Assessing ROSE for adequacy of EBUS-TBNA compared with a direct-to-cell block approach as a response to the COVID-19 pandemic

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Introduction: Rapid on-site evaluation (ROSE) has been used during the endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) procedure as standard practice. Because of the COVID-19 (coronavirus disease 2019) pandemic, our institute had had to discontinue ROSE and adopt a direct-to-cell block approach. In the present study, we aimed to determine whether this change has had significant effects on the cytopathology quality.

Materials and methods: A total of 1903 EBUS-TBNA cases from 734 patients were collected (1097 cases with ROSE for 452 patients; 806 cases without ROSE but with direct-to-cell block for 282 patients). The clinical and cytology data were analyzed using SAS, version 9.4, software to render calculated standardized residuals and a fitted multivariate generalized linear model.

Results: On average, a biopsy from a patient with ROSE was 0.936 ($=\exp -0.066$) times less likely to be reported as satisfactory compared with a biopsy from a patient without ROSE, although the difference was not statistically significant ($P = 0.785$). The inadequacy rate of EBUS-TBNA was 6.4% higher on average for cases with ROSE compared with a direct-to-cell block approach. However, this difference was also not

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statistically significant. The proportions of biopsies reported as diagnostic for malignancy and other were significantly different between the ROSE and no-ROSE groups with a standardized residual of 1.80 ($P = 0.036$) and -2.27 ($P = 0.012$), respectively.

Conclusions Discontinuing ROSE and using a direct-to-cell block approach had no negative effects on cytopathology quality. This practice can be considered acceptable during the COVID-19 pandemic when social distancing and the shortage of staff and supplies have resulted in challenges to delivering quality care to cancer patients whose treatment cannot be postponed.

Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a revolutionized technique that has become the recommended modality for diagnosing and staging lung cancer and hilar and mediastinal lymph nodes (LNs) for other etiologies.[1] Numerous studies have demonstrated that EBUS-TBNA is an accurate, minimally invasive, and cost-effective procedure compared with other methods such as mediastinoscopy.[1,2] EBUS-TBNA uses a flexible bronchoscope equipped with ultrasound capabilities to view beyond the walls of the airways to detect in real time the precise locations of LNs or lesions. High-resolution, real-time ultrasound imaging enables direct visualization of the EBUS-TBNA needle as it penetrates the LN. Because nondiagnostic specimens will usually require repeat procedures, including bronchoscopy, thoracoscopy, transthoracic needle aspiration, or more invasive procedures, obtaining an accurate diagnosis the first time is critical for patient care because it reduces patient anxiety, possible complications, mobility, costs, future risks, and the interval to definitive treatment.

Immediate feedback from on-site review can help improve one's technique and needle positioning. Rapid on-site evaluation (ROSE) of the cytology aspirate has been used during the needle aspiration procedure to improve the diagnostic yield,[3-7] decrease unnecessary passes, and, ultimately, decrease the risk and complications associated with additional sampling, as well as decreasing the time and cost.[6,8-12] Some investigators have argued that the use of ROSE does not help obtain adequate specimens, can only confirm specimen adequacy after the fact,[13] and that more recent randomized studies found no differences in adequacy or diagnostic yield with and without ROSE.[8-10,14] However, most institutes have recommended the use of ROSE during TBNA, in particular to improve clinical decision-making, including triage samples for flow cytometry analysis, microbiology studies, or predictive molecular testing for personalized treatment.[6,7,9,12,14,15] The concordance rate between ROSE and the final pathologic diagnosis has been very high.[12,15-17]

Because of the coronavirus disease 2019 (COVID-19) pandemic and in response to the high-risk nature of obtaining EBUS-TBNA specimens, social distancing, and staff and supply shortages, our institution had decided abruptly to discontinue ROSE for EBUS-TBNA and, instead, adopted a direct-to-cell block approach. The main rationale for choosing a cell block preparation instead of liquid-based methods, such as ThinPrep or SurePath, was that the cell block can be used for future immunostains, special stains, or molecular tests, if needed. We collected real-world data to determine whether removing ROSE affected the adequacy of the samples obtained from the EBUS-TBNA procedures and the quality of care provided by cytopathology. If no significant effects on patient care were found, a direct-to-cell block approach could be used in the cytopathology service and still provide the standard of care to patients during the COVID-19 pandemic. If the effects were negative, methods to overcome this challenge must be found.

Materials and methods

Study cohort

The data for all patients who had undergone EBUS-TBNA at the Moffitt Cancer Center from January 1, 2019 to December 31, 2020 were collected from the database. Biopsy specimens taken from different sites (ie, lung, station 7 LN, station 11R LN) for the same patient were processed as individual cases. ROSE was performed from January 1, 2019 to March 23, 2020. From March 24, 2020 to December 31, 2020, when ROSE was unavailable, the samples were collected directly in a balanced salt solution (BSS) and processed as a cell block. Data collection included patient age and gender, specimen sites, total number of biopsies per patient, and the final cytopathologic diagnosis. The specimen collection sites included the lesion or mass and LNs, including stations 4L, 4R, 11L, 11R, 7, and others. The main cytopathologic diagnosis categories included unsatisfactory, no evidence of malignancy, atypical, suspicious for malignancy, diagnostic for malignancy, and other. The adequacy criteria (satisfactory versus unsatisfactory) were determined from the final cytopathologic diagnosis, not from the ROSE interpretation. Any diagnosis other than unsatisfactory was considered satisfactory. No adequacy criteria have been defined for cell blocks for LN sampling. The pathologists at our

institute consider a LN cell block adequate when ≥2 areas of lymphoid tissue fragments under a low power field or malignant cells are identified. The clinical indications for the procedure, number of passes for each biopsy site, on-site adequacy evaluation information, and diagnostic sub-categories (eg, malignancy − adenocarcinoma, squamous cell carcinoma, small cell carcinoma, metastasis) were not included or subcategorized in the present study. Any patients included in ROSE group but who had undergone another EBUS procedure later and were included in the no-ROSE group were automatically excluded by the statistical model design.

The Moffitt Cancer Center institutional review board approved the present study (approval no. MCC 21618). The institutional database was interrogated. We performed a retrospective review of the data from our database; thus, the study was classified as a low and negligible risk research project and written informed consent from the patients was deemed not necessary.

EBUS-TBNA and specimen processing

EBUS-TBNA was performed using an Olympus UC-180F endobronchial ultrasound fiberoptic bronchoscope, with a 22-guage Olympus TBNA needle, by bronchoscopists. The sites for TBNA were chosen from the clinical staging, radiologic studies, and intraprocedural findings. The contralateral LNs (N3 nodes) were biopsied first. Next, the ipsilateral LNs (N2 nodes), N1 LNs, and the lesion, if applicable, were biopsied to avoid potential needle contamination. The biopsy needle was flushed with saline when switching sites. The usual time required per biopsy site was 3 to 5 minutes. When ROSE was available, 3 to 4 continuous passes of each site were collected, with 2 slides prepared for on-site evaluation and the remaining 1 to 2 passes placed in BSS for cell block preparation. One slide was air-dried and stained using the Diff-Quik method on site, and the other slide was alcohol-fixed and later stained with Papanicolaou in the laboratory. On average, an additional 3 to 5 minutes were required for ROSE per biopsy site. If the ROSE resulted in a malignant diagnosis in an N3 LN, the procedure was terminated. However, the bronchoscopists were likely to continue to the next available LN if the positive LN had been an N2 LN. When ROSE was unavailable, all material was collected in BSS for cell block processing. Sedation was achieved with fentanyl and reversed if moderate sedation had been used or with remifentanil and propofol if monitored anesthesia care were available. This was in addition to local anesthesia with 2% lidocaine. Patients received continuous cardiac monitoring, including blood pressure and pulse oximetry.

Cell block preparation was performed in accordance with our institution's laboratory procedures. In brief, a clot was made from the cell pellet after specimen centrifugation to combine equal amounts of plasma and thrombin solution. The clot was then fixed in formalin, embedded in a paraffin block, and sectioned.

Statistical analysis

Two separate multivariate generalized linear models were built to assess the association of each repeated measure binary outcome to the main predictor, the ROSE group (yes versus no), by controlling for other covariates. The first model measured the repeated measure binary outcome satisfactory versus unsatisfactory and the second, the repeated measure binary outcome diagnostic for malignancy and suspicious for malignancy versus all other diagnostic categories. Both outcomes were measured by taking multiple biopsies from each patient. To build the model, the generalized estimating equation with the logit LINK function was used in SAS software, version 9.4. The final model was built using the backward selection method at an α level of 0.1. All the covariates that were not significant at an α level of 0.1 were eliminated. However, for both models, the ROSE group was forced into the models at every step of backward selection, even if not statistically significant at an α level of 0.1 because it was the primary interest of the present study. For the first outcome of satisfactory versus unsatisfactory, the full model included ROSE, specimen sites, total number of biopsies per patient, and patient gender and age. After backward selection, only ROSE and specimen sites remained in the final reduced model. For the second outcome of diagnostic for malignancy and suspicious for malignancy versus all other diagnostic categories, the full model included ROSE, specimen sites, total number of biopsies per patient, and gender. However, only ROSE, specimen sites, and the total number of biopsies per patient remained in the final reduced model.

Results

During the study period, a total of 1941 cases for 743 patients were retrieved. Nine patients (38 cases) had initially been included in the ROSE group but had had repeated visits during the period in which ROSE was not available and, thus, were automatically excluded from the study by the statistical model design. Thus, data from 1903 cases for 734 patients were collected (Table 1). In brief, 1097 cases for 452 patients were included in the ROSE group and 806 cases for 282 patients were in the no-ROSE group. The mean patient age for each group was 68.25 and 66.59 years, respectively. Both groups had had a slight male predominance. However, the difference in patient age and gender between these 2 groups was not statistically significant ($P = 0.442$ and $P = 0.658$, respectively).

In the satisfactory versus unsatisfactory outcome model, the variables comparing the two groups (ROSE and no-ROSE) included patient age, gender, total number of biopsy

Table 1 Comparison of patient demographics and adequacy measures.

ROSE	Study period	Total (n)	Mean age (years)	Male/female ratio	Unsatisfactory (n; %)	Satisfactory (n; %)
Yes	1/1/2019-3/23/2020	1097	68.25	1.13	64 (5.83)	1033 (94.17)
No	3/24/2020-12/31/2020	806	66.59	1.06	47 (5.83)	759 (94.17)

Abbreviation: ROSE, rapid on-site evaluation.

counts, and biopsy collection sites. The only significantly associated variable was the biopsy collection site (Table 2). On average and holding the specimen site variable constant, no difference was observed regarding adequacy (unsatisfactory versus satisfactory; Table 1) for the 2 ROSE groups ($P = 0.785$). However, a biopsy sample taken from LN 7 and LN 4R were 2.14 ($= \exp^{0.760}$) and 2.57 ($= \exp^{0.9456}$) times more likely to be reported as satisfactory compared with a biopsy taken from a lesion or mass. The differences were statistically different ($P = 0.0098$ and $P = 0.0041$, respectively; Table 2). The reason for the greater satisfactory rate with biopsies of LN 4R and 7 was that the LN location allows for better accessibility. It will be easier to obtain a satisfactory sample from lesions or masses located closer to the main bronchus or its branches than from peripheral lesions. Among the commonly biopsied LNs, station 4R includes the lower paratracheal LNs and station 7, the subcarinal LNs. They are not adjacent to a vital organ as are the LNs in station 4L, which are next to the aortic arch and left main pulmonary artery and, thus, will be easier to reach compared with a peripheral lesion.

When comparing the total number of biopsy sites performed for each patient in the ROSE and no-ROSE groups, the mean ± standard deviation for each group was 2.43 ± 2.30 and 2.86 ± 2.70, respectively, a statistically significant difference ($P < 0.0001$). The most frequently encountered biopsy count per patient was 1 in the ROSE group (35.4% of patients; Table 3 and Fig. 1). Approximately 23%, 19%, and 15% of patients in the ROSE group had had 3, 2, and 4 biopsies performed, respectively. Three patients had had 7, 8, and 10 biopsies on 2 separate visits in the ROSE group.

Table 2 Satisfactory outcome comparison using multivariate generalized linear model with generalized estimating equation.

Specimen collection site	P value	OR	95% CI
LN, 4L	0.8797	1.047	0.576-1.905
LN, 4R	0.0041[a]	2.570	1.350-4.910
LN, 11L	0.4216	1.321	0.670-2.607
LN, 11R	0.1559	1.641	0.828-3.254
LN, 7	0.0098[a]	2.139	1.201-3.810
LN, other	0.3139	1.666	0.617-4.502
Lesion	Ref	Ref	Ref

Abbreviations: CI, confidence interval; LN, lymph node; OR, odds ratio; Ref, reference.
[a]Statistically significant.

In contrast, the most frequently encountered biopsy count per patient in the no-ROSE group was 3 (28.01% of patients). Approximately 23%, 22%, and 17% of patients in the no-ROSE group had had 4, 1, and 2 biopsies, respectively. No repeat visit was observed in the no-ROSE group. As stated, EBUS-TBNA was terminated if a N3 node were interpreted as malignant during ROSE. We suspect this was the most important factor causing the difference in biopsy counts between these 2 groups.

The comparison of the frequency of the final cytopathologic diagnosis (Table 4) between the ROSE and no-ROSE groups revealed no statistically significant differences for the unsatisfactory, no evidence of malignancy, atypical, and suspicious for malignancy categories. However, a statistically significant difference was identified between the diagnostic for malignancy and other categories ($P = 0.036$ and $P = 0.012$, respectively). The malignancy diagnoses include non−small cell carcinoma, small cell carcinoma, large cell neuroendocrine carcinoma, squamous cell carcinoma, adenocarcinoma, neuroendocrine neoplasm, lymphoma, metastatic cancer, and other malignant neoplasm (ie, rhabdomyosarcoma). The diagnoses included in the other category were granuloma, predominant necrotic debris, cannot rule out a lymphoproliferative disorder, thymoma, and scant cellularity. Although the details of the clinical indications for EBUS-TBNA were not included in the present study, we suspect these differences resulted from unavoidable patient selection due to the COVID-19 pandemic. Patients with clinical and/or radiologic findings that were less suspicious were less likely to be advised to undergo an EBUS-TBNA procedure owing to the pandemic and more likely to be scheduled for closer observation. In contrast, if clinical suspicion remained high, EBUS-TBNA would have been performed.

Discussion

EBUS-TBNA is a very accurate, safe, and minimally invasive modality for the diagnosis and staging of lung cancer and mediastinal lymphadenopathy. Nakajima et al,[16] Wong et al,[12] and Mallya et al[15] have demonstrated a high concordance rate between the ROSE findings and the final surgical diagnosis. The success of TBNA can be influenced by many factors in addition to the use of ROSE, such as the instruments used, location and size of the LNs, experience of the proceduralist, the patient population, and disease

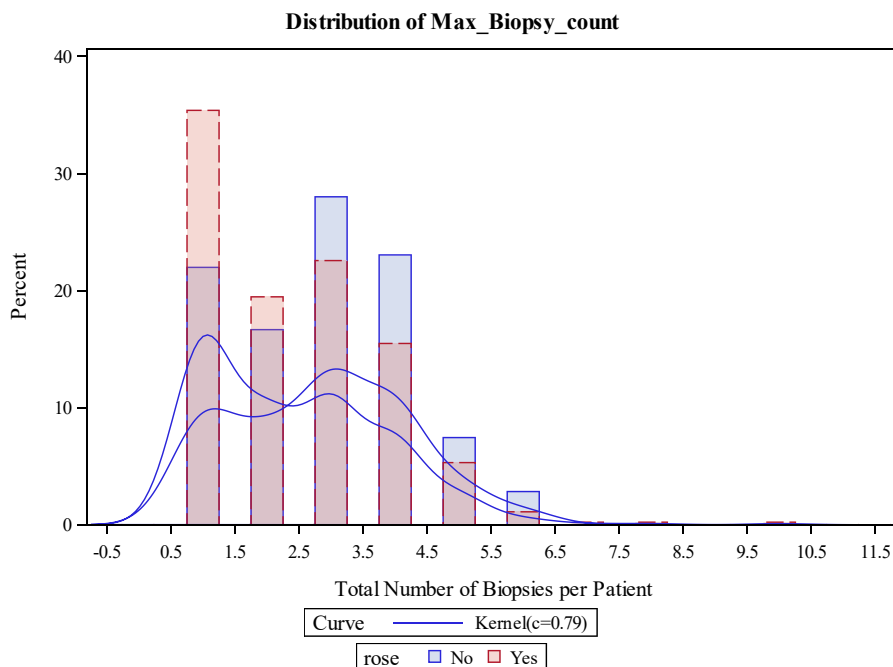**Table 3**   Summary of total number of biopsy counts per patient.

ROSE	Biopsy count								
	1	2	3	4	5	6	7	8	10
Yes	160 (35.4)	88 (19.47)	102 (22.57)	70 (15.49)	24 (5.31)	5 (1.11)	1 (0.22)	1 (0.22)	1 (0.22)
No	62 (21.99)	47 (16.67)	79 (28.01)	65 (23.05)	21 (7.45)	8 (2.84)	0 (0)	0 (0)	0 (0)

Data presented as n (%).
Abbreviation: ROSE, rapid on-site evaluation.

prevalence. The latter two factors can interfere with the diagnostic yield of certain diseases. Before EBUS had become available, needles were inserted into the LNs or lesions blindly. Hence, the experience of the bronchoscopist and the presence of an on-site cytopathologist were critical for an adequate diagnosis. Immediate feedback from the cytopathologist could help to adjust the needle positioning, improve the technique, and train proceduralists. The early studies from Davenport[3] and Diette et al[4] proved that the use of ROSE significantly increased the adequacy and diagnostic yield. However, the more recent randomized studies from Yarmus et al[10] and Trisolini et al[9] demonstrated no differences in adequacy or diagnostic yield between the study groups, indicating that the benefits of ROSE observed in previous studies might have resulted from selection bias. In addition, ROSE is time-intensive for the cytopathology service and is often poorly reimbursed. These limitations have prompted attempts to decrease the time and costs required for several methods, including using cyto-technologists only or using telecytology.

When the COVID-19 pandemic started, the high-risk nature of obtaining EBUS-FNA specimens, the requirements for social distancing, and other reasons meant that our institution had had to abruptly discontinue the use of ROSE for EBUS-TBNA and, instead, had adopted a direct-to-cell block approach. The present study was initiated as a quality project to compare the real-world data with prior information to determine whether removing the use of ROSE affected the adequacy of samples obtained via EBUS-TBNA and the quality of care provided by cytopathology. We performed a retrospective review of all patients who had undergone EBUS-TBNA during 2 different periods—before COVID-19 with ROSE in use and during COVID-19 when the use of ROSE was discontinued. The results from our study have also demonstrated no statistically significant differences in adequacy (satisfactory versus unsatisfactory) between the ROSE and no-ROSE groups. Trisolini et al[9] showed that the use of ROSE significantly decreased the complication rates of bronchoscopy ($P = 0.011$). TBNA is a minimally invasive, and thus very safe, procedure compared with other biopsy methods such as forceps biopsy, which had caused the complications in the study by Trisolini et al.[9] Other groups have also shown that the use of ROSE decreased the number of punctures and number of lesions sampled, reducing the overall risk and costs.[8,10,12] The same trend was also observed in our study

Figure 1   Distribution of total number of biopsy count per patient.

Table 4 Comparison of final cytopathology diagnosis.

ROSE	Unsatisfactory	No evidence of malignancy	Atypical	Suspicious for malignancy	Diagnostic for malignancy	Other
Yes	64 (5.83)	695 (63.35)	37 (3.37)	10 (0.91)	244 (22.24)	47 (4.28)
No	47 (5.83)	496 (61.54)	24 (2.98)	12 (1.49)	208 (25.81)	19 (2.36)
P value	0.499	0.209	0.314	0.122	0.036[a]	0.012[a]

Abbreviation: ROSE, rapid on-site evaluation.
Data presented as n (%).
[a]Statistically significant.

(Table 3 and Fig. 1). Our result have also demonstrated that the most frequent biopsy sites in the ROSE group was 1 but was 3 in the no-ROSE group. The mean number $\pm$ standard deviation of the biopsy sites per patient in the ROSE and no-ROSE groups in our study was 2.42 ± 1.40 and 2.85 ± 1.35, respectively ($P < 0.0001$). A comparison of the major complication rates and causes was beyond our study, and these data were not collected in the present study.

The current guidelines and studies have shown that 3 passes taken from each biopsy site will be sufficient to obtain an adequate specimen.[18,19] The bronchoscopists at our institute have consistently collected 3 to 4 passes at each biopsy site, regardless of the use of ROSE. Hence, although the outcomes of complication rates or costs were not measured in our study, we would not have expected to find differences between these 2 groups. In addition, our proceduralists are well-trained and very experienced and, thus, less likely to affect the adequacy outcomes between the 2 groups in the present study.

In our institute, the use of ROSE increases the time spent by both the cytopathology service and the bronchoscopy unit. Although additional time is required for ROSE, proceduralists in training might benefit from the immediate on-site evaluation to improve their technique. However, if a N3 node were diagnosed as malignant via ROSE, the procedure would have been terminated. The actual time spent per case varies widely and will depend on the clinical indication, radiologic findings, and proceduralist preference.

Our study showed a significantly higher rate of a malignant diagnosis and a lower rate of other diagnoses between the ROSE and no-ROSE groups. Although the clinical indications for TBNA were not included in our study, and no demographic differences were found between the 2 study groups, we suspect a patient selection factor could have been present because of the COVID-19 pandemic. It is common sense that the care of cancer patients should not be delayed even during a pandemic such as COVID-19. In addition, patients with clinically and radiologically more suspicious findings were more likely to undergo biopsy, with patients with less suspicious findings receiving closer monitoring.

Another factor that could have been affected by ROSE is sample triage. It has been reported that samples will be managed and processed better with ROSE, such as sending for microbiology culture or flow cytometry.[6,7,9] On further investigation in our study, 7 cases (all with concurrent flow cytometry results) from 5 patients and 11 cases (6 with concurrent flow cytometry results) from 8 patients had had a diagnosis of lymphoma in the ROSE and no-ROSE groups, respectively. Flow cytometry analysis was ordered by the clinician on the basis of the patient's medical history and clinical and radiologic findings. Regarding the 5 cases for which flow cytometry was not ordered, the diagnosis of lymphoma was determined from the immunostains and molecular studies performed on the cell block. However, 3 of the 7 cases in the ROSE group had had a diagnosis of Hodgkin lymphoma, which cannot be made using flow cytometry analysis. Additional samples can be collected for molecular studies, which is important for personalized treatment.[9,17] In the present study, we did not evaluate whether the cellularity of the cell block for each case had been sufficient for molecular studies. However, because all the samples collected in the no-ROSE group had been processed as cell blocks, the cellularity of the cell block was expected to be higher. Additional molecular studies can be performed on formalin-fixed, paraffin-embedded cell block sections on request.

Our study was a retrospective review of the adequacy of EBUS-TBNA specimens from a single specialized cancer institute. Thus, the patient population and disease prevalence will be quite different from those of the general population. Although no differences were found in patient age and gender before and during the COVID-19 pandemic, patient selection was unavoidable because of the pandemic.

Conclusions

The use of ROSE did not affect the adequacy rate for EBUS-TBNA biopsies compared with a direct-to-cell block approach in our study, suggesting that the discontinuation of the use of ROSE was a reasonable decision during the COVID-19 pandemic. Not using ROSE also decreased the time and cost burden to the cytopathology service but still provided the same quality of care to patients during the pandemic. However, the clinical indication, proceduralist preference, and the need for sample triage are important

factors to consider on a case-by-case basis when determining whether ROSE would be required. If the use of ROSE is deemed clinically critical, it should be performed with caution during the COVID-19 pandemic.

Funding sources

Conflict of interest disclosures

The authors made no disclosures.

Acknowledgments

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