State of the art: peripheral diagnostic bronchoscopy

Eric T. Sumner^, Jiwoon Chang^, Pranjal R. Patel^, Harmeet Bedi, Brian D. Shaller^

Division of Pulmonary, Allergy and Critical Care Medicine, Stanford University School of Medicine, Stanford, CA, USA

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

Correspondence to: Eric T. Sumner, DO. Stanford Medical Center, 300 Pasteur Drive, Stanford, CA 94305, USA; Division of Pulmonary, Allergy and Critical Care Medicine, Stanford University School of Medicine, Stanford, CA, USA. Email: etsumnerdo@gmail.com.

Abstract: Lung cancer is the leading cause of cancer related death worldwide and in the United States according to the World Health Organization and National Cancer Institute. Improvements in the diagnosis and treatment of lung cancer are of the utmost importance. A prompt diagnosis is a crucial factor to improve outcomes in the treatment of lung cancer. Although the implementation of lung cancer screening guidelines and the overall steady growth in the use of computed tomography have improved the likelihood of detecting lung cancer at an earlier stage, the diagnosis of peripheral pulmonary lesions (PPLs) has remained a challenge. The bronchoscopic techniques for PPL sampling have historically offered modest diagnostic yields at best in comparison to computed tomography guided transthoracic needle aspiration (TTNA). Fortunately, recent advances in technology have ushered in a new era of diagnostic peripheral bronchoscopy. In this review, we discuss the introduction of advanced intraprocedural imaging included digital tomosynthesis (DT), augmented fluoroscopy (AF), and cone beam computed tomography. We discuss robotic assisted bronchoscopy with a review of the currently available platforms, and we discuss the implementation of novel biopsy tools. These technologic advances in the bronchoscopic approach to PPLs offer greater diagnostic certainty and pave the way toward peripheral therapeutics in bronchoscopy.

Keywords: Peripheral pulmonary lesion (PPL); robotic-assisted bronchoscopy (RAB); cone beam computed tomography (CBCT); diagnostic bronchoscopy

Introduction

Lung cancer is the second-most diagnosed cancer in the United States, and despite advances in its diagnosis and treatment, it remains the leading cause of cancer-related mortality (1). It is estimated that 1.6 million new pulmonary nodules will be detected in the United States every year (2), and this is likely to increase in the coming years with growing adoption of the updated United States Preventive Services Task Force lung cancer screening guidelines (3).

Data from the National Lung Screening and NELSON trials suggest that the majority of such nodules are located in the periphery of the lung (4,5). The National Comprehensive Cancer Network and American College of Chest Physicians guidelines recommend tissue sampling and staging with the least invasive technique. Bronchoscopy offers a minimally-invasive approach to the sampling of peripheral pulmonary lesions (PPLs), along with the ability to diagnose and stage in a single procedure. Unfortunately, many commonly-implemented approaches to the bronchoscopic biopsy of

^ ORCID: Eric T. Sumner, 0000-0001-5720-220X; Jiwoon Chang, 0000-0002-8919-5195; Pranjal R. Patel, 0000-0003-4031-9545; Brian D. Shaller, 0000-0002-5620-8674.

PPLs, including virtual bronchoscopy, electromagnetic navigational (EMN) bronchoscopy, and radial endobronchial ultrasound (rEBUS), are plagued with middling diagnostic yield that averages around 70% (6). The historical deficiencies of bronchoscopic biopsy become even more concerning when compared to computed tomography (CT)-guided transthoracic needle aspiration (TTNA) (CT-TTNA), which—although not suitable for the staging of intrathoracic nodes—has a diagnostic yield of around 90% (7).

Recent advances in peripheral bronchoscopy show promise for improving the procedure's diagnostic yield. The introduction of robotic-assisted bronchoscopy (RAB) platforms, the development and application of advanced imaging technologies, and the implementation of more effective biopsy tools and tool-usage strategies have increased the overall diagnostic success of bronchoscopic sampling of PPLs. The success of these advancements improves the bronchoscopist's ability to successfully diagnose and stage in a single procedure with a high degree of accuracy and an excellent safety profile. Moreover, the enhanced visibility, reach, stability, and accuracy afforded with these new technologies open the door to future bronchoscopic therapies.

In this review, we discuss recent advancements in imaging modalities, robotic-assisted platforms, biopsy tools, and future directions in the field.

Advanced imaging modalities

Throughout much of its history, diagnostic bronchoscopy has been performed without high-fidelity intraprocedural imaging, thus depriving the bronchoscopist of opportunities to detect and compensate for significant but avoidable issues. Without the ability to visualize a target lesion, it is effectively impossible to account for CT-body divergence (CTBD, the change in a lesion's position in the intraprocedural lung environment relative to preprocedural imaging); and even when the proceduralist successfully navigates to their target, additional testing (for example, on-site cytologic evaluation) is required to confirm a successful biopsy. Awareness of these problems has spurred progressive integration of advanced imaging into bronchoscopy, and available data strongly support the adoption of advanced imaging modalities by bronchoscopists.

Cone beam CT (CBCT)

CBCT is a mode of CT imaging in which a specialized fluoroscopic C-arm obtains images during a roughly 190-degree rotation around an area of interest, then digitally converts them into multi-planar 3D reconstructions. Whereas multi-slice (fan beam) CT scanners emit a narrow X-ray beam from a linear array of emitters while the patient moves through the scanner, CBCT scanners emit a wider cone-shaped beam, thus imaging a larger volume of tissue during a single, brief (as short as five seconds) rotation around a static target.

One aspect of CBCT that distinguishes it from virtually all other tools for peripheral bronchoscopy is that it enables the proceduralist to definitively assess spatial relationships between biopsy instruments and all anatomic structures in all dimensions within the imaging field (*Figure 1A*). The ability to visualize tool-lesion orientation provides critical information for guiding adjustments and ultimately confirming successful penetration of the target (tool-in-lesion confirmation) (*Figure 1B-1D*).

Although most CBCT systems are built into procedural suites ("fixed"), there are several mobile systems whose smaller footprints and lower price-points make them excellent alternatives for those who may not have access to fixed systems. Many systems are also equipped with augmented fluoroscopy (AF, discussed below) for added guidance, and dedicated bronchoscopic navigation software that superimposes the bronchial tree and navigation pathway onto live fluoroscopy (AirWaze investigational device, Philips, Amsterdam, The Netherlands) has been developed (8). Lastly, the proliferation of RAB has stimulated interest in crosstalk between RAB and CBCT systems to improve navigation: the Ion shape-sensing RAB system (Intuitive Surgical, Sunnyvale, CA, USA) pairs with the Cios Spin mobile CBCT C-arm (Siemens Healthineers AG, Erlangen, Germany) to detect changes in target-location due to CTBD and adjust navigation information accordingly (9,10).

Data on procedural outcomes with CBCT—both fixed and mobile systems, and in concert with various bronchoscopic techniques—are overwhelmingly favorable, with diagnostic yields superior to non-CBCT approaches or comparable despite more challenging targets (11-17). When directly compared to EMN bronchoscopy or rEBUS-guided ultrathin bronchoscopy, the performance of CBCT-guided bronchoscopy is consistently superior, with diagnostic yields up to 94% and similar or more favorable safety profiles (18-20), and the success of CBCT-guided bronchoscopy does not seem to be impacted by certain target characteristics (such as the absence of an airway leading directly into the target, or lobar location) that may pose limitations for other bronchoscopic methods (20-22).
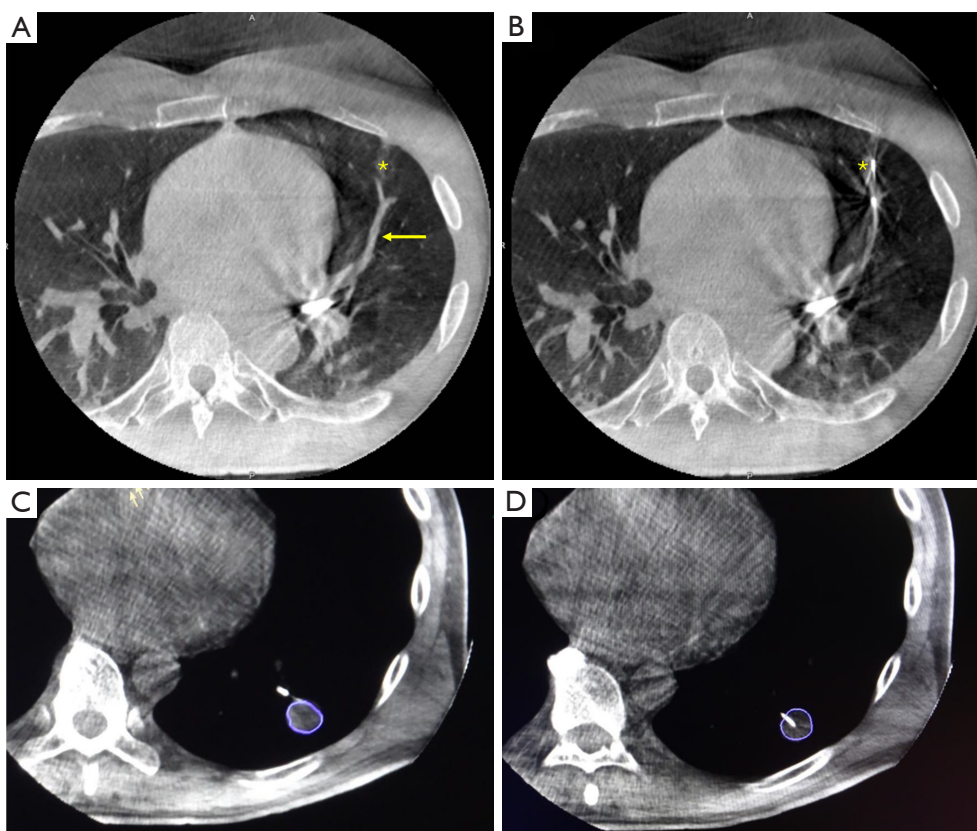
Figure 1 Example of intraoperative use of CBCT to confirm TIL. (A) CBCT imaging shows the target ground glass nodule (asterisk) and a large adjacent blood vessel (arrow). (B) Prior to obtaining a biopsy, re-imaging was performed to visualize the tip of the biopsy instrument relative to the target nodule (asterisk) and blood vessel. Sampling confirmed adenocarcinoma. (C) CBCT imaging revealed the biopsy instrument to be tangential to the target lesion (circle). On-site cytologic evaluation was non-diagnostic. (D) After adjusting the instrument and re-imaging, TIL confirmation was obtained. On-site cytologic evaluation of sample from target lesion (circle) showed adenocarcinoma. Images courtesy of Brian D. Shaller. CBCT, cone beam computed tomography; TIL, tool-in-lesion.

Although there are no prospective studies comparing CBCT-guided bronchoscopy to CT-TTNA, a recent single-center retrospective comparison found no difference in diagnostic yield and fewer adverse events with CBCT-guided bronchoscopy despite comparable target characteristics (23).

Potential downsides to CBCT include potentially higher costs (although one study suggests that CBCT-guided bronchoscopy may be more cost-effective than CT-TTNA), greater use of ionizing radiation as compared to 2D fluoroscopy alone (although this improves with user-experience), and an inherent learning curve for new users (21,24,25). As with all targeted peripheral bronchoscopy, CBCT-guided bronchoscopy should be performed under general anesthesia with optimal ventilatory settings to minimize CTBD and maximize diagnostic potential (26,27).

Digital tomosynthesis (DT)

DT uses image-processing algorithms to convert 2D images obtained by a conventional C-arm over a limited angle of rotation (usually 50–70 degrees) into reconstructions with limited depth-of-field. With the use of artificial intelligence (AI) and machine learning, many modern DT systems are now capable of generating CT-like multi-axial reconstructions from limited DT images.

Several commercially available bronchoscopy platforms use DT: the LungVision system (BodyVision Medical, Campbell, CA, USA) uses AI to create 3D reconstructions that resemble CT images, which may provide sufficient information on tool-target relationships to guide adjustments and obtain tool-in-lesion confirmation (*Figure 2A*). LungVision also provides AF guidance in

the form of a virtual airway roadmap and target overlay (discussed below), and data obtained from each DT sweep are used to update the AF overlay to account for limited degrees of CTBD. The Galaxy system (Noah Medical, San Carlos, CA, USA) is an EMN-guided RAB platform that uses DT to generate AI-enhanced multi-axial images, update the navigation pathway, and display a target overlay on AF (*Figure 2B*). The ILLUMISITE fluoroscopic navigation and EMN platform (Medtronic, Santa Clara, CA, USA) uses DT to update its virtual navigation data when the tip of the system's EMN catheter is closely approximated to the target, although neither CT-like reconstructions nor AF overlay are provided.

Outcomes using DT are generally positive. Studies using LungVision furnished diagnostic yields ranging from 75.4–81.8% (28-30). Publications on ILLUMISITE showed similar results, with diagnostic yields ranging from 79–87% (31-34). Although in-human data on the Galaxy system are not yet available, one study using 20 simulated nodules in pigs reported a successful sampling rate of 100% (35).

Although some DT systems appear to produce multi-axial images using a conventional C-arm, it bears remembering that these CT-like images are not fully accurate representations of what might be seen with actual CT due to some degree of AI-extrapolation. Studies comparing target-location as represented on DT to actual target-location on CBCT showed that although there is usually some degree of spatial overlap, the distance between the centers of the target on DT and the actual target on CBCT may deviate by as much as 16.2 mm (28,36).

AF

AF involves the virtual overlay of visual information from CT, CBCT, or DT onto real-time 2D fluoroscopic images. Structures of interest on multi-axial images are demarcated and subsequently superimposed on live fluoroscopy (*Figure 3*). Because AF-capable systems track the C-arm's position relative to one or more static points (the gurney of fixed CBCT systems, or a fiducial marker board for DT systems), the target overlay "moves" appropriately on live fluoroscopy when the C-arm is rotated, allowing the proceduralist to confirm tool-target alignment across multiple planes. Some AF-equipped platforms (LungVision and AirWaze investigational software) are capable to auto-segmenting the airways and overlaying an airway roadmap onto AF for additional guidance (*Figure 3A*).

Although AF is a feature of other imaging modalities rather than a standalone technology, data suggest that its use may improve diagnostic outcomes (21,37). There are virtually no downsides to AF, although the proceduralist must keep in mind that movement within the patient is not reflected in the AF overlay: for example, if a nodule begins to move due to CTBD, its virtual representation on AF will remain static (*Figure 3B*). Fortunately, the bronchoscopist may update the AF overlay as needed be performing additional CBCT spins or DT sweeps throughout the procedure.

RAB

In the last 6 years, RAB has emerged as a promising new technology in peripheral bronchoscopy. There are currently three RAB platforms available in the United States: the Monarch platform (Ethicon, Inc., Redwood City, CA, USA), the Ion endoluminal system (Intuitive Surgical, Sunnyvale, CA, USA), and the Galaxy system (Noah Medical). Data suggest that they may have greater reach (38) and higher rates of navigational success (35,39). One cadaver study found superior diagnostic yield when comparing RAB to peripheral bronchoscopy using conventional thin flexible bronchoscopes (39). All three platforms utilize a proprietary articulating bronchoscope controlled via one or more robotic arms, which is used to navigate along a predetermined virtual pathway to the PPL of interest. Although the use of pre-procedural CT images for airway-mapping and virtual navigation is similar to preexisting navigational bronchoscopy platforms, there are unique differences between how the three platforms operate (*Table 1*).

Monarch™ platform (Ethicon, Inc., Redwood City, CA, USA)

The Monarch™ platform is an EMN-guided system that utilizes a "mother-daughter" scope configuration consisting of an outer sheath and inner bronchoscope with 6 mm and 4.2 mm outer diameters (ODs), respectively. The inner bronchoscope also has a camera, light source, and 2.1 mm working channel (WC). The sheath and bronchoscope are mounted to separate robotic arms and steering is accomplished using a handheld controller. While the sheath and scope may be advanced, retracted, and articulated together, the system also allows for "uncoupling" and independent movement of the sheath and scope, such that the inner scope may be advanced beyond the tip of the
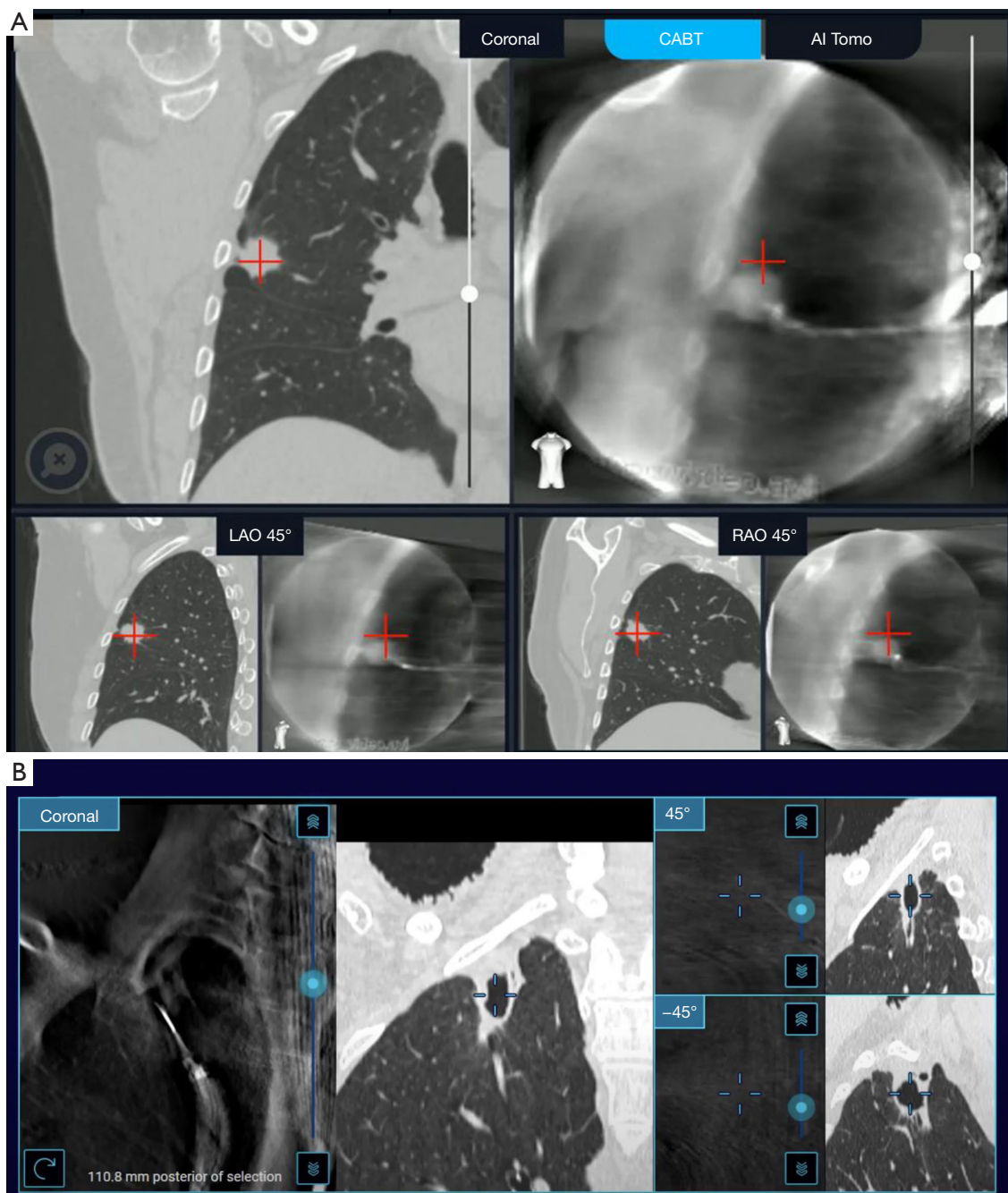
Figure 2 CT-like images rendered via digital tomosynthesis using (A) the LungVision system (BodyVision Medical, Campbell, CA, USA) and (B) the Galaxy robotic-assisted bronchoscopy platform (Noah Medical, San Carlos, CA, USA). Images courtesy of Joesph Cicenia. CABT, C-arm based tomography; AI, artificial intelligence; LAO, left anterior oblique; RAO, right anterior oblique; CT, computed tomography.
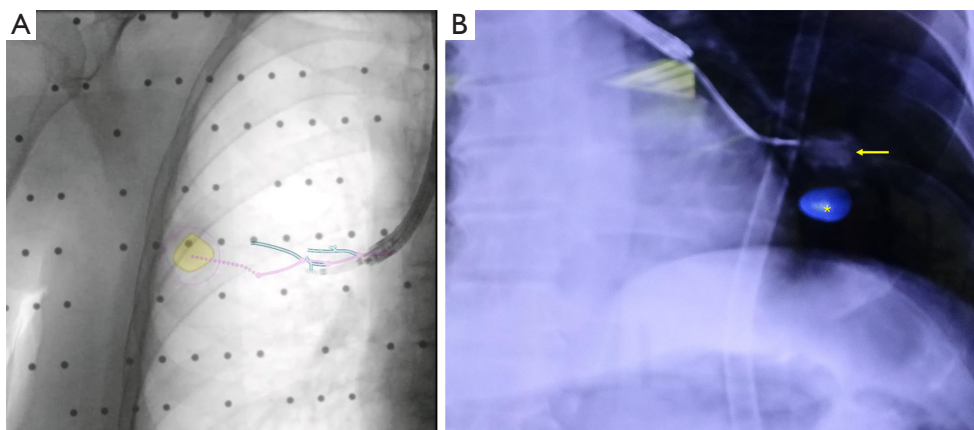
Figure 3 Representative images of augmented fluoroscopy. (A) Augmented fluoroscopy with the LungVision system (BodyVision Medical, Campbell, CA, USA), showing the regional airways (blue lines), suggested navigation pathway (pink line), and target lesion (yellow circle). Image courtesy of Joesph Cicenia. (B) Augmented fluoroscopy using a fixed cone beam CT system (Philips, Amsterdam, The Netherlands). Owing to the gradual development of atelectasis, the radio-opaque lesion (arrow) has changed position relative to where it was on cone beam CT imaging only a few minutes prior, while its virtual representation (asterisk) remains static. Image courtesy of Brian D. Shaller. CT, computed tomography.

Table 1 Comparison of robotic assisted bronchoscopy platforms

Platform features	Monarch™ Platform (Ethicon, Inc., Redwood City, CA, USA)	Ion Endoluminal Platform (Intuitive Surgical©, Sunnyvale, CA, USA)	Galaxy System™ (Noah Medical, San Carlos, CA, USA)
Bronchoscope	Sheath: 6 mm OD. Bronchoscope: 4.0 mm OD	Single bronchoscope: 3.5 mm OD	Single bronchoscope: 4.0 mm OD
Working channel	2.1 mm	2.0 mm	2.1 mm
Navigation	Electromagnetic	Shape-sensing	Electromagnetic
Vision during navigation	Yes	Yes	Yes
Vision during biopsy	Yes	No	Yes
Imaging integration	None	Cios Spin mobile CBCT C-arm (Siemens Healthineers AG, Erlangen, Germany)	TiLT + Technology™ digital tomosynthesis with augmented fluoroscopy

OD, outer diameter; CBCT, cone beam computed tomography; TiLT, Tool-in-Lesion Tomosynthesis.

sheath (or the sheath retracted proximally) for superior reach and articulation in smaller peripheral airways.

Ion™ endoluminal RAB platform (Intuitive Surgical©, Sunnyvale, CA, USA)

The Ion™ platform utilizes a single ultrathin bronchoscope with a 3.5-mm OD. In contrast to the Monarch and Galaxy platforms, vision and illumination are provided by a "vision probe" that is inserted through the 2.0-mm WC, and which must be removed to allow passage of biopsy tools (thus, endoscopic visualization is lost during biopsy maneuvers). The bronchoscope is controlled with a scroll wheel and ball mouse. The platform navigates using shape-sensing technology, which, unlike EMN, is not vulnerable to interference from adjacent ferromagnetic objects. Additionally, at present the Ion™ is the only RAB platform that supports integration with mobile CBCT, allowing for intraprocedural 3D imaging and updated target registration. This integration may help adjust for CTBD and one study suggests it may allow users to target more challenging lesions (9).

Galaxy System™ (Noah Medical, San Carlos, CA, USA)

The Galaxy System™ utilizes a single thin bronchoscope with a 4.0-mm OD that has an integrated camera, light source, and 2.1 mm WC. Whereas the Monarch and Ion bronchoscopes may be reprocessed by their respective manufacturers and used for more than one procedure, the Galaxy bronchoscope is approved for single use only, thus obviating concerns for contamination or possible damage during cleaning. The bronchoscope is mounted to a single robotic arm and controlled with a handheld controller. Like the Monarch system, airway road mapping and navigational guidance are accomplished using EMN. After initial navigation, the Galaxy System™ can utilize any standard fluoroscopic C-arm and proprietary DT software (TiLT + Technology™) to detect and compensate for finite degrees of CTBD. Additionally, the target lesion may be demarcated on DT images for additional AF guidance.

Clinical experience

Real-world data for the Monarch and Ion platforms demonstrate a very high navigational success rate ranging from 88.6% to 98.7% (40-43). The diagnostic yield for the Monarch and Ion platforms in published studies ranges from 69.1% to 81.7%, depending on variable factors such as target lesion characteristics and strictness of diagnostic criteria (40-43). A recent meta-analysis including data from ten studies with 725 lesions biopsied with either the Monarch or Ion platform furnished a pooled diagnostic yield of 80.4%, with the additional finding that the diagnostic yield was significantly higher in studies where transbronchial cryobiopsy (TBCB) was performed (90.0% vs. 79.0%, P<0.01) (44). These two RAB platforms also have excellent safety profiles with a pooled complication rate of 3% (44).

Preclinical data on the Galaxy platform with integrated DT using pigs with simulated lung nodules show rates of successful navigation and sampling of 100% (35). In-human data for the Galaxy platform are limited. Preliminary results of the FRONTEIR study presented as an abstract show a 100% successful navigation rate, 100% tool-in-lesion confirmation, and an estimated diagnostic yield of 86% to 93% (depending on follow-up results). Although these data are not yet peer-reviewed, they are nonetheless encouraging (45).

RAB versus EMN

While existing clinical data for RAB suggest improved diagnostic yield compared to EMN, data directly comparing the two technologies are lacking. A single center retrospective cohort study found no significant difference in diagnostic yield or complication rates when comparing RAB and DT-EMN (34). Procedural times are comparable with a median time of 51 to 64 minutes for RAB (40-43) and 52 minutes for EMN (6). Cost effectiveness of RAB in comparison to EMN is a point of discussion, however, peer reviewed cost analysis data are not yet available to our knowledge. We eagerly await the results of the RELIANT trial, which will add a prospective randomized control trial examining RAB versus EMN to the literature (46).

Biopsy modalities

The selection of the most effective biopsy tools is critical to maximizing diagnostic yield. Although observations from the AQuIRE registry supported transbronchial needle aspiration (TBNA) as the highest-yield biopsy modality for PPLs, recent data suggest that other tools, such as the flexible cryoprobe, may provide superior specimens and diagnostic outcomes. An understanding of the evidence behind different biopsy tools will better enable the bronchoscopist in selecting those best suited to their institutional practice and patient population.

Traditional methods for bronchoscopic biopsy of PPLs include TBNA, transbronchial forceps biopsy (TBBx), and bronchial brushing. In recent years, the introduction of the 1.1 mm cryotherapy probe has added mini cryobiopsy to the bronchoscopists armamentarium. Most recently, the iNod™ system has introduced real-time ultrasound guided TBNA as another biopsy modality to consider for PPLs.

TBNA

Fine needle aspiration is a versatile technique for sampling endobronchial lesions, PPLs, and intrathoracic lymph nodes. Specimens obtained via needle aspiration are well suited for rapid on-site cytologic evaluation, and samples may vary in size and architecture (or lack thereof) depending on the gauge of needle used. The TBNA technique was first described by Ko-Pen Wang in 1984, with a diagnostic yield of 47.8% for the diagnosis of

PPLs (47). Since its introduction, studies of TBNA have furnished diagnostic yields ranging from 31.5% to 86.6% (48-55), with a recent meta-analysis reporting a diagnostic yield of 53% (56). The substantial variability in outcomes is at least in part dependent on the navigational method used to reach the lesion, presence of a bronchus sign, nodule characteristics, and whether on-site cytologic evaluation was performed (56,57). Complications such as major bleeding and pneumothorax occur in less than 9% of cases (56).

Transbronchial forceps biopsies

TBBx has been used to collect tissue samples since the advent of the bronchoscope (58). As with TBNA, TBBx is often performed under fluoroscopic guidance; however, it tends to procure larger specimens with some degree of preserved tissue architecture as compared to TBNA (59). The diagnostic yield of TBBx for PPL-sampling ranges between 54% and 86.9%, and improves with larger lesions, the presence of a bronchus sign, an increased number of samples procured, and when used in combination with EMN, rEBUS, or RAB (57,60-62). Complications occur in less than 5% of cases, making it a safe and versatile technique.

Bronchial brushings

Bronchial brushing consists of agitating a small, semiflexible brush within the airway or target lesion to obtain a cytologic specimen. The diagnostic yield of bronchial brushing ranges between 47% and 54%, and does not seem to improve with the more advanced navigation techniques (57,60).

TBCB

The cryoprobe has traditionally been used to perform endobronchial tumor debulking, blood clot extraction, and foreign body retrieval (63-65); however, recent data have highlighted its potential superiority to other instruments for the biopsy of PPLs (51,55). The cryoprobe operates on the basis of the Joule-Thomson effect, wherein the adiabatic expansion of a compressed gas leads to rapid cooling at the probe's distal tip. Commercially-available flexible cryoprobe systems use compressed carbon dioxide or liquid nitrogen to rapidly cool the tip of the probe to around –79 ℃, at which point crystallization of water molecules within tissues results in tissue-adhesion to the probe tip. After a few seconds of cooling, the probe and frozen tissue specimen are rapidly

retracted (either through the WC of the bronchoscope or *en bloc* with the bronchoscope, depending on the particular probe and scope used). TBCB has several advantages over TBNA, TBBx, and bronchial brushings, including the procurement of much larger specimens and preservation of tissue architecture due to lack of crush artifact, and studies of TBCB report diagnostic yields in the range of 60–97.2% (49-55).

Table 2 presents a comparison of different bronchoscopic biopsy techniques. Despite concerns regarding the increased potential for complications with TBCB, rates of major bleeding (defined as CTCAE Grade ≥2, Nashville Scale Grade ≥2, or article specific definition) and pneumothorax are exceedingly low and comparable to other tools (0 to 1.4% and 0 to 5.4% respectively). It is worth noting that studies are quite heterogenous with regards to sample size, study design, size of nodules sampled, and type of tools utilized, and that the use of different navigational and adjunctive imaging technologies also impacts diagnostic success. Despite these variables, two studies have reported a diagnostic yield above 90% with use of the 1.1-mm flexible cryoprobe, which is higher than what has been reported for other instruments (51,55).

In addition to potentially providing a higher diagnostic yield, TBCB specimens are more likely to provide sufficient tissue for molecular analysis and assessment of architecture as compared to TBNA or TBBx (51,55).

The superiority of the cryoprobe in providing better quality specimens and higher diagnostic yield can be attributed to three main factors. First, the probe freezes onto tissue circumferentially, whereas traditional tools such as TBNA and forceps typically biopsy in only one plane. This allows the probe to successfully biopsy targets even when the probe may be only tangential to their edge, thus potentially facilitating successful biopsy of lesions with eccentric rEBUS views. Second, rapid freezing of the target lesion preserves tissue architecture, including crucial nuclear details necessary for molecular analysis, substantially reducing the amount of crush artifact typically seen with forceps biopsies. Finally, the bronchoscopist has the ability to control the length of the freeze cycle, thus having some degree of control over the size of specimen procured.

Although the use of the cryoprobe has not overtaken TBNA or TBBx, its popularity is increasing as the evidence supporting its use—particularly when combined with more advanced bronchoscopic techniques such as RAB and CBCT—grows. Further studies with larger sample sizes and better control of cofounding variables are warranted to

Table 2 Summary of recent studies comparing the diagnostic yield of various biopsy tools utilized for peripheral pulmonary lesion diagnosis

First author	Year	Study design	No. of lesions	Navigation technique	Diagnostic yield by biopsy tool (%)				Complications (%)	
					TBNA	TBBx	TBCB[†]	Bronchial brushings	Major bleeding	Pneumothorax
Gildea (48)	2021	P	416	EMN	86.6	86.9	N/A	77.6	1.4	3.1
Verhoeven (49)	2021	P	225	EMN, rEBUS, CBCT	46.7	70.6	68.4	30.3	N/A	N/A
Benn (50)	2022	P	45	EWC, rEBUS	69	60	60	N/A	0	0
Bhadra (51)	2024	R	222	RAB, rEBUS, CBCT	68	77	75	28	0.5	1.5
Kim (52)	2023	P	50	rEBUS	N/A	N/A	92	N/A	0	0
Meng (53)	2023	R	52	RAB, CBCT	42.3	57.7	76.9	N/A	N/A	N/A
Oki (54)	2023	P	50	Ultrathin scope, rEBUS	N/A	54	62	N/A	0	0
Oberg (55)	2022	R	120	RAB, rEBUS	31.5	77.8	97.2	N/A	0	5.4

[†], cryobiopsies performed using 1.1-mm cryoprobe. P, prospective; R, retrospective; EMN, electromagnetic navigation; rEBUS, radial endobronchial ultrasound; CBCT, cone beam computed tomography; EWC, extended working channel; RAB, robotic-assisted bronchoscopy; TBNA, transbronchial needle aspiration; TBBx, transbronchial forceps biopsy; TBCB, transbronchial cryobiopsy; N/A, not applicable as this was not performed/reported in the study.

better elucidate the unique benefits of TBCB.

Real-time ultrasound guided peripheral TBNA

The Boston Scientific iNod™ System is a single use biopsy tool comprised of a rEBUS probe and a 25-G biopsy needle. The device can be used through a 2.0-mm WC and allows for real-time ultrasound visualization of TBNA of PPLs. A multicenter prospective pilot study that included twenty-three patients revealed a diagnostic yield of 70%. Of note, the PPLs sampled in this study tended to be solid (95.8%), have a bronchus sign (95.8%), and were relatively large (median diameter 36 mm) (66).

Future directions

Advances in imaging modalities, RAB, and biopsy tools have allowed for more accurate PPL-targeting and tissue-sampling. With precise navigation, real-time tool-in-lesion confirmation, and the ability to perform nodal staging concurrently, diagnostic bronchoscopy may now even be performed on the same day prior to the surgical resection under a single anesthetic event for localized early-stage lung cancer. While there is a lack of data to recommend this combined approach, this integrated pathway may eliminate the delay between diagnosis and definitive treatment, and

potentially decrease resource-utilization and redundant procedures (67,68).

Accurate targeting of ground glass, part-solid, or small solid nodules also facilitates fiducial marker-placement and dye-marking, which can be used to guide stereotactic body radiation therapy or surgical resection. While CT-TTNA can also be used to mark PPLs, a bronchoscopic approach appears to be associated with fewer complications, such as pneumothorax (69,70).

Development of new tools has improved accuracy, stability, and reach of peripheral bronchoscopy. Well-designed trials comparing various RAB platforms combined with sophisticated imaging and biopsy equipment are needed to validate the effectiveness of new technologies in peripheral bronchoscopy. Furthermore, since these same technologies may also be applied to treat peripheral tumors via therapeutic modalities such as radiofrequency ablation, microwave ablation, photodynamic therapy, and cryoablation, progress in the realm of peripheral diagnostics is intrinsically linked to progress in the nascent field of peripheral therapeutics (71,72).

Conclusions

The introduction of high-fidelity intraprocedural imaging, RAB platforms, and enhanced methods of

5418

Sumner et al. Peripheral bronchoscopy state of the art

tissue-acquisition are improving the diagnostic yield of peripheral bronchoscopy without compromising its safety. With comparable diagnostic yields, the added benefit of concomitant nodal staging, and a favorable safety profile, bronchoscopic biopsy may be the preferred method for the diagnostic workup of suspicious lung lesions. Furthermore, factors such as increased stability and the ability to confirm tool-anatomy relationships with 3D imaging have opened the door to ablative therapies in the periphery. Additional investigation into outcomes with different combinations of technologies and tools, continued work on the integration of advanced imaging with RAB, and the pursuit of successful ablative modalities all lend shape to an exciting and promising future for the field of peripheral bronchoscopy.

Acknowledgments

Footnote

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-346/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-346/coif). B.D.S. has worked as a consultant for both Ethicon (a subsidiary of Johnson & Johnson) and Noah Medical. H.B. has received support from Phillips in studying the efficacy of their LungSuite software, which is related to a portion of the topic of this review. H.B. has received support from Siemens, Philips, and GE as sponsors of the annual CBCT educational course held at Stanford. The other authors have no 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.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the

formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33.
2. Gould MK, Tang T, Liu IL, et al. Recent Trends in the Identification of Incidental Pulmonary Nodules. Am J Respir Crit Care Med 2015;192:1208-14.
3. US Preventive Services Task Force; Krist AH, Davidson KW, et al. Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2021;325:962-70.
4. National Lung Screening Trial Research Team; Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
5. Yousaf-Khan U, van der Aalst C, de Jong PA, et al. Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval. Thorax 2017;72:48-56.
6. Folch EE, Pritchett MA, Nead MA, et al. Electromagnetic Navigation Bronchoscopy for Peripheral Pulmonary Lesions: One-Year Results of the Prospective, Multicenter NAVIGATE Study. J Thorac Oncol 2019;14:445-58.
7. DiBardino DM, Yarmus LB, Semaan RW. Transthoracic needle biopsy of the lung. J Thorac Dis 2015;7:S304-16.
8. Pritchett MA, Williams JC, Schirmer CC, et al. Cone-beam CT-based Navigation With Augmented Fluoroscopy of the Airways for Image-guided Bronchoscopic Biopsy of Peripheral Pulmonary Nodules: A Prospective Clinical Study. J Bronchology Interv Pulmonol 2024;31:175-82.
9. Abia-Trujillo D, Folch EE, Yu Lee-Mateus A, et al. Mobile cone-beam computed tomography complementing shape-sensing robotic-assisted bronchoscopy in the small pulmonary nodule sampling: A multicentre experience. Respirology 2024;29:324-32.
10. Menon A, Husta B, Bergemann R, et al. Impact of Intra-operative Mobile Cone Beam CT on Shape-sensing Robotic-assisted Bronchoscopy: Improving Accuracy. American Thoracic Society International Conference Abstracts: American Thoracic Society; 2023:A4463.
11. Reisenauer J, Duke JD, Kern R, et al. Combining Shape-Sensing Robotic Bronchoscopy With Mobile Three-Dimensional Imaging to Verify Tool-in-Lesion and Overcome Divergence: A Pilot Study. Mayo Clin Proc Innov Qual Outcomes 2022;6:177-85.

12. Cheng GZ, Liu L, Nobari M, et al. Cone beam navigation bronchoscopy: the next frontier. J Thorac Dis 2020;12:3272-8.

13. Pritchett M, Muller L, Ost D, et al. Integration of shape-sensing robotic-assisted bronchoscopy and cone-beam CT for the biopsy of pulmonary nodules. Chest 2021;160:A1622-A1624.

14. Salahuddin M, Bashour SI, Khan A, et al. Mobile Cone-Beam CT-Assisted Bronchoscopy for Peripheral Lung Lesions. Diagnostics (Basel) 2023;13:827.

15. Benn BS, Romero AO, Lum M, et al. Robotic-Assisted Navigation Bronchoscopy as a Paradigm Shift in Peripheral Lung Access. Lung 2021;199:177-86.

16. Styrvoky K, Schwalk A, Pham D, et al. Shape-Sensing Robotic-Assisted Bronchoscopy with Concurrent use of Radial Endobronchial Ultrasound and Cone Beam Computed Tomography in the Evaluation of Pulmonary Lesions. Lung 2022;200:755-61.

17. Cumbo-Nacheli G, Velagapudi RK, Enter M, et al. Robotic-assisted Bronchoscopy and Cone-beam CT: A Retrospective Series. J Bronchology Interv Pulmonol 2022;29:303-6.

18. Verhoeven RLJ, Fütterer JJ, Hoefsloot W, et al. Cone-Beam CT Image Guidance With and Without Electromagnetic Navigation Bronchoscopy for Biopsy of Peripheral Pulmonary Lesions. J Bronchology Interv Pulmonol 2021;28:60-9.

19. Kheir F, Thakore SR, Uribe Becerra JP, et al. Cone-Beam Computed Tomography-Guided Electromagnetic Navigation for Peripheral Lung Nodules. Respiration 2021;100:44-51.

20. DiBardino DM, Kim RY, Cao Y, et al. Diagnostic Yield of Cone-beam-Derived Augmented Fluoroscopy and Ultrathin Bronchoscopy Versus Conventional Navigational Bronchoscopy Techniques. J Bronchology Interv Pulmonol 2023;30:335-45.

21. Pritchett MA, Schampaert S, de Groot JAH, et al. Cone-Beam CT With Augmented Fluoroscopy Combined With Electromagnetic Navigation Bronchoscopy for Biopsy of Pulmonary Nodules. J Bronchology Interv Pulmonol 2018;25:274-82.

22. Podder S, Chaudry S, Singh H, et al. Efficacy and Safety of Cone-Beam CT Augmented Electromagnetic Navigation Guided Bronchoscopic Biopsies of Indeterminate Pulmonary Nodules. Tomography 2022;8:2049-58.

23. Patel P, Shaller BD, Chang J, et al. Diagnostic Accuracy and Procedural Outcomes for Peripheral Pulmonary Lesion Biopsy: Comparing Transthoracic Needle Aspiration to Cone-beam CT Computed Tomographic Bronchoscopy. Chest 2023;164:A5294-A5295.

24. Kops SEP, Verhoeven RLJ, Vermeulen RJ, et al. Cone beam CT-guided navigation bronchoscopy: a cost-effective alternative to CT-guided transthoracic biopsy for diagnosis of peripheral pulmonary nodules. BMJ Open Respir Res 2022;9:e001280.

25. Verhoeven RLJ, van der Sterren W, Kong W, et al. Cone-beam CT and Augmented Fluoroscopy-guided Navigation Bronchoscopy: Radiation Exposure and Diagnostic Accuracy Learning Curves. J Bronchology Interv Pulmonol 2021;28:262-71.

26. Pritchett MA, Lau K, Skibo S, et al. Anesthesia considerations to reduce motion and atelectasis during advanced guided bronchoscopy. BMC Pulm Med 2021;21:240.

27. Bhadra K, Setser RM, Condra W, et al. Lung Navigation Ventilation Protocol to Optimize Biopsy of Peripheral Lung Lesions. J Bronchology Interv Pulmonol 2022;29:7-17.

28. Pritchett MA. Prospective Analysis of a Novel endobronchial augmented fluoroscopic navigation system for diagnosis of peripheral pulmonary lesions. J Bronchology Interv Pulmonol 2021;28:107-15.

29. Pertzov B, Gershman E, Izhakian S, et al. The LungVision navigational platform for peripheral lung nodule biopsy and the added value of cryobiopsy. Thorac Cancer 2021;12:2007-12.

30. Cicenia J, Bhadra K, Sethi S, et al. Augmented fluoroscopy: a new and novel navigation platform for peripheral bronchoscopy. J Bronchology Interv Pulmonol 2021;28:116-23.

31. Aboudara M, Roller L, Rickman O, et al. Improved diagnostic yield for lung nodules with digital tomosynthesis-corrected navigational bronchoscopy: Initial experience with a novel adjunct. Respirology 2020;25:206-13.

32. Avasarala SK, Roller L, Katsis J, et al. Sight unseen: diagnostic yield and safety outcomes of a novel multimodality navigation bronchoscopy platform with real-time target acquisition. Respiration 2022;101:166-73.

33. Dunn BK, Blaj M, Stahl J, et al. Evaluation of Electromagnetic Navigational Bronchoscopy Using Tomosynthesis-Assisted Visualization, Intraprocedural Positional Correction and Continuous Guidance for Evaluation of Peripheral Pulmonary Nodules. J Bronchology Interv Pulmonol 2023;30:16-23.

34. Low SW, Lentz RJ, Chen H, et al. Shape-Sensing Robotic-Assisted Bronchoscopy vs Digital Tomosynthesis-

Corrected Electromagnetic Navigation Bronchoscopy: A Comparative Cohort Study of Diagnostic Performance. Chest 2023;163:977-84.

35. Bhadra K, Rickman OB, Mahajan AK, et al. "Tool-in-lesion" Accuracy of Galaxy System-A Robotic Electromagnetic Navigation BroncHoscopy With Integrated Tool-in-lesion-Tomosynthesis Technology: The MATCH Study. J Bronchology Interv Pulmonol 2024;31:23-9.

36. Pritchett MA, Bhadra K, Mattingley JS. Electromagnetic navigation bronchoscopy with tomosynthesis-based visualization and positional correction: three-dimensional accuracy as confirmed by cone-beam computed tomography. J Bronchology Interv Pulmonol 2021;28:10-20.

37. Yu W, Zhou P, Chen K, et al. Bronchoscopy-guided intervention therapy with extracorporeal membrane oxygenation support for advanced cancer metastasis to the central airway: a case report. Medicine (Baltimore) 2020;99:e19488.

38. Chen AC, Gillespie CT. Robotic Endoscopic Airway Challenge: REACH Assessment. Ann Thorac Surg 2018;106:293-7.

39. Yarmus L, Akulian J, Wahidi M, et al. A Prospective Randomized Comparative Study of Three Guided Bronchoscopic Approaches for Investigating Pulmonary Nodules: The PRECISION-1 Study. Chest 2020;157:694-701.

40. Chen AC, Pastis NJ Jr, Mahajan AK, et al. Robotic Bronchoscopy for Peripheral Pulmonary Lesions: A Multicenter Pilot and Feasibility Study (BENEFIT). Chest 2021;159:845-52.

41. Chaddha U, Kovacs SP, Manley C, et al. Robot-assisted bronchoscopy for pulmonary lesion diagnosis: results from the initial multicenter experience. BMC Pulm Med 2019;19:243.

42. Fielding DIK, Bashirzadeh F, Son JH, et al. First Human Use of a New Robotic-Assisted Fiber Optic Sensing Navigation System for Small Peripheral Pulmonary Nodules. Respiration 2019;98:142-50.

43. Kalchiem-Dekel O, Connolly JG, Lin IH, et al. Shape-Sensing Robotic-Assisted Bronchoscopy in the Diagnosis of Pulmonary Parenchymal Lesions. Chest 2022;161:572-82.

44. Zhang C, Xie F, Li R, et al. Robotic-assisted bronchoscopy for the diagnosis of peripheral pulmonary lesions: A systematic review and meta-analysis. Thorac Cancer 2024;15:505-12.

45. Saghaie T, Williamson J, Philips M, et al. Preliminary results of the FRONTIER STUDY: First Human Use of a New Robotic Electromagnetic Navigation Bronchoscopy with Integrated Tool-in-Lesion Tomosynthesis (TiLT) technology (Galaxy System) for Small Peripheral Pulmonary Nodules. In Proceedings of the 2023 Annual Conference, American Association for Bronchology and Interventional Pulmonology, Chicago, IL, USA, 24–26 August 2023.

46. Paez R, Lentz RJ, Salmon C, et al. Robotic versus Electromagnetic bronchoscopy for pulmonary LesIon AssessmeNT: the RELIANT pragmatic randomized trial. Trials 2024;25:66.

47. Wang KP, Haponik EF, Britt EJ, et al. Transbronchial needle aspiration of peripheral pulmonary nodules. Chest 1984;86:819-23.

48. Gildea TR, Folch EE, Khandhar SJ, et al. The Impact of Biopsy Tool Choice and Rapid On-Site Evaluation on Diagnostic Accuracy for Malignant Lesions in the Prospective: Multicenter NAVIGATE Study. J Bronchology Interv Pulmonol 2021;28:174-83.

49. Verhoeven RLJ, Vos S, van der Heijden EHFM. Multi-modal tissue sampling in cone beam CT guided navigation bronchoscopy: comparative accuracy of different sampling tools and rapid on-site evaluation of cytopathology. J Thorac Dis 2021;13:4396-406.

50. Benn BS, Gmehlin CG, Kurman JS, et al. Does transbronchial lung cryobiopsy improve diagnostic yield of digital tomosynthesis-assisted electromagnetic navigation guided bronchoscopic biopsy of pulmonary nodules? A pilot study. Respir Med 2022;202:106966.

51. Bhadra K, Setser RM, Condra W, et al. A Cone Beam CT Bronchoscopy Study of the Ultrathin Cryoprobe for Biopsy of Peripheral Lung Lesions. J Bronchology Interv Pulmonol 2024;31:117-25.

52. Kim SH, Mok J, Kim S, et al. Clinical outcomes of transbronchial cryobiopsy using a 1.1-mm diameter cryoprobe for peripheral lung lesions - A prospective pilot study. Respir Med 2023;217:107338.

53. Meng WD, Lum M, Yu E, et al. Performance of Biopsy Tools in Procurement of Lung Tissue in Robot-Assisted Peripheral Navigation: A Comparison. Respiration 2023;102:1007-15.

54. Oki M, Saka H, Kogure Y, et al. Ultrathin bronchoscopic cryobiopsy of peripheral pulmonary lesions. Respirology 2023;28:143-51.

55. Oberg CL, Lau RP, Folch EE, et al. Novel Robotic-Assisted Cryobiopsy for Peripheral Pulmonary Lesions. Lung 2022;200:737-45.

56. Mondoni M, Sotgiu G, Bonifazi M, et al. Transbronchial needle aspiration in peripheral pulmonary lesions: a systematic review and meta-analysis. Eur Respir J 2016;48:196-204.

57. Mondoni M, Rinaldo RF, Carlucci P, et al. Bronchoscopic sampling techniques in the era of technological bronchoscopy. Pulmonology 2022;28:461-71.

58. Andersen HA, Fontana RS, Harrison EG Jr. Transbronchoscopic lung biopsy in diffuse pulmonary disease. Dis Chest 1965;48:187-92.

59. Miller RJ, Casal RF, Lazarus DR, et al. Flexible Bronchoscopy. Clin Chest Med 2018;39:1-16.

60. Khandhar SJ, Bowling MR, Flandes J, et al. Electromagnetic navigation bronchoscopy to access lung lesions in 1,000 subjects: first results of the prospective, multicenter NAVIGATE study. BMC Pulm Med 2017;17:59.

61. Chen A, Chenna P, Loiselle A, et al. Radial probe endobronchial ultrasound for peripheral pulmonary lesions. A 5-year institutional experience. Ann Am Thorac Soc 2014;11:578-82.

62. Kato A, Yasuo M, Tokoro Y, et al. Virtual bronchoscopic navigation as an aid to CT-guided transbronchial biopsy improves the diagnostic yield for small peripheral pulmonary lesions. Respirology 2018;23:1049-54.

63. Fruchter O, Kramer MR. Retrieval of various aspirated foreign bodies by flexible cryoprobe: in vitro feasibility study. Clin Respir J 2015;9:176-9.

64. Hetzel J, Eberhardt R, Herth FJ, et al. Cryobiopsy increases the diagnostic yield of endobronchial biopsy: a multicentre trial. Eur Respir J 2012;39:685-90.

65. Sehgal IS, Dhooria S, Behera D, et al. Use of cryoprobe for removal of a large tracheobronchial foreign body during flexible bronchoscopy. Lung India 2016;33:543-5.

66. Yarmus LB, Mallow C, Pastis N, et al. First-in-Human Use of a Hybrid Real-Time Ultrasound-Guided Fine-Needle Acquisition System for Peripheral Pulmonary Lesions: A Multicenter Pilot Study. Respiration 2019;98:527-33.

67. Patel PP, Duong DK, Mahajan AK, et al. Single Setting Robotic Lung Nodule Diagnosis and Resection. Thorac Surg Clin 2023;33:233-44.

68. Ross PS, Sutter P, Sutter J, et al. Fast Track Nodule Pathway: Same Day Robotic Diagnosis and Resection. Chest 2021;160:A82.

69. Moran DE, Parikh M, Sheiman RG, et al. Comparison of technical success and safety of transbronchial versus percutaneous CT-guided fiducial placement for SBRT of lung tumors. J Med Imaging Radiat Sci 2021;52:409-16.

70. Potts K, Ravikumar N, Hogarth DK, et al. The role of bronchoscopy as a novel approach in preoperative lung marking for early-stage lung cancer. Transl Cancer Res 2023;12:221-5.

71. Folch E, Guo Y, Senitko M. Therapeutic Bronchoscopy for Lung Nodules: Where Are We Now? Semin Respir Crit Care Med 2022;43:480-91.

72. Steinfort DP, Herth FJF. Bronchoscopic treatments for early-stage peripheral lung cancer: Are we ready for prime time? Respirology 2020;25:944-52.