Endoscopic ultrasound guided fine-needle aspiration for the staging of non-small cell lung cancer and the diagnosis of mediastinal masses

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Assessment report

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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 Dr John Gillespie, Mr Koji Makino, Mr Marc Bevan, Ms Keira Robinson, Ms Corinne LeReun and Dr Liesl Birinyi-Strachan from M-TAG Pty Ltd, a unit of IMS Health. The report was endorsed by the Minister for Health and Ageing on 29 August 2007.

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The procedure

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. EUS-FNA can be applied to obtain tissue samples to inform diagnosis of lesions in the mediastinum.

This review evaluates the use of EUS-FNA in the staging of non-small cell lung cancer (NSCLC) and the diagnosis of mediastinal masses of unknown origin.

EUS-FNA has a potential positive impact on people's health outcomes (including quality of life). Unnecessary invasive surgical procedures can be avoided by improving the accuracy of staging NSCLC. EUS-FNA may also improve diagnosing mediastinal masses of unknown origin, leading to changes in patient management, which may result in improved survival outcomes. EUS-FNA offers potential benefits in terms of patient quality of life, as well as possible economic benefits.

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 M-TAG Pty Ltd, a unit of IMS Health, was engaged to conduct a systematic review of literature on endoscopic ultrasound guided fine-needle aspiration for the staging of non-small cell lung cancer and the diagnosis of mediastinal masses of unknown origin.

MSAC's assessment of EUS-FNA for NSCLC staging and mediastinal mass diagnosis

Clinical need

In 2001, there were 8275 diagnoses of lung cancer reported in Australia. There were 7039 lung cancer deaths in 2001, resulting in 44,978 person-years of life lost before the age of 75 years. NSCLC accounts for 84 per cent of lung cancers. NSCLC is treatable; the treatment protocol is determined by the stage of disease. The standard treatment option for early stage tumours is surgical resection. Therapy for patients with more advanced tumours can involve radical chemoradiation or palliative treatment. At diagnosis, most patients are found to have advanced disease. About 60 per cent of NSCLC patients

present with sufficiently localised disease to attempt curative surgical resection. The overall five-year survival rate for NSCLC is 14 per cent.

Primary mediastinal masses comprise a diverse group of lesions including neoplastic, congenital and inflammatory conditions. Secondary mediastinal masses are generally metastatic tumours. Treatment for mediastinal masses depends on the lesion type, extent and malignant status. Treatment options include surgical resection, chemotherapy, radiotherapy and therapies appropriate for benign conditions such as sarcoidosis.

Research questions

The research questions addressed were:

Non-small cell lung cancer

To what extent is endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) safe, effective, and cost-effective in the pre-treatment staging of patients with presumed or known NSCLC relative to current clinical practice or in comparison to current techniques for biopsy of mediastinal lymph nodes?

Mediastinal masses

To what extent is EUS-FNA: safe, effective, and cost-effective in the diagnosis of patients with known mediastinal masses of unknown origin relative to current clinical practice or in comparison to current techniques for biopsy of mediastinal masses?

Safety

Safety data relating to the use of EUS-FNA in NSCLC staging and diagnosis of mediastinal masses were drawn from reports relating to 1649 patients undergoing this test. EUS-FNA use for diagnosis and/or staging of lung cancer and mediastinal lesions appears to be associated with a low risk of serious adverse events (0.12%, 95% CI: [0.01, 0.44]). There are a small number of mild adverse events associated with EUS-FNA such as sore throat (2.12%, 95% CI: [1.48, 2.94]), pain (0.67%, 95% CI: [0.33, 1.19]), and nausea or vomiting (0.24%, 95% CI: [0.07, 0.62]). Poor reporting and other factors mean that a degree of uncertainty exists about the incidence of these events.

Effectiveness

Direct evidence

A randomised controlled trial by Larsen et al (2005) provided direct evidence of EUS-FNA use in the pre-treatment staging of NSCLC. This trial suggests that the introduction of routine EUS-FNA would reduce the number of futile thoracotomies.

This study was unable to assess the impact of EUS-FNA on patient survival. Differences were found between prior tests and the current clinical practice group from those identified in the clinical pathway developed for NSCLC patients in this assessment. Larsen et al (2005) reported that some patients in the current clinical practice group received EUS-FNA and all patients had prior bronchospcopy with transbronchial needle aspiration. This difference limits applicability of this trial to the NSCLC patient population that was considered for this assessment. For this reason, it was considered that this study provided limited direct evidence for EUS-FNA in NSCLC staging.

Linked evidence

Is it accurate?

Systematic review

Systematic reviews by Kramer and Groen (2003) and Toloza et al (2003) assessed the diagnostic performance of EUS-FNA for NSCLC staging. These reviews reported similar diagnostic performance among invasive staging technologies. Kramer and Groen (2003) concluded that EUS-FNA had potential to be used to perform mediastinal tissue sampling more accurately than other invasive staging modalities. Toloza et al (2003) reported similar diagnostic performance among invasive staging modalities. These reviews were considered to offer limited value because of their lack of comparative evidence.

Linked evidence

Staging of NSCLC

Results from a medium quality, applicable study by Annema et al (2005) suggested that EUS-FNA may be more sensitive than mediastinoscopy: 75.9 per cent (95% CI: [56.5, 89.7]) versus 65.5 per cent (95% CI: [45.7, 82.1]) respectively. EUS-FNA was slightly less specific than mediastinoscopy in identifying advanced disease: 96.9 per cent (95% CI: [89.2, 99.6]) versus 100 per cent (95% CI: [94.4, 100.0]) respectively. There was a large degree of overlap between the 95 per cent confidence intervals for sensitivity and specificity between the technologies. This study was considered to provide the best available comparative evidence for this assessment.

A low quality comparative study by Larsen et al (2005b) of EUS-FNA and mediastinoscopy had limited applicability because a sequence of prior tests were included that were not applicable to the NSCLC patient population considered in this assessment.

Diagnosis of mediastinal masses of unknown origin

A low quality, non-comparative study by Larsen et al (2002) assessed EUS-FNA diagnostic accuracy for mediastinal masses. This study indicated that EUS-FNA was a sensitive (92.3%) and specific (100%) diagnostic test and considered to be applicable to the mediastinal mass patient population considered in this assessment. The absence of comparative data meant that conclusions could not be made about the relative performance of EUS-FNA for mediastinal mass diagnosis when compared with current clinical practice.

Does EUS-FNA change patient management?

A patient management study by Chong et al (2005) reported the impact of EUS-FNA testing in a mixed mediastinal mass/mediastinal lymphadenopathy/lung cancer population. Reported results suggested that EUS-FNA could impact on patient management, principally by avoiding surgeries (42% of patients) or further invasive investigations (16% of patients) such as mediastinoscopy.

This patient group was considered to reflect clinical practice, but the applicability of this group may be limited because of inclusion of patients with small cell lung cancer (SCLC). It was also possible that this study included patients for lung cancer diagnosis, among whom no mediastinal masses were observed.

This management study was considered to provide evidence of the impact of EUS-FNA on patient management. This study's results should be interpreted with caution because of potential differences in the study population compared with the patient population considered for this assessment.

Summary of evidence for effectiveness

Evidence of effectiveness for EUS-FNA use in staging NSCLC and diagnosing mediastinal masses was reviewed.

Staging of NSCLC

There was limited, medium quality evidence to indicate that:

> EUS-FNA is more sensitive, but slightly less specific than mediastinoscopy for NSCLC staging and can alter patient management, reducing the number of surgical and invasive procedures performed. The impact of EUS-FNA on patient survival and quality of life remains unclear.

Diagnosis of mediastinal masses of unknown origin

There was insufficient evidence to indicate that:

> EUS-FNA has equal or improved diagnostic performance in the diagnosis of mediastinal masses of unknown origin when compared with current clinical practice.

Cost-effectiveness

Staging of NSCLC

A decision analytic model was constructed to assess the cost-effectiveness of introducing EUS-FNA to NSCLC staging compared with mediastinoscopy.

The base case analysis demonstrated that the staging algorithm commencing with EUS-FNA was found to be cost saving when compared with mediastinoscopy. Both arms of the model were shown to offer largely comparable outcomes in terms of patients' mean life expectancy, although a negligible difference was demonstrated that favoured the current algorithm slightly over the staging algorithm beginning with EUS-FNA.

The average cost savings associated with the EUS-FNA strategy were estimated to be $2570 per patient when compared with mediastinoscopy. This would allow up to half of patients to undergo further tests after EUS-FNA without incurring any additional costs.

The base case analysis demonstrated that compared with mediastinoscopy, the EUS-FNA strategy was associated with an insignificant impact on on patient life years (decreased by 0.001 life years). This suggested a negligible overall difference between final outcomes of testing strategies.

Impacts of varying the test accuracy estimates were explored by using 95 per cent confidence limits. These sensitivity analyses reinforced the base case finding that both arms were largely comparable in outcome (ie, patients' likelihood of survival following

invasive staging). Sensitivity analysis performed on other variables in the current model also confirmed that the base case simulation results were robust. Of these, a sensitivity analysis derived an estimate of 0.5 per cent fatal complication rate associated with mediastinoscopy (advisory panel estimate). Under this scenario, there were minimal differences between the EUS-FNA strategy and mediastinoscopy.

Diagnosis of mediastinal mass of unknown origin

A lack of evidence meant that comparative assessment of diagnostic accuracy was not possible. Formal economic evaluation was not performed, but a simple cost analysis that quantified estimated cost savings associated with EUS-FNA use instead of other modalities was conducted.

Recommendation

MSAC has considered safety, effectiveness and cost-effectiveness for endoscopic ultrasound guided fine needle aspiration (EUS-FNA) for the staging of presumed or known non-small cell lung cancer and the diagnosis of mediastinal masses compared with current clinical practice and techniques for biopsy of mediastinal lymph nodes.

MSAC finds EUS-FNA for the staging of non-small cell lung cancer when compared with current clinical practice/ techniques for biopsy of mediastinal lymph nodes and the diagnosis of mediastinal masses is as safe as current clinical practice, as effective, and cost saving.

MSAC **recommends that public funding** is supported for EUS-FNA for pre-treatment staging of patients with presumed or known non-small cell lung cancer and the diagnosis of mediastinal masses.

–The Minister for Health and Ageing accepted this recommendation on 27 August 2007–

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of endoscopic ultrasound guided fine-needle aspiration, which is a diagnostic test for the staging of non-small cell lung cancer and the diagnosis of mediastinal masses of unknown origin. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

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

This report summarises the assessment of current evidence for endoscopic ultrasound guided fine-needle aspiration for the staging of non-small cell lung cancer and the diagnosis of mediastinal masses of unknown origin.

Background

The procedure

Diagnostic sonography is a technique that uses high-frequency sound waves (ultrasound) to visualise internal body structures. Endoscopic ultrasound (EUS) examination is performed using a particular endoscope modified by a high-frequency ultrasound transducer on its tip (Fusaroli and Caletti 2005). This allows placement of an ultrasound transducer against the internal surface of the oesophagus. When placed in the oesophagus, EUS is capable of imaging masses and lymph nodes in the mediastinum (Barawi and Gress 2000). In particular, EUS can image the posterior mediastinum via the oesophagus and can identify mediastinal lymph nodes in the subcarinal, para-oesophageal and paratracheal regions, but not the pretracheal or intrapulmonary regions (Jacobson et al 2003). Other important indications can be derived by placing the ultrasound transducer against the luminal surface of the gastro-intestinal (GI) surface. The endoscopic approach overcomes many of the problems encountered with visualisation using an external approach by minimising air and adipose tissue between the transducer and the imaged structure. It also avoids difficulties that arise due to intervening calcified structures. EUS first appeared in clinical practice around 1985 and has now become a widely integrated technique (Fusaroli and Caletti 2005).

A range of EUS probes with transducers operating in the range 5–20 MHz are available (American Society for Gastro-intestinal Endoscopy 2000; Vila Costas 2005). Probes operating at higher frequencies provide higher resolution images, but have reduced viewing depth. There are two basic designs of ultrasound endoscopes: those with radial scanners and those with linear scanners. Radial scanners provide a 270–360^{o} scan in a direction that is perpendicular to the long axis of the endoscope, and are primarily used for diagnostic imaging. Linear (or sector) scanners have a scanning plane parallel to the long axis of the scope and allow limited viewing (100–180^{o}) along the insertion direction.

The development of linear scanners allows real-time visualisation of a needle along the long axis of the echoendoscope in conjunction with sonographic monitoring of the depth of needle penetration. Linear scanners allow deep tissue sampling with EUS-guided fine-needle aspiration (EUS-FNA) using 22 gauge needles (Vila Costas 2005) or Tru-Cut biopsy ([TCB]; 19 gauge needle) (Bhutani and Logrono 2006; Vila Costas 2005). Drainage is also possible with 6 to 10 F prostheses (Vila Costas 2005). The linear instruments operate at 5 or 7.5 MHz and may also have colour Doppler imaging (CDI) capability for enhanced vascular imaging. By using the oesophagus as a window for access, EUS-FNA facilitates tissue diagnosis of masses and lymph nodes in the mediastinum (Barawi and Gress 2000; Bhutani and Logrono 2006). Radial EUS may be performed to visualise lesions and/or lymph nodes for FNA in patients where EUS-FNA is indicated for tissue diagnosis. Assessment of lesions and/or lymph nodes by EUS-FNA can be enhanced when an on-site cytopathologist is available at the endoscopy clinic: samples can be assessed for adequacy immediately (Bhutani and Logrono 2006; Jhala et al 2003).

At commencement of the EUS-FNA procedure, a linear endoscope is introduced to the patient's oropharynx by placing the tip of the scope on the back of the tongue (Kramer et al 2005). The endoscope is then inserted into the oesophagus while the patient swallows. In this position, the ultrasound endoscope can view the inferior pulmonary

lymph nodes by rotating 180° up to the aorta. The scope is then retracted 1–2 cm at a time, until the pulmonary arteries can be observed. After each retraction, a 360° view is taken of the surrounding structures or nodes. Retro-oesophageal, subaortic, subcarinal, para-oesophageal, and main bronchial (hilar) nodes can also be imaged with this procedure. Ultrasound images that appear hypoechoic (black) with sharp edges and a round shape are considered suspicious for malignancy and FNA can be performed at this time. It may also be necessary to puncture surrounding nodes of the suspected malignancy to stage the disease. To avoid a false positive diagnosis, biopsy of several tumours using the same needle must follow a successive order starting with the lesion suspected to be a distant metastasis, followed by local lymph nodes, and lastly, the primary lesion (Villmann and Săftoiu 2006).

Fine-needle aspiration involves introducing the needle with stylet into the EUS channel. The distance from the centre of the lymph node to the needle exit is measured on screen and the needle stopper found on the needle shaft is set to this distance. The needle is then introduced through the scope, the stylet retracted, and the lymph node punctured. Suction is then applied with a syringe. After 10 to 15 up-and-down vertical movements of the needle inside the node, the syringe is closed and the needle is retracted and removed. The specimen is smeared onto a glass slide and evaluated for adequacy by the attending cytopathologist (if present). Repeat samples can be taken at this time if necessary (Kramer et al 2005). Biopsied tissue on glass slides is then either air-dried, methanol-fixed or ethanol fixed followed by staining with Diff-Quik (Bardales et al 2006) or Romanowsky (Jhala et al 2003) for immediate reading and determination of specimen adequacy. Papanicolaou staining can be applied (Bardales et al 2006) for later reading. Usually one stain is prepared per smear. The remainder of the sample is arranged for cell-block processing. In some centres, EUS-FNA samples are obtained by the endoscopist, and then sent to the cytopathology laboratory for sample preparation. In other centres, a cytopathologist is present in the endoscopy suite and provides on-site sample analysis for immediate determination (Jhala et al 2003).

The cytopathologist is responsible for providing an accurate on-site diagnosis, or at least a confirmation of an adequate tissue sample, in as few needle passes as possible. This preliminary information aids in the decisions regarding therapeutic intervention or patient referral to specialists. Immediate reading of the specimens thus optimises the accuracy of diagnosis as well as minimises time to diagnosis. Fewer needle passes minimises patient discomfort and later complications (Bardales et al 2006).

Although EUS ± FNA is considered to be safe by most practitioners, complications have been associated with these procedures occasionally (Adler et al 2005; Erickson 2004). Reported serious adverse events include haemorrhage, which may require transfusion; and perforation, which may require surgical repair. Limited data indicate that EUS is associated with a similar risk of perforations compared with standard upper-GI endoscopy (Adler et al 2005). EUS-FNA is thought to have a higher risk of complications than EUS alone, due to the invasiveness of the FNA technique. However, the overall risk of complications from EUS-FNA is relatively low (1.6%) (Bardales et al 2006) and major complications are much less frequent (advice from the advisory panel). Major complications from EUS-FNA include: infections of cystic lesions, bleeding, pancreatitis, and duodenal perforation (Erickson 2004). However, potential risk factors for EUS-FNA reflect the nature and site of the lesion. For example, aspiration of pancreatic cystic lesions has a higher risk for infection and pancreatitis while aspiration of mediastinal lesions has the potential risk of mediastinitis (Bardales et al 2006). The use of

colour Doppler assessment to identify and avoid vasculature along the path of the needle during EUS-FNA minimises the risk of perforation and bleeding (Bardales et al 2006).

Needle tract seeding of malignant cells during the FNA procedure could potentially result in unresectable disease and poor survival due to the transfer of malignant cells to other sites. The incidence of needle tract seeding may be difficult to assess, because surgical resection removes the needle pathway, and positive response to chemotherapy eliminates evidence. This holds true only when the needle pathway is resected and is not likely to apply when EUS-FNA is used to sample mediastinal masses and the oesophagus is not resected.

Another consideration for potential complications with EUS-FNA is the level of experience of the operators. Extensive training will be required to avoid a potential increase in EUS+/–FNA related morbidity and mortality as the technology becomes more widespread and if the procedure is carried out by less experienced operators.

Training

Extensive experience in diagnostic EUS is recognised as a requirement for performing EUS-FNA (Erickson 2004). Acquired skills that are necessary before and after the actual EUS-FNA procedure have been proposed as reasons for a steeper learning curve (Chang 2004). These include patient evaluation, assessment of pre-test probability of disease, review of other imaging studies (eg CT, MRI), and a thorough knowledge of the indications, risks, benefits and expected outcomes of the procedure (Chang 2004).

In Australia, a conjoint committee of the Royal Australian College of Surgeons, Royal Australian College of Physicians and the Gastroenterological Society of Australia has developed professional training guidelines for gastro-intestinal endoscopy (Conjoint Committee for the Recognition of Training in Gastro-intestinal Endoscopy 2006). The following components of these guidelines apply to EUS:

- EUS trainees are required to have successfully completed recognised upper gastro-intestinal endoscopy training before applying for EUS training
- Training should be conducted by centre(s) that perform at least 200 EUS procedures annually in their training programs
- Trainees must provide evidence that 250 procedures, 200 of which were performed independently, were undertaken during training. At least 100 procedures should have beenperformed for gastro-oesophageal lesions/tumours, and at least 100 for pancreato-biliary masses
- EUS guided FNA procedures can be claimed for either gastro-oesophageal or pancreatobiliary conditions
- Catheter probe EUS (using a gastroscope) can be included in the tally, but should not amount to more than 10 per cent of all procedures.

Intended purpose

This review evaluates the use of EUS-FNA in two clinical areas: the pre-treatment staging of non-small cell lung cancer (NSCLC) and the diagnosis of mediastinal masses of unknown origin.

Improvements in staging NSCLC and diagnosing mediastinal masses may lead to improved patient management (curative and palliative treatment planning), and potentially, to improved survival and quality of life.

Reference standard

Investigatation of accuracy of novel diagnostic tests requires that diagnoses made with a new test are compared with true disease status. Often it is not feasible to determine patients' disease status unequivocally. This means that a proxy measure—such as another diagnostic test or clinical judgement—must be used for many disease states. The best available measure of disease is called the reference standard; the new test is known as the index test.

Histological examination of specimens obtained during surgery or on biopsied tissue is the reference standard for cancer diagnoses. Long-term clinical follow up is an acceptable alternative reference standard when findings for neoplasia are found to be negative by the index test or comparator.

Surgical staging is the reference standard for staging cancers. This involves surgical resection with pathological and histological examination of the excised specimen. Long-term clinical follow-up is an acceptable alternative reference standard for patients who are considered ineligible candidates for surgery because of advanced disease or co-morbidities. Long-term clinical follow-up must include reporting the clinical follow-up period and outcomes consistent with malignant or benign disease.

Non-small cell lung cancer

Clinical need

Lung cancer is the leading cause of cancer deaths worldwide (Ferlay et al 2004) and is a considerable health issue in Australia. In 2004, lung cancer was the fifth most common (notifiable[1]) malignancy in Australia, and the leading cause of cancer death, responsible for 19.1 per cent of all cancer mortality (Australian Institute of Health and Welfare [AIHW] 2006).

Lung cancer has four main histologic classifications: squamous cell carcinomas, adenocarcinomas, large cell carcinomas and small cell carcinomas (Cancer Council Australia 2004). The behaviour and management of squamous cell carcinomas, adenocarcinomas, and large cell carcinomas are similar and are often grouped together as non-small cell lung cancer (NSCLC). Small cell lung cancer (SCLC) has a distinct natural history and management. NSCLC accounts for approximately 75 per cent of all lung cancers (Maghfoor and Perry 2005).

[1] These data exclude non-melanocytic skin cancers, which are not reported

Tobacco smoking is the largest single cause of lung cancer in Australia. In 2001, 84 per cent and 77 per cent of lung cancers in men and women respectively were attributable to smoking (Australian Institute of Health and Welfare [AIHW] and Australasian Association of Cancer Registries [AACR] 2004). In 2004–2005, almost one in four adults (23%) currently smoked (Australian Bureau of Statistics 2006). A 2001 national survey found that Indigenous adults aged 18 years and over in Australia were twice as likely as non-Indigenous adults to be current smokers (51% and 24% respectively) (Australian Bureau of Statistics 2002). Other risk factors for lung cancer include environmental tobacco smoke, smoking cannabis, medical exposure to radiation, previous lung disease, genetic susceptibility, asbestos exposure, and exposure to other environmental carcinogens (Cancer Council Australia 2004).

Most people with lung cancer have some sign or symptom of the disease, but 5–15 per cent are asymptomatic, and their tumours are frequently diagnosed incidentally from routine chest x-rays (Minna 2001). Lung cancer symptoms are caused by the primary tumour, locoregional spread, regional lymphatic involvement, metastatic disease and effects of tumour products (such as ectopic hormone production) (Minna 2001). Primary tumour symproms may include cough, haemoptysis, wheeze and stridor, dyspnoea, and post-obstructive pneumonitis (Minna 2001). Locoregional spread may cause pain from pleural or chest wall involvement, cough, and dyspnoea (Minna 2001). Thoracic regional spread can cause tracheal obstruction, oesophageal compression with dysphagia, hoarseness from laryngeal nerve paralysis, phrenic nerve paralysis, and sympathetic nerve paralysis with Horner's syndrome (Minna 2001).

Incidence and mortality

The most recent reported data of cancer incidence and mortality in Australia were from 2001. In that year, 8275 new diagnoses of lung cancer were reported[2]—5384 were male (yielding an age-standardised rate for Australia of 61.4/100,000); and 2891 were female (age-standardised rate for Australia of 27.7/100,000). The overall age-standardised rate for Australia in 2001 was 42.6/100,000 (AIHW and AACR 2004). The 2006 projected incidence of lung cancers in Australia is 9187 (3411 females: 5776 male) (AIHW, AACR & NCSG: McDermid 2005).

Lung cancer was responsible for 7039 deaths in 2001 (4657 male; 2382 female), resulting in 44,978 person-years of life lost (before 75 years of age), the highest number of person-years of life lost among all notifiable cancers in Australia (AIHW and AACR 2004). The age-standardised mortality for Australia in 2001 was 53.7/100,000 and 22.6/100,000 for males and females respectively. The overall age-standardised mortality for Australia in 2001 was 36.3/100,000.

In 2001, there were 17,264 separations for malignant neoplasm of bronchus or lung, resulting in 141,711 patient-days in hospital. The average length of stay was 9.8 days (AIHW 2005). There were 102 separations for malignant neoplasm of trachea, resulting in 302 patient-days in hospital in 2001. The average length of stay was 6.5 days (AIHW 2005).

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[2] 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 ICD-10 classification, code C33 is 'malignant neoplasm of trachea' and code C34 is 'malignant neoplasm of bronchus and lung' (World Health Organisation 2003)

Eligible population

The estimated number of patients who would undergo EUS-FNA for diagnosis of NSCLC was based on an assumption that all included patients met the following criteria:

1. Patients with suspected or known NSCLC without known extrathoracic metastases. Palliative treatment is reserved for patients with distant metastases or stage IV disease (Caddy et al 2005). stage IV patients were therefore excluded from the estimate

2. Patients who were deemed candidates for curative treatment

3. Patients whose malignancies were limited to nodal stations accessible by the EUS scope. EUS has limited range with respect to structures anterior or lateral to the trachea or lymph nodes that are in the lobar (station 12) or interlobar (station 11) regions (Annema et al 2004; LeBlanc et al 2003; Lloyd and Silvestri 2001). This is presumably due to air interference in these regions (LeBlanc et al 2003; Lee et al 1992). EUS readily images the retrotracheal (station 3), subaortic (station 5), subcarinal (station 7), para-oesophageal (station 8), inferior pulmonary (station 9) and main bronchial (tracheobronchial or hilar) (station 10) regions (LeBlanc et al 2003) (see Table 1).

Patients with nodal metastases restricted to stations 3P, 5, 7, 8, 9, 10 (and possibly 2R, 4R and 4L in some clinical circumstances) were considered eligible for this procedure. The right lower paratracheal (4R), subcarinal (station 7) and para-oesophageal (station 8) nodes are most commonly involved in lung cancer (Annema et al 2004; Richardson and Peake 2004; advice from the advisory panel).

Table 1 Lymph nodes stations and corresponding accessibility for EUS

Lymph node descriptions	Lymph node station	Accessible by EUS endoscope (yes/no)
Superior mediastinal	1	No
Left upper paratracheal	2L	No[a]
Right upper paratracheal	2R	No[a]
Right lower paratracheal	4R	No[a]
Pre-vascular	3A	No
Retro-oesophageal	3P	Yes
Subaortic (aortopulmonary window)	5	Yes
Para-aortic	6	No
Subcarinal	7	Yes
Para-oesophageal	8	Yes
Inferior pulmonary	9	Yes
Main bronchial (hilar)	10	Yes
Interlobar	11	No
Lobar	12	No

[a] These stations my be sampled if lymph nodes are enlarged, but are difficult to sample reliably under most circumstances (Annema et al, 2004; US Guidelines for invasive staging 2003). Lymph node station 4L may be accessible in some clinical circumstances
Note: Significant discordance in nodal stations exist between the Japanese Naruki map and those reported in Table 1 (Watanabe et al 2002)

A pattern of care study conducted in Victoria reported that about 84 per cent of lung cancers are found to be NSCLC on pathological diagnosis (Richardson et al 2000). As many as 40 per cent of detected NSCLC have progressed to distant metastases at diagnosis (Caddy et al 2005). Based on the projected number of 9401 diagnoses being made in 2007 (AIHW, AACR & NCSG: McDermid, 2005) it was determined that 7897 would be NSCLC, and of these, 4739 patients (60%), may be eligible to undergo EUS staging annually.

The pattern of care analysis conducted in Victoria reported that 21 per cent of NSCLC patients did not undergo anti-tumour therapy (Richardson et al 2000). Of these untreated patients, 40 per cent had comorbid conditions such as ischaemic heart disease, chronic obstructive airway disease, atherosclerotic disease, or diabetes mellitus (Canstat 2002; Richardson et al 2000).

A pattern of care study conducted in south-western Sydney by Vinod et al (2003) showed that 28 per cent of this population did not undergo active treatment during the course of their illness. A multivariate analysis of data indicated that the most likely determinants for lack of specialist care and a pathological diagnosis were low scores on the Eastern Cooperative Oncology Group (ECOG) performance status scale[3], limited ability to speak English, and increasing age at diagnosis.

An estimatation of patients who should receive treatment is not clear from these patterns of care data (advice from the advisory panel). Approximately 15 per cent of patients with NSCLC may have severe comorbidities, such as emphysema, or be too frail for curative surgery or full dose radiotherapy (advice from the advisory panel). This figure is

[3] The ECOG scale is a measure of cancer patients' ability to carry out normal activities. This measure is a 5 point scale where the lowest rating of 0 indicates asymptomatic and a rating of 5 is deceased.

considered here as an estimate of the proportion of NSCLC patients without distant metastases who would not be considered for treatments that require staging.

Analysis indicated that 4029 people with NSCLC (85% of diagnoses of NSCLC without distant metastases) may be considered for active therapy every year. The introduction of PET scanning in cancer assessment has reduced requirements for invasive testing over the last few years. Where PET is available, it was estimated that a maximum of 20 per cent of the estimated 4029 patients would require invasive staging and be considered eligible to undergo EUS-FNA (advice from the advisory panel). If PET is unavailable, it was estimated that up to 40 per cent of the 4029 patients would be considered as candidates to undergo EUS-FNA (advice from the advisory panel). Based on the estimate of 4029 people with NSCLC who do not have distant metastases and who require staging to determine treatment, the minimum to maximum range considered eligible for EUS-FNA would be 806 to 1612 NSCLC patients. The algorithm used to determine the potential NSCLC eligible population for EUS-FNA is shown in Figure 1.

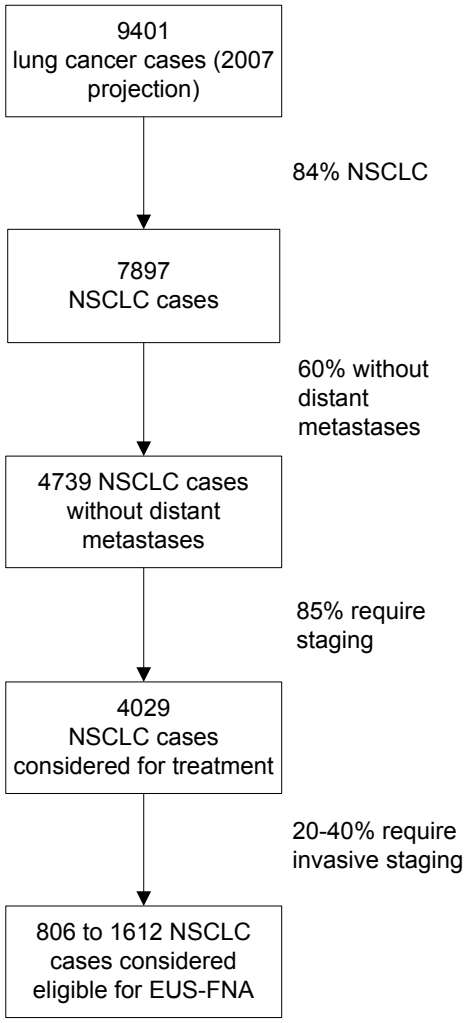

Figure 1 **Patient eligibility algorithm for EUS-FNA**

Current treatment

Survival after diagnosis of lung cancer is extremely poor and decreases with age and extent of disease (Cancer Council Australia 2004). NSW data covering the period 1980–1995 indicated the five-year relative survival from localised lung cancer to be 23.2 per cent in comparison with 1.0 per cent of patients whose disease had metastasised to distant organs (Supramaniam et al 1998). More recent American data from 1995–2000 showed the five-year relative survival from local disease to be 49.4 per cent compared with 2.1 per cent of distant disease (American Cancer Society 2005)[4].

Between 1992 and 1997 one-year relative survival for people diagnosed with NSCLC was approximately 35.6 per cent for males and 38.4 per cent for females. Five-year relative survival was 12.0 per cent and 15.8 per cent for males and females respectively (AIHW and AACR 2005).

NSCLC management is dependent on the extent of disease, position of the primary tumour and the patient's health (National Cancer Institute [NCI] 2006). Surgical resection is the optimal treatment for NSCLC but is only possible where patients are suitable candidates and tumours are early stage (Cancer Council Australia 2004). Most patients however present with advanced disease: only 30–35 per cent of patients with NSCLC present with sufficiently localised disease to attempt curative surgical resection (Maghfoor and Perry 2005). Up to 40 per cent of patients with NSCLC have distant metastases at diagnosis (Caddy et al 2005).

At diagnosis, patients with NSCLC can be divided into three groups, reflecting the extent of disease and the treatment approach (NCI 2006). The first group of patients have tumours that are surgically resectable (generally stage I, stage II and selected stage III patients) (see Table 51, **Appendix G**, for stage classification of NSCLC). Patients with resectable disease who are not suitable for surgery are candidates for curative radiation therapy. The second group includes patients with locally advanced (T3–T4) and/or regionally (N2–N3) advanced NSCLC. Selected patients with locally advanced tumours may benefit from combined modality treatments. Patients with unresectable or N2–N3 disease are treated with a combination of radiation and chemotherapy. Certain patients with T3 or N2 disease can be treated effectively with surgical resection and either pre-operative or postoperative chemotherapy or chemoradiation therapy. The final group includes patients with distant metastases (M1) identified at diagnosis. These patients can be treated with radiation therapy or chemotherapy for palliation of symptoms from the primary tumour.

Because currently available therapies for patients with NSCLC are often unsuccessful, well-matched patients (ie suitable candidates for therapies in development) may be considered for clinical trials (NCI 2006).

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[4] Survival data from the US and Australia may not be comparable because definitions of lung cancer staging differ. The American Cancer Society defines lung cancer stages as localised, regional or distant (Young et al 2000), and the AIHW applies TNM staging (Mountain 1997). The term 'localised' in NSW data between 1980 and 1985 is considered to include more advanced disease than the American definition of 'localised'.

Mediastinal masses

Clinical need

Primary mediastinal tumours represent a variety of different diseases, including neoplastic, congenital and inflammatory conditions (Strollo et al 1997a). Approximately 60 per cent of surgically resected lesions are neurogenic tumours, thymomas or benign cysts. Lymphomas, teratomas, and granulomatous diseases make up 30 per cent, and vascular lesions account for the remaining 10 per cent of mediastinal masses.

Because certain mediastinal tumours and other masses are usually found in particular areas of the mediastinum, this area is generally subdivided to facilitate better descriptive localisation of specific tumours (Eggerstedt 2003). The boundaries of the mediastinum itself are considered to be the pleural cavities laterally, the thoracic inlet superiorly and the diaphragm inferiorly (Duwe et al 2005). The mediastinum is further divided into three areas: anterior, middle and posterior (Eggerstedt 2003; Duwe et al 2005). The anterior compartment extends from the posterior surface of the sternum to the anterior surface of the pericardium and great vessels. The middle mediastinum is classified as the area between the posterior limit of the anterior compartment and the anterior longitudinal spinal ligament. The posterior compartment is the area posterior to the heart and trachea.

The most common primary tumours in the anterior mediastinum are of thymic, lymphatic or germ cell origin (Eggerstedt, 2003) and include: thymoma, thymic carcinoma, thymic carcinoid, thymolipoma, lymphoma, germ cell tumours and parathyroid adenoma (Strollo et al 1997a). Non-neoplastic conditions include thymic cysts, lymphangioma and intrathoracic goitre (Strollo et al 1997a). Thymoma is the most common primary tumour of the anterior mediastinum, accounting for 20 per cent of anterior mediastinal neoplasms in adults: males and females are affected equally and most are over 40 years of age (Strollo et al 1997a). Thymoma incidence has been reported at 0.15 cases per 100,000 (Strollo et al 1997a).

Primary tumours of the middle and posterior mediastinum make up about half of all mediastinal masses (Strollo et al 1997b). The most common tumours of the middle and posterior compartments are of lymphatic and neurogenic origin respectively (Eggerstedt et al 2003). Mediastinal cysts are also common in the middle and posterior mediastinum (Strollo et al 1997b).

Lymphomas can occur in any of the mediastinal compartments: 45 per cent of anterior mediastinal masses in children are lymphomas, and in adults, they are the second most common anterior mediastinal mass (Eggerstedt et al 2003). Lymphoma—both Hodgkin's and non-Hodgkin's—can affect the mediastinum, and it is uncommon for either to be limited to the mediastinum at the time of diagnosis (Strollo et al 1997b). The primary form of mediastinal lymphoma constitutes 10 per cent of disease incidence, Hodgkin's lymphoma accounts for between 50 and 70 per cent of mediastinal lymphoma, and non-Hodgkin's lymphoma makes up from 15 to 25 per cent (Duwe et al 2005).

Most mediastinal masses are asymptomatic and are found incidentally during chest x-ray or imaging studies of the thorax performed for other reasons (Eggerstedt 2003). Symptoms, if present, are usually associated with compression of the respiratory tract (local symptoms) and may include persistent cough, dyspnoea and stridor. Other possible non-specific symptoms include weight loss, fever, malaise, and vague chest pain. Certain

mediastinal masses may be associated with systemic or biochemical abnormalities typically caused by the release of excess hormones, antibodies or cytokines (Duwe et al 2005). An example is hypercalcaemia, caused by parathyroid adenoma.

The likelihood of malignancy is chiefly influenced by three factors: symptoms, mass location and patient age. About two-thirds of all mediastinal tumours are benign (Strollo et al 1997a) and over 75 per cent of asymptomatic patients have benign lesions. In contrast, almost two-thirds of symptomatic patients have malignancies. Masses in the anterior compartment have a high likelihood of malignancy: rates of malignancies detected in anterior, middle and posterior sites have been reported at 59 per cent, 29 per cent and 16 per cent respectively (Duwe et al 2005). Age is also a predictor of malignancy: many lymphomas and germ cell tumours present between the second and fourth decades (Duwe et al 2005). About a third of mediastinal tumours are found to be malignant in patients aged less than 20 or over 40 years old; and about half are found to be malignant in patients aged between 20 and 40 years (Eggerstedt 2003).

Eligible population

Patients who may potentially undergo EUS-FNA for diagnosis of mediastinal masses of unknown origin constitutes a diverse patient group. These patients may include those with benign conditions, primary mediastinal tumours or mediastinal metastases from unknown primary tumours.

Around 1000 mediastinoscopies were conducted in 2004–2005 (AIHW 2005). It was estimated that around 65 per cent of these procedures were conducted to investigate mediastinal masses of unknown origin (advice from the advisory panel). If EUS-FNA were to be used rather than mediastinoscopy, the maximum annual number of patients considered eligible for EUS-FNA to investigate mediastinal masses of unknown origin is estimated to be 650 patients. This maximum estimate is also considered to include those patients investigated using other procedures (such as transthoracic needle aspiration [TTNA]) who would also be considered eligible for EUS-FNA. In the event of patients who are not considered for mediastinoscopy because of safety issues or who are too unwell, 650 may underestimate the number of patients considered for the less invasive procedure of EUS-FNA.

Current treatment

Surgical resection is the optimal treatment for most mediastinal neoplasms. Patients with either invasive or non-invasive thymomas are candidates for surgical resection. Complete surgical excision is attempted for most patients with thymomas to limit invasion and improve survival. Adjunctive chemotherapy and radiation treatment may be used for thymoma patients with locally invasive or metastatic disease or inoperable tumours (Duwe et al 2005).

Early stage Hodgkin's lymphoma (stage PS 1A) of the mediastinum is generally treated using radiotherapy; stages I or II are treated using chemoradiation; therapy for stages III and IV involves chemotherapy (Eggerstedt et al 2003). Patients with non-Hodgkin's lymphoma are treated with chemotherapy (Eggerstedt et al 2003).

Mediastinal tumours of mesenchymal origin are surgically resected if possible, and may involve neo-adjuvant chemotherapy or postoperative radiotherapy, depending on the

particular tumour subtype. Surgical resection is the treatment of choice for some benign lesions, ectopic endocrine tumours and intrathoracic thyroid goitres.

Existing procedures

The aim of intrathoracic staging for NSCLC is to assess mediastinal lymph node involvement. Evaluation of mediastinal masses can determine the nature of the lesion and establish its malignant status. Histological assessment of mediastinal masses may be indicated for patients who have masses that are clearly invasive. Evaluation of mediastinal lymph nodes and masses is used to assess patients' prognoses and clinical management. Histological and cytological assessment of mediastinal lymph nodes and masses use needle biopsy or surgical biopsy techniques to obtain tissue samples. Invasive tests include mediastinoscopy, mediastinotomy, video-assisted thoracoscopy (VAT), transbronchial needle aspiration (TBNA), and transthoracic needle aspiration (TTNA) (Toloza et al 2003). As with other invasive technologies, such as EUS-FNA, these procedures carry a risk of procedural mortality. Techniques such as mediastinoscopy, mediastinotomy, VAT and TTNA are generally considered to be significantly more invasive than EUS-FNA.

Mediastinoscopy

Standard cervical mediastinoscopy is a surgical technique that involves making a small incision above the suprasternal notch, with dissection extending to the pretracheal fascia. An endoscope (mediastinoscope) is inserted through this incision, into the mediastinum and toward the carina. The patient's neck is hyperextended to facilitate insertion of the mediastinoscope. Anterior mediastinal lymph nodes are exposed by blunt dissection performed paratracheally, bilaterally and subcarinally. The four paratracheal lymph node stations (levels 2R, 2L, 4R and 4L) and subcarinal lymph node station (level 7) can then be sampled under direct or video-assisted view. Access to lymph node station 3 may be possible using extended cervical mediastinoscopy. Access to lymph nodes in the posterior and inferior mediastinum is limited using this technique. Standard cervical mediastinoscopy requires general anaesthesia and is associated with risk of bleeding, pneumothorax, wound infection and left laryngeal nerve injury. Mediastinoscopy may be contraindicated for patients with severe cervical arthritis, which may prevent adequate neck extension, or with cutaneous tracheotomy (Semik et al 2004).

Extended cervical mediastinoscopy is an extension of standard mediastinoscopy that enables biopsy of lymph nodes at the subaortic (aortopulmonary window; level 5) and para-aortic station (level 6). This procedure is performed through the same incision as standard mediastinoscopy. The mediastinoscope is passed between the brachiocephalic artery and the left carotid artery over the aortic arch to the aortopulmonary window. A substernal procedure enables biopsy of the thymus and any tumours or cysts found in the prevascular area (Eggerstedt 2003). Extended cervical mediastinoscopy presents risks of bleeding and embolic stroke.

Mediastinotomy

Anterior mediastinotomy can access the same lymph node stations as extended cervical mediastinoscopy, but this procedure requires another incision parasternally, usually at the second or third intercostal space. This procedure is associated with a risk of bleeding, and of damage to the pleura or internal mammary artery. Anterior mediastinotomy may

be used where standard cervical mediastinoscopy is considered or was found to be inadequate (Eggerstedt 2003).

Video-assisted thoracoscopy

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

Transbronchial needle aspiration

Transbronchial needle aspiration (TBNA) involves passing a needle catheter through the working channel of a bronchoscope. The needle is guided to the area overlying the targeted mediastinal lymph node. The needle catheter is advanced through the tracheal or carinal wall into the mediastinal lymph node and a biopsy sample obtained by aspiration. Histologic examination of tissue may be possible if larger gauge needles are used to obtain core samples. Several needle passes may be required to obtain an adequate sample. On-site examination of aspirated samples by a cytopathologist may enhance diagnostic yield—immediate feedback enables the endoscopist to obtain additional aspirated samples if necessary. The TBNA procedure can sample from anterior mediastinal lymph node stations, and is limited because it is usually carried out blind. Guidance by imaging techniques such as real-time CT-fluoroscopy, endobronchial ultrasound, and virtual bronchoscopy may enhance TBNA diagnostic yield. TBNA complications include laryngospasm and endobronchial bleeding.

Transthoracic needle aspiration

Transthoracic needle aspiration (TTNA) involves passing a biopsy needle percutaneously to the targeted mediastinal lymph node or mass. Needle guidance may use CT, fluoroscopy or endoscopic ultrasound. TTNA may require several needle passes to obtain an adequate sample, and like TBNA, an on-site cytopathologist may enhance diagnostic yield. Larger gauge needles may be used to obtain core biopsy samples. TTNA is also limited in the range of lymph node stations that can be sampled. Differentiation of thymomas, lymphomas, and germ cell tumours may be possible when tissue obtained from a core needle biopsy is subjected to histologic staining methods (Eggerstedt 2003). TTNA complications include intrathoracic bleeding and pneumothorax. Pericarditis and pericardial tamponade may occur if the pericardium is penetrated.

Comparator

Non-small cell lung cancer

EUS-FNA likely to be used in the Australian healthcare setting as a replacement diagnostic test for patients with known or suspected NSCLC, with suspected lymphadenopathy in EUS-FNA accessible lymph node stations,. Therefore, the comparator for this test is:

Current techniques for biopsy of mediastinal lymph nodes—mediastinoscopy, mediastinotomy, video-assisted thoracoscopy biopsy, transbronchial needle aspiration or transthoracic needle aspiration.

This test is likely to be used in the Australian healthcare setting as a supplementary diagnostic test for patients who would only be considered for biopsy if EUS-FNA were available. Therefore, the comparator for this test is:

Current clinical practice.

Mediastinal masses

This test is likely to be used in the Australian healthcare setting as a replacement diagnostic test for patients with mediastinal masses of unknown origin in EUS-FNA accessible areas of the mediastinum. Therefore, the comparator for this test is:

Current techniques for biopsy of mediastinal masses—mediastinoscopy, mediastinotomy, video-assisted thoracoscopy biopsy, transbronchial needle aspiration or transthoracic needle aspiration.

This test is likely to be used in the Australian healthcare setting as a supplementary diagnostic test for patients who would only be considered for biopsy if EUS-FNA were available. Therefore, the comparator for this test is:

Current clinical practice.

Marketing status of the device/technology

EUS components are available from Phillips, Hitachi, Olympus and Aloca, who manufacture processors; and Pentax and Olympus who build endoscopes. These manufacturers offer a range of devices that enable radial, linear and curvilinear endosonography and fine-needle aspiration (FNA) biopsy procedures to be performed.

Pentax FG-32UA ultrasound endoscopes (radial and linear) are registered with the Therapeutic Goods Administration (TGA). The Australian Registry of Therapeutic Goods (ARTG) listing number is Aust L 13212. Hitachi ultrasound diagnostic scanners (various models) are also registered with the TGA (ARTG listing number Aust L 81013). Olympus endoscopic ultrasound equipment (various products) is listed with the TGA (ARTG listing number AUST L 71621). Toshiba and Hitachi endoscopic ultrasound products are not currently listed with the TGA; however, both manufacturers have general ultrasound equipment listed (Aust L 18113 and Aust L 81013, respectively).

EUS has current USA marketing approval for diagnostic ultrasound imaging or fluid flow analysis of the human body, including the gastro-intestinal tract, biliary, pancreatic duct and surrounding organs, intraluminal ultrasound for upper airways and tracheobronchial tree, urinary tract and female reproductive tract.

Current reimbursement arrangement

Medicare Benefits Schedule funding for use of EUS in staging and diagnosing upper gastro-intestinal disorders is currently in progress following MSAC assessment.

Approach to assessment

Research questions and clinical pathways

Non-small cell lung cancer

The PPICO criteria (target population, prior tests, index test, comparator, outcomes) developed *a priori* for evaluation of EUS-FNA use for patients with presumed or known non-small cell lung cancer (NSCLC) is given in Table 2.

Table 2 PPICO criteria for EUS-FNA use for patients with presumed or known NSCLC

Population	Prior tests	Index test	Comparator	Outcomes
Patients with presumed or known NSCLC identified by prior tests	CT and/or PET (where available)	EUS-FNA	Current clinical practice	Change in clinical management
			Current techniques for biopsy of mediastinal lymph nodes[a]	Change in clinical outcomes
				Diagnostic accuracy

Abbreviations: CT, computed tomography; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration; NSCLC, non-small cell lung cancer; PET, positron emission tomography

[a] Transbronchial needle aspiration, video-assisted thorascopy biopsy, transthoracic needle aspiration, mediastinoscopy, or mediastinotomy

The research question for this indication, based on these criteria, was as follows:
To what extent is endoscopic ultrasound guided fine-needle aspiration (EUS-FNA):

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

in the pre-treatment staging of patients with presumed or known NSCLC relative to current clinical practice or in comparison with current techniques for biopsy of mediastinal lymph nodes?

The clinical pathway for the evaluation of patients with presumed or known NSCLC is shown in Figure 2. This flowchart displays the clinical management pathway to the point of patient diagnosis.

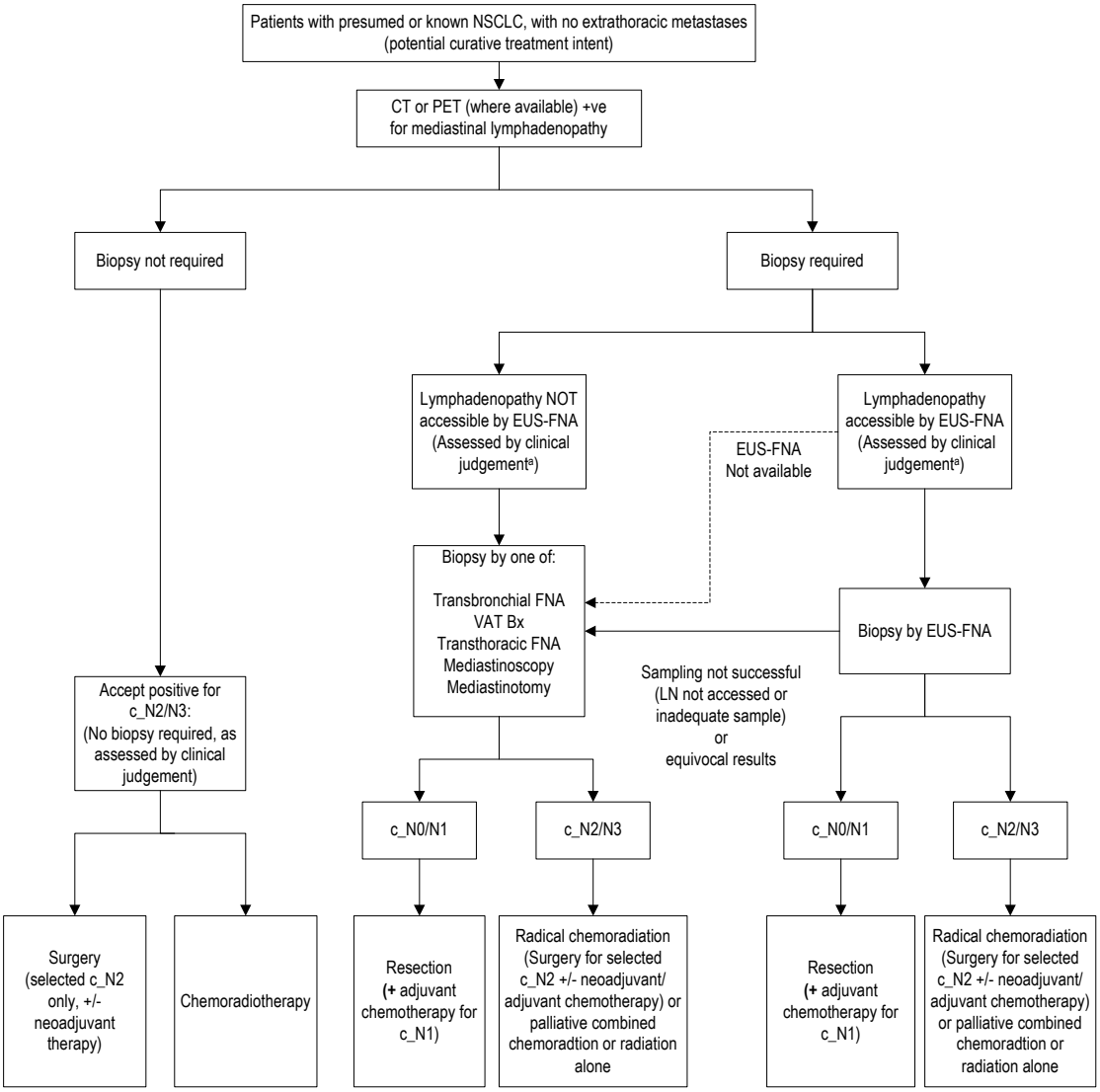

Figure 2 Clinical pathway for the evaluation of patients with presumed or known non-small cell lung cancer

Abbreviations: Bx, biopsy; C, clinical stage; CT, computed tomography; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration; FNA, fine-needle aspiration; N, regional lymph nodes; NSCLC, non-small cell lung cancer; P, pathological stage; PET, positron emission tomography; VAT, video-assisted thoracoscopy

[a] In general, lymph node stations accessible by EUS-FNA are: 3P, 5, 7, 8, 9, 10L (lymph node classification according to American Joint Committee on Cancer [2002], Lung Cancer, in *AJCC Cancer Staging Manual*, ed. Greene, Springer, New York, NY pp. 167–177). Other lymph nodes may also be accessible by EUS-FNA (2L 2R, 4R and 4L) depending on the clinical situation

Mediastinal mass of unknown origin

The PPICO criteria (target population, prior tests, index test, comparator, outcomes) developed *a priori* for evaluation of EUS-FNA use for patients with mediastinal mass of unknown origin is given in Table 3.

Table 3 PPICO criteria for the use of EUS-FNA in patients with a mediastinal mass of unknown origin

Population	Prior tests	Index test	Comparator	Outcomes
Patients with known mediastinal masses, identified by prior tests, with or without symptoms	Chest radiograph and/or CT	EUS-FNA	Current clinical practice	Change in clinical management
			Current techniques for biopsy of mediastinal masses[a]	Change in clinical outcomes
				Diagnostic accuracy

Abbreviations: CT, computed tomography; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration
[a] Transbronchial FNA, video-assisted t thoracoscopic biopsy, thoracotomy/sternotomy biopsy, CT-guided core biopsy, transthoracic needle aspiration, mediastinoscopy, or mediastinotomy

The research question for this indication, based on these criteria, was as follows:
To what extent is EUS-FNA:

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

in the diagnosis of patients with known mediastinal masses of unknown origin relative to current clinical practice or in comparison with current techniques for biopsy of mediastinal masses?

The clinical pathway for the evaluation of patients with a mediastinal mass of unknown origin is shown in Figure 3. This flowchart displays the clinical management pathway to the point of patient diagnosis.

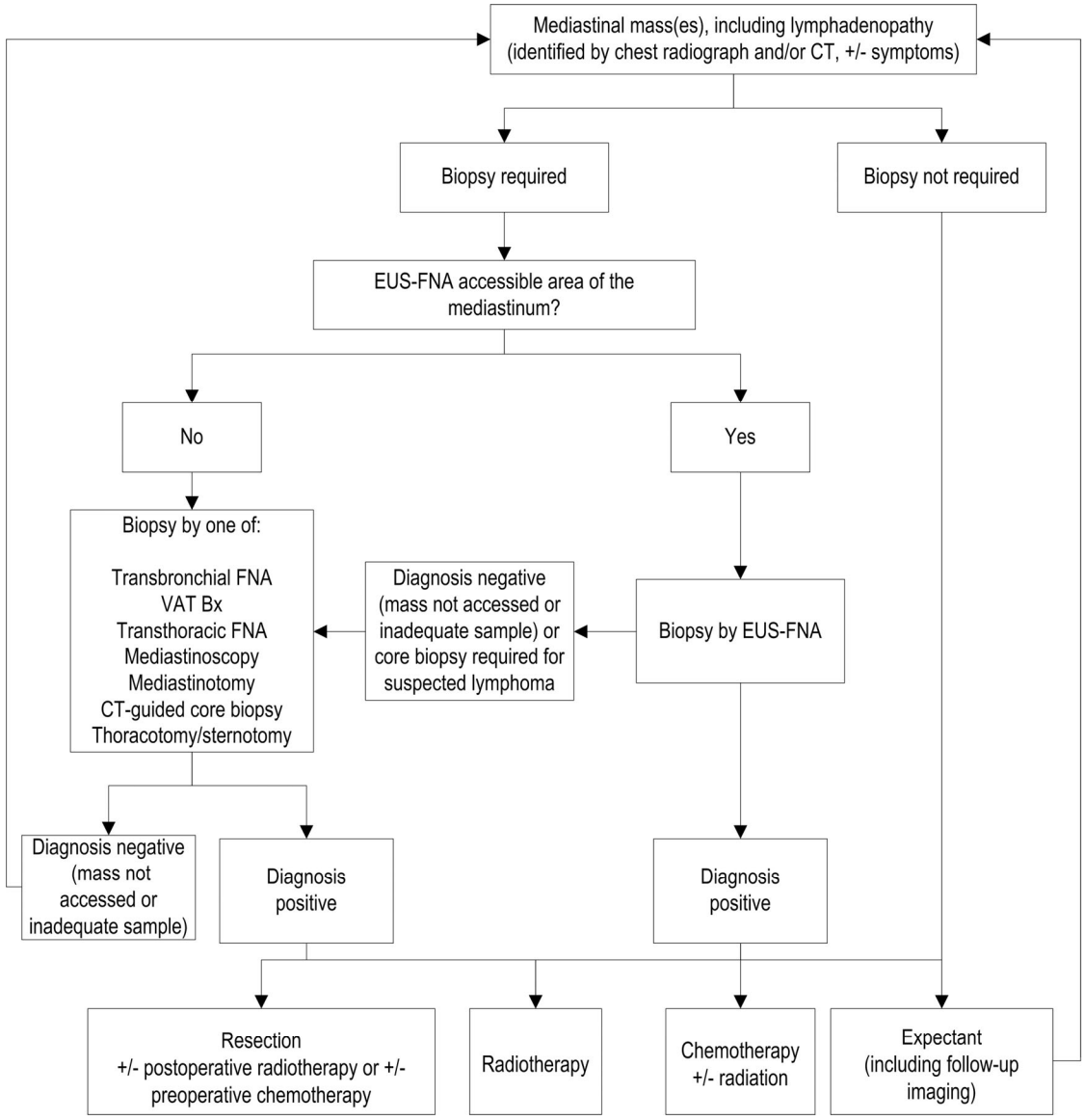

Figure 3 Clinical pathway for evaluation of patients with mediastinal masses of unknown origin

Abbreviations: Bx, biopsy; CT, computed tomography; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration; FNA, fine-needle aspiration; VAT, video-assisted thoracoscopy

Assessment framework

Types of evidence

A systematic review of the medical literature was undertaken to identify relevant studies examining the value of EUS-FNA for diagnosis of mediastinal masses of unknown origin and the pre-treatment staging of NSCLC. Direct evidence regarding the impact of EUS-FNA 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 regarding the impact of EUS-FNA on clinical management and diagnostic accuracy was assessed.

Review of the literature

The medical literature was searched to identify all relevant studies and reviews published to 2006. Searches were conducted in the primary databases indicated in Table 4.

Search strategy

Primary databases

Table 4 Electronic databases searched for EUS-FNA review

Database	Period covered/date searched
Medline[a]	1966 to August week 2, 2006
EMBASE[a]	1980 to 2006, week 32
PreMedline[a]	15 August 2006
Cochrane Library	Issue 3, 2006 (10 August 2006)

[a] Initial searches of these databases for management/outcomes studies were conducted as follows: Medline 1966 to July week 2, 2006; EMBASE 1980 to 2006, week 28; PreMedline 19 July 2006

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

- endosonography, endoscopic ultrasound, EUS, echoendoscopy, interventional ultrasound
- fine-needle aspiration, fine-needle biopsy, FNA, aspiration biopsy, puncture biopsy, suction biopsy
- mediastinum, mediastinal
- non-small cell lung cancer, non-small cell lung tumour, non-small cell pulmonary cancer, non-small cell pulmonary tumour, NSCLC and staging, lymph nodes, lymph gland, lymphoid nodule, lymphatic gland, lymphatic node, lymphatic metastases, lymphatic tissue.

Complete details of the literature searches performed using the primary databases are presented in **Appendix H**. The list of secondary databases searched is also presented in **Appendix H**.

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

Selection criteria

Non-small cell lung cancer

Table 5 Selection criteria for studies of EUS-FNA in patients with presumed or known NSCLC

Research question: To what extent is EUS-FNA safe, effective and cost-effective in the pre-treatment staging of patients with presumed or known NSCLC relative to current clinical practice or in comparison with current techniques for biopsy of mediastinal lymph nodes?

Selection criteria	Inclusion	Exclusion
Study design		
All studies	Studies with ≥ 10 patients[a]	Non-systematic reviews, letters and opinion pieces, non-human or *in vitro* studies
Direct evidence studies	Studies comparing health outcomes with and without the use of EUS-FNA	
Accuracy studies	Studies investigating the diagnostic accuracy of EUS-FNA	Studies incorporating EUS-FNA results in the reference standard
Management studies	Pre-test post-test management studies	
Population	Patients with presumed or known NSCLC, with no extrathoracic metastases	Patient population of mixed indications with inadequate data separation
Prior tests	Not specified for inclusion or exclusion criteria	
Index test	Use of EUS ± FNA for staging of NSCLC as currently approved by the TGA	Intraductal ultrasound; catheter or mini-probes; intra-operative endosonography
Comparator	Current clinical practice Current techniques for biopsy of mediastinal lymph nodes[b]	
Reference standard		
Accuracy studies	Histopathology Surgical staging Long-term clinical follow up	Inadequate reporting of reference standard
Outcomes		
Direct evidence studies	Effect on health outcomes	Inadequate data reporting
Accuracy studies	Diagnostic performance	
Management studies	Effect on clinical management	

Abbreviation: TGA, Therapeutic Goods Administration

[a] Studies with less than 10 patients were included for the assessment of adverse event and safety data

[b] Transbronchial needle aspiration, video-assisted thoracoscopic biopsy, transthoracic needle aspiration, mediastinoscopy, or mediastinotomy

Mediastinal mass of unknown origin

Table 6 Selection criteria for studies of EUS-FNA in patients with a mediastinal mass of unknown origin

Research question: To what extent is EUS-FNA safe, effective and cost-effective in the diagnosis of patients with known mediastinal masses of unknown origin relative to current clinical practice or in comparison to current techniques for biopsy of mediastinal masses?

Selection criteria	Inclusion	Exclusion
Study design		
All studies	Studies with ≥ 10 patients[a]	Non-systematic reviews, letters and opinion pieces, non-human or *in vitro* studies
Direct evidence studies	Studies comparing health outcomes with and without the use of EUS-FNA	
Accuracy studies	Studies investigating the diagnostic accuracy of EUS-FNA	Studies incorporating EUS-FNA results in the reference standard
Management studies	Pre-test, post-test management studies	
Population	Patients with known mediastinal masses, with or without symptoms	Patient population of mixed indications with inadequate data separation[b]
Prior tests	Not specified for inclusion or exclusion criteria	
Index test	Use of EUS ± FNA for diagnosis of mediastinal masses/ as currently approved by the TGA	Intraductal ultrasound; catheter or mini-probes; intra-operative endosonography
Comparator	Current clinical practice Current techniques for biopsy of mediastinal lymph nodes[c]	
Reference standard		
Accuracy studies	Histopathology Surgical staging Long-term clinical follow up	Inadequate reporting of reference standard
Outcomes		
Direct evidence studies	Effect on health outcomes	Inadequate data reporting
Accuracy studies	Diagnostic performance	
Management studies	Effect on clinical management	

Abbreviation: TGA, Therapeutic Goods Administration

[a] Studies with less than 10 patients were included for the assessment of adverse event and safety data

[b] Studies with a mixed population of lung cancer and mediastinal/mass were not excluded, however, in this patient group clinical, follow up was not an appropriate reference standard

[c] Transbronchial needle aspiration, video-assisted thoracoscopic biopsy, thoracotomy/sternotomy biopsy, CT-guided core biopsy, transthoracic needle aspiration, mediastinoscopy, or mediastinotomy

Search results

Results from safety and effectiveness searches and management and health outcomes searches were pooled. The QUOROM (quality of reporting of meta-analyses) flowchart in Figure 4 summarises the exclusion of studies. A total of 511 non-duplicate references were identified by the search, of which 161 were reviewed for safety data, and eight were included in the effectiveness review.

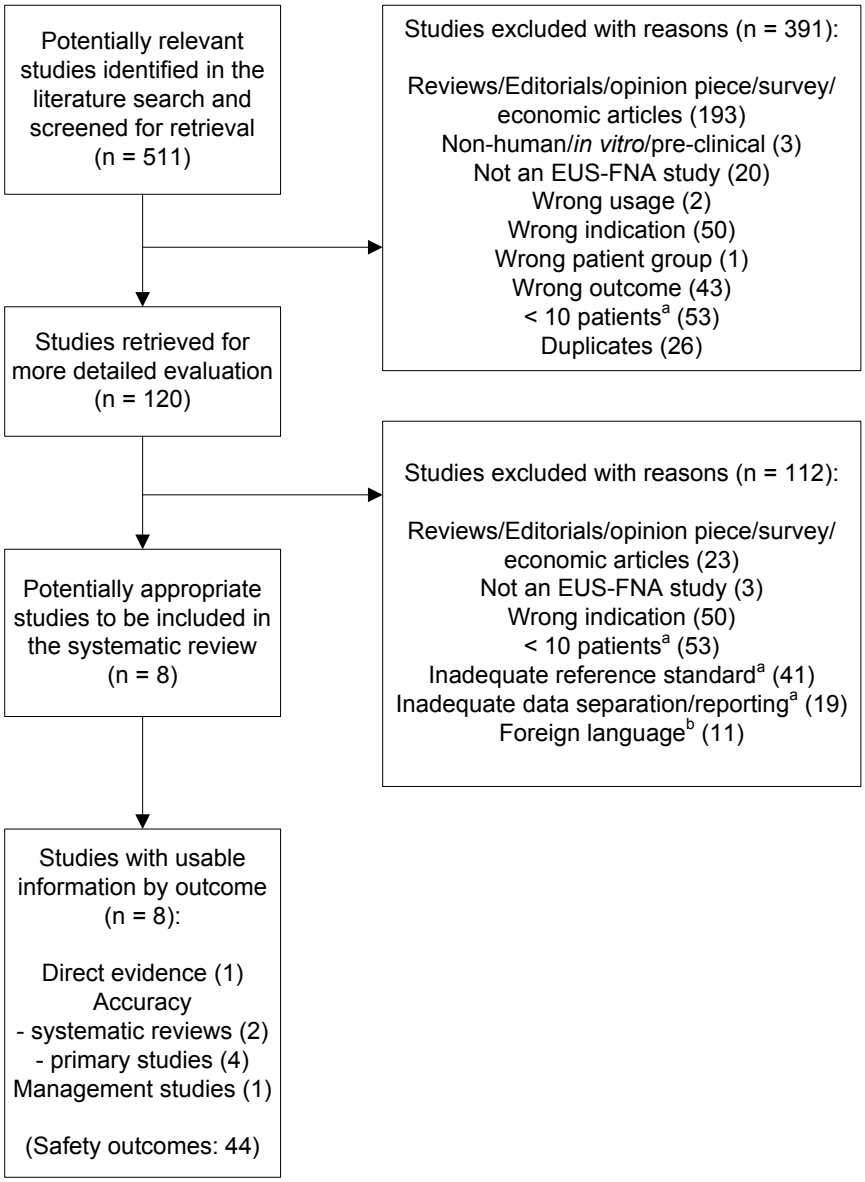

Figure 4 QUOROM flowchart used to identify and select studies for the literature review of EUS-FNA

[a] These studies were reviewed for the assessment of safety

[b] Due to time limitations, these studies were not reviewed

Adapted from Moher et al (1999)

Data extraction

Data extraction was performed with the aid of a *pro forma* based on the following key parameters: trial characteristics, study population characteristics, tests used and outcomes reported. This follows the procedure for the collection of data outlined in the *Cochrane Reviewers' Handbook* (Higgins et al 2005).

Statistical methods

Methodological considerations

Direct evidence of the value of EUS-FNA relative to current clinical practice, when used in the relevant patient group, was required to justify reimbursement under Medicare. This ideally should be in the form of studies reporting effects on patient-centred health outcomes. Alternatively, evidence of greater diagnostic accuracy than the comparator, with linked evidence indicating change in management and treatment will affect health outcomes is required.

In circumstances where an additional diagnostic test is to be used in the clinical pathway, confirmation of an effect on management change is a key component of the evidence base. The most appropriate design for investigation of effects on management change is a pre-test, post-test case series study. Where a pre-test management plan is not reported, the study outcomes do not truly represent change in patient management, and thus, outcomes are likely to be biased.

The ideal design for a study of the 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).

Diagnostic performance

The evaluation of the accuracy of a new diagnostic test involves comparing the new test with its comparators and the 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 assess sensitivity, specificity, accuracy, diagnostic odds ratio and likelihood ratios.

Sensitivity is defined as the proportion of all patients with a specified condition whose results are positive. Specificity is the proportion of all patients, who do not have the specified condition, who test negative. Test accuracy is represented by the proportion of patients whom the test correctly identified as positive or negative. The diagnostic odds ratio (DOR) is an expression of the odds of positive test results occurring in patients with the specified condition, compared with those who do not have the condition. A DOR of 100 provides convincing evidence of the test's ability to discriminate between the presence or absence of the condition.

The likelihood ratio of a positive test is the probability that a positive result will be found in a person with, as opposed to without, the condition. The likelihood ratio of a negative test is the probability that a negative result will be found in a person with, as opposed to

without, the condition. A positive ratio of >10 and a negative ratio of <0.1 provide convincing diagnostic evidence. A positive likelihood ratio of >5 and a negative likelihood ratio of <0.2 provide strong diagnostic evidence (Medical Services Advisory Committee 2005). Bayes' theorem indicates that the post-test odds of a condition are equal to the pre-test odds of the condition multiplied by the likelihood ratio. The post-test probability of a condition can be determined for any given pre-test probability using this approach.

Statistical methods

All confidence intervals (CI) calculated to assess safety and diagnostic accuracy outcomes were exact binomial CIs. Calculating a CI around proportions (particularly sensitivity and specificity) is usually performed using a normal approximation for a binomial distribution. This analytic approach is not appropriate when proportions are too close to 0 or 1, or when sample sizes are too small. This was the case in this assessment, and therefore, exact binomial CIs were used.

Appraisal of the evidence

Appraisal of the evidence was conducted at three stages.

Stage 1: Appraisal of the applicability and quality of individual studies included in the review.

Stage 2: Appraisal of the precision, size and clinical importance of the primary outcomes used to determine the safety and effectiveness of the test.

Stage 3: Integration of this evidence in order to draw conclusions about the net clinical benefit of the index test in the context of Australian clinical practice.

Appraisal of the quality and applicability of individual studies

The quality and applicability of the included studies was assessed according to pre-specified criteria according to the study design (**Appendix E**).

Ranking the evidence

Studies evaluating the direct impact of the test or treatment on patient outcomes were ranked according to the study design using the levels of evidence designated by the National Health and Medical Research Council (NHMRC) (Table 7).

Table 7 NHMRC levels of evidence for studies of effectiveness

Level of evidence	Study design
I	Evidence obtained from a systematic review of level II studies
II	Evidence obtained from properly designed randomised controlled trials
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies with concurrent controls: non-randomised experimental trials, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies without concurrent controls: historical control studies, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test outcomes

Source: NHMRC 2005

Studies of diagnostic accuracy were ranked according to the NHMRC levels of evidence for diagnoses (Table 8).

Table 8 NHMRC levels of evidence for diagnosis

Level of evidence	Study design
I	Evidence obtained from a systematic review of level II studies
II	Evidence obtained from studies of test accuracy with: an independent blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation
III-1	Evidence obtained from studies of test accuracy with: an independent blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation
III-2	Evidence obtained from studies of test accuracy with: a comparison with reference standard that does not meet the criteria required for level II or III-1 evidence
III-3	Evidence obtained from diagnostic case-control studies
IV	Evidence obtained from studies of diagnostic yield (no reference standard)

Source: NHMRC 2005

Studies were also graded according to the pre-specified quality and applicability criteria (Table 9).

Table 9 Grading system used to rank included studies

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 and to avoid bias? High quality = no potential for bias based on pre-defined key quality criteria Medium quality = some potential for bias in areas other than those pre-specified as key criteria Poor quality = poor reference standard and/or potential for bias based on key pre-specified criteria	Q1 high quality Q2 medium quality Q3 poor reference standard poor quality or insufficient information

Expert advice

An advisory panel with expertise in medical and radiation oncology, thoracic medicine, thoracic surgery, gastroenterology/endoscopy and consumer affairs was established to evaluate the evidence and provide advice to MSAC from a 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**.

Results of assessment

Summary

When used for the diagnosis and/or staging of lung cancer and mediastinal lesions endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) appears to be associated with a low risk of serious adverse events (0.12%; 95% CI: [0.01, 0.44]). A small number of mild adverse events such as sore throat, pain, nausea and vomiting are associated with EUS-FNA, but a degree of uncertainty exists about their incidence.

A randomised controlled trial (RCT), Larsen et al (2005), provided direct evidence about use of EUS-FNA in non-small cell lung cancer (NSCLC) pre-treatment staging. This trial suggested that introducting routine EUS-FNA would reduce numbers of futile thoracotomies, and avoid unnecessary surgeries. The direct evidence however had only limited applicability to the current review because of study design and patient population issues.

A linked evidence approach was used to evaluate the use of EUS-FNA in NSCLC staging and diagnosing mediastinal masses of unknown origin.

A medium quality (Annema et al 2005) and three low quality comparative and non-comparative diagnostic accuracy studies (Larsen et al 2005b; Eloubeidi et al 2005; and Larsen et al 2002) were identified in the literature search. The best available evidence indicated that EUS-FNA may be more sensitive 75.9% (95% CI: [56.5, 89.7]) than mediastinoscopy 65.5% (95% CI: [45.7, 82.1]) and slightly less specific 96.9% (95% CI: [89.2, 99.6]) than mediastinoscopy 100% (95% CI: [94.4, 100.0]) in identifying advanced disease as part of pre-treatment staging of NSCLC. It was noteworthy that a large degree of overlap exists between the 95% confidence intervals for sensitivity and specificity between the technologies.

A low quality non-comparative study assessing the diagnostic accuracy of EUS-FNA in the diagnosis of mediastinal masses was identified (Larsen et al 2002). Study outcomes for this indication showed that EUS-FNA was a sensitive (92.3%) and specific (100%) diagnostic test.

A patient management study presenting the impact of EUS-FNA testing in a mixed mediastinal mass/lung cancer population was also identified (Chong et al 2005). Results suggested that EUS-FNA can impact patient management, primarily by avoiding surgery (42%) or further invasive investigations, such as mediastinoscopy (16%).

Treatment effectiveness was not examined for NSCLC staging because EUS-FNA's primary purpose is to improve patient management; therefore, evidence indicating the treatment's effectiveness is not required as part of the scope of this assessment report.

Treatment effectiveness was not examined for diagnosis of mediastinal masses of unknown origin because there was insufficient evidence relating to diagnostic accuracy and change in patient management.

Is it safe?

The safety of endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) in diagnosis and/or staging of lung cancer and mediastinal lesions was assessed by reviewing studies identified and retrieved from the literature search outlined in Figure 4 for reported adverse events (Table 10). A total of 161 relevant studies were reviewed for safety; of these, 44 (28%) reported on the safety of EUS-FNA in assessment of lung cancer and mediastinal lesions. It is likely that a number of these studies present overlapping patient cohorts. Consequently, where studies from the same research centre were found to have overlapping recruitment periods, only the most complete study was used in the safety analysis (35 studies).

Of the studies reviewed, 3.52 per cent (95% CI: [2.68, 4.52]) of patients experienced adverse events. The number of patients experiencing adverse events is potentially underestimated. It is possible that overlapping patient cohorts between studies involving the same research centres were included in the current assessment of safety. This would artificially inflate the number of patients who were included in EUS-FNA safety assessments. Accurate assessment was not possible because of inadequate recruitment periods reporting.

There have been two serious adverse events—mediastinitis and suppurative infection—reported in association with use of EUS-FNA for diagnosis and/or staging of lung cancer and mediastinal lesions. The most frequently reported adverse events associated with EUS-FNA were sore throat (35/1649), and pain (11/1649). Small proportions of patients experienced nausea and vomiting (n = 4; 0.24%), and limited ('small' in the literature) haemorrhages (n = 2; 0.12%). There was one event each of stridor, cough, hypotension and fever. It is noteworthy that most adverse events presented in the safety analysis originated from a single small study (Emery et al 2004).

Adverse events associated with mediastinoscopy are not presented, due to the limited and skewed patient population who underwent mediastinoscopies in the EUS-FNA studies.

Table 10 Reported adverse events associated with EUS-FNA performed for diagnosis and/or staging of lung cancers and mediastinal lesions

	EUS-FNA		
	n/1649	Percentage	95% CI
Total events	58[a]	3.52	2.68, 4.52
Mediastinitis	1	0.06	0.002, 0.34
Suppurative infection	1	0.06	0.002, 0.34
Stridor	1	0.06	0.002, 0.34
Cough	1	0.06	0.002, 0.34
Sore throat	35	2.12	1.48, 2.94
Nausea and vomiting	4	0.24	0.07, 0.62
Pain	11	0.67	0.33, 1.19
'Small' haemorrhage	2	0.12	0.01, 0.44
Hypotension	1	0.06	0.002, 0.34
Fever	1	0.06	0.002, 0.34

Abbreviations: CI, confidence interval; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration
[a] This is potentially an overestimate as it is unclear whether individual patients may have experienced multiple adverse events due to inadequate reporting of some studies

Use of EUS-FNA for staging and/or diagnosis of lung cancer and mediastinal lesions appeared to be associated with a low risk of serious adverse events.

Is it effective?

Direct evidence

Does it improve health outcomes?

A randomised controlled trial (RCT) by Larsen et al (2005) provides direct evidence concerning the impact of EUS-FNA on non-small cell lung cancer (NSCLC) staging (Table 11). This study was classified as level II evidence according to the NHMRC levels of evidence for studies of effectiveness (Table 7). The aim of this study was to determine the value of routine EUS-FNA compared with current clinical practice. The trial primarily focused on management outcomes and reported disease recurrence as a health outcome.

This study enrolled patients with suspected or recently diagnosed NSCLC who were candidates for invasive staging before curative surgery. Patients underwent bronchoscopy with transbronchial needle aspiration (TBNA) as a prior test; this differs from the target population of this assessment and potentially limits its applicability. Patients were randomised to either a routine EUS-FNA diagnostic arm (in addition to mediastinoscopy) or a current clinical practice diagnostic arm where staging was performed by mediastinoscopy; EUS-FNA was reserved for patients with either enlarged lymph nodes or mediastinal invasion detected by CT.

Table 11 Included study characteristics comparing routine EUS-FNA with current clinical practice for staging NSCLC

Author (year) Country	Patient characteristics (n)	Prior tests	Test characteristics	Treatment
Larsen et al (2005) Denmark	**Included**: Patients with suspected or newly diagnosed NSCLC who are candidates for invasive staging prior to curative surgery (104) **Excluded**: Patients with a poor medical condition; refusal of surgery; verified N2/3, T4 or M1 disease or small cell lung cancer; pregnancy; age <18 years	Chest CT, bronchoscopy (with TBNA), clinical evaluation, lung function tests, TTNA, PET	**EUS-FNA**: Olympus GF-UC160P-OL5 or Olympus GF-UC140P-AL5 or Pentax EG 3830 linear scanner; 22 gauge needle; all lymph nodes with ≥1 criterion of malignancy were sampled; 1–3 passes per lesion; presence of cytologist during EUS-FNA procedure was unknown **Mediastinoscopy**: Accessed stations 2/4R, 2/4L, 7	Surgical resection; surgical resection with induction chemotherapy; chemo/radiotherapy alone

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

The study by Larsen et al (2005) was assessed for study bias (Table 12). Larsen et al (2005) reported a secure randomisation method and an adequate patient follow up. The trial was open-label, and consequently, there was potential for bias in the reported outcomes. However, RCTs examining diagnostic test health outcomes must be open-label by design so the diagnostic test can affect patient management and outcomes.

Table 12 Assessment of study bias, Larsen et al (2005)

Trial	Randomisation	Blinding	Patient follow up
Larsen et al (2005)	Randomisation was performed using computer-generated random assignment	Patients and physicians were not blinded	104 patients were randomised. 53 patients to the routine EUS-FNA group and 51 patients to current clinical practice All patients were included in the analysis

Abbreviations: EUS-FNA, endoscopic ultrasound guided fine-needle aspiration

The primary outcome of this study was avoidance of futile thoracotomies (Table 13). Futile thoracotomy was defined as either explorative (open and close) or disease recurrence/death after a potentially curative thoracotomy. There was a significant difference in futile thoracotomies between routine EUS-FNA (9%) and current clinical practice (25%). No significant difference was detected in the number of explorative thoracotomies (2% vs 10%) or the number of patients experiencing disease recurrence/death (8% vs 16%) when subgroups of futile thoracotomies were examined.

Table 13 Study outcomes, Larsen et al (2005)

Trial	Outcomes	Routine EUS-FNA[a] n (%)	Current clinical practice[b] n (%)	*p* value
Larsen et al (2005)	Futile thoracotomies	5 (9)	13 (25)	0.03
	Explorative thoracotomies	1 (2)	5 (10)	0.11
	Disease recurrence/death	4 (8)[c]	8 (16)[d]	0.17

Abbreviation: EUS-FNA, endoscopic ultrasound guided fine-needle aspiration
[a] 50 patients received EUS-FNA and 49 patients received mediastinoscopy
[b] 14 patients received EUS-FNA and 46 patients received mediastinoscopy
[c] The median follow up time in this group was 1.3 years (range 0.2–2.4 years)
[d] The median follow up time in this group was 1.4 years (range 0.2–2.4 years)

The current clinical practice diagnostic arm in this study differs from the current clinical practice in Australia (some patients were assessed using EUS-FNA). Inclusion of patients examined using EUS-FNA in this arm potentially reduces applicability of these results. EUS-FNA was used in the management of 27 per cent (n = 14) of patients in the current clinical practice group; it is likely that the difference in futile thoracotomies was underestimated. It is also noteworthy that EUS-FNA was used in the current clinical practice group for patients with either enlarged lymph nodes or mediastinal invasion detected by CT. The differences in futile thoracotomies between the groups reflect differences in the management of patients with negative CT scans, because all patients with whose CT scans were positive had the same diagnostic work up regardless of the diagnostic arm to which they were assigned.

Larsen et al (2005) suggested that introducing routine EUS-FNA could reduce the number of futile thoracotomies. This study did not show a significant difference in the number of patients whose disease recurred. The results of this study had limited applicability to the target population.

Linked evidence

A linked evidence approach was undertaken to verify the diagnostic accuracy of EUS-FNA and its affect on patient management. This approach was necessary because available direct evidence focused primarily on management outcomes and was limited in applicability to NSCLC patient groups. This study was unable to address the potential affects of false positive staging results using EUS-FNA because patient survival was not assessed.

The appropriate reference standards for this assessment are histopathology, surgical staging and long-term clinical follow up (Table 5 and Table 6). Many studies retrieved for this review used cytology results obtained from EUS-FNA sampling as the reference standard. This issue was identified by Detterbeck et al (2003) who concluded that no conclusion could be made about EUS-FNA specificity without using another appropriate confirmatory procedure in NSCLC pre-treatment staging. EUS-FNA cytology results was considered to be an unsatisfactory reference standard for this review.

Identified studies

The literature search identified six diagnostic accuracy studies eligible for review: two were systematic reviews (Kramer and Groen 2003; Toloza et al 2003) and four were primary studies (Annema et al 2005; Larsen et al 2005b; Eloubeidi et al 2005; Larsen et al 2002). A patient management study (Chong et al 2005) was also identified.

Diagnostic accuracy studies

Systematic reviews

The systematic review by Kramer and Groen (2003) (Table 14) evaluated the diagnostic accuracy of several invasive and non-invasive techniques for NSCLC staging. Application of NHMRC quality criteria (NHMRC guidelines, **Appendix E**) indicated that this review was classified as low quality: limited details were reported for the search strategy; inclusion/exclusion criteria were not specified; validity assessment of included trials was lacking; and heterogeneity was neither reported nor explored. Summary measures of results and estimates of precision were not reported. It was not possible to assess the validity of this systematic review because characteristics of included patient populations were reported inadequately.

The authors of this systematic review included instances of both meta-analyses and primary studies where pathology results for lymph nodes were verified surgically. It was not reported whether lymph node pathology results were verified for all patients regardless of test results. The authors also reported that many outcomes were supported by clinical, rather than surgical follow up. This suggests that some patients' lymph node diagnoses were not verified surgically. It was not clear whether this systematic review included studies that used appropriate reference standards.

The results of this systematic review are summarised in Table 15. The authors concluded that EUS-FNA had the potential to facilitate mediastinal tissue sampling more accurately than TBNA, TTNA or mediastinoscopy, with fewer complications and lower costs.

It is evident from the data presented in Table 15 that there is extensive heterogeneity in the measures of diagnostic performance for EUS-FNA and the other NSCLC staging modalities. However, sources of heterogeneity were not systematically examined in this review. Considered with the lack of summary measures for diagnostic performance, the absence of a robust analysis for sources of heterogeneity means that the comparative performance of EUS-FNA and other NSCLC staging modalities cannot be assessed.

The systematic review by Toloza et al (2003) (Table 14) evaluated the diagnostic accuracy of a number of invasive techniques in the staging of NSCLC. Application of NHMRC quality criteria (NHMRC guidelines, **Appendix E**) indicated that this review was classified as low quality: a lack of validity assessment of included trials, heterogeneity was neither reported nor explored and the presented results differed from the stated objective of the systematic review. The validity of the systematic review was also reduced as the results were presented for lung cancer, not NSCLC specifically.

The systematic review by Toloza et al (2003) included studies on the basis of a reference standard consisting of histological confirmation or long-term clinical follow up (greater than one year). No distinction was made between fine-needle aspiration (which obtains a cytology sample) and needle biopsy (which obtains a histology sample). Further examination of the endoscopic ultrasound guided needle aspiration (EUS-NA) studies identified found that this inclusion criterion was applied only to results that were determined negative by the index test. Errors in data extraction, with potential to affect the meta-analysis conclusion, were detected.

Toloza et al (2003) presented a meta-analysis of the diagnostic accuracy of EUS-NA, transbronchial needle aspiration (TBNA), transthoracic needle aspiration (TTNA) and mediastinoscopy (Table 15). This review reported similar diagnostic performance among the technologies, and acknowledged that comparative evidence was required to identify the most appropriate technology for lung cancer staging.

Table 14 Characteristics systematic reviews assessing the diagnostic accuracy of EUS-FNA

Systematic review	Objective	Search strategy (included studies)	Inclusion/exclusion criteria	Methodology	Comment[a]
Kramer and Groen (2003)	To review the test performance characteristics of concepts in the mediastinal staging of NSCLC, evaluating traditional and modern staging modalities	A brief search strategy was described using PubMed, SUMSearch and reference lists of identified studies. The time period covered by the literature search was not reported. Search terms included: lung cancer staging; computed tomography; magnetic resonance; positron emission; mediastin*; thoracoscop*; thoracotom*; endoscop*; bronchoscop*; ultraso*; biopsy* and punct* (n = 49)	No inclusion or exclusion criteria were pre-specified.	No description of how the literature search and data analysis were performed Results presented for studies where lymph nodes were surgically verified Results of included studies were individually summarised Variation in individual study results was not investigated An assessment of the quality of included studies was not undertaken Sources of heterogeneity were not investigated Summary results were not reported	Low quality —Limited details reported for search strategy and inclusion/exclusion criteria. —No quality assessment was reported —Heterogeneity not investigated —Reference standards used in included studies not clearly reported Validity: —Inadequate reporting – not possible to assess included patient populations
Toloza (2003)	To determine the test performance characteristics of TBNA, TTNA, EUS-NA and mediastinoscopy in staging NSCLC	A brief search strategy was described using Medline, Healthstar, Cochrane library, reference lists and grey literature Literature search was completed in 2001 Search terms included: lung neoplasm, bronchial neoplasm, mediastinoscopy, neoplasm staging, neoplasm metastasis, lymphatic metastasis, biopsy, needle biopsy, CT, mediastinum radiography, emission–CT and sensitivity, specificity (n = 38)	Studies with the following characteristics were included: published in a peer reviewed journal, study size >20 patients[b], patient groups not included in subsequent study, confirmation of biopsy results by histology or long-term clinical follow up (>1 year), availability of data to re-calculate diagnostic accuracy measures Articles in English were included	The literature search and data extraction were completed by two independent reviewers Results of included studies were individually summarised An assessment of the quality of included studies was not undertaken Sources of heterogeneity were not explored Results presented were for lung cancer (NSCLC + SCLC) Results were presented as pooled diagnostic accuracy measures (variance measured by range or 95% CI)	Low quality —No quality assessment was reported —Objective did not correspond with presented results —Heterogeneity not reported Limited validity —Summary results are presented for lung cancer (NSCLC + SCLC)

Abbreviations: CI, confidence interval; CT, computed tomography; EUS-NA, endoscopic ultrasound guided needle aspiration; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; TBNA, transbronchial needle aspiration; TTNA, transthoracic needle aspiration

[a] Quality determined after applying the quality criteria in Appendix E

[b] Studies examining mediastinoscopy were required to have > 50 patients

Table 15 Results of systematic reviews assessing the diagnostic accuracy of EUS-FNA and other NSCLC staging modalities

Trial	Summary of results
Kramer and Groen (2003)	Diagnostic accuracy of EUS-FNA for the staging of NSCLC: Sensitivity–range = 54 to 97% Specificity–range = 71 to 100% PPV–range = 64 to 100% NPV–range = 64 to 95% Diagnostic accuracy of TBNA for the staging of NSCLC: Sensitivity–range = 36 to 74% Specificity–range = 92 to 100% PPV–range = NR NPV–range = NR Diagnostic accuracy of TTNA for the staging of NSCLC: Sensitivity = 98% Specificity = 100% PPV–NR NPV–NR Diagnostic accuracy of mediastinoscopy for the staging of NSCLC: Sensitivity–range = 44 to 92% Specificity[a]–range = 100% PPV[a]–range = 100% NPV–range = 62 to 93% Diagnostic accuracy of extended cervical mediastinoscopy for the staging of NSCLC: Sensitivity–range = 69 to 81% Accuracy–range = 91 to 94% Specificity–NR PPV–NR NPV–range = 89 to 91% Diagnostic accuracy of CT for the staging of NSCLC: Sensitivity–range = 33 to 83% Specificity–range = 66 to 90% PPV–range = 46 to 71% NPV–range = 68 to 86% Diagnostic accuracy of PET for the staging of NSCLC: Sensitivity–range = 71 to 91% Specificity–range = 67 to 94% PPV–range = 67 to 90% NPV–range = 77 to 97% Diagnostic accuracy of MRI for the staging of NSCLC: Sensitivity–range = 64 to 71% Specificity–range = 48 to 91% PPV–NR NPV–NR

Trial	Summary of results
Toloza (2003)	Diagnostic accuracy of EUS-NA for the staging of lung cancer:
	Sensitivity 88% (95% CI: [82, 93])
	Specificity 91% (95% CI: [77, 97])
	PPV 98% (range: 96–100%)
	NPV 77% (range: 68–100%)
	Diagnostic accuracy of TBNA for the staging of lung cancer:
	Sensitivity 76% (95% CI: [72, 79])
	Specificity 96% (95% CI: [91, 100])
	PPV 100%
	NPV 71% (range: 36–100%)
	Diagnostic accuracy of TTNA for the staging of lung cancer:
	Sensitivity 91% (95% CI: [74, 97])
	Specificity 100%
	PPV 100%
	NPV 78% (range: 42–100%)
	Diagnostic accuracy of mediastinoscopy for lung cancer staging:
	Sensitivity 81% (95% CI: [76, 85])
	Specificity 100%
	PPV 100%
	NPV 91% (range: 58–97%)

Abbreviations: CI, confidence interval; CT, computed tomography; EUS-NA, endoscopic ultrasound guided needle aspiration; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration; MRI, magnetic resonance imaging; NPV, negative predictive value; NR, not reported; PET, positron emission tomography; PPV, positive predictive value; TBNA, transbronchial needle aspiration; TTNA, transthoracic needle aspiration

[a] Range not reported as values were the same in all studies

Primary studies

Review of the literature identified four primary studies that examined the diagnostic accuracy of EUS-FNA: Annema et al 2005, Larsen et al 2005b, Eloubeidi et al 2005, and Larsen et al 2002. Diagnostic accuracy was examined separately in patients with presumed or known non-small cell lung cancer (NSCLC) and in patients with mediastinal mass of unknown origin.

Non-small cell lung cancer

Diagnostic accuracy of EUS-FNA in the pre-treatment staging of NSCLC was examined in four studies identified in the literature review: two compared EUS-FNA with mediastinoscopy (Annema et al 2005; Larsen et al 2005b). The other two studies (Eloubeidi et al 2005; Larsen et al 2002) were non-comparative, and are presented in **Appendix C** as supportive evidence. The characteristics of the comparative studies are presented in Table 16. These studies were classified as level III-2 evidence according to the NHMRC levels of evidence for diagnostic tests (Table 8). However, there were differences in the quality and applicability of these studies that were not accounted for in the NHMRC levels of evidence.

Neither of the studies enrolled patients on a consecutive basis and only the study by Annema et al (2005) reported blinding of the treating physician and patient to the EUS-FNA results. The study by Larsen et al (2005b) is of limited applicability to the target population. This study included TBNA and TTNA as prior tests, and this differs from the research question as outlined in Table 2.

Both studies clearly described the index test, reference standard and comparator. The study by Larsen et al (2005b) reported patients with an inconclusive final diagnosis (3.3%); however, these patients' data were not used to calculate the diagnostic accuracy of EUS-FNA. Annema et al (2005) were the only study that reported an onsite cytopathologist evaluating the adequacy of EUS-FNA sample. This was also the only study that reported surgical confirmation of all patients after undergoing EUS-FNA.

It is possible that the reference standards used in these studies may have affected the reported diagnostic accuracy of EUS-FNA for NSCLC staging. The diagnostic accuracy of EUS-FNA and mediastinoscopy, its comparator in the Annema et al (2005) study, may have been affected by both verification and incorporation bias. Positive mediastinoscopy results were treated as a final diagnosis and were not verified by thoracotomy. This may have overestimated the diagnostic accuracy of mediastinoscopy. The other trial by Larsen et al (2005b) confirmed positive EUS-FNA results with long-term clinical follow up (greater than one year), and confirmed negative EUS-FNA results with surgery. Long-term clinical follow up was regarded as an adequate reference standard in this review. It is of concern that this reference standard may not have been sufficiently sensitive to detecting false positive results in patients with early stage disease.

It was not appropriate to combine results in a meta-analysis due to differences in study characteristics.

Table 16 Characteristics of the included comparative studies assessing the diagnostic accuracy of EUS-FNA in NSCLC pre-treatment staging

Author (year) Country	Study design	Patient characteristics (n)	Test characteristics	Study quality
Annema (2005) Netherlands	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard 2000–2003	Patients with proven NSCLC without signs of distant metastases after conventional staging and are candidates for surgical resection **Exclusion**: Patients with inadequate (n = 4) or cancelled (n = 1) mediastinoscopies or lack of surgical verification (n = 2) or physician changing therapeutic strategy (n = 1) **Prior tests**: CT (n = 100)	**Index test**: Pentax FG 34 UX linear scanner; 22G needle; unclear selection of lymph nodes for sampling; median 3 needle passes (sampled nodes only); onsite cytopathologist; accessed stations 3, 4L, 5, 7, 8, 9 **Comparator**: Cervical mediastinoscopy; experienced pathologist; accessed stations 2L, 2R, 4L, 4R, 7 **Reference standard**: Thoracotomy (n = 80); Mediastinoscopy (n = 20)	C1, P1, Q2 *Quality*: Medium Non-consecutive patient enrolment *Applicability*: Applicable
Larsen (2005b) Denmark	Prospective, non-consecutive patient enrolment November 2001–February 2004	Patients with suspected or newly diagnosed NSCLC who after prior tests are candidates for invasive staging prior to curative surgery **Exclusion**: Poor medical condition; refusal of surgery; verified N2/3, T4 or M1 disease or small cell lung cancer; pregnancy; age <18 years **Prior tests**: Chest CT, bronchoscopy (with TBNA), clinical evaluation, lung function tests, TTNA, PET (n = 60)	**Index test**: Olympus GF-UC160P-OL5 or Olympus GF-UC140P-AL5 or Pentax EG 3830 linear scanner; 22G needle; all lymph nodes with ≥1 criterion of malignancy were sampled; 1–3 passes per lesion; cytologist unknown **Comparator**: Cervical mediastinoscopy; experienced pathologist; accessed stations 2R, 2L, 4R, 4L, 7 **Reference standard**: Thoracotomy (29); EUS-FNA+ long-term clinical follow up (29); inconclusive (2)	C1, P2, Q3 *Quality*: Low Non-consecutive patient enrolment Unblinded *Applicability*: limited Enrolled patients with a previous TBNA or TTNA

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

In the pre-treatment staging of NSCLC, the comparative study by Annema et al (2005) found that EUS-FNA may be more sensitive–75.9 per cent (95% CI: [56.5, 89.7]) versus mediastinoscopy 65.5 per cent (95% CI: [45.7, 82.1]) and slightly less specific 96.9 per cent (95% CI: [89.2, 99.6]) versus mediastinoscopy 100 per cent (95% CI: [94.4, 100.0]) in identifying advanced disease. This conclusion should be considered carefully due to the large degree of overlap in the 95 per cent confidence intervals for both EUS-FNA and mediastinoscopy in regards to sensitivity and specificity. In addition, the population included in this study is not large (n = 100).

The authors of this study concluded that reduction in specificity of EUS-FNA was due to two false positive samples which were caused by misinterpretation of EUS images that in turn led to the accidental sampling of the primary tumour instead of a mediastinal node.

The diagnostic accuracy of both EUS-FNA and mediastinoscopy decreased when nodes were included that were not accessible by both techniques (nodal stations 2L, 2R, 4R, 5, 8, 9). However, sensitivity differences between the tests remain similar (61.1% vs 52.8%).

Table 17 Accuracy of the EUS-FNA compared with mediastinoscopy in NSCLC pre-treatment staging (Annema et al 2005)

Author (year)	Prevalence	Sensitivity (95% CI)		Specificity (95% CI)		Accuracy (95% CI)	
	n/N (%)	EUS-FNA	Med	EUS-FNA	Med	EUS-FNA	Med
Annema (2005)	29/93 (31.2)[a,b]	75.9 (56.5, 89.7)	65.5 (45.7, 82.1)	96.9 (89.2, 99.6)	100.0 (94.4-100.0)	90.3 (82.4–95.5)	89.2 (81.1–94.7)

Abbreviations: CI, confidence interval; EUS-FNA, endoscopic ultrasound guided fine-needle biopsy; Med, mediastinoscopy
[a] Prevalence of late-stage NSCLC
[b] EUS-FNA failed to obtain representative material in eight per cent of included patients: these patients were not included in the analysis of staging accuracy

Data from this applicable medium quality study suggest that EUS-FNA offers a reasonable increase in sensitivity with a small decrease in specificity compared with mediastinoscopy in the pre-treatment staging of NSCLC.

The study by Larsen et al (2005b) was part of the Larsen et al (2005) randomised controlled trial. EUS-FNA was compared with mediastinoscopy in patients who had prior TBNA/TTNA diagnostic tests as part of the trial. EUS-FNA was associated with a considerable increase in overall diagnostic accuracy when compared with mediastinoscopy (EUS-FNA 93.1%, 95% [CI: 83.3, 98.1] vs mediastinoscopy 56.9%, 95% [CI: 43.2, 69.8]) for the assessment of paratracheal and subcarinal lymph nodes (Table 18) in this study. The difference in the overall diagnostic accuracy between the techniques assessed in this study can be explained by the difference in sensitivity (EUS-FNA 87.1%, 95% [CI: 70.2, 96.4] vs mediastinoscopy 19.4%, 95% [CI: 7.5, 37.5]), as 100 per cent specificity was reported for both techniques.

The diagnostic accuracy of both techniques may have been affected by the use of long-term clinical follow up as the reference standard for patients who tested positive by EUS-FNA and/or mediastinoscopy. This has the potential to overestimate the specificity of these techniques.

The prior tests used to select the patient group may also have affected the diagnostic accuracy of both techniques. In this study all patients were evaluated using TBNA and TTNA. The protocols used in the diagnosis of these patients are outside the target

population of this assessment report; hence, the applicability of the diagnostic accuracy results is limited. The authors of this study stated that the earlier TBNA/TTNA diagnostic tests may have skewed the data against mediastinoscopy.

Table 18 Accuracy of EUS-FNA compared with mediastinoscopy in NSCLC pre-treatment staging (Larsen et al 2005b)

Author (year)	Prevalence n/N (%)	Sensitivity (95% CI)		Specificity (95% CI)		Accuracy (95% CI)	
		EUS-FNA	Med	EUS-FNA	Med	EUS-FNA	Med
Larsen (2005b)	31/58 (53.5)[a,b]	87.1 (70.2, 96.4)	19.4 (7.5, 37.5)	100.0 (87.2, 100.0)	100.0 (87.2, 100.0	93.1 (83.3–98.1)	56.9 (43.2–69.8)

Abbreviations: EUS-FNA, endoscopic ultrasound guided fine-needle biopsy; Med, mediastinoscopy
[a] Prevalence of late-stage NSCLC
[b] Patients with inconclusive final diagnosis were not evaluated in the assessment of diagnostic accuracy

The data from this limited applicability, low quality study suggest that EUS-FNA offers a major increase in sensitivity compared with use of mediastinoscopy in NSCLC pre-treatment staging. This result should be interpreted with caution due to concerns regarding the prior tests and reference standard.

Two comparative studies of EUS-FNA and mediastinoscopy were identified in this review; the sensitivity and overall diagnostic accuracy varied considerably between these studies and appeared to be affected by the choice of prior tests and reference standard. Of these two studies, the better quality applicable study appeared to indicate that EUS-FNA may be more sensitive but slightly less specific than mediastinoscopy. This conclusion should be interpreted in light of the large overlap in the sensitivity and specificity confidence intervals between the two staging procedures.

Mediastinal mass of unknown origin

Larsen et al (2002) examined the diagnostic accuracy of EUS-FNA in diagnosing mediastinal masses of unknown origin as well as NSCLC pre-treatment staging. This study was classified as level III-2 evidence according to the NHMRC levels of evidence for diagnostic tests (Table 8). The diagnostic accuracy of EUS-FNA for mediastinal masses only is reported in this section of the assessment report. Study characteristics are presented in Table 19.

Larsen et al (2002) recruited patients who had mediastinal lesions or enlarged lymph nodes detected by CT. Patients were enrolled on a non-consecutive basis and physicians and patients were not blinded to the EUS-FNA results. It was reported that some patients had an inconclusive final diagnosis but none were in the mediastinal mass/lymphadenopathy patient group.

The study clearly described the index test, reference standard and comparator. With all tests considered suitable for the diagnosis of mediastinal masses of unknown origin.

Table 19 Characteristics of the included study assessing the diagnostic accuracy of EUS-FNA in the diagnosis of mediastinal masses of unknown origin

Author (year) Country	Study design	Patient characteristics (n)	Test characteristics	Study quality
Larsen et al (2002) Denmark	Non-consecutive patient enrolment April 1993–December 1999	Patients with an established diagnosis of lung cancer and mediastinal invasion and/or enlarged lymph nodes by CT, or patients with a mediastinal solid lesion or enlarged lymph nodes of unknown origin as detected by CT **Prior tests**: CT (n = 84)	**Index test**: Pentax FG-32UA or Pentax FG-34UA or Pentax FG-36UA linear scanner; 22G needle; unclear selection of lymph nodes for sampling; 1–3 passes per lesions; cytopathologist unknown **Reference standard**: Thoracotomy (19); Mediastinoscopy (1); EUS-FNA + long-term clinical follow up (59); inconclusive (5)	CX, P1, Q3 *Quality*: Low Non-consecutive patient enrolment Unblinded *Applicability*: Applicable

Abbreviations: CT, computed tomography; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration

Larsen et al (2002) assessed the non-comparative value of EUS-FNA in the diagnosis of mediastinal masses (Table 20). This study reported EUS-FNA diagnostic accuracy of 94.0 per cent (95% CI: [83.5, 98.7]), 92.3 per cent (95% [CI: 79.1, 98.4]) sensitivity and 100 per cent (95% CI: [71.5, 100]) specificity.

Table 20 Accuracy of the EUS-FNA in the diagnosis of mediastinal masses of unknown origin

Author (year)	Prevalence n/N (%)	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
Larsen et al (2002)	39/50 (78.0)	92.3 (79.1, 98.4)	100.0 (71.5, 100)	94.0 (83.5, 98.7)

Data from this applicable, low quality study suggest that EUS-FNA is a sensitive and specific diagnostic test for the diagnosis of mediastinal masses of unknown origin.

Patient management

Chong et al (2005) reported the impact of EUS/EUS-FNA on patient management as determined by the use of a pre-test management plan. This prospective, Australian study aimed to determine the impact of EUS/EUS-FNA in a series of patients with mixed indications. The impact of EUS/EUS-FNA was determined by any alteration in diagnosis, subsequent patient management or requirement of additional investigations following EUS/EUS-FNA. The characteristics of this study are presented in Table 21.

Of the patients initially enrolled in the study, 70 per cent had adequately completed pre-test and post-test management plans by the referring physician. A small proportion of these patients (19.5%) underwent EUS/EUS-FNA for various mediastinal/lung indications (only one of the patients received EUS). While this patient group may reflect clinical practice, the applicability of this group to the target populations stated in the research questions may be limited. The applicability of this group could be affected by the inclusion of patients with small cell lung cancer (SCLC). This could not be accurately determined because patients' disease profiles were inadequately reported in the study. It was also possible that patients undergoing diagnosis of lung cancer without any

mediastinal mass observed were also included. This patient group was not covered by either of the target populations (Table 2 and Table 3) and could not be adequately determined from the report.

Table 21 Studies included in the assessment of the effect of EUS on patient management

Author (year) Country	Study design	Patient characteristics (n)	Test characteristics	Physicians determining management
Chong et al (2005) Australia	Prospective pre-test, post-test case series August 2002–June 2004	Patients with mixed indications[a] referred to EUS/EUS-FNA for diagnosis or staging Exclusion: Incomplete pre-test and post-test management plans (231)	Olympus GF-UM20 or Olympus GF-UM160 or Olympus GF-UC140P scanner Performed by single experienced gastroenterologist	Referring doctors: physicians (62%), surgeons (38%)

Abbreviations: EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration

[a] Mixed indications, including oesophageal (32.5%), gastric (15.2%), pancreaticobiliary (31.1%), lung/mediastinal disease (19.5%) and duodenal (1.7%)

The results of the study by Chong et al (2005) are presented in Table 22. Results were presented for all mediastinal/lung indications combined; hence, it was not possible to examine the change in management for mediastinal masses or NSCLC separately. For all mediastinal/lung indications, management was changed in 76 per cent of patients undergoing EUS/EUS-FNA. Treatment was altered from planned surgery in 42 per cent of patients. Additional invasive investigations such as mediastinoscopy were avoided for 16 per cent of patients. EUS/EUS-FNA resulted in a change of diagnosis for 4 per cent of patients and changes in staging for a further 13 per cent of patients. It was unclear how patients' revised status affected management.

Table 22 Effect of EUS/EUS-FNA on change in patient management for mediastinal/lung indications

Author (year)	Overall change n/N (%)	Surgery avoided n/N (%)	Invasive diagnostic procedure avoided n/N (%)	Change in diagnosis n/N (%)	Change in staging n/N (%)
Chong et al (2005)	34/45 (75.6)	19/45 (42.2)	7/45 (15.6)	2/45 (4.4)	6/45 (13.3)

The results of this study suggest that EUS/EUS-FNA can impact the management of patients referred for various mediastinal/lung indications. This was achieved primarily through avoiding surgeries or further invasive investigations such as mediastinoscopy. These results should be interpreted with caution due to potential differences in the study population compared with this assessment's target population.

Treatment effectiveness

Where EUS-FNA was used to stage NSCLC, the primary purpose was to improve patient management; therefore, evidence of the effectiveness of treatment are not required in terms of this assessment report.

It was assumed that new patients diagnosed with advanced disease through the use of EUS-FNA will not substantially differ in terms of treatment protocols from patients currently identified with advanced disease.

Due to the limited evidence for the diagnostic accuracy of EUS-FNA in patients with mediastinal masses of unknown origin and the diverse nature of mediastinal masses (and their diverse treatments), evidence of the effectiveness of treatment were not presented in this report.

What are the economic considerations?

Summary

Staging of NSCLC

A decision analytic model was constructed to assess the cost-effectiveness of introducing EUS-FNA in NSCLC staging when compared with mediastinoscopy.

The base case analysis demonstrated that the staging algorithm commencing with EUS-FNA was found to be cost saving when compared with mediastinoscopy. The two arms were shown to offer largely comparable outcomes in terms of patients' mean life expectancy, although a negligible difference was demonstrated slightly favouring the current algorithm over the staging algorithm beginning with EUS-FNA.

The average cost savings associated with the EUS-FNA strategy were estimated to be $2570 per patient when compared with mediastinoscopy. This would allow a large proportion of patients (up to 50%) to receive further tests following EUS-FNA without incurring any additional costs.

The base case analysis demonstrated that the EUS-FNA strategy was associated with an insignificant impact on patient life years (decreased by 0.001) compared with mediastinoscopy, suggesting an insignificant difference between the two testing strategies in their final outcomes overall.

Impacts of varying the test accuracy estimates were explored by using the 95 per cent confidence limits. These sensitivity analyses reinforced the base case finding that the two arms are largely comparable in outcome (ie the patient's likelihood for survival following invasive staging). Sensitivity analysis performed on other variables included in the current model also confirmed that the base case simulation results were robust.

Diagnosis of mediastinal mass of unknown origin

No comparative assessment of diagnostic accuracy was possible due to a lack of evidence. No formal economic evaluation was performed. Instead, a simple cost analysis was conducted, quantifying estimated cost savings associated with the use of EUS-FNA in place of other modalities.

This section examines whether the introduction of endoscopic ultrasound fine-needle aspiration (EUS-FNA) under the proposed indications represents value-for-money for the Australian healthcare system. A decision analytic model was employed to examine the cost-effectiveness of EUS-FNA in the pre-treatment staging of non-small cell lung cancer (NSCLC). A simple cost analysis was conducted for EUS-FNA in the diagnosis of mediastinal mass of unknown origin.

The available evidence suggest that the use of EUS-FNA as a first-line biopsy modality in NSCLC pre-treatment staging is likely to improve the overall sensitivity of detecting unresectable NSCLC, thereby avoiding unnecessary surgery. This was also demonstrated by Chong et al (2005). Given that surgeries such as thoracotomy are associated with fatal complication risks, this outcome may have an important impact on patient survival. Avoiding unnecessary surgery associated with the use of EUS-FNA also provides significant healthcare cost savings.

There is limited reliable clinical evidence describing specificity of the EUS-FNA test. Incomplete specificity contributes to the risk of assigning false positive results and over staging patients with earlier stage disease (ie N0/N1). These patients may consequently receive less than optimal management, compromising their survival. There are also important economic implications associated with false positive results. The potential implications of incomplete specificity on the relative cost-effectiveness of EUS-FNA are examined in this section.

The current analysis aims to perform a comprehensive and generalisable cost-effectiveness evaluation of EUS-FNA when a range of economic and health outcome implications are incorporated in the evaluation.

There is little evidence regarding the use of EUS-FNA in the diagnosis of mediastinal masses of unknown origin. Larsen et al (2002) suggest that EUS-FNA is a sensitive and specific test for the diagnosis of mediastinal masses of unknown origin. Comparative assessment of diagnostic accuracy was not possible due to the lack of evidence.

The balance of evidence may suggest that the introduction of EUS-FNA as a first-line biopsy modality is at least as accurate as other biopsy modalities in the diagnosis of mediastinal masses of unknown origin. Although there is no evidence available to make a conclusive assessment, EUS-FNA is a less invasive procedure, and is likely to be associated with better safety (Aabakken et al 1999; Kramer et al 2004). This also suggests that the quality-of-life profile of EUS-FNA is superior to other modalities. Chong et al (2005) demonstrated that the introduction of EUS-FNA in the diagnosis of mediastinal mass can result in reducing the number of unnecessary surgeries.

Given that EUS-FNA is likely to be less costly than other biopsy modalities, it could present a dominant strategy when compared with the current strategy. The current analysis performs a simple cost analysis in order to quantify the likely cost savings.

Estimated extent of financial implications

The expected extent of EUS-FNA use under the proposed indications was determined in **Section 7** of the application dossier. It was estimated that approximately 3500 patients would be eligible for EUS-FNA for either NSCLC staging or diagnosis of mediastinal masses of unknown origin. The Applicant anticipates that of those 3500 eligible, only 1,750 patients would receive EUS-FNA per year after three years of listing on the

Medicare. Based on the per-procedure cost of $2,374.55 (see Table 29), the total annual costs can be estimated to be $4.2 million each year.

The current evaluation estimated that the number of eligible population to be between 806 and 1612 cases per year for the staging of NSCLC; this number was estimated to be no higher than 650 for the diagnosis of mediastinal mass of unknown origin. Based on the per-procedure cost of $2374.55 (see Table 29), these estimates translate to the annual costs of $1.9–3.8 million for NSCLC staging and $1.5 million for mediastinal mass diagnosis. However, these costs should be interpreted with some caution due to the degree of uncertainty in the estimates of eligible populations.

The number of patients who undergo the subsidised use of EUS–FNA will be limited by the capacity to perform EUS-FNA in Australia. A previous MSAC assessment of EUS for several gastroenterological indications (Ref: MSAC 1072, 2006) showed that 11 centres were equipped to perform EUS-FNA in Australia. It was estimated that each site was able to perform 120 procedures a year (ie a total of 1320 procedures per year). This level of utilisation is associated with the total annual costs of $3.1 million.

These estimates derived based on the epidemiological data represent the national level. Depending on the setting in which the patients receive treatment, the subsidisation costs may be borne by the private sector.

The financial implications of making EUS-FNA available are likely to be lower in practice than the aforementioned estimates. This is because EUS-FNA is likely to replace other mediastinal node biopsy modalities in some patients, thereby generating cost offsets. As demonstrated in the following analysis, the use of EUS-FNA may be associated with overall cost savings. This is dependent on the extent of substitution.

In practice, the capacity allocated for the indications considered in the current assessment may compete with other indications, thereby potentially reducing the financial implications specifically related to NSCLC staging and diagnosis of mediastinal mass of unknown origin.

Published evidence on the cost-effectiveness of EUS-FNA

There is a limited body of published evidence concerning the cost-effectiveness of EUS-FNA under the indications being considered. The literature search conducted as a part of this evaluation identified four studies, and their findings are briefly described below. Aabakken et al (1999) examined the potential impact on patients' survival. No Australian studies were found.

A modelled cost analysis by Eloubeidi et al (2005) compared EUS-FNA with mediastinoscopy for NSCLC staging. Subsequent testing was not considered following indication of a positive result from the respective first-line diagnostic test. The model was based on a hypothetical cohort of NSCLC patients presenting with enlarged anterior and posterior mediastinal lymph nodes identified by using non-invasive imaging techniques. The study concluded that the use of EUS-FNA as a first-line staging modality would generate substantial cost-savings.

Kramer et al (2004) performed a prospective cost analysis of EUS-FNA in the cytological assessment of mediastinal and/or upper retroperitoneal tumours identified by positron-emission tomography (PET). Patients with suspected or pathologically

established lung cancer were included in the study (n = 81). EUS-FNA was used as the first-line modality, and subsequent mediastinoscopy and/or exploratory thoracotomy were not considered following positive EUS-FNA (indicating the presence of non-operable disease) results. The addition of EUS-FNA to the staging algorithm was demonstrated to avoid unnecessary surgical procedures for 62 per cent of patients, thereby reducing staging costs by 40 per cent.

Harewood et al (2002) performed a modelled cost-minimisation analysis of alternative staging algorithms in patients with known or suspected NSCLC in whom enlarged lymph nodes at level 7 (subcarinal) are detected on computed tomography (CT). A suite of five alternative staging algorithms was considered using one of the following techniques as the primary modality: EUS-FNA biopsy, mediastinoscopy (with biopsy), transbronchial needle aspiration (TBNA) biopsy, and CT-guided transthoracic needle aspiration biopsy, and PET. The algorithm commencing with EUS-FNA was demonstrated to be the least costly strategy.

Aabakken et al (1999) compared the cost-effectiveness of EUS-FNA with mediastinoscopy/mediastinotomy (MED) in the pre-operative staging of patients with NSCLC. All patients with negative results underwent thoracotomies (ie no subsequent minimally invasive tests). A decision analytic model was employed to perform the evaluation. Effectiveness of each staging algorithm arm was expressed in terms of life expectancy (ie life years).

The model was based on patients with verified NSCLC and pathologically enlarged mediastinal lymph nodes, defined as nodes of more than 10 mm short axis measurement, detected by CT scan. Due to the lymph node accessibility of these instruments, only patients with one or more enlarged station 5, 6, or 7 nodes were included in the model. The average cost per year of expected survival was US$1729 for the EUS strategy, and US$2411 for the MED strategy. An incremental cost-effectiveness ratio was not reported. The report did not clearly describe the effectiveness of EUS-FNA relative to MED. Both tests were assumed to be perfectly specific, while the sensitivity estimate of MED was superior to EUS-FNA. This assumption indicates that the overall effectiveness in the EUS-FNA arm was likely to have compared unfavourably with the MED arm.

Assessment of value-for-money of EUS-FNA in the staging of NSCLC

Why an economic model is required

As previously noted, there is little published evidence regarding the cost-effectiveness of EUS-FNA. A review of the literature did not identify any economic evaluations relevant to the Australian setting. Hence, it was considered appropriate and necessary to perform an economic evaluation.

A modelled evaluation was deemed necessary to fully explore the economic and health outcomes implications of listing EUS-FNA. Some elements of the overall economic and clinical implications lie outside the primary clinical trials or persist far longer than the trial duration. In particular, no survival data were collected in the pivotal trials. A modelled evaluation enables the analysis to examine potential impacts on the patient survival. It also allows the relative cost-effectiveness of alternative strategies to be expressed using a convenient measurement such as incremental costs per life year gained.

The relationship between clinical and economic implications of alternative strategies was modelled using data inputs that are relevant to the Australian setting. This also allows the model to appropriately reflect Australian practice in NSCLC pre-treatment staging.

A modelled evaluation enables a comprehensive and generalisable assessment to be made regarding the relative cost-effectiveness of EUS-FNA. The model-based simulation analysis can also provide valuable information for decision makers by allowing exploration of alternative assumptions and scenarios that characterise uncertainties associated with the evaluation results.

Population in the model

The hypothetical patient cohort included in the current model reflects the patient population who would be eligible for treatment with EUS-FNA if the procedure were available under Medicare.

Under this indication, the subsidised use of the EUS-FNA procedure is limited to patients with suspected or known NSCLC without CT or PET-defined extrathoracic metastases. Patients with stage IV disease were deemed ineligible for inclusion because those with distant metastases or stage IV disease are not considered for curative resection (Caddy et al 2005).

The current model assumed that hypothetical patients in the model were 65 years old at the commencement of the simulation. This is consistent with cancer registry data from Western Australia reported by Hall et al (2004).

The Advisory Panel estimated that 18 per cent of patients who are currently considered for invasive staging have N0/N1 stage disease, while the remaining patients (82%) have N2/N3 stage disease.

The prevalence of each cancer stage in the overall NSCLC population at diagnosis differs considerably from the aforementioned estimates, as reported by Delaney et al (2003). Findings from Delaney et al (2003) are summarised in Table 23. These data were extracted from the South Australian Network of Hospital-Based Cancer Registries (Delaney et al 2003). It is reasonable to expect that these South Australian data are representative of the overall Australian patient population.

Table 23 Baseline prevalence of each cancer stage (Delaney et al 2003)

Cancer stage (NSCLC)	Proportion	
	All	Excluding stage IV
Stage I–II	0.33	0.49
Stage IIIA	0.16	0.24
Stage IIIB	0.19	0.28
Stage IV	0.32	–

Note: Figures may not add to 1.00 due to rounding

The above data suggest that the stage I–II disease group account for 49 per cent of the potential patient population, after excluding distant metastases cases (ie stage IV). This proportion represents a proxy for the proportion of patients diagnosed with N0/N1 stage disease. The remaining patients have N2/N3 stage disease (ie stage IIIA and IIIB patients). The proportion of stage IV patients excluded in Table 23 is considered in line

with the proportion of patients with distant metastases excluded in the estimate of EUS-FNA eligible population presented in Figure 1.

In practice, a large proportion of NSCLC patients (60–80%) are not considered for invasive staging (see Figure 1). This affects the prevalence of each cancer stage in the patients who are potentially considered for mediastinal lymph node biopsy–with 18 per cent of patients considered N0/1 and 82 per cent considered N2/3 (advice from the advisory panel).

Structure of the economic model

A decision analytic model was constructed to assess the cost-effectiveness of introducing EUS-FNA in NSCLC staging when compared with current practice.

A decision tree analysis was considered to be the most appropriate method for this evaluation. The pre-treatment staging process of NSCLC is typically a short-term, one-off event. The process is completed with the diagnosis of mediastinal lymph node metastases, which determines downstream patient management. This type of analysis attains simplicity and transparency in the evaluation, while allowing sufficient complexity to be incorporated in the model to mimic actual clinical practice.

Structure of the decision model is presented graphically in Figure 5. The current model structure based on Figure 2 described the clinical pathway for the evaluation of patients with presumed or known NSCLC. Alternative strategies labelled as EUS-FNA strategy and current strategies were established.

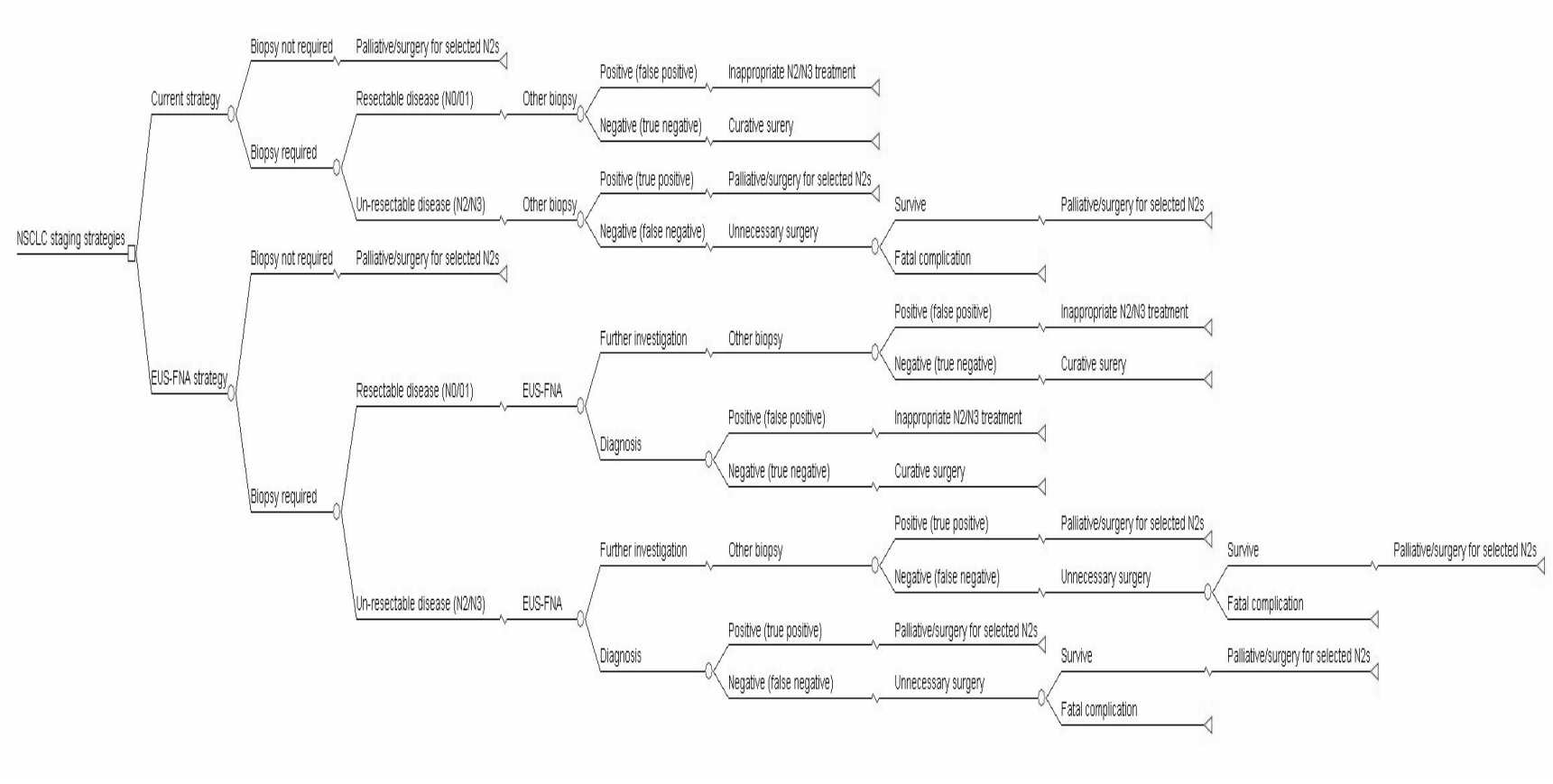

Figure 5 Structure of decision analytic model used in the cost-effectiveness analysis

Note: The model structure is based on the clinical flowchart for NSCLC staging presented in Figure 2

Note that positive and negative test results means positive and negative for N2 and/or N3 nodes respectively

The current algorithm arm represents a simplified replication of the current staging procedure for patients with NSCLC following CT or PET identified mediastinal lymph node metastases. The clinical evidence for the diagnostic performance of EUS-FNA and mediastinoscopy come from a study where patients were staged regardless of mediastinal lymph node size on CT (Annema et al 2005). Although this differs from the clinical flowchart presented in Figure 2, this patient population was considered appropriate and applicable to clinical practice (advice from the advisory panel).

As presented in Figure 1, the advisory panel indicated a large proportion of treatable patients are not considered for invasive staging (ie 60–80%). With the availability of EUS-FNA, patients who have not received mediastinal node biopsy previously are likely to be considered appropriate candidates. This shows that EUS-FNA is less invasive than the majority of existing modalities and is likely to offer a further improvement in safety. Although the extent of this change in the staging algorithm is expected to be limited, the model is designed to explore potential economic and health outcome implications.

To facilitate the simulation process, patients were allocated into one of two separate arms in accordance with the patient's true cancer stage.

The presence of false results was incorporated in the model, and the associated economic and health outcomes implications were appropriately captured, as noted in the decision tree nodes. It was assumed that patients who receive unnecessary surgery because of a false negative result proceed into the management strategy suitable for N2/N3 stage disease. Patients who receive a false positive result undergo inappropriate N2/N3 management, compromising their survival in the model.

The likely staging algorithm after the introduction of EUS-FNA is represented by the EUS-FNA algorithm arm.

More patients are expected to be considered as appropriate candidates for invasive staging if EUS-FNA becomes available. The current model allows the associated economic and health outcome implications to be adequately assessed.

A small group of patients would require further investigation using other modalities for various reasons (eg lymph nodes not accessed by EUS-FNA). Of those patients considered to have mediastinal lymph nodes accessible, EUS-FNA is expected to be prioritised over other biopsy modalities. This again reflects that EUS-FNA is less invasive than the majority of other modalities and likely to offer a further improvement in safety.

The model aims only to cover the pre-treatment staging algorithm which in turn determines the appropriate downstream clinical management. The cytological determination of disease stage represents the final event in the current model. Once a patient was diagnosed, the total costs associated with the staging procedure were calculated, and the appropriate downstream clinical management was determined. Patients diagnosed with N0/N1 disease proceed to undergo surgery and, for N1 patients, adjuvant chemotherapy. Patients diagnosed with N2/N3 disease receive palliative care or undergo curative intervention that involves radical chemoradiation, surgery with or without neoadjuvant or adjuvant chemotherapy (see Figure 2). Costs of the cancer treatment were accrued at this stage. The anticipated life expectancy was also determined in accordance with the relevant disease stage and the administered treatment.

All costs were estimated from the perspective of the Australian healthcare system. Indirect and societal costs were not considered in the current analysis. It is unlikely that the introduction of EUS-FNA would be associated with significant indirect or societal costs. There is a potential where the less invasive nature of EUS-FNA compared with mediastinoscopy and other invasive biopsy procedures may allow patients to be speedily discharged. Furthermore, indirect costs are difficult to estimate accurately; therefore, their inclusion can introduce further uncertainty into economic analyses.

The simulation was performed using TreeAge Pro 2006 Suite (TreeAge Software, Inc).

Variables used in the economic model

Clinical variables

Variables included in the model to describe the characteristics of alternative staging algorithms are summarised in Table 24. Estimated life expectancies and derivation of these estimates are also presented below.

Table 24 Clinical and treatment algorithm variables included in the model

Variable	Description	Value	Source
Baseline patient demographics			
Prevalence of each N stage	Prevalence of each cancer stage at baseline		Expert opinion (see Table 23)
Baseline			
N0/N1		17.5%	
N2/N3		82.5%	
Diagnostic accuracy			
EUS-FNA	Accuracy of biopsy modalities in diagnosing mediastinal node metastasis		Annema et al (2005)
Sensitivity		0.759	
Specificity		0.969	
Other biopsy modalities[1]			
Sensitivity		0.655	
Specificity		1.00	
Parameters relation to treatment algorithm			
Probability of requiring further investigation	Proportion of patients who require further investigation using other modalities after EUS-FNA	10%	Expert opinion
Probability of not performing biopsy	Proportion of patients not considered for biopsy after CT or PET		
EUS-FNA available		0%	Expert opinion
Current		2.5%	
Fatal complication	Risk of fatal complication associated with unnecessary thoracotomy	4.5%	Thoracic Surgery Database (see Table 28)
Life expectancy			
Surgery, N0/N1	Life expectancy following the diagnosis of NSCLC by intervention and disease stage	3.46 years	Dietlein et al (2000) (see **Appendix F**)
Palliative, N0/N1		2.20 years	
N2/N3		1.57 years	

Abbreviations: CT, computed tomography; EUS-FNA, endoscopic ultrasound fine-needle aspiration; PET, positron-emission tomography

[1] Mediastinoscopy data (Annema et al 2005)

The advisory panel estimated that 18 per cent of patients who are currently considered for mediastinal node biopsy have N0/N1 stage disease, while the remaining patients

(82%) have N2/N3 stage disease. The availability of EUS-FNA is expected to shift a small group of patients currently not considered for invasive staging to the biopsy required patient group. To accommodate this practice in the current analysis, the current algorithm arm transits 2.5% of the baseline patient population to the biopsy non-required path, while no patients flow onto this path in the EUS-FNA algorithm. In accordance with the expert opinion, the analysis described here assumes that this shift affects only N2/N3 patients. The baseline prevalence of each cancer stage was re-calculated accordingly.

The estimated proportion of patients for each cancer stage at baseline, and in the biopsy-required and the biopsy non-required groups are shown in Table 25.

Table 25 Prevalence of each cancer stage

Disease stage	Baseline prevalence[2]	Prevalence in patients who are:	
		Considered for biopsy[1]	Currently not considered for biopsy[1]
N0/N1 stage	17.5%	18%	0
N2/N3 stage	82.5%	82%	100%

[1] Based on expert opinion

[2] Based on the assumption that 2.5% of N2/N3 patients transit to the biopsy not-required group

All patients in the biopsy non-required group were assumed to have diagnoses of N2/N3 stage disease. The progression of patients into the biopsy-required and the biopsy non-required groups in the current strategy arm is graphically represented in Figure 6. In the EUS-FNA strategy arm, no patients are assumed to transit to the patient group who do not require a biopsy; the baseline prevalence estimates represent the prevalence within the biopsy required patient group.

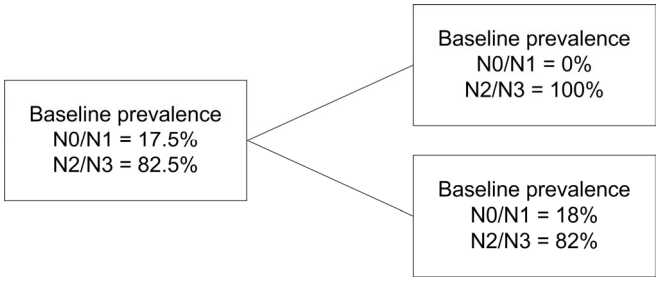

Figure 6 Prevalence of each cancer stage (the current strategy arm)

The accuracy of NSCLC staging is driven by diagnostic accuracy of the employed biopsy instrument(s) in detecting lymph node metastases. Sensitivity and specificity of EUS-FNA and mediastinoscopy were derived from Annema et al (2005). As discussed above, Annema et al (2005) represented the best available source of evidence regarding the comparative assessment of test accuracy to date.

The relevant findings from Annema et al (2005) are summarised in Table 26. EUS-FNA was more sensitive than mediastinoscopy (75.9% vs 65.5%) but had slightly lower specificity (96.9% vs 100.0%). As indicated in Table 26, the 95 per cent confidence

intervals for both EUS-FNA and mediastinoscopy in regards to sensitivity and specificity overlap each other.

Table 26 Accuracy of EUS-FNA compared with mediastinoscopy in pre-treatment staging of NSCLC

Author (year)	Sensitivity (%)		Specificity (%)	
	EUS-FNA	Mediastinoscopy	EUS-FNA	Mediastinoscopy
Annema et al (2005)	75.9 (95% [CI: 56.5, 89.7])	65.5 (95% [CI: 45.7, 82.1])	96.9 (95% [CI: 89.2, 99.6])	100.0 (95% [CI: 94.4, 100])

Abbreviation: CI, confidence intervals

A series of sensitivity analyses were performed to investigate the impact of varying test accuracy estimates on the relative cost-effectiveness of EUS-FNA. This was done using 95% confidence intervals for sensitivity and specificity as shown in Table 26.

The advisory panel suggested that the specificity of EUS-FNA reported in Annema et al (2005) may underestimate the actual specificity of EUS-FNA in practice, and cited a range between 97 and 99.5 per cent. This range approximately corresponds to the upper 95 percent confidence interval value.

A small group of patients who receive EUS-FNA are considered for further investigation using other biopsy modalities. This may occur as a result of inadequate sampling or equivocal results. For the base case analysis, the current model assumed that 10 per cent of patients follow this pathway. This estimate was provided by the advisory panel.

The life expectancy of patients was determined from published evidence. There is little Australian evidence regarding patient survival by disease stage for NSCLC. Survival data stratified by disease stage and treatment received by the patient were necessary for this analysis, which allows any potential impacts on the patient's life expectancy arising from differential accuracy of the two staging pathways to be assessed appropriately.

A modelled cost-effectiveness analysis of FDG-PET performed by Dietlein et al (2000) employed the estimates summarised in Table 27. These estimates were derived using the declining exponential approximation of life expectancy (DEALE) method (Beck et al 1982). Adjustments were made to reflect the patient population under consideration, Australian individuals aged 65. Further details are provided in **Appendix F**. The estimated life expectancies were discounted at 5 per cent per annum before being entered into the model.

Table 27 Estimated life expectancies of patients diagnosed with NSCLC

Disease stage and treatment	Dietlein et al (2000)	Current model	
		Undiscounted	Discounted
Surgery, N0/N1	4.5 years	3.70 years	3.46 years
Palliative, N0/N1 (resectable patients)	2.6 years	2.30 years	2.20 years
N2/N3	1.8 years	1.60 years	1.57 years

Source: Dietlein et al (2000), **Appendix F**

Risk of fatal complication caused by unnecessary thoracotomy has been reported to be negligible (Steinbaun et al 1995), although the advisory panel recognised that a small risk exists. There is also a small risk of fatal complication in curative thoracotomy. Pneumonectomy and lobectomy are consistently described with mortality rates of

6–8 per cent and 2–4 per cent, respectively (British Thoracic Society 2001). These estimates are roughly consistent with Australian data since 1992, which were drawn from Victorian and South Australian hospitals and collated in the Thoracic Surgery Database (Table 28).

Table 28 Thoracic surgical procedures for NSCLC and postoperative death

NSCLC surgical procedure	Number of patients (%)	Mortality (30 day or in-hospital)
Lobectomy	1132 (63%)	34 (3.0%)
Pneumonectomy	260 (15%)	21 (8.1%)
Segmentectomy	80 (4%)	2 (2.5%)
Wedge resection	144 (8%)	4 (2.4%)
Unresectable[1]	177 (10%)	8 (4.5%)
Total	1793 (100%)	69 (4%)

Source: Thoracic Surgery Database
[1] Unnecessary thoracotomy
Note: Data extract from Thoracic Surgery Database covering Victorian and South Australian Hospitals, commenced in 1992. This database was developed and is maintained by Mr Simon Knight, Thoracic Surgeon, Austin Health, Victoria

The mortality risk associated with unnecessary thoracotomy was reported to be 4.5 per cent (Table 28). The base case analysis was performed using this estimate. It is likely to overestimate the postoperative mortality risk because it may include mortalities from other causes such as cancer death. The potential existence of selection bias should also be noted. This is because the characteristics of patients included in this database may not reflect the patient population considered in this evaluation. Sensitivity analysis was performed to investigate uncertainty associated with this estimate. The current model does not incorporate mortality associated with curative surgery as both arms are equally affected.

The current model does not incorporate potential complications caused during the staging procedures. The available evidence suggests that EUS-FNA is a safe procedure that is not likely to cause complications with significant clinical or economic implications. In contrast, mediastinoscopy has been reported to be associated with a small complication risk (Aabakken et al 1999; Kramer et al 2004).

Omission of the complication risks from the analysis may bias against the EUS-FNA algorithm arm, providing a conservative estimate of the relative cost-effectiveness of EUS-FNA. Furthermore, the advisory panel recognised the presence of a small fatal complication risk associated with mediastinoscopy in practice, and recommended this to be explored in the current assessment report. It was considered appropriate to explore the impact of this fatal complication risk with a sensitivity analysis as evidence for this risk were not determined from a systematic review of the literature. This sensitivity analysis has the potential for bias in favour of EUS-FNA when similar fatal complication risks for EUS-FNA are not considered. However, no evidence for a fatal complication risk associated with EUS-FNA was identified during the systematic review conducted during this assessment (see page 31). However, as EUS-FNA is considered a relatively new procedure, rare fatal complications may occur as procedure numbers increase (advice from the advisory panel).

Cost variables

Variables used to incorporate the cost inputs in the cost-effectiveness evaluation are summarised in Table 29. Derivation of these estimates is presented below.

Table 29 Cost variables included in the model

Variable	Description	Value	Source
Cost of procedure	Resource costs per mediastinal node biopsy		
EUS-FNA		$2374.55	Application document, MBS (see Table 30)
Other biopsy modality		$4682.00	MBS (see Table 33)
Unnecessary surgery		$14,053.00	MBS (see Table 34)
Cost of cancer treatment	Resource cost associated with treatment of NSCLC at various stage		
N0/N1 stage		$17,053.00	MBS (see Table 34), Rosenthal et al (1992), MSAC (2003)
N2/N3 stage		$25,000.00	

The cost of EUS-FNA was estimated primarily from information provided by the applicant, as shown in Table 30. Where more recent data were available, estimates were updated accordingly. The total costs of EUS-FNA were estimated to be $2,374.55 per procedure. It was assumed that this estimate represents the average per-procedure costs across private and public sectors.

Table 30 Total cost of EUS-FNA per procedure

Costs	Estimates	Source
Capital equipment costs	$993.00	Application document (see **Appendix F**)
Proposed professional fee	$803.30	Application document (see Table 31)
Other medical services (including anesthesia and pathology)	$278.25	MBS (see Table 32)
FNA disposable needle	$300.00	Application document
Total	$2374.55	

Major capital equipment cost was estimated at $993 per procedure. It was assumed that each EUS-FNA equipped site had capacity to perform 120 procedures per year. Further details on the derivation of this estimate are provided in **Appendix F**.

No MBS items currently exist for procedures involving EUS-FNA. As such, the proposed professional fee for EUS-FNA was derived using the multiple operation rule, and current MBS fees (Table 31). The Applicant suggested that therapeutic endoscopic retrograde cholangiopancreatography (ERCP) was an appropriate comparator to base this estimation: EUS-FNA and ERCP were considered to require similar resource requirements and skill level to perform, and training requirements for competence in both procedures were equally demanding. Details are shown in Table 31.

Table 31 Estimated EUS-FNA professional fees per procedure using comparator items (as proposed by the Applicant)

MBS item number, description	Fee (multiple operation rule weight)
30491 Bile duct, endoscopic stenting of (including endoscopy and dilatation)	$480.60 (100%)
30485 Endoscopic sphincterotomy with or without extraction of stones from common bile duct	$487.50 (50%)
30484 Endoscopic retrograde cholangiopancreatography	$315.80 (25%)
Total costs according to multiple operation rule	**$803.30**

Source: Medicare Benefits Schedule Book November 2005
Abbreviation: MBS, Medicare Benefits Schedule

Estimated costs of other medical services associated with EUS-FNA are presented in Table 32.

Table 32 Other costs associated with EUS-FNA per procedure

MBS item number, description	Fee
17603 Examination of a patient in preparation for the administration of an anaesthetic relating to a clinically relevant service, being an examination carried out at a place other than an operating theatre or an anaesthetic induction room	$37.15
20520 Initiation of management of anaesthesia for all closed chest procedures	$102.90
23043 Anaesthesia, perfusion or assistance at anaesthesia (56 minutes to 1:00 hour)	$68.60
73049 Cytology of material obtained directly from a patient by fine-needle aspiration of solid tissue or tissues	$69.60
Total costs per procedure	**$278.25**

Abbreviation: MBS, Medicare Benefit Schedule

Cost of other biopsy modalities was estimated from the National Hospital Cost Data collection. It was assumed that the Australian Refined Diagnosis-Related Groups (AR-DRG) E02A, E02C and E02B appropriately represented the resource requirements associated with this procedure (Department of Health and Ageing 2005). Public sector estimates were employed. The AR-DRG costs were weighted using the number of separations to derive the mean costs per procedure, as shown in Table 33. The same methodologies were applied to estimate mediastinal node biopsy costs in the MSAC assessment report on positron emission tomography (PET) for NSCLC and solitary pulmonary nodules (MSAC 2003).

Table 33 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	$14,430	1860
E02B Other respiratory system operating procedures with severe complications and comorbidities	$5529	1870
E02C Other respiratory system operating procedures without catastrophic or severe complications and comorbidities	$2573	9348
Weighted average per separation	**$4682**	

Source: National Hospital Cost Data Collection, Round 8 (2003–04)

A similar estimate was reported by an observational study performed in Australia. Yap et al (2005) determined costs associated with mediastinoscopy for the staging or treatment of proven histological NSCLC. This study was undertaken at the Austin Hospital, Melbourne, during the period 1 July 2000 to 30 June 2001. The mean cost was estimated to be $4160 per procedure, based on data from 10 mediastinoscopic procedures.

Estimation of costs for cancer treatment requires the consideration of several factors. Management of diagnosed cancer varies according to the extent of disease progression, which requires different levels of healthcare resources and associated economic costs.

It was assumed that the total costs associated with the treatment of N0 disease include curative surgery, while additional costs for adjuvant chemotherapy are required for the treatment of N1 disease.

The cost of surgery was again estimated from the National Hospital Cost Data Collection. It was assumed that the AR-DRG codes E01A and E01B appropriately represent the resource requirements associated with this procedure. Estimates for public sector were employed. The costs for these DRGs were weighted using the number of separations in order to derive the mean costs per procedure, as shown in Table 34. This was consistent with the estimate reported in Yap et al (2005). The mean cost of thoracotomy was estimated to be $15,642 per procedure (Yap et al 2005). This estimate was also used for the unnecessary surgery as a result of a false negative test result.

Table 34 Estimated costs of curative surgery per procedure

AR–DRG code, description	Average cost per separation	Number of separations
E01A Major chest procedure with catastrophic complications and comorbidities	$20,209	1270
E01B Major chest procedure without catastrophic complications and comorbidities	$10,686	2322
Weighted average per separation	**$14,053**	

Source: National Hospital Cost Data Collection, Round 8 (2003–2004)

It was difficult to accurately estimate chemotherapy costs. Rosenthal et al (1992) estimated the cost of treating small cell lung cancer at Westmead Hospital, New South Wales. The cost of chemotherapy per patient with limited disease was estimated to be $3937 (in 1990 dollars). This is equivalent to approximately $6000 in the current value, determined using the total health price index reported by the Australian Institute of Health and Welfare (2002; 2006)[5]. Although Rosenthal et al (1992) are outdated and the studies were conducted for patients with small cell lung cancer that typically has a more aggressive clinical course than NSCLC at diagnosis, this study was still considered useful in deriving a proxy value.

Assuming that 50 per cent of the N0/N1 group receive adjunct chemotherapy, the average cost of treating a N0/N1 stage NSCLC can be estimated to be $17,053 per patient.

Patients with N2/N3 disease receive palliative care or curative intervention that involves radical chemoradiation, surgery with or without neoadjuvant or adjuvant chemotherapy.

The MSAC assessment report regarding PET for NSCLC and solitary pulmonary nodules (MSAC 2003) estimated the costs associated with un-resectable disease to be $20,000 as shown in Table 35. These were based on expert opinion (advisory panel).

[5] These may represent conservative estimates. Indicative cost estimates provided by the advisory panel were based on a small sample of patients (n = 3) and suggest that radiotherapy costs approximately $7,000 per patient, and chemotherapy costs approximately $3,500 (single agent)/$8,500 (multiple drugs) per patient. The sensitivity analysis demonstrated that these cost inputs had negligible implications for the relative cost-effectiveness of the treatment strategies under consideration.

Table 35 Estimated costs of NSCLC treatment per episode (MSAC 2003)

Costs	Estimate	Range
Surgical cure	$15,000	$10,000–$20,000
Un-resectable cancer	$20,000	$15,000–$25,000

Source: MSAC assessment report (MSAC reference 16), 2003

The advisory panel suggested that this was likely to underestimate the costs of current N2/N3 cancer treatment due to the increased usage of chemoradiation therapy. The current model utilised an estimate of $25,000 for the base case analysis. Sensitivity analysis was performed in order to address this uncertainty (see Table 40).

Table 35 shows that surgical cure was previously estimated to cost $15,000, which is comparable to the estimate derived using AR-DRG categories (Table 34).

These cost estimates were assumed to account for all the healthcare resource implications over time that are specific to the cancer episode the hypothetical patient was suffering during the simulation.

Results

Base case analysis

The following tables summarise the base case results of the cost-effectiveness analysis comparing the NSCLC staging algorithm involving EUS-FNA and the current practice. No discounting was performed on the cost estimates. Patients' life expectancy was discounted at 5 per cent per annum.

The results should be interpreted in the context of assumptions made in performing the simulation. In particular, the assumptions relating to test accuracy of the two modalities should be taken into consideration in interpreting the following results (Annema et al 2005; see Table 26).

Table 36 indicates that the staging algorithm beginning with EUS-FNA was associated with costs lower than that of current practice. The use of EUS-FNA was demonstrated to provide a relatively large reduction in the pre-treatment staging costs ($6678 vs $4485). Cancer treatment costs were largely comparable between the arms. When compared with the current algorithm, the average cost savings associated with the EUS-FNA strategy were estimated to be $2570 per patient.

Table 36 Estimated cost of pre-treatment staging and treatment

Strategy	Average cost per patient			Incremental costs associated with EUS-FNA
	Staging procedure[1]	Cancer treatment	Total	
EUS-FNA algorithm	$5757	$23,415	$29,172	–
Current algorithm	$8444	$23,299	$31,742	–$2570

Note: Figures may not add up due to rounding
[1] Includes costs of unnecessary surgery

The effectiveness of each treatment pathway was captured in terms of patients' life years in the model, as shown in Table 37. Only a negligible difference was demonstrated, slightly favouring the current algorithm over the staging algorithm beginning with EUS-FNA. There were 1.880 life years gained with the EUS-FNA strategy and 1.881 life

years gained with the current strategy, resulting in an insignifcant reduction in life years with the EUS-FNA strategy (0.001, ie less than a day).

Table 37 Estimated life expectancies

Strategy	Life expectancies	Additional life years associated with EUS-FNA
EUS-FNA algorithm	1.880	–
Current algorithm	1.881	–0.001

Note: Figures may not add up due to rounding

By combining the economic and clinical outcomes presented in **Table 36** and **Table 37**, the incremental cost-effectiveness of the EUS-FNA strategy was evaluated. This is shown in Table 38.

Table 38 Incremental cost-effectiveness ratio

Strategy	Incremental costs associated with EUS-FNA	Additional life years associated with EUS-FNA	Cost per life year gained
EUS-FNA algorithm versus current algorithm	–$2570	–0.001	EUS-FNA cost saving, but slightly less effective

The staging algorithm commencing with EUS-FNA was found to be cost saving, but was associated with inferior outcomes (ie lower life expectancy) when compared with the current algorithm. The outcome difference was very marginal between the arms and unlikely to be clinically meaningful.

Table 36 and Table 37 indicate that the simulation results logically reflect the diagnostic test accuracy information incorporated in the model. Patients in the EUS-FNA algorithm arm were more likely to avoid unnecessary surgeries than those in the current algorithm arm, which offered important cost savings. This is despite the expected change in the clinical practice whereby a larger proportion of patients would be considered for mediastinal node biopsy with the availability of EUS-FNA, and additional investigations using other modalities would be conducted in some patients following EUS-FNA.

The base case analysis assumed that EUS-FNA is associated with a false positive rate of 3.1 per cent, while mediastinoscopy provides complete specificity (ie no false positive). A false positive result leads to inappropriate downstream cancer management, which consequently compromises patient survival. In contrast, an improvement in sensitivity offered by EUS-FNA avoids unnecessary surgery for patients with N2/N3, which in turn avoids fatal complications potentially caused by the surgical procedure. The simulation results indicate that the number of life years saved from avoided surgeries largely compensate for the loss of life years attributable to false positive results.

It is noteworthy that the incremental difference in the number of life years between the arms was negligible. The specificity estimate incorporated in the base case analysis was suggested to be an underestimate by the advisory panel, possibly biasing against the EUS-FNA algorithm arm in the current model. Therefore, the life expectancy may not be lower than the current strategy in practice and, if so, the EUS-FNA strategy would represent a dominant option given its cost savings. Sensitivity analysis presented below demonstrates that the simulation results are very sensitive to altering the specificity rate.

The current model did not explore quality-of-life implications of these alternatives. As shown, the EUS-FNA strategy is likely to reduce post-procedural quality-of-life impact when compared with the current strategy. Quality-of-life implications of unnecessary surgery can be substantial (Ferguson 2003; Mangione et al 1997). The results of the current evaluation may provide a conservative view of the patient outcomes provided by EUS-FNA.

Conducting a comparative assessment of the findings from the current model and other available published evidence was difficult because of differences in the approaches and assumptions employed among studies. However, the introduction of EUS-FNA in the pre-treatment staging of NSCLC was consistently demonstrated to provide cost savings. The current model incorporates the best available evidence regarding test accuracy (Annema et al 2005). Hence, the sensitivity of EUS-FNA is assumed to be superior to mediastinoscopy, the comparator modality in the current model. This contrasts with the findings reported by Aabakken et al (1999). All the reviewed studies assumed that EUS-FNA and comparator modalities were associated with complete specificity. The current study differs in this aspect.

Sensitivity analysis

The validity and generalisability of these results are dependent on the accuracy of the data inputs and assumptions used in the model. The results from the economic evaluation should be interpreted in the context of the key underlying assumptions, in particular, those relating to the test accuracy.

Table 39 summarises findings from analyses, examining the impact of varying assumptions regarding the test accuracy. These analyses were performed using the 95 per cent confidence limits for specificity and sensitivity calculated from Annema et al (2005), while an additional analysis incorporated an assumption of complete specificity for EUS-FNA and mediastinoscopy.

Table 39 Sensitivity analysis—assumptions regarding test accuracy

	Average cost per patient (incremental cost of EUS-FNA)	Average life years per patient (incremental life years with EUS-FNA)	Cost per life year gained
Base case analysis			
EUS-FNA algorithm	$29,172	1.880	EUS-FNA cost saving, but slightly less effective
Current algorithm	$31,742 (–$2570)	1.881 (–0.001)	
1. Specificity of EUS-FNA: Upper 95% CI value (99.6%)			
EUS-FNA algorithm	$29,138	1.885	EUS-FNA algorithm dominates current algorithm
Current algorithm	$31,742 (–$2604)	1.881 (0.004)	
2. Specificity of EUS-FNA: Lower 95% CI value (89.2%)			
EUS-FNA algorithm	$29,269	1.865	EUS-FNA cost saving, but slightly less effective
Current algorithm	$31,742 (–$2474)	1.881 (–0.017)	
3. Sensitivity of EUS-FNA: Upper 95% CI value (89.7%)			
EUS-FNA algorithm	$27,847	1.887	EUS-FNA algorithm dominates current algorithm
Current algorithm	$31,742 (–$3895)	1.881 (0.006)	
4. Sensitivity of EUS-FNA: Lower 95% CI value (56.5%)			
EUS-FNA algorithm	$31,034	1.870	EUS-FNA cost saving, but slightly less effective
Current algorithm	$31,742 (–$708)	1.881 (–0.011)	
5. Specificity of mediastinoscopy: Lower 95% CI value (94.4%)[a]			
EUS-FNA algorithm	$29,180	1.879	EUS-FNA algorithm dominates current algorithm
Current algorithm	$31,820 (–$2640)	1.869 (0.014)	
6. Sensitivity of mediastinoscopy: Upper 95% CI value (82.1%)			
EUS-FNA algorithm	$28,995	1.881	EUS-FNA cost saving, but slightly less effective
Current algorithm	$30,026 (–$1030)	1.891 (–0.010)	
7. Sensitivity of mediastinoscopy: Lower 95% CI value (45.7%)			
EUS-FNA algorithm	$29,383	1.879	EUS-FNA algorithm dominates current algorithm
Current algorithm	$33,790 (–$4407)	1.870 (0.009)	
8. Complete specificity for both modalities			
EUS-FNA algorithm	$29,133	1.886	EUS-FNA algorithm dominates current algorithm
Current algorithm	$31,742 (–$2609)	1.881 (0.005)	

Note: Figures may not add up due to rounding

[a] Upper 95% CI value of specificity was 100% for mediastinoscopy (ie the base case estimate)

The base case analysis assumed that EUS-FNA was more sensitive 75.9 per cent (95% [CI: 56.5, 89.7]) versus mediastinoscopy 65.5% (95% [CI: 45.7, 82.1]) and slightly less specific 96.9 per cent (95% [CI: 89.2, 99.6]) versus mediastinoscopy 100 per cent (95% [CI: 94.4, 100.0]). These data were derived from the study by Annema et al (2005). These assumptions should be considered carefully due to the large degree of overlap in the 95 per cent confidence intervals for both EUS-FNA and mediastinoscopy in regard to sensitivity and specificity.

Analyses 1–7 reinforce the interpretation of findings from the base case analysis: the two alternative staging algorithms were largely comparable in terms of their health outcomes (ie life years). Analysis 1 demonstrated that the relative effectiveness of the EUS-FNA algorithm arm was sensitive to altering the specificity estimate; and Analysis 5 showed that the specificity of mediastinoscopy also represents an important determinant. In these analyses, the EUS-FNA algorithm arm was found to represent a dominant strategy, providing superior effectiveness and cost savings. In contrast, the relative cost-effectiveness of EUS-FNA deteriorated when the lower 95 per cent confidence interval for its specificity estimate was incorporated (Analysis 2). In this analysis, the reduction in

life expectancy with the EUS-FNA strategy became slightly more pronounced, providing 0.017 fewer life years (approximately 6 days). The sensitivity estimates were also found to be important determinants when the 95 per cent confidence limits were employed in the analyses (Analysis 3, 4, 6 and 7). Analysis 8 assumed 100 per cent specificity for EUS-FNA and mediastinoscopy. The EUS-FNA algorithm arm dominated the current strategy. This was an expected outcome; the sensitivity improvement offered by EUS-FNA reduces numbers of unnecessary surgical procedures and, as a result, limits fatal complications. Table 40 summarises findings from sensitivity analysis performed on other variables included in the current model.

Table 40 Sensitivity analysis—other assumptions

	Average cost per patient (incremental cost of EUS-FNA)	Average life years per patient (incremental life years with EUS-FNA)	Cost per life year gained
Base case analysis			
EUS-FNA algorithm	$29,172	1.880	EUS-FNA cost saving, but slightly less effective
Current algorithm	$31,742 (–$2,570)	1.881 (–0.001)	
1. 0.5% risk of fatal complication associated with mediastinoscopy			
EUS-FNA algorithm	$29,159	1.879	EUS-FNA algorithm dominates current algorithm
Current algorithm	$31,610 (–$2,451)	1.872 (0.007)	
2. Reduction in the fatal complication risk of unnecessary thoracotomy by 50% (ie 2.25%)			
EUS-FNA algorithm	$29,289	1.887	EUS-FNA cost saving, but slightly less effective
Current algorithm	$31,898 (–$2,609)	1.891 (–0.004)	
3. Life expectancy of N0/N1 patient with inappropriate care: 2.98 years			
EUS-FNA algorithm	$29,172	1.884	EUS-FNA algorithm dominates current algorithm
Current algorithm	$31,742 (–$2,570)	1.881 (0.003)	
4. Deterioration on the quality of life after unnecessary surgery (by 12%; Ferguson 2003)			
EUS-FNA algorithm	$29,172	1.856	EUS-FNA algorithm dominates current algorithm
Current algorithm	$31,742 (–$2,570)	1.850 (0.007)	
5. 20% requiring further biopsy tests after EUS-FNA			
EUS-FNA algorithm	$29,747	1.880	EUS-FNA cost saving, but slightly less effective
Current algorithm	$31,742 (–$1,995)	1.881 (–0.001)	
6. 50% requiring further biopsy tests after EUS-FNA			
EUS-FNA algorithm	$31,471	1.880	EUS-FNA cost saving, but slightly less effective
Current algorithm	$31,742 (–$271)	1.881 (–0.001)	
7. Higher cost of unnecessary surgery ($20,000)			
EUS-FNA algorithm	$30,406	1.880	EUS-FNA cost saving, but slightly less effective
Current algorithm	$33,384 (–$2,978)	1.881 (–0.001)	
8. Higher costs of cancer treatment			
EUS-FNA algorithm	$33,776	1.880	EUS-FNA cost saving, but slightly less effective
Current algorithm	$36,321 (–$2,545)	1.881 (–0.001)	
9. Baseline prevalence of cancer stages			
EUS-FNA algorithm	$25,715	2.470	EUS-FNA cost saving, but slightly less effective
Current algorithm	$27,834 ($2,119)	2.484 (–0.014)	

10. No discounting			
EUS-FNA algorithm	$29,172	1.946	EUS-FNA cost saving, but slightly less effective
Current algorithm	$31,742 (–$2,570)	1.948 (–0.002)	
11. Discounting at 10% per annum			
EUS-FNA algorithm	$29,172	1.830	EUS-FNA cost saving, but slightly less effective [a]
Current algorithm	$31,742 (–$2,570)	1.830 (0.000)	

Note: Figures may not add up due to rounding
[a] No difference is shown in the table due to rounding

Analysis 1 explores the fatal complication risk of mediastinoscopy. The advisory panel recognised the presence of a small mortality risk associated with mediastinoscopy. Under this scenario, the EUS-FNA arm was demonstrated to offer additional life years when compared with the current algorithm arm. The difference was considered marginal. This sensitivity analysis has the potential for bias in favour of EUS-FNA when similar fatal complication risks for EUS-FNA are not considered. However, no evidence for a fatal complication risk associated with EUS-FNA was identified during the systematic review conducted during this assessment (see page 31).

Analysis 2 relates to the fatal complication risk of unnecessary thoracotomy. The incremental difference in the life years deteriorated slightly against the EUS-FNA algorithm arm when the risk was reduced by half. This is an expected outcome because the improved sensitivity offered by EUS-FNA now translates to that patient's life years to a lesser extent than the base case. No significant change was observed from the base case results.

Analysis 3 assumed that inappropriate management of N0/N1 patients due to over staging (ie false positive results) results in the average reduction of life years by six months. This was about 1.3 years in the base case. Under this assumption, the EUS-FNA arm offered a slight improvement in the number of life years gained when compared with the current algorithm arm (by 0.003 life years).

Ferguson (2003) incorporated a utility deterioration of 12 per cent during postoperative recovery following thoracotomy in a cost-effectiveness analysis. Analysis 4 applied this rate over the 12-month period following surgery in order to account for potential quality-of-life implications caused by unnecessary surgery. The EUS-FNA algorithm arm was demonstrated to offer additional quality-adjusted life years of 0.007, when compared with the current algorithm arm (ie approximately 2.5 quality-adjusted days).

The following two analyses examined the effects of altering variables that affect the patient flow through the staging algorithms on the relative cost-effectiveness of EUS-FNA (Analysis 5 and 6). Analysis 6 demonstrated that even when EUS-FNA was used as a supplementary test in more than 50 per cent of patients, the EUS-FNA strategy still remains cost-neutral to the current strategy. The outcome difference between the arms remains largely unaffected, although small improvements in the EUS-FNA arm were observed. This is because further investigations were performed in the model using mediastinoscopy that was associated with better specificity than EUS-FNA.

The cost of unnecessary surgery was estimated using the public sector data from the National Hospital Cost Data Collection. Analysis 7 examined the relative cost-effectiveness of EUS-FNA where the cost was set at $20,000. This estimate

corresponds to the upper range estimate for the costs of surgical cure employed in the MSAC assessment report regarding PET for NSCLC and solitary pulmonary nodules (see Table 35; MSAC 2003). No material difference in costs was observed.

Analysis 8 incorporated alternative estimates for the costs of cancer treatment. The N0/N1 NSCLC was assumed to incur $20,000 (MSAC 2003), N2/N3 assumed to incur $30,000. No material impact was again observed for the incremental cost difference between the arms.

Analysis 9 employed the prevalence of each cancer stage reported in Delaney et al (2003; see Table 23) as the baseline prevalence of N0/1 and N2/3 cases. It was assumed that 49% of patients suffer from N0/N1 cases, while the remaining patients (51%) suffer from N2/N3 cases. Under this assumption, the outcome difference between the two arms became slightly more pronounced, favouring the current algorithm arm. This is because the number of N0/N1 patients receiving inappropriate care is greater than that of the base case scenario. The difference was nonetheless marginal (ie 5 days).

No material change was observed in the relative cost-effectiveness of EUS-FNA after having varied the discount rate (analysis 10 and 11).

In summary, the presence of uncertainty surrounding assumptions regarding the test accuracy and other parameters used to populate the model does not allow a firm conclusion on the relative cost-effectiveness of EUS-FNA in the staging of NSCLC to be made. The balance of evidence suggests that the EUS-FNA strategy offers large cost savings when compared with the current staging strategy. The model demonstrated that the patient's likelihood for survival overall is largely comparable between the two arms.

The above analyses highlighted the importance of assumptions regarding the test accuracy (**Table 39**). As noted above, the Advisory Panel considered that the EUS-FNA base case specificity estimate for EUS-FNA was underestimated in Anemma et al (2005), biasing against the EUS-FNA algorithm arm in the current model. The economic model employed in this assessment demonstrated that the staging algorithm starting with EUS-FNA would allow a large proportion of patients to receive further tests without incurring any additional costs when compared with the current strategy

The EUS-FNA strategy is also likely to reduce post-procedural quality-of-life impact when compared with the current strategy. The results of the current evaluation may represent a conservative view on the patient outcomes provided by EUS-FNA.

Assessment of value-for-money of EUS-FNA in the diagnosis of mediastinal mass of unknown origin

There is little evidence regarding the use of EUS-FNA in the diagnosis of mediastinal mass of unknown origin. No comparative assessment of diagnostic accuracy was possible due to a lack of evidence.

Larsen et al (2002) suggest that EUS-FNA is a sensitive and specific test for the diagnosis of mediastinal masses of unknown origin. As discussed in the previous section, EUS-FNA is likely to have a better safety and quality-of-life profile than mediastinoscopy.

Due to limited evidence, no formal economic evaluation was performed in the current report. Instead, a simple cost analysis comparing the diagnostic test using EUS-FNA and

other test modalities was performed. Doing so assumes that the introduction of EUS-FNA as a first-line biopsy modality under this indication (as described in Figure 3) is at least as accurate as the current diagnostic algorithm (ie a cost-minimisation analysis).

The likely costs of diagnostic procedures using EUS-FNA and other instrument(s) are presented in Table 41. Derivation of these estimates is presented above (Table 30, Table 33).

Table 41 Costs of diagnostic procedures using EUS-FNA or other instruments

Diagnostic test	Estimate	Source
EUS-FNA	$2,374.55	Application document, MBS (see Table 30)
Other biopsy modality	$4,682.00	MBS (see Table 33)
Cost savings associated with EUS-FNA	**–$2307.45**	

Hence, the use of EUS-FNA in place of alternative minimally invasive diagnostic test instruments such as mediastinoscopy is estimated to generate a cost saving of $2307.45 per procedure. The analysis also indicates that, given the estimated procedure costs, the introduction of EUS-FNA would remain cost-neutral to the Australian healthcare system up to the point where approximately 50 per cent of all patients who receive EUS-FNA are also tested using existing test instruments.

It should be noted that the validity of this analysis rests on the assumption that the introduction of EUS-FNA provides diagnostic accuracy that is comparable with the current diagnostic algorithm. The current analysis did not consider quality-of-life issues and broader economic implications, such as the cost savings associated with avoided unnecessary surgery (Chong et al 2005), because the absence of evidence did not allow a reliable and generalisable evaluation to be performed.

Research recommendations

Non-small cell lung cancer

The evaluators advise that the evidence base for the use of EUS-FNA in the staging of NSCLC would be improved by addressing the following research question in a randomized controlled trial.

To what extent does EUS-FNA impact patient survival and quality of life in the pre-treatment staging of patients with presumed or known NSCLC (as assessed by CT and/or PET) relative to mediastinoscopy?

This research question was designed to address the uncertainty in the evidence regarding the trade-off between patient survival (potentially affected by false positive EUS-FNA results leading to patients being inappropriately treated for advanced disease) and quality of life (potentially affected by true positive EUS-FNA results leading to avoidance of unnecessary surgery).

Mediastinal mass of unknown origin

The evaluators advise that the evidence base for the use of EUS-FNA in the diagnosis of mediastinal mass of unknown origin needs to address the following research question in a prospective diagnostic accuracy trial.

What is the diagnostic performance of EUS-FNA in the diagnosis of patients with a mediastinal mass/lymphadenopathy of unknown origin (as assessed by chest radiograph and/or CT) relative to current clinical practice?

This research question was designed to address the uncertainty in the evidence regarding the comparative diagnostic performance of EUS-FNA to other diagnostic technologies used in current clinical practice.

Conclusions

Safety

Safety data relating to the use of EUS-FNA in the staging of NSCLC and diagnosis of mediastinal masses were drawn from reports relating to a total of 1,649 patients receiving this test. EUS-FNA for the diagnosis or staging of lung cancer and mediastinal lesions appears to be associated with a low risk of serious adverse events (0.12%, 95% [CI: 0.01, 0.44]). There are a small number of mild adverse events such as sore throat (2.12%, 95% [CI: 1.48, 2.94]), pain (0.67%, 95% [CI: 0.33, 1.19]), and nausea/vomiting (0.24%, 95% [CI: 0.07, 0.62]) associated with EUS-FNA. However, due to a number of factors, such as poor study reporting, a degree of uncertainty exists in regards to the incidence of these events.

Effectiveness

Direct evidence

A randomised controlled trial conducted by Larsen et al (2005) provided direct evidence of EUS-FNA in the pre-treatment staging of NSCLC. This trial suggested that the introduction of routine EUS-FNA would reduce the number of futile thoracotomies, but was unable to assess the impact of EUS-FNA on patient survival. In addition, there are differences in the prior tests and the current clinical practice group from those identified in the clinical pathway developed for NSCLC patients in this assessment. These differences limit the applicability of this trial to the NSCLC patient population as considered for this assessment. For this reason, it is considered that this study provides limited direct evidence for EUS-FNA in NSCLC staging.

Diagnostic accuracy

Systematic review

Two low quality systematic reviews were identified which assessed the diagnostic performance of EUS-FNA for NSCLC staging. These reviews reported similar diagnostic performance among the invasive staging technologies. One systematic review concluded that EUS-FNA has the potential to perform mediastinal tissue sampling more accurately than other invasive staging modalities. The other review reported similar diagnostic performance among invasive staging modalities. However, these reviews are considered to be of limited value due to the absence of comparative evidence.

Linked evidence

Staging of NSCLC

One medium quality, applicable study appeared to indicate that EUS-FNA may be more sensitive 75.9% (95% [CI: 56.5, 89.7]) vs mediastinoscopy 65.5% (95% [CI: 45.7, 82.1]) and slightly less specific 96.9% (95% [CI: 89.2, 99.6]) vs mediastinoscopy 100% (95% [CI: 94.4, 100.0]) in identifying advanced disease; in the pre-treatment staging of NSCLC. However it is noteworthy that there is a large degree of overlap between the 95 per cent confidence intervals for sensitivity and specificity between the two technologies. This

study was considered the best available comparative evidence identified in this assessment.

Another low quality comparative study of EUS-FNA and mediastinoscopy was also identified. This study had limited applicability due to a sequence of prior tests that was not applicable to the NSCLC patient population considered in this assessment.

Diagnosis of mediastinal masses of unknown origin

A single low quality, non-comparative study assessing the diagnostic accuracy of EUS-FNA in the diagnosis of mediastinal masses was identified. This study indicated that for this indication EUS-FNA was a sensitive (92.3%) and specific (100%) diagnostic test. This study was considered applicable to the mediastinal mass patient population considered in this assessment. However, due to the absence of comparative data no conclusions can be made regarding the relative performance of EUS-FNA for mediastinal mass diagnosis in comparison to current clinical practice.

Does EUS-FNA change patient management?

A single patient management study was identified that reported the impact of EUS-FNA testing in a mixed mediastinal mass/mediastinal lymphadenopathy/lung cancer population. The results of this study suggest that EUS-FNA can impact the management of patients, primarily through the avoidance of surgery (42% of patients) or further invasive investigations (16% of patients) such as mediastinoscopy.

This patient group is considered to reflect clinical practice; however the applicability of this group may be limited due to the inclusion of small cell lung cancer (SCLC) patients. In addition, it is also possible that this study included patients for lung cancer diagnosis, with no mediastinal mass observed.

This management study is considered to provide evidence of EUS-FNA's impact on patient management. However, the results of this study should be interpreted with caution due to potential differences in the study population compared with the patient population considered in this assessment.

Summary of evidence for effectiveness

Evidence for the effectiveness of EUS-FNA for the staging of NSCLC and diagnosis of mediastinal masses was reviewed.

Staging of NSCLC

There was limited medium quality evidence that:

> EUS-FNA is more sensitive, but slightly less specific than mediastinoscopy for NSCLC staging and can alter patient management, reducing the number of surgical and invasive procedures performed. The impact of EUS-FNA on patient survival and quality of life remains unclear.

Diagnosis of mediastinal masses of unknown origin

There was insufficient evidence that:

> EUS-FNA has equal or improved diagnostic performance in the diagnosis of mediastinal masses of unknown origin in comparison to current clinical practice.

Cost-effectiveness

Staging of NSCLC

A decision analytic model was constructed to assess the cost-effectiveness of introducing EUS-FNA in NSCLC staging when compared with mediastinoscopy.

The base case analysis demonstrated that the staging algorithm commencing with EUS-FNA was found to be cost saving when compared with mediastinoscopy. The two arms were shown to offer largely comparable outcomes in terms of patients' mean life expectancy, although a negligible difference was demonstrated slightly favouring the current algorithm over the staging algorithm beginning with EUS-FNA.

The average cost savings associated with the EUS-FNA strategy were estimated to be $2570 per patient when compared with mediastinoscopy. This would allow a large proportion of patients (up to 50%) to receive further tests following EUS-FNA without incurring any additional costs.

The base case analysis demonstrated that the EUS-FNA strategy was associated with an insignificant impact on patient life years (decrease by 0.001) compared with mediastinoscopy, suggesting an insignificant difference between the two testing strategies in their final outcomes overall.

Sensitivity analyses reinforced the base case finding that the two arms are largely comparable in outcome (ie the patient's likelihood for survival following invasive staging).

Diagnosis of mediastinal mass of unknown origin

No comparative assessment of diagnostic accuracy was possible due to a lack of evidence. No formal economic evaluation was therefore performed. Instead, a simple cost analysis was conducted, quantifying estimated cost savings associated with the use of EUS-FNA in place of other modalities.

Recommendation

MSAC has considered safety, effectiveness and cost-effectiveness for endoscopic ultrasound guided fine needle aspiration (EUS-FNA) for the staging of presumed or known non-small cell lung cancer and the diagnosis of mediastinal masses compared with current clinical practice and techniques for biopsy of mediastinal lymph nodes.

MSAC finds EUS-FNA for the staging of non-small cell lung cancer when compared with current clinical practice/ techniques for biopsy of mediastinal lymph nodes and the diagnosis of mediastinal masses is as safe as current clinical practice, as effective, and cost saving.

MSAC **recommends that public funding** is supported for EUS-FNA for pre-treatment staging of patients with presumed or known non-small cell lung cancer and the diagnosis of mediastinal masses.

–The Minister for Health and Ageing accepted this recommendation on 27 August 2007–

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, nuclear medicine, surgery, specialist 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
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Mary Turner	Australian Health Ministers' Advisory Council representative
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Ms Catherine Farrell	Acting Assistant Secretary, Department of Health and Ageing
Associate Professor Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Donald Perry-Keene	endocrinology
Dr Ray Kirk	health research
Dr David Gillespie	gastroenterology

Dr Ewa Piejko	general practice
Dr Brian Richards	Principal Medical Adviser, Department of Health and Ageing
Ms Sheila Rimmer	consumer health issues
Dr David Wood	orthopaedic surgery
Professor Frederick Khafagi	nuclear medicine
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Advisory panel

Advisory panel for MSAC application 1104

Endoscopic ultrasound guided fine-needle aspiration for the staging of non-small cell lung cancer and the diagnosis of mediastinal masses

Dr Kwun Fong (Chair) Thoracic medicine	Member of MSAC
Dr Ray Kirk Health research	Member of MSAC
Dr Robert Chen Consultant gastroenterologist	Co-opted gastroenterologist
Dr Bruce Latham General pathology	Royal Australiasian College of Physicians nominee
Associate Professor Paul Mitchell Medical oncology	Medical Oncology Group of Australia nominee
Dr Hugh Dixson Nuclear medicine	Australian and New Zealand Physicians in Nuclear Medicine nominee
Associate Professor Louis Irving Respiratory medicine	Thoracic Society of Australia and New Zealand nominee
Associate Professor David Ball Radiation oncology	Royal Australian and New Zealand College of Radiologists nominee
Dr Gavin Michael Wright Thoracic surgeon	Thoracic Society of Australia and New Zealand nominee
Ms Robin Toohey Consumer nominee	Consumers' Health Forum of Australia nominee

Evaluators for MSAC application 1104

Dr John Gillespie BSc (Hons) PhD	M-TAG Pty Ltd A unit of IMS Health
Mr Marc Bevan BSc (Hons)	M-TAG Pty Ltd A unit of IMS Health
Mr Koji Makino BCom MCom GradCertPharmEc	M-TAG Pty Ltd A unit of IMS Health
Ms Keira Robinson BSc (Hons) MSc	M-TAG Pty Ltd A unit of IMS Health
Ms Corinne Le Ruen BA(Ec) BA(Statistics)	M-TAG Pty Ltd A unit of IMS Health
Dr Liesl Birinyi-Strachan BSc (Hons) PhD	M-TAG Pty Ltd A unit of IMS Health

Appendix C Supplementary NSCLC data

Two non-comparative studies evaluating the diagnostic accuracy of EUS-FNA in the pre-treatment staging of NSCLC were identified in the literature review (Eloubeidi et al 2005; Larsen et al 2002). The characteristics of these studies are presented in Table 42. These studies were classified as level III-2 evidence according to the NHMRC levels of evidence for diagnostic tests (Table 8).

The study by Eloubeidi et al (2005) is of limited applicability to the target population, as this study included mediastinoscopy as a prior test; this was regarded as comparator, not as prior tests, in the target population (Table 2).

It is possible that the reference standards used in these studies may have affected the reported diagnostic accuracy of EUS-FNA for NSCLC staging. These trials commonly confirmed positive EUS-FNA results with long-term clinical follow up (greater than one year), and confirmed negative EUS-FNA results with surgery (Eloubeidi et al 2005, Larsen et al 2002). Long-term clinical follow up was regarded as an adequate reference standard in this review. It is of concern that this reference standard may not have been sufficiently sensitive to detecting false positive results in patients with early stage disease.

Table 42 Characteristics of the included non-comparative studies assessing the diagnostic accuracy of EUS-FNA in NSCLC pre-treatment staging

Author (year) Country	Study design	Patient characteristics (n)	Test characteristics	Study quality
Eloubeidi (2005) USA	Retrospective, non-consecutive patient enrolment July 2000–July 2004	Patients with biopsy proven lung cancer who had a mediastinoscopy-proven benign lymphadenopathy in the anterior mediastinum **Prior tests**: CT, PET, mediastinoscopy (n = 33)	**Index test**: Radial Olympus GF-UM130 scanner followed by Olympus UC-30P or Olympus UCT 140 linear scanner; 22G needle; unclear selection of lymph nodes for sampling; cytopathologist unknown **Reference standard**: Surgery (n = 16); EUS-FNA + long-term clinical follow up (n = 17)	CX, P2, Q3 *Quality*: Low Non-consecutive patient enrolment Unblinded *Applicability*: limited Enrolled patients with a previous negative mediastinoscopy
Larsen (2002) Denmark	Non-consecutive patient enrolment April 1993–December 1999	Patients with an established diagnosis of lung cancer and mediastinal invasion and/or enlarged lymph nodes by CT or patients with a mediastinal solid lesion or enlarged lymph nodes of unknown origin as detected by CT **Prior tests**: CT (n = 84)	**Index test**: Pentax FG-32UA or Pentax FG-34UA or Pentax FG-36UA linear scanner; 22G needle; unclear selection of lymph nodes for sampling; 1–3 passes per lesions; cytopathologist unknown **Reference standard**: Thoracotomy (19); Mediastinoscopy (1); EUS-FNA + long-term clinical follow up (59); Inconclusive (5)	CX, P1, Q3 *Quality*: Low Non-consecutive patient enrolment Unblinded *Applicability*: Applicable

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

The study by Larsen et al (2002) assessed the non-comparative value of EUS-FNA in the diagnosis of mediastinal masses/lymphadenopathy and NSCLC staging. The diagnostic accuracy of EUS-FNA for NSCLC pre-treatment staging is reported in Table 43. This study reported EUS-FNA diagnostic accuracy at 93.1 per cent (95% [CI: 77.2, 99.2]); 90.0 per cent (95% [CI: 68.3, 98.8]) sensitivity and 100.0 per cent (95% [CI: 66.4, 100.0]) specificity. The diagnostic accuracy of this technique may have been affected by the use of long-term clinical follow up as the reference standard for EUS-FNA positive patients, leading to an overestimation of the specificity of this technique.

Table 43 Accuracy of the EUS-FNA in NSCLC pre-treatment staging (Larsen et al 2002)

Author (year)	Prevalence n/N (%)	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
Larsen (2002)	20/29 (69.0)[a,b]	90.0 (68.3–98.8)	100.0 (66.4–100.0)	93.1 (77.2–99.2)

[a] Prevalence of late-stage NSCLC
[b] Patients with inconclusive final diagnosis were not evaluated in the assessment of diagnostic accuracy

The data from this applicable, low quality study suggest that EUS-FNA is a sensitive and specific diagnostic test for NSCLC pre-treatment staging. The reference standard used in this study may have contributed to an overestimation of specificity.

The study by Eloubeidi et al (2005) assessed the non-comparative value of EUS-FNA for NSCLC pre-treatment staging after a prior negative mediastinoscopy (Table 44). The use of EUS-FNA in this patient group is outside the target population of this assessment report; hence, the applicability of the diagnostic accuracy results is limited. This study reported similar results as Larsen et al (2002): diagnostic accuracy of 97.0 per cent (95% CI: [84.2, 99.9]), 92.9 per cent (95% CI: [66.1, 99.8]) sensitivity, and 100.0 per cent (95% CI: [82.4, 100.0]) specificity. As was the case in the other study, the diagnostic accuracy of this technique may have been affected by the use of long-term clinical follow up as the reference standard for EUS-FNA positive patients.

Table 44 Accuracy of the EUS-FNA in NSCLC pre-treatment staging (Eloubeidi et al 2005)

Author (year)	Prevalence n/N (%)	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
Eloubeidi et al (2005)	14/33 (42.4)[a]	92.9 (66.1, 99.8)	100.0 (82.4, 100.0)	97.0 (84.2, 99.9

[a] Prevalence of late-stage NSCLC

The data from this limited applicability, low quality study suggest that EUS-FNA is a sensitive and specific diagnostic test for the NSCLC pre-treatment staging. The reference standard used in this study may have contributed to an overestimation of specificity.

Appendix D Studies included in the review

Table 45 Characteristics and results of randomised controlled trials assessing the affect of EUS-FNA on patient management

Author (year) Country Study Design	Population Characteristics	Test Characteristics	Study outcomes	Study quality
Larsen et al (2005) Denmark Diagnostic RCT	**Inclusion:** Patients with suspected or newly diagnosed NSCLC who are candidates for invasive staging prior to curative surgery (104) **Exclusion:** Patients with a poor medical condition; refusal of surgery; verified N2/3, T4 or M1 disease or small cell lung cancer; pregnancy; Age <18 years **Prior tests:** Chest CT, bronchoscopy (with TBNA), clinical evaluation, lung function tests, TTNA, PET	**EUS-FNA:** Olympus GF-UC160P-OL5 or Olympus GF-UC140P-AL5 or Pentax EG 3830 linear scanner; 22 gauge needle; all lymph nodes with >1 criterion of malignancy were sampled; 1–3 passes per lesion; presence of cytologist during EUS-FNA procedure was unknown **Mediastinoscopy:** Accessed stations 2/4R, 2/4L, 7	**Futile thoracotomies:** routine EUS-FNA[a] 5 (9%), current clinical practice[b] 13 (25%), $p = 0.03$ **Explorative thoracotomies:** routine EUS-FNA[a] 1 (2%), current clinical practice[b] 5 (10%), $p = 0.11$ **Disease recurrence/death:** routine EUS-FNA[a] 4 (8%)[c], current clinical practice[b] 8 (16%)[d], $p = 0.17$	Randomisation was performed using computer-generated random assignment Patients and physicians were not blinded 104 patients were randomised. 53 patients to the routine EUS-FNA group and 51 patients to current clinical practice All patients were included in the analysis

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

[a] 50 patients received EUS-FNA and 49 patients received mediastinoscopy

[b] 14 patients received EUS-FNA and 46 patients received mediastinoscopy

[c] The median follow up time in this group was 1.3 years (range 0.2–2.4 years)

[d] The median follow up time in this group was 1.4 years (range 0.2–2.4 years)

Table 46 Characteristics and results of systematic reviews assessing the diagnostic accuracy of EUS-FNA

Systematic Review	Objective	Search strategy inclusion/exclusion criteria (included studies)	Methodology	Results	Comment[a]
Kramer and Groen (2003)	To review the test performance characteristics of concepts in the mediastinal staging of NSCLC, evaluating traditional and modern staging modalities.	A brief search strategy was described using PubMed, SUMSearch and reference lists of identified studies. The time period covered by the literature search was not reported. Search terms included: lung cancer staging; computed tomography; magnetic resonance; positron emission; mediastin*; thoracosp*; thoracotom*; endoscop*; bronchoscop*; ultraso*; biopsy* and punct* (n = 49)	No inclusion or exclusion criteria were pre-specified. No description of how the literature search and data analysis were performed. Results presented for studies where lymph nodes surgically verified. Results of included studies were individually summarised. Variation in individual study results was not investigated An assessment of the quality of included studies was not undertaken Sources of heterogeneity were not investigated Summary results were not reported.	**Diagnostic accuracy of EUS-FNA for the staging of NSCLC:** Sn 54 to 97%, Sp 71 to 100%, PPV 64 to 100%, NPV 64 to 95% **Diagnostic accuracy of TBNA for the staging of NSCLC:** Sn 36 to 74%, Sp 92 to 100%, PPV – NR, NPV – NR **Diagnostic accuracy of TTNA for the staging of NSCLC:** Sn 98%, Sp 100%, PPV – NR, NPV – NR **Diagnostic accuracy of mediastinoscopy for the staging of NSCLC:** Sn 44 to 92%, Sp 100%, PPV 100%, NPV 62 to 93% **Diagnostic accuracy of extended cervical mediastinoscopy for the staging of NSCLC:** Sn 69 to 81%, Acc 91 to 94%, Sp NR, PPV – NR, NPV 89 to 91% **Diagnostic accuracy of CT for the staging of NSCLC:** Sn 33 to 83% Sp 66 to 90% PPV 46 to 71%, NPV 68 to 86% **Diagnostic accuracy of PET for the staging of NSCLC:** Sn 71 to 91%, Sp 67 to 94%, PPV 67 to 90%, NPV 77 to 97% **Diagnostic accuracy of MRI for the staging of NSCLC:** Sn 64 to 71%,Sp 48 to 91%,PPV – NR, NPV - NR	*Low quality* —Limited details reported for search strategy and inclusion/exclusion criteria. —No quality assessment was reported —Heterogeneity not investigated —Reference standards used in included studies not clearly reported *Validity:* —Inadequate reporting – not possible to assess included patient populations

Systematic Review	Objective	Search strategy inclusion/exclusion criteria (included studies)	Methodology	Results	Comment[a]
Toloza (2003)	To determine the test performance characteristics of TBNA, TTNA, EUS-NA and mediastinoscopy in staging NSCLC	A brief search strategy was described using Medline, Healthstar, Cochrane library, reference lists and grey literature Literature search was completed in 2001 Search terms included: lung neoplasm, bronchial neoplasm, mediastinoscopy, neoplasm staging, neoplasm metastasis, lymphatic metastasis, biopsy, needle biopsy, CT, mediastinum radiography, emission-CT and sensitivity, specificity Studies with the following characteristics were included: published in a peer reviewed journal, study size >20 patients[b], patient groups not included in subsequent study, confirmation of biopsy results by histology or long-term clinical follow up (>1 year), availability of data to re-calculate diagnostic accuracy measures Articles in English were included (n = 38)	The literature search and data extraction were completed by two independent reviewers Results of included studies were individually summarised An assessment of the quality of included studies was not undertaken Sources of heterogeneity were not explored Results presented were for lung cancer (NSCLC + SCLC) Results were presented as pooled diagnostic accuracy measures (variance measured by range or 95% CI)	**Diagnostic accuracy of EUS-NA for the staging of lung cancer:** Sn 88% (95% CI: [82, 93]), Sp 91% (95% CI: [77, 97]), PPV 98% (range: 96–100%), NPV 77% (range: 68–100%) **Diagnostic accuracy of TBNA for the staging of lung cancer:** Sn 76% (95% CI: [72, 79]), Sp 96% (95% CI: [91, 100]), PPV 100%, NPV 71% (range: 36–100%) **Diagnostic accuracy of TTNA for the staging of lung cancer:** Sn 91% (95% CI: [74, 97]), Sp 100%, PPV 100%, NPV 78% (range: 42–100%) **Diagnostic accuracy of mediastinoscopy for lung cancer staging:** Sn 81% (95% CI: [76, 85]), Sp 100%, PPV 100%, NPV 91% (range: 58–97%)	*Low quality* — No quality assessment was reported — Objective did not correspond with presented results — Heterogeneity not reported *Limited validity* — Summary results are presented for lung cancer (NSCLC + SCLC)

Abbreviations: CI, confidence interval; EUS-NA, endoscopic ultrasound guided needle aspiration; NPV, negative predictive value; NR, not reported; NSCLC, non-small cell lung cancer; PPV, positive predictive value; SCLC, small cell lung cancer; TBNA, transbronchial needle aspiration; TTNA, transthoracic needle aspiration

[a] Quality determined after applying the quality criteria in **Appendix E**

[b] Studies examining mediastinoscopy were required to have >50 patients

Table 47 Characteristics and results of studies assessing the diagnostic accuracy of EUS-FNA

Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
Annema (2005) Netherlands Prospective, non-consecutive patient enrolment Blinded comparison to reference standard 2000–2003	Patients with proven NSCLC without signs of distant metastases after conventional staging and are candidates for surgical resection **Exclusion:** Patients with inadequate (n = 4) or cancelled (n = 1) mediastinoscopies or lack of surgical verification (n = 2) or physician changing therapeutic strategy (n = 1) **Prior tests:** CT (n = 100)	**Index test:** Pentax FG 34 UX linear scanner; 22G needle; unclear selection of lymph nodes for sampling; median 3 needle passes (sampled nodes only); onsite cytopathologist; Accessed stations 3, 4L, 5, 7, 8, 9 **Comparator:** Cervical mediastinoscopy; experienced pathologist; Accessed stations 2L, 2R, 4L, 4R, 7 **Reference standard:** Thoracotomy (n = 80); Mediastinoscopy (n = 20)	**NSCLC** *Prevalence:* 29/93 (31.2%)[a] *EUS-FNA (95% CI):* Sn 75.9 (56.5–89.7), Sp 96.9 (89.2–99.6), Acc 90.3 (82.4–95.5) *Mediastinoscopy (95% CI):* Sn 65.5 (45.7–82.1), Sp 100.0 (94.4–100.0), Acc 89.2 (81.1–94.7)	C1, P1, Q2 *Quality:* Medium Non-consecutive patient enrolment *Applicability:* Applicable
Eloubeidi (2005) USA Retrospective, non-consecutive patient enrolment July 2000–July 2004	Patients with biopsy proven lung cancer who had a mediastinoscopy-proven benign lymphadenopathy in the anterior mediastinum **Prior tests:** CT, PET, mediastinoscopy (n = 33)	**Index test:** Radial Olympus GF-UM130 scanner followed by Olympus UC-30P or Olympus UCT 140 linear scanner; 22G needle; unclear selection of lymph nodes for sampling; cytopathologist unknown **Reference standard:** Surgery (n = 16); EUS-FNA + long-term clinical follow up (n = 17)	**NSCLC** *Prevalence:* 14/33 (42.4%)[a] *EUS-FNA (95% CI):* Sn 92.9 (66.1–99.8), SP 100.0 (82.4–100.0), Acc 97.0 (84.2–99.9)	CX, P2, Q3 *Quality:* Low Non-consecutive patient enrolment Unblinded *Applicability:* limited Enrolled patients with a previous negative mediastinoscopy
Larsen (2002) Denmark Non-consecutive patient enrolment April 1993 – December 1999	Patients with an established diagnosis of lung cancer and mediastinal invasion and/or enlarged lymph nodes by CT or patients with a mediastinal solid lesion or enlarged lymph nodes of unknown origin as detected by CT **Prior tests:** CT (n = 84)	**Index test:** Pentax FG-32UA or Pentax FG-34UA or Pentax FG-36UA linear scanner; 22G needle; unclear selection of lymph nodes for sampling; 1–3 passes per lesions; cytopathologist unknown **Reference standard:** Thoracotomy (19); Mediastinoscopy (1); EUS-FNA + long-term clinical follow up (59); Inconclusive (5)[b]	**NSCLC** *Prevalence:* 20/29 (69.0)[a] *EUS-FNA (95% CI):* Sn 90.0 (68.3–98.8), Sp 100.0 (66.4–100.0), Acc 93.1 (77.2–99.2) **Mediastinal mass** *Prevalence:* 39/50 (78.0) *EUS-FNA (95% CI):* Sn 92.3 (79.1–98.4), Sp 100.0 (71.5–100.0), Acc 94.0 (83.5–98.7)	CX, P1, Q3 *Quality:* Low Non-consecutive patient enrolment Unblinded *Applicability:* Applicable

Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
Larsen (2005b) Denmark Prospective, non-consecutive patient enrolment November 2001 – February 2004	Patients with suspected or newly diagnosed NSCLC who after prior tests are candidates for invasive staging prior to curative surgery **Exclusion:** Poor medical condition; refusal of surgery; verified N2/3, T4 or M1 disease or small cell lung cancer; pregnancy; Age <18 years **Prior tests:** Chest CT, bronchoscopy (with TBNA), clinical evaluation, lung function tests, TTNA, PET (n = 60)	**Index test:** Olympus GF-UC160P-OL5 or Olympus GF-UC140P-AL5 or Pentax EG 3830 linear scanner; 22G needle; all lymph nodes with >1 criterion of malignancy were sampled; 1–3 passes per lesion; cytologist unknown **Comparator:** Cervical mediastinoscopy; experienced pathologist; Accessed stations 2R, 2L, 4R, 4L, 7 **Reference standard:** Thoracotomy (29); EUS-FNA+ long-term clinical follow up (29); Inconclusive (2)[b]	**NSCLC** *Prevalence:* 31/58 (53.5%)[a] *EUS-FNA (95% CI):* Sn 87.1 (70.2–96.4), Sp 100.0 (87.2–100.0), Acc 93.1 (83.3–98.1) *Mediastinoscopy (95% CI):* Sn 19.4 (7.5–37.5), Sp 100.0 (87.2–100.0), Acc 56.9 (43.2–69.8)	C1, P2, Q3 *Quality:* Low Non-consecutive patient enrolment Unblinded *Applicability:* limited Enrolled patients with a previous TBNA or TTNA

Abbreviations: Acc, accuracy; CT, computed tomography; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration; NSCLC, non-small cell lung cancer; PET, positron emission tomography; Sn, sensitivity; Sp, specificity; TBNA, transbronchial needle aspiration; TTNA, transthoracic needle aspiration

[a] Prevalence of late-stage NSCLC

[b] Patients with inconclusive final diagnosis were not evaluated in the assessment of diagnostic accuracy

Table 48 Characteristics of a study assessing the impact of EUS-FNA on patient management and results for mediastinal/lung indications

Author (year) Country Study Design	Population characteristics, physicians	Test characteristics	Study outcomes[a]	Comment
Chong et al (2005) Australia Prospective pre-test, post-test case series August 2002 – June 2004	Patients with mixed indications[b] referred to EUS/EUS-FNA for diagnosis or staging Exclusion: Incomplete pre-test and post-test management plans (231) **Physicians determining management:** Referring doctors: physicians (62%), surgeons (38%)	Olympus GF-UM20 or Olympus GF-UM160 or Olympus GF-UC140P scanner Performed by single experienced gastroenterologist	**Overall change:** 75.6% **Surgery avoided:** 42.2% **Invasive diagnostic procedure avoided:** 15.6% **Change in diagnosis:** 4.4% **Change in staging:** 13.3%	Data reporting did not allow a separate analysis of mediastinal and NSCLC indications Potential reduced applicability to target population

Abbreviations: EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration

[a] Refers to mediastinal mass/mediastinal lymphadenopathy and lung cancer indications

[b] Mixed indications, including oesophageal (32.5%), gastric (15.2%), pancreaticobiliary (31.1%), lung/mediastinal disease (19.5%) and duodenal (1.7%)

Appendix E 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?
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?

Case-control study, *cont*	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 (i.e. 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 F Additional information for economic evaluation

Estimation of life expectancy

The declining exponential approximation of life expectancy (DEALE) method (Beck et al 1982) was used to derive life expectancy (LE) estimates used in the economic model. The DEALE utilises mortality parameters under the assumption that population survival follows a declining exponential curve in which LE is the reciprocal of the annual mortality rate. When excess illness is considered, LE becomes the inverse of the sum of the ASR and the disease specific mortality rate (DSR) (Formula 1)

$$LE = \frac{1}{ASR + DSR} \qquad \text{(Formula 1)}$$

The age, sex and race specific mortality rate (ASR) for an otherwise healthy individual is obtained by taking the reciprocal of the corresponding LE. Data specific to an Australian, 65-year-old cohort were used in the estimation (65 years of age was the mean age of diagnosis for any non-small cell lung cancer [NSCLC] in the Australian population according to Hall et al 2004). ASR estimates were calculated using tables of vital statistics provided by the Australian Bureau of Statistics. DSRs for various stages of NSCLC were based on estimates from Deitlein et al (2000). Although DSR figures were primarily extracted from American medical literature, these statistics are valid in the Australian population given that the five year survival estimates for lung cancer patients are similar—12 per cent and 15.8 per cent for Australian males and females, respectively; 11 per cent and 16 per cent for American males and females, respectively (Australian Institute of Health and Welfare 2001).

Major capital equipment costs

Table 49 Determination of capital cost per procedure

Cost of investment	Year 0	Year 1	Year 2	Year 3
Undepreciated value of equipment [a]	$319,145	$239,359	$159,573	$79,786
Depreciation over a year [b]	$79,786	$79,786	$79,786	$79,786
Opportunity cost of investment [c]	$25,500	$19,125	$12,750	$6,375
Maintenance costs [d]	$31,915	$31,915	$31,915	$31,915
Annual total costs	$137,201	$130,826	$124,451	$118,076
Present value of cost stream [e]	$137,201	$124,596	$112,881	$101,999
Total present value of cost stream [f]		$476,677		
Return on investment				
Number of procedures performed annually [g]	120	120	120	120
Total number of procedures performed		480		
Calculated capital cost per procedure		**$993**		

[a] Cost of equipment ($319,145) supplied by the applicant. Undepreciated value of equipment based on assumption that 159 procedures are performed annually per machine and all of those procedures are for the indication examined in this analysis
[b] Assumes straight-line depreciation, 4-year lifetime of equipment and $0 residual value
[c] Calculated by considering an interest rate of 7.99 per cent for purchase costs. Interest rate provided by Medfin Finance, Sydney
[d] Proposed by the Applicant
[e] Discounted at 5%
[g] Proposed by the Applicant

Appendix G Staging classification

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

Lung cancer

The TNM staging of lung cancer as described by the American Joint Committee on Cancer (AJCC) is presented in Table 50 and the stage classification is presented in Table 51.

Table 50 TNM classification of 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 visualized 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; however, in a few patients, multiple cytopathologic examinations of pleural fluid are negative for tumour. In these cases, fluid is non-bloody and is not an exudate. Such patients may be further evaluated by videothoracoscopy 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 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, pp167–177

Table 51 Staging of lung cancer 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, pp167–177

Appendix H Literature search

Medline search strategy

Two search strategies were used to identify relevant studies of EUS-FNA for the diagnosis of mediastinal masses of unknown origin and the pre-treatment staging of NSCLC in Medline. The search strategy used to identify diagnostic accuracy studies is presented in Table 52 and the strategy to identify management/outcome studies is presented in Table 53.

Table 52 EUS-FNA for the diagnosis of mediastinal masses of unknown origin and the pre-treatment staging of NSCLC (diagnostic accuracy), Medline search strategy (1966 to August Week 2 2006)

Keywords / search history		Results
1.	endosonography/	3956
2.	endoscopy/	28401
3.	ultrasonography/ or ultrasonography, interventional/	60257
4.	2 and 3	552
5.	ultrasonics/ and endoscop$.ti,ab.	90
6.	(endosonograph$ or echo?endoscop$ or eus).ti,ab.	3182
7.	(endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab.	2912
8.	(interventional adj (ultrason$ or ultrasound)).ti,ab.	64
9.	or/1,4-8	7007
10.	exp biopsy, needle/	37230
11.	((aspiration or puncture or suction) adj biopsy).ti,ab.	6114
12.	((fine-needle adj (aspiration or biopsy)) or fna$1).ti,ab.	14086
13.	or/10-12	41766
14.	9 and 13	996
15.	(endoscopic ultrasound adj5 fine-needle aspiration).ti,ab.	242
16.	(eus fna$1 or (eus guided adj3 biopsy)).ti,ab.	282
17.	(endoscopic ultrasonography adj5 fine-needle aspiration).ti,ab.	63
18.	or/14-17	1013
19.	carcinoma, non-small-cell lung/	17867
20.	lung neoplasms/	113943
21.	(nsclc or ((nonsmall or non small) adj cell lung)).ti,ab.	17207
22.	((lung or pulmonary) adj3 (cancer or neoplasm$)).ti,ab.	56126
23.	or/19-22	123936
24.	18 and 23	158
25.	neoplasm staging/	76009
26.	(stage or staging or restaging).ti,ab.	321084
27.	exp lymph nodes/	52089
28.	lymphatic metastasis/	48903
29.	sentinel lymph node biopsy/	3329
30.	(lymph node$ or lymph gland or lymphoid nodule).ti,ab.	91001
31.	(lymphatic adj (gland or node or metastasis or tissue)).ti,ab.	1406
32.	carcinoma, non-small-cell lung/us	65
33.	lung neoplasms/us	306
34.	exp lung/us	421
35.	or/25-34	462459
36.	24 and 35	145
37.	mediastinum/	4329
38.	mediastinal neoplasms/	9438
39.	(mediastinum or mediastinal).ti,ab.	25200
40.	or/37-39	29374
41.	18 and 40	189
42.	or/36,41	237

Table 53 EUS-FNA for the diagnosis of mediastinal masses of unknown origin and the pre-treatment staging of NSCLC (management/outcomes), Medline search strategy (1966 to July Week 2 2006)

Keywords / search history		Results
1.	endosonography/	3909
2.	endoscopy/	28141
3.	ultrasonography/ or ultrasonography, interventional/	59880
4.	2 and 3	541
5.	ultrasonics/ and endoscop$.ti,ab.	90
6.	(endosonograph$ or echo?endoscop$ or eus).ti,ab.	3129
7.	(endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab.	2880
8.	(interventional adj (ultrason$ or ultrasound)).ti,ab.	64
9.	or/1,4-8	6915
10.	exp biopsy, needle/	36779
11.	((aspiration or puncture or suction) adj biopsy).ti,ab.	6078
12.	((fine-needle adj (aspiration or biopsy)) or fna$1).ti,ab.	13960
13.	or/10-12	41273
14.	9 and 13	975
15.	(endoscopic ultrasound adj5 fine-needle aspiration).ti,ab.	236
16.	(eus fna$1 or (eus guided adj3 biopsy)).ti,ab.	275
17.	(endoscopic ultrasonography adj5 fine-needle aspiration).ti,ab.	61
18.	or/14-17	992
19.	exp decision making/	65917
20.	disease management/	4700
21.	"outcome assessment health care"/	24489
22.	(impact adj5 management).ti,ab.	2240
23.	management plan$1.ti,ab.	1609
24.	((management or diagnosis) adj3 (change$1 or alter$)).ti,ab.	8358
25.	or/19-24	104832
26.	18 and 25	44
27.	survival/	2381
28.	exp survival analysis/	80233
29.	exp mortality/	177494
30.	fatal outcome/	29473
31.	mo.fs.	275012
32.	prognosis/	242302
33.	disease-free survival/	21755
34.	disease progression/	42867
35.	recurrence/	113931
36.	(outcome or survival or mortality or death).ti,ab.	921195
37.	(progression or natural course or natural history).ti,ab.	165336
38.	(recur$ or recrudescence or relaps$).ti,ab.	300389
39.	or/27-38	1559492
40.	18 and 39	197
41.	or/26,40	226
42.	41 and carcinoma, non-small-cell lung/	13
43.	41 and exp lung neoplasms/	25
44.	41 and mediastinal neoplasms/	15
45.	41 and (nsclc or ((nonsmall or non small) adj cell lung)).ti,ab.	14

Keywords / search history		Results
46.	41 and ((lung or pulmonary) adj3 (cancer or neoplasm$)).ti,ab.	27
47.	41 and (mediastinum or mediastinal).ti,ab.	41
48.	or/42-47	55

EMBASE search strategy

Two search strategies were used to identify relevant studies of EUS-FNA for the diagnosis of mediastinal masses of unknown origin and the pre-treatment staging of NSCLC in EMBASE. The search strategy used to identify diagnostic accuracy studies is presented in Table 54 and the strategy to identify management/outcome studies is presented in Table 55.

Table 54 EUS-FNA for the diagnosis of mediastinal masses of unknown origin and the pre-treatment staging of NSCLC (diagnostic accuracy), EMBASE search strategy (1980 to Week 32 2006)

Keywords / search history		Results
1.	endoscopic echography/	4157
2.	echography/ and endoscopy/	1186
3.	echography/ and endoscop$.ti,ab.	2861
4.	ultrasound/ or ultrasound transducer/	32228
5.	endoscopy/	25376
6.	4 and 5	370
7.	(endosonograph$ or echo?endoscop$ or eus).ti,ab.	3310
8.	(endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab.	3104
9.	(interventional adj (ultrason$ or ultrasound)).ti,ab.	67
10.	or/1-3,6-9	9022
11.	needle biopsy/	8384
12.	aspiration biopsy/	12613
13.	((aspiration or puncture or suction) adj biopsy).ti,ab.	4640
14.	((fine-needle adj (aspiration or biopsy)) or fna$1).ti,ab.	12250
15.	or/11-14	24224
16.	10 and 15	1046
17.	(endoscopic ultrasound adj5 fine-needle aspiration).ti,ab.	273
18.	(eus fna$1 or (eus guided adj3 biopsy)).ti,ab.	332
19.	(endoscopic ultrasonography adj5 fine-needle aspiration).ti,ab.	78
20.	or/16-19	1064
21.	lung non small cell cancer/	14644
22.	lung carcinoma/	13809
23.	(nsclc or ((nonsmall or non small) adj cell lung)).ti,ab.	13621
24.	((lung or pulmonary) adj3 (cancer or neoplasm$)).ti,ab.	43475
25.	or/21-24	57839
26.	20 and 25	146
27.	cancer staging/	59888
28.	staging/	2157
29.	(stage or staging or restaging).ti,ab.	252444
30.	exp lymph node/	32863
31.	exp lymph node biopsy/	6136
32.	lymph node metastasis/	28091
33.	(lymph node$ or lymph gland or lymphoid nodule).ti,ab.	68677
34.	(lymphatic adj (gland or node or metastasis or tissue)).ti,ab.	916
35.	or/27-34	337916
36.	26 and 35	126
37.	exp mediastinum/	7172
38.	exp mediastinum tumor/	4673
39.	(mediastinum or mediastinal).ti,ab.	17945
40.	or/37-39	20443
41.	20 and 40	227
42.	or/36,41	255

Table 55 EUS-FNA for the diagnosis of mediastinal masses of unknown origin and the pre-treatment staging of NSCLC (management/outcomes), EMBASE search strategy (1980 to Week 28 2006)

Keywords / search history		Results
1.	endoscopic echography/	4082
2.	echography/ and endoscopy/	1176
3.	echography/ and endoscop$.ti,ab.	2836
4.	ultrasound/ or ultrasound transducer/	31933
5.	endoscopy/	25210
6.	4 and 5	368
7.	(endosonograph$ or echo?endoscop$ or eus).ti,ab.	3255
8.	(endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab.	3075
9.	(interventional adj (ultrason$ or ultrasound)).ti,ab.	65
10.	or/1-3,6-9	8913
11.	needle biopsy/	8309
12.	aspiration biopsy/	12499
13.	((aspiration or puncture or suction) adj biopsy).ti,ab.	4627
14.	((fine-needle adj (aspiration or biopsy)) or fna$1).ti,ab.	12186
15.	or/11-14	24025
16.	10 and 15	1006
17.	(endoscopic ultrasound adj5 fine-needle aspiration).ti,ab.	270
18.	(eus fna$1 or (eus guided adj3 biopsy)).ti,ab.	320
19.	(endoscopic ultrasonography adj5 fine-needle aspiration).ti,ab.	78
20.	or/16-19	1023
21.	diagnostic accuracy/	96796
22.	medical decision making/	37236
23.	exp disease management/	558851
24.	dm.fs.	60532
25.	outcomes research/	55910
26.	outcome assessment/	172924
27.	(impact adj5 management).ti,ab.	3475
28.	management plan$1.ti,ab.	1550
29.	((management or diagnosis) adj3 (change$1 or alter$)).ti,ab.	12181
30.	or/21-29	694640
31.	20 and 30	492
32.	exp survival/	175126
33.	exp mortality/	177211
34.	fatality/	37963
35.	prognosis/	140372
36.	recurrent disease/	41250
37.	disease course/	120634
38.	relapse/	18880
39.	(outcome or survival or mortality or death).ti,ab.	752387
40.	(progression or natural course or natural history).ti,ab.	141487
41.	(recur$ or recrudescence or relaps$).ti,ab.	247838
42.	or/32-41	1262423
43.	20 and 42	249
44.	or/31,43	591
45.	44 and lung non small cell cancer/	52

Keywords / search history		Results
46.	44 and exp lung carcinoma/	61
47.	44 and exp lung tumor/	105
48.	44 and exp mediastinum tumor/	51
49.	44 and (nsclc or ((nonsmall or non small) adj cell lung)).ti,ab.	41
50.	44 and ((lung or pulmonary) adj3 (cancer or neoplasm$)).ti,ab.	75
51.	44 and (mediastinum or mediastinal).ti,ab.	115
52.	or/45-51	173

PreMedline search strategy

Two search strategies were used to identify relevant studies of EUS-FNA for the diagnosis of mediastinal masses of unknown origin and the pre-treatment staging of NSCLC in PreMedline. The search strategy used to identify diagnostic accuracy studies is presented in Table 56 and the strategy to identify management/outcome studies is presented in Table 57.

Table 56 EUS-FNA for the diagnosis of mediastinal masses of unknown origin and the pre-treatment staging of NSCLC (diagnostic accuracy), PreMedline search strategy (15 August 2006)

Keywords / search history		Results
1.	(endosonograph$ or echo?endoscop$ or eus).ti,ab.	140
2.	(endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab.	121
3.	(interventional adj (ultrason$ or ultrasound)).ti,ab.	1
4.	or/1-3	210
5.	((aspiration or puncture or suction) adj biopsy).ti,ab.	89
6.	((fine-needle adj (aspiration or biopsy)) or fna$1).ti,ab.	298
7.	or/5-6	315
8.	4 and 7	50
9.	(endoscopic ultrasound adj5 fine-needle aspiration).ti,ab.	13
10.	(eus fna$1 or (eus guided adj3 biopsy)).ti,ab.	21
11.	(endoscopic ultrasonography adj5 fine-needle aspiration).ti,ab.	3
12.	or/8-11	52
13.	(nsclc or ((nonsmall or non small) adj cell lung)).ti,ab.	743
14.	((lung or pulmonary) adj3 (cancer or neoplasm$)).ti,ab.	1622
15.	or/13-14	1668
16.	12 and 15	8
17.	(stage or staging or restaging).ti,ab.	9871
18.	(lymph node$ or lymph gland or lymphoid nodule).ti,ab.	1953
19.	(lymphatic adj (gland or node or metastasis or tissue)).ti,ab.	74
20.	or/17-19	11288
21.	16 and 20	7
22.	(mediastinum or mediastinal).ti,ab.	453
23.	12 and 22	10
24.	or/21,23	11

Table 57 EUS-FNA for the diagnosis of mediastinal masses of unknown origin and the pre-treatment staging of NSCLC (management/outcomes), PreMedline search strategy (19 July 2006)

Keywords / search history		Results
1.	(endosonograph$ or echo?endoscop$ or eus).ti,ab.	151
2.	(endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab.	118
3.	(interventional adj (ultrason$ or ultrasound)).ti,ab.	1
4.	or/1-3	210
5.	((aspiration or puncture or suction) adj biopsy).ti,ab.	88
6.	((fine-needle adj (aspiration or biopsy)) or fna$1).ti,ab.	299
7.	or/5-6	316
8.	4 and 7	54
9.	(endoscopic ultrasound adj5 fine-needle aspiration).ti,ab.	15
10.	(eus fna$1 or (eus guided adj3 biopsy)).ti,ab.	24
11.	(endoscopic ultrasonography adj5 fine-needle aspiration).ti,ab.	4
12.	or/8-11	55
13.	(impact adj5 management).ti,ab.	96
14.	management plan$1.ti,ab.	66
15.	((management or diagnosis) adj3 (change$1 or alter$)).ti,ab.	218
16.	or/13-15	369
17.	12 and 16	1
18.	(outcome or survival or mortality or death).ti,ab.	27412
19.	(progression or natural course or natural history).ti,ab.	5067
20.	(recur$ or recrudescence or relaps$).ti,ab.	7631
21.	or/18-20	36098
22.	12 and 21	15
23.	or/17,22	16
24.	(nsclc or ((nonsmall or non small) adj cell lung)).ti,ab.	682
25.	((lung or pulmonary) adj3 (cancer or neoplasm$)).ti,ab.	1529
26.	(mediastinum or mediastinal).ti,ab.	464
27.	or/24-26	1956
28.	23 and 27	1

Cochrane Library search strategy

The search strategy used to identify relevant studies of EUS-FNA for the diagnosis of mediastinal masses of unknown origin and the pre-treatment staging of NSCLC in the Cochrane Library is presented in **Table 58**.

Table 58 EUS-FNA for the diagnosis of mediastinal masses of unknown origin and the pre-treatment staging of NSCLC, Cochrane Library search strategy (Issue 3 2006)

Keywords / search history		Results
1.	MeSH descriptor Endosonography explode all trees	154
2.	MeSH descriptor Endoscopy explode all trees	7846
3.	MeSH descriptor Ultrasonography explode all trees	4381
4.	MeSH descriptor Ultrasonography, Interventional explode all trees	291
5.	(#3 OR #4)	4381
6.	(#2 AND #5)	98
7.	MeSH descriptor Ultrasonics explode all trees	202
8.	(endoscop*)	8758
9.	(#7 AND #8)	8
10.	(endosonograph* OR echoendoscop* OR echo-endoscop* OR eus)	221
11.	(endoscop* near (echo* OR ultrason* OR ultrasound))	219
12.	(interventional near (ultrason* OR ultrasound))	349
13.	(#1 OR #6 OR #9 OR #10 OR #11 OR #12)	690
14.	MeSH descriptor Biopsy, Needle explode all trees	729
15.	(aspiration OR puncture OR suction) near biopsy	204
16.	(fine-needle NEAR (aspiration OR biopsy))	280
17.	(fna*)	124
18.	(#14 OR #15 OR #16 OR #17)	909
19.	(#13 AND #18)	83
20.	"endoscopic ultrasound" near "fine-needle aspiration"	15
21.	"eus fna*" .ti,ab.	0
22.	"eus guided" near biopsy.ti,ab.	0
23.	"endoscopic ultrasonography" near "fine-needle aspiration"	2
24.	(#19 OR #20 OR #21 OR #22 OR #23)	83
25.	MeSH descriptor Carcinoma, Non-Small-Cell Lung explode all trees	1127
26.	MeSH descriptor Lung Neoplasms explode all trees	2824
27.	(nsclc)	1128
28.	(nonsmall OR non small) NEAR "cell lung"	2208
29.	(#27 OR #28)	2308
30.	(lung OR pulmonary) near (cancer OR neoplasm*)	4774
31.	(#25 OR #26 OR #29 OR #30)	4906
32.	(#24 AND #31)	10
33.	MeSH descriptor Neoplasm Staging explode all trees	2696
34.	(stage or staging or restaging)	20620
35.	MeSH descriptor Lymph Nodes explode all trees	368
36.	MeSH descriptor Lymphatic Metastasis explode all trees	1053
37.	MeSH descriptor Sentinel Lymph Node Biopsy explode all trees	67
38.	"lymph node*" or "lymph gland" or "lymphoid nodule"	1681
39.	(lymphatic near (gland OR node OR metastasis OR tissue))	1199
40.	(#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39)	21981

Keywords / search history		Results
41.	(#32 AND #40)	8
42.	MeSH descriptor Mediastinum explode all trees	80
43.	MeSH descriptor Mediastinal Neoplasms explode all trees	52
44.	(mediastinum OR mediastinal)	610
45.	(#42 OR #43 OR #44)	610
46.	(#24 AND #45)	11
47.	(#41 OR #46)	14

Secondary databases

Searches of the following secondary databases/sites were also performed:

- Agencia de Evaluación de Tecnologías Sanitarias, España (Spain)
- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) (Quebec, Canada)
- Agence Nationale d'Accreditation et d'Evaluation en Santé (France)
- Agency for Healthcare Research and Quality (USA)
- Alberta Heritage Foundation for Medical Research (Canada)
- Austrian Institute of Technology Assessment
- British Columbia Office of Health Technology Assessment (Canada)
- Blue Cross Blue Shield Association Technology Evaluation Center (USA)
- Canadian Agency for Drugs and Technologies in Health (CADTH) (formerly Coordinating Office for Health Technology Assessment [CCOHTA])
- Catalan Agency for Health Technology Assessment (CAHTA)
- Centre for Health Program Evaluation (Monash University, Australia), Monash University Evidence Centre Reports (Australia)
- Centers for Medicare and Medicaid Services (USA)
- Centre for Reviews and Dissemination (University of York, UK)
- Current Controlled Trials metaRegister and ISRTCN register
- Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)
- Department of Health Publications (UK)
- ECRI (formerly Emergency Care Research Institute) (USA)

- Finnish Office for Health Technology Assessment (FinOHTA)
- German Institute for Medical Documentation and Information (DIMDI)
- Harvard Centre for Risk Analysis: Program on the Economic Evaluation of Health Technology (USA)
- Health Council of the Netherlands
- Health Economics Research Group (Brunel University, UK)
- Health Information Research Unit (HIRU) internal database (McMaster University, Canada)
- Health Technology Advisory Committee (Minnesota Department of Health, USA)
- Health Technology Assessment International Conference Proceedings
- Health Technology Board for Scotland (UK)
- Institute for Clinical Evaluative Sciences (Canada)
- Institute for Medical Technology Assessment Erasmus MC (Netherlands)
- International Network of Agencies for Health Technology Assessment (INAHTA)(Sweden)
- International Society of Technology Assessment in Health Care (Montreal, Canada)
- Israel Centre for Technological Assessment of Health Care Services
- Medion Database (Netherlands)
- Monash University Evidence Centre Reports (Australia)
- National Guidelines Clearinghouse (USA)
- National Health and Medical Research Council Australia publication list
- National Health Service Health Technology Assessment Programme (UK)
- National Information Center on Health Services Research and Health Care Technology (HSTAT database) (USA), National Library of Medicine Health Services/Technology Assessment Text (HSTAT) (USA)
- New Zealand Health Technology Assessment
- Scottish Intercollegiate Guidelines Network (SIGN) (Scotland)

- Swedish Council on Technology Assessment in Health Care (SBU)
- Swiss Centre for Technology Assessment (TA-SWISS)
- Swiss Network for Health Technology Assessment (SNHTA).

Abbreviations

AACR	Australasian Association of Cancer Registries
AHMAC	Australian Health Ministers' Advisory Council
AIHW	Australian Institute of Health and Welfare
AJCC	American Joint Committee on Cancer
ARTG	Australian Registry of Therapeutic Goods
CDI	colour Doppler imaging
CI	confidence interval
CT	computed tomography
DEALE	declining exponential approximation of life expectancy
DOR	diagnostic odds ratio
EBUS	endobronchial ultrasound
ECOG	Eastern Cooperative Oncology Group
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound
FNA	fine-needle aspiration
GI	gastro-intestinal
MBS	Medicare Benefits Schedule
MED	mediastinoscopy
MRI	magnetic resonance imaging
MSAC	Medical Services Advisory Committee
NCI	National Cancer Institute
NCSG	National Cancer Strategies Group
NHMRC	National Health and Medical Research Council
NPV	negative predictive value
NSCLC	non-small cell lung cancer

PET	positron emission tomography
PPV	positive predictive value
pTNM	pathological tumour-node-metastasis
QUOROM	quality of reporting of meta-analyses
RCT	randomised controlled trial
SCLC	small cell lung cancer
TBNA	transbronchial needle aspiration
TCB	Tru-Cut biopsy
TGA	Therapeutic Goods Administration
TTNA	transthoracic needle aspiration
VATS	video-assisted thoracoscopy surgery
WHO	World Health Organization

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