State-of-the-Art Modalities for Peripheral Lung Nodule Biopsy

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KEYWORDS

• Peripheral pulmonary nodules • Electromagnetic navigational bronchoscopy • ENB • Radial ultrasound • Solitary pulmonary nodule • Lung cancer

KEY POINTS

- Lung nodules are being increasingly detected, particularly with lung cancer screening with low-dose computed tomography.
- Although the vast majority of lung nodules are benign, many often require tissue diagnosis.
- Several modalities to obtain diagnostic tissue from peripheral lung nodules are available.
- Bronchoscopic modalities such as radial ultrasound and electromagnetic navigational bronchoscopy are being increasingly used because of their superior safety profile and improving diagnostic yield.
- Although these modalities continue to become more advanced, newer and complementary technologies appear promising.

INTRODUCTION

A solitary pulmonary nodule is defined as a single, well-demarcated radiographic opacity measuring less than 3 cm in diameter, and is surrounded by lung tissue. It may be solid, subsolid, or ground glass. Solitary pulmonary nodule is a specific clinical entity with fairly well-known risk-ascertainment clinical prediction tools. Multiple pulmonary nodules can be an entirely different clinical problem. Peripheral pulmonary nodules (PPN) pose significant diagnostic challenges to pulmonologists because, unlike endobronchial lesions, there is lack of direct visualization of PPN during bronchoscopy that results in unsatisfactory reach of diagnostic instruments to the nodule. Conventional bronchoscopy and transbronchial biopsies have a low sensitivity (14%–63%) for diagnosing malignant lesions.[1,2] The yield is particularly low (30%) for PPN less than 2 cm in diameter.[1,2]

With the advent of low-dose computed tomography (CT) lung cancer screening, pulmonologists are expected to dedicate a significant portion of their practice dealing with PPN. The National Lung Cancer Screening Trial demonstrated lung nodules in at least 39% of the participants, of which 72% required further investigation.[3] PPN greater than 2 cm in diameter may carry risk of malignancy in the range of 64% to 82%.[4] Although several characteristics of a nodule may determine the probability of a nodule being malignant or benign, none of them can be conclusive on their own, except perhaps complete calcification. Comparison with prior images is extremely helpful, but older images may not always be available.

Although several modalities of performing biopsy of PPN are available, each has its own pros and cons. For instance, CT-guided transthoracic needle biopsy of PPN has a higher sensitivity for

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malignant lesions (up to 90%) compared with bronchoscopic techniques; it is also fraught with higher complication rates (24% in some studies). This article reviews the techniques, diagnostic abilities, and limitations of commonly used modalities available for PPN biopsy and briefly describes promising innovations in this area (Fig. 1).

CONVENTIONAL BRONCHOSCOPY

Conventional transbronchial biopsy for diagnosis of peripheral lung nodules has been almost phased out. Although it is true that larger lesions may well be successfully sampled with traditional transbronchial lung biopsy with fluoroscopy, the challenges with smaller, particularly peripheral lesions are obvious. Although conventional bronchoscopy is still an excellent tool for endobronchial lesions, its diagnostic sensitivity for smaller nodules (<2 cm) in the periphery of the lung is dismal. A review of literature suggests the diagnostic yield of conventional bronchoscopy for PPN is 43% to 65%, much less for smaller peripheral lesions, about 14% to 31%.[5] Table 1 provides a summary of key studies over a 20-year period from 1967 to 1995 with little improvement in diagnostic yields over time, particularly for small nodules. Even extending CT fluoroscopy, conventional bronchoscopy does appear to improve the yield.[6]

Newer advanced technologies such as electromagnetic navigational (EMN) bronchoscopy have replaced conventional bronchoscopy in the diagnosis of peripheral lung nodules.

RADIAL PROBE ULTRASOUND

Radial probe endobronchial ultrasound (RP-EBUS, Olympus Medical Systems, Tokyo, Japan) is a technology that uses ultrasound properties to provide a minimally invasive modality to visualize the airways structure and the lung parenchyma. Originally intended to visualize the airway and mediastinal structures, RP-EBUS is now mainly used to visualize and sample PPN. It consists of a miniature ultrasound probe (20–30 MHz) with a rotating tip that allows a 360° view of the target lesion (Fig. 2A). It is one of the very few image-guided modalities for diagnosis of PPN that offers real-time confirmation of the PPN. The probe may be threaded through the working channel of a flexible bronchoscope, and given its small diameter, it can be advanced all the way to the periphery of the lung. The RP-EBUS image of normal lung parenchyma has a "snowstorm" appearance, whereas a solid lesion had a dark and "solid" appearance (Fig. 2B, C). However, RP-EBUS does not possess the ability to sample the target lesion by itself. The RP-EBUS has to be retracted and the biopsy instruments passed in its place. Given the difference in caliber and flexibility between RP-EBUS and the biopsy tools, it is not always possible for the biopsy tools to retrace the same path traversed by the RP-EBUS. To overcome this challenge, a guide sheath (GS) (also called extended working channel – EWC) is first threaded into the working channel of the bronchoscope through which the RP-EBUS is passed. After the RP-EBUS reaches the target lesion, the GS is then advanced over the RP-EBUS and positioned just

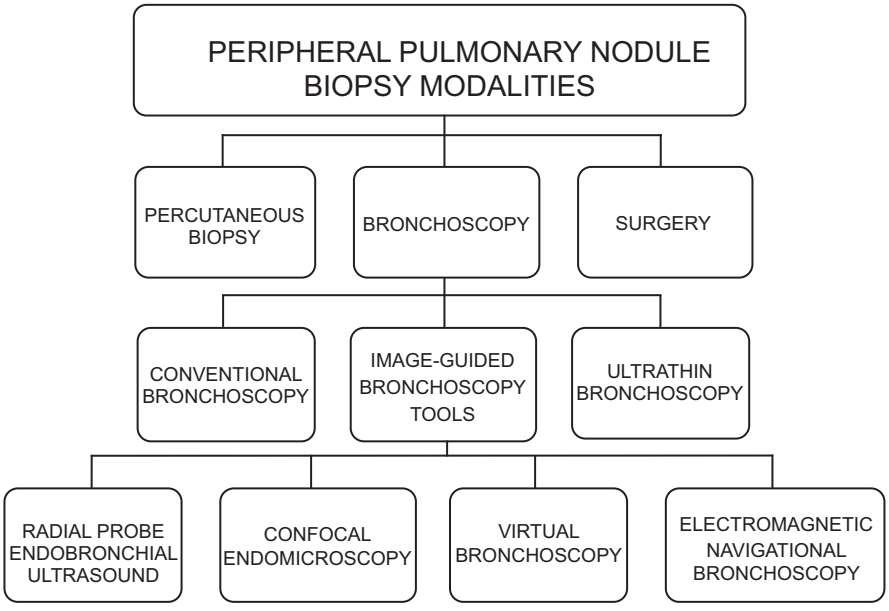

Fig. 1. Currently available PPN biopsy modalities.

Table 1
Conventional bronchoscopy: diagnostic yield and other characteristics

Study, y	Number of PPN	PPN Size-Related Information	Overall Diagnostic Yield (%)
Oswald et al,[52] 1971	435	NA	28
Zavala,[66] 1975	137	NA	71
Naidich et al,[53] 1988	65	≤20 mm DY 21% ≥20 mm DY 57%	41
Bilaceroglu et al,[54] 1998	92	20–50 mm	64
De Roza et al,[55] 2016	226	≤20 mm DY 63% ≥20 mm DY 84%	80

Abbreviations: DY, diagnostic yield; NA, not available.

proximal to the target lesion. The RP-EBUS is then removed, and biopsy instruments are passed through the GS so there is direct access to the target lesion. This RP-EBUS-GS method is popular in centers that do not use navigational bronchoscopy. Occasionally, a curette with an angulated flexible tip is used to navigate through difficult turns and the GS is advanced over the curette. This allows the RP-EBUS to be advanced to difficult to reach locations.

Based on a large meta-analysis, the overall diagnostic yield of all techniques using RP-EBUS is about 73% for lung cancer.[7] Used as standalone, RP-EBUS has a diagnostic yield of about 69% for diagnosis of PPN.[8] In this study, use of GS with RP-EBUS has a diagnostic yield of 84% compared with 48% if GS was not used along with RP-EBUS. Interestingly, whether used as adjunct with ENB, or as standalone, RP-EBUS seems to have similar diagnostic yields (73% vs 71.4%).[9] A recent systematic review of 57 studies and 7872 lesions showed an overall diagnostic yield for RP-EBUS at 70.6%.[10]

In addition to size of the target lesion, the position of the radial probe position of RP-EBUS in relation to PPN has been shown to impact diagnostic yields.[8] The location of the probe directly within the lesion was 8 times more likely to have success with adequate sampling than when the probe was eccentric or tangential to the lesion (diagnostic yield 84% vs 48%).

The RP-EBUS-GS is much more cost-effective than navigational bronchoscopies, but also requires more experience and detailed study of CT chest findings so a "mental preprocedural planning" may be performed before the procedure. In the United States, RP-EBUS is more widely used along with one of the navigational bronchoscopy techniques, rather than a standalone modality for biopsy of PPN.

CONFOCAL LASER ENDOMICROSCOPY

Confocal laser endomicroscopy (CLE, Cellvizio, Mauna Kea Tchnologies, Paris, France) is a novel technology that uses a fiber-optic probe and laser

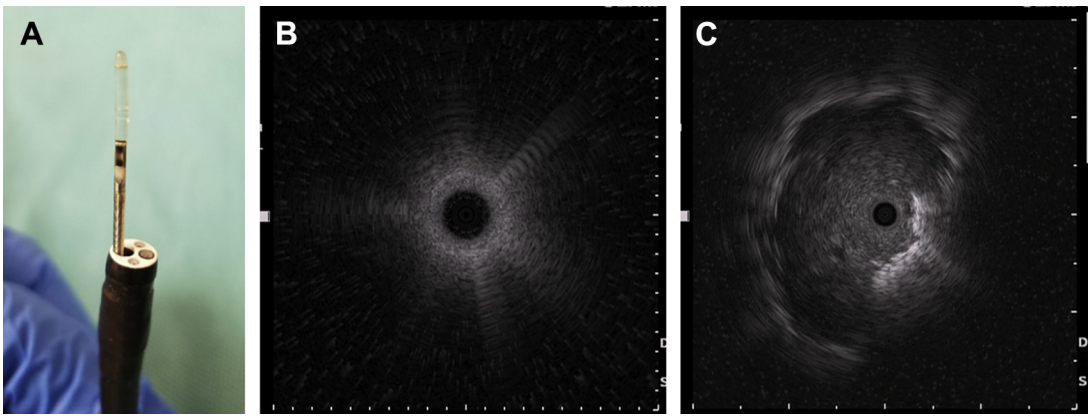

Fig. 2. (*A*) Radial ultrasound probe. (*B*) RP-EBUS image of normal lung parenchyma. Note the "snowstorm" appearance. (*C*) RP-EBUS image of a solid nodule. Note the dark "solid" appearance of the nodule.

to provide in vivo microscopy during endoscopy. It provides direct microscopic examination of the bronchial mucosa and the alveolar structures. Using 488-nm wavelength laser, the CLE provides a fluorescence image of the target area. The image shows fluorescence of elastin in the connective tissue matrix of the bronchial mucosa or the alveolar walls. The generated image covers an area that is 600 μm in diameter around the probe, which is in direct contact with tissue.[11] Images may be obtained with still images or video of the area. Normal lung parenchyma is identified by the thin structure of the alveolar walls and the thicker, more solid-appearing structures of blood vessels (Fig. 3A). A solid lesion such as cancer shows disruption of normal alveolar structures and may show alveolar thickening, distortion, and friability within the alveolar tissue (Fig. 3B).

Efforts have been made to try to compare optical-based images with conventional microscopy in patients with lung cancer to get a better understanding of the endomicroscopic findings.[12] Because CLE images show fluorescence of connective tissue matrix, disruption of the alveolar structure is a common finding. There may also be areas of interruption of the connective tissue that can correspond to infiltration by tumor. Direct examination of cellular structure in the lungs is unavailable with current confocal laser endomicroscopic tools. Fluorescein has been used to examination mucosa with gastrointestinal endoscopy; however, this has not been able to be used with lung imaging.[13] Development

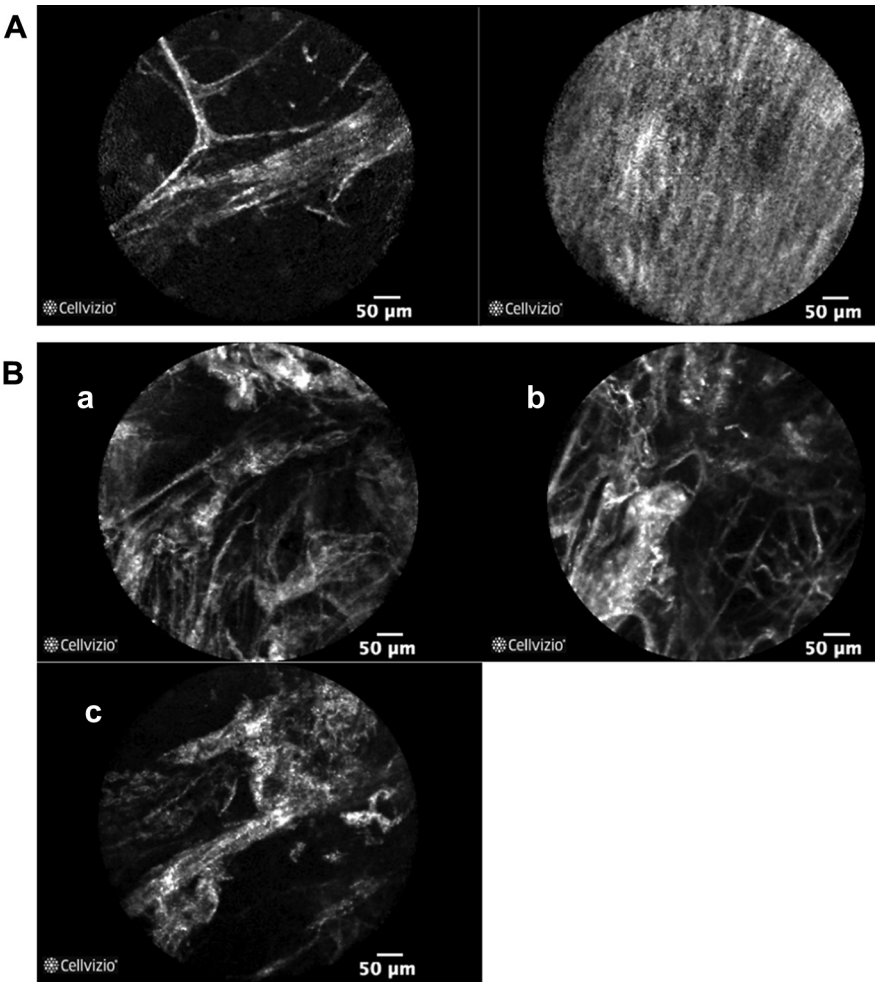

Fig. 3. (*A*) Panel A shows thin structure of alveolar walls and thicker structure of vessels. Panel B shows normal bronchial mucosa with longitudinally directed elastin fibers. (*B*) CLE: Panel a shows disruption of normal alveolar architecture and friability of the tissue in a patient with adenocarcinoma. Panel b shows abnormal alveolar structure with thickening and clumping of the connective tissue in a patient with adenocarcinoma. Panel c shows thickening of the alveolar structure with clumping of tissue along the end of the structure in a patient with squamous cell carcinoma.

of fluorescent markers may help in the utility of endomicroscopy for direct "optical biopsy"; however, its best use currently is real-time confirmation of PPN and to aid in obtaining biopsies from PPN. Just like RP-EBUS, it is often used as an adjunct tool with navigational bronchoscopy. Some centers prefer the use of CLE to RP-EBUS because CLE offers a better view of lung parenchyma, especially the alveolar vessels, and therefore, it may also be used while selecting appropriate sites for transbronchial lung biopsy and cryobiopsy in interstitial lung disease.

NAVIGATIONAL BRONCHOSCOPY

The limitations of conventional bronchoscopy in its ability to obtain biopsies from PPN and the higher rates of complications associated with transthoracic needle aspiration (TTNA) led to the concept of navigational bronchoscopy. Navigational bronchoscopy technology uses images from a chest CT scan to reconstruct a 3-dimensional (3D) map of the airways and the surrounding lung tissue. This is used to create "virtual bronchoscopy," a bronchoscopic view and pathway from the trachea to the target lesion. Several different navigational bronchoscopy platforms are now available for commercial use: they differ in how this virtual bronchoscopic path is used to aid real-time bronchoscopy in reaching a target lesion. The most common navigational bronchoscopy systems are discussed in this article.

VIRTUAL BRONCHOSCOPIC NAVIGATION

Virtual bronchoscopic navigation (VBN), also called virtual navigational bronchoscopy, is a technique that uses chest CT images to create a 3D reconstruction of the airways and the lung. A virtual bronchoscopic view of the airways is obtained, and the software allows a virtual pathway from the central airways all the way up to the selected target lesion in the lung periphery. This virtual pathway to the target lesion acts as a map to allow the bronchoscopist to guide the bronchoscope and the biopsy instruments through the smaller airways to reach the PPN. The accuracy of reconstructing the airways, particularly the smaller ones, depends on the quality of the CT images. Thus, thinner slices and high-volume CT data result in more accurate virtual images. Although several VBN platforms are available, none possess the ability for real-time tracking of instruments during the actual procedure, which led to its successors, the electromagnetic navigational bronchoscopy (ENB) systems. Even without real-time tracking ability, VBN can be used in conjunction with radial probe endobronchial ultrasonography (RP-EBUS) and ultrathin bronchoscopy to improve the diagnostic yield of PPN biopsies.

Pooled diagnostic yield using VBN is in the range of 72% to 74%.[7,14] For smaller lesions (diameter $\leq$2 cm), the yield is lower at around 67%.[14] Whether use of VBN results in improved diagnostic yield in PPN is unclear: one trial demonstrated superior diagnostic yield with VBN and RP-EBUS use in lesions $\leq$30 mm diameter (80% compared with 67%),[15] whereas the same investigators had demonstrated earlier in another randomized trial no significant improvement in diagnostic yield for $\leq$30-mm lesion using VBN-assisted techniques (67% compared with 60%).[16] Of note, the former study used RP-EBUS with VBN and the latter study used ultrathin bronchoscopy with VBN.

A recent advance in the VBN system is the Bronchoscopic Transparenchymal Nodule Access (BTPNA) system (Archimedes System/Broncus Medical, Inc, San Jose, CA, USA). In BTPNA, VBN guides navigation to the nearest airway in the target lesion's vicinity. The software creates a tunneled path through the lung parenchyma and around the blood vessels directly to the peripheral lesion, which can then be sampled and treated. This may be particularly useful in lesions lacking the "air bronchus sign." In a human trial in 12 patients, this technique was successfully applied to 10 patients (track could not be created in 2 patients), and in all 10 cases where a transparenchymal track could be created, the diagnostic yield for BTPNA was 100%.[17] This promising technique needs validation with wider use in different PPN locations, and in a larger number of patients.

ELECTROMAGNETIC NAVIGATIONAL BRONCHOSCOPY

Inability of VBN to track and actually guide instruments into the PPN has led to the newer EMN bronchoscopy systems. Addition of electromagnetic tracking to virtual bronchoscopy allows real-time positional guidance and directional cues, allowing bronchoscopists to use these virtual road maps to guide instruments to the PPN. The most widely used ENB systems are the superDimension (Medtronic, Minneapolis, MN, USA) and the newer Veran SPiN system (Veran Medical Technologies, St Louis, MO, USA). The vast majority of the literature stems from cases performed on various iterations of the superDimension system.

ELECTROMAGNETIC NAVIGATION: SUPERDIMENSION SYSTEM

Similar to VBN, thin-cut CT images of the chest are reconstructed to create a 3D map of the airways and the parenchyma. Good-quality reconstruction

especially of smaller airways is contingent on CT images with higher resolution and overlap. The manufacturers provide recommendations on CT scan specifications for their respective platforms.

There are 3 phases to achieve to perform ENB.

1. Planning phase

   In this phase, the system software re-creates a dynamic multiplanar (axial, sagittal, coronal planes) 3D map of the lung and parenchyma from the CT chest images. Using this dynamic multiplanar map, the target lesion is marked (Fig. 4A). Using an intuitive "drag-and-drop" method, the operator then links the target to the nearest visible airway. The software automatically then creates a pathway from the trachea to the target. After review of the path, the operator moves on to the next step, which displays a "virtual fly through" (Fig. 4B), which can be reviewed by the operator before proceeding to the registration phase. The next step is to identify landmarks on the virtual airway in case manual registration needs to be performed during the procedure. These registration points are usually easily identifiable landmarks such as the main carina and lobar bronchi (Fig. 4C). Once the registration is complete, these data are saved in the dedicated laptop and then exported to a USB for transfer to the procedure platform.

2. Registration phase

   In this phase, an electromagnetic field is created around the patient and sensors are placed on the patient. The patient lies on a magnetic board such that the entire chest lies within the borders of the magnetic board. The board creates an electromagnetic field around the patient. Sensors are attached to the patient's chest that help synchronize the virtual landmarks registered in the planning phase to the actual anatomy of the patient. This is achieved by passing a locatable guide (LG) (through a 2.8-mm-diameter working channel bronchoscope) throughout the central airways and the lobar bronchi. During this process, the LG passively makes several hundreds of positional data points and matches them to the virtual 3D tracheobronchial tree. Once

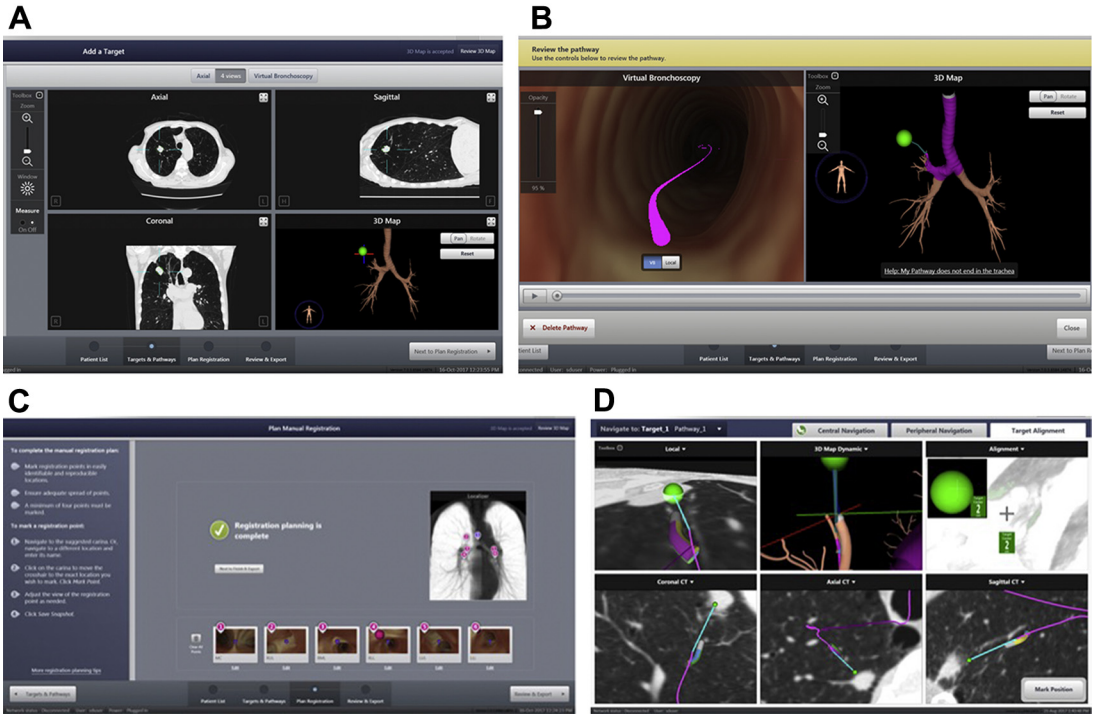

Fig. 4. (*A*) Planning phase: multiplanar views of the target lesion. (*B*) Planning phase: virtual path ("fly through") to the target. (*C*) Planning phase: registration of prominent landmarks (main carina and lobar bronchi) in case manual registration is required during the procedure. (*D*) Navigation phase: multiplanar views of the virtual images as the LG approaches the target lesion. Please note that the target lesion is represented by the green dot, and the tip of the LG is shown to be 2 cm away from the lesion. Also note that the lesion is aligned satisfactorily with the LG in all planes.

the software has enough data points, the virtual bronchoscopic image will appear on the screen. When successful, the estimated error is less than 4 mm. At this point, the scope is withdrawn to the trachea, and the navigation phase is ready to begin.

3. Navigation phase

The bronchoscope is wedged into the subsegmental bronchus leading to the lesion as determined by the virtual bronchoscopic path. The probe or the LG is then advanced into toward the lesion. The LG is rotated slowly so that it is advanced along the purple line on the virtual images. The purple line leads to the target lesion, which is represented as a green sphere. The LG is advanced as close to the green sphere as possible, and the EWC (or "edge" catheter), which accompanies the LG, is fixed at this position. Ideally, multiplanar confirmation of satisfactory position of the LG in relation to the target lesion should be done (**Fig. 4**D). The LG is then removed, and at this juncture, the RP-EBUS or CLE probe may be passed through the EWC to obtain real-time confirmation of the target lesion. Biopsy instruments, such as transbronchial aspiration needle, several kinds of brushes, and/or biopsy forceps, may then be passed through the EWC to obtain biopsies from the target lesion. Fluoroscopy can used to ensure the biopsy instruments function and to assess, if visible, that the lesion is being sampled without catheter displacement.

Table 2 summarizes major studies using ENB technique, diagnostic yield, and pneumothorax rates. Furthermore, in a large meta-analysis of 39 studies (11 studies with ENB) using image-guided bronchoscopy for diagnosis of PPN, the pooled diagnostic yield for ENB was 67%.[7] This number was not much different in another meta-analysis of 16 studies with ENB, with a pooled diagnostic yield of 65%.[18] In addition, ENB samples demonstrate adequate tissue acquisition for histologic subtyping as well as mutational analysis.[19] A multicenter, prospective trial (NAVIGATE Trial) with a 2-year follow-up study of subjects is currently

Table 2
Electromagnetic navigation bronchoscopy: adjunct technology and diagnostic yield

Study, y	Technology	Anesthesia	Number of PPN	Mean Size (mm)	AFTRE (mm)	Diagnostic Yield (%)	PTX (%)
Hautmann et al,[56] 2005	ENB, Fluoro	CS	16	22	6.2	66	0
Becker et al,[57] 2005	ENB, Fluoro	GA	29	39.8	NA	69	3.3
Schwarz et al,[58] 2006	ENB, Fluoro	CS	13	33.5	6.6	69	0
Gildea et al,[23] 2006	ENB, Fluoro	CS	58	22.8	NA	74	3.4
Wilson & Bartlett,[26] 2007	ENB, Fluoro, ROSE	CS	222	21	8.7	60	1.2
Makris et al,[59] 2007	ENB	GA/CS	40	23.5	4.6	62.5	7.5
Eberhardt et al,[60] 2007	ENB	GA/CS	93	24	4	67	2.2
Eberhardt et al,[22] 2007	ENB	GA/CS	39	26	NA	74	6
Bertoletti et al,[61] 2009	ENB	Nitrous oxide	53	31	3.9	77	4
Lamprecht et al,[62] 2009	ENB, PET-CT, ROSE	GA	13	30	4.7	77	0
Seijo et al,[21] 2010	ENB, ROSE	CS	51	25	4	66.7	0
Eberhardt et al,[32] 2010	ENB, RP-EBUS	GA/CS	54	23.3	3.6	75.5	1.9
Mahajan et al,[63] 2011	ENB, Fluoro	CS	49	20	NA	77	10
Pearlstein et al,[64] 2012	ENB, ROSE	GA	101	28	NA	85	5.8
Lamprecht et al,[25] 2012	ENB, PET-CT, ROSE	GA	112	27	4	84	1.8
Karnak et al,[27] 2013	ENB, ROSE	CS	35	23	4.4	91	3.9
Loo et al,[65] 2014	ENB, PET-CT, ROSE	GA	50	26	NA	94	0
Ozgul et al,[9] 2016	ENB, RP-EBUS	CS	56	30	5.8	71.5	1.7
Raval & Amir,[34] 2016	ENB	CS	61	19.3	NA	83.3	2

Abbreviations: CS, conscious sedation; ENB, electromagnetic navigation bronchoscopy; Fluoro, fluoroscopy; GA, general anesthesia; NA, not available; PTX, pneumothorax; ROSE, rapid onsite cytologic evaluation.

underway, and it is hoped this comprehensive study will answer key questions pertaining to ENB.[20]

Factors Affecting Diagnostic Yield

Although successful navigation to the target lesion occurs in more than 90% of cases, the diagnostic yield remains lower. This apparent paradox is explained by several factors affecting diagnostic yield with ENB:

1. Bronchus sign: The presence of a bronchus (on CT scan) leading to the PPN increases the overall diagnostic yield from 67% to 88%.[21]
2. Location of PPN: Although there are mixed reports, lower lobe location of PPN particularly close to the diaphragm may have a lower diagnostic yield compared with upper lobe location (77% vs 29%).[22] The reason for this is likely the respiration-related movement of the diaphragm may result in navigation error as the CT scans to create the virtual map is performed during a single breath-hold (superDimension) and does not take into account the movement of the nodule during respiration.
3. Lesion size: Lesions less than 30 mm may have a low diagnostic yield compared with larger lesions (72% compared with 82%[23]).
4. Learning curve: There are nuances to using the ENB technology, and therefore, it is reasonable to conclude that experience is an important determinant of diagnostic yield with this technology. Not surprisingly, there are data to support this.[24,25]
5. AFTRE (average fiducial target registration error): AFTRE is the difference in the location of the tip of the LG in actual patient compared with its expected location on the virtual 3D airway map created from the CT images. AFTRE of less than 4 mm has been associated with better diagnostic yields.[26,27] With the newer versions of the software, this is less likely to be a concern.
6. Identification of the lesion on fluoroscopy: Although touted to be important and commonly used in the United States, data from Europe note no difference in published yields with or without fluoroscopy.
7. Anesthesia: Pooled data from the Wang Memoli meta-analysis[7] suggest the diagnostic yield for ENB is better with GA compared with conscious sedation (69% vs 57%). However, a retrospective study of 120 patients did not demonstrate a significant difference.[28] The investigators favor general anesthesia for patient comfort as well as for when trainees are involved with the procedure.
8. Biopsy tools: Although 40 years of data have suggested that the use of the peripheral transbronchial needle aspiration (TBNA) is associated with higher yield even without navigation, it is still not commonly used.[29] Sixteen percent of the cases in the AQuIRE Registry used the peripheral TBNA, but it was associated with higher yield.[30] The Cleveland Clinic experience showed that a dedicated peripheral needle was associated with a yield of 63%, but when combined with bush and forceps, yield was 83%.[31] The use of a simple aspiration catheter is associated with higher yields than transbronchial forceps biopsy.[32]

ELECTROMAGNETIC NAVIGATION: VERAN SYSTEM

This ENB platform (SPiN System; Veran Medical Technologies) has attempted to overcome certain challenges, such as the effect of respiratory motion while obtaining biopsies. In addition, the Veran system offers real-time tracking mechanisms of the biopsy instruments during the procedure. Another feature that is unique to this system is its ability to perform navigational TTNA at the same sitting, an option that may come in handy if the navigational bronchoscopy is unable to obtain satisfactory samples from PPN.

Just like other EMN systems, the SPiN/Veran System generates a 3D map of the lungs based on an inspiration/expiration CT Scan Protocol. Stickers containing electromagnetic sensors (**Fig. 5**A) are placed on the patient's chest before CT scans and remain in place during the procedure to help guide navigation and track patient breathing. The planning phase is similar to the superDimension system but allows for automatic registration if the CT scan is performed with the skins sensors on the patient. Therefore, the CT chest scan with this system needs to be performed on the same day as the procedure. Although this may create logistical challenges, a hidden advantage may be the same-day CT scan may show regression or resolution of nodules in 7% of patients, thus obviating a procedure in these patients.[33] Often the SPiN planning software converts the scans and creates a dynamic 3D map that allows customization of views and selection of targets. The electromagnetic sensor–equipped stickers enable automatic registration and dynamic referencing throughout the entire procedure (**Fig. 5**B). Respiratory gating technology communicates with the electromagnetic sensors to track respiratory movement. The dedicated biopsy instruments contain electromagnetic sensors at the tip to allow continuous tracking of the

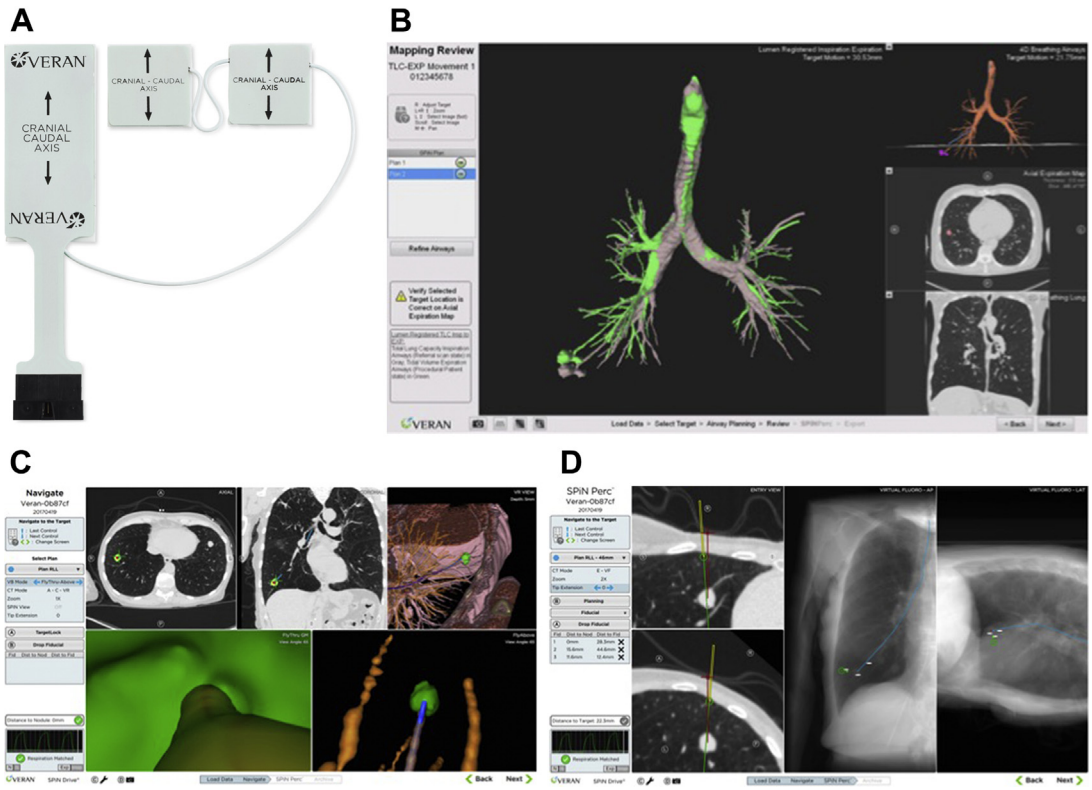

Fig. 5. (*A*) Electromagnetic sensors, "vPad." (*B*) Respiratory gating. (*C*) Navigation to target with instrument tracking. (*D*) Navigational TTNA when navigational bronchoscopy fails to reach the target lesion. (*Courtesy of* Veran Medical Technologies, St Louis, MO; with permission.)

instruments to the target lesion (Fig. 5C). The manufacturer touts that fluoroscopy is not required for navigation success, and there are additional instruments that have tracking probes built in for added success.

The Veran system offers the flexibility of performing electromagnetic navigation transthoracic needle aspiration (ETTNA) of the target lesion as well (Fig. 5D). ETTNA may be performed as the first step or as an additional procedure if the navigational bronchoscopy is unsatisfactory. Transition from EMN to ETTNA may be seamlessly performed in the same sitting because the magnetic sensors are already attached to the patient and the target lesion selected in the planning software.

In a study of 50 patients with PPN sizes 19.3 ± 10.7 mm and 54 mm, the overall diagnostic yield for ENB using the Veran system was noted to be 83.3%. The yield was 77% for lesions without bronchus sign.[34]

In a pilot study to evaluate the safety and feasibility of the ETTNA feature of this system, ETTNA was found to be feasible in 96% of cases. The pneumothorax rate was 21%, and chest tube placement occurred 8% of cases. The diagnostic yield for ETTNA alone was 83% and increased to 87% ($P = .0016$) when ETTNA was combined with EMN.[35] Some centers use the ETTNA feature for dye marking or fiducial marker placement just before thoracic surgery.

There have been no comparative trials to compare the 2 navigation systems, but the authors suspect these are similar based on experience and limited available data.

ULTRATHIN BRONCHOSCOPY

A major limitation of traditional bronchoscopes is their inability to traverse beyond the subsegmental bronchi due to their relatively large circumference (4.9 mm to 6.1 mm in diameter), thus having to thread biopsy tools from a distance and resulting in lower diagnostic yields for PPN. Ultrathin bronchoscopes, as the name indicates, are much thinner than a standard flexible bronchoscope, ranging in diameter from approximately 2.8 to 3.5 mm (Fig. 6). Compared with a standard flexible bronchoscope, the thinner bronchoscope has the ability to navigate beyond fifth- or sixth-order airways and close to a PPN while retaining visualization, in theory making biopsy attempts more reliable to obtain accurate samples from a

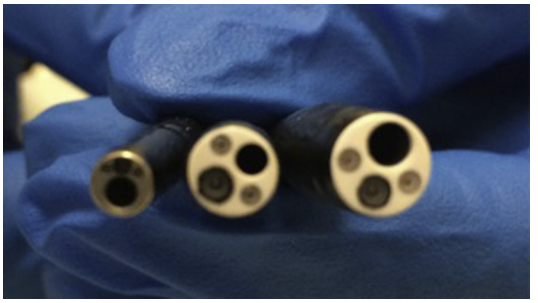

Fig. 6. Ultrathin bronchoscope on the left in comparison with standard bronchoscopes. Newer-generation ultrathin scopes are thinner than the one shown here.

target lesion. Dedicated miniaturized biopsy instruments can be used to obtain biopsies though the smaller working channel. However, secretions in the smaller airways may result in poor visualization as the ultrathin scope is advanced, and the smaller working channel may not be as efficient as a standard working channel in suctioning out secretions.

Ultrathin bronchoscopy is often combined with other techniques, such as virtual bronchoscopy, EMN, or RP-ultrasound for PPN tissue sampling, especially with the advent of a 1.4-mm-diameter RP-EBUS.[36] Used as a standalone tool, ultrathin bronchoscopy for PPN has a diagnostic yield of 57% to 70%.[7,36,37]

A combination of RP-EBUS and ultrathin bronchoscopy has a reported overall diagnostic yield of 69%.[36] In this study, the diagnostic yield for a lesion less than 20 mm diameter was 36% compared with 77% for lesions larger than 20 mm. A hybrid tracking system that uses electromagnetic and image-based techniques to track the location of the bronchoscope within the airways has been reported.[38] A combination of ultrathin bronchoscopy (3 mm diameter), virtual bronchoscopy, and RP-EBUS may result in a slightly better diagnostic yield of 74%.[39] Despite these advantages, the sensitivity of ultrathin bronchoscopy used alone or in combination with other technologies for diagnosis of PPN is not conclusively superior to other bronchoscopic modalities.

PERCUTANEOUS APPROACH

TTNA of PPN may be performed under CT or fluoroscopic guidance. CT-guided aspiration and biopsies result in a higher diagnostic yield compared with fluoroscopy,[29] and therefore, most commonly used TTNA modality. The most widely used technique is a coaxial system; a larger-bore needle is inserted into the lesion under CT guidance, and a smaller needle is passed through the larger one. Thus, a single chest wall and pleural puncture allows for multiple samples to be obtained.

In a study of 203 patients[40] at an academic institution who underwent CT-guided TTNA of PPN, the sensitivity of CT-guided TTNA for lung cancer was 93%. The investigators also noted that the overall complication rate was 25%. Incidence of pneumothorax was 24%, with 7% of all patients requiring a chest tube. This trend has been consistent over time. A recent meta-analysis of 8133 procedures undergoing CT-guided core biopsies and 462 procedures undergoing needle aspiration demonstrated overall complication rates for core biopsy and needle aspiration at 38.8% and 24%, respectively. Pneumothorax rates for core biopsies and needle aspiration were 25% and 19%, respectively. The largest cross-sectional study noted a pooled risk of 15% of pneumothorax and 6.6% of needing a chest tube and 1% risk of clinically significant bleeding.[41] Several factors have been implicated, including the type/size of needle used, number of passes, location of lesion, degree of emphysematous disease, distance of PPN from the pleura, and procedure duration.[42]

Of interest lately is tissue adequacy for mutational analysis for lung cancer. CT-guided TTNA, particularly core biopsy, appears to have high sample adequacy in this regard. The average number of cells obtained by CT-guided needle biopsy is 500 cells per biopsy,[43] and samples may have nearly 100% adequacy for histologic and endothelial growth factor receptor mutation analysis.[43–45]

FUTURE DIRECTIONS

Cone Beam Computed Tomography

Cone beam CT scanning is a technique whereby a virtual target can be obtained and overlaid on fluoroscopic images with various tools co-opted from digital segmented angiography (**Fig. 7**). One study noted a 91% navigational success with a biopsy yield of 67% for lesions greater than 2 cm and 75% for lesions less than 2 cm.[46] Ng and colleagues[47] described the technique of combining navigational bronchoscopy and cone beam CT with a robotic arm CT scanner.

The ability to perform real-time multiplanar confirmation with 3D reconstruction is a useful tool to confirm position of an instrument or the accuracy of a guidance technology. Portable systems can be used, but these have many limitations in their current configurations. Presently, another drawback of this technology is the high-dose radiation burst with its use; personnel have to leave the room, or stand behind a shield while cone beam CT “spin” is in use to obtain a

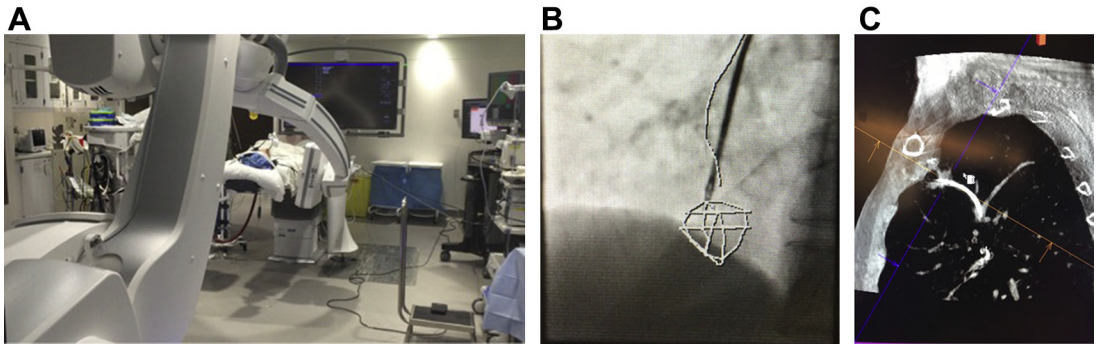

Fig. 7. (*A*) Cone beam CT preparation for image acquisition. Note that all personnel are out of the room, and the bronchoscopy and other instruments are separated from the system and secured. (*B*) Cone beam CT with target overlay on the fluoroscopy images with pathway (DynaCT Siemens). (*C*) Image captured from cone beam CT of a peripheral TBNA directed into a spiculated lesion in the left upper lobe, using ENB.

CT image. However, there are also data to suggest that the cumulative radiation dose per procedure is similar to CT-TTNA or low-dose CT scan procedures.[46] Furthermore, virtual targeting has the same drawbacks of other navigation systems wherein the lung is not static and the lesion may be moving. Also, error may be introduced with patient movement or atelectasis. This could be one of the areas for technology refinement, along with the addition of 4-dimensional motion tracking so that image acquisition can be made portable. Because cone beam CT is an adjunctive image acquisition tool, it can be used with other guidance systems like ENB, but considerations for interference with images and the possibility of the 2 systems giving different information are possible in the authors' experience.

Modality Selection/Multimodality Approach

Although each individual nonsurgical modality available for diagnosis of PPN has its own advantages and limitations, currently it is not possible to offer a recommendation on any one or combination as the diagnostic modality of choice. The only exception is the combination ENB and radial EBUS probe. This is because of the inability of the safer bronchoscopic techniques to offer comparable diagnostic yields as percutaneous CT-guided biopsy technique, which in turn has a higher complication rate. Several factors affect the choice of a diagnostic tool for PPN:

1. Availability of a specific diagnostic modality
2. Wait times to undergo a specific procedure
3. Diagnostic yield of a specific diagnostic test
4. Complication rates of a specific diagnostic test
5. Need for hilar and mediastinal nodal staging
6. PPN characteristics, such as location, size, and presence or absence of bronchus sign
7. High pretest probability of malignancy of a PPN may result in upfront surgical resection
8. Clinician preference
9. Patient preference (CT biopsy vs bronchoscopic biopsy)
10. Cost for the patient, cost for the institution; some techniques may be cost prohibitive especially in developing countries

Professional societies' guidelines[48,49] for management of incidentally detected PPNs remain the best approach to initial assessment and management of PPN. PPN with high risk for malignancy may be directly referred to surgery. However, there seems to be increasing evidence to suggest that in select cases such as somewhat central location of indication of PPN, preoperative tissue sampling of thoracic nodes may have to be performed for accurate nodal staging. This is because of a higher incidence of false negative PET scans in such cases.[50] In such instances, there is variation in practice on whether bronchoscopic diagnostic testing should be limited to nodal sampling, or extend the procedure to obtain biopsy from the PPN in the same sitting. There is no such dilemma in intermediate-risk PPN or in patients who are deemed nonsurgical candidates. In these cases, nonsurgical biopsy is preferred to determine malignant or benign nature of the lesion. Factors enlisted above come into play while choosing one or more of the diagnostic modalities for obtaining diagnostic tissue from PPN. The authors usually perform a combination of navigation bronchoscopy with real-time confirmation of the lesion with RP-EBUS and use rapid onsite cytologic evaluation. For lesions deemed nearly impossible to reach with navigational bronchoscopy, image-guided percutaneous modality is preferred. This approach may be done in a single

setting with the newer Veran Navigation system, which allows both navigational bronchoscopy and navigational percutaneous sampling. However, navigational percutaneous sampling is still not real-time and is subject to the same pitfalls as EMN with regard to error, and the risk of percutaneous biopsy is still the same. A bronchoscopy technique offers the additional benefit of being able to perform EBUS nodal staging at the same time. On the other hand, a PPN abutting the chest wall may be more reliably sampled with percutaneous techniques with reduced risk of pneumothorax. No matter what guidance technique is used, there is still a need to obtain invaluable tissue samples. Even the choice of the inexpensive biopsy instruments has direct impact. Regardless, there continues to be a diagnostic drop-off between "localization" and actual acquisition of diagnostic tissue.[51]

SUMMARY

Given the widespread adoption of lung cancer screening programs, it is not hard to foresee that the incidence of peripheral lung nodules will only increase. Many of these nodules will require tissue sampling as part of management. Several modalities for sampling PPNs are available; none is perfect though. Bronchoscopic techniques have a better safety profile, but relatively lower diagnostic yield. With technological advances, in the not too distant future, bronchoscopic techniques such as navigational bronchoscopy may have diagnostic yields comparable to CT-guided biopsy and may well become the modality of choice for biopsy of PPN. They have the ability to provide additional information such as lymph node staging with endobronchial ultrasound, and perhaps even be able to offer therapeutic options in the future. Presently, the choice of modality for biopsy of PPN depends on probability of malignancy, physician preference, availability of resources in individual institutions, lesion location, the need for concomitant nodal staging, presence of risk factors for complications such as pneumothorax, and patient preference. As these emerging technologies undergo further refinement, a major factor determining the choice of modality will be the ability to obtain enough tissue for molecular markers.

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