Abstract

Intrathoracic lymphadenopathy is a common problem encountered in clinical practice and is caused by a wide variety of diseases. Traditionally, the mediastinal lymph nodes were sampled using conventional transbronchial needle aspiration (TBNA), or surgical methods such as mediastinoscopy, and thoracotomy (open or video-assisted thoracoscopic surgery). However, surgical modalities including mediastinoscopy are invasive, expensive, and not universally available. Moreover, they are associated with considerable morbidity and mortality. Conventional TBNA although minimally invasive has a low diagnostic yield. In the last decade, endobronchial ultrasound-guided TBNA (EBUS-TBNA) has emerged as the diagnostic procedure of choice in evaluating undiagnosed intrathoracic lymphadenopathy. EBUS-TBNA is also currently the preferred modality in the mediastinal staging of lung cancer. The procedure is minimally invasive, safe, and can be performed as a day-care procedure. In the era of personalized medicine in lung cancer, optimizing the procedure, sample collection, and processing are crucial, as more tissue is required for performing a wide array of molecular tests. Despite its widespread use and acceptance, the diagnostic sensitivity of EBUS-TBNA is still low. To maximize the yield, cytologists and physicians should be aware of the technical details of the procedure. Herein, we discuss the technique of performing EBUS-TBNA, its indications, contraindications, and the processing of the samples at our bronchoscopy suite. We also highlight the challenges faced by the cytologists and clinicians while processing EBUS aspirates.

Keywords: Bronchoscopy, cytology, endoscopic ultrasound, ROSE, sarcoidosis, tuberculosis

INTRODUCTION

Intrathoracic lymphadenopathy is a common problem encountered in pulmonary medicine. A wide range of diseases can present with intrathoracic lymphadenopathy including malignant (lung cancer, lymphoma, and others) and benign disorders (tuberculosis, sarcoidosis, and others). A definite diagnosis is thus crucial in the management of these disorders. Several techniques are available for sampling the enlarged mediastinal lymph nodes, including mediastinoscopy, thoracotomy [open or video-assisted thoracoscopic surgery (VATS)], computed tomography (CT)-guided transthoracic sampling, conventional transbronchial needle aspiration (TBNA), and recently endobronchial ultrasound (EBUS)-guided TBNA. Invasive surgical procedures such as mediastinoscopy are considered the reference standard in evaluating intrathoracic lymphadenopathy (especially in lung cancer staging).[1,2] However, mediastinoscopy is not only invasive, expensive, and requires considerable expertise, but it is also associated with significant morbidity and mortality.

CT-guided transthoracic sampling of mediastinal and hilar nodes is a less invasive alternative, but the rates of pneumothorax are unacceptably high (up to 48%).[3] The introduction of TBNA using flexible bronchoscope provided a minimally invasive alternative to surgical sampling of intrathoracic nodes with a reduced incidence of complications.[4] However, the sensitivity of this conventional or “blind” (unguided) TBNA procedure is low, operator dependent, and varies with the location and size of the mediastinal lymph node.[5,6] In fact, the variable and poor yield of conventional TBNA has discouraged pulmonary physicians from practicing it widely.[7]

The advent of EBUS has enabled sampling of intrathoracic nodes under real-time vision. EBUS-TBNA is a safe and minimally invasive procedure and is currently the preferred modality in the mediastinal staging of lung cancer. The procedure is minimally invasive, safe, and can be performed as a day-care procedure. In the era of personalized medicine in lung cancer, optimizing the procedure, sample collection, and processing are crucial, as more tissue is required for performing a wide array of molecular tests. Despite its widespread use and acceptance, the diagnostic sensitivity of EBUS-TBNA is still low. To maximize the yield, cytologists and physicians should be aware of the technical details of the procedure. Herein, we discuss the technique of performing EBUS-TBNA, its indications, contraindications, and the processing of the samples at our bronchoscopy suite. We also highlight the challenges faced by the cytologists and clinicians while processing EBUS aspirates.

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procedure in the evaluation of undiagnosed mediastinal adenopathy and staging of lung cancer.\cite{6-13} Herein, we discuss the techniques involved in performing a successful EBUS-TBNA and the challenges faced.

**What are the instruments used for the EBUS-TBNA procedure?**

A dedicated bronchoscope with a convex ultrasound transducer incorporated at the distal end (echoendoscope) is used for EBUS-TBNA [Figure 1]. The distal end has a balloon which can be inflated with saline, allowing optimal contact of the ultrasound transducer with the airway. The bronchoscope has a working channel through which the TBNA needle can be introduced. The commonly used needle is a 22G needle, while TBNA needles of varying sizes are also available commercially (19G, 21G, and 25G). Novel needle design, such as the ProCore\textsuperscript{TM} needle (provides a core tissue for histopathology along with cytology samples) or the flexible 19G needle, have been claimed to yield superior sample for analysis, but requires further research.\cite{14,15}

**What are the indications and contraindications of EBUS-TBNA?**

The most common indications include the diagnosis and staging of lung cancer, and evaluation of undiagnosed intrathoracic lymphadenopathy.\cite{13,16,17} In addition, lung and mediastinal masses adjacent to the larger airways are also accessible to sampling by EBUS-TBNA. Uncommonly, EBUS has also been used to sample left adrenal gland.\cite{18} Rarely, pulmonary embolism (thromboembolic as well as tumor) may be diagnosed incidentally, while performing EBUS.\cite{19,20} EBUS has also been employed for fiducial placement and transbronchial needle injection of chemotherapeutic or photodynamic therapeutic agents to manage centrally placed malignant tumors and local recurrence of lung cancer, respectively.\cite{21,22}

Anecdotal reports suggest a role of EBUS in diagnosing and treating mediastinal bronchogenic cyst.\cite{23}

The usual contraindications for performing flexible bronchoscopy also applies to EBUS-TBNA. Most of these contraindications are relative. Broadly, these include patients at a higher risk of bleeding or a higher risk of developing pulmonary or cardiovascular decompensation (severe hypoxemia, poorly controlled heart failure, cardiac arrhythmias, recent myocardial infarction, and others), either due to EBUS-TBNA itself or the sedation used for the procedure. EBUS-TBNA is generally a safe procedure, and complications are rare, even in children.\cite{13,24,25} However, a potential risk of mediastinitis and pericarditis exists.\cite{26,27}

**How to perform EBUS-TBNA?**

In general, EBUS-TBNA is performed as a day-care procedure in the bronchoscopy suite, under conscious sedation (with the subject breathing spontaneously) or under general anesthesia. The lymph node stations that are accessible by EBUS-TBNA include stations 2R/L, 3P, 4R/L, 7 10R/L, and 11R/L.\cite{28} At our center, we perform EBUS-TBNA under conscious sedation using intravenous midazolam and fentanyl.\cite{13} After an overnight fast, subjects are administered intramuscular atropine (0.6 mg) and promethazine (25 mg), 15 min before the procedure. Topical lignocaine (10%) is sprayed over the oropharynx, and lignocaine solution (2 mL aliquots of 1% lignocaine) is instilled bronchoscopically over the vocal cords and airways.\cite{29} The EBUS scope is then introduced through the oral cavity. After a quick inspection of the airway, the mediastinal and hilar nodes are visualized using EBUS. The use of the Doppler imaging helps in identifying vascular structures, adding to the safety of the TBNA procedure. The size of the lymph node is measured and the endosonographic characteristics are noted.\cite{30,31} Subsequently, the needle along with its sheath is suitably positioned, and under real-time ultrasound guidance the node is punctured. An internal stylet provided with the needle serves to clear the bronchial cartilage, which could enter the needle during penetration of the airway. Following this step, the needle is moved back and forth (usually 10–20 “revolutions”) within the node, under real-time ultrasound guidance. The EBUS-TBNA needle comes with a 20 mL vacuum (VacLok\textsuperscript{TM}) syringe, which is attached to the needle while performing fine-needle aspiration (FNA). The entire procedure is repeated (number of passes in each node) till sufficient material is available for various investigations (including samples for microbiology and flow cytometry). In general, we obtain two or three passes from each enlarged lymph node.

**What is EUS-B-FNA?**

The mediastinal lymph nodes can also be accessed with an echoendoscope introduced into the esophagus. Once the scope is in the esophagus, ultrasonography is used to identify various landmarks and lymph node stations. Puncturing the node and obtaining the sample are performed, as described above. Initially, this procedure was described using a dedicated endoscopic ultrasound (EUS) by gastroenterologists. Alternatively, the same EBUS scope can also be introduced in to the esophagus to perform “EUS with echobronchoscope-guided...
What are the challenges with EBUS-TBNA?

Availability and cost

EBUS-TBNA has been widely adopted across the globe. Though available in larger cities, this newer diagnostic modality is not yet universally available across India. In a recent survey of bronchoscopy practices conducted among 669 respiratory physicians throughout India, only 27% were performing EBUS-TBNA. On the contrary, 74% of the respondents were using conventional TBNA. Although EBUS-TBNA is cost effective and safer than the more invasive surgical procedures (such as mediastinoscopy or VATS), it still incurs considerable expense. A significant proportion of patients visiting our bronchoscopy suite are economically disadvantaged, and cannot afford a EBUS-TBNA needle. The situation is likely to be same throughout our country, though data are lacking. Besides, even where EBUS-TBNA is available, the facilities for ROSE are not available uniformly. The reasons for this include, a deficiency of the required infrastructure, the additional cost, and the availability of a skilled cytologist on-site.

Skills and training

As with other interventional procedures, the safety and diagnostic yield of EBUS-TBNA depends on the skills and expertise of the operator, which in turn requires adequate training. Consensus based on expert opinion suggested that at least 40 EBUS-TBNA should be performed for becoming proficient in the procedure. A recent meta-analysis concluded that performing at least 37–44 procedures is essential to overcome the initial learning curve. Also, training on a simulator was shown to be as good as the traditional apprenticeship-based training. Lack of formal training opportunities and sufficient experience could be a major factor why only 27% of our bronchoscopists were performing EBUS-TBNA. In fact, nearly half of the respiratory physicians acquired their bronchoscopy skills after completing their fellowship, indicating the lacuna in the current training.

Lack of uniformity in the technique and its impact on diagnostic yield

Despite widespread use, the technical aspects of the EBUS-TBNA are not yet standardized. Apart from the patient-related factors such as the size, location, and etiology of the lymphadenopathy, procedure-related factors also play a major role in the diagnostic yield of EBUS-TBNA. The size of the needle used, the use of internal stylet, the number of jabs, the number of nodes sampled, the number of passes in each node, the amount to suction employed during EBUS-TBNA, and the use of ROSE differs widely across different centers. The commonly available needles (21G and 22G) appear to be similar, especially in sarcoidosis. Whether the newer needles (19G needle or needles capable of providing core tissue) could improve the diagnostic performance of EBUS-TBNA remains to be seen. So far, none of them have been shown to be superior to the currently used needles. The apparent advantage gained by a larger needle is often offset...
by the hemorrhage which accompanies its use. A randomized trial of EBUS-TBNA in subjects with sarcoidosis showed that the number of revolutions within the node (10 or 20) did not affect the diagnostic yield or adequacy. Whether this holds true for other diseases such as lung cancer is not known. Similarly, the quality of the aspirate and diagnostic performance of EBUS-TBNA have been found to be similar with or without the use of an internal stylet.

ROSE has the potential to improve diagnostic performance by ensuring adequacy of the specimens and providing feedback to the operator before concluding the procedure. However, the existing literature is equivocal and does not suggest a clear benefit of using ROSE to improve the diagnostic performance of EBUS-TBNA or shorten the procedure duration. In resource-limited settings where ROSE is not feasible, training of respiratory physicians and implementing telecytology is an attractive option. Several questions still remain unanswered, such as the optimal number of nodes and the optimal number of passes in each node to improve the sensitivity of EBUS-TBNA.

Low diagnostic yield

While it is true that a positive result obtained by EBUS-TBNA may obviate the need for a more invasive procedure such as mediastinoscopy or VATS, the diagnostic sensitivity of EBUS-TBNA is generally low. The sensitivity of EBUS-TBNA at our center, and the AQuIRE (American College of Chest Physicians Quality Improvement Registry, Education, and Evaluation Registry) were only 61.2% (of the total 972 participants) and 51.3% (n = 1299), respectively. Also, the sensitivity may be even lower, when performed outside academic centers. Liquid-based cytology preparations when available, can improve the diagnostic sensitivity of EBUS-TBNA as compared to conventional smears (82.1% vs. 56% in one study). Further, the diagnostic performance may be different in different settings. For example, the pooled sensitivity of EBUS-TBNA in mediastinal restaging following neo-adjuvant chemotherapy (67%) is lower than that of initial mediastinal staging in treatment-naive lung cancer (88%).

Thus, in general, a negative EBUS-TBNA requires either confirmation by a second procedure or close follow up.

The role of cytologists

The advancements in lung cancer, especially non-small cell lung cancer (NSCLC) necessitates a multitude of molecular tests to be performed, and the advent of minimally invasive diagnostics such as EBUS-TBNA, would mean that the cytologists would have very little tissue at their disposition. Thus, the role of cytologist in the current era cannot be overemphasized. Available literature suggests that the samples obtained from EBUS-TBNA and resected surgical specimens are both equally sufficient, even for performing a complete mutational testing panel. In a prospective study of 306 lung cancer patients undergoing EBUS-TBNA, 96.9% had sufficient samples for epidermal growth factor receptor (EGFR) mutation testing by Sanger sequencing, Kirsten rat sarcoma (KRAS) gene mutation testing by Cobas real-time polymerase chain reaction, and anaplastic lymphoma kinase (ALK) rearrangement tested by fluorescence in situ hybridization. A recent meta-analysis showed that the pooled probability to obtain sufficient sample for EGFR and ALK testing was 94.5% and 94.9%, respectively.

Whether EBUS-TBNA sample is adequate to test for programmed death ligand-1 (PD-L1) expression, a marker useful to predict response to immunotherapy (anti-PD-1/anti-PD-L1 therapy), remains uncertain. Though some reports suggest that the sample obtained from EBUS-TBNA or small biopsy is as good as surgically resected specimens; data to the contrary are also available. Most of these data are retrospective in nature, and large multicenter prospective studies would be required.

Thus, the judicious use of the limited material available from EBUS-TBNA is of paramount importance and requires a skilled cytologist. As with clinicians, cytologists require formal training and should be well versed with the existing recommendations of ancillary testing.

Conclusions

In summary, the introduction of EBUS-TBNA in clinical practice has revolutionized the management of intrathoracic lymphadenopathy. EBUS-TBNA has replaced mediastinoscopy as the initial procedure in the staging of lung cancer and is currently the preferred modality for the investigation of intrathoracic lymphadenopathy. Several challenges need to be addressed to improve the yield of EBUS-TBNA, especially in the era of personalized medicine where the need for tissue is greater than ever before. The feedback which the cytologist provides to the clinician is vital to improve the overall diagnostic performance of EBUS-TBNA.

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Conflicts of interest

There are no conflicts of interest.

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