Diagnostic Value of Non-Real-Time Radial Probe Endobronchial Ultrasound (RP-EBUS) Guided Positioning Method for Peripheral Pulmonary Lesions

Background: The aim of this study was to analyze the diagnostic value of thin bronchoscopy lung biopsy for peripheral pulmonary lesions under non-real-time guidance of radial ultrasound (RP-EBUS).

Material/Methods: We used a retrospective analysis of ultrasound images of 165 patients with peripheral pulmonary disease admitted to Suzhou Municipal Hospital Affiliated to Nanjing Medical University from February 2016 to December 2018 who were given RP-EBUS examination. Ultrasound images were obtained for all patients. There were 76 patients treated using traditional positioning method as the control group; 89 patients were treated by probe combined with bronchoscopy positioning method as the research group where the biopsy of the lesion along the path of the ultrasound probe was taken. The positive rate of the 2 methods was observed, and the factors affecting the quality of ultra-thin bronchoscopy under RP-EBUS non-real-time guidance were analyzed.

Results: The detection rate of the study group was 77.64%, which was significantly higher than that in control group, which was 63.16% ($\chi^2=5.238, P<0.05$). The number of biopsies in the study group was 6±1.25, which was significantly lower than that of the control group which was 9±1.87 ($t=4.116, P<0.05$). The diagnostic positive rate of the RP-EBUS probe was significantly higher than that of the RP-EBUS probe ($\chi^2=5.081, P<0.05$).

Conclusions: The diagnostic positive rate of RP-EBUS non-real-time guided subtotal bronchoscopy lung biopsy for peripheral lung disease using probe combined with bronchoscopy positioning method was higher than the traditional positioning method, and the number of biopsies in the study group was significantly lower than that in the control group, which was related to the size, location, whether the probe was wrapped, or the characteristics of the ultrasound image.

MeSH Keywords: Alagille Syndrome • Bronchoscopy • Diagnostic Test Approval

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Background

Most of periphery pulmonary diseases occur outside the segmental bronchus in the lung. The evaluation of the lesion degree and the diagnosis of lesions are particularly important for choosing treatment methods [1]. There are numerous diagnosis and treatment methods used in the clinic setting. Among them, percutaneous lung puncture has been widely used in the clinic with high accuracy. The limitation of such a strategy is that it results in high radiation exposure for patients, and patients may concurrently suffer from pneumothorax, massive hemoptysis, or even air embolism. In addition, the operation risks are extremely high for lesions close to the large hilar and central airways. Although surgical thoracoscopic biopsy with a high accuracy rate is reasonably regarded as a golden diagnostic standard, the limitation is that it is an invasive approach that requires surgery. It appears to be excessively used to treat benign and small lesions. Moreover, the cost of surgical biopsy is high, which could impose a certain burden on some patients [2–4]. Bronchoscopy is a minimally invasive technique that has been used for biopsy of lesions, but the limitation is that the accuracy is restricted by the lesion size. The smaller the lesion, the higher the diagnostic inaccuracy. The diagnostic accuracy is merely 30% when the diameter of the lesion is below 20 mm. Biopsy guided by bronchoscopy ultrasound imaging has greatly improved diagnostic accuracy, however, the cost is high, and the hospital’s popularity is low. The radial ultrasound non-real-time guided bronchoscopy examination used in this study had a bronchoscope with an outer diameter of 4 mm to reach the distal airway and to scan 360° around the tissue within 4 cm with independent biopsy channels which therefore penetrate deep into the 5–10 grade bronchus. This approach could greatly increase the diagnostic accuracy [5,6]. This study is to investigate the diagnostic value of non-real-time guided radial probe endobronchial ultrasound (RP-EBUS) in conjunction with reasonable positioning methods for the diagnosis of peripheral pulmonary lesions. This study retrospectively analyzed 165 patients with peripheral pulmonary lesions who were treated in Suzhou Municipal Hospital Affiliated to Nanjing Medical University from February 2016 to December 2018. The results are reported thereby.

Material and Methods

Demographic information

A retrospective analysis of 165 patients with peripheral pulmonary disease admitted to our hospital from February 2016 to December 2018 was performed in the study. Suzhou Municipal Hospital Affiliated to Nanjing Medical University approved this study. Patients should meet the following recruiting criteria: 1) patients aged at least 18 years without past medical history of lung diseases; 2) the patient’s lesion is below the segmental bronchial opening and the lesion is embedded in the lung parenchyma; 3) the patient has no contraindications to bronchoscopy; 4) the patient has no abnormal pulmonary function and no respiratory tract bleeding; 5) patients and their family members sign the informed consent form. A total of 65 patients with malignant lung lesions and 100 patients with benign lung lesions were recruited in the study. There were 101 males and 64 females with the age range of 25 to 80 years old and the average age is 54.6±6.28 years. There were no significant differences in gender, age, admission time, smoking history, lesion size, and pathological type between patients in the 2 groups (P>0.05).

Study methods

A total of 165 patients were treated by RP-EBUS. Equipment: flexible bronchoscope (BF-P260F, Olympus, Japan); intracavitary ultrasound host (EVIS EUS EU-ME2, Olympus, Japan); ultrasound probe driver (MAJ-1720, Olympus, Japan); and radial endobronchial ultrasound probe (UM-S20-17S, 20MHz Japan, Olympus).

There were 76 patients who were treated using the traditional positioning method (the total number of lesions was 83) as the control group. There were 89 patients who were treated by the probe with the bronchoscope in conjunction with the positioning method (the total number of lesions was 92) as the treatment group. The 2 medical groups in our hospital performed the diagnosis as well as treatments. A biopsy of the lesion was performed along the probe path, from which the ultrasound image was obtained. The specific procedure of RP-EBUS transbronchial lung biopsy (TBLB) was as follows: carefully examine the chest computed tomography (CT) images of the patient to determine the lesion area before surgery. After 6 hours of fasting, the patient took the supine position. The anesthesia to the patient’s throat was performed with 2% lidocaine. Fentanyl and midazolam injections were intravenously administered to maintain patients sedated. Intraoperative monitoring of heart rate, heart rhythm, pulse oxygen, and blood pressure were performed. The disinfected bronchoscope was inserted intranasally. The airway was anesthetized with lidocaine under the guidance of the bronchoscope, and the lungs were carefully observed by the bronchoscope. Based on the lesion area identified from pulmonary CT imaging, the bronchoscope was delivered to the sub-segment opening of the target position. Then the radial ultrasound probe was delivered to the target sub-segment, and the patient’s lesion area was scanned by ultrasound after adjusting the EUBS gain, contrast, and scanning range to observe the images.

In the conventional positioning method, the operator starts to withdraw the probe when the operator feels an obvious resistance. More effort is needed to measure the distance from the
resistance end to the lesion area (A), and the distance from the resistance end to the lesion disappearing site when the probe is slowly withdrawn (B). The distance and path of the operation should be evaluated twice. Surgeons need to withdraw the ultrasound probe and put it into the biopsy forceps along the insertion path. Similarly, the probe is withdrawn when obvious resistance is detected by the operator to the distance of (A+B)/2 depth where the specimen could be obtained for biopsy. For this study, there were 6 operators, 3 in each group. Within each group, there was 1 director, 1 deputy chief physician, and 1 attending physician. All operators have accepted professional training with respiratory endoscopy skills.

In the proposed positioning method, the insertion depth of the bronchoscope was marked when the lesion spot appeared on the probe image. The distance from the entrance port of the bronchoscopy biopsy channel to the lesion spot (A) and the distance from the entrance port of the bronchoscopy biopsy channel to the lesion image disappearance area (B) were measured through slow advancement of the probe. Surgeons then remove the ultrasound probe and mark the distance from the end of the biopsy forceps to the (A+B)/2 of the biopsy forceps. In general, clinicians should be mindful of the need to keep the insertion path and depth of the bronchoscope unchanged and insert the biopsy forceps to the (A+B)/2 marking spot at the entrance port of the biopsy tunnel, where the biopsy specimen could be obtained.

Golden diagnostic standards

Histopathology was obtained by TBLB. Patients with TBLB who failed to confirm pathological diagnosis would undergo CT-guided percutaneous lung biopsy, surgical thoracoscopic biopsy or surgical resection with additional 3 months of clinical imaging follow-up. Comparative analysis was performed to pathological and diagnostic results to identify the correlation rate. Patients who failed to be diagnosed were not included in the analysis.

Observation indicators

To compare the difference between the detection rate of the lesions and the number of biopsies required by the 2 positioning methods, the non-real-time guided bronchoscope diagnosis, RP-EBUS, was used to diagnose benign and malignant pulmonary lesions. The size of the lesion and the distance from the lesion to the pleura are measured according to the CT chest image. RP-EBUS was applied to evaluate the difference of diagnostic rates between lesions more than 2 cm and less than 2 cm, and to identify factors affecting the positive diagnostic rate of RP-EBUS, which were indispensable to understand adverse effects of this strategy. The pleura, the size of the lesion, whether the ultrasound edge is continuous, whether the internal echo is uniform, whether the lesion is surrounded by the RP-EBUS probe and the ranging method will affect the positive rate of detection. Whether or not the RP-EBUS passes the lesion would not affect the diagnostic positive rate.

Statistical analysis

In this study, SPSS 20.0 software was used for statistical data analysis. The t-test analysis was performed for measurement results, which were expressed as “(x±s)”. The χ² test was performed for counting data, which were expressed as (n, %). P<0.05 was considered as statistically significant.

Results

The detection rates of lesions and the number of biopsies between the 2 positioning methods

The detection rate of lesions in the treatment group was 77.64%, which was significantly higher than that of the control group of 63.16% (χ²=5.238, P<0.05). The number of biopsies in the treatment group was 6±1.25, which was significantly lower than that of the number of biopsies in the control group, which was 9±1.87 (t=4.116, P<0.05) as shown in Table 1. Figure 1A–1F show ultrasound images. The images were taken after bronchoscopy, the lower left corner of the image is the bronchoscope guided by the radial ultrasound probe in the airway, the right side of the color map is the representative real-time ultrasound image. G represents the gain value, C represents the contrast. The positive rate of lesions >2 cm was significantly higher than ≤2 cm (χ²=4.161, P<0.05). The positive rate of lesions not close to the pleura was significantly higher than that of the pleura (χ²=3.988, P<0.05).

The relationship between the characteristics of peripheral pulmonary lesions and the diagnostic rate of bronchoscopy with the non-real-time guided RP-EUBS

The data from patients in the treatment group were analyzed. The statistical results indicated from the non-real-time guided bronchoscope diagnostic method showed that the proximity of the lesion spot to the pleura, the size of the lesion, the continuous status of the ultrasound edge, uniformity of the internal echo signal, and the condition of the RP-EBUS probe surrounding the lesion could affect the positive detection rate, whereas the condition of RP-EBUS passing through the lesion did not affect the positive diagnostic rate. Among them, the positive detection rate with lesions over 2 cm was significantly higher than those less than 2 cm (χ²=5.281, P<0.05). The positive detection rate of lesions away from the pleura was significantly higher than that close to the pleura (χ²=15.463, P<0.05). The diagnostic positive rate of ultrasound edge with
discontinuity was significantly higher than that of continuous ultrasound edge ($\chi^2 = 4.283, \text{P}<0.05$). The diagnostic positive rate of nonuniform ultrasound internal echo was significantly higher than that of uniform internal echo ($\chi^2 = 5.372, \text{P}<0.05$). The diagnostic positive rate of the lesion surrounding the RP-EBUS probe was significantly higher than that of the lesion without the RP-EBUS probe ($\chi^2 = 6.016, \text{P}<0.05$). All the data are as summarized in Table 2.

### Complications status

Of all the cases in this study, 3 patients had chest pain and 4 patients had hemoptysis. All affected patients were relieved without special treatment. There were no serious complications including pneumothorax, severe hypoxemia, and arrhythmia.

### Discussion

For the diagnosis of peripheral pulmonary lesions, the use of conventional bronchoscopy in the early time could detect some large lesions. However, the limitation was that conventional bronchoscopy could only penetrate the 4th and 5th grade of bronchial lumen, which was relatively shallow and extremely limited in the process of diagnosis leading to a lower diagnostic rate [7–9]. With the continuous advancement of medical instrument, the American Thoracic Surgeon Association recommended that RP-EBUS could be used in the respiratory track for the diagnosis of pulmonary lesions in 2007 [10]. The non-real-time guided RP-EBUS diagnosis adopted and improved domestically, which had achieved good results. The outer diameter of the probe used in RP-EBUS is as small as 1.8 mm, which is beneficial to the expand the visual field. This probe can penetrate deeper into tissues around the bronchi and the lesion at the distal end. The microscopic angle can be detected within 360°. The image has a clearer overall quality and higher resolution, which is beneficial to enhance the observation of subtle changes in the lesion and has been widely used in clinical practices [11,12]. Yong et al. found that the positive diagnostic rate of RP-EBUS assisted ultra-thin bronchoscopy biopsy to detect peripheral pulmonary lesions was significantly improved, and the diagnostic rate of malignant peripheral pulmonary lesions was significantly higher than that of benign lesions (P<0.05). Li et al. showed that the positive diagnostic rate of peripheral lung cancer by RP-EBUS assisted ultra-thin bronchoscopy biopsy could reach 61.33%. Similarly, the positive diagnostic rate of peripheral lung cancer with hypoechoic and strong peripheral echo zone was dramatically high, when the lesion was over 2 cm in diameter, surrounding the RP-EBUS probe, and away from the pleura, regardless of the number of

### Table 1. Comparison of the detection rate of 2 types of lesions and the number of biopsies.

| Group                                           | Study (n=89) | Control (n=76) | $\chi^2$ | P     |
|-------------------------------------------------|--------------|----------------|----------|-------|
| Male/Female                                     | 58/31        | 43/33          | 1.923    | >0.05 |
| Age (years)                                     | 29–80        | 25–81          | 1.282    | >0.05 |
| Diameter of lesion                              | ≤2 cm        | 61 (68.53)     | 51 (67.11)| 0.546 | >0.05 |
|                                                | >2 cm        | 28 (31.46)     | 25 (32.89)| 0.238 |       |
| Lesion proximity to pleura                      | Yes          | 24 (26.97)     | 22 (28.95)| 0.914 | >0.05 |
|                                                | No           | 65 (73.03)     | 54 (71.05)| 0.304 |       |
| Continuous edge of ultrasound                   | Yes          | 27 (30.34)     | 24 (31.58)| 0.221 | >0.05 |
|                                                | No           | 62 (69.66)     | 52 (68.42)| 0.105 |       |
| Uniform internal echo                           | Yes          | 32 (35.96)     | 25 (32.89)| 0.297 | >0.05 |
|                                                | No           | 57 (64.04)     | 51 (67.11)| 0.397 |       |
| Lesion surrounding the RP-EBUS probe            | Yes          | 68 (76.4)      | 57 (75)  | 0.198 | >0.05 |
|                                                | No           | 21 (23.6)      | 19 (25)  | 0.219 |       |
| RP-EBUS probe penetrating through the lesion     | Yes          | 36 (39.33)     | 27 (35.33)| 0.547 | >0.05 |
|                                                | No           | 53 (59.55)     | 49 (64.47)| 0.822 |       |
| Pathological type                                | Benign       | 55 (61.8)      | 50 (65.79)| 0.152 | >0.05 |
|                                                | Damaging     | 22 (24.66)     | 14 (17.78)| 0.244 |       |
| Positive detection rate                         | 77.64% (69/89)| 63.16% (48/76)| 5.238    | <0.05 |
| Number of biopsies                              | 6±1.25       | 9±1.87         | 4.116    | <0.05 |
A  
B  
C  
D  
E  
F  

Figure 1. Three representative images of the treatment group. (A) Posterior segment of the right upper lobe. Transbronchial lung biopsy (TBLB) histopathology: mucosal chronic organizing inflammation; diagnosis: organizing pneumonia. (B) Right lateral lobe. TBLB histopathology: adenocarcinoma; diagnosis: lung adenocarcinoma. (C) Anterior segment of the left upper lobe. TBLB histopathology: adenocarcinoma; diagnosis: lung adenocarcinoma. Three representative images of the control group (D) Right anterior basal segment. Transbronchial lung biopsy (TBLB) histopathology: adenocarcinoma; diagnosis: lung adenocarcinoma. (E) Right anterior segment of the lateral lobe of the right lung. TBLB histopathology: mucosal chronic inflammation. Percutaneous lung biopsy confirmed pathological diagnosis: lung squamous cell carcinoma. (F) Right upper tip segment. TBLB histopathology: mucosal chronic inflammation; surgical histopathology confirmed diagnosis: pulmonary sclerosing hemangioma.

Table 2. Relationship between pathological features of peripheral lesions of the lung and diagnostic detection rate of ultra-thin bronchoscopy under non-real-time guidance of RP-EBUS.

| Group                        | Total cases (89) | Positive cases (69) | Positive rate | \( \chi^2 \) | \( P \) |
|------------------------------|------------------|---------------------|---------------|-------------|---------|
| Diameter of lesion           |                  |                     |               |             |         |
| \( \leq 2 \text{ cm} \)     | 61               | 43                  | 70.49\%       | 4.161       | <0.05   |
| \( >2 \text{ cm} \)         | 28               | 26                  | 92.86\%       |             |         |
| Lesion proximity to pleura   |                  |                     |               |             |         |
| Yes                          | 24               | 15                  | 62.50\%       | 3.988       | <0.05   |
| No                           | 65               | 54                  | 83.08\%       |             |         |
| Continuous edge of ultrasound|                  |                     |               |             |         |
| Yes                          | 27               | 16                  | 59.26\%       | 4.283       | <0.05   |
| No                           | 62               | 53                  | 85.48\%       |             |         |
| Uniform internal echo        |                  |                     |               |             |         |
| Yes                          | 32               | 15                  | 46.88\%       | 5.372       | <0.05   |
| No                           | 57               | 54                  | 94.74\%       |             |         |
| Lesion surrounding the RP-EBUS probe |      |                     |               |             |         |
| Yes                          | 68               | 59                  | 86.74\%       | 5.081       | <0.05   |
| No                           | 21               | 10                  | 47.62\%       |             |         |
| RP-EBUS probe penetrating through the lesion |      |                     |               |             |         |
| Yes                          | 36               | 27                  | 75.00\%       | 1.121       | >0.05   |
| No                           | 53               | 42                  | 79.25\%       |             |         |
sampling and the condition of the RP-EBUS probe penetrating the lesion ($P<0.05$) [13]. It is obvious that the positive detection rate of RP-EBUS assisted bronchoscope biopsy is affected by factors including the size of the lesion, the characteristics of the ultrasound image, the location of the lesion and the condition of lesion surrounding the probe. Meanwhile, it can effectively improve the lesion detection rate of peripheral pulmonary disease in comparison with traditional bronchoscopy.

This study found that the positive diagnostic rate of the RP-EBUS probe in conjunction with bronchoscopy and the positioning method was higher than that of the traditional approach. The detection rate of the treatment group was 77.64%, which was significantly higher than that of the control group (63.16%, $\chi^2=5.238$, $P<0.05$). The number of biopsy procedures (6±1.25) was significantly lower than that of the control group (9±1.87) ($t=4.116$, $P<0.05$). The non-real-time guided RP-EUBS bronchoscopy diagnosis was able to detect positive results regardless of the proximity of lesion to the pleura, the size of the lesion, the continuity condition of edge of the ultrasound, the uniformity condition of the internal echo signal, the lesion surrounding status to the RP-EBUS probe, and the condition of the RP-EBUS probe penetrating the lesion. Among them, the positive detection rate with lesions over 2 cm was significantly higher than that with lesions less than 2 cm ($\chi^2=4.161$, $P<0.05$). The positive detection rate of lesions away from the pleura was significantly higher than that close to the pleura ($\chi^2=3.988$, $P<0.05$). The positive diagnostic rate of ultrasound edge with discontinuity was significantly higher than that of continuous ultrasound edge ($\chi^2=4.283$, $P<0.05$). The positive diagnostic rate of nonuniform ultrasound internal echo was significantly higher than that of uniform internal echo ($\chi^2=5.372$, $P<0.05$). The positive diagnostic rate of the lesion surrounding the RP-EBUS probe was significantly higher than that of the lesion without the RP-EBUS probe ($\chi^2=5.081$, $P<0.05$). Based on the accumulated experience, it was found that the traditional positioning method of biopsy would more likely result in the false negative results, which were attributed to several reasons. In the traditional positioning method, the flexibility of the probe and the biopsy forceps was different due to the different diameter of their tips. In this regard, the traditional method relies on the probe to feel the obvious resistance so as to assist positioning. The effect of the patient’s breathing amplitude on the diameter of the distal lumen may result in different locations where resistance was encountered leading to inconsistence of the biopsy site to the probe position. We employed the probe in conjunction with the bronchoscope to measure the positioning method to avoid inconsistence. When the insertion path and depth of the bronchoscope are kept unchanged, the biopsy cannot be performed until the marked point is adjusted in place if the marker point fails to reach the bronchoscopy biopsy entrance port where the biopsy forceps is inserted. The traditional positioning method increases the number of biopsies. In addition, inconsistence between the biopsy spot and the probe positioning results in the inability to obtain the required biopsy tissue volume or even the failure to reach the lesion ($\chi^2=6.016$, $P<0.05$). For the lesions with a diameter of more than 2 cm, the positive detection rate is higher. The underlying reason is that when the lesion diameter is less than 2 cm, the degree of lesion invasion to the bronchus is very low, which cannot be fully detected by the probe. This leads to the false negative results. The lesions with discontinuous edge of ultrasound imaging have an invasive growth tendency with high malignancy and the unclear boundary between the lesions and the surrounding tissues. If the boundary between of the lesion and the surrounding tissue is clearer under ultrasound imaging with good activities, the biopsy could be difficult and the diagnosis rate of TBLB is low. The nonuniform characteristic of ultrasound images of the lesion is associated with histopathological hemorrhage, necrosis, granuloma and fibrosis, and these abnormalities are useful for obtaining histological pathological diagnosis. The lesions highly close to the pleura have small peripheral bronchial lumens, which make the probe inaccessible and cause false negatives. When the lesion is surrounding the RP-EBUS probe, the biopsy may not reach the targeted diseased tissue but the bronchial wall, leading to a false negative. When the lesion is surrounding the RP-EBUS probe, the probe can be subjected to a 360° scan to increase the chance of obtaining the diseased tissue during the biopsy. There is no statistically significant difference in the condition of probe penetration in the lesion. In addition, the positive diagnostic rate is also related to the operator’s skills which can be improved through accumulated exercises.

Conclusions

In summary, the positive diagnostic rate of the proposed method for peripheral pulmonary lesions diagnosis is higher than that of the traditional positioning method. It is due to non-real-time guided RP-EBUS in conjunction with bronchoscopy and the positioning method. The diagnostic results are associated with the size and site of the lesion, the surrounding condition of the lesion with the probe, and the characteristics of the ultrasound image. Improving the techniques through reasonable positioning methods could further enhance the diagnosis accuracy. This strategy is safe and worthy of wide clinical applications.
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