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Diagnostic value of combination of rapid on-site evaluation and radial endobronchial ultrasound for peripheral pulmonary infectious lesions

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Peripheral pulmonary lesions (PPLs) are surrounded by lung parenchyma and invisible under an endoscope. The detection rate of PPLs by routine bronchoscopy is low. Radial endobronchial ultrasound (R-EBUS) can overcome those limitations, as it can locate peripheral bronchial lesions through a characteristic ultrasound signal.

Rapid on-site evaluation (ROSE) is a real-time rapid cytological interpretation technology accompanied by tissue sampling. ROSE is helpful in improving the diagnostic rate of R-EBUS for PPLs, especially lung cancer.[1] However, the utility of ROSE during R-EBUS for peripheral pulmonary infectious lesions (infectious PPLs) is unclear. This study aimed to analyze the diagnostic value and safety of R-EBUS combined with ROSE in infectious PPLs. The study was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University (No. 2019-017). The informed consent form was signed by the patient or his or her authorized legal representative.

In this retrospective study, 280 patients who underwent R-EBUS were diagnosed with peripheral pulmonary infectious diseases at the Third Affiliated Hospital of Soochow University, from January 2019 to August 2021, 114 of whom accepted ROSE (ROSE group) and 166 of whom did not accept ROSE (non-ROSE group).

The inclusion criteria are the following: (1) hospitalized patients without gender limitation and age ≥ 16 years; (2) bronchoscopy showed peripheral lung lesions; (3) no contraindications related to bronchoscope; and (4) complete clinical information and available follow-up data.

The exclusion criteria are the following: (1) visible lesions and stenosis in the airways; (2) patients with contraindications to accept bronchoscope; (3) suspicion of malignant tumors and non-infectious lesions (sarcoidosis, interstitial lung disease, etc); and (4) incomplete follow-up and clinical data.

Fiberoptic bronchoscope (BF-P260F; Olympus, Tokyo, Japan), processor monitor (EU-ME1; Olympus), ultrasonic host (MAJ-935; Olympus), and R-EBUS with a 1.4 mm diameter (UM-S20-17S; Olympus) were used for R-EBUS. All operations were performed by three pulmonologists familiarized with the procedures. During the operation, the bronchoscope was delivered to the bronchial lesion site based on computed tomography (CT). Visible bronchial segments were continuously examined until a characteristic ultrasound signal indicating the presence of solid lesions [Supplementary Figure 1A, http://links.lww.com/CM9/B341]. Then, the EBUS probe was removed, and the sampling instrument was inserted through the guide sheath to obtain tissue samples.

The specimen was fixed in Diff Quick A solution (Diff-Quik; Baso Ltd, Guangzhou, Guangdong, China) and stained for 30 s, slowly soaked in phosphate buffer, dried gently, and then stained with Diff Quick B solution (Diff-Quik; Baso Ltd), for 40 s. Preliminary diagnostic information was obtained by observing the composition of cells and the changes in morphology under the microscope by an experienced pulmonologist with professional training. If the sample was obtained successfully, preliminary diagnosis could be carried out, tissue sampling would be stopped, and sample would be sent for conventional analyses; otherwise, the operation was repeated by adjusting the position and angle of the bronchoscope to ensure timely obtainment of new

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samples. Hematoxylin and eosin staining or special staining combined with clinical, medical imaging, and blood test analyses were considered criteria for diagnosing infectious PPLs.[2] Three diagnostic categories were shown in the present study, including pulmonary tuberculosis (TB), pulmonary mycosis, and other pneumonia. If the initial diagnosis was not confirmed, CT-guided percutaneous lung puncture, operation, or secondary bronchoscopic biopsy would be selected in consideration of the conditions and the preferences of the patient at the follow-up visit. For pneumonia with unknown pathogen, the final diagnosis was made by clinical and imaging follow-up at least 6 months after anti-infective therapy.

Bronchoscopy is an invasive procedure that can cause hypoxemia, bleeding, infection, arrhythmia, pneumothorax, and other complications. The most common complication was bleeding. According to the literature, it could be divided into minimal (<5 mL), mild (5–20 mL), moderate (21–100 mL), and severe bleeding (>100 mL).[3]

The basic information, clinical symptoms, imaging manifestations, histopathological diagnosis of bronchoscopy biopsy tissue, microbial culture, the result of ROSE, and the complications of the patients were collected.

The statistical analysis was performed using IBM SPSS 26 software (IBM, Armonk, NY, USA). Descriptions for categorical variables were based on percentages and frequencies and for continuous variables were means and standard deviations if the data were normally distributed or medians (Q_1, Q_3) if the data were non-normally distributed. Mann-Whitney *U* tests (for non-parametric variables), chi-squared tests or fisher's exact tests were used to compare the data between the two groups, and two-tailed $P < 0.05$ was considered statistically significant.

The age, gender, clinical symptoms, lesion distribution, and lesion types of the two groups were described in Supplementary Table 1, http://links.lww.com/CM9/B341, and there were no significant differences between the two groups.

The differences in initial diagnostic rate between the ROSE and non-ROSE groups are presented in Table 1. The initial diagnosis rate of pulmonary TB in the ROSE group was significantly higher than that in the non-ROSE group (88.9% [24/27] *vs*. 60.0% [18/30], $\chi^2 = 6.116$, $P = 0.013$).

Among 114 patients in the ROSE group, 21 cases of ROSE smear that were considered TB revealed granulomatous inflammation with necrosis in tissue and epithelioid cells [Supplementary Figure 1B, http://links.lww.com/CM9/B341]. Some neutrophils and necrosis were seen in four cases that were considered aspergillus infection, with some *Aspergillus* filaments [Supplementary Figure 1C, http://links.lww.com/CM9/B341]. Epithelial cell proliferation, neutrophils, lymphocytes, and other inflammatory cells were found in 48 cases that were considered pneumonia.

The diagnostic rates of R-EBUS in the ROSE and non-ROSE groups under different conditions were shown in Supplementary Table 2, http://links.lww.com/CM9/B341. The R-EBUS diagnostic rate of lesions with a diameter ≤3 cm in the ROSE group (42.4% [14/33]) was significantly higher than that in the non-ROSE group (21.9% [14/64], $\chi^2 = 4.478$, $P = 0.034$). The diagnostic rates of lesions located in the upper lobe of the right and left lungs in the ROSE group were significantly higher than those in the non-ROSE group (right lung: 68.4% [26/38] *vs*. 46.0% [23/50], $\chi^2 = 4.398$, $P = 0.036$; left lung: 70.6% [12/17] *vs*. 38.2% [13/34], $\chi^2 = 4.747$, $P = 0.029$). In addition, the diagnostic rate of the ROSE group was also significantly higher than that in the non-ROSE group (68.2% [58/85] *vs*. 52.8% [66/125], $\chi^2 = 4.985$, $P = 0.026$) when the ultrasound probe got access to the lesions.

Among 280 cases, pneumothorax occurred in one case, which occurred in the non-ROSE group and improved after symptomatic treatment of oxygen inhalation. There were 27 cases with mild and moderate bleeding: six in the ROSE group and 21 in the non-ROSE group. All of them improved after drug hemostasis. The incidence of bleeding complications in the ROSE group was 5.3% (6/114), which was significantly lower than that in the non-ROSE group (12.7% [21/166], $\chi^2 = 4.233$, $P = 0.040$).

The diagnostic efficacy of transbronchial lung biopsy (TBLB) was related to tissue sample size, especially in infectious diseases. The larger the tissue sample size, the higher the proportion of patients diagnosed with infection is.[4] Therefore, for peripheral pulmonary infectious diseases, confirming the obtainment of sufficient sampling tissue with diagnostic significance has become an important issue for clinicians.

ROSE can guide the process of interventional diagnosis, such as puncture and lavage in real-time, preliminarily assess the sufficiency and quality of samples, and guide further auxiliary examination, including immunohistochemistry and microbial culture, which is helpful to diagnosis and treatment.

Table 1: Initial diagnostic rate of patients in the ROSE group and non-ROSE group.

Items	ROSE group ($n = 114$)	Non-ROSE group ($n = 166$)	χ^2 values	*P* values
Pulmonary TB	24/27 (88.9)	18/30 (60.0)	6.116	0.013
Pulmonary mycosis	11/14 (78.6)	14/19 (73.7)	0.106	0.745
Other pneumonia	32/73 (43.8)	48/117 (41.0)	0.146	0.703
Total	67/114 (58.8)	80/166 (48.2)	3.033	0.082

Data are presented as the number initially diagnosed in ROSE or non-ROSE group/the number finally diagnosed (percentage). ROSE: Rapid on-site evaluation; TB: Tuberculosis.

We found that the initial diagnostic rate of pulmonary TB in the ROSE group was 88.9%, which was significantly higher than 60.0% in the non-ROSE group. Pulmonary TB lesions were prone to necrosis and cavities, which could easily affect the quality of the samples and lead to false negatives. ROSE assisted with R-EBUS biopsy could well make up for this defect, improve the qualified rate of specimens, and thus enhance the diagnostic rate. Another advantage of ROSE is that it is able to distinguish the pathological features of TB, such as granuloma with necrosis, in time during the bronchoscopy. Identifying these features during the process of ROSE can help to guide doctors to submit specimens for microbial culture or X-pert testing and other non-culture detection techniques of etiology, thereby improving the diagnosis rate of TB.

This study also found that the diagnostic rate of the ROSE group was significantly higher than that of the non-ROSE group for infectious lesions with a diameter of $\leq$3 cm. For small infectious lesions, it is difficult to obtain satisfactory ultrasound images because less bronchi are involved, which affects the guide-sheath biopsy sampling. ROSE can provide real-time feedback during the operation to ensure the quality of tissue sampling, and simultaneously guide microbial staining or microbial culture, which is conducive to improving the diagnostic rate.

ROSE can reduce the incidence of complications of bronchoscopy by avoiding additional TBLB. In the present study, the incidence of bleeding in the ROSE group was lower than that in the non-ROSE group. When a ROSE diagnostic result indicates infectious lesions (such as TB, fungi, etc), the samples can be analyzed by (cultured or non-cultured) pathogen detection techniques directly, thus avoiding extra biopsies and reducing the incidence of bleeding and other complications while maintaining the diagnostic rates.

There are some limitations to our study. First, the effects of ROSE on the frequency of biopsies and operation time were not noted. Second, this study was a retrospective, non-randomized, single-center study. For infectious PPLs, prospective multicenter studies with more samples are required to evaluate the value of ROSE combined with R-EBUS in the diagnosis.

In conclusion, ROSE combined with R-EBUS has a high diagnostic value for infectious PPLs, especially for pulmonary TB. Fewer complications and lower associated risks were reported using this combined procedure.

Conflicts of interest

None.

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