EUS-FNA is an accurate method for mediastinal staging of patients with non small cell lung cancer (NSCLC), and therefore EUS-FNA provides an alternative for surgical evaluation of the mediastinum. Due to the complementary reach in analyzing different mediastinal regions, additional staging by EUS-FNA to mediastinoscopy improves preoperative staging of NSCLC and therefore reduces the number of futile thoracotomies. Preliminary data suggest an important role for EUS-FNA in the assessment of mediastinal tumor invasion as well as mediastinal restaging after prior chemo (radiation) therapy. For interstitial lung diseases, EUS-FNA has been demonstrated to be an accurate method in diagnosing sarcoidosis. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a novel diagnostic method by which mediastinal, hilar, and intrapulmonary nodes can be aspirated under real-time ultrasound control from the trachea or main bronchi. EBUS-TBNA can be performed in an ambulatory setting and has been proven to be accurate in mediastinal staging of patients with NSCLC. Like EUS-FNA, EBUS-TBNA is an alternative for mediastinoscopy. EUS-FNA and EBUS-TBNA have a complementary reach for various mediastinal nodal stations, and recent studies indicate that complete and accurate locoregional staging of NSCLC can be achieved by the combination of EUS-FNA and EBUS-TBNA.

Keywords: EUS-FNA, EBUS-TBNA, pulmonary

On a daily basis, chest physicians and thoracic surgeons are faced with the challenge to evaluate mediastinal lesions. Due to the high incidence of lung cancer, 170,000 new cases in the USA and 1.3 million worldwide, mediastinal staging of non small cell lung cancer (NSCLC) compromises by far the largest subset of patients in which mediastinal analysis is indicated. Although imaging methods such as computed tomography (CT) and positron emission tomography (PET) provide detailed information regarding size and metabolic activity of mediastinal nodes, tissue samples are frequently needed for accurate nodal assessment. Therefore, to date, mediastinoscopy is frequently performed for regional lung cancer staging in those cases in which tissue verification is indicated. Although mediastinoscopy has a sensitivity of 81% and excellent specificity (100%), it has limitations in its diagnostic reach, is invasive, and requires clinical admission. By 1995, it was reported that transesophageal ultrasound-guided fine needle aspiration (EUS-FNA), originally designed for the analysis and staging of gastrointestinal malignancies, had a high diagnostic potential for mediastinal staging of lung cancer. In the following section, the procedure, indications, limitations, and impact on patient management of EUS-FNA in pulmonary medicine will be discussed.

EUS-FNA: Instruments and Procedural Technique

The same linear array ultrasonic equipment that is used in gastroenterology is utilized for the assessment of mediastinal lesions. For accurate mediastinal analysis, tissue samples are required, and therefore linear and not radial equipment is needed. Various ultrasonic endoscopes that are commercially available (for instance Pentax FG 34UX, or Olympus GF UC 140 P) are equipped with curved linear array ultrasound transducers that transmit ultrasound waves with frequencies between 5 and 10 MHz parallel to the axis of the scope and therefore permit a real-time controlled aspiration. For the actual tissue sampling, various needle types (Vizeon, Medi-Globe 222 480, Wilson-Cook Echo tip -1-22 or Olympus NA -10J-10) and sizes (19-, 22-, 25-gauge) are available, but studies almost exclusively have been performed with 22-gauge needles. The use of suction is under debate, and for an optimal yield, five needle passes are advised. Rapid on-site cytology (ROSE) is advocated to obtain optimal yield. For regional lung cancer staging, the Mountain classification is used (Fig. 1).
Patients are investigated in left lateral position under conscious sedation using midazolam. Initially, the scope is introduced into the stomach from where the celiac axis, celiac nodes, and left adrenal gland can be inspected. A thorough mediastinal staging is performed by 360-degree rotations of the echoendoscope at intervals of 3 to 4 cm proceeding from the gastroesophageal junction to the upper esophageal sphincter. Using this technique, mediastinal nodes can be detected in following regions: the pulmonary ligament (stations 9R and 9L), the lower paraesophageal area (stations 8R and 8L), the subcarinal area (station 7), paratracheal to the left (station 4L, Fig. 2, LN1), the aorto-pulmonary window (station 5, Fig. 2, LN2), and the para-aortal region (station 6) (Hawes RH, Fockens P: Endosonography 2006, p 57-72, ISBN1-4160-2953-2). The latter two lymph node stations often cannot be aspirated due to the interposition of the pulmonary artery and aorta (Fig. 2, LN2). EUS has limitations in detecting the lower paratracheal nodes on the right (station 4R) (Fig. 3) as well as the upper paratracheal stations (2R and 2L), unless they are grossly enlarged, due to the presence of air in the trachea.

Figure 1  Regional lung cancer staging map, according to Mountain.\textsuperscript{11}
EUS-FNA Results

Mediastinal staging of lung cancer is beyond doubt the main indication for EUS-FNA. The vast majority of studies have been performed in selected patients with enlarged mediastinal nodes at chest CT. The accuracy of EUS-FNA in this subset of patients ranges between 91% and 100%. Three studies evaluated the role of EUS-FNA in patients with (suspected) lung cancer without signs of mediastinal nodal involvement at chest CT. The lower accuracy of EUS-FNA (range 76% to 89%) might be explained by sampling errors, technical difficulty to sample small nodes, or just the fact that the nodes have not been aspirated due to their normal sonographic appearance. Evaluating patients with suspected mediastinal involvement at positron emission tomography (PET) by EUS-FNA has been proposed as a minimally invasive and accurate (range 77-97%) staging strategy. Staging by EUS-FNA in addition to mediastinoscopy improves preoperative staging due to the complementary reach of various mediastinal nodal stations. EUS-FNA has major impact on patient management, as 70% of scheduled mediastinoscopies can be prevented by EUS-FNA. EUS-FNA has also been suggested for mediastinal restaging after induction chemo (radiation) therapy, and therefore provides an alternative for remediastinoscopy. Besides targeting mediastinal nodes, intrapulmonary tumors can be detected and aspirated by EUS-FNA, provided they are located adjacent to the esophagus (Fig. 4). In two studies in patients with a centrally located intrapulmonary mass without mediastinal involvement at chest CT, EUS-FNA (after a prior non-diagnostic bronchoscopy) was able to establish a diagnosis in 97% and 100% of patients. If intrapulmonary tumors can be detected at EUS, the presence or absence of mediastinal or aortic invasion (Fig. 5) can be assessed successfully.

EUS-FNA also has an important role in assessing mediastinal metastases in patients with (previous) extra thoracic tumors and radiological suspicion of mediastinal involvement. EUS-FNA is expected to be incorporated in the diagnostic workup of patients with sarcoidosis—the most common cause of interstitial lung disorder—a disease in
which mediastinal nodes are frequently affected. Bronchoscopy with TBNA and peripheral lung biopsies have a diagnostic yield in assessing granulomas in 65% of patients. The disadvantages of peripheral lung biopsies are the risk of pneumothoraces and hemoptysis. Three studies have evaluated the role of EUS-FNA in diagnosing sarcoidosis and reported a yield of noncaseating granulomas without necrosis in 82% to 94% of patients.

**EBUS-TBNA in Pulmonary Medicine**

Flexible bronchoscopy allows inspection of the airways and biopsying of endobronchial lesions. In case tissue sampling of mediastinal lymph nodes is indicated, they can be aspirated by transbronchial needle aspiration (TBNA). As these nodes cannot be identified during conventional bronchoscopy, the actual aspiration is “blind” (Fig. 6) and the site of aspiration is selected based on the CT scan (Fig. 3). The yield of TBNA varies widely (range 39-78%) as reported by a recent meta-analysis and is critically dependent on the prevalence of mediastinal metastases in the population under investigation. Unfortunately, TBNA is only performed by 10% to 30% of bronchoscopists, and the main reason for its limited use is the absence of real-time needle monitoring. The first attempt to overcome this problem was the development of endobronchial ultrasound (EBUS) mini probes. These probes can be inserted in the working channel of a bronchoscope, and after inflation of a water-filled balloon, provide a 360° ultrasound image in a plane surrounding the ultrasound transducer. After localizing the target node, the ultrasound probe has to be removed and using the same working channel, a “blind” TBNA can be performed. Herth and coworkers demonstrated that TBNA after EBUS localization improved diagnostic yield in all nodal stations, except in the subcarinal area, compared with conventional TBNA. By the end of 2003, Krasnik and coworkers reported the first experiences with an EBUS-TBNA scope, which permitted real-time ultrasound-guided transbronchial needle aspiration of mediastinal nodes. As real-time EBUS-TBNA is a promising future technique, it will be discussed in detail below.

**EBUS-TBNA: Instruments and Procedural Technique**

The EBUS-TBNA bronchoscope (Olympus BF 160F-OL8) (Fig. 7) has an outer diameter of 6.9 mm and incorporated at its distal end is a curved linear ultrasound transducer (frequency 7.5 MHz, scanning range 50 degrees) as well as a 35-degree forward oblique optical system. A 22-gauge needle system (Olympus NA-201SX-4022) can be attached to the bronchoscope (Fig. 8). After adjustment of the length of the sheath, a needle can be inserted in a plane parallel to the scanning direction (Fig. 7), thus permitting a real-time ultrasound controlled aspiration. The distal end of the needle has an echogenic dimpled tip (Fig. 9) that improves its visibility on ultrasound images.

EBUS-TBNA can be performed in an ambulatory setting, and most investigators use conscious sedation with midazolam. Before the examination, the oropharynx is anesthetized with a lidocaine spray. After the (oral) introduction of the ultrasonic bronchoscope, the trachea and right and left main bronchus can be inspected. To visualize the mediastinal nodes, the ultrasound transducer has to make firm contact with the tracheo/bronchial wall. A balloon option is available, to increase surface contact between ultrasound transducer and the tracheal wall, but in the majority of cases, good ultrasound images can be obtained without use of the balloon. A Doppler system is available to detect flow, which can be helpful in the discrimination between solid lesions and vascular structures (Fig. 10). After adjustment of the length of the sheath, a real-time controlled aspiration of a lymph...
node can be performed. In case a cartilage ring is encountered during TBNA, the scope is moved a little bit up or down to find an intercartilage space. After positioning of the needle into the node (Fig. 11), the stylet of the needle is removed and suction is applied. After moving the needle back and forth several times, suction is removed and the needle is withdrawn. EBUS can visualize the upper (stations 2R and 2L) and lower (stations 4R and 4L) paratracheal nodes, the subcarinal area (station 7), as well as the hilar (stations 10R and 10L) and intrapulmonary nodes (stations 11R and 11L). In addition to lymph nodes, centrally located tumors abutting the larger airways and undetectable by conventional bronchoscopy can be identified by EBUS.

**EBUS-TBNA Results**

After the initial report in 2003, 3 medium-sized and 1 large study have been performed, all addressing mediastinal lymph node staging in patients with (suspected) non-small cell lung cancer. In a study of 70 patients with enlarged mediastinal nodes at chest CT, Yasafuku and coworkers reported a sensitivity, specificity, and accuracy for EBUS-TBNA in assessing mediastinal nodes of 96%, 100%, and 97%, respectively. In a subsequent study of 105 patients with non-small cell lung cancer, 29 mediastinoscopies, 8 thoracotomies, 4 thoracoscopies, and 9 CT-guided lung biopsies were precluded due to EBUS-TBNA findings. Very recently, Herth and colleague studied 502 patients with (suspected) lung cancer and enlarged mediastinal nodes and reported a sensitivity of 94% and a specificity of 100% for mediastinal staging. The same author evaluated EBUS-TBNA in 100 patients without signs of mediastinal lymph node enlargement (<10 mm short axis) on CT. The sensitivity, specificity, and accuracy of EBUS-TBNA in this subset of patients were 92%, 100%, and 96%, respectively.

**Clinical Perspectives**

EUS-FNA and EBUS-TBNA are accurate, minimally invasive, and safe diagnostic methods for mediastinal staging of non-small cell lung cancer. It has to be realized that the diagnostic reach of both methods in assessing various mediastinal nodal stations is complementary. The role of mediastinoscopy in lung cancer staging is issue of debate due to the introduction of ultrasonic endoscopic methods. Surgical staging by mediastinoscopy can be prevented to a large extent by both EUS and EBUS. The concept of complete endoscopic lung cancer staging by the combination of EUS-FNA and EBUS-TBNA has been postulated by Vilman and colleagues, who reported an accuracy of 100% in a small study of 33 patients. These findings were confirmed by Wallace and his group, who presented data on 84 patients with (suspected) lung cancer who all underwent bronchoscopy with conventional TBNA, EBUS-TBNA, and EUS-FNA in 1 ambulatory setting.
setting. The sensitivity of mediastinal staging for combined EUS-FNA + EBUS-TBNA (97%) was superior to either EUS-FNA + TBNA (95%), EBUS-TBNA + TBNA combined (89%), and EUS (89%), EBUS (83%) or conventional TBNA (73%) alone (Wallace MD, Endoscopy 2006, 38, p4, abstract). It has to be realized that EUS and EBUS results have been obtained by a selected group of dedicated investigators, and it remains to be seen whether the reported accuracy remains high after large-scale implementation. In the near future, both EUS-FNA and EBUS-TBNA beyond doubt will be implemented in diagnostic and (re) staging strategies for lung cancer (Table 1). As a result, the need for surgical staging and the number of exploratory and futile thoracotomies will be reduced. For extra thoracic malignancies that metastasize to the mediastinal nodes, EUS and possible EBUS can be of value in confirming or excluding mediastinal spread. Aside from its role in (lung) cancer, EUS is expected to play a role in diagnosing sarcoidosis and cysts.

### Conclusions

In conclusion, by now there is substantial evidence that both EUS-FNA and EBUS-TBNA are accurate and safe diagnostic methods for the analysis of mediastinal lymph nodes. For regional staging of lung cancer and evaluation of mediastinal masses, it is expected that EUS-FNA and EBUS-TBNA will substitute surgical methods to a large extent.

### References

Pulmonary interventions

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