

# Efficacy of rapid on-site cytological evaluation (ROSE) by a pulmonologist in determining specimen adequacy and diagnostic accuracy in interventional diagnosis of lung lesions

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## Abstract

**Objective:** To evaluate the efficacy of rapid on-site cytological evaluation (ROSE) in determining specimen adequacy and diagnostic accuracy in the interventional diagnosis of lung lesions.

**Methods:** This retrospective study included 127 consecutive cases of lung lesions, which were sampled by bronchoscopy or transthoracic fine needle aspiration, and diagnosed on ROSE followed by histopathology. ROSE was performed by a trained pulmonologist and the diagnosis of ROSE was compared with the final diagnosis.

**Results:** The sensitivity of ROSE in determining adequacy of specimens was 97.5% and specificity in determining inadequacy was 85.7%. The diagnostic efficacy of ROSE for assessing malignancy (sensitivity of 94.5% and specificity of 100%) and non-malignancy (sensitivity of 97.8% and specificity of 100%) was excellent. The sensitivity of ROSE for diagnosing small cell carcinoma (100%) was highest, followed by adenocarcinoma (89.2%) and squamous cell carcinoma (75.0%). Performance of ROSE by a trained pulmonologist also determined tuberculosis with a high diagnostic sensitivity (83.3%) and specificity (100%).

**Conclusions:** A trained pulmonologist can reliably carry out ROSE to ensure the adequacy of the sample, distinguish between malignancy and non-malignancy, and make a preliminary diagnosis in a large number of cases.

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## Keywords

Cytology, lung lesion, rapid on-site evaluation, diagnostic accuracy, interventional pulmonology, malignancy

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## Introduction

Interventional pulmonology is defined as “the art and science of medicine as related to the performance of diagnostic and invasive therapeutic procedures that require additional training and expertise beyond that required in a standard pulmonary medicine training programme” by the European Respiratory Society/American Thoracic Society.<sup>1</sup> Rapid development of diagnostic bronchoscopy and guidance technology, such as endobronchial ultrasound (EBUS), together with transthoracic fine needle aspiration (FNA) under computed tomographic (CT) guidance (CT-FNA) has raised diagnostic yield and reduced complications. This has led to minimally invasive interventional techniques being widely considered as the preferential diagnostic approaches for lung lesions. Moreover, 70% of lung cancer is unresectable in the advanced stages. Management of these patients includes personalized medicine where treatment decisions are made on the basis of specific histology and molecular characteristics of the tumor.<sup>2</sup> Therefore, interventional diagnostic techniques play an important role in this situation.

The rapid on-site cytological evaluation (ROSE) system provides immediate feedback regarding adequacy of the specimens obtained during the examination and guides the operators to modify the sampling technique, and the site and depth sampled. Therefore, ROSE decreases the number of passes required for an adequate sample, improves the diagnostic yield, reduces the

risk of complications, and reduces costs.<sup>3–5</sup> Ideal ROSE reporting has two components of on-site adequacy and diagnostic category. There are various criteria for determining on-site adequacy, including a certain amount of lymphocytes, the presence of diagnostic smears, and abundant pigment-laden macrophages.<sup>6</sup> The International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society have provided a standardized classification for diagnosis of lung cancer considering small biopsies and cytology.<sup>7</sup> This classification cytomorphologically describes adenocarcinoma as a flat, cohesive sheet of relatively uniform-appearing glandular cells characterized by mild variability in nuclear sizes, a delicate cytoplasm, and a low level of disruption of polarity. Additionally, squamous cell carcinoma is described as a flat mosaic sheet of malignant epithelial cells characterized by a dense (or opaque) cyanophilic cytoplasm, and obviously hyperchromatic nuclei with small chromocenters and/or nucleoli.

The extent to which a pulmonary physician, who often performs ROSE, can master these cytological characteristics to aid interventional diagnosis of lung lesions is unclear. Therefore, we evaluated the efficacy of ROSE for determining specimen adequacy and diagnostic accuracy in lung lesions. We retrospectively compared the diagnosis of ROSE with the final diagnosis made on formalin-fixed and paraffin-embedded tissue obtained by biopsy during interventional sampling and/or on resected tissue from operable lesions.

## Materials and methods

Patients with pulmonary/mediastinal mass lesions that were sampled through minimally invasive techniques and diagnosed by ROSE followed by histopathology were included. Cases without ROSE or histopathological diagnosis were ruled out. Our retrospective study included 127 consecutive cases of pulmonary/mediastinal mass lesions during July 2018 to April 2019. For each patient, age and sex, techniques used for sampling, the site of sampling, the original ROSE report, and diagnosis made on histopathology were recorded. This retrospective study was approved by the Institutional Review Board of Hubei Public Health Clinical Center, the central Hospital of Wuhan (2020–196). All patients signed informed consent forms of sampling by interventional techniques and written informed consent for this study was waived.

The following techniques were used by pulmonologists on the basis of radiological characteristics of the lung lesions: transbronchial biopsy (TBB); endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) (22-gauge needle; Olympus Corporation, Tokyo, Japan and EBUS PENTAX; Miyagi Factory HOYA Corporation, Tokyo, Japan); transbronchial lung biopsy (TBLB) either directly or under radial probe endobronchial ultrasound guidance (UM-S20–20R; Olympus Corporation); and CT-FNA either alone or in combination. Surface anesthesia and/or general anesthesia with a laryngeal mask airway were freely decided by the operators.

ROSE was performed in the procedural room by a pulmonary physician who received training in cytopathology for 3 months. Every sample, brush, clamp, or needle aspiration was first evaluated by ROSE. A minimal amount of the specimen was smeared on slides, air dried, and stained with Diff-Quik (BA4150; Baso Diagnostics Corporation, Zhuhai, China.).

The remaining specimen was kept for pathological tests and/or microbial tests. The staining process for ROSE was as follows. A drop of stain A (Diff-Quik, BA4150; Baso Diagnostics Corporation) was placed on freshly prepared air-dried smear for 30 s, washed with phosphate-buffered saline, stained with solution B for 40 s, and washed with phosphate-buffered saline. The smear was observed for specimen adequacy and diagnostic category. Adequacy of the smear for EBUS-TBNA was assessed<sup>6</sup> as follows: (1) adequacy of lymphocytes where more than 41 lymphocytes were observed in the most cellular area of the slide on  $\times 40$  magnification; (2) abundant pigment-laden macrophages; and (3) diagnostic smears (malignancy or granulomas) were present. For other specimens, on-site adequacy was assessed by the presence of relatively abundant and well-visualized lesional material as proposed by Burlingame et al.<sup>8</sup> The sampling stopped until ROSE reported an adequate specimen, and when inadequacy persisted, the biopsy was stopped on the basis of the operators' and the patients' tolerance.

ROSE also provided the diagnostic category, such as malignant, atypical, or negative for malignancy. Additionally, a specific diagnosis was further provided if possible because a pulmonologist can combine clinical features, radiological findings, and cytological characteristics together to make a diagnosis. Some cytological criteria of malignancy have been previously reported.<sup>4,7</sup> Aggregates of epithelioid histiocytes associated with a necrotic background and a moderate amount of lymphocytes in cytological images, together with other features, such as symptoms of fever and cough, a positive result of interferon gamma release assay, and a tree-in-bud pattern, necrosis, or cavity in radiological images indicated the probable diagnosis of tuberculosis. Granulomatous inflammation without obvious necrosis in cytological images

and symmetrical bilateral lymphadenopathy in radiological images highly indicated sarcoidosis.

The final diagnosis was made using histopathology and/or microbial tests, and polymerase chain reaction was used if necessary. For some cases, such as sarcoidosis, patients were followed up after treatment to confirm the diagnosis. Nonspecific inflammation was defined as inflammatory cells that were aggregated in tissues without definite microbial results. The diagnosis made by the pulmonologist who performed ROSE was compared with the final diagnosis.

In our study, the sampling method was decided by the operators and the proficiency of operators was different, which might be considered as investigator bias. Therefore, four experienced pulmonologists who participated in the study chose a sampling method and performed interventional sampling procedures independently to reduce investigator bias. The histopathological diagnosis was made by at least two pathologists who did not know the diagnosis of ROSE. However, the bias in performing ROSE could not be entirely eliminated because there was one pulmonologist who was not blinded to the patients and the diagnosis of ROSE depended on the experience of this pulmonologist.

The efficacy of ROSE in assessing specimen adequacy was shown by the sensitivity, specificity, positive predictive value, and negative predictive value. The efficacy of ROSE for sub-classifying the morphological type of lung lesions was shown by diagnostic sensitivity. SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA) was used for analysis.

## **Results**

The mean ( $\pm$ standard deviation) age of the patients was  $54.9 \pm 11.7$  years and there were 72 men and 55 women. As shown in

Table 1, six (4.7%) cases were undiagnosed because these patients refused surgery or other techniques for sampling after failing to obtain an adequate specimen by bronchoscopy. Three (2.4%) cases were diagnosed as atypical cells. A total of 94.5% (69 cases) of the 73 malignant cases were pulmonary source tumors and 5.5% (4 cases) were non-pulmonary source tumors. Adenocarcinoma accounted for the majority of lung cancer, followed by squamous cell carcinoma and small cell carcinoma. One patient received CT-FNA immediately after failing to obtain adequate tissue by TBLB, and the diagnosis of adenocarcinoma was finally made. In the non-malignant group, the diagnosis was mostly nonspecific inflammation and tuberculosis. The majority of specimens were obtained by TBB (53 cases) and EBUS-TBNA (30 cases), followed by TBLB (24 cases) and CT-FNA (21 cases). The distribution of the lesions sampled is shown in Table 2. The right lower lobe location was slightly preferred (26 cases). The locations of EBUS-TBNA were 4R and 7 lymph node stations, and both 4R and 7 lymph nodes were sampled in two patients.

The efficacy of ROSE for determining adequacy is shown in Table 3. ROSE successfully confirmed adequacy in most cases. However, three cases were falsely determined as inadequate by ROSE, while they were diagnosed as adenocarcinoma, primary tracheal leiomyoma, and atypical cells on histopathology. Notably, there was one case in our study in which ROSE was adequate and the case was diagnosed as adenocarcinoma, but histopathology suggested an inadequate specimen. Although ROSE failed in determining adequacy in this case, it resulted in the correct diagnosis because the patient was confirmed as having adenocarcinoma by histopathology after surgery in another hospital. The sensitivity of ROSE in determining adequacy was 97.5% and specificity in determining

**Table 1.** Distribution of specimen types that were sampled by interventional diagnostic techniques on the basis of the final diagnosis.

Categories	Percentage (number of cases/ total number of cases)	Diagnosis	Percentage (number of cases/ total number of cases)					
			TBB	TBLB	EBUS-TBNA	CT-FNA		
Malignancy	57.5 (73/127)							
Pulmonary source tumors	94.5 (69/73)	Adenocarcinoma Squamous cell carcinoma Small cell carcinoma Sarcomatoid carcinoma	16 14 4	6 1	4 2 4 2	12 4 1		
Non-pulmonary source tumors	5.5 (4/73)	Lymphoma Adenoid cystic carcinoma	1			1		
Non-malignancy	35.4 (45/127)	Metastatic malignancy Sarcoidosis Tuberculosis Nonspecific inflammation Aspergillosis	5 6 6 6	3 3 12 1	3 3 8	1 2		
Other	7.1 (9/127)	Leiomyoma Atypical cells Undiagnosed	1 2 4		1 1 2	1 2		

TBB, transbronchial biopsy; TBLB, transbronchial lung biopsy; EBUS-TBNA, endobronchial ultrasound-transbronchial needle aspiration; CT-FNA, fine needle aspiration under computed tomographic guidance.

**Table 2.** Sampling locations of different interventional diagnostic techniques.

Sampling locations	Interventional diagnostic techniques used (n)			EBUS-TBNA
	TBB	TBLB	CT-FNA	
LUL	6	6	5	
LLL	13	4	3	
RUL	9	7	6	
RML	7	3	2	
RLL	17	4	5	
Trachea	1			
4R lymph nodes				11
4L lymph nodes				6
7 lymph nodes				15

TBB, transbronchial biopsy; TBLB, transbronchial lung biopsy; CT-FNA, fine needle aspiration under computed tomographic guidance; EBUS-TBNA, endobronchial ultrasound-transbronchial needle aspiration; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe.

**Table 3.** Efficacy of ROSE in assessing specimen adequacy.

Adequacy by ROSE	Adequacy by histopathology	
	Positive (n)	Negative (n)
Positive	117	1
Negative	3	6
Total	120	7

ROSE, rapid on-site cytological evaluation.

inadequacy was 85.7%. The positive predictive value was 99.2% and the negative predictive value was 66.7%. The sensitivity of ROSE in determining adequacy was highest in the CT-FNA group, followed by the TBB group and the EBUS-TBNA group (Figure 1). ROSE was more sensitive when the lesion was more precisely located and a larger specimen was obtained.

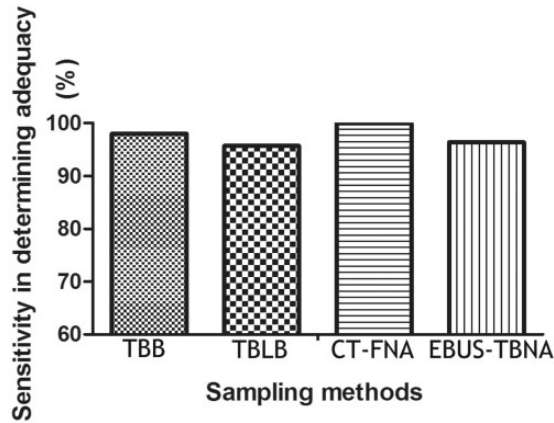
The association between ROSE and histopathology, as well as the diagnostic sensitivity and specificity of ROSE in various

lung lesions, are shown in Table 4. The diagnostic efficacy of ROSE for determining malignancy (sensitivity of 94.5% and specificity of 100%) and non-malignancy (sensitivity of 97.8% and specificity of 100%) was excellent. ROSE was used to further make a specific diagnosis when possible. The sensitivity of ROSE for diagnosing small cell carcinoma was highest, followed by adenocarcinoma and squamous cell carcinoma. In the non-malignant group, ROSE also determined tuberculosis with a high diagnostic sensitivity (83.3%) and specificity (100%).

We summarized several cytomorphological characteristics in relation to the histotype of the tumor and tuberculosis (Figure 2). Adenocarcinoma showed small clusters of uniform-appearing glandular cells with a delicate cytoplasm (Figure 2a). For squamous cell carcinoma, tumor cells with large nuclei, macronucleoli, and varying nuclear/cytoplasmic ratios were observed in a dirty, necrotic background, and keratinization was occasionally observed (Figure 2b). Small cell carcinoma cells had a scant cytoplasm, and their nuclei were round, oval, or spindle-shaped. Additionally, these cells showed nuclear molding with a dispersed granular chromatin pattern (Figure 2c). For tuberculosis, aggregates of epithelioid histiocytes associated with a necrotic background with a moderate amount of lymphocytes were observed (Figure 2d).

## Discussion

With the development of interventional pulmonology, an increasing amount of lung lesions can be sampled by minimally invasive techniques.<sup>1</sup> ROSE is recommended in the sampling process to improve diagnostic accuracy, reduce the risk of complications, and enable appropriate specimen triage.<sup>9-11</sup> With ROSE, the yield of conventional TBNA is similar to that of EBUS-TBNA



**Figure 1.** Sensitivity of rapid on-site cytological evaluation in determining adequacy of specimens for TBB, TBLB, CT-FNA, and EBUS-TBNA.

TBB, transbronchial biopsy; TBLB, transbronchial lung biopsy; CT-FNA, fine needle aspiration under computed tomographic guidance; EBUS-TBNA, endobronchial ultrasound-transbronchial needle aspiration.

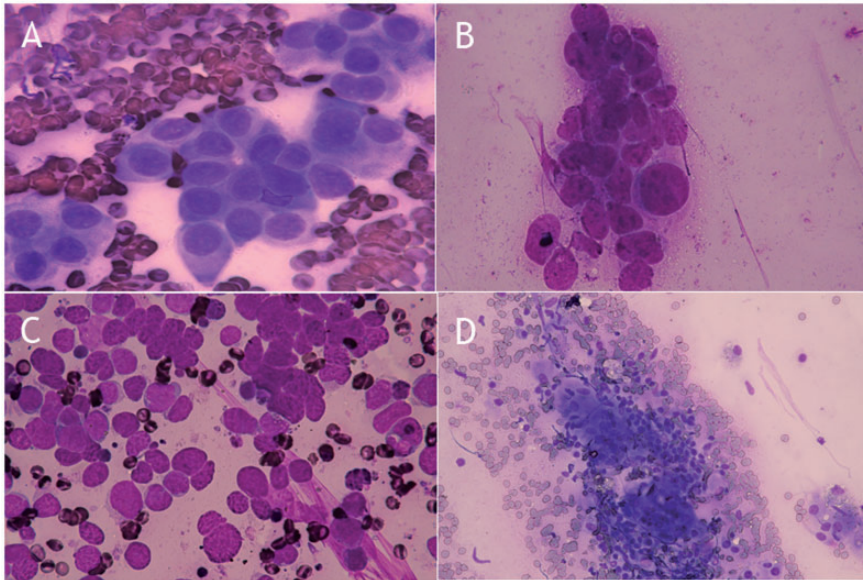
**Table 4.** Efficacy of ROSE in diagnostic accuracy.

Diagnosis	ROSE (number of cases)	Histopathology (number of cases)	Diagnostic efficacy of ROSE (%)	
			Sensitivity	Specificity
Malignancy	69	73	94.5	100
Adenocarcinoma	33	37	89.2	100
Squamous cell carcinoma	15	20	75.0	100
Small cell carcinoma	10	10	100	100
Sarcomatoid carcinoma	0	2		
Lymphoma	1	1		
Adenoid cystic carcinoma	0	1		
Metastatic malignancy	0	2		
Unclassified	10	0		
Non-malignancy	44	45	97.8	100
Sarcoidosis	1	3		
Tuberculosis	10	12	83.3	100
Nonspecific inflammation	32	28	100	96.0
Aspergillosis	1	1		
Leiomyoma	0	1		
Atypical cells	5	3		
Undiagnosed	9	6		

ROSE, rapid on-site cytological evaluation.

and this is especially relevant in the case of sarcoidosis.<sup>12</sup> Even at centers where an EBUS facility is available, conventional TBNA with ROSE can provide a diagnostic yield similar to EBUS. This is useful in

settings where EBUS-TBNA is not available. With ROSE, the diagnostic yield may be optimized.<sup>13</sup> Because ROSE is just beginning to be used in China, the experience of this technique should be



**Figure 2.** Cytomorphological characteristics with rapid on-site cytological evaluation (stained with Diff-Quik). In adenocarcinoma, small clusters of uniform-appearing glandular cells with a delicate cytoplasm can be seen (100× magnification) (a). In squamous cell carcinoma, tumor cells with large nuclei, macronucleoli, and varying nuclear/cytoplasmic ratios in a dirty necrotic background can be seen (100× magnification) (b). In small cell carcinoma, tumor cells with a scant cytoplasm, nuclear molding, and dispersed granular chromatin can be seen (100× magnification) (c). In tuberculosis, aggregates of epithelioid histiocytes associated with a necrotic background and a moderate amount of lymphocytes can be seen (40× magnification) (d).

summarized and many questions need to be clarified. Unfortunately, few studies have focused on the diagnostic accuracy of ROSE by comparing it with histopathology.

Consistent with a study by Anila et al.,<sup>14</sup> we found that ROSE had excellent efficacy in determining adequacy of specimens. In three cases, ROSE resulted in a false negative result of inadequacy and these cases were diagnosed as adenocarcinoma, primary tracheal leiomyoma, and atypical cells by histopathology. In our study, Minnesota Criteria<sup>6</sup> and criteria proposed by Burlingame et al.<sup>8</sup> were used to determine on-site adequacy. Currently, there are no uniform criteria for on-site adequacy of ROSE. Moreover, a small amount of specimens, mass red cell contamination, and a lack of experience in cytopathology by a

pulmonologist might account for these false negative results. Additionally, in one patient, there was a false positive result in determining adenocarcinoma by ROSE and inadequacy with histopathology. This patient was finally diagnosed with adenocarcinoma after surgery. A similar situation was previously reported,<sup>14</sup> and there was speculation that a difficult biopsy or intolerance of the patient caused few specimens to be obtained. Additionally, fragmentation of specimens into pieces and diagnostic material with a different distribution might have caused this situation. However, falsely determined adequacy appeared to be an advantage, instead of a limitation, of ROSE in our study.

ROSE was useful in determining malignancy and in preliminarily identifying



subtypes of lung tumors in our study, which would help to define the number of samples to be taken. In cases of squamous cell or small cell carcinoma, a single sample may be sufficient, whereas multiple samples are required for adenocarcinoma to permit biomolecular characterization. Additionally, tuberculosis can also be preliminarily diagnosed by ROSE when symptoms, imaging features, and cytological characteristics are considered together. Several studies<sup>4,7,15</sup> have reported cytological characteristics of common lung diseases. These studies showed the presence of nucleoli and small/medium cell clusters in adenocarcinoma and the presence of large cluster-forming cells and extensive necrosis in squamous cell carcinoma. Additionally, single cells with molding and moderate necrosis were characteristic of small cell carcinoma, and granulomatous inflammation with a large amount of necrosis was indicative of tuberculosis.

Training a pulmonologist to perform ROSE when a cytopathologist is not available regularly is an alternative. A trained pulmonologist can reliably assess adequacy and malignancy for endosonography-derived samples.<sup>16</sup> Furthermore, an 81% overall agreement was reported between a pulmonologist and cytopathologist in evaluating ROSE when determining adequacy of specimens.<sup>17</sup> Some “user-friendly” criteria of ROSE have been reported to histologically classify cytological specimens.<sup>4,15</sup> A pulmonologist can better combine clinical features and cytological characteristics together to make a diagnosis compared with a cytopathologist. Therefore, the pulmonologist who performed ROSE in our study not only assessed adequacy, but also provided a preliminary diagnosis of the most frequent lung diseases, and the diagnostic accuracy was high.

In conclusion, ROSE is comparable with histology in ensuring the adequacy of samples and sub-classifying the morphological

type of lung lesions in many cases. This would be beneficial in clinical practice. A trained pulmonologist can reliably carry out ROSE.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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