INVITED REVIEW SERIES:
UPDATE IN INTERVENTIONAL PULMONOLOGY
SERIES EDITORS: FABIEN MALDONADO, ERIC S. EDELL, PATRICK J. BARRON AND REX C. YUNG

Novel bronchoscopic strategies for the diagnosis of peripheral lung lesions: Present techniques and future directions

CHRISTOPHER GILBERT,¹ JASON AKULIAN,² RICARDO ORTIZ,³ HANS LEE³ AND LONNY YARMUS³

¹Sections of Interventional Pulmonology, Pennsylvania State University, Hershey, Pennsylvania, ²University of North Carolina, Chapel Hill, North Carolina and ³Johns Hopkins University, Baltimore, Maryland, USA

ABSTRACT
The diagnosis of the peripheral lung lesion has been a long-standing clinical challenge—balancing accuracy with patient safety. With recent data revealing mortality benefits with lung cancer screening via low-dose computed tomography, now more than ever, clinicians will be challenged with the task of providing the means to provide a safe and minimally invasive method of obtaining accurate tissue diagnostics for the pulmonary nodule. In this review, we present available technologies to aid clinicians in attempts at minimally invasive techniques and the data supporting their use. In addition, we review novel tools under investigation that may further increase yield and provide additional benefit in obtaining an early diagnosis of lung cancer.

Key words: bronchoscopy, lung cancer, pulmonary nodule, transthoracic needle aspiration.

Abbreviations: 3-D, three-dimensional; BTPNA, bronchoscopic trans-parenchymal nodule access; CP-EBUS, convex probe-endobronchial ultrasound; CT, computed tomography; DGS, disposable guide sheath; EBUS, endobronchial ultrasound; ENB, electromagnetic navigational bronchoscopy; H-EBUS, hybrid endobronchial ultrasound; LG, locatable guide; PPN, peripheral pulmonary nodule; ROI, region of interest; RP-EBUS, radial probe endobronchial ultrasound; TTNA, traditional transthoracic needle aspiration; VNB, virtual navigational bronchoscopy.

INTRODUCTION
The diagnosis of the peripherally located pulmonary nodule has remained a diagnostic dilemma. In the setting of new guidelines for lung cancer screening, the identification of pulmonary nodules will become more common,¹ and the need for safe but also effective diagnostic modalities remain. Within this review, we present the current technologies available for the evaluation of the pulmonary nodule, as well as offering insight into the new, emerging technologies that will continue to improve our approach.

RADIAL ENDOBRONCHIAL ULTRASOUND
Radial probe-endobronchial ultrasound (RP-EBUS), first reported in 1990 in the assessment of tracheobronchial wall integrity and mediastinal adenopathy,² has become increasingly used in the diagnostic evaluation of peripheral pulmonary nodules (PPN). This form of endobronchial ultrasound (EBUS) utilizes a 20-MHz miniaturized ultrasonic probe (UM-S20-17S, Olympus, Tokyo, Japan) with radial side scanning properties, producing a 360-degree ultrasound image of the surrounding lung parenchyma (Fig. 1).
reflective properties of the lung parenchyma make this technology particularly attractive as PPN tend to be hypoechoic, resulting in a sharply defined interface with normal lung parenchyma when viewed on ultrasound.

When employed in the evaluation of PPN, after initial planning using computed tomography (CT) imaging, the RP-EBUS probe is deployed within a disposable guide sheath (DGS) via a flexible bronchoscope after the scope has reached its limit in traversing the airway. Once the bronchoscope can no longer be advanced, the probe is then passed distally until either the PPN of interest is seen or the visceral pleura is encountered. When the PPN is seen on ultrasound imaging, the DGS is fixed in place using stoppers placed prior to RP-EBUS probe insertion into the bronchoscopic working channel. Once the DGS is fixed in place, the RP-EBUS probe is removed, followed by brushing, needle aspiration, transbronchial biopsy, directed lavage and/or fiducial marker placement.

This method of evaluating PPN was first published by Herth et al. in 2002, who reported a diagnostic yield of 80% in 50 lesions sampled not using a DGS. This was followed in 2004 by four studies evaluating the use of RP-EBUS, three of which utilized a DSG. These studies reported diagnostic yields ranging from 58% to 82%, confirming Herth’s previous study. In 2005, Becker and Asahina each reported the first combined use of RP-EBUS, DSG and navigation bronchoscopy (electromagnetic navigational bronchoscopy (ENB) and virtual navigational bronchoscopy (VNB)) with comparable diagnostic yields of 69% and 63%, respectively. In a well-designed trial, Eberhardt et al. evaluated RP-EBUS, ENB and a combination of the two. They were able to show that alone RP-EBUS and ENB had diagnostic yields of 69% and 59%, respectively, but when combined the yield significantly improved to 88%. Asano reported a diagnostic yield of 84.4% when combining an ultrathin bronchoscope, VNB, RP-EBUS and a DSG in 31 patients with 32 PPN. Two comprehensive meta-analyses have been performed evaluating RP-EBUS. The first in 2011 by Steinfort et al. included 1420 patients in 16 studies and reported a point specificity and sensitivity of 1.0 and 0.73, respectively, for the detection of lung cancer. The effect of lesion size on diagnostic yield was also evaluated with a significant difference in pooled diagnostic yield when comparing lesions ≤20 mm with those >20 mm (56.3% vs 77.7%). In 2012, Wang Memoli et al. reported the results of an even larger meta-analysis that included all forms of ‘guided bronchoscopy’. This analysis included 3052 lesions from 39 studies that involved the use of RP-EBUS, ENB, VNB, DSG, ultrathin bronchoscopy or a combination of modalities. The pooled diagnostic yield is reported to be 70% for all modalities; however, when individual modalities were evaluated, RP-EBUS without DSG had a 71.1% pooled diagnostic yield, while addition of a DSG had the highest reported pooled diagnostic yield of 73.2%. The pooled diagnostic yield was again shown to be significantly greater in those lesions larger than 20 mm (60.9% vs 82.5%, P < 0.001).

Factors that have been shown to significantly affect PPN visualization and diagnostic yield when utilizing RP-EBUS + DGS include the size of the lesion (≤20 mm vs >20 mm), distance from the hilum (≤50 mm vs >50 mm), lobar distribution, the presence of malignancy and positioning of the probe in relation to the lesion (eccentric vs within). Of these, the characteristics that have been most reproducibly reported have been size of the lesion and probe positioning in relation to the lesion.

The safety profile of RP-EBUS-guided biopsy of PPN has been shown to be quite favourable. In the two previously mentioned meta-analyses, the rates of pneumothorax were 1% and 1.5%, respectively, with approximately half the patients requiring intercostal tube drainage. No episodes of significant bleeding were reported in either study. In addition to its excellent safety profile, the RP-EBUS system is the least expensive of the bronchoscopic guidance modalities given that the probe is reusable and has shown itself to be easily employed in combination with other guidance systems.

Despite the largest body of literature among bronchoscopic guidance modalities, limitations and questions regarding applicability of RP-EBUS remain. The technology continues to rely on the

---

Figure 1  (a) Radial probe ultrasound bronchoscope (EBUS) image; note the hypoechoic lesion surrounding the probe with a sharply defined interface with lung parenchyma. (b) Radial probe EBUS.
bronchoscopist’s three-dimensional (3-D) understanding of airway architecture and the ability to pilot a bronchoscope then RP-EBUS probe to the intended PPN while navigating increasingly small airways and numerous branch points. Without these abilities, the bronchoscopist could easily evaluate the wrong set of airways and conclude that the PPN is either unreachable or no longer exists, potentially delaying diagnosis and treatment. The other most prominent limitation of RP-EBUS involves the ultrasound image and the reflective properties of the lung. While solid PPN create a well-demarcated interface between normally aerated lung parenchyma and themselves, ground-glass nodules return a poor or no ultrasound signal that can cause these lesions to be poorly represented when trying to evaluate them.

Despite these limitations, the reported pooled diagnostic yields comparable with transthoracic needle aspiration with a fraction of the risk of pneumothorax make RP-EBUS-guided bronchoscopy, with or without combining it with an additional guidance modality, an attractive alternative to percutaneous modalities.

**ENB**

ENB is based on the principle of: (i) creating a magnetic field around the patient; (ii) a sensor device to detect location within the magnetic field space; (iii) an interface to allow for displaying position within the space and input desired target location(s); and (iv) data from a CT scan for 3-D reconstruction to overlap the magnetic field. Ultimately, the CT scan 3-D reconstruction is superimposed on the real anatomy of the patient based on the magnetic field and sensor. In many ways, ENB mimics current Global Positioning System technology, which we use in our vehicles, with a magnetic field substituting for a satellite network and a sensor device acting as our vehicle.

In the United States, there are two commercially available systems that use ENB: i-Logic (Covidien, Mansfield, MA, USA) and SPiNDrive (Veran Medical Technologies, Inc., St Louis, MO, USA). (Fig. 2) Both systems require initial CT scan imaging with preferred protocols for planning ENB targets and to overlay the magnetic field to the CT scan anatomy. If an appropriately formatted CT scan is unavailable, then repeat CT scanning is required to utilize the software and technology. The SPiNDrive system uses a sensor pad during the CT scan to obtain additional information for navigation to compensate for respiratory movement and recommends same-day imaging as the bronchoscopy. Both have similar planning systems using computer software to target the lesion of interest based on CT images. The i-Logic system uses a board that is placed underneath the patient to create its magnetic field, while the SPiNDrive uses an array to project the field over the patient.

The major differences between the two systems are in the sensor device. The i-Logic locatable guide (LG) is similar to a probe that can pass through a larger bronchoscopic working channel with a catheter guide sheath. The catheter comes in various angles (45, 90 and 180) and offers some steerability of the catheter during navigation. Instead of a LG, the SPiNDrive uses their always-on tipped track technology; the sensor tracking is built into the biopsy instruments (i.e. forceps, brush and needle) allowing for direct navigation of their biopsy instrument. In addition, a phantom bronchoscopy catheter is also available with steerability that functions similar to a guide sheath. An interesting feature of the SPiNDrive system is a transthoracic needle software/needle system to biopsy lesions similar to CT needle biopsy, which will be reviewed later in this article. Unlike CT needle biopsy, the images are not in real time, but offer navigation assistance for needle insertion to the target lesion. This is a major departure from navigational bronchoscopy and may allow for additional access to lesions that could not be reached with bronchoscopy. There currently are no peer-reviewed studies using the Veran SPiNDrive system; however, a single-centre prospective study is
currently underway with study completion expected in late 2014.

A recent meta-analysis found the pooled diagnostic yield (ENB) to be 64.9% (95% confidence interval: 59.2—70.3); however, the methodological quality of the studies included were found to be poor. The largest series (retrospective) reported using the i-Logic system reported a diagnostic yield for peripheral lesion (mean size 2.1 cm, standard deviation 1.4 cm) of 55.7%, but when including lymph node biopsies, the yield increased to 70%. A small prospective study (89 patients) showed an ENB yield of 67%, which was independent of size of the peripheral lesion and without the use of fluoroscopy. The largest prospective study was a randomized controlled trial with three arms comparing ENB, RP-EBUS, and a combined ENB and RP-EBUS. The results were similar for ENB in other studies with a diagnostic yield of 59%; this was similar to the yield of RP-EBUS (69%). However, the combined technology arm had a significant increase in diagnostic yield (88%) compared with either RP-EBUS or ENB alone. In another series by the same authors, the diagnostic yield was much higher (93% vs 48%) when confirmed with RP-EBUS compared with ENB navigation to target where the lesion was not seen by RP-EBUS. The use of RP-EBUS with ENB has not been replicated by other investigators.

The overall safety of ENB is comparable with historical data of standard bronchoscopy procedures and superior to CT needle biopsy. In the largest retrospective series, there was an overall 3.2% rate of complication; 3/266 patients had a pneumothorax with none requiring a chest tube. There is one small series reporting the safety of ENB with implantable defibrillators/pacemakers, which found no disruptions or arrhythmias from the magnetic field. Another area that ENB has been used is to place fiducial markers to guide radiation therapy to the lung. In one small comparative study, the pneumothorax rate was smaller when compared with a transcutaneous implantation of the fiducial markers.

Several factors that may influence EMN yield: (i) location, upper or middle lobe had better yields; (ii) presence of a bronchus sign on CT imaging; (iii) combined use of RP-EBUS; (iv) catheter suctioning as a sampling technique; (v) lower registration error; (vi) deep sedation; and (vii) nodule size. The last factor of nodule size has been a consistent determinant in bronchoscopy. Peripheral lesions that are less than 2 cm show a decreased yield compared with >2 cm even when using ENB.

While both technologies are impressive in their engineering and concept, there remains limited data on their performance. Like many other medical technologies, the rate of published studies lags far behind technological changes. This is concerning due to the difficulty with assessing strengths and limitations of different systems and when/how to best apply ENB. Further investigations are needed for the added value of combination of technologies, for example, the use of RP-EBUS or fluoroscopy with ENB. Currently, there are no studies directly comparing other minimally invasive biopsies to ENB such as CT or ultrasound-guided needle biopsies.

VNB

VNB is an advanced diagnostic tool available for the investigation of peripheral pulmonary lesions. VNB systems are designed to provide additional guidance for the bronchoscopist, assisting in the plotting of an appropriate course through the bronchial tree. Preformatted, preprocedural CT scanning is required, of which specific requirements for scan resolution and image thickness are available per manufacturer’s guidelines. After uploading CT data to the navigational software platform, a 3-D bronchial tree and roadmap is created. During procedural planning, a region(s) of interest (ROI) is identified and software provides a virtual roadmap of the bronchial tree, hopefully obtaining access to the ROI.

The software platform also offers additional aides in localizing the ROI. Multiple different views are often available, including views of the vascular tree, fluoroscopic views and the ability to rotate a ROI in almost any plane or direction. VBN can be utilized preprocedureally or during the procedure. Intra-procedural use often requires an additional operator, but has demonstrated improvement in proper pathway selection in a simulation setting. Unfortunately, data regarding the efficacy of the above mentioned additional software aids remains non-existent.

Worldwide only two systems are commercially available that have been investigated in humans. The Bf-NAVI System (Olympus) and the LungPoint System (Broncus Medical, Mountain View, CA, USA) are available, however, only LungPoint is available in the United States (Fig. 3). The current literature offers varying data regarding efficacy of VNB. The Bf-NAVI system has been more extensively studied in humans, whereas the LungPoint system has only a single study of 25 patients available. A recent meta-analysis has suggested an overall diagnostic yield of 72% when utilizing VNB; however, the data remain heavily weighted in the Bf-NAVI system. LungPoint VNB has a number of preclinical studies suggesting improved ability in selection of proper bronchial pathways and improved localization of phantom lesions. Limitations to these non-human studies include the use of a 2.4-mm ROI lesion and that half of the participating bronchoscopists were pulmonary fellows. The single human study comprises a 25-patient pilot study of peripheral pulmonary lesions less than 42 mm in size. Utilizing VNB and an ultrathin bronchoscope (2.8 mm external diameter), more than 50% of the lesions were directly visualized, and overall diagnostic yield was 80% (all patients with a visualized lesion obtained a diagnosis).

As previously mentioned, the Bf-NAVI has been more extensively studied, including two randomized trials in patients undergoing bronchoscopy for PPN, with most studies coming from the same core group of Japanese authors. Initial work on the Bf-NAVI VNB system was reported in a 37-patient feasibility study. Patients underwent bronchoscopy with VNB guidance and single-plane fluoroscopy or CT fluoroscopy. Biopsy forcesps were advanced to the lesion in 33 (as confirmed by CT fluoroscopy) and diagnostic
material was obtained in 31 lesions. A prospective non-randomized trial identified no increase in diagnostic yield when comparing RP-EBUS alone to VNB and RP-EBUS in PPN. A larger randomized trial utilizing the same concept (RP-EBUS alone vs RP-EBUS and VNB) identified a significant increase in diagnostic yield for both malignant and non-malignant diseases. This was followed by another larger, randomized, controlled trial in which 334 patients were randomized to undergo VNB with fluoroscopy versus standard bronchoscopy with fluoroscopy. No overall difference in diagnostic yield was identified; however, in subgroup analysis there appeared to be some improvement in those with lesions in the right upper lobe, fluoroscopically invisible lesions and lesions located in the peripheral one third.

Drawbacks for the use of VNB do exist. While the overall cost of the system and software requires a large up-front cost, the lack of needed catheters, probes, etc., make it somewhat attractive. However, an often overlooked cost includes the potential cost and radiation exposure associated with CT scanning. In patients undergoing CT scans without the appropriate protocol for the respective planning software, repeat scanning is a requirement for both VNB and ENB. While not well studied at this point, this remains a potentially significant barrier to patients and insurance carriers. Also, as suggested by the recent Asano et al. study, in those bronchoscopists with advanced training, the use of VNB appears to offer no advantage over standard fluoroscopy. VNB may offer improvements in regards to training or those with less experience, but in adequately trained bronchoscopists it appears to offer no particular advantage. A major drawback to using VNB technology is its lack of real-time procedural guidance. Some have likened the guidance to printing travel directions out prior to leaving on a trip. If one were to make a wrong turn at any point, no feedback can be offered to suggest one is headed in the wrong direction, rather one will continue down the wrong pathway, all with the false sense of navigational assurance that the correct destination has been chosen. This lack of real-time guidance can be demonstrated in a recent swine model of VNB. The simple act of wedging a bronchoscope near a ROI can cause significant displacement, with the authors noting ‘...the wedging maneuver could pose a substantive problem as one could risk that no part of the tumor is within the preoperative CT image location’.

In conclusion, while the VNB technology remains attractive, current literature does not support its widespread adoption at this point, and limitations of the technology need to be considered. This remains especially true in light of other available technologies. Further study is required with this technology and the combination of other advanced diagnostic procedures.

**NAVIGATION TRANSTHORACIC NEEDLE ASPIRATION**

Traditional transthoracic needle aspiration (TTNA) is a percutaneous approach to lung nodule biopsy that utilizes guidance by CT and/or fluoroscopy. Unlike most bronchoscopic approaches, which are usually limited in access to 4–5th generation airways, TTNA allows the operator to biopsy peripheral nodules without relying on central airway anatomy to reach the target. This approach allows TTNA users to reach...
diagnostic yields of 90%.

While this diagnostic yield is higher than any other non-surgical approach, the disadvantage is that TTNA results in a pneumothorax rate of 15–25% whereas traditional bronchoscopic approaches have rates of less than 1.5%. For this reason, TTNA is recommended by the American College of Chest Physicians for lung nodules present without a bronchus sign only when RP-EBUS is unavailable. Despite the safety profile, TTNA remains a very useful tool when all other bronchoscopic procedures fail.

Recently, a navigation TTNA technique that promises to resolve the issue of choosing between a bronchoscopic procedure and a percutaneous one has been developed. The underlying idea of the technology is that the operator can perform a bronchoscopic procedure, such as EBUS or ENB, and then if unable to localize the lesion given airway anatomy, transition to navigation assisted TTNA within the same procedure (Fig. 4). Currently, there is only one marketed device that uses this approach (Veran Medical Technologies, Inc.). The navigation software used for this TTNA is the same as used for ENB (SPiNDrive 2.0) (see above section). The exception is the location of the electromagnetic sensor, which in the TTNA version is located in a stylet that is used to first percutaneously navigate to the lesion before a core biopsy is taken.

Whether this approach would lessen the pneumothorax rate is doubtful in theory because there’s no major intraoperative deviation in protocol from traditional CT-guided TTNA. The supposed advantage of such an approach is not safety, however. Theoretically, the convenience offered by such an approach could decrease the number of procedures a patient must go through to reach an answer. Although there currently are no peer-reviewed studies using the TTNA Veran SPiNPerc system, a single-centre prospective study is currently underway with study completion expected in late 2014.

Bronchoscopic trans-parenchymal nodule access (BTPNA) is another emerging technology that theoretically would allow biopsy of peripheral nodules not accessible through traditional bronchoscopy. The principle behind BTPNA is that navigation software generates a bronchoscopic path, similar to ENB, from the bronchus to a position adjacent to the nodule. Unlike ENB, BTPNA would not be limited by the distance of parenchyma separating the airway and nodule.

Silvestri et al. performed an animal pilot using BTPNA on canines. Following anaesthetization, fiducial markers were placed bronchoscopically, and a CT scan was then performed in order to generate point of entry plans using BTPNA software (Archimedes, Broncus Medical). The software generates a straight line path from the central airway, through the parenchyma and to the lesion (Fig. 5). A straight path tunnel was then created with a balloon catheter.
Fluoroscopy computer-enhanced software provided a virtual pathway to guide the sheath to a position that is adjacent to the lesion (Fig. 6). In the animal study, 10 canines underwent the procedure (44 tunnels), with no reports of pneumothorax. Whether this is applicable to a human population is not yet known, and the authors speculate that pneumothorax rates are likely to be higher in a clinical population, especially patients with emphysema. Human studies are currently underway to assess the safety profiles and efficacy in humans.

HYBRID EBUS

Like traditional bronoscopes, convex probe-endobronchial ultrasound (CP-EBUS) scopes are limited in airway accessibility by their external diameter. Two other factors that limited airway accessibility by CP-EBUS were the conventional 30-degree oblique viewing field and the limited degree of flexion. These limitations often required the bronchoscopist to utilize a standard bronchoscope in order to perform full airway examination. Recently, a new EBUS scope (Fujinon, Tokyo, Japan) has been introduced that may reduce the need for supplemental bronchoscopes during lung cancer diagnosis and staging. This hybrid EBUS scope (H-EBUS) offers a higher degree of flexion, a narrower external diameter and a 10-degree oblique viewing field (Fig. 7).

A randomized controlled trial in press comparing the new H-EBUS scope to a CP-EBUS scope revealed several advantages to using an H-EBUS scope. While there were no differences in overall adequacy and diagnostic yield for lymph node sampling, the H-EBUS allowed for visualization of significantly more airway segments, and in patients requiring nodal staging for lung cancer, the need to convert to a standard bronchoscope was significantly less when using the H-EBUS scope as compared to the CP-EBUS scope.

THIN-EBUS

As discussed above, due to the size of the current model Olympus CP-EBUS scope, there are recognized limitations in regards to accessing N1 nodes especially in the peripheral zone. A prototype CP-EBUS (BF-Y0046, Olympus) has been recently presented by Wada et al. featuring a thinner diameter (5.9 mm compared with the standard 6.9 mm) and improved bending angle (170 degrees upward compared with the standard 120 degrees). As a result of these advancements, the prototype scope was able to access deeper into the bronchial tree, including the ability to access the upper lobe as well. Despite the need for smaller needle gauges, lymph node sampling from lobar and segmental lymph nodes remained adequate.
CONCLUSION

The diagnosis and characterization of peripheral lung lesions remains a common clinical management issue. Recent advances in bronchoscopic and minimally invasive techniques have allowed clinicians to provide a continued increase in diagnostic yield and safety. Established techniques continue to improve with technological advances and education. Continued interest in novel interventions will provide physicians with additional tools to further improvements in diagnostic yields.

REFERENCES


33 Oshige M, Shirakawa T, Nakamura M, Mineshita M, Kurimoto N, Miyazawa T, Becker HD. Clinical application of virtual