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8

### Endosonography in bronchopulmonary disease

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The diagnostic approach to diseases of the mediastinum is divided into two phases: (1) imaging techniques and (2) procedures for obtaining tissue samples for cytologic and histologic examination. The latter has for many years represented a considerable challenge to the clinician. Often invasive procedures in general anaesthesia as mediastinoscopy or thoracoscopy have been necessary. However, the sampling of tissue from the mediastinum has been revolutionized by EBUS and EUS, since they give access to the middle and the posterior compartment via the trachea and the oesophagus, respectively. Both EUS FNA and EBUS-TBNA of mediastinal nodes and tumors can provide a specimen adequate for interpretation in over 95% of cases with a specificity of close to 100% and a sensitivity ranging between 88% and 96%. A growing number of studies including randomized trials and meta-analyses have demonstrated a major impact of EUSFNA as well as EBUS-TBNA on management of patients with lung cancer as well as in patients with unknown lesions in the mediastinum. The aim of the present review is to discuss the current role of endosonography in bronchopulmonary diseases focusing on endosonographically guided biopsy via the esophagus, trachea and main bronchi. The concept of complete echo-endoscopic staging of lung cancer is postulated as virtually all mediastinal nodes as well as regions relevant to pulmonal medicine (liver and adrenal glands) can be reached by these two methods in combination.

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## Introduction

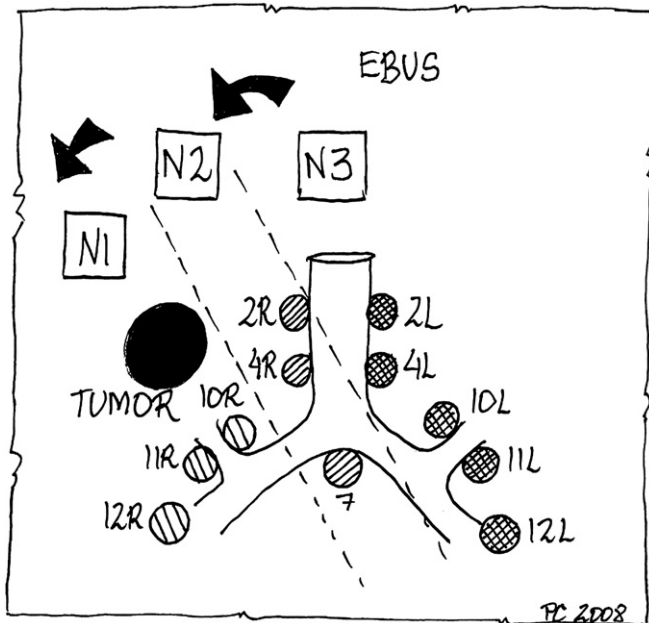
Endoscopic ultrasound scanning (EUS) from the gastrointestinal tract has become an integrated diagnostic modality in modern gastroenterology allowing high resolution ultrasound images to be obtained of the gastrointestinal tract (GI tract), adjacent organs and structures. After the development of EUS-guided fine needle aspiration biopsy (EUS-FNA), it became clear that EUS-FNA allows access to the posterior mediastinum with tissue acquisition under real-time ultrasound guidance through the oesophageal wall. EUS-FNA as well as histological true-cut needle biopsy (EUS-TCB) can be performed from all lesions outlined in the mediastinum adjacent to the esophagus [1]. In addition, also many organs and regions relevant to bronchopulmonary neoplastic diseases may be targeted via the upper GI tract (adrenals, liver, retroperitoneal lymph nodes).

However, a region anterior to the trachea cannot be visualized via the oesophagus. In recent years the addition of endobronchial ultrasound has been developed including real-time endobronchial guided fine needle biopsy (EBUS-TBNA).

The aim of the present review is to discuss the current role of endosonography in bronchopulmonary diseases focusing on endosonographically guided biopsy via the esophagus, trachea and main bronchi.

## Primary diagnosis of mediastinal lesions and mediastinal staging

Improvement of established procedures and development of new techniques continue to expand the diagnostic armamentarium for diagnosis of tumours in the mediastinum and in the lungs. Flexible bronchoscopy and trans-thoracic needle aspiration have for many years been the most common used techniques to obtain a tissue diagnosis. The former is especially valuable if there is endobronchial tumour visible, whereas the latter is used to biopsy peripheral lesions not visible at bronchoscopy.



**Fig. 1.** Illustration of Mediastinal lymph node stations according to the Mountain/Dressler classification in relation to lymph node metastases staging of lung cancer (i.e. local lymph node metastases N-1, ipsilateral lymph node metastases N-2, contralateral lymph node metastases N-3). When taking biopsies from the lymph nodes in the mediastinum, it is important to start with N-3 nodes, proceed to N-2 nodes and end with N-1 nodes to avoid spread of malignant cells to lymph nodes, that brings the patient in a stage not considered eligible for surgical resection (N2 and N3).

However, many tumours are not visible at bronchoscopy and small peripheral tumours may be difficult to biopsy CT-guided, even if electromagnetic navigation systems are used. Secondly, accurate staging of lung cancer is important to identify patients who will benefit from surgical resection. Patients with metastases in N2 and N3 lymph nodes are not considered eligible for surgical resection (Fig. 1). Unfortunately CT and PET have limited sensitivity and specificity in the differentiating benign tissue from malignant tissue.

### *Tumours in the mediastinum*

Mediastinal masses can be associated with systemic syndromes or endocrine or autoimmune effects or symptoms due to compression or invasion of adjacent intra-thoracic structures (cough, dyspnoea, dysphagia, pain, superior vena cava syndrome), but the incidental discovery of a mediastinal mass, that produces no symptoms, is the most common setting in which the clinician encounters primary mediastinal disease [2]. The precise frequencies of individual disorders vary among series probably because of differences in referral sources and patient populations, but neurogenic tumours, and developmental cysts account for around 60% of all mediastinal masses. Lymphoma and germ cell tumours such as teratoma and seminoma account for about one fourth, and a large number of other lesions, both benign and malignant, constitute the remaining 15% [2] (Table 1).

The diagnostic approach to diseases of the mediastinum is divided into two phases: (1) imaging techniques and (2) procedures for obtaining tissue samples for cytologic and histologic examination. The latter has for many years represented a considerable challenge to the clinician. Often invasive procedures in general anaesthesia as mediastinoscopy or thoracoscopy have been necessary. However, the sampling of tissue from the mediastinum has been revolutionized by EBUS and EUS, since they give access to the middle and the posterior compartment via the trachea and the oesophagus, respectively (Fig. 2a + b). The anatomic relationship between trachea, oesophagus and the mediastinum is easily appreciated on axial images produced by CT (Fig. 3).

### *Lung tumours*

Benign tumours of the lung account for 2–5% of primary lung tumours. Most primary malignant pulmonary tumours are bronchogenic carcinomas. Lymphomas and sarcomas comprise the largest group of non-bronchogenic neoplasms. Lung cancer is the leading cause of cancer-related mortality in

**Table 1**

Disorders presenting as a mass in the mediastinum.

#### **Anterior mediastinum**

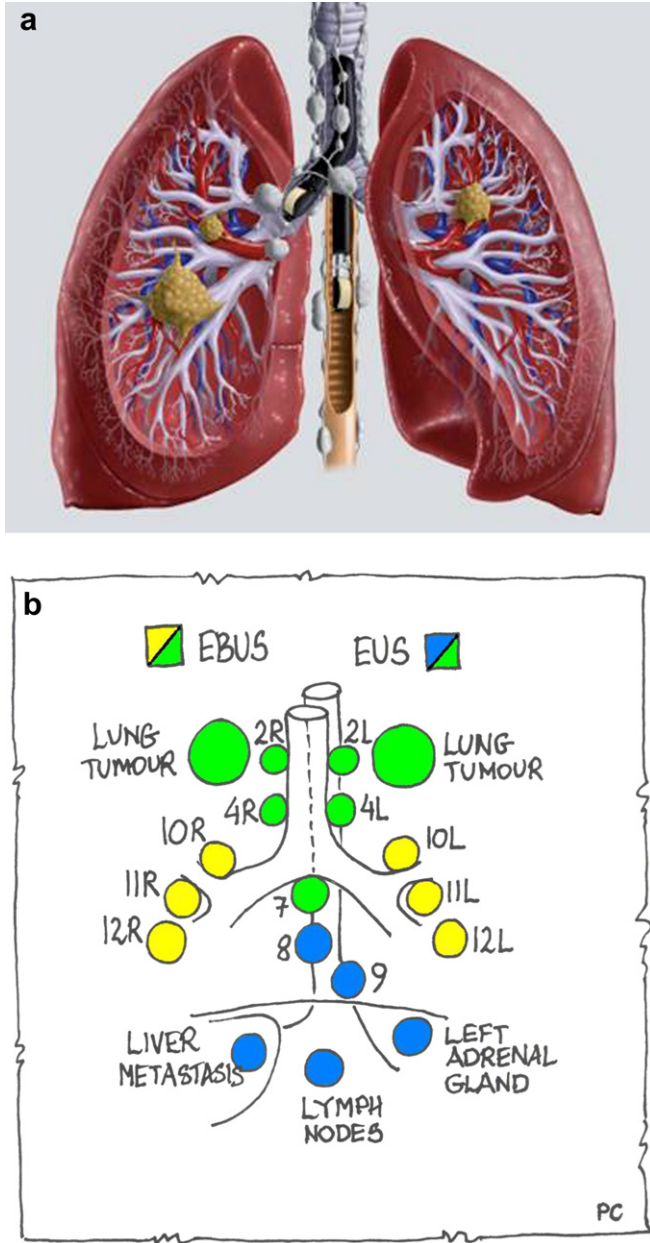
- Thymic neoplasms
- Germ cell tumors
- Lymphoma
- Thyroid and parathyroid neoplasms
- Mesenchymal tumors
- Diaphragmatic hernia
- Primary carcinoma

#### **Middle mediastinum**

- Lymphadenopathy: reactive and granulomatous inflammation or metastasis
- Lymphoma
- Developmental cysts
- Vascular enlargements
- Diaphragmatic hernia

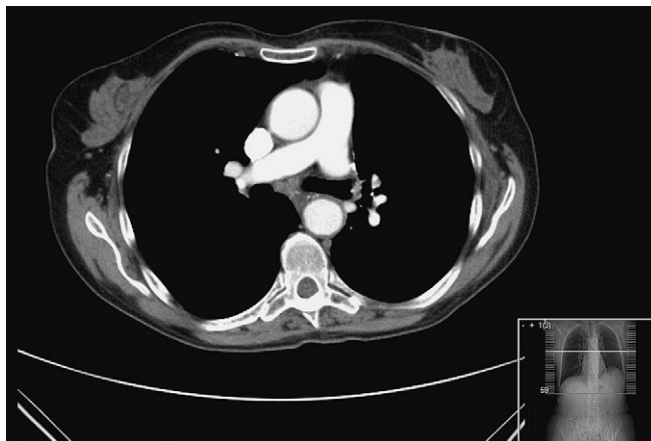
#### **Posterior mediastinum**

- Neurogenic tumors
- Meningocele
- Oesophageal lesions
- Diaphragmatic hernia



**Fig. 2.** a. Illustration of the thorax with EBUS and EUS endoscopes placed in the trachea and oesophagus, respectively. b. Schematic illustration showing the most important regions that can be reached by EUS and EBUS.

the Western countries [3]. Most cases are non-small cell lung cancer (NSCLC), and correct staging is important for rational allocation to surgery which is curative in case of localised disease, whereas the current recommended treatment of small cell lung cancer (SCLC) and disseminated NSCLC involves chemotherapy and radiotherapy. Surgery cannot generally be recommended in patients with NSCLC T4 and/or N2–N3 and/or M1 lesions (stage IIIB–IV). Accurate staging of mediastinal lymph node involvement, therefore, is a critical aspect of the management of non-metastatic NSCLC. Recently, the



**Fig. 3.** CT of the chest in a patient with an enlarged subcarinal lymph node (station 7).

International Association for the Study of Lung Cancer (IASLC) has proposed significant modifications to the existing TNM and stage grouping classifications [4].

### **EUS guided biopsy in bronchopulmonary disease**

Established indications of EUS-FNA in the mediastinum are either to obtain a diagnosis from an unknown primary lesion (Fig. 4a + b) or to sample tissue from mediastinal lymph nodes in order to stage lung cancer (LC), or to diagnose other diseases involving lymph nodes and structures of the mediastinum i.e. TB, Sarcoidosis, histoplasmosis, mesothelioma or metastases from other malignant primary lesions. If lymphoma is suspected EUS-TCB of an enlarged mediastinal lymph node is preferred [5,6].

#### *Instruments and procedure*

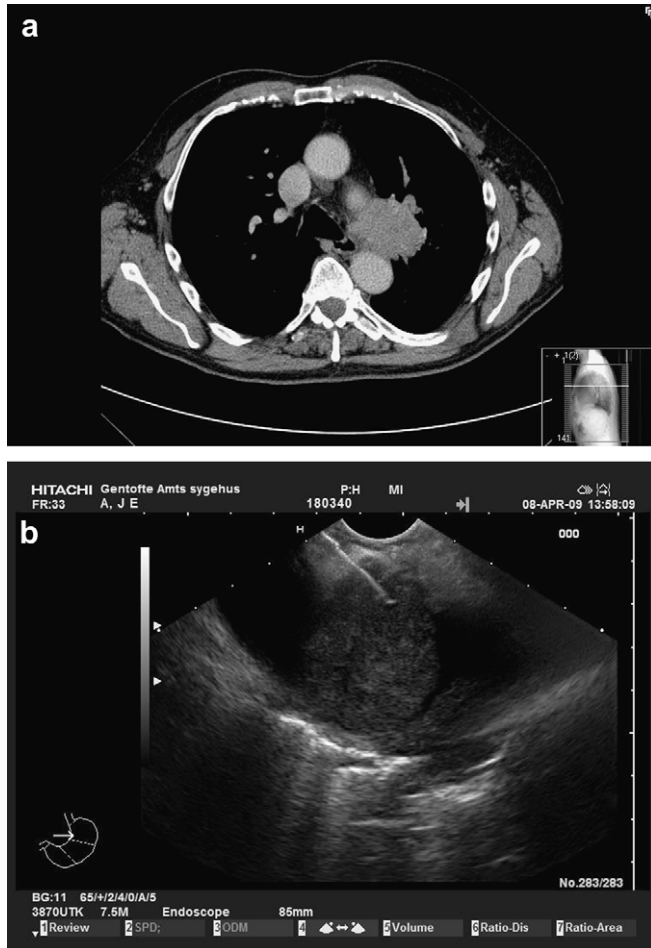
A wide range of dedicated EUS endoscopes with linear transducers suitable for monitoring of a needle during biopsy are available. These EUS endoscopes use frequencies between 5 and 10 MHz with a penetration at 5 MHz of around 6–8 cm. The examination is performed in a fastening patient under conscious sedation and most frequently as an out-patient procedure.

EUS-FNA 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 (Fig. 5a + b). After the lesion has been outlined the needle is advanced under real time ultrasonic guidance. Lesions down to the size of 5 mm may be targeted and cells collected for cytology (Fig. 6).

If histological material is needed, a dedicated needle device can be used in order to obtain tru-cut biopsies. Generally, EUS-FNA is the method of preference for most lesions but EUS-TCB may be of additional help for differential diagnosis of patients with either lymphomas or to differentiate between 2 distinct tumours [5].

### **EUS-FNA for diagnosis and staging of lung cancer**

More than 150 studies have been published, addressing EUS-FNA and lung cancer. EUS-FNA studies have demonstrated high diagnostic values challenging both other imaging modalities as well as surgical procedures used for tissue acquisition in the mediastinum. Two large meta-analyses have been published showing a pooled sensitivity and specificity of 88% and 96% and 83% and 97%, respectively [7,8] in the diagnosis of mediastinal lymph node metastases. In patients with enlarged lymph nodes on



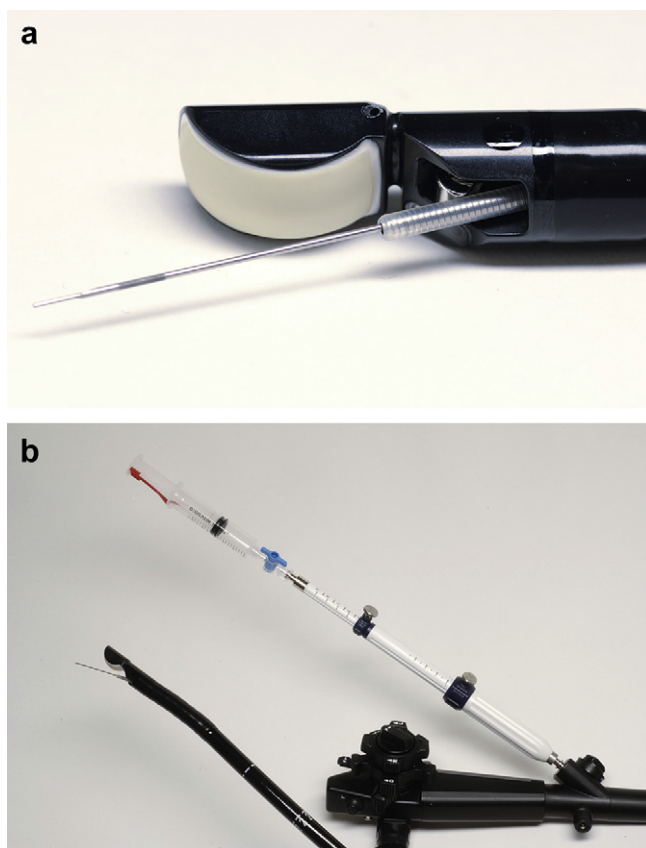
**Fig. 4.** a. CT of the chest of a patient with a left sided centrally located lung tumor. b. EUS-FNA from the same tumour shown in Fig. 4a

CT, the sensitivity rose to 90%, demonstrating that even CT node negative patients are diagnosed with lymph node metastases by EUS-FNA.

A recent study has demonstrated that EUS could be used as the first diagnostic test after CT scan of the chest as both a tissue diagnosis and locally advanced diseases was assessed in a single test [9]. In this study, including 116 patients, EUS-FNA was found to have superior sensitivity compared to both PET and CT for detection of mediastinal lymph node metastases.

#### *EUS-FNA and clinical Impact*

Several clinical impact studies have been published. In the first study published [10] in 84 patients selected for EUS-FNA by CT, a board of thoracic specialists was asked to decide the further course of the patient if EUS-FNA had not been available. In 18 of 37 patients (49%) a thoracotomy/-scopy was avoided as a result of EUS-FNA. In 28 of 41 patients (68%) a mediastinoscopy was avoided. In a randomized study from Larsen et al [11], 53 patients were randomly assigned to routine EUS-FNA and 51 patients to a conventional strategy (CWU) including EUS-FNA if CT demonstrated enlarged lymph nodes in the mediastinum. In the routine EUS-FNA group five patients (9%) underwent a futile thoracotomy,



**Fig. 5.** a. The distal end of a EUS endoscope with its transducer and a needle extending from the biopsy channel outlet. b. A EUS endoscope (Pentax EG 3870U).

compared with 13 (25%) in the CWU group ( $P = 0.03$ ), indicating that the routinely use of EUS-FNA in LC staging significantly reduces the number of futile thoracotomies when compared to a conventional staging strategy. These results argue very strongly for a standard staging strategy with EUS-FNA in all NSCLC patients.

In the largest study to date [12] in 242 consecutive patients with suspected ( $n = 142$ ) or proven ( $n = 100$ ) lung cancer and enlarged ( $>1$  cm) mediastinal LNs at chest CT, EUS-FNA prevented 70% of scheduled surgical procedures because of the demonstration of LN metastases in non-small-cell lung cancer (52%), tumor invasion (T4) (4%), tumor invasion and LN metastases (5%), SCLC (8%), or benign diagnoses (1%). Sensitivity, specificity, and accuracy for EUS in mediastinal analysis were 91%, 100% and 93%, respectively.

It is beyond doubt today that EUS-FNA makes a huge impact on the clinical management of lung cancer patients.

#### *EUS-FNA in CT node negative patients*

Several studies have now documented that EUS-FNA is able to demonstrate mediastinal lymph node metastases in around 25% of lung cancer patients without enlarged mediastinal lymph nodes by CT [13,14]. Wallace evaluated EUS-FNA in 69 patients with NSCLC and lymph nodes less than 1 cm by CT [13]. A sensitivity of 61% and a specificity of 98% for advanced LC was found by EUS-FNA. EUS detected advanced disease in 25% (17/69) of the CT negative patients. A study with 47 CT negative



**Fig. 6.** EUS-FNA from subcarinal lymph node. Note the needle echo inside the echo poor lymph node.

patients found a lower figure of 11% [14]. These results suggest that EUS-FNA should be performed in all patients with lung cancer irrespective of the size of lymph nodes demonstrated by CT.

#### *EUS-FNA and PET*

The place of EUS-FNA against PET/CT is a matter of discussion and no final conclusions can be drawn at present [15,16]. That the 2 methods are complementary seems obvious [17], but should PET/CT precede EUS-FNA or vice-versa? Should EUS-FNA only be performed in a subgroup of PET/CT patients or vice versa? Some data may be retracted from the present literature although no randomized studies are published. When comparing the 2 modalities most studies seem to show superior accuracy of EUS-FNA in the detection of mediastinal involvement. In all studies published, PET positive diagnoses seems to be a problem underlining the need for tissue confirmation. A study found that PET correctly diagnosed mediastinal lymph node status in 77% of 72 patients, and EUS fine-needle aspiration was correct in 94% of patients ( $P = 0.012$ ). The overall sensitivity, specificity, and accuracy of PET were 61%, 91%, and 77% compared with 87%, 100%, and 94% for EUS-FNA [18]. Annema [19] evaluated EUS-FNA in 36 patients with NSCLC suspected of mediastinal involvement (N2/N3 disease) by PET. EUS-FNA confirmed mediastinal involvement in 25 of the patients (69%). EUS-FNA correctly identified 25 of the 28 patients (89%) with clinically verified N2/N3 disease, EUS was suspicious in one and false negative in two patients (sensitivity 93%). PET was false positive in 8 of the 36 PET positive patients (22%).

The largest study to date [20] included 104 consecutive patients with suspicious nodes on PET or CT. The reference standard included thoracotomy with complete lymphadenectomy in patients with lung cancer or if EUS-FNA was benign, repeat clinical imaging, or long-term follow-up. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of EUS-FNA were 92.5%, 100%, 100%, 94%, and 97%, respectively. EUS-FNA was more accurate and had a higher positive predictive value than the PET or CT ( $P < 0.001$ ) scan in confirming cancer in the posterior mediastinal lymph nodes. However, it seems that EUS-FNA will have an important role to confirm or exclude a PET suspicion of mediastinal disease in patients with NSCLC.

#### *EUS-FNA and mediastinoscopy*

Mediastinoscopy (MS) and EUS-FNA are often considered as complementary, MS covering the anterior- and EUS the posterior mediastinum [21,22]. A few studies have addressed the role of EUS-FNA



against mediastinoscopy. A small randomized study with 40 patients randomised to either EUS-FNA or surgical staging concluded that the need for surgical staging is reduced if EUS-FNA is performed routinely [23]. For patients allocated to EUS-FNA, surgical staging was only needed in 32% ( $P < 0.001$ ). The sensitivity to detect malignant lymph node invasion was 93% (95% confidence interval, 66–99%) for EUS-FNA and 73% (95% confidence interval, 39–93%) for surgical staging ( $P = 0.29$ ). Complication rate was 0% for EUS-FNA and 5% for surgical staging ( $P = 1.0$ ). The median hospital stay was significantly shorter for EUS-FNA than for surgical staging (0 vs. 2 nights;  $P < 0.001$ ).

Annema et al [24] investigated the additional value of EUS-FNA to mediastinoscopy in a prospective, non-randomized multicenter trial in 107 consecutive patients with potential resectable non-small cell lung cancer. The patients underwent thoracotomy with tumor resection if mediastinoscopy was negative. The combination of EUS-FNA and mediastinoscopy identified more patients with tumor invasion or lymph node metastases (36%) compared with either mediastinoscopy alone (20%) or EUS-FNA (28%) alone. This indicated that 16% of thoracotomies could have been avoided by using EUS-FNA in addition to mediastinoscopy. However, 2% of the EUS-FNA findings were false-positive. In a recent study with 120 patients the false negative rate of EUS-FNA was 25.3%. EUS-FNA sensitivity was 91.7%, 78.1% and 43.8% for bulky disease, enlarged mediastinal nodes or normal nodes on CT scan, 50% and 96.6% for right- and left-sided tumours, and 80.6%, 78.9%, 23.8% and 25.0% for the lymph node stations 7, 5/6, 4R, and 4L. A 38.3% respectively 100% cut-down of mediastinoscopies leads in 7.5% respectively 20.8% to incorrect treatment decisions indicating that EUS-FNA is a useful supplement to and not the replacement of mediastinoscopy [25].

### EUS-FNA in non-lung cancer

A growing number of studies have demonstrated that other diagnoses from mediastinal lesions can be obtained by EUS-FNA. According to the literature diagnoses obtained by EUS-FNA are TB, lymphoma, sarcoidosis, histoplasmosis, malignant mesotheliomas, metastases from other primary tumors such as renal cancer, breast cancer, gynecological cancer, esophageal cancer, gastric cancer and pancreatic cancer.

In patients with suspected sarcoidosis a tissue proof of non-caseating granulomas is strongly recommended to exclude malignant diseases or tuberculosis, especially when treatment is considered. EUS-FNA seems to be well suited for this. Fritscher-Ravens found a sensitivity of 94% of EUS-FNA in 19 patients suspected of sarcoidosis [26]. Another study by Mishra found a sensitivity of 86% in 7 patients [27].

Annema [28] included 51 patients with suspected sarcoidosis stages I and II. Thirty-six patients (71%) previously underwent a non-diagnostic bronchoscopy. All patients were clinically followed (median 18 months) and surgical–pathological verification occurred in those patients with EUS aspirates that contained unrepresentative material. EUS-FNA demonstrated non-caseating granulomas without necrosis in 41 of 50 patients (82%) with the final diagnosis of sarcoidosis.

Wildi et al [29] showed in 124 patients with mediastinal lymphadenopathy 35 cases of granulomas (group 1) by EUS-FNA; in the other 89 cases (group 2) no granulomas were detected. The definite diagnoses in group 1 were sarcoidosis ( $n = 25$ ), indefinite ( $n = 7$ ), no sarcoidosis ( $n = 3$ ). The definite diagnoses in group 2 were sarcoidosis ( $n = 3$ ), indefinite ( $n = 9$ ), no sarcoidosis ( $n = 77$ ). Of the 77 cases with no sarcoidosis, 44 were diagnosed with other diseases. The other 33 showed non-specific changes in the FNA and sarcoidosis was excluded by negative non-EUS pathology ( $n = 17$ ) and clinical presentation. The sensitivity and specificity for EUS-FNA were 89% (95% CI 82–94) and 96% (95% CI 91–98), respectively, after exclusion of the indefinite cases in both groups. EUS-FNA seems to be an accurate method for diagnosing sarcoidosis in an unselected group of patients with mediastinal lymphadenopathy.

No large series of EUS-FNA for diagnosis of TB is at present published but studies are ongoing (Personal experience). EUS-guided FNA is accurate and feasible in diagnosing TB. The importance of this experience cannot be overemphasized especially in the era of drug resistant tuberculosis and acquired immune deficiency syndrome.

If mediastinal lymphoma is suspected it seems advisable to perform EUS guided TCB either alone or in addition to EUS-FNA [5,6]. However, if flow cytometry is available EUS-FNA may be sufficient for subclassification [30]. More data are needed for this indication.

### *EUS-FNA and complications*

EUS-FNA is generally considered to be a safe method. Most complications reported are case studies [31,32]. Barawi prospectively studied the incidence of complications associated with EUS-FNA [32]. In 842 mediastinal EUS-FNA procedures, 1 infection, 2 hemorrhages, and 1 inexplicable transient hypotension were reported. FNA of a cystic mediastinal lesion should be avoided, or when necessary be preceded by prophylactic antibiotics [33].

### **EBUS and EBUS-TBNA for bronchopulmonary diseases**

The clinical availability of endobronchial ultrasound (EBUS) has opened up fascinating novel diagnostic possibilities for lung and mediastinal diseases, especially for the diagnosis and staging of lung cancer. Radial EBUS applications can be helpful for the detection of peripheral lung lesions and the assessment of mediastinal tumor invasion. The focus of this review will be on linear EBUS-TBNA, which permits real-time ultrasound-guided aspiration of mediastinal and hilar lymph nodes and centrally located lung tumors.

#### *Radial EBUS*

The development of endobronchial ultrasound started in the 1990s [34]. Mechanical radial EBUS probes transmit ultrasound waves with frequencies between 5 and 30 MHz in a plane of 90 degree angle to the axis of the scope. Structures up to 3 cm around the probe can be visualized in a 360 degree plane. Images can either be obtained by directed contact with the so-called EBUS mini-probes, or indirectly by positioning the ultrasound transducer in a water-filled balloon. Mediastinal and hilar nodes can be detected but not aspirated in a real-time fashion with radial EBUS [35,36]. Therefore, the currently available linear EBUS scopes – which permit real-time guided TBNA – are the first choice for mediastinal staging. In skilled hands, the radial EBUS method can be helpful in selected patients to detect mediastinal tumor invasion (T4). Herth et al prospectively compared radial EBUS with CT and found a sensitivity of 89–25% and specificity of 100–89% in differentiating airway infiltration and compression by the tumor [36].

EBUS mini-probes, with an outer diameter of 1.7 mm, can be used for the detection of peripheral lung lesions invisible by conventional bronchoscopy, and are especially suitable for lesions larger than 20 mm [37]. A real-time ultrasound guided aspiration of the lung lesion is not possible with this method. However, with the guided sheath (GS) technique, biopsy of peripheral lung lesions after detection by EBUS mini probes can be performed [38]. Obviously, a pre-requisite for success is an airway leading to such a peripheral lesion.

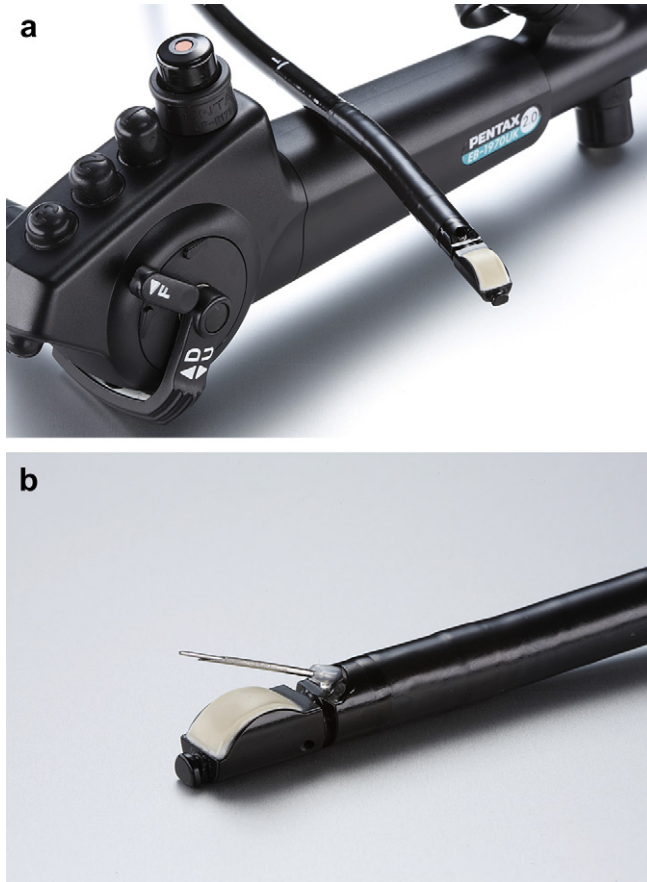
### **EBUS-TBNA**

#### *Instruments and procedure*

With convex electronic linear endobronchial ultrasound, ultrasound waves are transmitted with frequencies between 5 and 12 MHz along the same axis of the bronchoscope. Linear EBUS, commercially introduced in 2004, permits real-time visualization of the needle in the target lesion [39]. Undoubtedly, this has been the most clinically relevant development in the field of endobronchial ultrasound. The main indications of linear EBUS-TBNA are (1) mediastinal/hilar (re) staging of lung cancer, (2) diagnosing centrally located lung tumors not visible at conventional bronchoscopy, (3) analysis of mediastinal lesions and (4) demonstrating granulomas in patients with suspected sarcoidosis.

A real-time EBUS-TBNA examination is commonly performed in an outpatient setting under a low dose midazolam and takes approximately 15–20 minutes. Premedication of codeine is advised to reduce symptoms of cough. In some institutions, EBUS-TBNA is performed under propofol sedation or general anaesthesia.

EBUS-TBNA scopes (Olympus XBF-UC 160 F/Pentax EB 1970, UK) (Fig. 7a + b) are introduced orally into the trachea. With an outer diameter of 7 mm, EBUS scopes can be introduced till the segmental



**Fig. 7.** a. EBUS endoscope with proximal handle end as well as the distal end with transducer (Pentax EB 1970 UK). b. Distal end of the EBUS Pentax endoscope with needle extending from the biopsy channel outlet.

airways. In addition to an ultrasound transducer, an optical source is available which is positioned under a 30 degree (ERCP like) angle (Fig. 8). Therefore, EBUS scopes have limitations regarding the inspection of the tracheal-bronchial tree. In order to visualize mediastinal or hilar nodes, the ultrasound transducer has to be pressed against the wall of the trachea or larger airways. At that moment the optical images only shows the mucosa adjacent to the transducer. The EBUS investigator constantly has both an optical and an ultrasound image available but largely loses the optical one once the ultrasound transducer is positioned against the bronchial wall and alternatively, the ultrasound images will be lost in the absence of contact of the transducer to the airway wall. A needle can be advanced in the field of the ultrasound beam, thus performing a real-time ultrasound guided TBNA (Fig. 9). For an optimal yield, at least 3 needle passes per station are advised [40]. To date, 22 gauge needles are standard; larger 19 Gauge needles are in development. Most investigators use suction to aspirate lymph node material. Complications have seldom (0.15%) been reported [41]. Once a pneumothorax [42] and severe hypoxemia has been reported [40]. Obviously, haemoptysis is possible in case of aspiration a pulmonary vessel.

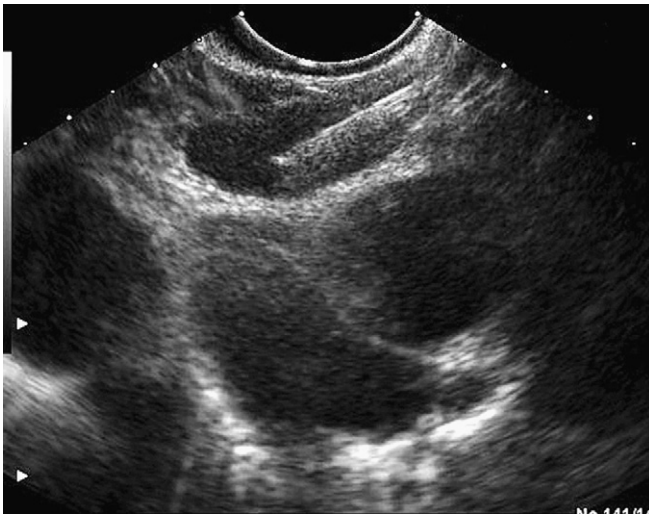
The diagnostic reach of EBUS-TBNA is related to those mediastinal and hilar nodes that are located immediately adjacent to the trachea and larger airways (Fig. 2b). They comprise the upper and lower para-tracheal nodes (stations 2 and 4 on both sides) and the subcarinal area (station 7). EBUS has a unique feature by being able to sample tissue from the hilar (station 10) (Fig. 10) and the intra pulmonary nodes (station 11) (N1 stations). These nodal regions rarely can be reached safely by any other diagnostic method.



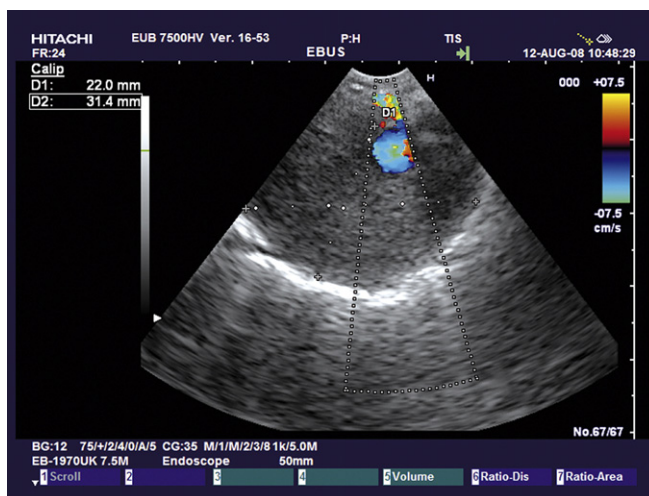
**Fig. 8.** Bronchoscopic image seen through an EBUS endoscope. The transducer can be seen at the bottom of the image.

### **EBUS-TBNA for diagnosis and staging of lung cancer**

Undoubtedly, lymph node staging in patients with (suspected) lung cancer is the major indication for an EBUS-TBNA investigation. In a recent meta-analysis [41] describing over 1299 patients from 11 different studies EBUS-TBNA had a pooled sensitivity of 93% (95% CI 0.91–0.94) and a pooled specificity of 100% (95% CI 0.99–1.00) [39,40,42–50]. P Sensitivity was not correlated with the prevalence of mediastinal metastases. Patients selected based on CT and/or PET findings suggestive of mediastinal involvement had a higher pooled sensitivity (94%, 95% confidence interval 0.93–0.96) in comparison with



**Fig. 9.** Ultrasonic image obtained during EBUS-TBNA of a 1 cm mediastinal lymph node. Note the reflexions from the needle inside the lymph node.



**Fig. 10.** EBUS image of a lesion located at the lung hilum with colour Doppler signals from a vessel inside the lesion (Pentax EB 1970 UK).

those without any selection on CT or PET (0.76, 95% CI 0.65–0.85). These data were confirmed in a recent study in 226 patient – unselected by CT, in which EBUS had a sensitivity of 89% and NPV of 84% [51].

One study focused exclusively on patients without mediastinal enlargement at chest CT (short axis <10 mm) found that EBUS still had a high sensitivity of 92% and NPV of 96% [45].

Regarding mediastinal restaging after neoadjuvant chemotherapy, one report of 124 patients found a sensitivity of EBUS-TBNA of 77% – comparable to EUS-FNA and redo-mediastinoscopy) and an NPV of 20% [52]. So, EBUS-TBNA can be used to confirm persistent nodal disease but has poor value in excluding it.

In patients with suspected lung cancer, integrated CT-PET is increasingly used as an initial staging test. Analyzing those patients with suspected mediastinal involvement on PET-CT with EBUS-TBNA currently qualifies as a minimally invasive staging strategy for patients with suspected lung cancer. In several studies, it has been demonstrated that EBUS-TBNA has a sensitivity between 90 and 95% and NPV between 60 and 97% in analyzing mediastinal nodes that were suspect on CT-PET [42,53,54].

In patients with suspected lung cancer, the primary lung lesion cannot be reached by conventional white light bronchoscopy in around 30% of cases due to the absence of abnormalities in the larger airways. In those patients with centrally located lung tumors, but without endoluminal abnormalities on conventional bronchoscopy, EBUS-TBNA, could identify and aspirate these lesions in the vast majority of cases [55,56]. Therefore EBUS-TBNA is an alternative to CT guided biopsy.

The impact of EBUS-TBNA (establishing a tissue diagnosis, prevention of CT guided biopsies or surgical staging or exploratory thoracotomy) depends on the specific population under investigation. Obviously, in those subsets of patients with a very high prevalence of mediastinal malignancy, the impact is high, in comparison for instance to patient cohorts in which normal sized nodes without FDG uptakes at FDG-PET are investigated. In patients with enlarged (short axis >10 mm) [57] or PET positive nodes [54], patient management is influenced by EBUS-TBNA outcome in 49–71% of cases.

Current lung cancer staging guidelines (ACCP/ESTS) position EBUS-TBNA as an alternative diagnostic method for surgical staging to confirm the presence of mediastinal metastases [56,58,59]. Surgical staging is currently still advised in the absence of mediastinal spread at EBUS-TBNA, in patients with suspected mediastinal involvement on (CT/PET) imaging, due to limitations in the negative predictive value of EBUS-TBNA.

### EBUS-TBNA in non-lung cancer

The role of EBUS-TBNA for lymphomas is still under discussion and is related to the quantity of tissue from the lymph node that can be obtained. Although a sensitivity of 91% and NPV for of 93% for EBUS has

been reported [56,60] with 22 G needles, cytological material alone often proves to be insufficiently for a definite lymphoma classification. The mini-forceps biopsy, in which a forceps is introduced in the subcarinal space via a previously made small hole by conventional TBNA, enables large tissue samples to be taken under ultrasound guidance. Not surprisingly, the diagnostic yield for lymphomas using mini forceps biopsy was significantly increased in comparison to 22 and 19 G needles [56,61].

Sarcoidosis is the most common interstitial lung disease, which involves mediastinal or hilar lymph nodes in 90% of patients. In patients with a clinical and radiological suspicion of sarcoidosis, assessment of non-caseating granulomas is indicated to diagnose sarcoidosis [62]. Three studies, that investigated 15, 50 and 65 patients with suspected sarcoidosis by EBUS-TBNA, demonstrated non-caseating granulomas in 93%, 85% and 92% of patients [63–65]. These data have been obtained in selected cohorts with a high prevalence of sarcoidosis and whether the established yield remains as high in other patients populations where tuberculosis and histoplasmosis are endemic remains to be seen. The high yield of EBUS-TBNA in assessing granulomas is comparable with EUS-FNA [28]. To date, transbronchial lung biopsies are currently advised in the consensus statement [66] to detect granulomas, which involve a risk of pneumothoraces and hemoptysis. A randomized trial between transbronchial lung biopsies and endosonography for the detection of granulomas is currently conducted.

### **Combined EUS-FNA and EBUS-TBNA for staging of lung cancer**

For patients with localized NSCLC, optimal mediastinal nodal staging is important to select the best treatment option. No single mediastinal tissue sampling method can reach all mediastinal nodal stations. Previously, it has been shown that additional staging of EUS-FNA to mediastinoscopy improves nodal staging [24] and spare futile thoracotomies [11]. EBUS-TBNA and mediastinoscopy have a similar range in detecting mediastinal nodal stations according to a comparison trial especially regarding assessment of subcarinal nodes [43]. In 2005 the concept of complete echo-endoscopic staging of lung cancer was postulated by investigating patients with both EUS-FNA and EBUS-TBNA [47] as virtually all mediastinal nodes can be reached by these two methods combined (Fig. 2a) and in addition to this, the transoesophageal approach is able to reach regions in the upper abdomen, relevant to staging of LC (Fig. 11).

Herth et al reported in patients with enlarged nodes on chest CT that the combined EUS and EBUS approach produced successful biopsies in 97% and established a diagnosis in 94% of patients [67]. In a prospective trial in 138 patients with (suspected) lung cancer and mediastinal masses, the combination of EUS and EBUS had a sensitivity of 93% and a negative predictive value of 97% regarding mediastinal nodal staging [49]. The ASTER trial – a recently completed randomized trial in which optimal surgical staging was compared to complete echo endoscopic staging (EUS + EBUS) under local sedation – will learn us whether the combined endosonographic approach will be an alternative for surgical staging (Clinical trials. gov. nr identifier NCT00432640).

In current lung cancer staging guidelines, EUS and EBUS are suggested as an alternative to surgical mediastinal staging to confirm mediastinal spread [58,59]. However, in the absence of mediastinal metastases at either EUS/EBUS surgical staging is still advised due to limitations in the negative predictive value [58,59]. In the future, it will be under the discussion whether, in specific subsets of patient's, surgical staging can be omitted after endosonography. Part of the discussion will be how many surgical staging procedures are needed to identify one patient false negatively staged by EUS/EBUS.

### **The future of EUS-FNA and EBUS-TBNA**

Evaluation of mediastinal adenopathy and mass lesions are usually challenging owing to their non-specific clinical presentation and a low diagnostic yield obtained by routine investigations. However, these strategies have now been challenged by far less invasive methods represented by EUS-FNA and EBUS-TBNA. EUS and EBUS gives in combination an excellent overview of mediastinal structures and have been shown to yield a diagnosis even when other invasive modalities like CT-guided FNA, bronchoscopy and mediastinoscopy are negative or inconclusive. Both EUS FNA and EBUS-TBNA of mediastinal nodes can provide a specimen adequate for interpretation in over 95% of cases with a specificity of close to 100% and a sensitivity ranging between 88% and 96%.



Fig. 11. EUS showing the left adrenal gland with a 1-cm round lesion.

Radial EBUS will probably have a place in the diagnostic armamentarium also but will only be used in selected centers for the analysis of peripheral lung lesions and the assessment of mediastinal tumor invasion. EBUS-TBNA is a more recent development than EUS-FNA and it is expected that linear EBUS, by which mediastinal and hilar nodes and centrally located tumors are aspirated in a real-time fashion under ultrasound guidance will spread rapidly and evolve as an indispensable diagnostic method for the diagnosis and staging of lung cancer as well as EUS-FNA. The implementation of EUS-FNA among pneumologists will depend on the psychological barrier that still exists to diagnose and stage lung cancer from the esophagus. However, according to current evidence, the 2 methods seem to be complementary in order to obtain optimal diagnostic results as well as to avoid more invasive and risky diagnostic procedures [47,49].

### Practice points

- EUS and EBUS are alternative methods for surgical staging to detect mediastinal metastases in patients with NSCLC
- EUS and EBUS have a complementary diagnostic reach and together can reach virtually all mediastinal nodes
- Implementation of endosonography in lung cancer staging protocols reduces surgical staging by at least half and prevents futile thoracotomies

### Research agenda

- Randomised trials between surgical staging and complete echo-endoscopic staging of the mediastinum are indicated
- Implementation trails for endosonographic methods are needed to ensure spread of these minimally invasive diagnostic and staging methods for patients with lung cancer

## Summary

Evaluation of mediastinal adenopathy and mass lesions are usually challenging owing to their non-specific clinical presentation and a low diagnostic yield obtained by routine investigations. However, these strategies have now been challenged by 2 far less invasive methods. Both EUS-FNA and EBUS-TBNA of mediastinal lesions can provide a specimen adequate for interpretation in over 95% of cases with a specificity of close to 100% and a sensitivity ranging between 88% and 96%. Many studies including randomized trials have demonstrated a major impact of EUS-FNA as well as EBUS-TBNA on management of LC patients as well as in patients with unknown lesions in the mediastinum. Implementation of endosonography in lung cancer staging protocols reduces surgical staging by at least half and prevents futile thoracotomies. It is also documented that both methods alone are able to demonstrate mediastinal lymph node metastases in around 25% of NSCLC patients without enlarged mediastinal lymph nodes on CT. Both methods are considered important to confirm or exclude a PET suspicion of mediastinal spread due to a high percentage of false positive diagnoses by PET. Although the concept of complete echo-endoscopic staging of lung cancer was postulated in 2005, surgical staging is currently still advised in the absence of mediastinal spread at EBUS-TBNA or EUS-FNA, due to limitations in the negative predictive value of the 2 methods. Apart from LC, a growing number of studies have also demonstrated that a variety of other mediastinal lesions can be diagnosed by EUS-FNA and EBUS-TBNA.

EUS and EBUS are complementary methods if optimal diagnostic results should be reached as well as to reduce more invasive and risky diagnostic procedures. It is expected that these 2 methods will be implemented as routine procedures for staging of NSCLC and diagnosis of various mediastinal lesions.

## Conflict of interest

None Declared.

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