


Diagnostic Value of Virtual Bronchoscopic Navigation Combined With Endobronchial Ultrasound Guided Transbronchial Lung Biopsy for Peripheral Pulmonary Lesions

Technology in Cancer Research & Treatment
 Volume 20: 1-6
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 DOI: 10.1177/1533033821989992
journals.sagepub.com/home/tct


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Abstract

Objective: X-ray guided transbronchial ultrasound-guided transbronchial lung biopsy (EBUS-TBLB) can improve the diagnostic yield of peripheral pulmonary lesions (PPLs), but it needs special requirements. The purpose of this study was to investigate the clinical value of virtual bronchoscopy navigation (VBN) combined with EBUS-TBLB in the diagnosis of PPLs without X-ray guidance. **Methods:** The 105 patients with PPLs underwent EBUS-TBLB with or without VBN randomly. The diagnostic yield, the operation time and complications were evaluated in the 2 groups. **Results:** No significant difference was found between the VBN+EBUS group and the EBUS group (76.0% vs. 65.5%, $P = 0.287$). The operation time of VBN+EBUS group was significantly shorter than that of EBUS group (20.6 ± 12.8 min vs. 28.6 ± 14.3 min, $P = 0.023$). No severe procedure related complications occurred. **Conclusions:** VBN can shorten the operation time. The combination of VBN and EBUS-TBLB is a safe and effective diagnosis technique for PPLs.

Keywords

endobronchial ultrasound, virtual bronchoscopic navigation, peripheral pulmonary lesions, transbronchial lung biopsy, diagnosis

Received: September 21, 2020; Revised: December 16, 2020; Accepted: December 29, 2020.

How to diagnose the PPLs quickly and accurately has always been a clinical difficulty.¹ Computed tomography-guided percutaneous lung biopsy has a high diagnostic yield and is used to diagnose the peripheral lung diseases, but it is often accompanied by pneumothorax, hemorrhage and other complications.^{2,3} Transbronchial lung biopsy (TBLB) has fewer complications, but the diagnostic yield of peripheral lung lesions is lower.⁴ In recent years, VBN has been applied in clinical practice. Many studies showed that VBN combined with EBUS can improve the diagnosis yield of peripheral lung diseases, but VBN combined with EBUS-TBLB is rarely used in PPLs.⁵⁻⁹ The aim of this study was to investigate the clinical value of VBN combined with EBUS-TBLB in the diagnosis of PPLs.

Materials and Methods

Patients

A total of 105 patients with PPLs were recruited, who underwent EBUS-TBLB alone or combined with VBN from January

2016 to December 2017. Inclusion criteria: the diameter of PPLs ≤ 30 mm, and no lesion was found under bronchoscope.

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Exclusion criteria: patients with cerebral hemorrhage and myocardial infarction in the past 3 months; patients with active hemorrhage and severe cardiopulmonary insufficiency can not tolerate bronchoscopy and do not cooperate with them. The patients were randomly divided into VBN+EBUS group (50 cases) and EBUS group (55 cases). Since other studies have shown that the diagnostic yield is related to the size of the lesion and the doctor's skills, the randomized grouping was based on the size of the lesion, and bronchoscopy physicians adopt a randomized grouping design to ensure that these factors were balanced in the study group. Independent, blinded, trial staff randomly assigned the patients before bronchoscopy. All patients underwent chest computed tomography (CT) before EBUS (Figure 1). The study protocol was approved by the ethics committee of Nanjing Chest Hospital (approval no. NJXK16208). All subjects were fully informed of the examination content, risk and signed the informed consent.

Procedure

All patients underwent multi-slice spiral CT scan. The DICOM data of CT scan were imported into the computer, and the virtual bronchoscope image of the target bronchus was automatically created by VBN software, and the focus guidance path was established (Figure 2 A, B). Two groups of patients were carried out under local anesthesia, fasting and water prohibition for 6 hours before operation, 2% lidocaine was inhaled by atomization, and 2% lidocaine was dripped into nose and trachea at the same time. In the VBN+EBUS group, bronchoscopy was guided to the target's sub segment bronchi through the VBN system, and then the ultrasound probe was extended to the corresponding sub segment. After detecting the low echo

area (Figure 2 C), the ultrasound probe was slowly withdrawn and the sub segment bronchus opening was measured to indicate the focus distance of the area. Then according to the measured distance, use the ultrasonic probe twice repeatedly to observe whether the operation path is correct. Withdraw the ultrasound probe and send it into the biopsy forceps along the positioning bronchial subsegment, and take the biopsy materials at the same location distance from the ultrasound focus. In the EBUS group, according to the location of the focus determined by chest CT, the ultrasonic probe was pushed to the corresponding segment, the same as the operation steps of EBUS group. All the above groups were biopsied 5 times. Finally, the tissue samples were fixed with 4% formaldehyde solution and sent to pathological examination by smear (Figure 2 D). Operation time: the time from arrival of bronchoscope to carina to departure of bronchoscope from glottis.

Diagnostic Criteria

The cases with malignant histology and /or cytology results are defined as positive cases, and the cases with non malignant pathological results are determined as follows according to the clinical situation: follow-up observation, anti infection, anti tuberculosis, percutaneous lung puncture and surgical biopsy to further clarify. All pathological results should be sent to the department of pathology for unified diagnosis. If there is any doubt, the second pathologist should cooperate in the diagnosis.

Statistical Analysis

The data were processed by SPSS 20.0 software, the measurement data were described by mean \pm standard deviation, the

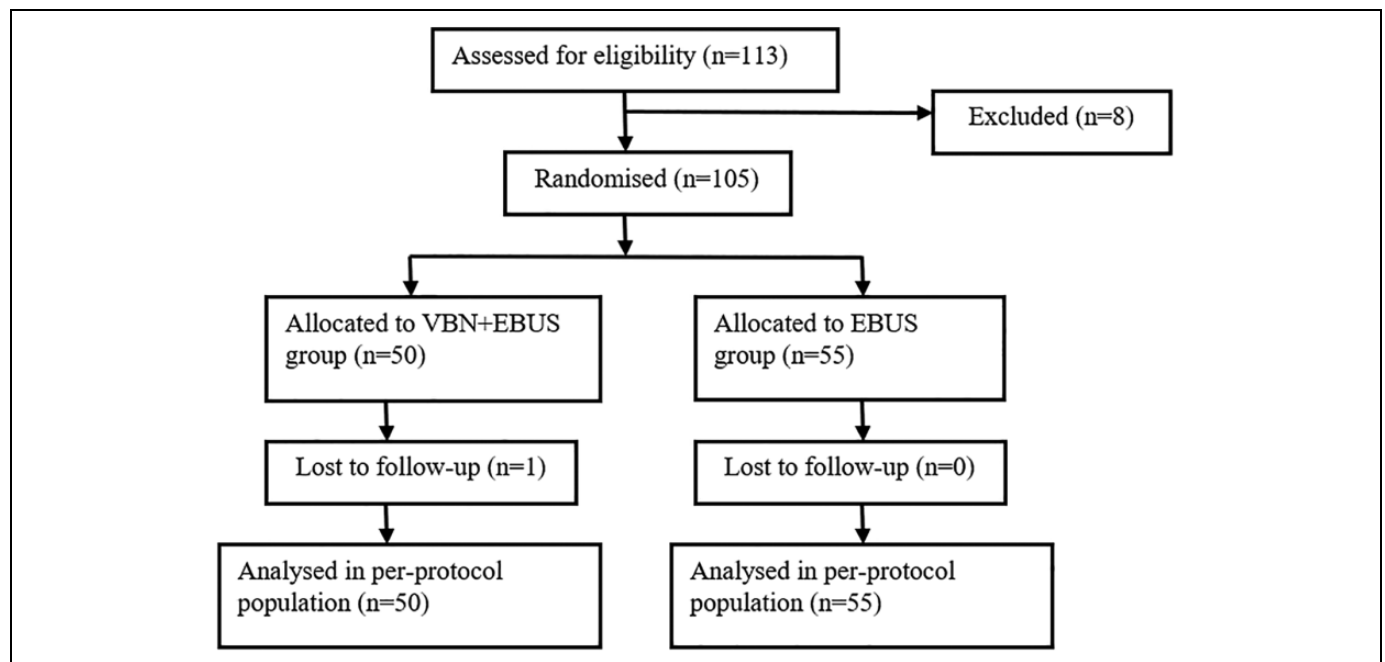


Figure 1. Flow diagram of the eligible patients and the interventional process of the study.

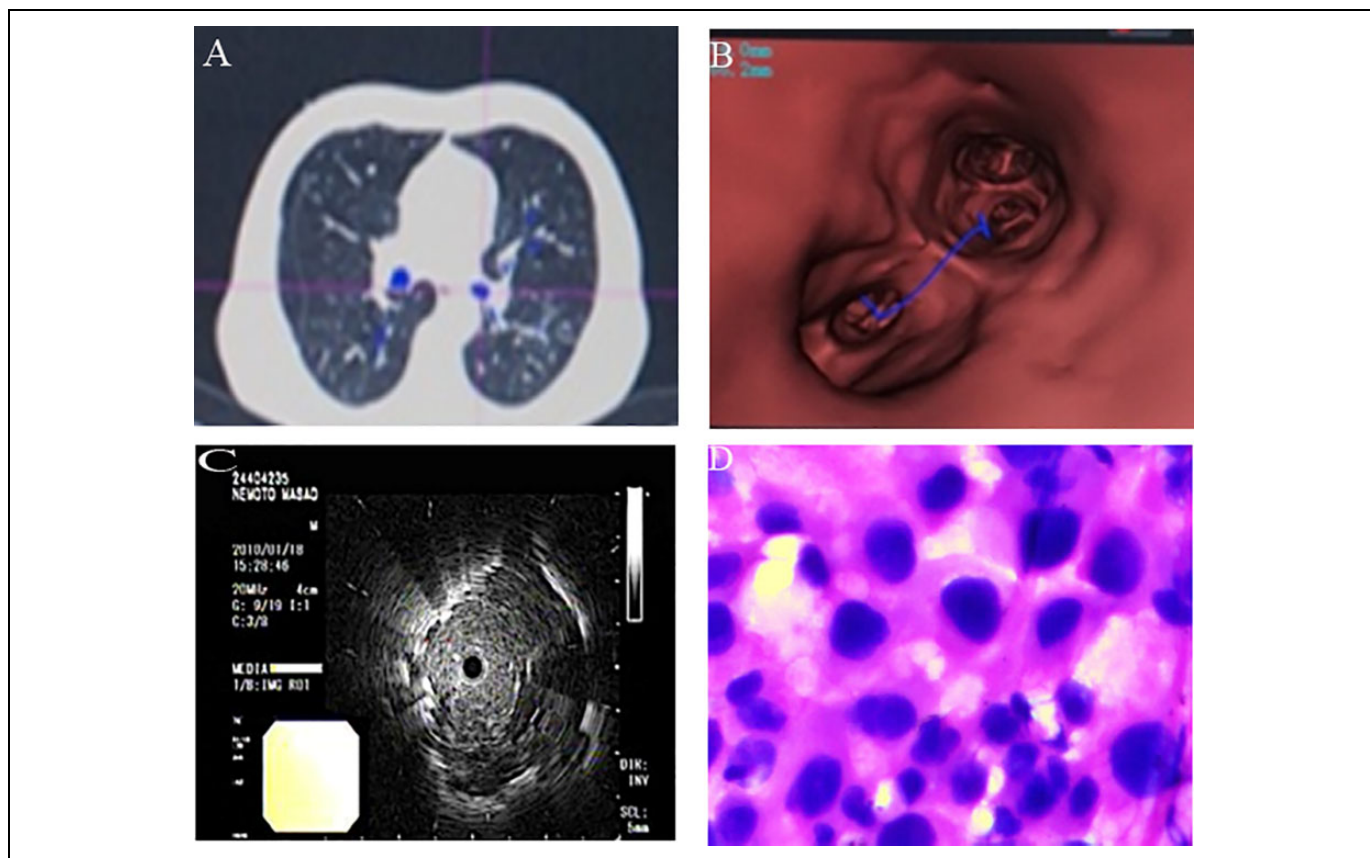


Figure 2. (A) The coronal position setting navigation path. (B) VBN demonstrated a precise route to the peripheral nodule. (C) EBUS showed a low-echoic nodule surrounded by a highly reflective interface produced between the aerated lung and the lesion. (D) Adenocarcinoma of the lung was diagnosed from EBUS guided TBLB.

comparison of measurement data was analyzed by single factor ANOVA, and the comparison between the count data groups was tested by χ^2 , with $P < 0.05$ as the difference.

Result

Clinical Characteristics

Among 105 PPLs patients, 50 cases were in VBN+EBUS group, with an average age of (55.8 ± 10.6) years and a diameter of (27.3 ± 2.7) mm. There were 55 cases in EBUS group, with an average age of (56.5 ± 10.2) years and diameter of (28.4 ± 2.6) mm. In VBN+EBUS group, the number of lesions in right and left lung was not significantly different from that in EBUS group (Table 1).

Diagnosis of EBUS-TBLB

There was no significant difference in diagnosis yield between VBN+EBUS group and EBUS group (76.0% vs. 65.5%, $P = 0.287$) (Table 2).

In VBN+EBUS group, there were 26 malignant tumors, including 25 primary lung cancer and 1 metastatic lung cancer, 12 benign diseases, including 10 infectious disease, and 2 other benign condition; in EBUS group, there were 25 malignant

tumors, including 23 primary lung cancer and 2 metastatic lung cancer, 11 benign diseases, including 10 infectious disease, and one other benign condition (Table 2).

Effect of EBUS-TBLB on Diagnostic Yield

In PPLs with diameter < 20 mm, the diagnostic yield of VBN+EBUS group was higher than that of EBUS group (70.0% vs. 52.0%, $P = 0.047$). In the 2 groups, the diagnostic yield of patients with ultrasound probe within or adjacent to the lesion was significantly higher than that of patients with ultrasound probe outside the lesion (VBN+EBUS group 92.0%, 76.5%, 25.0%, $P < 0.05$; EBUS group 84.6%, 63.2%, 20.0%, $P < 0.05$) (Table 2).

When the diameter of lesions ≥ 20 mm, there was no significant difference in the diagnostic yield between VBN+EBUS group and EBUS group (80.0% vs. 76.6%, $P = 0.488$). There was no significant difference in the diagnosis yield of different location lesions between the 2 groups (Table 2).

Results of Outcome Measures

The operation time of VBN+EBUS group was significantly shorter than that of EBUS group (20.6 ± 12.8 min vs. 28.6

Table 1. Baseline Characteristics and Final Diagnosis.

Variables	VBN+EBUS group	EBUS group	P
Age (years)	55.8 ± 10.6	56.5 ± 10.2	0.465
Gender (male/female)	30/20	30 /25	0.357
Lesion size (mm)	27.3 ± 2.7	28.4 ± 2.6	0.487
<20 mm, n (%)	20/50 (40.0%)	25/55 (45.5%)	0.573
20-30 mm, n (%)	30/50 (60.0%)	30/55 (54.5%)	0.172
Probe location			
Within the lesion	25 (50.0%)	26 (47.3%)	
Adjacent to the lesion	17 (34.0%)	19 (34.5%)	
Outside the lesion	8 (16.0%)	10 (18.2%)	
Lesion location			
Right upper lobe, n (%)	12 (24.0%)	15 (27.3%)	0.831
Right middle lobe, n (%)	8 (16.0%)	8 (14.5%)	0.535
Right lower lobe, n (%)	15 (30.0%)	15 (27.3%)	0.839
Left upper lobe, n (%)	5 (10.0%)	5 (9.1%)	0.572
Left lower lobe, n (%)	10 (20.0%)	12 (21.8%)	0.521
Final diagnosis			
Malignant disease			
Primary lung cancer n (%)	25 (50.0%)	23 (41.8%)	
Metastatic lung cancer n (%)	1 (2.0%)	2 (3.6%)	
Non-malignant disease			
Infectious disease n (%)	10 (20.3%)	10 (18.2%)	
Other benign condition n (%)	2 (4.0%)	1 (1.8%)	

EBUS, endobronchial ultrasound; VBN, virtual bronchoscopic navigation.

± 14.3 min, $P = 0.023$). The number of biopsies and hemorrhage rate in EBUS group were higher than those in VBN+EBUS group ($P < 0.05$) (Table 3).

Complications

In the 2 groups, 16 patients had bleeding in the lumen, 4 in VBN+EBUS group and 12 in EBUS group, respectively. During the operation, the bleeding stopped after the treatment of 1:1000 ice salt water, adrenaline, thrombin, etc. through the bronchoscope biopsy channel, no moderate and severe bleeding and pneumothorax complications occurred.

Discussion

Conventional bronchoscopy can reach 4-5 grade bronchus. With the help of ultra-fine bronchoscopy, intratracheal ultrasound and virtual navigation, the operation field can be extended to 6, 7 grade or even more distal bronchus, which makes our positioning of pulmonary nodules more accurate. Lung tissue biopsy guided by multiple technologies may improve the diagnosis yield of pulmonary nodules.

The diagnostic yield of traditional lung biopsy for pulmonary nodules is lower than 20%.¹⁰ According to ACCP guideline, radial ultrasound guided lung biopsy should be preferred in the diagnosis of pulmonary nodules, which can be used as an important means of diagnosis.⁹ A number of researches showed that, compared with the traditional lung biopsy technology, EBUS guided lung biopsy can significantly improve the diagnosis yield of PPLs.¹⁰ Some researchers considered that, endobronchial ultrasound failed to achieve self navigation

Table 2. Clinical Factors Associated With Diagnostic Yield.

Factors	VBN+EBUS group	EBUS group	P
Diagnostic yields	38/50 (76.0%)	36/55 (65.5%)	0.287
Gender			
Male	22/30 (73.3%)	23/30 (76.7%)	0.766
Female	16/20 (80.0%)	13/25 (52.0%)	0.066
Lesion size (mm, median; range)			
<20 mm, n (%)	14/20 (70.0%)	13/25 (52.0%)	0.047
20-30 mm, n (%)	24/30 (80.0%)	23/30 (76.7%)	0.488
Probe location			
Within the lesion	23/25 (92.0%)	22/26 (84.6%)	0.668
Adjacent to the lesion	13/17 (76.5%)	12/19 (63.2%)	0.481
Outside the lesion	2/8 (25.0%)	2/10 (20.0%)	0.618
Lesion location			
Right upper lobe, n (%)	11/12 (91.7%)	12/15 (80.0%)	0.396
Right middle lobe, n (%)	6/8 (75.0%)	3/8 (37.5%)	0.131
Right lower lobe, n (%)	10/15 (66.7%)	11/15 (73.3%)	0.690
Left upper lobe, n (%)	3/5 (60.0%)	2/5 (40.0%)	0.527
Left lower lobe, n (%)	8/10 (80.0%)	8/12 (66.7%)	0.484
Final diagnosis			
Malignant disease n (%)	29/35 (82.9%)	25/35 (71.4%)	0.788
Non-malignant disease n (%)	9/15 (60.0%)	11/20 (55.0%)	0.123

EBUS, endobronchial ultrasound; VBN, virtual bronchoscopic navigation.

Table 3. Comparison of Index Between the 2 Groups.

Index	VBN+EBUS group	EBUS group	P
Number of biopsy (n)	3.5 ± 0.6	5.8 ± 0.5	0.032
Hemorrhage rate [n (%)]	4 (8.0)	12 (21.8)	0.043
The operation time (min)	20.6 ± 12.8	28.6 ± 14.3	0.023

EBUS, endobronchial ultrasound; VBN, virtual bronchoscopic navigation.

positioning, so 8%-20.8% of the lesions could not be detected.^{11,12} Virtual navigation technology is one of the new technologies developed in recent years. The image got by high-resolution chest CT without septum scanning is guided into the virtual navigation software system. The three-dimensional reconstruction has the same pixel value range to the inner surface of the bronchus, endows artificial pseudo color and simulates the condition in the lumen, and obtains the dynamic reconstruction image similar to that in the lumen of the bronchus. Before operation, according to the prompt of chest CT, the operation path can be determined by calibrating the lung focus. The virtual navigation technology can observe the 0-6 grade bronchi.

The diagnosis yield of lesions with diameter <20 mm was lower than that of the lesions with diameter ≥ 20 mm. Although the specific location of PPLs was confirmed by VBN, the PPLs with diameter less than 10 mm could not be performed by EBUS-TBLB. The diagnostic yield of PPLs > 20 mm was higher than that of 10-20 mm group with or without VBN, which was consistent with foreign studies.¹³ It shows that the larger lesions are easy to be detected and obtained by EBUS. It can be seen that the diameter of the

lesions was positively correlated with the diagnosis yield. In the lesions with diameter <2.0 cm, the diagnosis yield of VBN+EBUS group was significantly higher than that of EBUS group. The main reason is that the smaller the diameter of PPLs, the less the number of bronchial branches involved in the lesion, which to a certain extent, requires the accuracy of bronchial path to the target lesion. In VBN+EBUS group, with the help of VBN system, ultrasound probe can accurately extend to the target lesion, so EBUS has an increased detection rate of lesions.

The location of ultrasound probe is an important factor affecting the diagnostic yield of EBUS-TBLB.^{14,15} Our study indicated that the diagnostic yield of patients with ultrasound probe within or adjacent to the lesion was significantly higher than that of patients with ultrasound probe outside the lesion, indicating that the ultrasound probe location was closely related to the diagnostic yield. In addition, the operation time of VBN+EBUS group was significantly shorter than that of EBUS group, suggesting that VBN can shorten the operation time. Finally, this study suggests that there was no difference between the 2 groups of complications. It can be seen that VBN is a safe and effective technology for diagnosis of PPLs.

According to previous reports, EBUS-TBLB guided sheath and/or combined with fluoroscopy guidance can improve the diagnostic yield of biopsy.¹⁶ In practice, there is no matching X-ray fluoroscopy system in this endoscope, and it is very difficult to occupy the fluoroscopy room due to the large number of patients in radiology department. In addition, domestic doctors and patients are not willing to accept radiation exposure, not combined with X-ray fluoroscopy guidance is more in line with the domestic reality. Guide sheath can help the group to fix the lesion position displayed by EBUS, so that the biopsy forceps will not deviate after withdrawing from the probe. However, the cost of guide sheath and management is high. In addition, it has been reported that the diagnostic yield of EBUS for PPLs without guide sheath was 66.4%-77.0%, suggesting that EBUS has a good diagnostic yield.^{17,18} According to the results of this study, no combined use of guide sheath or X-ray had no effect on the diagnostic yield.

There were 2 limitations of our study. First, it was a single center study. Second, the sample size was small. Next, we will continue to expand the sample size and conduct multicenter studies to further verify our data.

In conclusion, VBN combined with EBUS has a high diagnostic value for PPLs, which can reduce the operation time and provide a safe and effective auxiliary technology for PPLs.

Acknowledgments

We gratefully acknowledge Professor Jiwang Wang for technical assistance. We thank Ms Qian Zhang for advice and discussions.

Author Contribution

Chun Hua Xu and Yan Wang are contributed equally to this work.


Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by the Research Project of Jiangsu "333" High Level Talented Training Project (BRA 2017032); the National Natural Science Foundation of China (Grant Number 81700068); the Key Program of Nanjing Medical Science and technique Development Foundation and the Personnel Training Project of Nanjing Medical Science and technique Development Foundation (ZKX18047).

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