Online supplement

Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS)

Peter Vilmann[1], Paul Frost Clementsen[2,11], Sara Colella[2], Mette Siemsen[3], Paul De Leyn[4], Jean-Marc Dumonceau[5], Felix J. Herth[6], Alberto Larghi[7], Enrique Vasquez-Sequeiros[8], Cesare Hassan[7], Laurence Crombag[9], Daniël A. Korevaar[10], Lars Konge[11], Jouke T. Annema[9]

[1] Department of Surgical Gastroenterology, Endoscopy Unit, Copenhagen University Hospital Herlev, Copenhagen, Denmark

[2] Department of Pulmonary Medicine, Gentofte University Hospital, Hellerup, Denmark

[3] Department of Thoracic Surgery, Rigshospitalet, Copenhagen Hospital Union, Copenhagen, Denmark

[4] Department of Thoracic Surgery, University Hospitals Leuven, Belgium

[5] Gedyt Endoscopy Center, Buenos Aires, Argentina

[6] Department of Pneumology and Critical Care Medicine, Thoraxklinik, University of Heidelberg, Heidelberg, Germany

[7] Digestive Endoscopy Unit, Catholic University, Rome, Italy

[8] Department of Gastroenterology, University Hospital Ramón y Cajal, Universidad de Alcala, Madrid, Spain

[9] Department of Respiratory Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

[10] Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

[11] Centre for Clinical Education, University of Copenhagen and the Capital Region of Denmark, Copenhagen, Denmark

Appendices

Appendix e1 Key questions, level of evidence, and conclusions supporting the Guideline recommendations

Topic	Key questions	Summary of available evidence	Conclusions	Working group recommendation
1 Peripherally located lung cancer with abnormal mediastinum (enlarged or FDG-PET-avid nodes)	– What is the sensitivity of EBUS and EUS in combination for mediastinal nodal staging in patients with suspected or proven peripherally located lung cancer and abnormal mediastinum at imaging? – Does the combination of EBUS and EUS result in a significant improvement of the sensitivity regarding mediastinal nodal staging in comparison with each of the techniques alone? – What is the next investigation when EBUS and EUS show no nodal metastases?	Data were extrapolated from the cited meta-analyses and randomized clinical trials. Other prospective nonrandomized clinical trials were also considered. No meta-analyses or randomized clinical trials assessed the role of the combined technique only in patients with abnormal mediastinum at imaging.	– The pooled sensitivity for mediastinal nodal staging for EBUS and EUS performed in combination was 86% (95%CI 82%–90%) (evidence level 1–). – The pooled sensitivities of EBUS or EUS alone were 94% (95%CI 93%–96%) and 90% (95%CI 84%–94%), respectively (evidence level 1–). –The sensitivity of EBUS + EUS followed by surgical staging vs. surgical staging: 94% (95%CI 85%–98%) vs. 79% (95%CI 66%–88%) (evidence level 1++). A patient with a negative result from complete endosonography should be considered for progression to surgical staging for the confirmation of that result, in order to avoid an unnecessary thoracotomy (evidence level 2+). – The pooled increase in sensitivity of adding EUS to EBUS is 13% (95%CI 8%–20%), and the pooled increase in sensitivity of adding EBUS to EUS is 21% (95%CI 13%–30%) (evidence level 1–). According to a recent RCT, the EBUS procedure should be performed first. Starting with EUS-FNA could be a reasonable alternative, especially in patients with low cardiorespiratory function (evidence level 1+).	For mediastinal nodal staging in patients with suspected or proven NSCLC with abnormal mediastinal and/or hilar nodes at CT and/or PET, endosonography is recommended over surgical staging as the initial procedure (Recommendation grade A). The combination of EBUS-TBNA and EUS-(B)-FNA is preferred over either test alone (Recommendation grade C). If the combination of EBUS and EUS-(B) is not available, we suggest that EBUS alone is acceptable (Recommendation grade C). Subsequent surgical staging is recommended, when endosonography does not show malignant nodal involvement (Recommendation grade B).

			[18,25,27,28,31–38]	
2 and **3** Peripheral lung cancer without abnormal mediastinal lymph nodes (no enlarged or FDG-PET-avid nodes)	– What is the sensitivity of EBUS and EUS in combination for mediastinal staging in patients with suspected or proven peripheral lung cancer and normal mediastinum at radiological imaging? – Does the combination of EBUS and EUS result in significant improvement of sensitivity regarding mediastinal nodal staging in comparison with each of the techniques alone? – What is the next investigation when EBUS and EUS show negative results?	Data were extrapolated from the cited meta-analyses and randomized clinical trials. Other prospective nonrandomized clinical trials were also considered. No meta-analyses or randomized clinical trials assessed the role of the combined technique only in patients with normal mediastinum at imaging. The role of routine surgical staging after a negative endosonography should be further investigated.	– The sensitivity for mediastinal staging of EBUS, only followed by EUS-B in patients with inaccessible or difficult-to-reach nodes, was 38% in one study, which increased to 73% by adding mediastinoscopy (evidence level 2+). – The sensitivity for mediastinal staging for EBUS and EUS performed in combination with two scopes in this group of patients was 68% in one study (evidence level 2+). -The sensitivity for mediastinal staging of EBUS and EUS performed in combination with two scopes was 71% and 75% in two small subgroup analyses of larger trials (evidence level 2–). – The pooled sensitivities of EBUS or EUS alone were 76% (95%CI 65%–85%) and 58% (95%CI 39%–75%), respectively (evidence level 1–). – No studies investigated the role of combined EBUS and EUS with a single scope in patients with normal mediastinal lymph nodes (evidence level 4). – For patients with negative results from complete endosonography, there should be multidisciplinary consideration on whether surgical staging should be undertaken for confirmation of that result, in order to avoid unnecessary thoracotomy (evidence level 2–). [9–11,21,29–31,46–48]	For mediastinal nodal staging in patients with suspected or proven non-small-cell peripheral lung cancer without mediastinal involvement at CT or CT-PET, we suggest that EBUS-TBNA and/or EUS-B-FNA should be performed before therapy, provided that one or more of the following conditions is present: (i) enlarged or FDG-PET-avid ipsilateral hilar nodes; (ii) primary tumor without FDG uptake; (iii) tumor size ≥3 cm (**Fig. 3a–c**) (Recommendation grade C). If endosonography does not show malignant nodal involvement, we suggest that mediastinoscopy is considered especially in suspected N1 disease (Recommendation grade C). If PET is not available and CT does not reveal enlarged hilar or mediastinal lymph nodes, we suggest performance of EBUS-TBNA and/or EUS-FNA and/or mediastinoscopy for further staging (Recommendation grade C). In patients with suspected or proven <3 cm peripheral non-small-cell lung cancer with normal mediastinal and hilar nodes at CT and/or PET, we suggest initiation of therapy without further mediastinal staging (Recommendation grade C).
4 and **7** Centrally located	– What is the value of EBUS/EUS in staging of centrally located	No meta-analyses or randomized clinical trials assess	– In selected cases tumor invasion of the heart, mediastinum and the vessels can be	For mediastinal staging in patients with centrally located suspected or proven non-small-cell lung

lung cancer	lesions? – What is the value of EBUS/EUS in diagnosing centrally located lesions suspected for lung cancer?	the role of the combined technique only in patients with centrally located tumors.	detected (T4) by EUS/EBUS. The advantage of using both techniques is that, in selected cases, the tumor can be reached from the esophagus and/or from the trachea, depending on its location (evidence level 4). – The sensitivity for EBUS in diagnosing lung tumors that are invisible by conventional bronchoscopy was 82% in one study and 91.4% in another study, and was around 96% for EUS (evidence level 2–). [12,13,15,21,27,29,49–51,63–65]	cancer without mediastinal or hilar involvement at CT and/or PET, we suggest performance of EBUS-TBNA with or without EUS-(B)-FNA in preference to surgical staging (**Fig. 4**) (Recommendation grade D). If endosonography does not show malignant nodal involvement, mediastinoscopy may be considered (Recommendation grade D). For diagnostic purposes, in patients with a centrally located lung tumor that is not visible at conventional bronchoscopy, endosonography is suggested, provided the tumor is located immediately adjacent to the larger airways (EBUS) or esophagus (EUS). (Recommendation grade D).
5 Restaging after neoadjuvant therapy	– What is the sensitivity and NPV of endosonography (EBUS/ EUS) for mediastinal restaging after induction chemo- and/or radiotherapy in patients with NSCLC?	There are no RCTs on these topics. Few studies have been performed and most have a small sample size. The reference standard, however, is adequate in most studies.	– Sensitivity and NPV for EUS for mediastinal restaging after induction chemo- and/or radiotherapy in patients with NSCLC range from 44% to 75% and from 42% to 91.6%, respectively, in 5 studies (evidence level 2–). – Sensitivity and NPV of EBUS for mediastinal restaging after induction chemo- and/or radiotherapy in patients with NSCLC range from 67% to 76% and from 20% to 78%, respectively, in 2 studies (evidence level 2+). – Sensitivity and NPV of combined EBUS-TBNA and EUS-B-FNA for mediastinal restaging after induction chemotherapy in patients with NSCLC were 67% and 73%, in one study (evidence level 2+) [22,52–62]	For mediastinal nodal restaging following neoadjuvant therapy, EBUS-TBNA and/or EUS-(B)-FNA is suggested for detection of persistent nodal disease but, if negative, subsequent surgical staging is indicated (Recommendation grade C).
6 How many lymph nodes should be sampled?	– How many lymph node stations should be sampled to consider mediastinal staging as “complete”?	For endosonography, there is no agreement about how many and which lymph node stations should be sampled and which level of thoroughness is necessary for different situations.	– At least three stations should be sampled in patients with high risk of mediastinal lymph node metastases (evidence level 4). [21,22]	A complete assessment of mediastinal and hilar nodal stations is recommended, and sampling of at least three different mediastinal nodal stations (4R, 4L, 7) (**Figs 1, 5**) is suggested in patients with NSCLC and an abnormal mediastinum (Recommendation grade D).

8 EUS for adrenal glands	– What is the feasibility of EUS for detection in the left and right adrenal glands? – Are specific EUS imaging characteristics predictive for metastatic involvement? – What are the sensitivity and NPV of EUS-FNA of adrenal glands suspicious for metastatic lung cancer involvement?	There are no meta-analyses and no RCTs. The vast majority of studies had a retrospective design. Additionally, only half of the selected studies included patients with lung cancer.	– EUS of the left adrenal gland is feasible in the vast majority (97%–100%) of patients with lung cancer (evidence level 2–). – Loss of seagull shape of the adrenal gland on EUS imaging seems to be predictive of malignancy (evidence level 2–). – Sensitivity of EUS left adrenal gland metastases in patients with lung cancer ranges from 86% to >90%, and NPV ranges from 70% to >90%, but the number of studies is limited. (evidence level 2–). – Detection and aspiration of the right adrenal gland by EUS is feasible in selected cases (evidence level 2–). – EUS-FNA of suspicious left adrenal gland is feasible and safe in the absence of clinical signs of a pheochromocytoma (evidence level 4) [66–80]	In patients with a left adrenal gland suspected of a distant metastasis, we suggest performance of EUS-FNA, while the use of EUS-B with a transgastric approach is at present experimental (Recommendation grade D).
9 and **10** Training	– Which steps should be included in the training curriculum for endosonography? – What is the impact of simulator-based training on patient care?	We await results from randomized trials exploring the effect of simulation-based training in endosonography. However, we believe that evidence from high quality RCTs from other surgical and endoscopic domains can be extrapolated to endosonography.	– The quality and the safety of endosonography are dependent on the level of experience of the operator (evidence level 2–). – The training curriculum for endosonography should include two steps: a simulator-based training followed by supervised practice on patients (evidence level 4-). – No data are available about the effects of the simulator-based program for endosonography on patient care (evidence level 4).	For optimal endosonographic staging of lung cancer, we suggest that individual endoscopists should be trained in both EBUS and EUS-B in order to perform complete endoscopic staging in one session (Recommendation grade D). We suggest that new trainees in endosonography follow a structured training curriculum consisting of simulation-based training followed by supervised practice on patients (Recommendation grade D).

			[81–88]	
11 Competence assessment	– How many procedures must a trainee perform before being being considered competent in endosonography?	All available evidence on acquisition of skills in endosonography show substantial variability between trainees, making it impossible to define a certain number of procedures required for credentialing. Perhaps because of the lack of standardized certification programs in endosonography, there are no studies that actually show that ensuring basic competence and monitoring of outcomes leads to better patient care.	–There is no standard number of procedures that can be used as a criterion for considering a trainee to be competent (evidence level 4) –The acquisition of competence in endosonography varies between operators, but basic competence should be ensured before operators perform the procedures by themselves (evidence level 4). [16,17,61,88–100]	We suggest that competence in EBUS-TBNA and EUS-FNA for staging lung cancer be assessed using available validated assessment tools (Recommendation grade D).

95%CI, 95% confidence interval; CT, computed tomography; EBUS-TBNA, endobronchial ultrasound with real-time guided transbronchial needle aspiration; EUS-B, endoscopic ultrasound, using the EBUS scope; FDG, fluorodeoxyglucose; FNA, fine needle aspiration; NPV, negative predictive value; PET-CT, positron emission tomography-CT; PPV, positive predictive value; RCT, randomized controlled trial; vs., versus.

Appendix e2. Search strategy for key questions

1 Search terms: EUS[All Fields] AND EBUS[All Fields] AND staging[All Fields] AND ("lung neoplasms"[MeSH Terms] OR ("lung"[All Fields] AND "neoplasms"[All Fields]) OR "lung neoplasms"[All Fields] OR ("lung"[All Fields] AND "cancer"[All Fields]) OR "lung cancer"[All Fields]) AND combination[All Fields]

2, 3 Search terms: EUS[All Fields] AND EBUS[All Fields] AND staging[All Fields] AND ("lung neoplasms"[MeSH Terms] OR ("lung"[All Fields] AND "neoplasms"[All Fields]) OR "lung neoplasms"[All Fields] OR ("lung"[All Fields] AND "cancer"[All Fields]) OR "lung cancer"[All Fields]) AND combination[All Fields]

4, 5 Search terms: (centrally[All Fields] AND located[All Fields] AND ("lung neoplasms"[MeSH Terms] OR ("lung"[All Fields] AND "neoplasms"[All Fields]) OR "lung neoplasms"[All Fields] OR ("lung"[All Fields] AND "cancer"[All Fields]) OR "lung cancer"[All Fields])) AND (("mediastinum"[MeSH Terms] OR "mediastinum"[All Fields] OR "mediastinal"[All Fields]) AND ("lymph nodes"[MeSH Terms] OR ("lymph"[All Fields] AND "nodes"[All Fields]) OR "lymph nodes"[All Fields] OR ("lymph"[All Fields] AND "node"[All Fields]) OR "lymph node"[All Fields])) AND staging[All Fields] AND ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "diagnosis"[MeSH Terms])

6 Search terms: (((EBUS[All Fields] AND EUS[All Fields] AND (combined[All Fields] AND technique[All Fields]) AND ("mediastinum"[MeSH Terms] OR "mediastinum"[All Fields]) AND ("lymph nodes"[MeSH Terms] OR ("lymph"[All Fields] AND "nodes"[All Fields]) OR "lymph nodes"[All Fields] OR ("lymph"[All Fields] AND "node"[All Fields]) OR "lymph node"[All Fields]) AND ("lung neoplasms"[MeSH Terms] OR ("lung"[All Fields] AND "neoplasms"[All Fields]) OR "lung neoplasms"[All Fields] OR ("lung"[All Fields] AND "cancer"[All Fields]) OR "lung cancer"[All Fields])))

7 Search terms: ((("Endoscopic Ultrasound-Guided Fine Needle Aspiration"[Mesh] OR (("Ultrasonography, Interventional"[Mesh] OR Ultrasound[tiab] OR ultrasonograph*[tiab] OR EUS[tiab]) AND ("Biopsy, Fine-Needle"[Mesh] OR Fine Needle[tiab] OR FNA)) OR EUS-FNA[tiab] OR echoendoscop*[tiab] OR echo-endoscop*[tiab]))) AND (("Adrenal Glands"[Mesh] OR adrenal[tiab]))

8 Search terms: ((("Lung Neoplasms"[Mesh] OR lung neoplasm*[tiab] OR lung cancer*[tiab] OR pulmonary neoplasm*[tiab] OR pulmonary cancer*[tiab])) AND ("Combined Modality Therapy"[Mesh] OR neoadjuvant[tiab] OR therapy[tiab] OR treatment[tiab] OR treated[tiab] OR chemotherap*[tiab] OR chemoradiat*[tiab] OR combined modality[tiab])) AND ((("Endoscopic Ultrasound-Guided Fine Needle Aspiration"[Mesh] OR (("Ultrasonography, Interventional"[Mesh] OR Ultrasound[tiab] OR ultrasonograph*[tiab] OR EUS[tiab]) AND ("Biopsy, Fine-Needle"[Mesh] OR Fine Needle[tiab] OR FNA)) OR EUS-FNA[tiab] OR echoendoscop*[tiab] OR echo-endoscop*[tiab])) OR ((Endobronchial ultrasound[tiab] OR

EBUS[tiab]) AND (transbronchial needle aspiration*[tiab] OR TBNA[tiab]) OR EBUS-TBNA[tiab]))

Appendix e3. Evaluation of single studies according to the Scottish Intercollegiate Network (SIGN) system [26]

First author, year	Study design	Intervention	Participants	Reference standard	Results	Conclusions	Level of evidence Limits and comments	Recommendations
Gu, 2009 [29]	Systematic review and meta-analysis	EBUS for mediastinal staging in lung cancer patients	11 studies, 1299 patients	Histopathology in 5 studies, and histopathology or clinical follow-up in 6	EBUS-TBNA: – Sensitivity: 0.93 (95%CI 0.91–0.94) - Specificity: 1.00 (95%CI 0.99–1.00). The subgroup of patients who were selected on the basis of CT- or PET-positive results had higher pooled sensitivity (0.94, 95%CI 0.93–0.96) than the subgroup of patients without any selection by CT or PET (0.76, 95%CI 0.65–0.85) ($P < 0.05$). Only two complications occurred (0.15%).	EBUS-TBNA is an accurate, safe and cost-effective tool in lung cancer staging. The selection of patients who had positive results of suspected lymph node metastasis on CT or PET may improve the sensitivity of EBUS-TBNA.	Directly applicable 1– Limits: – Reference standard included clinical follow-up in some studies	1–5
Micames, 2007 [30]	Systematic review and meta-analysis	EUS for mediastinal staging in lung cancer patients	18 studies, 1201 patients	Histopathology in 10 studies, and histopathology or clinical follow-up in 8	EUS-FNA: – Sensitivity: 0.83 (95%CI 0.78%–0.87%) – Specificity: 0.97 (95%CI 0.96–0.98) The subgroup of patients who were selected on the basis of CT-positive results had higher pooled sensitivity (90%, 95%CI 84%–94%) than the subgroup of patients without mediastinal abnormalities on CT (58%; 95%CI 39%–75%).	EUS-FNA is a safe modality for the invasive staging of lung cancer that is highly sensitive when used to confirm metastasis to mediastinal lymph nodes seen on CT scans. In addition, among lung cancer patients with normal mediastinal adenopathy on CT scans, despite lower sensitivity, it has the potential to prevent unnecessary surgery in a large proportion of cases missed by CT scanning.	Directly applicable 1– Limits: – Reference standard included clinical follow-up in some studies	1–5

Zhang, 2013 [25]	Systematic review and meta-analysis	Accuracy of the combination of EBUS-TBNA and EUS-FNA procedures and clarification of its current role for mediastinal lymph node staging of lung cancer	8 studies, RCT 1 Prospective 7 822 patients	Surgery in 4 studies, and surgery and clinical follow-up in 4	Combined approach: – Sensitivity: 86% – Specificity: 100% – Positive likelihood ratio: 51.77 – Negative likelihood ratio : 0.15 – Diagnostic odds ratio (DOR): 416.83 – Area under the curve (AUC): 0.99 Complications: 1 pneumothorax, 1 lymph node abscess	The combined technique is more sensitive than EBUS-TBNA or EUS-FNA alone. The diagnostic power of this combined technique is accurate.	1– Directly applicable Limits: – Reference standard included clinical follow-up in some studies – Heterogeneity across studies	1, 6
Annema, 2010 [18]	RCT Multicenter study	Combination of EBUS and EUS (conventional endoscope) in detecting N2/N3 disease in lung cancer patients Primary outcome: sensitivity for N2/N3 disease Secondary outcome: rate of unnecessary thoracotomy	n = 241 Consecutive patients potentially operable for NSCLC – n = 118 surgical staging group – n = 123 endosonography staging group, followed by surgical staging	Surgery (thoracotomy with node dissection)	Primary outcome: sensitivity for N2/N3 metastases: Sensitivity – Surgery alone: 79% – Endosonography (EBUS + EUS) alone: 85% – Endosonography followed by surgical staging: 94% NPV – Surgery alone: 86% – Endosonography alone: 85% – Endosonography followed by surgical staging: 93% Abnormal mediastinum: – Sensitivity for endosonography of 86%, but 97% when it is followed by surgical staging. Thoracotomy was unnecessary in 21 patients (18%) in the surgical group and in 9 patients (7%) in the endosonography group. Complication rate was similar in both groups.	Among patients with (suspected) NSCLC, a staging strategy combining endosonography and surgical staging compared with surgical staging alone resulted in greater sensitivity for mediastinal nodal metastases and fewer unnecessary thoracotomies	For statement 1: 1++ Directly applicable Limits: – Only tertiary hospitals For statement 2–: Extrapolated Limits: – Small sample	1, 2, 3, 6

Wallace, 2008 [31]	Prospective comparative study Single-center study	Combination of EBUS and EUS (regular) in mediastinal lymph node staging in lung cancer	n = 138 consecutive patients	Surgery (thoracotomy with node dissection, lobectomy with mediastinal exploration, mediastinoscopy, or thoracoscopy) or clinical follow-up	The overall sensitivity of the combined technique was 93% and the NPV was 97%. Sensitivity: – EBUS alone: 69% – EUS alone: 69% – EBUS+EUS: 93% Moreover: – If mediastinoscopy had been performed only when results from endosonography were negative, this surgical procedure would have been avoided in 28% of patients (39/138).	EBUS-TBNA has higher sensitivity than “blind” TBNA and that EUS plus EBUS may allow near-complete minimally invasive mediastinal staging in patients with suspected lung cancer. These results require confirmation in other studies but suggest that EUS plus EBUS may be an alternative approach for mediastinal staging in patients with suspected lung cancer. Suboptimal reference standard	2+ Directly applicable Limits: – Not randomized – Single-center Reference standard included clinical follow-up	1, 2, 3, 6
Dooms, 2014 [47]	Prospective multicenter study	Endosonography (EBUS, only followed by EUS-B if patients had inaccessible or difficult to reach lymph nodes) and mediastinoscopy for mediastinal nodal staging of cN1 lung cancer.	n = 100 consecutive patients	Surgery (thoracotomy or video-assisted thoracic surgery [VATS] resection)	Of the 100 patients with cN1 on imaging, 24 patients were diagnosed with N2 disease. Invasive mediastinal nodal staging with endosonography alone had a sensitivity of 38%, which was increased to 73% by adding a mediastinoscopy. The NPVs were 81% and 91%, respectively; 10 mediastinoscopies were needed to detect 1 additional N2 disease missed by endosonography.	Endosonography alone has unsatisfactory sensitivity for detecting mediastinal nodal metastasis in cN1 lung cancer, and the addition of a confirmatory mediastinoscopy is of added value.	2+ Limits: – EUS-(B) only performed in 25% of patients	1
Rintoul, 2005 [101]	Prospective comparative study Single-center study	Combination of EBUS and EUS for mediastinal nodal staging (EUS has been done only when the assessment of postero-inferior mediastinal lymph nodes was needed)	n = 20 Selected patients underwent EBUS and 7 patients EUS and EBUS	Mediastinoscopy Clinical follow-up	EBUS-TBNA: Diagnosis of malignant lymph nodes: 11 out of 18 patients Negative for N2/N3: 7 patients: – 5 true-negative – 2 false-negative Procedure time: – EBUS-TBNA: 30 min – EUS-FNA: 45 min	EBUS with real-time TBNA offers improved sensitivity and accuracy for staging of the middle mediastinum, and, combined with endoscopic ultrasound, should allow investigation of the majority of the mediastinum.	2– Not directly applicable Limits: – Small sample of patients, – EUS not in all cases – Not consecutive patients – Reference standard included clinical follow-up	1

Oki, 2014 [37]	Prospective study	EBUS-TBNA was followed by EUS-FNA with a single bronchoscope in the preoperative hilar and mediastinal staging of NSCLC	n = 150 (of whom 146 were included in analysis)	Surgery (resection with node dissection, or resection with node examination), or (in a small number of patients) clinical follow-up	Sensitivity per patient: – EBUS-TBNA: 52% – EUS-FNA: 45% – Combined approach: 73% Corresponding negative predictive value: – EBUS-TBNA: 88% – EUS-FNA: 86% – Combined approach: 93%	The combined endoscopic approach with EBUS-TBNA and EUS-FNA is a safe and accurate method for preoperative hilar and mediastinal staging of NSCLC, with better results than with each technique by itself.	2+ Limits: – Single-center	1
Vilmann, 2005 [32]	Prospective cohort study Single-center study	Combination of EBUS and EUS for mediastinal lymph node staging	n = 33 (of whom 28 were included in analysis) Selected patients	Surgery (thoracotomy) or clinical follow-up	Diagnostic accuracy: 100%	EUS-FNA and EBUS-TBNA appear to be complementary methods. A combined approach with both EUS-FNA and EBUS-TBNA may be able to replace more invasive methods for evaluating lung cancer patients with suspected hilar or mediastinal metastases, as well as for evaluating unclear mediastinal or hilar lesions	2- Directly applicable Limits: – Small sample of patients – Not consecutive patients – Reference standard included clinical follow-up	1
Szlubowski, 2010 [41]	Prospective comparative study Multicenter study	Combination of EBUS and EUS for mediastinal lymph node staging	n = 120 Selected patients To assess the diagnostic yield of the combined approach in the radiologically normal mediastinum in NSCLC staging.	Surgery (pulmonary resection with node dissection, or transcervical extended bilateral mediastinal lymphadenectomy [TEMLA])	Overall sensitivity: 68% Overall NPV: 91% Overall PPV: 91% Prevalence of N2-N3 disease: 22% Station 4R: high rate of false negatives Station 4L: sensitivity for the combined procedure was 90%, significantly higher compared with the single techniques alone. Station 7: sensitivity for the combined procedure was 92%, significantly higher compared with the single techniques alone.	In the radiologically normal mediastinum, the combined technique is a highly effective and safe technique in NSCLC staging and, if negative, a surgical diagnostic exploration of the mediastinum may be omitted.	2+ Directly applicable	2, 3

Varadarajulu, 2004 [50]	Retrospective study Single-center study	EUS-FNA for diagnosing lung masses adjacent to or abutting the esophagus after unrevealing CT-guided biopsy or bronchoscopy	n = 18 patients	Mean follow-up: 205 days	Diagnostic yield: 100%, no complication 10 patients had mediastinal invasion. In 6 out of the 10 patients mediastinal lymph nodes were involved: – Station 7: 5 lymph nodes – Station 8: 1 lymph nodes Out of 6, in 3 patients FNA was performed and a diagnosis was not reached; in the other 3, lymph nodes were difficult to reach because of the position of the tumor. 8 patients had no mediastinal invasion; of these EUS-FNA detected a metastasis in only 1 (station 8).	In this study, EUS-guided FNA of lung mass was safe, and it established a diagnosis in all patients with accessible lesions.	2– Directly applicable Limits: – Small sample – Retrospective study	4, 5
Szlubowski, 2014 [62]	Prospective study	Combination of EBUS-TBNA and EUS-B-FNA for mediastinal lymph node restaging after induction therapy	n =106 NSCLC patients with confirmed N2 disease who had undergone induction chemotherapy	Transcervical extended bilateral mediastinal lymphadenectomy (TEMLA)	Sensitivity: 67% NPV: 73%	The combination of EBUS-TBNA and EUS-B-FNA is a reasonable and safe technique in mediastinal restaging in NSCLC patients afterinduction therapy.	2+ Directly applicable	
Hernandez, 2007 [51]	Review of prospective cohort Single-center study	EUS-FNA for diagnosing centrally located primary lung cancers	n = 17 patients 9 lesions at hilum 8 lesions in upper lobe 4/17 had lymph node abnormalities at EUS of which 3 were confirmed for metastases	Clinical follow up	Diagnostic yield: 100% Complication: 1 case of hemoptysis that needed hospitalization	EUS-FNA is a safe, relatively cost-effective, and accurate initial diagnostic modality for the diagnosis of lung lesions adjacent to the esophagus or invading the mediastinum.	2– Directly applicable Limits: – Small sample – Retrospective study	4, 5

Vazquez-Sequeiros, 2013 [63]	Review of prospective cohort Multicenter study	EUS-FNA after unsuccessful CT-guided lung biopsy or bronchoscopy for diagnosing indeterminate central mediastinal lung masses	n = 73 patients Mean tumor size in short axis: 26 mm CT/PET-CT Tumor close to the cervical/upper part of the esophagus	Clinical follow-up (12 months) Surgical staging/treatment Autopsy	62 patients had a diagnosis from the lung infiltrates with EUS (1 hamartoma, 47 NSCLC, 8 SCLC, 6 metastatic cancer). 11 patients had no diagnosis because EUS did not visualize the lung infiltrates. Sensitivity: – in 73 patients: 80.8% – excluding 11 patients: 96.7% Complication: 1 tension pneumothorax	Good accuracy and safety of EUS-FNA for evaluation of central mediastinal lung masses	2+ Directly applicable Limits: – Only EUS-FNA was considered – Only lung tumor	4, 5
Annema, 2005 [64]	Retrospective cohort Single-center study	EUS-FNA following a nondiagnostic bronchoscopy for diagnosing centrally located lung tumors	n = 32 patients Mean tumor size at CT: 45 mm No lymph node involvement Location: Left upper lobe: 7 Right upper lobe: 15 Left lower lobe: 7 Right lower lobe: 3	Surgery (only in 11 patients)	– 31 out of 32 patients (97%) had a diagnosis of malignancy – Only 1 patient had the diagnosis after pneumonectomy (lymphoma) – 11 patients underwent operation and were referred to surgery. – 39% of patients were staged as having T4 disease.	EUS-FNA qualifies as the next diagnostic step in patients with suspected lung cancer and a nondiagnostic bronchoscopy if the intrapulmonary mass is located adjacent or near the esophagus. In these cases, EUS-FNA may replace computed tomography of the chest (CT)-guided biopsies and reduce the number of exploratory thoracotomies.	2- Directly applicable Limits: – Small sample	4, 5
Tournoy, 2009 [65]	Retrospective Multicenter study	EBUS-TBNA after a nondiagnostic conventional bronchoscopy for diagnosing central parenchymal lung lesions	n = 60 patients CT or CT-PET Mean size of tumor: 25 mm	Transthoracic needle aspiration biopsy or surgical diagnostic procedure (98% of patients)	The primary tumor was visible with EBUS in all cases. Lung cancer was diagnosed in 46 patients (77%) Overall sensitivity: 82% Overall NPV: 23%	EBUS-TBNA can be considered as a diagnostic test in patients with a centrally located lung lesion after a previous nondiagnostic conventional bronchoscopy.	2- Directly applicable Limits: – Small sample	4, 5

					Sensitivity: – For lung tumor <25 mm: 78% – For lung tumor > 25 mm: 86% No serious complication			
Verma, 2013 [15]	Review of prospective cohort Single-center study	EBUS-TBNA for diagnosing central lung parenchymal lesions	n = 37 patients CT scan Mean size in short axis: 8–82 mm	Surgery (not in all patients)	32/37 had a final diagnosis 30/37 had diagnosis of lung cancer Sensitivity of EBUS-TBNA for detecting: – Malignancy: 91.4% – Benign process: 86.5%	EBUS-TBNA is an effective and safe method for tissue diagnosis of parenchymal lesions that lie centrally close to the airways. EBUS-TBNA should be considered the procedure of choice for patients with centrally located lesions without endobronchial involvement.	2– Directly applicable Limits: – Surgical reference not done in all patients	
Kang, 2013 [35]	Randomized clinical trial	EUS-B-FNA +EBUS-TBNA for mediastinal lymph node staging Primary outcome: – Diagnostic accuracy for N2/N3 disease Secondary outcomes: – Procedure sequence – Diagnostic added benefits of the second procedure – Procedure time – Number of nodal stations aspirated – Procedure tolerance – Cardiorespiratory parameters – Medication	n = 162 Consecutive patients were randomized into 2 groups: – Group A: 82 patients, EBUS-TBNA then EUS-B-FNA (of whom 74 were included in analysis) – Group B: 80 patients, EUS-B-FNA then EBUS-TBNA (of whom 74 were included in analysis	Surgery (open thoracotomy with node dissection, or video-assisted thoracic surgery [VATS])	Primary outcome: Values achieved with the first procedure, then with the second added: Group A: – Diagnostic accuracy: 91.9% then 93.2% – Sensitivity: 82.4%, then 85.3% – NPV: 87%, then 88.9% These values were not significant. Group B: – Diagnostic accuracy: 86.5%, then 97.3% – Sensitivity: 60%, then 92% – NPV: 83.1%, then 96.1% These values were significant. Secondary outcomes: – Procedure time; number of lymph node stations sampled and number of aspirations; amount of medication, cardiorespiratory parameters; patient tolerance:	Using a combination of EBUS-TBNA and EUS-B-FNA in mediastinal staging, the diagnostic values and the patient satisfaction were not different between group A and group B. The necessity for EBUS-TBNA following EUS-B-FNA suggests that EBUS-TBNA is a better primary procedure in endoscopic mediastinal staging.	1+ Directly applicable Limits: – Suboptimal performance of EUS-B (selective sampling, low number of aspirations, little time spent)	6

		requests – Complications			similar in both groups – Complications: hypoxia similar in both groups; in group B, 1 pneumomediastinum was observed after EBUS but did not require specific treatment			
Ohnishi, 2011 [33]	Prospective comparative study	Combination of EBUS and EUS for mediastinal lymph node staging To compare the diagnostic yield of CT-PET and the combination of EBUS/EUS-FNA	n = 120 Consecutive patients	Surgery (resection with N staging)	CT-PET: – Accuracy: 73.6% – Sensitivity: 47.4% – Specificity: 87.5% – PPV: 66.7% – NPV: 75.9% – False-negative: 20 EBUS+EUS – Accuracy: 90% – Sensitivity: 71.8% – Specificity: 100% – PPV: 100% – NPV: 86.6% – False-negative: 11 The number of false-negative results was 14 with only EBUS and 20 with only EUS.	The combined endoscopic approach using EUS-FNA and EBUS-TBNA provided excellent diagnostic performance. Therefore, this approach is strongly recommended before surgery or mediastinoscopy to avoid futile thoracotomy and surgical intervention.	2+ Directly applicable	6
Hwangbo, 2010 [36]	Prospective study Single-center study	Combination of EBUS and EUS (single scope) for mediastinal lymph node staging	n = 143 Consecutive patients	Surgery (node dissection)	EBUS alone: – Sensitivity: 84.4% – NPV: 93.3% – Diagnostic accuracy: 95.1% EBUS + EUS-B-FNA – Sensitivity: 91.1% – NPV: 96.1% – Diagnostic accuracy: 97.2% (not significant values) Among 473 mediastinal nodal stations having at least one node ≥5 mm that were evaluated, the proportion of mediastinal nodal stations accessible by EBUS-	Following EBUS-TBNA in the mediastinal staging of potentially operable lung cancer, the accessibility to mediastinal nodal stations increased by adding EUS-B-FNA, and an additional diagnostic gain might be obtained by EUS-B-FNA.	2+ Directly applicable Limits: – Single-center – EUS-B only used for those nodes not accessible by EBUS	6

					TBNA was 78.6%; the proportion increased to 84.8% by combining EUS-B-FNA with EBUS-TBNA (*P* = .015). Mean procedure time: – EBUS-TBNA: 18.9 min – EUS-B-FNA: 38 min			
Herth, 2010 [34]	Prospective comparative study Multicenter study	Combination of EBUS and EUS (single scope) for mediastinal lymph node staging	n = 139 Consecutive patients	Surgery (thoracoscopy or open thoracotomy) or clinical follow-up	Sensitivity: – EBUS alone: 89% – EUS alone: 92% – Combined approach: 96% NPV: – EBUS alone: 92% – EUS alone: 82% – Combined approach: 95% Mean procedure time: – EBUS-TBNA: 14 min – EUS-B-FNA: 16 min No patient intolerance No complications	The two procedures can be performed with a dedicated linear endobronchial ultrasound bronchoscope in one setting and by one operator. They are complementary and provide better diagnostic accuracy than either one alone. The combination may be able to replace more invasive methods as a primary staging method for patients with lung cancer.	2+ Directly applicable Limits: – Reference standard included clinical follow-up	6
Lee, 2014 [39]	Retrospective study	EUS-B-FNA was performed after EBUS-TBNA when mediastinal lymph nodes were not accessible using EBUS-TBNA or when tissue sampling using EBUS-TBNA alone was inadequate.	n = 44 (37 included in analysis)	Surgery: – Mediastinoscopy – Pulmonary resection with mediastinal node dissection	EBUS: Sensitivity: 79% NPV: 57% Combined approach: Sensitivity: 100% NPV: 100%	Use of a combination of EBUS-TBNA and EUS-B-FNA can afford better sensitivity and accuracy of mediastinal N-staging compared with use of EBUS-TBNA alone	2– Limits: – Reference standard included mediastinoscopy – Only included patients with inaccessible nodes during EBUS-TBNA – Retrospective study	
Liberman, 2014 [40]	Prospective study	Combined EBUS/EUS for mediastinal lymph node staging	n = 166	Surgery: – Mediastinoscopy	EBUS: – Sensitivity: 72% – NPV: 88% EUS: – Sensitivity: 62% – NPV: 85%	The combined EBUS/EUS procedure can replace surgical mediastinal staging in patients with potentially resectable NSCLC.	2– Limits: – Reference standard included mediastinoscopy	

					Combined approach: – Sensitivity: 91% – NPV: 96%			
Chang, 1996 [71]	Consecutive patients Single-center study	EUS: imaging and characterization of left adrenal gland	n = 31 Indication for EUS: diagnosis and staging of GI and lung malignancies.	Radiological follow-up	Left adrenal gland visualized by EUS in 97% of patients	Technically feasible	2– Not directly applicable Limits: – Small – Several GI malignancies	7
Uemura, 2013 [79]	Retrospective cohort study	EUS: Detection rate for right adrenal gland Diagnostic ability of EUS-FNA for adrenal metastases in lung cancer	n = 150 Indication for EUS: staging of lung cancer	No reference standard	Visualization: – Right adrenal gland: 87% – Left adrenal gland: 100% Diagnostic accuracy for adrenal metastases 100%	Technically feasible	2– Directly applicable Only a few with actual metastasis	7
Eloubeidi, 2004 [72]	Consecutive patients. Data collection prospectively as an ongoing observational study in one center and by retrospective cohort design at the other center.	EUS-FNA left adrenal gland: feasibility and safety	n = 31 Indications for EUS-FNA: enlarged adrenal gland on imaging and known or suspected malignancies 2 EUS referral centers	No reference standard	Adequate tissue obtained in 100%. No complications.	Technically feasible, including aspiration	2– Directly applicable	7
Stelow, 2005 [102]	Retrospective review of cytology files	EUS-FNA of left adrenal gland (1 right adrenal gland): comparison of EUS-FNA and non-EUS-guided FNA for utility of cell block immunohistochemistry.	n = 22 (24 cases) Indications for EUS-FNA: in 86%, staging for malignancies 1 center	No reference standard	Diagnostic material was present in all cases	Technically feasible, including aspiration, to detect left adrenal gland metastases	2– Not directly applicable	7

DeWitt, 2006 [103]	Retrospective case series	EUS-FNA of left adrenal gland: report experience	n = 38 Indication for EUS-FNA: lung mass in 14, left adrenal gland mass in 5, pancreatic mass in 14 1 center	Surgery, clinical and/or radiological follow-up	24% nondiagnostic 0% false-negative results in lung cancer cases. No complications	Technically feasible, including aspiration, to detect and exclude left adrenal gland metastases	2– Not directly applicable	7
Eloubeidi, 2008 [104]	Prospective	EUS-FNA (lymph nodes, pancreatic masses, liver etc): diagnostic accuracy and complications	n = 540 n = 15 for adrenal gland Indications for EUS-FNA of adrenal gland: unknown 1 center	Death from disease progression; radiological and/or clinical follow-up	Sensitivity: 100% NPV: 100%	Technically feasible, including aspiration, to detect and exclude left adrenal gland metastases	2– Not directly applicable	7
Ang TL, 2007 [73]	Prospective	EUS or EUS-FNA for left adrenal gland	n = 119 Consecutive patients	No reference standard	Overall prevalence of left adrenal gland mass: 3.4%	EUS-FNA is a safe and useful technique for evaluation of left adrenal gland masses.	2– Not directly applicable Not all patients had lung cancer	7
Bodtger, 2009 [74]	Retrospective	Evaluation of impact of EUS-FNA of left adrenal gland on TNM staging	n = 40	No reference standard	EUS-FNA of enlarged left adrenal gland altered TNM staging in 70% of patients, and treatment in 48%. Malignant left adrenal gland lesion was found in 28% of patients and was associated with shorter survival.	EUS-FNA of an enlarged left adrenal gland in patients with known or suspected lung cancer had a significant impact on TNM staging, treatment, and survival. The impact of routine visualization of the left adrenal gland in lung cancer work-up needs to be prospectively validated.	2– Directly applicable	7

Schuurbiers, 2011 [75]	Retrospective	EUS-FNA sensitivity for left adrenal metastases in lung cancer patients with an adrenal gland suspicious at radiological imaging	n = 85	Imaging, no surgical reference	EUS-FNA findings: – 62% of patients, left adrenal gland metastases – 29%, benign lesions – 1%, colon carcinoma metastasis – 1%, primary adrenocortical carcinoma In 5.9%, aspirates had no representative material. False negatives: 2/85 Sensitivity: 86% NPV: 70%	EUS-FNA is a sensitive, safe and minimally invasive technique to provide tissue proof of left adrenal metastases in patients with (suspected) lung cancer.	2– Directly applicable	7
Von Bartheld, 2011 [58]	Retrospective Single-center study	EUS-FNA for mediastinal restaging	n = 58 Inclusion: stage III NSCLC and tissue proven lymph node metastases N2/N3, who underwent EUS-FNA for restaging after chemoradiotherapy	Surgical-pathological staging of nodal metastases	Sensitivity: 44% False negative rate: 58% NPV: 42%	For mediastinal restaging of stage III NSCLC, EUS-FNA is a minimally invasive and safe method to confirm persistent nodal metastases but has a low NPV.	2– Directly applicable	8
Stigt, 2009 [57]	Prospective Single-center study.	EUS-FNA for mediastinal restaging	n = 28 Inclusion: NSCLC stage III and pathologically proven nodal disease. Restaging was performed on the same nodes after chemoradiotherapy	Thoracotomy with mediastinal lymph node dissection if restaging with EUS showed no tumor cells	NPV: 91.6% Diagnostic accuracy: 92.3%	Restaging with EUS-FNA after induction chemoradiotherapy is well tolerated and reliably predicts the absence of nodal metastasis. Although changes in mediastinal FDG-PET uptake show a high concordance with EUS-FNA, pathological confirmation is still superior and therefore necessary.	2– Directly applicable	8

Zielinski, 2013 [59]	Retrospective Single-center study	EBUS-TBNA and/or EUS-FNA for mediastinal restaging Aim: compare diagnostic yield of EBUS and/or EUS with transcervical extended mediastinal lymphadenectomy (TEMLA)	n = 88 – 32 EBUS-TBNA – 6 EUS – 50 Combined EBUS and EUS Inclusion: NSCLC with previously endosonographically proven metastatic mediastinal nodes and neoadjuvant treatment	TEMLA in the case of negative results of endoscopy	Endosonography: – Sensitivity: 64.3% – NPV 82.1%	The results of this largest reported series comparing endoscopic and surgical primary staging and restaging of NSCLC showed a significantly higher diagnostic yield of TEMLA when compared with that of EBUS or EUS.	2– Directly applicable	8
Annema, 2003 [55]	Prospective Single-center study	EUS-FNA for mediastinal restaging	n = 19 Inclusion: patients with NSCLC and proven IIIA-N2 disease who had been treated with induction chemotherapy were referred for mediastinal restaging by EUS-FNA	When EUS-FNA restaged the mediastinum as N0, surgical resection of the tumor with lymph node sampling or dissection	PPV: 100% NPV: 67% Sensitivity: 75% Specificity: 100% Diagnostic accuracy: 83%	EUS-FNA qualifies as an accurate, safe and minimally invasive diagnostic technique for the restaging of mediastinal lymph nodes after induction therapy in NSCLC.	2– Directly applicable	8
Varadarajulu, 2006 [56]	Pilot study: Retrospective analysis of prospectively collected data. Single-center study	EUS-FNA for mediastinal restaging	n = 14 Inclusion: patients with NSCLC and biopsy-proven N2 disease who underwent restaging by EUS following chemoradiation therapy	Those staged as N0 by EUS underwent tumor resection with complete lymph node dissection	Diagnostic accuracy: 86%	EUS-FNA appears to qualify as an accurate, safe and minimally invasive diagnostic technique for restaging of mediastinal lymph nodes after chemoradiation therapy in NSCLC patients.	2– Directly applicable	8

Herth 2008 [60]	Prospective	EBUS-FNA sensitivity and accuracy for restaging the mediastinum after induction chemotherapy in patients with NSCLC	n = 124 Consecutive patients	Thoracotomy	Sensitivity: 76% Specificity: 100% PPV: 100% NPV: 20% Diagnostic accuracy: 77%	EBUS-TBNA is a sensitive, specific, accurate, and minimally invasive test for mediastinal restaging of patients with NSCLC. However, because of the low negative predictive value, tumor-negative findings should be confirmed by surgical staging before thoracotomy.	2+ Directly applicable	8
Szlubowski, 2010 [61]	Prospective	EBUS-TBNA sensitivity and diagnostic yield in restaging of NSCLC patients after neoadjuvant therapy	n = 61 Consecutive patients	Transcervical extended mediastinal lymphadenectomy (TEMLA)	Sensitivity: 67% Specificity: 86% Diagnostic accuracy: 80% PPV: 91% NPV: 78%	EBUS-TBNA is an effective and safe technique for mediastinal restaging in NSCLC patients. In patients with negative results of EBUS-TBNA, a surgical restaging of the mediastinum might not be mandatory.	2+ Directly applicable	8
Steinfort, 2011 [81]	Prospective	EBUS-TBNA sensitivity for malignancy and evaluation the effect of procedural learning curve on diagnostic sensitivity	n = 215 Consecutive patients (analysis of the first 215 patients undergoing EBUS-TBNA at one institution)	Surgery	Sensitivity for malignancy was 92% Significant improvement in diagnostic performance was seen after 20 procedures were completed, and diagnostic accuracy did not peak until after 50 procedures	EBUS-TBNA is able to accurately confirm histologically a large number of disease processes, both malignant and benign, in all clinical indications studied. The procedure is safe even when carried out by practitioners with minimal prior experience. Diagnostic performance continues to improve beyond performance of 50 cases.	2–	9
Stather, 2013 [82]	Retrospective	Determination of the impact of trainee participation during advanced diagnostic bronchoscopy on procedure time, sedation use, and complications	670 procedures; a trainee participated in 512 (84.3%) examinations	Not applicable	Trainee participation led to: – Increased complication rate (4.7% vs. 1.1%, $P = 0.076$) – Increased procedure length (58.3 minutes vs. 37.7 minutes, $P = 0.001$) – Increased dose of propofol (178 mg vs. 137 mg, $P = 0.002$)	Trainee participation in advanced diagnostic bronchoscopy increased procedure time, increased the amount of sedation used, and resulted in a trend to increased complications.	2–	9

Cook, 2011 [84]	Systematic review and meta-analysis	To summarize the outcomes of technology-enhanced simulation training for health professions learners in comparison with no intervention	137 randomized studies	Simulation Not applicable	Pooled effect sizes for: – Time skills: 1.14 – Process skills: 1.09 – Product skills: 1.18 – Time behaviors: 0.79 – Other behaviors: 0.81 – Direct effects on patients: 0.50	In comparison with no intervention, technology-enhanced simulation training in health professions education is consistently associated with large effects for outcomes of knowledge, skills, and behaviors, and moderate effects for patient-related outcomes.	1+ Large heterogeneity (I^2 > 50%)	10
Konge, 2013 [85]	Prospective comparative	To design an evidence-based and credible EBUS certification based on a virtual-reality EBUS simulator test	n = 22 participants, divided into 3 groups: – Experienced EBUS operators (group 1, n = 6) – Untrained novices (group 2, n = 8) – Simulator-trained novices (group 3, n = 8).	Not applicable	Successfully sampled lymph nodes and procedure time were the only simulator metrics that showed statistically significant differences. None of the novices met the pass/fail standard.	Virtual reality simulators could be an important first line in credentialing before trainees proceed to supervised performance on patients.	2–	10
Stather, 2011 [86]	Prospective comparative	To validate a computer EBUS simulator in differentiating between operators of varying clinical EBUS experience	n = 22 participants, divided into groups: – A, novice bronchoscopists, no EBUS experience (n = 4) – B, expert bronchoscopists, no EBUS experience (n = 5) – C, basic clinical EBUS training (n = 9) – D, EBUS experts (n = 4)	Not applicable	Significant differences between groups were noted for: – Total procedure time – Percentage of lymph nodes identified – Percentage of successful biopsies. Group D performed significantly better than all other groups for: – Total procedure time – Percentage of lymph nodes identified Group C performed significantly better than groups A and B for: – Total procedure time – Percentage of lymph nodes identified – Percentage of successful biopsies.	An EBUS simulator can accurately discriminate between operators with different levels of clinical EBUS experience.	2–	10
Stather, 2012 [87]	RCT	To compare two methods used to teach EBUS-TBNA: wet laboratory (lab) vs. computer EBUS-	n = 12 participants – 6 wet lab group – 6 EBUS-TBNA simulator group	Not applicable	No significant differences between the computer EBUS-TBNA simulator group and the wet lab group in procedure time and percentage of successful biopsies.	Computer EBUS-TBNA simulation and wet lab simulation are effective methods of learning basic EBUS-TBNA skills, and appeared to be complementary.	1–	10

		TBNA simulation			The computer simulator group performed significantly better than the wet lab group in the percentage of lymph nodes correctly identified. Wet lab simulation was associated with increased learner confidence in operating the real EBUS-TBNA bronchoscope. All participants responded that wet lab and computer EBUS-TBNA simulation offered important complementary learning opportunities.			
Annema, 2010 [93]	Prospective multicenter trial	To test a training and implementation strategy for EUS for the diagnosis and staging of lung cancer	n = 551 Consecutive patients	Surgery (not in all patients)	Implementation center: – EUS sensitivity: 83% – EUS diagnostic accuracy: 89% – Surgery avoided: 51% Expert center: – EUS sensitivity: 82% – EUS diagnostic accuracy: 88% – Surgery avoided: 54% A single complication occurred in each group.	Chest physicians who participate in a dedicated training and implementation program for EUS in lung cancer staging can obtain results similar to those of experts for mediastinal nodal staging.	2+	11
Konge, 2013 [94]	Prospective cohort study	To establish whether there is a minimum training requirement for EUS	n = 4 participants (91 EUS-FNA procedures)	Not applicable	The performances of the participants improved significantly and became more consistent, but were still highly variable even in the latter part of the learning curves. Only 2 of the participants reached the mean score of experienced operators; this was after 17 and 23 procedures, respectively.	Pulmonologists with knowledge of lung cancer staging and experience in bronchoscopy quickly improved their performance of EUS-FNA. 20 procedures were not enough to secure consistent and competent performance of all trainees.	2– Small sample	11
Konge, 2012 [99]	Prospective comparative study	To explore the reliability and validity of a newly developed EUS Assessment Tool (EUSAT) designed	n = 30 procedures 6 EUS- FNA trainees 6 EUS- FNA experts	Not applicable	Reliability, Cronbach's *α*: – Intra-rater: 0.80 – Inter-rater: 0.93 The assessment tool demonstrated construct validity by discriminating between trainees	Competency in mediastinal staging of NSCLC using EUS and EUS-FNA can be assessed in a reliable and valid way using the EUSAT assessment tool.	2– Small sample	11

		to measure competence in EUS-FNA for mediastinal staging of NSCLC			and experienced physicians			
Davoudi, 2012 [100]	Prospective multicenter comparative study	To assess the validity and the reliability of the EBUS Skills and Tasks Assessment Tool (EBUS-STAT)	24 operators at three levels of EBUS-TBNA experience: – 8 beginners – 8 intermediates – 8 experienced	Not applicable	Intertester reliability between testers was very high (r = 0.9991). Mean EBUS-STAT scores: – Beginners: 31.1/100 – Intermediates: 74.9/100 – Experienced: 93.6/100 Each group differed significantly from the others. Self-assessments corresponded closely to actual EBUS-STAT scores (r^2 = 0.81).	The EBUS-STAT can be used to reliably and objectively score and classify EBUS-TBNA operators from novice to expert.	2+ Small sample	11

95%CI, 95% confidence interval; CT, computed tomography; CT-PET, integrated computed and positron emission tomography; EBUS-TBNA, endobronchial ultrasound with real-time guided transbronchial needle aspiration; EUS-B, endoscopic ultrasound, using the EBUS scope; FDG, fluorodeoxyglucose; FNA, fine needle aspiration; GI, gastrointestinal; NPV, negative predictive value; NSCLC, non-small-cell lung cancer; PET, positron emission tomography; PPV, positive predictive value; RCT, randomized controlled trial; vs., versus.

References

1 Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013; 49: 1374–1403

2 Rivera MP, Mehta AC, American College of Chest P. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007; 132: 131S–148S

3 Vansteenkiste J, De Ruysscher D, Eberhardt WE et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24 Suppl 6: vi89–98. doi: 10.1093/annonc/mdt241. Epub 2013 Jul 16

4 Libshitz HI, McKenna RJ Jr. Mediastinal lymph node size in lung cancer. AJR Am J Roentgenol 1984; 143: 715–718

5 Lardinois D, Weder W, Hany TF et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. NEJM 2003; 348: 2500–2507

6 Tournoy KG, Maddens S, Gosselin R et al. Integrated FDG-PET/CT does not make invasive staging of the intrathoracic lymph nodes in non-small cell lung cancer redundant: a prospective study. Thorax 2007; 62: 696–701

7 De Wever W, Stroobants S, Coolen J et al. Integrated PET/CT in the staging of nonsmall cell lung cancer: technical aspects and clinical integration. Eur Respir J 2009; 33: 201–212

8 Fischer BM, Mortensen J, Hansen H et al. Multimodality approach to mediastinal staging in non-small cell lung cancer. Faults and benefits of PET-CT: a randomised trial. Thorax 2011; 66: 294–300

9 Hishida T, Yoshida J, Nishimura M et al. Problems in the current diagnostic standards of clinical N1 non-small cell lung cancer. Thorax 2008; 63: 526–531

10 Watanabe S, Asamura H, Suzuki K et al. Problems in diagnosis and surgical management of clinical N1 non-small cell lung cancer. Ann Thorac Surg 2005; 79: 1682–1685

11 Cerfolio RJ, Bryant AS, Ojha B et al. Improving the inaccuracies of clinical staging of patients with NSCLC: a prospective trial. Ann Thorac Surg 2005; 80: 1207–1213; discussion 1213–1204

12 Cerfolio RJ, Bryant AS, Eloubeidi MA. Routine mediastinoscopy and esophageal ultrasound fine-needle aspiration in patients with non-small cell lung cancer who are clinically N2 negative: a prospective study. Chest 2006; 130: 1795–1795

13 Detterbeck FC, Jantz MA, Wallace M et al. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007; 132: 202S–220S

14 Pedersen BH, Vilmann P, Folke K et al. Endoscopic ultrasonography and real-time guided fine-needle aspiration biopsy of solid lesions of the mediastinum suspected of malignancy. Chest 1996; 110: 539–544

15 Verma A, Jeon K, Koh WJ et al. Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of central lung parenchymal lesions. Yonsei Med J 2013; 54: 672–678

16 Silvestri GA, Hoffman BJ, Bhutani MS et al. Endoscopic ultrasound with fine-needle aspiration in the diagnosis and staging of lung cancer. Ann Thorac Surg 1996; 61: 1441–1445; discussion 1445–1446

17 Vilmann P, Annema J, Clementsen P. Endosonography in bronchopulmonary disease. Best Pract Res Clin Gastroenterol 2009; 23: 711–728

18 Annema JT, van Meerbeeck JP, Rintoul RC et al. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. JAMA 2010; 304: 2245–2252

19 Wiersema MJ, Vilmann P, Giovannini M et al. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. Gastroenterology 1997; 112: 1087–1095

20 Herth FJ, Eberhardt R, Vilmann P et al. Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. Thorax 2006; 61: 795–798

21 De Leyn P, Dooms C, Kuzdzal J et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg 2014; 45: 787–798

22 Silvestri GA, Gonzalez AV, Jantz MA et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American

College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143 (5 Suppl): e211S–250S

23 Rintoul RC, Glover MJ, Jackson C et al. Cost effectiveness of endosonography versus surgical staging in potentially resectable lung cancer: a health economics analysis of the ASTER trial from a European perspective. Thorax 2014; 69: 679–681

24 Sharples LD, Jackson C, Wheaton E et al. Clinical effectiveness and cost-effectiveness of endobronchial and endoscopic ultrasound relative to surgical staging in potentially resectable lung cancer: results from the ASTER randomised controlled trial. Health Technol Assess 2012; 16: 1–75, iii–iv

25 Zhang R, Ying K, Shi L et al. Combined endobronchial and endoscopic ultrasound-guided fine needle aspiration for mediastinal lymph node staging of lung cancer: a meta-analysis. Eur J Cancer 2013; 49: 1860–1867

26 Scottish Intercollegiate Guidelines Network. Available at: http://www.sign.ac.uk/guidelines/fulltext/50/annexoldb.html

27 Tournoy KG, Keller SM, Annema JT. Mediastinal staging of lung cancer: novel concepts. Lancet Oncol 2012; 13: e221–e229

28 Darling GE, Maziak DE, Inculet RI et al. Positron emission tomography-computed tomography compared with invasive mediastinal staging in non-small cell lung cancer: results of mediastinal staging in the early lung positron emission tomography trial. J Thorac Oncol 2011; 6: 1367–1372

29 Gu P, Zhao YZ, Jiang LY et al. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. Eur J Cancer 2009; 45: 1389–1396

30 Micames CG, McCrory DC, Pavey DA et al. Endoscopic ultrasound-guided fine-needle aspiration for non-small cell lung cancer staging: A systematic review and metaanalysis. Chest 2007; 131: 539–548

31 Wallace MB, Pascual JM, Raimondo M et al. Minimally invasive endoscopic staging of suspected lung cancer. JAMA 2008; 299: 540–546

32 Vilmann P, Krasnik M, Larsen SS et al. Transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy: a combined approach in the evaluation of mediastinal lesions. Endoscopy 2005; 37: 833–839

33 Ohnishi R, Yasuda I, Kato T et al. Combined endobronchial and endoscopic ultrasound-guided fine needle aspiration for mediastinal nodal staging of lung cancer. Endoscopy 2011; 43: 1082–1089

34 Herth FJ, Krasnik M, Kahn N et al. Combined endoscopic-endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes through a single bronchoscope in 150 patients with suspected lung cancer. Chest 2010; 138: 790–794

35 Kang HJ, Hwangbo B, Lee GK et al. EBUS-centred versus EUS-centred mediastinal staging in lung cancer: a randomised controlled trial. Thorax 2014; 69: 261–268

36 Hwangbo B, Lee GK, Lee HS et al. Transbronchial and transesophageal fine-needle aspiration using an ultrasound bronchoscope in mediastinal staging of potentially operable lung cancer. Chest 2010; 138: 795–802

37 Oki M, Saka H, Ando M et al. Endoscopic ultrasound-guided fine needle aspiration and endobronchial ultrasound-guided transbronchial needle aspiration: Are two better than one in mediastinal staging of non-small cell lung cancer? J Thorac Cardiovasc Surg 2014; 148: 1169–1177

38 Annema JT. Letter to the Editor. J Thorac Cardiovasc Surg 2015; 149: 942

39 Lee KJ, Suh GY, Chung MP et al. Combined endobronchial and transesophageal approach of an ultrasound bronchoscope for mediastinal staging of lung cancer. PLoS One 2014; 9: e91893

40 Liberman M, Sampalis J, Duranceau A et al. Endosonographic mediastinal lymph node staging of lung cancer. Chest 2014; 146: 389–397

41 Szlubowski A, Zieliński M, Soja J et al. A combined approach of endobronchial and endoscopic ultrasound-guided needle aspiration in the radiologically normal mediastinum in non-small-cell lung cancer staging – a prospective trial. Eur J Cardiothorac Surg 2010; 37: 1175–1179

42 von Bartheld MB, van Breda A, Annema JT. Complication rate of endosonography (endobronchial and endoscopic ultrasound): a systematic review. Respiration 2014; 87: 343–351

43 Varela-Lema L, Fernandez-Villar A, Ruano-Ravina A. Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: a systematic review. Eur Respir J 2009; 33: 1156–1164

44 Asano F, Aoe M, Ohsaki Y et al. Complications associated with endobronchial ultrasound-guided transbronchial needle aspiration: a nationwide survey by the Japan Society for Respiratory Endoscopy. Respir Res 2013; 14: 50

45 Harewood GC, Pascual J, Raimondo M et al. Economic analysis of combined endoscopic and endobronchial ultrasound in the evaluation of patients with suspected non-small cell lung cancer. Lung Cancer 2010; 67: 366–371

46 Toloza E, Harpole L, Detterbeck F, McCrory DC. Invasive staging of non-small cell lung cancer: a review of the current evidence. Chest 2003; 123 Suppl 1: 157S–166S

47 Dooms C, Tournoy KG, Schuurbiers O et al. Endosonography for mediastinal nodal staging of clinical N1 non-small cell lung cancer: a prospective multicenter study. Chest 2015; 147: 209–215

48 Annema JT. When will we finally adopt endoscopic ultrasound? Chest 2014; 146: e117

49 Ghosh S, Nanjiah P, Dunning J. Should all patients with non-small cell lung cancer who are surgical candidates have cervical mediastinoscopy preoperatively? Interact Cardiovasc Thorac Surg 2006; 5: 20–24

50 Varadarajulu S, Hoffman BJ, Hawes RH, Eloubeidi MA. EUS-guided FNA of lung masses adjacent to or abutting the esophagus after unrevealing CT-guided biopsy or bronchoscopy. Gastrointest Endosc 2004; 60: 293–297

51 Hernandez A, Kahaleh M, Olazagasti J et al. EUS-FNA as the initial diagnostic modality in centrally located primary lung cancers. J Clin Gastroenterol 2007; 41: 657–660

52 Vansteenkiste J, De Ruysscher D, Eberhardt WE et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24 Suppl 6: vi89–vi98

53 de Cabanyes CS, Detterbeck FC. A systematic review of restaging after induction therapy for stage IIIa lung cancer: prediction of pathologic stage. J Thorac Oncol 2010; 5: 389–398

54 De Leyn P, Stroobants S, De Wever W et al. Prospective comparative study of integrated positron emission tomography-computed tomography scan compared with remediastinoscopy in the assessment of residual mediastinal lymph node disease after induction chemotherapy for mediastinoscopy-proven stage IIIA-N2 non-small-cell lung cancer: a Leuven Lung Cancer Group Study. J Clin Oncol 2006; 24: 3333–3339

55 Annema JT, Veselic M, Versteegh MI et al. Mediastinal restaging: EUS-FNA offers a new perspective. Lung Cancer 2003; 42: 311–318

56 Varadarajulu S, Eloubeidi M. Can endoscopic ultrasonography-guided fine-needle aspiration predict response to chemoradiation in non-small cell lung cancer? A pilot study. Respiration 2006; 73: 213–220

57 Stigt JA, Oostdijk AH, Timmer PR et al. Comparison of EUS-guided fine needle aspiration and integrated PET-CT in restaging after treatment for locally advanced non-small cell lung cancer. Lung Cancer 2009; 66: 198–204

58 von Bartheld MB, Versteegh MI, Braun J et al. Transesophageal ultrasound-guided fine-needle aspiration for the mediastinal restaging of non-small cell lung cancer. J Thorac Oncol 2011; 6: 1510–1515

59 Zielinski M, Szlubowski A, Kolodziej M et al. Comparison of endobronchial ultrasound and/or endoesophageal ultrasound with transcervical extended mediastinal lymphadenectomy for staging and restaging of non-small-cell lung cancer. J Thorac Oncol 2013; 8: 630–636

60 Herth FJ, Annema JT, Eberhardt R et al. Endobronchial ultrasound with transbronchial needle aspiration for restaging the mediastinum in lung cancer. J Clin Oncol 2008; 26: 3346–3350

61 Szlubowski A, Herth FJ, Soja J et al. Endobronchial ultrasound-guided needle aspiration in non-small-cell lung cancer restaging verified by the transcervical bilateral extended mediastinal lymphadenectomy – a prospective study. Eur J Cardiothorac Surg 2010; 37: 1180–1184

62 Szlubowski A, Zielinski M, Soja J et al. Accurate and safe mediastinal restaging by combined endobronchial and endoscopic ultrasound-guided needle aspiration

performed by single ultrasound bronchoscope. Eur J Cardiothorac Surg 2014; 46: 262–266.

63 Vazquez-Sequeiros E, Levy MJ, Van Domselaar M et al. Diagnostic yield and safety of endoscopic ultrasound guided fine needle aspiration of central mediastinal lung masses. Diagn Ther Endosc 2013; 2013: 150492. doi: 10.1155/2013/150492. Epub 2013 May 30

64 Annema JT, Veseliç M, Rabe KF. EUS-guided FNA of centrally located lung tumours following a non-diagnostic bronchoscopy. Lung Cancer 2005; 48: 357–361

65 Tournoy KG, Rintoul RC, van Meerbeeck JP et al. EBUS-TBNA for the diagnosis of central parenchymal lung lesions not visible at routine bronchoscopy. Lung Cancer 2009; 63: 45–49

66 Abrams HL, Spiro R, Goldstein N. Metastases in carcinoma; analysis of 1000 autopsied cases. Cancer 1950; 3: 74–85

67 Stone WZ, Wymer DC, Canales BK. Fluorodeoxyglucose-positron-emission tomography/computed tomography imaging for adrenal masses in patients with lung cancer: review and diagnostic algorithm. J Endourol 2014; 28: 104–111

68 Pieterman RM, van Putten JW, Meuzelaar JJ et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. N Engl J Med 2000; 343: 254–261

69 Osman Y, El-Mekresh M, Gomha AM et al. Percutaneous adrenal biopsy for indeterminate adrenal lesion: complications and diagnostic accuracy. Urol Int 2010; 84: 315–318

70 Mody MK, Kazerooni EA, Korobkin M. Percutaneous CT-guided biopsy of adrenal masses: immediate and delayed complications. J Comput Assist Tomogr 1995; 19: 434–439

71 Chang KJ, Erickson RA, Nguyen P. Endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration of the left adrenal gland. Gastrointest Endosc 1996; 44: 568–572

72 Eloubeidi MA, Seewald S, Tamhane A et al. EUS-guided FNA of the left adrenal gland in patients with thoracic or GI malignancies. Gastrointest Endosc 2004; 59: 627–633

73 Ang TL, Chua TS, Fock KM et al. EUS-FNA of the left adrenal gland is safe and useful. Ann Acad Med Singapore 2007; 36: 954–957

74 Bodtger U, Vilmann P, Clementsen P et al. Clinical impact of endoscopic ultrasound-fine needle aspiration of left adrenal masses in established or suspected lung cancer. J Thorac Oncol 2009; 4: 1485–1489

75 Schuurbiers OC, Tournoy KG, Schoppers HJ et al. EUS-FNA for the detection of left adrenal metastasis in patients with lung cancer. Lung Cancer 2011; 73: 310–315

76 Eloubeidi MA, Black KR, Tamhane A et al. A large single-center experience of EUS-guided FNA of the left and right adrenal glands: diagnostic utility and impact on patient management. Gastrointest Endosc 2010; 71: 745–753

77 Buxbaum JL, Eloubeidi MA. Transgastric endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) in patients with esophageal narrowing using the ultrasonic bronchovideoscope. Dis Esophagus 2011; 24: 458–461

78 Eloubeidi MA, Morgan DE, Cerfolio RJ, Eltoum IA. Transduodenal EUS-guided FNA of the right adrenal gland. Gastrointest Endosc 2008; 67: 522–527

79 Uemura S, Yasuda I, Kato T et al. Preoperative routine evaluation of bilateral adrenal glands by endoscopic ultrasound and fine-needle aspiration in patients with potentially resectable lung cancer. Endoscopy 2013; 45: 195–201

80 Haseganu LE, Diehl DL. Left adrenal gland hemorrhage as a complication of EUS-FNA. Gastrointest Endosc 2009; 69: e51–e52

81 Steinfort DP, Hew MJ, Irving LB. Bronchoscopic evaluation of the mediastinum using endobronchial ultrasound - A description of the first 216 cases performed at an Australian tertiary hospital. Intern Med J 2011; 41: 815–824

82 Stather DR, Maceachern P, Chee A et al. Trainee impact on advanced diagnostic bronchoscopy: an analysis of 607 consecutive procedures in an interventional pulmonary practice. Respirology 2013; 18: 179–184

83 Annema JT, Rabe KF. Why respiratory physicians should learn and implement EUS-FNA. Am J Respir Crit Care Med 2007; 176: 99

84 Cook DA, Hatala R, Brydges R et al. Technology-enhanced simulation for health professions education: a systematic review and meta-analysis. JAMA 2011; 306: 978–988

85 Konge L, Annema J, Clementsen P et al. Using virtual-reality simulation to assess performance in endobronchial ultrasound. Respiration 2013; 86: 59–65

86 Stather DR, Maceachern P, Rimmer K et al. Validation of an endobronchial ultrasound simulator: differentiating operator skill level. Respiration 2011; 81: 325–332

87 Stather DR, Maceachern P, Chee A et al. Wet laboratory versus computer simulation for learning endobronchial ultrasound: a randomized trial. Can Respir J 2012; 19: 325–330

88 Polkowski M, Larghi A, Weynand B et al. Learning, techniques, and complications of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Guideline. Endoscopy 2012; 44: 190–206

89 Folch E, Majid A. Point: are >50 supervised procedures required to develop competency in performing endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal staging? Yes. Chest 2013; 143: 888–891

90 Eisen GM, Dominitz JA, Faigel DO et al. Guidelines for credentialing and granting privileges for endoscopic ultrasound. Gastrointest Endosc 2001; 54: 811–814

91 Wani S, Cote GA, Keswani R et al. Learning curves for EUS by using cumulative sum analysis: implications for American Society for Gastrointestinal Endoscopy recommendations for training. Gastrointest Endosc 2013; 77: 558–565

92 Vilmann P, Saftoiu A. Endoscopic ultrasound-guided fine needle aspiration biopsy: equipment and technique. J Gastroenterol Hepatol 2006; 21:1646–1655

93 Annema JT, Bohoslavsky R, Burgers S et al. Implementation of endoscopic ultrasound for lung cancer staging. Gastrointest Endosc 2010; 71: 64–70, 70

94 Konge L, Annema J, Vilmann P et al. Transesophageal ultrasonography for lung cancer staging: learning curves of pulmonologists. J Thorac Oncol 2013; 8: 1402–1408

95 Bolliger CT, Mathur PN, Beamis JF, Becker HD et al. ERS/ATS statement on interventional pulmonology. European Respiratory Society/American Thoracic Society. Eur Respir J 2002; 19: 356–373

96 Ernst A, Silvestri GA, Johnstone D. Interventional pulmonary procedures: Guidelines from the American College of Chest Physicians. Chest 2003; 123: 1693–1717

97 Kinsey CM, Channick CL. Counterpoint: are >50 supervised procedures required to develop competency in performing endobronchial ultrasound-guided transbronchial needle aspiration for lung cancer staging? No. Chest 2013; 143: 891–893

98 Du Rand IA, Barber PV, Goldring J et al. Summary of the British Thoracic Society guidelines for advanced diagnostic and therapeutic flexible bronchoscopy in adults. Thorax 2011; 66: 1014–1015

99 Konge L, Vilmann P, Clementsen P et al. Reliable and valid assessment of competence in endoscopic ultrasonography and fine-needle aspiration for mediastinal staging of non-small cell lung cancer. Endoscopy 2012; 44: 928–933

100 Davoudi M, Colt HG, Osann KE et al. Endobronchial ultrasound skills and tasks assessment tool: assessing the validity evidence for a test of endobronchial ultrasound-guided transbronchial needle aspiration operator skill. Am J Respir Crit Care Med 2012; 186: 773–779

101 Rintoul RC, Skwarski KM, Murchison JT et al. Endobronchial and endoscopic ultrasound-guided real-time fine-needle aspiration for mediastinal staging. Eur Respir J 2005; 25: 416–421

102 Stelow EB, Debol SM, Stanley MW et al. Sampling of the adrenal glands by endoscopic ultrasound-guided fine-needle aspiration. Diagn Cytopathol 2005; 33: 26–30

103 DeWitt J, Alsatie M, LeBlanc J et al. Endoscopic ultrasound-guided fine-needle aspiration of left adrenal gland masses. Endoscopy 2007; 39: 65–71

104 Eloubeidi MA, Tamhane A. Prospective assessment of diagnostic utility and complications of endoscopic ultrasound-guided fine needle aspiration. Results from a newly developed academic endoscopic ultrasound program. Dig Dis 2008; 26: 356–363