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Review

Inheritance and innovation of the diagnosis of peripheral pulmonary lesions

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***Abstract*:** As the leading cause of cancer-related deaths worldwide, early detection and diagnosis are crucial to reduce the mortality of lung cancer. To date, the diagnosis of the peripheral pulmonary lesions (PPLs) remains a major unmet clinical need. The urgency of diagnosing PPLs has driven a series of development of the advanced bronchoscopy-guided techniques in the past decades, such as radial probe-endobronchial ultrasonography (RP-EBUS), virtual bronchoscopy navigation (VBN), electromagnetic navigation bronchoscopy (ENB), bronchoscopic transparenchymal nodule access (BTPNA), and robotic-assisted bronchoscopy. However, these techniques also have their own limitations. In this review, we would like to introduce the development of diagnostic techniques for PPLs, with a special focus on biopsy approaches and advanced guided bronchoscopy techniques by discussing their advantages, limitations, and future prospects.

Keywords: bronchoscopy, diagnosis, peripheral pulmonary lesion

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Background

To date, lung cancer remains the leading cause of cancer-related deaths worldwide.[1] Early detection and diagnosis are crucial to reduce the mortality of lung cancer. As the most promising tool for lung cancer screening, low-dose computed tomography (LDCT) has been widely used in recent years, resulting in abundant peripheral pulmonary lesions (PPLs) being detected. Although a series of novel techniques for obtaining biopsy specimens have been devised and improved continually, the diagnosis of PPLs remains a big challenge for pulmonary physicians. This review will provide a concise overview of the development of diagnostic techniques for PPLs, with a special focus on biopsy approaches and advanced guided bronchoscopy techniques by discussing their advantages, limitations, and prospects.

The development of diagnostic systems for PPLs

Early stage before flexible bronchoscope

Prior to the invention of fiberoptic bronchoscopes, PPLs were diagnosed mainly by exfoliative cytology, with a diagnostic rate of 23.7–40%.[2–4] In 1952, Dr. H Metras designed a bronchial catheter, which was first introduced into the bronchus under fluoroscopy, and was widely applied in the following years.[5] In 1967, Dr. Eitaka Tsuboi introduced a curet through the modified Metras catheter into the lesions under fluoroscopy and obtained biopsy specimens, promoting the development of interventional respiration.[6] However, the bronchial catheter can only reach the proximal bronchus, which greatly limits the diagnosis of PPLs. Therefore, it was urgent to design a flexible endoscope which can adapt to and enter the distal bronchus.

The stage of fiberoptic bronchoscopy

In 1967, Dr. Ikeda designed a flexible bronchoscope that could change the curvature according to the shape of the bronchus to reach the distal ones. In addition, its powerful light conduction ability allowed people to observe the internal structure and lesions of the bronchi.[7] Throughout the 1970s–1980s, various instruments adapted to the bronchoscope for biopsy through the working channel were designed, such as brush, forceps, curette, needle, and needle brush, greatly improving the biopsy rate. Nevertheless, the diagnostic

Table 1. Overview of biopsy techniques for PPLs.

Biopsy technique	Diagnostic yield	Complication rate	Advantage	Disadvantage
TBNA	44–61%	0.43% pneumothorax 0.49% hemorrhage	A positive predictor for diagnostic yield	Need further improvement for PPLs in some specific locations
TBLB	53.8–60%	1–5% pneumothorax	Obtain relatively large tissues	Difficult to penetrate through the bronchial wall
PCNA	92.1–97.7%	20.5% pneumothorax 2.8% hemorrhage	High diagnostic sensitivity	Relatively high complication rate and high radiation dose

PCNA, percutaneous needle aspiration; PPL, peripheral pulmonary lesion; TBLB, transbronchial needle aspiration; TBNA, transbronchial lung biopsy.

yield of PPLs by fiberoptic bronchoscopy alone remained low.[8–10] The reason might be that the bronchial wall and parabronchial lesions were invisible in fiberoptic bronchoscopy, leading to inaccurate location and inaccessible biopsy.

Advanced guided bronchoscopy techniques

In recent years, new techniques emerge in endlessly. Guided bronchoscopy techniques developed from fluoroscopy to ultrasound, virtual navigation, and electromagnetic navigation. The development of diagnostic guided bronchoscopy techniques not only improved the clarity of endoscope images but also enhanced the accessibility of PPLs. To adapt the more distant bronchus, smaller bronchoscopes and steerable guides were designed, which improved the positive diagnostic rate of PPLs.[11–14] Newer bronchoscopy techniques, such as robot-assisted bronchoscopy and Lung Pro, have also been put into use. The combination of guided bronchoscopy techniques, new biopsy instruments can promote strength and avoid weaknesses.

The commonly used biopsy techniques

Transbronchial needle aspiration

Transbronchial needle aspiration (TBNA) was first described in 1949 by Dr. Eduardo Schieppati[15] and developed by Dr. Kopen Wang for rigid bronchoscope and flexible bronchoscope in 1978[16] and 1983,[17] respectively, which remains one of the most commonly used sampling techniques (Table 1). Under the guidance of X-ray or other navigation techniques, insert the needle into the lesion and aspirate for 3–5 times under negative pressure to obtain the specimens, which is helpful for the diagnosis of PPLs and staging of lung cancer. A systematic review and meta-analysis published in European Respiratory Journal in 2016 reported the diagnostic rate of TBNA for PPLs was 53% [95% confidence interval (CI): 44–61%], with a rare complication incidence, mainly pneumothorax and moderate bleeding.[18] The subgroup analyses suggested that the presence of CT bronchus sign, lesions size >3 cm and rapid on-site evaluation (ROSE) employment are the positive predictive factors of diagnostic yield.[18]

At present, the MW-319 needle (15 mm/3 mm × 140 cm, 19G/21G; CONMED Corporation) is recommended for TBNA and mainly used for central pulmonary lesions due to its enhanced hardness. On the contrary, the SW-221 needle (13 mm × 140 cm, 21G; CONMED Corporation) is commonly applied for PPLs. The SW-221 needle can partially retract the internal stylet, making it less stiff and easier to reach apical or superior segmental lesions for biopsy. The improvement of the puncture needles for PPLs has never stopped. For example, the PeriView FLEX (NA-403D-2021; Olympus Medical Systems), a new type of TBNA needle, came out. The smaller diameter of the PeriView FLEX makes it more suitable for the ultrathin bronchoscope working channel.[19] What's more, with a spiral pattern on the needle, PeriView FLEX is conferred flexibility

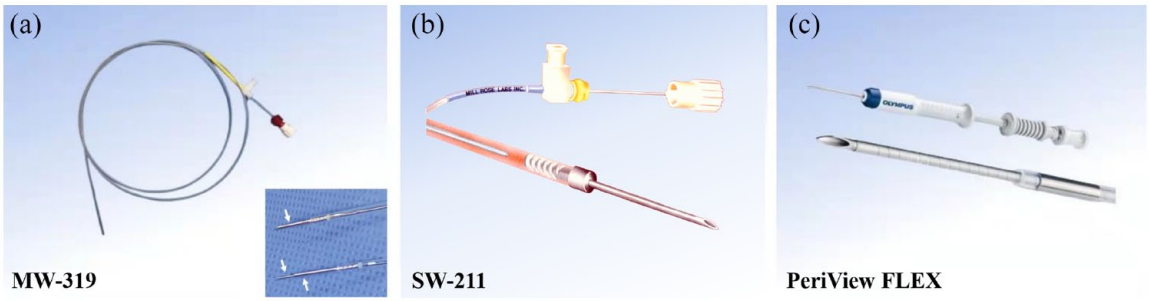

Figure 1. The image of MW-319 (a), SW-221 (b), and PeriView FLEX(c). (The image of PeriView FLEX needle is from the Olympus official website.)

to reach PPLs through the angulation.[20] The employment of PeriView FLEX increased the diagnostic rate of PPLs to 68–70%.[19,20] More importantly, TBNA with PeriView FLEX is the only method to diagnose PPLs in some specific locations, such as the apical segment[20] (Figure 1).

Transbronchial lung biopsy

Transbronchial lung biopsy (TBLB) can obtain lung tissue by biopsy forceps, curettes, and brushes. Clinically, biopsy forceps are predominantly used, which can obtain relatively large tissue to improve the positive diagnostic rate. Some studies have shown that the diagnostic yield of TBLB without fluoroscopy is 53.8–60%,[21,22] while it can increase more than 10% when combined with fluoroscopy.[23,24] It is confirmed that the combination of navigation bronchoscopy can improve the diagnostic rate of TBLB.[25–27] Recently, a prospective randomized controlled trial conducted in China suggested that the diagnostic rate of TBLB could reach 81.7% with the assistance of ultrathin bronchoscopy, VBN, RP-EBUS, and other novel technologies.[28] The diameter and location of the lesion would affect the diagnostic rate of TBLB, that is, the big size and located in the right lung and the lower lung are positive predictors of the diagnostic rate.[22] The presence of bronchial signs on CT was also a positive factor in the diagnostic rate.[29] In addition, repeated biopsy will significantly improve the diagnostic rate. Studies have shown that the diagnostic rate can be high enough for 3–4 repeated biopsies,[30,31] while some scholars discovered that it can still be improved for more than six repeated biopsies.[32] The main complication is pneumothorax, with an incidence of 1–5%,[24,33] which is generally safe and feasible.

Percutaneous needle aspiration/transthoracic needle aspiration

Compared with the traditional bronchoscopy technique, CT-guided percutaneous needle aspiration (PCNA) has great advantages in the diagnosis of PPLs, which can take biopsy through percutaneous approach under real-time guidance. DiBardino and colleagues conducted a systematic review and meta-analysis involving 48 articles suggesting that the diagnostic yield of PCNA under CT guidance can reach 92.1%.[34] Recently, it can even up to 97.7% in a prospective study.[35] A retrospective analysis demonstrated that the diagnostic sensitivity of CT-guided PCNA for lesions close to the chest wall was significantly higher than those away from (100% *vs* 80%, $p = 0.04$).[36] The size of the lesions did not have a noticeable impact on the diagnostic rate.[37] The high diagnostic yield of PCNA makes it appear to be the prior method for the diagnosis of PPLs, while it also has some limitations. First, PCNA has a high risk of complications, and a meta-analysis revealed that the incidence of bleeding and pneumothorax in PCNA was 2.8% and 20.5%, respectively.[34] Subgroup analysis implied that pulmonary diseases and lesions away from the chest wall were risk factors for complications.[36,37] In addition, the high radiation dose is also a drawback of this technology. In recent years, emerging guidance techniques have been applied to PCNA, including ultrasound and electromagnetic navigation, with diagnostic rates of 88.7%[34,38] and 83%,[39] respectively, but they also have a high risk of pneumothorax.[34,38,39] Finally, PCNA cannot

Table 2. Overview of guided bronchoscopy techniques for PPLs.

Guided technique	Diagnostic yield	Characteristic	Limitation
Fluoroscopy	41.4–74.4%	Simple and affordable; real-time guidance and biopsy	High radiation exposure
RP-EBUS	72–82.5%	Ultrasonic echo with no radiation	Not real-time confirmation and biopsy
VBN	57.1–67.1%	Construct a virtual bronchial approach	Lacked of a real-time adjustment
ENB	38.5–73%	Electromagnetic effect with no radiation	The probe may deviate by respiration
BTPNA	83.3–86.3%	Create a vascular-less channel from the bronchial wall to PPLs	Safety issue needs to be further validated
Robotic-assisted bronchoscopy	69.1–80%	Adjust the angle of biopsy instruments flexibly	Fluoroscopy and human control required

BTPNA, bronchoscopic transparenchymal nodule access; ENB, electromagnetic navigation bronchoscopy; PPL, peripheral pulmonary lesion; RP-EBUS, radial probe – endobronchial ultrasonography; VBN, virtual bronchoscopy navigation.

perform mediastinal staging in the meanwhile, which is not conducive to the formulation of therapeutic schedules.

Comparison of TBNA, TBLB, and PCNA

Several prospective randomized controlled trials have demonstrated that PCNA has a higher diagnosis sensitivity to PPLs than TBNA or TBLB, especially when the lesions are close to the chest wall and have a smaller diameter.[40–43] Nonetheless, the complication probability of PCNA was notably higher than that of TBNA and TBLB.[40–43] As a traditional technology, TBLB alone has a low biopsy rate, and the participation of guiding technology is required to improve the positive diagnostic rate furtherly. The main reason is that TBLB alone often fails to break through the bronchial wall, resulting in poor sampling. Therefore, TBNA may be the preferred choice for the lesions lacking bronchial signs on CT (27% *vs* 17%).[44] Two studies discovered that when both TBNA and TBLB were completed simultaneously, 9.5%[45] and 21%[44] of patients were diagnosed with TBNA but not with TBLB, respectively. A prospective multicenter study (AQuIRE Registry) published in the American Journal of Respiratory and Critical Care Medicine in 2016 indicated that novel navigation techniques did not improve the diagnostic yield of PPLs, while TBNA was a positive predictor.[45] Hence, TBNA is still of great value in the diagnosis of PPLs.

The development of guiding technology

Fluoroscopy

In the face of these invisible PPLs in traditional bronchoscopy, the combination of guiding technology turns to be critical, in which fluoroscopy was the first one to be introduced into bronchoscopy (Table 2). Several studies have shown that the diagnostic yield of PPLs under fluoroscopy guidance alone is 41.4–74.4%,[23,46–50] which is similar to that of central pulmonary lesions.[47] A retrospective comparative study indicated that the diagnostic rate of TBLB under fluoroscopy was markedly higher than that without guidance (41.4% *vs* 29.5%, $p=0.036$), and there was no significant difference in the incidence of pneumothorax, which were 1.2% and 0.6%, respectively.[23] The combination of fluoroscopy and other novel navigation technologies will be described in detail later.

The main factors affecting the diagnostic rate of fluoroscopy-guided bronchoscopy include the size and location of PPLs. A retrospective study confirmed that the diagnostic rate of PPLs larger than 2 cm can reach 72.2% under fluoroscopy guidance, while for those smaller than 2 cm was only 33.3%.[46] A two-center prospective study found that the diagnostic rate of PPLs located in the lower lobe was lower than those of non-lower lobes, but there was no statistical difference ($p=0.091$).[48] Moreover, Uchida *et al.*[50] conducted

a prospective study and discovered that performing ROSE in patients with suspected peripheral lung cancer can increase the diagnostic rate by 23% during fluoroscopy-guided bronchoscopy, which was independent of the experience of physicians. As a result, ROSE is an effective method for bronchoscopy in the diagnosis of PPLs.

The leading drawback of fluoroscopy-guided technology is the radiation. Clark *et al.*[51] expressed that the patient undergoing fluoroscopy-guided bronchoscopy was exposed to a radiation dose of 0.26 m Sv averagely. Considering the patient has respiratory disease, although the dose of radiation is not too high to accept, the possibility of long-term follow-up imaging examination makes it hard to be ignored.

Radial probe–endobronchial ultrasonography (RP-EBUS)

In order to reduce the radiation exposure of patients and interventional pulmonary physicians in the operation, the ultrasound-guided technology–RP-EBUS was designed. Another advantage of RP-EBUS is that those invisible parabronchial and bronchial wall lesions in conventional bronchoscopy can be detected through the echo level. RP-EBUS provides a 360° ultrasound view of the two-dimensional plane where the device probe is located, which enables real-time localization of distal lesions.

In 2002, Herth first used EBUS technology to guide bronchoscopy biopsy in the diagnosis of PPLs, confirming the feasibility.[52] Triller *et al.*[53] conducted a prospective controlled trial and suggested that the difference between TBLB guided by EBUS and fluoroscopy showed no statistical significance in the diagnosis of PPLs, and EBUS was more advantageous due to its no radiation. A retrospective study conducted by Boonsarngsuk *et al.*[46] revealed that the addition of EBUS guidance on the basis of X-ray fluoroscopy could further improve the diagnostic rate (57.9% *vs* 82.5%, $p = 0.004$), especially in the lesions with diameter less than 20 mm (33.3% *vs* 79.3%, $p = 0.001$). In another retrospective analysis of 174 patients, Boonsarngsuk *et al.*[54] found that performing TBLB, brushing, and BAL simultaneously under EBUS guidance could achieve the greatest diagnostic yield. A meta-analysis of 51 studies with 7601 patients displayed that EBUS had a diagnostic sensitivity of 72%, specificity of 99%, and an incidence of pneumothorax of 0.7%.[55] In particular, the diagnostic rate of PPLs has been further improved after ultrathin bronchoscopy and microultrasound probes were designed and widely used.[56] In view of the efficacy and safety, American College of Chest Physicians (ACCP) guideline recommends RP-EBUS as the preferred guiding technology for patients with suspected lung cancer (Grade 1C).[57]

However, the success of R-EBUS is related to whether the lesion and airway branch are connected, close, or far away. If the pulmonary nodule is not passed directly by the bronchi, which means there is no bronchial sign on CT, its diagnostic yield will be greatly reduced. Minezawa *et al.*[58] conducted a retrospective study and classified target lesions with bronchial accessibility on CT as type A, those without bronchial accessibility as type C, and those in between as type B. The corresponding positive diagnostic rates reported were 83.7%, 65.3%, and 28.6%, respectively, with significant statistical differences.[58] Several other studies have shown similar results.[36,59–67] The reason is that RP-EBUS cannot confirm the relative position of the lesion and bronchus. The diagnostic rate can be improved when the probe is completely inserted into the lesion. When the probe is only unilaterally close to the lesion, we cannot confirm the positional relationship between the probe and the lesion, which brings uncertainty to the direction of the biopsy. At that time, it is necessary to combine CT to determine the biopsy direction. A prospective randomized controlled trial showed that TBNA has a clear diagnostic advantage over TBLB and brush when the probe is close to the lesion.[68] The size and location of the lesions also have a great influence on the diagnostic rate. Several studies have confirmed that the diagnostic rate of lesions less than 2 cm, located in the upper lobe, and proximal to the chest wall would be reduced markedly.[37,63,66,69–74] There are other studies showing that solid nodules are associated with a higher diagnostic yield.[62,63,74] Dr Xu carried out a prospective study on the value of ROSE in the diagnosis of PPLs under EBUS guidance, and pointed out that ROSE could increase the diagnostic rate (85.7% *vs* 70.3%, $p = 0.018$) and shorten the operation time (24.6 ± 6.3 min *vs* 31.5 ± 6.8 min, $p < 0.01$).[75,76]

Moreover, because of the deficiency of working channel, after RP-EBUS locates and confirms the

lesion, the probe needs to be withdrawn before sampling, which may lead to deviation during the sampling process due to breathing movement or placement of biopsy instrument. To overcome this problem, a guide sheath (GS) was introduced into the EBUS probe. After locating the lesion, withdraw the probe with GS left *in situ* to ensure the biopsy from the right position. Nevertheless, Kramer and Annema,[70] Ho *et al.*,[77] and Huang *et al.*,[78] clarified that the diagnostic yield did not have an obvious improvement after the introduction of GS, which may be related to the movement or dislodgement of the sheath caused by stiff biopsy tools.[79] On the contrary, Oki *et al.*[80] conducted a multicenter randomized trial showing that histological specimens had a higher diagnostic yield in the GS group (55.3% *vs* 46.6%, $p = 0.033$), and the diagnostic yield of upper lobe lesions could be significantly improved upon using GS (63.1% *vs* 42.9%, $p = 0.003$).

Nowadays, the application of non-invasive analysis technology in EBUS-guided bronchoscopy to assist in the diagnosis of PPLs is emerging. As a non-invasive quantitative imaging analysis method, radiofrequency spectrum is of great significance in differentiating malignant or benign PPLs in EBUS-guided bronchoscopy. Ishiwata *et al.*[81] discovered that malignant PPLs had a lower intercept, lower midband-fit and higher slope than benign PPLs, with intercept showing the best diagnostic performance. In addition, confocal laser microendoscopy (CLE), known as 'optical biopsy', enables real-time observation of the cytological morphology of target lesions. Fuchs *et al.*[82] performed airway acriflavine staining in 32 patients with suspected neoplasma and used CLE to observe the airway lesions. They concluded that it could be distinguished from normal mucosa, inflammation, or regeneration and neoplastic tissue by the morphological features of the cytoplasm and nucleus, with an accuracy of 91.0%, a sensitivity of 96.0%, and a specificity of 87.1%.

Virtual bronchoscopy navigation

By uploading the preoperative CT to the computer workstation, virtual bronchoscopy navigation (VBN) can construct a three-dimensional image of the human bronchus, and design the optimal virtual bronchial approach to the target lesion. Shinagawa *et al.*[83] confirmed that the bronchi created by VB were highly consistent with those seen under ultrathin bronchoscopy. Miyoshi *et al.*[84] demonstrated that VBN could improve the diagnostic rate of PPLs (57.1% *vs* 33.3%, $p = 0.008$) through a retrospective study. On the contrary, Asano *et al.*[85] came to the conclusion that there was no significant difference in the diagnostic rate between the VBN-assisted group and the non-VBN-assisted group (67.1% *vs* 59.9%, $p = 0.173$) in a prospective multicenter controlled trial. Asano *et al.*[85] also noticed that VBN played a positive role in the diagnosis of PPLs in the right upper lobe and invisible in X-ray fluoroscopy, which are usually difficult to be diagnosed by other bronchoscopy technologies. The imaging quality of VBN depends on the preoperative CT data. Furthermore, since VBN is not a real-time imaging technology and lacks of a real-time adjustment for navigation errors, it is necessary to be assisted with locating technology. Lately, several studies have pointed out that the diagnostic yield of VBN combined with X-ray fluoroscopy for PPLs was 62.5–81.6%[83,86–89] and that combined with EBUS-GS was 63.3–84.4%.[90–94]

Like other bronchoscopy technologies, the size and location of PPLs are the determining factors for diagnostic yield. The lesions larger than 3 cm and located in the left lower lobe have a higher diagnostic sensitivity.[95,96] For the lesions smaller than 3 cm, the diagnostic sensitivity of non-solid lesions was evidently lower than that of solid and partially solid lesions (odds ratio = 0.161, 95% CI: 0.033–0.780, $p = 0.023$).[96]

As a well-developed bronchoscopy navigation technology, VBN is now trying to be applied in pre-procedure for EBUS-guided bronchoscopy. In order to evaluate the feasibility and effectiveness of pre-procedural VBN, Xu *et al.*[97] carried out a single-center prospective study. They verified that with VBN assistance did not clearly improve the diagnostic rate of PPLs (76.0% *vs* 65.5%, $p = 0.287$) but could shorten the operation time clearly (20.6 ± 12.8 min *vs* 28.6 ± 14.3 min, $p = 0.023$). Two other studies suggested similar results.[98,99]

Although VBN may improve diagnostic yield and shorten operation time, the technology is expensive and complicated so that not all hospitals are equipped. Currently, manual bronchial branch mapping techniques are emerging, which do not rely on the advanced navigational tools like VBN, and have been applied to EBUS-guided

bronchoscopy. Kho *et al.*[100] performed manual bronchial branch mapping of preoperative CT via the bronchial branch reading technology of DICOM software and then identified target lesions by EBUS according to the pre-planned airway road map, resulting in 98.9% successful rate. Our group created a hierarchical clock-scale hand-drawn mapping (HBN) for bronchoscopic navigation. That is, based on the 'clock' scale, mark each bronchial opening according to CT images, when the preoperative CT image spatial structure is consistent with bronchoscopic observation. We also conducted a comparative study between HBN and VBN, and the results showed that there was no significant difference in the diagnostic yield between the two groups (75.00% *vs* 61.90%, $p=0.25$), but the HBN group had a shorter planning pathway time (1.32 *vs* 9.79 min, $p<0.001$), total operation time (23.63 *vs* 28.02 min, $p=0.002$), as well as operating cost (758.31 ± 125.21 *vs* 1327.70 ± 116.25 USD, $p<0.001$).[101]

Electromagnetic navigation bronchoscopy

Electromagnetic navigation bronchoscopy (ENB) is a bronchoscopy navigation technology that utilizes electromagnetic effect for real-time guidance in a virtual tracheobronchial tree. To date, there are two systems: SuperDimension (Medtronic) and SPiNDrive (Olympus Medical Systems). ENB is designed to accurately locate the lesion and reach the vicinity of the lesion, making it available for the precise biopsy of PPLs.

Through a retrospective study, Brown *et al.*[102] figured out that the diagnostic rate of early lung cancer was increased meaningfully after the introduction of ENB (23.4% *vs* 40%, $p<0.0001$). By contrast, AQuIRE Registry found that the positive diagnostic rate was only 38.5% when using ENB alone, and even subgroup analysis suggested that ENB was associated with a lower diagnostic rate.[45] Besides, Chee *et al.*[103] revealed that EBUS combined with ENB improved the location of PPLs compared with EBUS alone (93% *vs* 75%), while did not promote the diagnostic rate (50% *vs* 43%). The lower diagnostic yield is in part related to the fact that accuracy of electromagnetic navigation is susceptible to respiratory motion. The probe position drifts and deviates from the actual position during respiration resulting in a discrepancy between the virtual and true anatomic location of the nodule. Most importantly, ENB alone cannot confirm the biopsy site within the lesion in real time like R-EBUS.

Recently, researchers have recognized the fact that ENB requires the support of X-ray fluoroscopy, CBCT or EBUS for adjustment before biopsy to achieve a higher diagnostic rate.[70,104–108] One-year data from a prospective, multicenter, global cohort study (NAVIGATE study) found that the diagnostic rate of ENB combined with pre-biopsy adjustment can reach 73%.[109] Studies have shown that PPLs with diameter $\geqslant 2$ cm and located in the upper lobe or middle lobe are important univariate predictors.[70,109,110] There is also an apparent correlation between morbidity and diagnostic yield in the study population.[70,111] Bellinger *et al.*[112] confirmed that the diagnostic sensitivity of Tsuboi I (bronchus directly enters into the lesion) and Tsuboi II (bronchus is infiltrated by the lesion) was significantly higher than Tsuboi III (bronchus curves around the lesion).

Two meta-analyses published by Folch *et al.*[111] and McGuire *et al.*[113] showed that the diagnostic rate of ENB after correction can reach 77% and 76.4%, respectively, and the risk of pneumothorax was less than 2%. However, the combination also increases the risk of radiation exposure to patients inevitably. Cho *et al.*[114] demonstrated the feasibility of ENB combined with O-arm imaging system for the diagnosis of PPLs. Nevertheless the study showed that an average of 4.33 O-arm rotations was required in each case, with an average radiation dose of 3.73 mSv, which is equivalent to a CT radiation dose.[114] Dramatic radiation exposure goes against the orientation of ENB.

To avoid the discrepancy and additional radiation exposure, the 4D ENB system was put into use. The 4D ENB system requires inspiratory and expiratory CT scans prior to operation and utilizes an electromagnetic tip-tracked biopsy instrument to perform real-time located biopsy. The study confirmed that the diagnostic yield was 68.3%, which was still lower than that of other bronchoscopy technologies in previous studies.[115]

Bronchoscopic transparenchymal nodule access

The presence of bronchial signs on CT has an important positive impact on the diagnosis of PPLs by bronchoscopy navigation technology. For that reason, bronchoscopic transparenchymal nodule access (BTPNA) has been designed to

improve the diagnostic rate of bronchial sign-negative PPLs. With the help of Archimedes VBN system (Bronchus medical, Inc, San Jose, California USA), establish a virtual bronchial image and select a virtual route. Subsequently, the operator uses a coring needle to puncture the point of entry (POE) and then dilates the accompanying balloon catheter. In this way, a vascularless channel from the bronchial wall to PPL is created. Through the created channel, the biopsy instruments can be introduced and reach the bronchial sign-negative PPLs successfully.

Silvestri *et al.*[116] demonstrated the feasibility and safety of BTPNA in canine models. Sterman *et al.*[117] made a study with 31 canine models, and verified the high diagnostic rate (90.3%) and low risk of BTPNA, without pneumothorax and moderate bleeding.

Herth *et al.*[118] performed the first human trial to evaluate the feasibility of BTPNA for entering the nodules and making biopsy. The study showed that 10 of 12 patients successfully created the channel and obtained sample, with no adverse events during the 6-month follow-up. The two failed PPLs were located in the apical section of the left upper lobe. Due to the limitation of the bronchoscope angulation and the proximity to the aorta and pulmonary artery, it was impossible to establish a straight-line tunnel. In addition, it was also pointed out that six of seven cases with PPLs invisible under fluoroscopy could be diagnosed by BTPNA. Harzheim *et al.*[119] also reported the same diagnostic rate, and two cases (33.3%) developed pneumothorax, of which one case (16.7%) required drainage. Recently, Sun *et al.*[120] conveyed that the diagnostic rate of BTPNA was significantly higher than that of guided TBNA (86.3% *vs* 67.2%), with the low incidence of pneumothorax (1.9%) and mild bleeding (1.0%) in a prospective single-arm multicenter study. Furthermore, for those lesions without bronchial signs, less than 2 cm, located in the upper lobe and proximal to the chest wall, which might be difficult to be diagnosed by other conventional bronchoscopy technologies, the diagnostic rate of BTPNA did not significantly decrease.

For bronchial sign-negative PPLs, BTPNA seems to be a promising method. Trials with large sample are needed to further verify the safety before it can be widely carried out.

Robotic-assisted bronchoscopy

Very recently, robot-assisted bronchoscopy not only improves the ability to locate the lesion but is capable to adjust the angle of TBNA, and also takes full advantage of radiology, such as C arm and cone beam CT. To date, there are two types of robotic-assisted bronchoscopy devised by distinct principles, namely Monarch system and Ion system.

Monarch system (Auris Health) is consisted of an inner scope and an outer sheath, the lesion can be reached via direct visualization. The bronchoscope can reach a more distal airway by 4-way steering control. The biopsy procedure is performed under the direction of the magnetic navigation system. Chen and colleagues compared the efficacy of Monarch robotic endoscopic system and thin conventional bronchoscopy with the same outer diameter in human cadaveric lungs. The study demonstrated that the robotic bronchoscopy can enter the eighth generation bronchi on average, much higher than thin bronchoscopy.[121] Chen and colleagues then successfully diagnosed 97% of lung lesions in cadavers by Monarch system and concluded that neither lesion diameter, appearance in EBUS, nor distance from the chest wall would affect the diagnostic yield.[122] Rojas-Solano *et al.*[123] performed the Monarch robotic system in humans for the first time and identified 93.3% of pulmonary nodules without the occurrence of pneumothorax or severe bleeding. A multicenter retrospective study held in the United States suggested that the diagnostic rate of Monarch robotic system ranged from 69.1% to 77% (conservative and maximum estimate). The performance of nodules in EBUS was a predictor of diagnostic yield, whereas diameter, density, and location were not.[124] Recently, the first prospective, multicenter study (BENEFIT) to evaluate the efficacy and safety of the Monarch system noted a 96.2% localization accuracy rate and a 3.7% incidence of pneumothorax, of which 1.9% required drainage.[125]

For the other type of robotic-assisted system, that is Ion system (Intuitive Surgical), the outer tube equipped with a camera can reach the lesion by four-way steering control. The real-time virtual shape of the catheter is the predominant indicator to confirm it is in the right place, followed by the validation through fluoroscopy. The biopsy is carried out after removing the

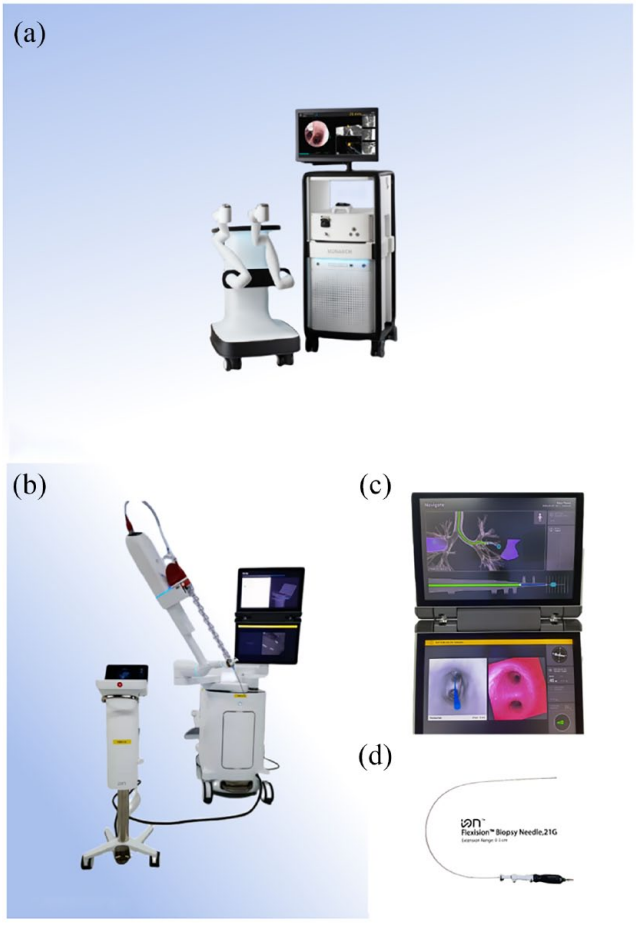

Figure 2. The image of Monarch System (a) and Ion System (b). (c) The working interface of Ion system. (d) The biopsy needle for Ion system (21G). (The image of Monarch System is from the Internet.)

visualizing optic. Fielding *et al.*[126] first used Ion system in humans and included 29 patients totally. Among the PPLs with an average diameter of 1.2 cm and bronchial sign absent of 41.4%, the overall diagnostic rate was 79.3%, and the diagnostic rate for malignancy was 88%. There were no pneumothorax or excessive bleeding events in the trial. A prospective randomized comparative trial showed that the diagnostic rate of Ion robotic system guidance was clearly higher than that of ENB ($p = 0.022$) and RP-EBUS ($p < 0.001$) guidance[127] (Figure 2).

Of note, both systems require a controller, and also require a C-arm or cone beam CT to confirm the position of biopsy instruments. Robot-assisted bronchoscopy uses remote direction control instead of manual control, but in fact it still relies on human judgment and operation.

Emerging insights beyond biopsy approaches and advanced guided bronchoscopy

LDCT is considered an important screening tool for lung cancer, but its high false-positive rate means that many patients are unnecessarily subjected to invasive diagnostic testing. To reduce unnecessary invasive examinations, our team established a diagnostic classifier combining chest CT features with large airway epithelium transcriptomics signatures obtained by bronchial brush.[128] The results suggested an area under the curve (AUC) of 0.903, a sensitivity of 90.0%, a negative predictive value (NPV) of 0.811, and a positive predictive value (PPV) of 0.851.[128] The advanced model can availably predict the risk of malignant lung nodules, and has a tendency to exclude diagnosis due to its high NPV. Moreover, the classifier performed well regardless of lesion size, location, or smoking status.

Currently, Lambin *et al.*[129] from Holland proposed the concept of radiomics that do not rely on bronchoscopy. He attempted to capture intratumoral spatial and temporal heterogeneity through non-invasive imaging method, which might be related to genomic and proteomics patterns. Many scholars have made contributions to the application of radiomics in the diagnosis of pulmonary nodules. Dhara *et al.*[130] identified benign and malignant nodules of 891 patients by quantifying the imaging characteristics, with an accuracy of 95.05%. Chen *et al.*[131] extracted 76 features that were statistically significant in identifying the diagnosis from 750 imaging features and precisely predicted 84% of pulmonary nodules. Wu *et al.*[132] and Zhu *et al.*[133] set up the radiomic trait for histologic subtype classification, and the AUC can reach 0.893 in the validation cohort.[133] In addition, a recent review described a clear correlation between radiomics and genomics, and established radiogenomics to identify the molecular biological basis of imaging phenotypes.[134] At present, the radiomics technology is still in the stage of being further verified and improved.

Limitations

This review mainly discusses the current blue map of diagnostic techniques for PPLs. Although the relevant literatures have been read in detail, since emerging new technologies developed rapidly, it is possible that a few latest technologies are not fully covered in this review.

Conclusion

The innovation of advanced bronchoscopy techniques has vastly contributed to the diagnosis of PPLs, while their combination with fluoroscopy is still the key point to improve the diagnostic rate. In the future, additional efforts are in urgent need in the following aspects: (1) devise more precise navigation systems to accommodate respiratory motion; (2) visualization of the guidance-location-biopsy steps with minimum radiation exposure; (3) improve biopsy instruments, including TBNA needle; (4) employ minimally invasive and non-invasive technologies, and consider adopting artificial intelligence (AI) technology; (5) PPLs ablation right after diagnosis is also an important objective; and (6) carry out further studies to verify the value of emerging technologies such as BTPNA and robotic bronchoscopy. With unmet clinical needs in the diagnosis of PPLs, we as interventional pulmonary physicians should keep on learning and devising new techniques, and inheriting and utilizing old methods. Clinical practitioners, researchers, and industry should work together to improve the long-term survival of lung cancer.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Yang Xia: Conceptualization; Writing – review & editing.

Qin Li: Writing – original draft.

Changgao Zhong: Writing – original draft.

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