



Endobronchial ultrasound bronchoscopy: current uses, innovations and future directions

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Radial probe endobronchial ultrasound (RP-EBUS) and convex probe EBUS (CP-EBUS) have transformed the approach to diagnosis and management of intrathoracic disease. RP-EBUS, has improved the diagnostic yield of bronchoscopic biopsy of peripheral pulmonary nodules. CP-EBUS is the initial diagnostic tool of choice for mediastinal and hilar lymph node staging of lung cancer. Both EBUS modalities have been used in a variety of novel ways to enhance the minimally invasive diagnostic and treatment capabilities of the bronchoscopist in benign and malignant disease. Thin convex probe EBUS and electromagnetic navigated EBUS are promising advances in endobronchial ultrasound technology that may allow for enhanced diagnostic capabilities in the future. Future research and technological developments will likely continue to expand the application of EBUS in thoracic disease.

Keywords: Radial probe endobronchial ultrasound (RP-EBUS); convex probe endobronchial ultrasound; ultrasound; chest imaging

Received: 12 April 2018; Accepted: 14 June 2018; Published: 29 June 2018.

doi: 10.21037/amj.2018.06.06

View this article at: <http://dx.doi.org/10.21037/amj.2018.06.06>

Introduction

Ultrasound has thoroughly transformed modern point of care medicine in many fields. In the field of chest medicine, the ability to perform ultrasound inside the thorax via the airways and esophagus has fundamentally changed the approach to certain types of chest disease. With new minimally invasive options, intrathoracic ultrasound is being used in applications ranging from less invasive staging of the mediastinum in the setting of cancer, to targeted delivery of chemotherapeutic agents. In this review we will discuss the traditional use of radial probe endobronchial ultrasound (RP-EBUS), convex probe endobronchial ultrasound (CP-EBUS) as well as the innovative ways endobronchial ultrasonography (EBUS) is being used and the future directions of EBUS for diagnosis and treatment of thoracic disease.

RP-EBUS

The radial ultrasound probe became commercially available in the 1990's and provides a 360-degree ultrasound view of the airway and structures external to the airway (1,2). In its earliest iterations a balloon on the tip of the radial probe was used to oppose the airway wall and allow for, among other things, evaluation of extent of tumor infiltration into the airway (3). In a study of 131 patients with central thoracic malignancy, RP-EBUS was able to reliably distinguish between compression of the airway versus airway involvement with superior sensitivity to chest CT (4). The balloon tipped radial probe was also used to identify the location of mediastinal and hilar lymph nodes. After the node was located, the probe was removed and conventional transbronchial needle aspiration (TBNA) was done at the confirmed site. While this advance in EBUS technology

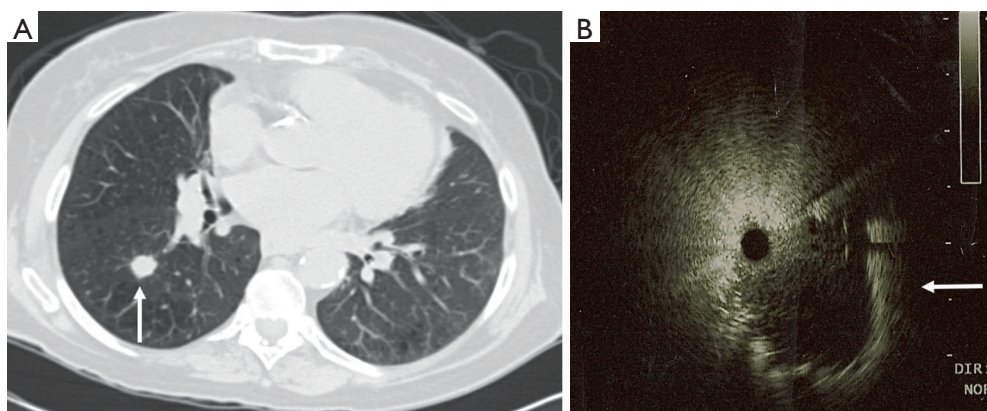


Figure 1 Radial probe endobronchial ultrasound of a pulmonary nodule. (A) Chest computed tomography demonstrating pulmonary nodule (arrow); (B) eccentric radial probe EBUS view of the pulmonary nodule (arrow).

resulted in improvement in yield of TBNA for lymph node staging (5), it was somewhat cumbersome to use in this context given that it needed to be removed and exchanged for the sampling instrument such as a needle. Though the balloon tip radial probe is utilized less in contemporary interventional pulmonology, RP-EBUS has continued to evolve in the management of chest disease.

The miniaturization of the radial probe has allowed for imaging of peripheral lesions beyond the segmental airways. In this capacity, the ultrasound probe, albeit typically without a balloon, can be placed through the working channel of the bronchoscope and extended into the periphery to identify intrapulmonary nodules (6). Utilization of this technique has evolved in several ways. The radial probe can be extended through the bronchoscope to identify the lesion, leaving the bronchoscope in the appropriate subsegment and replacing the probe with biopsy tools. The addition of a guide sheath may improve diagnostic yield (7). The radial probe can be directed to the nodule via a sheath catheter and after the probe has been removed biopsy of the nodule can be done with or without fluoroscopy through the catheter that has been directed to the nodule. Using the latter technique, diagnostic yield for peripheral pulmonary nodules 2–3 cm can be as high as 72%, at single centers versus yields as low as 20% for bronchoscopy alone (7,8). If a concentric view is obtained, where the nodule encircles the probe, the diagnostic yield improves to 84% and has similar, if not improved yield, compared to computed tomography (CT) guided biopsy, with fewer complications (Figure 1) (7,9). When RP-EBUS has been combined with electromagnetic navigational bronchoscopy (ENB) the diagnostic yield for peripheral nodules is increased versus

either technique alone (10,11). TBNA of the peripheral pulmonary nodule can also improve diagnostic yield by nearly 10% versus brush biopsy or forceps biopsy (12).

Further, imaging features noted on RP-EBUS have also been used to help risk stratify pulmonary nodules as malignant versus nonmalignant. In a study of 69 patients with peripheral pulmonary lesions undertaken by a group of experienced RP-EBUS practitioners, RP-EBUS was used to classify lesions into one of three categories based on ultrasound appearance: homogenous pattern, hyperechoic dots and linear arcs pattern, and heterogeneous pattern. Benign disease was most common in patients with homogenous pattern nodules (92%), while the majority of patients with hyperechoic dots and linear arcs pattern or heterogeneous pattern had malignant disease (99%) (6).

Recently RP-EBUS has also played a role in treatment of malignancy. RP-EBUS has been used to determine depth of tumor invasion, proximity to vasculature and other tumor characteristics in patients undergoing therapeutic bronchoscopy. In a study of 1,174 cases where RP-EBUS was used to evaluate endobronchial lesions, therapy changed in 43% of cases based on ultrasound findings (13). RP-EBUS has also been used to guide decisions regarding surgery, radiotherapy or photodynamic therapy for centrally located lung cancers (14,15). With the advent of stereotactic body radiation therapy (SBRT) for treatment of early stage non-small cell lung cancer (NSCLC), RP-EBUS has also been employed to deliver fiducial markers to guide radiotherapy (16,17).

The major limitation of RP-EBUS is the inability to perform real-time ultrasound guided procedures. Even with the use of a guide sheath to direct sampling after

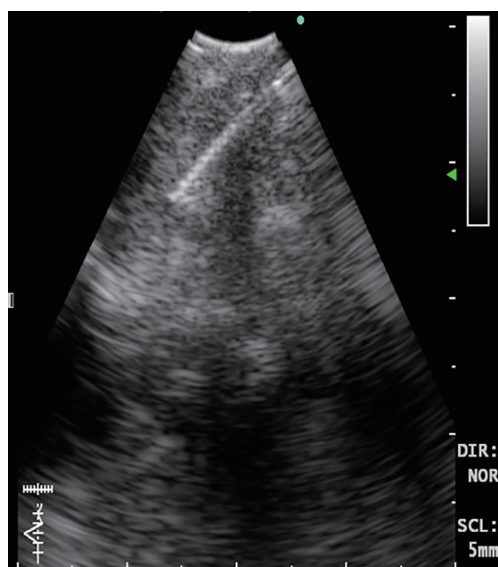


Figure 2 Convex probe endobronchial ultrasound guided transbronchial needle aspiration of a lymph node. Arrow denotes needle tip.

identification of the lesion, positioning can be lost, and sampling error can occur.

Convex probe endobronchial ultrasound

The CP-EBUS allows for real-time ultrasound guided tissues sampling. The CP-EBUS incorporates a convex transducer at the tip of a flexible bronchoscope to provide an ultrasound image that is parallel to the insertion direction of the bronchoscope (18). Some incorporate a saline filled balloon on the tip to improve approximation with the airway, while others utilize direct contact by the probe. A Doppler mode allows for assessment of vasculature and an instrument channel permits biopsy under direct visualization (*Figure 2*).

CP-EBUS is now the recommended initial diagnostic modality for mediastinal lymph node staging of lung cancer (19,20). When compared to CT and PET for lymph node staging EBUS with real time TBNA has demonstrated higher sensitivity (76.9%, 80.0%, and 92.3% respectively) and specificity (55.3%, 70.1%, and 100% respectively) (21). Prior to the advent of CP-EBUS, mediastinoscopy was the predominant technique used for mediastinal staging. Several studies have compared EBUS-TBNA with mediastinoscopy and have found equivalent diagnostic sensitivity, accuracy and NPV with fewer complications (22-24).

In one comparison CP-EBUS had higher diagnostic yield, sensitivity, specificity and negative predictive value versus mediastinoscopy (91%, 87%, 100%, and 78% *vs.* 78%, 68%, 100%, and 59%, respectively) (24). CP-EBUS can access mediastinal and hilar lymph nodes with improved site selection and reduced sampling errors versus mediastinoscopy or conventional transbronchial needle aspiration (TBNA) although stations 5, 6, 8 and 9 are not readily accessible (25-27). With appropriate expertise the same convex probe equipped bronchoscope can be used to perform transesophageal endoscopic ultrasound guided biopsy (EUS) to reach posterior and inferior mediastinal nodes and may provide the most complete approach to minimally invasive mediastinal staging when combined with EBUS-TBNA (28,29). The diagnostic yield of EBUS-TBNA for mediastinal staging of lung cancer appears to be similar across community and academic settings (23). In addition, EBUS-TBNA appears to be more cost effective than mediastinoscopy for lymph node staging in part because of lower need for post procedural hospitalization, but also because EBUS-TBNA can be performed in the endoscopy suite as opposed to the operating room (30,31).

CP-EBUS is also useful following treatment of NSCLC when there is concern for recurrence or disease progression and has started to replace redo mediastinoscopy (32). Repeat mediastinoscopy after prior mediastinoscopy, surgical dissection or neoadjuvant therapy is complicated by adhesions and fibrosis that increase complications while decreasing diagnostic yield (33,34). EBUS-TBNA has been evaluated in patients with recurrence postoperatively with excellent sensitivity and specificity for redo staging (32,35).

In addition to lymph node sampling, CP-EBUS can be used to diagnose nodules and masses that abut the mediastinum and proximal airways. In a study of 140 patients with mediastinal masses EBUS-TBNA was diagnostic in 131 patients with no complications (36). Biopsy of peripheral lung tumors is limited by the outer diameter of the CP-EBUS bronchoscope and in most cases cannot extend beyond the lobar bronchus, though basilar segmental bronchi may be accessed in the lower lobes of some patients (18).

With the identification of driver genetic mutations as therapeutic targets in the treatment of NSCLC, the need for adequate tissue samples to facilitate testing for multiple mutations has arisen. In a study of 126 samples obtained via EBUS-TBNA, mutation analysis was performed for epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene (KRAS) with success rates of 97% and 93%, respectively (37). Additional studies have

validated adequate tumor and lymph node tissue acquisition using EBUS-TBNA for identifying a variety of molecular alterations in non-small cell lung cancer (38-40).

Fiducial placement in central lesions using CP-EBUS has also been described (41). In this technique the transbronchial needle can be loaded with the fiducial marker with the stylet removed and the stylet can be used to deploy the marker under direct visualization. Several variations on this technique have been described using CP-EBUS to deploy fiducial markers (41-43).

Though CP-EBUS has been most often described in the diagnosis and staging of lung cancer, it also plays a significant role in the diagnosis of mediastinal adenopathy and other disease entities such as sarcoidosis, lymphoma and infectious disease. EBUS-TBNA has been used for the evaluation of mediastinal adenopathy without a primary lung cancer with reported diagnostic yield as high as 92% (44). EBUS-TBNA is commonly used for evaluation of adenopathy in the setting of suspected sarcoid and in a study of 50 patients had a diagnostic yield of 83.3% (45). There has been concern in the past that EBUS-TBNA would yield insufficient tissue for diagnosis of lymphoma based on mediastinal and hilar lymph nodes sampling, however, Moonim *et al.* conducted a prospective study of 100 patients with suspected lymphoma and in *de novo* lymphoma diagnosis was made in 88% of cases, while relapse was diagnosed in 100% of cases (46). Sensitivity for subtyping was highest in low-grade non-Hodgkins lymphoma and was lowest in Hodgkin's disease (100% and 79% respectively). Others have supported that the reliability of EBUS-TBNA for diagnosis of lymphoma is influenced by subtype with much lower diagnostic yields in the setting of follicular and marginal zone lymphoma (47-49). Transbronchial forceps biopsy through the prior TBNA insertion site may improve diagnostic yield in these situations and can be done with real-time EBUS guidance (48). EBUS-TBNA has been employed to differentiate malignant from infectious disease and has been particularly useful in areas with high incidence of tuberculous mediastinal lymphadenitis and histoplasmosis (50-53).

The primary limitation of CP-EBUS is the diameter of the bronchoscope and inability to reach peripheral airways as previously mentioned. The endobronchial image may also be lower quality resolution in some instances compared to white light bronchoscopy without EBUS.

Complications and contraindications

The complications associated with RP-EBUS are

primarily associated with biopsy and therefore are akin to transbronchial biopsy without RP-EBUS. Pneumothorax and bleeding occur at similar rates of 0.8-4.2% and 0-5.6% respectively, though significant hemorrhage may be lower in RP-EBUS with use of a guide sheath due to what is thought to be the tamponade effect of the sheath (54-56). Infection is a rare complication reported in the use of RP-EBUS (54). Compared to CT guided needle biopsy of peripheral pulmonary nodules, RP-EBUS guided biopsy has significantly lower complication rates (27% vs. 3%) (57).

Due to the rigid tip of the CP-EBUS bronchoscope, mucosal injury can occur and full thickness bronchial disruption has been reported (58). Outside of this rare complication, the majority of complications as reported in a multicenter study involving 7,345 cases are associated with biopsy, with hemorrhage being the most common complication (0.68% of cases) followed by infection (mediastinitis, pneumonia, pericarditis, cyst infection; 0.19%) and pneumothorax (0.03%). In the same study needle breakage was a complication reported in 0.20% of cases and can be prevented by avoiding excessive bending and torque on the needle (59).

The contraindications to RP-EBUS and CP-EBUS are similar to that of bronchoscopy. In non-emergent cases, bronchoscopy should be delayed 6 weeks in the setting of recent myocardial infarction, decompensated heart failure, life threatening arrhythmia, or exacerbation of asthma or chronic obstructive pulmonary disease (60). Patients should be healthy enough to undergo general anesthesia or conscious sedation for the procedure and should not have significant hemodynamic instability or hypoxemia prior to procedure. Anticoagulants and antiplatelets should be held as appropriate based on the planned procedure. In general, clopidogrel should be held 5 to 7 days prior to TBNA, endobronchial or transbronchial biopsy (61,62). Aspirin is generally considered safe to continue during TBNA and TBBX (63). INR should be <1.5 in patients on warfarin and bridging with low molecular weight heparin (LMWH) should be considered in high risk conditions, with LMWH dose held on the day of the procedure (60). The timing for discontinuing direct oral anticoagulants prior to bronchoscopy with biopsy is based on the specific drug and renal function of the patient (64). Other relative contraindications include severe pulmonary hypertension, elevated intracranial pressure, bulky anterior mediastinal masses and pregnancy (60).

New frontiers and future investigation in EBUS

There are many novel ways EBUS is being used in the

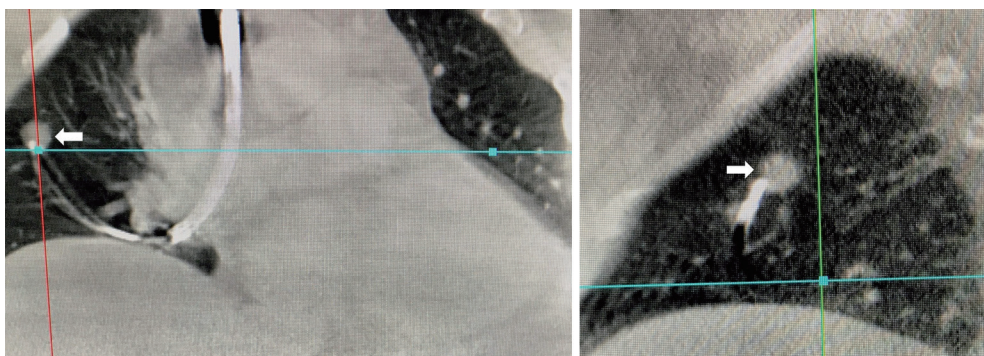


Figure 3 Radial probe endobronchial ultrasound localization of a peripheral pulmonary nodule combined with cone beam computed tomography.

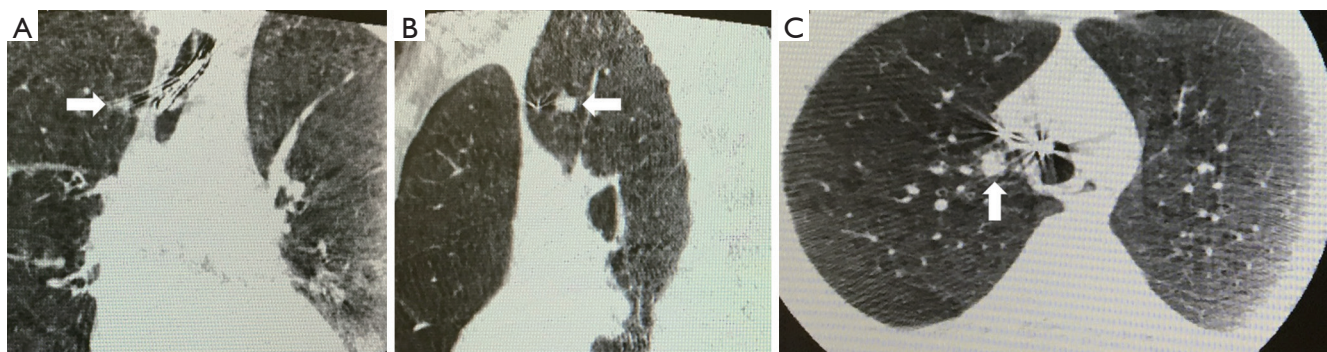


Figure 4 Convex probe endobronchial ultrasound with cone beam computed tomography to identify and biopsy a central pulmonary nodule. (A) Coronal image; (B) sagittal image; (C) axial image. White arrow identifying the pulmonary nodule.

diagnosis and treatment of intrathoracic disease. We and others have combined RP-EBUS and CP-EBUS with cone beam CT to facilitate biopsy of difficult to locate central and peripheral pulmonary nodules (Figures 3,4) (65). A randomized controlled trial is currently underway to determine if this technique improves diagnostic yield (NCT02978170). For thyroid malignancy EBUS has been used for diagnosis and staging in patients with lesions not amenable to percutaneous biopsy (66). It has also been used to evaluate for airway invasion in the setting of esophageal and thyroid cancer and has higher sensitivity and specificity than magnetic resonance imaging or CT (67). EBUS may also play a role in diagnosis and treatment of cardiac disease and has been used to facilitate pericardiocentesis for posterior loculated pericardial effusions (68). Among 32 patients with CT proven pulmonary embolism, EBUS was utilized in a pilot study to confirm a diagnosis of central pulmonary embolism in every patient with an average procedure time of only five minutes (69). EBUS has been

utilized for bronchogenic cyst drainage in patients who were not good surgical candidates and for treatment of cyst recurrence after partial resection (70,71).

Recently, CP-EBUS been used to access lymph nodes previously thought to be reserved for mediastinoscopy. In a retrospective series, 10 cases were described where CP-EBUS was used to achieve adequate sample in 10/10 cases and diagnosis in 9/10 cases of station 5 lesions or intrapulmonary artery lesions. The authors used transpulmonary or intrapulmonary aspiration with no procedure-related complications (72).

EBUS may also play a role in the direct instillation of treatment into a pulmonary lesion. EBUS transbronchial needle injection (TBNI) has been used to inject chemotherapy into pulmonary lesions and may be a therapeutic option for patients who are not candidates for systemic therapy or radiation (73,74). We recently used RP-EBUS to allow for identification of a non-resolving mycetoma in a patient with refractory hemoptysis. After

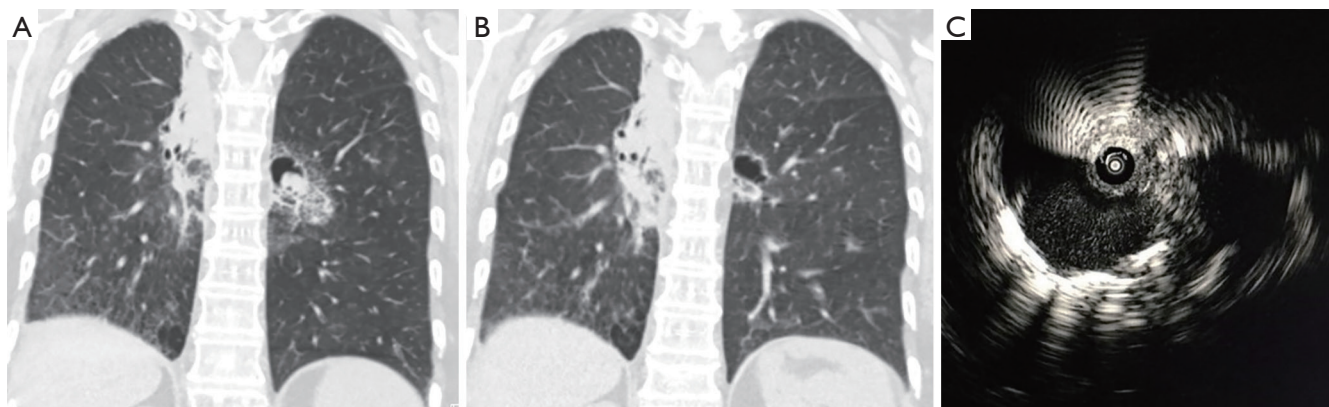


Figure 5 Radial probe endobronchial ultrasound of a mycetoma. (A) Chest computed tomography demonstrating mycetoma prior to therapy; (B) chest computed tomography of the mycetoma after therapy; (C) radial probe endobronchial ultrasound visualization of the mycetoma.

localizing the lesion using RP-EBUS voriconazole and tranexamic acid were injected into the cavity via a guide sheath. On follow up imaging the mycetoma had resolved with decrease in size of the cavity and resolution of hemoptysis (Figure 5).

Several technological advances are poised to extend the application of EBUS in thoracic disease. A human feasibility study was recently done where a tracking sensor was attached to a prototype CP-EBUS bronchoscope to permit electromagnetic navigated EBUS-TBNA using preoperative CT to identify 100% of the targeted lymph nodes (75). Recently, a new thin convex probe EBUS (TCP-EBUS) has been trialed in the porcine lung and a human *ex vivo* lung study (76,77). The 5.9 mm tip of the TCP-EBUS, 170 degree upward angle and decreased forward oblique view (20 degrees) allowed for 22.1 mm greater maximum reach and 10.3 mm further endoscopic visibility *vs.* the current CP-EBUS that has a 6.9 mm tip, 135 degree upward angle and forward oblique view of 35 degrees (77). In the future the TCP-EBUS may be used to reach more peripheral pulmonary nodules and intrapulmonary lymph nodes.

Conclusions

Radial probe EBUS and convex probe EBUS continue to alter the approach to intrathoracic disease. RP-EBUS has improved the diagnostic yield of bronchoscopic peripheral pulmonary nodule biopsy. CP-EBUS is the diagnostic tool of choice for mediastinal and hilar lymph node staging of lung cancer. Both EBUS modalities have been used in a

variety of novel ways to enhance the minimally invasive diagnostic and treatment capabilities of the bronchoscopist. TCP-EBUS and electromagnetic navigated EBUS are promising advances in endobronchial ultrasound that may allow for enhanced diagnostic capabilities in the future. Technological developments will likely continue to expand the application of EBUS in the diagnosis and treatment of thoracic disease.

Acknowledgements

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Amit Mahajan, Sandeep J. Khandhar and Erik E. Folch) for the series “Management of Complex Airway and Pleural Diseases” published in *AME Medical Journal*. The article has undergone external peer review.

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/amj.2018.06.06>). The series “Management of Complex Airway and Pleural Diseases” was commissioned by the editorial office without any funding or sponsorship. WS Krinsky is a part-time employee for the Medtronic corporation, he is also a consultant/CSO for Gala Therapeutics, consultant for Innovital systems and consultant for Peytant Solutions. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/amj.2018.06.06

Cite this article as: Warren WA, Sobieszczyk MJ, Sarkar S, Krinsky WS. Endobronchial ultrasound bronchoscopy: current uses, innovations and future directions. *AME Med J* 2018;3:70.