The Evolution of Transbronchial Lung Biopsy Guidance

Mohamad Fahmi Alatas, Asri Liqditta Bies*, Prasenohadi, Dicky Soehardiman, Wahju Aniwdyaningsih, Mia Elhidsi, Ginanjar Arum Desianti, Tina Reisa, Menaldi Rasmin

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Persahabatan General Hospital, Jakarta

Corresponding Author:
Asri Liqditta Bies | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Persahabatan General Hospital, Jakarta | biesasriliqdita@gmail.com

Submitted: January 15th, 2024
Accepted: March 3rd, 2025
Published: March 8th, 2025

Respir Sci. 2025; 5(2): 141-52
https://doi.org/10.36497/respirsci.v5i2.170

Creative Commons Attribution-NonCommercial 4.0 International License

Abstract

Histological confirmation of lung lesions is necessary prior to determining further management. Imaging preparation is needed to find the biopsy site such as a computed tomography scan. Imaging helps to trace the position of lung lesions that are peripheral and not visualized by bronchoscope. However, along with the discovery of small lesions and peripheral location, two-dimensional imaging alone remains suboptimal. Therefore, to reach lung lesions peripherally would need to a guide through the bronchial. Subsequently, the method of guiding transbronchial biopsy evolved. Namely, real-time fluoroscopy, radial-probe endobronchial ultrasound, virtual bronchoscopy navigation and electromagnetic bronchoscopy navigation are guiding modalities with each of their advantages and disadvantages. Several biopsy modalities are used in combination to increase the accuracy of diagnosis. Careful analysis in planning and an understanding of the limitations and advantages of diagnostic modalities must be considered in deciding which method to choose.

Keywords: bronchoscopy, peripheral pulmonary lesions, transbronchial biopsy

INTRODUCTION

Lung cancer contributes 9.5% of all incidence of cancer of both sexes in Indonesia, leading into the second rank but first ranked of mortality.[1] For many years, lung biopsy was performed surgically. However, when solitary pulmonary nodules were routinely resected, it turned out that half of them were benign and did not require surgery with its side effects. This is why there is a demand for histological confirmation before surgery. The challenge is to find the path to the lesion because calculating the location of the lesion from an X-ray or computed tomography scan (CT scan) and trying to approach it only with an endoscopic view has a very low success rate.[2]

Real-time control of transbronchial biopsy under fluoroscopy showed better visualization. Although it provides good visualization, large radiation associated with duration exposure is a drawback. Thus, the development of transbronchial

biopsy techniques continues to occur in order to improve the accuracy of diagnosis.[2]

Bronchoscopy can be divided into diagnostic and therapeutic procedures. Diagnostic bronchoscopy has been mostly performed as a basic procedure by pulmonologists in proving lung lesions. Simple bronchoscopy procedures have been carried out in many hospitals, while advanced procedures are only done in referral hospitals. Another peripheral pulmonary lesion (PPL) biopsy is a transthoracic lung biopsy with the lesion attached to the chest wall. Currently, there are several guided biopsy methods for PPLs such as CT scan, fluoroscopy, radial probe endobronchial ultrasound (RP-EBUS), electromagnetic bronchoscopy navigation (EBN), and virtual bronchoscopy navigation (VBN).[3]

TRANSBRONCHIAL LUNG BIOPSY

Peripheral pulmonary lesion is non-directly visible through bronchoscopy. It is often an accidental finding while screening lung cancer with low-dose CT scans. The location, size of the lesion, and sampling technique play a role in the diagnostic result. Small PPL <2 cm gives a diagnostic yield of only 30%. While lesions >4 cm give a diagnostic yield of up to 80%.[2,3]

The positivity rate was reported to increase using advanced imaging and navigation techniques by up to 74% for small PPL <2 cm. Intuitively, bronchoscopists think that achieving good positivity depends on the proximity of the lesion to the airway, the angle at which it is located, and the number of samples taken.[2,3]

A meta-analysis by Rivera et al mentioned transbronchial needle aspiration biopsy (TBNA) in combination with TBB was superior to TBB alone. Operators usually estimate the three-dimensional bronchi regarding a two-dimensional planar axial section of the CT scan. Sometimes this method is less accurate for more peripheral bronchi than subsegmental bronchi. Diagnostic results depend not only on the size of the lesion but also on bronchus signs on CT scans, fluoroscopic visibility, and operator skills.[3]

Transbronchial lung biopsy (TBLB) is a biopsy procedure obtaining lung nodules by using flexible forceps positioned distally through a working channel of flexible bronchoscopy. The procedure can be obtained with or without guidance. Blind TBLB called for without guidance lung biopsy typically for lung parenchyma diffuse disease. This modality requires a unique technique and is not often used as it has considerable additional risks such as sensory feedback from a moderately sedated patient.[4]

Guided TBLB is depicted as a biopsy with imaging, such as fluoroscopy as confirmation precise position of biopsy tools through a working channel of a bronchoscope. The diagnostic yield increased by several specimen collections around 6-10 specimens. When performed with bronchial brushing and needle aspiration biopsy may increase the diagnostic yield. The success of lung

transplantation also has a role for transbronchial biopsy in determining cellular contraindications.[4]

Recently, a conventional TBLB refers to TBLB with CT scan guidance and confirmation under fluoroscopy. Peripheral pulmonary lesions, particularly beyond the sub-segmental bronchi, are more difficult than the central lesion. The bronchoscope and biopsy instrument passes through the bronchi and branches reaching the biopsy target. Therefore, innovation was carried out and developed because the diagnostic value of conventional transbronchial biopsy is not good, especially in very peripheral lesions. Plus, the lesion is less than two centimeters.[4,5]

Indications and Contraindication

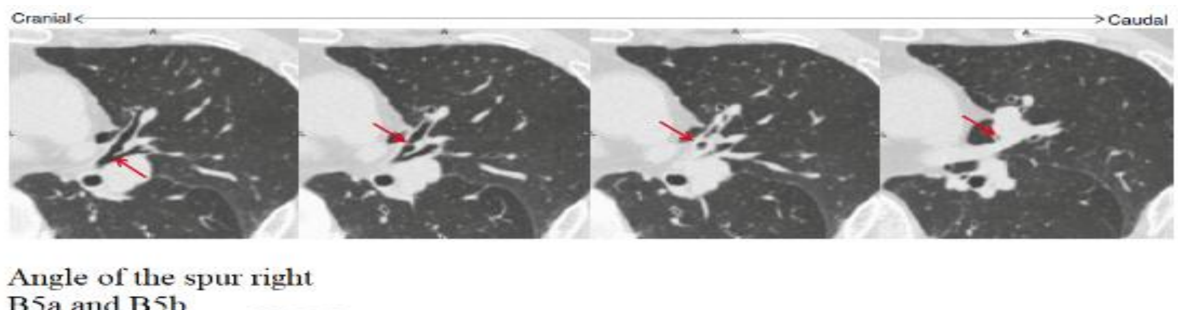
A transbronchial lung biopsy can be performed in focal and diffuse lung diseases. High-resolution computed tomography (HRCT) and CT scan findings in diffuse lung pathology may be an indication for a transbronchial lung biopsy. However, clinical correlation and other non-invasive diagnostic considerations should be made beforehand. In focal lung lesions with a peripheral location, CT scan-guided identification and localization can aid in identification. The use of the procedure together with fluoroscopy and the development of navigation technologies such as VBN, ENB, and cone beam computed tomography can increase the positivity rate of TBB.[2,6]

The most common complications of the TBLB procedure were bleeding (<4%), pneumothorax (<2%), and death (<0.05%). The risk of bleeding can increase to 89% in patients taking anticoagulant drugs, so if a TBLB is still needed, anticoagulant administration should be stopped five days before the procedure. Severe hypoxemia despite oxygen administration, unstable cardiovascular status, no patient consent, and unavailability of trained resources and equipment are absolute contraindications.[2,4]

Meanwhile, relative contraindications are a cough that is not controlled with drugs, hypercoagulation, thrombocytopenia, renal failure, large pulmonary blisters, and malformations of blood vessels at the site of the lesion. Pulmonary hypertension is still debated as a contraindication.[2,4]

Procedure Preparation Guidance

Kurimoto defines the bronchial tree reading method in CT scans into three steps. The first step is to observe the lung field from the apex to the diaphragm and then determine the lesion's location to be the biopsy's target. The second step follows the outline of the bronchial tree via the axial section of the lung window. Follow from the trachea to the carina then move to the right and left main bronchi and their branches. Observations following the bronchial route to the target lesion for biopsy can be repeated to confirm the location. For example, the lesion is located on B5a and B5b mainly occupying B5b as seen in Figure 1.[7]



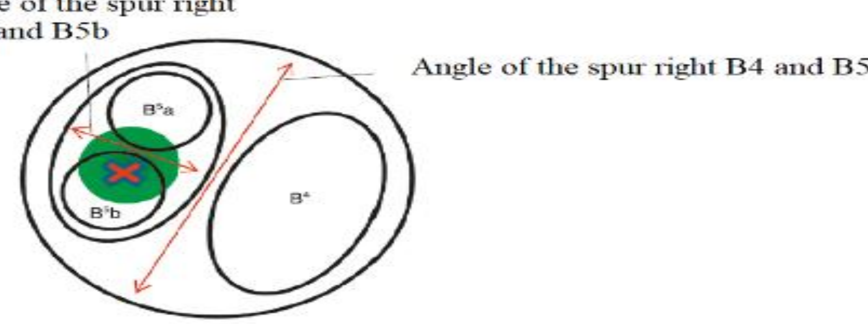


Figure 1. Middle lobe bronchial branch[7]

Biopsy was directed at B5b. On a CT scan, the first branches of the middle lobe bronchus go to B4 and B5. After finding the branching angles of B4 and B5 then follow them in a medial direction. An axial CT scan is followed caudally until a biopsy target lesion is seen.[7]

The third step is to rotate and reverse the position of the CT scan image so that the position of the lesion is in the same direction as the bronchoscope visualization. For example, a lesion located in the middle lobe, lingula, right and left lower lobe makes it easy to read the location by reversing the CT scan image. For the upper lobe left lung lesion rotate 90^0 clockwise axial lung window CT scan then follow the left main bronchus from caudal to cranial. The bronchoscope visualization will be similar to the direction of the CT scan.[7,8]

A systematic review and meta-analysis in 2018 showed that the guidance of bronchial signs on CT scans correlated with better diagnostic values compared to those without bronchial signs. However, there are some confounding factors such as the size and distance of the lesion from the hilum as a determinant of TBLB.[7,8]

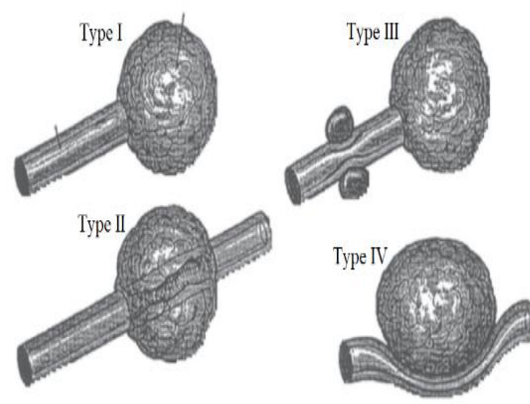


Figure 2. Bronchus sign classification by Tsuboi[2]

Tsuboi classified bronchial signs into four types (Figure 2). The first type is the bronchial lumen over to the lesion. Type two, where the lesion grows to enfold the bronchi into the lumen. The biopsy technique for type 2 involves inserting forceps deep enough into the lesion.[2,9]

Type three is bronchi compressed by the lesion so that the bronchial lumen is

narrowed and there is no infiltration of the lesion into the bronchial lumen. This type is impossible to reach the lesion so it often gives a negative result. Type four is narrowed proximal bronchial lumen due to infiltration of the lesion into the bronchial sub-epithelium or due to suppression of lymph nodes while the lesion is distal to the bronchial lumen. This type makes it difficult for the forceps to enter the distal lumen.[2,9]

TRANSBRONCHIAL LUNG BIOPSY WITH FLUOROSCOPY GUIDANCE

Fluoroscopy is designed to display the shadow of the body's organs at the actual time. Important components of fluoroscopy are X-ray tubes and shadowing devices that are connected to the monitor screen. A common type of fluoroscopy is the C-Arm type, an arm-shaped letter c. Fluoroscopy C-arm consists of an x-ray tube beneath the patient's table and a shadow capture above the patient's table. This position is called the under-couch position and provides the least radiation exposure.[2]

Radiation hazard effects on patients are derived from the light fraction absorbed into the body's organs while health workers come from scattered radiation. The modern fluoroscopy system has an element that can minimize the light fraction without reducing the quality of the image. Measurement several times becomes a method that can reduce radiation exposure during biopsy procedures.[2]

Fluoroscopy serves to confirm forceps instruments to generate good diagnostic results. The operator performs bronchial inspection and its branches. This is to see endobronchial abnormalities while determining the location of the biopsy according to the CT scan guidance. The flexible bronchoscopy is then directed to the intended segmental bronchus. Furthermore, forceps are inserted into the bronchoscope through a working channel.[2,3]

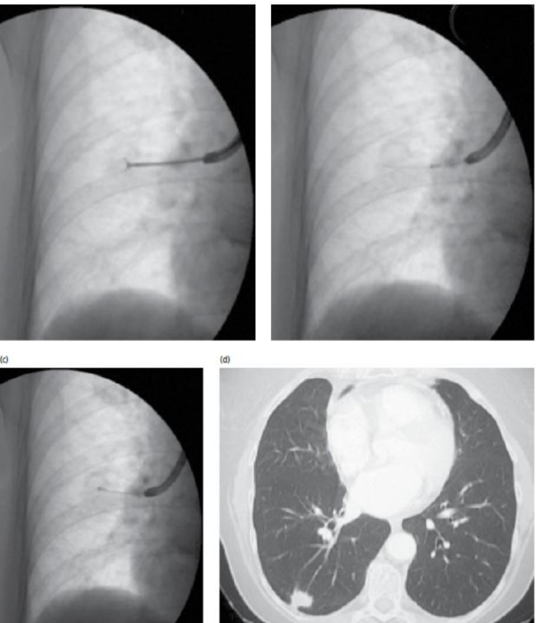


Figure 3. Biplane fluoroscopy to obtain lung specimens from selected areas[2]

Once the forceps have been seen distally from the working channel and precisely in the right subsegmental bronchi, fluoroscopy is activated to confirm the position. Forceps then gently push forward until resistance to confirm the distal of the bronchus branch. Forceps retracted around one centimeter for the space to open the forceps' jaw. Then gently push forward the open jaw forceps and grip for sampling for a while to

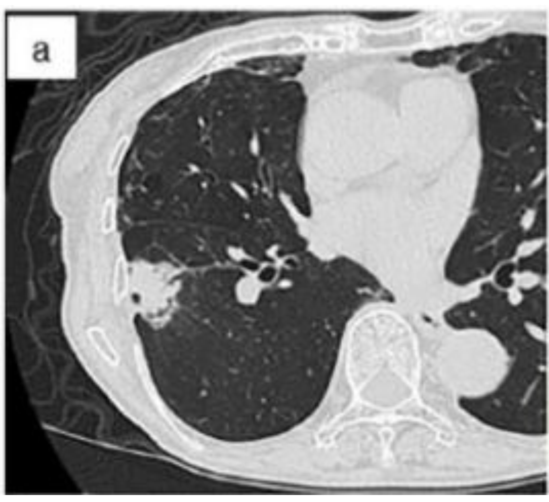
minimize bleeding. Forceps are then pulled with the technique of turning the bronchoscope. Biplane fluoroscopy can be seen in Figure 3. At the end of the biopsy, it is necessary to do a fluoroscopy to confirm pneumothorax as a complication.[2,3]

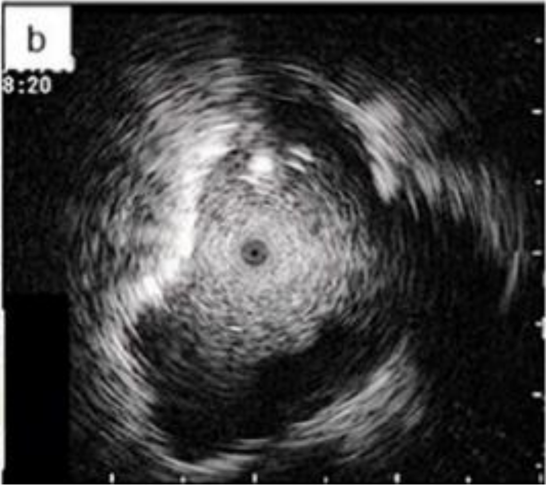
TRANSBRONCHIAL LUNG BIOPSY WITH RADIAL PROBE ENDOBRONCHIAL ULTRASOUND

Radial probe endobronchial ultrasonography (RP-EBUS) is a flexible catheter with a straight-shaped probe ultrasonography at the distal end of the catheter that can be rotated 360^0 to provide a circular sonographic picture. This tool is widely used to confirm the location of PPL before carrying TBLB, especially without a clear bronchus sign on the CT scan. The size of the RP-EBUS with an outer diameter of 1.4 mm is very small so it can easily reach the most peripheral bronchi branch.[10,11]

The position of RP-EBUS in the middle of the lesion as shown in Figure 4b gives a better diagnostic value than the adjacent or proximal position of the lesion Figure 4c. The positivity rate reached 86.7%. Several factors that affect the diagnostic yield of RP-EBUS have been identified including lesions and the location of the lesion as well as the location of the radial probe in relation to the lesion.[10,11]

The advantage of RP-EBUS guidance is the ability to accurately and in real-time identify PPL. The operator can observe the position of the probe within the lesion, adjacent to the lesion, or away from the lesion. When inspecting with RP-EBUS, if the bronchi are in or next to the lesion, then a biopsy guided by the EBUS guide sheet (GS) can produce good diagnostic value with minimal complications.[2,10]





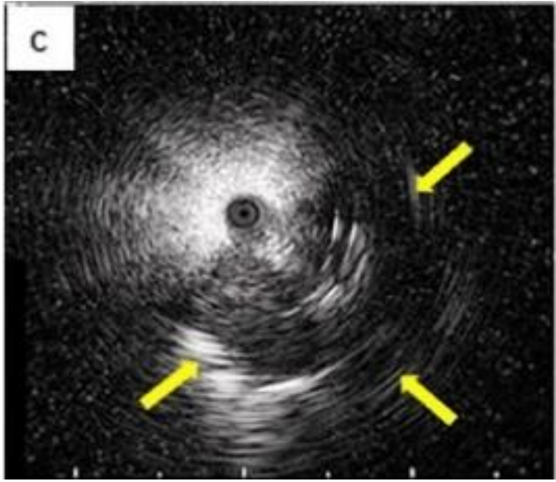


Figure 4. Bronchus sign and RP-EBUS image[10]

The key to this method is ensuring that the bronchoscope remains in its last position while the RP-EBUS is visualizing the target lesion for the biopsy. A plastic sheath called the GS makes it even easier for the forceps to reach the lesion when the radial probe is removed from the working channel.[2,10]

Observe endobronchial in three distances when bronchoscopy visualization showed abnormalities. Distance view to observe the condition of the surrounding bronchial mucosa. Intermediate view to observe the distribution of blood vessels using narrow-band imaging (NBI) features. Close view to observe the pattern of blood vessels. When the lesion is visualized with EBUS, the entire lesion is scanned by moving the probe from distal to proximal. Observe the structures within the lesion, such as echo view, vascular structure, and hyperechoic line boundaries.[2]

Classification of EBUS images is divided into three types. Type I is a homogeneous appearance divided into types Ia and Ib. Type Ia is a homogeneous appearance with patent blood vessels without compression. This type is thought to be an acute inflammation such as pneumonia. Type Ib is a homogeneous appearance without a blood vessel appearance. This type is thought to be chronic inflammation.[7]

Type II is a hyperechoic appearance inside the lesion divided into type IIa and IIb. Type IIa is hyperechoic without blood vessels and type IIb is hyperechoic with blood vessels. Type III is a heterogeneous appearance divided into types IIIa and IIIb. Type IIIa is a heterogeneous appearance spread linearly as if the bronchial lumen is compressed. Type IIIb is a non-linear heterogeneous appearance with a presumably poorly differentiated solid lesion.[7] This classification can be seen in Table 1.

Peripheral lesions that are not visualized on RP-EBUS have a low diagnostic yield when the biopsy is performed without other guidance. Another cause of the non-visible PPL is its location in the upper lobe, so it is difficult for GS to reach. Another cause is beyond the peripheral location close to the visceral pleura so the GS cannot reach until the smallest endobronchial.[11,12]

Table 1. The classification of EBUS images[7]

Type	I		II		III	
Internal echo	Homogeneous		Hyperechoic points		Heterogeneous	
Subtype	Ia	Ib	IIa	IIb	IIIa	IIIb
Open vessel	o	---	---	o	---	---
Hyperechoic linear echo	o	---	---	---	o	---
EBUS						

Xu et al revealed similar results to the study by Yamada et al, RP-EBUS TBB guidance diagnostic results depending on the position of the probe in the lesion. If the position of the probe is in the lesion it will give the best results compared to a position near or even far from the lesion. Guidance RP-EBUS coupled with GS is to provide the best diagnostic results with minimal complications.[11,12]

VIRTUAL BRONCHOSCOPY NAVIGATION

Virtual navigation bronchoscopy is a three-dimensional bronchoscopy method with virtual guidance of the bronchial route and its branches to reach the target biopsy lesion. Virtual navigation is carried out using software that has been applied to the system. The procedure of VBN consists of planning and guidance. The planning phase is the process before bronchoscopy by preparing virtual images of the bronchi and their branches to the target lesion for the biopsy. The guidance phase is the procedure of virtually directing the bronchoscope to the lesion. Currently, several navigation system products can be used by Japanese manufacturers (Bf-NAVI®) and the United States (LungPoint® and DirectPath®).[13,14]

Image from DirectPath® (Figure 5), an axial lung window CT scan shows the target location in the right eighth segment and is marked with a red circle. The bronchi and their branches are extracted by the system at the planning stage and shown in blue lines. The additional bronchial tree can be extracted manually. The blue line in the bronchial tree is the virtual route to the target lesion. The yellow circle represents the tip of the virtual bronchoscope. The green line extending from the yellow circle represents the virtual bronchoscope direction. On the left side of the image is a screen view of a virtual bronchoscope which can be compared with the view of a real bronchoscope. In this case, the figure shows the fifth generation of the bronchial tree and the blue line goes to the right B8aiiαγ.[13,14]

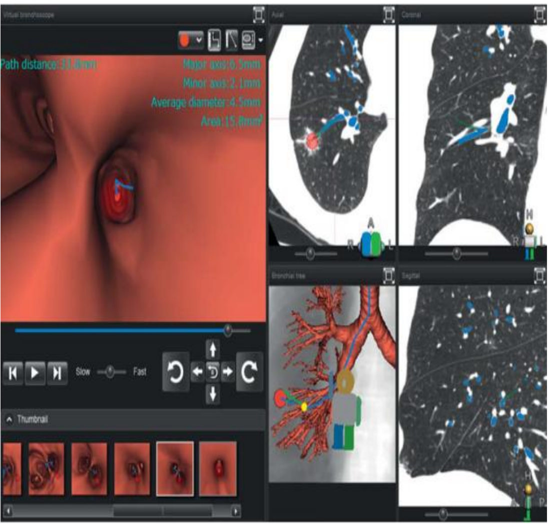


Figure 5. Virtual bronchoscopy navigation image[15]

A prospective randomized controlled trial concluded that the diagnostic value is up to 80% in small PPL measuring less than 30 mm in combination with VBN and RP-EBUS guidance. Several factors have yet to be proven between the positivity of the diagnostic results and virtual navigation guidance. These factors are the difference in lung volumes when holding a full inspiratory breath when a CT scan was performed. Meanwhile, when bronchoscopy is performed, the breathing condition is spontaneous so that

navigational discrepancies can occur, such as the normal narrowing of the bronchi during the breathing process.[13]

ELECTROMAGNETIC BRONCHOSCOPY NAVIGATION GUIDANCE

The first attempt at EBN in humans was in 2006.[14] Electromagnetic bronchoscopy navigation is a three-dimensional virtual navigation method of bronchial trees based on CT scan images. An electromagnetic sensor is attached to the distal bronchoscope through the working channel. A flat board is placed under the patient's bed cushion to emit electromagnetic waves, ensuring the biopsy target lesion will be captured in a square prism.[11,16]

The EBN method is not only useful for very peripheral lesions but also for small central lesions. Currently, there are two electromagnetic navigation software, namely superDimension® and SPiNDrive®. In principle, the EBN navigation system is like airplane navigation. The EBN guidance method consists of two stages consist of planning and procedures.[11,16]

Successful of the procedure depends on a good planning stage. The software reconstructs a three-dimensional view which is an axial, coronal, and sagittal view based on the CT scan results. The operator controls the bronchoscope according to virtual endobronchial guidance while comparing the actual view. The path to the target biopsy lesion is then determined by means of a cross. The planning stage data that has been made is then stored. At the procedure stage, the bronchoscope is directed toward the lesion then the guide sheet and locatable guide are inserted into the working channel. A locatable guide will provide position data to the system.[16]

A meta-analysis study in 2014 showed that EBN represents 65% of diagnostic value. Several factors contributed to the higher value such as the lesion size of more than 30 mm and the presence of bronchial signs. Pneumothorax occurs in around 3.1%, and bleeding with mild to moderate variations of around 1.6% are complications of the EBN method.[11]

Data collected in Hong Kong in 2019 shows that the diagnostic value of BNE is higher for lesions not visualized with RP-EBUS or fluoroscopy. One of the weaknesses of the EBN method is the high operational costs. Therefore, best planning is needed especially for a small probability of diagnostic value.[17]

OTHER TRANSBRONCHIAL LUNG BIOPSY GUIDANCE

The latest innovations in achieving biopsy target lesions are bronchoscopy trans-parenchymal nodule access (BTPNA)/transbronchial access tool (TBAT). A clinical trial that has been carried out since 2018, EAST-2 assessed the benefits and safety of the BTPNA method. The first human case report was by Herth and colleagues.[11,18]

Herth demonstrated sampling using a combination of Archimedes guidance and

fluoroscopy, although some samples were unable to see nodules by fluoroscopy giving the best diagnostic value of 83%. The BTPNA method can be used for lesions that are more centrally located or without bronchial signs.[11,18]

The BTPNA technique creates a path to a peripheral lesion through the lung parenchyma. This technique is integrated with Archimedes. Archimedes is a VBN system integrating bronchoscopy, CT scan data, and continuous fluoroscopy views to generate real-time airway views in a three-dimensional construct. A coring needle punctures the planned entry based on BTPNA guidance and then is dilated by a balloon catheter. The blunt dissection style sheath is inserted into the biopsy target. The BTPNA method increases the ability to access peripheral lung lesions with bronchoscopy. However, further research is still needed to assess its diagnostic positivity and safety.[11,18]

Robotic bronchoscopy is now being developed. This guidance was first performed in humans by Fielding et al. The advantage of robotic bronchoscopy is that it maintains the stable position of the flexible bronchoscope when peripheral lesions are visualized so that the lesion can be seen continuously and facilitates biopsy. There were several clinical trials of robotic bronchoscopy for the diagnosis of PPLs, including NCT04182815 and NCT04740047. Those clinical trials had been completed but are still in review to be published.[11,19]

CONCLUSION

Various transbronchial biopsy guidance continues to be developed to achieve the best diagnostic results for PPL. Pre-procedure planning following guidance are the two common steps. The diagnostic results are higher if there are bronchial signs at the pre-procedure stage based on a chest CT scan. Careful analysis in planning and an understanding of the limitations and advantages of diagnostic modalities must be considered in deciding which method to choose

REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63.
2. Wang KP, Mehta AC, Turner JF. Flexible Bronchoscopy. 4th ed. Wiley-Blackwell; 2020.
3. Livi V, Barisione E, Zuccatosta L, Romagnoli M, Praticò A, Michieletto L, et al. Competence in navigation and guided transbronchial biopsy for peripheral pulmonary lesions. Panminerva Med. 2019;61(3):280–9.
4. Küpeli E, Feller-Kopman D, Mehta AC. Diagnostic Bronchoscopy. In: Murray and Nadel's Textbook of Respiratory Medicine. Elsevier; 2016. p. 372-382.e5.
5. Ost DE, Ernst A, Lei X, Kovitz KL, Benzaquen S, Diaz-Mendoza J, et al.

Diagnostic Yield and Complications of Bronchoscopy for Peripheral Lung Lesions. Results of the AQuIRE Registry. Am J Respir Crit Care Med. 2016;193(1):68–77.
6. Wahidi MM, Rocha AT, Hollingsworth JW, Govert JA, Feller-Kopman D, Ernst A. Contraindications and Safety of Transbronchial Lung Biopsy via Flexible Bronchoscopy. Respiration. 2005;72(3):285–95.
7. Kurimoto N, Morita K. Bronchial Branch Tracing. Springer Singapore; 2020. 4–18 p.
8. Ali MS, Sethi J, Taneja A, Musani A, Maldonado F. Computed Tomography Bronchus Sign and the Diagnostic Yield of Guided Bronchoscopy for Peripheral Pulmonary Lesions. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2018;15(8):978–87.
9. Imabayashi T, Matsumoto Y, Uchimura K, Furuse H, Tsuchida T. Computed Tomography Bronchus Sign Subclassification during Radial Endobronchial Ultrasound-Guided Transbronchial Biopsy: A Retrospective Analysis. Diagnostics. 2023;13(6):1064.
10. Kurihara Y, Tashiro H, Takahashi K, Tajiri R, Kuwahara Y, Kajiwara K, et al. Factors related to the diagnosis of lung cancer by transbronchial biopsy with endobronchial ultrasonography and a guide sheath. Thorac Cancer. 2022;13(24):3459–66.
11. Ishiwata T, Gregor A, Inage T, Yasufuku K. Bronchoscopic navigation and tissue diagnosis. Gen Thorac Cardiovasc Surg. 2020;68(7):672–8.
12. Herth FJF, Ernst A, Becker HD. Endobronchial ultrasound-guided transbronchial lung biopsy in solitary pulmonary nodules and peripheral lesions. European Respiratory Journal. 2002;20(4):972–4.
13. Ernst A, Anantham D. Bronchus Sign on CT Scan Rediscovered. Chest. 2010;138(6):1290–2.
14. Schwarz Y, Greif J, Becker HD, Ernst A, Mehta A. Real-Time Electromagnetic Navigation Bronchoscopy to Peripheral Lung Lesions Using Overlaid CT Images. Chest. 2006;129(4):988–94.
15. Asano F, Eberhardt R, Herth FJF. Virtual Bronchoscopic Navigation for Peripheral Pulmonary Lesions. Respiration. 2014;88(5):430–40.
16. Leong S, Ju H, Marshall H, Bowman R, Yang I, Ree AM, et al. Electromagnetic navigation bronchoscopy: A descriptive analysis. J Thorac Dis. 2012;4(2):173–85.
17. Cheng SL, Chu CM. Electromagnetic navigation bronchoscopy: the initial experience in Hong Kong. J Thorac Dis. 2019;11(4):1697–704.
18. Harzheim D, Sterman D, Shah PL, Eberhardt R, Herth FJF. Bronchoscopic Transparenchymal Nodule Access: Feasibility and Safety in an Endoscopic Unit. Respiration. 2016;91(4):302–6.
19. Giri M, Dai H, Puri A, Liao J, Guo S. Advancements in navigational bronchoscopy for peripheral

pulmonary lesions: A review with special focus on virtual bronchoscopic navigation. Front Med (Lausanne). 2022;9:989184.