Appendix E – Clinical evidence tables

Short Title	Title	Study Characteristics	Risk of Bias
Annema 2010	Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial	**Study type** • Randomised controlled trial *This is the ASTER RCT, which has a mirror publication - Sharples 2012. ASTER is short for: Assessment of Surgical sTaging versus Endosonographic ultrasound in lung cancer: a Randomised clinical trial. Data in Sharples 2012 was also used in this analysis.* **Study details** • Study location *Netherlands, Belgium, UK* • Study setting *Leiden University Medical Center, the Netherlands; the University Hospitals of Ghent and Leuven in Belgium; and Papworth Hospital United Kingdom.* • Study dates *February 2007 to April 2009* • Duration of follow-up *Study inclusion, preliminary findings, and complications were evaluated 1 year after start of the study. Patients were followed up for survival for 6 months after staging.* • Sources of funding *Local support for data collection at Ghent University Hospital was provided by the Zorg-programma Oncologie Gent (ZOG) (Ghent University Hospital). Data collection in Papworth Hospital was supported by the UK National Health Service R&D Health. Two of the*	**Quality assessment (RCT)** Random sequence generation • Unclear risk of bias *Details of the randomisation method are not provided.* Allocation concealment • Unclear risk of bias *No mention of allocation concealment.* Blinding of outcome assessment • Unclear risk of bias *No mention of how aware pathologists and radiologists were of the trial taking place.* Blinding of participants and personnel • Unclear risk of bias *Blinding is not possible for a study of this nature.* Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		investigators were supported in part by the National Institute for Health Research Cambridge Biomedical Research Centre. • Lung cancer staging system used *European Society of Thoracic Surgeons Guidelines 2007* **Inclusion criteria** • Suspected N2 or N3 mediastinal lymph node involvement **Exclusion criteria** • <18 years of age • Not fit enough to undergo thoracotomy and lung resection • Significant concurrent malignant disease • Any condition that contraindicated the intervention or mediastinoscopy • Known extrathoracic malignant disease • Received previous treatment for lung cancer • Uncorrected coagulopathy • Unlikely to be staged accurately by any surgical staging procedure • Pregnancy • Inability to consent **Sample characteristics** • Sample size *241 people* • Split between study groups *Straight to surgical staging (mediastinoscopy) = 117 (one person dropped out because they had bone metastasis); EUS-FNA followed by EBUS-TBNA = 123*	Other sources of bias • Low risk of bias Overall risk of bias • Moderate *Details of randomisation are not provided* Directness • Directly applicable **QUADAS 2** Was a random sample of patients enrolled? • Unclear *Details of the randomisation method are not provided.* Was a case-control design avoided? • Yes Did the study avoid inappropriate exclusions? • Yes RISK Could the selection of patients have introduced bias? • Low CONCERN Is there concern that the included patients do not match the review question?

Short Title	Title	Study Characteristics	Risk of Bias
		• Loss to follow-up *All 241 people were followed up.* • %female *Straight to surgical staging = 74% male, 26% female; EUS-FNA then EBUS-TBNA = 80% male, 20% female* • Mean age (SD) *Straight to surgical staging = 65 (9); EUS-FNA then EBUS-TBNA = 65 (9)* • Nodal staging on initial PET/CT scan *Straight to surgical staging = N0: 13%; N1: 14%; N2: 56%; N3: 17%; EUS-FNA then EBUS-TBNA = N0: 7%; N1: 16%; N2: 63%; N3: 13%* **Interventions** • EUS-FNA followed by EBUS-TBNA • Straight to surgical staging (mediastinoscopy) **Downstream investigations and/or treatments** • EUS-FNA followed by EBUS-TBNA arm *58/123 were found to have locally advanced disease. They proceeded to multimodality treatment. 65/123 were without locally advanced disease. They proceeded to surgical staging. 6/65 had locally advanced disease at surgical staging and had multimodality treatment. 59/65 were without locally advanced disease. 58/59 had a thoracotomy. 1/59 had a second endoscopy. Of the 58 who had a thoracotomy, 6/58 had locally advanced disease and 52/58 were without locally advanced disease.* • Straight to surgical staging arm *117/118 went straight to surgical staging. 1/118 did not because they were found to have bone metastasis. At surgical staging, 42/117 had*	• Low Were the index test results interpreted without knowledge of the results of the reference standard? • Unclear *Information about blinding was not provided.* If a threshold was used, was it pre-specified? • Yes RISK Could the conduct or interpretation of the index test have introduced bias? • Unclear Concerns regarding applicability • Low Is the reference standard likely to correctly classify the target condition? • Yes Were the reference standard results interpreted without knowledge of the results of the index test? • Unclear *Details regarding blinding were not provided.* RISK Could the reference standard, its conduct, or its interpretation have introduced bias?

Short Title	Title	Study Characteristics	Risk of Bias
		locally advanced disease. They proceeded to multimodality treatment. 75/117 were without locally advanced disease. Of these, 70/75 underwent thoracotomy, 3/75 refused thoracotomy, 1/75 had endoscopy, 1/75 deteriorated clinically. Of these 75 without locally advanced disease on surgical staging, 16 were found to have locally advanced disease and 59 were found to be without locally advanced disease. **Protocol outcome measures** • Diagnostic sensitivity *Sensitivity = people who the intervention deemed positive [and were confirmed N2/3 by pathology] / (people who the intervention deemed positive [and were confirmed N2/3 by pathology] + people who the intervention deemed negative who were subsequently shown to have N2/3 at thoracotomy [confirmed by pathology])* • Diagnostic negative predictive value *NPV = people who the intervention deemed negative [and were confirmed negative by thoracotomy with pathology] / (people who the intervention deemed negative [and were confirmed negative by thoracotomy with pathology] + people who the intervention deemed negative but had N2/3 as confirmed by thoracotomy and pathology])* • Safety: pneumothorax *This was the only complication that was relevant to EUS-FNA and EBUS-TBNA* • Safety: other complications • Quality of life *The EQ-5D questionnaire was completed using standard proforma at baseline, at the end of staging (after surgical staging but before thoracotomy) and after 2 months and 6 months for all patients recruited at Papworth Hospital. This information was collected for patients in the*	• Unclear CONCERN Is there concern that the target condition as defined by the reference standard does not match the review question? • Low Was there an appropriate interval between index test(s) and reference standard? • Unclear *Timings are not provided.* Did all patients receive a reference standard? • Yes Did patients receive the same reference standard? • Yes Were all patients included in the analysis? • Yes RISK Could the patient flow have introduced bias? • Low Overall quality • Moderate

Short Title	Title	Study Characteristics	Risk of Bias
		continental European centres who were recruited after April 2008. Between February 2007 and April 2008, EQ-5D data were not available from the continental European centres. As this represented a block of time for which no patient completed the EQ-5D, this information was reasonably assumed to be missing at random. **Non-protocol outcome measures** • No. of avoidable thoracotomies *Rate of unnecessary thoracotomies was defined as either exploratory thoracotomy, unexpected presence of mediastinal nodal metastases (pN2/N3) or tumor invasion of the mediastinum at thoracotomy (pT4), pM1, thoracotomy for SCLC or benign disease (other than carcinoid or hamartoma), or death within 30 days after surgery.* • Percentage (or number) of people who died during a specified follow-up period *Patients were followed up for survival for 6 months after staging.*	
Kang 2014	EBUS-centred versus EUS-centred mediastinal staging in lung cancer: a randomised controlled trial	**Study type** • Randomised controlled trial **Study details** • Study location *South Korea* • Study setting *National Cancer Center in Goyang, South Korea* • Study dates *June 2011 to February 2012* • Duration of follow-up *3-5 days after the intervention*	**Quality assessment (RCT)** Random sequence generation • Low risk of bias Allocation concealment • Low risk of bias Blinding of outcome assessment • Unclear risk of bias *Blinding of pathology laboratory staff was not mentioned.* Blinding of participants and personnel

Short Title	Title	Study Characteristics	Risk of Bias
		• Sources of funding *This work was supported by National Cancer Center Grant* • Lung cancer staging system used *Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2:706–14.* **Inclusion criteria** • Histologically confirmed or strongly suspected, potentially operable non-small cell lung cancer **Exclusion criteria** • <18 years of age • Not fit enough to undergo thoracotomy and lung resection • Any condition that contraindicated the intervention or mediastinoscopy • Any medication that contraindicated the intervention or mediastinoscopy • Pregnancy • >80 years of age • M1 disease • Inoperable T4 disease • Mediastinal infiltration or extranodal invasion of the mediastinal lymph node visible on chest CT • Confirmed supraclavicular lymph node metastasis • Pancoast tumours • Ground glass-dominant (>50% in diameter) T1 nodule (≤3 cm)	• Unclear risk of bias *Blinding is not really possible.* Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Unclear risk of bias *The inclusion criteria are vague with regards to imaging or the standards/guidelines that were used.* Overall risk of bias • Moderate Directness • Indirectly applicable *The inclusion criteria are vague with regards to imaging or guidelines/standards used. In addition, all participants underwent a bronchoscopy just before the interventions of interest.* **QUADAS 2** Was a random sample of patients enrolled? • Yes

Short Title	Title	Study Characteristics	Risk of Bias
		• Drug reaction to lidocaine, midazolam, fentanyl **Sample characteristics** • Sample size *148 people* • Split between study groups *74 in each arm* • Loss to follow-up *None* • %female *Bronchoscopy, then EBUS-TBNA, then – if required – EUS-FNA = 21% female, 79% male; Bronchoscopy, then EUS-FNA, then – if required – EBUS-TBNA = 29% female, 71% male* • Mean age (SD) *Bronchoscopy, then EBUS-TBNA, then – if required – EUS-FNA = 63.21 years (7.91); Bronchoscopy, then EUS-FNA, then – if required – EBUS-TBNA = 62.94 years (8.39)* • Nodal staging on initial PET/CT scan *Bronchoscopy, then EBUS-TBNA, then – if required – EUS-FNA = N0: 35%; N1: 11.25%; N2: 32.5%; N3: 21.25%; Bronchoscopy, then EUS-FNA, then – if required – EBUS-TBNA = N0: 35%; N1: 11.3%; N2: 27.5%; N3: 26.3%* **Interventions** • Bronchoscopy, EBUS-TBNA then EUS(B)-FNA if necessary on mediastinal nodes inaccessible or difficult to access by EBUS-TBNA • Bronchoscopy, EUS(B)-FNA then EBUS-TBNA if necessary on mediastinal nodes inaccessible or difficult to access by EUS(B)-FNA	Was a case-control design avoided? • Yes Did the study avoid inappropriate exclusions? • Unclear *The inclusion criteria are vague with regards to imaging or the standards/guidelines that were used.* RISK Could the selection of patients have introduced bias? • Unclear CONCERN Is there concern that the included patients do not match the review question? • Low Were the index test results interpreted without knowledge of the results of the reference standard? • Unclear *Blinding is not mentioned.* If a threshold was used, was it pre-specified? • Yes RISK Could the conduct or interpretation of the index test have introduced bias? • Unclear

Short Title	Title	Study Characteristics	Risk of Bias
		Downstream investigations and/or treatments • Recommendation of open thoracotomy or video-assisted thoracic surgery with systematic lymph node dissection to people whose endoscopic staging results did not show mediastinal masses **Protocol outcome measures** • Diagnostic accuracy *The diagnostic standard for a malignant result was the pathological confirmation of malignancy by any tissue sampling (EBUS-TBNA, EUS-FNA or surgical biopsy). The diagnostic standard for a benign result was the surgical confirmation of lesions showing no malignancy. The diagnostic accuracy, sensitivity and negative predictive value (NPV) for the detection of mediastinal metastasis (N2 or N3) were calculated using the standard definitions.* • Diagnostic sensitivity • Diagnostic negative predictive value • Safety: pneumothorax • Patient acceptability	Concerns regarding applicability • Low Is the reference standard likely to correctly classify the target condition? • Yes Were the reference standard results interpreted without knowledge of the results of the index test? • Unclear *Blinding is not mentioned* RISK Could the reference standard, its conduct, or its interpretation have introduced bias? • Low Was there an appropriate interval between index test(s) and reference standard? • Unclear *Timing is not mentioned* Did all patients receive a reference standard? • Yes Did patients receive the same reference standard? • Yes Were all patients included in the analysis?

Short Title	Title	Study Characteristics	Risk of Bias
			• Yes RISK Could the patient flow have introduced bias? • Low Overall quality • Moderate
Larsen 2005	Endoscopic ultrasound guided biopsy performed routinely in lung cancer staging spares futile thoracotomies: preliminary results from a randomised clinical trial	**Study type** • Randomised controlled trial **Study details** • Study location *Denmark* • Study setting *Gentofte University Hospital* • Study dates *November 2001 to February 2004* • Duration of follow-up *The median follow-up time from inclusion date was 1.3 years (range 0.2-2.4 years) in the routine EUS-FNA group and 1.4 years (range 0.2-2.4 years) in the group that had EUS-FNA only if CT showed invasion adjacent to the oesophagus* • Sources of funding *Not disclosed* • Lung cancer staging system used *American College of Chest Physicians. Lung cancer. Invasive staging: the guidelines. Chest 2003; 123: 167-175*	**Quality assessment (RCT)** Random sequence generation • Low risk of bias Allocation concealment • Low risk of bias Blinding of outcome assessment • Unclear risk of bias *Blinding of pathologists was not mentioned.* Blinding of participants and personnel • Unclear risk of bias *Not possible* Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		Inclusion criteria • Suspected or diagnosed lung cancer after CT/PET, bronchoscopy, TBNA/TTNA, lung function tests and general examination **Exclusion criteria** • <18 years of age • Not fit enough to undergo thoracotomy and lung resection • Pregnancy • Verified N2/3-, T4- or M1-disease or small-cell lung cancer **Sample characteristics** • Sample size *59 people* • Split between study groups *EUS-FNA for all = 28; EUS-FNA only if CT showed invasion adjacent to the oesophagus = 31* • Loss to follow-up *Three people in the EUS-FNA for all group did not undergo EUS-FNA because one became medically unfit, one person had had M1-disease (contra-lateral lung metastasis) verified before EUS-FNA was performed and one patient refused EUS-FNA on the day of examination.* • %female *EUS-FNA for all = 43% female, 57% male; EUS-FNA only if CT showed invasion adjacent to the oesophagus = 47% female, 53% male* • Mean age (SD) *EUS-FNA for all = 64 years (10); EUS-FNA only if CT showed invasion adjacent to the oesophagus = 65 years (10)*	Other sources of bias • Low risk of bias Overall risk of bias • Low **QUADAS 2** Was a random sample of patients enrolled? • Yes Was a case-control design avoided? • Yes Did the study avoid inappropriate exclusions? • Yes RISK Could the selection of patients have introduced bias? • Low CONCERN Is there concern that the included patients do not match the review question? • Low Were the index test results interpreted without knowledge of the results of the reference standard? • Unclear

Lung cancer: diagnosis and management: evidence reviews for effectiveness of non-ultrasound-guided TBNA, EBUS-TBNA or EUS-FNA for people with a probability of mediastinal malignancy (March 2019)

Short Title	Title	Study Characteristics	Risk of Bias
		• Nodal staging on initial PET/CT scan *CT stage (I-V): EUS-FNA for all = IA: 9%; IB: 6%; IIB: 4%; IIIA: 19%; IIIB: 36%; IV: 26%; EUS-FNA only if CT showed invasion adjacent to the oesophagus = IA: 12%; IB: 4%; IIB: 6%; IIIA: 25%; IIIB: 35%; IV: 18%* **Interventions** • Mediastinoscopy + EUS-FNA for all • Mediastinoscopy + EUS-FNA only if CT showed invasion adjacent to the oesophagus **Downstream investigations and/or treatments** • Surgical resection or multimodal therapy *Provided mediastinal metastases were demonstrated by EUS-FNA, or if direct mediastinal organ invasion was demonstrated by EUS, in concordance with a CT suspicion, a malignant cytological diagnosis obtained by EUS-FNA was taken as final proof of malignancy in the mediastinum. The options for post-staging treatment of NSCLC, during the study period, were in general: 1) Surgical resection, provided no tumour-spread outside the lung was found; 2) Induction chemotherapy followed by resection in patients with ipsilateral mediastinal lymph node metastases (stage IIIA-N2); or 3) Chemo-/radiotherapy alone if contralateral mediastinal- or distant metastases were present (stage IIIB and IV).* **Protocol outcome measures** • Safety: other complications **Non-protocol outcome measures**	*Blinding of the pathologists was not mentioned.* If a threshold was used, was it pre-specified? • Yes RISK Could the conduct or interpretation of the index test have introduced bias? • Unclear Concerns regarding applicability • Low Is the reference standard likely to correctly classify the target condition? • Yes Were the reference standard results interpreted without knowledge of the results of the index test? • Unclear *Blinding of pathologists was not mentioned.* RISK Could the reference standard, its conduct, or its interpretation have introduced bias? • Low CONCERN Is there concern that the target condition as defined by the reference standard does not match the review question?

Short Title	Title	Study Characteristics	Risk of Bias
		• No. of avoidable thoracotomies *A thoracotomy was classified as futile/avoidable if: 1) An intended curative thoracotomy ended as an explorative thoracotomy without tumour resection; or 2) A resected patient died from lung cancer or had recurrent disease during follow up.* • Percentage (or number) of people who died during a specified follow-up period • Recurrence during a specified follow-up period	• Low Was there an appropriate interval between index test(s) and reference standard? • Unclear *Timing was not mentioned.* Did all patients receive a reference standard? • Yes Did patients receive the same reference standard? • Yes Were all patients included in the analysis? • Yes RISK Could the patient flow have introduced bias? • Low Overall quality • High
Navani 2015	Lung cancer diagnosis and staging with endobronchial ultrasound-guided transbronchial needle aspiration	**Study type** • Randomised controlled trial *They randomly assigned participants (1:1) to either conventional diagnosis and staging (CDS group) or EBUS-TBNA as an initial investigation after a staging CT scan followed by further diagnosis and staging techniques if needed (EBUS group). They used a telephone randomisation method with permuted computer-generated blocks of*	**Quality assessment (RCT)** Random sequence generation • Low risk of bias Allocation concealment • Low risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
	compared with conventional approaches: an open-label, pragmatic, randomised controlled trial	*four. Randomisation was stratified according to the presence of mediastinal lymph nodes that measured 1 cm or more in the short axis and by recruiting centre. An investigator undertook the informed consent process, followed by the telephone randomisation process done by research assistants. The random allocation sequence was kept in the randomisation centre and concealed from participants and investigators until the interventions were assigned. Because of the nature of the intervention, masking of participants and consenting investigators was not possible. However, pathologists and radiologists were unaware that patients were enrolled into a clinical trial. Data were obtained on paper-based case forms and entered by an independent clerk onto a secured trial database on a dedicated trial computer.* **Study details** • Study location *UK* • Study setting *University College London Hospital, Whittington Hospital, North Middlesex University Hospital, Princess Alexandra Hospital, Barnet General Hospital, and Nottingham University Hospital* • Study dates *June 2008 to July 2011* • Duration of follow-up *Not stated. However, the survival curve has data collected for just over a 4-year duration. The final diagnosis of nodal staging was established in both groups by clinical follow-up of at least 1 year and pathological changes noted with EBUS-TBNA, conventional TBNA, EUS-FNA, mediastinoscopy, or dissection of mediastinal lymph nodes.* • Sources of funding *UK Medical Research Council*	Blinding of outcome assessment • Unclear risk of bias *Because of the nature of the intervention, masking of participants and consenting investigators was not possible. However, pathologists and radiologists were unaware that patients were enrolled into a clinical trial.* Blinding of participants and personnel • Unclear risk of bias *Because of the nature of the intervention, masking of participants and consenting investigators was not possible. However, pathologists and radiologists were unaware that patients were enrolled into a clinical trial.* Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low

Short Title	Title	Study Characteristics	Risk of Bias
		• Lung cancer staging system used *7th edition of the tumour, node, metastasis (TNM) staging system 2012* **Inclusion criteria** • Suspected stage I to IIIA lung cancer on CT neck, thorax and upper abdomen **Exclusion criteria** • <18 years of age • Not fit enough to undergo thoracotomy and lung resection • Significant concurrent malignant disease • Any condition that contraindicated the intervention or mediastinoscopy • Any medication that contraindicated the intervention or mediastinoscopy • Known extrathoracic malignant disease • Supraclavicular lymphadenopathy • Pleural effusion **Sample characteristics** • Sample size *132 people with suspected lung cancer* • Split between study groups *EBUS-TBNA / EUS-FNA = 66 people; CDS (Bronchoscopy / CT-guided biopsy) = 66 people* • Loss to follow-up	Directness • Directly applicable **QUADAS 2** Was a random sample of patients enrolled? • Yes Was a case-control design avoided? • Yes Did the study avoid inappropriate exclusions? • Yes RISK Could the selection of patients have introduced bias? • Low CONCERN Is there concern that the included patients do not match the review question? • Low Were the index test results interpreted without knowledge of the results of the reference standard? • Yes If a threshold was used, was it pre-specified? • Yes

Lung cancer: diagnosis and management: evidence reviews for effectiveness of non-ultrasound-guided TBNA, EBUS-TBNA or EUS-FNA for people with a probability of mediastinal malignancy (March 2019)

Short Title	Title	Study Characteristics	Risk of Bias
		One patient (randomly assigned to CDS) declined all further investigations and withdrew consent before any investigations were done. • %female *EBUS-TBNA / EUS-FNA = 35% CDS (Bronchoscopy / CT-guided biopsy) = 30%* • Mean age (SD) *EBUS-TBNA / EUS-FNA = 71 years (IQR 62-78) CDS (Bronchoscopy / CT-guided biopsy) = 68 years (IQR 61-73)* • Smoking history *EBUS-TBNA / EUS-FNA = 28.1% CDS (Bronchoscopy / CT-guided biopsy) = 23.4%* • Nodal staging on initial PET/CT scan *EBUS-TBNA / EUS-FNA = N0: 32%; N1: 9%; N2: 51%; N3: 8%; CDS (Bronchoscopy / CT-guided biopsy) = N0: 30%; N1: 14%; N2: 50%; N3: 6%* **Interventions** • EBUS-TBNA as initial investigation. EUS-FNA if target node cannot be accessed by EBUS-TBNA *In the EBUS group, 64 (97%) of 66 underwent EBUS and two (3%) had EUS-FNA as an initial procedure. Five (8%) of 66 patients had a subsequent radiology-guided biopsy sample taken.* • Bronchoscopy or CT-guided biopsy (NHS conventional diagnosis and staging) *Participants allocated to conventional diagnosis and staging (CDS) underwent investigations as determined by the local multidisciplinary team. The investigators suggested an algorithm for CDS in the trial protocol based on the most recently available NICE guidance (2005) at*	RISK Could the conduct or interpretation of the index test have introduced bias? • Low Concerns regarding applicability • Low Is the reference standard likely to correctly classify the target condition? • Yes Were the reference standard results interpreted without knowledge of the results of the index test? • Unclear RISK Could the reference standard, its conduct, or its interpretation have introduced bias? • Low CONCERN Is there concern that the target condition as defined by the reference standard does not match the review question? • Low Was there an appropriate interval between index test(s) and reference standard? • Yes

Short Title	Title	Study Characteristics	Risk of Bias
		the time the trial started. The trial management group agreed that allowing the responsible multidisciplinary teams to determine the patients' investigations would provide the best comparator group. This allowed the control CDS group to emulate clinical practice, giving the trial strong external validity. In the CDS group, 44 (67%) of 66 patients initially underwent a bronchoscopy and 29 (44%) had a radiology-guided biopsy sample taken. 5 underwent conventional TBNA, 1 underwent a mediastinoscopy. 2 underwent a PET-CT scan. **Protocol outcome measures** • Diagnostic accuracy *Diagnostic accuracy percentages were included for the EBUS-TBNA/EUS-FNA arm but not for the conventional diagnosis and staging arm. Therefore, these numbers were excluded because our protocol's inclusion criteria are RCTs where the results of one arm are compared against the other.* • Safety: mortality • Safety: in-patient admission • Safety: pneumothorax • Safety: other complications • Timing: time to treatment decision *Time from first outpatient appointment with the respiratory specialist to treatment decision by the multidisciplinary team, after completion of the diagnosis and staging procedures.* • Timing: time to diagnosis and staging *Percentage of people who had diagnosis and staging completed by 14 days* • No. of investigations / person	Did all patients receive a reference standard? • Yes Did patients receive the same reference standard? • Yes Were all patients included in the analysis? • Yes RISK Could the patient flow have introduced bias? • Low Overall quality • High

Short Title	Title	Study Characteristics	Risk of Bias
		Non-protocol outcome measures • Proportion of people diagnosed and staged with one investigation • No. of avoidable thoracotomies *An avoidable thoracotomy was defined as an open and close procedure, unexpected mediastinal nodal metastases (pN2/pN3), pT4 or pM1a/b disease, resection of benign disease or disease recurrence, or death within 1 year of thoracotomy.* • Duration of survival (time) • Duration of survival (Hazard Ratio)	
Tournoy 2008	Endoscopic ultrasound reduces surgical mediastinal staging in lung cancer: a randomized trial. American Journal of Respiratory & Critical Care Medicine	**Study type** • Randomised controlled trial **Study details** • Study location *Belgium* • Study setting *Ghent University Hospital. EUS-FNA was performed in an outpatient setting* • Study dates *December 2005 to January 2007* • Duration of follow-up *Participants were followed up until discharge after the procedure (1 to 22 nights, with a median of 2 nights)* • Sources of funding *Not mentioned. The authors disclosed that they did not have a financial relationship with a commercial entity that had an interest in the study.* • Lung cancer staging system used	**Quality assessment (RCT)** Random sequence generation • Unclear risk of bias *Method not mentioned* Allocation concealment • Unclear risk of bias *Not mentioned* Blinding of outcome assessment • Unclear risk of bias *Not mentioned* Blinding of participants and personnel • Unclear risk of bias *Not possible* Incomplete outcome data

Short Title	Title	Study Characteristics	Risk of Bias
		Not stated. In the reference section, the following guidelines were referred to: Detterbeck FC, DeCamp MM Jr, Kohman LJ, Silvestri GA. Lung cancer: invasive staging: the guidelines. Chest 2003;123:167S–175S. Detterbeck FC, Jantz MA, Wallace MB, Vansteenkiste J, Silvestri GA; American College of Chest Physicians. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines, 2nd ed. Chest 2007;132:202S–220S. **Inclusion criteria** • Proven or suspected NSCLC • Suspected mediastinal lymph node invasion on CT/PET *Their guidelines for invasive mediastinal exploration were enlarged (>1-cm short axis) mediastinal lymph nodes and/or FDG uptake in the mediastinal lymph nodes, tumours abutting the mediastinum regardless of FDG uptake in the lymph nodes, and absence of FDG uptake in the primary tumour.* **Exclusion criteria** • Not fit enough to undergo thoracotomy and lung resection • Any condition that contraindicated the intervention or mediastinoscopy • Any medication that contraindicated the intervention or mediastinoscopy • Unresectable tumour • No distant metastasis • Former therapy for lung cancer • Concurrent other malignancy **Sample characteristics**	• Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Moderate Directness • Directly applicable **QUADAS 2** Was a random sample of patients enrolled? • Unclear *Method not mentioned* Was a case-control design avoided? • Yes Did the study avoid inappropriate exclusions? • Yes RISK Could the selection of patients have introduced bias?

Short Title	Title	Study Characteristics	Risk of Bias
		• Sample size *40 people* • Split between study groups *EUS-FNA = 19; Straight to surgical staging = 21* • Loss to follow-up *None* • %female *EUS-FNA = 11% female, 89% male; Straight to surgical staging = 5% female, 95% male* • Mean age (SD) *EUS-FNA = 67 years (range 47-78); Straight to surgical staging = 61 years (range 42-74)* • Nodal staging on initial PET/CT scan *EUS-FNA = N2: 79%; N3: 21%; T1: 5%; T2: 84%; T3: 0%; T4: 11%; Straight to surgical staging = N2: 67%; N3: 33%; T1: 10%; T2: 76%; T3: 5%; T4: 10%* **Interventions** • Straight to surgical staging (mediastinoscopy) • Mediastinoscopy + EUS-FNA for all **Downstream investigations and/or treatments** • Surgical staging if required, then thoracotomy if required **Protocol outcome measures** • Diagnostic sensitivity • Diagnostic specificity • Diagnostic negative predictive value	• Low CONCERN Is there concern that the included patients do not match the review question? • Low Were the index test results interpreted without knowledge of the results of the reference standard? • Unclear If a threshold was used, was it pre-specified? • Yes RISK Could the conduct or interpretation of the index test have introduced bias? • Unclear Concerns regarding applicability • Low Is the reference standard likely to correctly classify the target condition? • Yes Were the reference standard results interpreted without knowledge of the results of the index test? • Unclear

Short Title	Title	Study Characteristics	Risk of Bias
		• Diagnostic positive predictive value • Safety: in-patient admission • Safety: other complications	RISK Could the reference standard, its conduct, or its interpretation have introduced bias? • Low CONCERN Is there concern that the target condition as defined by the reference standard does not match the review question? • Low Was there an appropriate interval between index test(s) and reference standard? • Unclear *Not mentioned* Did all patients receive a reference standard? • Yes Did patients receive the same reference standard? • Yes Were all patients included in the analysis? • Yes RISK Could the patient flow have introduced bias? • Low Overall quality • Moderate