

Diagnosis and staging of lung cancer with the use of one single echoendoscope in both the trachea and the esophagus: A practical guide

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ABSTRACT

Accurate staging of non-small cell lung cancer (NSCLC) is crucial for allocation to surgical, medical or multimodal treatment. EUS and endobronchial ultrasound (EBUS) have gained ground in the diagnosis and staging of lung cancer in addition to radiological imaging (e.g., computed tomography, fluoroscopy, and magnetic resonance imaging), nuclear medicine techniques (e.g. positron emission tomography, PET), combined techniques (e.g., fluorodesoxyglucosepositron emission tomography scanning), and sonographic imaging including conventional transcutaneous mediastinal and lung ultrasound. By using one single echoendoscope in both the trachea and the esophagus, surgical staging procedures (e.g. mediastinoscopy and video assisted thoracoscopy) can be avoided in a considerable proportion of patients with NSCLC.

Key words: diagnosis; staging; echoendoscope

INTRODUCTION

Accurate staging of non-small cell lung cancer (NSCLC) is crucial for allocation to surgical, medical, or

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multimodal treatment. EUS and endobronchial ultrasound (EBUS) have gained ground in the diagnosis and staging of lung cancer in addition to radiological imaging (*e.g.*, computed tomography [CT], fluoroscopy, and magnetic resonance imaging), nuclear medicine techniques (*e.g.*, positron emission tomography [PET]), combined techniques (*e.g.*, fluorodeoxyglucose-PET scanning), and sonographic imaging including conventional transcutaneous mediastinal and lung ultrasound. By using one single echoendoscope in both the trachea and the esophagus, surgical staging procedures (*e.g.*, mediastinoscopy and video-assisted thoracoscopy) can be avoided in a considerable proportion of patients with NSCLC.

Transesophageal ultrasound is excellent for the left and lower paraesophageal structures plus structures under the diaphragm, whereas EBUS provides access to structures close to the large airways. Thus, the two procedures are complementary. EUS-guided fine-needle aspiration (EUS-FNA) can be performed either with a conventional curvilinear gastrointestinal echoendoscope (EUS) or by using the EBUS-scope in the esophagus (EUS-B).^[1]

For mediastinal nodal staging in patients with suspected or proven NSCLC, combining EBUS-guided transbronchial needle aspiration (EBUS-TBNA) and EUS-FNA/EUS-B-FNA is preferred over either test alone.^[1] EUS-B-FNA is a safe and feasible procedure for the biopsy of the left adrenal gland,^[1-8] lung tumors,^[9] retroperitoneal lymph nodes (LNs), and the liver.^[10] Furthermore, in case reports, it has been demonstrated that EUS-B-FNA makes it possible to take biopsies from pleura^[11] and difficult-to-assess posterior mediastinal structures^[12] and to aspirate ascites^[13] and pericardial fluid.^[14] Moreover, the small-caliber EBUS-scope may be preferential compared to the gastrointestinal echoendoscope for sampling of mediastinal and upper abdominal lesions in toddlers^[15-17] and in adult patients with esophageal stenosis.^[4,18]

The traditional apprenticeship method has been the cornerstone of training for many years. Trainees observe experienced practitioners and train under supervision to acquire the necessary skills and competences. Unfortunately, this approach results in prolonged procedure time and increased risk of complications.^[19]

Individual learning curves for EUS-B-FNA and EBUS-TBNA vary a lot with the number needed to

overcome the initial learning curve of EBUS ranging from 10 to 100 in different studies (mean: 37–44 procedures).^[20] Simulation-based training provides a safe environment to develop and refine technical skills before performing the procedures in patients.^[21] No patient wants to be a part of a learning curve.

HOW TO LEARN ENDOBRONCHIAL ULTRASOUND

The European Respiratory Society (ERS) has launched a structured training program on EBUS-TBNA, comprising a three-part comprehensive process build on the best available evidence in medical education.^[22] Part 1 is a theoretical introduction comprising self-directed online modules and a course, including lectures and live transmissions of procedures. This part ends with a theoretical test developed and externally reviewed by international experts in the field. Part 2 consists of intensive simulation-based training and clinical observation at selected European centers. The operators practice on the GI Branch Mentor simulator (Simbionix®, Cleveland, Ohio, USA) using a training program that was proven superior to initial apprenticeship training in an international randomized controlled trial.^[23] The simulation-based training ends with a validated simulator test.^[24] Part 3 is performing procedures under supervised training in the clinical setting. The basis for the educational program is to use a systematic approach using the six defined home base landmarks, see below (The anatomical home base landmark scheme),^[25] and each participant finishes the entire training program by submitting videotaped procedures following this approach for final assessment. These assessments are done by an international panel of blinded raters using the validated EBUSAT assessment tool for measuring competences.^[23] Each of the three tests mentioned above (*i.e.*, the theoretical test, the simulation-based test, and the clinical test) has established standards for competency that must be met. This competency-based approach is superior to the procedure-based approach in earlier guidelines on training requirements for EBUS that suggested forty procedures for acquisition of competence.^[26] However, a certain (arbitrary) number of procedures does not ensure basic competency as all trainees learn at different paces. The newest European guidelines^[1] recommend that competency in EBUS-TBNA as well as EUS-(B)-FNA for staging lung cancer should be ensured using validated assessment tools [Figure 1].

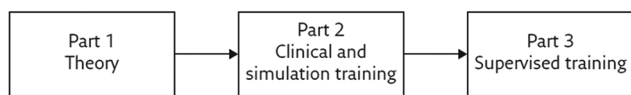


Figure 1. The European Respiratory Society has launched a structured training program on EBUS-TBNA, comprising a three-part comprehensive process. EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration

HOW TO LEARN TRANSESOPHAGEAL ULTRASOUND WITH THE USE OF ENDOBRONCHIAL ULTRASOUND ENDOSCOPE

Unfortunately, no simulator for education in transesophageal ultrasound for lung cancer diagnosis and staging exists in contrast to what is the case for EBUS. Therefore, we still have to practice transesophageal ultrasound on patients. The only study exploring learning curves for EUS-FNA for lung cancer staging found that acquisition of skills varied between operators and that twenty procedures were not enough to ensure basic competency.^[27] We do not have data for EUS-B-FNA, but probably the results would be similar. We recommend using the EUSAT assessment tool for assessing technical ability.^[28] Due to the absence of EUS-B simulator, we recommend to learn EBUS-TBNA (see above) before learning EUS-B-FNA. Due to the difficulty level for EUS-B-FNA,^[29] we recommend learning transesophageal ultrasound in the mediastinum in patients with abnormal mediastinal tumors and/or LNs before starting the search for small structures below the diaphragm. We recommend to use a systematic approach using the six landmarks, see below (The anatomical home base landmark scheme).^[30]

THE ENDOBRONCHIAL ULTRASOUND EQUIPMENT, A SHORT DESCRIPTION

The integration of flexible bronchoscopy and EUS technology allows conventional endoscopic imaging simultaneously side by side with the radial or longitudinal sonographic view. The corresponding alignment of side-viewing optics and curvi-linear transducer of the EBUS scope is the prerequisite for sampling of mediastinal LNs and other suspicious lesions for improved staging. The equipment is produced by three companies [Table 1]. EBUS uses frequencies of 5–12 MHz with a theoretical depth of penetration up to 120 mm. It is recommended to use 7.5 MHz as a routine and change the frequency, if necessary. The endoscopic and ultrasound images

are delivered simultaneously, and they allow a precise visualization of the mucosa and of the tracheobronchial landmarks and a high definition of the ultrasound images. EBUS systems can perform elastography for tissue analysis^[31-34] as well as contrast-enhanced Doppler EBUS.^[35] The procedure is performed with a dedicated needle assembly, which consists of a long steel needle, a sheath, and a handle for manipulation of the needle. The needle assembly is attached to the working channel of the endoscope. After the lesion has been outlined, the needle is advanced under real-time ultrasonic guidance. Aspiration needles are available for EBUS-scopes with a diameter of 25, 22, and 21 Gauge (G), with a meta-analysis demonstrating no significant differences in terms of diagnostic yield, sample adequacy, safety, and mean number of needle passes between 21 and 22G needles.^[36] Flexible 19G needles are available for EBUS-scopes with a working channel of 2.2 mm.^[37] A higher tissue yield was claimed for the larger needle diameter, but clinical relevance with regard to predictive biomarker analyses is still unproven.^[38] Experience with core-biopsy needles designed for use with EBUS-scopes^[39-41] and EBUS-guided intranodal forceps biopsy^[41] is still limited.

NEEDLES

A detailed description of different needle types is beyond the scope of this paper. Most often, a 22G needle is used, but other sizes are also available. Different companies produce needles, that are slightly different, but the main principles when using them are the same.^[42] Some studies have shown that needle gauge size has no significant impact on diagnostic yield. However, in selected cases where additional tissue may be needed, sampling with a 19G EBUS needle following standard aspiration with a 22G needle results in an increase in the diagnostic yield.^[43] In a randomized study including 500 subjects undergoing EBUS-TBNA, the efficacy of 19G was similar to that of 21G needle.^[44] The criteria for selecting the appropriate needle type depending on the sampling indication are still under debate.

ANATOMY

A detailed description of the anatomy is beyond the scope of this paper, and we refer to textbooks. Knowledge of endosonographic anatomy and its relation to the TNM lung cancer staging system is crucial, but not all anatomical borders have clinical

Table 1. Established EBUS equipment

	Diameter (mm)	Working channel (mm)	Working length (mm)	Field of view	Depth penetration (mm)	Frequency (MHz)	Scan modus	Comment
EB19-J10U Video EBUS-scope (Pentax)	7.3	2.2	600	100° /45° Oblique optic	2-50	5.0-13.0	Electronic 75° curved linear array	Compatible with Hitachi Hi-Vision Scanner
BF-UC190F Video-EBUS-scope (Olympus)	6.6	2.2	600	80° /20° Oblique optic	2-50	5.0-12.0	Electronic 65° curved linear array	Compatible with EU-ME2, Hitachi Aloka ProSound F75
EB-530US Video-EBUS-scope (Fujifilm)	6.7	2.0	610	120° /10° Oblique optic	3-100	5.0-12.0	Electronic 60° curved linear array	Compatible with SU-1-S/H Compatible with SU-8000

EBUS: endobronchial ultrasound

relevance in staging of the lung cancer patient. In a patient with NSCLC and N1 disease, surgery may be relevant, which is normally not the case for N2 disease. Thus, the border between stations 10 and 11 is not clinically relevant because both stations represent N1 (or N3, if located contralaterally to the primary tumor) disease. In contrast to this, the border between stations 4L and 10L is essential in a patient with a left-sided lung tumor as it denotes the border between N2 and N1 disease. Similarly, the border between stations 4R and 10R is essential in a patient with a right-sided lung tumor. Furthermore, for obvious reasons, it is mandatory to know the border between right- and left-sided LN stations. Incorrect upstaging could prevent the patient from receiving potentially curative therapy, and incurrent downstaging may cause the patient to undergo unnecessary surgery. Therefore, we should remember the following three important borders:

1. The border between stations 4R and 10R is the lower border of the azygos vein
2. The border between stations 4L and 10L is the upper border of the left pulmonary artery
3. The border between stations 4R and 4L is the left border of the trachea. Thus, a LN located in front of the trachea may be station 4R.

BEFORE YOU START

Check before starting the procedure that the endoscope as well as the ultrasonic picture and the endoscopic picture are all functioning satisfactory and that the wished frequency and depth are chosen. Check that the dot on the ultrasonic picture is located on the right side of the picture. It shows you where the proximal part of the endoscope is located. If the dot accidentally is on the left side, the ultrasonic picture

is inverted, which may be confusing. Let the dot stay on the right side also when you proceed to EUS-B even if most gastroenterologists prefer the dot on the left side.^[45] EBUS (-TBNA) and EUS-B (-FNA) may be performed with the patient in the supine position (preferred position for the pulmonologist), but also with the patient lying on his left side (preferred by the gastroenterologist).

HOW TO PERFORM ENDOBRONCHIAL ULTRASOUND-GUIDED TRANSBRONCHIAL NEEDLE ASPIRATION

Following a conventional bronchoscopy, the operator introduces the EBUS-endoscope in the airways. Remember that you cannot see straight because the transducer is in the way. It can be difficult to get access to the trachea with an aggravated vision. If you see the vocal cords in the middle of the picture, you will have to bend the tip of the endoscope forward until they are in the lower part of the picture, and then you can proceed. The operator performs a systematic EBUS with localization of the six landmarks before searching for other structures:

1. Find the landmarks in the following order: 4L→7→10L→10R→azygos→4R before starting to look for other structures
2. Take the biopsies in the following order: N3→N2→N1→lung tumor to prevent an accidentally upstaging of the patient with lung cancer.

HOW TO PERFORM EUS-B-FNA

Thereafter, the operator can introduce the EBUS-endoscope into the esophagus and continue with an EUS-B procedure. Retract the EBUS scope from

the trachea to a level just above the vocal cords and turn it slightly to the left and backward in the patient under very gentle pressure and encourage the patient to swallow. Right rotation (clockwise) of the handle moves the transducer to the right side of the body, when the transducer is directed ventrally, that is, it is above the diaphragm. Right rotation moves the transducer to the left side of the body when the transducer is directed dorsally, that is, it is below the diaphragm.

1. Find the landmarks in the following order: liver→ abdominal aorta→left adrenal gland→7→4 L→4R before starting to look for other structures
2. Take the biopsies in the following order: M1b→N3→N2→N1→lung tumor.

Use a new needle when you shift from EBUS to EUS-B if necessary, that is, do not risk moving malignant cells from the mediastinum to structures that may upstage the patient accidentally. In the case of one-needle approach, EUS-B is recommended first and thereafter proceed to EBUS. We recommend to sample in the order as follows to avoid relevant needle tract seeding: “M1b → N3 → N2 → N1 → lung tumor” independently from the location of the EBUS scope in the airways or in the upper gastrointestinal tract. For each sample, we give the information of the sampled station and in addition the needle pathway (transgastric, transesophageal, transbronchial, and transtracheal) to avoid any confusion. Others recommend using a new needle when shifting from structures below the diaphragm to structures above or if you biopsy at different locations, but there is no supportive published evidence.

THE ANATOMICAL HOME BASE LANDMARK SCHEME

Two sets of six anatomically defined home base landmarks (HBLs) each serve as the basis for simulation and hands-on- training, for assessment and certification of examiners and for standardisation of examination in clinical practice. The identification of HBL is helpful if the orientation is lost during imaging. Systematic clockwise or counterclockwise rotation of the echoendoscope tip and angulation of the instrument should be performed from each position to ascertain close contact with the tracheobronchial wall. Instead of trying to remember and understand all anatomical structures at once, you should start by learning the *six simple landmarks* for EBUS and EUS-B that you could always go back to.

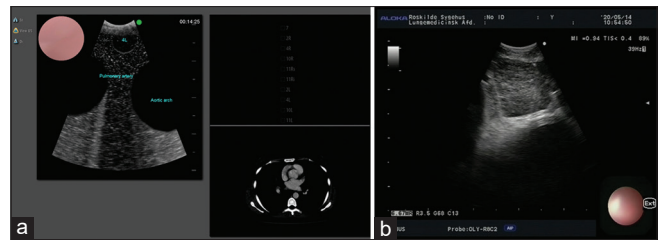


Figure 2. Station 4L, simulator (a) and ultrasound (b) picture

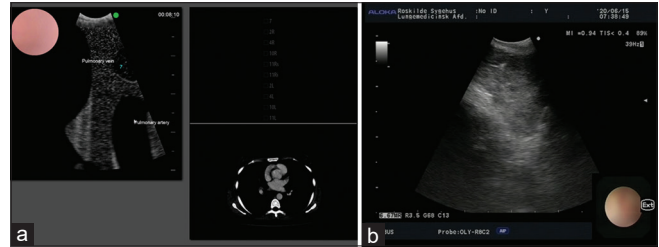


Figure 3. Station 7, simulator (a) and ultrasound (b) picture

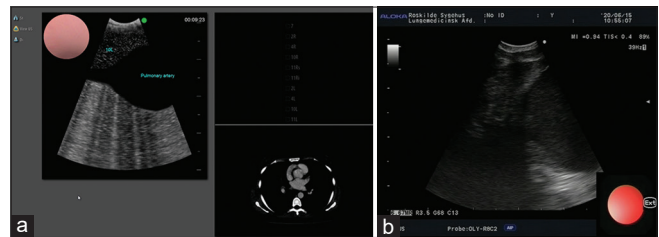


Figure 4. Station 10L, simulator (a) and ultrasound (b) picture

The six endobronchial ultrasound landmarks

The six EBUS landmarks are shown in Figures 2-7

Seek out the six EBUS landmarks systematically in the order mentioned.

1. Station 4L: Turn the endoscope counterclockwise and look for station 4L between the arch of the aorta and the left pulmonary artery. These vessels resemble the ears of Mickey Mouse – the so-called Mickey Mouse window [Figure 2]
2. Station 7: lies below the carina, with the EBUS scope in the right or the left main bronchus facing medially [Figure 3]
3. Station 10L: look upward with the transducer in the left upper lobe bronchus. Search for the upper part of the left pulmonary artery, which forms the boundary between station 4L and 10L [Figure 4]
4. Station 10R: look upward with the transducer in the right upper lobe bronchus searching close to the right main bronchus. Station 10R lies caudal to the inferior border of the azygos vein close to the right main bronchus [Figure 5]
5. The azygos vein: Look for the azygos vein by turning the transducer to the right in the trachea [Figure 6].

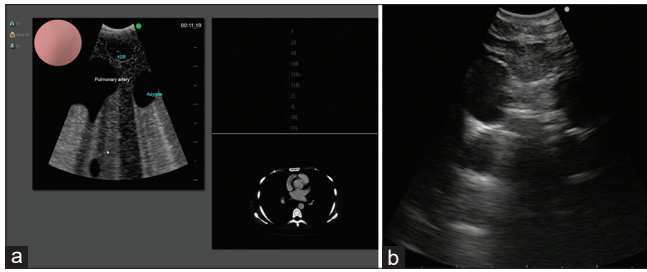


Figure 5. Station 10R, simulator (a) and ultrasound (b) picture

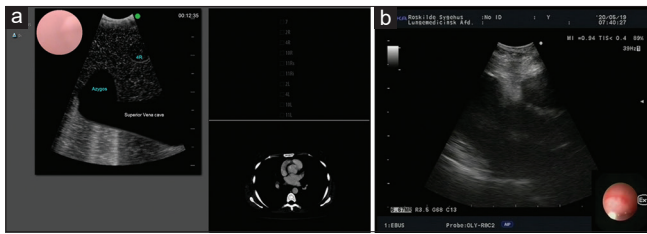


Figure 7. Station 4R, simulator (a) and ultrasound (b) picture

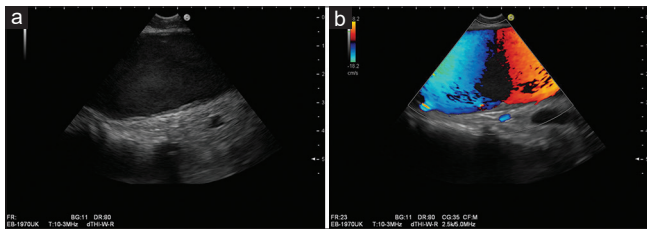


Figure 9. EUS-B abdominal aorta using B-mode (a) and color Doppler (b)

Note that the azygos vein is in communication with the superior vena cava – this can be demonstrated by turning the scope counterclockwise

6. Station 4R: This LN is found at the right or in front of the trachea above the azygos vein. The inferior border of the azygos vein marks the inferior border of station 4R [Figure 7].

The six EUS-B landmarks

The six EUS-B landmarks are shown in Figures 8-13.

Seek out the six EUS-B landmarks systematically in the order mentioned:

1. The liver: Introduce the endoscope into the esophagus and slide down. Turn the handle slightly counterclockwise and find the left liver lobe with the liver veins [Figure 8]
2. Aorta: Then turn the endoscope clockwise until the abdominal aorta with the origins of celiac trunk and superior mesenteric artery is found. If you get lost, you can always go back to this position [Figure 9]
3. The left adrenal gland: Now, turn the endoscope further clockwise and press the big wheel gently until you find

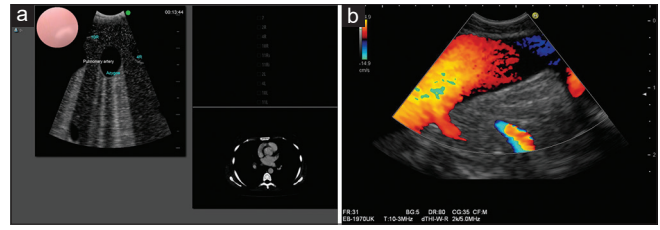


Figure 6. Station azygos vein, simulator (a) and Doppler ultrasound (b) picture

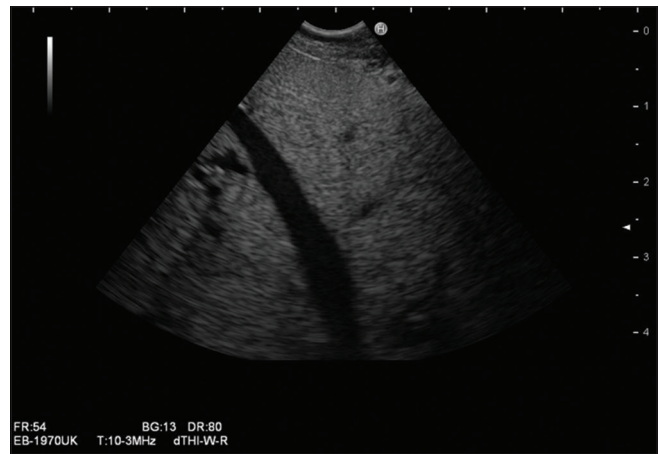


Figure 8. EUS-B (left) liver



Figure 10. EUS-B left adrenal gland

- the left adrenal gland close to the upper pole of the left kidney. The left adrenal gland resembles a bird [a seagull, Figure 10]
4. Station 7: Go to the mediastinum by retracting the endoscope, where you find the subcarinal LN, station 7, between the left atrium and the right pulmonary artery [Figure 11]
5. Station 4L: Retract the endoscope a little bit until you see the reflections from the trachea as parallel black and white lines. By counterclockwise rotation, station 4L is located between the aortic arch and the left pulmonary artery [Figure 12]

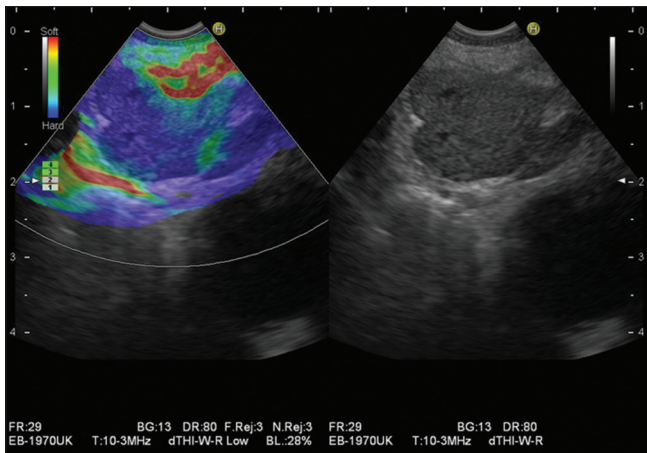


Figure 11. EBUS-B station 7, ultrasound elastography picture of a large lymph node with soft hilum (upper right, red and green colors) and stiffer lymph node parenchyma (blue)

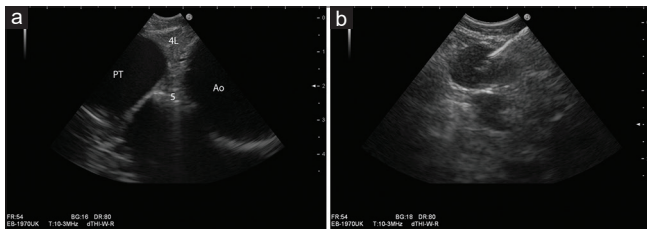


Figure 12. EBUS-B Station 4L, conventional B-mode ultrasound (a) and biopsy (b)

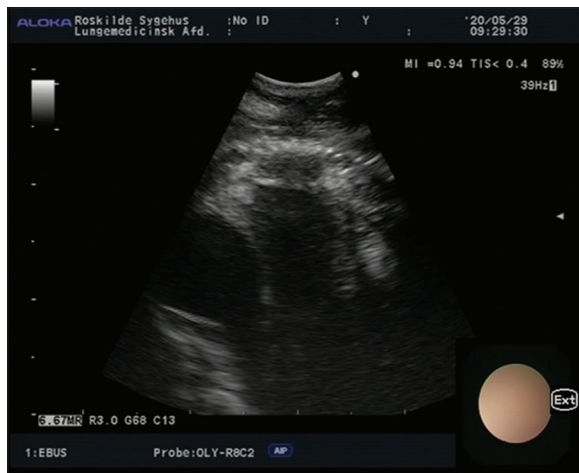


Figure 13. EBUS-B station 4R, conventional B-mode ultrasound

6. Station 4R: Rotate clockwise until you pass the trachea and find the azygos vein. Where it disappears into the superior caval vein, you find station 4R. However, it is often hidden behind the trachea [Figure 13].

INDICATIONS

The focus of the present paper is the diagnosis and staging of lung cancer. For other indications, please

see the papers of Colella *et al.*^[42] and Jenssen *et al.*^[30] In short, the European guidelines^[1] give the following recommendations when focusing at five clinical situations:

1. Abnormal mediastinum and/or hilar nodes at CT and/or PET in a patient with suspected or proven NSCLC: The combination of EBUS-TBNA and EUS, with the use of a gastrointestinal (EUS-FNA) or EBUS (EUS-B-FNA) scope, is preferred over either test alone. If the combination of EBUS and EUS-(B) is not available, EBUS alone is acceptable. Subsequent surgical staging is recommended, when endosonography does not show malignant nodal involvement
2. No mediastinal involvement at CT and/or PET/CT in patients with suspected or proven peripheral NSCLC: EBUS-TBNA and/or EUS-(B)-FNA should be performed, provided that one or more of the following conditions are present: (a) enlarged or fluorodeoxyglucose (FDG)-PET-avid ipsilateral hilar nodes; (b) primary tumor without FDG uptake; and (c) tumor size ≥ 3 cm
3. No involvement of mediastinal or hilar node plus lung tumor < 3 cm in size at CT and/or PET/CT in patients with suspected or proven peripheral NSCLC: Initiation of therapy without further mediastinal staging is suggested
4. No involvement of mediastinal or hilar nodes plus centrally located lung tumor at CT and/or PET in patients with suspected or proven NSCLC: It is suggested to perform EBUS-TBNA with or without EUS-(B)-FNA
5. Re-staging: For mediastinal nodal re-staging following neoadjuvant therapy, EBUS-TBNA and/or EUS-(B)-FNA is suggested for detection of persistent nodal disease, but, if this is negative, subsequent surgical staging is indicated.

A complete assessment of mediastinal and hilar nodal stations (all the above situations except^[3]) includes sampling of at least three different mediastinal nodal stations (4R, 4L, and 7) as well as abnormal LNs as suggested by CT or PET-CT.^[1] In patients with a centrally located lung tumor not visible at conventional bronchoscopy, sampling guided by endosonography is suggested, provided the tumor is located immediately adjacent to the larger airways (EBUS) or esophagus (EUS-[B]).^[1]

CONTRAINDICATIONS

In all patients undergoing invasive procedures, careful attention to antithrombotic therapy that may increase

Table 2. Factors potentially influencing the diagnostic yield of EBUS-TBNA

Factor	Influence	Evidence
ROSE	Reduced number of needle passes, but no influence on diagnostic yield	Meta-analysis ^[51]
Needle size (21G vs. 22G)	No influence on diagnostic yield	Meta-analysis ^[36]
Needle size (19G vs. 22/21G)	The results are equivocal. Larger volume sample and higher yield of tumor cells may theoretically be obtained with the 19G needle compared with the 22G needle, but may give a risk of more bloody material	Prospective comparative trials ^[38,52,53]
Number of needle passes	100% adequacy and 95% sensitivity achieved with three needle passes per LN with no further increase with further passes performed (mediastinal staging of patients with NSCLC)	Prospective RCT ^[54]
Stylet use	No influence on specimen adequacy rate and on diagnostic yield (two RCTs) Decreased average procedure time by nonuse of stylet (1 RCT)	Prospective RCTs ^[55,56]
Suction <i>versus</i> no suction	No influence on specimen adequacy rate and on diagnostic yield (two RCTs) Suction may improve tissue-core acquisition (one RCT)	Prospective RCTs ^[55,57]

RCT: Randomized controlled trial, LN: Lymph node, NSCLC: Non-small cell lung cancer

the risk of bleeding must be kept in mind, for example in patients with mechanical heart valves, atrial fibrillation, or deep-vein thrombosis. The indication must be balanced with the contraindication. Contraindications to EBUS and EUS-B are recent myocardial infarction or ischemia, poorly controlled heart failure, significant hemodynamic instability, severe exacerbations in chronic obstructive pulmonary disease or asthma, and severe coagulopathy.

TECHNICAL DETAILS OF SAMPLING, SPECIMEN PREPARATION, AND PROCESSING

The technical performance of tissue acquisition as well as handling and preparation of tissue samples is described in detail in recent guidelines.^[46-48] In short, the quality of samples may be influenced by several factors, such as size and type of the needle, number of needle passes, use of suction or slow-pull technique, availability of rapid on-site cytological evaluation (ROSE), and specimen processing (smear cytology, liquid cytology, and cell-block technique). However, evidence is limited and confined only to EBUS-TBNA [Table 2]. For EUS-guided sampling, a complementary approach combining cytopathological and histopathological processing is recommended to optimize diagnostic yield.^[46,49] However, evidence for this approach is only preliminary for EBUS-TBNA.^[50] Specimen obtained for the diagnosis of lung cancer using EBUS-TBNA and EUS-B-FNA should be adequate for immunohistochemical staining including PD-L1 analysis and for molecular profiling. Therefore, for molecular evaluation, additional passes, needles yielding a higher amount of tumor cells (19G, core needles), or histological processing (cell-block) may be useful approaches.^[46,48]

CONCLUSION

Using a single echoendoscope in both the trachea (EBUS) and the esophagus (EUS-B) allows mediastinal staging of lung cancer in one procedure.

This “single-scope, double investigation” with the EBUS equipment can be performed safely after conventional bronchoscopy in the same session. Evidence-based simulator training is recommended and is – concerning EBUS – offered via the European Respiratory Society. No EUS-B simulator training is available despite an apparent need and increasing interest.

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Conflicts of interest

There are no conflicts of interest.

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