

# State of the art lecture: EUS and EBUS in pulmonary medicine

J. T. Annema<sup>1</sup>, K. F. Rabe<sup>1</sup>

<sup>1</sup> Division of Pulmonary Medicine, Leiden University Medical Center, Leiden, The Netherlands

## Introduction

The development of linear echo-endoscopes has opened up fascinating new diagnostic possibilities for patients with various lung diseases. Transoesophageal ultrasound-guided fine needle aspiration (EUS-FNA) and transbronchial ultrasound-guided needle aspiration (EBUS-TBNA) are both minimally invasive diagnostic techniques that enable real-time controlled aspirations of mediastinal lymph nodes and centrally located lung tumours. By demonstrating mediastinal metastases, surgical procedures can frequently be avoided. In this short survey, we provide an overview concerning results obtained by EUS and EBUS in pulmonary medicine and discuss how these novel methods can be used in clinical practise.

## EUS- FNA

Linear echo-endoscopes (Fig. 1) were originally developed for diagnostic purposes in gastro-enterology. By incorporating an ultrasound transducer at the tip of an endoscope, para-oesophageal lesions can be aspirated under real-time ultrasound guidance. In 1996, it was suggested that EUS was also a useful diagnostic method for mediastinal lesions of unknown origin [1]. Initial EUS studies for mediastinal abnormalities were often performed by gastro-enterologists who frequently first performed a radial EUS – which provides a 360 degree overview of the para-oesophageal area. Once suspected lesions were identified, they were aspirated those using linear equipment. As ultrasound criteria of lymph nodes alone – such as shape, size, demarcation and echo pattern – are not accurate enough to distinguish between malignant and benign nodes, fine needle aspirations are needed for an accurate assessment [2–4]. Nodes as small as 4 mm can be aspirated [5], and on site cytology is advocated in order to assess whether representative material has been obtained [6]. For its use in pulmonary medicine, we believe that linear equipment should be used primarily, as in the overwhelming majority of cases tissue verification is needed. An EUS investigation is performed under ambulatory conditions, often under conscious sedation, and takes on average 20–25 minutes. EUS-FNA should be performed in a standardized fashion in order to visualize the left adrenal gland, left liver lobe and all mediastinal nodes that that can be assessed from the oesophagus. EUS in particular provides access to nodes in the lower mediastinum (station 7,8,9) (Fig. 2). Nodes located in the aorta-pulmonary window

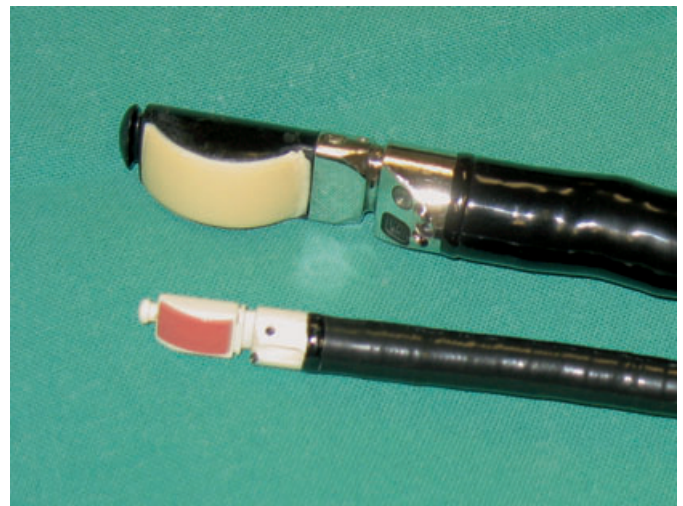


Fig. 1 Linear oesophageal (Pentax FG 34 UX) and bronchial (bottom) endo-echo scopes (Olympus BF UC 160F).

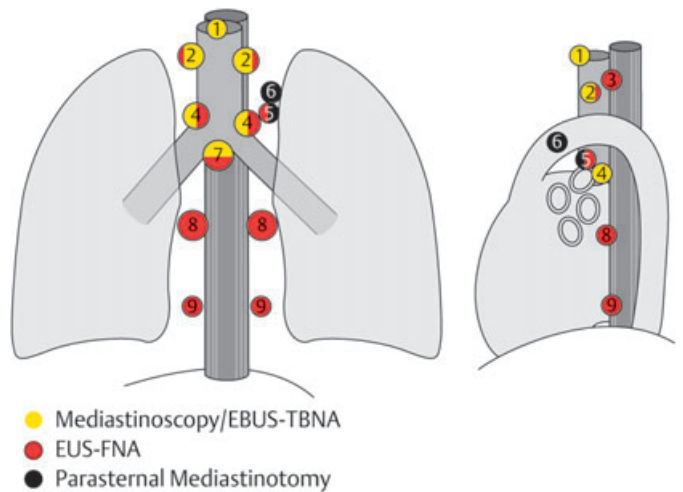


Fig. 2 Staging methods and their range in assessing regional lymph node stations [48] in non-small cell lung cancer [49].

(station 5) and adjacent to the aorta (station 6) can easily be identified but not all these nodes can be safely targeted due to intervening vascular structures. Lymph nodes located pre- and para-tracheally (station 2 and 4) often cannot be detected by EUS due to intervening air, especially in those located on the right side of the trachea. The diagnostic reach of EUS is complementary with that of mediastinoscopy and EBUS [7] (Fig. 2).

## EBUS-TBNA

Transbronchial needle aspiration (TBNA) of mediastinal lesions has been reported since the 1940's and can be performed during routine bronchoscopy. The sensitivity varies enormously (17–84%) and is dependent on the prevalence of mediastinal metastases in the population under investigation and experience of the investigators [8]. Currently, “blind” TBNA is only performed by 27% of chest physicians [9] – the main reason for its limited use being the lack of real time monitoring of the needle [10]. The yield of TBNA can be increased, especially for those nodes lo-

**Correspondence:** Jouke Annema, MD, PhD · Department of Pulmonology C3 P · Albinusdreef 2 · PO box 9600 · 2300 RC Leiden · Leiden University Medical Center · Leiden · The Netherlands · Phone: 0031-71-5262950 · Fax: 0031-71-5266927 · E-mail: j.t.annema@lumc.nl

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cated outside the subcarinal region [11], by using endobronchial ultrasound (EBUS) to locate the node prior to TBNA [12]. To achieve images with radial EBUS, an ultrasound probe and a water filled balloon are needed. A limitation of this radial EBUS “localisation method” is that the aspiration itself is still being performed in a blind fashion. Very recently, linear EBUS probes with a side viewing optic and a curved linear array ultrasound transducer have been developed by which hilar and mediastinal lymph nodes can be aspirated under real-time ultrasound control from the trachea bronchial tree [13]. With EBUS-TBNA the para-tracheal (stations 2 and 4), subcarinal (station 7) hilar and intrapulmonary nodes (stations 10 and 11) can be reached. EBUS investigations occur both under local and general anaesthesia and take around 20 minutes. In the near future, further technological improvements are expected, especially regarding the quality of the ultrasound signal. Due to their size and side viewing optic a complete inspection of the bronchial system is not possible. The diagnostic range of EBUS overlaps with that of mediastinoscopy and is complementary with EUS (Fig. 2) [7], [13–15].

### Diagnosis and staging of lung cancer

Undoubtedly, mediastinal lymph node staging in patients with (suspected) lung cancer is the main indication for EUS and EBUS. Additionally, EUS and EBUS might be helpful in the assessment of mediastinal tumour invasion (T4) or – in the case of EUS-left adrenal metastases (M1). For EUS-FNA, the vast majority of studies have been performed in selected lung cancer patients with enlarged mediastinal nodes on computed tomogram (CT) of the chest for which it has accuracy above 90% [14–21]. Two studies addressed the value of EUS in small nodes for which an accuracy of 73% and 82% has been reported [22,23]. For mediastinal restaging after neo adjuvant chemotherapy an accuracy of 83% has been assessed [24]. EUS in combination with mediastinoscopy improves loco regional staging [17,25] and thus prevents futile thoracotomies [26]. Regarding EBUS-TBNA, two medium sized studies reported an accuracy of more than 96% in distinguishing benign from malignant mediastinal nodes in patients with (suspected) lung cancer [13,27]. Analysis of lesions that are suspect for malignancy based of FDG-PET by either EUS-FNA [18,28,29] or TBNA after EBUS localisation [30] has been advocated as a minimally invasive staging strategy for patients with NSCLC.

In up to 30% of patients with suspected lung cancer, no tissue diagnosis is obtained by bronchoscopy. In those patients with enlarged mediastinal nodes, tissue proof of mediastinal malignancy – either by EUS or EBUS – provides both a diagnosis and loco-regional staging in a single test [16,27]. In those patients with suspected lung cancer and the primary tumour located adjacent to the oesophagus, intrapulmonary tumours can be visualised and aspirated by EUS [31,32]. In one study in 32 patients, EUS established a tissue diagnosis in 97% of patients after a prior non-diagnostic bronchoscopy [31]. It has been reported that EUS can assess mediastinal tumour invasion provided the tumour is detected by EUS [17,33,34]. In 97 patients with left sided tumours located adjacent to the aorta EUS (Fig. 3) had an accuracy for mediastinal tumour invasion of 92% [34]. Cells from the left adrenal

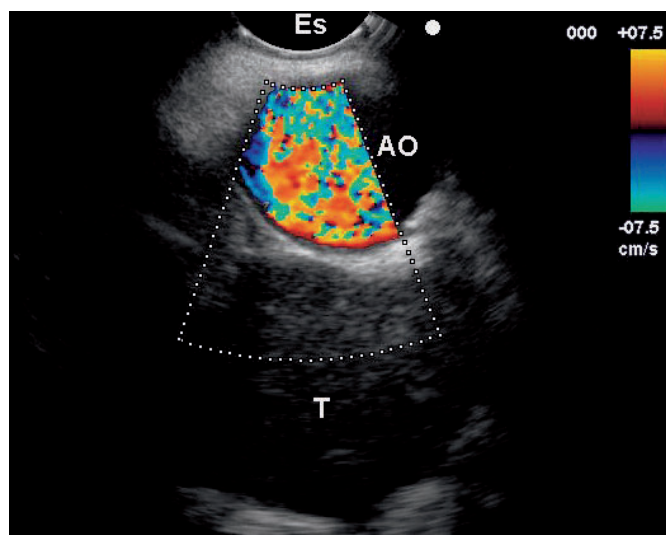


Fig. 3 Left upper lobe tumor (T) located adjacent to the aorta (AO) without sonographic signs of tumor invasion (T4) (Es = esophagus).

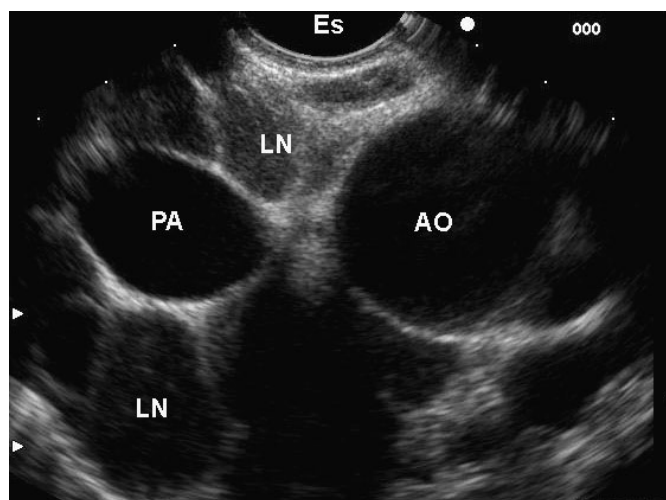


Fig. 4 Multiple iso-echoic mediastinal and hilar lymph nodes (LN) located adjacent to the esophagus (ES), aorta (AO), and pulmonary artery (PA) in a patient with sarcoidosis.

gland can be aspirated by EUS-FNA from the stomach. In a study of 31 patients with suspected malignancy and enlarged left adrenal glands, EUS-FNA demonstrated metastases in 42% of patients [35]. Whether the left adrenal gland should be investigated routinely during EUS – regardless of its size at CT is subject of debate [36].

### Granulomatous diseases

Sarcoidosis and tuberculosis are common diseases in which a tissue diagnosis or culture is often needed for diagnostic and treatment purposes. As the mediastinal nodes are frequently involved in these diseases, EUS and EBUS might be helpful in the diagnostic process. EUS-FNA has been demonstrated to have a yield of 82% [37] and sensitivity of 89–94% [38,39] by assessing non-caseating granulomas in mediastinal nodes in patients with suspected sarcoidosis. Ultrasonic images frequently display a typical pattern of clustered iso-echoic nodes (Fig. 4) [37] with some-

times prominent vessels [38]. Studies regarding the diagnostic value of EBUS-TBNA in patients with suspected sarcoidosis are ongoing. For the diagnosis of sarcoidosis, bronchoscopy with TBNA and transbronchial lung biopsies have a yield in assessing granulomas of around 66% [40]. We expect an important role or both EUS and probably EBUS in the diagnostic workup for patients with sarcoidosis as EUS has a high yield in demonstrating granulomas and no risk of haemoptysis and pneumothoraces, complications that are described for transbronchial biopsies. Samples obtained by EUS can be sent for culture for Tuberculosis [19] as well as PCR analysis.

## Miscellaneous

EUS can be useful for the diagnosis of other diseases besides lung cancer and granulomatous disorders. Mediastinal cysts – comprising 20% of mediastinal lesions – are often difficult to diagnose. On EUS, cysts frequently have a specific round form with an echo free interior, although the content of cysts can be very variable [41]. Although EUS could be helpful in the differential diagnosis of a mediastinal lesion, it is not recommended to aspirate cysts due to the risk of infection and mediastinitis [41,42]. Obviously, mediastinal metastases other than from pulmonary malignancies can be assessed by either EUS or EBUS. EUS-FNA has been demonstrated to assess mediastinal metastases from head and neck neoplasms [43], colon, renal, bladder carcinoma carcinomas and melanomas [44]. Although it has been reported that EUS with flow cytometry can be used for the diagnosis of lymphomas [6,45,46], the diagnostic role of EUS for this indication is under debate as haematologists often prefer large histological samples for the initial diagnostic assessment.

## Impact on patient management

One of the big advancements of EUS and EBUS is related to the fact that these methods enable minimally invasive tissue sampling of regions that are otherwise only accessible by invasive surgical procedures such as mediastinoscopy/ tomy, or even open thoracotomy. In operable patients with (suspected) lung cancer and enlarged mediastinal nodes, EUS and prevented 70% of scheduled mediastinoscopies [16,20]. As EUS and mediastinoscopy are complementary in their diagnostic reach [17,25,26] additional staging of EUS to mediastinoscopy improves staging [17,25] and reduces futile thoracotomies [26]. In patients with lung cancer without enlarged nodes, EUS findings changed patient management in 25% of cases [22,23]. By demonstrating left adrenal metastases, EUS prevented CT guided biopsies [22] which usually require a separate patient appointment. In a recent study in 105 patients with (suspected) lung cancer and enlarged hilar or mediastinal nodes, EBUS-TBNA prevented mediastinoscopies in 29, thoracotomies in 8, thoracoscopies in 4 and CT guided needle biopsies in 9 patients (total 48%) [27].

## Future goals and perspectives

In 2006, there is a substantial body of evidence that EUS-FNA is an accurate method for the diagnosis and staging of lung cancer

with a large impact on patient management. Therefore, in our opinion, it is not the question if but how and on which scale and within which time frame EUS will be implemented in the daily practice in pulmonary medicine. For several indications more data are needed, in particular regarding small nodes, mediastinal restaging and the assessment of tumour invasion. As the EBUS-TBNA scopes have been available for just a few years, as yet limited data are available. The first results of EBUS in the diagnosis and staging lung cancer are promising [13,14,27]. EUS and EBUS are complementary in their diagnostic reach [7] and combined endoscopic staging by both methods (Fig. 1) has been suggested [14,15]. For those lesions/ nodal stations that can be reached by either method, more comparison studies [7] are needed. For such studies not only yield and diagnostic accuracy, but also feasibility tolerability and patient preference should be taken into account. Lung cancer staging algorithms are under debate [47] with the rapidly increasing clinical availability of EUS, EBUS and PET. Each of these techniques as well as existing methods such as mediastinoscopy and VATS have their specific limitations and to date it is not clear what the optimal staging algorithm for lung cancer should be. Prospective staging studies between EUS, EBUS, PET mediastinoscopy and VATS should investigate several staging strategies. For sarcoidosis, comparative studies between conventional bronchoscopy with blind TBNA and TBLB, EBUS-TBNA and EUS-FNA should be performed that do not only take diagnostic yield but also complications and patient tolerability and preference into account.

Training and implementation of EUS will be important issues in the years to come. The lack of training facilities for EUS provides a barrier for further implementation. It remains to be seen whether the published results, mostly obtained by “dedicated enthusiasts” in expert centres, will be reproducible by less experienced investigators. Most courses that are organised in expert centers provide participants with a good overview of the indications for EUS (Table 1), but in order to get acquainted with EUS, hands-on training over a longer period seems to be the desirable. To perform mediastinal EUS in pulmonary medicine on a top level, there is more to it than just aspirating a para-oesophageal node. Investigators should be aware of indications and limitations of EUS as well as alternative approaches to solve the diagnostic problem under investigation. Additionally, a thorough knowledge of the various mediastinal nodal stations should be present.

**Table 1** Indications for EUS-FNA in Pulmonary Medicine

Suspected lung cancer, enlarged (> 1 cm) mediastinal lymph nodes <sup>#</sup>
Suspected lung cancer, primary tumour located adjacent to the esophagus
Mediastinal staging of non-small cell lung cancer <sup>#</sup>
Mediastinal involvement at FDG-PET in (suspected) lung cancer <sup>#</sup>
Mediastinal restaging after induction chemotherapy
Assessment of tumour invasion (T4) in centrally located tumours
Suspected mediastinal metastasis from extra thoracic tumours
Suspected Sarcoidosis
Suspected Tuberculosis
Suspected Cysts (no FNA)

<sup>#</sup> Indications also for EBUS-TBNA

In conclusion, both EUS-FNA and EBUS-TBNA are fascinating novel diagnostic methods that enable tissue verification of mediastinal and intrapulmonary lesions in a minimally invasive way and, therefore, prevent surgical interventions to a large extent. More training facilities are urgently needed in order to ensure that all patients get access to these novel diagnostic methods.

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