Review Article

Convex-probe Endobronchial Ultrasound: A Decade of Progress

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Abstract

Ever since the invention of the flexible bronchoscope, perhaps no other innovation in the field of interventional pulmonology has caused so much excitement the world over, as the convex probe endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA). While it took over a decade from 1992 to 2004 for the radial EBUS to evolve into the commercial convex probe EBUS scope, another exciting decade has gone by with the technology being thoroughly researched and appraised. The current evidence suggests that EBUS-TBNA can replace mediastinoscopy as the first investigation in the mediastinal staging of lung cancer. The use of EBUS-TBNA has been extended to several other areas including the diagnosis of undefined mediastinal lymphadenopathy, evaluation of intra-parenchymal lesions and others. In fact, EBUS-TBNA is the preferred modality for accessing mediastinal lesions in contact with the airways. The procedure not only has a high diagnostic efficiency (80%-90% for most indications) but is also safe compared to alternative options, such as image-guided fine needle aspiration and mediastinoscopy in the diagnosis of mediastinal lymphadenopathy. Apart from the traditional use of EBUS to perform TBNA, the last decade has seen the evolution of its transoesophageal use, development of novel EBUS-TBNA needles to obtain better histological specimens and a smaller EBUS scope. This review summarises the developments made in this field over the years since its inception. **[Indian J Chest Dis Allied Sci 2016;58:21-35]**

Key words: Lung cancer; Bronchoscopy; EBUS-TBNA; Airways; Lymphadenopathy; Mediastinal staging.

Introduction

Mediastinal and/or hilar lymphadenopathy is a common problem encountered in clinical practice.[1] The common causes for intra-thoracic lymphadenopathy include malignant conditions such as lung cancer and lymphoma, and benign causes such as tuberculosis and sarcoidosis. An accurate diagnosis of these conditions requires sampling of the intra-thoracic lymph nodes.[2] The usual modalities for diagnosing mediastinal lymphadenopathy include conventional transbronchial needle aspiration (TBNA), computed tomography (CT)-guided transthoracic fine needle aspiration (FNA) and surgical techniques including mediastinoscopy. Conventional TBNA is associated with a variable yield ranging from 17%-61% and 6%-90% in mediastinal staging of lung cancer and diagnosis of sarcoidosis, respectively.[3-5] The CT-guided transthoracic FNA can access virtually all mediastinal nodal stations, and can provide a yield as high as 80%.[6] However, there is a very high chance (about 60%) of pneumothorax when the lung parenchyma is traversed, a situation that is fairly common while accessing mediastinal or hilar lymph nodes.[6] Mediastinoscopy is considered as the reference standard for the evaluation of mediastinal adenopathy. However, not only one is unable to access all the lymph node stations (stations 5, 6, 8, 10, 11) but also the procedure requires general anesthesia and may be associated with procedural morbidity and mortality.[7,8] The discovery of endobronchial ultrasound (EBUS) has revolutionised the field of bronchoscopy because it provides 'eyes' to the bronchoscopist for visualising the mediastinum as well as extends his view to peripheral pulmonary lesions that are not seen with the conventional bronchoscope.

The use of EBUS was first described by Hurter and Hanrath in 1992.[9] Broadly, EBUS can be classified into the radial probe EBUS and the convex probe EBUS. The radial probe EBUS is an ultrasound catheter that can be passed through the working channel of the flexible bronchoscope. The catheter has a miniature ultrasound transducer at its tip; the transducer rotates and produces a 360-degree circular image around the central position of the probe. There are two types of radial EBUS probes, namely, the peripheral probes that are used for localising peripheral pulmonary lesions and the central probes, which have balloon sheaths, and are mainly used for the assessment of airway walls and identification of peribronchial lymph nodes.[10] On the other hand, the convex probe EBUS is a flexible bronchoscope with a convex ultrasound probe

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at its distal end that enables sampling of lymph nodes adjacent to the airways under real-time ultrasound guidance. The EBUS-TBNA, as compared to conventional TBNA, allows direct visualisation of the target lesion, and because the nodes can be visualised in real-time, it enables sampling of smaller nodes, thereby improving the diagnostic sensitivity. More than a decade has elapsed since the publication of the first report of EBUS-TBNA.[11] In this review, we summarise the current concepts on the use of convex probe EBUS-TBNA in the diagnosis of mediastinal lesions.

Indications

The convex probe EBUS-TBNA is commonly used for the following indications: (i) mediastinal staging of lung cancer; (ii) diagnosis of mediastinal lymphadenopathy of undefined aetiology; (iii) investigation of suspected granulomatous lymphadenitis including tuberculosis and sarcoidosis; and (iv) diagnosis of peri-bronchial and para-oesophageal lung masses. The use of convex probe EBUS has also been described in the following situations: (i) diagnosis and treatment of endotracheal and mediastinal bronchogenic cysts; (ii) diagnosis of pulmonary embolism, thromboembolic as well as tumour; (iii) fiducial placement for malignant central lung lesions; and (iv) transbronchial needle injection of chemotherapeutic agents for the local control of recurrent non-small cell lung carcinoma (NSCLC).

Equipment

The equipment comprises of a dedicated ultrasound bronchoscope (also called echobronchoscope or EBUS scope), an ultrasound processing system, a video processor and a light source.[12] The EBUS scope used at our center, the Olympus BF-UC180F (Olympus Medical Systems, Japan) has been chosen as a reference to elucidate the features of the ultrasound bronchoscope in the subsequent discussion. The other echo-bronchoscopes available in the market have similar features with a few variations (Table 1).

The echobronchoscope consists of a control section (the handle) and an insertion tube with an ultrasound transducer at the tip, placed ahead of the camera and light source (Figure 1). The Olympus scope is a hybrid fibre-videoscope that has image guide fibers in the insertion tube, which transmit the image to a charge-coupled device placed inside the control section. The diameter of the insertion tube is larger (6.9 mm at the tip and 6.2 mm in the rest of the length) than the commonly used 'therapeutic' bronchoscopes (for comparison, the Olympus BF-1T180 has a maximum outer diameter of

Table 1. Characteristics of various echobronchoscopes available for clinical use.

	Olympus BF-UC180F		**Pentax EB-1970UK**	**Fujifilm EB-530US**
Endoscopic system	Hybrid (fiberoptic image guide bundles with CCD in control section)		Video (CCD in the tip)	Video (CCD in the tip)
Distal end outer diameter	6.9 mm		7.4 mm	6.7 mm
Insertion tube diameter	6.2 mm		6.3 mm	6.3 mm
Channel inner diameter	2.2 mm		2.0 mm	2.0 mm
Working length	600 mm		600 mm	610 mm
Field of view	80°		100°	120°
Direction of view	35° forward oblique		45° forward oblique	10° forward oblique
Depth of field	2-50 mm		2-50 mm	3-100 mm
Angulation range	Up 120°, down 90°		Up 120°, down 90°	Up 130°, down 90°
Ultrasound Processor	**EU-ME1**	**EU-ME2**		**SU-8000**
Frequency	5, 6, 7.5, 10, 12 MHz	5, 6, 7.5, 10, 12 MHz	5-10 MHz	5, 7.5, 10, 12 MHz
Scanning range	60°	60°	75°	65°
Display range	2,3,4,5,6,7,8,9,12 cm	2,3,4,5,6,7,8,9,12 cm		
Scanning mode	B mode/Colour Doppler/ Power Doppler	B mode/Pulse wave Doppler/High resolution flow/Tissue harmonic echo/Elastography	B mode/Pulse wave Doppler/High resolution flow/Tissue harmonic echo/Elastography	B mode/M mode/ Colour Doppler/ Power Doppler/ Pulse wave Doppler
Compatible Needle*	Olympus NA-201SX-4021/4022 (21G and 22G) needles, Mediglobe SonoTip, Cook EchoTip		Mediglobe SonoTip, Cook EchoTip	Olympus NA-201SX-4021/4022 (21G and 22G) needles, Mediglobe SonoTip, Cook EchoTip

*May require additional adaptors for compatibility

Definition of abbreviations: CCD=Charge-coupled device

6.0 mm). The scope has a 35° anterior viewing angle (as compared to 0° for the usual flexible bronchoscopes) and 80° field of vision.

Due to this viewing angle, the maneuvering of the scope in the tracheobronchial tree has been described as akin to moving in a narrow tunnel while lying on one's back and looking up and ahead.[12] The scope tip offers a 120° anterior and 90° posterior flexion, which makes it difficult to maneuver the scope into the upper lobes. The compatible ultrasound processor (EU-ME1, Olympus Medical Systems, Japan) works at a frequency of 5-15 MHz and offers a scanning depth of up to 12 cm and a scanning range of 60°. A disposable latex balloon can be placed over the transducer and can be inflated with normal saline through a special balloon channel housed inside the scope. The ultrasound transducer should be in perfect contact with the airway wall to provide an echo-free window for the transmission of the ultrasonic waves. The balloon over the transducer may be filled with saline to provide better coupling. There is a single suction-cum-instrumentation channel (2.2 mm diameter), that allows the entry of the aspiration needle.

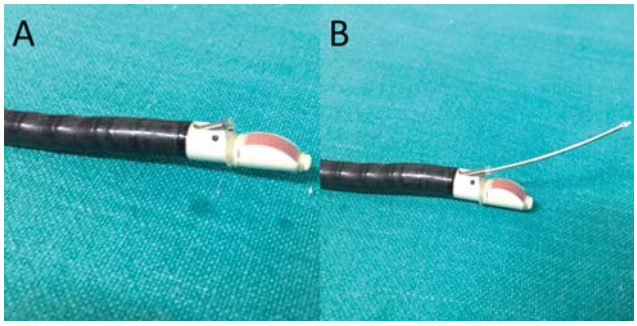

Figure 1. The endobronchial ultrasound bronchoscope is a flexible bronchoscope with a convex ultrasound transducer at its tip (Panel A). The needle can be passed through the working channel of the echobronchoscope and exits at an angle of 30 degrees (Panel B).

A dedicated EBUS-TBNA needle with a 21- or 22-gauge (Vizishot, NA-201 SX-4021A or NA-201 SX-4022A; Olympus Medical, Japan) is recommended for use with the EBUS scope, although other needles may also be used (Table 2). The assembly has a safety lock, a sheath lock and a needle lock. The safety lock fixes the assembly to the working channel port. The sheath lock allows adjusting and fixing of the length of the sheath. The needle lock allows fixing of the working length of the 4-cm long puncture needle located at the tip. There is a stylet at the most proximal end of the needle assembly, which is used for pushing out the bronchial and cartilaginous tissue from the needle bore at the time of puncturing, and the tissue core or blood clot obtained during aspiration. The needle comes out of the instrumentation channel outlet at the distal end at an angle of 30° (Figure 1).

Procedure

We use the Olympus EBUS scope with a compatible endoscopic ultrasound unit (EU-ME1; Olympus Medical Systems, Japan) to perform EBUS-TBNA. The procedure can be performed either under moderate sedation or general anesthesia as an out-patient or a day-care procedure. Deep sedation or general anesthesia is preferred while performing EBUS-TBNA for lung cancer staging, as the procedure is likely to be prolonged.[13] At our center, the procedure is performed on an out-patient basis under moderate to deep sedation.[14] All patients receive nebulised lignocaine (4% solution, 2.5 mL) immediately before the procedure, coupled with injection of 0.6 mg atropine and 25 mg promethazine intramuscularly. Intravenous midazolam and pentazocine are used as agents for sedation and analgesia, respectively. Topical 10% lignocaine spray is squirted in the oropharynx augmented with 'spray-as-you-go' 1% lignocaine over the vocal cords and the airways.[15] The procedure is performed in the supine position via the oral route. The external diameter of the EBUS scope is 6.9 mm, which is significantly larger than that of the usual flexible bronchoscope, and thus, the procedure is not comfortable transnasally. As the scope has an anterior oblique viewing angle, it takes about 5-10 procedures to get acclimatised. While intubating the trachea, the scope is positioned such that the anterior commissure of the vocal cords is seen in the lower quadrant of the endoscopic view

Table 2. Comparison of various EBUS-TBNA needles available for use with the EBUS scopes.

	Olympus Vizishot	Cook EchoTipProCore	Medi-Globe SonoTip II Standard and Flex (SonoTip EBUS Pro and Pro Flex)
Needle gauge	21G and 22G	21G and 25G	22G
Minimum channel inner diameter needed	2.0 mm	2.0 mm	2.0 mm
Needle length	4 cm	5 cm	4 cm
Additional feature		Core trap (bibevel design) to capture a histological sample	Flex version is a dimensionally stable nitinol needle that resists deformation

Definition of abbreviations: EBUS-TBNA=Endobronchial ultrasound-guided transbronchial needle aspiration

facilitating easy entry into the trachea with a slight retroflexion (Figure 2). After a quick airway inspection, the EBUS scope is positioned at the approximate location of the target lymph node, guided by the CT of the thorax. The EBUS scope is then anteflexed to make contact with the airway wall. Subtle back and forth

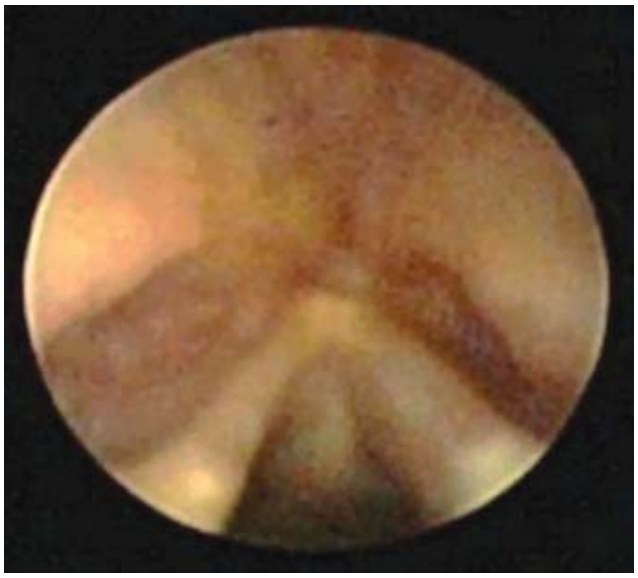

Figure 2. Endoscopic view while intubating the trachea with the echobronchoscope. Due to the presence of optics at a 35 degrees anterior viewing angle, the scope has to be positioned such that the anterior commissure is at the lower quadrant of the endoscopic field of vision.

movements of the scope are made while also rotating it from side to side in order to identify the best ultrasound view of the lymph node. If a good image cannot be obtained, the balloon surrounding the ultrasound transducer is inflated with 0.25-0.5 mL of normal saline to facilitate coupling. In the ultrasound image, lymph nodes appear grey while the blood vessels appear black. Further differentiation can easily be made using the colour Doppler mode. The dimensions of the lymph nodes are documented by measuring the diameter of the nodes on EBUS along an axis perpendicular to that of the airway, once the best view of the node is identified.[16] The TBNA specimens are obtained using a dedicated, disposable, 21- or 22-gauge, Vizishot needle (NA-201SX-4021 or NA-201SX-4022, Olympus Medical Systems, Japan), using the "jabbing" method under real-time ultrasound control (Figure 3). Continuous suction is applied with a dedicated 20mL syringe (VACLOK syringe) while the catheter is moved back and forth for up to a maximum of 20 times. In general, three aspirates are obtained from each lymph node. Aspirated material is sent for cytological examination and microbiological analysis including stain for acid-fast bacilli, mycobacterial cultures and Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA). We use the same needle for obtaining samples from all stations. For a procedure performed only for a diagnostic purpose, the largest lymph

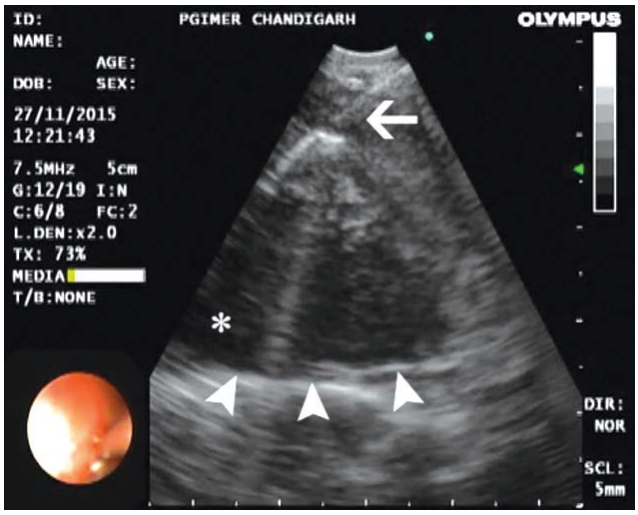

Figure 3. Endosonographic and bronchoscopic (inset) view of the EBUS-TBNA needle traversing the subcarinal lymph node. The border of the lymph node is demarcated by arrow heads. There is large hypoechoic area in the lymph node (asterisk) and the needle can be see entering the necrotic area (arrow). The aspirate was frank pus; the stain for acid-fast bacilli and Xpert MTB/RIF was positive.

***Definitions of abbreviations*: EBUS-TBNA=Endobronchial ultrasound-transbronchial needle aspiration; MTB=*Mycobacterium tuberculosis*; RIF=Rifampicin.**

nodes are accessed first. In general, we perform TBNA of the largest-sized lymph nodes from at least three stations in patients with multi-station involvement.

The use of rapid on-site cytological examination (ROSE) has been shown to reduce the number of lymph node passes without a reduction in procedural yield in some,[17-20] but not all studies.[21] It can significantly shorten the duration of the procedure as the procedure can be terminated once the diagnosis is achieved. We do not perform ROSE at our centre due to logistics (requirement of cytologist/technician at the bronchoscopy suite). However, it may be employed at centres, where it is feasible.

The EBUS scope can also be used to perform the transoesophageal endoscopic ultrasound (EUS) fine needle aspiration, a procedure termed as EUS with an echobronchoscope guided FNA (EUS-B-FNA).[22] The EUS-B-FNA is performed in the supine position by introducing the EBUS scope into the oesophagus. For this, the echobronchoscope is inserted orally and gently negotiated posterior to the larynx. It is then turned 180° to face the posterior pharyngeal wall, and advanced into the oesophagus. Subsequent manipulation of the bronchoscope is performed using vascular landmarks as there is limited endoluminal visualisation due to the collapsed oesophagus. The scope is pushed distally and at about 40-42 cm from the incisor teeth, the left lobe of the liver is visualised anteriorly. The bronchoscope is then rotated 180° anti-clockwise to visualise the longitudinal descending aorta; the scope is then pulled cranially tracing the descending aorta. At approximately 24 cm from

incisors, the longitudinal aorta becomes circular and is seen in cross section; this is the aortic arch. At this level, the bronchoscope is rotated clockwise and the scope is anteflexed. With this maneuver, the aorta becomes further circular and another vascular structure appears in cross section on the left, the pulmonary artery; and the lymph node located anteriorly between the two is the station 4L lymph node. From the neutral position with the left lobe of the liver in view, the left ventricle and left atrium are seen as pulsatile thick walled anechoic structures, once the bronchoscope is gradually withdrawn. On further withdrawal, the left atrium disappears and ring artifacts appear, caused by the air in the trachea. This is the carina and the space between the carina and the left atrium is the subcarinal space (station 7 lymph nodes). The para-oesophageal (station 8) lymph nodes are easy to identify on either side of the oesophagus. Aspiration of the lymph nodes and specimen processing are performed similar to EBUS-TBNA. When both EBUS-TBNA and EUS-B-FNA are planned in the same patient, EBUS-TBNA should always be performed before EUS-B-FNA.

The EBUS and EUS are complementary techniques that provide access to different parts of the mediastinum.[23] The advantage of EUS-B-FNA is that both EBUS and EUS can be performed by the same operator in the same sitting using the same equipment.[24] The EUS-B-FNA not only provides access to lesions located posterior to the oesophagus but also to lymph nodes located in the para-oesophageal area (station 8), and pulmonary ligament (station 9) lymph nodes. These stations cannot be accessed with the use of EBUS. Even the left para-tracheal lymph node (station 4L) is, on occasion, easier to access with EUS-B-FNA. The use of EUS-B-FNA in addition to EBUS-TBNA has been shown to provide significant increment in the diagnostic yield compared to EBUS alone. The additional diagnostic gain of EUS-B-FNA over EBUS-TBNA was 7.6% in the diagnosis of undefined mediastinal adenopathy.[25]

Lung Cancer

Endobronchial ultrasound has been recommended as the first procedure for the diagnosis and staging of lung cancer involving the mediastinum.[26] Mediastinal staging of lung cancer is recommended when there is a lung mass with no distant metastases, and there are discrete appearing mediastinal lymph nodes on CT chest or lymph nodes with activity on positron emission tomography (PET).[8] Mediastinal staging is also recommended in those with a radiologically normal mediastinum (no abnormal mediastinal lymph node on CT and PET) and a central tumour or an abnormal N1 lymph node.[8] For this purpose, EBUS-TBNA, EUS-FNA or combined EBUS-TBNA/EUS-FNA is preferred over surgical staging.[8] The pooled sensitivity and specificity of EBUS-TBNA for mediastinal staging of lung cancer were 90%-93% and 99%-100%, respectively in two different meta-analyses.[27,28] The yield of EBUS-TBNA in mediastinal staging for lung cancer is almost similar or even better when compared to mediastinoscopy.[29-31] As EBUS-TBNA is much less resource-intensive and may be conveniently performed in endoscopy suite, it scores over mediastinoscopy as the first investigation for mediastinal staging. Besides, it gives better access to some of the lymph node stations, such as posterior subcarinal (station 7). Surgical staging (with mediastinoscopy) may be performed when EBUS-TBNA is negative, which further increases the sensitivity of detection of lymph node metastasis before subjecting the patient to surgery.[30] In one study, surgical staging alone, endosonography (EBUS-TBNA plus EUS-FNA) alone, and a strategy of surgical staging following a negative endosonographic assessment yielded sensitivities of 79%, 85%, and 94%, respectively.[30] The pooled false negative rate of EBUS is approximately 25%, which means that a negative result on EBUS still requires confirmation by a surgical technique, preferably mediastinoscopy.[32]

EBUS-TBNA should ideally be combined with EUS-FNA for mediastinal staging of lung cancer.[33] Zhang *et al*[34] reported a sensitivity and specificity of 86% and 100%, respectively, for the combined technique in a meta-analysis. EBUS-TBNA can also be combined with EUS-B-FNA for this purpose with an increase in sensitivity from 80% to 91%.[25] While a trans-oesophageal approach to the lymph nodes (whether by EUS-FNA or EUS-B-FNA) provides definite practical/technical advantages during mediastinal sampling, the usefulness of the combined approach has been challenged. In a recent study, it was found that adding EUS-FNA to EBUS-TBNA increased the yield; however, adding EBUS-TBNA to EUS-FNA did not augment the diagnostic sensitivity.[35] If EUS/EUS-B is not available, EBUS-TBNA alone is considered acceptable.[33] Apart from mediastinal lymph node sampling, an additional advantage of the EUS-FNA technique in staging of lung cancer is that it provides additional access to the left adrenal gland.[36] The left adrenal gland might also be accessed with EUS-B-FNA according to preliminary studies.[37,38]

Technique of lung cancer staging

There are certain technical aspects that should be borne in mind while performing EBUS for staging purposes. As the aspirate from each lymph node/station needs to be examined separately to demarcate the site of involvement, a separate needle should ideally be used for each station. However, this may not always be feasible due to cost constraints. The alternative is to access the highest N station first; i.e., N3 followed by N2 and then N1, to prevent falsely upstaging the tumour.[39]

In general, lymph nodes having a short axis diameter ≥10 mm are accessed with EBUS-TBNA. However, lymph nodes as small as 5 mm in short axis may be targeted during a staging examination.[40] Further, about 10% of patients with T1 tumours who do not have significant mediastinal lymph node enlargement on CT chest may harbor malignancy in these nodes that may be identified with the help of EBUS-TBNA (89% sensitivity, 100% specificity).[40] When performing EBUS for mediastinal staging, three aspirations should be performed from each node.[41] If ROSE is utilised, aspirations should be repeated till an adequate sample (consisting of tumour cells or showing a predominance of lymphocytes) is obtained or a maximum of five passes are performed.[42] Either 21G or 22G needle can be used as the diagnostic yield and sample adequacy are similar between the two.[43] There is also evidence that application of suction while performing TBNA does not alter the yield.[44] However, in our practice, we always use suction of 10-20 cm H_2O using a vaclok syringe.

The thoroughness of mediastinal staging has been classified as level A (complete), level B (systematic), level C (selective), and level D (poor).[45] Level A staging involves sampling of each visible node in each station (1, 2R, 2L, 3, 4R, 4L, 7, 8; and 5, 6 if left upper lobe tumour), ≥3 passes per node or ROSE. Level B staging implies sampling nodes in each station sampled (2R, 2L, 4R, 4L, 7, and 5, 6 if left upper lobe tumour), ≥3 passes per node or ROSE. Level C staging is sampling of ≥1 station, which must include a node suspicious on chest imaging or ≥1 cm on endosonography, or if <3 passes are performed with no ROSE. The staging examination is classified as level D if it involves visual assessment only, or if no node is biopsied or if there is no lymphatic tissue in the aspirates. In general, at least level B staging should be performed; however, in certain situations, a selective approach may be sufficient (for example, if a node at an N3 station is found positive on ROSE, further sampling can be abandoned).[42] Whether level A staging is better than level B staging remains unknown.

Restaging of lung cancer

EBUS-TBNA has also been utilised for restaging of stage III lung cancer after induction chemotherapy.[46] The sensitivity in this setting is lower than that in primary staging. Studies have reported sensitivities ranging from 50% to 76% and negative predictive values ranging from 20% to 88%.[46-50] Despite the lower sensitivity, the procedure is useful as it helps in avoiding surgical staging in patients with a positive result on EBUS-TBNA. Surgical restaging by mediastinoscopy may be fraught with technical difficulties due to fibrotic changes in the mediastinum secondary to lung cancer therapy.

Molecular testing in lung cancer

In patients with NSCLC, especially adenocarcinoma, there is a need to obtain specimens for testing several genetic mutations as these decide future therapy.[51,52] Several studies have shown that EBUS-TBNA specimens are sufficient for this purpose.[51,52] An average of four passes has been found adequate to accomplish this objective.[53]

Endosonographic features

There are certain important characteristics of lymph nodes that may be observed on endosonography. These include: size, shape (round, oval or triangular), margin (indistinct or distinct), echogenicity (homogeneous or heterogeneous), presence or absence of central hilar structure, and presence or absence of central necrosis sign.[54] Round shape, distinct margin, heterogeneous echogenicity, and presence of coagulation necrosis sign are predictive factors for malignant involvement of the lymph nodes.[54] Absence of an intra-nodal vessel may also predict malignancy.[55] However, only ultrasonographic features do not obviate the need for obtaining a tissue specimen, as none of these signs have absolute specificity.[56] However, these signs guide the interventionist on the choice of nodes and the specific areas within the node in question that are to be sampled on priority.

Tuberculosis

Tuberculosis is a common cause of isolated mediastinal lymphadenopathy especially in countries with a high burden of tuberculosis. EBUS-TBNA has been widely investigated in the diagnosis of intrathoracic tuberculous lymphadenopathy. In the largest study involving 156 patients, EBUS-TBNA was diagnostic of tuberculous in 146 (94%) patients. Microbiological investigations of EBUS-TBNA aspirate yielded a diagnosis in 82 (53%) patients; in 27 (17%) patients, acid-fast bacilli were demonstrated; while in 74 (47%) patients, *Mycobacterium tuberculosis* bacilli were grown on culture.[57] A recent meta-analysis[58] comprising of eight studies (809 patients) found a pooled sensitivity and specificity of EBUS-TBNA for the diagnosis of tuberculous lymphadenitis of 80% and 100%, respectively. Recently, the use of Xpert MTB/RIF (Cepheid, Sunnyvale, CA), a novel cartridge-based, automated diagnostic polymerase chain reaction (PCR) assay that can identify *Mycobacterium tuberculosis* and resistance to rifampicin on EBUS-TBNA aspirates in about two hours, has been described. In one study,[59] a single Xpert MTB/RIF assay demonstrated a sensitivity of 72.6% for the diagnosis of culture-positive tuberculosis in patients who underwent EBUS-TBNA. The Xpert MTB/RIF also helps in differentiating tuberculosis from sarcoidosis. In a recent study, the

specificity and the positive predictive value of Xpert MTB/RIF in the diagnosis of tuberculosis were 98% and 93%, respectively.[60]

The ultrasound characteristics of lymph nodes on EBUS are also helpful in diagnosing tuberculosis. In a recent study,[61] a combination of a positive tuberculin skin test and either heterogeneous echotexture of lymph node or the presence of coagulation necrosis sign had a specificity of 98% and a positive predictive value of 91% for differentiating tuberculosis from sarcoidosis in patients with granulomatous mediastinal lymphadenopathy. In another study,[60] the presence of any of the four features, namely positive Xpert MTB/RIF, positive tuberculin skin test, heterogeneous echotexture of the lymph nodes, or the presence of endosonographic coagulation necrosis sign, yielded a sensitivity and negative predictive value of 83% and 88%, respectively in the diagnosis of tuberculosis *versus* sarcoidosis. As the same ultrasound features (heterogeneous echotexture or coagulation necrosis) that were found to be predictors of malignant lymph nodes in a previous study,[54] are also seen in tuberculous lymph nodes; these characteristics are not helpful in differentiating malignant from benign lymphadenopathy in countries with a high tuberculosis burden.

Sarcoidosis

According to the European Respiratory Society/American Thoracic Society/World Association of Sarcoidosis and Other Granulomatous Disorders consensus statement, a diagnosis of sarcoidosis is made in patients presenting with a compatible clinical and radiologic profile, demonstration of non-caseating granulomas, and exclusion of known causes of granulomatous inflammation.[62] Apart from biopsy of the skin or peripheral lymph nodes, the safest and easiest procedure for the diagnosis of sarcoidosis is TBNA because the hilar and mediastinal lymph nodes are the most frequently involved sites in this disorder. The EBUS-TBNA has also been used for obtaining tissue for confirmation of diagnosis in sarcoidosis.[63,64] In a recent meta-analysis,[65] the pooled sensitivity of EBUS-TBNA in the diagnosis of sarcoidosis was 78%. A large randomised study, the GRANULOMA trial,[66] found endosonographic needle aspiration (either EBUS or EUS) of lymph nodes superior to conventional bronchoscopic biopsies in the demonstration of granuloma with a sensitivity of 74%. The EBUS-TBNA is also superior to conventional TBNA alone in the diagnosis of sarcoidosis. The results from four randomised trials[67-70] suggest that the diagnostic yield of EBUS is about one-and-a-half times higher (77% *versus* 50%) than the conventional TBNA (Figure 4). Thus, it seems that even if EBUS-TBNA is used as a diagnostic modality, the diagnosis will still remain unconfirmed in one of the four patients being investigated. We had previously suggested that a combination of bronchoscopic procedures including TBNA, transbronchial lung biopsy (TBLB), and endobronchial biopsy (EBB) is required to optimise the yield in the diagnostic work-up of sarcoidosis.[71] In a recent randomised trial,[68] we have shown that although EBUS-TBNA individually has the highest diagnostic yield in sarcoidosis among bronchoscopic techniques, it needs to be combined with conventional bronchoscopy procedures including TBLB and EBB for the best yield. The presence of ROSE is helpful as it obviates the need for TBLB (and its antecedent complications).[72,73] A larger needle size has been shown to improve the diagnostic yield while performing conventional TBNA.[74] However, a recent large randomised trial[75] found similar yield in detecting granulomas with either a 21G or 22G EBUS-TBNA needle in patients with sarcoidosis. Importantly, the lack of availability of EBUS-TBNA should not be a major limitation in the diagnosis of sarcoidosis as conventional TBNA when combined with EBB and TBLB provides diagnostic efficacy similar to EBUS-TBNA.[68]

The differentiation between tuberculosis and sarcoidosis is often difficult given the remarkable clinical, radiological and histopathological similarities.[76] However, it is extremely important to differentiate between the two conditions, as tuberculosis if mis-diagnosed and treated as sarcoidosis can have disastrous consequences. We have often seen patients being treated with both glucocorticoids and anti-tuberculosis

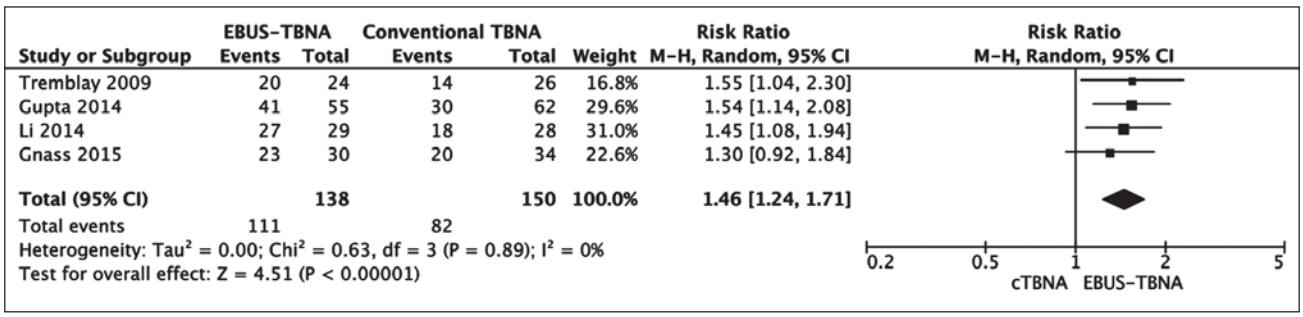

Figure 4. Forest plot showing the diagnostic yield of EBUS-TBNA versus conventional TBNA. The diagnostic yield was significantly higher with EBUS-TBNA (risk ratio with 95% confidence intervals, random effects model).

Definitions of abbreviations: **EBUS-TBNA=Endobronchial ultrasound-transbronchial needle aspiration**

therapy as the clinician is unable to differentiate between the two. At our centre, we rarely if ever, adopt this principle; we follow a simple algorithm to differentiate between the two entities (Figure 5).

EBUS for Other Indications

Apart from the conventional indications, EBUS has also been used for the diagnosis of lympho-reticular malignancy,[77] pulmonary artery tumours,[78] bronchogenic cyst (diagnosis and treatment),[79] assessment of thyroid nodules,[80] and other conditions.

Lymphoreticular malignancy

The current practice guidelines for lymphoma generally advocate against the use of needle aspiration as a diagnostic modality because it does not provide sufficient material for immunophenotyping and molecular techniques.[81] Recent evidence, however, suggests a role of EBUS-TBNA in the diagnosis of lymphoma.[82,83] In a retrospective study,[84] EBUS-TBNA had a sensitivity and specificity of 91% and 100%, respectively for diagnosis of lymphoma. In another study,[85] lymphoma could be subtyped by performing immunocytochemistry analysis on the EBUS-TBNA samples. In a prospective study[83] comprising of suspected *de novo* and relapsed patients with lymphoma, EBUS-TBNA correctly identified *de novo* and relapsed lymphoma in 88% and 100%, respectively. The sensitivity of EBUS-TBNA in correctly subtyping the lymphoma into high-grade non-Hodgkin lymphoma, low-grade non-Hodgkin lymphoma and Hodgkin lymphoma was 90%, 100%, and 79%, respectively.[83] Thus, EBUS-TBNA can obviate the need of invasive procedures such as mediastinoscopy in the diagnostic evaluation of patients with suspected lymphoma.[82-84] Moreover, the availability of needles that allow EBUS-guided biopsy of the nodes (described below), is likely to change the outlook of EBUS-TBNA in the work-up of lymphoma.

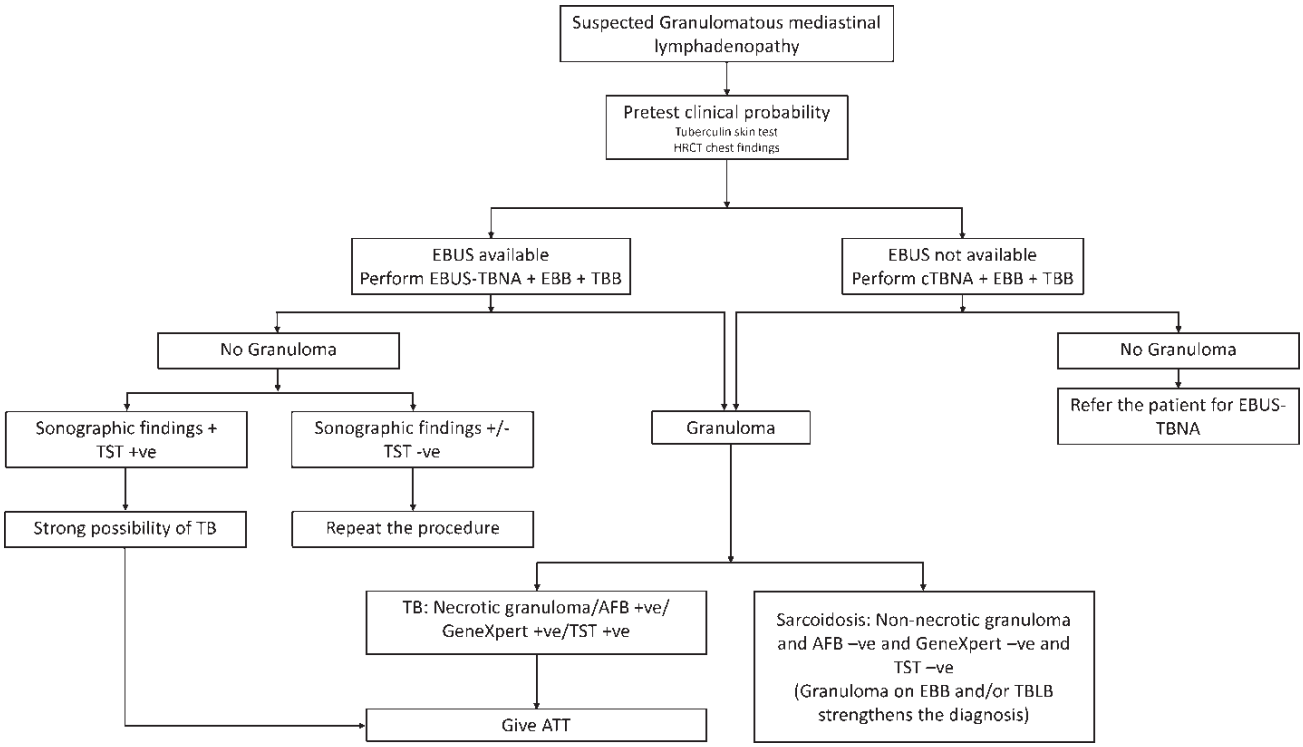

Figure 5. Algorithm followed at our center to differentiate tuberculosis (TB) from sarcoidosis. All patients with suspected granulomatous mediastinal lymphadenopathy undergo tuberculin skin test (TST) and computed tomography (CT) of the chest, both contrast-enhanced and high-resolution CT (HRCT). Presence of peribronchovascular nodules on HRCT chest suggest sarcoidosis while centrilobular nodules and cavitation indicates tuberculosis. The presence of distinct endosonographic features of lymph nodes such as heterogeneous appearance or coagulation necrosis along with a positive TST strongly suggests tuberculosis. The presence of non-necrotic granuloma with absent acid-fast bacilli (AFB), negative Xpert MTB/RIF along with a negative TST, points towards sarcoidosis. Findings of necrotising granulomata, positive AFB or Xpert MTB/RIF, and/or a positive TST, strongly suggest tuberculosis. The presence of granulomas on endobronchial biopsy (EBB) from a visually normal bronchial mucosa and/or granuloma on transbronchial lung biopsy (TBLB) in a patient with a normal lung parenchyma on HRCT chest strongly supports the diagnosis of sarcoidosis. In situations where the only positive finding is a non-necrotising granuloma, we rely on TST. If the TST is positive, we first administer only anti-tuberculosis treatment. If there is no response after two months of anti-tuberculosis therapy, a diagnosis of sarcoidosis is considered.

***Definitions of abbreviations*: MTB=*Mycobacterium tuberculosis*; RIF=Rifampicin.**

Pulmonary artery lesions

Endobronchial ultrasound has also been evaluated for its utility in the diagnosis of pulmonary thromboembolism. In a pilot study of 32 patients with pulmonary embolism,[86] EBUS detected 96% of the pulmonary emboli identified by CT pulmonary angiography (CTPA).[86] However, the bronchoscopists were not blinded to the results of CTPA.[86] The EBUS may have a role in evaluation of patients with suspected pulmonary thromboembolism (PTE) who have contraindications for CTPA, such as allergy to contrast agent, renal failure, pregnancy, patients receiving invasive mechanical ventilatory support and others.[86-88] Pulmonary artery sarcoma or tumour embolism can rarely mimic pulmonary thromboembolism. The diagnosis is usually confirmed on histological examination of samples obtained by surgical resection or right heart catheterisation. The EBUS-TBNA has also been shown to be beneficial in such instances.[78,89] In a systematic review, the use of EBUS enabled a confirmatory diagnosis in 90% (9/10) of the cases with suspected non-thrombotic endovascular lesions of the pulmonary artery.[89] In a pilot study[90] investigating the role of EBUS for the assessment of pulmonary artery dimensions, although significant correlation was demonstrated between the pulmonary artery dimensions measured on EBUS and CT, the limits of agreement were wide. A larger study is required for confirming the results of this pilot study.[90]

Mediastinal cysts

An accurate diagnosis of mediastinal cyst is generally made by surgical resection.[79] Other options for the diagnosis include aspiration of the cyst, either transthoracic or transbronchial (EBUS or conventional).[79,91] The presence of an anechoic lesion suggests mediastinal cyst and the diagnosis is confirmed by needle aspiration and cytological evaluation.[92] In a systematic review on the safety and efficacy of TBNA for bronchogenic cysts, 32 patients were identified who underwent TBNA for the diagnosis and management of mediastinal cysts.[79] The use of EBUS enabled real-time imaging and aspiration of the cystic content until the documentation of collapse of the cyst. Further, in patients who were managed with a therapeutic intent, no episode of recurrence of the cyst was documented at 14 months follow-up. Five (16.1%) patients developed complications including cyst rupture and cyst infection after EBUS-guided aspiration.[79]

Thyroid lesions

The diagnosis of thyroid lesions is usually accomplished by ultrasound-guided FNA. However, when the thyroid enlargement is intra-thoracic, the diagnosis requires mediastinoscopy or surgical excision.[93] The EBUS is an attractive alternative in these situations.[94-96] In a study of 12 cases with thyroid swelling,[80] EBUS enabled sampling in all patients and was diagnostic in 100% of the cases. Performance of EBUS for thyroid sampling was safe and no complication was reported.[80]

Other lesions

EBUS-TBNA (or EUS-B-FNA) is useful for sampling intra-parenchymal lung lesions adjacent to central airways,[97] and in one study,[98] EBUS-TBNA was diagnostic in 82% of the patients. EBUS has been used to diagnose rare conditions, such as anterior mediastinal schwannoma and pericardial mesothelioma in patients who presented with an anterior mediastinal mass.[99,100] Recently, EBUS has also been explored for its safety in intra-tumour injection of cisplatin-based chemotherapy in early stage NSCLC after chemotherapy and external beam radiation.[101-104] In a pilot study of five patients with advanced NSCLC,[105] instillation of cisplatin based chemotherapy directly into mediastinal lymph nodes and the tumour resulted in achieving disease control and increase in overall survival. However, larger trials are needed before incorporating EBUS-guided intra-tumour needle instillation of chemotherapy in the routine management of advanced stage lung cancers.[105]

Complications of EBUS

Endobronchial ultrasound is a minimally invasive method that is rarely associated with complications. In a systematic review of over 1500 EBUS procedures no major complications were encountered.[106] In another review,[27] complications were seen in only two (0.15%) cases. The various complications reported with EBUS include mediastinal abscess, empyema, mediastinal emphysema, pericarditis, sepsis, needle breakage, lung abscess and others. Most of these complications have been reported as case reports.[106-109] In a multicentre study evaluating the complications associated with EBUS-TBNA, problems were encountered in 19 (1.4%) of the 1317 patients.[110] Pneumothorax and sustained hypoxia were the most frequently encountered complications. Other complications included airway bleeding, hypotension and respiratory failure. One death was also encountered. In a multivariate analysis,[110] performing TBLB increased the risk of complications during EBUS. In another multicentre study of 3123 patients with 11753 EBUS procedures, only five (0.2%) serious complications (fever lasting >24 hours, infection of bronchogenic cyst, mediastinal abscess, pericarditis and pneumo-mediastinitis with empyema) were seen.[111] All complications were managed with antibiotics and four patients required hospitalisation.[111] In a meta-analysis of EBUS-TBNA comprising of 10 (n=1080 patients) studies, no serious complications were identified.[25] Occasionally,

complications are due to sedation and analgesia and side-effects resulting from drugs used for this purpose.

EUS-FNA or EBUS-TBNA

EBUS-TBNA and EUS-FNA are complementary techniques for accessing the mediastinum.[112] Clearly, a combined approach of EBUS-TBNA and EUS-FNA is superior to either technique alone in mediastinal staging of lung cancer.[34] An eternal debate has been about preferred choice of procedure in other situations.[113-115] The EBUS scope has limited depth of penetration and limited range of scanning (60°-70°) compared to the EUS scope (120°-180°).[113] On the other hand, EUS-FNA has access to fewer lymph node stations compared to EBUS-TBNA. The oesophagus is located posterior and to the left to the trachea, and thus, EUS-FNA allows excellent lymph node access only of the subcarinal (station 7), left para-tracheal (station 4L), para-oesophageal (station 8) and pulmonary ligament region (station 9).[116] Other lymph node stations, such as 10L, 5, 2R, 4R and 10R are easily accessed only when grossly enlarged. The station 6 can be accessed only through the transaortic approach, although a complicated technique without resorting to a transvascular puncture has recently been described.[117,118] The left adrenal gland can be easily accessed with the EUS although some centres have described the use of EUS-B-FNA for accessing the left adrenal gland.[37,38] On the other hand, EBUS allows excellent visualisation of the right and left para-tracheal (2R, 4R,2L, 4L), and the subcarinal region (7). In addition, EBUS provides easy access to the right and left hilar region (10R and 10L) and the right and left inter-lobar regions (11R and 11L).[11] Moreover, intra-pulmonary lymph nodes can also be accessed using the radial mini-probes. The EUS-B-FNA extends the reach of EBUS to station 8 and 9 lymph nodes.[119]

In our opinion, either procedure is effective when stations 4L and 7 are the predominant nodes. On the other hand, when right-sided para-tracheal lymph nodes, hilar or inter-lobar nodes are the predominant sites of involvement, EBUS is the preferred procedure. When stations 5 and 6 are the predominant sites, then EUS should be the preferred procedure. In patients with sarcoidosis, the addition of conventional bronchoscopy procedures significantly adds to the yield of endosonographic procedure. Thus, a bronchoscopist-performed procedure (EBUS-TBNA) should be the initial procedure of choice in these patients and should be combined with EBB and TBLB. Overall, the trans-oesophageal procedures are more comfortable to the patient and require less sedation.[120]

Future Directions

A new prototype of the EBUS scope has recently been evaluated.[121] The prototype echobronchoscope has a smaller (5.9 mm) external diameter compared to the existing EBUS scopes. Further, it has a better upward angulation (170°). Both these features would enable visualisation and sampling from lobar and segmental lymph nodes and allow better access to parenchymal lesions located adjacent to lobar and segmental bronchi.[121]

There are a few innovative biopsy techniques that have been described with the use of the convex EBUS scope with an aim to obtain a better tissue core for histological analysis. Herth *et al*,[122] in a series of 75 patients described the use of a 1.15 mm diameter mini-forceps (FB-56D-I; Olympus Medical) to obtain histological cores from subcarinal lymph nodes (larger than 2.5 cm in short axis). The yield of the mini-forceps biopsy (88%) was higher than that of the 22G (36%) and 19G (49%) needles. In a later report, Herth *et al*[123] have described the use of a needle forceps biopsy from mediastinal lymph nodes in 50 patients. The forceps used in this study was a sharp biopsy forceps (conical type; Olympus Medical) that is housed in a 1.5mm diameter sheath and has a 15mm long stiff distal end. It combines the characteristics of a needle (bevelled tip for penetrating through the airway wall) with that of forceps (serrated jaws that can be opened and closed). A specific diagnosis could be made in 86% of the patients in this study. Chen *et al*[124] also described the use of a 1.0mm diameter mini-forceps (M00546270, Boston Scientific) in 12 patients with a diagnostic yield of 67%.

The use of a new bibeveled needle (Table 2), the 22G EchoTipProCore EBUS needle (Cook Medical, Bloomington, IN) has been described to obtain a histological core for the successful diagnosis of Hodgkin's lymphoma.[125] Harris *et al*[126] have recently described a technique wherein they punctured the airway wall over the subcarinal lymph node by repetitive movements of the sheath of the EBUS-TBNA needle against the airway wall. Subsequently, they pushed a 1.15mm mini-forcep through the access path thus created, to obtain a histological sample. Harris *et al*[127] have also recently described the use of a water-based lubricant (HR Pharm, Inc. PA) for enhancing EBUS images, by allowing better coupling between the ultrasound probe and the airway wall.[127] This obviates the requirement of a balloon sheath. Apart from the routine ultrasound modes, namely the B-mode and Doppler, emphasis is being laid on a new imaging technology, namely the elastography, that may further add to the clinical utility of EBUS in the diagnostic evaluation of mediastinal diseases.[128] First described in breast malignancy,[129] elastography has also been useful in the assessment of mediastinal lymph nodes.[128] Izumo *et al*[130] have described three types of elastographic patterns on EBUS: type I with non-blue pattern (100% benign); type II with a mixture of blue and non-blue (mixed benign and malignant); type III with blue pattern (94% malignant). However, more evidence is needed to demonstrate the clinical utility of elastography

in the diagnostic evaluation of mediastinal pathologies.

Although mediastinal lymphadenopathy is a common problem in the pediatric population, few studies have described the utility of EBUS-TBNA in children.[131] The EBUS scope being a larger scope, is difficult to maneuver in children, especially smaller children. In children, EUS-B-FNA is an alternate and safe method of accessing the mediastinal lymph nodes. A recent multicenter study describing the utility of EBUS-TBNA and EUS-B-FNA in children, found that the endosonographic procedures helped in modifying the pre-procedure diagnosis in almost 40% of the patients.[132] The availability of a smaller EBUS scope (described above) would allow an even convenient performance of EBUS-TBNA/EUS-B-FNA in children.

Our Experience

We started performing convex probe EBUS at our centre in July 2011. The procedures are performed by pulmonary consultants or by fellows in training under the supervision of the consultants. Till date, 1005 procedures have been performed (Table 3). The most common indications for perming EBUS-TBNA at our centre are sarcoidosis (50.6%) and tuberculosis (23.5%), with only about-a-fifth of the procedures performed for suspected malignancy. The diagnostic yield (proportion with a definite diagnosis on cytology) of the procedure at our centre is 60.7% and an adequate sample (defined by either a definite cytological diagnosis or preponderance of lymphocytes) was obtained in 94.6% of the procedures.

Table 3. Clinical characteristics and diagnostic yield of 1005 patients who have undergone EBUS-TBNA at our centre

Characteristic	Value
Age (in years)	45.4±15.5
Female gender, No. (%)	387 (38.5)
Clinical diagnosis	
Sarcoidosis	509 (50.6)
Tuberculosis	236 (23.5)
Metastatic malignancy	218 (21.7)
Lymphoma	27 (2.7)
Others	15 (1.5)
Technique	
EBUS	929 (92.5)
EUS-B	22 (2.1)
Both	54 (5.4)
Adequate sample	94.6%
Diagnostic yield	60.7%

Definition of abbreviations: EBUS-TBNA=Endobronchial ultrasound-guided transbronchial needle aspiration; EUS=Endoscopic ultrasound

Conclusions

The convex probe EBUS-TBNA has been a revolutionary development in the field of interventional pulmonology. The technique has enabled sampling of mediastinal lesions under real-time ultrasound guidance, thereby significantly improving the diagnostic yield compared to conventional TBNA. This has decreased the requirement for invasive procedures, such as mediastinoscopy in sampling of mediastinal lymph nodes. Although its initial use was mainly for staging of lung cancer, its utility has subsequently been extended to any undefined mediastinal lymphadenopathy including sarcoidosis, tuberculosis and others. The technology is constantly evolving with smaller echobronchoscopes, better needle design and improvement in endoscopic and ultrasound characteristics. Despite all this, the negative predictive value of EBUS is not high enough to preclude mediastinoscopy. The challenge now is to integrate the existing technologies including conventional TBNA, EBUS-TBNA and mediastinoscopy into appropriate clinical algorithms so that the patient-care can be delivered in the safest and the most cost-effective manner. The technique should be incorporated into every pulmonary fellowship curriculum, as it has now become an integral part of the interventional pulmonology.

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