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Value of rapid on-site evaluation for ultrasound-guided thyroid fine needle aspiration

Danni Jiang[1], Yichen Zang[1], Dandan Jiang[2], Xiaojuan Zhang[1] and Cheng Zhao[1]

Abstract

Objective: Application of rapid on-site evaluation (ROSE) for thyroid fine needle aspiration (FNA) is controversial. Therefore, ROSE has not been universally applied. This study aimed to evaluate the value of ROSE for ultrasound-guided thyroid FNA.

Methods: A total of 997 patients with 1103 suspicious thyroid nodules had ultrasound-guided FNA performed from January 2016 to February 2018. There were 513 nodules with ROSE and 590 nodules without ROSE. The cytological nondiagnostic rate, needle passes, and procedural times of thyroid FNA with or without ROSE were compared. The nondiagnostic rates of subsets of suspicious thyroid nodules were further compared.

Results: There was no significant effect of ROSE on the nondiagnostic rate of FNA. However, FNA with ROSE significantly reduced the numbers of sub-centimeter, mixed solid-cystic, macro-calcified, and hypervascular nodules. There was a significantly smaller number of needle passes and less procedural times with ROSE than without ROSE. There was no significant difference in the complication rate of FNA with and without ROSE.

Conclusion: ROSE for thyroid FNA reduces the number of needle passes and procedural times. ROSE has a higher clinical application value in subsets of thyroid nodules, which tend to be difficult to diagnose with FNA.

Keywords

Thyroid nodule, fine needle aspiration biopsy, rapid on-site evaluation, nondiagnostic rate, needle passes, cytology, ultrasound

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[1]Department of Ultrasound, The Affiliated Hospital of Qingdao University, Qingdao, China
[2]Department of Breast Surgery, The Affiliated Hospital of Qingdao University, Qingdao, China

Corresponding author:
Cheng Zhao, Affiliated Hospital of Qingdao University, Jiangsu Rd, Shinan Qu, Qingdao, Shandong 266000, China.
Email: zhaochqd@sohu.com

Introduction

Fine needle aspiration (FNA) is the principal method for preoperative investigation of thyroid nodules, and is beneficial for triaging patients for clinical follow-up or surgical management.[1–3] However, some diagnostic challenges of FNA remain, such as inadequate specimens satisfying the diagnostic criteria, causing nondiagnostic results.[4,5]

Previous studies have shown that 2% to 33% of FNA procedures generate nondiagnostic results.[6,7] A repeat FNA is often recommended after 3 to 6 months for nondiagnostic nodules to determine the risk of malignancy.[8] However, repeated FNAs may increase the patient's discomfort and anxiety, as well as medical costs. Moreover, nondiagnostic lesions may cause treatment delays.[9]

To further improve adequacy of specimens, cytology technicians in many institutions perform rapid on-site evaluation (ROSE) of FNA specimens by staining cytological smears.[10] Studies have shown that ROSE can significantly decrease nondiagnostic thyroid FNA results by increasing sample adequacy.[11–15] Other studies have reported that this technique increases the procedural time and the cost for the patient, but fails to significantly decrease the nondiagnostic rates of FNA.[9,16] Therefore, application of ROSE for FNA is still controversial, and thus ROSE is not universally applied. In this study, we aimed to evaluate the value of ROSE for ultrasound-guided thyroid FNA and subsets of thyroid FNA.

Materials and methods

Study population and design

This study was approved by the Institutional Review Board of the Affiliated Hospital of Qingdao University. All of the patients provided written informed consent. A total of 1103 suspicious thyroid nodules with at least two suspicious signs were sampled by ultrasound-guided FNA from January 2016 to February 2018. In our institution, ROSE was first introduced in October 2016. Before this time, FNA was conducted without ROSE for all nodules. After this time, the majority of FNAs were conducted with ROSE, but some FNAs were not performed when the cytotechnologist was absent. For every suspicious nodule, specimens were obtained and smeared by two physicians with at least 5 years of ultrasound interventional experience and evaluated by one cytotechnologist and one pathologist. In our institution, all cases were divided into two groups according to the diameter of the nodule ($\leq$10 mm and $>$10 mm). The composition of nodules was assessed as solid dominant, mixed solid-cystic, and cyst dominant (cystic component $\geq$50%). Echogenicity of nodules was classified as hyperechoic, isoechoic, hypoechoic, and markedly hypoechoic. Calcification of nodules was categorized as microcalcification, macrocalcification (punctuate echogenic foci $>$ 1 mm in size), and negative. The shape of nodules was categorized as wider than tall and taller than wide. The margin of nodules was classified as a smooth or obscure boundary, lobulated or irregular, and extraglandular invasion. Vascularity of nodules was divided into hypervascular and hypovascular.[17,18]

Procedures

Each patient was placed in the supine position with the neck gently hyperextended and the overlying skin was cleansed with iodine. Local anesthetic was not routinely applied.[19] The best puncture point and path of the suspicious nodule were localized by using a GE-logic E8 ultrasound system equipped with a linear high frequency probe (6–15 MHz). With a freehand technique and direct ultrasound visualization,

a 23-gauge needle attached to a 5-mL plastic syringe was punctured into the suspicious lesion, such as the solid mural or suspicious calcification areas of the nodule. Aspirated material was placed onto glass slides and smeared.[17,20] One smear from each pass was stained with toluidine blue for ROSE by a cytotechnologist. Immediate assessment of adequacy and feedback for adequacy of the specimen were provided. If an appropriate specimen was obtained, the puncture was terminated immediately; if not, the physician repeated the puncture until a satisfactory specimen was obtained. The maximum number of passes for each nodule was four according to the recommendation of China ultrasound interventional guidelines. Each nodule without ROSE was typically punctured with two to four needle passes at the discretion of the physician by evaluating adequacy of the specimen by viewing the specimen and by touching.[9] The procedural time was defined as the time from placement of the first needle to completion of the puncture, including the time of ROSE. All specimens were subsequently fixed in 95% ethyl alcohol for hematoxylin–eosin (HE) staining later in the pathology laboratory for final analysis within 24 to 48 hours. Following the biopsy, the biopsy site was gently compressed with manual pressure for 10 to 20 minutes (at least 30 minutes for deep lesions).[20] An ultrasound examination was repeated to evaluate complications after the procedures.

Criteria for cytological diagnosis

Cytological results were classified into one of six categories according to The Bethesda System for reporting thyroid cytopathology[21,22] as follows: I, nondiagnostic or unsatisfactory (Figure 1a and 1b), which indicated failure to meet The Bethesda adequacy criteria, the presence of at least six groups of well-visualized follicular cells, and each group contained at least 10

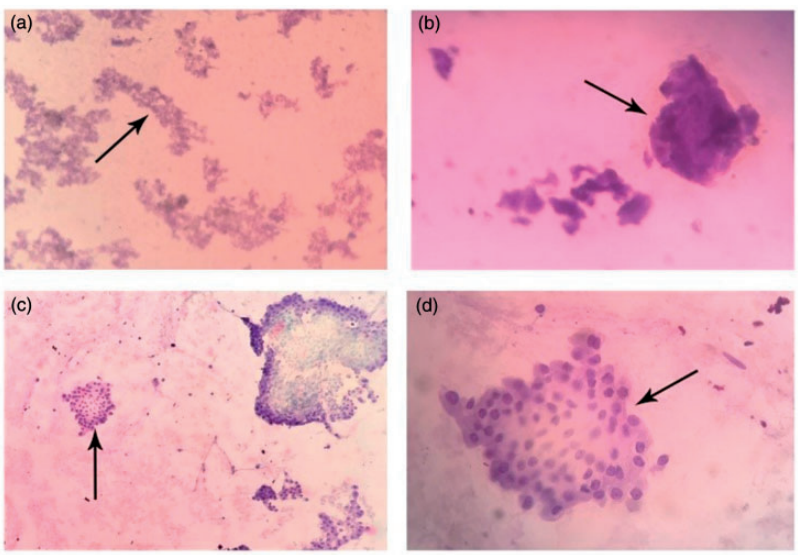

Figure 1. (a and b) Nondiagnosable specimens. The arrow indicates thick colloid. (c and d) Diagnosable specimens. The arrow indicates clusters of thyroid follicular cells. Toluidine blue stain was used; original magnifications: × 100 and × 400.

well-preserved epithelial cells of a solid lesion;[23] II, benign; III, atypia of undetermined significance or a follicular lesion of undetermined significance; IV, follicular or suspicious for follicular neoplasm; V, suspicious for malignancy; and VI, malignant. The percentage of category I in the total cytological results was the nondiagnostic rate. For the purpose of the present study, other than category I, the remaining five categories were combined and defined as successful and diagnosable (Figure 1c and 1d).

Statistical analysis

Data analysis was performed with IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Analysis was performed using Pearson's χ^2 or Fisher's exact test for categorical data and the two sample *t*-test for continuous data to determine statistical significance. P values ≤ 0.05 were considered statistically significant.

Results

Clinical data

There were 1103 nodules in 997 patients, including 513 nodules in 455 patients with ROSE and 590 nodules in 542 patients without ROSE. Table 1 shows the characteristics of patients who had FNA with and without ROSE. Of 434 nodules without ROSE in 400 patients, the procedural times were not recorded because the data were obtained retrospectively. Two and three patients had a self-limited post-procedure hematoma with and without ROSE, respectively.

FNA cytological results

Table 2 shows the cytological diagnostic rate of FNA with and without ROSE.

Table 1. Characteristics of patients who had fine needle aspiration with or without ROSE.

Variables	With ROSE	Without ROSE	t-test	χ^2	P value
Age (years)	45.7 ± 12.7	45.7 ± 12.4	0.08		0.939
Sex (M/F)	119/336	130/412		0.62	0.431
Nodule size (mm)	9.8 ± 7.3	9.5 ± 6.7	0.83		0.409
Mean needle passes	1.7 ± 0.6	2.8 ± 0.5	33.55		0.000
Mean procedural time (minutes)	8.3 ± 3.2	11.4 ± 2.4*	13.22		0.000
Complications	2/513	3/590		0.00	1.000

*The procedural time for nodules without ROSE refers to prospective thyroid nodules (n = 142). ROSE, rapid on-site evaluation; M, male; F, female

Table 2. Cytological diagnostic rate of fine needle aspiration with and without ROSE.

Category	With ROSE	Without ROSE	χ^2	P value
I	34/513 (6.6)	56/590 (9.5)	3.00	0.083
II	84/513 (16.4)	88/590 (14.9)	0.44	0.505
III	30/513(5.8)	49/590 (8.3)	2.49	0.114
IV	37/513 (7.2)	39/590 (6.6)	0.16	0.694
V	96/513 (18.7)	116/590 (19.7)	0.16	0.690
VI	232/513 (45.2)	242/590 (41.0)	1.98	0.159

Values are number (%). ROSE, rapid on-site evaluation.

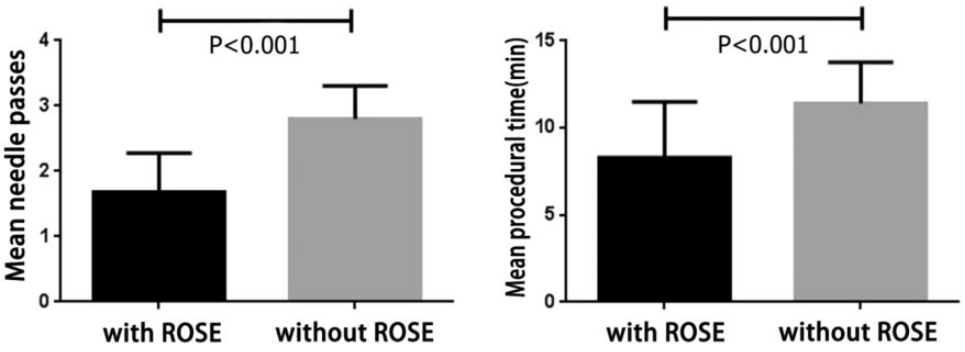

Figure 2. Needle passes and procedural times for thyroid nodule fine needle aspiration.

There was no significant effect of ROSE on the nondiagnostic rate of FNA).

Number of needle passes, procedural times, and complications in suspicious thyroid nodules in FNA with or without ROSE

The mean number of needle passes and procedural times were significantly reduced with ROSE compared without ROSE (1.7 ± 0.6 vs 2.8 ± 0.5, $P < 0.001$; 8.3 ± 3.2 vs 11.4 ± 2.4 minutes, $P < 0.001$; Figure 2). The incidence of complications with ROSE was not significantly different than that without ROSE (0.4% vs 0.5%).

Nondiagnostic rates of subsets of suspicious thyroid nodules in FNA with and without ROSE

The nondiagnostic rates of FNA with and without ROSE were further compared for subsets of thyroid nodules. The nondiagnostic rates of FNA with ROSE were significantly reduced in sub-centimeter nodules ($P = 0.006$), mixed solid-cystic nodules ($P = 0.041$), macrocalcified nodules ($P = 0.001$), and hypervascular nodules ($P = 0.036$). The nondiagnostic rates for the other types of nodules were not significant between FNA with and without ROSE (Table 3).

Discussion

The success of FNA depends on many factors, such as the experience of the physician and pathologist and the features of the nodules.[24,25] In the current study, all specimens were obtained by a team of experienced operators. Previous studies showed that the rates of specimen adequacy with and without ROSE were 76% to 96% and 66% to 94%, respectively.[5] Therefore, whether ROSE can significantly increase specimen adequacy and decrease the nondiagnostic rate of FNA are controversial.

The nondiagnostic rate of FNA is usually between 2% and 33%, but the ideal rate is 10%.[3,26] In our study, the nondiagnostic rate was 6.6% with ROSE, which was lower than 9.5% without ROSE, but this difference was not statistically significant. Therefore, we further investigated the value of ROSE in the nondiagnostic rate of FNA with subsets of suspicious thyroid nodules. We found that the nondiagnostic rates of sub-centimeter, mixed solid-cystic, macrocalcified, and hypervascular nodules were significantly reduced with ROSE.

Table 3. Nondiagnostic rate of subsets of suspicious thyroid nodules with and without ROSE.

Subsets of nodules	With ROSE	Without ROSE	χ^2	P value
Nodule size (mm)				
≤10	23/343 (6.7)	47/365 (12.9)	7.56	0.006
>10	11/170 (6.5)	9/225 (4.0)	1.23	0.267
Composition				
Solid dominant	31/474 (6.5)	43/542 (7.9)	0.73	0.394
Mixed solid-cystic	3/39 (7.7)	13/48 (27.1)	4.18	0.041
Cyst dominant	0	0	–	–
Echogenicity				
Hyperechogenicity/isoechogenicity	1/15 (6.7)	2/17 (11.8)	–	1.00*
Hypoechogenicity	23/360 (6.4)	42/430 (9.8)	2.96	0.085
Marked hypoechogenicity	10/138 (7.2)	12/143 (8.4)	0.13	0.721
Calcification				
Microcalcification	14/223 (6.3)	18/266 (6.8)	0.05	0.828
Macrocalcification	6/80 (7.5)	23/84 (27.4)	11.13	0.001
Negative	14/210 (6.7)	15/240 (6.3)	0.03	0.857
Shape				
Wider than tall	8/103 (7.8)	14/135 (10.4)	0.47	0.492
Taller than wide	26/410 (6.3)	42/455 (9.2)	2.49	0.115
Margin				
Smooth or obscure boundary	5/79 (6.3)	9/89 (10.1)	0.78	0.376
Lobulated or irregular	27/403 (6.7)	44/465 (9.5)	2.19	0.139
Extraglandular invasion	2/31 (6.4)	3/36 (8.3)	0.00	1.000
Vascularity				
Hypervascular	4/53 (7.5)	16/68 (23.5)	4.42	0.036
Hypovascular	30/460 (6.5)	40/522 (7.7)	0.48	0.488

Values are number (%). ROSE, rapid on-site evaluation.
*Calculated using Fisher's exact test.

The American Thyroid Association guidelines[27] recommend that nodules ≤10 mm should not undergo FNA, even if malignancy is suspected because of the difficult location and diagnosis. Sabel et al.[28] reported that the smaller the nodule, the higher the nondiagnostic rate and lower sensitivity of FNA. However, having these nodules checked because of the patient's psychological pressure and a tense physician–patient relationship in China are common.[25] Studies have shown that nodules with a cystic component or macrocalcification are highly associated with low cellularity and nondiagnostic results.[17] The reason for this finding is because the cystic component dilutes cells into the needle and macrocalcification is difficult to penetrate with a fine needle. This causes a significant reduction in the effectiveness of obtaining adequate follicular epithelial cells. Alexander et al.[29] showed that establishing a definite diagnosis in hypervascular nodules was difficult because they had too many blood cells and obscured the smears. We found that these nodules tended to be difficult to diagnose with FNA.

ROSE can decrease the nondiagnostic rate by improving adequacy of the specimen. For nodules with ROSE, if the first few needle passes did not obtain a satisfactory specimen, we immediately adjusted the

needle path and punctured parts to obtain more cells and improve adequacy of the specimen. Therefore, for the physician, ROSE obviously decreased the nondiagnostic rate of nodules, which tended to be difficult to diagnose with FNA.

A few studies have compared the number of needle passes between FNA with and without ROSE, but their findings were not clear.[16] In our study, the mean number of passes with ROSE was significantly lower than that without ROSE, which is in agreement with a previous report.[8] ROSE allows immediate on-site assessment of adequacy and timely feedback if an adequate specimen is obtained. In this case, the puncture is terminated immediately, thus reducing needle passes. Several previous studies have claimed that ROSE only prolonged the procedural times (from 12.5 to 44.4 minutes) and increased the patient's discomfort.[16] In our study, we found that FNA with ROSE had a faster procedural time than FNA without ROSE. The most likely explanation for this finding is that ROSE, as an ancillary technique, can decrease the number of needle passes. Additionally, in our study, specimens were stained with toluidine blue (approximately 2 minutes) and immediately assessed with a microscope by an experienced cytotechnologist. However, in previous studies, thyroid FNA usually required multiple needle passes and specimens were stained with Diff-Quik or HE stain (approximately 30 minutes), which involves more procedures and time. Although toluidine blue stain has less clear cytological morphology than Diff-Quik or HE stain, it can provide accurate judgment to evaluate adequacy of the specimen and it has a low cost. In our study, only a few patients experienced a self-limited post-procedural hematoma. There was no significant difference in the complication rate between FNA with and without ROSE. These data are well within published standards.[9] The most likely explanation for our finding is that regardless of whether ROSE is performed, the procedure is low risk and complications are extremely rare.[30] ROSE is unlikely to affect the rate of complications and cause discomfort of patients. Therefore, we can use ROSE as a secure ancillary technique for FNA of thyroid nodules. Additionally, ROSE is simple and requires little material, and thus it is cost-effective and will become popularized in rural hospitals.

There are some limitations in our study. First, for some subsets of suspicious thyroid nodules, the statistical power was low because only a few cases were compared. Second, because we did not investigate histopathological diagnosis for nodules, FNA might have false-negative and false-positive results. Third, we did not examine how ROSE affects the outcome of FNA with different experienced physicians.

In summary, ROSE is generally associated with an improvement in adequacy of specimens and thus decreases the nondiagnostic rate of FNA. However, the effect of ROSE greatly depends on the subsets of thyroid nodules. Our study shows that subcentimeter, mixed solid-cystic, macrocalcified, and hypervascular nodules with FNA can benefit the most from implementing ROSE. This information will be useful and improve the confidence of physicians. Additionally, ROSE can reduce the number of needle passes and procedural times. Therefore, popularizing ROSE, especially for suspicious nodules that are difficult to diagnose with FNA, is a goal worth achieving.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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