Introduction

Lung cancer remains the leading cause of death among all malignancies worldwide, representing 18.4% of all cancer-related mortality (1). Although transbronchial needle aspiration (TBNA) has been part of the diagnostic algorithm for lung cancers for decades (2,3), real-time ultrasound-guided TBNA has become mainstream only recently. Endobronchial ultrasound (EBUS) was first introduced in 1992 as a 360° rotating radial probe (4) which allowed visualization of mediastinal structures, vasculature, lymph nodes and tumors adjacent to the central airways. This technology however, was mostly a novelty due to the inability to perform concurrent biopsy of the visualized structures. The linear EBUS bronchoscope, with a separate working channel that allowed for real-time EBUS-TBNA, was introduced in 2002 (5) and rapidly became an essential tool for both diagnosing and staging of lung cancer. Given its utility in assessing mediastinal structures, EBUS has also gained a prominent role in the evaluation of non-cancer etiologies of mediastinal and hilar lymphadenopathy (6).

EBUS-TBNA has become the preferred method of mediastinal staging of lung cancer as per the American College of Chest Physicians (7). Since the introduction of
EBUS, many advances in techniques and tools for EBUS-guided biopsy have emerged over the past several years. Here, we review the recent advancements in equipment and tools related to linear EBUS-guided bronchoscopy and biopsy. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at http://dx.doi.org/10.21037/med-20-25).

**Data review**

Literature search was done via the PubMed® database. We included all types of articles and study design, including original research, meta-analyses, reviews, and abstracts. Only studies published in English were considered.

**Equipment**

*Bronchoscopes*

Although endoscopic ultrasound (EUS) was developed in the 1980s, it was not until years later that EBUS bronchoscopes became readily available due to the technical challenges in adapting this technology for the airways (8,9). After multiple prototypes, the linear (convex-probe, cp) EBUS bronchoscope was introduced into clinical practice in 2002 (5). The linear EBUS bronchoscopes have an elongated curved array ultrasound transducer at the distal tip with a camera and a light source that is offset at an angle (10-12). It allows for both direct visualization within the airways as well as ultrasonographic view of the lymph node, needle device, and vasculature with color flow doppler. Currently on the market, there are three companies that produce EBUS bronchoscopes: Olympus, Fuji and Pentax (Table 1).

| Company | Scope          | Working channel | Direction of view | Outer diameter | Field of view | Frequency | Method of image transmission |
|---------|----------------|-----------------|-------------------|----------------|---------------|-----------|-------------------------------|
| Olympus | BF-UC180F      | 2.2 mm          | Forward oblique 35 degrees | 6.9 mm         | 80 degrees    | 5–12 MHz | Fiberoptic                   |
| Fuji    | EB-530US       | 2.0 mm          | Forward oblique 10 degrees | 6.7 mm         | 120 degrees   | 5–12 MHz | Charge coupled device         |
| Pentax  | EB19-J10U      | 2.2 mm          | Forward oblique 45 degrees | 7.3 mm         | 100 degrees   | 5–13 MHz | Charge coupled device         |
|         | EB-1970UK      | 2.0 mm          | Forward oblique 45 degrees | 7.4 mm         | 100 degrees   | 5–10 MHz | Charge coupled device         |

by Pentax and Fuji is the imaging system. Olympus uses a fiberoptic system for transmitting the bronchoscopic images while the other manufacturers utilize a charge coupled device (CCD) chip within the distal tip of the scope. The images produced from CCD are higher quality digital images (13). However, the CCD chip has a larger footprint than the fiberoptic system, necessitating a smaller working channel at 2.0 mm, except for the most recent Pentax EBUS bronchoscope (EB19-J10U), which has a 2.2 mm working channel similar to the Olympus bronchoscope. The larger working channel allows for use of 19G and 21G needles which are incompatible with the other systems and may allow for enhanced suction capability. Importantly, it is worth mentioning that in general, due to the anterior location and smaller size of the working channel, the EBUS bronchoscopes have limited suction capacity. Thus, it is recommended to use a dedicated therapeutic bronchoscope for the clearance of secretions before airway inspection and after performing EBUS-TBNA.

The other differences include the smaller outer diameter of the Fuji scope which could make it more comfortable for patients, as well as the 10 degree forward oblique view as opposed to the 35–45 degree forward oblique view of Olympus and Pentax (14). This allows simultaneous visualization of the distal end of the scope as well as the ultrasound image, providing a familiar view for seasoned bronchoscopists interested in adding EBUS to their skill-set.

**Ultrasound processors**

Each EBUS bronchoscope requires a different ultrasound processor. From Olympus, there are the EU-ME1 and EU-ME2 processors. The EU-ME1 was launched in 2009 and at the time, was the first processor to combine electronic and mechanical scanning into one device, so that multiple scopes and ultrasound probes for both pulmonary and GI procedures, could all be connected to the same unit.
Since the introduction of EBUS-TBNA, multiple needles have emerged on the market. Needles of various sizes and designs are available for tissue acquisition (Figure 1). Currently, there are three companies that produce the majority of EBUS-TBNA needles: Olympus, Boston Scientific and Cook.

Olympus has designed the ViziShot and ViziShot 2 needles. The ViziShot includes a 21-gauge (21G) and 22G, while the ViziShot 2 class includes a 21G and 22G as well as a 19G Flex needle (Olympus Respiratory America, Redmond, WA). Due to the stiffness of the needle, there is often limited flexion of the distal tip of the EBUS bronchoscope when the needle is in the working channel (Table 2) (25). The second generation ViziShot 21G and 22G needles incorporate spiral laser cuts on the needle surface, which significantly increase flexibility and ultrasonographic needle visualization compared to the original ViziShot design. The ViziShot2 Flex 19G needle has the greatest flexibility, which increases the ability to sample from locations which require more scope angulation, such as 4L (25) or within the upper lobes (26). Additionally, with its larger lumen, the 19G needle was marketed as one which can obtain larger amounts of tissue to allow for enhanced histological analysis.

Boston Scientific produces the Expect 22G and 25G TBNA needles, Acquire fine needle biopsy (FNB) needle in 22G and 25G, and the CoreDx mini-forceps (Boston Scientific, Watertown, MA). The Expect needle is made from cobalt chromium, as opposed to stainless steel, which enhances its ability to penetrate through stiffer tissue or cartilage and withstand multiple passes. This may shorten procedural time (27) as less time is spent on failed passes or exchanging needles. The Acquire needle has a Franseen needle tip, which consists of 3-prongs that increases the overall cutting surface and is designed for enhanced tissue acquisition while minimizing fragmentation of the specimen. Additionally, the 3 needle points provide greater control at the puncture site. CoreDx mini-forceps is used in conjunction with EBUS-TBNA to obtain additional biopsy samples for histology evaluation.

Cook Medical has the EchoTip Ultra TBNA needles and the EchoTip ProCore FNB needles, both which include a 22G and 25G (Cook Medical, Bloomington, IN). The unique feature of the ProCore needle is a Menghini bevel with a lateral cutout just proximal to the tip of the needle, called a core trap, which is designed to facilitate additional tissue sampling. With the core trap, despite the smaller size of the 25G ProCore needle, it is able to obtain sufficient samples when compared to the 22G (28).
21G and 22G needles
Historically, the EBUS-TBNA 22G needle was developed first, followed shortly by the 21G needle. Multiple studies comparing the diagnostic yield of both sizes of needles, have not found a significant difference (29-31). There is a high success rate of diagnosis with both, with a diagnostic yield for malignancy of 96.6% with 21G needles and 95.3% with 22G needles (29) (Figures 2, 3). In a large retrospective review of over 1,200 patients who underwent EBUS-TBNA, there was similarly no difference in diagnostic yield or specimen adequacy between the 21G and 22G needles (32).

Although both needles achieved similar diagnostic yield, there was better characterization of non-malignant diseases and histologic preservation of malignant diseases with the 21G needle (29,30). Despite better characterization of benign diseases, especially sarcoidosis, with the 21G needle (29) the overall diagnostic ability of both the 21 and 22G needles for sarcoidosis is not as robust as in
non-small cell lung cancer (NSCLC). In two studies by Herth and colleagues, they found the diagnostic ability of the 22G needle for sarcoidosis to be 24–33% (33,34), while a different study found a higher rate of sarcoid diagnosis at 61%, but still much lower than the rate of NSCLC diagnosis at 80% (35). A systematic review of 15 studies evaluating use of EBUS-TBNA in sarcoidosis found a pooled diagnostic accuracy of 79%, with the yield ranging between 54–93% (36), highlighting the substantial variability in diagnostic sensitivities reported for sarcoidosis. The use of EBUS-TBNA to diagnose lymphoproliferative malignancies has also had similar pitfalls (34), with diagnostic sensitivities ranging from 38–90% (37-39). A meta-analysis of 14 studies evaluating EBUS-TBNA with 21G or 22G needles in diagnosing lymphoma reported a pooled sensitivity of 66% (40).

**19G needle**

Due to the limitations of the 21 and 22G needles, most notably the challenges with diagnostic accuracy in lymphoma and sarcoidosis, additional tools were created to address this issue. In 2015, the Olympus ViziShot 2 Flex 19G needle was introduced which was designed to provide larger tissue samples as well as greater flexibility, and several studies have evaluated the performance of the 19G needle in both malignant and benign disease.

Tyan et al. reported a diagnostic yield of 89% (42/47 patients) with the Vizishot Flex 19G needle (25). The majority of cases were done with conscious sedation and application of needle vacuum-suction during lymph node sampling. Despite the larger bore of the 19G needle, there were no complications seen except for mild bleeding, which did not require intervention other than local suctioning. Similarly, another group reported 13 patients who underwent EBUS-TBNA with 19G needle, in whom minor bleeding was seen in one patient which self-resolved (41).

Multiple studies evaluating the performance of 19G needle have shown no significant difference in diagnostic yield between the 19G needle, as compared to the 21G or 22G needles (42-44). Specimens from the 19G needle
were noted to be bloodier overall (59% with 19G vs. 19% with 22G) (43). However, this did not affect the diagnostic yield (45). Of interest, one study showed the 19G needle achieved less adequate samples compared to 22G (46% with 19G vs. 73% with 22G) (43), while another study showed the 19G needle achieved large volumetric and cohesive tissue samples (44).

Perhaps most significantly, a randomized controlled trial by Dooms et al. found no superiority with 19G in procuring tissue core for cell block (45). However, the 19G needle did achieve larger tissue surface area which may be beneficial for molecular marker testing in NSCLC. Subsequent prospective randomized trials comparing EBUS-TBNA samples obtained from 19G and 22G concluded that specimens acquired from the 19G needle had significantly more tissue, as well as significantly more tumor cells (46). These benefits were seen without any increase in complications (46,47). With advanced molecular testing in NSCLC becoming more customary, the 19G needle may obtain more tissue to support these tests (48).

Although overall diagnostic yield in NSCLC appeared to be similar with 19G as compared to 22G, there are a subset of conditions which require tissue architecture to diagnose and may benefit from larger bore needles. Several studies have compared the diagnostic yield in sarcoidosis and lymphoma when using different needle sizes. Pooled results from these studies show an overall increased diagnostic yield in both sarcoidosis and lymphoma with the 19G needle or mini-forceps, which are classified as “histology” tools, as compared to the 21G and 22G needles, which are classified as “cytology” tools (44). With “histology” tools, the diagnostic yield was 68% vs. 51% with “cytology” tools for sarcoidosis. Similarly, in lymphoma, the diagnostic yield with “histology” tools was 63% vs. 21% with “cytology” tools (24).

25G needle

There are limited data on the use of 25G needles in EBUS-TBNA. A retrospective study comparing the efficacy of the Boston Scientific Expect 25G to the Olympus ViziShot 22G needles in EBUS-TBNA, demonstrated comparable diagnostic accuracy and specimen adequacy (92%, 73/79 with both needles) (49). In the setting of next-generation sequencing, Stoy et al. showed that the 25G needle was able to obtain adequate tissue and similar diagnostic yield as the 22G needle (50). Of note, given the small caliber of the 25G needle, it is vulnerable to clotting after repeated lymph node sampling which could affect yield, but this may be countered with wiping the stylet with heparin after each use. Heparin priming of the needle did not increase blood contamination of the specimen, or negatively affect cytological or histological analysis (51).

Most of the experience with 25G needles is in the gastrointestinal (GI) literature for endoscopic ultrasound-fine needle aspiration (EUS-FNA) of pancreatic lesions. A recent meta-analysis of over 500 studies comparing 22G vs. 25G needles in EUS-FNA found no significant difference in diagnostic accuracy between the two needles (52). However, a meta-analysis from 2013 found that while the specificity was similar between both 22G and 25G needles (1.00 in 22G vs. 0.97 in 25G, P=0.97), the sensitivity for diagnosing malignancy was higher with the 25G needle (0.85 in 22G vs. 0.93 in 25G, P=0.0003) (53). The increased sensitivity with the 25G needle might theoretically be due to fewer bloody aspirates, facilitating cytological interpretation without compromising cellular yield, as well as both greater

Figure 3 Metastatic breast cancer diagnosed by EBUS-TBNA with an Olympus 22G ViziShot needle. (A) Pap stain at ×40. (B) Diff-Quik ×10.
needle flexibility and better to-and-fro traversal passage of the needle to the target lesion. Importantly, there was a discrepancy between diagnostic yield obtained from rapid on-site evaluation (ROSE) and cell blocks when the 25G needle was used for EUS-FNA. Although ROSE established malignancy in 100% of patients, it only resulted in a diagnostic cell block in 81% of cases with a 25G needle (54). Although these studies are from GI procedures, these results may extrapolate to EBUS-TBNA and may be important when choosing needle size.

**Fine needle aspiration (FNA) versus Fine needle biopsy (FNB)**

FNB needles were designed to obtain larger tissue and core samples for improved histological and cytological evaluation, compared to fine needle aspiration needles. The choice between FNA and FNB needles has been evaluated, mostly in the GI literature as well. A recent study assessing the efficacy of the Acquire FNB needle in EUS-FNB evaluation of intra-abdominal lesions found that a core was present in 90% of the samples (55). In a small prospective study of patients with pancreatic lesions, individuals were randomized to either EUS-FNA with Olympus 22G needle or EUS-FNB with Cook EchoTip ProCore 22G needle. Diagnostic yield was the same in both groups at around 83%, but definitive diagnosis was established with fewer punctures with FNB as compared to FNA (1.11 vs. 1.83, P<0.05) (56), which has been consistent in other studies as well (57). Similarly, a meta-analysis of nine studies comparing the ProCore FNB needle to standard FNA needles found no difference in diagnostic adequacy or accuracy, but the number of passes required for diagnosis was lower with FNB (58) (Figure 4).

Intranodal forceps, or mini-forceps, biopsy (IFB) were introduced as a means to obtain larger tissue samples. With EBUS-IFB, mini-forceps are passed through the bronchoscope into the target lymph node following a standard TBNA puncture (Figure 5, Video 1). Mini-forceps has a role in obtaining larger amounts of tissue which may aid in preserving histopathology for diagnosis of sarcoidosis and lymphoma (Figure 4B). With the use of IFB as compared to TBNA, the diagnostic yield for both sarcoidosis and lymphoma were increased (34,59). One study showed the rate of diagnosis for sarcoidosis increased from 24% to 88% and for lymphoma from 11% to 81% between 22G TBNA and IFB respectively (34). In malignant disease, IFB also has a role in obtaining additional tissue for molecular marker analysis (60). Despite larger samples, the safety profile of EBUS-IFB is similar to EBUS-TBNA, with an overall complication rate of 1.5% and no deaths in the published cases of EBUS-IFB (60).

**Tool selections**

With a multitude of TBNA needles to choose from, there is no clear “best needle” and each size and type of needle may have a role depending on the clinical situation. There was a recent survey of bronchoscopists evaluating different EBUS-TBNA needles which showed that providers rated the Boston Scientific Expect 25G and Olympus ViziShot 22G highest for ease of insertion, and Boston Scientific
Expect 22G for durability, but the highest overall rated needle was the Olympus ViziShot 22G (61). The variability and lack of overall consensus regarding needles highlights the subjective nature of needle preference, and the unique design features of each type of needle may be best suited for different clinical scenarios.

Often times the ultimate selection in tools may depend on a variety of factors, including local availability, operational costs, sampling location and histopathologic diagnostic requirements. Given the wide selection of needles, a single medical center may not stock all the options. Therefore, operators will need to be aware and comfortable with the use of the needles at their respective institutions.

**Cost analysis**

EBUS significantly reduced the cost of both diagnosing and staging lung cancer when compared to surgical staging. The ASTER study randomized patients with potentially resectable NSCLC to surgical staging or EBUS-TBNA, with subsequent surgical staging if EBUS-TBNA was negative (62). With this strategy, the average cost in the surgical arm was 10,459€ compared to 9,713€ with EBUS. The majority of the cost savings was from preventing unnecessary surgery, as mediastinoscopies were avoided in close to half the patients and thoracotomies were reduced by 11%. In addition, the sensitivity for nodal metastases (N2 or N3) was higher with EBUS at 94% compared to mediastinoscopy at 79% (62).

When EBUS-TBNA was compared to blind TBNA, there was still a cost savings associated with EBUS when accounting for the subsequent necessary surgical procedures for complete staging (63). With EBUS, more lymph nodes were sampled and overall diagnostic yield with EBUS was higher at 87%, compared to only 59% in the blind TBNA group. Therefore, there were less patients in the EBUS group who ultimately required surgery compared to those who received blind TBNA (11% vs. 24%), and the overall estimated average cost savings with EBUS was about $787 per procedure. Another study estimated an average savings of 1,450€ with EBUS-TBNA (64).

In addition to hospital financial savings, there was also time savings for the patients. The median time to treatment decision was 14 days with EBUS-TBNA as compared to 29 days with other methods, which included CT-guided biopsy, mediastinoscopy and positron emission tomography (PET) scan (65). PET scan previously had a prominent role in lung cancer staging, but studies have shown a high false negative rate with PET/CT staging. In 113 patients with NSCLC and radiographic N0 disease who underwent EBUS, there were 20 patients who were upstaged to N2 disease (66). Similarly, in 220 patients with N0 disease, there were a total of 45 patients (20.5%) who were upstaged by EBUS or surgery (67). Given the high false negative rate with PET/CT imaging, as well as the importance of obtaining tissue, EBUS-TBNA still has a role in radiographic N0 disease.

EBUS should be the initial diagnostic procedure of choice in patients with accessible mediastinal masses or lymphadenopathy. There was an average delay in diagnosis of 18 days in patients with small cell lung cancer who underwent other diagnostic procedures prior to EBUS (68). EBUS is an outpatient procedure with quick recovery time, so patients who received staging with EBUS as compared to surgery rated their quality of life higher as well (62). The use of EBUS-TBNA in lung cancer staging and diagnosis is cost-effective, limits treatment delays for patients and has superior diagnostic performance compared to PET/CT scan which can dramatically alter treatment decisions and prognosis (69).

**Future directions**

Since the introduction of EBUS about 20 years ago, its utility has grown rapidly from mediastinal lymph node sampling to now include a large variety of other clinical situations.

Peripheral lung nodules, which previously were deemed not amenable to EBUS are becoming increasingly
accessible via new technology. Electromagnetic navigational bronchoscopy with cone beam CT scan in conjunction with EBUS has been successfully used to biopsy peripheral or difficult to access pulmonary nodules (70). Additionally, the iNod system (Boston Scientific, Watertown, MA) allows for real-time biopsy of peripheral nodules under radial EBUS visualization. In addition to lymph node and lung nodule biopsies, there have also been reports of EBUS being used in thyroid biopsies for lesions not amenable to percutaneous biopsy (71,72). Beyond diagnostics, EBUS may also have a therapeutic role in facilitating lung cancer treatment via placement of fiducial markers to guide radiotherapy (73,74), transbronchial needle injection to deliver chemotherapy locally (75,76) and there is ongoing research regarding linear EBUS-guided ablation of central lesions.

There may also be a role for EBUS in non-biopsy and non-malignant clinical scenarios (77). Given frequent barriers in diagnosing pulmonary emboli (PE) and the ability of EBUS to view major mediastinal blood vessels, a pilot study was done in 2009 to evaluate the feasibility of EBUS in diagnosing central PE (78). In 32 patients, EBUS detected PE in 96% of the cases that were confirmed on CT scan. There is currently an ongoing clinical trial (NCT04047784) evaluating the role of EBUS in diagnosing PE in critically ill patients. EBUS may also develop a role in examining other mediastinal structures. There are cases of EBUS being used to facilitate drainage of mediastinal and bronchogenic cysts (79,80), as well as reports describing pericardiocentesis that are treated by EBUS-guided pericardiocentesis (81,82).

Conclusions

The field of interventional pulmonology is rapidly growing. EBUS, which is one of the landmark advancements in the field, has become widespread and indispensable in a short timeframe and continues to find a role in new clinical scenarios. With the increasing use of EBUS, major advancements in the equipment and tools for EBUS have been developed over the last several years. While randomized controlled clinical trials to evaluate the efficacy and outcomes of these novel EBUS devices are still needed, the rapid rate of growth and innovation hopefully signifies the trajectory of advancements still to come in interventional pulmonology.

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