Review Article

Ultrasound techniques in the evaluation of the mediastinum, part 2: mediastinal lymph node anatomy and diagnostic reach of ultrasound techniques, clinical work up of neoplastic and inflammatory mediastinal lymphadenopathy using ultrasound techniques and how to learn mediastinal endosonography

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Abstract: Ultrasound imaging has gained importance in pulmonary medicine over the last decades including conventional transcutaneous ultrasound (TUS), endoscopic ultrasound (EUS), and endobronchial ultrasound (EBUS). Mediastinal lymph node (MLN) staging affects the management of patients with both operable and inoperable lung cancer (e.g., surgery *vs.* combined chemoradiation therapy). Tissue sampling is often indicated for accurate nodal staging. Recent international lung cancer staging guidelines clearly state that endosonography should be the initial tissue sampling test over surgical staging. Mediastinal nodes can be sampled from the airways [endobronchial ultrasound combined with transbronchial needle aspiration (EBUS-TBNA)] or the esophagus [endoscopic ultrasound fine needle aspiration (EUS-FNA)]. EBUS and EUS have a complementary diagnostic yield and in combination virtually all MLNs can be biopsied. Additionally endosonography has an excellent yield in assessing granulomas in patients suspected of sarcoidosis. The aim of this review in two integrative parts is to discuss the current role and future perspectives of all ultrasound techniques available for the evaluation of mediastinal lymphadenopathy and mediastinal staging of lung cancer. A specific emphasis will be on learning mediastinal endosonography. Part 1 deals with an introduction into ultrasound techniques, MLN anatomy and diagnostic reach of ultrasound techniques and part 2 with the clinical work up of neoplastic and inflammatory mediastinal lymphadenopathy using ultrasound techniques and how to learn mediastinal endosonography.

Keywords: Guidelines; recommendations; lung cancer; sarcoidosis; staging; endoscopic ultrasound fine needle aspiration (EUS-FNA); endobronchial ultrasound combined with transbronchial needle aspiration (EBUS-TBNA); training

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Introduction

For a thorough mediastinal nodal evaluation including tissue sampling, a variety of techniques are available: endoscopic techniques (e.g., bronchoscopy), radiological methods (e.g., computed tomography, fluoroscopy, and magnetic resonance imaging), nuclear medicine techniques (e.g., positron emission tomography) and surgical procedures (e.g., mediastinoscopy and video-assisted thoracoscopy). Additionally ultrasound-derived techniques have been introduced that have changed the workflow in the evaluation of mediastinal diseases. Endobronchial ultrasound combined with transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound fine needle aspiration (EUS-FNA) have replaced surgical staging as the initial test of choice for mediastinal tissue evaluation (1-15). Regardless of its numerous advantages, ultrasound-derived techniques are still not utilized to their full potential in respiratory medicine.

The aim of this review in two integrative parts is to discuss the current role and future perspectives of ultrasound techniques for staging of lung cancer and for the evaluation of mediastinal lymphadenopathy. Part 1 deals with an introduction into ultrasound techniques, and part 2 does with the mediastinal lymph node (MLN) anatomy and diagnostic reach of ultrasound techniques, the clinical work up of neoplastic and inflammatory mediastinal lymphadenopathy using ultrasound techniques and how to learn mediastinal endosonography.

MLN anatomy and diagnostic reach of ultrasound techniques

To ensure efficient performance of all mediastinal ultrasound techniques, it is important to have a profound knowledge of mediastinal anatomy and insight how ultrasound images relate to the different nodal stations. According to the International Association for the Study of Lung Cancer (IASLC) classification MLN are divided into different lymph node regions (16). A more anatomically detailed description is given in the following paragraph. The supra-aortic region is defined as the compartment directly above the aortic arch, excluding the area posterior to the trachea, the right paratracheal region as the compartment anterior and lateral to the trachea below the brachiocephalic trunk and above the right bronchus, the aortopulmonary window as the compartment below the aortic arch and above pulmonary trunk, left pulmonary artery, and left main bronchus, the prevascular region as the compartment anterior to the ascending aorta, vena cava superior, and pulmonary trunk and behind the upper sternum, and the pericardial region as the compartment anterior and lateral to the heart. In the following paragraphs and *Table 1* mediastinal lymph node stations and their evaluability by ultrasound techniques are summarized.

MLN evaluation by (transesophageal) endoscopic ultrasound (EUS)

EUS-guided biopsy allows excellent LN evaluation mainly of the lower mediastinum including the subcarinal region 7, paraesophageal region 8 and pulmonary ligament region 9. EUS also allows access to the left paratracheal region (4L) and partially to the left hilar region (10L). EUS-FNA of region 5 is safe and effective if lymph nodes are considerably enlarged whereas in small lymph nodes FNA might be more difficult or impossible due to interposition of the pulmonary artery/aorta. The para-aortal lymph nodes (station 6) are even more difficult to assess; biopsy (from above the aortic arch) is often difficult avoiding the large mediastinal vessels (17), and the transaortic approach using a 25G-needle may be used only in selected cases (18). The right sided paratracheal and hilar located LN (2R, 4R, 10R) can only be evaluated when grossly enlarged. This can be explained by the anatomy of the esophagus which is located posterior and left-sided to the air-guiding trachea. Therefore, the trachea prevents visualization of the right sided mediastinal regions (19). The examination technique has been recently summarized in textbooks (20-22).

MLN evaluation by endobronchial ultrasound (EBUS)

EBUS-guided biopsy allows excellent LN evaluation of the right (2R, 4R) and left-sided (2L, 4L) paratracheal and the subcarinal regions (7). In addition EBUS provides also easy bilateral access to the hilar region 10 and to the interlobar region 11. Access to intrapulmonary lymph node regions 12-14 is possible only using radial mini-probes (EBUS-R) (23).

In conclusion EBUS and EUS allow complementary evaluation of almost all MLN localizations and combining both methods virtually all mediastinal nodes can be sampled.

MLN evaluation by transcutaneous mediastinal ultrasound (TMUS)

TMUS allows the standardized examination of the

Table 1 Modified lymph node classification according to the international association for the study of lung cancer (IASLC) and evaluable regions using EUS, EBUS and TMUS

No	Region	EUS	EBUS	TMUS
1	Low cervical, supraclavicular and sternal notch nodes regions	(–)	(–)	+++
2	Upper paratracheal region [left (2L), right (2R)]	+	+++	++
3a	Prevascular region	(–)	+	++
3p	Retrotracheal region	+++	+++	(–)
4	Lower paratracheal region [left (4L), right (4R)]			
	4L	++	+++	(+)
	4R	(+)	+++	++
5	Aortopulmonary window	–/+	–	+(+)
6	Para-aortal region	+	(-)	(–)
7	Subcarinal region	+++	+++	+
8	Lower paraesophageal region	+++	(–)	(–)
9	Pulmonary ligament	+++	+	(–)
10	Hilar lymph nodes	(+)	+++	(–)
11	Interlobar lymph nodes	(-)	++	(–)
12	Lobar lymph nodes	(-)	(++)[a]	(–)
13	Segmental lymph nodes	(-)	(++)[a]	(–)
14	Subsegmental lymph nodes	(-)	(++)[a]	(–)

Explanations: +++, ultrasound evaluation is always possible and FNA is easy to perform; ++, Ultrasound evaluation and FNA are often but not always possible; +, ultrasound evaluation and FNA are sometimes possible; –, ultrasound evaluation and FNA are restricted and only possible if LN is grossly enlarged. In the case of lung cancer, ipsilateral pulmonary LNs (hilar, lobar, segmental and subsegmental) are defined as N_1-LNs, ipsilateral mediastinal and subcarinal as N_2-LNs and supraclavicular and scalenus LNs as well as contralateral mediastinal LNs as N_3-LNs. [a], access to LN regions 12-14 is only possible using radial miniprobes (R-EBUS)! EUS, endoscopic ultrasound; EBUS, endobronchial ultrasound; TMUS, transcutaneous mediastinal ultrasound; FNA, fine needle aspiration.

supra-aortic region, prevascular region, right sided upper and lower paratracheal regions (regions 2R, 4R), aortopulmonary window (region 5) and subcarinal region (region 7) under most circumstances (24-30). In addition the precardial region can be easily evaluated.

Clinical work up of mediastinal lymphadenopathy using ultrasound techniques

Enlargement of MLNs is a frequent finding in inflammatory and neoplastic diseases. Conventional chest radiography and thoracic computed tomography are first line diagnostic methods to evaluate suspected mediastinal lymphadenopathy (2,31). In addition, ultrasound methods have gained importance mainly due to their ability to guide biopsy and interventions but also to their detailed spatial resolution. Ultrasound methods allow not only size-related criteria as shown for computed tomography and magnetic resonance imaging but also evaluation of the lymph node architecture (32,33), lymph node vascularity and perfusion (34-37), resistance index (38), lymph node elasticity (39-41) and changes of perfusion under antiangiogenetic treatment (34).

Several studies have tried to define typical ultrasound criteria for malignant MLNs. One North American and one European EUSstudy found MLNs in 86% and 62% of patients with benign diseases and healthy individuals (42,43). Almost all of these normal lymph nodes have a short diameter below 10 mm and a triangular, crescent or oval shape. Other features like homogeneity, central echogenic structure, and contour differed between individuals and nodes. Contrary to what is often claimed, in both studies number and size of MLNs did not differ between smokers and non-smokers (42,43). Catalano *et al.* (44) in 1994 in a cohort of 100 patients with esophageal cancer

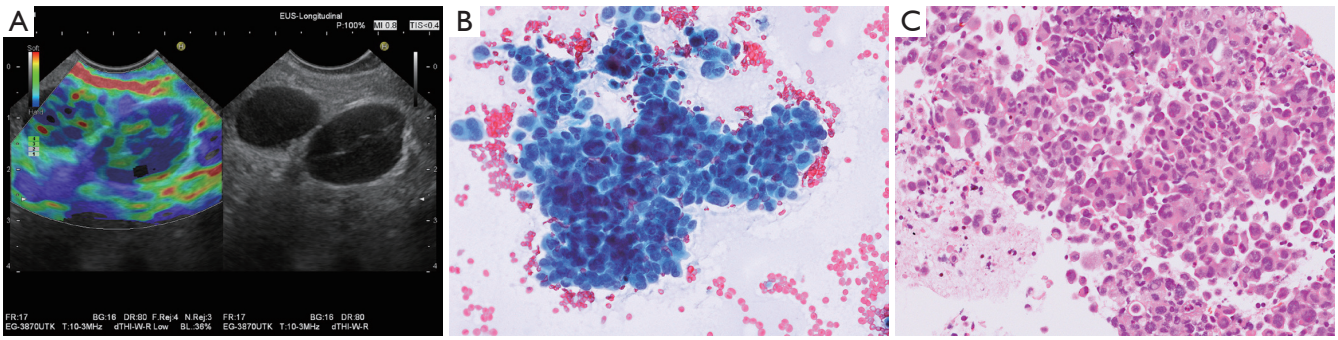

Figure 1 Hypoechoic periesophageal lymph nodes with compression of the hyperechoic hilum in a 49-year-old female patient 6 months after surgery for NSCLC. Elastography shows high and heterogeneous stiffness compared to surrounding connective tissue (A). EUS-FNA was performed using a 22 Gauge-aspiration needle. Smear cytology (B) (Papanicolaou, ×200) and histology (C) (hematoxylin-eosin, ×200) showed poorly differentiated adenocarcinoma. Molecular analysis of the aspirate proved KRAS-mutation in exon 2, but wild type of exon 3 and 4, wild type of exons 2, 3 and 4 of NRAS, wild type of EGFR-exons 18, 19, and 20 and no EML4/ALK-transition. Therefore, a targeted therapy was not possible. Cytological and histologic images: courtesy Dr. K. Zels, Königs Wusterhausen, Germany. EUS-FNA, endoscopic ultrasound fine needle aspiration.

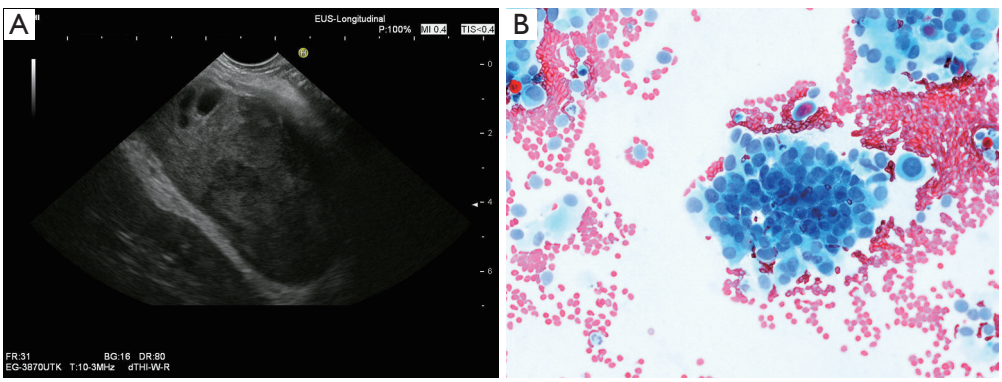

Figure 2 Large hypoechoic, heterogeneous mass lesion of the left adrenal with small cysts in a male patient with radiological suspicion of peripheral lung cancer (A). EUS-FNA was performed using a 22 Gauge-aspiration needle. Smear cytology (B) (Papanicolaou, ×200; immunocytochemistry: CK7 and EMA positive, CD56 and CK5/14 negative) gives proof of poorly differentiated adenocarcinoma, consistent with the clinical suspicion of left adrenal metastasis of NSCLC. Cytological image: courtesy Dr. K. Zels, Königs Wusterhausen, Germany. EUS-FNA, endoscopic ultrasound fine needle aspiration.

defined endosonographic features predictive of lymph node metastasis: hypo- echoic structure, distinct margin, roundness, and a diameter greater than 10 mm. Additionally, as the number of "malignant" echo features rises, the probability of malignancy increased. Malignancy could be predicted with 100% accuracy when all four features were present (44). These endosonographic criteria have been confirmed in further studies using EUS and EBUS. Additional predictive criteria for malignancy of lymph nodes have been added: absence of echogenic hilar structure and of central nodal vessel, echogenic coagulation necrosis, heterogeneous echo pattern (33,45-49). However, a definitive classification as either malignant or benign by endosonographic criteria is possible only in approximately 25% of MLNs (50). Classification of lymph nodes by EUS criteria alone is less reliable in mediastinal than in lymph nodes of other anatomical locations. Therefore, especially in MLNs EUS-guided fine needle aspiration (FNA) has a significantly higher accuracy than echo features alone (51) (*Figures 1,2*). However, the probability of malignancy is very low, if none of the malignant lymph node criteria is observed (33,52,53).

From a practical point of view it was suggested that

Table 2 Indications for EUS, EBUS and TMUS in pulmonary diseases modified according to Annema *et al*. (8,23,54)

Suspected lung cancer
Enlarged mediastinal lymph nodes
FDG-PET-positive mediastinal lymph nodes
Primary lung tumor adjacent to esophagus (EUS) or the airways (EBUS)
Staging of NSCLC
Mediastinal staging (regardless of nodal size at CT)
FDG-PET-positive mediastinal lymph nodes
Enlarged (short axis >10 mm) FDG-PET-negative mediastinal lymph nodes
Mediastinal restaging after neoadjuvant treatment (chemotherapy)
Suspected mediastinal tumor invasion (T4)
Suspected left adrenal or celiac lymph node metastasis (EUS)
Evaluation of mediastinal masses
Solitary (multiple) solid mediastinal masses
Suspected mediastinal metastases of extrathoracic tumors
Mediastinal lymphadenopathy of unknown origin
Suspected granulomatous disease (sarcoidosis, tuberculosis)
Suspected lymphoma

EUS, endoscopic ultrasound; EBUS, endobronchial ultrasound; TMUS, transcutaneous mediastinal ultrasound.

patients without any pathological sonographic lymph node criteria should not be biopsied whereas all other lymph nodes should be considered for biopsy (53).

A summary of possible indications for ultrasound techniques in the evaluation of mediastinal and lung diseases is summarized in *Table 2* (8,23,54).

Lung cancer

Lung cancer is one of the most common malignancies and accounts for very high cancer related mortality. In the absence of distant metastases, MLN staging is the most important factor that affects the management and prognosis of patients with lung cancer. Knowledge of locoregional tumor stage is important for planning the best choice of treatment including surgical resection, radiation and chemotherapy (2,31). Mediastinoscopy and thoracoscopy are invasive techniques and, therefore, should be avoided if not necessary.

Lymph node staging

It is obvious that there is an increasing need for minimally invasive techniques including EBUS and EUS techniques with needle aspiration for MLN staging. It has to be taken into account that results of transbronchial biopsy techniques (TBNA) relying on "blind" biopsy are disappointing (55). EBUS-TBNA has significantly improved the biopsy results (56-62). Promising results have been shown in a multicentric study of 502 patients with a mean lymph node diameter of 16 mm. The reported sensitivity was 94%, specificity 100%, and the positive predictive value 100% (63). Recent meta-analyses have shown a pooled sensitivity of EBUS-TBNA in the range of 88% to 93% (2,64-67). EUS-FNA has a comparable diagnostic yield. Two recent meta-analyses report on a pooled sensitivity of EUS-FNA in nodal staging of NSCLC of 83% and 89%, respectively (2,68).

EUS-FNA and EBUS-TBNA have a complementary diagnostic reach. In combination with both EUS and EBUS almost all important MLNs can be biopsied (59,62,69). Several studies have shown that a combined EUS- and EBUS-approach ("complete endosonographic mediastinal staging") improves lymph node staging versus each of the techniques alone (7-10,23). The sensitivity of both, EUS and EBUS for MLN staging is around 90% (2,23,67,70-73). Meta-analytic data show a substantial increase in sensitivity for mediastinal nodal staging in patients with proven or suspected lung cancer by combining EBUS-TBNA and EUS-FNA or transesophageal FNA using an EBUS-bronchoscope (EUS-B-FNA). Average increment in sensitivity was 21% compared with the esophageal approach alone (pooled data from seven studies) and 13% compared

with EBUS-TBNA alone (pooled data from nine studies) (5). Similar data were reported in another meta-analysis including only studies comparing EBUS-TBNA and EUS-B-FNA with an increase in sensitivity for lung cancer staging of 11% by combining both techniques *vs.* EBUS-TBNA alone (74). The accuracy of the combined approach using EUS-FNA plus EBUS-TBNA proved to be significantly higher than that of PET-CT alone (90.0% *vs.* 73.6%) (12). A randomized controlled study comparing two approaches to combined endosonographic mediastinal staging (EBUS first *vs.* EUS first) found no differences of efficacy and patient's satisfaction in both groups. However, EBUS-TBNA turned out to be the more efficient primary procedure in endoscopic mediastinal staging of potentially operable lung cancer (13). The published studies mainly include cohorts of patients with a relatively high prevalence of mediastinal lymphadenopathy (median 58% for EUS-FNA and EBUS-TBNA; 33% for the combined approach) (2). In studies with a low prevalence of MLN metastases sensitivity of both endosonographic techniques was considerably lower than in studies with a high prevalence (2). Moreover, it has to be taken into account that enlarged lymph nodes and PET-positive findings are the inclusion criteria for most published studies. Meta-analyses uniformly show that sensitivity of EUS-FNA and EBUS-TBNA for detection of metastatic invasion in patients selected on the basis of CT or PET positive results is significantly higher than in patients with negative CT findings or without any selection of CT or PET (66,68). This underlines the importance of biopsies to identify patients who need neoadjuvant treatment strategies.

The combined use of EUS and EBUS can prevent >50% of scheduled surgical staging procedures by providing tissue proof of advanced disease in patients with suspected lung cancer and enlarged or PET positive lymph nodes (75,76).

The results for re-evaluation after neoadjuvant treatment are generally more skeptical (less than 75%). Due to the reported low negative predicative value, negative lymph node findings should be surgically verified (8).

However, both EBUS and EUS have limitations in excluding malignant lymph node involvement. False negative EUS and EBUS findings occur either to sampling errors (lymph node found and biopsied but metastasis missed) or a detection error (lymph node not found).

EUS and EBUS *vs.* mediastinoscopy

Mediastinoscopy, a surgical staging procedure, has been regarded as the gold standard for a long period of time with a sensitivity of 78% for mediastinal nodal staging (72). The additional use of EUS to mediastinoscopy improved locoregional staging (cT4N2-3). The improved results were explained by the complementary diagnostic reach of various nodal stations and the ability of EUS to assess mediastinal tumor invasion (73). The use of mediastinoscopy after a negative endosonography improved the sensitivity of mediastinal nodal staging from 85% to 94% (8). The question which patients staged negative by endosonography should subsequently undergo surgical staging of the mediastinum is a matter of current discussions. It is recommended that in patients with suspicious lymph nodes on either CT or PET, negative endosonography findings should be surgically verified. In contrast there is evidence that patients with centrally located tumors or suspected hilar abnormalities do not benefit from additional surgical staging (23). However, in a very recent study in patients with suspected single level N1 disease, the sensitivity of EBUS for N2 disease was disappointingly low (38%) (77) suggesting a role for mediastinoscopy. However, in this cohort often only EBUS and not the EBUS-EUS combination was used.

It could be shown that in 10-25% of patients with negative CT and in 5-10% of patients with negative PET subsequent endosonographic examinations verify lymph node metastases (78-81).

In conclusion, a complete endosonography evaluation of the mediastinum is at least as good as mediastinoscopy but is associated with fewer complications and futile thoracotomies (8). Therefore, endosonography (and not mediastinoscopy) qualifies as the initial mediastinal tissue staging test (31). Negative endosonography findings however should be verified by surgical staging (5,82).

Proof of diagnosis

In about one third of patients with suspected lung cancer, conventional bronchoscopy fails to prove the diagnosis. In patients with suspected lung carcinoma adjacent to the trachea or bronchi without mucosal (endobronchial) abnormalities, EBUS is superior to CT for guidance of biopsy. The reasons include a better diagnostic yield and a much lower rate of complications including pneumothorax and bleeding in the case of perivascular tumor growth (83,84). In addition, EUS can be used to biopsy centrally located intrapulmonary periesophageal tumors if conventional methods fail (71). In a group of 123 patients with an undiagnosed but suspected malignant lung lesion (paratracheal, parabronchial, paraesophageal) or with a peripheral lung nodule and PET-positive MLNs who had

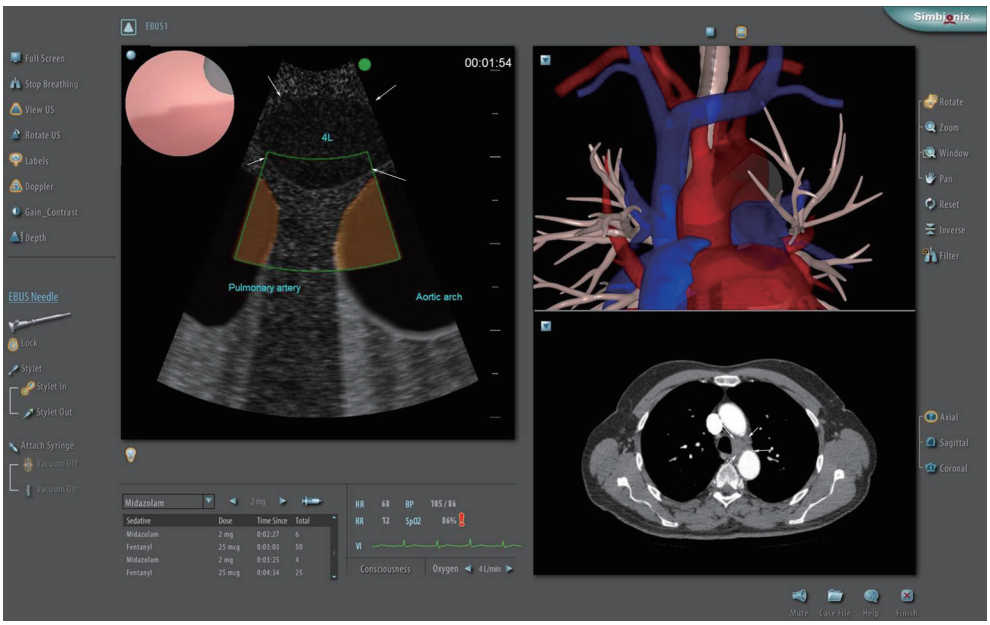

Figure 3 EBUS simulation case (Bronch Mentor-Simbionix). Right lower panel: CT scan of the chest showing a slightly enlarged left paratracheal node (arrows). Left panel: Bronchoscopic screen showing bronchial mucosa with sheath (upper left) and EBUS image showing the station 4L lymph node (arrows) located between the aortic arch and pulmonary artery. Panel right upper corner: anatomical image showing the position of the EBUS scope in the trachea.

undergone at least one diagnostic flexible bronchoscopy or CT-guided transthoracic needle aspiration attempt, EBUS-TBNA and/or EUS-FNA had a high diagnostic efficacy. The endosonographic approach to diagnosis of lung cancer avoided expensive surgical procedures in 106 cases and led to significant cost savings (85).

T-staging

EUS is helpful in selected cases to evaluate T4 (stage IIIB) in the case of possible aortic invasion (70). This specifically applies to invasion in vascular structures. However, more data are needed to make a more definite assessment on this topic.

M-staging

Adrenal gland

In addition, conventional EUS instruments allows the evaluation and biopsy of the left adrenal gland (86-88), which is often involved in metastatic lung carcinoma (89-93). FDG-PET uptake is helpful for detection of adrenal metastases. Focal lesions as the most important imaging sign but also increased size and loss of the typical "seagull shape" are predictors for malignant involvement (89). In addition, the left adrenal gland can be reached and sampled by EUS-FNA demonstrating a high yield (91,94,95). The right adrenal gland can be assessed using a transduodenal or transgastric approach, which is technically more demanding and sometimes dangerous if a decubitus or right sided position for visualization is required. EUS is inferior to transcutaneous ultrasound (TUS) in the evaluation of the right adrenal gland (96,97). TUS-guided biopsy is recommended (88,98). However, in cases transduodenal biopsy of suspected right sided adrenal metastases have shown to be feasible (99,100). A preoperative bilateral EUS examination and EUS-FNA of the adrenal glands in patients with potentially resectable lung cancer has a high diagnostic accuracy in detecting adrenal metastases (89,101) (*Figure 3*). Recently a few reports in abstract form have reported the use of the EBUS scope for the assessment of the left adrenal gland. However, more data are needed for a more definitive assessment.

Liver

In rare cases liver metastases are detectable only by EUS with CT-negative findings. In such cases the EUS-guided biopsy of the liver is helpful to proof the metastatic spread (98,102,103).

Other infradiaphragmal manifestations

In even more rare cases pancreatic metastases (or infiltration

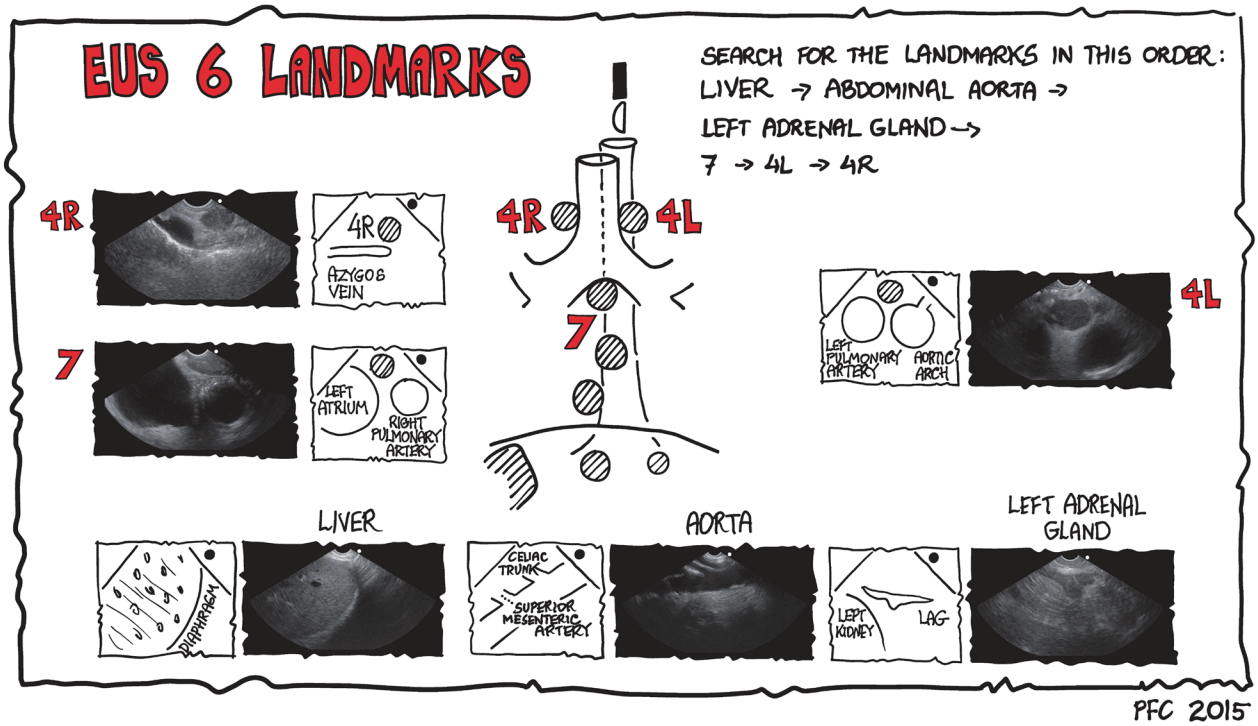

Figure 4 The six landmarks of endoscopic ultrasound (EUS) for lung cancer staging. Paul Clementsen is owner of the copyright.

of celiac or peripancreatic lymph nodes) are detectable only by EUS with CT-negative findings. In such cases the EUS-guided biopsy of the pancreas is helpful to prove the metastatic spread (98,104-107).

Mediastinal staging of extrathoracic malignancies

As has been shown for pancreatobiliary cancer, in up to 10% of extrathoracic malignancies metastasize to MLNs (108). Both EUS and EBUS have been successfully used for the assessment of tumor spread to MLNs (M1 disease) in patient cohorts with various extra-thoracic malignant diseases (109-116). In particular, the usefulness of EUS-guided sampling of MLNs has been reported in the staging of patients with gastric cancer, pancreatic cancer (108,117) breast cancer (118), upper GI cancer (119,120); head and neck cancer (121), colorectal cancer (122), and lymphoma (57,123-129). A recent meta-analysis (five studies, n=533 patients) showed a high value for EBUS-TBNA for the diagnosis of mediastinal and hilar lymph node metastases from extrathoracic malignancy. Pooled sensitivity was estimated 85% with a specificity of 99% (130). Procurement of specimens which are eligible for immunohistochemistry is important for reliable differentiation between mediastinal nodal metastases of extrathoracic cancer *vs.* non-small cell lung cancer.

How to learn pneumological endosonography

A systematic training in mediastinal endosonography should ideally be based on (I) theoretical knowledge, (II) performance on simulators and (III) supervised performance on patients. Each step should be completed by passing a validated exam before proceeding to the next step. However, there are no commercially available virtual reality simulators for mediastinal EUS-FNA, but it is possible to practice EBUS-TBNA on both the GI Bronch Mentor™ (Simbionix) (*Figure 4*) and the AccuTouch Flexible Bronchoscopy Simulator™ (GE Healthcare). A standardized test including pass/fail-standards has been developed for the GI Bronch Mentor (131,132).

Firstly the trainee should learn to recognize anatomic landmarks and mediastinal vessels (133) by observing the procedure (134,135). The next step is to learn to insert the endoscope and to "produce" the pictures, which is much more difficult than watching an experienced examiner doing

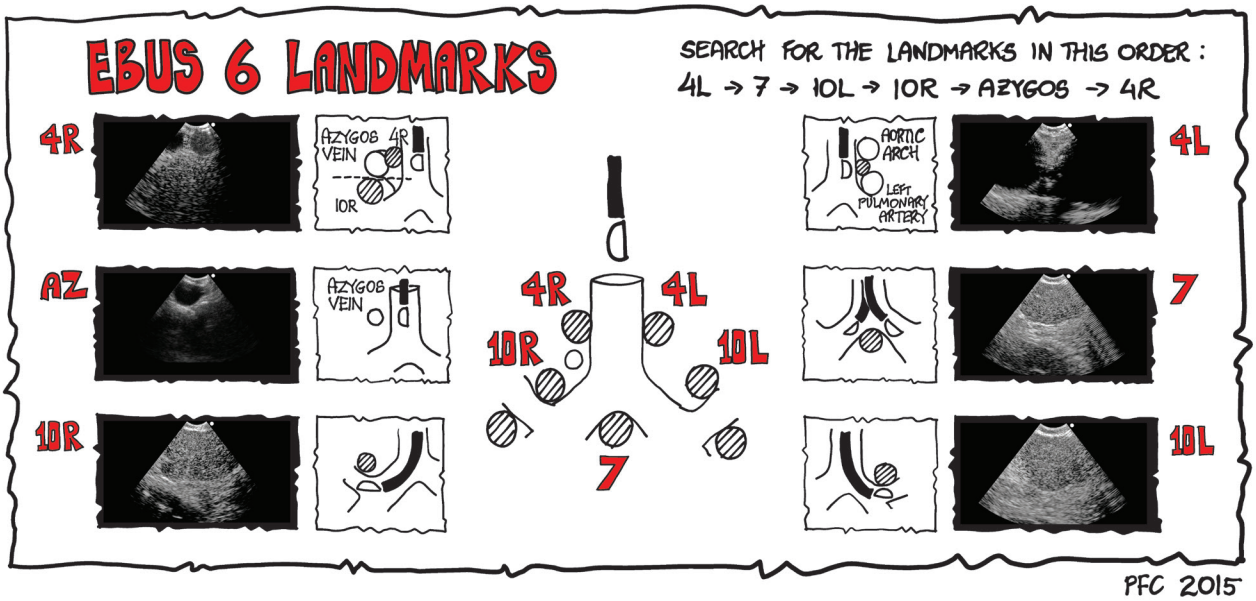

Figure 5 The six landmarks of endobronchial ultrasound (EBUS). Paul Clementsen is owner of the copyright.

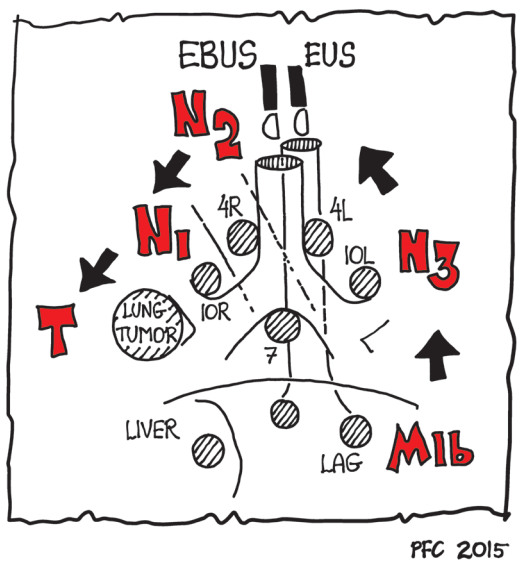

Figure 6 Systematic approach to endosonographic lung cancer staging. Paul Clementsen is owner of the copyright.

the procedure. The final task relates to correct positioning of the transducer, proper use of the needle sheath and handling of the needle when taking fine needle aspirates (123-126,136-140).

After passing a simulation-based test the trainee should perform the initial endosonography procedures in patients under supervision. The learning curve should be monitored by specific tools for assessment, since the number of procedures to obtain competence varies from trainee to trainee (127-129,131,141,142). For EBUS-TBNA, in a multicenter cohort of fellows in pulmonary medicine, the majority of trainees achieved first independent successful performance of EBUS-TBNA following a training protocol that included theoretical education and simulation sessions at an average of only 13 procedures (143). Another study with nine interventional pneumologists failed to observe such a steep learning curve and observed ongoing improvements for lymph node identification by EBUS and EBUS-TBNA skills even after 200 clinical cases (144).

The classical approach is to start by learning the six basic landmarks for EBUS and EUS and to practice finding them in the order mentioned (*Figures 4-6*) (145).

The six EUS landmarks (Figure 4)

- Liver (landmark I): introduce the endoscope into the esophagus and slide down below the diaphragm. Turn the endoscope counterclockwise to find the left liver lobe.
- Aorta (landmark II): turn the endoscope clockwise and find the aorta with the celiac trunk and the superior mesenteric artery.
- The left adrenal gland (landmark III): turn the endoscope

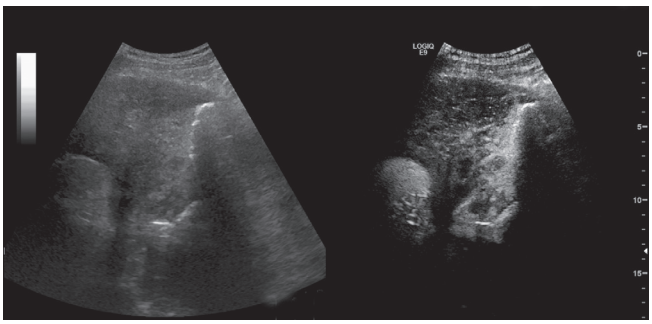

Figure 7 Mediastinal ultrasound using contrast enhanced ultrasound to demonstrate vital Hodgkin's disease by contrast enhancement.

further clockwise, move the transducer a little upwards to find the left adrenal gland (it resembles a small bird, seagull) close to the upper pole of the left kidney.

- Station 7 (landmark IV): retract the endoscope to the mediastinum and find station 7 below the carina close to the left atrium and the right pulmonary artery.
- Station 4L (landmark V): retract the endoscope a few centimeters, turn counterclockwise and find station 4L between the aortic arch and the left pulmonary artery (the vessels resemble the ears of Mickey Mouse).
- Station 4R (landmark VI): turn clockwise until you pass the trachea and find the azygos vein. Retract the endoscope slowly until the vein disappears into the superior cava vein and search for station 4R. If it is of normal size, it will, often hide behind the trachea.

The six EBUS landmarks (Figure 5)

- Station 4L (landmark I): turn the endoscope counter clockwise and find station 4L between the arch of the aorta and the left pulmonary artery.
- Station 7 (landmark II) is found below the carina with the endoscope in the right or the left main bronchus facing medially.
- Station 10L (landmark III) is found looking upwards with the transducer in the left upper lobe bronchus.
- Station 10R (landmark IV) is found looking upwards with the transducer in the right upper lobe bronchus.
- The azygos vein (landmark V): retract the endoscope and find the azygos vein paratracheal to the right.
- Station 4R (landmark VI) is found above the azygos vein. The inferior border of the azygos vein marks the border between station 4R and 10R.

Handling of the endoscope: a few tips and tricks

- Note carefully on the ultrasonic picture, if the endoscope is coming from the right or the left side. "The dot" shows where the proximal part of the endoscope on the ultrasonic picture is located. Avoid confusion with a mirror image.
- With the EUS endoscope, a rotation to the right (clockwise) moves the transducer to the right side of the patient, when the transducer is directed forward, i.e., above the diaphragm. The same rotation will move the transducer to the left side of the patient when the transducer is directed backwards below the diaphragm.
- When performing EBUS, it must be remembered that the view is typically in an oblique direction of 30 degrees, so it can be difficult to get access to the trachea.
- All regions should be inspected systematically with a 360 degrees rotation for every four centimeters. Do not overlook any structures that are not necessarily located according to the two times six landmarks.

Practical advice: systematic approach to endosonographic lung cancer staging

The order of recommended examinations (EBUS, EUS) depends mainly on the side and localization of the tumor determined by the CT findings. Biopsies should be performed under the premise that distant metastases (M1) are excluded first, followed by lymph node staging in the order N3 (contralateral lymph nodes) → N2 (ipsilateral mediastinal and subcarinal lymph nodes) → N1 (ipsilateral hilar lymph nodes) (*Figure 6*). For patients with suspected N2 disease infiltration of only single N2 lymph nodes (N2a, stage IIIA3) has to be differentiated from infiltration of more than one N2 lymph node region, clusters of involved lymph nodes in one or more N2 stations, or large N2 lymph nodes with extracapsular invasion (N2b, Stage IIIA4) (1-3,31,72,146).

Lymphoma

Mediastinal ultrasound

In a retrospective study [40 consecutive patients with Hodgkin's (n=29) and non-Hodgkin's (n=11)] MTUS was clearly superior to chest radiographs and comparable to CT for monitoring patients with mediastinal lymphomas (147) (*Figure 7*). Thymic enlargement due to involvement by Hodgkin disease is more frequently observed than previously reported.

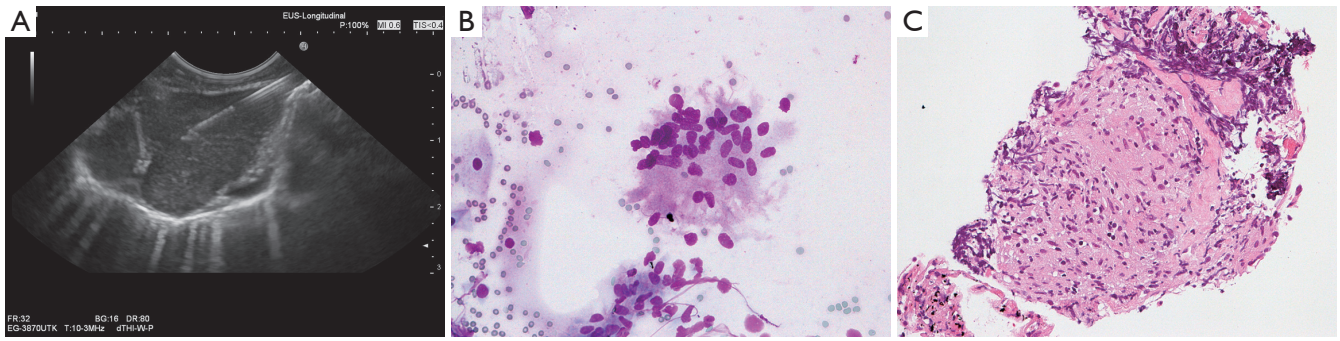

Figure 8 EUS-FNA using a 22 Gauge-aspiration needle of large hypo-echoic mediastinal lymph nodes (station 7) in 50-year-old women with dry cough (A). Smear cytology (May-Gruenwald-Giemsa, ×200) shows groups of epithelioid cells (B), histology (hematoxylin-eosin, ×200) demonstrates typical epithelioid granuloma without necrosis and with some multinuclear giant cells (C). Clinical diagnosis was sarcoidosis. Cytological and histologic images: courtesy Dr. S. Wagner, Königs Wusterhausen, Germany. EUS-FNA, endoscopic ultrasound fine needle aspiration.

Thymic gland involvement is sonographically visible due the hypoechoic structure. In contrast MTUS was not helpful to differentiate the normal-sized typical tongue-shaped thymus from surrounding fatty tissue after treatment due to the same echogenicity of the gland and the surrounding fat (148). Elastography and contrast enhanced techniques might overcome this problem but data are lacking (32).

It is of importance that lymphoma and other tumors in the anterior mediastinum can also be biopsied under ultrasound guidance via a suprasternal and strict parasternal approach. Using the parasternal approach non-visible lymphoma might get visible due to the shifting of the mediastinum from the decubitus to a strict left or right lateral position (22,26).

EUS-FNA and EBUS-TBNA

EUS-FNA and EBUS-FNA have a variable diagnostic yield for diagnosing and subtyping of non-Hodgkin Lymphoma of the posterior and inferior mediastinum. There are good data that EBUS/EUS is useful for the assessment of recurrent lymphoma, for the primary lymphoma diagnosis often a histology specimen—obtained by mediastinoscopy—is needed. However, cell block processing of material obtained by EUS-FNA or EBUS-TBNA may have nearly similar diagnostic yield as histology (149-152). Two large cohort studies demonstrated, that accuracy of EBUS-FBNA for diagnosis of mediastinal malignant lymphoma was 84% and 91%, with correct subtyping possible in >2/3 of cases (150,153).

Inflammatory diseases

Sarcoidosis and tuberculosis

Depending on the geographic distribution, sarcoidosis and tuberculosis are the two most important inflammatory causes of mediastinal lymphadenopathy (109,154-158).

Sarcoidosis

The typical imaging finding of sarcoidosis lymphadenopathy are symmetrically distributed clusters of MLNs around large vessels. The typically oval-shaped lymph nodes may reach a size of up to 60 mm with mixed echogenicity depending on the stage of the disease (156). Color Doppler imaging, contrast enhanced ultrasound techniques and elastography have shown that the lymph node architecture is typically not destroyed and a hilum can be displayed (159-161).

Both EUS-FNA and EBUS-TBNA are suitable for final diagnosis of sarcoidosis (*Figure 8*) whereas pure transbronchial biopsy fails in about one third of cases. Published data indicate that the sensitivity (80-90%) and accuracy of EUS-FNA and EBUS-TBNA are superior compared to simple mucosa biopsies without and with "blind" transbronchial puncture (155,162-165). Special techniques (cytology and cell-block analysis) might even improve the diagnostic yield of ultrasound-guided biopsies (162). A meta-analysis (14 studies including 2,097 patients) showed a diagnostic yield of 79% for diagnosis of sarcoidosis by EBUS-TBNA. Pooled sensitivity and specificity were 84% and 100%, respectively (166).

Complications may be encountered. Mediastinitis with abscess formation has been observed after transesophageal biopsy of MLNs (167). Therefore, prophylactically administered antibiotics may be considered for EUS-guided biopsies but studies on this topic are lacking. Similar complications haven not been observed in EBUS-TBNA, therefore, no prophylactically applied antibiotics are recommended.

In conclusion, for the diagnosis of sarcoidosis, endosonographic techniques are superior to the combination of endobronchial mucosa and transbronchial lymph node biopsies. Besides conventional cytological smears, cell blocks are recommended to increase the diagnostic yield.

Differential diagnoses

Under specific circumstances also depending on geographic and other epidemiological criteria tuberculosis and atypical mycobacteriosis have to be excluded in the case of unclear mediastinal lymphadenopathy. Several studies have shown acceptable diagnostic accuracy for the diagnosis of MLN tuberculosis by EUS-FNA and EBUS-TBNA. Cytopathological criteria, the search for acid-fast bacilli (stained red) using Ziehl-Neelsen-technique or Acridin-Orange-staining as well as culture techniques and PCR are helpful for final diagnosis (157,158,168-170). Concurrent systemic symptoms may be encountered (171).

Besides tuberculosis, atypical mycobacteriosis, sarcoidosis and other granulomatous diseases paraneoplastic "sarcoid like reaction" (SLR) have to be included in the differential diagnosis of granulomatous lymphadenopathy. SLR has been observed in the neighborhood of malignancies as well as sequelae of chemotherapy and radiation. Positron emission tomography (PET) may show false positive results in patients with SLR (172-174).

Mediastinal ultrasound in patients with cystic fibrosis

The respiratory tract is involved in almost all patients with cystic fibrosis and respiratory failure accounts for about 90% of morbidity and mortality in patients with cystic fibrosis. Extrapulmonary manifestations are also often encountered (175). Evaluation of TMUS in healthy subjects and patients with cystic fibrosis demonstrated that the lymph node detection rate in the paratracheal region and aortopulmonary window was significantly higher in patients with cystic fibrosis and the total lymph node volume was larger, respectively. Therefore, mediastinal ultrasound was helpful for the detection of inflammatory activity in patients with cystic fibrosis (176). Similar studies using EUS and EBUS have not been published.

Mediastinal ultrasound in patients with chronic virus hepatitis C

Mediastinal lymphadenopathy can be considered as an extrahepatic manifestation of chronic hepatitis C. TMUS was also able to detect slightly enlarged MLNs in patients with chronic virus hepatitis C. In patients with chronic hepatitis C a trend could be observed, that patients with larger perihepatic lymph nodes also reveal larger MLNs indicating a systemic pathomechanism. The mechanism of lymphadenopathy in the liver hilum (177-179) and mediastinum in patients with chronic hepatitis C and other viral and autoimmune liver diseases is yet unknown (180). Similar studies using EUS and EBUS have not been published. Therefore, normal lymph nodes were detectable more frequently in the paratracheal region and aortopulmonary window of cadavers compared to the respective mediastinal regions of healthy volunteers. A possible explanation of this finding lies in the better image resolution obtained by application of the transducer to the region of interest in cadavers. The difference in age may also have an impact.

Conclusions

Endobronchial, endoesophageal and TUS are complimentary approaches for the evaluation of the mediastinum, in particular in patients with non-small cell lung cancer and with mediastinal lymphadenopathy. All three techniques facilitate tissue acquisition from MLNs or masses for primary diagnosis or staging. Due to their high accuracy and low risk, ultrasound-guided sampling procedures should be considered to substitute for more invasive surgical techniques. Learning ultrasonographic evaluation of the mediastinum should be performed in a systematic manner based on the classical anatomical landmarks.

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Footnote

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