Improvement in Specimen Adequacy with Ultrasound-guided Fine-Needle Aspiration Biopsy (FNAB) of Thyroid Nodules Using Rapid On-site Evaluation (ROSE): A Cross-sectional Study

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Abstract

Background. Fine-needle aspiration biopsy (FNAB) is the most accurate and cost-effective method to evaluate thyroid nodule for possible malignancy. However, an adequate specimen is required for proper examination by a pathologist. Rapid on-site evaluation (ROSE), a service typically provided by pathologists, is the real-time evaluation for adequacy of FNAB smears which can help improve adequacy rates by allowing the submission of additional thyroid samples when the submitted samples are inadequate. This study aims to investigate if ROSE done by trained Endocrinologists can improve specimen adequacy in our patients.

Methods A total of 192 patients were included in this study and were divided in two groups: a ROSE group (*n*=96) and a non-ROSE group (*n*=96). In the ROSE group, the smear of thyroid aspirate was evaluated for adequacy by a trained Endocrinologist in real time. In the non-ROSE group, specimens are directly sent to the Pathologist.

Results ROSE done by Endocrinologists had 94% sensitivity, 46% specificity and 82% accuracy compared to a Pathologist. The adequacy rate under the ROSE group was 84.38% and 81.25% in non-ROSE group.

Conclusion Our study showed that ROSE can improve adequacy rate in our center. ROSE can also be used by physicians in the provinces who are performing FNAB of the thyroid without ultrasound guidance to improve specimen adequacy and lessen repeat biopsy.

Keywords: Rapid on-site evaluation (ROSE), thyroid fine-needle aspiration biopsy, FNAB, specimen adequacy rate

Introduction

Thyroid nodules are a common problem among Filipinos needing further diagnostic investigation. Thyroid cancer ranked 8th among the most common cancers among Filipinos.[1] The prevalence of goiter in the Philippines was reported to be at 6.7% in 1993.[2] The American Thyroid Association (ATA) in 2015 recommended ultrasound guided fine-needle aspiration biopsy (FNAB) as the procedure of choice in evaluating thyroid nodules. Fine needle aspiration biopsy is the most accurate and cost-effective method available to patient which carries minimal risk.[3] Complications encountered are usually minor such as local pain and hematoma.[4] A review of thyroid FNAB done in the Philippines in 2017 reported a wide range of sensitivity (30.7% - 73%), specificity (83 - 100%) and accuracy (72.8% - 87.2%) among different hospitals in the Philippines attributed to poor tissue sampling due to extensive practice of FNAB without ultrasound guidance.[5]

In the typical local setting, FNAB is done and the specimen is sent to the laboratory for processing. There is usually an interval of several days before the specimens are evaluated, initially for adequacy and then for thyroid cytology and classification. Since evaluation for specimen adequacy is not done at the time the FNAB is done, a submitted specimen may be inadequate and the chance to submit additional specimens is lost. Patients will need to undergo repeat biopsy if the submitted specimens are inadequate which results in additional costs, pain and patient dissatisfaction. In our country, Endocrinologists as part of their fellowship training acquire the skills in performing FNAB of thyroid and are further certified in workshop during their annual convention.

In a review of thyroid FNAB done at the Medical City Ortigas in 2017, 38.3% (319 out of 833) of the specimens were found to be non-diagnostic. Rapid on-site evaluation (ROSE) is a service that is typically provided by

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pathologists to evaluate the cellular adequacy of FNAB smears. ROSE has the potential to improve the adequacy rates of FNAB by allowing the physician doing the biopsy to submit additional specimens when the initially submitted samples were interpreted as inadequate. ROSE has been shown to improve per-case adequacy rate by 12%, with higher rates of improvement seen in locales with high baseline inadequacy rates[6]. However, in the local setting, ROSE is not routinely available either due to additional cost or generally not offered by health care facilities. In this study, we looked into the effectiveness and impact of ROSE done by trained Endocrinologists on adequacy rate in our institution.

Scientific Significance. This study aims to decrease repeat biopsy of the thyroid by improving sample adequacy through implementation of ROSE.

General Objective. To measure the impact of rapid on-site evaluation (ROSE) in ultrasound guided fine-needle aspiration biopsy of thyroid nodules.

Specific Objectives

1. To quantify improvement of thyroid FNAB specimen adequacy rate using ROSE.
2. To determine the repeat biopsy rate using ROSE.

Methodology

Study Design. This is a cross-sectional study carried out at The Medical City Ortigas by the Department of Internal Medicine - Section of Endocrinology in collaboration with the Department of Pathology.

Study Subjects. Inclusion criteria includes patients scheduled for thyroid FNAB with the following characteristics:

1. Thyroid nodule $\geq$ 1 cm in diameter who were able to meet the ATA sonographic pattern criteria for FNAB
2. Age $\geq$ 18 years old
3. Those who provided informed consent

Exclusion criteria:

1. Significant risk of bleeding (anti-platelet / anti-coagulant medications that cannot be safely withheld)
2. Known bleeding disorders

Sample Size. The sample size was calculated using the prevalence rate of goiter (6.7%) reported by Carlos-Raboca et. al. in 1993.[2] We used a confidence interval of 95% and a margin of error of 0.05. The total number of patients included in the study is 192.

$$n = [t^2 \times p\,(1 - p)] / m^2$$
$$n = [1.96^2 \times 6.7(1 - 6.7)] / 0.05^2$$
$$n = 96$$

Data Collection. Patients being worked-up for a thyroid nodule who fulfilled the inclusion and none of the exclusion criteria were included in the study after obtaining the informed consent in the Endocrine, Diabetes, and Thyroid center by the primary investigator. Each patient will be assigned randomly to either the non-ROSE or ROSE group using the fish-bowl method. The attending physician performs the ultrasound-guided fine-needle aspiration biopsy of the thyroid. For each thyroid nodule, at least two thyroid aspirate smears are done on glass slides. One smear per nodule will be stained using the following *Diff-Quik* method: 1) The thyroid aspirate is smeared thinly on glass slides and air dried. 2) The glass slide was dipped five times in methanol, 3) then they were dipped five times in eosin; and 4) five times in methylene blue. Each glass slide was allowed enough time to drip off completely before dipping again in a solution. The glass slides were then rinsed with distilled water until the runoff from the slides became clear. An assigned Thyroid clinic nurse collected the prepared specimens after the FNAB and presents it to the investigators for determination of specimen adequacy. An adequate specimen is defined as presence of six or more groups of 10 follicular cells. Specimens that did not fulfill this criterion were labeled as inadequate. In cases where the specimen was inadequate, the attending physician was asked by the Thyroid clinic nurse to provide another specimen for re-evaluation. Repeat biopsy was done until adequate specimen was collected. All the specimens obtained will be sent at the pathology department for evaluation. Patient assigned to non-ROSE group had their specimens sent directly to pathology after the fine-needle aspiration biopsy.

Administrative, Ethical and Regulatory Consideration. The study was approved by the institute's research ethics committee. Confidentiality and anonymity were maintained by assigning a specific number to each of the subjects and allowing only the primary investigator and co-investigator access to the data.

Results

A total of 192 cases were included in the research: 96 cases were assigned under the ROSE group while another 96 cases were assigned under non-ROSE group. Mean age of those under ROSE group was 47.98 years old $\pm$ 10.11, while mean age of those under non-ROSE group was 47.60 years $\pm$ 10.23. There were 81 female and 15 males both in ROSE and non-ROSE group respectively. There was no significant difference in the subjects both in ROSE and non-ROSE group (*Table I*).

The total number of inadequate specimens read by Endocrinologist were 18 on the first sample consisting of 13 true inadequate and 5 false inadequate specimens. A second sample was done among the 18 specimens and revealed 14 (78%) true adequate and 5 (28%) false adequate specimens. (*Figure 1*).

The adequacy rate of the first and second sample read by the Pathologist was 75%. (*Table II*).

True adequate thyroid specimen was 94% while the false adequate thyroid specimen was 54%. True inadequate thyroid specimen was 46% while the false inadequate thyroid specimen was 6%. (*Table III*).

Under the ROSE group, 84.38% of the cases considered adequate by the endocrinologist were confirmed to be

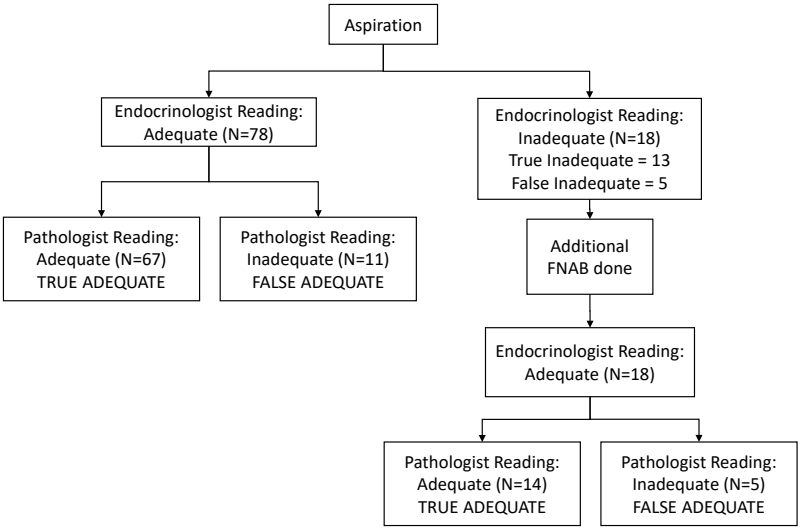

Figure 1. Outcomes of First and Second Sample under ROSE

Table I. Baseline Characteristics of Study Subjects

	Frequency (%); Mean ± SD			P-value
	Total (n=192)	ROSE (n=96)	Non-ROSE (n=96)	
Age	47.79 ± 10.14	47.98 ± 10.11	47.60 ± 10.23	0.799
Sex				1.000
Male	30 (15.63)	15 (15.63)	15 (15.63)	
Female	162 (84.38)	81 (84.38)	81 (84.38)	

Table II. First and Second Sample under ROSE read by a Pathologist

Pathologist		
Adequate	Inadequate	Total
86 (75%)	28 (25%)	114 (100%)

Table III. Frequency (%) of First and Second Sample Combined (ROSE group)

		Done by Pathologist		Total
		Adequate	Inadequate	
Done by Endocrinologist	Adequate	81 (94%)	15 (54%)	96
	Inadequate	5 (6%)	13 (46%)	18
	Total	86	28	114

Table IV. Adequacy rate of ROSE vs non-ROSE group

	Frequency (%)			p-value
	Total (n=192)	ROSE (n=96)	Non-ROSE (n=96)	
Adequate	159 (82.81)	81 (84.38)	78 (81.25)	0.566
Inadequate	33 (17.19)	15 (15.63)	18 (18.75)	

adequate by the pathologist while 81.25% was seen in the Non-ROSE group. (*Table IV*).

Discussion

Adequacy is defined as a measure of sampling performance. ROSE was previously reported to improve specimen adequacy if the baseline adequacy rate is low.[6] Chamorro *et. al*. in 2017 reported that inadequate specimen has 76% unsatisfactory diagnostic yield compared to only 2% if the specimen is adequate. Unsatisfactory diagnostic yield results to a decrease in likelihood that a specimen will provide the information needed to establish a diagnosis. ROSE significantly decreased their unsatisfactory samples by 30%. They also stated that ROSE was able to improve the diagnostic yield of specimens to 90.5% compared to 60% with conventional fine-needle aspiration biopsy.[7] Simsek *et al.* compared the non-diagnostic result of thyroid FNAB specimen with ROSE and non-ROSE.[8] In the ROSE group only 2% had non-diagnostic result while 15.7% in the non-ROSE group which was statistically significant (p = <0.0001). Zhu and Michael in 2007 reported that the non-diagnostic rate in ROSE was 5.9% while 31.8% in non-ROSE group which was also statistically significant (p = <0.001).[9]

Witt and Schmidt in 2013 identified the impact of ROSE in FNAB of thyroid lesions.[10] The average adequacy rate with ROSE was 92% while 83% in non-ROSE group which was statistically significant (p=0.002). There was modest improvement with the use of ROSE when the baseline adequacy rate with ROSE was >80%. Pastorello *et. al*. showed that ROSE has an adequacy rate of 93.4% while non-ROSE has 69.4% which was also statistically significant (p<0.0001).[11] However, in a study done by O'Malley *et al.*, the adequacy rate with ROSE was 55% while 50% in the non-ROSE group which was not statistically significant (p = 0.815).[12]

Pastorello *et. al*., Jiang *et.al*., De Koster *et. al*. and *Redman et. al* reported that ROSE can reduce number of needle passes to achieve an adequate specimen.[11,13-15] The aforementioned studies had reported different number of needle passes necessary to achieve an adequate specimen which were 1.48 ± 0.71, 1.7 ± 0.6 , 1.75 ± 0.86 and 3.2 ± 0.07 respectively. While in a study done by Zhu and Micheal in 2007, they noted that 4 – 6 needle passes per nodule can lessen non-diagnostic rates and no improvement was seen with additional needle passes.[9] Unfortunately, we were not

able to include the number of needle passes in our analysis.

The adequacy rate for ROSE and non-ROSE were 84.38% and 81.25% respectively. The difference in nodule characteristics, number of needle passes, needle gauge used and smear preparation were the factors that might influence the adequacy rate in both ROSE and non-ROSE group.

A Pathologist re-examined the ROSE specimens in our study. There was an increase in specimen adequacy after obtaining the repeat FNAB in the ROSE group (75% vs 84%). ROSE done by Endocrinologists had 94% sensitivity, 46% specificity and 82% accuracy compared to the examination done by the Pathologist. Our skill in identifying inadequate specimens can be enhanced by implementation of ROSE in all thyroid FNAB in our center.

Conclusion and Recommendations

Our study showed that ROSE can improve adequacy rate in our center. ROSE can also be used by physicians in the provinces who are performing FNAB of thyroid nodules without ultrasound guidance to improve specimen adequacy and lessen repeat biopsy. Further training and honing of skills by physician doing ROSE is recommended to further improve detection of inadequate specimens and also to reduce additional sampling from samples improperly labeled as inadequate.

We recommend further studies regarding use of ROSE in thyroid FNAB with focus on applicability in the local setting such as proper training of individuals in identifying specimen adequacy and its effect on other factors such as characteristics of the nodule, needle gauge used, number of needle passes and skill in smear preparation. We believe that ROSE done by properly trained individuals could decrease repeat biopsy rate, avoid additional expenditures and improve patient satisfaction.

Conflict of Interest: There is no conflict of interest among the authors of this paper.

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