Bronchoscopic biopsy of peripheral pulmonary lesions in 2020: a review of existing technologies

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (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: There are over 200,000 new cases of lung cancer diagnosed annually in the United States resulting in nearly 150,000 deaths, making lung cancer the most lethal of all forms of cancer. Only 1 in 6 lung cancers are diagnosed at an early stage an over half are diagnosed with distant metastasis. Despite advances in screening and treatment, the 5-year survival rate for all lung cancers remains low, around 20%. The advent of effective lung cancer screening with low-dose computed tomography has started to shift diagnosis to earlier stages. Screening, along with the ever-increasing use of chest CT, have led to an exponential increase in the detection of indeterminate lung nodules. For many nodules, effective diagnosis relies on invasive tissue sample collection. Advances in bronchoscopic technology have allowed for safe and increasingly effective tissue diagnosis of these nodules; however, inconsistencies across studies evaluating diagnostic yield remain. This review will provide an overview of the advanced bronchoscopic technologies currently in wide use, the quality of data supporting their use, some of the perceived weaknesses and strengths of each technology, and introduce promising emerging diagnostic platforms poised to advance the field. Ultimately, quality comparative research is needed to accurately characterize the diagnostic test performance of currently available bronchoscopic platforms, improve the efficacy of bronchoscopy-generated diagnostic yields while maintaining, their strong safety profile.

Keywords: Bronchoscopy; lung cancer; lung nodule; transbronchial biopsy; navigational bronchoscopy

Introduction

There have been significant advances in diagnostic bronchoscopy techniques over the last two decades. Since the advent of linear endobronchial ultrasound (EBUS) in 2002, there has been an explosion of new technologies entering the field (1). With these advances comes the hope of improving diagnostic yields. This was certainly true in the case of EBUS, which is now widely viewed as the gold-standard for mediastinal staging in newly diagnosed lung cancer (2). Lung nodules, however, remain a significant challenge in many cases. With an estimated annual incidence of 1.5 million, they are common, and when malignant, represent the earliest and more curable stage of lung cancer (3).

Differentiating benign from malignant nodules requires thorough risk-of-malignancy stratification. Factors associated with increased risk include location and size of the lesion, age, smoking status, exposure to other known carcinogens (e.g., radium), gender, race and co-existing lung disease such as emphysema or idiopathic pulmonary fibrosis. Decision making can be further guided by existing societal

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guidelines such as those promoted by the Fleischner society for incidentally found nodules or lung-RADS for nodules discovered while performing lung cancer screening (4,5). In addition to these guidelines, risk stratification calculators can be utilized (6,7).

A tissue diagnosis is often indicated following risk stratification (8). There are three major modalities for tissue acquisition of lung nodules: surgical resection, CT-guided transthoracic needle biopsy (CT-TTNB), and bronchoscopic biopsy. Clinicians are faced with the challenge of determining the least invasive and most efficacious way to obtain a tissue sample, weighing the risks of a procedure against the diagnostic yield. Of the two minimally-invasive diagnostic modalities, CT-TTNB has been touted for its impressive diagnostic yields. A recent meta-analysis of 48 TTNB case series, for example reported a pooled diagnostic accuracy of 92.1% (9). High diagnostic yields persisted even with small nodules <1 cm. Despite this high diagnostic yield, TTNB complications, most notably pneumothorax rates of 20–25% (3,10,11) have generated interest in alternative modalities. In addition, TTNB lacks the ability to perform simultaneous staging. Quality comparative trials are lacking in the CT-TTNB literature. There may be patient selection bias in the available reports. Additionally, data for nodules <2 cm is limited.

Bronchoscopic biopsy of peripheral pulmonary lesions has been associated with a wide variety of diagnostic yields, with some as high as 94% (12). A 2012 meta-analysis including multiple advanced bronchoscopic technologies reported a pooled diagnostic yield of 70%, with favorable complication rate compared to TTNB of 1.6% pneumothorax and 0.7% major bleeding. Additionally, the platform of bronchoscopy may allow for the targeting of multiple legions during the same procedure and the ability to perform simultaneous mediastinal staging, which has generated considerable interest in optimizing timely triage of patients with indeterminate pulmonary nodules (13).

A variety of novel bronchoscopic tools have emerged over recent years. In this review we will focus on several of these technologies, discussing their technical aspects and any available clinical data. Many of these technologies have only recently been introduced into clinical use, limiting available data, and many of these technologies are viewed as complementary and not studied in isolation making each component's contribution to diagnostic yield and safety difficult to ascertain. Robotic bronchoscopy will not be covered in this review as it is being covered in an accompanying article in this journal edition. The

technologies reviewed include: radial probe endobronchial ultrasound (REBUS), thin/ultrathin bronchoscopes, virtual bronchoscopic navigation (VBN), electromagnetic navigational bronchoscopy (ENB), cone beam CT (CBCT)-assisted bronchoscopy, digital tomosynthesis-assisted bronchoscopy, and bronchoscopic transparenchymal nodule access (BTPNA) and transbronchial access tools (TBAT).

REBUS

REBUS is a thin flexible ultrasound probe which comes in three sizes, the smallest of which has an outer diameter of 1.4 mm (UM-S20-17S, Olympus, Toyko, Japan) allowing it pass through the working channel of nearly all bronchoscopes. These can also be used through straight or curved guide sheaths advanced through the larger working channel of therapeutic bronchoscopes, allowing for more specific targeting in the peripheral lung. These probes provide a 360-degree view in a two-dimensional (2D) plane radiating outward from the spinning probe located near the tip of the device. They allow real-time localization of lesions distal to the physical reach of the bronchoscope or where direct visibility would otherwise be limited or not possible (a nodule located adjacent to an airway, for example). Solid lesions are often detected as a circle which completely surrounds the central probe (a concentric view, seen when the REBUS probe is advanced into an airway which leads directly into a peripheral lesion, *Figure 1A*) or a semicircle only visible on part of the screen (eccentric view, seen when the REBUS probe is directed into an airway which makes only peripheral contact with a lesion, *Figure 1B*). Ground glass opacities (GGOs) can sometimes be detected by the more subtle "blizzard" pattern (*Figure 1C*).

A 2011 meta-analysis of REBUS-guided bronchoscopy pooling the results of 16 studies including 1,420 patients with at least 6 months follow-up data reported a pooled diagnostic sensitivity of 73% (14). A larger meta-analysis which also included complementary technologies such as guide sheaths, ultrathin bronchoscopes, electromagnetic navigation, and virtual navigation, showed similar pooled sensitivities of 73% with GS and 71% without GS (13). A concentric REBUS signature is associated with higher diagnostic yield compared to an eccentric view, 87% *vs.* 42%, respectively (15). Complication rates are similar to those seen with standard non-guided transbronchial biopsy, with pneumothorax rate of 1%, of which 0.4% required chest tube placement (14).

While REBUS provides the proceduralist an opportunity
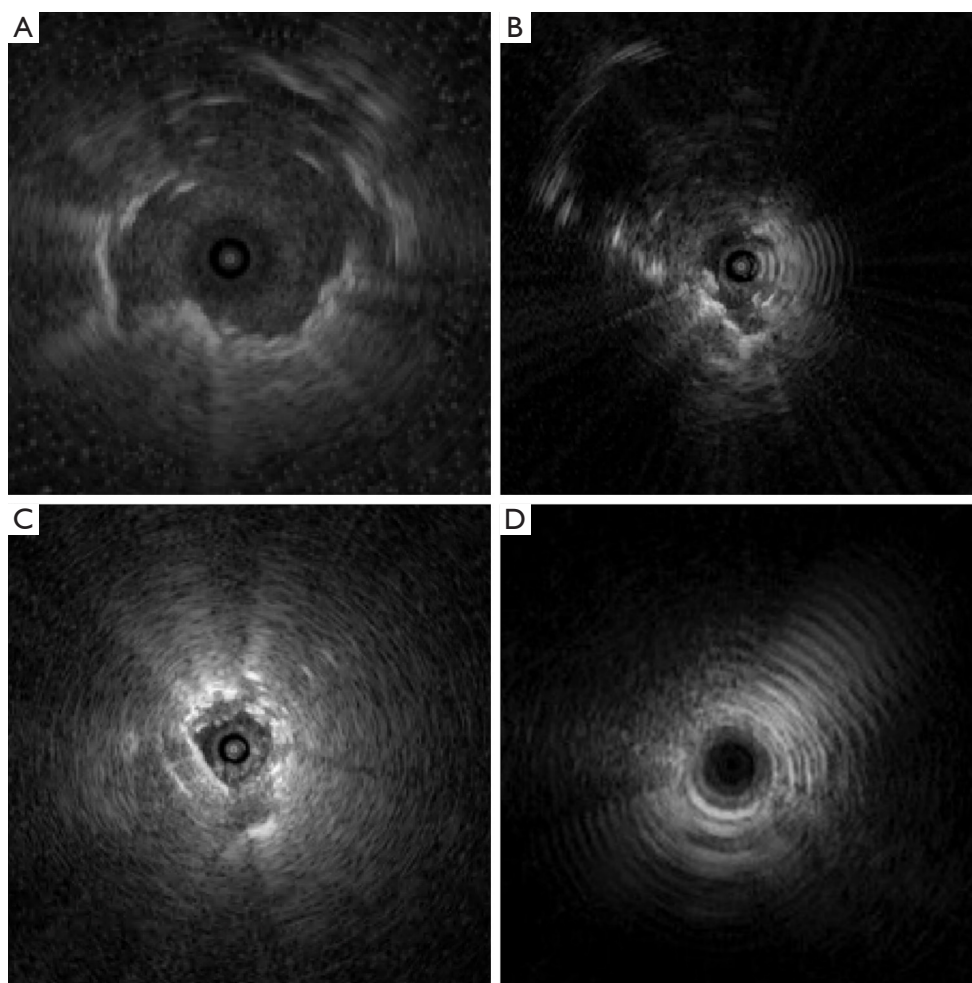
Figure 1 REBUS profiles of (A) concentric view of a lung nodule; (B) eccentric view of a lung nodule; (C) "blizzard sign" of slightly increased intensity and length of acoustic shadow associated with subsolid lesions; and (D) normal aerated lung. REBUS, radial probe endobronchial ultrasound.

to visualize lung nodules which may not be otherwise be visible with other modalities, it does have limitations. GGOs are visualized as a "blizzard" pattern (*Figure 1C*); in practice this pattern is often difficult to appreciate, especially with small lesions. Additionally, false positives are frequent as bleeding, saline, and atelectasis occur during the procedure and may be mistaken for the lung nodule, perhaps explaining the substantial drop-off rate between identification of lung nodules and actual diagnostic yield (16). Finally, these probes do not assist in more precise localization of a nodule located eccentrically to the probe/airway. An eccentric REBUS nodule signature tells the operator that the nodule is next to the airway but provides no information about where the nodule is

in three-dimensional (3D) space in relation to the airway. The operator must use other means to decide which way to manipulate the bronchoscope or guide sheath to accomplish successful access of the eccentric peripheral lesion.

Thin and ultrathin bronchoscopy

Thin or ultra-thin bronchoscopes do not have consensus definitions. When referenced in existing literature, they typically imply bronchoscopes with an outer diameter <4.0 and <3.0 mm, respectively (17,18). This is in contrast to the approximate 6.0 mm outer diameter of therapeutic or treatment bronchoscopes (19,20). The narrow outer diameter of thin and ultrathin bronchoscopes allow for improved access

to subsegmental airways, and, presumably, to peripheral lung nodules themselves. While standard bronchoscopes may be able to reach 3rd or 4th generation airways, UTBs are reported to reach up to the 9th generation (21).

A 2015 prospective multicentered randomized controlled trial examined the diagnostic yield of a thin bronchoscope with a guide sheath and an ultrathin bronchoscope which have an out diameter of 4 and 3 mm respectively (18). This study enrolled 310 patients with lung nodules <30 mm in size, of which 305 underwent bronchoscopy. Procedures were additionally guided by fluoroscopy, VBN, and REBUS in both groups. Despite only a 1 mm difference in diameter, ultrathin bronchoscopy was shown to be superior to thin bronchoscopy, with histological diagnostic yield in the ultrathin group of 74% (111 of 150 patients) *vs.* 59% (92 of 155 patients) in the thin bronchoscope with guide sheath group (absolute difference 14.6%, 95% CI: 5.8–23.4%). Importantly, unconfirmed but suspect benign diagnoses were confirmed by radiologic size stability and clinical compatibility during the follow-up period for at least 1 year after bronchoscopy. A recently published RCT examined the diagnostic yield between thin and ultrathin bronchoscopy. Three hundred and fifty-six patients with pulmonary nodules of a median size of 19 mm were randomized to bronchoscopy with a thin or ultrathin scope. The diagnostic yield was significant better in the ultrathin group (70.1% *vs.* 598.7%) (22).

This diagnostic yield has not been universally reported in studies of thin and ultrathin bronchoscope, however. A prospective 2018 trial comparing traditional fluoroscopically-guided transbronchial forceps biopsy using a standard 5.0 mm OD bronchoscope *vs.* thin bronchoscopy with REBUS ± guide sheath and fluoroscopic guidance demonstrated decidedly lower yields of 49% and 37%, respectively, despite expert bronchoscopists and a generous average lesion size of 31 mm (23). This study has been criticized for its use of cytobrushes instead of needle biopsies for rapid on-site cytology, fairly rigid methodology allowing for only 5 forceps transbronchial biopsies at the target site, and lack of sampling via transbronchial needle aspiration suggested by prior work to be the highest yield diagnostic tool in the peripheral lung (24,25), all of which might have unfavorably impacted diagnostic yield.

Overall, studies of thin and ultrathin bronchoscope suggest that narrower bronchoscopes used in conjunction with complementary technologies such as fluoroscopy, REBUS, guide sheaths, and navigational systems improves the ability to successfully access peripheral lung lesions,

though this has not been a universal finding. Complication rates were infrequently reported in these studies but case reports of pleural perforation have been made (26).

VBN

Accessing lung nodules necessitates accurate selection of branching bronchi, which represents a significant technical and spatial-reasoning challenge. VBN utilizes a helical CT scan to generate 3D images of the tracheobronchial tree (27). During bronchoscopy, the computerized navigational system recognizes the visual appearance of airways during bronchoscopic maneuvering and guides the user to make correct turns into subsequent subsegmental branches on the way to the operator pre-specified peripheral lesion. There are several VBN systems commercially available worldwide, including Bf-NAVI® (Cybernet System Inc., Tokyo, Japan), LungPoint® (Broncus Medical Inc., Mountain View, CA, USA), and DirectPath® (Cybernet System Inc.) (28).

A multicenter prospective study randomized 199 patients with lung nodules <30 mm to either VBN-assisted (VBNA) or non-VBN-assisted (NVBNA) groups. Guide sheaths were used in all procedures and sampling was also guided by REBUS probes and fluoroscopy. VBNA had significantly higher diagnostic yield than the NVBNA group (80% *vs.* 67%, respectively, P=0.03) (29). A 2014 systematic review of VBN showed an average diagnostic yield of 74% in all lesions and 67% in small lesions <20 mm. Other complementary technologies used in these studies included UTB, fluoroscopy, GS, and REBUS (28).

VBN appears helpful in planning procedures and aids operators in approximating the bronchoscope and the peripheral lesion by facilitating selection of correct subsegmental bronchi on the pathway to the lesion. VBN does not include a mechanism for making real time adjustments for CT-to-body divergence (the difference in nodule location between the pre-operative CT and real-time imaging) or provide electronic tool tip location feedback to the operator.

ENB

ENB systems utilize a pre-procedure CT scan-derived virtual tracheobronchial tree, on which target lesions are designated by the operator, similarly to VBN. During the procedure, an electromagnetic field is generated by a board placed under or above the patient's thorax and electromagnetic sensors are placed on the patient. These

sensors triangulate electromagnetic catheters or biopsy tools within the patient in real time. Currently there are two commercially-available ENB systems: superDimension (Medtronic, Minneapolis, MN, USA) and SPiNDrive (Veran Medical Technologies, Inc, St Louis, MO, USA). Within the superDimension platform, a blunt-tip electromagnetic probe affixed to the distal aspect of a curved guide sheath (with multiple degrees of curvature available) is used to direct the sheath toward the target lesion. Once in position, the electromagnetic guide is removed, leaving the guide sheath in place as a channel for biopsy instruments to be introduced. SPiNDrive, by contrast, utilizes tools with electromagnetically-tracked tips allowing for real time tracking as biopsy samples are collected, and also offers support for transthoracic needle aspiration via an electromagnetic tip-tracked transthoracic biopsy needle. A multicenter case series was recently published showing a diagnostic yield of 73.7% in 129 cases with an average nodule size of 27.31 mm. This increased to 81.1% when bronchoscopy was also performed (30).

A 2014 review showed pooled diagnostic yield from 15 studies containing results on 1,033 lung nodules demonstrated a 64.9% diagnostic rate for ENB (31). Eberhardt and colleagues reported a yield of 59% for ENB without assistance of fluoroscopy, increasing to 88% when REBUS probes were additionally used to guide the procedure (32). Complication rates similar to other bronchoscopic modalities have been reported, with a pooled pneumothorax rate of 3.1%, of which 1.6% required chest tube insertion, in the aforementioned meta-analysis (31). Several factors have been associated with higher yield such as nodule size and presence of a bronchus sign (33-35).

In more real-world use settings, the diagnostic yield of ENB has been mixed. The multicenter prospective NAVIGATE trial evaluating superDimension was recently published (36). This study included 1,157 lung lesions with an average size of 20 mm, with diagnostic yield of 73% (37). This is contrast to data from the AQuIRE (ACCP Quaility Improvement Registry, Evaluation, and Education) registry, in which a yield of 47.1% was noted when ENB and REBUS were used to biopsy lung nodules (25). There are many potential reasons for the discrepancy in these yields, including patient/nodule selection, operator/institution experience (median of 14 ENB cases per year per physician in AQuIRE *vs.* 45% of operators in NAVIGATE reporting 5–10 ENB cases per month and another 45% reported >10 per month), utilization of rapid on-site cytology during the procedure (31% in AQuIRE *vs.* 69% in NAVIGATE),

a high degree of interinstitutional practice variability in the AQuIRE registry, and underuse of transbronchial needle aspiration in the AQuIRE registry (only 16% of cases, with four or more needle passes in only 24% when actually utilized). The discrepancy in diagnostic yield centering on operator experience and appropriate biopsy tool selection also highlights the fact that advanced bronchoscopic technologies may have significant learning curves, implying the technologies themselves are not sufficient in guaranteeing high diagnostic yields.

There are some limitations to ENB systems, particularly CT-to-body divergence (35), which occurs due to respiration, body positioning, atelectasis, and cardiac motion. Nodules in the lower lobes, for example, have been demonstrated to move up to 2.5 cm between inspiratory and expiratory CT scans (38). Additionally, catheter-to-nodule deflection occurs as a result of stiff tools being placed through relatively pliable guide sheaths. For example, a curved guide sheath may be precisely aligned with the nodule without a tool inside it, but be significantly deflected when a biopsy tool is advanced through it.

Potential solutions to minimize CT-to-body divergence in ENB and VBN procedures include optimization of ventilator strategies to reduce the risk of atelectasis and use of near-real-time imaging with intraprocedural CBCT and/or digital tomosynthesis fluoroscopy. Instrument or catheter-based deflection has been addressed with continuous electromagnetic tracking of catheters and biopsy instruments.

ENB with fluoroscopic digital tomosynthesis [fluoroscopic navigation (F-Nav)]

One major limitation of all ENB and VNB platforms is the reliance on a pre-operative CT for planning and navigation as opposed to real-time imaging guidance. Though ENB is often used with 2D fluoroscopy, the resolution needed to see small or semi-solid lung nodules is frequently lacking. Digital tomosynthesis, also referred to as F-Nav, is a method for performing high-resolution limited-angle tomography at radiation dose levels comparable with standard projection radiography (39).

F-Nav consists of a traditional ENB, followed by a limited angle spin of the standard 2D fluoroscopic C-arm, with images recorded and processed to yield a digital tomosynthesis image of the nodule. This enhances the visual appearance of the lesion, revealing nodules not otherwise visible on standard 2D fluoroscopy, including
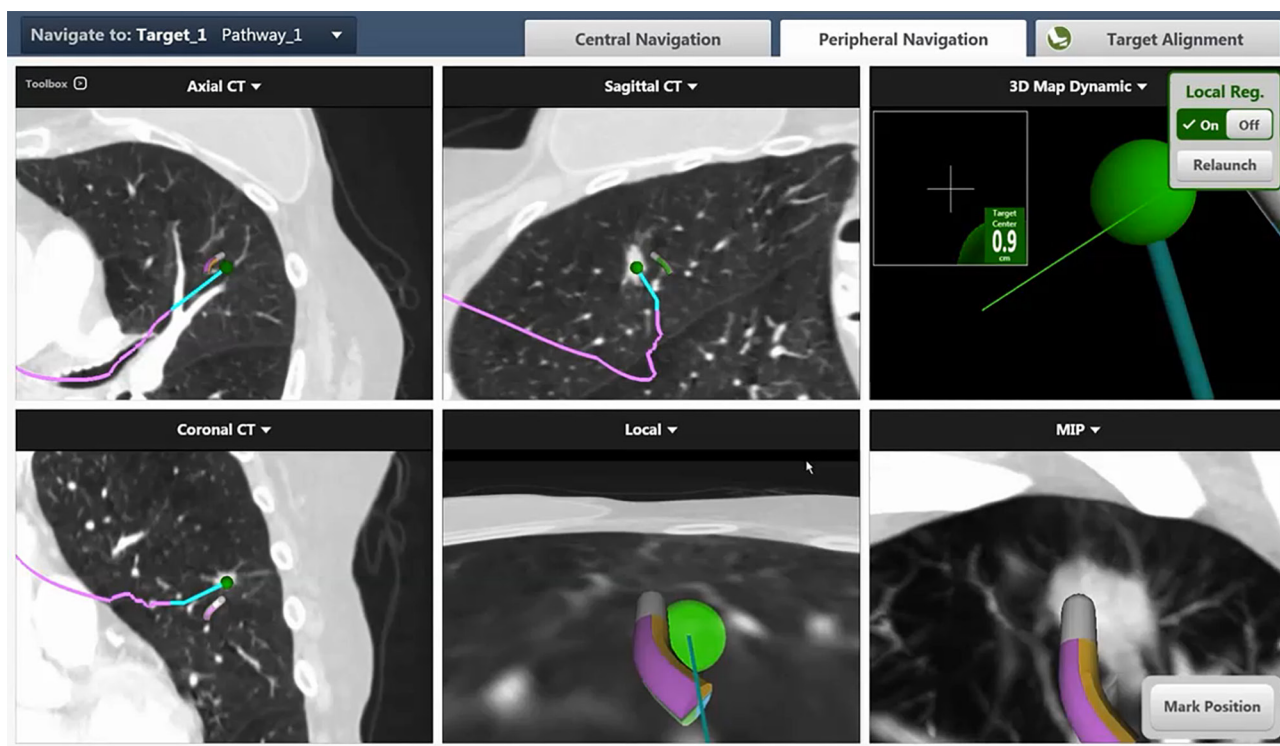
Figure 2 superDimension navigation screen showing axial, sagital, coronal CT views plus local maximal intensity projection and "3D map dynamic view" which are intended to help the user visualize and guide the curved guide sheath into correct alignment with the peripheral lesion. Local registration in "on" in this figure signifying a F-Nav was performed. 3D, three-dimensional; F-Nav, fluoroscopic navigation.

pure ground glass and cavitary lesions. Additionally, by marking the tip of the guide sheath and the lesion, the ENB system can update the real-time location of the nodule in the virtual workspace, directing the operator to manipulate the catheter in an optimal manner to direct biopsy tools into the lesion (*Figure 2*). This technology was the subject of a retrospective before-and-after study in which 168 consecutive nodules were analyzed at a single center. Standard ENB (ENB) with 2D fluoroscopy was used on 101 of the nodules. F-Nav was subsequently introduced and the remaining 67 cases were analyzed. ENB had a diagnostic yield of 54% while F-Nav had a diagnostic yield of 79% (P=0.0019), with comparable nodule sizes in both groups (median 15 *vs.* 16 mm). Complications rates were equivalent between the two groups with a pneumothorax rate of 1.5% and no significant bleeding (35). This emerging technology, currently commercially available as a component of the superDimension ENB system, will require additional study to confirm these results.

CBCT-guided bronchoscopy

CBCT-guided bronchoscopy offers near real-time high-resolution imaging which demonstrates the relationship between the target lesion and bronchoscope or guide sheath (*Figure 3*). The target lesion can subsequently be segmented at a workstation, creating a virtual lesion which is subsequently overlaid upon 2D fluoroscopy (resulting in so-called augmented fluoroscopy) during actual biopsy passes (*Figure 3B*). There limited existing data on this emerging technique. In one retrospective 2019 study, 75 consecutive patients with a total of 93 Lung nodules were evaluated after undergoing CBCT-guided bronchoscopy, with diagnostic yield of 83.7% and pneumothorax rate of 4% (40). Previously observed associations of diagnostic yield with the location, size, and presence of a bronchus sign were not observed. Another small feasibility trial reported achieving a diagnosis in 17 of 22 cases (77%), which included a transbronchial access to TBAT in seven cases (41). Another 20 case pilot study combining TB/UTB with cone
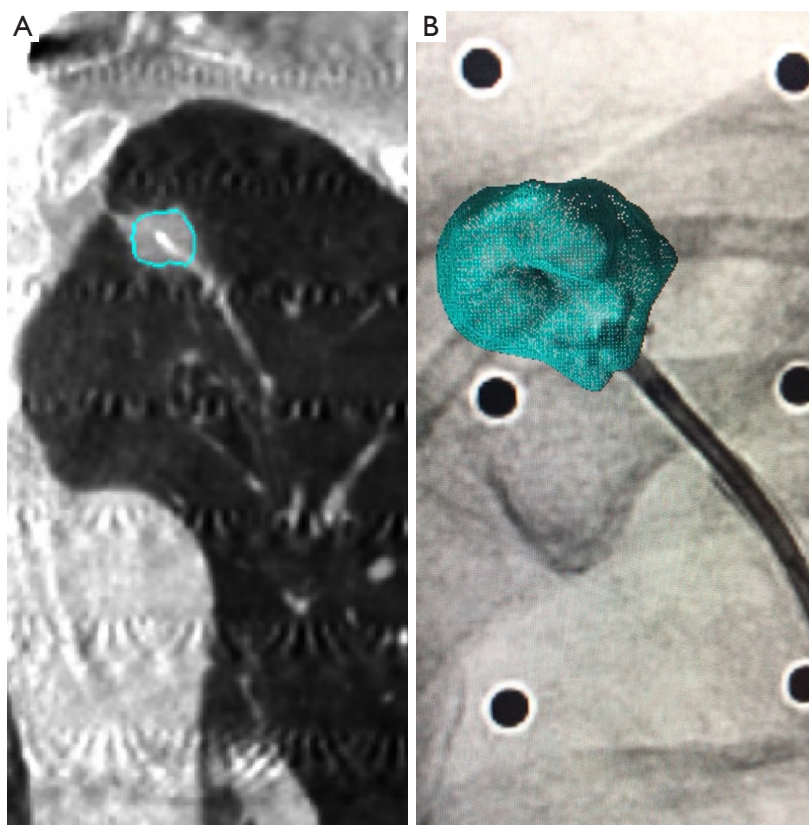
Figure 3 Cone beam-guided navigational bronchoscopy. (A) Coronal image showing center strike needle in lesion; (B) augmental fluoroscopy demonstrating biopsy forceps extending through a guide sheath into a peripheral lung nodule.

beam guidance reported a diagnostic yield of 70% (42).

BTPNA/TBAT

The presence of bronchus sign has been a positive predictor for diagnostic yield (33,35). A bronchus sign refers to the presence of a bronchus leading directly to the nodule (43). BTPNA and TBAT are new modalities designed to overcome the limitations of the airways in which bronchoscopes travel, specifically for nodules without a bronchus sign or without a nearby airway present. BTPNA generates a route through the lung parenchyma to a lung nodule while avoiding blood vessels. BTPNA is part of the VBN system Archimedes (Broncus Medical, Inc, San Jose, CA, USA). The first-in-human BTPNA report was in 2015, in which 12 patients underwent BTPNA with adequate biopsies in 83% and no significant complications (44). Much more research is required before making an informed assessment of it safety profile.

TBAT, a component of the CrossCountry system (Medtronic, Minneapolis, MN, USA), is another technology being investigated to access peripheral lesions without a bronchus sign. CrossCountry utilizes the superDimension ENB to generate a virtual pathway to the lesion. A needle guidewire advanced through the working channel of the bronchoscope is used to puncture the bronchial wall at a specified location, creating an entry point for a cone-shaped dilator followed by a GS. The first in human procedures using this technology were in 2015. In this report, 10 out 12 nodules were successfully accessed using Archimedes and fluoroscopy (83% yield) (44). A large multicenter trial involving TBAT (EAST-2 trial: ClinicalTrial.gov registration no. NCT02867371) is currently recruiting patients and will hopefully to provide further data on this technique's safety and diagnostic yield.

Conclusions

Advanced bronchoscopy for the diagnosis of peripheral lung lesions involves many complementary technologies, many

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of which seem to improve diagnostic yield. The bulk of extant data regarding advanced peripheral lung diagnostic techniques is derived from prospective observational or retrospective data, which has resulted in wide ranges of reported diagnostic efficacy. Advancements in lung cancer screening require safe, efficacious diagnostic tools for the pulmonology community to appreciate the long sought-after stage shift in lung cancer diagnosis. The modalities reviewed here had similar complication rates though many lack rigorous studies to best inform their safety profile. As the field continues to mature there will be increasing demand for high-quality multicenter randomized controlled trials to validate diagnostic yield and safety results to inform the pulmonology community how best to identify and characterize lung nodules.

Acknowledgments

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Fabien Maldonado and Robert Lentz) for the series "Novel Diagnostic Techniques for Lung Cancer" published in *Journal of Thoracic Disease*. The article was sent for external peer review organized by the Guest Editors and the editorial office.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd.2020.02.36). The series "Novel Diagnostic Techniques for Lung Cancer" was commissioned by the editorial office without any funding or sponsorship. RJL served as an unpaid Guest Editor for the series. FM served as the unpaid Guest Editor of the series and serves as an unpaid editorial member of *Journal of Thoracic Disease* from Aug 2019 to Jul 2021. FM reports grants and personal fees from Medtronic and personal fees from Erbe, outside the submitted work. OBR reports grants and personal fees from Medtronic, personal fees from Olympus America, personal fees from Auris, personal fees from Intuitive, personal fees from VERAN, outside the submitted work. JMK has 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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