BMC Pulmonary Medicine

RESEARCH

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Improved diagnostic yield of peripheral pulmonary malignant lesions with emphysema using a combination of radial endobronchial ultrasonography and rapid on-site evaluation

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Abstract

Background This is a retrospective cohort study from a single center of Chest Medical District of Nanjing Brain Hospital Affiliated to Nanjing Medical University, Jiangsu Province, China. It was aim to evaluate the diagnostic value of radial endobronchial ultrasound (R-EBUS) combination with rapid on-site evaluation (ROSE) guided transbronchial lung biopsy (TBLB) for peripheral pulmonary lesions in patients with emphysema.

Methods All 170 patients who underwent PPLs with emphysema received an R-EBUS examination with or without the ROSE procedure, and the diagnostic yield, safety, and possible factors influencing diagnosis were analyzed between the two groups by the SPSS 25.0 software.

Results The pooled and benign diagnostic yields were not different in the two groups ($P=0.224$, 0.924), but the diagnostic yield of malignant PPLs was significantly higher in the group with ROSE than the group without ROSE ($P=0.042$). The sensitivity of ROSE was 79.10%, the specificity, 91.67%, the positive predictive value, 98.15%, and the negative predictive value, 84.62%. The diagnostic accuracy, was 95.52%. In the group of R-EBUS + ROSE, the procedural time and the number of times of biopsy or brushing were both significantly reduced (all $P<0.05$). The incidence of pneumothorax (1.20%) and bleeding (10.84%) in the group of R-EBUS + ROSE were also less than those in the group of R-EBUS ($P<0.05$). The lesion's diameter ≥ 2 cm, the distance between the pleura and the lesion ≥ 2 cm, the positive air bronchograms sign, the location of the ultrasound probe within the lesion, and the even echo with clear margin feature of lesion ultrasonic image, these factors are possibly relevant to a higher diagnostic yield. The diagnostic yield of PPLs those were adjacent to emphysema were lower than those PPLs which were away from emphysema

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($P=0.048$) in the group without ROSE, however, in the group of R-EBUS + ROSE, there was no such difference whether the lesion is adjacent to emphysema or not ($P=0.236$).

Conclusion Our study found that the combination of R-EBUS and ROSE during bronchoscopy procedure was a safe and effective modality to improve diagnostic yield of PPLs with emphysema, especially for malignant PPLs. The distance between the pleura and the lesion ≥ 2 cm, the positive air bronchograms sign, the location of the ultrasound probe within the lesion, and the even echo with clear margin feature of lesion ultrasonic image, these factors possibly indicated a higher diagnostic yield. Those lesions' position is adjacent to emphysema may reduce diagnostic yield but ROSE may make up for this deficiency.

Keywords Radial endobronchial ultrasonography, Rapid on-site evaluation, Pulmonary peripheral lesions, Emphysema, Combined modality

Introduction

Many peripheral pulmonary lesions (PPLs) are actually lung cancer [1], therefore the pathological diagnosis of them is a noticeable issue for physicians. Emphysema refers to a pathological state of the structure of the distal end of the bronchioles [2], it can destroy lung tissue structure, affect ventilation function, and as the degree of emphysema worsens, it is more prone to pneumothorax, pulmonary infection and lung cancer [2–4]. Computer tomography (CT)-guided lung puncture biopsy (CT-GLPB) is conventional diagnostic method for PPLs with its [5] high diagnostic yield of nearly 90% [6, 7], but it also has a high incidence rate of pneumothorax, approaching 25.9% [5]. For patients with PPLs and emphysema, the risk of pneumothorax in CT-guided lung puncture biopsy will significantly increase.

Although radial endobronchial ultrasound (R-EBUS) in bronchoscope is considered a safer diagnostic tool for PPLs due to its much lower pneumothorax incidence rate than that of CT-GLPB, and without the diagnostic yield decrease [6], there was also a study suggested the presence of emphysema remained an independent high-risk factor for pneumothorax in R-EBUS examination [7]. However, a few studies showed that the R-EBUS was a secure tool with an acceptable diagnostic yield for PPLs patients with emphysema [8, 9]. These above studies indicate that the R-EBUS's value for patients with PPL and emphysema still deserve further attention and research.

A critical issue affecting the success or failure of R-EBUS' diagnosing PPL combined with emphysema is can we obtain sufficient specimens and reduce unnecessary sampling. Rapid on-site evaluation (ROSE) is a method to identify different cells morphology by the microscope on-site in bronchoscopy procedure in real time, and has been found it can shorten the R-EBUS bronchoscopy procedure time, reduce incidence of complications [10, 11], and increase the diagnostic yield of PPLs [12]. For PPLs patients with emphysema, it is necessary to minimize the number of sampling and shorten the procedural time as possible, therefore, our hypothesis is that ROSE may be helpful in the diagnosis of such patients.

However, till now, the role of R-EBUS combined with ROSE in the diagnosis of PPLs with emphysema remains unclear. Here, we made a retrospectively cohort study to investigate the accuracy and safety of the R-EBUS in bronchoscopy combined with ROSE for the diagnosis of PPL with emphysema.

Methods

Study design

This study is a retrospective cohort study belongs to observational studies. Its key elements, such as setting, participants, variables (Quantitative/qualitative), outcome data, and main results, were all described as follows.

Setting

Clinical records and a retrospectively maintained database of 220 consecutive bronchoscopy procedures at the Endoscopic Center of Chest Medical District of Nanjing Brain Hospital, between February 2015 and December 2021. All patients were follow-up until one year after Bronchoscopy examination.

Participants

Participants should meet both the inclusion and exclusion criteria as follows:

The inclusion criteria: i): The lesion in the chest CT image is located below the segmental bronchial and is surrounded by lung parenchyma. Meanwhile, the CT image presents emphysema feature. ii): For lesions which are determined to be partially solid, the solid component must reach > 50% of the PPL size [13]. iii): The lesion was invisible under the conventional bronchoscopy and no evidence of endobronchial injury, extrinsic compressive narrowing, submucosal lump, occlusion, apparent swelling and hypertrophy of mucosa, or bleeding of the bronchus. iv) Those who have obtained a positive pathological diagnosis or an assured diagnosis through follow-up, empirical treatment, and other means.

The exclusion criteria: (i) Patients being examined had fever, purulent phlegm or other obvious active infectious symptoms. (ii) Patients had active bleeding or abnormal coagulation. (iii) Patients failed to complete a whole bronchoscopy. (iv) Patients refused to provide their medical data.

According to the above criteria, a total of 170 cases were collected. All these patients signed written informed consents to express their willingness to provide data required for research.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Chest Medical District of Nanjing Brain Hospital Affiliated to Nanjing Medical University (April 2014, the committee's approval number: 2014-KL008-01) and was carried out in accordance with national law and the current revised Declaration of Helsinki. All patients provided written informed consent before enrollment.

Variables from pulmonary function test and emphysema severity

All patients received pulmonary function tests by a flow spirometer (Master Screen PFT System- 200, JAEGER, Germany) according to the guidelines of the American Thoracic Society [14]. According to the previous guideline literature [15], pulmonary spirometry parameters included forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and their ratio of actual/predicted, were selected and record.

Two experienced radiologists reviewed patients' thin-section CT scan images and evaluated emphysema severity. According to the previous guideline [16], 170 patients were classified into three groups: mild, moderate, and severe emphysema. Mild emphysema was described as scattered centrilobular lucent area, usually separated by large regions of normal lung, and involving an estimated 0.5-5% of a lung zone, or small (≤1 cm) parapleural lucencies. Moderate emphysema was defined as many well-defined lucencies occupying more than 5% area of any lung zone. Severe emphysema usually means confluent centrilobular, advanced destructive, and substantial paraseptal emphysema and their scopes exceed beyond above standards.

Equipment

Patient underwent flexible bronchoscopy (BF-P260F, Olympus, Japan) with an external diameter of 4.4 mm for complete inspection of airways before R-EBUS. The EBUS (EU-M30 S, Olympus, Japan) was integrated with a 20 MHz radial probe (a R-EBUS probe (UM-S20-17 S, Olympus, Japan) 2.0 mm in inside diameter. For ROSE, the Diff-Quick staining method (American Scientific Products, McGaw Park, IL) was used and cytological evaluation was processed with microscope (DM500, Lycra, Germany).

Procedures of bronchoscopy and ROSE

Bronchoscopy was applied under conscious sedation. Solid food and liquid fasting for 6 h before examination and 2% lidocaine aerosol inhalation were routine procedure.

During the operation, the heart rate, blood pressure, saturation of pulse oxygen, and clinical symptom were continuously monitored. The bronchoscope was inserted and observed each branching trachea. Then it was advanced forward to the target bronchus until unable to enter. Then a R-EBUS probe was inserted into the target bronchus through the working channel of the bronchoscope. When the ultrasonic image of the target lesion appeared, according to previous literature's classification as follows: (a) within: the lesion was completely surrounding the probe in the ultrasonic image; (b) adjacent to: a part of the lesion was visualized in the ultrasonic image; (c) invisible: no abnormal echogenicity was visualized [17]. The endoscopist adjusted the probe until the R-EBUS image was clear. Then, referring to previous report [12], the assistant fixed the bronchoscope at the marked site of the patient's cavum nasi. After the R-EBUS probe was withdrawn, the endoscopist sent the forceps to the marked predetermined depth for sequential transbronchial lung biopsy (TBLB) [18]and brushings [19].

For the ROSE group, the assistant removed the TBLB specimen from the biopsy forceps used a 5 ml sterile syringe needle and smeared it onto a glass slide and rolled it back and forth for nearly 5 s, in order to imprint cytology by materials [20]. Since DQ A solution, DQ B solution, phosphate buffer (PBS) and water have been poured respectively in glass vials with lids before this. individual ROSE slide is dipped in DQ A solution for 20 s and transferred to PBS vial washing DQ A solution. Then the slide is soaked in DQ B solution for 30 s and washed in water tank. Finally, residual liquid is removed from slide with bibulous paper. Glass vials holding DQ A solution, DQ B solution, and PBS should be sealed after use because of these solutions are volatilizable [20]. The entire process usually does not exceed 60 s [21]. Next, a trained respiratory physician followed the instructions and evaluated the cytological morphology on site [22].

Common ROSE cell morphologies are classified as follows: i): If the cell is irregular in shape or abnormal in size, or nuclear hyperchromatism, then a malignancy will be recommended. ii) If any pathogenic signs such as fungal hyphae or mycobacteria were found, a suspicion of special infection will be considered. The above two situations both suggested that the endoscopist should be terminated or continued as needed for diagnostic requirement. iii): If only bronchial epitheliums or histocytes but no any

Table 1 Baseline of clinical characteristics between the two groups

Variables	*R*-EBUS + ROSE[*n*/(%)]	*R*-EBUS [*n*/(%)]	*P*
Age (years)	69.55 ± 7.97	68.78 ± 7.12	0.505
≤ 60	22 (26.51%)	19 (21.84%)	0.478
>60	61 (73.49%)	68 (78.16%)	
Gender (Male/Female)			
Male	62 (84.34%)	69 (90.80%)	0.596
Female	21 (15.66%)	19 (9.20%)	
Smoke			
Yes	60 (72.29%)	71(81.61%)	0.150
No	23 (27.71%)	16 (18.39%)	
Mean diameter (cm)	36.56 ± 13.12	35.91 ± 11.92	0.657
≤ 2	9 (10.84%)	8 (9.20%)	0.741
>2	74 (89.16%)	79 (90.80%)	
Location [n (%)]			
URL*	29 (34.94%)	23 (26.44%)	0.488
MRL*	8 (9.64%)	12 (13.79%)	
LRL*	15 (18.07%)	14 (16.09%)	
ULL*	14 (16.87%)	13 (14.94%)	
LLL*	6 (7.22%)	15 (17.24%%)	
LLL*	11(13.25%)	10 (11.49%)	
Density of the lesion			
Solid	64 (77.11%)	71 (81.61%)	0.468
cavitary	19 (22.89%)	16 (18.39%)	
Air bronchograms sign			
Positive	28 (33.73%)	29 (33.33%)	0.780
Negative	55 (66.27%)	58 (66.67%)	
Distance from pleura (cm)			
≤ 2	33 (39.76%)	36 (41.38%)	0.830
>2	50 (60.24%)	51(58.62%)	
Severity of emphysema			
Mild	38 (45.78%)	45 (51.72%)	0.525
Moderate	27 (32.53%)	24 (27.59%)	
Severe	18 (21.69%)	18 (20.69%)	
Pulmonary function test			
FEV1 [a]/FEV1[P] (%)	64.66 ± 9.50	64.47 ± 9.04	0.766
(FEV1/FVC) [a] /(FEV1/FVC) [P] (%)	63.95 ± 8.80	64.46 ± 8.56	0.510
The lesion location to emphysema			
Adjacent to	26 (31.33%)	30 (34.48%)	0.662
Away from	57 (68.67%)	57 (65.52%)	

*URL = Upper lobe of the right lung; *MRL = Middle lobe of the right lung; *LRL = Low lobe of the right lung; *ULL = Upper lobe of the left lung; *LLL = Lingual lobe of the left lung; *LLL = Lower lobe of the left lung. [a] = Actual value, [P] = Predictive value

characteristic pathological cells were observed on the smear, the ROSE result is regarded as negative, then 3 ~ 5 times biopsy and brushings will be performed within the adjacent bronchial lumen at the same bronchial-tree level [11, 23]. Besides ROSE slides, other remaining specimens were saved as required and sent for routine examinations timely. The procedural time was defined as the interval from the insertion to withdrawal of the bronchoscope through the glottis [12].

Complications

Accord with previous literature [24], The severity of bleeding was classified into four grades: i): Minimal bleeding (< 5 ml); ii) Mild bleeding (5 ~ 20 ml); iii): Moderate bleeding (20 ~ 100 ml), and iv): Severe bleeding (> 100 ml). The minimal bleeding was not included in the category of complications. A chest X-ray radiograph was examined for every patient in following 24 h after the bronchoscopy. Patients with pneumothorax, including those who received oxygen therapy, thoracic puncture, and closed drainage with a catheter, were all recorded.

Statistical analysis

Statistical analysis was performed with a statistical program of SPSS 25.0 software (SPSS Institute, Stanford, USA). The Shapiro–Wilk test was used to test whether the measurement data were of normal distribution. The normally distributed data were presented as the mean ± SD, and data with skewed distribution would be recorded as the median (interquartile range [IQR]). The T-test was used to compare measurement data that were of normal distribution. The Chi-square test or Fisher exact test was used to compare rates or proportions. A probability(*P*) value of < 0.05 was considered significant.

Results

The baseline of clinical features was balanced and comparable (Table 1). As Table 2 indicated, in the group of R-EBUS + ROSE, the diagnostic yield of malignant and benign lesions was 85.94% (55/64) and 63.16% (12/19), respectively. The pooled diagnostic yield was 80.72% (67/83). Corresponding data in the group of R-EBUS were 71.43% (50/70), 64.71% (11/17), and 70.11% (61/87), respectively. The pooled and benign lesions' diagnostic yields between the two groups were not different ($P = 0.224$ and $= 0.924$), but the diagnostic yield of malignancy in the group with ROSE was significantly higher than in the group without ROSE (85.94% vs. 71.43%, $P = 0.042$).

Table 3 listed possible factors may influence diagnostic yield and showed that no matter in which group, the lesion's diameter ≥ 2 cm, the distance between the pleura and the lesion ≥ 2 cm, the positive air bronchograms sign, and the location of the ultrasound probe

Table 2 Final pathologic diagnoses in patients between the two groups

Variables	*R*-EBUS + ROSE [*n* (%)]	*R*-EBUS [*n* (%)]
Diagnosed cases by*R*-EBUS		
Malignancy	55	50
Squamous cell carcinoma	24	21
Adenocarcinoma	25	22
Small cell carcinoma	3	3
Metastatic malignancy	2	3
Lymphoma	1	1
Benign lesions	**12**	**11**
Pneumonia/abscess	4	5
Tuberculosis	4	3
Fungal infection	4	3
Diagnosed through other methods	**16**	**26**
Malignancy	**9**	**20**
Squamous cell carcinoma	2	4
Adenocarcinoma	2	4
Adenosquamous carcinoma	2	3
Small cell carcinoma	1	4
Metastatic malignancy	1	3
Lymphoma	1	2
Benign lesions	**7**	**6**
Pneumonia/abscess	2	2
Tuberculosis	1	1
Fungal infection	1	2
Organizing pneumonia	3	1

within the lesion, the even echo and clear margin of lesion ultrasonic image feature, these factors all indicated a higher diagnostic yield. Other factors such as age, smoking history, lesions' location, density, and the severity of emphysema did not influence diagnostic yield. As Table 4 showed, the sensitivity of ROSE was 79.10% (53/67), the specificity, was 91.67% (11/12), the positive predictive value (PPV), was 98.15% (53/54), and the negative predictive value, was 84.62% (11/13). The diagnostic accuracy, was 95.52% (64/67). In Table 5, compared with the R-EBUS group of R-EBUS, the procedural time in the group of R-EBUS+ROSE was shortened ((25.70±5.25) min vs. (27.29±4.55) min) and the number of times of biopsy ((3.29±0.97) vs. (3.78±0.88)) or brushing ((2.99±1.04) vs. (3.62±0.91)) were both significantly reduced, with the P=0.037, 0.001 and 0.000, respectively. Furthermore, the incidence of pneumothorax (1.20%) vs. (8.05%) and bleeding ((10.84%) vs. (24.14%)) in the group of R-EBUS+ROSE were also less than those in the group of R-EBUS, with the P=0.036 and 0.038. There is no patient died in this study, and the patients with pneumothorax and bleeding were all relieved by treatment, and only one patient received a chest tube drainage. It is interesting that in the group of R-EBUS without ROSE, the diagnostic yield of PPLs those were adjacent

Table 3 Factors possibly affecting diagnostic yields between two groups

Variables	*R*-EBUS + ROSE [*n* (%)]	*R*-EBUS [*n* (%)]
Age (years)		
≤60	18/22 (81.82%)	14/19 (73.68%)
>60	49/61(80.33%)	47/68 (69.11%)
P	0.880	0.983
Smoke		
Yes	49/60 (81.67%)	52/71 (73.24%)
No	18/23 (78.26%)	9/16 (56.25%)
P	0.726	0.168
Mean diameter(cm)		
<2	5/9 (55.56%)	3/8 (37.5%)
≥2	62/74 (83.78%)	58/79 (73.42%)
P	0.044*	0.035*
Location of lesion		
UL	34/43 (79.07%)	25/36 (69.44%)
M/LL	11/14 (78.57%)	19/27 (70.37%)
LL	22/26 (84.62%)	17/24 (70.83%)
P	0.833	0.993
Distance from pleura(cm)		
≤2	23/33 (69.70%)	21/36 (58.33%)
>2	44/50 (88.00%)	40/51 (78.43%)
P	0.040*	0.045*
Density of the lesion		
Solid	52/64 (81.25%)	51/71(71.83%)
Non-solid	15/19 (78.95%)	10/16 (62.50%)
P	0.824	0.464
Air bronchograms sign		
Yes	25/28 (89.29%)	24/29 (82.76%)
No	42/55 (76.36%)	37/58 (63.79%)
P	0.047*	0.036*
Position of the probe		
Within	45/51 (88.24%)	40/49 (81.63%)
Adjacent to/Outside	22/32 (68.75%)	21/38 (55.26%)
P	0.029*	0.023*
Ultrasonic image features		
Even echo with clear margin	27/29 (93.10%)	24/28 (85.71%)
Mix echo with unclear margin	40/54 (74.07%)	37/59 (62.71%)
P	0.037*	0.029*
Severity of emphysema		
Mild	33/38 (86.84%)	35/45 (77.78%)
Moderate ~ Severe	34/45 (75.56%)	26/42 (61.90%)
P	0.197	0.108
lesion position to emphysema		
Adjacent to	19/26 (73.08%)	17/30 (56.67%)
Away from	48/57 (84.21%)	44/57 (77.19%)
P	0.236	0.048*

*P <0.05

Table 4 ROSE compared with HE pathological results in R-EBUS + ROSE group

ROSE cytology	Hematoxylin Eosin (HE) pathology		Total
	Malignancy	Benign	
Malignancy	53	1	54
Benign	2	11	13
Total	55	12	67

Table 5 Procedural time and incidence of complications between two groups

Variables	*R*-EBUS + ROSE	*R*-EBUS	t/χ^2	*P*
procedural time (min)	25.70 ± 5.25	27.29 ± 4.55	2.111	0.037*
Number of biopsy (n)	3.29 ± 0.97	3.78 ± 0.88	3.435	0.001*
Number of brushing (n)	2.99 ± 1.04	3.62 ± 0.91	4.262	0.000*
Pneumothorax (n (%)])	1(1.20%)	7(8.05%)	2.009	0.036*
Bleeding (n (%)])	9 (10.84%)	21(24.14%)	4.292	0.038*

*P <0.05

to emphysema were lower than lesions those were away from emphysema (56.67% vs. 77.19%, P=0.048), but in the group of R-EBUS+ROSE, there was no such difference whether the lesion is close to emphysema or not (73.08% vs. 84.21%, P=0.236).

Discussion

In this study, the pooled diagnostic yields of the two groups were both beyond 70%: the R-EBUS+ROSE group: 80.72% and the R-EBUS group: 70.11%, which is nearly consistent with previous literature [25]. For malignant PPLs, the diagnostic yields of the two groups even reached 85.94% and 71.43%, respectively. We also found that the larger size of the PPL, the ultrasonic probe's location is within the lesion, the positive air bronchograms sign, the distance from pleura to the lesion is longer than 2 cm, these factors can improve the diagnostic yield, which support earlier researches [5, 26–29]. In addition, previous study [30] observed that the R-EBUS' images may helpful to identify the lesion's pathological characteristic, here, our data also indicated that the even echo with clear margin of R-EBUS image was a positive factor for higher diagnostic yield, especially for malignant PPLs, which was showed in representative cases in Fig. 1. These results above mentioned indicated that R-EBUS was a strong useful diagnostic tool for PPLs in patients with emphysema, which supported Lee [8] and Steinfort's views [10].

Regarding the rapid on-site evaluation (ROSE), both the existing literature and the clinical experience suggest that it can potentially reduce the complication rate of bronchoscopy by decreasing the procedural time and number of biopsies [10, 11]. However, the impact of

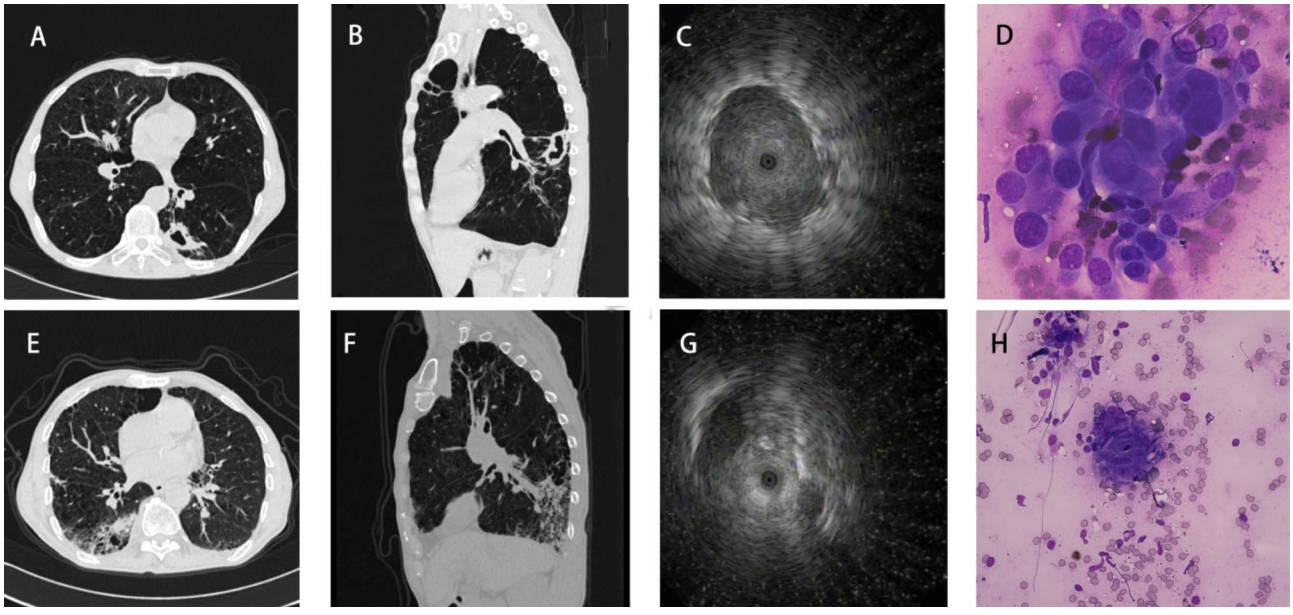

Fig. 1 Case1 (**A**-**D**): (**A**): Axial CT showed a cavitary PPL in the Lower lobe of the left lung, with thick walls and burrs. (**B**): Sagittal CT showed the severe emphysema and the lesion was adjacent to pulmonary bulla. (**C**): The R-EBUS probe was located within the lesion, and the latter presented a uniform low-density echo area with a high-echo band-like edge. (**D**): Tissue smear ROSE identified cells of different sizes, large and deeply stained nuclei, implied the possibility of adenocarcinoma. Case 2 (**E**-**H**): (**E**): Axial CT showed an Irregular shape PPL in the Lower lobe of the right lung, with adjacent emphysema and bullae. (**F**): Sagittal CT showed the PPL was surrounded by severe emphysema. (**G**): The R-EBUS probe was located within the lesion, and presented an uneven low-density echo area with discontinuous edge. (**H**): Tissue smear ROSE identified epithelial-like cells piled up, with roughly circular arrangement and rich cytoplasm, suggested the possibility of tuberculosis

ROSE on diagnostic yield varies among different diseases as well [12, 31]. Studies have found that ROSE may help improve the diagnostic yield in pulmonary parenchyma lesions than hilar/mediastinal diseases, especially for suspected malignancies [32]. One possible reason is that the ultrasound probe used for the transbronchial needle aspiration (TBNA) is directly embedded in the bronchoscope lens, allowing biopsies to be performed in real time when the EBUS examination is performed, the accuracy of sampling is relatively high. Comparatively, when an endoscopist examines a PPL, during the bronchoscopy, after the R-EBUS probe locates the PPL, the endoscopist needs to withdraw the R-EBUS probe from the bronchoscope and then send the biopsy forceps into the lesion. This is a non-real-time procedure and there is inevitably the possibility of displacement when sampling, and the quality of specimens needs to be evaluated, which is the role of ROSE. Thus, ROSE may have an advantage over EBUS-TBNA in the diagnosis of PPLs [12, 29].

In this study, our results found that the ROSE improved significantly the diagnostic yields of malignant PPLs, which is consistent with previous researches [10–12]. It is also found that the advantage of ROSE in improving the diagnostic yield of malignant PPL is significantly better than of benign PPL, which is supporting earlier reports [10–12]. We considered the main explanation for this difference is due to the discrepancy in cell morphology. As we know, malignant cells are usually large, with hyperchromatic nuclei and irregular shapes, which are relatively easier to identify. However, benign cells morphologies often various and non-specific, which leads to more difficulty in ROSE's identification [12, 29]. Nevertheless, for some specific infectious lesions that can present pathogenic characteristics, such as tuberculosis, aspergillus, sporozoites, ROSE may reach a significantly higher diagnostic yield (70–100%), which has been showed by several previous studies and our results this time [10–12].

In this study, the sensitivity, specificity, PPV, NPV and the coincidence rate with HE pathological diagnosis was 79.10%, 91.67%, 98.15%, 84.62%, and 95.52%, respectively, which were accord with previous report [11, 30]. The incidence of pneumothorax, bleeding, and the number of times in biopsies and brushings were all lower in the group with ROSE than in the group without ROSE, is also consistent with.

previous findings [11, 29, 33]. These advantages indicate that ROSE can really shorten the examination time and improve the efficiency of bronchoscopy, and it also can reduce the adverse physiological effects of carbon dioxide retention, blood oxygen and pH reduction, which is especially benefit to pulmonary diseases just as emphysema.

In this study, we also explored the effect of emphysema on the diagnostic yield and safety for patients. In pooled diagnostic yield in the group of R-EBUS was 70.11%, which is similar to Lee's work [8], 70.54%. But unlike Lee's results, in our study, the diagnostic yield of patients with mild emphysema had no statistical difference compared with patients with moderate ~ severe emphysema, whether in the group with or without ROSE. Some reasonable explanations may be considered as follows:1) The number of patients in our study was still relatively small (170 cases), and the proportions of severity of emphysema are not similar (our data: mild, moderate or severe, were 83, 87 vs. Lee's corresponding data: 70,59), which is cannot reflect the difference. 2) The mean size of PPLs in our study was larger compared with Lee's study ((36.56±13.12) mm vs. 28.00 mm) [8], larger sizes may contribute to higher diagnostic yield [34].

The incidence of pneumothorax is higher than that of Lee's study (8.05% vs. 0% (0/129)). This difference may be due to their application of guided-sheath (GS) and fluoroscopy but we did not. But even so, the incidence rate of pneumothorax was still significantly lower than the CT-guided needle biopsy, whether in the group with or without ROSE [5]. Meanwhile, we also found that all the 8 pneumothorax cases were happened in those PPLs whose locations were adjacent to emphysema (Fig. 1), indicated that those lesions which were adjacent to emphysema had higher pneumothorax risk than those were away from (1.20% vs. 8.05%) emphysema. However, in the 8 patients, only one patient was in the group of R-EBUS+ROSE, and the rest were all in the group without ROSE. This difference implies ROSE may help reduce the risk of pneumothorax incidence.

Another interesting phenomenon was also observed in this study. In the group of R-EBUS without ROSE, the diagnostic yield of PPL was not different, regardless of whether it was adjacent to emphysema (73.08% vs. 84.21%, $P=0.236$). But in the group of R-EBUS with ROSE, the diagnostic yield was higher in PPL which was adjacent to emphysema (56.67% vs. 77.19%, $P=0.048$). We speculate that ROSE can evaluate the quality of specimens in real-time to determine or adjust the biopsy position, which may overcome the sampling difficulty caused by twisting or narrowing of the distal airway due to emphysema. Previous literature such as Wang's found that ROSE promoted the diagnostic accuracy of special anatomical parts such as the distal bronchi of apical-posterior segments [12], and our findings support their view.

Our work has the following limitations: First, as a single-center, preliminary retrospective study of 170 cases. Although statistical analysis showed that baseline characteristics between the two groups were balanced and comparable, however, there is still potential inevitable bias. Second, in this study, the proportion of mild- moderate

emphysema cases (134 (78.82%)) and patients of lesions are away from the emphysema (114 (67.06%)) were relatively higher, while severe emphysema patients (36 (21.18%)) and lesions adjacent to emphysema were relatively less (56 (32.94%)), which also maybe lead to some biases. In part these limitations were due to a preliminary retrospective study. Therefore, more patients who meet the propensity score matching (PSM) requirements and have a balanced distribution of mild, moderate, and severe emphysema may make the results of study more valuable for clinical practice.

In general, our study showed that the combined modality of bronchoscopy, R-EBUS and ROSE may be an efficient and safe diagnostic procedure for patients underwent PPLs with emphysema. A large-sample, randomized prospective study is necessary to be performed in the future.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03208-1.

Supplementary Material 1

Supplementary Material 2

Author contributions

Qing Xie and Wei Wang wrote the main manuscript text; Yiling Qiu, Jiajia Sun, Huidi Hu, Jue Zou, Chunhua Xu and Qiang Zhang collected clinical and pathological data; Wei Wang and Qi Yuan prepared Fig. 1. The Primary corresponding author, Yan Wang, provided funding and managed the procedure of the entire project.

Funding

This work was supported by 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).

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are stored in a designated computer at Clinical Research Archives of Chest Medical District of Nanjing Brain Hospital Affiliated to Nanjing Medical University.

Declarations

Ethics approval and consent to participate

All authors of this paper certify that they have obtained the patient consent forms. In the forms, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published.

Consent for publication

All authors have signed to transfer the copyright of this article to *BMC Pulmonary Medicine*.

Competing interests

The authors declare no competing interests.

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Received: 16 January 2024 / Accepted: 8 August 2024
Published online: 20 August 2024

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