Article

Diagnostic Accuracy and Adequacy of Rapid On-Site Evaluation Performed by a Pulmonologist on Transbronchial Needle Aspi-Ration Specimens (DREPA): A Prospective Study

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Abstract: Introduction: Rapid on-site evaluation (ROSE) during transbronchial needle aspiration (TBNA) is conventionally performed by pathologists. However, availability of a pathologist in the bronchoscopy suite is often an issue. We aimed to study if a pulmonologist, after receiving a short period of training in cytopathology, is able to assess the adequacy of onsite samples during TBNA. Material and methods: A pulmonologist was initially trained by a pathologist in examining cytology slides and assessing sample adequacy on TBNA smears. During TBNA, one slide from each needle pass was stained on-site using rapid Giemsa stain and was labelled as ROSE slide. The remaining slides were sent to the pathology laboratory for definitive cytological analysis. The ROSE slides were examined by a pulmonologist and a pathologist blinded to each other's interpretation. Level of agreement between the pulmonologist and pathologist was assessed by estimating Cohen's kappa. Results: A total of 172 slides from 35 patients were prepared for ROSE and evaluated independently by pulmonologist and pathologist. For adequacy, the pulmonologist and pathologist agreed in 143 out of the 172 slides (83% agreement), κ 0.649 (p <0.001). For diagnostic categories, the pulmonologist and the pathologist agreed in 143 out of the 172 slides (83% agreement); κ 0.696 (p < 0.001). The sensitivity, specificity and accuracy of ROSE performed by the pulmonologist with respect to that performed by the pathologist was 66.2%, 96.8% and 83.1% respectively. Conclusion: After a short period of training in cytopathology, a pulmonologist can assess for adequacy of TBNA ROSE slides in the bronchoscopy suite.

Keywords: bronchoscopy; pathologist; pulmonologist; ROSE; TBNA

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1. Introduction

Transbronchial needle aspiration (TBNA) is a bronchoscopic procedure during which specimen is collected from lymph nodes/lesions outside the airway wall by inserting a needle through the airway wall. It is a well-established, minimally invasive technique. It is done in two ways, one is conventional TBNA (c-TBNA) in which specific landmarks during bronchoscopy are used to target a lymph node/mass lesion. The other is EBUS-TBNA, in which needle pass is done real-time using ultrasound (US) guidance through an endobronchial ultrasound (EBUS) video bronchoscope.

Rapid onsite evaluation (ROSE) is a procedure during which smears prepared during fine needle aspiration (FNA) are evaluated by the pathologist on-site, to ensure adequacy and render a preliminary broad diagnosis. Similarly, during TBNA, ROSE ensures adequacy of the sample and provides a preliminary diagnosis. It provides onsite guidance to the pulmonologist in either deciding to go for more needle passes or abort the procedure

in case an adequate sample is obtained. Studies have shown that the use of ROSE during TBNA reduces the number of needle passes, complication rates and the need for additional staging and diagnostic procedures [1,2]. A high agreement between ROSE and final pathological diagnosis has been shown [3].

ROSE is conventionally performed by pathologists. However, in most of the institutions availability of an on-site pathologist is often an issue due to lack of time, personnel, and resources. This problem could be circumvented by training the pulmonologist to assess the adequacy of samples during ROSE. In our study, we aimed to see if a pulmonologist, after a short period of training in cytopathology, is able to assess the adequacy of samples on-site during TBNA procedure. The objective of our study was to estimate the level of agreement between a pulmonologist and pathologist in assessing the adequacy of cytology slides on-site in the bronchoscopy suite.

2. Material and Methods

This was a hospital-based study carried out between January 2019 to June 2020. Patients more than 18 years of age who were posted for a TBNA procedure were enrolled in the study after taking informed written consent.

Before the enrolment of patients, pulmonologist was trained by the pathologists for performing ROSE in the bronchoscopy suite. During the training period which lasted one month, the pulmonologist analysed thirty ROSE slides under the supervision of pathologists. He was trained to identify squamous cells, ciliated columnar cells, lymphocytes, red blood cells, epithelioid cells, giant cells, atypical cells and the presence of granuloma and necrosis. As suggested by pathologists, the pulmonologist read relevant chapters from Orell and Sterrett's Fine needle aspiration cytology (5th edition) and Koss Diagnostic cytology (5th edition) during this training period. After receiving this initial training, this dedicated pulmonologist was involved in evaluating ROSE slides of patients enrolled in this study. Images of few ROSE slides used during training are shown in Figure 1.

The decision to perform conventional TBNA or EBUS TBNA was taken by the pulmonologist.–Bronchoscopy was performed under local anaesthesia using 2% lignocaine jelly and solution. Midazolam (1 mg/mL) and fentanyl (50 mcg/mL) were used for conscious sedation. For conventional TBNA (c-TBNA), Olympus BF-1T150 and BF-1TH190 flexible video bronchoscopes were used along with 21G TBNA needles for sampling the lesions. For EBUS TBNA, an Olympus BF-UC-180F bronchoscope with EU-ME1 ultrasound processor was used. 22G EBUS TBNA needles (NA-201SX-402, Olympus Medical) were used during EBUS TBNAs. Nasal/oral route was used for c-TBNA, while oral route was used for all EBUS procedures. These procedures were performed as per standard techniques [4–6]. Three to five punctures were done in a single lesion. Specimen collected in the lumen of the needle was flushed out by internal stylet and then blown over the slides. Four slides were made from each puncture. One slide from each puncture called a ROSE slide was immediately stained by the rapid Giemsa method.

This ROSE slide was coded using a number from a random number table and assessed independently initially by a pulmonologist and then by a pathologist sitting in another room. Thus, both the pulmonologist and pathologist were blinded to patient's clinical diagnosis and each other's findings. Olympus CX21i-LED (binocular version) biological microscope was used for microscopy. Adequacy of the sample was assessed using criteria proposed by Nayak et al. [7]. A sample was considered adequate if there was sufficient diagnostic material (e.g., tumour or granulomatous pathology) even in the absence of lymphoid tissue. The level of agreement between pulmonologist and pathologist was studied. The diagnostic categories used were granuloma, malignancy, negative for disease and non-diagnostic. The diagnostic category "negative for disease" was used when only lymphoid tissue was present without any specific diagnostic features. The sample was termed "non-diagnostic" when no lymphoid tissue and no specific diagnostic features were present.

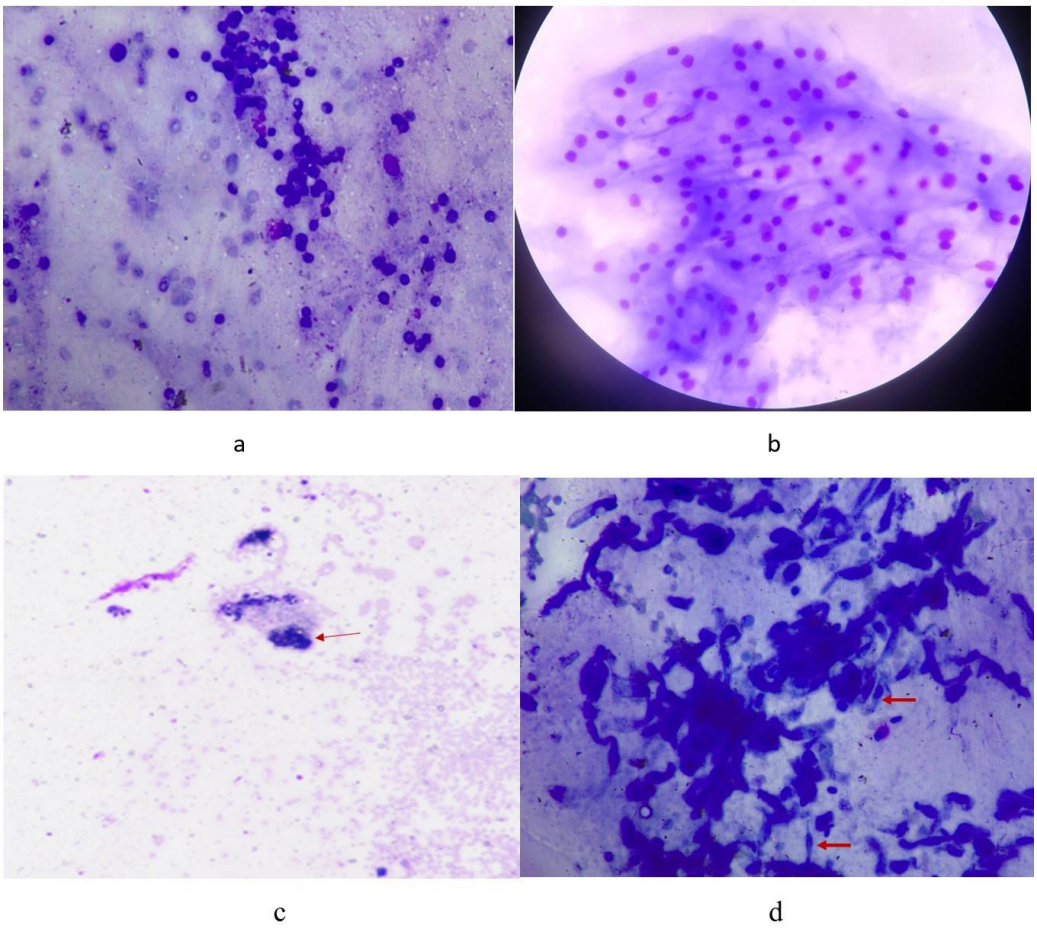

Figure 1. Images of few ROSE slides used during training of pulmonologists. (**a**) Rapid Giemsa stain; 400×; ROSE slide depicting numerous lymphocytes — Adequate; (**b**) Rapid Giemsa stain; 400×; TBNA smear showing sheet of benign squamous cells; (**c**) Rapid Giemsa stain; 100×; TBNA smear showing cluster of atypical cells (arrow); (**d**) Rapid Giemsa stain; 400×; TBNA smear showing endobronchial cells (arrow).

The remaining slides were wet fixed in 95% ethanol and were sent to the pathology laboratory for definitive cytologic evaluation. Needle rinses from each FNA pass was collected in 99% ethanol and saline if required. Sample in ethanol was processed as a cell block preparation. Sample in saline was sent for microbiological analysis. The workflow has been outlined in Figure 2.

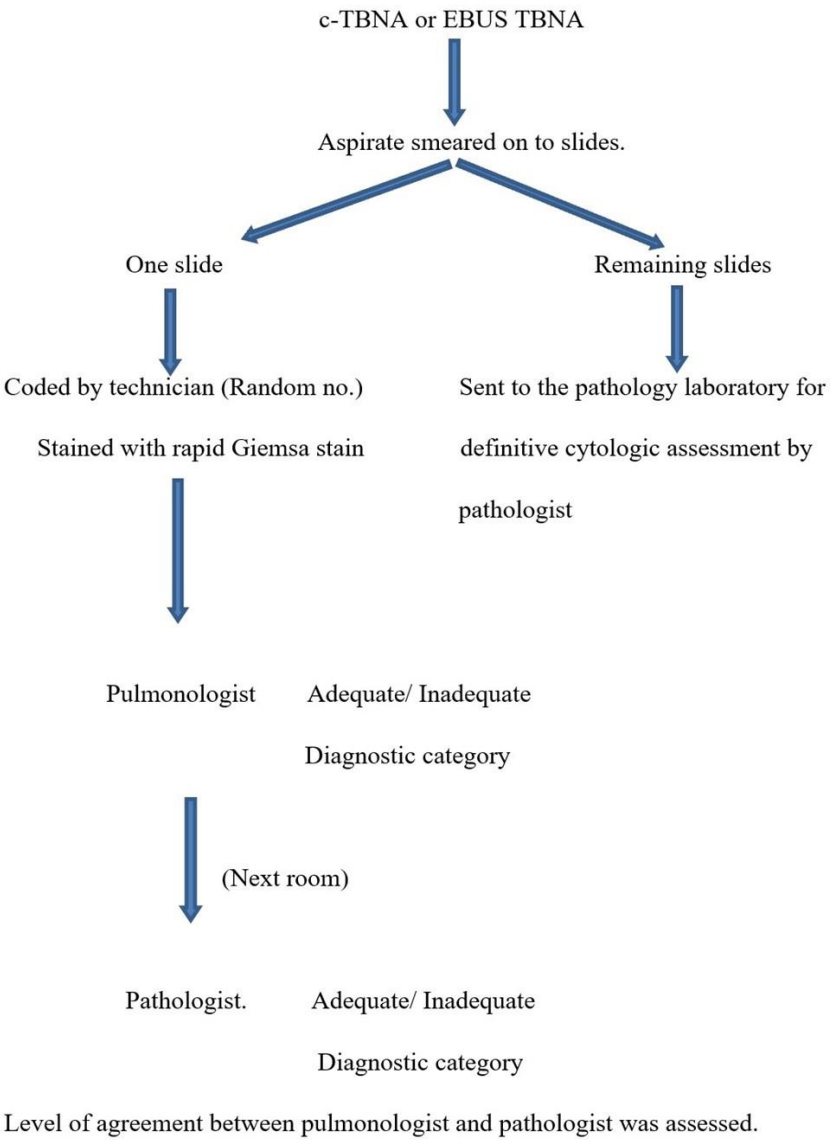

Figure 2. Workflow of our study.

The sample size (ROSE slides) calculated using the formula given by Temel et al. [8] was estimated to be 171 at 95% confidence interval, type II error of 0.2, 10% relative precision and 10% contingency. The level of agreement between the ROSE performed by pulmonologist and pathologist for adequacy and diagnostic categories was evaluated by calculating the Cohens kappa co-efficient (κ) [9].

$$\kappa = p_0 - p_e / 1 - p_e$$

p_0 — observed proportionate agreement, p_e — probability of random agreement.

The sensitivity, specificity, and accuracy of the pulmonologist for assessing the adequacy with respect to the pathologist was calculated. Statistical package for social sciences (SPSS) version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) was used for statistical analysis [10]. $p < 0.05$ was considered as significant.

3. Results

The median age of the patients was 55 (IQR 44.5–64) years. There were 26 males (77%) and 9 females (23%). Carcinoma lung with mediastinal lymph node involvement was the most common indication for TBNA in 24 (68.6%) patients, followed by sarcoidosis in 4 (11.4%), and pulmonary tuberculosis with mediastinal lymphadenopathy in 3 (8.6%) patients. Mediastinal lymph node metastases from an unknown primary in 2 (5.6%), carcinoma trachea with mediastinal lymph node involvement in 1 (2.9%), and mediastinal mass in 1 (2.9%) patient were some of the other indications. The characteristics of patients are shown in Table 1.

Table 1. Characteristics of study patients.

Number of study subjects (*n*)		35
Age in years (median; IQR)		55; (44.5–64)
Gender; *n* (%)	Males	26 (77%)
	Females	9 (23%)
Clinical diagnosis at presentation; *n* (%)	Pulmonary tuberculosis with mediastinal lymphadenopathy	3 (8.6%)
	Sarcoidosis	4 (11.4%)
	Carcinoma lung with mediastinal lymph nodal involvement	24 (68.6 %)
	Carcinoma trachea with mediastinal lymph node involvement	1 (2.9%)
	Mediastinal mass	1 (2.9%)
	Mediastinal lymph node metastases from an unknown primary	2 (5.6%)
Final cytological diagnosis; *n* (%)	Malignancy	19 (54.3%)
	Non-diagnostic	9 (25.8%)
	Granulomatous lymphadenitis	4 (11.4%)
	Necrotising granulomatous lymphadenitis	3 (8.5%)
Final diagnosis; *n* (%)	Non-small cell lung cancer	16 (14.7%)
	Small cell lung cancer	4 (11.3%)
	Sarcoidosis	4 (11.3%)
	Tuberculosis	3 (8.6%)
	Poorly differentiated malignancy	2 (5.7%),
	Aspergillus mediastinal lymphadenopathy	1 (2.9%)
	Reactive lymphadenopathy	1 (2.9%)
	Inflammatory polyp	1 (2.9%)
	Poorly differentiated sarcomatoid carcinoma	1 (2.9%)
	Adenoid cystic carcinoma	1 (2.9%)
	Fibrosing mediastinitis	1 (2.9 %)

A total of 172 slides were prepared for ROSE and evaluated independently by the pulmonologist and pathologist. 158 (91.9%) slides were prepared from samples obtained from mediastinal and hilar lymph nodes while 14 (8.1%) slides were prepared from samples obtained by puncturing a mass lesion. 107 slides (62.2%) were prepared from station 7, followed by 22 slides (12.8%) from station 4R, 18 slides (10.4%) from station10R, 12 slides (7%) from station 10L, and 6 slides (3.5%) from station 2R. 4 slides (2.3%) were prepared from material obtained from endobronchial needle aspiration (EBNA) of an endobronchial mass. The characteristics of various lesions which were sampled are elucidated in Table 2.

Table 2. Distribution of slides prepared from various lesions.

ROSE slides	*n* = 172	
Type of lesion; *n* (%)	Lymph node	158 (91.9%)
	Mass	14 (8.1%)
Stations sampled *n* (%)	2R	6 (3.5%)
	4R	22 (12.8%)
	4L	3 (1.8%)
	7	107 (62.2%)
	10R	18 (10.4%)
	10L	12 (7%)
	Mass (EBNA)	4 (2.3%)

Of the 172 slides evaluated independently by pulmonologist and pathologist, 54 slides were classified as adequate by the pulmonologist while 77 slides were classified as adequate by the pathologist. For adequacy, the pulmonologist and the pathologist agreed in 143 out of the 172 slides (83% agreement) with a kappa value (κ) of 0.649 (95% CI 0.533–0.766) considered as a substantial agreement ($p < 0.001$) (Table 3). Images of few ROSE slides assessed in the study have been shown in Figure 3.

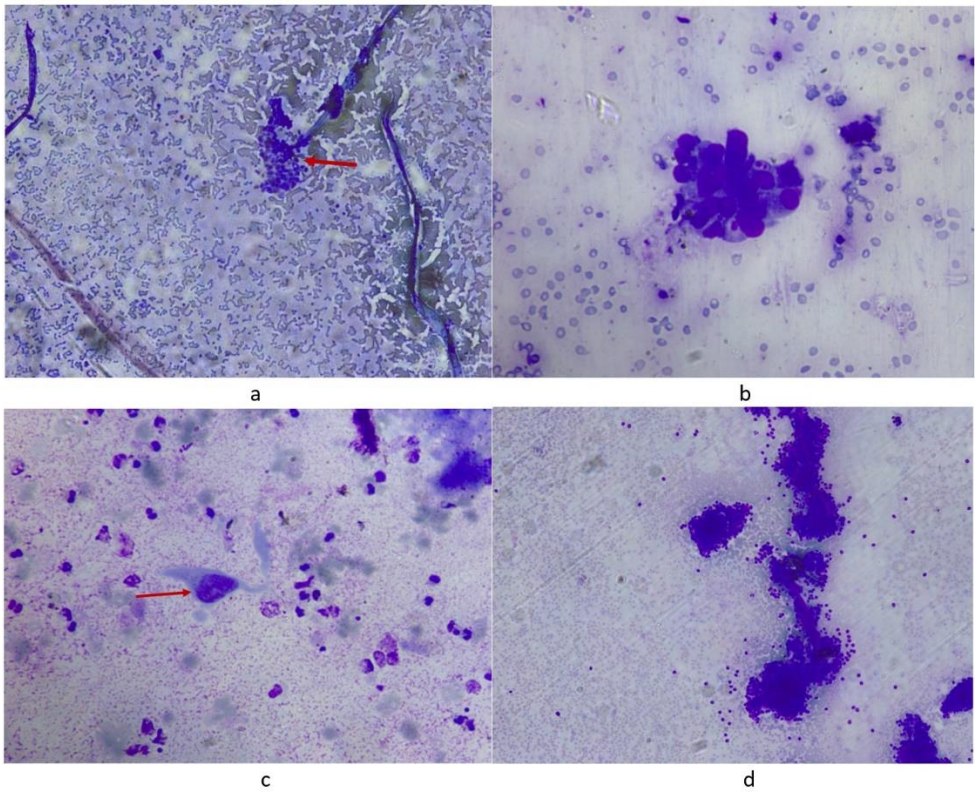

Figure 3. Images of few slides assessed in our study. (**a**) Rapid Giemsa stain; 100×; ROSE slide showing a cluster of atypical cells (arrow); (**b**) Rapid Giemsa stain; 400×; ROSE slide showing a cluster of atypical cells arranged in a rosette fashion; (**c**) Rapid Giemsa stain; 400×; ROSE slide showing a tadpole cell (arrow) reported as NSCLC (Magnification 400×). (**d**). Rapid Giemsa stain; 100×; ROSE slide depicting a cluster of basaloid cells with intervening basement membrane like matrix reported as adenoid cystic carcinoma.

For diagnostic categories on ROSE, 30 slides (17.4%) were classified as negative for disease by the pathologist, while 15 (8.7%) were classified as negative for disease by the pulmonologist. Forty-five (26.2%) were classified as malignant by the pathologist while 34 (19.8%) were classified as malignant by the pulmonologist. Only 95 (55.2%) slides were

non-diagnostic as per pathologist while 118 (68.6%) slides were non-diagnostic as per pulmonologist. Granuloma was seen in 2 (1.2%) slides by the pathologist while it was seen in 5 (2.9%) slides by the pulmonologist. A bar diagram depicting the distribution of diagnostic category on ROSE performed by pathologist and pulmonologist is shown in Figure 4. For diagnostic categories, the pulmonologist and the pathologist agreed in 143 out of the 172 slides (83% agreement) with a kappa value (κ) of 0.696 (95% CI 0.595–0.797) considered as a substantial agreement ($p < 0.001$) (Table 4). The sensitivity and specificity of ROSE performed by the pulmonologist with respect to that performed by the pathologist was 66.2% and 96.8% respectively. The accuracy of the pulmonologist was 83.1%.

Table 3. Level of agreement between ROSE performed by pathologist and pulmonologist for assessment of adequacy.

		ROSE Performed by the Pathologist		Total
		Adequate	Inadequate	
ROSE performed by the pulmonologist	Adequate	51	3	54
	Inadequate	26	92	118
Total		77	95	172

Observed agreement	**143 (83%)**
Measure of agreement—kappa	0.649 (95% CI 0.533–0.766) (Substantial)
***p* value**	<0.001

Table 4. Level of agreement between ROSE performed by pathologist and pulmonologist for assessment of diagnostic categories.

		ROSE Performed by a Pathologist				
		Granuloma	Malignancy	Negative	Non-diagnostic	Total
ROSE performed by a pulmonologist	Granuloma	2	0	0	3	5
	Malignancy	0	34	0	0	34
	Negative	0	0	15	0	15
	Non-diagnostic	0	11	15	92	118
	Total	2	45	30	95	172

Observed agreement	143 (83%)
Measure of agreement –kappa	0.696 (95% CI 0.595–0.797) (Substantial)
***p* value**	<0.001

The most common final cytological diagnosis was malignancy in 19 (54.3%) patients. No diagnosis on cytology could be achieved in 9 (25.8%) patients. Granulomatous lymphadenitis was seen in 4 (11.4%) patients. Necrotising granulomatous lymphadenitis was seen in 3 (8.5%) patients. The final diagnosis was the diagnosis obtained after evaluation of clinical, cytological, and histopathological findings. Most of the patients were diagnosed with non-small cell lung cancer 16 (45.7%) followed by small cell lung cancer 4 (11.3%) and sarcoidosis 4 (11.3%). 3 (8.6%) cases were of tuberculosis and 2 (5.7%) cases were of poorly differentiated malignancy. There was one (2.9%) patient each of aspergillus mediastinal lymphadenopathy, reactive lymphadenopathy, inflammatory polyp, poorly differentiated sarcomatoid carcinoma, adenoid cystic carcinoma and fibrosing mediastinitis.

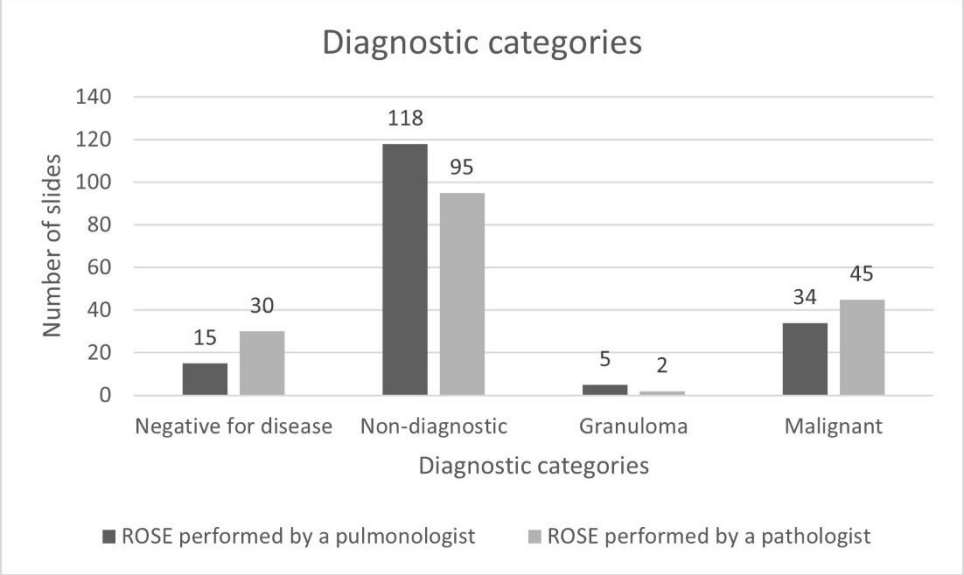

Figure 4. Bar diagram depicting distribution of diagnostic category on ROSE performed by pathologist and pulmonologist.

4. Discussion

ROSE plays an important role during TBNA. Though it has not shown to improve the diagnostic yield, it certainly helps in reducing the number of needle passes, need for additional biopsies and repeat procedures, thereby reducing the cost and complications associated with the procedure [1,2]. The major limiting factor with ROSE is the availability of onsite pathologist, especially in resource-constrained settings. Pathologists are required to reach the site where-procedure is being performed and wait till all the sites are sampled. Telecytology and cytotechnologists can help solve the problem to some extent. With telecytology, the pathologist can report the slides from the laboratory. Different telecytology systems like static imaging, dynamic real-time imaging using either live video stream or robotic microscopy, whole slide imaging have evolved [11]. Various studies have shown that the use of telecytology for ROSE is cost-effective and has a high concordance rate with onsite ROSE results [12–16]. However, the cost of infrastructure required and the availability of pathologist at the remote site at that exact time when the procedure is being performed will still be an issue. Cytotechnologists have been shown to demonstrate high agreement rates ranging from 70 to 90% with pathologists in ROSE [17–20]. However, in some countries, the use of cytotechnicians for ROSE may result in billing and medicolegal issues as a medical professional is not directly involved. In the US, medical professionals without CLIA license are allowed to use professional cytology billing codes for rapid assessment of fine-needle aspiration (FNA) samples [21].

Our study showed that pulmonologist after a short period of training in cytopathology is able to assess the adequacy of the cytologic smears during ROSE (83% agreement, κ 0.649, 95% CI 0.533–0.766, $p < 0.001$). Bonifazi et al. [22] in a prospective study, aimed to study the agreement between a pathologist and a pulmonologist in assessing the adequacy of specimens by ROSE during TBNA. The pulmonologist underwent three months of training under a board-certified cytopathologist. He also read textbooks on pulmonary cytopathology. Once the slides were prepared, they were stained by a rapid method using a Romanowsky type stain. They were first evaluated by the pulmonologist who assessed them for adequacy. The slides were then sent to the pathologist. Pathologist was blinded to the pulmonologists results. In 84 patients, a total of 362 ROSE's were performed. There was an 81% agreement between pulmonologists and cytopathologists with a kappa value of 0.73 ($p = 0.001$). Meena and colleagues [23], recruited 102 patients, in whom 164 separate sites were biopsied. Samples were obtained during EBUS TBNA, EUS TBNA and

percutaneous thoracic FNA. Diff Quik stain was used. The criteria by Jeffus et al. [24] were used to judge the adequacy of the samples when a lymph node was sampled. ROSE slides were first assessed by the procedural pulmonologist and then by the pathologist. The slides were assessed for adequacy and diagnostic category. As far as adequacy is concerned, there was a 98% agreement between pulmonologist and pathologist (κ, 0.72 ± 0.15). In the study by Hopkins et al. [25], the level of agreement between the two respiratory registrars and pathologist was 78% (κ, 0.568; 95% CI, 0.338–0.798) and 72% (κ, 0.448; 95% CI, 0.222–0.674) respectively.

In our study, for diagnostic categories, there was a substantial agreement between pulmonologist and pathologist (83% agreement, κ 0.696, 95% CI 0.595–0.797, $p < 0.001$). The disagreement was for 29 slides. In three slides that were non-diagnostic, artifacts were reported as granuloma by the pulmonologist. Atypical cells in eleven slides could not be identified by the pulmonologist and were reported as non-diagnostic by the pulmonologist. Fifteen slides that had adequate lymphocytes were reported as non-diagnostic by the pulmonologist. In the study by Meena et al. [23], for diagnostic category, there was an 86% agreement between pulmonologist and pathologist (κ, 0.89 ± 0.02). However, we believe that the role of a pulmonologist in ROSE should be limited to assessing the adequacy of samples and the diagnostic category should be assessed by a pathologist in the laboratory.

The skill of gastroenterologists in assessing the adequacy of specimens obtained during EUS-FNA from pancreatic masses has been shown to significantly improve after completion of a training program in cytopathology [26]. A curriculum to advance the knowledge and skills of cytotechnologists which includes ROSE has been outlined by the Cytotechnology Programs Review Committee (CPRC), the multi-society sponsored Committee on Accreditation under the Commission on Accreditation of Allied Health Education Programs (CAAHEP) [27]. The cytopathology division of the department of pathology of the University of Wisconsin has also developed an educational program for on-job training of cytotechnologists so that they become competent in assessing the adequacy of specimens during ROSE [28]. However, no such formal training program exists for pulmonologists in a majority of the pulmonary training centres across the world. In our study, the pulmonologist's gained theoretical knowledge by reading relevant chapters from standard cytopathology textbooks. They were trained by the pathologists to identify cells routinely seen in a rapid Giemsa stained TBNA smear. A structured training program needs to be devised to make pulmonologists competent in assessing the adequacy of specimens during ROSE. While the American society of cytopathologists (ASC) has taken a step forward in training cytotechnologists in ROSE [26], similar steps should also be taken for training pulmonologists especially for centres that have a heavy footfall of patients requiring TBNA.

There are currently no set standards for the training of pulmonologists in ROSE. Future studies may be planned which would standardize this and also look at the efficacy of pulmonologists in assessing the adequacy of specimens obtained during transthoracic FNAs and touch imprint cytology (ROSE-TIC) of transbronchial or image-guided transthoracic biopsies. In our study, we used the criteria used by Nayak et al. [7] for determining the adequacy of samples. However, in today's era of personalized medicine, especially for cases of lung cancer, a sample should be considered as adequate when sufficient material is also deemed to be available for mutation analysis. Larger multicenter studies may be conducted to look for inter-observer differences between pulmonologists in assessing on-site cytology specimens.

5. Conclusion

After a short period of training in cytopathology, a pulmonologist who regularly performs TBNAs is able to assess the adequacy of aspirated sample from the lesion and render a preliminary diagnosis of ROSE specimens without compromising its efficacy. The incorporation of a structured training of pulmonologists in ROSE into the interventional

pulmonology training curriculum is likely to benefit the outcome of this invasive and expensive diagnostic procedure.

Conflicts of Interest: None declared.

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