

Peripheral pulmonary lesion: novel approaches in endoscopic guidance systems and a state-of-the-art review

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Abstract

Diagnosis of peripheral pulmonary lesions (PPL) is the most challenging field in bronchoscopy and interventional pulmonology, which concerns early lung cancer diagnosis. Despite novel techniques and new approaches to the periphery of the lung, almost 25% of PPLs remain undiagnosed. Bronchoscopy with guide systems, virtual and/or electromagnetic navigation, robotic bronchoscopy, and transparenchymal nodule approaches tend to provide a higher percentage of reaching the lesion, but the diagnostic yield rarely exceeds 75%, regardless of the instruments used. Further studies are needed to evaluate what the main constraints of this discrepancy are and if a combined use of these techniques and instruments can provide an increased diagnostic yield.

Key words: peripheral pulmonary lesion, lung cancer, electromagnetic navigation bronchoscopy, virtual navigation bronchoscopy, bronchoscopic transparenchymal nodule access.

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Introduction

Lung cancer is the most fatal and the second most common cancer worldwide. A lung nodule can represent the earliest detectable stage of lung cancer, defined as a peripheral pulmonary lesion (PPL). It has been well demonstrated that the stage of diagnosis is inversely related to prognosis, with early detection leading to significant improvements in survival [1]. Diagnosis of PPLs suspected of malignancy remains a challenge. However, there are no clear guidelines for these various endobronchial modalities.

Moreover, with the ubiquitous use of diagnostic chest computed tomography (CT) scan and the implementation of lung cancer screening, the number of pulmonary nodules detected yearly continues to increase; as is obvious, as the number of patients with lung nodules increases, there will be increased demand to perform tissue sampling.

Since the low diagnostic rate for which concerns PPLs, over time, novel bronchoscopic approaches have been developed. We aimed to provide a comprehensive review of the novel bronchoscopic techniques and their diagnostic yield (DY). We performed literature research in PubMed by using the keywords "bronchoscopy" AND "lung cancer" AND "peripheral pulmonary lesion".

This review focuses on bronchoscopic navigation techniques and innovative imaging/tumor detection techniques. We aimed to describe recent advancements, including the identification of knowledge gaps and future perspectives to improve the diagnosis and treatment of PPLs.

PPL is actually considered the most challenging field in bron-

choscopy. Traditionally, there are three options for tissue sampling of the lung nodule: surgical resection, CT-guided transthoracic needle biopsy, or bronchoscopic biopsy. Over time, novel endoscopic approaches were developed to sample PPL. The first of them was transbronchial lung biopsy (TBLB) with fluoroscopy, which consists of a radiologic confirmation of which direction the forceps are walking across.

Traditional TBLB, guided only by fluoroscopy, has historically had a low DY, with diagnostic rates for nodules under 2 cm estimated to be 34% and still only 63% for lesions over 3 cm [2].

After that technique, advanced bronchoscopic technologies have been developed, and include thin/ultrathin bronchoscopes, radial probe endobronchial ultrasound (R-EBUS) with or without guide sheath (GS), virtual bronchoscopic navigation (VBN), electromagnetic navigational bronchoscopy, cone-beam CT (CBCT) assisted bronchoscopy, and robotic bronchoscopy (RB).

Radial endobronchial ultrasound and guide sheath

R-EBUS is a thin, flexible catheter with a rotating ultrasound transducer that produces a 360-degree ("radial") image; the catheter easily passes through the working channel of the scope. This provides a 360-degree view in a 2D plane radiating laterally outward from the probe tip [2] (Figure 1).

A 2011 meta-analysis of R-EBUS-guided bronchoscopy with 1420 patients reported a pooled diagnostic sensitivity of 73%. Complication rates were similar to non-guided bronchoscopy, with



a pneumothorax rate of 1%, with less than half of those requiring chest tube placement [3].

The largest (and more recent) meta-analysis assessing R-EBUS for diagnosis of PPL to date was in 2017 and found an overall weighted DY of 70.6%. DY was higher in nodules >2 cm, malignant nodules, and those with a positive bronchus sign. Not surprisingly, the yield was higher when the probe had a concentric view rather than an eccentric one [4].

The benefit of R-EBUS lies in its ability to provide guided imaging to distal locations, allowing for real-time operator feedback regarding nodule location before the biopsy. Larger nodules and the ability to obtain a concentric view further increase the likelihood of higher DY. A major limitation for R-EBUS is that an eccentric signature tells the operator that the nodule is next to the airway, but we do not know where the nodule is (*i.e.*, upper, lower, left, or right). Thus, improved techniques such as bronchoscope manipulation and GS are needed for improved DY [5]. Although GS (Figure 2, [6]) may have improved the ability to find the same pathway towards the target lesion, in a meta-analysis, a similar pooled DY (72.7%) was reported compared to R-EBUS without GS use (70.6%), probably due to dislodgment of the GS by the stiff biopsy tools [4,7,8].

Conversely, an randomized controlled trial (RCT) conducted by Oki *et al.* in which compared DY between TBLB plus GS and without GS, revealed that the DY of histological specimens from the GS group was significantly higher than that from the non-GS group (55.3% vs. 46.6%; $p=0.033$) [9].

The major limitations in R-EBUS procedures are misinterpretations of radial ultrasound signals in inexperienced operators and the fact that the radial probe is more flexible than forceps; thus, after the lesion is identified, the forceps cannot reach the target because of its stiffness.

Moreover, R-EBUS does not provide a real-time biopsy because when R-EBUS reaches the lesion, the probe has to be withdrawn to provide the biopsy tool insertion on the same working channel of the scope. An alternative option recently available is a real-time radial endobronchial ultrasonography with transbronchial needle aspira-

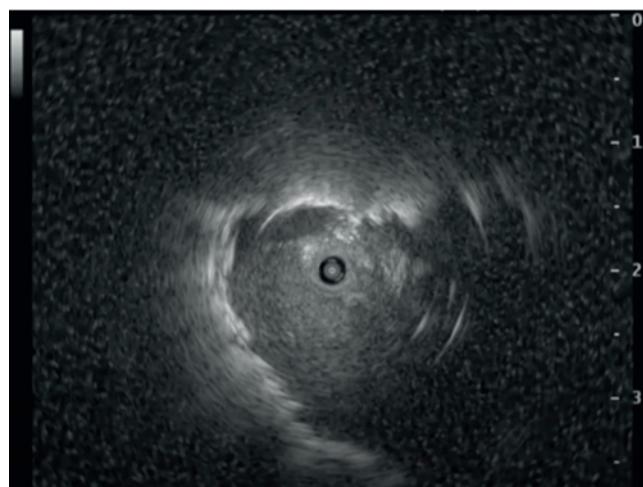


Figure 1. Radial probe endobronchial ultrasound.



tion (TBNA), in which TBNA and not TBLB can be performed, but a contemporary view (R-EBUS images and TBNA) is available; DY reported is 69% [10].

Thin/ultrathin bronchoscopy

The reasons to use thin/ultrathin bronchoscopy (TB/UTB) lie in the fact that the major limitation of conventional bronchoscopy is the anatomic constraints of the physical bronchoscope and its inability to reach distal subsegmental levels owing to the bronchoscope's large outer diameter (OD). Conversely, TB/UTB (OD<3 mm) can go deeper into the lung periphery, often reaching the ninth bronchial generation, gaining improved access to peripheral lesions for tissue sampling [11]. TB/UTB is often combined with other guided techniques, such as CT guidance, VBN, and R-EBUS, to improve lesion localization.

One retrospective study comprising 44 of 338 patients who underwent bronchoscopy evaluated whether substituting a TB with the UTB during multimodal bronchoscopy improved lesion ultrasound visualization and DY. After substitution, in cases where the radial probe was within the target lesion (a concentric view), the DY was 80%. The yield decreased to 72% when the probe is adjacent to the lesion (eccentric). Overall DY was 65% [12]. This demonstrated that substitution of TB for UTB as needed improved the position of the R-EBUS probe. With an improvement in view, there was an increase in DY.

A 2015 trial from Japan randomized 310 patients who underwent TBLB with R-EBUS, fluoroscopy, and VBN to either an ultrathin bronchoscope (3 mm) or a thin bronchoscope (4 mm) plus GS (TB+GS). The UTB could reach more distal bronchi (median 5th vs. 4th generation) and had a higher DY of 74% compared to 59% of the TB+GS group. Complications occurred in 3% vs. 5%, respectively [13].

In a trial from 2019, patients were randomized to undergo R-EBUS, VBN, and fluoroscopy-guided biopsy with a 3 mm UTB or

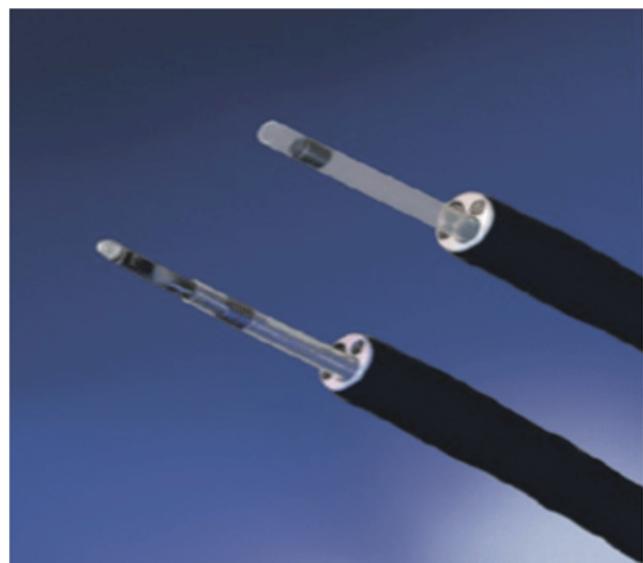


Figure 2. Guide sheath. Reproduced by Lachkar *et al.* (2020).

a 4 mm TB. In the TB group, small forceps with GS or standard forceps without GS were allowed. Nevertheless, overall DY was higher in the UTB group (70.1% vs. 58.7%) and had a shorter procedure duration (24.8 vs. 26.8 min) with fewer complications (2.8% vs. 4.5%) [11]. Again, we observe that multimodal bronchoscopy with the aid of UTB allows for higher DY than using TB alone.

Complications of TB/UTB are bleeding and pneumothorax, because of their capability to reach subpleural zones.

Virtual bronchoscopic navigation and electromagnetic navigation

Selecting the right branching bronchi from a 2D CT scan in order to accurately assess the lung lesion in a real-life three-dimensional setting is challenging. VBN software creates a virtual map of the airway that describes the route with the highest probability to reach the lesion based on a pre-procedural CT scan. During bronchoscopy, the navigational system recognizes the visual appearance of the airways and provides guidance towards the target lesion [14] (Figure 3). A limitation of VBN is that it lacks a real-time adjustment mechanism for navigation errors and does not provide real-time biopsy tool localization feedback.

To overcome this limitation, electromagnetic navigation (EMN)

combines a pre-procedural CT scan to create a virtual tracheobronchial tree, similar to VBN, with an electromagnetic field for real-time guidance. An electromagnetic plate is placed around the patient's chest, and biopsy instruments are guided towards the lesion based on the positional information of the electromagnetic sensor and pre-procedural CT scan [14] (Figure 4, [15]).

The major limitations of these two techniques are the difference between the lesion localization on pre-procedural CT scan and the real-time localization during the procedure due to respiration, body positioning, atelectasis and cardiac pulse (*i.e.*, the CT-to-body-divergence) [16]; to overcome this divergence, there are many adjustments (*i.e.*, anesthesia) or additional confirmatory tools that can be useful to reduce the difference between the CT scans and real images [R-EBUS, CBCT, augmented fluoroscopy (AF)] [17].

Multiple meta-analyses have been performed to demonstrate the usefulness of VBN and EMN, but the outcomes are mostly based on small, single-center analyses with a frequent retrospective design.

One RCT performed VBN in conjunction with the UTB and fluoroscopy and did not demonstrate a significantly higher DY in the VBN group (67.1% vs. 59.9%), while another RCT used VBN in conjunction with fluoroscopy and R-EBUS showed a significantly higher DY in the VBN group (80.4% vs. 67.0%) [18,19]. Lately, the first multi-center cohort study also prospectively evaluated the DY of EMN in 1157 lung lesions and reported a DY of 73% [20].

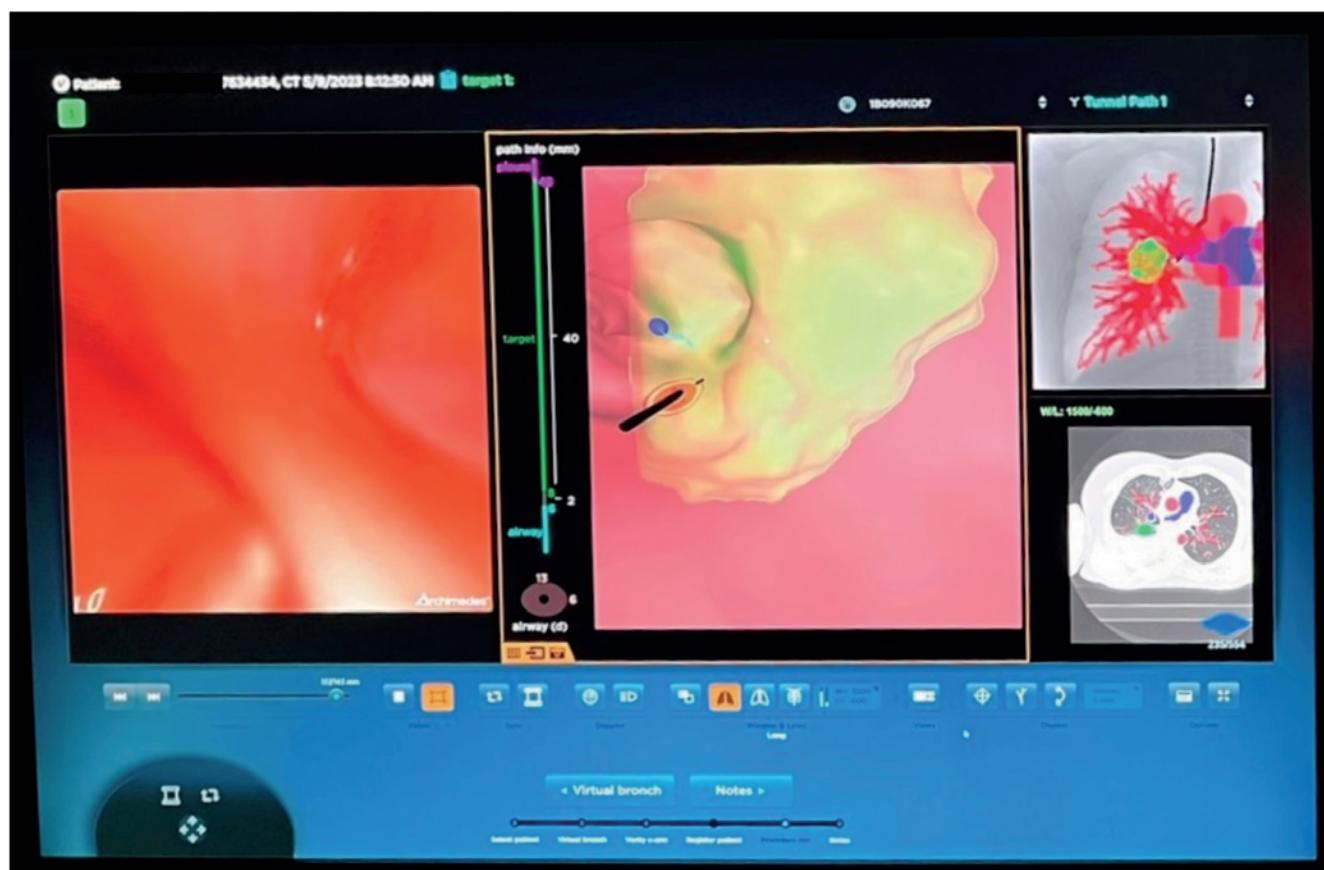


Figure 3. Virtual bronchoscopic navigation.



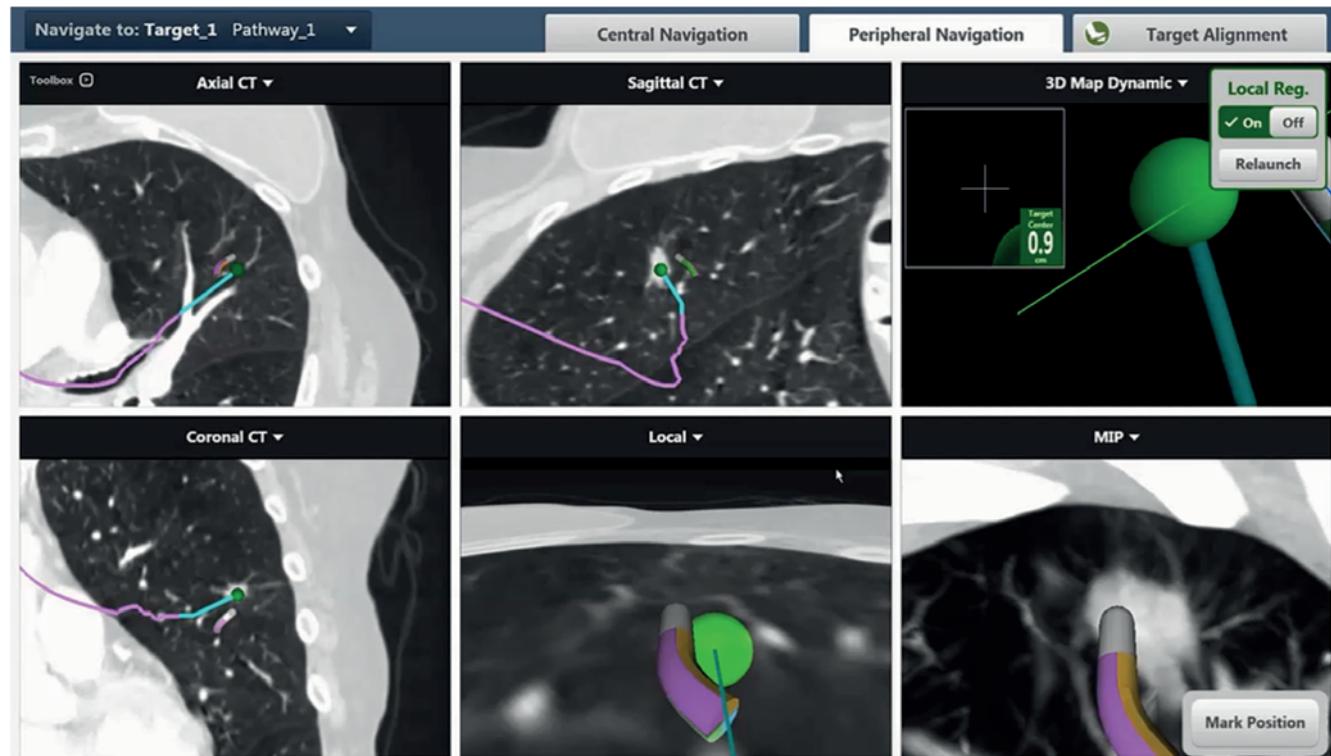


Figure 4. Electromagnetic navigation. Reproduced by Katsis *et al.* (2020).

Cone beam computed tomography and augmented fluoroscopy guided bronchoscopy

Fluoroscopy uses a C-arm X-ray for real-time, 2D visualization of the target lesion and biopsy tools. Although the technique is widely used, few small, randomized trials evaluated the use of fluoroscopy and suggest that the complementary use of fluoroscopy does not result in an improved DY [21,22]. This is probably the result of the two-dimensional imaging. The introduction of CBCT imaging seems to perform a better identification of the target, and this should result in an augmented DY.

CBCT, with its rotating arm, scans the patient's chest and performs a 3D visualization of the bronchial anatomy, the lesion, and the biopsy tools, in order to correctly reach the pulmonary lesion [23] (Figure 5). To have real-time guidance during biopsy passes, CBCT images of the target lesions can be overlaid on real-time fluoroscopy images, the so-called AF [23,24]. This technique allows the fluoroscopic visualization of small lesions and ground glass opacity that are invisible to conventional fluoroscopy [24,25]. Also, AF can be used for confirmation of the biopsy tool's site, and a real-time evaluation of the biopsy site can be performed (Figure 6).

First studies performing CBCT with AF, either in conjunction with EMN and/or R-EBUS, report a DY ranging from 70.2% to 83.7% [25-27]; one study reported a significantly improved navigational success using CBCT with AF and EMN of 89.9% but with a DY of 70.2%. This discrepancy between navigational success and DY was attributed to the rigidity of the biopsy tools, breathing

motions, and manipulation of the endoscope, causing displacement of the instruments [26].

Recently, a navigation and AF system has been developed (Body Vision Medical LTD, Israel). This system integrates preprocedural high-resolution CT to intraoperative real-time fluoroscopy using artificial intelligence algorithms. As a result, the system shows the exact projection of the target lesion on the fluoroscopic image, facilitating nodule localization and thus increasing DY. However, like the other guidance systems, even if the localization ratio of the nodule reaches 93-94%, its DY is still debated, ranging from 75% to 87% [27,28].



Figure 5. Cone-beam computed tomography. Reproduced with permission from Siemens Healthcare GmbH.



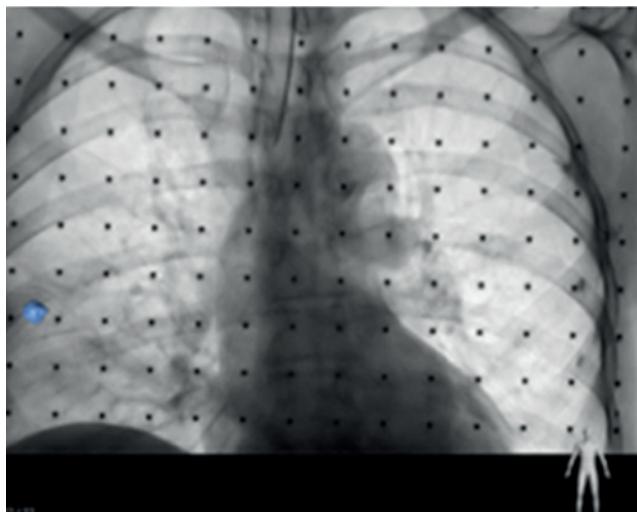


Figure 6. Augmented fluoroscopy. Reproduced from Cheng *et al.* (2020).

Regarding the radiation exposure, performing CBCT plus AF for the total procedure, it ranged from 11 to 29 mSv, which is comparable to the average radiation from CT-scan guided lung biopsy [29,30].

The major limitations of these techniques are their expense, so an exhaustive analysis of the number of procedures, single-procedure costs, and effective advantage has to be performed center-by-center.

Robotic bronchoscopy

Currently available bronchoscopic guidance tools have demonstrated an improved approximation of the PPL, but the DY remains limited. The innovative robotic bronchoscopic platforms (The Monarch™ platform, Auris Health, and Ion™ Endoluminal System, Intuitive Surgical) have been developed to overcome the limitations of other guidance tools by redesigning the distal ends of the bronchoscope [31]. A cadaver study compared the peripheral reach of the robotic bronchoscope with a conventional thin bronchoscope with the same OD and demonstrated a superior reach in all segmental bronchi compared to the conventional thin bronchoscope [32]. One of the major differences between the platforms is the design of the scope and working channel. The Monarch™ platform has a 4.4-mm scope and a 2.1-mm working channel, while the Ion™ Endoluminal System has a 3.5-mm scope and a 2.0-mm working channel, which is occupied by the camera during navigation. Another difference is about the navigation: while the Monarch™ platform uses EMN technology to navigate, the Ion™ Endoluminal System records the catheter tip and overlays it on the CT-scan to navigate.

The first prospective, multi-center study performed RB using the Monarch™ platform with R-EBUS in 54 patients with a median lesion size of 23 mm. In 51/53 patients (96.2%), the lesion was successfully localized using R-EBUS, but a DY of 74.1% was reported [33]. Another study evaluated the Ion™ Endoluminal System in 130 patients with 159 lung lesions (median lesion size 18 mm) under R-EBUS and/or fluoroscopy guidance, and successful navigation was achieved in 157/159 (98.7%) lesions. An overall DY of 81.7% was reported with an 79.8% sensitivity for malignancy [34].

Although the results of both studies are encouraging, the difference between the identification of the lesion and DY is still high, with 20% of PPLs undiagnosed. Moreover, these techniques are disturbed by the patient's breath, cardiac pulse, development of bleeding, and/or atelectasis. Also, like CBCT, RB is very expensive, and its widespread use is limited by costs.

Bronchoscopic transparenchymal nodule access

All the techniques mentioned above present a substantial limitation, that is, bronchial anatomy: in fact, if the lesion is not reached by a bronchus, biopsy cannot be performed or cannot provide a diagnosis. To overcome this limitation, bronchoscopic transparenchymal approaches have been developed to create a pathway towards the lesion.

Bronchoscopic transparenchymal nodule access (BTPNA) is part of the Archimedes VBN platform (Bronchus Medical, Inc., San Jose, California, USA), allowing integration of bronchoscopic images, CT data, and fluoroscopic images to generate a 3D transparenchymal route with avoidance of blood vessels. Based on the virtual guidance, a coring needle punctures the central airways to have direct access into the parenchyma. A balloon catheter dilates the point-of-entry, allowing a 2.0 mm working channel sheath with a stilet to be advanced to the target lesion under fluoroscopic/CT guidance. *Via* this tunneled tract, biopsy instruments are introduced and navigated safely towards the lesion [35] (Figure 7). The first study performed in humans was made by Herth *et al.* in 2015 [36]. In 10/12 patients (82%), the procedure was successfully performed with adequate tissue sampling. The most recent study of Sun performed in 114 patients revealed a BTPNA DY of 93.9% and sample adequacy for definite diagnosis in 75.4% of the cases [37].

The most recent study regarding Archimedes' VBN showed encouraging preliminary results, with a DY of 77% (7/9 patients)

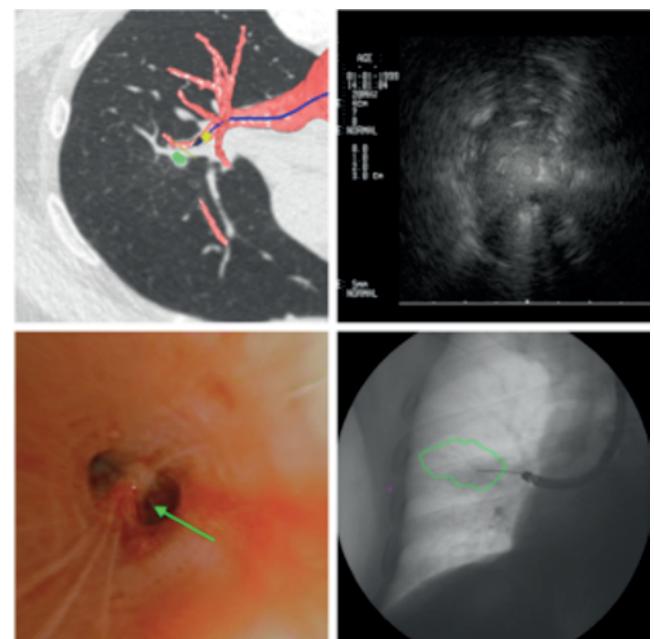


Figure 7. Bronchoscopic transparenchymal nodule access.



using Archimedes' VBN and BTPNA in patients who previously underwent conventional bronchoscopy with R-EBUS and fluoroscopy, with no diagnosis achieved. Interestingly, this study provided another way to sample PPL, by using miniforceps (CoreDx miniforceps, Boston Scientific, Watertown, MA) into the tunneled tract previously performed (FlexNeedle®, Broncus Medical®, San Jose, CA). This suggests a multimodal approach (needle, miniforceps), using different tools [38]. An alternative technique is the trans-bronchial access tool (TBAT, Medtronic, Minneapolis, Minnesota, USA), which can be integrated into the superDimension EMN system. To our knowledge, just a few case series have been reported with this technique [39-41].

Biopsy tools

The more different navigational systems there are, the same biopsy tools are available: biopsy forceps, miniforceps, and TBNA needles are currently used and described in the studies mentioned above. Biopsy tools are a limiting factor that can explain the divergence between localization and DY ratios. The use of flexible and smaller (1.1 mm) cryoprobes (ErbeCryo®2, Erbe Elektromedizin GmbH 2023, Germany), moving its use from interstitial lung diseases (ILDs) to PPLs diagnosis, represents a promising tool to improve DY of navigational bronchoscopy systems. Descriptions of biopsy tools are not the aim of the present review, but it is interesting to highlight the potential positive impact of cryobiopsy for PPLs. The 1.1 mm flexible cryoprobe (*i.e.*, mini-cryo) allows freezing and sampling a huge amount of tissue compared to conventional biopsy tools, increasing DY and obtaining adequate tissue for NGS [42]; its flexibility and dimensions make this probe suitable for all bronchoscopes (TB, UTB). Complications of cryobiopsy can be bleeding and pneumothorax, and consequently, management of potentially life-threatening complications should be considered before performing cryobiopsy (Figure 8).



Figure 8. Cryobiopsy.

Conclusions

The field of interventional pulmonology for peripheral lung lesion analysis and treatment is evolving rapidly. A desirable future concept is the one-step bronchoscopic approach, including navigation to the tumor, biopsy sample, and diagnosis for future treatments. PPL are the current challenge: several bronchoscopic guidance technologies have been developed that resulted in an improved DY of PPL [33,34], but data are still poor. Moreover, it is challenging to determine each individual technology's contribution to the DY. Actually, whatever navigational technique is used, DY now rarely exceeds 75% [33,34,43], with a key limiting factor being the lack of needle in target lesion confirmation [44]. Thus, novel techniques regarding needle imaging might be helpful tools to identify malignant lesions and confirm the right place for biopsy, enabling optimal tissue acquisition [45]. However, the data on these techniques are preliminary, and further research is needed.

In conclusion, in the last few years, technological developments have implemented the options for bronchoscopic tumor navigation and treatment [46]. For which concerns the interventional pulmonology, the one-step bronchoscope approach to diagnose (and treat) will become the future clinical practice.

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