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Endobronchial Ultrasound in the Diagnostic Evaluation of Sarcoidosis

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1. Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive mediastinal sampling technique which combines the use of ultrasound with conventional bronchoscopy in order to visualise and sample structures adjacent to the tracheo-bronchial tree such as mediastinal and hilar lymph nodes. The technique is commonly used in the staging and diagnosis of lung cancers but can also be used for the diagnosis of benign conditions affecting the mediastinum including sarcoidosis.

In asymptomatic stage I sarcoidosis (bilateral hilar adenopathy) with evidence of arthritis and erythema nodosum (Löfgren's syndrome) it may be possible to make a presumptive diagnosis based on clinical and radiological findings however in symptomatic patients and particularly where immunosuppressive therapy is being considered or exclusion of other causes of mediastinal lymphadenopathy is required (e.g. tuberculosis, histoplasmosis, silicosis or lymphoma) a tissue diagnosis may be sought. A diagnosis of sarcoidosis can be made in the presence of pathological evidence demonstrating non-caseating granulomata, in the absence of positive mycobacterial and fungal cultures and with supporting clinical and radiological evidence. Tissue for diagnosis should be obtained from the most accessible involved organ. Since pulmonary sarcoidosis is the most frequent form, bronchoscopic techniques are often the first line investigation.

Conventional flexible bronchoscopy is frequently performed in the diagnosis of sarcoidosis but is of limited use when central or peripheral airways are not affected. Endobronchial biopsy (EBB) where there is evidence of disease affecting the airways may assist with the diagnosis. Transbronchial lung biopsy (TBLB) can be performed where there is evidence of parenchymal disease however this technique carries a risk of bleeding and pneumothorax. Transbronchial needle aspiration (TBNA) can be useful in the context of mediastinal lymphadenopathy however this is a "blind" technique and as such diagnostic accuracy is variable and further

more there is risk of bleeding and damage to vascular structures. There are also limitations in terms of which nodes can be sampled using conventional TBNA. Mediastinoscopy remains the gold standard approach for sampling the mediastinal glands, particularly when other sampling techniques are non-diagnostic however this is an invasive procedure which requires a general anesthetic and is associated with morbidity. Many of the limitations associated with the aforementioned techniques can be overcome by the use of EBUS-TBNA. The following chapter describes the technique, its application in the diagnosis of sarcoidosis and the advantages of EBUS-TBNA over alternative mediastinal sampling techniques.

2. EBUS –TBNA - Technical issues

2.1. The EBUS scope

There are two probes available. The radial probe was initially developed in 1992. This is a high frequency probe (20-30MHz) which achieves a high resolution image but has limited depth penetration (4-5cm) and provides a 360 degree view. The radial probe is particularly useful for imaging of the airway wall however it does not allow real time identification of structures during sampling (table 1). The convex or linear probe EBUS scope integrates a convex transducer probe at the tip of a flexible bronchoscope (figure 1). The transducer has a frequency of 7.5 MHz and scans through the airway wall in a plane which is parallel to the insertion direction of the bronchoscope. Although images using the convex probe are of lower resolution there is improved depth of penetration (up to 9cm) and most importantly this probe enables real time imaging of the EBUS-TBNA needle throughout the sampling process thus reducing the risk of damage to vascular structures. The endoscopic image is viewed at an angle of 30 degrees forward oblique and the operator needs to compensate accordingly. The ultrasonic image is viewed at an angle of 90 degrees to the bronchoscope. The ultrasonic image of mediastinal structures is obtained by making direct contact between the probe and the airway wall. Improved image quality can be achieved by increasing the contact between the transducer and the airway wall using a balloon attached to the tip of the ultrasound which is filled with normal saline. The ultrasound image is processed and visualized with the conventional bronchoscopic image, on the same monitor (figure 2). The ultrasonic image can be frozen and the size of lesions or nodes can be measured in two dimensions. The use of colour flow and power Doppler also allows accurate identification of vascular structures adjacent to or within the area of interest. The linear probe is most commonly used in the sampling of mediastinal lymph nodes. Unless specified, the term EBUS in this chapter refers to linear probe EBUS.

	Radial Probe	Convex Probe
Frequency	20-30MHz	7.5MHz
Penetration (cm)	4-5	9
Applications	Assessment of airway wall	Sampling of mediastinal lesions e.g.
	Sampling of peripheral lesions	lymph nodes

Table 1. Comparison of radial probe vs convex probe

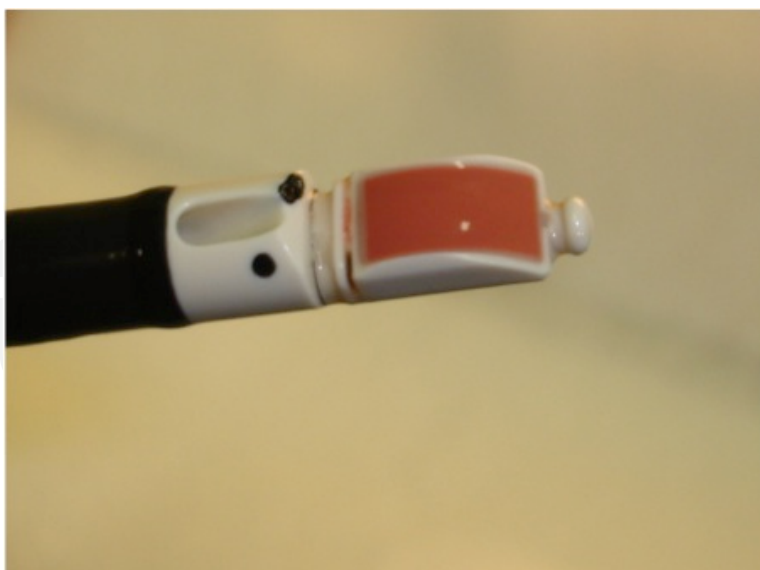


Figure 1. Linear EBUS probe



Figure 2. EBUS Scope Processor and Monitor

EBUS-TBNA is sometimes performed at the same time as flexible bronchoscopy which may be necessary when more detailed examination of the distal tracheobronchial tree or endobronchial biopsies are required. The external diameter of the EBUS-TBNA scope is wider than a conventional bronchoscope (6.9mm compared with 5-6mm) however endobronchial biopsies of more proximal airways can be carried out via the EBUS bronchoscope. As with flexible bronchoscopy, EBUS-TBNA procedure is commonly performed under light conscious sedation using intravenous midazolam and fentanyl as well as topical anaesthesia however some centres prefer to use deep sedation with propofol or a remifentanyl infusion with a laryngeal mask airway in order to minimize coughing. Typically the procedure is carried out as a day case. Adequate sedation is essential as EBUS-TBNA takes longer than a flexible bronchoscopy, particularly if multiple nodal stations are sampled. The patient is positioned in a supine position and the bronchoscopist stands behind the patient. In view of the wider diameter of the EBUS-TBNA scope, oral intubation is preferred. As described above the endoscopic view is 30 degrees forward oblique, therefore the bronchoscope needs to be flexed down in order to obtain a straight view. In order to pass the bronchoscope through the vocal cords the anterior angle of the glottis should be visualized with the bronchoscope in the neutral position. The mediastinal lymph nodes are examined by positioning the bronchoscope in the correct anatomical position and then by flexing and pressing the ultrasound probe onto the airway wall. The bronchoscope is adjusted so that the area for sampling is viewed in its maximum diameter at the centre of the ultrasound image. The Doppler mode is used to visualize vascular landmarks and can be used to identify vessels within lymph nodes. The size of the lymph node is measured using the calipers.

2.2. The sampling technique

For a more detailed review of this aspect, the reader is directed to other sources [1]. Sampling using the dedicated single use TBNA needle is ideally performed by two operators however it is possible for the technique to be carried out with a single operator. Currently 2 sizes of dedicated EBUS-TBNA sampling needles (21-gauge and 22-gauge) are available. The needle is housed within a sheath which is inserted into the 2.0mm working channel of the EBUS bronchoscope. The sampling needle has multiple small dimples along its shaft in order to increase the echogenicity and screen visualisation. 21 gauge needles are often preferred for suspected granulomatous disease as there is evidence to suggest that the histological structure of specimens is better preserved using the larger needle [2, 3].

Following intubation, lymph nodes are identified according to the International Staging System [4] with the aid of vascular landmarks and the Doppler mode. Mediastinal lymph nodes at stations 2-4, 7, 10 and 11 can be accessed for EBUS-TBNA (figure 3). The EBUS-TBNA sampling needle is inserted through the working channel and is positioned so that the tip of the needle sheath is just visible on the endoscopic image. This is extremely important in order to avoid damage to the bronchoscope channel when the needle exits. The needle is locked on to the working channel and the internal stylet is withdrawn slightly. The depth for sampling is determined (0.5-4 cm) and this distance is set using the safety calibrator (figure 4). Holding the bronchoscope against the airway wall the needle is then inserted using a "jabbing"

movement. The needle exits the working channel at angle of 20 degrees to the sheath of the insertion tube (figure 5). Following insertion of the needle the internal stylet is advanced and withdrawn within the needle lumen to clear any airway wall debris before it is completely removed. A 3-way vacuum syringe is attached to the needle and sampling commences by advancing and withdrawing the needle approximately 15 times within the node under direct vision (figure 6). Once sampling is complete the 3-way syringe is disconnected and then the needle is removed from the working channel. The internal stylet is used to expel the histological core tissue sample from the needle lumen onto a specimen collecting system. The stylet is removed and cleaned with saline and air is injected though the needle lumen to remove any remaining particles. The same node is usually sampled 2 to 3 times assuming a good sample is obtained at each pass. For benign disease such as granulomatous disease it may be preferable to do a limited number of passes in a greater number of lymph nodes in order to limit the total length of the procedure if conscious sedation is being used rather than general anaesthesia [5].

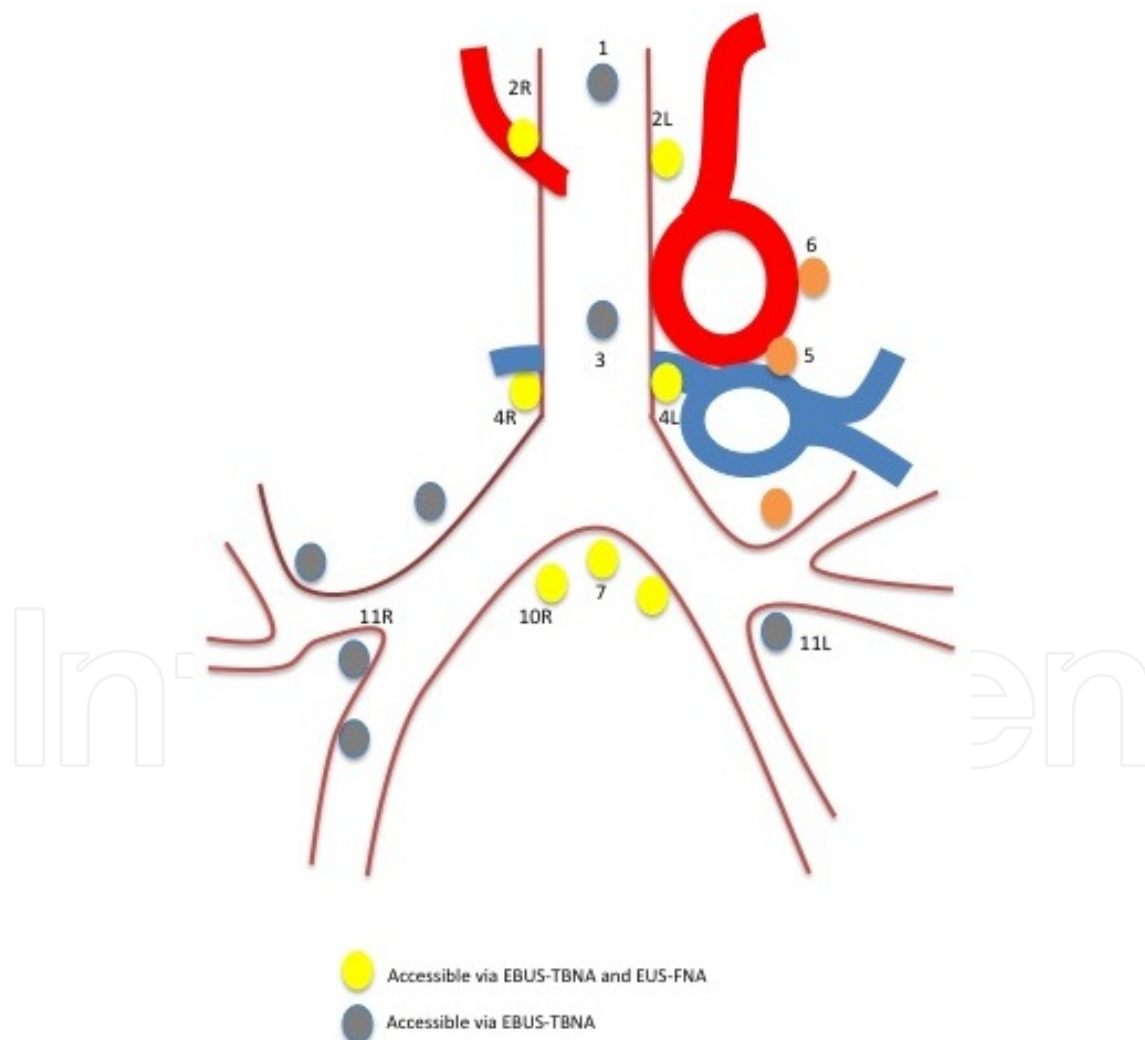


Figure 3. Diagrammatic representation of lymph node stations accessed via EBUS-TBNA/ EUS-FNA. EUS-FNA = endoscopic ultrasound-guided fine needle aspiration.

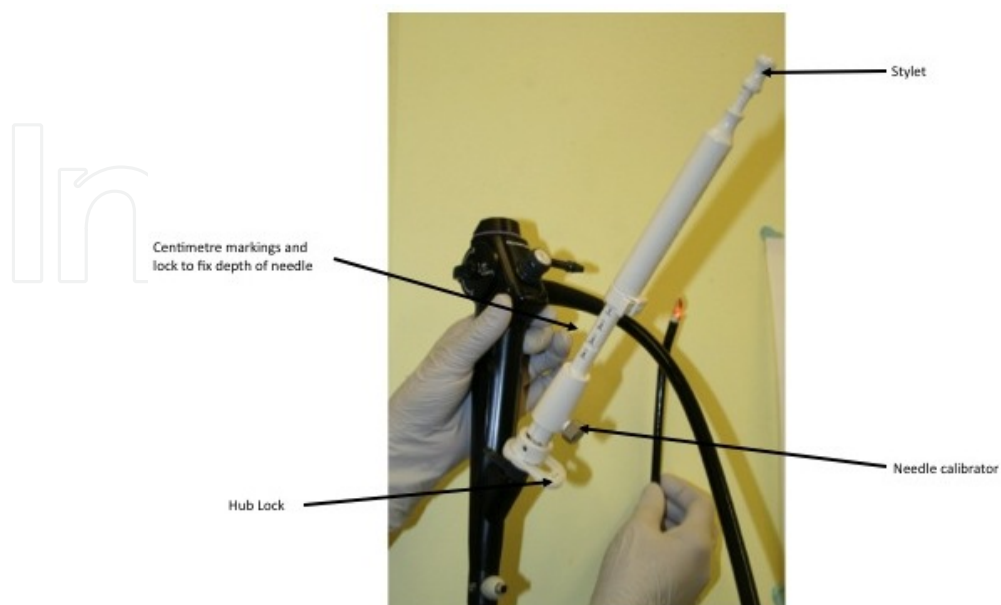


Figure 4. Sampling Needle inserted into working channel of EBUS scope

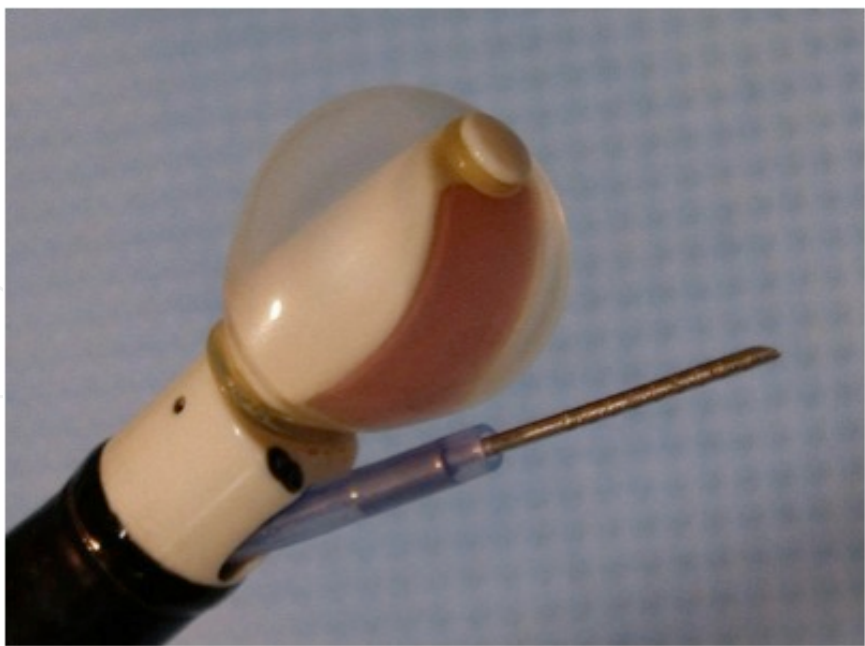


Figure 5. Tip of EBUS scope with balloon inflated and TBNA needle exiting

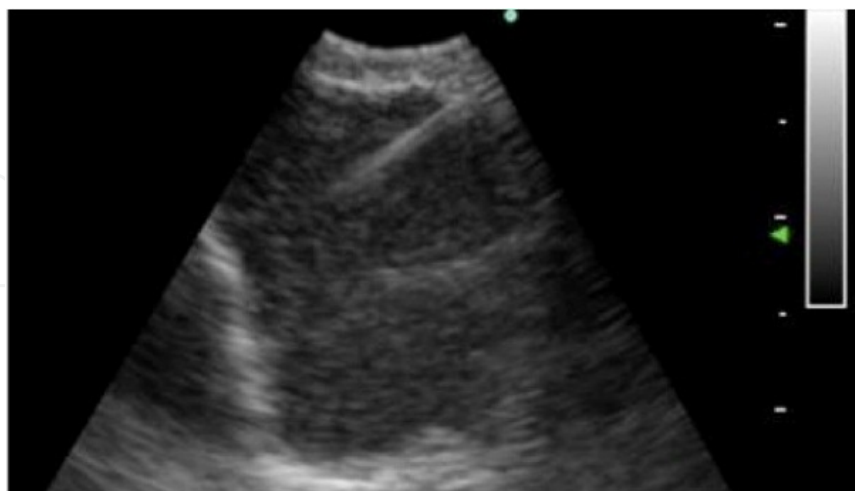


Figure 6. Ultrasound image of lymph node with EBUS-TBNA sampling needle in situ

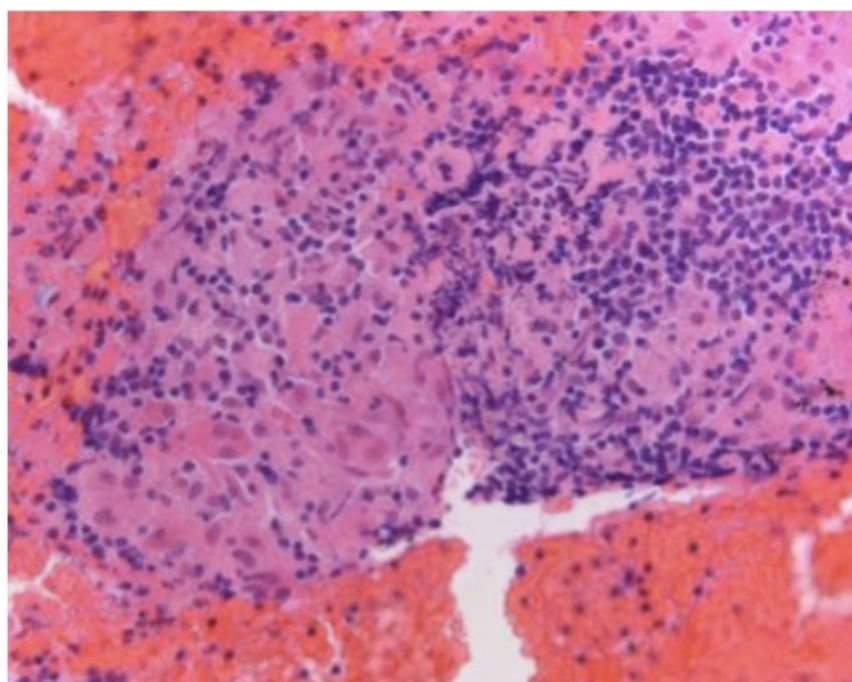


Figure 7. Histological sample obtained using EBUS-TBNA showing non-caseating granuloma

2.3. The specimen

The handling of the histological and cytological samples is extremely important. The diagnosis of sarcoidosis is established when clinical and radiological findings are supported by histological or cytological evidence of non-caseating epithelioid cell granulomas. Granulomas are defined by loose collections of non-pigmented epithelioid or spindle cell histiocytes with lymphocytes, necrotic material and neutrophils. In sarcoidosis numerous granulomas can be seen in FNA samples without evidence of necrosis [7]. It is important to exclude local sarcoid-like reactions and infective causes.

Many centres choose to utilise rapid on-site evaluation (ROSE) of cytology samples in order to confirm the adequacy of specimens however resources and cost are limiting factors. ROSE of specimens has been shown to increase diagnostic yield in some circumstances, however a recent meta-analysis examining the use of ROSE in cases of suspected sarcoidosis did not demonstrate a statistically significant increase ($p = 0.66$) in yield in studies where ROSE was carried out (165/206; 80.1% vs 282/347; 81.3%) [6]. ROSE allows a smaller number of passes to be carried per node. Once a diagnosis of granulomatous disease or malignancy is reached sampling of that particular node can be stopped. In order to minimize the number of false negative results, if no malignancy or granulomatous inflammation is seen, further sampling should be performed. Gross examination of the specimen can be helpful as adequate samples often appear creamy (rather than bloody, watery or mucoid) or may be black as a result of anthracosis [7].

Typically the EBUS-TBNA samples are smeared on to glass slides and air dried then fixed however some centres prefer to use liquid cytology bottles. Tissue cores are fixed in formalin or saline depending on whether culture for Mycobacterial disease is required. It has recently been reported that cell block analysis in addition to the Diff-Quick smear examination can reduce the false negative rate by 33%. Furthermore, Wang et al [8], found that of 37 patients who had EBUS-TBNA carried out, 100% of cell blocks contained non-necrotizing granulomas compared to 27% of smears. This may be because smearing samples between two slides disrupts the epithelioid groups in FNA samples which does not tend to occur during cell block preparation.

There is debate regarding the definition of an adequate tissue sample. In the absence of malignant cells or granulomatous cells it is clearly important to confirm that an adequate amount of lymphoid tissue is present in the sample. The negative predictive value of samples is far superior when lymphocytes are detected. Attempts have been made to quantify the number of cells required to define the adequacy of a sample. For example, [see 7] state that a sample containing at least 40 benign-appearing lymphocytes in a high-power field in the areas of highest cellularity of the smear constitutes an adequate sample. Likewise the identification of large numbers of anthracotic pigment and macrophages or large clusters of admixed lymphocytes and pigmented macrophages may further indicate an adequacy. If malignancy or granulomatous disease is seen with small numbers of lymphocytes this can also be considered to be adequate. The interpretation of adequacy is somewhat subjective and development of a standardised approach may help to reduce the number of false negative or positive results.

Sarcoid-like granulomata may be visualized in the context of malignancy such as non-small cell lung cancer, lymphoid and germ cell neoplasms and are thought to be a result of a local T cell-mediated immune reaction. It is therefore important to continue to attempt to exclude malignancy even if granulomatous inflammation is seen. Similarly granulomatous inflammation can be seen as a result of fungal or mycobacterial infections particularly in immunosuppressed patients and appropriate culture should be considered. The implication of EBUS-TBNA detection of granulomatous inflammation in patients with previously treated cancer and new mediastinal lymphadenopathy has been examined [9]. In this study, 17/153 (11%) of patients referred for EBUS-TBNA were found to have non-caseating granuloma. A subgroup of patients had a previous history of cancer and presented with mediastinal lymphadenopathy suspicious of cancer recurrence. All these patients had granulomatous inflammation confirmed via EBUS-TBNA and remained clinically stable during follow-up. The study highlights the importance of obtaining a tissue diagnosis in this subgroup of patients and supports the utility of EBUS-TBNA as a diagnostic tool in this circumstance. The differentiation between true sarcoidosis and sarcoid-like reaction must be made through clinical and radiological correlation.

2.4. Diagnostic yield of EBUS-TBNA

The diagnostic yield of EBUS-TBNA in sarcoid has been reported between 80-90% [10]. It is important to note that the highest sensitivity (92%) of EBUS-TBNA has been demonstrated in patients with stage I and II disease with nodes of >10mm however even in patients with nodes of <10mm and all stages of sarcoidosis the sensitivity is still adequate (85%) [11,12]. A recent meta-analysis of 15 studies of EBUS-TBNA in sarcoidosis described a yield between 54-93% with a pooled diagnostic accuracy of 79% (95% CI, 71-86%) however there was heterogeneity between studies included. There was also variability regarding the experience of the operators in these studies [6].

2.5. Contraindications

EBUS-TBNA is a well tolerated procedure. Patients should be fit enough to undergo flexible bronchoscopy in accordance with local guidelines [13]. Biopsies should not be carried out in patients who are currently taking warfarin and the international normalized ratio (INR) should be less than 1.4. Clopidogrel is normally withheld at least one week prior to the procedure although a small series of patients who had EBUS-TBNA whilst still taking clopidogrel (and a significant proportion also taking aspirin) did not report any bleeding complications [14]. The procedure should be avoided for 6 weeks after myocardial infarction and should not be carried out in patients with arrhythmia or severe hypoxaemia at rest [15].

2.6. Complications

EBUS-TBNA has been shown to be a safe, minimally invasive technique. Only 5 minor complications (minimal pneumothorax, minor bleeding, airway oedema/hypoxaemia, prolonged coughing) were reported in a recent systematic review of 532 patients undergoing EBUS-TBNA for suspected sarcoidosis [6]. Compared to mediastinoscopy which carries a 0.5%

risk of major complications and 1.4-2.3% risk of significant complications the risk of complications with EBUS-TBNA is lower [15]. Routine chest radiograph is not required following the procedure unless the patient reports specific symptoms (e.g. chest pain) during or after the procedure although some centres do a chest radiograph after sampling the hilar stations routinely [16].

2.7. Costs

The main costs of setting up an EBUS-TBNA service are due to equipment costs such as the EBUS bronchoscope, ultrasound processor and also the disposable EBUS needles (which are more expensive than conventional TBNA needles) and accessories (approximately £150-175). As the procedure takes longer than a conventional flexible bronchoscopy, the cost of additional staff time must be considered. If ROSE is required this is a further cost. Repair and servicing of the EBUS bronchoscope is more expensive than a flexible bronchoscope. Similar to conventional TBNA there is a risk of damage to the biopsy channel of the bronchoscope if the sheath of the EBUS-TBNA needle is not positioned correctly when the needle is advanced. Having taken into account the additional costs of EBUS-TBNA, since the technique has a higher sensitivity than conventional TBNA (particularly where distal or smaller node sampling is required, the overall cost saving potential from avoiding a mediastinoscopy is likely to be greater with this technique than with conventional TBNA [15].

2.8. Training and learning curve

EBUS-TBNA can be performed by pulmonologists. Training requires the operator to have had sufficient experience in all standard bronchoscopic techniques, including conventional TBNA. Experience with the interpretation of ultrasound is also useful e.g. thoracic ultrasound. Training of nursing staff is also required. The American College of Chest Physicians (ACCP) recommends that in order to achieve competence in EBUS-TBNA, 50 supervised procedures must be carried out. Furthermore in order to maintain competence it is recommended that a minimum of 20 procedures per year are carried out [17]. The learning curve and the number of procedures required to produce optimal results is high [18]. In fact a recent prospective study has demonstrated improving results up to 120 procedures [19].

3. Other diagnostic bronchoscopic techniques

3.1. Conventional TBNA

The use of TBNA in the diagnosis of sarcoidosis has been described since the 1980's. The technique of sampling lymph nodes using this method is a blind technique and diagnostic accuracy is likely to be dependant on the skill of the operator. The reported sensitivity of TBNA is variable, ranging from 46-90% [3]. It is also a technique which is underutilised by pulmonologists (10-30% uptake) because of concerns regarding diagnostic yield and fear of vascular injury [10]. There is also a belief that it is not useful (reported by 30% pulmonologists in one

study) and concerns about performing the technique without onsite pathology support [20]. EBUS-TBNA carries a lower risk of complications compared with conventional TBNA. Several studies have directly compared EBUS-TBNA with conventional TBNA. In one, small prospective study of patients with suspected sarcoidosis EBUS-TBNA was followed by conventional TBNA. The two techniques were found to be of similar efficacy with a positive diagnosis established in 93% of patients using EBUS-TBNA and/ or conventional TBNA [3]. Only one randomised controlled trial has directly compared EBUS-TBNA with conventional TBNA. This study demonstrated a superior diagnostic yield with EBUS-TBNA compared to conventional TBNA (using a 19-gauge needle) in patients with suspected sarcoidosis. An absolute increase in yield of 29.5% was demonstrated with EBUS-TBNA ($p < 0.05$; 95% confidence interval 8.6 to 55.4%). Sensitivity and specificity in the conventional TBNA group was 60.9% and 100% respectively compared with 83.3% and 100% in the EBUS-TBNA group. Of note, more lymph nodes were sampled in the EBUS-TBNA group but more passes were required in the TBNA group [21].

3.2. Bronchoalveolar Lavage (BAL)

BAL is a safe, minimally invasive and low cost technique which can be performed during flexible bronchoscopy but can also be performed via the EBUS bronchoscope. BAL samples can be used to support a diagnosis of sarcoidosis if a characteristic cytological predominance of lymphocytes is seen. A CD4+/CD8+ ratio of greater than 3.5 in the lymphocyte population has a high specificity (94%) for sarcoidosis. However a low ratio cannot be used to exclude a diagnosis of sarcoidosis [22]. BAL is also of use for microbiological testing particularly where mycobacterial disease is suspected.

3.3. Endobronchial and transbronchial lung biopsy

In patients with suspected sarcoidosis with evidence of parenchymal disease transbronchial lung biopsy (TBLB) can be used to obtain a diagnosis however the reported diagnostic yield is variable (44-90%) dependent on the number of sites sampled and the extent of the parenchymal disease [23]. TBLB has limited value in stage I disease and unlike EBUS-TBNA, TBLB carries a risk of pneumothorax and a higher risk of bleeding.

Endobronchial biopsy (EBB) can be carried out where there is evidence of airway involvement and even if the airways do not appear grossly abnormal EBB can further increase the yield with a 30% yield even in normal airways [24]. In practice EBB is typically performed when macroscopic disease is visible. EBUS-TBNA has been demonstrated to have superior diagnostic utility when compared with TBLB and endobronchial biopsy [3,25,26].

3.4. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA)

Transoesophageal EUS-FNA was first introduced in the early 1990s and was most commonly used by gastroenterologists to obtain tissue from pancreatic lesions. Subsequently this technique has been applied in the diagnosis of both intrabdominal and intrathoracic lesions. EUS-FNA enables access to lymph node stations 2L, 4L and most importantly

the lower mediastinum (7, 8, and 9). Nodes in the aortopulmonary window (5) and para-aortic nodes (6) can be visualized however sampling is limited by the proximity of vascular structures. The left adrenal gland and the left lobe of the liver can also be sampled. The accuracy of EUS-FNA is greater with ROSE. The technique can be combined with EBUS-TBNA and pulmonologists can train to carry out both procedures or (if appropriately trained) alternatively intubate the oesophagus with the EBUS bronchoscope, as described in some centres, EUS-B-FNA [27, 28]. The disadvantage of EUS-FNA without EBUS-TBNA is the range of nodes which can be accessed is more limited and it is not possible to sample hilar nodes. This is of particular relevance in sarcoidosis as hilar nodes and nodes anterolateral to the trachea are more commonly involved [7].

Diagnostic yield is high with EUS-FNA and has been reported as 82%, sensitivity 89% and specificity 96% [29]. When combined with EBUS-TBNA the yield is improved further and the range of nodes which can be sampled is greater.

3.5. Mediastinoscopy

Mediastinoscopy has been considered to be the gold standard mediastinal sampling method of choice particularly if other techniques such as TBLB are non-contributory. Mediastinoscopy is an invasive technique which requires a general anaesthetic and an overnight hospital stay. There are several approaches which allow access to different nodal stations and areas of the mediastinum. Cervical mediastinoscopy (via an incision at the suprasternal notch) allows access to the pretracheal, upper paratracheal (2R, 2L), lower paratracheal (4R, 4L), subcarinal (7) and hilar (10) nodes. The extended cervical mediastinoscopy also allows access to the anterior mediastinum including pre-aortic (6) and aortopulmonary window (5) nodes. There are currently no studies comparing EBUS-TBNA with mediastinoscopy in suspected sarcoidosis. Successful diagnosis with EBUS-TBNA may obviate the need for mediastinoscopy. This is not only likely to be more preferable to patients who may avoid an invasive procedure but there are also cost saving benefits as discussed previously.

3.6. Peripheral lymph node biopsy

Sarcoidosis involving peripheral lymph nodes is frequently asymptomatic. The incidence of peripheral lymph node involvement has been reported between 2-25%. High diagnostic yield with sampling of peripheral lymph nodes has been reported. In one study, at least one enlarged peripheral lymph node was found in 14.5% (79/546) of patients with a diagnosis of sarcoidosis [30]. The diagnostic yield of peripheral lymph node biopsy in these patients was 93% with no associated complications and significantly a lower cost compared to other techniques. The most common sites of involvement were the cervical nodes (31.3%) and supraclavicular nodes (29.9%). Ultrasound guided peripheral lymph node biopsy may be an option in patients who have contraindications to mediastinal sampling techniques.

The advantages and disadvantages of all these techniques are summarised in table 2.

Technique	Advantages over EBUS-TBNA	Disadvantages over EBUS-TBNA
Conventional TBNA	Lower cost More commonly performed by pulmonologists Shorter procedure time	Risk of complications/ injury ("blind" technique) Shorter needle throw therefore smaller tissue core Lower diagnostic yield Less extensive range of node sampling
EBB	Performed by pulmonologists Lower cost	Lower diagnostic yield
TBLB	Performed by pulmonologists Lower cost	Risk of complications Less useful in the absence of parenchymal disease
EUS-FNA	Improved access to some lymph node stations	Unable to access hilar nodes More commonly performed by gastroenterologists /radiologists
Mediastinoscopy	Larger histological tissue sample obtained High negative predictive value	Invasive procedure with risk of significant complications Generally performed by thoracic surgeons Requires general anaesthetic and overnight hospital stay Higher cost
Peripheral lymph node biopsy	Low cost (especially if ultrasound-guided without theatre) Low complication rate	Small proportion of patients with enlarged nodes

Table 2. Pros and cons of other non-EBUS sampling techniques in sarcoidosis involving mediastinum/nodal tissue and/or lung

4. Advantages and disadvantages of EBUS-TBNA

4.1. Compared to conventional TBNA

Unlike conventional TBNA, EBUS-TBNA allows access to a wider range of lymph nodes stations (2-4,7, 10 and 11) and therefore provides access to more distal locations. This is of particular relevance in granulomatous disease where sampling of multiple nodal stations can further increase diagnostic yield. This advantage is augmented further by combining EBUS-TBNA with EUS-FNA thereby enabling access to even more lymph node stations.

Conventional TBNA is a blind technique and therefore carries a risk of bleeding through potential damage to vascular structures. EBUS-TBNA carries a lower bleeding risk as it is performed under real time ultrasound guidance. The use of Doppler mode imaging allows accurate visualisation of vessels prior to sampling. Furthermore because sampling is carried out under direct vision it is possible for the EBUS-TBNA needle to be inserted further into the

sampling area with each pass compared with sampling during conventional TBNA. Larger cores of tissue can therefore be obtained compared with conventional TBNA. Once again this is particularly important in granulomatous disease.

The cost of equipment and additional staff time required in order to carry out EBUS-TBNA makes it a more expensive technique when compared with conventional TBNA, however as discussed earlier the overall cost saving gained from avoiding the need for mediastinoscopy is likely to be greater for EBUS-TBNA than with conventional TBNA.

4.2. Compared to mediastinoscopy

Mediastinoscopy has been considered to be the gold standard mediastinal sampling method of choice particularly if other techniques such as TBLB are non-contributory. Mediastinoscopy is an invasive technique which requires a general anaesthetic and an overnight hospital stay unlike EBUS-TBNA which is typically carried out under light conscious sedation as a day case procedure. Clearly there are financial advantages to a less invasive approach and it is likely to be more preferable to patients. Mediastinoscopy carries a risk of major complications (0.5%) and 1.4-2.3% risk of significant complications such as supraventricular arrhythmias. It also results in a neck scar and the development of adhesions following mediastinoscopy may hinder future attempts at lymph node sampling [16]. Previous neck surgery is a relative contraindication to mediastinoscopy. As discussed previously, the risk of complications with EBUS-TBNA is lower than with mediastinoscopy. The range of nodes which are accessible via EBUS-TBNA is greater than with mediastinoscopy particularly the hilar nodes. This is of relevance in granulomatous disease as the hilar nodes are frequently affected.

Smaller tissue samples are obtained with EBUS-TBNA compared to mediastinoscopy and as discussed earlier this can affect the adequacy of tissue samples obtained. For this reason the negative predictive value of EBUS-TBNA is lower. This is particularly relevant when sampling for malignancy. If there is concern that malignancy such as lymphoma is a possible cause for lymphadenopathy, mediastinoscopy should be the sampling technique of choice. Alternatively, a non-diagnostic EBUS-TBNA result should be considered for further investigation with mediastinoscopy. In experienced centres where adequate tissue samples are obtained through EBUS-TBNA the technique may be an alternative option for patients who have been deemed not fit for invasive mediastinoscopy.

5. Comparative studies of EBUS-TBNA with other mediastinal sampling techniques

Combining EBUS-TBNA with standard bronchoscopic techniques has been shown to improve diagnostic yield further. This is important as improved accuracy in non-invasive techniques may obviate the need for mediastinoscopy. A number of studies have evaluated combining EBUS-TBNA.

A prospective study carried out in an experienced centre examining the safety and efficacy of combining EBUS-TBNA with TBLB and EBB for the diagnosis of sarcoidosis in an unselected group of patients [26] demonstrate a sensitivity of standard bronchoscopic techniques (TBLB and EBB) of 35% ($P < 0.001$) compared with 85% with EBUS-TBNA. Combining the two techniques resulted in a diagnostic yield of 93% ($P < 0.0001$). In this study the relatively low sensitivity with TBLB and EBB was attributed to the fact that the majority of patients had stage I sarcoidosis without evidence of parenchymal disease.

Another study in which patients with clinical and radiological evidence of sarcoidosis underwent EBUS-TBNA, TBLB and BAL also supports a combined approach. The diagnostic accuracy was superior with EBUS-TBNA compared with TBLB ($p < 0.001$). Analysis of BAL samples demonstrated that the CD4/CD8 ratio was >3.5 in 65.7% of patients with a final diagnosis of sarcoidosis. The diagnostic yield for all modalities of sampling was very high (100%) in patients with stage II sarcoidosis, however EBUS-TBNA was superior to all other modalities for stage I disease. Of note, all patients underwent cross sectional imaging prior to the procedure and had nodes measuring $>10\text{mm}$ diameter. ROSE was also utilized [31].

There is evidence to support the use of combined flexible bronchoscopy and EUS-FNA +/- EBUS-TBNA in order to increase diagnostic yield. Tournoy et al, confirmed this in a study of patients with suspected sarcoidosis who did not have a definite diagnosis following standard bronchoscopic techniques (TBNA, TBLB and EBB) [32]. These patients were sent for EBUS-TBNA and/ or EUS-FNA. A definite diagnosis of sarcoidosis was established in 45% patients following standard flexible bronchoscopic procedures. However diagnostic yield increased by a further 39% with the addition of EBUS-TBNA and/ or EUS-FNA.

5.1. Newer techniques

EBUS-guided forceps or transbronchial needle forceps are currently under evaluation. This sampling tool is a combination of a needle and forceps which can be passed through the working channel of the EBUS scope. These forceps can potentially allow larger histological cores of tissue to be obtained. An initial pilot study has shown this tool to be safe and specific diagnosis was established in 86% of patients [33].

6. Conclusion

EBUS-TBNA is a safe, well tolerated and effective mediastinal sampling tool which can be used in the diagnosis of suspected sarcoidosis. As with all mediastinal sampling techniques, histological samples should be interpreted in the context of clinical and radiological findings. EBUS-TBNA has been shown to have a higher diagnostic yield compared to conventional bronchoscopic techniques such as EBB, TBLB and TBNA. Combining EBUS-TBNA with other modalities such as EUS-FNA may further increase diagnostic yield as may the use of newer sampling tools such as the transbronchial needle forceps. Improved accuracy and yield with this technique may obviate the need for further invasive sampling attempts such as mediastinoscopy. This consequently reduces the overall cost compared to other techniques and

importantly reduces the potential for procedure related complications. Future studies are required to further evaluate this technique in sarcoidosis as compared to existing sampling techniques.

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