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Rapid On-Site Cytologic Evaluation: A Feasibility Study Using Ancillary Interventional Pulmonary Personnel

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Abstract
Background: Ancillary health professionals helping in a procedural service is a common practice everywhere. ***Objectives:*** This was a proof-of-concept study to assess feasibility of using ancillary personnel for rapid on-site cytologic evaluation (ROSE) at interventional pulmonary procedures. ***Methods:*** After a training interval, a respiratory therapist (RT) performed ROSE on consecutive interventional pulmonary specimens. Sample sites included lymph nodes, lung, liver, and the left adrenal gland. RT findings were subsequently correlated with blinded cytopathology-performed ROSE and with final histopathology results, with primary foci of adequacy and the presence or absence of malignancy. ***Results:*** Seventy consecutive cases involved 163 separate sites for ROSE analysis. ***Adequacy:*** There was a high level of concordance between RT-performed ROSE (RT-ROSE) and cytopathology ROSE (CYTO-ROSE). They agreed upon the adequacy of 159 specimens. The Cohen's κ coefficient ± asymptotic standard error (ASE) was 0.74 ± 0.175, with $p < 0.0001$. ***Malignancy:*** RT-ROSE concurred highly with CYTO-ROSE, with agreement on 150 (92%) of the 163 specimens. Cohen's κ coefficient ± ASE was 0.83 ± 0.045, with $p < 0.0001$. When the comparison was for malignancy by case rather than individual site, Cohen's κ coefficient ± ASE was 0.68 ± 0.08, with $p < 0.0001$. ***Conclusion:*** This study demonstrates that ancillary personnel supporting an interventional pulmonary service can be trained to perform initial ROSE. Cytopathology can be called after sampling and staining have produced adequate samples. This setup streamlines ROSE evaluation with regard to time and cost.

Introduction

Rapid on-site cytologic evaluation (ROSE) gives the opportunity to establish adequacy and a preliminary diagnosis at the time of a procedure and can have a significant beneficial impact upon procedure duration while helping to maintain diagnostic accuracy. On the other hand, ROSE can create inefficiency for the proceduralist if he/she must wait for the cytopathologist and/or for the

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Table 1. Breakdown of sites sampled with final diagnoses

Final diagnosis	Cases, *n*	Site(s) of biopsy			
		lymph node	lung	liver	adrenal gland
Adenocarcinoma, lung primary	22	39	12		1
Squamous cell carcinoma, lung primary	11	22	2	1	
Benign lymph node	10	24			
Sarcoidosis	7	20	2		
Small cell lung cancer	4	8	2		
Adenocarcinoma metastatic to lung	4	7	2		
Hodgkin's lymphoma	3	2	1		
Inadequate	2	4	1		
Neuroendocrine carcinoma	1	0	1		
Metastatic renal cell carcinoma	1	2		1	
Metastatic melanoma	1	1			
T-cell lymphoma	1	1			
Germ cell tumor	1	2			
Blastomycosis	1	3	1		
Choriocarcinoma	1	1			
Total	**70**	**136**	**24**	**2**	**1**

cytopathologist, who must leave his/her office, travel, and process and review serial slides.

That pulmonologists can be trained to perform ROSE has been demonstrated [1, 2]. Pulmonologists were able to determine both adequacy and diagnostic category of cytologic specimens with high levels of concordance when compared with cytopathologists' readings. This capacity to prepare and screen specimens both obviated proceduralist wait times and economized cytopathologist time in the bronchoscopy suite [2]. In this follow-up study, we sought to determine how effectively support personnel in the bronchoscopy suite could be trained to independently evaluate cytologic samples obtained in the pulmonary procedure suite.

Methods

At our institution, interventional pulmonary performs several needle aspiration procedures for which ROSE is utilized; endobronchial ultrasound with transbronchial needle aspiration biopsy, esophageal ultrasound with transesophageal fine needle aspiration, and transcutaneous fine needle aspiration (FNA) biopsies. When transbronchial lung biopsies are performed for possible cancer, we also perform ROSE on touch preps from those biopsies. All biopsies are performed in a negative pressure room in the endoscopy suite. The interventional pulmonary attending and fellow perform the procedures, while a respiratory therapist (RT) assists both with the procedures and with slide preparation. The interventional pulmonary staff is experienced in ROSE analysis [2]. For the purposes of this study, the RT was trained for 3 months by the interventional pulmonary attending. Then, over the study period, the RT performed and documented ROSE (RT-ROSE) on consecutive cases.

Materials for ROSE were air dried and stained using Diff-Quik. Both classical ROSE components [3] were assessed and documented: (1) on-site adequacy and (2) when adequate, the presence or absence of malignancy. For lymph nodes, liver, and adrenal, a sample containing representative tissue and without evidence of malignancy was labelled "adequate and benign." Granulomas, if present, were identified. A sample containing malignant tissue was labelled adequate and positive. For lung biopsies, a sample was considered adequate only if it contained cellular material not typical of normal lung. That material, if present, was deemed "adequate and benign" if a finding such as granulomas was identified and "adequate and malignant" if malignant cells were identified.

For study samples, each biopsy was stained and then analyzed by the RT (RT-ROSE), who wrote down her diagnostic impression. The RT was aware of the same basic information that was subsequently given to pathology – very brief relevant history, nature and location of lesion, presence of mass if the biopsy was of possible nodal metastases. Once the RT had written her impression, a cytopathologist came and, blinded to the RT reading, performed ROSE (CYTO-ROSE). RT-ROSE findings were later correlated with CYTO-ROSE and with the final official histopathology report (CYTO-final). Although not a component of this study protocol, on-site analysis also included an assessment either by the interventional pulmonologist or by the cytopathologist (not by the RT) of specimen adequacy for subsequent molecular testing were it to become relevant (this is a routine component of all of our procedures).

Table 2. Specimen adequacy: RT-ROSE v CYTO-ROSE

	CYTO-ROSE		Total
	adequate	inadequate	
Nodes[a]			
RT-ROSE			
Adequate	134	1	**135**
Inadequate	0	1	**1**
Total	**134**	**2**	**136**
Lung[b]			
RT-ROSE			
Adequate	21	0	**21**
Inadequate	1	2	**3**
Total	**22**	**2**	**24**
Combined[c]			
RT-ROSE			
Adequate	158	1	**159**
Inadequate	1	3	**4**
Total	**159**	**4**	**163**

RT-ROSE, respiratory therapist-performed rapid on-site examination; CYTO-ROSE, cytopathologist-performed rapid on-site examination. [a] Kappa coefficient: 0.66 ± ASE of Kappa: 0.32 $p = 0.0147$. [b] Kappa coefficient: 0.78 ± ASE of Kappa: 0.21 $p = 0.0109$. [c] Kappa coefficient: 0.74±ASE of Kappa: 0.175 $p < 0.0001$.

Table 3. Malignancy: RT-ROSE v CYTO-ROSE

	CYTO-ROSE		Total
	malignant	benign	
Nodes[a]			
RT-ROSE			
Malignant	36	3	**39**
Benign	8	89	**97**
Total	**44**	**92**	**136**
Lung[b]			
RT-ROSE			
Malignant	17	0	**17**
Benign	2	5	**7**
Total	**19**	**5**	**24**
Combined[c]			
RT-ROSE			
Malignant	56	3	**59**
Benign	10	94	**104**
Total	**66**	**97**	**163**

RT-ROSE, respiratory therapist-performed rapid on-site examination; CYTO-ROSE, cytopathologist-performed rapid on-site examination. [a] Kappa coefficient: 0.81 ± ASE of Kappa: 0.055 $p < 0.0001$ [b] Kappa coefficient: 0.78 ± ASE of Kappa: 0.145 $p = 0.0005$ [c] Kappa coefficient: 0.83 ± ASE of Kappa: 0.045 $p < 0.0001$.

SPSS26 statistical software by International Business Machines was used for statistical data analysis. Two-by-two contingency tables were prepared for individual biopsy sites and for cases. Inter-rater reliability was assessed using a simple Cohen's κ coefficient and associated asymptotic standard errors (ASEs). Fisher's exact test was used, with $p < 0.05$ considered to be statistically significant.

Results

Over 70 consecutive cases, 163 separate sites were biopsied and subjected to ROSE. Patient ages ranged from 12 to 82 years (median, 64). Male:female ratio was 1:1. Procedures were as follows: 55 underwent endobronchial ultrasound with transbronchial needle aspiration biopsy, 17 underwent esophageal ultrasound with transesophageal fine needle aspiration, 13 underwent transbronchial lung biopsies (for which 3 utilized navigational bronchoscopy), and 4 underwent transthoracic lung FNAs (number of procedures is greater than number of cases, as some cases involved >1 biopsy approach). The 163 individual biopsy sites subjected to ROSE were as follows: lymph node – 136, lung – 24, liver – 2, left adrenal – 1. Table 1 lists procedures and final diagnoses.

For analysis, cases were subdivided into "nodes," "lung," and "combined," which included all 163 sites (lung, nodes, liver, and adrenal). Table 2 lists adequacy for both subgroups and the total study population. There were high levels of concordance for both subsets and for the total study sample (all kappa ≥ 0.66, all $p \leq 0.0147$). There was consensus on 161 (98.8%) specimens and discordance for only 2 sites (1.2%), one of each of which was called adequate by either the RT or the cytopathologist and inadequate by the other.

Table 3 lists results for diagnostic category – malignant versus benign. Once again, there were high levels of concordance for lung, nodes, and all biopsies combined (all kappa ≥ 0.78, all $p \leq 0.0005$). For biopsies evaluated separately ($n = 163$), there was consensus for 150/163 (92%). Finally, Table 4 lists malignancy by case ($n = 70$), grouping all biopsies performed on the same individual. For diagnosis of benign versus malignant by case there was consensus for 60/70 (86%). The kappa coefficient was 0.68, with $p < 0.0001$.

Although not the primary goal of the study, diagnosis of benign versus malignant by case for RT-ROSE was compared with CYTO-final. For this comparison, the

Table 4. Malignancy by case – RT-ROSE v CYTO-ROSE

	CYTO-ROSE		Total
	malignant	benign	
RT-ROSE			
Malignant	41	1	**42**
Benign	9	19	**28**
Total	**50**	**20**	**70**

RT-ROSE, respiratory therapist-performed rapid on-site examination; CYTO-ROSE, cytopathologist-performed rapid on-site examination. Kappa coefficient: 0.68 ± ASE of Kappa: 0.08 $p < 0.0001$.

Kappa coefficient ± ASE was 0.71 ± 0.086. Only 1 case (1.4%) which was on final histopathology found to be a reactive lymph node was called malignant by RT-ROSE. Eight cases (11.4%) called benign by RT-ROSE were called malignant on CYTO-final. Of these 8 cases, 3 were lymphomas, 2 were squamous-cell lung cancers, 1 was small-cell lung cancer, 1 was metastatic adenocarcinoma, and 1 a germ cell tumor.

Sub-analysis for RT-ROSE accuracy for diagnosis of granulomas was also performed. There were 9 cases with granulomas identified on final histopathology. RT-ROSE identified 6 and missed 3. In addition, RT-ROSE called granulomas on 2 cases not noted to have granulomas on final pathology. Cohen's κ coefficient (±ASE) was 0.66 ± 0.139, with a p value <0.0001.

Discussion

There are several potential benefits to ROSE. Most importantly, ROSE can confirm adequacy and that the final cytology report will reflect the organ being sampled [4]. This can result in a multifaceted procedural economy: (1) ROSE decreases the need for repeat diagnostic procedures [5]. (2) ROSE can decrease the number of needle passes, sites biopsied, and slides generated [6, 7]. (3) Finally, although not a component of the original ROSE criteria, an assessment of adequacy can include an assessment of adequacy of collected tissues for future molecular testing or flow cytometry [7, 8]; if this can be confirmed at time of procedure, it too can minimize the need for repeat procedures. A corollary is that although the presence of ROSE does not decrease the complications of the procedure being "ROSED," the decrease in a need for additional procedures is likely to decrease overall complications [5]. One would expect that on-site documentation of adequacy would increase diagnostic yield, but the collective data on pulmonary procedures have not demonstrated an increase in yield [5]. In addition, in the collected literature, the decrease in number of needle passes is counterbalanced by time spent by cytopathology, leading to no significant difference in procedure duration [5]; for traditional ROSE, one must wait for cytopathology to arrive, stain, and analyze.

While ROSE can create several efficiencies, it imposes a significant time burden upon the cytopathologist. Layfield et al. [9] demonstrated an average time expenditure of 55.3 min for a cytopathologist supporting bronchoscopy using FNA, with a resultant net financial loss. Cost exceeded compensation by USD 40–50 per case, a marked difference from routine surgical pathology, "for which a pathologist can generate approximately USD 638 per hour." [9] Cytopathologist performance of ROSE can decrease total medical expenditures but this is at the expense of the cytopathologist him/herself [9–11], leading to what Dhillon et al. [10] deemed a "compensation crisis."

If cytopathologist time per case can be decreased, the "compensation crisis" can be eliminated. Prior work has demonstrated the ability of a pulmonologist to interpret ROSE specimens [1, 3]. In our study, this markedly diminished on-site cytopathologist time, which averaged 4.02 min [2], far shorter than the 55.3 documented by Layfield et al. [9] (note that this did not include travel time, which was included in the Layfield figure). This shortening of the time involvement changes the cytopathologist's cost-benefit analysis dramatically and further increases the overall cost-benefit equation for ROSE [12]. In our prior study, this cytopathologist time savings involved time expense on the part of the pulmonologist, as procedures had to be paused for slide analysis [2]. Another solution is for a cytotechnologist to perform ROSE: although the literature is heterogenous, it has been recurrently demonstrated that cytotechnologists and other non-cytopathologists can perform ROSE with reasonable accuracy [6, 13–15]. For the procedure to generate income, however, a cytopathologist must be involved; cytotechnologist time would otherwise represent lost income.

This study has several limitations. Perhaps the greatest limitation is a probable lack of reproducibility. Our institution has several relatively unique characteristics which made this study feasible. First, we have interventional pulmonologists who actively stain and interpret cytology specimens. It is our belief that, just as pulmonologists do not rely solely upon radiologists for roentgenographic in-

terpretation, similarly interventional pulmonologists should be familiar with cytologic analysis. We (and others) have published data that demonstrate that we can achieve reasonable competence [1, 2], and our interventional fellows routinely participate in cytologic analysis. Second, we have support staff that is both dedicated to interventional pulmonary (and thus consistently present) and also willing to be trained in basic cytologic interpretation. Our institution thus has several features that may be relatively unique, such that others may not be able to reproduce and benefit from our approach. Finally, the visual learning involved in slide interpretation may not be as easy for some as it is for others, and our *n* of 1 in this case may represent an unusually "talented" individual, such that others with similar setup might still not be able to replicate our results. For these reasons, we consider this to be a proof-of-concept study more than a generalizable approach.

This study shows that a motivated supporting member of an interventional pulmonary can be trained to process and analyze ROSE samples with reasonable accuracy. There was excellent consensus between RT-ROSE and CYTO-ROSE for both on-site adequacy and diagnostic category. This capability allows maximal efficiency. The interventional pulmonologist does not have to pause to read each slide but can continue with the procedure and specimen collection. Slides are processed on site as soon as they are generated. When the RT has completed initial ROSE, the pulmonologist can pause briefly, and, if he/she concurs, the cytopathologist can be notified while the pulmonologist proceeds as indicated (more specimens for cell block, biopsy of other sites, and termination of procedure). The cytopathologist will arrive at the procedure with slides prepared and perform ROSE, with a small time commitment and a high likelihood of concurrence. Alternatively, the cytopathologist can be brought into the case using telecytology [16, 17].

In this proof-of-concept study, we have demonstrated that personnel supporting an interventional pulmonary service can perform initial ROSE. This capacity can streamline the ROSE process and can eliminate/minimize pragmatic and economic barriers to implementation. The authors strongly support the concept that a cytopathologist should be the final arbiter of pathology materials, including ROSE specimens. Our work is intended not to replace the cytopathologist but to facilitate collaboration and maximize efficiency for all.

Statement of Ethics

Ethics approval was not required, or the study has been granted an exemption from requiring ethics approval.

Conflict of Interest Statement

No disclosures or conflict of interest for any of the authors.

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Author Contributions

All the authors have contributed equally to the study design, collection documentation and statistical analysis of data. All the authors have also contributed equally to the organization, writing, and editing of tables resulting in the final manuscript.

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