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# Thyroid Ultrasound-Guided Fine-Needle Aspiration: The Positive Influence of On-Site Adequacy Assessment and Number of Needle Passes on Diagnostic Cytology Rate

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## Key Words

Thyroid · Fine-needle aspiration · Specimen adequacy · Image-guided intervention · Diagnostic accuracy

## Abstract

**Objective:** Nondiagnostic cytology is the most important limitation of thyroid ultrasound-guided fine-needle aspiration (US-FNA). This study aimed to identify factors associated with the adequacy rate of thyroid US-FNA. **Study Design:** Consecutive thyroid US-FNAs (2006–2013) were retrospectively included. Attending radiologists, radiology fellows and radiology residents performed US-FNA, usually involving 2–3 needle passes. In more recent years, rapid on-site adequacy assessment (ROSAA) was performed to ensure specimen adequacy. US characteristics, procedural variations and cytology results were extracted from US and pathology reports and statistically evaluated. **Results:** Diagnostic cytology was obtained in 64.6% of 1,381 thyroid US-FNAs. Factors associated with nondiagnostic cytology were ROSAA (74.6% diagnostic cytology, OR 0.55, 95% CI 0.42–0.71),  $\geq 3$  clinic visits for US-FNA of the same thyroid nodule (54.7%, OR 1.56, 95% CI 1.16–2.10) and increased intranodular vascularization (51.8%, OR 1.73, 95% CI 1.17–2.57). With ROSAA, an increasing number of needle passes demon-

strated improving adequacy rates. The adequacy rate was not operator-dependent. **Conclusion:** This study demonstrates that ROSAA improves the adequacy rate of thyroid US-FNA. Without ROSAA, we recommend performing at least 3 needle passes. Less diagnostic cytology is obtained from nodules with increased intranodular vascularization or from those undergoing US-FNA  $\geq 3$  times.

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## Introduction

The prevalence of thyroid nodules on ultrasound (US) is reported to be as high as 30–70%. As only 5% harbor a malignancy, fine-needle aspiration (FNA) is essential for their evaluation [1–4]. Adequate cytological diagnoses provided by FNA have resulted in a reduction of futile surgeries for benign thyroid nodules of up to 50% [1, 2, 5].

Although safe and cost-effective, the most important limitation of thyroid FNA is its high rate of nondiagnostic cytology with reported rates of up to 34% [1, 2, 6–11]. The established definition for adequate cytology is the presence of at least 6 groups of follicular cells, each containing 10–15 cells, preferably obtained from at least 2 aspirates of a nodule [2, 12, 13]. Nondiagnostic cytology leads to repeat FNA

procedures, futile diagnostic hemithyroidectomies and the associated additional costs. Rapid on-site adequacy assessment (ROSAA) during the FNA procedure provides immediate feedback and allows for repeat aspirates to ensure specimen adequacy. Studies evaluating the added diagnostic value of ROSAA have consistently demonstrated that the procedure decreases the rates of nondiagnostic specimens and false-negative cytology and the number of needle passes found to be necessary [4, 9, 10, 14–17].

Other factors that have been associated with nondiagnostic US-FNA results are the cystic content of a thyroid nodule, poor preparation of slides with smears that are too thick, blood obscuring the visualization of follicular cells, poor specimen fixation or an inadequate staining technique [1, 6, 16, 18]. Modified or alternative techniques, such as using a different type and size of biopsy needle or additional liquid-based cytology, are related to better adequacy rates [19–22]. In addition, both experience-based operator dependency and interobserver variance between cytotechnologists and cytopathologists have repeatedly been demonstrated [23–26].

This study was designed to evaluate the adequacy rate of all thyroid US-FNAs at our hospital and to identify factors associated with nondiagnostic cytology. Specifically, we hypothesized that the performance of thyroid US-FNA by an experienced radiologist or with additional ROSAA would improve the adequacy rates.

## Materials and Methods

### *Patient Selection*

With approval by the local Institutional Medical Ethics Committee, all consecutive thyroid US-FNAs in adult patients between 2006 and 2013 at the University Medical Center Utrecht were retrospectively included. Data were extracted from both US and cytopathology reports. Data recorded included the name of the operator, whether ROSAA was performed, the number of aspirates during one procedure, the thyroid nodule US characteristics and the number of clinic visits for repeated US-FNA of the same thyroid nodule. Four groups were used to categorize the 127 operators: 107 radiology residents, 13 radiology fellows, 6 attending radiologists (with 5–20 years of experience) and a separate category for our single, most experienced radiologist (with >20 years of experience). US-FNAs were excluded when they concerned residual tissue after previous thyroid surgery.

### *US-FNA Procedure*

US was performed using a Philips iU22 Ultrasound System (Philips Healthcare, Eindhoven, The Netherlands) with a linear 12- to 5-MHz transducer. FNA was performed using either a 21-gauge/1.5-inch (BD Microlance™ 3, No. 2) or 23-gauge/1.25-inch needle (BD Microlance 3, No. 14; Becton Dickinson and Co., Breda, The Netherlands). If a cytotechnologist was present for

ROSAA, for each needle pass, direct smears were made, air-dried and then stained by the Diff-Quik method. Immediate microscopic review of the slides determined the cytological adequacy based on presence of a minimum of 6 groups of follicular cells, each consisting of 10–15 cells [2, 12, 13]. In the case of an inadequate specimen and if time and the comfort of the patient allowed, an additional aspirate was obtained and ROSAA was repeated. The number of aspirates was registered. Finally, all obtained cytology was submitted to the cytopathology department for definite analysis. If no cytotechnologist was present, direct smears were made, marked and then submitted unstained. Two needle passes were standard procedure for US-FNAs without ROSAA.

### *Cytologic Assessment*

At the cytology laboratory, May-Grünwald-Giemsa staining was applied to all smears. Any additional residual material, placed in a container of CytoLyt® solution (Cytoc Corp., Marlborough, Mass., USA) during US-FNA, was processed using the Papanicolaou stain. Descriptive pathology reports were drafted for each specimen. Smears that could not be interpreted due to quantitative or qualitative reasons were classified as 'nondiagnostic'. The reports were descriptive and no further distinct diagnostic categories were reported.

### *Statistical Analysis*

Data analysis was performed using IBM SPSS Statistics (v20.0; IBM Corp., Armonk, N.Y., USA). Contingency tables were constructed to compare the different variables to the cytological outcome, i.e. diagnostic or nondiagnostic. The  $\chi^2$ , Fisher exact and independent-samples t tests were used for categorical data, categorical data plus small sample sizes and continuous or numeric data, respectively. A p value <0.05 was considered statistically significant. Multivariate analysis was performed for all factors significant on cross-tabulation. The Wald test was used to reduce the multivariate model until only factors that were independently and significantly associated with the outcome remained.

## Results

In total, 1,381 thyroid US-FNAs (mean maximum nodule diameter  $26.7 \pm 13.6$  mm) were included in the study (table 1). These were performed in 682 patients (86% females) with a mean age of 53.3 years ( $SD \pm 14.1$ ). Diagnostic cytology was obtained for 892 samples (64.6%). Benign cytology was reported in 793 (57.4%) cases, 54 (3.9%) had cytology of undetermined significance, including atypia and follicular or Hürthle cell proliferations and 45 (3.3%) were suspicious or positive for malignancy.

### *Cytological Adequacy*

Cytological adequacy was significantly higher with the performance of ROSAA (309/414, 74.6%) than without it (583/967, 60.3%;  $p < 0.001$ ; table 1). The first and second clinic visits for US-FNA of the same thyroid nodule yielded similar rates of adequate cytology (67.0 vs. 66.2%, re-

**Table 1.** Results for all thyroid FNAs

	Nondiagnostic	Diagnostic	p value
FNAs performed (n = 1,381)	35.4 (489)	64.6 (892)	
Sex, female	35.7 (424)	64.3 (765)	0.627
Age, years	54.1±14.1	52.8±14.0	0.101
<i>Procedural variations</i>			
Clinic visit for thyroid US-FNA			
1st	33.0 (249)	67.0 (506)	0.001
2nd	33.8 (128)	66.2 (251)	
3rd or more	45.3 (112)	54.7 (135)	
Operator of US-FNA			
Radiology resident	36.1 (338)	63.9 (597)	0.576
Radiology fellow	29.7 (35)	70.3 (83)	
Most experienced radiologist X	35.8 (77)	64.2 (138)	
Other attending radiologists	34.5 (39)	65.5 (74)	
Rapid on-site adequacy assessment			
No	39.7 (384)	60.3 (583)	<0.001
Yes	25.4 (105)	74.6 (309)	
<i>Thyroid nodule characteristics</i>			
Maximum diameter, mm	25.8±13.6	27.1±13.6	0.120
Nodularity			
Solitary	32.5 (102)	67.5 (212)	0.292 <sup>1</sup>
Multinodular	36.4 (385)	63.6 (672)	
Unknown	20.0 (2)	80.0 (8)	
Consistency			
Solid	27.6 (47)	72.4 (123)	0.054
Mixed solid-cystic	36.5 (107)	63.5 (186)	
Cystic	29.8 (34)	70.2 (80)	
Unknown	37.4 (301)	62.6 (503)	
Sonographic appearance			
Hypoechoogenic	36.9 (58)	63.1 (99)	0.813
Isoechoogenic	28.9 (11)	71.1 (27)	
Hyperechoogenic	37.8 (14)	62.2 (23)	
Unknown	35.3 (406)	64.7 (743)	
Homogeneity			
Homogenous	30.8 (4)	69.2 (9)	0.816 <sup>1</sup>
Inhomogenous	34.2 (119)	65.8 (229)	
Unknown	35.9 (366)	64.1 (654)	
Increased intranodular vascularization			
Yes	48.2 (54)	51.8 (58)	0.006
No	25.5 (12)	74.5 (35)	
Unknown	34.6 (423)	65.4 (799)	
Intranodular calcifications			
Yes	32.8 (44)	67.2 (90)	0.324
No	26.9 (14)	73.1 (38)	
Unknown	36.1 (431)	63.9 (764)	

Values are expressed as % (n) or mean ± SD. All variables can be compared according to a diagnostic or nondiagnostic cytology result.

<sup>1</sup> Calculated using the Fisher exact test.

spectively), but the third and subsequent visits less often resulted in a diagnostic specimen (54.7%,  $p < 0.001$ ). Increased intranodular vascularization on Doppler US was associated with a significantly higher nondiagnostic rate (48.2%,  $p = 0.006$ ). Other US characteristics, such as nodule size and consistency, showed no significant associa-

tion. Finally, no operator dependency was demonstrated. The mean number of US-FNAs performed by each operator group was 8.7 (range 1–31) for radiology residents, 9.0 (range 1–19) for radiology fellows and 18.8 (range 1–45) for attending radiologists. Our single, most experienced radiologist performed 215 US-FNAs.

**Table 2.** Multivariate analysis

	OR <sup>1</sup>	95% CI	p value
<i>Clinic visit for thyroid US-FNA</i>			
1st	1	ref.	
2nd	1.01	0.77–1.31	0.950
3rd or more	1.56	1.16–2.10	0.003
<i>Rapid on-site adequacy assessment</i>			
No	1	ref.	
Yes	0.55	0.42–0.71	<0.001
<i>Increased intranodular vascularization</i>			
No or unknown	1	ref.	
Yes	1.73	1.17–2.57	0.006

<sup>1</sup> Adjusted ORs for variables associated with nondiagnostic cytology.

### Multivariate Analysis

Multivariate analysis revealed a significant association with nondiagnostic cytology for  $\geq 3$  clinic visits (OR 1.56, 95% CI 1.16–2.10), ROSAA (OR 0.55, 95% CI 0.42–0.71) and strong intranodular vascularization (OR 1.73, 95% CI 1.17–2.57; table 2).

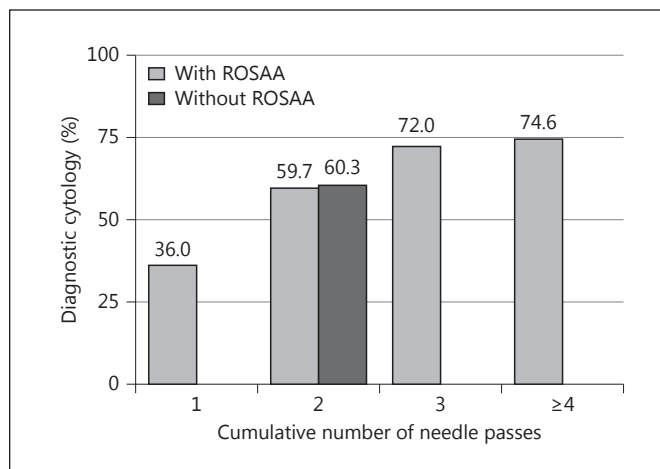
### Number of Needle Passes

Additionally, a subanalysis was performed of the number of needle passes per procedure. This was only registered for US-FNAs when ROSAA was performed. A mean number of 1.75 needle passes (SD  $\pm 0.86$ ) was needed to acquire a diagnostic specimen. With  $\leq 3$  aspirates, 72.0% (298/414) of all US-FNAs were diagnostic, while this was 59.7% (247/414) in the case of  $\leq 2$  aspirates (fig. 1).

### Discussion

Despite its reliability and cost-effectiveness for distinguishing between benign and malignant thyroid nodules, the nondiagnostic rate of thyroid FNA, which varies from 2 to 34% in the literature, remains a major clinical issue [1, 2, 6–10, 19]. Our study identified multiple factors that were significantly associated with adequacy rate: adequacy increased with ROSAA but decreased with  $\geq 3$  clinic visits and with strong intranodular vascularization.

Consistently higher adequacy rates of thyroid FNA with the application of ROSAA have led to recommendations for ROSAA to become routine [4, 9, 10, 15, 16, 27].



**Fig. 1.** US-FNA adequacy rate (%) compared to cumulative number of needle passes.

The absolute 14.3% (39.7–25.4%) decrease in nondiagnostic rate that our study demonstrated is greater than the average of 9% that was reported in a meta-analysis by Witt and Schmidt [28]. This result supports their finding that the increase in adequacy rate with ROSAA correlates with the adequacy rate without ROSAA, and that adequacy improves more when the initial nondiagnostic rate is higher [28].

Before ROSAA was implemented, common practice at our institution was to acquire no more than 2 aspirates per FNA procedure. This resulted in 60.3% adequate cytology. A subanalysis of our results demonstrated that 72.0% diagnostic specimens were obtained when ROSAA was combined with  $\leq 3$  needle passes. This was 59.7% with ROSAA and  $\leq 2$  needle passes, i.e. similar to the former adequacy rate. Without ROSAA, the operating radiologist blindly estimates the number of needle passes needed for adequate cytology. More aspirates then likely result in higher adequacy rates. Studies that performed 4–6 passes as standard protocol have reported nondiagnostic rates as low as 5.5% [17, 29, 30]. By providing feedback for immediate repeat biopsies and/or redirection of the needle within the thyroid nodule, ROSAA might not only improve adequacy but also decrease the number of needle passes necessary for institutions where protocol prescribes acquiring relatively many aspirates [17]. However, we propose that solely obtaining more aspirates per nodule – without ROSAA – might achieve an equal improvement in adequacy rate. Hereby minimizing additional costs, effort and procedure time, this could be the preferred, more cost-effective option for some institu-

tions, instead of implementing ROSAA. We would recommend performing at least 3–4 needle passes.

We did not demonstrate the influence of operator experience on adequacy rate, despite the vast evidence of operator dependency in the literature on FNA of the thyroid as well as other organs [9, 24, 26]. Ljung et al. [26] defined an experienced operator as one who performs at least 100 FNAs of various body sites per year. For thyroid FNAs, specifically, it has been suggested that an operator has to perform at least 200 procedures before achieving high adequacy rates [9, 24, 30]. As >100 operators performed the thyroid US-FNAs in our study (most of them were radiology residents), the individual and general level of experience was limited and may have had a negative effect on the overall diagnostic rate. Even our most specialized radiologist merely performed 215 out of 1,381 thyroid US-FNAs over the course of 8 years, an average of 27 procedures per year, with a success rate similar to the mean (64.2 vs. 64.6%). Centralizing thyroid FNA procedures to specialized centers and educating a small number of dedicated head-and-neck radiologists could substantially improve adequacy rates by reducing the influence of operator inexperience [25, 26].

Our study demonstrated that strong intranodular vascularization on Doppler US was significantly associated with lower adequacy rates. Other studies confirm what we experience in daily practice: blood contamination is one of the main qualitative reasons for nondiagnostic thyroid cytology, and FNA of a hypervascular nodule will often result in bloody aspirates [4, 19]. Strong intranodular vascularization is rarely mentioned in the literature as a predictor of nondiagnostic cytology [31]. It is, however, described as a possible predictor of malignancy, emphasizing the need for adequate cytology [7, 12, 32]. In contrast to the results of previous studies, other US characteristics, such as consistency or nodule size, were not significantly related to the adequacy rate of thyroid US-FNAs in our study [6, 33].

Even though the subsequent clinic visits after the second US-FNA were related to a significantly lower adequacy rate, a third or fourth US-FNA still yielded diagnostic cytology for a substantial 54.7% of patients in our population. Cost-benefit analysis, consequences and the associated morbidity of surgical intervention as well as the risks associated with delayed treatment for undetected malignancies cause a clinical dilemma of deciding between diagnostic surgery or an additional FNA [34]. A diagnostic hemithyroidectomy is recommended for nodules with a repeatedly nondiagnostic US-FNA and suspicious US or clinical characteristics, because approximately 10% harbor a malignancy [5, 27]. Weighing the low risk of aggres-

sive thyroid cancer against the roughly 50% of prevented surgeries upon diagnostic cytology of the third US-FNA, we believe that performing a third US-FNA is beneficial and safe, provided that the time interval between subsequent US-FNAs is appropriately minimized.

The ultimate goal of this study was to improve the adequacy rate of thyroid US-FNA at our hospital, by first addressing those factors that could improve quality with minor adjustments or minimal additional resources. Moreover, our study shows the value of an institutional assessment of quality of care. We believe that quality assessment of the existing primary diagnostic tools should always be done before more complex measures are added to the diagnostic routine. The resolution might be as simple as performing a few extra needle passes per procedure, leaving additional diagnostics such as molecular testing for BRAF mutations, promising but costly, for the fewer cases that remain nondiagnostic despite improved basic procedures. Guidelines for improvement, like the ones existing for breast cancer, could support this process [35]. Nevertheless, it all starts with a critical assessment of the institution's own performance and acknowledgement of the bottlenecks. The 35% nondiagnostic rate in our study might not be as exceptionally high as it seems when compared to previously published rates. Large interinstitutional variations inevitably exist, but publication bias presumably leaves worse rates unpublished and the general nondiagnostic rate higher than the reported average of 17% [28, 36].

The most important limitation of this study was its retrospective design. Data regarding multiple variables were missing for many US-FNAs, mostly US characteristics due to limited reports. The number of needle passes for most of the non-ROSAA US-FNAs was also missing, thereby impeding a full evaluation of our hypothesis regarding the number of needle passes in this subset.

Secondly, even when ROSAA was performed, the US-FNA procedure was often discontinued before adequate material had been acquired. Possible reasons for this are time limitations for the procedure, repeatedly bloody specimens, the stress of the patient and disagreement between the on-site and final adequacy assessments. Further research is needed at our institution to analyze the optimal number of needle passes and its presumed relation to the adequacy rate with and without ROSAA.

Potential confounders were addressed during data collection and analysis. Other than the procedural variations that were determined, no differences in US-FNA or cytology assessment procedures were demonstrated throughout the years. A potential confounding factor is that our

most experienced radiologist was specifically requested as the operator for a number of thyroid FNAs, mostly repeated procedures. Performing the more difficult FNAs may have reduced his adequacy rate. This possible relation could not be objectified due to limited reports.

## Conclusions

This study demonstrated that ROSAA improved the adequacy rate of thyroid US-FNA. When ROSAA is not performed, we recommend obtaining  $\geq 3$  aspirates. Diag-

nostic cytology is less often obtained from nodules with increased intranodular vascularization or during US-FNA that is performed  $\geq 3$  times. The adequacy rate of thyroid US-FNA was not operator-dependent in this study. Almost equally important, the results of our study underline the importance of institutional quality assessment of basic diagnostic procedures.

## Disclosure Statement

The authors declare that no conflicts of interest exist.

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