Adequacy Criteria of Rapid On-Site Evaluation for Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration: A Simple Algorithm to Assess the Adequacy of ROSE

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Background. **Rapid on-site evaluation (ROSE) for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has been advocated to qualitatively diagnose biopsy samples. However, adequate ROSE criteria during EBUS-TBNA are unclear. The aim of this study was to determine adequacy criteria of ROSE in EBUS-TBNA samples and suggest an appropriate algorithm.**

Methods. **Patients who underwent EBUS-TBNA for nodal evaluation between March and July 2013 at Seoul National University Hospital were included prospectively. The ROSE slides were reviewed independently by two pathologists, and the results were compared to the final pathologic results. Diagnostic yields, sensitivity, specificity, and accuracy were calculated in order to make nodal evaluations.**

Results. **EBUS-TBNA was performed on 300 lymph nodes in 133 patients. Samples were nondiagnostic in 7.7%, 6.3%, and 1.7% of the cytologic, histologic, and overall pathologic results, respectively. On the ROSE slides, a large tissue core size (≥2 cm), microscopic anthracotic pigment (MAP), and increased lymphocyte density (LD; ≥40 cells/field [40×, mean of 10 fields]) were significantly associated with adequate final cytologic or histologic results. Malignant cells were not statistically associated with adequacy but were considered a parameter indicating an adequate diagnosis. Using four sequential criteria, tissue core size, the presence of malignant cell, MAP, and LD ≥40 cells/field, the sensitivity and accuracy rates of ROSE increased from 64.4% to 98.6% and from 64.7% to 97.3%, respectively.**

Conclusions. **A high adequacy rate of ROSE in EBUS-TBNA can be achieved by sequentially applying four criteria: tissue core size, malignant cells, MAP, and increased LD.**

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Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has become an important tool in diagnostic bronchoscopy. Histologic and cytologic specimens are obtained from the mediastinal and hilar lymph nodes (LNs) using EBUS-TBNA in both malignant and benign diseases. EBUS-TBNA is preferred to cervical mediastinoscopy, especially when staging non-small cell lung cancer, because of its decreased invasiveness, excellent diagnostic accuracy, and applicability to a broad spectrum of nodal stations. Previous studies reported a diagnostic accuracy for EBUS-TBNA of 93% to 97.02%, which is comparable to that of cervical mediastinoscopy [1–3]. Efforts to improve the diagnostic accuracy of EBUS-TBNA have been evaluated, such as the number of punctures per target LN [4], specimen processing [5, 6] and rapid on-site evaluation (ROSE) [7].

ROSE has been used to augment the quality of specimens obtained by conventional TBNA, EBUS-TBNA, and other type of fine needle aspiration [8–11]. Potentially, the combination of ROSE and EBUS-TBNA could improve the diagnostic yield and reduce procedure-related complications. ROSE during EBUS-TBNA has been associated with a decreased incidence of repeat biopsy procedures and fewer punctures [7, 12], and may reduce post-procedure complications [7]. Furthermore, high agreement between ROSE and final pathologic results was also reported [13]. Despite these advantages, many institutions are unable to adopt ROSE due to a shortage of resources and personnel, especially pathologists. Notably,

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some pulmonologists have attempted to perform ROSE and have produced good results [14].

For pulmonologists who perform ROSE, easy and simple criteria are mandatory. Several retrospective studies suggested diagnostic ROSE criteria including the presence of malignant cells, a sufficient number of benign lymphoid cells, germinal center fragments, ≥3 punctures per LN, and the presence of anthracotic pigment-laden macrophages [15–18]. However, there is no organized algorithm available, and pulmonologists found some criteria difficult to use. Therefore, the present study aims to define adequate diagnostic criteria of ROSE for EBUS-TBNA and suggest a simple ROSE algorithm for use by pulmonologists.

Material and Methods

Patients

Patients who underwent EBUS-TBNA between March and July 2013 at a tertiary referral hospital in Korea were prospectively enrolled. All patients who were required evaluation of the hilar or mediastinal LNs by EBUS-TBNA were included. Patients who underwent puncture of a primary mass alone were excluded. All patients provided informed written consent, and the protocol was approved by the institutional review board of Seoul National University Hospital (IRB No: 1301-083-459).

EBUS-TBNA Procedure

Bronchoscopy was performed by four staff members of the Pulmonology Department or by supervised pulmonary fellows. A real-time linear probe (BF-UC260F-OL8; Olympus, Tokyo, Japan) was used for EBUS and a 22-guage needle (NA-201SX-4022; Olympus) for TBNA. EBUS-TBNA was performed with the patient under moderate sedation and local anesthesia using lidocaine. Sedation was induced using fentanyl (50 μg) and midazolam (2 mg); additional sedation was administered as needed. After white-light bronchoscopic evaluation, the EBUS scope was inserted. The mediastinal and hilar LNs were examined visually, and the targeted LNs were punctured. Each LN specimen was evaluated on a glass slide for visible anthracotic pigments or necrosis, and the nodal station was classified according to the seventh TNM classification. The procedure time and number of punctures were recorded. The number of punctures and the decision to end sampling were dependent on the clinical situation, as well as on the judgment of the operator.

Preparation of EBUS-TBNA and ROSE Specimens

The entire aspirate was expelled onto a glass slide, and the tissue core was fixed in 10% formalin for hematoxylin and eosin staining. The length of the tissue core was recorded. The remaining aspirate was expressed onto a glass slide and smeared using a second glass slide. One smear was air-dried and stained immediately with a rapid Giemsa-type stain (Diff-Quick [DQ], Fisher Scientific, Kalamazoo, MI) for ROSE in the bronchoscopy room, and the second was fixed in 95% alcohol for permanent cytologic examination using Papanicolaou stain. Specimen processing is summarized in Figure 1.

EBUS-TBNA Pathologic Diagnosis and Evaluation of Diagnostic Accuracy Using DQ Slides

The specimens that were fixed in formalin and 95% alcohol were processed according to the routine practice of the Department of Pathology. DQ-stained slides for ROSE were collected for analysis and later analyzed independently by 2 blinded pathologists for diagnostic adequacy. The slides were evaluated and graded according to the microscopic anthracotic pigments (MAP) (absent, scattered, and conglomerated), malignant cells (absent, background lymphocytes, and tumor cell only), and lymphocyte density (LD, <40, 40 to 200, and >200 cells/field, 40× magnification, mean of 10 fields). Representative samples are illustrated in Figure 2. When the two interpretations were discordant, the final decision was determined by consensus.

The final pathology reports were considered the diagnostic gold standard. If the pathology results were diagnostic, whether positive or negative, for malignant cells, then the EBUS-TBNA was considered adequate. If the pathology results were inadequate, blood only, or no tissue, then the EBUS-TBNA were deemed inadequate.

Statistical Analysis

Diagnostic yields, sensitivity, specificity, and accuracy were calculated for nodal evaluations. The χ^2 or Fisher's exact test were used to compare categorical variables and the Mann-Whitney *U*-test for continuous variables. Odds ratios (ORs) were calculated using the binary logistic regression model. A $p < 0.05$ was considered statistically significant. SPSS 19.0 statistical software (Chicago, IL) was used for analysis.

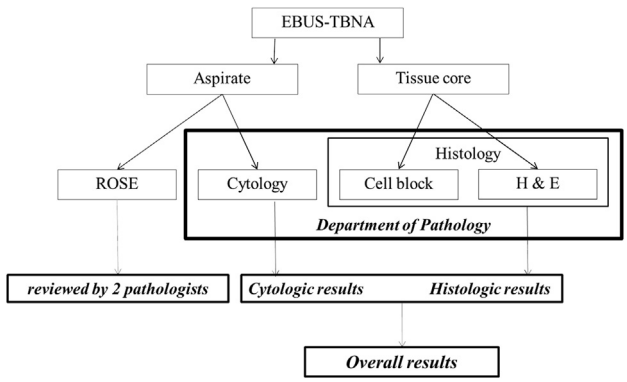

Fig 1. Tissue Preparation of Specimens Procured by EBUS-TBNA. The entire aspirate was expelled on a glass slide, and the tissue core was separated from the aspirate. The tissue core was processed for histologic evaluation, and the remaining aspirate was smeared for rapid on-site evaluation (ROSE) and cytologic evaluation. The cytologic and histologic specimens were evaluated routinely, and ROSE slides were evaluated independently by two pathologists. (EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration; H & E = hematoxylin and eosin.)

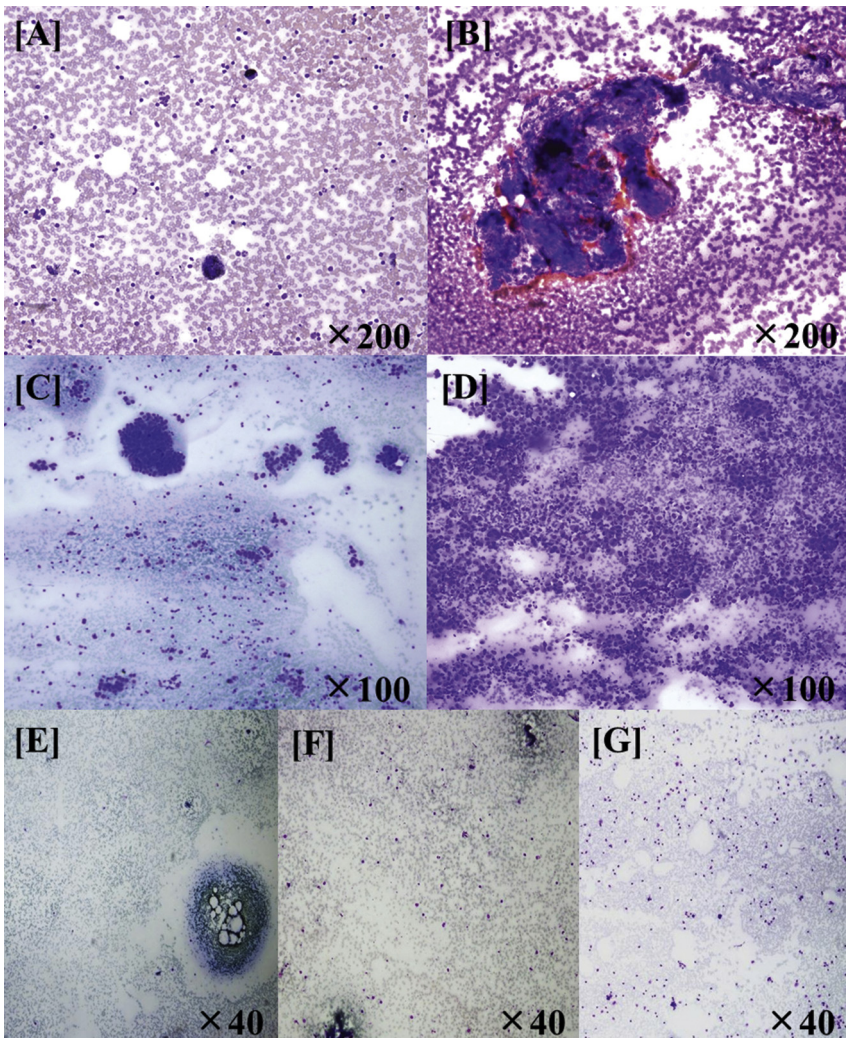

Fig 2. Representative Microscopic Grading Using ROSE. Microscopic anthracotic pigments (scattered [A], conglomerated [B]), malignant cells (background lymphocytes [C], tumor cells only [D]), and mean lymphocyte density per 10 fields at 40× (<40 cells [E], 40–200 [F], >200 [G]). (ROSE = rapid on-site evaluation.)

Results

Baseline Characteristics

A total of 152 patients were eligible, and 19 patients were excluded: 16 patients declined to participate and 3 patients underwent EBUS-TBNA for evaluation of a primary mass. Finally, 133 patients were enrolled, and 300 LNs were evaluated by ROSE. Table 1 summarizes the baseline characteristics of the 133 patients. The median age was 67 years, and males comprised 67.7% of the population. The majority (75.9%) of patients underwent EBUS-TBNA for diagnosis or staging of lung cancer. The final diagnoses included lung cancer (75.9%), metastasis from extrathoracic cancer (8.3%), lymphoma (2.3%), tuberculosis (3.8%), sarcoidosis (5.3%), and other (4.7%; Table 2).

Procedure-related variables are summarized in Table 3. A median of 2 LNs per patient were evaluated by ROSE. The median time and punctures per node were 11 min and three attempts, respectively. During the procedure, the median doses of midazolam and fentanyl for moderate sedation were 3 mg and 50 μg, respectively.

The median LN size was 12.3 mm. The most common nodal station of EBUS-TBNA was 7 (30.7%), followed by 4R (30.4%). The median maximal standardized uptake

Table 1. Baseline Characteristics of the Patient Population

Variables	Values
Age, years	67 (56–73)
Male	90 (67.7)
Smoking status	
Never smoker	53 (39.8)
Ex-smoker	49 (36.8)
Current smoker	31 (23.3)
Reasons for EBUS-TBNA	
Lung cancer diagnosis or staging	101 (75.9)
Suspicious metastasis from extrathoracic cancer	7 (5.3)
Evaluation of mediastinal lymphadenopathy	25 (18.8)

Data are presented as n (%) or the median (interquartile range).

EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration.

Table 2. Final Diagnoses in the Patient Population

Diagnoses	Values
Lung cancer	100 (75.2)
NSCLC	95
Squamous cell carcinoma	28
Adenocarcinoma	54
SqCC + SCLC	1
Neuroendocrine differentiation	1
Poorly differentiated carcinoma	1
NSCLC, not otherwise specified	10
SCLC	6
Extensive disease	4
Limited disease	2
Metastasis from extrathoracic cancer	10 (7.5)
Lymphoma	3 (2.3)
Tuberculosis	6 (4.5)
Sarcoidosis	7 (5.3)
Anthracosis	3 (2.3)
Other[a]	2 (1.5)

[a] Reactive lymph nodes, mediastinal hemangioma.

Data are presented as n or n (%).

NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; SqCC = squamous cell carcinoma.

value (SUV_{max}) was 4.7 (interquartile range, 3.3–7.7) in 121 patients who also underwent fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT). The final pathologic diagnosis of the LNs are summarized in Table 4. The majority of LNs were diagnosed as normal (59.2%), but malignant cells were identified in 28.8% of LNs. Approximately 1.5% of the specimens were non-diagnostic.

Findings of EBUS-TBNA Specimens

Table 5 details the procedure-related parameters and ROSE-related parameters. A tissue core ≥2 cm was obtained in 63.7% of LNs. Gross anthracotic pigmentation within the aspirate was found in 32% of LNs, and gross necrosis was found in 6.3% of LNs. MAP and tumor cells were observed on microscopic examination in 87% and 4.7% of specimens, respectively. An LD ≥40 was observed in 81.7% of specimens.

Table 3. EBUS-TBNA Procedure Parameters

Variables	Values
Lymph nodes per person	2 (1–3)
Passes per node	3 (2–4)
Total procedure time (min)	26 (20–43)
Pre-EBUS bronchoscopic time (min)	5 (3–8)
EBUS time per person (min)	22 (15–33)
EBUS time per node (min)	11 (8–15)
Sedatives	
Midazolam (mg)	3 (3–5)
Fentanyl (μg)	50 (50–50)

Data are presented as the median (interquartile range).

EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration.

Table 4. Characteristics of the Evaluated 300 Lymph Nodes

Variables	Values
Size (mm)	12.3 (10.3–14.9)
SUVmax on FDG-PET[a]	4.7 (3.3–7.5)
Nodal station	
1R	2 (0.6)
2R	20 (6.3)
4R	96 (30.4)
4L	42 (13.3)
7	97 (30.7)
10R	13 (4.1)
10L	1 (0.3)
11R	24 (7.6)
11L	14 (4.4)
12R	7 (2.2)
Overall pathology	
Malignancy	89 (28.2)
Atypical	12 (3.8)
Lymphocyte with no tumor	187 (59.2)
Granuloma	19 (6.0)
Anthracosis	4 (1.3)
Nondiagnostic	5 (1.6)

[a] SUV_{max} was evaluated in 278 lymph nodes using FDG-PET.

Data are presented as n (%) or the median (interquartile range).

FDG-PET = fluorodeoxyglucose-positron emission tomography/computed tomography; SUV_{max} = maximal standardized uptake value.

Among all the parameters, ≥3 punctures per node, the presence of tumor cells, MAP, and high LD in smears were significantly related to adequate results on permanent aspiration cytology. On permanent tissue histology, a core tissue size ≥2 cm, MAP, and high LD in smears were significantly related to adequate results. When determining the adequacy of cytology or histology as overall adequate on pathology, a core tissue ≥2 cm ($p = 0.06$), MAP ($p = 0.017$), and LD ≥40 cells/field (40×; $p = 0.004$) were correlated to overall adequate results on univariate analysis (Table 6).

Algorithm for Adequacy Evaluation

The 3 variables that were associated with overall adequete results (tissue core ≥2 cm, presence of MAP, and LD ≥40 cells/field at 40×) and the presence of malignant cells indicating a definitive diagnosis were constructed into an algorithm to improve the diagnostic accuracy of ROSE. As shown in Figure 3, the accuracy for adequacy of the specimen was increased from 64.7%, using only the first criterion, to 97.0% using the following four sequential criteria: (1) core size ≥2 cm, (2) presence of malignant cells, (3) presence of MAP, and (4) LD ≥40 cells/field (40×). The sensitivity for adequacy of the specimen was also much improved: from 64.4% using only the first criterion, to 98% using the same four sequential criteria.

Table 5. Parameters Evalauted to Gauge the Adequacy of ROSE

Parameters	Values
Procedure-related parameters	
Passes per node	3 (2–4)
Core size	
Absent	11 (3.7)
<1 cm	47 (15.7)
≥1 and <2 cm	51 (17.0)
≥2 cm	191 (63.7)
ROSE-related parameters	
Gross findings	
Gross anthracosis	96 (32)
Gross necrosis	19 (6.3)
Microscopic findings	
MAP	
Absent	39 (13.1)
Scattered	29 (9.7)
Conglomerated	232 (77.3)
Malignant cells	
Absent	239 (79.9)
Lymphocytes background	47 (15.7)
Tumor cell only	14 (4.7)
LD	
<40/x40	55 (18.3)
40–200/x40	44 (14.7)
>200/x40	201 (67)

Data are presented as n (%) or the median (interquartile range).

LD = lymphocyte density; MAP = microscopic anthracotic pigment; ROSE = rapid on-site evaluation.

Comment

In this study, we evaluated ROSE criteria and proposed an algorithm to assess the adequacy of ROSE. The scheme included both procedure-related parameters and microscopic findings as follows: number of punctures (≥3 per node), length of core tissue (≥2 cm), the gross appearance of aspirated specimens (pus-like or anthracotic), presence of tumor cells, presence of MAP, and high LD in aspirates. Among these factors, we selected four clear objective criteria based on producing overall adequate results. The first criterion requires assessment of the specimen determining whether the core size is ≥2 cm on gross inspection. For small specimens (<2 cm), the algorithm proceeds to the second criterion, which searches for visible malignant cells on ROSE. If there are no visible malignant cells, the third criterion is to determine the presence of MAP. If MAP is not observed, then the LD is estimated. We found that a stepwise application of these four criteria increased the diagnostic adequacy of ROSE (Fig 3). This study is the first known attempt to create a scientific algorithm to assess the adequacy of ROSE.

ROSE can help pulmonologist when performing TBNA gauge whether to repeat or end the procedure by determining the adequacy of specimens. Recent randomized controlled trials reported that ROSE reduces the median number of needle punctures, complication rates, and the procedure time for TBNA [7, 19]. However, despite these benefits, there is limited application of ROSE in general daily practice because a trained cytopathologist is required to perform it. To encourage greater adoption of ROSE in clinical practice, several studies have investigated the accuracy of clinicians other than cytopathologists, including pulmonologists [14] and cytotechnologists [20] at assessing ROSE specimens. A recent study assessed the accuracy of cytotechnologists at gauging the adequacy of 3,032 ROSE specimens obtained by fine needle aspirate. In the study, ROSE was assessed as adequate in 75.2% of specimens and inadequate in 12.1% by cytotechnologists. Among the cases considered adequate by ROSE, 99.6% of the specimens were deemed adequate in the final report [20].

There have been a few studies investigating adequacy criteria of ROSE for EBUS-TBNA. One study suggested several criteria including any smear with at least 100 lymphocytes in at least five fields at 100× and <2 aggregates of bronchial cells/100× field, the presence of germinal center fragments, and significant pathological findings positive for malignancy or granuloma [17]. However, some parameters were subjective, especially germinal center fragments and granuloma. In our study,

Table 6. Univariate Analysis of Variables Assessing the Specimen Adequacy

	Cytology Adequacy		Histology Adequacy		Overall Adequacy	
Variables	n = 277	*p* Value	n = 281	*p* Value	n = 295	*p* Value
Passes ≥3	172 (62.1)	0.003	171 (60.9)	0.107	178 (60.3)	0.162[a]
Core ≥2 cm	179 (64.6)	0.233	185 (65.8)	0.003	190 (64.4)	0.06[a]
Gross necrosis	19 (6.9)	0.379[a]	17 (6.0)	0.343[a]	19 (6.4)	>0.999[a]
Gross anthracosis	91 (32.9)	0.272	92 (32.7)	0.291	96 (32.5)	0.181[a]
Malignant cells	61 (22)	0.006[a]	60 (21.4)	0.138[a]	61 (20.7)	0.587[a]
Presence of MAP	245 (88.4)	0.018[a]	248 (88.3)	0.025[a]	259 (87.8)	0.017[a]
LD ≥40/40×	235 (84.8)	<0.001[a]	237 (84.3)	<0.001[a]	244 (82.7)	0.004

[a] Fisher's exact test.

Data are presented as n (%).

LD = lymphocyte density; MAP = microscopic anthracotic pigment.

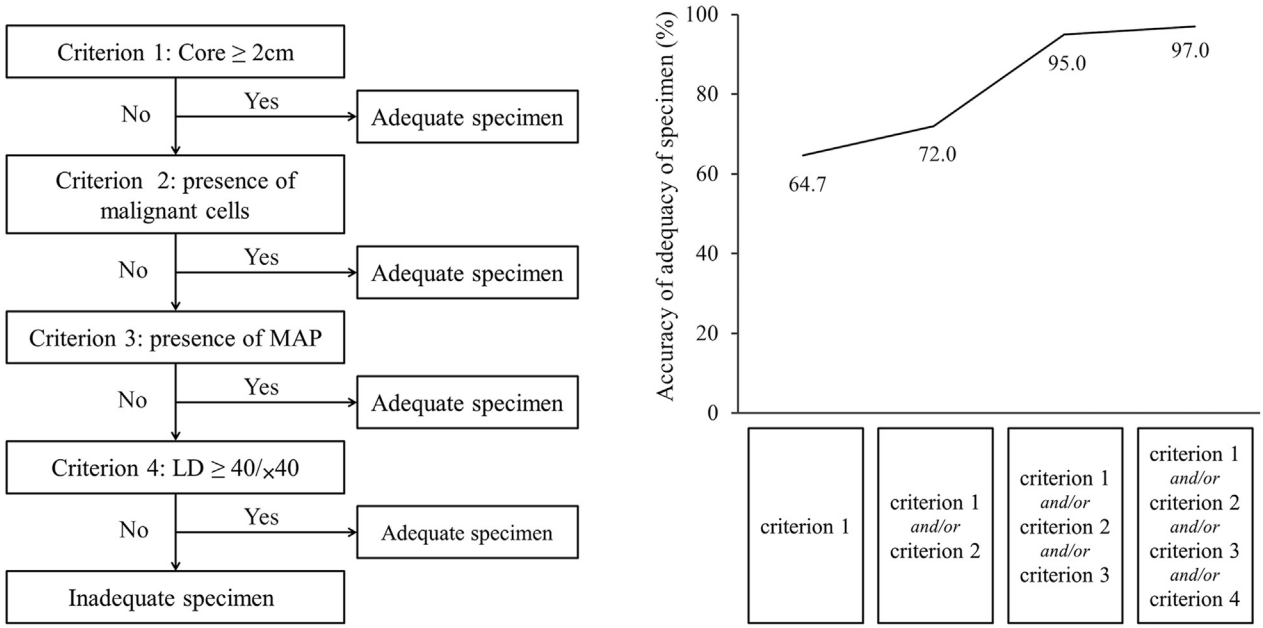

Fig 3. Proposed Algorithm to Evaluate the Adequacy of ROSE. A sequential approach comprising four criteria (core size ≥ 2 cm, presence of malignant cells, presence of microscopic anthracotic pigments [MAP], and mean lymphocyte density [LD] ≥ 40 cells/10 fields at 40×) resulted in a high diagnostic accuracy of 97% for rapid on-site evaluation (ROSE).

we presented objective microscopic criteria: visible malignant cells, MAP, and LD. These criteria can be used easily by pulmonologists to evaluate the adequacy of ROSE. Furthermore, they will inform pulmonologists when deciding whether or not to repeat the procedure. If any of the adequacy criteria are not met, EBUS-TBNA should be repeated to ensure an adequate specimen is retrieved. It is important to reduce the number of punctures and biopsies; not only to shorten procedure time but also to decrease the risk of procedure-related complications.

This study has several limitations. First, although the slides were created during the EBUS-TBNA procedure, we did not assess ROSE during the procedure, as explained in the Material and Methods section. Thus, we were unable to evaluate any potential advantages of ROSE during EBUS-TBNA; such as reduction of procedure-related complications, decreased incidence of repeat procedures, and fewer punctures [7, 12]. Second, we made this adequacy algorithm of ROSE using our own cohort, and did not validate it using a different cohort. In order for this algorithm to be applicable in clinical practice, further validation using other cohorts is required. Third, because this study was conducted in a clinic that would be considered a high-volume EBUS-TBNA center, it may not be possible to generalize the results herein and apply them to small-volume centers. Fourth, the tissue acquisition technique may vary between institutions. For example, some institutions may use a no-suction technique [21]. However, we used the standard suction technique as recommended by the device manufacturer.

In conclusion, a high rate of adequate ROSE specimens can be obtained during EBUS-TBNA by sequential application of criteria including tissue core size, presence of malignant cell, presence of MAP, and increased LD. This algorithm is simple and easy for clinicians to apply to ROSE.

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