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Transbronchial and transoesophageal (ultrasound-guided) needle aspirations for the analysis of mediastinal lesions

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ABSTRACT: A tissue diagnosis of mediastinal nodes is frequently needed for accurate lung cancer staging as well as the assessment of mediastinal masses. Transbronchial needle aspiration (TBNA) is a safe procedure that is performed during routine bronchoscopy. Provided mediastinal metastases are confirmed, TBNA has a high impact on patient management. Unfortunately, TBNA remains underused in current daily practice, mainly due to the lack of real-time needle visualisation. The introduction of echo-endoscopes has overcome this problem.

Endobronchial ultrasound-guided TBNA (EBUS-TBNA) allows real-time controlled tissue sampling of paratracheal, subcarinal and hilar lymph nodes. Mediastinal lymph nodes located adjacent to the oesophagus can be assessed by transoesophageal ultrasound-guided fine needle aspiration (EUS-FNA). Owing to the complementary reach of EBUS-TBNA and EUS-FNA in assessing different regions of the mediastinum, recent studies suggest that complete and accurate mediastinal staging can be achieved by the combination of both procedures.

It is expected that implementation of minimally invasive endoscopic methods of endobronchial ultrasound-guided transbronchial needle aspiration and transoesophageal ultrasound-guided fine needle aspiration will reduce the need for surgical staging of lung cancer significantly.

KEYWORDS: Endobronchial ultrasound-guided transbronchial needle aspiration, transoesophageal ultrasound-guided fine needle aspiration, transbronchial needle aspiration

The assessment of mediastinal lymph nodes and masses is important for both diagnostic purposes and (lung) cancer staging. Imaging methods, such as computed tomography (CT) and positron emission tomography (PET), indicate size and metabolic activity, respectively, of mediastinal nodes with a sensitivity and specificity of 57–82% (CT) and 84–89% (PET), respectively [1]. Surgical staging by mediastinoscopy has a high sensitivity (81%) and specificity (100%) [2, 3]. However, it is an invasive procedure that requires general anaesthesia and clinical admission. Endoscopic techniques provide a minimally invasive alternative for surgical

staging. In this part of this series, the background, indications and results of fine needle aspiration techniques that can be performed during bronchoscopy and oesophagoscopy will be discussed.

TRANSBRONCHIAL NEEDLE ASPIRATION

Merely a curiosity at its inception, flexible bronchoscopy has emerged as an essential diagnostic and therapeutic modality for a variety of lung diseases [4, 5]. The addition of transbronchial needle aspiration (TBNA) not only improved bronchoscopy's diagnostic yield, it further extended the role of bronchoscopy in

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the evaluation of mediastinal pathology, and in the diagnosis and staging of bronchogenic carcinoma [3, 6–8]. The first description of sampling mediastinal lymph nodes through the tracheal carina using a rigid bronchoscope was by SCHIEPPATI [9, 10], an Argentinian physician who presented the technique at the Argentine Meeting of Bronchoesophagology in 1949. In 1978, WANG *et al.* [11] demonstrated that it was feasible to sample paratracheal nodes using TBNA. In 1979, OHO *et al.* [12] introduced a flexible needle that could be utilised through a flexible fibrebronchoscope and in 1983, WANG and co-workers [13, 14] reported the use of TBNA for lung cancer staging and developed new types of needles. Subsequent publications highlighted the use of the technique in the diagnosis of endobronchial and peripheral lesions and the ability of TBNA to provide a diagnosis even in the absence of endobronchial disease [15–23]. In the present instalment in this series, the role of TBNA in the management of mediastinal lesions is examined and technical considerations essential to the TBNA procedure are addressed.

Equipment

All needle systems for transbronchial aspiration consist of: a retractable, sharp, bevelled, flexible needle; a flexible catheter; a proximal control device to manipulate the needle, the stylet, or both; and a proximal port through which suction can be applied. To obtain cytology specimens, 20–22-gauge needles are usually used, while 19-gauge needles are needed to obtain a “core” of tissue for histology [16, 24]. Histology specimens are commonly obtained using a 19-gauge histology needle. Several systems are available commercially as a dual-needle system involving 21- and 19-gauge bevelled, retractable needles [7].

Procedure

Selection of the proper site for needle insertion to increase diagnostic yield may be facilitated by reviewing the CT scan of the chest. TBNA can be performed safely and successfully for unexpected endobronchial lesions encountered during routine flexible bronchoscopy [25]. To prevent needle damage to the working channel of the fibrebronchoscope, the fiberbronchoscope should be kept as straight as possible, with its distal tip in the neutral position during catheter insertion. The bevelled end of the needle must be secured within the metal hub during its passage through the working channel. The needle is advanced and locked in place only after the metal hub is visible beyond the tip of the working channel. The catheter can then be retracted, keeping the tip of the needle distal to the end of the fibrebronchoscope. The scope is then advanced to the target area and the tip of the needle is anchored in the intercartilaginous space in an attempt to penetrate the airway wall as perpendicularly as possible (fig. 1) [26].

The following techniques may be used to insert the needle through the airway wall. 1) The “jabbing method”, whereby the needle is thrust through the intercartilaginous space with a quick, firm jab to the catheter, while the scope is fixed at the nose or mouth. 2) The “hub against the wall method”, whereby the distal end of the catheter (the metal hub) can be placed directly in contact with the target, with the needle in the retracted position, and held firmly while the needle is pushed out of the catheter for its spontaneous penetration through the

FIGURE 1. Bronchoscopic view of a transbronchial needle aspiration of a subcarinal node.

tracheobronchial wall. 3) The “piggyback method”, whereby, once the needle is advanced and locked in position, the catheter is fixed against the proximal end of the insertion port, using the index finger in a single port scope or the little finger in a dual port scope, to prevent recoil when resistance is met; the bronchoscope and catheter are then pushed forward as a single unit, until the entire needle penetrates the tracheobronchial wall. 4) The “cough method”, named because, while the physician is applying the jabbing or piggyback technique, the patient is asked to give a hard cough to encourage the spontaneous penetration of the needle. All of these techniques can be used alone or in combination to achieve penetration of the needle through the tracheobronchial wall [7, 26].

With the needle inserted, suction is applied at the proximal port using a syringe. Aspiration of blood indicates inadvertent penetration of a blood vessel. In this case, suction is released, the needle is retracted and a new site is selected for aspiration. When there is no blood in the aspirate, the catheter is moved up and down with continuous suction, in an attempt to shear off cells from the mass or lymph node. The needle is withdrawn from the target site after suction is released. The tip of the scope is straightened and the needle assembly is pulled out of the scope in a single, smooth motion [26].

Proper handling of the specimen is a crucial and under-appreciated aspect of the procedure. The specimen for cytology is prepared by using air from a 60-mL syringe to “blow” the specimen out to the slide (smear technique) [5] before smearing it using another slide.

The technique of obtaining a histology specimen *via* TBNA requires use of the 19-gauge needle assembly and is a variation on the technique used to obtain cytology specimens. Once the

TABLE 1 Factors influencing diagnostic yield of transbronchial needle aspiration

Presence of lymph node enlargement on computed tomography scan
Type of needle employed
Site of the tumour and lymph node
Lymph node size
Number of aspirates performed
Availability of rapid on-site cytopathologic examination
Ability and experience of the operators
Nature of the lesion (malignancy, type of malignancy)

metal hub is visible beyond the tip of the fibrebronchoscope, the 19-gauge needle is advanced beyond the metal hub and locked in place. The automatically advanced 21-gauge needle is used to puncture the airway wall and anchored at the target site using any of the techniques previously described. The 21-gauge needle acts as a trocar for the 19-gauge needle and prevents its plugging by bronchial wall tissue. Using a syringe, suction is applied at the proximal port to ascertain the safety of the location. This is followed by the insertion of the 19-gauge needle to its fullest extent. Under continuous suction, the 19-gauge needle is moved up and down, 4–5 times, to obtain a core of tissue [7, 26].

At least two satisfactory core specimens are obtained at each location and multiple passes may be required to increase the diagnostic yield. Rapid on-site evaluation of the specimen by the cytopathologist for sample adequacy has been shown to increase diagnostic yield [7].

Results

The diagnostic yield of TBNA in the assessment of hilar–mediastinal lymph nodes involvement in lung cancer varies greatly in the published literature, from 15%, reported by SHURE and FEDULLO [27], to >85%, obtained by SCHENK *et al.* [17]. Recently, a meta-analysis regarding TBNA for the mediastinal staging for nonsmall cell lung cancer demonstrated that TBNA is highly specific for the identification of mediastinal metastases, whereas the sensitivity depends heavily on the study population under investigation [28]. In studies that included patients with a prevalence of mediastinal metastases of 34%, sensitivity was only 39%, whereas in a population with a prevalence of 81% it was 78%. There are several reasons that explain the wide variety of diagnostic yield of TBNA (table 1).

A higher sensitivity is obtained in patients with established lymph node enlargement on CT. In the study by SHURE and FEDULLO [27], the sensitivity increased from 15 to 38% if only subjects with evidence of lymphadenopathy at CT were considered. UTZ *et al.* [29] reported a positive subcarinal TBNA in 36% out of 88 patients with lung cancer, but this value rose to 43% in the 67 cases with radiographic evidence of mediastinal adenopathy, while it was only 10% in the 21 patients without imaging evidence of subcarinal lymph node enlargement.

It seems that the kind of needle employed can influence the results and that the use of histology needles, introduced by WANG *et al.* [13], can further improve the sensitivity of the

technique. SCHENK *et al.* [16] studied the sensitivity of 22- and 19-gauge needles at identical endotracheal locations in 64 patients, 55 with proven malignant mediastinal adenopathy. The sensitivity of the 19-gauge needle (85.5%) was statistically higher than that of the 22-gauge needle (52.7%; $p<0.0001$). In 20 patients, only the 19-gauge needle was diagnostic, while the 22-gauge needle was exclusively diagnostic in two patients. Overall, the 19-gauge needle correctly identified 47 mediastinal nodal stages in patients, while the 22-gauge needle was diagnostic in only 29 patients. The sensitivity of the combined cytology and histology samples was higher (89.1%) than either individual sampling. In a prospective multi-institutional study conducted in 360 patients, HARROW *et al.* [25] found that needle size influenced the frequency of positive TBNA recovery. Aspirates were positive with a histology needle in 57%, and positive with a cytology needle in 41%.

A further element that can influence the sensitivity of TBNA is the site of the lymph node. For mediastinal and hilar lymph node mapping, the Mountain Dressler classification is used (fig. 2). In a study carried out by PATELLI *et al.* [8] on 194 procedures, the overall sensitivity of the technique in assessing lymph node metastases was 71%, but TBNAs performed in the left paratracheal station, with a sensitivity of 52%, have been significantly less sensitive than those performed in the right paratracheal (sensitivity 84%) or in the subcarinal stations (sensitivity 79%). The higher sensitivity of TBNA reported for cancer located in the right lung in comparison to left lung neoplasms, had already been reported by WANG *et al.* [24], in a study carried out on 39 patients. The overall sensitivity of TBNA was 76%, broken down as 92% for right lung and 56% for left lung tumours. Likewise, HARROW *et al.* [25] found a higher sensitivity in the right-sided tumours than those originating from the left lung, and that right paratracheal and subcarinal lymph nodes aspirates were more likely to provide a positive cytology than left paratracheal TBNA.

In the same study, HARROW *et al.* [25] underline the fact that lymph node size can influence the results of TBNA, showing that tumour-positive aspirates increased linearly from lymph nodes of <1 cm to lymph nodes of 2–2.5 cm. None of the TBNAs performed on lymph nodes of <5 mm were positive, but 15 (15%) out of 103 samples from nodes of 5–9 mm were diagnostic for malignancy. For lymph nodes >2.5 cm, the diagnostic yield did not increase further.

Another factor that may modify the sensitivity of the technique is the number of aspirates performed at each lymph node station. CHIN *et al.* [31], studied the effect of each successive TBNA specimen in 79 patients with (suspected) lung cancer. They reported a tumour-positive aspiration in the initial specimen in 42% of patients and this value rose incrementally with successive aspirates up to 57% at the seventh sample. The increase in yield was small after the fourth needle pass, and no diagnosis of cancer was obtained after the seventh aspirate. The authors recommended the performance of at least four TBNAs for a single node station in order to obtain adequate material, but seven passes will maximise yield [31]. In the same study, the role of rapid on-site cytopathologic examination (ROSE) was examined in relation to the diagnostic yield of TBNA. The results demonstrate that the presence of ROSE was associated with a yield of 71%, which was higher than the

FIGURE 2. Mediastinal and hilar lymph node map for lung cancer staging. Nodes are colour and numerically coded. a) Superior mediastinal nodes (red: highest mediastinal; dark blue/2R: upper paratracheal nodes; orange/4R/4L: lower paratracheal nodes, including azygos nodes); inferior mediastinal nodes (pale blue/7: subcarinal nodes; grey/8: paraoesophageal nodes (below carina); brown/9: pulmonary ligament nodes); and N₁ nodes (yellow/10: hilar nodes; green/11: interlobar nodes; pink/12, 13, 14L/12, 13, 14R: lobar, segmental and subsegmental nodes). b) Superior mediastinal nodes (dark pink/3: pre-vascular and retrotracheal nodes); and aortic nodes (black/5: subaortic nodes; dark red/6: para-aortic (ascending aorta or phrenic) nodes). Ao: aorta; PA: pulmonary artery. Reproduced with permission from [30].

value obtained if ROSE was absent (25%). That ROSE improved the results of TBNA had already been demonstrated by DAVENPORT [32], who found a significant increase in the percentage of specimens containing malignant cells in 73 aspirates performed using ROSE in comparison with 134 routinely processed TBNAs (56 *versus* 31%). In the same way, DIETTE *et al.* [33], in a study including 204 bronchoscopies where not only TBNA but also the results of bronchial and transbronchial biopsies and brushing were evaluated, obtained a better yield when ROSE was used (81 *versus* 50% without ROSE).

Perhaps the most important factor that can influence the results of TBNA is the ability and the experience of the operators. HAPONIK and STURE [22] demonstrated that the diagnostic yield on TBNA performed by 14 bronchoscopists increased from 21.4 to 47.6% during a 3-yr period of training and of educational intervention. DE CASTRO *et al.* [34] reported that the diagnostic yield of an expert bronchoscopist was 77%, while the yield of a pulmonologist without specific experience on TBNA was 23.5%. This value rose to 78% after a training of 24 months. The role of experience in performing TBNA is also supported by the analysis of the results of more recent studies, which consistently report sensitivities of TBNA >70% [8, 25].

In addition to lung cancer staging, TBNA can be used for diagnostic purposes, in lung cancer and other pathological conditions of the hilar–mediastinal area. In the study by HARROW *et al.* [25], TBNA was exclusively diagnostic of carcinoma in 65 (18%) out of 360 patients. In a study conducted to determine the diagnostic yield of TBNA in 166 patients with mediastinal lesions, SHARAFKHANEH *et al.* [35] obtained a diagnosis in 104 patients (61%) and in 69% of patients with malignancies. In this study, the TBNA yield was higher for malignant lesions when compared with benign disease; among malignancy, it was higher for small cell carcinoma (87%). The lowest yield among malignancy was for lymphoma (50%), while the best results among benign conditions were obtained for sarcoidosis (63%) [35]. CETINKAYA *et al.* [36], studying 60 patients with mediastinal lymphadenopathy, were able to make a diagnosis in 45 (75%). TBNA was the only diagnostic tool in 30 (50%), including patients with carcinoma, tuberculosis, lymphoma and carcinoma.

The possibility of diagnosing sarcoidosis with TBNA was already known before the introduction of flexible needles. Using a rigid needle through a rigid bronchoscope, PAULI *et al.* [20] obtained a diagnosis in 66.3% out of 258 patients with suspected sarcoidosis. In a series of 59 patients with undiagnosed mediastinal lymph adenopathy, KELLY and WANG [37] reported a diagnosis of sarcoidosis with a flexible needle in 17 patients. With the use of the histology needle, the sensitivity of TBNA for the diagnosis of sarcoidosis may increase up to 90% [38]. In a study on 51 patients with suspected sarcoidosis, MORALES *et al.* [39] reported that the addition of TBNA to the lung biopsy increased the diagnostic yield from 60 to 83% for stage I and from 76 to 86% for stage II sarcoidosis. TBNA seems to provide a better yield in stage I sarcoidosis (53–90%) than in stage II (42–50%) [40]. BILACEROGLU [41] studied 74 patients, all suspected of having sarcoidosis, and found that TBNA had sensitivities of 61 and 42% in stage I and II disease, respectively. TRISOLINI *et al.* [42],

in a study conducted on 55 patients with hilar–mediastinal adenopathy (32 of whom were proven to have stage I sarcoidosis), obtained a positive TBNA in 23 (72%) and reported that in the patients who underwent TBNA and transbronchial lung biopsy, the yield of TBNA (73%) exceeded that of lung biopsy (40%).

A number of hilar–mediastinal pathological processes besides sarcoidosis have been identified using TBNA. The following diseases have been assessed by TBNA: tuberculous adenitis [43]; lymphoma [35, 36]; post-transplantation lymphoproliferative disorder [44]; thymoma [45]; and carcinoid [46] metastases from nonlung cancer diseases [4]. The specificity of the technique is very high (96–100%) [40, 46], although false-positive results have been reported [47, 48]. To reduce this risk, TBNA of hilar–mediastinal lymph nodes should be performed following some precautions, such as always sampling the lymph nodes before the bronchial lesion (in order to avoid the possible contamination of the main bronchi or trachea with cellular material from the more distal airways) and avoiding puncturing an area where the mucosa is involved by the pathological process [43].

Complications

The numerous papers on TBNA confirm the safety of the procedure. No cases of mortality related to TBNA have been described. The rare complications reported are pneumothorax [24], pneumomediastinum [25, 15], haemomediastinum [49], bacteraemia [50] and pericarditis [51]. None of these complications determined major clinical consequences. The cases of haemomediastinum [49, 51], one caused by histology needle [49], showed spontaneous resolution of the mediastinal haematoma after 1 week. One of the major complications of TBNA is the possible severe damage to the working channel of the scope [18]. This is more frequent with nonretractable needles (that should no longer be available) and can be avoided if the operator takes care in introducing and extracting the needle from the bronchoscope with the tip completely retracted in the sheath.

Use of TBNA in clinical practice

Despite the impact of TBNA on patient management, surveys demonstrate that only 10–30% of pulmonologists regularly use TBNA [22, 52]. The main reasons for the limited use of TBNA are lack of needle monitoring [53], difficulties in performing the procedure and a belief, despite the evidence in the literature, that TBNA is not useful [52]. Training in TBNA is urgently advocated as it will optimise the care of patients with lung cancer [54].

ENDOBONCHIAL ULTRASOUND

The integration of ultrasound technology and flexible fibrebronchoscopy enables imaging of lymph nodes, lesions and vessels located beyond the tracheobronchial mucosa. In this section, different types of endobronchial ultrasound (EBUS) probes are discussed, as well as indications and results regarding mediastinal lymph node staging.

EBUS mini-probe: radial scanning

Equipment and procedure

The first available EBUS application was the radial endobronchial ultrasound (EBUS) probe (the so-called mini-probe). An

ultrasound transducer with a frequency of 20 MHz is positioned at the tip of the probe (fig. 3). The probe is conventionally inserted through the working channel of a flexible bronchoscope [55, 56]. The probe is positioned near the target area, where a balloon surrounding the probe has to be inflated with water in order to ensure coupling with the airway wall and transmission of the ultrasound waves (fig. 3). EBUS images detail the airway wall as well as parabronchial structures such as lymph nodes (fig. 4) and vessels. Once a target lymph node is identified, the transducer is removed and a needle is inserted through the working channel to obtain a sample [57, 58]. Consequently, the actual TBNA procedure is performed without real-time needle monitoring.

Indications and results

Several studies have been conducted using EBUS for the localisation of mediastinal nodes. In a prospective study of 242 patients with enlarged mediastinal nodes (mean diameter 1.7 cm) at chest CT, all target nodes could be identified by EBUS, independently of size or location. Adequate samples were obtained in 86% of cases and malignant lymph node involvement was assessed in 72% of cases [58]. A large (n=200) randomised trial, between conventional TBNA and TBNA after EBUS localisation, for mediastinal staging of enlarged nodes demonstrated that EBUS guidance significantly increased the yield of TBNA in all stations (84 *versus* 58%), except in the subcarinal region (86 *versus* 74%) [59].

Real-time EBUS-TBNA: linear scanning

Equipment and procedure

An ultrasound transducer integrated into a bronchoscope with a separate working channel would potentially increase the yield of TBNA by allowing real-time needle monitoring within the area of interest. Recently, such a linear or longitudinal EBUS scope has been developed (BF-UC160F-OL8; Olympus Medical Systems, Tokyo, Japan; fig. 5). The scope has an outward diameter of 6.9 mm, a 35-degree forward oblique

FIGURE 3. Endobronchial ultrasound mini-probe (Olympus UM-2R/3R; Olympus Medical Systems, Tokyo, Japan) demonstrating the ultrasound probe with a 20 MHz transducer (a). The mini-probe is inserted in the working channel of a fibrebronchoscope and the balloon on the tip is inflated with water to achieve coupling with the airways (b).

FIGURE 4. Radial endobronchial ultrasound image demonstrating a hypoechoic lymph node adjacent to the ultrasound transducer that is located in the anechoic space of the water-filled balloon.

optic, a 2.0 mm working channel and a 7.5 MHz curved linear array ultrasound scanner. EBUS-TBNA can be performed in an ambulatory setting under conscious sedation using midazolam [60, 61]. Although a balloon option is available, its use is seldom necessary for the visualisation of mediastinal nodes. The actual TBNA is performed by direct transducer contact with the wall of the trachea or bronchus. When a lesion is outlined, a 22-gauge full-length steel needle is introduced through the biopsy channel of the endoscope. Power Doppler examination may be performed before the biopsy to avoid unintended puncture of vessels. Under real-time ultrasonic guidance, the needle is placed in the lesion (fig. 6). Suction is applied with a syringe, and the needle is moved back and forth inside the lesion.

FIGURE 5. Linear real-time endobronchial ultrasound-guided transbronchial needle aspiration scope (BF-UC160F-OL8; Olympus Medical Systems, Tokyo, Japan).

FIGURE 6. a) Computed tomogram demonstrating a lymph node located paratracheal to the right (station 4R).

Indications and results

Mediastinal and hilar (fig. 7) nodal staging is the main indication for EBUS-TBNA. Additionally, intrapulmonary tumours located adjacent to the main bronchi can be aspirated [62]. KRASNIK *et al.* [62] reported on 11 patients in whom 15 lesions were punctured in the following regions: 10L (n=4), 10R (n=4), 4L (n=1), 4R (n=3), 1 (n=1), 7 (n=1) and 2R (n=1). Biopsies obtained through EBUS-TBNA showed malignant cells in 13 lesions and benign cells in two. YASUFUKU *et al.* [60] investigated 70 patients with suspected lung cancer and enlarged mediastinal (n=58) or hilar (n=12) nodes with EBUS-TBNA. The sensitivity, specificity and accuracy of EBUS-TBNA in distinguishing benign from malignant lymph nodes were 96, 100 and 97%, respectively. In a subsequent study from the same group, in 108 patients with (suspected) lung cancer and enlarged mediastinal nodes on CT, EBUS-TBNA had a sensitivity of 95%, specificity of 100% and accuracy of 96% in assessing mediastinal nodes [61]. EBUS-TBNA had a considerable impact on patient management as 29 mediastinoscopies, four video-assisted thoracic surgery (VATS) procedures, eight thoracotomies and nine CT-guided lung biopsies were prevented due to EBUS-TBNA findings [61]. In the largest study to date, by HERTH *et al.* [63], real-time EBUS-TBNA was performed in 502 patients with (suspected) lung cancer and enlarged mediastinal nodes on chest CT. A total of 572 lymph nodes were punctured and 535 (94%) resulted in a diagnosis. Biopsies were taken from all reachable lymph node stations (2L, 2R, 3, 4R, 4L, 7, 10R, 10L, 11R and 11L) and had a mean (range) diameter of 1.6 (0.8–3.2) cm. In this large series, a sensitivity of 94% and a specificity of 100% for mediastinal staging was reported. In contrast to all prior studies, which were performed in selected patients with enlarged mediastinal nodes on chest CT, EBUS-TBNA was evaluated in a prospective study in 100 patients with nonsmall

FIGURE 7. Patient with an adenocarcinoma and an enlarged lymph node at the left hilum (station 10L). a) Bronchoscopic view of the carina between the left upper and lower lobes in the left hilar region. b) Computed tomography scan demonstrating lymph node station 10L. c) Position of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) scope in the left main bronchus. d) EBUS-TBNA of the hilar node with the needle clearly visible.

cell lung cancer without enlarged nodes at chest CT. Surgical verification was performed in all patients. In assessing mediastinal nodal status, EBUS-TBNA had a sensitivity of 92% a specificity of 100% and a negative predictive value of 96% [64].

To date, no complications have been reported in EBUS-TBNA studies. Results so far indicate that real-time EBUS-TBNA is a safe and accurate method (table 2) for the mediastinal staging in patients with (suspected) lung cancer.

TRANSESOPHAGEAL ULTRASOUND-GUIDED FINE NEEDLE ASPIRATION

Initially designed for the staging of gastrointestinal malignancies, transoesophageal ultrasound-guided fine needle aspiration (EUS-FNA) has proven to be an accurate diagnostic method for the diagnosis and staging of lung cancer and the assessment of sarcoidosis [65]. Lymph nodes in the following areas can be detected by EUS: paratracheally to the left (station 4L); the aortopulmonary window (station 5); lateral to the aorta (station 6); in the subcarinal space (station 7); adjacent to the lower oesophagus (station 8); and near the pulmonary ligament (station 9) [66]. Although clearly visible with EUS, part of the nodes located in the aortopulmonary window and those located adjacent to the aorta cannot be aspirated due to the position of pulmonary artery and aorta. Upper paratracheal nodes (station 2) and those located in the lower paratracheal region to the right (station 4R) often cannot be assessed by EUS owing to the presence of air between the ultrasound transducer and area of interest.

Ultrasound features that predispose for malignant nodal involvement are a hypoechoic core, sharp edges, a round shape and a short axis diameter >10 mm. Sonographic signs of

TABLE 2 Results of real-time endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal lymph node staging in patients with (suspected) lung cancer

First author [Ref.]	Year	Patients	Sensitivity	Specificity	Accuracy	PPV	NPV
YASUFUKU [60]	2004	70	96	100	97	100	92
YASUFUKU [61]	2005	108	95	100	96	100	90
HERTH [63]	2006	502	94	100	94	100	
HERTH [#] [64]	2006	100	92	100		100	96

Data are presented as n or %. PPV: positive predictive value; NPV: negative predictive value. [#]: lymph nodes, short axis <1 cm.

benignancy are a hyperechoic core (fat), central calcification (old granulomatous disease), ill-defined edges and an elongated oval shape [67]. Regarding lymph node staging, it has been demonstrated that ultrasound features are not as accurate as aspirates [3] and therefore aspirates are needed. During EUS-FNA, the needle is passed through the working channel of the endoscope, through the oesophageal wall and guided ultrasonographically toward the lesion of interest in the mediastinum. Lymph nodes as small as 5 mm can be aspirated [68].

Equipment and procedure

For the analysis of mediastinal lesions, tissue sampling is essential. Linear and not radial ultrasound equipment is needed. Curved linear array ultrasound transducers (fig. 8) are available from various companies and typically scan with a frequency of 7.5 MHz (range 5–10 MHz). EUS-FNA is usually performed under local anaesthesia and conscious sedation using midazolam. It is important to perform EUS-FNA in a standardised fashion in order to visualise all mediastinal regions that can be detected from the oesophagus [66]. The echo-endoscope is initially introduced up to the level of the coeliac axis and gradually withdrawn upwards for a detailed mediastinal imaging. Since the ultrasound waves are emitted parallel to the long axis of the endoscope, the entire needle can be visualised approaching a target in the sector-shaped sound field. Pulse and colour Doppler ultrasonography imaging can be performed in cases of suspected vascular structures (fig. 9). For the aspirations, 22-gauge needles are standard, although smaller (25-gauge) and larger needles (19-gauge) can be used as well. Aspirations occur under real-time ultrasound control, by advancing the needle through the oesophageal wall into the target lesion (fig. 10). After removal of the stylet, the needle is moved back and forth within target lesions. Most investigators use suction, although its added benefit in terms of diagnostic yield is still the subject of debate [69]. In the absence of on-site cytology, at least four needle passes are required for optimal yield [70]. EUS-FNA is contraindicated in patients with a Zenker's diverticulum, or bleeding tendency.

FIGURE 8. Linear transoesophageal ultrasound-guided fine needle aspiration scope (GF-UC140P; Olympus Medical Systems, Tokyo, Japan).

Indications and results

The diagnosis and mediastinal staging of lung cancer is by far the most common indication for EUS-FNA in pulmonary medicine. For mediastinal staging, most studies have been performed in selected patients with enlarged or PET positive nodes. Sensitivity (range 72–100%), specificity (range 88–100%), negative predictive value (range 39–100%) and accuracy (77–100%) have been reported (table 3). In the three studies performed in patients without enlarged nodes, sensitivities between 35 and 61% and accuracies between 76 and 89% regarding mediastinal staging are reported [81, 82, 87]. The decreased accuracy in small nodes may be due to sampling

FIGURE 9. Transoesophageal ultrasound scan demonstrating lymph nodes at station 4L (LN1) and station 5 (LN2). Notice the aorta (Ao) with colour Doppler signal and the pulmonary artery (PA). Es: oesophagus.

FIGURE 10. A small lymph node (LN) located paratracheal to the left. a) Computed tomography of the node. b) Transoesophageal ultrasound-guided fine needle aspiration of the node. Notice the node's close relation to both the trachea and the oesophagus (Es). N: needle; PA: pulmonary artery.

error, technical difficulty in sampling small nodes or the fact that nodes with a normal sonographic appearance are just not biopsied [88]. EUS-FNA has been suggested as a restaging method after induction chemoradiotherapy, for which accuracies of 83% and 86% were reported [89, 90].

EUS-FNA provides a minimally invasive alternative for surgical staging as it can prevent ~70% of scheduled mediastinoscopies [76, 85, 86]. Thanks to its complementary diagnostic reach, the addition of EUS to mediastinoscopy improves staging [83] and, therefore, reduces the number of futile thoracotomies [91].

EUS-FNA has a yield of 82% [92–94] in assessing granulomas in patients with suspected sarcoidosis. Patients with sarcoidosis often present with multiple, clustered, well-demarcated nodes [92] that are frequently well vascularised [93]. EUS-FNA provides an alternative to bronchoscopy and peripheral lung biopsies (including a risk of haemoptysis and pneumothorax) should be performed where available prior to a mediastinoscopy. EUS-FNA can also be used for the mediastinal staging for extrathoracic tumours, for instance for suspected

TABLE 3 Results of real-time transoesophageal ultrasound-guided fine needle aspiration in mediastinal lymph node staging in patients with (suspected) lung cancer

First author [Ref.]	Year	Patients	Sensitivity	Specificity	PPV	NPV	Accuracy
SILVESTRI [71]	1996	27	89	100	100	82	93
GRESS [72]	1997	24	93	100	100	90	96
WILLIAMS [73]	1999	82	87	100	100	73	90
FRITSCHER-RAVENS [67]	2000	153	92	100	100	92	95
WALLACE [74]	2001	107	87	100	100	68	90
WIERSEMA [75]	2001	33	100	88	96	100	97
LARSEN [76]	2002	79	92	100	100	80	94
FRITSCHER-RAVENS [77]	2003	33	88	100	100	89	91
ANNEMA [78]	2004	36	93	100	100	80	94
KRAMER [79]	2004	81	72	100	100	39	77
SAVIDES [80]	2004	59	96	100	100	97	98
WALLACE [81]	2004	69 [#]	61	98	94	79	83
LEBLANC [82]	2004	72 [#]	35	100	100	73	76
ANNEMA [83]	2005	100	76	97	92	91	91
ELOUBEIDI [84]	2005	93	93	100	100	96	97
ANNEMA [85]	2005	215	91	100	100	74	93
TOURNOY [86]	2005	67	100	100	100	100	100
FERNANDEZ-ESPARRACH [87]	2006	47 [#]	50	100	100	88	89

Data are presented as n or %. PPV: positive predictive value; NPV: negative predictive value. [#]: lymph nodes, short axis <1 cm.

mediastinal metastases of mammarian or renal carcinoma [95]. Bronchogenic and paraoesophageal cysts can be visualised well by EUS [96]. EUS-FNA of mediastinal nodes is considered safe, as no serious complications have been reported. FNA of acystic mediastinal lesions, however, should be avoided, owing to the risk of mediastinitis [96, 97].

CLINICAL CONSIDERATIONS

How will the recent clinical availability of EBUS-TBNA and EUS-FNA affect clinical practice? Despite the advancement in imaging methods such as PET-CT, tissue sampling of mediastinal nodes will often be indicated to confirm or exclude mediastinal malignancy. In the current authors' opinion, conventional TBNA is a standard procedure (just like taking biopsies of endobronchial lesions), which should be part of a routine bronchoscopic investigation. In each patient with suspected lung cancer and enlarged mediastinal nodes at chest CT who is referred for bronchoscopic evaluation, a TBNA of the suspected nodes should be considered as it affects patient management to a large extent, provided mediastinal metastases are assessed.

For tissue sampling of mediastinal lymph nodes after conventional TBNA, the present authors prefer minimally invasive methods such as EBUS-TBNA and EUS-FNA to more invasive procedures such as mediastinoscopy and VATS. EUS-FNA [76, 85] and EBUS-TBNA [61] have been shown to prevent mediastinoscopies to a large extent. EBUS-TBNA and EUS-FNA have a complementary reach [98, 99] in analysing mediastinal nodes whereby EBUS has access to the paratracheal, subcarinal and hilar regions and EUS to the lower mediastinum and aortopulmonary window. Preliminary results indicate that, by combining of EUS-FNA and EBUS-TBNA, an accuracy >95% for mediastinal staging can be

obtained [99]. Although the concept of complete and accurate mediastinal staging is tempting, more studies are needed to confirm these initial findings.

WORKING RECOMMENDATIONS

In each patient with suspected lung cancer and enlarged mediastinal nodes who is referred for a bronchoscopic evaluation, conventional TBNA of enlarged lymph nodes should be undertaken as it has a large impact on patient management in case mediastinal metastases are confirmed.

In each patient that is a candidate for mediastinoscopy either EUS-FNA or EBUS-TBNA should be considered as an accurate, safe and minimally invasive alternative.

CONCLUSION

Transbronchial needle aspiration of mediastinal lymph nodes should be regarded as a routine procedure in conventional bronchoscopy. The novel diagnostic methods of endobronchial ultrasound-guided transbronchial needle aspiration and transoesophageal ultrasound-guided fine needle aspiration enable ultrasound-controlled mediastinal tissue sampling. Beyond doubt, implementation of these techniques will drastically alter lung cancer staging algorithms in the near future. Thanks to its minimally invasive approach, safety record, accuracy and diagnostic reach, complete ambulant endoscopic staging of lung cancer might be the future.

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