are presented in Table 4. EBUS imaging can be used alone or to guide sampling procedures such as endobronchial biopsy (EBBX), transbronchial needle aspiration (TBNA) or transbronchial biopsy (TBBX). This assessment focussed on the use of EBUS-TBNA for non-small cell lung cancer (NSCLC) staging and the diagnosis of mediastinal/hilar masses, EBUS imaging with or without endobronchial biopsy for depth diagnosis of endobronchial cancers, and EBUS-TBBX for diagnosis of peripheral lung lesions.

The advisory panel indicated that currently endobronchial biopsies are seldom performed for depth diagnosis of endobronchial cancers.

Endobronchial ultrasound-transbronchial biopsy

The EBUS-TBBX procedure consists of a radial ultrasound miniprobe sited in the working channel of a flexible bronchoscope to reach the periphery of the lungs (Figure 1). Patients undergoing the procedure are sedated or administered general anaesthesia. The bronchoscope is normally introduced orally and manoeuvred into the target lung location using fluoroscopic navigation. The 20 MHz radial probe then makes perpendicular scans to create a 360° cross sectional image (Koh et al 2007). The radial probe has a saline-filled balloon to improve ultrasound imaging. When the target lesion is visible, the probe inside the working channel is removed and replaced by biopsy forceps which are used to obtain tissue samples (Chung et al 2007). Slight movement when removing the probe and introducing the forceps can sometimes mean that sampling is unsuccessful.

Transbronchial biopsy, conventionally with fluoroscopic guidance, can be performed to aid diagnosis of peripheral lung lesions. EBUS-TBBX may help in locating lesions less than 3 cm diameter that may not be well visualised by fluoroscopy (Herth et al 2006a).

The introduction of a guide sheath, a cover placed over a probe in the working channel of a bronchoscope, may improve peripheral lesion biopsy sampling.
The radial probe cannot perform real time ultrasound guidance for biopsy sampling because it is removed to introduce biopsy forceps. The guide sheath helps to keep the bronchoscope location fixed during the removal of the probe and insertion of the forceps (Koh et al 2007). This also improves success when obtaining tissue samples and increases capacity to sample target peripheral lesions. Use of guide sheaths has potential to reduce bleeding during the procedure.

Figure 1 Radial EBUS probe with guide sheath (UM-S20-20R) (left) and linear EBUS TBNA scope tip (XBF-UC260F-OL8) (right)

Source: Olympus Australia Pty Ltd http://www.olympusaustralia.com.au

Endobronchial ultrasound-transbronchial needle aspiration

The EBUS-TBNA procedure currently involves use of a hybrid bronchoscope with three channels that accommodate a camera; the linear probe, and a working channel.

Similar to the EBUS-TBBX procedure, the bronchoscope is introduced into the bronchus while patients are under either conscious sedation or general anaesthesia. The linear EBUS probe is a 5–20 MHz convex transducer which performs scans parallel to the direction of the bronchoscope (Herth et al 2005). EBUS-TBBX was conducted using a radial probe before the linear probe was developed (Yasufuku et al 2007).

The linear probe and hybrid bronchoscope enables biopsy sampling to be performed without removing the probe and negates the need for a guide sheath (Zimmermann 2005). Disposable 22-gauge needles are typically used to collect aspirated tissue in TBNA procedures; core biopsy samples can also be obtained in some cases.
The ultrasound image is visualised together with a conventional bronchoscopy image on a monitor, making this a real time procedure.

Practical innovations have increased the range of functions of EBUS-TBNA. Linear probes can be used with rapid on-site evaluations (ROSE) of transbronchial aspirates by a cytopathologist to confirm tissue sufficiency, quantity and quality to inform both provisional diagnoses and ensuing laboratory requirements. These factors offer capacity to improve diagnostic yield and avoid repeat procedures, their additional costs and diagnostic delays.

Intended purpose

This assessment evaluated EBUS-guided procedures for non-small cell lung cancer staging, diagnosis of mediastinal/hilar masses, depth diagnosis of endobronchial cancers and diagnosis of peripheral lung lesions.

Clinical need

The impact of lung cancer both globally and in Australia is profound. Almost a fifth (19.1%) of all cancer deaths during 2004 in Australia was attributable to lung cancer, making it the leading cause of cancer death (AIHW 2006).

Tobacco smoking is the largest single cause of lung cancer in Australia. In 2001, 84 per cent and 77 per cent of diagnosed lung cancers in males and females, respectively, was attributable to smoking (AIHW and AACR 2004). In 2004–2005 almost a quarter of adults (23%) were current smokers (Australian Bureau of Statistics [ABS] 2006). A national survey of Indigenous Australians conducted in 2001 found that adults aged 18 years and over were twice as likely as non-Indigenous adults to be current smokers (51% and 24% respectively) (ABS 2002). Other risk factors for development of lung cancer include environmental tobacco smoke, cannabis use, medical exposure to radiation, previous lung disease, genetic susceptibility, asbestos exposure, and exposure to other environmental carcinogens (Cancer Council Australia 2004).

Although 5 to 15 per cent of people with lung cancer are asymptomatic—these cancers are often diagnosed incidentally from routine chest x-rays—most people present with some sign or symptom. Lung cancers manifest with symptoms caused by the primary tumour, locoregional spread, regional lymph node growth, metastatic disease, and from effects of tumour products, such as ectopic hormone production. Primary lung tumour symptoms may include cough, haemoptysis, wheeze and stridor, dyspnoea, and post obstructive pneumonitis. Locoregional spread may cause pain from pleural or chest wall involvement, cough and dyspnoea. Regional spread to the thorax may result in tracheal obstruction, oesophageal compression with dysphagia, hoarseness from laryngeal nerve paralysis, phrenic nerve paralysis and sympathetic nerve paralysis with Horner's syndrome (Minna 2001).

Improvements in lung cancer staging and diagnosis may lead to better patient management by avoiding invasive diagnostic procedures and providing more accurate curative and palliative treatment planning leading to improved survival and quality of life.

Incidence and mortality

Lung cancer accounted for 8.9 per cent of all cancers in 2003 when 8249 diagnoses were reported[1] (AIHW and AACR 2007). Of the reported 8249 diagnoses, 5281 occurred in males (resulting in an age-standardised rate for Australia of 57.1/100,000) and 2968 in females (resulting in an age-standardised rate for Australia of 27.1/100,000). The overall age-standardised rate for Australia in 2003 was 40.4/100,000.

Between 85 and 90 per cent of lung tumours are non-small cell lung cancers (NSCLC). NSCLC is subcategorised into three major sub-groups: squamous cell carcinoma, adenocarcinoma and large cell (undifferentiated) carcinoma.

Squamous cell carcinomas often occur near the bronchus and represent 25 to 30 per cent of all lung cancers (American Cancer Society 2007). Around 40 per cent of lung cancers are adenocarcinomas and generally develop in the bronchioles and alveoli (American Cancer Society 2007). The remaining 10 to 15 per cent of lung cancers are large-cell (undifferentiated) tumours that can occur in lung tissue (American Cancer Society 2007).

Lung cancer was responsible for 6988 deaths in 2003 (4506 in males and 2482 in females), resulting in 43,325 person-years of life lost (before 75 years of age) due to premature cancer death. This represents the highest number of person-years of life lost among all notifiable cancers in Australia (AIHW and AACR 2007). The age-standardised mortality for Australia in 2003 was 49.1/100,000 for males and 22.4/100,000 for females. The overall age-standardised mortality for Australia in 2003 was 34.2/100,000.

Lung cancer survival is poor, and rates decrease with patients' age and extent of disease (Cancer Council Australia 2004). New South Wales data from 1980–1995 showed a 23.2 per cent five-year relative survival rate for localised lung cancer compared with 1.0 per cent survival among patients with distant metastases (Supramaniam et al 1998). American data from 1995 to 2000 showed a 49.4 per cent five-year relative survival rate for localised disease and 2.1 per cent among patients with distant metastases (American Cancer Society 2005).[2]

Between 1992 and 1997, the one-year relative survival rate for patients diagnosed with NSCLC was approximately 35.6 per cent for males and 38.4 per cent for females;

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[1] Australian incidence data for lung cancer is described by *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10) codes C33–C34 (Australian Institute of Health and Welfare (AIHW) 2005). According to the ICD-10 classification, code C33 is 'malignant neoplasm of trachea' and code C34 is 'malignant neoplasm of bronchus and lung' (World Health Organization 2003).

[2] Differing definitions of lung cancer staging mean that USA and Australian survival data may not be comparable. The American Cancer Society defines lung cancer stage as localised, regional or distant (Young et al 2000) and the AIHW apply TNM staging reported by Mountain (1997). The term 'localised' used to describe NSW data from 1980 to 1985 is considered to include more advanced disease than the American definition of localised.

five-year relative survival was 12.0 per cent and 15.8 per cent for males and females respectively (AIHW and AACR 2005).

Eligible population

The projected number of diagnoses of lung cancer for 2008 in Australia is 9611 (5975 in males and 3636 in females) (AIHW, AACR & National Cancer Strategies Group [NCSG]: McDermid 2005).

In 2003–2004 there were 17,670 separations for malignant neoplasm of bronchus or lung, resulting in 137,458 patient-days in hospital. The average length of stay for most patients was 7.8 days (AIHW 2005).

Central, mediastinal and hilar tumours

The estimated number of patients who would undergo EBUS-guided procedures for assessment of central, mediastinal and hilar tumours was based on calculations for similar indications presented in the MSAC assessment report *Endoscopic ultrasound guided fine-needle aspiration for the staging of non-small cell lung cancer and the diagnosis of mediastinal masses* (MSAC, 2008). The opinion of the advisory panel was that the estimated patient population eligible for EUS-FNA was similar to the eligible patient population for EBUS-guided procedures. EUS-FNA has potential to replace between 1456 and 2262 procedures per year (Table 1).

Table 1 Estimated number of patients per year eligible to undergo pathological assessment for NSCLC staging and the diagnosis of mediastinal masses of unknown origin

Description	Number of patients
NSCLC staging	806–1612
Diagnosis of mediastinal mass of unknown origin	650
Total	1456–2262

Source: MSAC Application 1104, 2007

The estimated eligible patient population for NSCLC staging considered in the EUS-FNA report was calculated by taking the projected 2007 incidence of lung cancer and then deriving the proportion of patients who would require invasive staging. This was determined by identifying the proportion of patients with NSCLC; the proportion of patients without distant metastases; the proportion of patients suitable for curative treatment; and proportion of patients who require pathological staging.

The number of people requiring investigation for diagnosis of mediastinal masses of unknown origin was based on the number of mediastinoscopies performed in 2004–2005. The EUS-FNA advisory panel used these data to inform the estimated proportion of mediastinoscopies conducted for investigation of mediastinal masses of unknown origin

The estimated EUS-FNA patient population equates to an approximation of the eligible patient population for EBUS-guided procedures for assessment of central,

mediastinal/hilar tumours. The estimated patient population for EBUS-guided procedures would be affected by the following factors:

- patients undergoing EBUS-TBNA for diagnosis of hilar masses
- patients undergoing EBUS for depth diagnosis of endobronchial cancers
- substitution of comparators by EBUS-TBNA would be affected by the ability of each procedure to access different thoracic locations.

Based on the previous EUS-FNA estimated patient population, and taking these factors into account, the advisory panel estimated that an eligible population for EBUS guided procedures for assessment of central, mediastinal, and hilar tumours, was between 2200 and 3200 patients per year.

The advisory panel indicated that there is potential for EBUS-TBNA to be used for patients with non-malignant conditions.

Peripheral lung lesions

The estimated number of patients who would undergo EBUS-TBBX for diagnosis of peripheral lung lesions was calculated based on the current use of comparator procedures (see page 14). The most recently reported AIHW data (2003–2004) indicates that EBUS-TBBX has the potential to replace up to 2981 procedures per year (Table 2).

Table 2 Rates of comparator procedures for peripheral lung lesion diagnosis 2003–2004

ICD-10-AM code	Description	Number of procedures
38412-00	Percutaneous needle biopsy of lung	2725
38418-02	Biopsy of lung	256
Total		2981

Source: http://www.aihw.gov.au
Abbreviation: ICD-10-AM, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification

The estimate of the potential size of the eligible patient population (between 2200 and 3200 patients) would be affected by the following additional factors:

- a proportion of the reported procedures may be for indications other than diagnosis of peripheral lung lesions
- a proportion of patients referred for pathological diagnosis of peripheral lung lesions may not be covered by the ICD-10-AM codes cited
- a single patient may undergo multiple procedures
- substitution of comparators by EBUS-TBBX would be affected by the ability of each procedure to access different thoracic locations.

Based on the use of comparator procedures, and taking into account the additional factors, the advisory panel estimated that the eligible population for EBUS-TBBX for diagnosis of peripheral lung lesions was between 1500 and 3000 patients per year.

The number of eligible patients with peripheral lesions less than 3 cm diameter who would undergo EBUS-TBBX was estimated based on results from the current assessment (page 22). The number of eligible patients was calculated from data presented in the included peripheral lung lesion studies. Of the 10 included studies, five reported the proportion of patients with lesions less than 3 cm diameter (summarised in Table 3).

Table 3 Number of patients with peripheral lung lesions < 3 cm diameter

Author (year)	Reported number of patients with peripheral lung lesions (< 3 cm)	Total number of patients with peripheral lung lesions	%
Eberhardt et al (2007)[a]	266	517	51
Herth et al (2002)	17	21	80
Kurimoto et al (2004)	92	124	74
Paone et al (2005)	47	87	54
Shirakawa et al (2004)	30	50	60

[a] Results adapted from Eberhardt et al (2007) Table 1

An estimate was derived from the studies listed in Table 3 by averaging the proportion of patients in the included studies that reported results of peripheral lung lesions less than 3 cm diameter. This was calculated at 64 per cent. This proportion was then applied to the estimated range of the total eligible peripheral lung lesion patient population (1500–3000 patients per year). The estimated eligible patient population with peripheral lung lesions less than 3 cm was between 1000 and 1900 patients per year.

Current treatment

Management of NSCLC is dependent on the extent of disease, primary tumour location and patient's health (National Cancer Institute 2007). Optimal treatment for NSCLC is surgical resection (Cancer Council Australia 2004), but this is feasible only for suitable patients with early stage tumours. Most patients present with advanced disease; up to 40 per cent have distant metastases at diagnosis (Caddy et al 2005). Between 30 and 35 per cent of patients with NSCLC have disease that is sufficiently localised to attempt curative surgical resection (Maghfoor and Perry 2005).

Endobronchial cancer treatment options are dependent on the depth of bronchial wall invasion. Surgical resection may be considered for tumours that have invaded the bronchial wall. Appropriate treatments for carcinomas *in situ* include photodynamic therapy, brachytherapy, electrocautery, cryotherapy, and Nd-YAG laser therapy. Watchful waiting may also be an option for carcinomas *in situ*.

At diagnosis, patients with invasive NSCLC can be staged into one of three groups, reflecting the extent of disease and the treatment approach (National Cancer Institute 2007). The first group of patients have tumours that are surgically resectable (generally stage I, stage II and selected stage III patients) (see Table 63, **Appendix H**, for NSCLC staging). Patients with resectable disease who are unsuitable for surgery are often

candidates for curative radiotherapy. The second group includes patients with locally advanced (T3–T4) or regionally advanced (N2–N3) NSCLC.

Some patients with locally advanced tumours may benefit from combined therapies. Patients with unresectable or N2–N3 disease are treated with radiotherapy and chemotherapy. Some patients with T3 or N2 disease can be treated effectively with surgical resection and neo-adjuvant or adjuvant chemotherapy or chemoradiation. The final group includes patients with distant metastases (M1) identified at diagnosis. These patients may undergo palliative radiotherapy or chemotherapy.

Aside from lung cancer, other malignancies such as lymphoma and metastatic disease, can occur in the thoracic region. Treatment for these conditions is planned based on both the disease and individual patient needs and may include surgical resection, chemotherapy, radiotherapy and palliative care.

A range of benign lesions can present in the peripheral pulmonary, hilar and mediastinal regions. Treatment protocols for their management are designed appropriate to the nature of the condition.

Existing procedures

Imaging techniques

Computed tomography

Computed tomography (CT) imaging is a non-invasive medical imaging technique that generates three-dimensional images of the target location based on a series of two-dimensional x-ray images. CT scanning is one of the most common tools used for studying the thoracic region, particularly the chest. CT produces detailed, cross-sectional views of all types of tissue that assist to determine the size and location of thoracic lesions (Eggerstedt 2003). CT is often performed before TTNA, TBNA or TBBX.

Virtual bronchoscopy

Virtual bronchoscopy is an imaging technique based on CT to generate high quality two- and three-dimensional images that enable non-invasive intraluminal evaluation of the airways to be made (De Wever et al 2004).

Positron emission tomography

Positron emission tomography (PET) is a non-invasive imaging procedure that provides metabolic rather than morphological information about tumours. It uses positron-emitting radioisotopes that decay quickly. A positron camera surrounds the patient to produce cross-sectional images. Because tumour cells tend to take up glucose more avidly than normal cells, the labelled glucose analogue [F-18]-FDG (2-[18F] fluoro-2-deoxyglucose) is particularly useful for tumour imaging. [F-18]-FDG is administered intravenously and the PET scanner maps its distribution. PET is often performed to assess the malignant potential of lesions before biopsy sampling, and to rule out the presence of more widespread disease.

Electromagnetic navigation bronchoscopy

Electromagnetic navigation bronchoscopy is a minimally invasive guidance system for use with bronchoscopic biopsy tools, such as forceps, brush, and needles within the bronchial tree (Schwarz et al 2006, Eberhardt et al 2007). A sensor probe in the bronchoscope emits low-frequency electromagnetic waves that, in conjunction with an electromagnetic location board, generate an image (Schwarz et al 2003). Images aid clinicians to position the bronchoscope and to biopsy through the extended working channel (Eberhardt et al 2007).

White light bronchoscopy and autofluorescence bronchoscopy

White light bronchoscopy is a minimally invasive technique that uses a bronchoscope equipped with white light illumination and camera to examine the lungs.

Autofluorescence bronchoscopy (AFB) uses blue rather than white light for illumination. Blue light can assist the bronchoscopist to visually distinguish between pre-malignant and malignant tissue to detect dysplasia, carcinoma *in situ*, and early invasive cancers not visible using standard white light bronchoscopy (Häußinger et al 2005).

Narrow band imaging

Narrow band imaging (NBI) uses the intrinsic properties of two narrow band wavelengths to produce enhanced imaging of capillaries and surrounding mucosa. NBI uses narrow blue band light (390–445 nm) to visualise capillaries in the surface layers of mucosal membranes, and the narrow green band light (530–550 nm) aids in imaging blood vessels in the membranes. These specific narrow wavelengths are absorbed readily by circulating haemoglobin which can distinguish capillaries from blood vessels and improve mucosal surface imaging. Other benefits of NBI are reduced examination times and fewer unnecessary biopsies (Hirata et al 2007).

Fluoroscopy

Fluoroscopy is a real time x-ray technique in which x-rays are transmitted onto an image-intensifier screen (rather than film). The images produced are then collected by a charge-coupled device (CCD) video camera for immediate playback, or recorded for later review. Fluoroscopy is often used during bronchoscopy to guide insertion of biopsy forceps to obtain transbronchial tissue.

Sampling techniques

Transbronchial needle aspiration and transbronchial biopsy

Transbronchial needle aspiration (TBNA) and transbronchial biopsy (TBBX) can be performed based on previous CT results or using real time imaging, such as fluoroscopy or electromagnetic navigation bronchoscopy.

Both techniques use the transbronchial route, but differ in sampling method. TBNA involves sampling targeted central, mediastinal and hilar lymph nodes generally using a 22-gauge needle (usually a Wang needle) to obtain a cytological sample (Govert et al 1999).

TBBX generally involves collecting peripheral lung lesion tissue samples for histological examination using biopsy forceps. Bronchial washings and brushings are also usually obtained (Mazzone et al 2002). Bronchial washing involves aspirating a small amount of saline to displace surface tissue from the targeted lesion. Bronchial brushing takes cell scrapings from the suspected peripheral lung lesion. Both bronchial washing and bronchial brushing produce cytological samples.

Transthoracic needle aspiration and transthoracic biopsy

Transthoracic needle aspiration (TTNA) is an alternative to transbronchial sampling procedures for investigation of pulmonary lesions. TTNA is performed at CT or with fluoroscopic guidance and does not require general anaesthesia. A small incision is made in the patient's chest to facilitate needle entry (Klein et al 2000). Transthoracic biopsy (TTBX) and TTNA are related procedures. TTNA uses a finer, smaller needle to obtain cytological samples and TTBX is performed using a larger needle to obtain core biopsies for histological examination.

Endoscopic ultrasound fine-needle aspiration

Endoscopic ultrasound (EUS) uses an echoendoscope to place an ultrasound transducer close to the luminal surface of the oesophagus. EUS-guided fine-needle aspiration (FNA) can be used for tissue sampling. When the echoendoscope is placed next to the internal surface of the oesophagus, EUS-FNA enables both visualisation and tissue sampling of masses and lymph nodes in the mediastinum.

Mediastinoscopy

Standard cervical mediastinoscopy is a surgical technique that requires a small incision to be made above the suprasternal notch through which an endoscope (mediastinoscope) is inserted through the mediastinum toward the carina. Biopsy samples are then obtained from accessible areas (Semik et al 2004).

Mediastinotomy

Anterior mediastinotomy can access the same lymph node stations as cervical mediastinoscopy, but requires a second incision parasternally, usually at the second or third intercostal space. Mediastinotomy may be used to evaluate mediastinal masses where standard cervical mediastinoscopy is considered, or has been found to be unsuitable (Eggerstedt 2003).

Video-assisted thoracoscopy

Thoracoscopy involves using an endoscope (thoracoscope) which is inserted through a small incision in the chest to enable examination of the thoracic cavity. Biopsy can be performed through this or other incisions. Video-assisted thoracoscopy enables the operating team to view and assist in the procedure. Techniques have been developed to obtain biopsy tissue from mediastinal masses, including lymphoma (Eggerstedt 2003). Thoracoscopy can be used to access left-sided lymph node stations that cannot be accessed by standard mediastinoscopy and to access inferior pulmonary ligament and para-oesophageal lymph nodes (Pass 2005).

Lymph node stations

Most of these diagnostic tests can access a wide range of nodes, from the superior mediastinal nodes (stations 1–4) to the N1 nodes (stations 10–12). Nodal accessibility of the diagnostic tests are summarised in Table 4.

Transthoracic needle aspiration (TTNA) can theoretically access the widest range of nodes, but because nodes are generally situated deep in the chest close to other organs, may not always be feasible. Mediastinal and hilar nodes are infrequently sampled by the TTNA approach because of their depth and proximity to surrounding vital organs. TTNA is only occasionally possible for certain nodes if sufficiently large and situated where a needle can reach the lesion, without traversing vital structures.

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can access all mediastinal lymph node stations that are accessible by mediastinoscopy, as well as N1 nodes. Lymph node stations accessible are the highest mediastinal (station1), upper and lower para-tracheal (stations 2R, 2L and 4R, 4L, respectively), subcarinal (station 7), hilar (station 10), interlobar (station 11) and lobar (station 12) lymph nodes.

The regional lymph node classification for lung cancer staging is shown in Figure 2.

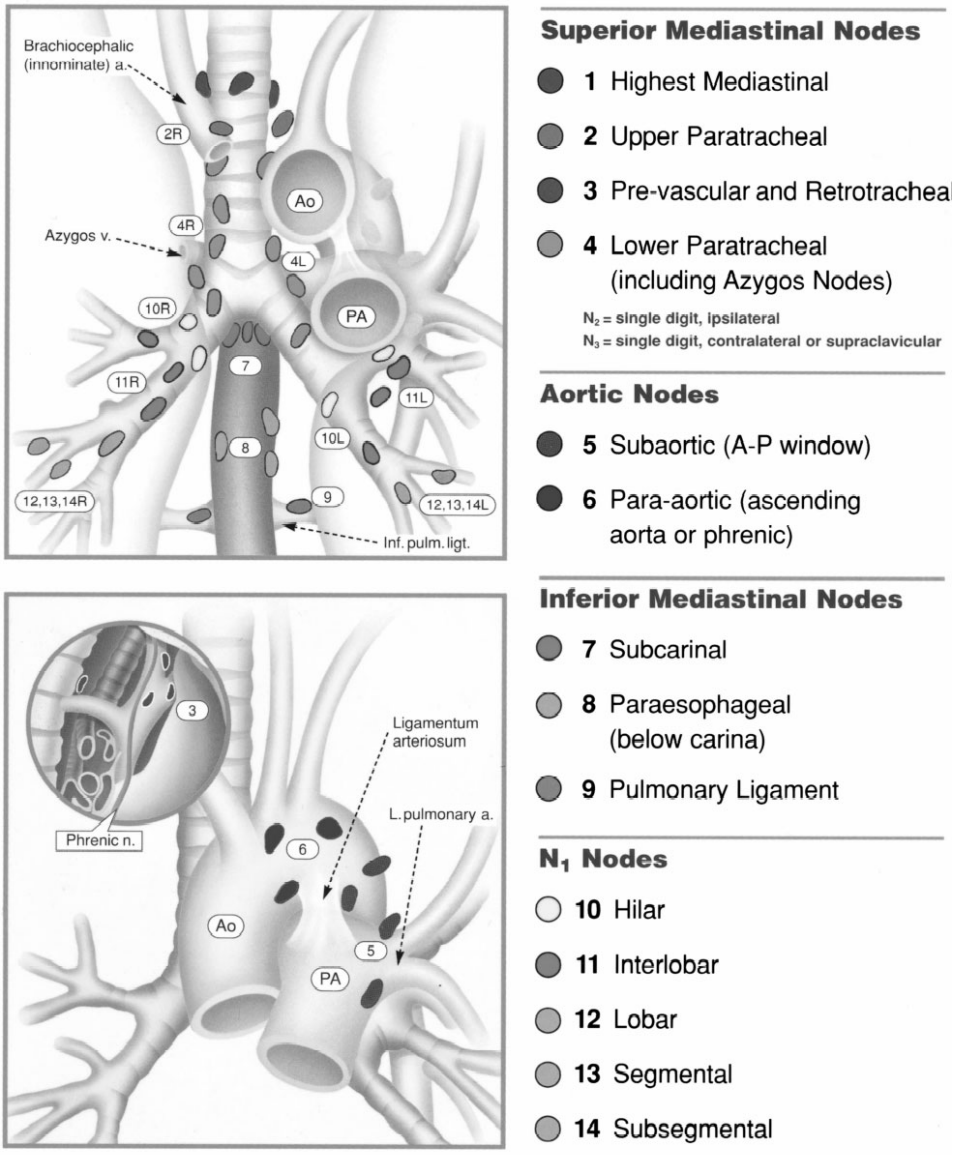

Figure 2 Regional lymph node stations for lung cancer staging

Source: Mountain and Dresler 1997

Table 4 Comparative nodal accessibility

Diagnostic tests	Accessible nodes/ locations														
	1	2R	2L	3	4R	4L	5	6	7	8	9	10R	10L	11	12
TBNA															
EUS-FNA															
EUS-FNA +TBNA															
Mediastinoscopy															
Thoracoscopy															

Abbreviations: EUS-FNA, endoscopic ultrasound-fine needle aspiration; TBNA, transbronchial needle aspiration; TTNA, transthoracic needle aspiration

Source: Herth 2005, Mentzer et al 1997, Zwischenberger et al 2002

Comparator

Endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) is likely to be used in the Australian healthcare setting as a replacement test for non-small cell lung cancer (NSCLC) staging and diagnosis of mediastinal/hilar masses. Comparators for this test were:

- endoscopic ultrasound-fine needle aspiration (EUS-FNA)
- mediastinoscopy
- mediastinotomy
- transbronchial needle aspiration (TBNA)
- transthoracic needle aspiration (TTNA)
- video-assisted thoracoscopy (VAT).

Of these, the advisory panel identified mediastinoscopy and TBNA as major comparators.

EBUS with or without endobronchial biopsy (EBBX) is likely to be used in the Australian healthcare setting as a replacement test for depth diagnosis of endobronchial cancers. The comparator for this test was:

- endobronchial biopsy (EBBX).

EBUS-TBBX is likely to be used in the Australian healthcare setting as a replacement diagnostic test for peripheral lung lesions. The comparators for this test were:

- transthoracic needle aspiration (TTNA)
- transbronchial biopsy (TBBX)
- fluoroscopy- transbronchial biopsy (TBBX)
- electromagnetic navigation bronchoscopy-transbronchial biopsy (ENB-TBBX).

Of these, the advisory panel identified fluoroscopy-TBBX and TTNA as the major comparators.

Marketing status of the technology

EBUS components are presently available only from Olympus. Olympus market a range of devices that includes radial and linear ultrasound probes and biopsy tools including needles and guide sheaths.

The Therapeutic Goods Administration (TGA) lists EBUS on the Australian Register of Therapeutic Goods (ARTG). The ARTG listing numbers for EBUS devices and components are presented in Table 5.

Table 5 Australian Register of Therapeutic Goods listing for EBUS devices and components

ARTG number	Manufacturer	Description
119797	Olympus Australia Pty Ltd	Endotherapy device, non-active, single use
118369	Olympus Australia Pty Ltd	Monitor, visual display unit
120820	Olympus Australia Pty Ltd	Light source, endoscope, line powered
120819	Olympus Australia Pty Ltd	Endoscopic video image processor
AUST L 71621	Olympus Optical Co Tokyo Japan	Endoscopes non-sterile
AUST L 15710	Olympus Optical Co Tokyo Japan	Endoscopes non-sterile

The applicant provided details of an Aloka ultrasound system (Prosound Alpha-5) that can support linear EBUS imaging probes. This device was suggested as an alternative to the Olympus ultrasound processor.

Current reimbursement arrangement

Specific EBUS-guided procedures are not currently funded under the Medicare Benefits Schedule (MBS). MBS item 41892 *Bronchoscopy with one or more endobronchial biopsies or other diagnostic or therapeutic procedures* could potentially be applied to EBUS-guided procedures.

Approach to assessment

Research questions and clinical pathways

Non-small cell lung cancer staging

The PPICO criteria (target population, prior tests, index test, comparator, outcomes) developed *a priori* to evaluate endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) in nodal staging of patients with presumed or known non-small cell lung cancer (NSCLC) are indicated in Table 6.

Table 6 PPICO criteria for the use of EBUS-TBNA in the invasive (nodal) staging of patients with presumed or known NSCLC

Population	Prior tests	Intervention/test	Comparator	Reference standard	Outcomes
Patients with presumed or known NSCLC with mediastinal/hilar lymphadenopathy identified by prior tests	Clinical assessment CT +/– PET (where available)	EBUS-TBNA EBUS-TBNA and EUS-FNA	Current techniques for biopsy of mediastinal/ hilar lymph nodes[a]	Histology sample Clinical follow-up of adequate length	Change in clinical outcomes[b] Change in clinical management[c] Diagnostic accuracy[d] Safety outcomes[e]

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; NSCLC, non-small cell lung cancer; PET, positron emission tomography; TBNA, transbronchial needle aspiration; TTNA, transthoracic needle aspiration; VAT, video-assisted thoracoscopy

[a] EUS-FNA, mediastinoscopy, mediastinotomy, TBNA, TTNA, or VAT

[b] Survival (disease-free survival, overall survival); morbidity (disease recurrence, disease progression); quality of life

[c] Alterations in treatment plan (eg exploratory surgery, surgical resection, excision by minimally invasive techniques, chemotherapy, radiotherapy, palliative treatments, imaging surveillance); alterations in diagnostic plan (eg other diagnostic/staging procedures)

[d] Sensitivity and specificity estimates; positive and negative likelihood ratios; summary diagnostic measures (eg diagnostic odds ratio, summary receiver operating characteristics)

[e] Adverse event reports; adverse events known to be associated with EBUS or its comparators (eg perforation, tears, bleeding, infection, tumour seeding; scope damage); patient discomfort/tolerance to the procedure

The research question for this indication based on these criteria was:

To what extent is endobronchial ultrasound guided transbronchial needle aspiration:

- safe, and
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in the invasive nodal staging of patients with presumed or known NSCLC with mediastinal/hilar lymphadenopathy relative to current techniques for biopsy of mediastinal/hilar lymph nodes?

The clinical pathway for the nodal staging of patients with presumed or known NSCLC is shown in Figure 3. The flowchart illustrates the clinical management pathway to the point of patient diagnosis.

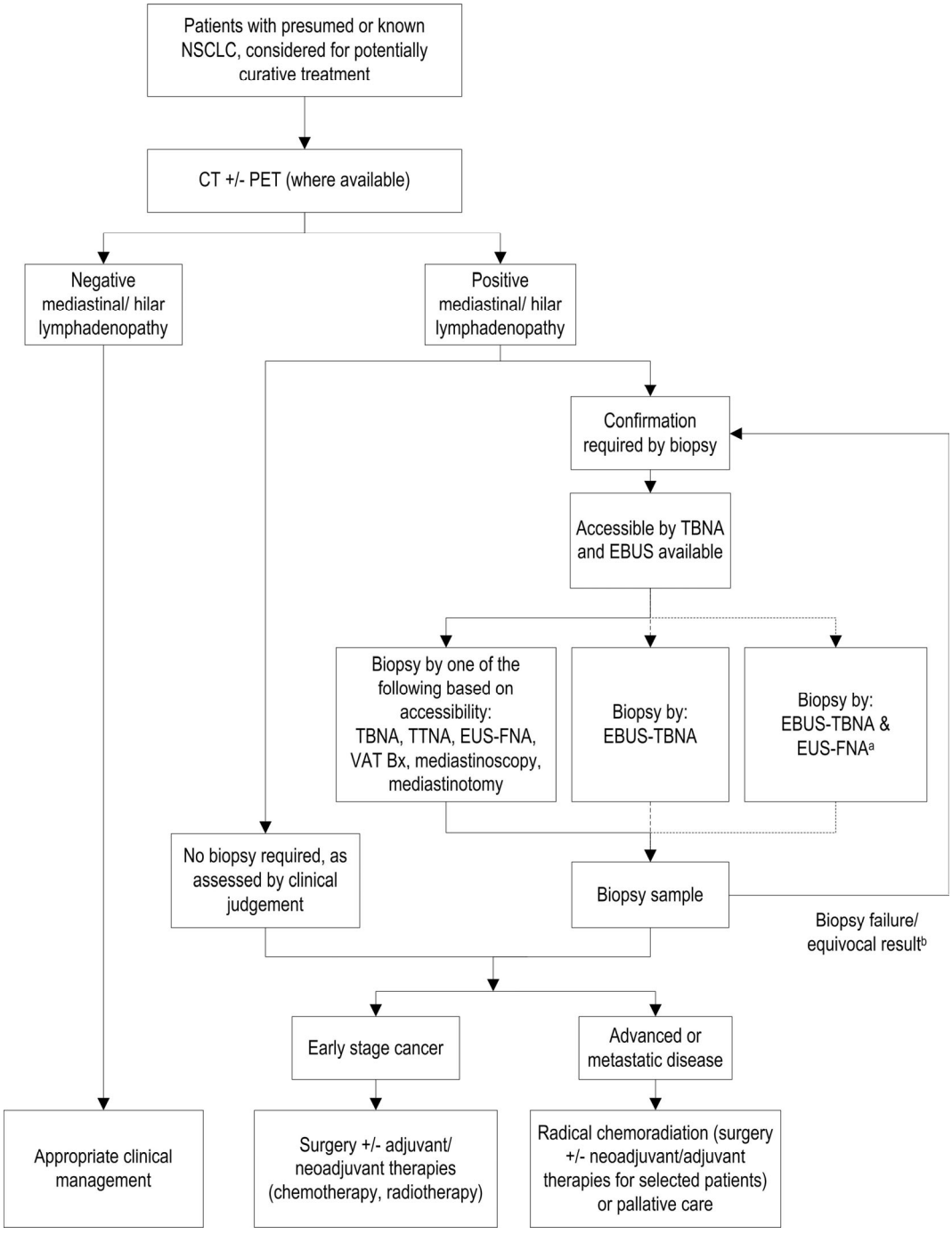

Figure 3 Clinical pathway for invasive (nodal) staging of patients with presumed or known NSCLC

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; NSCLC, non-small cell lung cancer; PET, positron emission tomography; TBNA, transbronchial needle aspiration; TTNA, transthoracic needle aspiration; VAT, video-assisted thoracoscopy

[a] EBUS and EUS-FNA procedures are undertaken in the same session in any order to theoretically enable access to the whole of the mediastinum as they are complementary techniques (Other considerations, p. 70)

[b] Biopsy unsuccessful (tumour not accessed or inadequate sample) or equivocal result

Note: The broken lines indicate the proposed positions of EBUS-TBNA in the clinical pathway. An alternative biopsy technique may be used when re-testing

Mediastinal/hilar masses of unknown origin

The PPICO criteria developed *a priori* to evaluate endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) for invasive diagnosis of patients with mediastinal/hilar masses of unknown origin is indicated in Table 7.

Table 7 PPICO criteria for the use of EBUS-TBNA in the invasive diagnosis of patients with mediastinal/hilar masses of unknown origin

Population	Prior tests	Intervention/test	Comparator	Reference standard	Outcomes
Patients with mediastinal/ hilar masses of unknown origin (including lymphadenopathy) identified by CT +/– x-ray +/– symptoms	Clinical assessment CT +/– x-ray	EBUS-TBNA EBUS-TBNA and EUS-FNA	Current techniques for biopsy of mediastinal/ hilar masses[a]	Histology sample Clinical follow-up of adequate length	Change in clinical outcomes[b] Change in clinical management[c] Diagnostic accuracy[d] Safety outcomes[e]

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; TBNA, transbronchial needle aspiration; TTNA, transthoracic needle aspiration; VAT, video-assisted thoracoscopy

[a] EUS-FNA, mediastinoscopy, mediastinotomy, TBNA, TTNA or VAT

[b] Survival (disease-free survival, overall survival); morbidity (disease recurrence, disease progression); quality of life

[c] Alterations in treatment plan (eg exploratory surgery, surgical resection, excision by minimally invasive techniques, chemotherapy, radiotherapy, palliative treatments, imaging surveillance); alterations in diagnostic plan (eg other diagnostic/staging procedures)

[d] Sensitivity and specificity estimates; positive and negative likelihood ratios; summary diagnostic measures (eg diagnostic odds ratio, summary receiver operating characteristics)

[e] Adverse event reports; adverse events known to be associated with EBUS or its comparators (eg perforation, tears, bleeding, infection, tumour seeding; scope damage); patient discomfort/tolerance to the procedure

The research question for this indication, based on these criteria, was as follows.

To what extent is endobronchial ultrasound guided transbronchial needle aspiration:

- safe, and
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in the invasive diagnosis of patients with mediastinal/hilar masses of unknown origin relative to current techniques for biopsy of mediastinal/hilar masses?

The clinical pathway for the invasive diagnosis of patients with mediastinal/hilar masses of unknown origin illustrates clinical management to the point of patient diagnosis (Figure 4).

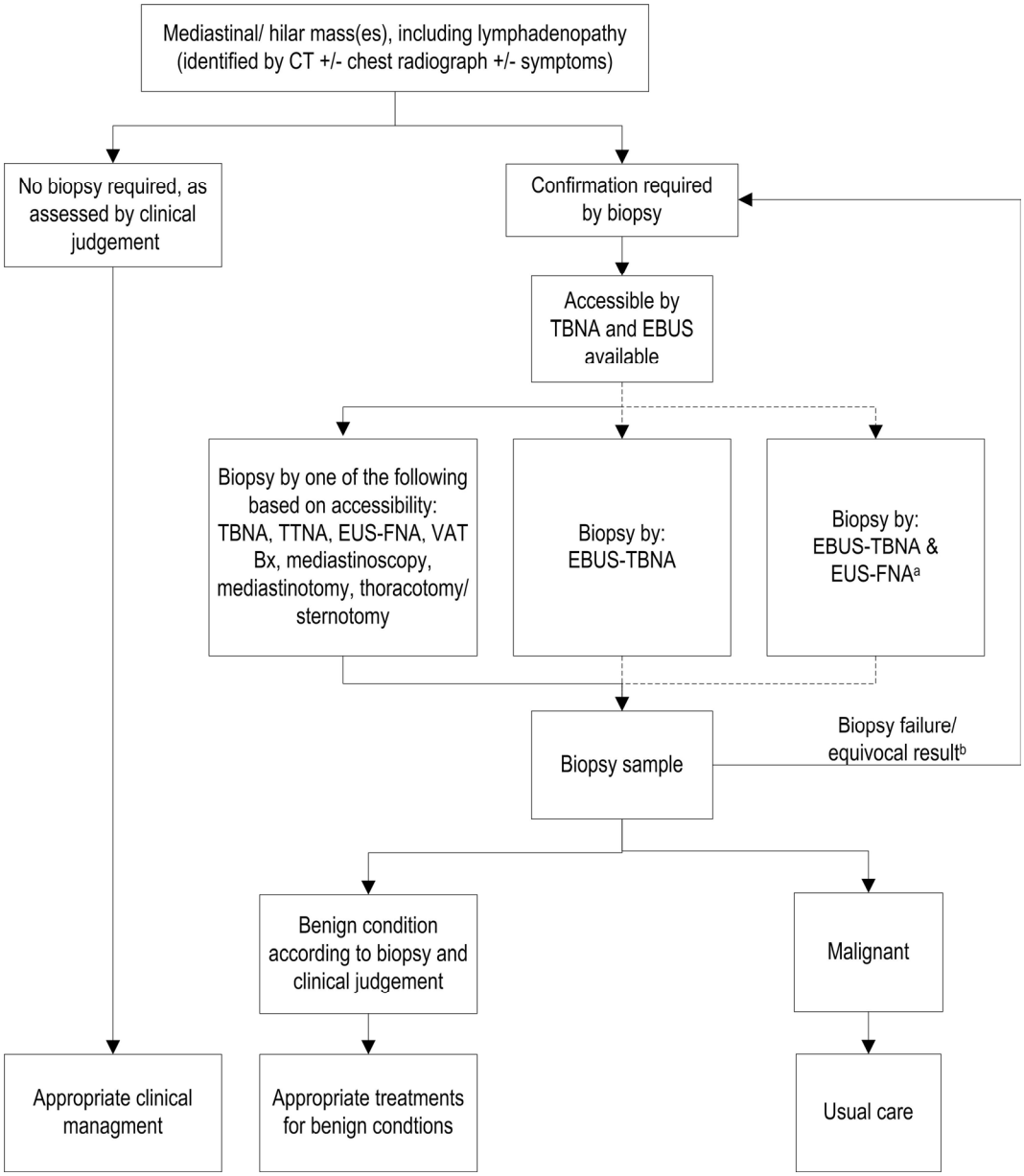

Figure 4 Clinical pathway for the invasive diagnosis of patients with mediastinal/hilar masses of unknown origin

Abbreviations: Bx, biopsy; CT, computed tomography; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; PET, positron emission tomography; TBBX, transbronchial biopsy; TTNA, transthoracic needle aspiration; VAT, video assisted thoracoscopy

[a] EBUS and EUS-FNA procedures are undertaken in the same session in any order to theoretically enable access to the whole of the mediastinum as they are complementary techniques (Other considerations, p. 70)

[b] Biopsy unsuccessful (tumour not accessed or inadequate sample) or equivocal result

Note: The broken line indicates the proposed positions of EBUS-TBNA in the clinical pathway

Depth diagnosis of endobronchial cancers

The PPICO criteria developed *a priori* to evaluate endobronchial ultrasound (EBUS) with or without endobronchial biopsy (EBBX) for diagnosing the depth of endobronchial cancers are indicated in Table 8.

Table 8 PPICO criteria for the use of EBUS with or without EBBX in diagnosing the depth of endobronchial cancers

Population	Prior tests	Intervention/ test	Comparator	Reference standard	Outcomes
Patients with presumed or known NSCLC without mediastinal/ hilar lymphadenopathy identified by prior tests	Clinical assessment CT +/– PET (where available)	EBUS +/– EBBX	EBBX	Histology sample Clinical follow-up of adequate length	Change in clinical outcomes[a] Change in clinical management[b] Diagnostic accuracy[c] Safety outcomes[d]

Abbreviations: CT, computed tomography; EBBX, endobronchial biopsy; EBUS, endobronchial ultrasound; NSCLC, non-small cell lung cancer; PET, positron emission tomography

[a] Survival (disease-free survival, overall survival); morbidity (disease recurrence, disease progression); quality of life

[b] Alterations in treatment plan (eg exploratory surgery, surgical resection, excision by minimally invasive techniques, chemotherapy, radiotherapy, palliative treatments, imaging surveillance); alterations in diagnostic plan (eg other diagnostic/staging procedures)

[c] Sensitivity and specificity estimates; positive and negative likelihood ratios; summary diagnostic measures (eg diagnostic odds ratio, summary receiver operating characteristics)

[d] Adverse event reports; adverse events known to be associated with EBUS or its comparators (eg perforation, tears, bleeding, infection, tumour seeding, scope damage); patient discomfort/tolerance to the procedure

The research question for this indication, based on these criteria, was as follows.

To what extent is endobronchial ultrasound with or without endobronchial biopsy:

- safe, and
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in the invasive staging (tumour depth) of patients with presumed or known NSCLC without mediastinal/hilar lymphadenopathy relative to endobronchial biopsy?

The clinical pathway for the depth diagnosis of endobronchial cancers to the point of patient diagnosis is shown in Figure 5.

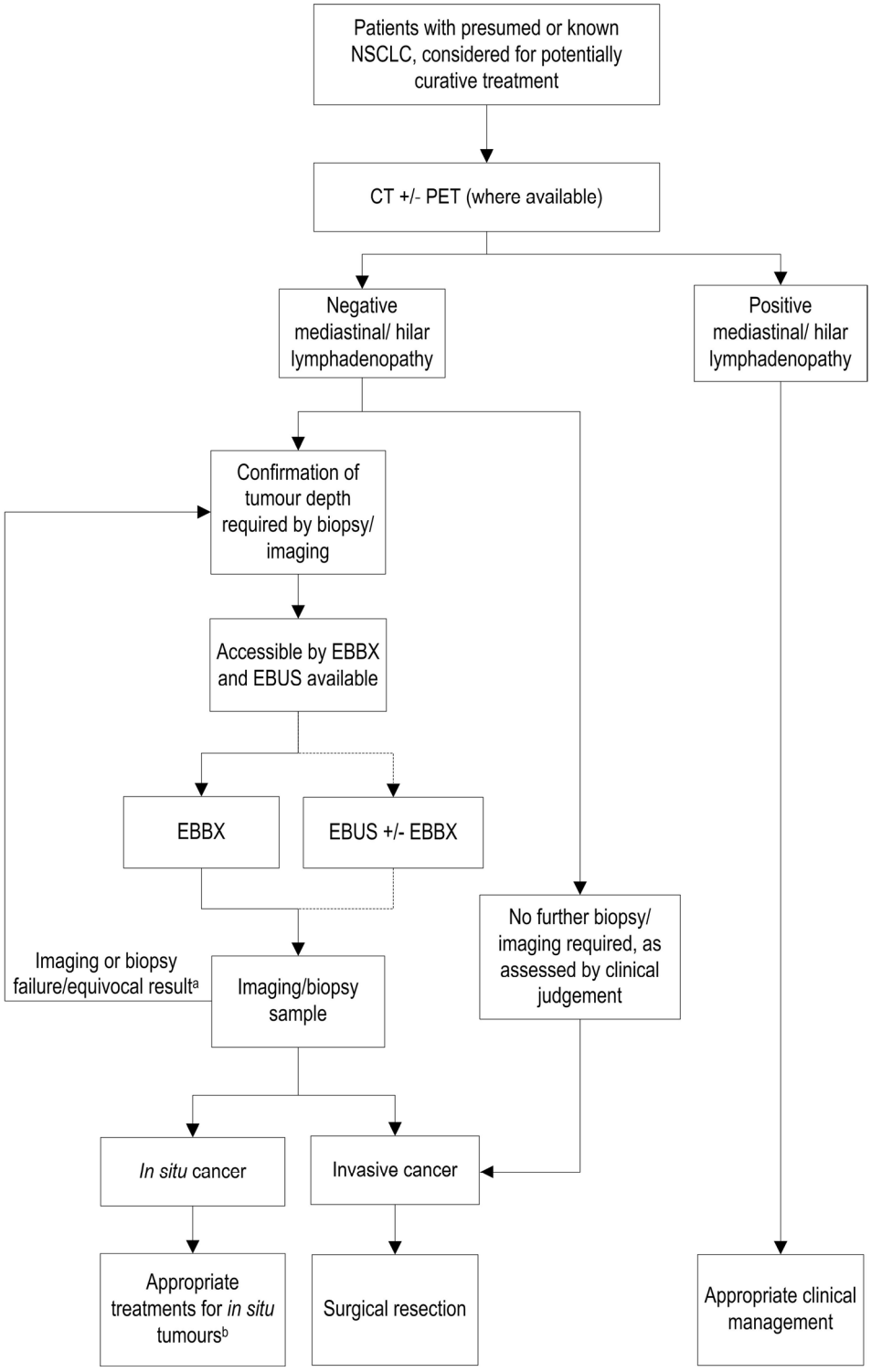

Figure 5 Clinical pathway for depth diagnosis of endobronchial cancers

Abbreviations: CT, computed tomography; EBBX, endobronchial biopsy; EBUS, endobronchial ultrasound; NSCLC, non-small cell lung cancer; PET, positron emission tomography

[a] Imaging/biopsy unsuccessful (tumour not accessed or inadequate sample/image) or equivocal result

[b] Appropriate treatments include photodynamic therapy, brachytherapy, electrocautery, cryotherapy and Nd:YAG laser therapy

Note: The broken lines indicate the proposed positions of EBUS +/–EBBX in the clinical pathway. An alternative biopsy technique may be used when re-testing

Peripheral lung lesion

The PPICO criteria developed *a priori* to evaluate endobronchial ultrasound transbronchial biopsy (EBUS-TBBX) for diagnosis of patients with peripheral lung lesions are indicated in Table 9.

Table 9 PPICO criteria for the use of EBUS-TBBX in the invasive diagnosis of patients with peripheral lung lesions

Population	Prior tests	Intervention/test	Comparator	Reference standard	Outcomes
Patients with a peripheral lung lesion identified by prior tests	Clinical assessment CT +/– PET (where available and indicated)	EBUS-TBBX	TTNA or TBBX[a]	Histology sample Clinical follow-up of adequate length	Change in clinical outcomes[b] Change in clinical management[c] Diagnostic accuracy[d] Safety outcomes[e]

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; PET, positron emission tomography; TBNA, transbronchial needle aspiration; TBBX, transbronchial biopsy; TTNA, transthoracic needle aspiration

[a] Including CT-guidance, fluoroscopic guidance and electromagnetic guidance

[b] Survival (disease-free survival, overall survival); morbidity (disease recurrence, disease progression); quality of life

[c] Alterations in treatment plan (eg exploratory surgery, surgical resection, excision by minimally invasive techniques, chemotherapy, radiotherapy, palliative treatments, imaging surveillance); alterations in diagnostic plan (eg other diagnostic/staging procedures)

[d] Sensitivity and specificity estimates; positive and negative likelihood ratios; summary diagnostic measures (eg diagnostic odds ratio, summary receiver operating characteristics)

[e] Adverse event reports; adverse events known to be associated with EBUS or its comparators (eg perforation, tears, bleeding, infection, tumour seeding, scope damage, pneumothorax); patient discomfort/tolerance to the procedure

The research question for this indication, based on these criteria, was as follows.

To what extent is endobronchial ultrasound guided transbronchial biopsy:

- safe, and
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in the invasive diagnosis of patients with peripheral lung lesions relative to transthoracic needle aspiration or transbronchial biopsy?

The clinical pathway for the invasive diagnosis of patients with peripheral lung lesions is displayed in Figure 6.

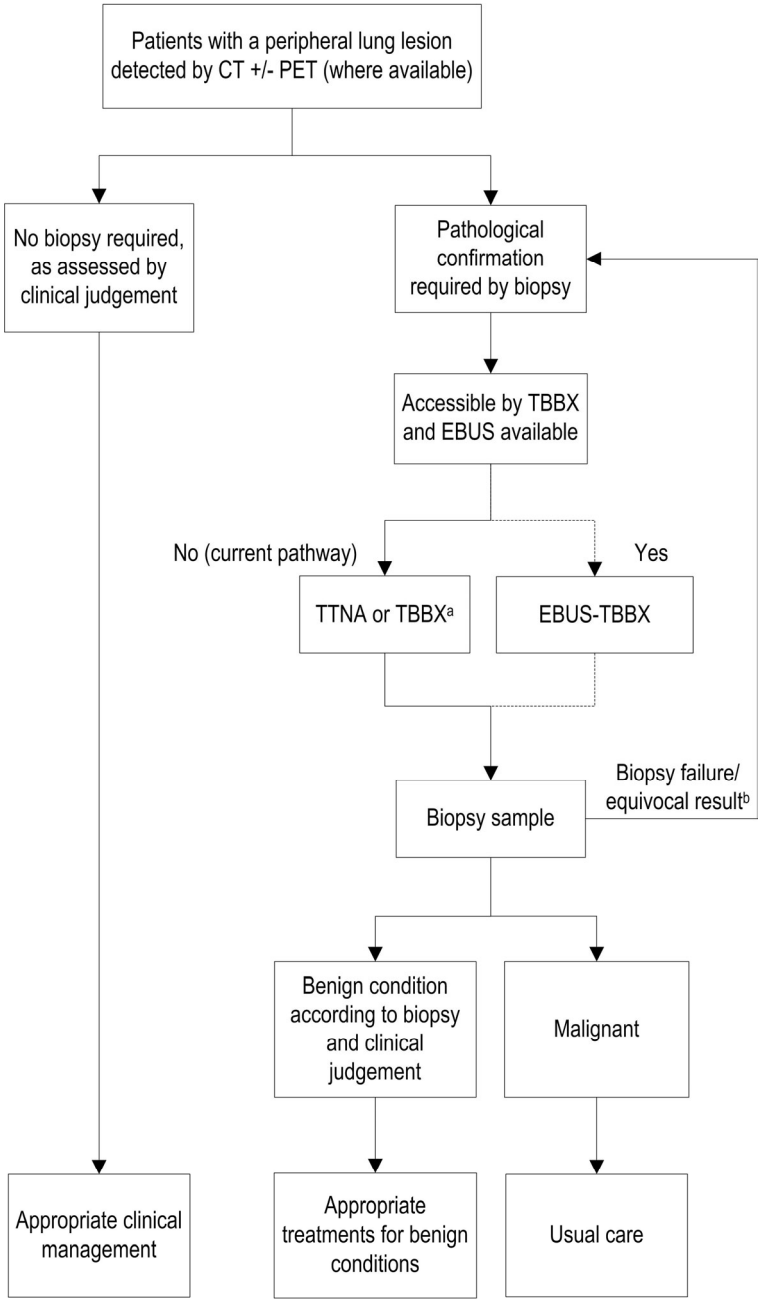

Figure 6 Clinical pathway for invasive diagnosis of patients with peripheral lung lesions

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; PET, positron emission tomography; TBBX, transbronchial biopsy; TTNA, transthoracic needle aspiration

[a] Including CT-guidance, fluoroscopic guidance and electromagnetic guidance

[b] Biopsy unsuccessful (tumour not accessed or inadequate sample) or equivocal result. There may be occasions where EBUS returns a benign result but because of clinical judgment further invasive testing is indicated

Note: The broken lines indicate the proposed position of EBUS-TBBX in the clinical pathway. An alternative biopsy technique may be used when re-testing

Assessment framework

Types of evidence

A systematic review of the clinical literature identified relevant studies that examined the value of endobronchial ultrasound (EBUS)-guided procedures for non-small cell lung cancer (NSCLC) staging, diagnosis of mediastinal/hilar masses of unknown origin, depth diagnosis of endobronchial cancers, and diagnosis of peripheral lung lesions. Direct evidence regarding the impact of EBUS-guided procedures on health outcomes was sought. The literature search was not limited by outcomes or comparators. In the absence of studies providing direct evidence, indirect evidence indicating the impact of EBUS guided procedures on clinical management and diagnostic accuracy was assessed.

Review of the literature

The clinical literature was searched to identify all relevant studies and reviews published to June 2007.

Search strategy

Primary databases

Searches were conducted in the primary databases indicated in Table 10. A review of the MEDION database did not identify any additional, non-duplicate, relevant citations.

Table 10 Electronic databases searched during the review of EBUS-guided transbronchial sampling procedures

Database	Date searched
Medline and EMBASE[a]	4 June 2007
PreMedline[b]	7 June 2007
Cochrane Library	4 June 2007 (Issue 2, 2007)

[a] Using the EMBASE.com interface
[b] Using the PubMed interface

The search terms included the following (as determined from the PPICO criteria):

- EBUS, endobronchial ultrasound, endobronchial echography, bronchoscopy *and* ultrasound or echography

Comprehensive details of the literature searches performed using the primary databases are presented in **Appendix F**.

Secondary databases

A review of databases maintained by health technology assessment (HTA) agencies was undertaken to identify existing reports of EBUS-guided procedures. The list of secondary databases searched is presented in **Appendix F**.

Additional searches were conducted to locate quality of life, epidemiological and economic information, as required.

Citation lists

The citation lists of included studies were searched to identify any additional studies.

Selection criteria

Selection criteria presented in Table 11, Table 12, Table 13 and Table 14 were applied to the citations identified in the literature search results. Studies that did not meet the pre-specified inclusion criteria were excluded from further analysis. Studies with small patient numbers (less than 10 patients) or data inadequacies were also excluded.

Table 11 Selection criteria for studies of EBUS-TBNA in the invasive (nodal) staging of patients with presumed or known NSCLC

Characteristic	Inclusion criteria	Exclusion criteria
Publication type	Clinical studies	Studies of < 10 patients
Patient	Patients with presumed or known NSCLC with mediastinal/hilar lymphadenopathy	
Prior tests	CT +/– PET	
Intervention/test	EBUS-TBNA; EBUS-TBNA and EUS-FNA	Non-standard/obsolete EBUS procedure
Comparators	Current techniques for biopsy of mediastinal/ hilar lymph nodes[a]	
Reference standard	Histopathology	
	Long-term clinical follow-up	
Outcome	Change in clinical management	Inadequate data reporting
	Change in clinical outcomes	
	Diagnostic accuracy	
Language	English language articles[b]	

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; FNA, fine needle aspiration; NSCLC, non-small cell lung cancer; PET, positron emission tomography; TBNA, transbronchial needle aspiration; TTNA, transthoracic needle aspiration; VAT, video-assisted thoracoscopy

[a] EUS-FNA, mediastinoscopy, mediastinotomy, TBNA, TTNA or VAT

[b] Non-English language articles were excluded unless they appeared to provide a higher level of evidence than English language articles

Table 12 Selection criteria for studies of EBUS-TBNA in invasive diagnosis of patients with mediastinal/hilar masses of unknown origin

Characteristic	Inclusion criteria	Exclusion criteria
Publication type	Clinical studies	Studies of < 10 patients
Patient	Patients with mediastinal/ hilar masses of unknown origin (including lymphadenopathy)	
Prior tests	CT	
Intervention/test	EBUS-TBNA; EBUS-TBNA and EUS-FNA	Non-standard/obsolete EBUS procedure
Comparators	Current techniques for biopsy of mediastinal/ hilar masses[a]	
Reference standard	Histopathology	
	Long-term clinical follow-up	
Outcome	Change in clinical management	Inadequate data reporting
	Change in clinical outcomes	
	Diagnostic accuracy	
Language	English language articles[b]	

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; FNA, fine needle aspiration; TBNA, transbronchial needle aspiration; TTNA, transthoracic needle aspiration; VAT, video-assisted thoracoscopy

[a] EUS-FNA, mediastinoscopy, mediastinotomy, TBNA, TTNA or VAT

[b] Non-English language articles were excluded unless they appeared to provide a higher level of evidence than English language articles

Table 13 Selection criteria for studies of EBUS with or without EBBX in the depth diagnosis of endobronchial cancers

Characteristic	Inclusion criteria	Exclusion criteria
Publication type	Clinical studies	Studies of < 10 patients
Patient	Patients with presumed or known NSCLC	Patient population of mixed indications with inadequate data separation
Prior tests	CT +/– PET	
Intervention/test	EBUS +/– EBBX	Non-standard/obsolete EBUS procedure
Comparators	EBBX	
Reference standard	Histopathology	
	Long-term clinical follow-up	
Outcome	Change in clinical management	Inadequate data reporting
	Change in clinical outcomes	
	Diagnostic accuracy	
Language	English language articles[a]	

Abbreviations: CT, computed tomography; EBBX, endobronchial biopsy; EBUS, endobronchial ultrasound; NSCLC, non-small cell lung cancer; PET, positron emission tomography

[a] Non-English language articles were excluded unless they appeared to provide a higher level of evidence than English language articles

Table 14 Selection criteria for studies of EBUS-TBBX in the invasive diagnosis of patients with peripheral lung lesions

Characteristic	Inclusion criteria	Exclusion criteria
Publication type	Clinical studies	Studies of < 10 patients
Patient	Patients with peripheral lung lesions	Studies limited to only lung cancer cases; studies limited to benign diagnoses only
Prior tests	CT +/– PET	
Intervention/test	EBUS-TBBX	Non-standard/obsolete EBUS procedure
Comparators	TTNA or TBBX[a]	
Reference standard	Histopathology	Inadequate reporting of reference standard
	Long-term clinical follow-up	
Outcome	Change in clinical management	Inadequate data reporting
	Change in clinical outcomes	
	Diagnostic accuracy	
Language	English language articles[b]	

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; PET, positron emission tomography; TBBX, transbronchial biopsy; TTNA, transthoracic needle aspiration

[a] Including CT-guidance, fluoroscopic guidance and electromagnetic guidance

[b] Non-English language articles were excluded unless they appeared to provide a higher level of evidence than English language articles

Search results

The QUOROM (quality of reporting of meta-analyses) flowchart (Figure 7) summarises reasons for exclusion of studies. A total of 712 non-duplicate references were identified: 39 were reviewed for safety data; 21 for effectiveness; and one was included in the economics review. A paper prepared for the Committee for Evaluation and Diffusion of Innovative Technologies (CEDIT) was potentially relevant to the review, but could not be obtained.

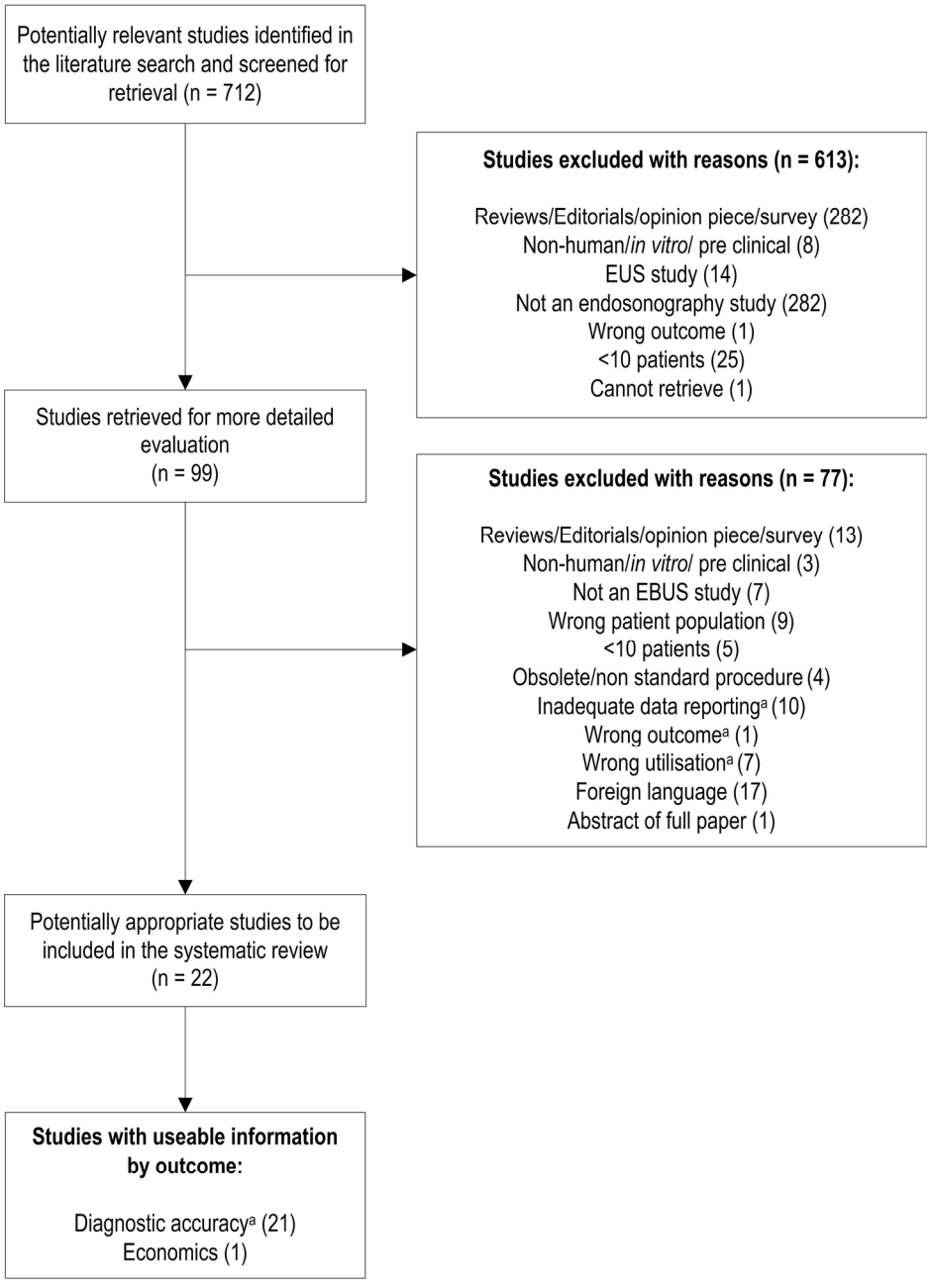

Figure 7 QUOROM flowchart used to identify and select studies for EBUS-guided procedure literature review

[a] These studies were reviewed for the assessment of safety
Adapted from Moher et al (1999)

Study appraisal

Direct evidence concerning the value of EBUS-guided procedures relative to current clinical practice, when used for the relevant patient group, is required to justify public funding. Such evidence should ideally be sourced from studies reporting effects on patient-centred health outcomes. Otherwise, evidence indicating that the diagnostic test being assessed has greater diagnostic accuracy than the comparator, along with linked evidence of management change, and that treatment will affect health outcomes, is required.

Data indicating an effect on management change is a key component of the evidence base where an additional diagnostic test is to be included in the clinical pathway. The most appropriate design to investigate effects on management change is a pre-test/post-test case series study. Studies that do not report pre-test management plan outcomes may not truly reflect change in patient management. Reported outcomes from these studies must be treated with a high index of suspicion about possible bias.

The ideal study design to establish comparative accuracy of diagnostic tests is one in which each test is performed in a population with a defined clinical presentation, in a consecutive series. The study should be an independent, blinded comparison with a valid reference standard (NHMRC 2005).

Assessment of eligible studies

Evidence retrieved from literature searches was assessed according to the NHMRC dimensions of evidence (Table 15) where applicable. There are three main domains: strength of the evidence, size of the effect, and relevance. Evidence strength is derived directly from the literature identified for a particular diagnostic test. Evidence of effect size and relevance require expert clinical input as part of the determination process.

An aspect of the strength of the evidence domain is the level of evidence of the study, which was assigned using the NHMRC levels of evidence outlined in Table 16. The quality and applicability of the included studies was assessed according to pre-specified criteria (**Appendix G**).

Table 15 NHMRC dimensions of evidence

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design[a]
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The *p* value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the null value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

Source: NHMRC (2005)
[a] See Table 16

Table 16 Designations of levels of evidence according to research question

Level	Intervention[b]	Diagnosis[e]
I [a]	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard[f] among consecutive patients with a defined clinical presentation[g]
III-1	A pseudo-randomised controlled trial (ie alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard[f] among non-consecutive patients with a defined clinical presentation[g]
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial[c] Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study[d] Interrupted time series without a parallel control group	Diagnostic case-control study[g]
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[h]

Source: NHMRC (2005)
[a] A systematic review can only be assigned a level of evidence as high as the studies it contains, except where those studies present level II evidence
[b] Study design definitions are provided in *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b) pp 7–8
[c] This also includes controlled pre-test/post-test studies and indirect comparisons (ie use A vs B and B vs C, to determine A vs C)
[d] Comparing single arm studies ie case series from two studies
[e] The dimensions of evidence apply only to diagnostic accuracy studies. Assessments of diagnostic tests effectiveness need to consider test impact on patient management and health outcomes. See MSAC (2004) *Guidelines for the assessment of diagnostic technologies* www.msac.gov.au
[f] Reference standard validity should be determined in the context of the disease under review. Criteria to determine reference standard validity should be pre-specified. This can include the choice of the reference standard(s) and timing in relation to the index test. Reference standard validity can be determined by appraising study quality. See Whiting et al (2003) 'The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews'. *BMC Med Res Methodol* 3 (25)
[g] Well designed population based case-control studies (population based screening studies that assess test accuracy with a random sample of controls) capture populations with representative spectrum of disease that meet requirements for a valid assembly of patients. In some cases, the assembled population is not representative of test use in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of people known to be disease free. In this situation patients with borderline or mild disease expression and other conditions mimicking the disease are excluded. This can lead to exaggeration of sensitivity and specificity (spectrum bias) because the study participants will not be representative of patients seen in practice
[h] Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative in the absence of reliable reference standard

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harmful events are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results
Note 2: When a level of evidence is attributed in the text of a document, it should be framed according to its corresponding research question eg level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence

The quality of diagnostic accuracy studies was ranked using the composite grading system described in Table 17. In accordance with MSAC guidelines, diagnostic accuracy studies are described according to the extent that they achieve the component factors of study validity.

Table 17 Grading system for appraisal of studies evaluating diagnostic tests

Validity criteria	Description	Grading system
Appropriate comparison	Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?	P1 applicable P2 limited P3 different population
Quality of study	Was the study designed to avoid bias?	
	High quality = no potential for bias based on pre-defined key quality criteria	Q1: high quality
	Fair quality = some potential for bias in areas other than those pre-specified as key criteria	Q2: fair quality
	Poor quality = poor reference standard and/or potential for bias based on key pre-specified criteria	Q3: poor quality

Source: Medical Services Advisory Committee (2005). *Guidelines for the assessment of diagnostic technologies*. Canberra, Commonwealth of Australia

Data analysis

The characteristics of the study, patient population, prior tests, index test, comparator, reference standard, and outcomes measures were extracted from each study. Results of eligible studies were statistically synthesised (meta-analysed) and pooled results presented where appropriate.

Data extraction

A single reviewer extracted relevant information using a standardised data extraction form designed specifically for this assessment. Any uncertainties were resolved by discussion with another reviewer and/or clinical advisers.

Measurement of test accuracy

Evaluating the accuracy of diagnostic tests involves comparing a new test with its comparators and a reference standard—the best available proxy for the true condition status. The new diagnostic test and its comparators can be independently compared with the reference standard to determine measures of test accuracy such as sensitivity, specificity and predictive values.

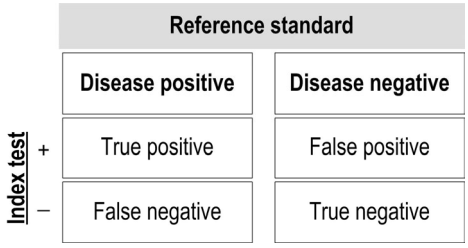

Figure 8 Data used to calculate measures of test accuracy

- True positive = number of patients who test positive and are classified positive by the reference standard
- False negative = number of patients who test negative and are classified positive by the reference standard
- False positive = number of patients who test positive and are classified negative by the reference standard
- True negative = number of patients who test negative and are classified negative by the reference standard.

Sensitivity is defined as the proportion of all patients with a specified condition whose results are determined to be positive according to the index test. Sensitivity is calculated by dividing the true positive (TP) value by the sum of the true positive and the false negative (FN):

$$\frac{TP}{TP+FN}$$

Specificity is the proportion of all patients, who do not have the specified condition, whose results are negative according to the index test. Specificity is calculated by dividing the true negative (TN) by the sum of the true negative and false positive (FP):

$$\frac{TN}{TN+FP}$$

The positive predictive value (PPV) is the proportion of patients with a positive index test result who have the specified condition. The equation to calculate PPV is:

$$\frac{TP}{TP+FP}$$

The *negative predictive value* (NPV) of a test is the proportion of patients with a negative index test result who do not have the specified condition. The equation to calculate NPV is:

$$\frac{TN}{TN+FN}$$

The limited body of evidence assessing the comparative diagnostic accuracy of EBUS-guided procedures meant that diagnostic yield (the numbers of patients receiving a diagnosis divided by the number of patients assessed) was used as a measure of diagnostic test performance. This measure did not consider the number of false positive and false negative results that may be associated with the findings. The diagnostic yield of EBUS-guided procedures and their comparators are therefore likely to overestimate the diagnostic capabilities of these procedures.

Statistics

Confidence intervals for safety and efficacy proportions were estimated at 95 per cent probability levels assuming a normal distribution. However, some safety events are rare, and hence, proportions take extreme values with large standard errors and skewed distributions. In these instances confidence intervals were large and resulted in some negative values for lower limits. These negative values were set to zero in this study.

Expert advice

An advisory panel with expertise in oncology, nuclear medicine, respiratory medicine, thoracic surgery, and consumer affairs was established to evaluate the evidence and provide advice to MSAC from the clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the advisory panel is provided at **Appendix B**.

Assessment of the body of evidence

The overall body of evidence was assessed. A level of evidence ranking from A (excellent) to D (poor) was assigned to each component outlined in the body of evidence matrix presented in Table 18.

Table 18 Body of evidence assessment matrix

Component	A Excellent	B Good	C Satisfactory	D Poor
Volume of evidence	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a systematic review/multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent; and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studies in body of evidence are the same as the target population	Population/s studies in the body of evidence are similar to the target population	Population/s studied in body of evidence different to target population but it is clinically sensible to apply this evidence to the target population	Population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Source: NHMRC (2005). NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Pilot Program 2005–2006. National Health and Medical Research Council, Canberra. Available from: www.nhmrc.gov.au/consult/docfeedback.htm

Results of assessment

Summary

A linked evidence approach was applied to evaluate use of endobronchial ultrasound (EBUS)-guided procedures for staging non-small cell lung cancer (NSCLC), diagnosis of mediastinal/hilar masses, depth diagnosis of endobronchial cancers and diagnosis of peripheral lung lesions. EBUS-guided procedures appear to be as safe as other minimally-invasive diagnostic tests. The most frequently reported adverse events were bleeding and pneumothorax. These mainly occurred among patients who underwent EBUS- or fluoroscopy-guided transbronchial biopsy. There also appeared to be a trend towards a higher frequency of pneumothoraces using electromagnetic navigation bronchoscopy-transbronchial biopsy.

Evidence indicates that the diagnostic yield of EBUS-transbronchial needle aspiration (TBNA) is greater than TBNA alone for NSCLC staging and diagnosis of mediastinal/hilar masses. Sensitivity and diagnostic yield of EBUS-TBNA were at least equivalent to endoscopic ultrasound fine needle aspiration (EUS-FNA) among specific subgroups. There was no evidence to assess the impact of EBUS-TBNA on patient management. Treatment effectiveness was not examined and deemed unnecessary because it was considered that EBUS-TBNA would not identify any unique patient groups that were substantially different from current Australian clinical practice.

No trials were identified that compared the diagnostic performance of EBUS with or without endobronchial biopsy (EBBX) to EBBX alone in the depth diagnosis of endobronchial cancers. In the absence of diagnostic accuracy evidence, substantiation of patient management and treatment effectiveness was not sought.

EBUS-transbronchial biopsy (TBBX) sensitivity is equivalent to fluoroscopy-TBBX in the diagnosis of peripheral lung lesions. Evaluated studies also indicated that the diagnostic yield of EBUS-TBBX was greater than TBBX and at least equivalent to other methods (electromagnetic, fluoroscopic) of guided-TBBX. The diagnostic yield of EBUS-TBBX may be higher than other methods of guided-TBBX for diagnosis of smaller peripheral lesions. There was no evidence to inform assessment of the impact of EBUS-TBBX on patient management. Treatment effectiveness was not examined because it was considered that EBUS-TBBX could not identify any unique patient groups that differed substantially from those seen in Australian clinical practice.

Is it safe?

There were 39 studies reviewed for safety data. Of these, 30 reported endobronchial ultrasound (EBUS)-guided procedures in relevant patient populations. It was likely that there was some overlap among reported patient populations which could artificially inflate the population size and potentially lead to underestimation of adverse event rates. The current safety analysis used the patient populations reported for each study so conclusions based on these data should be interpreted cautiously.

The studies that were assessed reported the safety of a variety of EBUS procedures—EBUS imaging, EBUS-transbronchial needle aspiration (TBNA), EBUS-transbronchial biopsy (TBBX) and electromagnetic navigation bronchoscopy (ENB)/EBUS-TBBX—and comparators—white light/autofluorescence bronchoscopy, TBNA, EUS-fine needle aspiration (FNA), TBBX, fluoroscopy-TBBX and ENB-TBBX. There were no comparative safety data for other major comparators such as mediastinoscopy, transthoracic needle aspiration (TTNA) or endobronchial biopsy (EBBX).

Most studies reported no complications. Adverse events were generally associated only with use of some form of transbronchial biopsy. The only exception was a large study (n = 648) conducted by Herth et al (2001) that combined the safety events using various EBUS procedures. This study reported that 5.3 per cent of patients required supplementary oxygen during the procedure and 2.8 per cent of patients experienced transient cardiac arrhythmias.

With the exception of findings reported by Herth et al (2001), the most frequently reported complications were pneumothorax and bleeding (Table 19). Study authors used terms such as bleeding and moderate bleeding, but because some studies did not clearly report cut-off criteria to categorise bleeding extent, all blood loss events were combined in a single analysis.

All pneumothorax and bleeding events occurred in patients who underwent transbronchial biopsy. The rate of pneumothorax and bleeding adverse events were similar for EBUS-TBBX (1.7% and 1.4%, 655 patients) and fluoroscopy-TBBX (1.1% and 2.2%, 92 patients). There also appeared to be a trend towards a higher frequency of pneumothoraces using ENB-TBBX (5.1%, 39 patients) or ENB/EBUS-TBBX (6.2%, 65 patients), but as indicated by the large confidence intervals, this may reflect the small number of patients included in each analysis.

A safety consideration raised in the literature with relevance to the current review was that fluoroscopy-TBBX and EBUS procedures with fluoroscopic navigation have the potential to expose patients and staff to radiation. The advisory panel indicated that procedure-related radiation is not a major safety issue in Australia because adequate protective measures are applied as a matter of course.

The advisory panel indicated that a single case report of needle breakage (using the dedicated EBUS-linear biopsy apparatus) was presented at a clinical meeting in 2007. No other cases are known to have been reported.

EBUS-guided procedures for non-small cell lung cancer (NSCLC) staging, diagnosis of mediastinal/hilar masses, depth diagnosis of endobronchial cancers and diagnosis of

peripheral lung lesions appear to be as safe as other minimally-invasive diagnostic tests for these indications.

Table 19 Pneumothorax and bleeding adverse events associated with EBUS-guided procedures and comparator technologies

Technique	N	Pneumothorax		Bleeding	
		n	% (95% CI)	n	% (95% CI)
EBUS-guided procedures					
EBUS	182	0	0.00	0	0.00
EBUS-TBNA	1449	0	0.00	0	0.00
EBUS-TBBX	655	11	1.67 (0.64, 2.50)	9	1.37 (0.44, 2.09)
ENB/EBUS-TBBX	65	4	6.15 (0.31, 12.00)	3	4.62 (0.00, 9.70)
Comparators					
WL/AF bronchoscopy	178	0	0.00	0	0.00
TBNA	100	0	0.00	0	0.00
EUS-FNA	220	0	0.00	0	0.00
TBBX	215	3	1.40 (0.00, 3.00)	7	3.26 (0.88, 5.63)
Fluoroscopy-TBBX	92	1	1.09 (0.00, 3.21)	2	2.17 (0.00, 5.15)
ENB-TBBX	39	2	5.13 (0.00, 12.05)	0	0.00

Abbreviations: AF, autofluorescence; CI, confidence interval; EBUS, endobronchial ultrasound; ENB, electromagnetic navigation bronchoscopy; EUS-FNA; endoscopic fine-needle aspiration; TBBX, transbronchial biopsy; TBNA, transbronchial needle aspiration; WL, white light

Is it effective?

Linked evidence

A linked evidence approach was undertaken to evaluate the diagnostic accuracy of EBUS-guided procedures and their impact on patient management and treatment. This approach was necessary because direct evidence indicating the impact of EBUS-guided procedures on health outcomes was not available.

Diagnostic accuracy

The literature search identified 21 diagnostic accuracy studies eligible for review. Of the 21 diagnostic studies, three were excluded because they reported superseded variations of the EBUS procedure (Goldberg et al 1994, Hurter et al 1992, Shannon et al 1996). No patient management or treatment effectiveness evidence was identified.

Nodal staging of NSCLC and diagnosis of mediastinal/hilar masses of unknown origin

No comparative studies were identified that investigated diagnostic accuracy or diagnostic yield of EBUS-guided procedures for nodal staging of NSCLC or mediastinal/hilar masses of unknown origin. The patient population for inclusion was therefore expanded to include studies reporting evaluation of EBUS-guided procedures in mixed populations of patients who were primarily referred for NSCLC staging or

diagnosis of mediastinal/hilar masses of unknown origin. This patient population was assumed to represent clinical practice and applicable to this assessment.

There were 11 studies identified that investigated the diagnostic accuracy or diagnostic yield of EBUS-TBNA in the mixed patient population. Of these, six were excluded from the review on the basis of: evaluation of EBUS diagnostic performance without tissue sampling (Okamoto et al 2002); evaluation conducted using an unusual radial probe, double channel bronchoscope procedure (Kanoh et al 2005); the population was limited to patients whose lymph nodes were not enlarged (Herth et al 2006b); EBUS-TBNA performance was reported per procedure not per patient (Wallace et al 2007); EBUS-TBNA diagnostic performance was not reported (Herth et al 2001, Herth et al 2002).

Of the 11 identified studies, three (Herth et al 2004, Herth et al 2005, Vilmann et al 2005) compared EBUS-TBNA with appropriate comparators; the characteristics of these studies are presented in Table 20.

Of the remaining eight of the 11 identified studies; three were non-comparative assessments of EBUS-TBNA use in NSCLC staging (insert citations for these three studies); four were non-comparative studies assessing EBUS-TBNA in the mixed patient population (insert citations for these four studies); and one study compared EBUS-TBNA with CT and PET imaging in the mixed patient population (insert citation). Details of these eight included studies are presented as supportive evidence in **Appendix C**.

A diagnostic yield (level IV) study by Herth et al (2004) compared EBUS-TBNA with TBNA among patients with enlarged mediastinal lymph nodes. The reported characteristics indicated this to be a high-quality study applicable to the Australian clinical setting.

Another high-quality study conducted by Herth et al (2005) compared the diagnostic yield (level IV) of EBUS-TBNA with EUS-FNA among patients with enlarged mediastinal lymph nodes. The applicability of this study to current clinical practice was reduced because nodes that were not assessable by both techniques were excluded. Therefore, some nodes that were assumed to be accessible using either EBUS-TBNA or EUS-FNA in clinical practice were excluded from the analysis presented in this study. Consequently, results from this study could only be interpreted in the context of the limited patient population.

Vilmann et al (2005) recruited patients with known or suspected lung cancer for staging using both EBUS-TBNA and EUS-FNA. The reported patient characteristics indicate that it was probable that patients without lymph node enlargement were included in the study. This study was classified as providing level III-2 evidence because an inadequate reference standard was used, and patient enrolment and assessor blinding reporting was inadequate. Applicability of this study was further limited by use of TBNA and TTNA as prior tests—this diagnostic work-up does not apply to Australian clinical settings.

Table 20 Characteristics of the included comparative studies assessing diagnostic accuracy and yield of EBUS-TBNA among patients referred for lung cancer staging or diagnosis of mediastinal/hilar masses of unknown origin

Author (year) Country	Study design	Patient characteristics (n)	Test characteristics	Quality and applicability
Herth et al (2004) Germany & USA	Prospective, parallel group RCT[a] Blinding of pathologists June 2001–March 2002	**Inclusion:** Patients referred for lung cancer staging or diagnosis of mediastinal lymphadenopathy of unknown origin *(mediastinal lymph node enlarged)* **Exclusion:** No patients were excluded (n = 200) **Prior test:** CT	**Index test: EBUS-TBNA** [system EU-M 20 and 30, radial probe UM2R/3R, Olympus]; conventional bronchoscope (Excera and p 40D, Olympus); 22 gauge needle; general anaesthesia or conscious sedation; no ROSE **Comparator: TBNA** 22 gauge needle; general anaesthesia or conscious sedation; no ROSE **Reference standard:** Cytology; histology	IV C1, P1, Q1 *Quality:* High *Applicability:* Applicable
Herth et al (2005) Germany	Prospective, cross-over RCT Blinding of pathologists Jan 2002–Jan 2004	**Inclusion:** Patients referred for lung cancer staging or diagnosis of a mediastinal lymphadenopathy of unknown origin *(mediastinal lymph nodes >1 cm)* **Exclusion:** Patients with enlarged lymph nodes not in the following stations 2R, 2L, 3, 4R, 4L, 7, 10R and 10L (n = 160) **Prior test:** CT	**Index test: EBUS-TBNA** [system EU-M 20 and 30, radial probe UM2R/3R, Olympus); conventional bronchoscope (p 20 and p 40D, Olympus); 22 gauge needle; conscious sedation; no ROSE **Comparator: EUS-FNA** [FU36 Pentax or UC 30P Olympus]; 22 gauge needle; conscious sedation; no ROSE **Reference standard:** Cytology; histology	IV C1, P2, Q1 *Quality:* High *Applicability:* Limited Exclusion of relevant lymph node stations
Vilmann et al (2005) Denmark	Prospective, non-consecutive patient series Blinding, not reported	**Inclusion:** Patients with known or suspected lung cancer **Exclusion**: No patients were excluded (n = 33) **Prior test**: CT, PET, TBNA, TTNA	**Index test: EBUS-TBNA** [system EU-C60, Olympus); linear scanning hybrid bronchoscope (XBF-UC40P, Olympus); 22 gauge needle; general anaesthesia; no ROSE; number of aspirates determined by macroscopic appearance of each sample. **Comparator: EUS-FNA** [GF-UCT160, Olympus]; 22 gauge needle; general anaesthesia; no ROSE **Reference standard**: Cytology; histology; clinical/radiological follow-up	III-2 C1, P2, Q3 *Quality*: Poor Inadequate reference standard Unblinded *Applicability*: Limited Unclear lymph node status Enrolled patients with a previous TBNA or TTNA

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration; PET, positron emission tomography; ROSE, rapid on site evaluation; TBNA, transbronchial needle aspiration; TTNA, transthoracic needle aspiration

[a] Two randomisations, Group A: subcarinal lymph nodes, Group B: lymph node stations 2, 3, 4 or aortopulmonary window

The comparative studies by Herth et al (2004), Herth et al (2005) and Vilmann et al (2005) reported diagnostic yield results (see Table 21). Additional data extracted from each study are presented in **Appendix D**.

Herth et al (2004) reported that EBUS-TBNA had a higher diagnostic yield than TBNA (77% vs 63%, respectively). This study also assessed the yield of these tests in two specific sub-groups—Group A: enlarged subcarinal lymph nodes, and Group B: enlarged lymph nodes at stations 2, 3, 4 or the aortopulmonary window. Herth et al (2004) observed that the relative difference in yields was increased in Group B (74% vs 54%) and maintained by Group A (80% vs 72%). When the diagnostic criteria for benign lymph nodes were expanded to include patients with non-malignant lymphocytes, but without a specific benign diagnosis, the yield of both techniques increased, but the relative difference remained similar (85% vs 66%). It is noteworthy that the yield calculated from the tabulated results was different from the yield reported in the text of the paper (EBUS-TBNA 80% vs TBNA 71%); regardless, the yield of EBUS-TBNA remained higher than TBNA.

Herth et al (2005) and Vilmann et al (2005) examined the comparative yield of EBUS-TBNA and EUS-FNA. These studies indicated that EBUS-TBNA obtained equivalent or moderately higher diagnostic yields than EUS-FNA in their respective patient populations. The results of both studies also suggest that EBUS-TBNA combined with EUS-FNA may obtain higher yields than either test alone. The relative yield of the different techniques remained similar in the study by Herth et al (2005) when the diagnosis of benign pathology was expanded to include patients with non-malignant lymphocytes but without specific benign diagnoses.

Table 21 Diagnostic yields of included comparative studies assessing EBUS-TBNA among patients referred for NSCLC staging and diagnoses of mediastinal/hilar masses of unknown origin

Author (year)	n/N (%)	Diagnostic test	Specific diagnostic yield[a]		Non-specific diagnostic yield[b]		Level of evidence
			n/N	% (95% CI)	n/N	% (95% CI)	
Herth et al (2004)	NR	EBUS-TBNA	77/100	77.00 (68.75, 85.25)	85/100	85.00 (78.00, 92.00)	IV C1 P1 Q1
		TBNA	63/100	63.00 (53.54, 72.63)	66/100	66.00 (56.72, 75.28)	
Herth et al (2005)	NR	EBUS-TBNA	137/160	85.63 (80.19, 91.06)	142/160	88.75 (83.85, 93.65)	IV C1 P2 Q1
		EUS-FNA	121/160	75.63 (68.97, 82.28)	126/160	78.75 (72.41, 85.09)	
		EBUS-TBNA/ EUS-FNA	151/160	94.38 (90.80, 97.95)	155/160	96.88 (94.18, 99.57)	
Vilmann et al (2005)	NR	EBUS-TBNA	NR	NR	32/33	96.97 (91.92, 100.00)	III-2 C1 P2 Q3
		EUS-FNA	NR	NR	32/33	96.97 (91.92, 100.00)	
		EBUS-TBNA/ EUS-FNA	NR	NR	33/33	100.00	

Abbreviations: CI, confidence interval; EBUS, endobronchial ultrasound; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration; NR, not reported; TBNA, transbronchial needle aspiration

[a] Per patient diagnostic yield when the diagnosis of a benign lymph node was restricted to requiring a specific diagnosis

[b] Per patient diagnostic yield when diagnosis of a benign lymph nodes was expanded to patients with non malignant lymphocytes but without specific benign diagnoses

When the non-specific diagnostic yields of the included comparative trials (Table 21) and the supportive non-comparative trials (Table 54) were examined, a trend toward higher yield with linear EBUS-TBNA (approximately 95%) compared with radial EBUS-TBNA (approximately 85%) was noted. No direct comparisons of these techniques were identified for this patient population.

The low quality, limited applicability study by Vilmann et al (2005) also reported the comparative sensitivity, specificity and predictive values of EBUS-TBNA and EUS-FNA (Table 22). The reported positive results from this study were not confirmed because malignant cytological diagnosis established using these techniques was taken as confirmation of malignancy. (This indicates that the reference standard was inadequate). For the purpose of this assessment, the reported specificity and positive predicted value (PPV) were not used as measures of test accuracy. The PPV was applied only as an assumption in conjunction with the negative predicted value (NPV) to calculate an approximate sensitivity for each diagnostic test. The study found that EBUS-TBNA appeared to be as sensitive as EUS-FNA (85% vs 80% respectively) in assessing malignant lymph nodes in a mixed patient population. The study also found that when these techniques were combined sensitivity was superior to either test alone (100%). Issues concerning study quality, applicability and the small patient population meant that the study's accuracy results were of limited value.

Table 22 Accuracy of EBUS-TBNA compared with EUS-FNA in patients referred for NSCLC staging and diagnosis of mediastinal/hilar masses of unknown origin

Author (year)	Prevalence n/N (%)	Diagnostic test	Sensitivity (95% CI)[a]	Negative predictive value (95% CI)	Level of evidence
Vilmann et al (2005)	20/28 (71.43)[b]	EBUS-TBNA	85.00 (77.41, 92.59)	72.73 (56.35, 89.30)	III-2 C1 P2 Q3
		EUS-FNA	80.00 (65.18, 94.81)	66.67 (49.21, 84.13)	
		EBUS-TBNA/ EUS-FNA	100.00	100.00	

Abbreviations: CI, confidence interval; EBUS, endobronchial ultrasound; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration; TBNA, transbronchial needle aspiration

[a] Sensitivity was calculated assuming PPV = 100%

[b] Excluded two patients whose samples were inadequate and three patients whose final diagnoses were inconclusive from analysis of diagnostic accuracy

Available evidence indicated that the diagnostic yield of EBUS-TBNA was better than TBNA for NSCLC staging and diagnosis of mediastinal/hilar masses of unknown origin. Evidence also suggested that the sensitivity and diagnostic yield of EBUS-TBNA were at least equivalent to EUS-FNA among subgroups of patients who had prior TBNA/TTNA testing, or to investigate lymph node enlargement accessible by both EBUS-TBNA and EUS-FNA.

Individual rankings for components of the body of evidence are shown in Table 23. Evidence is limited due to the small number of level III and level IV diagnostic studies currently available. These studies do not fully address the diagnostic performance of EBUS-TBNA compared with the major comparators—TBNA and mediastinoscopy.

Table 23 Assessment of the comparative body of evidence for EBUS-TBNA in NSCLC staging and diagnosis of mediastinal/hilar masses of unknown origin

Component	Rank	Reason
Volume of evidence	D	A small number of comparative diagnostic yield (IV) and low-quality diagnostic accuracy studies (III) were identified
Consistency	B	The reported outcomes were generally consistent in comparative trials when radial EBUS-TBNA and linear EBUS-TBNA were considered separately
Clinical impact	D	The reported diagnostic yield of EBUS-TBNA was greater than TBNA. No studies reported diagnostic accuracy of EBUS-TBNA compared with TBNA
		No studies were identified that compared the diagnostic performance of EBUS-TBNA with mediastinoscopy
		The reported sensitivity and diagnostic yield of EBUS-TBNA was at least equivalent to EUS-FNA in selected patient subgroups
Generalisability	B	The study populations did not correspond to the research questions, however it was presumed that the reported populations were representative of clinical practice and therefore relevant to the current assessment
Applicability	C	The diagnostic yield evidence of EBUS-TBNA compared with TBNA was applicable to the Australian healthcare setting
		The evidence of EBUS-TBNA compared with EUS-FNA had limited applicability to the Australian healthcare setting

Abbreviations: EBUS, endobronchial ultrasound; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration; TBNA, transbronchial needle aspiration

Endobronchial cancer depth diagnosis

No trials were identified that compared diagnostic accuracy of EBUS with or without EBBX to EBBX alone in the depth diagnosis endobronchial carcinomas for patients whose lymph nodes were not enlarged.

All nine potentially relevant studies were excluded from the assessment for a range of reasons: EBUS performance was reported per procedure not per patient (Miyazu et al 2002, Takahashi et al 2003); lymphadenopathy status was unclear (Baba et al 2002, Herth et al 2003b, Kotsianos-Hermle et al 2007, Kurimoto et al 1998, Takemoto et al 2000); and EBUS was used to diagnose benign/malignant status of central lesions (Becker et al 2000, Herth et al 2003a).

Peripheral lung lesions

There were 10 studies identified that investigated the diagnostic accuracy or diagnostic yield of EBUS-TBBX in the diagnosis of peripheral lung lesions. Of the 10 studies, five were excluded from the review because they evaluated the diagnostic performance of EBUS imaging alone without tissue sampling (Chao et al 2006, Kurimoto et al 2002, Omori et al 2002), or limited the patient population to patients with lung cancer (Yang et al 2004), or reported the performance of EBUS-TBBX per lesion not per patient (Asahina et al 2005).

Of the 10 studies, four compared radial EBUS-TBBX with other appropriate forms of guided or unguided TBBX (Eberhardt et al 2007, Herth et al 2002, Paone et al 2005, Shirakawa et al 2004); the characteristics of these studies are presented in Table 25. Of the remaining six, five were non-comparative studies of radial EBUS-TBBX and one an RCT that investigated variations of the radial EBUS-TBBX procedure. Details of these studies are presented as supportive evidence in **Appendix C**.

Of the 10 identified studies, Shirakawa et al (2004) recruited patients who had peripheral lung lesions and normal visible airways. The EBUS-TBBX procedure reported in the study used a radial EBUS probe (with guide sheath), fluoroscopic navigation, and curette support to obtain histological and cytological biopsy samples. Curette supports are used occasionally in Australia and the reported procedure is applicable to the Australian clinical setting. Patients were enrolled on a randomised basis, but assessors were not blinded to the test results. Although patients were randomly enrolled to undergo EBUS-TBBX, their results (comparative sensitivity, specificity and predictive values) were compared with a fluoroscopy-TBBX historical control (Table 24). Confirmation of positive results was not clear in this study (the reference standard was inadequate). Reported specificity and positive predictive value (PPV) were not used as measures of test accuracy for this assessment. PPV was applied as an assumption only with NPV to calculate an approximate sensitivity for each diagnostic test. The study suggested that EBUS-TBBX may be equally as sensitive as fluoroscopy-TBBX for the diagnosis of peripheral lung lesions (71% vs 70%, respectively). The diagnostic accuracy results of this study had limited value because of quality and applicability deficits coupled with the limitations of a small patient population. This study was regarded as low quality and limited applicability providing level III-3 evidence.

Table 24 Accuracy of EBUS-TBBX compared with fluoroscopy-TBBX in patients with peripheral lesions

Author (year)	Prevalence n/N (%)	Diagnostic test	Sensitivity (95% CI)[a]	NPV (95% CI)	Level of evidence
Shirakawa et al (2004)	24/49 (48.98)	EBUS-TBBX	70.83 (58.10, 83.56)	78.13 (66.56, 89.70)	III-3 C1 PX Q3
	23/42 (54.76)[b]	Fluoroscopy-TBBX	69.57 (55.65, 83.48)	73.08 (59.67, 86.49)	

Abbreviations: CI, confidence interval; EBUS, endobronchial ultrasound; NPV, negative predictive value; TBBX, transbronchial biopsy
[a] Sensitivity was calculated assuming 100% PPV
[b] Historical control group

Of the 10 identified studies, three were RCTs that assessed the diagnostic yield of EBUS-TBBX compared with ENB-TBBX (Eberhardt et al 2007), fluoroscopy-TBBX (Herth et al 2002) or TBBX (Paone et al 2005). These studies were classified as providing level IV evidence and had limited applicability to Australian clinical practice because they did not report fluoroscopic navigation use in conjunction with EBUS. Differences in quality among these studies could not be accommodated by NHMRC levels of evidence. Only the study by Paone et al (2005) reported blinding the assessors to the test results.

Of the 10 studies, only two compared EBUS-TBBX with fluoroscopy-TBBX (Shirakawa et al 2004, Herth et al 2002), one of the major comparators identified by the advisory panel. No evidence was identified that compared EBUS-TBBX with TTNA, the other major comparator in this indication.

Table 25 Characteristics of the included comparative studies assessing the diagnostic accuracy/yield of EBUS-TBBX in patients with peripheral lung lesions

Author (year) Country	Study design	Patient characteristics	Test characteristics	Quality and applicability
Eberhardt et al (2007) Germany, USA	Prospective, parallel group RCT Blinding, not reported Jan 2003–Aug 2006	**Inclusion:** Patients with peripheral lung lesions or solitary pulmonary lesions with no endobronchial abnormalities found on CT **Exclusion:** Patients < 18 years of age; patients who did not give informed consent; pregnant patients, patients with implantable cardiac devices, patients who had non-diagnostic bronchoscopies who declined surgical biopsy (n = 118) **Prior tests:** CT	**Index test: EBUS-TBBX (GS)** [radial probe UM-BS20-26R, Olympus]; conventional bronchoscope (IT160, Olympus); guide sheath; biopsy forceps; moderate sedation or general anaesthesia **Comparator: ENB-TBBX** (superDimension/Bronchus system, superDimension); conventional bronchoscope (IT160, Olympus); biopsy forceps; moderate sedation or general anaesthesia **Reference standard:** Histology	IV C1, P2, Q2 *Quality:* Medium Blinding unclear *Applicability:* Limited No fluoroscopic navigation of EBUS procedure
Herth et al (2002) Germany, USA	Prospective, cross-over RCT Unblinded Nov 2000–Feb 2001	**Inclusion:** Patients with peripheral lung lesions **Exclusion:** No reported exclusions (n = 50) **Prior tests:** CT	**Index test: EBUS-TBBX** [radial probe UM-3R, UM-4R, US20-20R, Olympus]; conventional bronchoscope (BF 1T-30, BF 1T 40 and BF XT 20, Olympus); bronchial forceps; general anaesthesia or conscious sedation; ≥ 4 biopsy specimens were obtained **Comparator: fluoroscopy-TBBX** (Super 50 CP, Phillips); conventional bronchoscope (BF 1T-30, BF 1T 40 and BF XT 20, Olympus); general anaesthesia or conscious sedation; at least 4 biopsy specimens were obtained **Reference standard:** Histology	IV C1, P2, Q2 *Quality:* Medium Unblinded *Applicability:* Limited No fluoroscopic navigation of EBUS procedure
Paone et al (2005) Italy	Prospective, parallel group RCT Blinding of pathologists Jan 2001–Sep 2003	**Inclusion:** Patients with peripheral lung lesions **Exclusion:** Patients who were < 18 years of age, outpatients, did not give informed consent, did not accomplish complete follow-up, did not accept randomisation, underwent lung surgery before bronchoscopy, primary lesion at another site, lung lesion disappeared at follow-up, lost to follow-up (n = 206) **Prior tests:** CT	**Index test: EBUS-TBBX** [system EU-M30 with radial probe, Olympus]; conventional bronchoscope (BF-B3 or BF-T20, Olympus); bronchial forceps; local anaesthesia; ≥ 5 biopsy specimens were obtained **Comparator: TBBX** target lesion localised by prior CT; conventional bronchoscope (BF-B3 or BF-T20, Olympus); bronchial forceps; local anaesthesia; ≥ 5 biopsy specimens were obtained **Reference standard:** Cytology; histology; clinical/radiological follow-up	IV C1, P2, Q1 *Quality*: High *Applicability*: Limited No fluoroscopic navigation of EBUS procedure

Author (year) Country	Study design	Patient characteristics	Test characteristics	Quality and applicability
Shirakawa et al (2004) Japan	Randomised patient series with historical control Unblinded Jan 2001–Dec 2001	**Inclusion:** Patients with peripheral lung lesions and normal visible airways **Exclusion:** Patients who were not randomised to EBUS, patients who did not undergo EBUS, patients with spontaneous bleeding, patients with no final diagnosis (n = 49) **Prior tests:** X-ray	**Index test: EBUS-TBBX (GS)** [radial probe UM-3R, UM-4R, US-20-20R, Olympus]; conventional bronchoscope (BS 1T-240R, Olympus); guide sheath; bronchial forceps and bronchial brushing; unclear anaesthesia; fluoroscopy and curette support **Fluoroscopy-TBBX;** unclear details **Reference standard:** Cytology; histology; clinical/radiological follow-up; other examinations	III-3 C1, P2, Q3 *Quality*: low Inadequate reference standard Unblinded Unclear comparator details *Applicability*: Applicable

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; ENB, electromagnetic navigation bronchoscopy; GS, guide sheath; RCT, randomised controlled trial; TBBX, transbronchial biopsy

Herth et al (2002) indicated that the yield obtained using EBUS-TBBX was equivalent to fluoroscopic-TBBX (80% vs 76%, respectively). It was also reported that EBUS-TBBX yield was maintained, but fluoroscopic-TBBX decreased when a subgroup of patients with peripheral lesions less than 3 cm diameter was assessed (81% vs 57%).

Paone et al (2005) reported that EBUS-TBBX generated a considerably higher yield than TBBX alone (76% vs 52%, respectively) and that the difference was maintained regardless of lesion size.

Eberhardt et al (2007) reported individual and combined yields for EBUS-TBBX, ENB-TBBX. EBUS-TBBX demonstrated a trend toward higher diagnostic yield than ENB-TBBX (69% vs 59%), but the use of the combined techniques was superior to either alone (88%). The relative difference in yield between techniques was generally maintained when subgroups of patients based on lesion size were examined.

The primary diagnostic yield results from the RCTs conducted by Herth et al (2002), Paone et al (2005) and Eberhardt et al (2007) are presented in Table 26. Additional data extracted from these RCTs are presented in **Appendix D**.

Table 26 Diagnostic yield of the included comparative studies assessing EBUS-TBBX in patients with peripheral lung lesions

Author (year)	Prevalence n/N (%)	Diagnostic test	Diagnostic yield		Level of evidence
			n/N	% (95% CI)	
Herth et al (2002)	45/50 (90)	EBUS-TBBX	40/50	80.00 (68.91, 91.09)	IV C1 P1 Q2
		Fluoroscopy-TBBX	38/50	76.0 (64.16, 87.84)	
Paone et al (2005)	144/206 (69.9)	EBUS-TBBX	66/87	75.86 (66.87, 84.85)	IV C1 P1 Q1
		TBBX alone	62/119	52.1 (43.13, 61.08)	
Eberhardt et al (2007)	82/118 (69.49)	EBUS-TBBX	27/39	69.23 (54.75, 83.72)	IV C1 P1 Q2
		ENB-TBBX	23/39	58.97 (43.54, 74.41)	
		ENB/EBUS-TBBX	35/40	87.5 (77.25, 97.75)	

Abbreviations: CI, confidence interval; EBUS, endobronchial ultrasound; ENB, electromagnetic navigation bronchoscopy TBBX, biopsy

The available evidence suggests that EBUS-TBBX sensitivity is equivalent to fluoroscopy-TBBX for diagnosis of peripheral lung lesions. Evaluated studies also indicated that the diagnostic yield of EBUS-TBBX was greater than TBBX alone and at least equivalent to other methods (electromagnetic, fluoroscopic) of guided-TBBX. The available evidence also suggested that the diagnostic yield of EBUS-TBBX alone may be superior to other methods of guided-TBBX for diagnosis of smaller peripheral lesions.

Individual rankings for components of the body of evidence are shown in Table 27. Evidence was limited because of the low number of level III and level IV diagnostic studies, which offered limited applicability, and did not fully address diagnostic performance of EBUS-TBBX compared with fluoroscopy-TBBX and TTNA.

Table 27 Assessing the comparative body of evidence for EBUS-TBBX in the diagnosis of peripheral lung lesions

Component	Rank	Reason
Volume of evidence	D	A small number of comparative diagnostic yield (IV) and low-quality diagnostic accuracy studies (III) were identified
Consistency	B	The reported outcomes for EBUS-TBBX were generally consistent in the comparative trials
Clinical impact	D	The reported sensitivity and diagnostic yield of EBUS-TBBX was equivalent to fluoroscopy-TBBX
		No studies were identified that compared diagnostic performance of EBUS-TBBX with TTNA
		The reported diagnostic yield of EBUS-TBBX was greater than TBBX and at least equivalent to ENB-TBBX
		EBUS-TBBX diagnostic yield may be greater than other methods of guided-TBBX in diagnosing smaller peripheral lesions
Generalisability	A	The study populations corresponded with the patient population identified in the research question
Applicability	D	Evidence for EBUS-TBBX diagnostic yield compared with fluoroscopy-TBBX had limited applicability to the Australian healthcare setting
		Evidence for EBUS-TBBX diagnostic yield compared with TBBX and ENB-TBBX had limited applicability to the Australian healthcare setting

Abbreviations: EBUS, endobronchial ultrasound; ENB, electromagnetic navigation bronchoscopy; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration; TBBX, transbronchial biopsy; TTNA, transthoracic needle aspiration

Patient management

No pre-test/post-test case series studies were identified that assessed the impact of EBUS-guided procedures on patient management.

Improvements in lung cancer staging and diagnosis may lead to better patient management by avoiding invasive diagnostic procedures and providing more accurate curative and palliative treatment planning leading to improved survival and quality of life.

Treatment effectiveness

It was considered that use of EBUS guided procedures for non-small cell lung cancer (NSCLC) staging, diagnosis of mediastinal/hilar masses of unknown origin, and diagnosis of peripheral lung lesions would not identify any unique patient groups that were substantially different from those currently seen in Australian clinical practice. Evidence of treatment effectiveness for these indications was therefore not presented in this assessment.

No treatment effectiveness evidence was identified among patients undergoing EBUS imaging for the depth diagnosis of endobronchial carcinomas.

Economic considerations

Summary

A decision analytic model was constructed to assess cost implications of endobronchial ultrasound (EBUS)-guided procedures when compared with current modalities. A cost analysis of EBUS-transbronchial needle aspiration (TBNA) relative to TBNA alone was performed for non-small cell lung cancer (NSCLC) staging and diagnosis of mediastinal/hilar masses of unknown origin; a cost analysis of EBUS-transbronchial biopsy (TBBX) relative to TBBX alone was conducted for diagnosis of peripheral lung lesions less than 3 cm diameter. There were insufficient clinical data available to inform a cost analysis for the depth diagnosis of endobronchial cancers.

The analysis indicated that use of EBUS-TBNA in NSCLC staging and diagnosis of mediastinal masses was estimated to generate a cost saving of $347 per patient; EBUS-TBBX for diagnosis of peripheral lung lesions less than 3 cm diameter was estimated to generate a cost saving of $364 per patient. This reflected the economic benefits associated with improved yield offered by using EBUS guidance for these procedures.

These results should be interpreted in the context of data inputs and assumptions made in the analyses. The current analysis assumed that the use of EBUS-guidance had no impact on the overall diagnostic accuracy of sampling procedures. Should EBUS use influence TBNA or TBBX diagnostic accuracy, patients' prognoses would likely be affected, creating important health outcomes and economic implications. No relevant data were available to allow evaluation of these outcomes.

Sensitivity analyses indicated that the yield represents the most critical variable in the analysis. This result was anticipated because the most significant clinical benefit was likely to result from avoiding expensive and invasive follow-up surgical procedures.

Epidemiological data indicated that the estimated total annual cost of employing EBUS-TBNA was between $2.5 and $3.6 million for assessment of central, mediastinal and hilar tumours. The total annual cost of EBUS-TBBX for use in diagnosis of peripheral lung lesions less than 3 cm diameter was estimated to be between $1.2 and $2.2 million.

The use of EBUS-guided procedures generated cost savings compared with current procedures. The total cost saving was expected to be between $763,994 and $1.1 million for implementation of EBUS-TBNA in the assessment of NSCLC and mediastinal/hilar masses; and from $363,802 to $691,224 for implementation of EBUS-TBBX in diagnosing of peripheral lung lesions less than 3 cm diameter.

It should also be noted the cost savings of EBUS presented may represent conservative estimates. This is because EBUS-guided procedures could replace more invasive biopsy modalities, such as mediastinoscopy, for some patients as a first line therapy in the assessment of lung cancer, thereby generating greater cost offsets.

Background and approach

This section examines whether the introduction of EBUS-guided procedures under the proposed indications represent value-for-money for the Australian healthcare system.

In practice, a variety of guiding and biopsy techniques are applied in transbronchial biopsy (TBBX) sampling (see Figures 3–6). Because comparative data are limited, evaluation of all techniques was not possible. For example, mediastinoscopy is often considered to be the preferred procedure applied in non-small cell lung cancer (NSCLC) staging and for diagnosis of mediastinal/hilar masses, but no data comparing mediastinoscopy with EBUS-transbronchial needle aspiration (TBNA) were identified in the course of this evaluation. The following analysis compares EBUS-guided sampling procedures with alternative techniques for which sufficient clinical data were available.

A systematic review of the literature demonstrated a paucity of published evidence regarding potential changes in staging/diagnostic accuracies that would occur as a result of using EBUS in place of the existing alternatives. A full economic evaluation that comparatively assessed alternative strategies in terms of costs and final patient outcomes (such as life years) was not considered to be feasible.

Current evidence indicated that the diagnostic yield of EBUS-TBNA was greater than TBNA alone (77 % vs 63%; Herth et al 2004) for staging NSCLC and diagnosis of mediastinal/hilar masses. Improved diagnostic yield reduces the need for repeat or follow-up procedures. This represents a potential source of healthcare cost savings.

Herth et al (2004) conducted a randomised comparative study in which EBUS-TBNA was compared with TBNA alone—one of the major comparators identified by the advisory panel. The study's patient and test characteristics were adequately reported and are likely to be applicable to Australian clinical practice. EBUS-TBNA was also reported to achieve equivalent or moderately higher diagnostic yield rates than EUS-fine needle aspiration (FNA) (Herth et al 2005; Vilmann et al 2005). However, the advisory panel indicated that EUS-FNA was a possible adjunct to, rather than a comparator for, EBUS-TBNA in Australia.

A cost analysis of EBUS-TBNA relative to TBNA alone in NSCLC staging and for diagnosis of mediastinal/hilar masses was performed using data from Herth et al (2004). The cost analysis aimed to quantify cost implications associated with the improved diagnostic yield offered by EBUS-guidance.

There were no trials identified that compared the diagnostic performance of EBUS with or without endobronchial biopsy (EBBX) in the depth diagnosis of endobronchial cancers. An economic analysis was therefore not conducted for this indication.

Herth et al (2002) indicated that EBUS-TBBX and fluoroscopic-TBBX offered equivalent yields for diagnosis of patients with peripheral lung lesions. Because fluoroscopy is used in both EBUS-TBBX and fluoroscopic-TBBX, the only cost difference between them is associated with EBUS guidance. This means that EBUS-TBBX procedures are expected to incur an additional cost to fluoroscopic-TBBX. From the economic perspective, EBUS-TBBX does not represent a preferred strategy—it provides no clinical benefit at higher cost when compared with fluoroscopic-TBBX.

However, a subgroup analysis conducted by Herth et al (2002) demonstrated EBUS-TBBX to be superior to fluoroscopic-TBBX in diagnosing lesions less than 3 cm diameter (81% vs 57%, respectively). In the current evaluation, a cost analysis of EBUS-TBBX relative to fluoroscopic-TBBX was performed to quantify cost implications associated with the improved diagnostic yield offered by EBUS guidance among patients with peripheral lung lesions less than 3 cm diameter.

EBUS-TBBX was shown to achieve a higher yield rate than TBBX and electromagnetic navigation bronchoscopy (ENB)-TBBX (Paone et al 2005, Eberhardt et al 2007). The advisory panel did not consider TBBX or ENB-TBBX to be major comparators for small peripheral lesions in the Australian setting.

The economic analysis was therefore restricted to quantification of the cost implications associated with the improved diagnostic yield offered by EBUS guidance:

1. A cost comparison of EBUS-TBNA vs TBNA alone for use in NSCLC staging and for diagnosis of mediastinal/hilar masses of unknown origin.

2. A cost comparison of EBUS-TBBX vs fluoroscopic-TBBX for diagnosis of peripheral lung lesions less than 3 cm diameter.

There are two types of EBUS imaging systems currently available in Australia. The first generation system requires different set-ups to perform EBUS-guided procedures with linear and radial probes. The second generation system—Aloka ultrasound imaging—is a single set-up system designed to perform EBUS-guided procedures and other imaging studies, such as abdominal and transrectal ultrasounds.

Because the Aloka system is compatible only with a linear probe, it represents an alternative to the first generation EBUS system to conduct EBUS-TBNA for diagnosing NSCLC and mediastinal masses. Conversely, the Aloka system is not suitable to conduct EBUS-TBBX procedures for use in diagnosing peripheral lung lesions because of the requirement for radial probe technology.

The literature review did not identify any clinical evidence relating to the Aloka system; presented evidence relates to the first generation system. Consequently, cost analyses conducted relate to the first generation system only. It is anticipated that use of the Aloka system to perform EBUS-TBNA procedures will increase. Hence, to better inform MSAC decision making, the likely financial implications of EBUS funding were estimated based on both the first generation and Aloka systems.

Estimated extent of financial implications

EBUS-guided sampling procedure cost analyses were performed for NSCLC staging, diagnoses of mediastinal/hilar masses and peripheral lung lesions less than 3 cm diameter. The likely financial implications of public funding of EBUS-guided biopsy sampling procedures were also determined based on these indications.

The likely financial implications of EBUS use in NSCLC staging and diagnosis of mediastinal/hilar masses were quantified using the estimated procedural costs for

EBUS-TBNA. Estimated EBUS-TBBX costs were applied to quantify associated financial implications for diagnosing peripheral lung lesions less than 3 cm diameter.

Per procedure costs of EBUS-guided techniques were first estimated. These costs were then multiplied by the estimated number of eligible patients to determine the total anticipated expenditure for EBUS-guided techniques.

Cost analyses of EBUS-guided techniques (EBUS-TBNA or EBUS-TBBX) indicated that the improved yield offered by the use of EBUS guidance over current practices should lead to cost savings by reducing the need for follow-up procedures; total cost savings for implementing EBUS for the Australian health system were also determined.

Estimated cost of EBUS-guided TBNA or TBBX per procedure

There are two types of EBUS imaging systems currently available in Australia—the first generation system and the Aloka system. Because their associated costs differ, the estimated costs of conducting EBUS-guided procedures were determined for both systems. All estimates were assumed to represent average costs among private and public sectors.

Cost of EBUS guidance

Table 28 presents costs of each health resource item required for both EBUS guidance systems. The total cost includes expenditure required for capital equipment, probes and professional fees. All cost information was provided by the Applicant.

Both radial and linear probes are used with first generation systems and are associated with different resource requirements and costs. Thus, separate procedural cost estimates were derived for the first generation system using both probes. A single cost for the Aloka system was determined because it incorporates use of linear probes only. Use of the Aloka system was assumed to incur the same professional fees as the first generation imaging system.

Table 28 Total cost of EBUS guidance per procedure

Costs	First generation system		Aloka	Source
	via linear probe	via radial probe	via linear probe	
Equipment/consumables costs				
Capital equipment costs[a]	$56.00	$76.00	$75.00	Application document (see **Appendix I**)
Ultrasonic probe	$44.00	$58.00	$46.00	Application document
Total				
Professional fees associated with EBUS guidance	$327.85	$327.85	$327.85	Application document (MBS item 38448)[b]
Total—EBUS guidance	**$427.85**	**$461.85**	**$448.85**	
Average cost	**$444.85**		**—**	

Abbreviation: EBUS, endobronchial ultrasound

[a] Assumes 12 procedures per week per centre, amortising the capital costs over a period of five years

[b] Item 38448: *Mediastinum, cervical exploration of, with or without biopsy*

Note: Different capital equipment costs were suggested by the applicant for first generation EBUS equipment employing linear and radial probes (total costs of $101,020 and $156,400, respectively, for linear and radial EBUS guidance)

Capital equipment costs for the first generation system using linear and radial probes were estimated at $56 and $76 per procedure respectively. Capital equipment costs for the Aloka system were estimated at $75 per procedure.

These estimates were based on equipment costs and the predicted number of procedures performed each year. Expert opinion indicated that each centre equipped with EBUS currently performs four to five procedures per week and this rate could increase to 10 to 12 procedures per week should public funding be approved for EBUS-guided procedures. The current analysis assumed that each site would perform 12 procedures on average per week should EBUS be publicly subsidised. Capital costs per procedure were estimated by amortising total capital costs and assuming that 624 procedures were performed per year (=12×52 weeks) over a period of five years. Further details on the derivation of this estimate are provided in **Appendix I**.

The costs of linear probes were estimated to be $44 and $46 per procedure for the first generation and Aloka systems, respectively. The same capital equipment costs estimating methodology was applied to derive linear probe costs, given that their corresponding utilisation life spans are duplicated.

Radial probes used with the first generation system were expected to be replaced after approximately 100 procedures. In practice, EBUS-guided techniques can be performed with two modes of radial probes, depending on physicians' preferences and diagnostic site. The cost of the radial probe was estimated to be $5825 and was calculated by averaging the cost of two probes. The radial probe cost per procedure was therefore estimated to be $58 (=$5825 ÷ 100).

It was assumed that MBS item 38448 (*Mediastinum, cervical exploration of, with or without biopsy*) provides a reasonable estimate of the professional fee for EBUS-guided procedures (see Table 28). Although EBUS guided procedures are less invasive and carry lower risks compared with mediastinoscopy, they are more time-consuming and require a higher level of training, than non-EBUS bronchoscopic procedures.

The total costs for first generation EBUS guidance using linear and radial probes were estimated to be $428 and $462 per procedure, respectively. Similarly, costs for the Aloka system were estimated to be $449 per procedure.

EBUS-guided TBNA can be undertaken with either linear or radial probes for diagnosing NSCLC and mediastinal/hilar masses. The estimated costs of the first generation EBUS guidance with linear and radial probes were comparable (Table 28). For simplicity, the following analysis of first generation EBUS guided systems for TBNA was performed using the average costs of EBUS guidance for both probe types—$445 per procedure.

EBUS-guided TBBX for diagnosis of peripheral lung lesions is undertaken using radial probes only. The estimated cost of $462 for first generation EBUS guided procedures using radial probes was applied to calculate the following cost analysis of EBUS guidance for TBBX.

Cost of EBUS-guided TBNA or TBBX per procedure

The total costs of EBUS-TBNA and EBUS-TBBX were estimated and presented in Table 29 and Table 31, respectively.

As well as costs associated with EBUS guidance (Table 28), total EBUS-guided TBNA procedure costs included professional fees, consumables and other medical services. Table 29 presents the costs of each identified health resource item.

Table 29 Total cost of EBUS-TBNA per procedure

Costs	First generation[a]	Aloka	Source
Cost of EBUS guidance per procedure	$444.85	$448.85	Estimated
Professional fee for TBNA	$188.90	$188.90	MBS 38812[b]
Disposable needle	$175.00	$175.00	Application document
Disposable balloon	$24.00	$24.00	Application document
Other medical services	$287.40	$287.40	MBS (see Table 30)
Total	**$1120.15**	**$1124.15**	

Abbreviation: EBUS, endobronchial ultrasound; TBNA, transbronchial needle aspiration
[a] The total EBUS-TBNA cost per procedure was estimated based on the health resource usage for EBUS-TBNA with linear probe
[b] The Applicant proposed MBS Item 38412. This item was replaced by 38812 Percutaneous needle biopsy of lung (November 2007)
Note: The fee for MBS Item 41892 Bronchoscopy with 1 or more endobronchial biopsies or other diagnostic or therapeutic procedures is $212.25. The fee for MBS Item 41898 Fibreoptic bronchoscopy with 1 or more transbronchial lung biopsies, with or without bronchial or bronchoalveolar lavage, with or without the use of interventional imaging is $232.05

The total costs of EBUS-TBNA per procedure were estimated to be $1120 using the first generation system and $1124 for the Aloka system. The total costs included professional fees for TBNA and other medical services, such as anaesthesia management and cytology evaluation. Costs for these services were estimated to be $287 (see Table 30).

In addition to standard diagnostic cytology, rapid on-site evaluation (ROSE) may be conducted for some patients during TBNA. The associated costs were not included in the current cost calculation.

Table 30 Other costs associated with EBUS-TBNA per procedure

MBS item number, description	Fee
17610 Anaesthetist, pre-anaesthesia consultation	
– a brief consultation involving a targeted history and limited examination (including the cardio-respiratory system)	
– and of not more than 15 minutes duration	$38.80
20520 Initiation of management of anaesthesia for all closed chest procedures	$107.40
23043 Anaesthesia, perfusion or assistance at anaesthesia (56 minutes to 1.00 hour)	$71.60
73049 Cytology of material obtained directly from a patient by fine needle aspiration of solid tissue or tissues	$69.60
Total costs per procedure	$287.40

Abbreviation: MBS, Medicare Benefits Schedule
Source: Medicare Benefits Schedule Book November 2007

The total cost for EBUS-TBBX was estimated based on the cost of the first generation EBUS system with radial probe (Table 31).

Based on the expert opinion of the advisory panel, MBS item 41898 *Fibreoptic bronchoscopy with 1 or more transbronchial lung biopsies, with or without bronchial or bronchoalveolar lavage, with or without the use of interventional imaging* was assumed to represent an appropriate professional fee for TBBX sampling procedures. The current MBS fee for fluoroscopy was also included because the EBUS-TBBX procedure requires fluoroscopic guidance.

A guide sheath set consisting of a sheath for probe, biopsy forceps and cytology brush is required for TBBX. The cost of the guide sheath kit was estimated to be $131, by averaging the costs of both available guide sheath kits.

Other medical services costs associated with TBBX were assumed to be same as TBNA ($287, see Table 30). Therefore, the total cost of EBUS-TBBX was estimated to be $1176 per procedure.

Table 31 Total cost of EBUS-TBBX per procedure

Costs	Estimates	Source
Cost of EBUS guidance per procedure	$461.85	Estimated (see Table 28)
Professional fee for fluoroscopic-TBBX		
– TBBX	$232.05	MBS 41898[a]
– Fluoroscopy	$63.75	MBS 60506[b]
Disposable guide sheath kit	$131	Estimated
Other medical services (including anaesthesia and pathology)	$287.40	MBS (see Table 30)
Total	$1176.05	

Abbreviations: EBUS, endobronchial ultrasound; TBBX, transbronchial biopsy

[a] Item 41898 Fibreoptic bronchoscopy with 1 or more transbronchial lung biopsies, with or without bronchial or bronchoalveolar lavage, with or without the use of interventional imaging

[b] Item 60506 Fluoroscopy using a mobile image intensifier, in conjunction with a surgical procedure lasting less than 1 hour

The costs of EBUS-guided biopsy sampling procedures are difficult to estimate because there are no reliable cost data available for Australian practice. For example, the Applicant suggested that MBS item 38448 (Table 28) and MBS item 38812 (Table 29) were likely associated with equivalent resource requirements and skill level as EBUS-TBNA. Based on these cost estimates, the total professional fee for EBUS-TBNA was estimated to be $517. Similarly, the total professional fee for EBUS-TBBX was estimated to be $624, covering EBUS-guidance, TBBX and fluoroscopy procedures (Table 32). These estimates are assumed to appropriately represent the professional fees for EBUS-guided procedures.

In addition, MBS item 30690[3] and MBS item 30694[4] represent the professional fees associated with EBUS-guided sampling procedures at $509. If those existing items were to represent the procedure fee for EBUS-guided sampling procedures, the total costs associated with the use of EBUS guidance would be less than that estimated in this assessment. Nonetheless, as also suggested by the Applicant, EBUS professional fees should account for the additional time required by clinicians to conduct the procedure.

[3] MBS item 30690 *Endoscopic ultrasound-endoscopy with ultrasound imaging, with or without biopsy, with fine needle aspiration, including aspiration of the locoregional lymph nodes if performed, for the staging of 1 or more of oesophageal, gastric or pancreatic cancer, not in association with another item in this subgroup and not being a service associated with the routine monitoring of chronic pancreatitis.*

[4] MBS item 30694 *Endoscopic ultrasound-endoscopy with ultrasound imaging, with or without biopsy, with fine needle aspiration for the diagnosis of 1 or more of pancreatic, biliary or gastric submucosal tumours, not in association with another item in this subgroup and not being a service associated with the routine monitoring of chronic pancreatitis.*

Table 32 Summary of professional fees for EBUS-guided procedures

Professional fee	Estimates	Source
Professional fee for EBUS-TBNA		
– EBUS guidance	$327.85	See Table 28
– TBNA	$188.90	See Table 29
Total professional fee for EBUS-TBNA	$516.75	
Professional fee for EBUS-TBBX		
– EBUS guidance	$327.85	See Table 28
– TBBX	$232.05	See Table 31
– Fluoroscopy	$63.75	See Table 31
Total professional fee for EBUS-TBBX	**$623.65**	

Abbreviation: EBUS, endobronchial ultrasound; TBNA, transbronchial needle aspiration; TBBX, transbronchial biopsy

Estimated extent of financial implications

The total likely costs of both techniques for each indication were determined from the estimated procedural costs of EBUS-guided techniques and the estimated eligible population.

The likely financial implications for use of EBUS in NSCLC staging and diagnosis of mediastinal/hilar masses were quantified by applying the estimated procedural costs of EBUS-TBNA. The estimated costs of EBUS-TBNA using the first-generation EBUS system and the Aloka system were similar (Table 29). This signified that the likely financial implications of implementing both systems would be parallel. Thus, the expected financial implication for use of EBUS-TBNA in NSCLC staging and diagnosis of mediastinal/hilar masses were quantified by applying the cost estimates of EBUS-TBNA with the first-generation system.

Similarly, estimated EBUS-TBBX costs were applied to quantify the financial implications for diagnosis of peripheral lung lesions less than 3 cm. The likely total financial costs of implementing EBUS-TBNA and EBUS-TBBX were estimated and presented in Table 33 and Table 34, respectively.

Table 33 Estimated total costs of EBUS-TBNA for assessment of NSCLC and mediastinal/hilar masses

	The first generation system		Source
	Lower estimate	Upper estimate	
Eligible population	2200	3200	See Table 1
Costs of EBUS-TBNA per procedure	$1120		See Table 29
Estimated total costs of EBUS-TBNA for all eligible populations	$2,464,330	$3,584,480	

Abbreviations: EBUS, endobronchial ultrasound; TBNA, transbronchial needle aspiration

The current evaluation estimated that the eligible population was in the range of 2200–3200 patients annually for assessment of NSCLC and mediastinal/hilar masses (Table 1). These eligible population estimates translate to an annual cost of between $2.5 and 3.6 million for performing EBUS-guided sampling procedures.

Table 34 Estimated total costs of EBUS-TBBX for diagnosis of peripheral lung lesions

	The first generation system		Source
	Lower estimate	Upper estimate	
Eligible population	1000	1900	See Table 2
Costs of EBUS-TBBX per procedure	$1176		See Table 31
Total costs of EBUS-TBBX for all eligible populations	$1,176,050	$2,234,495	

Abbreviations: EBUS, endobronchial ultrasound; TBBX, transbronchial biopsy

Based on AIHW data for the current use of comparator procedures, it was estimated that approximately 1500–3000 procedures are being performed for patients with peripheral lung lesions annually (see Table 2). The advisory panel indicated that of these, between 1000 and 1900 patients with peripheral lung lesions less than 3 cm would potentially be eligible for EBUS-TBBX. This would generate annual total costs of between $1.2 and $2.2 million.

These cost estimates do not account for possible cost offsets arising from substitution effects due to public funding of EBUS-guided sampling procedures, or potential cost savings such as reduced need for follow-up procedures due to improved diagnostic yield from EBUS guidance.

The following cost analysis demonstrates that using TBNA without EBUS-guidance as a comparator for NSCLC staging and diagnosing mediastinal masses EBUS-TBNA would generate a cost saving of $347 per patient using first generation imaging system. This reflects the lower follow-up costs of EBUS-TBNA because of its improved yield, compared with TBNA alone, which more than offset the additional procedural costs associated with EBUS-guidance. Similarly, use of EBUS-TBBX rather than fluoroscopic-TBBX would generate a cost saving of $364 per procedure when used in the diagnosis of peripheral lung lesions less than 3 cm diameter.

The extent of total cost-savings was estimated for both indications under consideration using the estimated eligible patient populations, as shown in Table 35 and Table 36.

Table 35 Estimated total cost savings offered by EBUS-TBNA for assessment of NSCLC and mediastinal/hilar masses in the Australian health system

	The first generation system		Source
	Lower estimate	Upper estimate	
Eligible population	2200	3200	See Table 1
Cost saving associated with EBUS-TBNA per procedure	$347		See Table 29
Total cost savings associated with EBUS-TBNA	$763,994	$1,111,264	

Abbreviation: EBUS, endobronchial ultrasound; TBNA, transbronchial needle aspiration

Based on per procedure cost savings associated with EBUS-TBNA over TBNA alone, and the estimated eligible population requiring assessments for NSCLC or mediastinal/hilar masses (see Table 1), the total cost saving of implementing EBUS-TBNA was expected to fall in the range of between $763,994 and $1.1 million (see Table 35).

Similarly, based on the per procedure cost saving associated with EBUS-TBBX over fluoroscopic-TBBX, and the estimated eligible population requiring diagnosis of

peripheral lung lesions less than 3 cm diameter (Table 2), the total cost saving for implementing EBUS-TBBX was expected at between $363,802 and $691,224 (Table 36).

Table 36 Estimated total cost savings of EBUS-TBBX for diagnosis of peripheral lung lesions < 3 cm diameter for the Australian health system

	First generation system		Source
	Lower estimate	Upper estimate	
Eligible population	1000	1900	See Table 2
Cost saving associated with EBUS-TBBX per procedure	$364		See Table 31
Total cost savings associated with EBUS-TBBX	$363,802	$691,224	

Abbreviation: EBUS, endobronchial ultrasound; TBBX, transbronchial biopsy

These estimates should be interpreted with some caution due to the degree of uncertainty in estimating eligible populations and numbers of procedures performed.

It was estimated in the analysis that each centre had capacity to perform up to 12 procedures per week in practice. There are currently seven centres with EBUS equipment in Australia, for a maximum capacity of approximately 4400 EBUS procedures per annum. The capacity to perform EBUS procedures has been increasing in Australia, and this trend is likely to accelerate should public funding become available. Given the eligible patient population (Table 33 and Table 34), it is possible that some centres might not operate at full capacity, which would consequently increase capital equipment costs per procedure. However, should EBUS-guided procedures be approved for other indications, such as diagnosis of endobronchial cancers and peripheral lesions greater than 3 cm diameter, full use of services may be absorbed. Furthermore, the Aloka ultrasound imaging system is able to perform other imaging studies, such as endoscopic ultrasound (EUS). Accordingly, if the Aloka system was used to perform EBUS-TBNA and other imaging procedures, more procedures could be performed with each system, resulting in reduced capital costs per procedure. Nevertheless, capital equipment costs per procedure are unlikely to differ significantly from estimates applied in the current analysis.

It should also be noted that the presented overall cost savings for EBUS may be conservative because EBUS-guided procedures could replace more invasive and more costly biopsy modalities. That is, for some patients, EBUS-TBNA may replace procedures such as mediastinoscopy as a first line approach for staging NSCLC and diagnosis of mediastinal/hilar masses of unknown origin, thereby generating greater cost offsets attributable to the diagnostic process.

Published evidence regarding endobronchial ultrasound cost-effectiveness

There are very few published economic evaluations of EBUS for the indications considered by this assessment. The literature search did not identify any Australian studies. A cost assessment was conducted in Germany (Herth et al 2003), and a précis of findings is presented. Improvement in diagnostic yield offered by implementing EBUS-guided TBNA was demonstrated to offset associated additional costs when compared with TBNA and mediastinoscopy.

Herth et al (2003) conducted a cost comparison involving EBUS-TBNA, TBNA and mediastinoscopy for mediastinal staging of lung cancer among 100 patients in Germany. Follow-up mediastinoscopy was provided as the follow-up staging procedure when the EBUS-TBNA and TBNA yields were inadequate. Per procedure costs of €180, €57 and €1620 were reported for EBUS-TBNA, TBNA and mediastinoscopy, respectively. TBNA was associated with requirement for follow-up mediastinoscopies among 40 per cent of patients. The mediastinoscopy follow-up rate among EBUS-TBNA patients was 25 per cent. Costs per patient cost for lymph node staging were estimated to be €585 for EBUS-TBNA, €705 for the TBNA arm, and €1620 for patients undergoing mediastinoscopy.

Cost analyses of EBUS-guided techniques

A decision analytic model was developed to quantify cost implications associated with improvements in the yield rate provided by EBUS-guided procedures compared with current practice.

Two cost analyses were conducted. The first considered EBUS-TBNA relative to TBNA alone and was performed for NSCLC staging and diagnosis of mediastinal/hilar masses of unknown origin. The second analysis compared costs for diagnosis of peripheral lung lesions less than 3 cm with and without EBUS. The biopsy procedure was fluoroscopic-TBBX, as per Herth et al (2002). A cost analysis of EBUS-guided sampling was not conducted in the assessment of endobronchial carcinoma because of the absence of relevant clinical data.

In Australia, mediastinoscopy is often considered to be the preferred procedure for NSCLC staging and diagnosis of mediastinal/hilar masses, but no clinical evidence comparing mediastinoscopy with EBUS-TBNA was identified during this assessment. A cost analysis comparing EBUS-TBNA with mediastinoscopy was not conducted.

Analytical approach

A simple decision analytic model was constructed to compute the expected costs of alternative strategies. Figure 9 presents a schematic diagram of the decision tree. This was based on clinical pathway presented in Figure 3, Figure 4 and Figure 6.

The model structure illustrates two alternative strategies that are differentiated by the use of EBUS guidance during the primary diagnostic procedure. This model was used for both of the indications under consideration.

In the absence of EBUS, TBNA alone is performed in the staging of NSCLC and for diagnosis of mediastinal/hilar masses. If the primary diagnostic procedure was inconclusive due to insufficient diagnostic yield, a follow-up mediastinoscopy procedure was performed (the gold-standard diagnostic procedure) (Figure 9).

Similarly, in the absence of EBUS, fluoroscopic-TBBX is performed in the diagnosis of peripheral lung lesions less than 3 cm diameter. Expert opinion suggested that, if the primary diagnostic procedure was to be inconclusive, CT-guided TTNA would represent a preferred secondary diagnostic procedure. Any further unsatisfactory yield from CT-guided TTNA would be followed by surgical resection via video-assisted thorascopic surgery (VATS) or thoracotomy where clinical suspicion for malignancy is high and the

patient deemed fit for surgery. Surgical resection is the gold-standard diagnostic test and can often be therapeutic. VATS is usually the favoured surgical approach for diagnostic investigation; it is both less invasive and costly than thoracotomy. Consequently, the base case analysis incorporated VATS as the follow-up procedure for those who had non-diagnostic CT-guided TTNA. A scenario of performing thoracotomy instead of VATS was explored in the sensitivity analysis.

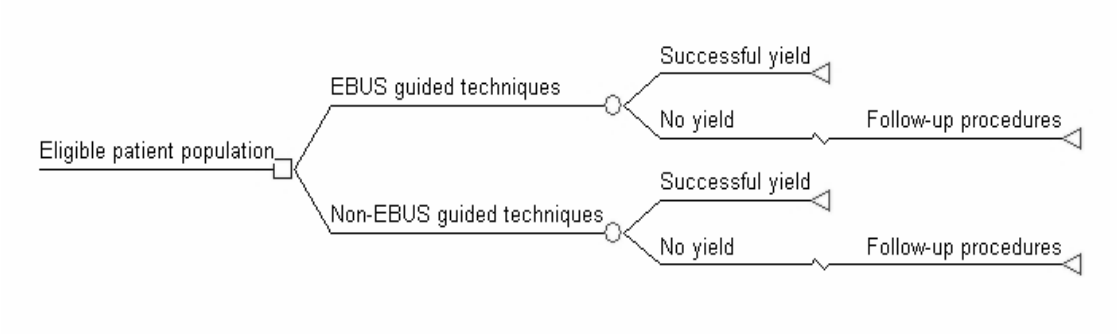

Figure 9 Structure of the current economic model

The model aims to cover only the pre-treatment algorithm which in turn determines the appropriate downstream clinical management. Given that a diagnosis would not be made unless sufficient diagnostic material were obtained, the current approach appropriately captures cost differences between the strategies.

The current model does not incorporate simulation of final patient outcomes such as life years or quality-adjusted life years (QALYs) due to the lack of relevant data. It is assumed that the final diagnostic accuracies remain equivalent across the strategies under consideration and these outcomes are unaffected by the introduction of EBUS.

Modelled population

The modelled population is represented by a hypothetical cohort of patients who would be eligible for EBUS-guided techniques if they were available.

The current model is based on two hypothetical patient groups. The first analysis relates to a mixed group of patients, including those with known NSCLC and mediastinal lesions. The second analysis relates to a patient population with peripheral lung lesions less than 3 cm diameter. Cost analysis was not possible for the patient population who were considered for EBUS-guided biopsy sampling as part of the depth assessment of bronchial carcinoma due to a lack of relevant clinical data.

Selection of these patient populations was driven by the availability of clinical data. Clinical inputs used in the first analysis were derived from Herth et al (2004) that included patients with NSCLC and mediastinal mass.

Clinical input used in the second analysis was derived from Herth et al (2002) that included patients with peripheral lung lesions. This analysis was based on a sub-group analysis of patients with lesions less than 3 cm diameter. For this reason, the model outputs should be interpreted within the context of a patient population with peripheral lung lesions less than 3 cm diameter.

The patient and test characteristics were adequately reported in these studies and are likely to be applicable to Australian clinical practice.

Variables used in the economic model

Clinical variables

Clinical data relating to estimated yield rates included in the model are summarised in Table 37.

Table 37 Clinical variables included in the model

Variable	Description	Value	Source
Biopsy sample yield			
For NSCLC staging and diagnosis of mediastinal/hilar masses of unknown origin			
EBUS-TBNA	Proportion of patients receiving final diagnosis/staging following the procedure	77%	Herth et al (2004)
TBNA alone		63%	
For diagnosis of peripheral lung lesions < 3 cm diameter			
EBUS-TBBX	As above	81%	Herth et al (2002)
Fluoroscopic-TBBX		57%	

Abbreviations: EBUS, endobronchial ultrasound; TBNA, transbronchial needle aspiration; TBBX, transbronchial biopsy

Cost inputs

Relevant cost inputs are summarised in Table 38. All costs were estimated from the perspective of the Australian healthcare system and are expressed in Australian dollars.

Table 38 Cost variables included in the model

Variable	Description	Value	Source
Cost of EBUS-guidance for TBNA	Resource cost associated with one episode of diagnosis	$444.85	See Table 28
Cost of EBUS-guidance for TBBX		$461.85	See Table 28
Cost of diagnostic follow-up			
Mediastinoscopy		$5658.00	See Table 39
CT-guided TTNA plus VATS if necessary		$3440.22	See Table 42

Abbreviations: EBUS, endobronchial ultrasound; TBNA, transbronchial needle aspiration; TBBX, transbronchial biopsy; CT, computerised tomography; VATS: video-assisted thorascopic surgery

Only direct healthcare costs were included in the analysis. The introduction of EBUS guidance was likely to have negligible implications for indirect/societal costs.

As demonstrated, two EBUS imaging systems are currently available with differing EBUS guidance cost estimates. The cost estimate used in the current analysis related to the first generation system. This is because clinical data input used in the analyses extracted from Herth et al (2002) and Herth et al (2004) both reported the yield rate of EBUS-guided procedures with the use of the first generation imaging system.
A sensitivity analysis was conducted by applying the cost estimate of EBUS guidance using the Aloka system.

The model includes the costs of EBUS-guidance associated with the primary diagnostic sampling procedure for NSCLC staging and diagnosis of mediastinal/hilar masses only (see Table 38). This is because it was assumed that all patients in both arms undergo

TBNA during bronchoscopy. For this reason, the only difference between the arms is appropriately represented by the additional costs of EBUS guidance.

Although this approach is a general representation of current Australian practice, as advised by the expert panel, EBUS-guidance would obviate the need for a separate bronchoscopy to perform TBNA in some cases. This creates important cost implications. To address this uncertainty, a sensitivity analysis was performed to examine a scenario in which bronchoscopy fees were added to the non-EBUS arm. (Mediastinoscopy is performed for patients who do not achieve a satisfactory diagnostic yield from the primary diagnostic procedure.)

The cost of mediastinoscopy was determined from the National Hospital Cost Data collection. It was assumed that the Australian Refined Diagnosis Related Groups (AR-DRGs) E02A, E02C and E02B appropriately represented the resource requirements associated with this procedure (Department of Health and Ageing 2006). Public sector estimates were employed. AR-DRG costs were weighted using the number of separations to derive the mean costs per procedure (Table 39).

Table 39 Estimated costs of mediastinal node biopsy per procedure

AR-DRG code, description	Average cost per separation	Number of separations
E02A Other respiratory system operating procedures with catastrophic complications and comorbidities	$18,966	561
E02B Other respiratory system operating procedures with severe complications and comorbidities	$8660	481
E02C Other respiratory system operating procedures without catastrophic or severe complications and comorbidities	$3240	3684
Weighted average per separation	**$5658**	

Source: National Hospital Cost Data Collection, Round 9 (2004–05)

The total cost of mediastinoscopy was estimated at $5658 per procedure. This is consistent with the cost estimated by Yap et al (2005) who determined costs associated with mediastinoscopy for staging or treatment of histologically proven NSCLC in Australia. This study was undertaken at the Austin Hospital, Melbourne, between 1 July 2000 and 30 June 2001. The costs of mediastinoscopy ranged from $3867 to $8597, with a mean cost of $4981 (converted to 2005 price; AIHW 2007).

The model includes only the costs of EBUS-guidance associated with the primary diagnostic sampling procedure for diagnosis of peripheral lung lesions less than 3 cm (Table 38). This reflects clinical practice after the introduction of EBUS-TBBX—EBUS-guidance is performed in addition to fluoroscopic-guidance to perform TBBX. The advisory panel noted that this represents standard practice for EBUS-TBBX.

CT-guided TTNA is performed for patients who fail to achieve a satisfactory diagnostic yield from the primary diagnostic procedure; VATS is then performed for diagnosis if CT-guided TTNA gives an unsatisfactory diagnostic yield. A systematic review conducted by Wahidi et al (2007) found that CT-guided TTNA was associated with a diagnostic yield of 79 per cent in the patient population under consideration.

The costs of CT-guided TTNA were estimated to be $670 per procedure (Table 40). A lack of relevant information meant that it was not considered feasible to estimate the CT-guided TTNA costs directly using a DRG-based approach. Consequently, the likely resource requirements were informed by expert opinion and from Gould et al (2003), and applied together with current MBS fees for benefit.

Table 40 Estimated costs of CT-guided TTNA per procedure

MBS item number, description	Fee
57345 Computed tomography, in conjunction with a surgical procedure using interventional techniques	$241.60
38812 Percutaneous needle biopsy of lung	$188.90
73049 Cytology of material obtained directly from a patient by fine needle aspiration of solid tissue or tissues	$69.60
72823 Tissue pathology level 4 – 1 tissue block	$97.95
58503 Chest (lung fields) by direct radiography	$47.15
Disposable needle	$24.53
Total costs per procedure	**$669.73**

Source: Medicare Benefits Schedule Book November 2007
Abbreviation: MBS, Medicare Benefits Schedule

No relevant information was available to inform direct estimation of VATS costs using a DRG-based approach. Several overseas studies compared procedural costs of VATS and thoracotomy consistently demonstrating that the costs of VATS were roughly 80 per cent of thoracotomy costs (Crisci and Coloni 1996, Gould et al 2003, Nakajima et al 2000). The mean cost of thoracotomy could be estimated as $16,491 per procedure, based on the National Hospital Cost Data Collection (Table 41). This is comparable with cost estimates reported by Yap et al (2005) that were based on data from 41 thoracotomy procedures. The estimated cost of thoracotomy in the study ranged from $8822 to $52,871, with the mean cost of $18,728 (converted to 2005 pricing; AIHW 2007). The cost of VATS can therefore be estimated as $13,192, which accounts for 80 per cent of estimated thoracotomy costs.

Table 41 Estimated costs of thoracotomy per procedure

AR–DRG code, description	Average cost per separation	Number of separations
E01A Major chest procedure with catastrophic complications and comorbidities	$23,476	1340
E01B Major chest procedure without catastrophic complications and comorbidities	$12,273	2219
Weighted average per separation for thoracotomy	**$16,491**	

Source: National Hospital Cost Data Collection, Round 9 (2004–2005)

Overall, each patient who failed to achieve a satisfactory yield with the primary procedure would incur an average follow-up cost of $3440 (Table 42).

Table 42 Estimated costs of follow-up procedures for the diagnosis of peripheral lung lesions < 3 cm

Variable	Value	Source
Total cost of CT-guided TTNA	$669.73	See Table 40
Cost of VATS if failed with CT-guided TTNA		
– Total costs of VATS	$13,192	See Table 41
– % of CT-guided TTNA recipients requiring follow-up using VATS	21%	Wahidi et al (2007)
– Expected costs per patient who require follow-up	$2770	Estimated
Total cost of diagnostic follow-up[a]	**$3440.22**	

Abbreviations: TTNA, transthoracic needle aspiration; CT, computerised tomography; VATS: video-assisted thorascopic surgery
[a] Expected costs per patient who fail to achieve a satisfactory yield with the primary procedure (ie fluoroscopy-guided TBBX or EBUS-TBBX)

Results

Base case analysis

Base case results are summarised in Table 43. The use of EBUS-guidance in addition to TBNA alone/fluoroscopy-TBBX is expected to generate a moderate cost saving for the Australian healthcare system.

Table 43 Summary of costs and incremental costs

Costs	Primary biopsy cost	Follow-up cost[a]	Total
For NSCLC staging and diagnosis of mediastinal/ hilar masses of unknown origin			
EBUS-TBNA	$444.85	$1301.34	$1746.19
TBNA alone	$0.00	$2093.46	$2093.46
Incremental costs	$444.85	–$792.12	–$347.27
For diagnosis of peripheral lung lesions < 3 cm diameter			
EBUS-TBBX	$461.85	$653.64	$1115.49
Fluoroscopic-TBBX	$0.00	$1479.29	$1479.29
Incremental costs	$461.85	–$825.65	–$363.80

Abbreviations: EBUS, endobronchial ultrasound; TBNA, transbronchial needle aspiration; TBBX, transbronchial biopsy
[a] Represents the costs associated with unsuccessful yield from the primary procedure, necessitating secondary procedures

The initial staging/diagnostic costs for patients referred for NSCLC staging or diagnosis of mediastinal masses of unknown origin were $445 higher in the EBUS-TBNA group. These represent additional costs associated with use of EBUS-TBNA over TBNA alone; follow-up costs were $792 lower in the EBUS-TBNA arm. Overall, the use of EBUS-TBNA for NSCLC staging and for diagnosis of mediastinal masses was estimated to generate a cost saving of $347 per patient.

The initial diagnostic costs associated with peripheral lung lesion less than 3 cm diameter were $462 higher in the EBUS group. However, follow-up costs were more than $800 lower in the EBUS-TBBX arm. Overall, the use of EBUS-TBBX for diagnosis of peripheral lung lesions less than 3 cm diameter was estimated to generate a cost saving of $364 per patient.

Sensitivity analysis

A series of one-way sensitivity analyses was performed to assess the impact of uncertainty on all input variables and robustness of results.

The following sensitivity analyses were conducted to compare costs of EBUS-TBNA relative to TBNA alone (Table 44):

- It is possible that the yield rates included in the current model may not reflect the actual rates observed in Australia. A sensitivity analysis was conducted by varying the yield rate of EBUS-TBNA, while maintaining a constant rate for TBNA alone (sensitivity analysis 1, Table 44). The 95 per cent confidence interval (CI) values reported Herth et al (2004) (Table 21) were used to explore this uncertainty.

- In the base case analysis, mediastinoscopy was used to represent the secondary biopsy procedure in the event of insufficient primary yield for this indication. The associated costs were estimated using AR-DRGs and verified by comparison with findings from an Australian observational study by Yap et al (2005). Resource requirements associated with mediastinoscopies may vary so the analysis was conducted using the reported cost range for mediastinoscopy ($3867–$8597) from Yap et al (2005) (sensitivity analysis 2, Table 44).

- The current capital costs of EBUS-guidance per procedure were estimated by amortising the total capital costs on the assumption of 624 procedures being conducted annually (=12 procedures per week ×52 weeks) over a period of five years. With the increasing number of centres performing the EBUS-guided procedures, some centres may not operate at maximum capacity (ie 12 procedures per week). This would lead to higher capital cost of EBUS-guidance per procedure and therefore higher total costs of EBUS-guidance. A sensitivity analysis was conducted by assuming that each centre performs eight EBUS procedures per week (sensitivity analysis 3, Table 44).

- The cost of bronchoscopy was excluded from the base case analysis because it was assumed to affect both arms. However, the advisory panel indicated that in some circumstances EBUS-TBNA does not generate a separate bronchoscopy fee. A sensitivity analysis was therefore conducted by including the bronchoscopy fee in the non-EBUS arm (sensitivity analysis 4, Table 44).

Table 44 Results of sensitivity analyses for EBUS-TBNA vs TBNA alone

Patients with NSCLC and mediastinal/hilar masses			
Analysis	**Expected costs**		**Incremental costs**
	EBUS-TBNA	**TBNA**	
Base case analysis	$1746.19	$2093.46	–$347.27
1.Varying the yield rate of EBUS-guided procedure			
Reduced to 68.75%	$2122.98	$2093.46	$119.52
Increased to 85.25%	$1279.41	$2093.46	–$814.06
2. Varying the cost of mediastinoscopy			
Reduced to $3867	$1334.26	$1430.79	–$96.53
Increased to $8597	$2422.16	$3180.89	–$758.73
3. Varying the number of procedures performed per centre per annum			
416 procedures per centre	$1783.19	$2093.46	–$310.27
4. Including the cost of bronchoscopy in the non-EBUS arm			
Bronchoscopy cost ($160.75)[a]	$1746.19	$2254.21	–$508.02

[a] Item 41889 *Bronchoscopy as an independent procedure* (source: MBS)

Sensitivity analysis 1 indicated that the 95 per cent confidence interval (CI) values for diagnostic yield profoundly affected the base case findings. In particular, when the lower limit of the CI estimate was applied, the cost savings associated with use of EBUS-guidance in the base case analysis were no longer observed. Under this scenario, use of EBUS-guidance was estimated to generate additional costs of $120, since the yield improvement offered by EBUS-guidance did not generate sufficient savings to offset the additional costs associated with use of EBUS.

Sensitivity analysis 2 indicated that the results are relatively sensitive to the cost of mediastinoscopy. When the cost of mediastinoscopy increased to $8597, the use of EBUS-guided procedures generated a bigger cost saving. When the cost of mediastinoscopy decreased to $3867, the cost saving associated with EBUS-TBNA use diminished.

Under sensitivity analysis 3, the procedural costs of EBUS-guidance were estimated to be slightly higher than the base case analysis. As expected, the cost savings associated with the EBUS arm declined from the base case level; however, no significant impacts were observed. Inclusion of bronchoscopy costs in the non-EBUS arm improved the cost advantage associated with the EBUS-TBNA arm (sensitivity analysis 4).

Similar sensitivity analyses were conducted for EBUS-TBBX (Table 45):

- A sensitivity analysis was also conducted by varying the yield rate of EBUS-TBBX. The yield rate of EBUS-TBBX used in the base case analysis was derived from Herth et al (2002). The number of subjects included in the sub-group analysis was considered to be too small to accurately calculate the CI. For this reason, the yield rate was arbitrarily increased and decreased by 10 per cent (see sensitivity analysis 1, Table 45). This range was comparable to the 95 per cent CIs for EBUS-TBNA.

- Both VATS and thoracotomy are considered appropriate follow-up strategies after an unsatisfactory CT-guided TTNA. VATS was used as the follow-up procedure in the base case analysis. A sensitivity analysis in which thoracotomy is used in place of VATS was conducted (see sensitivity analysis 2, Table 45).

- As per sensitivity analysis 3 for EBUS-TBNA, a sensitivity analysis was also conducted for the EBUS-TBBX analysis by assuming that each centre performs eight EBUS-TBBX procedures per week, rather than the base case assumption of 12 procedures per week.

Table 45 Results of sensitivity analyses for EBUS-TBBX vs fluoroscopic-TBBX

Patients with peripheral lung lesions < 3 cm diameter			
Analysis	**Expected costs**		**Incremental costs**
	EBUS-TBBX	**Fluoroscopic-TBBX**	
Base case analysis	**$1115.49**	**$1479.29**	**–$363.80**
1. Varying the yield rate of EBUS-guided procedure			
Reduced by 10% (73%)	$1394.15	$1479.29	–$85.14
Increased by 10% (89%)	$836.83	$1479.29	–$642.46
2. Varying the cost of the surgical resection (replacing VATS with thoracotomy)			
Thoracotomy cost ($16,491)	$1247.09	$1777.12	–$530.03
3. Varying the number of procedures performed per centre per annum			
416 procedures per centre	$1140.49	$1479.29	–$338.80

Sensitivity analysis indicated the yield rate of EBUS-TBBX had a substantial effect on the results (Table 45). When yield rate of EBUS-TBBX dropped by 10 per cent (73%), the cost savings associated with EBUS-TBBX were minimal compared with fluoroscopic-TBBX. The cost differences between the arms increased in favour of EBUS-TBBX when the higher yield rate was applied in the analysis (89%).

Sensitivity analysis 2 indicated that the EBUS-TBBX strategy was shown to offer further cost savings when compared with the base case analysis, when thoracotomy was used as the third line follow-up procedure. Given that thoracotomy is more expensive than VATS, this is an expected outcome because the improvement in yield offered by the use of EBUS-guidance reduced the need for the more costly follow-up procedure.

Sensitivity analysis 3 indicated that higher costs of EBUS-guidance due to reduced total procedures performed per annum resulted in less cost savings. No notable change was observed compared with the base case findings.

Discussion

Accurate NSCLC staging and diagnosis of mediastinal/hilar masses of unknown origin and peripheral lung lesions are vital for prognostic and therapeutic decision making.

The use of EBUS procedures was shown to improve the likelihood of successfully obtaining TBNA material of diagnostic quality for NSCLC staging and diagnosis of mediastinal/hilar masses (Herth et al 2004). A decision analytic model, comparing EBUS-TBNA with TBNA alone, was used to evaluate associated cost implications.

Although EBUS did not improve yield in diagnosis of peripheral lung lesions greater than 3 cm diameter, it was shown to offer improvement when performed for peripheral lung lesions less than 3 cm diameter (Herth et al 2002). To this end, a model was used to compare EBUS-TBBX with fluoroscopic-TBBX in this patient sub-group.

No analysis was carried out for EBUS procedures in the depth diagnosis of endobronchial cancers due to the lack of relevant clinical data.

The current model estimated that EBUS-TBNA would generate a mean cost saving of $347 per patient when compared with TBNA alone for NSCLC staging and diagnosis of mediastinal/hilar masses. This finding is consistent with the analysis of Herth et al (2003).

The use of EBUS-TBBX was estimated to generate a cost saving of $364 per patient in the diagnosis of peripheral lung lesions less than 3 cm diameter when compared with fluoroscopic-TBBX.

Sensitivity analyses demonstrated that only a small change in yield rates in the model significantly affected the results. This was anticipated because yield rate represents the key factor in the model, influencing the likelihood of avoiding the more costly follow-up procedure.

The break-even yield rate for EBUS-TBNA, at which the cost advantage of EBUS guidance is lost, was approximately 71 per cent according to the current model. This break-even yield rate fell within the 95 per cent confidence intervals calculated from Herth et al (2004). As such, the cost advantage demonstrated for EBUS-TBNA in the base case analysis should be interpreted with caution.

The break-even point was also estimated to be 71 per cent for EBUS-TBBX. The use of EBUS-TBBX was reported to offer a yield rate of 81 per cent in the diagnosis of peripheral lung legions less than 3 cm diameter, well over the break-even point of 71 per cent based on the current model. This indicates that EBUS-TBBX could be considered as a preferred strategy over fluoroscopic-TBBX.

Improved yield offered by EBUS guidance was the main focus of the current analyses. The use of EBUS-guidance was assumed to have no impact on the overall diagnostic accuracy of sampling procedures (TBNA and TBBX). Should the use of EBUS influence diagnostic accuracy of TBNA or TBBX, patients' prognoses would likely be affected. This would potentially create important health outcomes and economic implications. No relevant data were available to inform evaluation of these outcomes.

A variety of biopsy techniques could be considered as appropriate comparators (Figures 3–6). The current model elected TBNA alone and fluoroscopic-TBBX as comparators for EBUS-TBNA and EBUS-TBBX, respectively. This reflected the limited availability of comparative data between EBUS-guided procedures and other modalities.

Mediastinoscopy is often used as a first-line invasive staging procedure in practice for NSCLC staging and diagnosis of mediastinal/hilar masses of unknown origin. Mediastinoscopy is a considerably more expensive procedure than EBUS-TBNA. Given the reported yield rates for EBUS-TBNA, these procedures are very likely to offer cost advantages over mediastinoscopy as the first-line staging/diagnostic procedure. At a yield rate of 77 per cent obtained by EBUS-TBNA, its expected costs, plus mediastinoscopy if necessary, were estimated at $2426 per patient. This level of cost advantage means that with the assumption of a perfect yield for mediastinoscopy, EBUS-TBNA would still represent a superior alternative even if its yield rate were far worse than the levels reported in the available evidence—as low as 20 per cent.

Mediastinoscopy has been reported to be associated with a small risk of complication (Aabakken et al 1999, Kramer et al 2004). Avoiding mediastinoscopy by using EBUS technology is likely to generate health benefits. These benefits were not captured by the current model. The current analyses are therefore likely to be conservative and to underestimate the cost advantages of EBUS procedures.

VATS or thoracotomy were employed as the final diagnostic procedures in the model for diagnosis of peripheral lung lesions less than 3 cm diameter. The model was designed to determine the overall costs associated with the diagnostic algorithm, and not the costs associated with downstream clinical management of patients following confirmed diagnosis; VATS or thoracotomy can offer both therapeutic and diagnostic interventions in some cases. This means some patients would undergo VATS or thoracotomy for treatment as well as diagnosis.

Given that a higher proportion of patients in the fluoroscopic-TBBX arm underwent VATS or thoracotomy, more people in this arm may potentially have undergone therapeutic surgical resection simultaneously with the (more invasive) diagnostic procedure than patients in the EBUS-TBBX arm in the model. Accordingly, fewer patients in the fluoroscopic-TBBX arm would have required an additional therapeutic intervention after the diagnostic procedure outside the model, potentially reducing the costs of downstream management for these patients, which was not captured in the model.

Accordingly, the cost savings demonstrated for the EBUS arm may not be fully realised in practice. However, given the small incremental difference in the proportion of patients undergoing surgical resection, this is likely to have a negligible cost implication.

Clinical observation could represent an alternative to surgical resection (ie VATS and thoracotomy) for diagnosis of peripheral lung lesions. This strategy is most appropriate for patients at very low risk of malignancy and/or those at high risk of surgical resection complication. This could however potentially delay diagnosis and treatment in patients with malignant nodules (Gould et al 2007). The current analysis did not explore the cost implications of employing clinical observation as a follow-up procedure.

It is noted that most centres equipped to provide EBUS-guided sampling services are currently located in public hospitals. Based on the available evidence (Table 46), private hospitals represented 33 per cent of the total separations relating to respiratory system procedures in 2002–2003; the remainder were in the public hospital system. This trend might also develop for EBUS-guided sampling procedures. As a result, health resource utilisation for implementing EBUS-guided sampling procedures in the public hospital system would be reduced.

Table 46 Separation statistics for respiratory system procedures by public and private hospitals

AR-DRG code, description	Public patient separations	Private patient separations
E02A Other respiratory system operating procedures with catastrophic complications and comorbidities	1864	632
E02B Other respiratory system operating procedures with severe complications and comorbidities	1919	800
E02C Other respiratory system operating procedures without catastrophic or severe complications and comorbidities	8619	4765
Total number of separations	12,402	6197

Source: National Hospital Cost Data Collection, Round 7 (2002–2003). The data from Round 8 and Round 9 were not used because of the absence of the comparative private hospitals separations with those DRG codes

The introduction of EBUS-guided procedures for NSCLC staging and diagnoses of mediastinal masses and peripheral lung lesions less than 3 cm diameter may generate modest cost savings for the Australian healthcare system. A reliable assessment of the potential impact of EBUS-guided procedures in terms of patient outcomes is not possible due to lack of relevant data.

Other considerations

This section raises matters relating to endobronchial ultrasound (EBUS) that may not have been addressed by the identified evidence indicating the clinical safety, effectiveness and cost-effectiveness of EBUS procedures. Advice from the expert advisory panel and issues raised by the evaluators is presented. Information provided information is additional to evidence identified during the systematic literature review.

Generalisability of evidence

The Thoraxklinik (University of Heidelberg, Germany) is credited as a collaborating centre in most studies presenting EBUS technology and procedural information. The unique status of Thoraxklinik should be considered when reviewing this report because it may limit the generalisability of the evidence.

Endobronchial ultrasound and endoscopic ultrasound

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) are complementary techniques. EBUS provides better access to anterior and superior mediastinal lymph nodes, and EUS is better able to access to posterior and inferior mediastinal lymph nodes (Table 4). Combining EBUS and EUS should theoretically enable access to the whole of the mediastinum. It was assumed that a reasonable evaluation approach to confirm diagnoses of mediastinal masses would involve CT/PET scanning followed by EBUS-TBNA and/or EUS-FNA. This single procedure evaluation strategy could potentially minimise the number of procedures patients undergo, and provide accurate staging of mediastinal masses. This approach could also provide benefits for patients considered medically unfit to undergo surgical diagnostic procedures (Rintoul et al 2005). Larger randomised controlled trials that examined accuracy of combined EBUS-TBNA and EUS-FNA in staging mediastinal masses, compared with currently available studies that considered surgical techniques, are required. If combined, the resulting procedure would be more expensive because Australian clinical practice requires two different specialists to perform the procedures.

Prospective studies

A number of relevant prospective studies are under way that should be considered as part of the decision making process about reimbursement of EBUS (see Table 47). Studies being conducted by Tournoy and Annema (NCT00432640) and Rintoul (ISRCTN97311620) combine EBUS with EUS for comparison with mediastinoscopy (the reference standard) and may be particularly informative. No prior parallel group randomised controlled trial (RCT) has been conducted to ascertain the capability of the combined techniques versus mediastinoscopy.

Emerging experience indicates the possible use of EBUS-TBNA for patients who do not have abnormal lymph nodes detected by CT and/or PET (Herth et al 2006a).

Table 47 Characteristics of potentially relevant ongoing trials using EBUS-guided procedures

Trial register details	Study characteristics
ISRCTN97311620 Robert Rintoul Identified using Current Controlled Trials Register	**Study design**: Parallel group RCT **Population**: Patients with presumed or known NSCLC with mediastinal lymphadenopathy identified by prior tests (n = 142) **Prior tests**: CT **Index test**: EBUS-TBNA and EUS-FNA **Comparator**: Mediastinoscopy **Reference standard**: Negative histology samples will be confirmed with surgical resection **Outcomes**: *Primary* Sensitivity of lymph node staging; *Secondary* Utility; assessment of the rate of avoided surgical procedures
NCT00432640 Kurt Tournoy & Jouke Annema Identified using ClinicalTrials.gov register	**Study design**: Open-label parallel group RCT **Population**: Patients with presumed or known NSCLC with mediastinal lymphadenopathy identified by prior tests (n = 150) **Prior tests**: NR **Index test**: EBUS-TBNA/EUS-FNA **Comparator**: Mediastinoscopy **Reference standard**: NR **Outcomes**: *Primary* Sensitivity of lymph node staging; *Secondary* Assessment of mediastinal tumour invasion (T4); assessment of the rate of avoided surgical procedures; assessment of the negative predictive value; assessment of the difference in the cost for lymph node staging; assessment of the complication rates; assessment of the rate of futile thoracotomies
NCT00372203 Shaf Keshavjee Identified using ClinicalTrials.gov register	**Study design:** Prospective, open-label patient series **Population**: Patients with presumed or known NSCLC who require staging using mediastinoscopy or patients who have mediastinal masses of unknown origin (n = 180) **Prior tests**: NR **Index test**: EBUS-TBNA **Comparator:** Mediastinoscopy **Reference standard**: NR **Outcomes**: *Primary* sensitivity of lymph node diagnosis
NCT00415337 Han-Pin Kuo Identified using ClinicalTrials.gov register	**Study design:** Prospective/retrospective cross-sectional study **Population:** Patients with peripheral lung lesions identified by prior tests (n = NR) **Prior tests**: NR **Index test**: EBUS +/-TBBX (GS) **Comparator**: NR **Reference standard**: NR **Outcomes**: NR
NCT00398970 Jon Hardie Identified using ClinicalTrials.gov register	**Study design:** Open-label parallel group RCT **Population:** Patients with lesions suspected of malignancy in the lung (n = 240) **Prior tests**: Bronchoscopy **Index test**: EBUS-TBBX (GS) **Comparator**: TBBX **Reference standard**: NR **Outcomes**: Diagnostic yield

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; EUS-FNA, endoscopic fine-needle aspiration; GS, guide sheath; NR, not reported; NSCLC, non-small cell lung cancer; RCT, randomised controlled trial; TBBX, transbronchial biopsy; TBNA, transbronchial needle aspiration

Research recommendations

After reviewing the body of evidence addressing each research question the evaluators have made specific research recommendations using a modified EPICOT (evidence, population, intervention, comparison, outcome, time stamp) format (Brown et al 2006). As well as the standard EPICOT elements, the research recommendations also address the prior test element. After reviewing the current evidence it was considered appropriate to combine the NSCLC staging and diagnosis of mediastinal/hilar mass indications.

The research recommendations outlined in Table 48 were formulated to address the gaps identified in the body of evidence for use of EBUS-TBNA in NSCLC staging of and diagnosis of mediastinal/hilar masses.

A systematic review of the literature did not identify any comparative evidence of the effectiveness of EBUS-TBNA versus mediastinoscopy, which is one of the major comparators identified by the advisory panel.

The systematic review identified evidence that indicated the comparative diagnostic yield of EBUS-TBNA and TBNA. There was insufficient evidence to address the uncertainty in comparative effectiveness between procedures.

Table 48 Research recommendations for use of EBUS-TBNA in NSCLC staging and diagnosis of mediastinal/hilar masses

Element	Description
Evidence	The reported diagnostic yield of EBUS-TBNA was greater than TBNA. There were no studies that reported diagnostic accuracy of EBUS-TBNA compared with TBNA
	No studies were identified that compared the diagnostic performance of EBUS-TBNA with mediastinoscopy
	The reported sensitivity and diagnostic yield of EBUS-TBNA was at least equivalent to EUS-FNA in selected patient subgroups
Population	Patients with presumed or known NSCLC with mediastinal/ hilar lymphadenopathy identified by prior tests
	Patients with mediastinal/ hilar masses of unknown origin (including lymphadenopathy) identified with CT +/- x-ray +/- symptoms
	Mixed patient population with presumed or known NSCLC with mediastinal/ hilar lymphadenopathy identified by prior tests or diagnosis of mediastinal lymphadenopathy of unknown origin (including lymphadenopathy) identified with CT +/- x-ray +/- symptoms
Prior tests	Clinical assessment; CT +/- PET
Intervention/test	EBUS-TBNA; EBUS-TBNA and EUS-FNA
Comparator[a]	Mediastinoscopy; TBNA
Outcome	Sensitivity and specificity (compared with a histological reference standard)
	Diagnostic yield[b]
	Treatment alterations (eg assessment of the rate of avoided surgical procedures)
	Patient survival
	Quality of life
	Adverse events
Time stamp	June 2007

Abbreviations: CT, computer tomography; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; FNA, fine needle aspiration; NSCLC, non-small cell lung cancer; PET, positron emission tomography; TBNA, transbronchial needle aspiration

[a] The research recommendation was formulated based on the major comparators identified by the advisory panel. Other comparators for this indication included EUS-FNA, mediastinotomy, TTNA, or VAT

[b] Comparisons versus mediastinoscopy

The research recommendations outlined in Table 49 were formulated to address the gap identified in the body of evidence for use of EBUS with or without EBBX in depth diagnosis of endobronchial cancers.

A systematic review of the evidence did not identify any comparative evidence of EBUS with or without EBBX versus EBBX.

Table 49 Research recommendations for the use of EBUS with or without EBBX in the depth diagnosis of endobronchial cancers

Element	Description
Evidence	No trials were identified that compared the diagnostic accuracy of EBUS +/- EBBX to EBBX in depth diagnosis of endobronchial cancers in patients without enlarged lymph nodes
Population	Patients with presumed or known NSCLC without mediastinal/ hilar lymphadenopathy identified by prior tests
Prior tests	Clinical assessment
	CT +/- PET
Intervention/test	EBUS +/- EBBX
Comparator	EBBX
Outcome	Sensitivity and specificity (compared with a histological reference standard)
	Diagnostic yield
	Treatment alterations (eg changes in planned photodynamic therapy or surgery)
	Patient survival
	Quality of life
	Adverse events
Time stamp	June 2007

Abbreviations: CT, computer tomography; EBUS, endobronchial ultrasound; EBBX, endobronchial biopsy; NSCLC, non-small cell lung cancer; PET, positron emission tomography

The research recommendations outlined in Table 50 were formulated to address two gaps identified in the body of evidence for use of EBUS-TBBX in diagnosis of peripheral lung lesions.

A systematic review of the literature did not identify any comparative evidence of EBUS-TBBX versus TTNA, which was one of the major comparators identified by the advisory panel.

The systematic review identified evidence indicating comparative diagnostic performance of EBUS-TBBX and fluoroscopy-TBBX. The EBUS-TBBX procedures reported had limited applicability to the Australian clinical setting.

Table 50 Research recommendations for the use of EBUS-TBBX in the diagnosis of peripheral lung lesions

Element	Description
Evidence	The reported sensitivity and diagnostic yield of EBUS-TBBX was equivalent to fluoroscopy-TBBX
	No studies were identified that compared the diagnostic performance of EBUS-TBBX with TTNA
	The reported diagnostic yield of EBUS-TBBX was greater than TBBX and at least equivalent to ENB-TBBX
	The diagnostic yield of EBUS-TBBX may be greater than other methods of guided-TBBX in diagnosis of smaller peripheral lesions
Population	Patients with peripheral lung lesions identified by prior tests
	Patients with peripheral lung lesions < 3 cm identified by prior tests
Prior tests	Clinical assessment
	CT +/- PET
Intervention/test	EBUS-TBBX (with fluoroscopic navigation)
Comparator a	Fluoroscopy-TBBX
	TTNA
Outcome	Sensitivity and specificity (compared with a histological reference standard)
	Diagnostic yield
	Treatment alterations (eg assessment of surgical procedures avoided rate)
	Patient survival
	Quality of life
	Adverse events
Time stamp	June 2007

Abbreviations: CT, computer tomography; EBUS, endobronchial ultrasound; ENB, electromagnetic navigation bronchoscopy; TBNA, transbronchial needle aspiration; TTNA, transthoracic needle aspiration; PET, positron emission tomography

[a] The research recommendation was formulated based on the major comparators identified by the advisory panel. Other comparators for this indication included TTNA, TBBX and electromagnetic guided TBBX

Conclusions

Safety

Endobronchial ultrasound (EBUS)-guided procedures for non-small cell lung cancer (NSCLC) staging, diagnosis of mediastinal/hilar masses, depth diagnosis of endobronchial cancers and diagnosis of peripheral lung lesions appear to be as safe as other minimally-invasive diagnostic tests. The most frequently reported adverse events were bleeding and pneumothorax. These mainly occurred among patients who underwent EBUS- or fluoroscopy-guided transbronchial biopsy.

Effectiveness

A linked evidence approach was used to evaluate use of EBUS-guided procedures for NSCLC staging, diagnosis of mediastinal/hilar masses, depth diagnosis of endobronchial cancers and diagnosis of peripheral lung lesions.

The evidence indicated that the diagnostic yield of EBUS-transbronchial needle aspiration (TBNA) was greater than TBNA alone in NSCLC staging and for diagnosis of mediastinal/hilar masses. There was limited evidence suggesting that the sensitivity and diagnostic yield of EBUS-TBNA were at least equivalent to endoscopic ultrasound fine-needle aspiration (EUS-FNA) in specific sub-groups. No evidence was available to assess EBUS-TBNA impact on patient management. Treatment effectiveness evidence was not examined because it was considered that EBUS-TBNA would not identify any unique patient groups that were substantially different from those currently seen in Australian clinical practice. There was insufficient evidence to address uncertainty concerning the clinical impact of EBUS-TBNA compared with its major comparators, TBNA and mediastinoscopy.

No trials were identified that compared the diagnostic performance of EBUS with or without endobronchial biopsy (EBBX) to EBBX alone in diagnosing the depth of endobronchial cancers. In the absence of evidence indicating diagnostic accuracy, patient management and treatment effectiveness-related evidence was not sought.

The evidence suggested that EBUS-TBBX sensitivity was equivalent to fluoroscopy-TBBX in the diagnosis of peripheral lung lesions. The evaluated studies also indicated that the diagnostic yield of EBUS-TBBX was greater than TBBX and at least equivalent to other methods (electromagnetic, fluoroscopic) of guided-TBBX. The evidence further suggested that the diagnostic yield of EBUS-TBBX may be greater than other methods of guided-TBBX in diagnosing smaller peripheral lesions (less than 3 cm diameter). There was no evidence to assess the impact of EBUS-TBBX on patient management. There was insufficient evidence to address uncertainty surrounding the clinical impact of EBUS-TBBX compared with the major comparators, fluoroscopy-TBBX and TTNA. Treatment effectiveness evidence was not examined because it was considered that EBUS-TBBX would not identify any unique patient groups that were substantially different from those currently seen in Australian clinical practice.

Economic analyses

A decision analytic model was constructed to assess cost implications of EBUS-guided procedures when compared with current procedures. A cost analysis of EBUS-TBNA relative to TBNA alone was performed for NSCLC staging and diagnosis of mediastinal/hilar masses of unknown origin. A cost analysis of EBUS-TBBX relative to TBBX was conducted for diagnosis of peripheral lung lesions less than 3 cm.

A cost analysis was not conducted for the depth diagnosis of endobronchial cancers because clinical data were limited.

The analysis indicated that use of EBUS-TBNA for NSCLC staging and diagnosis of mediastinal masses was estimated to generate a cost saving of $347 per patient. The use of EBUS-TBBX for diagnosis of peripheral lung lesions less than 3 cm diameter was estimated to generate a cost saving of $364 per patient. This reflected the economic benefits associated with improved yield offered by the use of EBUS guidance.

The presented results should be interpreted in the context of data inputs and assumptions applied in the model. A reliable assessment of the potential impact of EBUS-guided procedures in terms on patient outcomes is not possible due to a lack of relevant data.

Recommendation

MSAC has considered the safety, effectiveness and cost-effectiveness of endobronchial ultrasound (EBUS)-guided procedures for the investigation of non-small cell lung cancer, mediastinal/hilar masses, endobronchial cancer and peripheral lung lesions compared to mediastinoscopy and transbronchial needle aspiration.

The MSAC finds that the EBUS-guided procedures for the staging of non-small cell lung cancer, and the investigation of mediastinal/hilar masses and peripheral lung lesions is safer, more effective and likely to be cost saving when compared to mediastinoscopy and transbronchial needle aspiration.

MSAC finds that, though safe, there is insufficient evidence on the effectiveness and cost-effectiveness of the EBUS-guided procedure for the evaluation of endobronchial cancer.

MSAC recommends that public funding should be **supported** for EBUS-guided procedures for the staging of non-small cell lung cancer, and the investigation of mediastinal/hilar masses and peripheral lung lesions.

MSAC recommends that public funding should **not be supported** for the EBUS-guided procedure for the evaluation of endobronchial cancer.

— The Minister for Health and Ageing accepted this recommendation on 20 May 2008—

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures, and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, radiology, nuclear medicine, oncology, surgery, internal medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers and health administration and planning:

Member	Expertise or affiliation
Dr Stephen Blamey (Chair)	General surgery
Associate Professor John Atherton	Cardiology
Associate Professor Michael Cleary	Emergency medicine
Associate Professor Paul Craft	Clinical epidemiology and oncology
Professor Geoff Farrell	Gastroenterology
Dr Kwun Fong	Thoracic medicine
Professor Richard Fox	Medical oncology
Dr Bill Glasson	Ophthalmology
Professor Jane Hall	Health economics
Professor John Horvath	Chief Medical Officer Department of Health and Ageing
Associate Professor Terri Jackson	Health economics
Professor Brendon Kearney	Health administration and planning
Associate Professor Frederick Khafagi	Nuclear medicine
Dr Ray Kirk	Health research
Dr Ewa Piejko	General practice
Dr Ian Prosser	Haematology

Member	Expertise or affiliation
Ms Sheila Rimmer	Consumer health issues
Dr Judy Soper	Radiology
Professor Ken Thomson	Radiology
Dr David Wood	Orthopaedics
Mr Peter Woodley	Assistant Secretary Medical Benefits Schedule (MBS) Policy Development Branch, Department of Health and Ageing

Appendix B Advisory panel

Advisory panel for MSAC application 1108

Dr Kwun Fong (Chair) Thoracic medicine	Member of MSAC
Associate Professor Frederick Khafagi (Second Chair) Nuclear medicine	Member of MSAC
Mr Phillip Antippa Cardiothoracic surgery	Nominated by the Australasian Society of Cardiovascular Surgeons
Dr Martin Phillips Respiratory medicine	Nominated by the Thoracic Society of Australia and New Zealand
Dr Marshall Plit Thoracic medicine & Lung transplation	Nominated by the Thoracic Society of Australia and New Zealand
Dr Morgan Windsor Cardio & Thoracic surgery & Upper gastrointestinal surgery	Nominated by the Australasian Society of Cardiac and Thoracic Surgeons
Ms Robin Toohey Independent consumer representative	Nominated by the Consumers' Health Forum

Appendix C Supportive data

Nodal staging of non-small cell lung cancer and diagnosis of mediastinal/hilar masses of unknown origin

There were eight studies identified that presented supportive evidence of EBUS-TBNA use for patients primarily referred for NSCLC staging or diagnoses of mediastinal/hilar masses of unknown origin (Herth et al 2003b, Herth et al 2006b, Krasnik et al 2003, Plat et al 2006, Rintoul et al 2005, Yasufuku et al 2004, Yasufuku et al 2005, Yasufuku et al 2006). The characteristics of these studies are summarised in Table 51.

A low-quality comparative diagnostic accuracy study by Yasufuku et al (2006) assessed the diagnostic sensitivity of EBUS-TBNA, CT and PET imaging for mediastinal lymph nodes. This study did not compare EBUS with the conventional comparators and was not included in the primary analysis. Because the comparison did not involve a blinded independent comparison with a valid reference standard, it was regarded as providing level III-2 evidence. This study offers limited applicability to the Australian clinical setting because the sensitivity evaluation of CT and PET imaging included patients who did not present with mediastinal/hilar lymphadenopathy.

Of the eight identified studies, four non-comparative studies assessed sensitivity (Krasnik et al 2003; level III-2 evidence) and diagnostic yield (Herth et al 2003b, Herth et al 2006b, Plat et al 2006; level IV evidence) of EBUS-TBNA in a mixed patient population. All studies that assessed diagnostic yield of EBUS-TBNA were high quality, but the diagnostic accuracy study was regarded as low quality. All studies were applicable to Australian clinical practice, but it should be noted that Herth et al (2003b) used a larger gauge needle than is common practice in this country. Herth et al (2006b) reported diagnostic accuracy values, but a 2×2 table (Figure 8) could not be reconstructed. Diagnostic accuracy results were not reported adequately by this study so they were excluded from the current review. Only diagnostic yield results were assessed.

The identified literature included three low quality non-comparative studies that assessed the diagnostic sensitivity of EBUS-TBNA (Yasufuku et al 2004, Yasufuku et al 2005) and EBUS-TBNA/EUS-FNA (Rintoul et al 2005) for mediastinal lymph nodes. It is noteworthy that Yasufuku et al (2004) and Yasufuku et al (2005) indicated that there was a partial overlap in the enrolled patient populations. These studies did not involve blinded independent comparisons with valid reference standards and were consequently regarded as providing level III-2 evidence. These studies present evidence that is likely to be applicable to the Australian clinical setting.

Table 51 Characteristics of the included supportive studies assessing the diagnostic accuracy/yield of EBUS-TBNA in patients referred for lung cancer staging and/or diagnosis of mediastinal/hilar mass of unknown origin

Author (year) Country	Study design	Patient characteristics	Test characteristics	Quality and applicability
Herth et al (2003b) Germany	Prospective, consecutive patient series Jan 1999–Jan 2000	**Inclusion:** Patients referred for lung cancer staging or diagnosis of mediastinal lymphadenopathy of unknown origin **Exclusion:** No reported exclusions (n = 242) **Prior tests:** CT	**Index test: EBUS-TBNA** [system EU-M 20 and 30, radial probe UM2R/3R, Olympus]; conventional bronchoscope (p 20 and p 40D, Olympus); 19G and 22G needle; general anaesthesia or conscious sedation; no ROSE **Reference standard:** Cytology; histology	IV CX, P2, Q1 *Quality:* High *Applicability:* Applicable 19G tissue sampling needle
Herth et al (2006b) Germany	Prospective, consecutive patient series Jun 2002–Sep 2004	**Inclusion:** Patients referred for lung cancer staging or diagnosis of mediastinal lymphadenopathy of unknown origin **Exclusion:** No reported exclusions (n = 502) **Prior tests:** X-ray, CT	**Index test: EBUS-TBNA** [system EU-60, Olympus]; linear scanning hybrid bronchoscope (XBF-UC260F-OL8, Olympus); 22G needle; moderate sedation and local anaesthesia or general anaesthesia; no ROSE; 2 aspirates per node were obtained **Reference standard:** Cytology; histology; clinical/radiological follow-up	IV CX, P1, Q1 *Quality:* High *Applicability:* Applicable
Krasnik et al (2003) Denmark	Direction unclear, non-consecutive patient series Unblinded	**Inclusion:** Patients referred for lung cancer staging, diagnosis of mediastinal/hilar lymphadenopathy of unknown origin or assessment of mediastinal tumour recurrence **Exclusion:** No reported exclusions (n = 11) **Prior tests:** CT, bronchoscopy	**Index test: EBUS-TBNA** [system EU-C60, Olympus]; linear scanning hybrid bronchoscope (XBF-UC40P, Olympus); 22G needle; general anaesthesia **Reference standard**: Cytology; histology	III-2 CX, P2, Q3 *Quality*: Low Unblinded Inadequate reference standard *Applicability*: Applicable Patients assessed for tumour recurrence
Plat et al (2006) Belgium	Prospective, consecutive patient series Jan 2003–Jun 2004	**Inclusion:** Patients referred for lung cancer staging or diagnosis of mediastinal lymphadenopathy of unknown origin **Exclusion:** No reported exclusions (n = 33) **Prior tests:** CT, PET	**Index test: EBUS-TBNA** [system EU-M20, radial probe UM-BS20-26R, Olympus]; conventional bronchoscope (Excera, Olympus); local anaesthesia and conscious sedation; no ROSE; 4–6 punctures were obtained **Reference standard:** Cytology; histology; clinical/radiological follow-up	IV CX, P1, Q1 *Quality:* High *Applicability:* Applicable

Author (year) Country	Study design	Patient characteristics	Test characteristics	Quality and applicability
Rintoul et al (2005) UK	Direction unclear, non-consecutive patient series Unblinded	**Inclusion:** Patients with known or suspected lung cancer and a mediastinal lymphadenopathy of > 1 cm or paratracheal or parabronchial masses **Exclusion:** Patients were excluded from analysis based on imaging results (n = 18) **Prior tests:** CT	**Index test: EBUS-TBNA/EUS-FNA** [system EU-C2000, Olympus]; linear scanning hybrid bronchoscope (XBF-UC260F-OL8, Olympus); 22G needle. **EUS-FNA** (GF-UC240P-AL5, Olympus); 22G needle. Local anaesthesia and sedation; no ROSE; 2–3 needle passes were obtained. **Reference standard:** Cytology, histology, clinical/radiological follow-up	III-2 CX, P1, Q3 *Quality*: Low Unblinded Inadequate reference standard *Applicability*: Applicable
Yasufuku et al (2004) Japan	Prospective, non-consecutive patient series Unblinded Mar 2002–Sep 2003	**Inclusion:** Patients with known or suspected lung cancer and mediastinal and/or hilar lymphadenopathy of > 1 cm **Exclusion:** No reported exclusions (n = 70) **Prior tests**: X-ray, CT	**Index test: EBUS-TBNA** [system EU-C2000, Olympus]; linear scanning hybrid bronchoscope (XBF-UC260F-OL8, Olympus); 22G needle; local anaesthesia and sedation; ROSE; 1–5 needle passes were obtained **Reference standard**: Cytology, histology, clinical/radiological follow-up	III-2 CX, P1, Q3 *Quality*: Low Unblinded Inadequate reference standard *Applicability*: Applicable
Yasufuku et al (2005) Japan	Prospective, non-consecutive patient series Unblinded Jun 2002–Apr 2004	**Inclusion:** Patients with known or suspected lung cancer and mediastinal and/or hilar lymphadenopathy of > 1 cm **Exclusion:** Patients with a final diagnosis of a benign disease; patients with a final diagnosis of malignant disease other than NSCLC, patients with extensive N2, N3 disease on CT (n = 108) **Prior tests:** CT	**Index test: EBUS-TBNA** [system EU-C2000, Olympus]; linear scanning hybrid bronchoscope (XBF-UC260F-OL8, Olympus); 22G needle; local anaesthesia and sedation; ROSE; 1–5 needle passes were obtained **Reference standard:** Cytology, histology, clinical/radiological follow-up	III-2 CX, P1, Q2 *Quality*: Low Unblinded Inadequate reference standard Inadequate data reporting *Applicability*: Applicable
Yasufuku et al (2006) Japan	Prospective, consecutive patient series CT & PET blinded Dec 2003–Mar 2005	**Inclusion:** Patients with known or suspected lung cancer **Exclusion:** Patients who were not further evaluated (n = 102) **Prior tests:** CT, PET, other tests	**Index test: EBUS-TBNA** [system EU-C2000, Olympus]; linear scanning hybrid bronchoscope (XBF-UC260F-OL8, Olympus); 22G needle, conscious sedation; ROSE; maximum of 5 needle passes were obtained **Comparator: CT** (Light Speed, GE medical systems), multidetector row, injection of contrast material **Comparator: PET** (PET Advance Nxi, GE medical systems), 300 Mbq injection of FDG **Reference standard**: Cytology, histology, clinical/radiological follow-up	III-2 C1, P2, Q3 *Quality*: Low Inadequate blinding Inadequate reference standard *Applicability*: Limited Included patients with negative lymphadenopathy

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; EUS-FNA, endoscopy ultrasound-fine needle aspiration; FDG, fluorodeoxyglucose; G, gauge; PET, positron emission tomography; ROSE, rapid on site evaluation; TBBX, transbronchial biopsy; TBNA, transbronchial needle aspiration; TTNA, transthoracic needle aspiration

Yasufuku et al (2006) reported the comparative sensitivity, specificity and predictive values of EBUS-TBNA, CT and PET (Table 52). The reported positive results were not confirmed, because malignant cytological diagnoses by EBUS-TBNA were taken as final proof of malignancy (inadequate reference standard). Therefore, the reported specificity and positive predictive value (PPV) could not be used as measures of test accuracy for this review. The PPV was applied only as an assumption in conjunction with the negative predictive value (NPV) to calculate approximate sensitivities for each diagnostic test. Yasufuku and colleagues (2006) found that the sensitivity of linear EBUS-TBNA (92%) was greater than CT and PET imaging (77% and 80%, respectively) in the diagnosis of involved mediastinal lymph nodes. It is noteworthy that the prevalence reported by this study was considerably lower than the rate reported by Vilmann et al (2005). This may be indicative of differences in patient populations that could affect indirect comparisons.

Table 52 Diagnostic accuracy of included supportive studies comparing EBUS-TBNA with CT and PET imaging in patients referred for NSCLC staging and diagnoses of mediastinal/hilar masses of unknown origin

Author (year)	Prevalence n/N (%)	Diagnostic test	Sensitivity (95% CI)[a]	NPV (95% CI)	Level of evidence
Yasufuku et al (2006)	26/102 (25.49)	EBUS-TBNA	92.31 (87.14, 97.48)	97.44 (94.37, 100.00)	III-2 C1, P2, Q3
		CT	76.92 (68.74, 85.10)	87.50 (81.08, 93.92)	
		PET[b]	80.00 (72.24, 87.86)	91.53 (86.13, 96.93)	

Abbreviations: CI, confidence interval; CT, computed tomography; EBUS-TBNA, endobronchial ultrasound transbronchial needle aspiration; NPV, negative predictive value; PET, positron emission tomography

[a] Sensitivity was calculated assuming a 100% PPV

[b] An apparent data reporting error was detected in this calculation

The reported sensitivity and NPV of the non-comparative studies are summarised in Table 53. The study by Krasnik et al (2003) reported a sensitivity of 91 per cent for linear EBUS-TBNA in the mixed patient population. This was a small study (n = 11); all enrolled participants had malignant lymph nodes. The studies by Yasufuku and colleagues (2004, 2005) reported different sensitivities for linear EBUS-TBNA—100 per cent in the 2004 study and 95 per cent in the 2005 study—in patients referred for lung cancer staging (overlapping patient population). It is noteworthy that both studies calculated the sensitivity with failed TBNA procedures contributing to the false results but it was only possible to recalculate (failed TBNA procedures excluded) the Yasufuku et al (2004) results. The non-comparative study by Rintoul et al (2005) reported a sensitivity of 85 per cent for the combination of linear EBUS-TBNA and EUS-FNA in the mixed patient population.

The reported positive results were not confirmed in any of the non-comparative diagnostic accuracy studies because a malignant cytological diagnosis made using these techniques was taken as final proof of malignancy (inadequate reference standard). Therefore, for the purpose of this review the reported specificity and PPV were not used as measures of test accuracy. The PPV was only used as an assumption in conjunction with the NPV to calculate an approximate sensitivity for each diagnostic test.

Table 53 Diagnostic accuracy of the included non-comparative supportive studies assessing EBUS-TBNA in patients referred for NSCLC staging and diagnoses of mediastinal/hilar masses of unknown origin

Author (year)	Prevalence n/N (%)	Diagnostic test	Sensitivity (95% CI)[a]	NPV (95% CI)	Level of evidence
Patients primarily referred for NSCLC staging and diagnosis of a mediastinal/hilar mass of unknown origin					
Krasnik et al (2003)	11/11 (100.00)	EBUS-TBNA	90.91 (73.92, 100.00)	0.00	III-2 CX, PX, Q3
Patients referred for lung cancer staging					
Rintoul et al (2005)	13/18 (72.22)	EBUS-TBNA/EUS-FNA	84.62 (67.95, 100.00)	71.43 (50.56, 92.30)	III-2 CX, P1, Q3
Yasufuku et al (2004)	45/68 (66.18)	EBUS-TBNA	100.00	100.00	III-2 CX, P1, Q3
Yasufuku et al (2005)[b]	74/108 (68.52)	EBUS-TBNA	94.59 (90.32, 98.86)	89.47 (83.68, 95.26)	III-2 CX, P1, Q2

Abbreviations: CI, confidence interval; EBUS, endobronchial ultrasound; TBNA, transbronchial needle aspiration
[a] Sensitivity was calculated assuming a 100% PPV
[b] An apparent data reporting error was detected in this calculation

The reported diagnostic yield results from five non-comparative studies are presented in Table 54. The yields obtained for patients referred for lung cancer staging (97%) and the mixed patient population (82–95%) were generally concordant with the yields observed in the comparative trials presented in Table 21.

Table 54 Diagnostic yield of the included supportive studies assessing EBUS-TBNA in a mixed patient population (including NSCLC)

Author (year)	Prevalence n/N (%)	Diagnostic test	Specific diagnostic yield[a]		Non-specific diagnostic yield [b]		Level of evidence
			n/N	% (95% CI)	n/N	% (95% CI)	
Patients primarily referred for NSCLC staging and diagnoses of mediastinal/hilar masses of unknown origin							
Herth et al (2003b)	NR	EBUS-TBNA	172/242	71.07 (65.36, 76.79)	207/242	85.54 (81.11, 89.97)	IV CX, PX, Q1
Herth et al (2006b)	493/502 (98.21)	EBUS-TBNA	470/502	93.63 (91.49, 95.76)	476/502	94.82 (92.88, 96.76)	IV CX, P1, Q1
Plat et al (2006)	27/33 (81.82)	EBUS-TBNA	NR	NR	27/33	81.82 (68.66, 94.98)	IV CX, P1, Q1
Patients referred for lung cancer staging							
Yasufuku et al (2004)	NR	EBUS-TBNA	NR	NR	68/70	97.14 (93.24, 100.00)	III-2 CX, P1, Q3
Yasufuku et al (2005)	NR	EBUS-TBNA	NR	NR	105/108	97.22 (94.12, 100.00)	III-2 CX, P1, Q2

Abbreviations: CI, confidence interval; EBUS, endobronchial ultrasound; NR, not reported; TBNA, transbronchial needle aspiration
[a] Per patient diagnostic yield when the diagnosis of a benign lymph node was restricted to requiring a specific diagnosis
[b] Per patient diagnostic yield when the diagnosis of a benign lymph node was expanded to patients with negative lymphocytes but without a specific benign diagnosis

Peripheral lung lesions

Supportive evidence indicating the use of EBUS-TBBX in peripheral lung lesions diagnosis was identified in studies by Becker et al (2005), Chung et al (2007), Dooms et al (2007), Herth et al (2006a), Kikuchi et al (2004), Kurimoto et al (2004). The characteristics of these studies are summarised in Table 55.

A high-quality diagnostic yield RCT by Chung et al (2007) assessed the value of measuring the distance between the bronchial orifice and the peripheral lesion using radial EBUS. This study did not compare EBUS with the conventional comparators and was not included in the primary analysis. This study was classified as providing level IV evidence.

The high-quality non-comparative studies by Chung et al (2007), Dooms et al (2007), and Herth et al (2006a) assessed the diagnostic yield of EBUS-TBBX among patients with peripheral lung lesions. Because they did not report the use of fluoroscopic navigation in conjunction with the EBUS procedure these studies offer limited applicability to Australian clinical practice. The applicability of the study by Herth et al (2006a) was further limited because patients had been fluoroscopically examined previously. These studies were classified as providing level IV evidence.

Table 55 Characteristics of included supportive studies that assessed diagnostic yield of EBUS-TBBX among patients with peripheral lung lesions

Author (year) Country	Study design	Patient characteristics	Test characteristics	Quality and applicability
Becker et al (2005) Germany	Direction unclear, non-consecutive patient series Jul 2003–Dec 2003	**Inclusion:** Patients with a peripheral lung lesions not visible using bronchoscopy **Exclusion:** Patients with distorted airways due to previous surgery (n = 29) **Prior tests:** CT	**Index test: ENB/EBUS-TBBX** ENB (superDimension/Bronchus system, superDimension) and EBUS-TBBX (radial probe UM-BS20-26R, Olympus), conventional bronchoscope (EXERA IT160, Olympus); bronchial forceps and bronchial brushing; general anaesthesia; fluoroscopy and curette support **Reference standard**: Histology, clinical/radiological follow-up	IV CX, P2, Q1 *Quality:* High *Applicability:* Applicable
Chung et al (2007) Taiwan	Prospective, parallel group RCT Blinding of pathologists Oct 2004–Jul 2005	**Inclusion:** Patients with a solitary pulmonary lesion not visible using bronchoscopy **Exclusion:** Lesion invisible using EBUS (n = 113) **Prior tests:** X-ray, CT	**Index test: EBUS-TBBX (GS)** [system EU-M30S, radial probe UM-S20-20R, Olympus]; conventional bronchoscope (P260F, Olympus); guide sheath; biopsy forceps; local anaesthesia; distance measuring; 3–5 biopsy specimens were obtained **Index test: EBUS-TBBX (GS)** [system EU-M30S, radial probe UM-S20-20R, Olympus]; single channel bronchoscope (P260F, Olympus); guide sheath; biopsy forceps; local anaesthesia; 3–5 biopsy specimens were obtained **Reference standard**: Cytology, histology	IV C1, P2, Q1 *Quality:* High *Applicability:* Limited No fluoroscopic navigation of EBUS procedure

Author (year) Country	Study design	Patient characteristics	Test characteristics	Quality and applicability
Dooms et al (2007) Germany & Belgium	Prospective, consecutive (test-based) patient series Jan 2005–May 2005	**Inclusion**: Patients with a peripheral lung lesion or solitary pulmonary lesion, not visible using bronchoscopy **Exclusion**: Patients with a spiral CT showing a pulmonary infiltrate or a subpleural lesion lying entirely within 10 mm from the pleura (n = 50) **Prior tests:** CT	**Index test: EBUS-TBBX** [system EU-M20, radial probe UM-BS20-26R, Olympus]; conventional bronchoscope (IT160, Olympus); biopsy forceps; local anaesthesia; at least 4 biopsy specimens were obtained **Reference standard**: Cytology, histology	IV CX, P2, Q1 *Quality:* High *Applicability:* Limited No fluoroscopic navigation of EBUS procedure
Herth et al (2006a) Germany & USA	Prospective, consecutive patient series Jan 2003–Jan 2004	**Inclusion:** Patients with a solitary pulmonary lesion **Exclusion:** Patients with a solitary pulmonary nodule visible using fluoroscopy (n = 54) **Prior tests:** CT, fluoroscopy	**Index test: EBUS-TBBX (GS)** [radial probe UM-3R, UM-4R, US2020R, Olympus]; conventional bronchoscope (BF T160, Olympus); guide sheath; bronchial forceps; general anaesthesia or conscious sedation; 4–6 biopsy specimens were obtained **Reference standard**: Histology	IV CX, P2, Q1 *Quality:* High *Applicability:* Limited Enrolled patients with previous fluoroscopy No fluoroscopic navigation of EBUS procedure
Kikuchi et al (2004) Japan	Direction unclear, non-consecutive patient series Dec 2002–Jul 2003	**Inclusion:** Patients with a peripheral pulmonary lesion (< 30 mm in mean diameter) not visible using bronchoscopy **Exclusion:** No reported exclusions (n = 24) **Prior tests:** CT	**Index test: EBUS-TBBX (GS)** [system EU-M30S, radial probe XUM-S20-17R, Olympus]; conventional bronchoscope (BF-P-260F, BF-P-240, BF-P-200, Olympus); guide sheath; bronchial forceps and bronchial brushing; local anaesthesia; curette and fluoroscopy support **Reference standard**: Cytology, histology; clinical/radiological follow-up	IV CX, P2, Q1 *Quality:* High *Applicability:* Applicable
Kurimoto et al (2004) Japan	Prospective, consecutive patient series May 2001–Nov 2002	**Inclusion:** Patients with solitary pulmonary lesions **Exclusion:** No reported exclusions (n = 150) **Prior tests:** X-ray, CT	**Index test: EBUS-TBBX (GS)** [system EU-M30, radial probe UM-S20-20R, Olympus]; conventional bronchoscope (BF 1T-30, 40 or 240R, Olympus); guide sheath; bronchial forceps and bronchial brushing; unclear anaesthesia; curette and fluoroscopy support; at least 1 biopsy specimen was obtained **Reference standard**: Cytology, histology, clinical/radiological follow-up; other examinations	IV CX, P2, Q1 *Quality:* High *Applicability:* Applicable

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; ENB, electromagnetic navigation bronchoscopy; GS, guide sheath; RCT, randomised controlled trial; TBBX, transbronchial biopsy

The reported diagnostic yields of the six studies listed in Table 55 are summarised in Table 56. Chung et al (2007) reported that the yield of radial EBUS-TBBX can be improved by measuring the distance between the bronchial orifice and the peripheral lesion (79% with distance measuring, 57% without distance measuring).

The non-comparative EBUS-TBBX diagnostic yield studies by Dooms et al (2007), Herth et al (2006a), Kikuchi et al (2004), and Kurimoto et al (2004) reported yields ranging from 58 per cent to 77 per cent. The single non-comparative diagnostic yield study of ENB/EBUS-TBNA by Becker et al (2005) reported a yield of 69 per cent, which is considerably lower than the 88 per cent yield obtained for ENB/EBUS-TBNA by Eberhardt et al (2007).

These yields are generally concordant with observed yields in the comparative trials presented in Table 26.

Table 56 Diagnostic yield reported by the included supportive studies that assessed EBUS-TBBX among patients with peripheral lung lesions

Author (year)	Prevalence n/N (%)	Diagnostic test	Diagnostic yield		Level of evidence
			n/N	% (95% CI)	
Becker et al (2005)	24/29 (82.76)	ENB/EBUS-TBBX	20/29	68.97 (52.13, 85.80)	IV CX PX Q1
Chung et al (2007)	82/113 (72.57)	EBUS-TBBX (distance)	45/57	78.95 (68.36, 89.53)	IV C1 P1 Q1
		EBUS-TBBX	32/56	57.14 (44.18, 70.10)	
Dooms et al (2007)	NR	EBUS-TBBX	34/50	68.00 (55.07, 80.93)	IV CX P1 Q1
Herth et al (2006a)	39/54 (72.22)	EBUS-TBBX	38/54	70.37 (58.19, 82.55)	IV CX P1 Q1
Kikuchi et al (2004)	18/24 (75.00)	EBUS-TBBX	14/24	58.33 (38.61, 78.06)	IV CX PX Q1
Kurimoto et al (2004)	101/150 (67.33)	EBUS-TBBX	116/150	77.33 (70.63, 84.03)	IV CX PX Q1

Abbreviations: CI, confidence interval; EBUS, endobronchial ultrasound; ENB, electromagnetic navigation bronchoscopy; NR, not reported; TBBX, biopsy

Appendix D Included studies

Table 57 Characteristics and results of studies assessing the diagnostic accuracy and/or diagnostic yield of EBUS guided procedures

Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
Becker et al (2005) Germany Direction unclear, non-consecutive patient series Jul–Dec 2003	**Inclusion**: Patients with a peripheral lung lesions not visible using bronchoscopy **Exclusion**: Patients with distorted airways due to previous surgery (n = 29) **Prior tests**: CT	**Index test**: ENB/EBUS-TBBX ENB [superDimension/Bronchus system, superDimension] & EBUS-TBBX [radial probe UM-BS20-26R, Olympus], conventional bronchoscope (EXERA IT160, Olympus); bronchial forceps and bronchial brushing; general anaesthesia; fluoroscopy and curette support **Reference standard**: Histology, clinical/radiological follow-up	Peripheral lung lesion **Prevalence**: 24/29 (82.76%) ENB/EBUS-TBBX: Total yield 20/29 (68.97%)	IV CX, P2, Q1 Quality: High Applicability: Applicable
Chung et al (2007) Taiwan Prospective, parallel group RCT Blinding of pathologists Oct 2004–Jul 2005	**Inclusion**: Patients with a solitary pulmonary lesion not visible using bronchoscopy **Exclusion**: Lesion invisible using EBUS (n = 113) **Prior tests**: X-ray, CT	**Index test**: EBUS-TBBX (GS) [system EU-M30S, radial probe UM-S20-20R, Olympus]; conventional bronchoscope (P260F, Olympus); guide sheath; biopsy forceps; local anaesthesia; distance measuring; 3–5 biopsy specimens were obtained Index test: EBUS-TBBX (GS) [system EU-M30S, radial probe UM-S20-20R, Olympus]; single channel bronchoscope (P260F, Olympus); guide sheath; biopsy forceps; local anaesthesia; 3–5 biopsy specimens were obtained **Reference standard**: Cytology; histology	Peripheral lung lesion **Prevalence**: 82/113 (72.57%) EBUS-TBBX (distance): Total yield 45/57 (78.95%) EBUS-TBBX: Total yield 32/56 (57.14%)	IV C1, P2, Q1 Quality: High Applicability: Limited No fluoroscopic navigation of EBUS procedure
Dooms et al (2007) Germany & Belgium Prospective, consecutive (test-based) patient series Jan 2005–May 2005	**Inclusion**: Patients with a peripheral lung lesion or solitary pulmonary lesion, not visible using bronchoscopy **Exclusion**: Patients with a spiral CT showing a pulmonary infiltrate or a sub-pleural lesion lying entirely within 10 mm from the pleura (n = 50) **Prior tests**: CT	**Index test**: EBUS-TBBX [system EU-M20, radial probe UM-BS20-26R, Olympus]; conventional bronchoscope (IT160, Olympus); biopsy forceps; local anaesthesia; at least 4 biopsy specimens were obtained **Reference standard**: Cytology; histology	Peripheral lung lesion **Prevalence**: NR EBUS-TBBX: Total yield 34/50 (68.00%)	IV CX, P2, Q1 Quality: High Applicability: Limited No fluoroscopic navigation of EBUS procedure

Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
Eberhardt et al (2007) Germany & USA Prospective, parallel group RCT Blinding, not reported Jan 2003–Aug 2006	**Inclusion**: Patients with a peripheral lung lesion or a solitary pulmonary lesion with no endobronchial abnormalities using CT **Exclusion**: Patients < 18 years of age; patients who did nor give informed consent; pregnant patients, patients with implantable pacemakers or defibrillators, patients with a non-diagnostic bronchoscopy who refused surgical biopsy (n = 118) **Prior tests**: CT	**Index test**: EBUS-TBBX (GS) [radial probe UM-BS20-26R, Olympus]; conventional bronchoscope (IT160, Olympus); guide sheath; biopsy forceps; moderate sedation or general anaesthesia **Comparator**: ENB-TBBX (superDimension/Bronchus system, superDimension); conventional bronchoscope (IT160, Olympus); biopsy forceps; moderate sedation or general anaesthesia **Reference standard**: Histology	Peripheral lung lesion **Prevalence**: 82/118 (69.49) EBUS-TBBX: Total yield 27/39 (69.23%); < 3 cm yield 23/32 (71.88%); > 3 cm yield 4/7 (57.14%) ENB-TBBX: Total yield 23/39 (58.97%); < 3 cm yield 14/26 (53.85%); > 3 cm yield 9/13 (69.23%) ENB/EBUS-TBBX: Total yield 35/40 (87.50%); < 3 cm yield 30/34 (88.24%); > 3 cm yield 5/6 (83.33%)	IV C1, P2, Q2 Quality: Medium Blinding unclear Applicability: Limited No fluoroscopic navigation of EBUS procedure
Herth et al (2002) Germany & USA Prospective, cross-over RCT Unblinded Nov 2000–Feb 2001	**Inclusion**: Patients with a peripheral lung lesion **Exclusion**: No reported exclusions (n = 50) **Prior tests**: CT	**Index test**: EBUS-TBBX [radial probe UM-3R, UM-4R, US20-20R, Olympus]; conventional bronchoscope (BF 1T-30, BF 1T 40 and BF XT 20, Olympus); bronchial forceps; general anaesthesia or conscious sedation; at least 4 biopsy specimens were obtained **Comparator**: Fluoroscopy-TBBX (Super 50 CP, Phillips); conventional bronchoscope (BF 1T-30, BF 1T 40 and BF XT 20, Olympus); general anaesthesia or conscious sedation; at least 4 biopsy specimens were obtained **Reference standard**: Histology	Peripheral lung lesion **Prevalence**: 45/50 (90.00%) EBUS-TBBX: Total yield 40/50 (80.00%); < 3 cm yield 17/21 (80.95%); > 3 cm yield 23/29 (79.31%) Fluoroscopy-TBBX: Total yield 38/50 (76.00%); < 3 cm yield 12/21 (57.14%); > 3 cm yield 26/29 (89.66%)	IV C1, P2, Q2 Quality: Medium Unblinded Applicability: Limited No fluoroscopic navigation of EBUS procedure
Herth et al (2003b) Germany & USA Prospective, consecutive patient series Jan 1999–Jan 2000	**Inclusion**: Patients referred for lung cancer staging or diagnosis of mediastinal lymphadenopathy of unknown origin **Exclusion**: No reported exclusions (n = 242) **Prior test**: CT	**Index test**: EBUS-TBNA [system EU-M 20 and 30, radial probe UM2R/3R, Olympus); conventional bronchoscope (p 20 and p 40D, Olympus); 19G and 22G needle; general anaesthesia or conscious sedation; no ROSE **Reference standard**: Cytology; histology	Mixed population **Prevalence**: NR EBUS-TBNA: Specific yield 172/242 (71.07%); Non-specific yield 207/242 (85.54%)	IV CX, P2, Q1 Quality: High Applicability: Applicable 19G tissue sampling needle

Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
Herth (2004) Germany & USA Prospective, parallel group RCT Blinding of pathologists Jun 2001–Mar 2002	**Inclusion**: Patients referred for lung cancer staging or diagnosis of mediastinal lymphadenopathy of unknown origin (mediastinal lymph node enlarged) **Exclusion**: No reported exclusions (n = 200) **Prior test**: CT	**Index test**: EBUS-TBNA [system EU-M 20 and 30, radial probe UM2R/3R, Olympus]; conventional bronchoscope (Excera and p 40D, Olympus); 22G needle; general anaesthesia or conscious sedation; no ROSE **Comparator**: TBNA 22G needle; general anaesthesia or conscious sedation; no ROSE **Reference standard**: Cytology, histology	Mixed population **Prevalence**: NR EBUS-TBNA: Specific yield 77/100 (77.00%); Non-specific yield 85/100 (85.00%) Conventional TBNA: Specific yield 63/100 (63.00%); Non-specific yield 66/100 (66.00%)	IV C1, P1, Q1 Quality: High Applicability: Applicable
Herth et al (2005) Germany Prospective, cross-over RCT Blinding of pathologists Jan 2002–Jan 2004	**Inclusion**: Patients referred for lung cancer staging or diagnosis of a mediastinal lymphadenopathy of unknown origin (mediastinal lymph nodes > 1 cm) **Exclusion**: Patients with enlarged lymph nodes excluding 2R, 2L, 3, 4R, 4L, 7, 10R or 10L (n = 160) **Prior test**: CT	**Index test**: EBUS-TBNA [system EU-M 20 and 30, radial probe UM2R/3R, Olympus]; conventional bronchoscope (p 20 and p 40D, Olympus); 22G needle; conscious sedation; no ROSE **Comparator**: EUS-FNA [FU36 Pentax or UC 30P Olympus]; 22G needle; conscious sedation; no ROSE **Reference standard**: Cytology, histology	Mixed population **Prevalence**: NR EBUS-TBNA/ EUS-FNA: Specific yield 151/160 (94.38%); Non-specific yield 155/160 (96.88%) EBUS-TBNA: Specific yield 137/160 (85.63%); Non-specific yield 142/160 (88.75%) EUS-FNA: Specific yield 121/160 (75.63%); Non-specific yield126/160 (78.75%)	IV C1, P2, Q1 Quality: High Applicability: Limited Exclusion of relevant lymph node stations
Herth et al (2006a) Germany & USA Prospective, consecutive patient series Jan 2003–Jan 2004	**Inclusion**: Patients with solitary pulmonary lesion, candidates for diagnostic bronchoscopy **Exclusion**: Patients with a solitary pulmonary nodule visible using fluoroscopy (n = 54) **Prior tests**: CT, fluoroscopy	**Index test**: EBUS-TBBX (GS) [radial probe UM-3R, UM-4R, US2020R, Olympus]; conventional bronchoscope (BF T160, Olympus); guide sheath; bronchial forceps; general anaesthesia or conscious sedation; 4–6 biopsy specimens were obtained **Reference standard**: Histology	Peripheral lung lesion **Prevalence**: 39/54 (72.22%) EBUS-TBBX: Total yield 38/54 (70.37%)	IV CX, P2, Q1 Quality: High Applicability: Limited Enrolled patients with previous fluoroscopy No fluoroscopic navigation of EBUS procedure

Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
Herth et al (2006b) Germany & Denmark Prospective, consecutive patient series Jun 2002–Sep 2004	**Inclusion**: Patients referred for lung cancer staging or diagnosis of mediastinal lymphadenopathy of unknown origin **Exclusion**: No reported exclusions (n = 502) **Prior tests**: X-ray, CT	**Index test**: EBUS-TBNA [system EU-60, Olympus]; linear scanning hybrid bronchoscope (XBF-UC260F-OL8, Olympus); 22G needle; moderate sedation and local anaesthesia or general anaesthesia; no ROSE; 2 aspirates per node were obtained **Reference standard**: Cytology, histology, clinical/radiological follow-up	Mixed population **Prevalence**: 493/502 (98.21%) EBUS-TBNA: Specific yield: 470/502 (93.63%); Non-specific yield: 476/502 (94.82%)	IV CX, P1, Q1 Quality: High Applicability: Applicable
Kikuchi et al (2004) Japan Direction unclear, non-consecutive patient series Dec 2002–Jul 2003	**Inclusion**: Patients with a peripheral pulmonary lesion (< 30 mm in mean diameter) not visible using bronchoscopy **Exclusion**: No reported exclusions (n = 24) **Prior tests**: CT	**Index test**: EBUS-TBBX (GS) [system EU-M30S, radial probe XUM-S20-17R, Olympus]; conventional bronchoscope (BF-P-260F, BF-P-240, BF-P-200, Olympus); guide sheath; bronchial forceps and bronchial brushing; local anaesthesia; curette and fluoroscopy support **Reference standard**: Cytology, histology, clinical/radiological follow-up	Peripheral lung lesion **Prevalence**: 18/24 (75.00%) EBUS-TBBX: Total yield 14/24 (58.33%); < 3 cm yield 14/24 (58.33%)	IV CX, P2, Q1 Quality: High Applicability: Applicable
Krasnik et al (2003) Denmark Direction unclear, non-consecutive patient series Unblinded	**Inclusion**: Patients referred for lung cancer staging, diagnosis of mediastinal/hilar lymphadenopathy of unknown origin or assessment of mediastinal recurrence of carcinoma **Exclusion**: No reported exclusions (n = 11) **Prior tests**: CT, bronchoscopy	**Index test**: EBUS-TBNA [system EU-C60, Olympus); linear scanning hybrid bronchoscope (XBF-UC40P, Olympus); 22G needle; general anaesthesia **Reference standard**: Cytology, histology	Mixed population **Prevalence**: 11/11 (100.00%) EBUS-TBNA: Non-specific yield 27/33 (81.82%); TP 10; FN 1; TN 0; FP 0; Sn 90.91%; NPV 0.00%	III-2 CX, P2, Q3 Quality: Low Unblinded Inadequate reference standard Applicability: Applicable Patients assessed for tumour recurrence

Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
Kurimoto et al (2004) Japan Prospective, consecutive patient series May 2001– Nov 2002	**Inclusion**: Patients with a solitary pulmonary lesion **Exclusion**: No reported exclusions (n = 150) **Prior tests**: X-ray, CT	**Index test**: EBUS-TBBX (GS) [system EU-M30, radial probe UM-S20-20R, Olympus]; conventional bronchoscope (BF 1T-30, 40 or 240R, Olympus); guide sheath; bronchial forceps and bronchial brushing; unclear anaesthesia; curette and fluoroscopy support; at least 1 biopsy specimen was obtained **Reference standard**: Cytology, histology, ,clinical/radiological follow-up, other examinations	Peripheral lung lesion **Prevalence**: 101/150 (67.33%) EBUS-TBBX: Total yield 116/150 (77.33%); < 3 cm yield 92/124 (74.19%); > 3 cm yield 24/26 (92.31%)	IV CX, P2, Q1 Quality: High Applicability: Applicable
Paone et al (2005) Italy Prospective, parallel group RCT Blinding of pathologists Jan 2001– Sep 2003	**Inclusion**: Patients with a peripheral lung lesion **Exclusion**: Patients who were < 18 years of age, outpatients, did not give informed consent, did not accomplish a complete follow-up, did not accept randomisation, underwent lung surgery before bronchoscopy, primary lesion at another site, lung lesion disappeared at follow-up, lost to follow-up (n = 206) **Prior tests**: CT	**Index test**: EBUS-TBBX [system EU-M30 with radial probe, Olympus]; conventional bronchoscope (BF-B3 or BF-T20, Olympus); bronchial forceps; local anaesthesia; at least 5 biopsy specimens were obtained Comparator: TBBX, target lesion localised by prior CT; conventional bronchoscope (BF-B3 or BF-T20, Olympus); bronchial forceps; local anaesthesia; at least 5 biopsy specimens were obtained **Reference standard**: Cytology, histology, clinical/radiological follow-up	Peripheral lung lesion **Prevalence**: 144/206 (69.90%) EBUS-TBBX: Total yield 66/87 (75.86%); < 3 cm yield 35/47 (74.47%); > 3 cm yield 33/40 (82.50%) TBBX: Total yield 62/119 (52.10%); < 3 cm yield 18/58 (31.03%); > 3 cm yield 47/61 (77.05%)	IV C1, P2, Q1 Quality: High Applicability: Limited No fluoroscopic navigation of EBUS procedure
Plat et al (2006) Belgium Prospective, consecutive patient series Jan 2003– Jun 2004	**Inclusion**: Patients referred for lung cancer staging or diagnosis of mediastinal lymphadenopathy of unknown origin **Exclusion**: No reported exclusions (n = 33) **Prior tests**: CT, PET	**Index test**: EBUS-TBNA [system EU-M20, radial probe UM-BS20-26R, Olympus); conventional bronchoscope (Excera, Olympus); local anaesthesia and conscious sedation; no ROSE; 4–6 punctures were obtained **Reference standard**: Cytology, histology, clinical/radiological follow-up	Mixed population **Prevalence**: 27/33 (81.82%) EBUS-TBNA: Non-specific yield 27/33 (81.82%)	IV CX, P1, Q1 Quality: High Applicability: Applicable

Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
Rintoul et al (2005) UK Direction unclear, non-consecutive patient series Unblinded	**Inclusion**: Patients with known or suspected lung cancer and mediastinal lymphadenopathy of > 1 cm or paratracheal or parabronchial masses, **Exclusion**: Patients were excluded from analysis based on imaging results (n = 18) **Prior tests**: CT	**Index test**: EBUS-TBNA/EUS-FNA [system EU-C2000, Olympus]; linear scanning hybrid bronchoscope (XBF-UC260F-OL8, Olympus); 22G needle. EUS-FNA (GF-UC240P-AL5, Olympus); 22G needle. Local anaesthesia and sedation; no ROSE; 2–3 needle passes were obtained. **Reference standard**: Cytology, histology, clinical/radiological follow-up	NSCLC Staging **Prevalence**: 13/18 (72.22%) EBUS-TBNA/EUS-FNA: TP 11; FN 2; TN 5; FP 0; Sn 84.62%; NPV 71.43%	III-2 CX, P1, Q3 Quality: Low Unblinded Inadequate reference standard Applicability: Applicable
Shirakawa et al (2004) Japan Randomised patient series with historical control Unblinded Jan 2001–Dec 2001	**Inclusion**: Patients with a peripheral lung lesion and normal visible airways **Exclusion**: Patients who were not randomised to EBUS, patients who did not undergo EBUS, patients with spontaneous bleeding, patients with no final diagnosis (n = 49) **Prior test**: X-ray	**Index test**: EBUS-TBBX (GS) [radial probe UM-3R, UM-4R, US-20-20R, Olympus]; conventional bronchoscope (BS 1T-240R, Olympus); guide sheath; bronchial forceps and bronchial brushing; unclear anaesthesia; fluoroscopy and curette support **Comparator**: Fluoroscopy-TBBX; unclear details **Reference standard**: Cytology, histology, clinical/radiological follow-up, other examinations	Peripheral lung lesion **Prevalence**: 24/49 (48.98%) EBUS-TBBX: TP 17; FN 7; TN 25; FP 0; Sn 70.83%; NPV 78.13% Fluoroscopy-TBBX: TP 16; FN 7; TN 19; FP 0; Sn 69.57%; NPV 73.08%	III-3 C1, P2, Q3 Quality: low Inadequate reference standard Unblinded Unclear comparator details Applicability: Applicable
Vilmann et al (2005) Denmark Prospective, non-consecutive patient series Blinding, not reported	**Inclusion**: Patients with known or suspected lung cancer **Exclusion**: No patients were excluded (n = 33) **Prior tests**: CT, PET, TBNA, TTNA	**Index test**: EBUS-TBNA [system EU-C60, Olympus]; linear scanning hybrid bronchoscope (XBF-UC40P, Olympus); 22G needle; general anaesthesia; no ROSE; number of aspirates determined by macroscopic appearance of each sample **Comparator**: EUS-FNA [GF-UCT160, Olympus]; 22G needle; general anaesthesia; no ROSE **Reference standard**: Cytology, histology, clinical/radiological follow-up	Mixed population **Prevalence**: 27/33 (81.82%) EBUS-TBNA/ EUS-FNA: Non-specific yield 33/33 (100.00%); TP 20; FN 0; TN 8; FP 0; Sn 100.00%; NPV 100.00% EBUS-TBNA: Non-specific yield 32/33 (96.97%); TN 17; FN 3; TN 8; FP 0; Sn 85.00%; NPV 72.73% EUS-FNA: Non-specific yield 32/33 (96.97%); TN 16; FN 4; TN 8; FP 0; Sn 80.00%; NPV 66.67%	III-2 C1, P2, Q3 Quality: Poor Inadequate reference standard Unblinded Applicability: Limited Unclear lymph node status Enrolled patients who had undergone previous TBNA or TTNA

Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
Yasufuku et al (2004) Japan Prospective, non-consecutive patient series Unblinded Mar 2002–Sep 2003	**Inclusion**: Patients with known or suspected lung cancer and mediastinal and/or hilar lymphadenopathy of >1 cm **Exclusion**: No reported exclusions (n = 70) **Prior tests**: X-ray, CT	**Index test**: EBUS-TBNA [system EU-C2000, Olympus]; linear scanning hybrid bronchoscope (XBF-UC260F-OL8, Olympus); 22G needle; local anaesthesia and sedation; ROSE; 1–5 needle passes were obtained **Reference standard**: Cytology, histology, clinical/radiological follow-up	NSCLC staging **Prevalence**: NR EBUS-TBNA: Non-specific yield 68/70 (97.14%); TP 45; FN 0; TN 23; FP 0; Sn 100.00%; NPV 100.00%	III-2 CX, P1, Q3 Quality: Low Unblinded Inadequate reference standard Applicability: Applicable
Yasufuku et al (2005) Japan Prospective, non-consecutive patient series Unblinded Jun 2002–Apr 2004	**Inclusion**: Patients with known or suspected lung cancer and mediastinal and/or hilar lymphadenopathy of > 1 cm **Exclusion**: Patients with a final diagnosis of a benign disease; patients with a final diagnosis of malignant disease other than NSCLC, patients with extensive N2, N3 disease on CT (n = 108) **Prior tests**: CT	**Index test**: EBUS-TBNA [system EU-C2000, Olympus]; linear scanning hybrid bronchoscope (XBF-UC260F-OL8, Olympus); 22G needle; local anaesthesia and sedation; ROSE; 1–5 needle passes were obtained **Reference standard**: Cytology, histology; clinical/radiological follow-up	NSCLC staging Prevalence: NR EBUS-TBNA: Non-specific yield 105/108 (97.22%); TP 70; FN 4; TN 34; FP 0; Sn 94.59%; NPV 89.47%	III-2 CX, P1, Q2 Quality: Low Unblinded Inadequate reference standard Inadequate data reporting Applicability: Applicable
Yasufuku et al (2006) Japan Prospective, consecutive patient series CT & PET blinded Dec 2003–Mar 2005	**Inclusion**: Patients with known or suspected lung cancer **Exclusion**: Patients who were not further evaluated (n = 102) **Prior tests**: CT, PET, other tests	**Index test**: EBUS-TBNA [system EU-C2000, Olympus]; linear scanning hybrid bronchoscope (XBF-UC260F-OL8, Olympus); 22G needle, conscious sedation; ROSE; maximum of 5 needle passes were obtained Comparator: CT (Light Speed, GE medical systems), multidector row, injection of contrast material **Comparator**: PET (PET Advance Nxi, GE medical systems), 300 Mbq injection of FDG **Reference standard**: Cytology, histology, clinical/radiological follow-up	Mixed population **Prevalence**: 26/102 (25.49%) EBUS-TBNA: TP 24; FN 2; TN 76; FP 0; Sn 92.31%; NPV 97.44% CT: TP 20; FN 6; TN 42; FP 34; Sn 76.92%; NPV 87.50% PET: TP 20; FN 5; TN 54; FP 23; Sn 80.00%; NPV 91.53%	III-2 C1, P2, Q3 Quality: Low Inadequate blinding Inadequate reference standard Applicability: Limited Included patients with negative lymphadenopathy

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; EBUS-TBNA, endobronchial ultrasound transbronchial needle aspiration; FN, false negative; FP, false positive; NPV, negative predictive value; NR, not reported; NSCLC, non-small cell lung cancer; PET, position emission tomography; ROSE, rapid on site evaluation; Sn, sensitivity; TBBX, transbronchial biopsy; TBNA, transbronchial needle aspiration; TP, true positive; TTNA, transthoracic needle aspiration

Appendix E Excluded studies

Excluded: inadequate data reporting

Asahina H, Yamazaki K, Onodera Y et al. 2005. "Transbronchial biopsy using endobronchial ultrasonography with a guide sheath and virtual bronchoscopic navigation". *Chest* 128: 1761–176.

Baba M, Sekine Y, Suzuki M et al. 2002. "Correlation between endobronchial ultrasonography (EBUS) images and histologic findings in normal and tumor-invaded bronchial wall". *Lung Cancer* 35: 65–71.

Herth FJF, Ernst A, Schulz M et al. 2003a. "Endobronchial ultrasound reliably differentiates between airway infiltration and compression by tumor". *Chest* 123: 458–462.

Kotsianos-Hermle D, Scherr M, Wirth S et al. 2007. "Visualization of bronchial lesions using multidetector CT and endobronchial ultrasound (EBUS)". *Eur J Med Res* 12: 84–89.

Kurimoto N, Murayama M, Morita K et al. 1998. "Clinical applications of endobronchial ultrasonography in lung diseases". *Endosc* 30 Suppl 1: A8–12.

Miyazu Y, Miyazawa T, Kurimoto N et al. 2002. "Endobronchial ultrasonography in the assessment of centrally located early-stage lung cancer before photodynamic therapy". *Am J Respir Crit Care Med* 165: 832–837.

Ono R, Suemasu K, Matsunaka T 1993. "Bronchoscopic ultrasonography in the diagnosis of lung cancer". *Japan Clin Oncol* 23: 34–40.

Takahashi H, Sagawa M, Sato M et al. 2003. "A prospective evaluation of transbronchial ultrasonography for assessment of depth of invasion in early bronchogenic squamous cell carcinoma". *Lung Cancer* 42: 43–49.

Takemoto Y, Kawahara M, Ogawara M et al. 2000. "Ultrasound-guided flexible bronchoscopy for the diagnosis of tumor invasion to the bronchial wall and mediastinum". *J Bronchol* 7: 127–132.

Wallace WAH, Monaghan HM, Salter DM et al. 2007. "Endobronchial ultrasound-guided fine-needle aspiration and liquid-based thin-layer cytology". *J Clin Pathol* 60: 388–391.

Excluded: foreign language

Becker HD 1996. "Endobronchial ultrasound—A new perspective in bronchoscopy". *Ultraschall in der Medizin* 17: 106–112.

Becker HD, Messerschmidt E, Ott S 1997. "Endobronchial ultrasound". *Atemwegs und Lungenkrankheiten* 23: 218–224.

Faber J, Pierard P, Prigogine T et al. 2006. "Endobronchial ultrasound and PET positive mediastinal lymph nodes". *Rev malad respirat* 23: 37–42.

Harada M 2005. "Recent advances in photodynamic therapy; an expanding role in non-small cell lung cancer". *Japan J Lung Cancer* 45: 687–692.

Herth FJF, Hecker E, Hoffmann H et al. 2002. "Endobronchial ultrasound for local tumour and lymph node staging in patients with centrally growing lung cancer". *Ultraschall in der Medizin* 23: 251–255.

Hurter T, Hanrath P 1990. "Endobronchial sonography in the diagnosis of pulmonary and mediastinal tumours". *Deutsche Medizinische Wochenschrift* 115: 1899–1905.

Kurimoto N, Murayama M, Kohama Y et al. 1997. "Clinical application of endobronchial ultrasound in the diagnosis of bronchial and peri-bronchial diseases". *Japan J Clin Radiol* 42: 143–150.

Kurimoto N, Hayashi K, Murayama M et al. 1999. "Endobronchial ultrasonography for lung cancer". *Nippon Geka Gakkai zasshi* 100: 724–728.

Matsuo K, Watanabe Y 2002. "Endobronchial ultrasonography for diagnosis of lung neoplasms". *Nippon rinsho .Japan J Clin Med* 60 Suppl 5: 191–194.

Monso E, Andreo F, Rosell A et al. 2007. "Usefulness of endobronchial ultrasonography with real-time needle aspiration for lung cancer staging". *Medicina Clinica* 128: 481–485.

Morocz E, Strausz J 2002. "Endobronchial ultrasonography". *Orvosi hetilap* 143: 2875–2879.

Morocz E, Strausz J 2004. "Endobronchial ultrasonography in post-intubation tracheal stenosis". *Orvosi hetilap* 145: 1507–1510.

Ono R 1996. "Bronchoscopic brachytherapy: development of bronchoscopic ultrasonography and brachytherapy for early stage lung cancer of hilar type". *Nippon rinsho Japan J Clin Med* 54: 1337–1342.

Postmus P 2002. "Endobronchial detection and treatment of pre-neoplastic lesions". *Revue de Pneumologie Clinique* 58: 3S22–3S24.

Tsurupa DI, Sadchikova IA, Blashentseva SA et al. 1995. "The interpretation of the data from the ultrasonic examination of patients with acute and chronic suppurative lung and pleural diseases". *Vestnik Khirurgii Imeni I.I.Grekova* 154: 17–21.

Votruba J, Stastny B 2002. "Endobronchial ultrasonography". *Endoskopie* 11: 23–26.

Woelke K, Rausch V, Granetzny A 2006. "Mediastinal lymph node staging with endobronchial ultrasound (EBUS) and mediastinoscopy—A comparison of both methods". *Atemwegs- und Lungenkrankheiten* 32: 343–344.

Excluded: wrong utilisation

Chao TY, Lie CH, Chung YH et al. 2006. "Differentiating peripheral pulmonary lesions based on images of endobronchial ultrasonography". *Chest* 130: 1191–1197.

Herth FJF, Becker HD, LoCicero J et al. 2002. "Endobronchial ultrasound in therapeutic bronchoscopy". *Eur Respir J* 20: 118–121.

Herth FJF, Becker HD, LoCicero III J et al. 2003. "Endobronchial ultrasound improves classification of suspicious lesions detected by autofluorescence bronchoscopy". *J Bronchol* 10: 249–252.

Kurimoto N, Murayama M, Yoshioka S et al. 2002. "Analysis of the internal structure of peripheral pulmonary lesions using endobronchial ultrasonography". *Chest* 122: 1887–1894.

Okamoto H, Watanabe K, Nagatomo A et al. 2002. "Endobronchial ultrasonography for mediastinal and hilar lymph node metastases of lung cancer". *Chest* 121: 1498–1506.

Omori S, Takiguchi Y, Hiroshima K et al. 2002. "Peripheral pulmonary diseases: Evaluation with endobronchial US—Initial experience". *Radiol* 224: 603–608.

Excluded: wrong intervention

Diacon AH, Schuurmans MM, Theron J et al. 2005. "Utility of rapid on-site evaluation of transbronchial needle aspirates" (structured abstract) *Respiration* 72: 182–188.

Jakob H, Lorenz J, Clement T et al. 1990. "Mediastinal lymph node staging with transesophageal echography in cancer of the lung". *Eur J Cardiothor Surg* 4: 355–358.

Khoo KL, Ho KY, Nilsson B et al. 2006. "EUS-guided FNA immediately after unrevealing transbronchial needle aspiration in the evaluation of mediastinal lymphadenopathy: A prospective study". *Gastroint Endosc* 63: 215–220.

Obata K, Ueki J, Dambara T et al. 1999. "Repeated ultrasonically guided needle biopsy of small subpleural nodules". *Chest* 116: 1320–1324.

Singh MM, Gupta RK, Gupta RK et al. 1987. "Ultrasonically guided fine needle aspiration biopsy (FNAB) of intrathoracic lesions". *Indian J Chest Dis Allied Sci* 29: 81–89.

Sortini D, Feo CV, Carrella G et al. 2003. "Thoracoscopic localization techniques for patients with a single pulmonary nodule and positive oncological anamnesis: A prospective study". *J Laparoendosc Adv Surg Tech–Part A* 13: 371–375.

Yuan A, Yang PC, Chang DB et al. 1992. "Ultrasound-guided aspiration biopsy of small peripheral pulmonary nodules". *Chest* 101: 926–930.

Exclude: review, letter etc

Esteva H, Becker HD 2005. "Value of fiberoptic bronchoscopy in patients undergoing surgery for solitary pulmonary nodules". *Chest* 128: 474

Feller-Kopman D, Lunn W, Ernst A 2005. "Autofluorescence bronchoscopy and endobronchial ultrasound: A practical review". *Ann Thor Surg* 80: 2395–2401.

Gambhir SS, Shepherd JE, Shah BD et al. 1998. "Analytical decision model for the cost-effective management of solitary pulmonary nodules". *J Clin Oncol* 16: 2113–2125.

Gasparini S 2005. "It is time for this 'ROSE' to flower". *Respiration* 72: 129–131.

Harewood GC, Wiersema MJ, Edell ES et al. 2002. "Cost-minimization analysis of alternative diagnostic approaches in a modeled patient with non-small cell lung cancer and subcarinal lymphadenopathy (Provisional record)". *Mayo Clin Proceed* 77: 155–164.

Herth FJF, Becker HD 2000. "Endobronchial ultrasound of the airways and the mediastinum". *Monaldi Arch Chest Dis* 55: 36–44.

Janssen J, Gasparini S, Mehta A 2006. "Endoscopic ultrasound-guided biopsy in the chest". *Eur Respir J* 27: 238–239.

Kurimoto N, Miyazawa T 2004. "Endobronchial ultrasonography". *Sem Respirat Critical Care Med* 25: 425–431.

Layfield LJ, Bentz JS, Gopez EV 2001. "Immediate on-site interpretation of fine-needle aspiration smears: A cost and compensation analysis". *Cancer* 93: 319–322.

Souquet PJ 1998. "Place of transbronchial or transoesophageal endosonography guided aspiration biopsy in the initial management of lung cancer". *Acta Endoscopica* 28: 1–5.

Trisolini R, Agli LL, Patelli M 2004. "Conventional vs endobronchial ultrasound-guided transbronchial needle aspiration of the mediastinum". *Chest* 126: 1005–1006.

Turner JF 2002. "Endobronchial ultrasound and peripheral pulmonary lesions: Localization and histopathologic correlates using a miniature probe and the flexible bronchoscope". *Chest* 122: 1874–1875.

Wang KP 2006. "EUS-guided FNA immediately after unrevealing transbronchial needle aspiration in the evaluation of mediastinal lymphadenopathy: a prospective study". *Gastrointest Endosc* 64: 468–469.

Excluded: non-standard/obsolete procedure

Goldberg BB, Steiner RM, Liu JB et al. 1994. "US-assisted bronchoscopy with use of miniature transducer-containing catheters". *Radiol* 190: 233–237.

Hurter T, Hanrath P 1992. "Endobronchial sonography: Feasibility and preliminary results". *Thorax* 47: 565–567.

Kanoh K, Miyazawa T, Kurimoto N et al. 2005. "Endobronchial ultrasonography guidance for transbronchial needle aspiration using a double-channel bronchoscope". *Chest* 128: 388–393.

Shannon JJ, Bude RO, Orens JB et al. 1996. "Endobronchial ultrasound-guided needle aspiration of mediastinal adenopathy". *Am J Respir Crit Care Med* 153: 1424–1430.

Excluded: wrong outcome

Herth FJF, Becker HD, Manegold C et al. 2001. "Endobronchial ultrasound (EBUS)—Assessment of a new diagnostic tool in bronchoscopy for staging of lung cancer". *Onkologie* 24: 151–154.

Excluded: wrong patient population

Herth FJF, Ernst A, Eberhardt R et al. 2006. "Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically normal mediastinum". *Eur Respir J* 28: 910–914.

Irani S, Hess T, Hofer M et al. 2006. "Endobronchial ultrasonography for the quantitative assessment of bronchial mural structures in lung transplant recipients". *Chest* 129: 349–355.

Iwamoto Y, Miyazawa T, Kurimoto N et al. 2004. "Interventional bronchoscopy in the management of airway stenosis due to tracheobronchial tuberculosis". *Chest* 126: 1344–1352.

Miyazawa T, Miyazu Y, Iwamoto Y et al. 2004. "Stenting at the flow-limiting segment in tracheobronchial stenosis due to lung cancer". *Am J Respir Crit Care Med* 169: 1096–1102.

Nishimura Y, Osugi H, Inoue K et al. 2002. "Bronchoscopic ultrasonography in the diagnosis of tracheobronchial invasion of esophageal cancer". *J Ultrasound Med* 21: 49–58.

Osugi H, Nishimura Y, Takemura M et al. 2003. "Bronchoscopic ultrasonography for staging supracarinal esophageal squamous cell carcinoma: Impact on outcome". *World J Surg* 27: 590–594.

Wakamatsu T, Tsushima K, Yasuo M et al. 2006. "Usefulness of preoperative endobronchial ultrasound for airway invasion around the trachea: Esophageal cancer and thyroid cancer". *Respiration* 73: 651–657.

Wong M, Yasufuku K, Nakajima T et al. 2007. "Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis". *Eur Respir J* 29: 1182–1186.

Yang MC, Liu WT, Wang CH et al. 2004. "Diagnostic value of endobronchial ultrasound-guided transbronchial lung biopsy in peripheral lung cancers". *J Formosan Med Assoc = Taiwan yi zhi* 103: 124–129.

Excluded: abstract of full paper

Herth FJF, Ernst A, Becker HD 2003. "Conventional vs endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA)—a randomised trial". *Eur Respir J* 22: 205s.

Exclude: endosonography case report

Herth FJF, Krasnik M, Yasufuku K et al. 2006. "Endobronchial ultrasound-guided transbronchial needle aspiration". *J Bronchol* 13: 84–91.

Kramer H, Nieuwenhuis JA, Groen HJM et al. 2004. "Pulmonary tuberculosis diagnosed by esophageal endoscopic ultrasound with fine-needle aspiration". *Int J Tubercul Lung Dis* 8: 272–273.

Martinez-Monge R, Subtil JC, Lopez-Picazo JM 2006. "Transoesophageal endoscopic-ultrasonography-guided 125I permanent brachytherapy for unresectable mediastinal lymphadenopathy". *Lancet Oncol* 7: 781–783.

Miyazu Y, Miyazawa T, Iwamoto Y et al. 2001. "The role of endoscopic techniques, laser-induced fluorescence endoscopy and endobronchial ultrasonography in choice of appropriate therapy for bronchial cancer". *J Bronchol* 8: 10–16.

Rosario F, Da Costa JD, Dionisio J et al. 2006. "Endobronchial ultrasound may reveal the presence of previously undiagnosed thyroid carcinoma". *Thyroid* 16: 515–516.

Excluded: animal/in vitro study

Kurimoto N, Murayama M, Yoshioka S et al. 1999. "Assessment of usefulness of endobronchial ultrasonography in determination of depth of tracheobronchial tumor invasion". *Chest* 115: 1500–1506.

Nakamura Y, Endo C, Sato M et al. 2004. "A new technique for endobronchial ultrasonography and comparison of two ultrasonic probes: Analysis with a plot profile of the image analysis software NIH image". *Chest* 126: 192–197.

Yasufuku K, Chhajed PN, Sekine Y et al. 2004. "Endobronchial ultrasound using a new convex probe: a preliminary study on surgically resected specimens". *Oncol Reports* 11: 293–296.

Appendix F Literature search

Search strategies were used to identify relevant studies of EBUS guided transbronchial sampling procedures for non-small cell lung cancer staging, diagnosis of peripheral lung lesions and the diagnosis of mediastinal/hilar masses. The Medline and EMBASE databases were search using the EMBASE.com interface. The PreMedline database was search using the PubMed interface. The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register (CMR), Health Technology Assessment (HTA), NHS Economic Evaluation Database (NHSEED databases were search using the Cochrane Library interface. The search results for EMBASE.com are presented in Table 58, the results from PubMed are presented in Table 59 and the results from the Cochrane Library search are presented in Table 60.

Table 58 EMBASE.com search results: EBUS procedures for NSCLC staging and diagnosis of peripheral lung, mediastinal and hilar masses (4 June 2007)

	Keywords / search history	Results
1.	'bronchoscopy'/exp	21888
2.	'bronchoscope'/exp	1069
3.	#1 OR #2	22485
4.	'ultrasound'/exp	44242
5.	'echography'/exp	285250
6.	#4 OR #5	322345
7.	#3 AND #6	626
8.	'endobronchial echography':de	9
9.	'endobronchial ultrasonography':de	14
10.	'endobronchial ultrasound':de	15
11.	'endobronchial ultrasound driven biopsy':de	1
12.	'endobronchial ultrasonography with a guide sheath':de	1
13.	'endobronchial ultrasound guided transbronchial needle aspiration':de	1
14.	'endoscopic transbronchial real time echography guided biopsy':de	1
15.	#8 OR #9 OR #10 OR #11 OR #12 OR #13 or #14	39
16.	'endobronchial *3 echography':ti,ab	2
17.	'endobronchial *3 ultrasonogram':ti,ab	2
18.	'endobronchial *3 ultrasound':ab,ti	99
19.	'endobronchial *3 ultrasonography':ab,ti	59
20.	'endobronchial *3 ultra sonography':ab,ti	1
21.	'endobronchial us':ab,ti OR ebus:ab,ti	87
22.	#16 OR #17 OR #18 OR #19 OR #20 OR #21	166
23.	#7 OR #15 OR #22	704

Table 59 PubMed search results for EBUS procedures for NSCLC staging and diagnosis of peripheral lung, mediastinal and hilar masses (7 June 2007)

	Keywords / search history	Results
1.	endobronchial[tiab] AND echography[tiab]	1
2.	endobronchial[tiab] AND ultrasonogram[tiab]	3
3.	endobronchial[tiab] AND ultrasound[tiab]	97
4.	endobronchial[tiab] AND ultrasonography[tiab]	54
5.	endobronchial[tiab] AND "ultra sonography"[tiab]	0
6.	"endobronchial us"[tiab] OR ebus[tiab]	67
7.	#1 or #2 or #3 or #4 or #5 or #6	152
8.	#1 or #2 or #3 or #4 or #5 or #6 Limits: MEDLINE	135
9.	#7 NOT #8	17

Table 60 Cochrane Library search results for EBUS procedures for NSCLC staging and diagnosis of peripheral lung, mediastinal and hilar masses (4 June 2007)

	Keywords / search history	Results
1.	MeSH descriptor Bronchoscopy explode all trees	368
2.	MeSH descriptor Bronchoscopes explode all trees	41
3.	#1 OR #2	389
4.	MeSH descriptor Endosonography explode all trees	171
5.	MeSH descriptor Ultrasonography explode all trees	4808
6.	MeSH descriptor Ultrasonography, Interventional explode all trees	331
7.	#4 OR #5 OR #6	4808
8.	#3 AND #7	8
9.	(endobronchial near echography)	0
10.	(endobronchial near ultrasonogram)	0
11.	(endobronchial near ultrasound)	9
12.	(endobronchial near ultrasonography)	3
13.	(endobronchial near "ultra sonography")	0
14.	"endobronchial us" or ebus	7
15.	#9 OR #10 OR #11 OR #12 OR #13 OR #14	12
16.	#8 OR #15	16

Table 61 HTA websites searched in this review

Australia	Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S) http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
	Centre for Clinical Effectiveness, Monash University http://www.med.monash.edu.au/healthservices/cce/evidence/
	Health Economics Unit, Monash University http://chpe.buseco.monash.edu.au
Austria	Institute of Technology Assessment / HTA unit http://www.oeaw.ac.at/ita/e1-3.htm
Canada	Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/site/index.php?home
	Institute of Health Economics (IHE) http://www.ihe.ca/index.html
	Canadian Coordinating Office for Health Technology Assessment (CCHOTA) http://www.ccohta.ca/entry_e.html
	Canadian Health Economics Research Association (CHERA/ACRES)—Cabot database http://www.mycabot.ca
	Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org
	Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca
	Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm
	Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca
Denmark	Danish Institute for Health Technology Assessment (DIHTA) http://www.dihta.dk/publikationer/index_uk.asp
	Danish Institute for Health Services Research (DSI) http://www.dsi.dk/engelsk.html
Finland	FINOHTA http://finohta.stakes.fi/EN/index.htm
France	L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) http://www.anaes.fr/
Germany	German Institute for Medical Documentation and Information (DIMDI) / HTA http://www.dimdi.de/dynamic/en/index.html
The Netherlands	Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/adviezen.php
New Zealand	New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/
Norway	Norwegian Knowledge Centre for the Health Services http://www.kunnskapssenteret.no/index.php?show=38&expand=14,38
Spain	Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS) http://www.isciii.es/htdocs/en/index.jsp
	Catalan Agency for Health Technology Assessment (CAHTA) http://www.aatrm.net/html/en/Du8/index.html
Sweden	Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/www/index.asp
	Center for Medical Health Technology Assessment (CMT) http://www.cmt.liu.se/english?l=en
Switzerland	Swiss Network on Health Technology Assessment (SNHTA) http://www.snhta.ch/home/portal.php
United Kingdom	National Health Service Quality Improvement: Scotland (NHS QIS) http://www.nhshealthquality.org/nhsqis/43.0.140.html
	National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.hta.nhsweb.nhs.uk/
	University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/
	National Institute for Clinical Excellence (NICE) http://www.nice.org.uk/
United States	Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/techix.htm
	Harvard School of Public Health—Cost-Utility Analysis Registry http://www.tufts-nemc.org/cearegistry/
	US Blue Cross/ Blue Shield Association Technology Evaluation Center http://www.bcbs.com/consumertec/index.html

Appendix G Quality criteria

Study design	Quality checklist
Systematic review	Was the research question specified?
	Was the search strategy documented and adequate?
	Were the inclusion and exclusion criteria specified, appropriate and applied in an unbiased way?
	Was a quality assessment of included studies undertaken?
	Were the methods of the study appraisal reproducible?
	Were the characteristics and results of the individual studies summarised?
	Were the methods for pooling the data appropriate?
	Were sources of heterogeneity explored?
	Was a summary of the main results and precision estimates reported?
Studies evaluating effectiveness of an intervention on health outcomes	
Randomised controlled trial	Were the inclusion and exclusion criteria specified?
	Was the assignment to the treatment groups really random?
	Was the treatment allocation concealed from those responsible for recruiting subjects?
	Was there sufficient description about the distribution of prognostic factors for the treatment and control groups?
	Were the groups comparable at baseline for these factors?
	Were outcome assessors blinded to the treatment allocation?
	Were the care providers blinded?
	Were the subjects blinded?
	Were all randomised participants included in the analysis?
	Was a point estimates and measure of variability reported for the primary outcome?
Cohort study	Were subjects selected prospectively or retrospectively?
	Was the intervention reliably ascertained?
	Was there sufficient description about how the subjects were selected for the new intervention and comparison groups?
	Was there sufficient description about the distribution of prognostic factors for the new intervention and comparison groups? Were the groups comparable for these factors?
	Did the study adequately control for potential confounding factors in the design or analysis?
	Was the measurement of outcomes unbiased (ie blinded to treatment group and comparable across groups)?
	Was follow-up long enough for outcomes to occur?
	What proportion of the cohort was followed-up and were there exclusions from the analysis?
	Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?

Study design	Quality checklist
Case-control study	Was there sufficient description about how subjects were defined and selected for the case and control groups?
	Was the disease state of the cases reliably assessed and validated?
	Were the controls randomly selected from the source of population of the cases?
	Was there sufficient description about the distribution of prognostic factors for the case and control groups? Were the groups comparable for these factors?
	Did the study adequately control for potential confounding factors in the design or analysis?
	Was the new intervention and other exposures assessed in the same way for cases and controls and kept blinded to case/control status?
	How was the response rate defined?
	Were the non-response rates and reasons for non-response the same in both groups?
	Was an appropriate statistical analysis used?
	If matching was used, is it possible that cases and controls were matched on factors related to the intervention that would compromise the analysis due to over-matching?
Case series	Was the study based on a representative sample selected from a relevant population?
	Were the criteria for inclusion and exclusion explicit?
	Did all subjects enter the survey at a similar point in their disease progression?
	Was follow-up long enough for important events to occur?
	Were the techniques used adequately described?
	Were outcomes assessed using objective criteria or was blinding used?
	If comparisons of sub-series were made, was there sufficient description of the series and the distribution of prognostic factors?
Study of diagnostic accuracy	Was the spectrum of patients representative of the patients who will receive the test in practice?
	Were selection criteria clearly described?
	Is the reference standard likely to correctly classify the target condition?
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
	Did patients receive the same reference standard regardless of the index test result?
	Was the reference standard independent of the index test (ie the index test did not form part of the reference standard)?
	Was the execution of the index test described in sufficient detail to permit replication of the test?
	Was the execution of the reference standard described in sufficient detail to permit its replication?
	Were the index test results interpreted without knowledge of the results of the reference standard?
	Were the reference standard results interpreted without knowledge of the results of the index test?
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
	Were uninterpretable/ intermediate test results reported?
	Were withdrawals from the study explained?

Appendix H Staging classification

The most widely accepted staging system for pathological staging of cancer is the TNM (tumour, node, metastasis) cancer staging system. Cancer staging involves defining the extent of spread of the primary tumour, spread to regional lymph nodes, and the presence or absence of metastases. Accurate cancer staging is essential to inform clinical management decisions. The increasing range of surgical, non-surgical and palliative treatment options has increased clinical emphasis on cancer staging.

The TNM staging for lung cancer, as described by the American Joint Committee on Cancer (AJCC), is presented in Table 62. The stage classification is presented in Table 63.

Table 62 TNM classification for lung cancer

Classification	Lung cancer
Tumour	
TX	Primary tumour cannot be assessed, or tumour is proven by the presence of malignant cells in sputum or bronchial washings but is not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1	A tumour that is ≤ 3 cm in greatest dimension, is surrounded by lung or visceral pleura and is without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie not in the main bronchus)
T2	A tumour with any of the following features of size or extent: • > 3 cm in greatest dimension • Involves the main bronchus and is ≥ 2 cm distal to the carina • Invades the visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3	A tumour of any size that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or, tumour in the main bronchus < 2 cm distal to the carina but without involvement of the carina; or, associated atelectasis or obstructive pneumonitis of the entire lung
T4	A tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina; or, separate tumour nodules in the same lobe; or, tumour with a malignant pleural effusion[a]
Node	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes including involvement by direct extension of the primary tumour
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Metastasis	
MX	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastasis present

[a] Most pleural effusions associated with lung cancer are due to tumour; multiple cytopathologic examinations of pleural fluid are negative for tumour in some patients. Pleural fluid is blood-free and is not an exudate in these circumstances. These patients may be evaluated further using video-thoracoscopy and direct pleural biopsies. When these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient's disease should be staged as T1, T2, or T3.
Source: Lung Cancer. In American Joint Committee on Cancer: AJCC Staging Manual. 6th ed. New York, NY: Springer, 2002, pp 167–177

Table 63 Lung cancer staging by TNM grouping

Stage	TNM grouping
Occult carcinoma	TX, N0, M0
0	Tis, N0, M0
IA	T1, N0, M0
IB	T2, N0, M0
IIA	T1, N1, M0
IIB	T2, N1, M0
	T3, N0, M0
IIIA	T1, N2, M0
	T2, N2, M0
	T3, N1, M0
	T3, N2, M0
IIIB	Any T, N3, M0
	T4, any N, M0
IV	Any T, any N, M1

Source: Lung Cancer. In American Joint Committee on Cancer: AJCC Staging Manual. 6th ed. New York, NY: Springer, 2002, pp 167–177

Appendix I Additional information for economic evaluation

Major capital equipment costs of the first generation EBUS imaging system with radial probe

Table 64 Capital costs of EBUS with radial probe—low utilisation level

Cost of investment	Year 1	Year 2	Year 3	Year 4	Year 5
Undepreciated value of equipment[a]	$156,400	$125,120	$93,840	$62,560	$31,280
Depreciation over a year[b]	$31,280	$31,280	$31,280	$31,280	$31,280
Maintenance cost[c]	$12,915	$12,915	$12,915	$12,915	$12,915
Interest costs of investment and maintenance[d]	$25,411	$22,912	$20,412	$17,913	$15,414
Total cost per year	$56,691	$54,192	$51,692	$49,193	$46,694
Present value of cost stream[e]	$56,691	$51,611	$46,886	$42,495	$38,415
Total present value of cost stream[f]			$236,098		
Return on investment					
Number of procedures performed annually[g]	416	416	416	416	416
Total present value of number of procedures performed[h]			2080		
Calculated capital cost per procedure[i]			**$114**		

[a] Cost of equipment ($156,400) supplied by applicant., including costs of a processor, probe driver, broncho-videoscope, video processor and other miscellaneous components. A cost of probe is not included because a probe has to be replaced after 100 procedures
[b] Assumes straight-line depreciation, 5 year lifetime of equipment and $0 residual value
[c] Proposed by applicant
[d] Calculated by considering an interest rate of 8.0% for purchase and maintenance costs. Interest rate provided by Medfin Finance, Sydney
[e] Present value represents the total value costs that need to be reimbursed to the investor to justify their investment
[f] This value represents the total value of costs that needs to be reimbursed to the investor to justify their investment
[g] Expert opinion (assuming 8 procedures per week, translating to 416 procedures per year)
[h] Sum of the number of procedures
[i] Total present value of cost stream divided by the total present value of procedures performed

Table 65 Capital costs of EBUS with radial probe—high utilisation level

Cost of investment	Year 1	Year 2	Year 3	Year 4	Year 5
Undepreciated value of equipment[a]	$156,400	$125,120	$93,840	$62,560	$31,280
Depreciation over a year[b]	$31,280	$31,280	$31,280	$31,280	$31,280
Maintenance cost[c]	$12,915	$12,915	$12,915	$12,915	$12,915
Interest costs of investment and maintenance[d]	$25,411	$22,912	$20,412	$17,913	$15,414
Total cost per year	$56,691	$54,192	$51,692	$49,193	$46,694
Present value of cost stream[e]	$56,691	$51,611	$46,886	$42,495	$38,415
Total present value of cost stream[f]			$236,098		
Return on investment					
Number of procedures performed annually[g]	624	624	624	624	624
Total present value of number of procedures performed[h]			3120		
Calculated capital cost per procedure[i]			**$76**		

[a] Cost of equipment ($156,400) supplied by applicant., including costs of a processor, probe driver, broncho-videoscope, video processor and other miscellaneous components. A cost of probe is not included because a probe has to be replaced after 100 procedures
[b] Assumes straight-line depreciation, 5 year lifetime of equipment and $0 residual value
[c] Proposed by applicant
[d] Calculated by considering an interest rate of 8.0% for purchase and maintenance costs. Interest rate provided by Medfin Finance, Sydney
[e] Present value represents the total value costs that need to be reimbursed to the investor to justify their investment
[f] This value represents the total value of costs that needs to be reimbursed to the investor to justify their investment
[g] Expert opinion (assuming 12 procedures per week, translating to 624 procedures per year)
[h] Sum of the number of procedures
[i] Total present value of cost stream divided by the total present value of procedures performed

Major capital equipment costs of the first generation EBUS imaging system with linear probe

Table 66 Capital costs of EBUS with linear probe—low utilisation level

Cost of investment	Year 1	Year 2	Year 3	Year 4	Year 5
Undepreciated value of equipment[a]	$101,020	$80,816	$60,612	$40,408	$20,204
Depreciation over a year[b]	$20,204	$20,204	$20,204	$20,204	$20,204
Maintenance cost[c]	$12,915	$12,915	$12,915	$12,915	$12,915
Interest costs of investment and maintenance[d]	$20,986	$19,372	$17,757	$16,143	$14,529
Total cost per year	$41,190	$39,576	$37,961	$36,347	$34,733
Present value of cost stream[e]	$41,190	$37,691	$34,432	$31,398	$28,575
Total present value of cost stream[f]			$173,286		
Return on investment					
Number of procedures performed annually[g]	416	416	416	416	416
Total present value of number of procedures performed[h]			2080		
Calculated capital cost per procedure[i]			**$83**		

[a] Equipment cost ($101,020) supplied by Applicant (processor, light source, video processor, miscellaneous component costs) linear probe excluded
[b] Assumes straight-line depreciation, 5 year lifetime of equipment and $0 residual value
[c] Proposed by Applicant
[d] Calculated by considering an interest rate of 8.0% for purchase and maintenance costs. Interest rate provided by Medfin Finance, Sydney
[e] Present value represents the total value costs that need to be reimbursed to the investor to justify their investment
[f] This value represents the total value of costs that needs to be reimbursed to the investor to justify their investment
[g] Expert opinion (assuming 8 procedures per week, translating to 416 procedures per year)
[h] Sum of the number of procedures
[i] Total present value of cost stream divided by the total present value of procedures performed
Note: The cost of linear probe per procedure was estimated using the same methodology as that for capital cost calculation

Table 67 Capital costs of EBUS with linear probe—high utilisation level

Cost of investment	Year 1	Year 2	Year 3	Year 4	Year 5
Undepreciated value of equipment[a]	$101,020	$80,816	$60,612	$40,408	$20,204
Depreciation over a year[b]	$20,204	$20,204	$20,204	$20,204	$20,204
Maintenance cost[c]	$12,915	$12,915	$12,915	$12,915	$12,915
Interest costs of investment and maintenance[d]	$20,986	$19,372	$17,757	$16,143	$14,529
Total cost per year	$41,190	$39,576	$37,961	$36,347	$34,733
Present value of cost stream[e]	$41,190	$37,691	$34,432	$31,398	$28,575
Total present value of cost stream[f]			$173,286		
Return on investment					
Number of procedures performed annually[g]	624	624	624	624	624
Total present value of number of procedures performed[h]			3120		
Calculated capital cost per procedure[i]			**$56**		

[a] Equipment cost ($101,020) supplied by Applicant (processor, light source, video processor, miscellaneous component costs) linear probe excluded
[b] Assumes straight-line depreciation, 5 year lifetime of equipment and $0 residual value
[c] Proposed by applicant
[d] Calculated by considering an interest rate of 8.0% for purchase and maintenance costs. Interest rate provided by Medfin Finance, Sydney
[e] Present value represents the total value costs that need to be reimbursed to the investor to justify their investment
[f] This value represents the total value of costs that needs to be reimbursed to the investor to justify their investment
[g] Expert opinion (assuming 12 procedures per week, translating to 624 procedures per year)
[h] Sum of the number of procedures
[i] Total present value of cost stream divided by the total present value of procedures performed
Note: The cost of linear probe per procedure was estimated using the same methodology as that for capital cost calculation

Major capital equipment costs of Aloka EBUS imaging system

Table 68 Capital costs of Aloka EBUS—low utilisation level

Cost of investment	Year 1	Year 2	Year 3	Year 4	Year 5
Undepreciated value of equipment[a]	$155,400	$124,320	$93,240	$62,160	$31,080
Depreciation over a year[b]	$31,080	$31,080	$31,080	$31,080	$31,080
Maintenance cost[c]	$12,915	$12,915	$12,915	$12,915	$12,915
Interest costs of investment and maintenance[d]	$25,331	$22,848	$20,364	$17,881	$15,398
Total cost per year	$56,411	$53,928	$51,444	$48,961	$46,478
Present value of cost stream[e]	$56,411	$51,360	$46,662	$42,294	$38,237
Total present value of cost stream[f]			$234,964		
Return on investment					
Number of procedures performed annually[g]	416	416	416	416	416
Total present value of number of procedures performed[h]			2080		
Calculated capital cost per procedure[i]			**$113**		

[a] Equipment cost ($101,020) supplied by Applicant (processor, light source, video processor, miscellaneous component costs) linear probe excluded
[b] Assumes straight-line depreciation, 5 year lifetime of equipment and $0 residual value
[c] Proposed by applicant
[d] Calculated by considering an interest rate of 8.0% for purchase and maintenance costs. Interest rate provided by Medfin Finance, Sydney
[e] Present value represents the total value costs that need to be reimbursed to the investor to justify their investment
[f] This value represents the total value of costs that needs to be reimbursed to the investor to justify their investment
[g] Expert opinion (assuming 8 procedures per week, translating to 416 procedures per year)
[h] Sum of the number of procedures
[i] Total present value of cost stream divided by the total present value of procedures performed
Note: The cost of linear probe per procedure was estimated using the same methodology as that for capital cost calculation

Table 69 Capital costs of Aloka EBUS—high utilisation level

Cost of investment	Year 1	Year 2	Year 3	Year 4	Year 5
Undepreciated value of equipment[a]	$155,400	$124,320	$93,240	$62,160	$31,080
Depreciation over a year[b]	$31,080	$31,080	$31,080	$31,080	$31,080
Maintenance cost[c]	$12,915	$12,915	$12,915	$12,915	$12,915
Interest costs of investment and maintenance[d]	$25,331	$22,848	$20,364	$17,881	$15,398
Total cost per year	$56,411	$53,928	$51,444	$48,961	$46,478
Present value of cost stream[e]	$56,411	$51,360	$46,662	$42,294	$38,237
Total present value of cost stream[f]			$234,964		
Return on investment					
Number of procedures performed annually[g]	624	624	624	624	624
Total present value of number of procedures performed[h]			3120		
Calculated capital cost per procedure[i]			**$75**		

[a] Equipment cost ($101,020) supplied by Applicant (processor, light source, video processor, miscellaneous component costs) linear probe excluded
[b] Assumes straight-line depreciation, 5 year lifetime of equipment and $0 residual value
[c] Proposed by applicant
[d] Calculated by considering an interest rate of 8.0% for purchase and maintenance costs. Interest rate provided by Medfin Finance, Sydney
[e] Present value represents the total value costs that need to be reimbursed to the investor to justify their investment
[f] This value represents the total value of costs that needs to be reimbursed to the investor to justify their investment
[g] Expert opinion(assuming 12 procedures per week, translating to 624 procedures per year)
[h] Sum of the number of procedures
[i] Total present value of cost stream divided by the total present value of procedures performed
Note: The cost of linear probe per procedure was estimated using the same methodology as that for capital cost calculation

Abbreviations

AACR	Australian Association of Cancer Registries
ABS	Australian Bureau of Statistics
AFB	autofluorescence bronchoscopy
AHMAC	Australian Health Ministers' Advisory Council
AIHW	Australian Institute of Health and Welfare
AJCC	American Joint Committee on Cancer
AR-DRG	Australian Refined Diagnosis Related Groups
ARTG	Australian Register of Therapeutic Goods
Bx	biopsy
CCD	charge coupled device
CT	computed tomography
EBBX	endobronchial biopsy
EBUS	endobronchial ultrasound
ENB	electromagnetic navigation bronchoscopy
EPICOT	evidence, population, intervention, comparison, outcome, time stamp
EUS	endoscopic ultrasound
18F-FDG	2-[18F] fluoro-2-deoxyglucose
FN	false negative
FNA	fine-needle aspiration
FP	false positive
HTA	health technology assessment
MBS	Medicare Benefits Scheme
MSAC	Medical Services Advisory Committee
NBI	narrow band imaging
NCSG	National Cancer Strategies Group

NHMRC	National Health and Medical Research Council
Nd-YAG	neodymium-doped yttrium aluminium garnet
NR	not reported
NSCLC	non-small cell lung cancer
NPV	negative predictive value
PET	positron emission tomography
PPICO	population, prior tests, index test, comparator, outcomes
PPV	positive predictive value
QALY	quality-adjusted life year
QUADAS	Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews
QUOROM	quality of reporting of meta-analyses
RCT	randomised controlled trials
ROSE	rapid on site evaluation
TBBX	transbronchial biopsy
TBNA	transbronchial needle aspiration
TGA	Therapeutic Goods Administration
TN	true negative
TP	true positive
TTBX	transthoracic biopsy
TTNA	transthoracic needle aspiration
VAT	video-assisted thoracoscopy

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