



Unsatisfactory Ultrasound-Guided Fine Needle Aspiration of Thyroid Nodule: Which Factors Limit Cytology Result?

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Abstract

Objective: The purpose of this study is to focus on which factors affect or limit fine-needle aspiration-cytology (FNAC) results of thyroid nodule, in order to increase the satisfactory cytologic results and to avoid unnecessary FNAC in patients with asymptomatic benign nodules and highly possible unsatisfactory results.

Materials and Methods: The records of 217 thyroid nodules in 179 patients referred to the radiology department at Lerdsin Hospital for US-guided FNAC between January 2010 and December 2013 were retrospectively reviewed. Cytologic specimens of the FNAC were classified as unsatisfactory (non-diagnostic) and satisfactory (diagnostic) results and analyzed by mean of Logistic regression analysis, based on patient's age, gender, nodule size, number and solid-cystic composition of nodule.

Results: The cytologic result was satisfactory for diagnosis in 154 specimens (71%) and unsatisfactory in 63 specimens (29%). Patient's age, gender, number and size of nodule of the unsatisfactory result group were not different from the satisfactory result group but the nodule composition was different. Percentage of the unsatisfactory aspiration increased as the cystic component increased, ranging from 15.3% in solid nodules to 59.3% in predominant cystic nodules (cystic $\geq 75\%$). Upon the binary logistic regression analysis, the predominant cystic nodule was the only significant predictor of unsatisfactory result (p -value < 0.001) while solid nodules, predominant solid nodules and solid-cystic nodules are not significant. Unsatisfactory FNAC result of the predominant cystic nodules was about 8 times higher than the solid nodule (crude odds ratio = 8.087, p -value < 0.001).

Conclusion: To optimize the usefulness of FNAC, we should realize that solid-cystic composition of the thyroid nodules influence the non-diagnostic and diagnostic cytology.

Introduction

Thyroid nodules represent a common problem, with an estimated prevalence of 4-10% in the adult population for palpable nodules¹⁻³. The prevalence of non-palpable thyroid nodules appears to be higher with ultrasonographic(US) examination, approximately 10-40%^{1,4}. Most of thyroid nodules are benign. Only 5-10% of these are malignant.^{1,3-5} Unfortunately, no specific sonographic characteristics of malignancy have been published and there is overlap of sonographic characteristic findings in benign and malignant nodules. Fine-needle aspiration cytology (FNAC) is minimally invasive procedure that is usually performed on an out-patient basis. Real-time ultrasonography guidance permits visualization of the needle tip within the nodule resulting in decreased needle misplacement and increased FNAC accuracy of the non-palpable nodules. It has become the standard of care for the initial diagnostic workup of a thyroid nodule. Although the majority of FNAC are adequate for diagnosis, 5-20% are inadequate^{1,4,6}. The achievement of FNAC results requires not only an US guidance aspiration technique skill to obtain adequate material for cytology but also awareness of limitation of FNAC. The purpose of this study is to focus on which factors affect or limit material adequacy for FNAC, based on nodule size, number and US features so we can decide which nodules should be subjected to US-guided fine needle aspiration and which thyroid nodules need not be subjected to fine-needle aspiration because of high possibility of inadequate specimen.

Materials and Methods

We reviewed the records of all patients referred to the radiology department at Lerdsin Hos-

pital for evaluation of thyroid nodule with US-guided FNAC between January 2010 and December 2013. For each thyroid nodule that FNAC was performed, gray-scale US was used to evaluate the US features, which included number, size and composition .

Maximum diameter of each nodule was reported and classified as ≤ 1 cm ,1.1-2.0 cm and >2 cm.

Number of nodules was classified as single nodule or multiple nodules on US examination.

In case of multiple nodules, FNAC was performed in the prominent nodule or suspicious nodule.

Composition was classified as a solid, a predominantly solid nodule ($\leq 25\%$ cystic), a solid-cystic ($25\% < \text{cystic} < 75\%$) and a predominantly cystic nodule ($\geq 75\%$ cystic, including 100% cystic).

US-guided FNAC was performed by the same interventional radiologist, using a high-resolution (11.5 MHz) linear-array transducer. A 21-gauge needle with 10 ml disposable syringe was used. A perpendicular puncture was done with limited local anesthesia. When the needle tip reached the target nodule, the needle was observed as a small echogenic spot within the nodule on the US monitor. After the needle tip was placed in the appropriate area of the target nodule, the needle was moved up and down with aspiration for a few seconds under US guidance. After a sample was obtained, it was smeared promptly onto a glass slide. The smears were quickly fixed in 95% ethyl alcohol. We obtained 4-6 slides by performing 2-3 punctures from each nodule. All specimens were processed using the Papanicolaou staining method. All slides were reviewed and interpreted by a cytopathologist at Lerdsin Hospital.

Cytologic specimens of the FNA were classi-

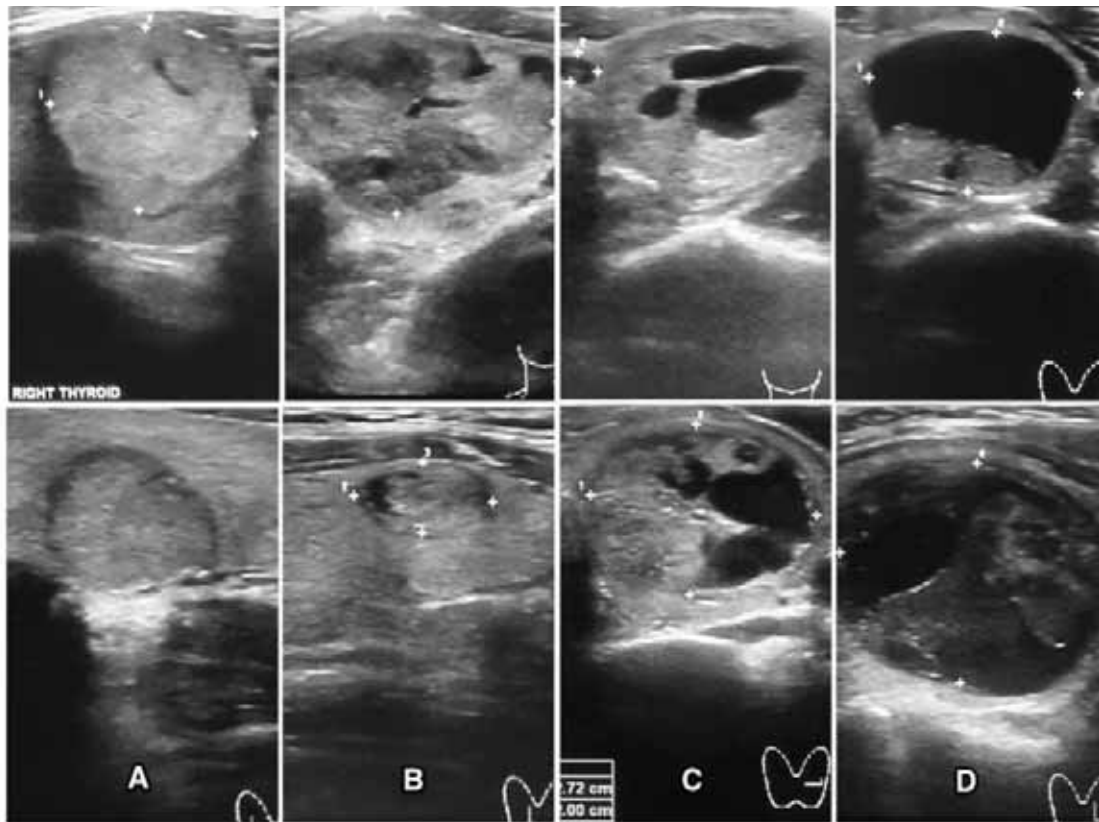


Fig. 1 US features of thyroid nodules. A - solid, B - predominantly solid, C -solid-cystic, D - predominantly cystic

fied as unsatisfactory (non-diagnostic) and satisfactory(diagnostic).

Specimens were considered unsatisfactory (non-diagnostic) if insufficient cellular material, air drying artifact or blood contamination was found. Satisfactory specimens (benign, intermediate and malignant/suspicious of malignancy) were including nodular goiter, follicular lesion, follicular lesion with cystic degeneration, Hashimoto thyroiditis, hemorrhagic cyst, presence of atypical cells, suspicious of papillary thyroid carcinoma.

Results of FNAC of thyroid nodules were retrospectively analysed. The Ethic Committee of Lerdsin Hospital has approved the study.

Statistics

Descriptive statistics were presented according to nodule or patient. Binary logistic regression analysis was performed using SPSS software (version 17.0, SPSS, Inc., Chicago, IL). Patient's age gender and number of nodule (single or multiple) were analyzed as dichotomous variables. Patient's age (10 year interval from 20-29 years to 60-69 years and more than 70 years) , nodule size (≤ 1 cm, 1.1-2.0 cm or >2 cm.) and solid-cystic composition (solid , cystic $\leq 25\%$, $25 < \text{cystic} < 75\%$, or cystic $\geq 75\%$) were analyzed as categorical variables. Significance was accepted at $P < 0.05$. Adjusted odds ratio and crude odds ratio were calculated.

Results

FNAC of 217 thyroid nodules were performed in 179 patients (16 men and 163 women), aged from 20 to 87 years (mean 49.88). The aspiration was performed twice in 16 patients and three times in 1 patient on follow-up, due to unsatisfactory cytological result or nodule growth. The indication was single nodule in 54 patients and dominant nodule of multiple nodules in 125 patients. In multiple nodules, FNAC of 2 nodules per patient were done in 18 patients and 3 nodules per patient in 1 patient. A total of 217 cytological diagnoses were reviewed. The maximum diameter of nodules vary from 0.4-4.8 cm (mean 2.05 cm. SD. = 0.9651). The cytologic result was satisfactory for diagnosis in 154 specimens (71%) and unsatisfactory in 63 specimens (29%). The demographic and US features were compared between these 2 groups (table 1). Patient's age, gender, nodule composition, nodule size and number of nodules were evaluated as possible predictors of an unsatisfactory FNAC. Gender, age, nodule size and number of the unsatisfactory result group were not different from the satisfactory result group but the nodule composition was different. Percentage of the unsatisfactory aspiration increased as the cystic component increased, ranging from 15.3% in solid nodules, 15.9% in predominant solid nodules, 23.8% in solid-cystic nodules to 59.3% in predominant cystic nodules (table 2). Upon the binary logistic regression analysis, the predominant cystic nodule was the only significant predictor of unsatisfactory result (p -value < 0.001) while solid nodules, predominant solid nodules and solid-cystic nodules are not significant. Unsatisfactory FNAC result of the predominant cystic nodules (cystic $\geq 75\%$) was about 8 times higher than the solid nodule (crude odds ratio = 8.087, p -value < 0.001).

Discussion

Thyroid nodules are very common in the general population, but malignancy is relatively rare. Ultrasonography (US) is increasingly able to detect thyroid nodules, and the differentiation between malignant and benign nodules has been raising issues among both physicians and patients. Thyroid FNAC is a well-established method and its main goal is to differentiate malignant from benign nodules. Its reliability depends on several factors, such as the skill of the interventional radiologist or the experience of the cytopathologist. Although use of ultrasonography in FNAC increases significantly the sensitivity, specificity and accuracy compared with conventional palpation-guided FNAC^{7,8,9}, unsatisfactory cytology is frequently troubled.

The aims of our study are to define to which factors unsatisfactory results are related, in order to increase the satisfactory cytologic results and to avoid unnecessary FNAC in patients with benign, asymptomatic and highly probable unsatisfactory result.

We used 2 categories (satisfactory and unsatisfactory). All patients were recorded for their demographic features, that is, age and gender and US features of nodules were recorded in the term of single vs. multiple, size and solid-cystic composition. In our study, unsatisfactory results were found in 29%. Almost all of unsatisfactory cytology were insufficient cellular material for diagnosis. The rests are limited by air-drying artifact and blood contamination.

We found that the patient's age, gender, nodule size and number with unsatisfactory cytology were not different from those with satisfactory cytology and were not the predictive factors for non-diagnostic specimens ($P > 0.05$) upon the binary

Table 1 Demographic and US features between satisfactory and unsatisfactory result groups.

| Factors | Total | Satisfactory | Unsatisfactory |
|---|-------------------|-------------------|-------------------|
| Number of nodules | 217 | 154 (71%) | 63 (29%) |
| Age (mean \pm SD.) | 49.88 \pm 13.92 | 48.20 \pm 13.96 | 53.97 \pm 13.02 |
| Female | 201 | 147 (95.5%) | 54 (85.7%) |
| Male | 16 | 7 (4.5%) | 9 (14.3%) |
| Single nodule | 59 | 36 (23.4%) | 23 (36.5%) |
| Multiple nodules | 158 | 118 (76.6%) | 40 (63.5%) |
| Size (mean \pm SD, cm) | 2.05 \pm 0.96 | 1.98 \pm 0.89 | 2.23 \pm 1.10 |
| solid | 72 | 61 (39.6%) | 11 (17.5%) |
| predominantly solid nodule (cystic \leq 25%) | 44 | 37 (24.0%) | 7 (11.1%) |
| solid-cystic (25% < cystic < 75%) | 42 | 32 (20.8%) | 10 (15.9%) |
| predominantly cystic nodule (cystic \geq 75%) | 59 | 24(15.6%) | 35 (55.6%) |

logistic regression analysis. The predominant cystic nodule was the only significant predictor of unsatisfactory result (p -value < 0.001).

Cystic composition was a significant problem in our study, with unsatisfactory specimens reaching 59% in nodules more than 75% cystic. We found that the highest proportion of unsatisfactory specimens occurred in nodules with the greatest cystic content. In our study, 16 simple thyroid cysts were included in the predominant cystic nodule group and showed no satisfactory cytology, due to insufficient cellular materials in all cysts. It could be due to dilution effect of the sample and

scant thyroid follicular cell in the cystic content. In spite of US-guided FNAC, there is a risk of unsatisfactory cytology, especially the nodule with prominent cystic portion. We may assume that the unsatisfactory cytology is influenced more by lesion composition than by mistaken targeting. Aspiration is normally done when the US shows the tip of needle in the solid portion of the nodule to avoid aspiration of the cystic portion. However cystic content is usually contaminated in the samples, especially in the greater cystic nodule. It may dilute specimens, resulting in insufficient cellular material¹⁰. If the nodule has a large cystic portion, aspiration of the

Table 2 Binary logistic regression analysis of patient age, gender, nodule composition ,nodule size and number of nodules as possible predictors of an unsatisfactory FNAC.

| Factors | NO. | Satisfactory | Unsatisfactory | p-value | Adjusted OR | Crude OR | 95% CI |
|----------------------|-----|--------------|----------------|---------|-------------|----------|----------------|
| solid | 72 | 61 (84.7%) | 11 (15.3%) | | 1 | 1 | |
| predominantly solid | 44 | 37 (84.1%) | 7 (15.9%) | 0.978 | 0.984 | 1.049 | 0.374- 2.944 |
| solid-cystic | 42 | 32 (76.2%) | 10 (23.8%) | 0.110 | 2.378 | 1.733 | 0.665-4.514 |
| predominantly cystic | 59 | 24 (40.7%) | 35 (59.3%) | <0.001 | 10.140 | 8.087 | 3.541- 18.469 |
| size \leq 1.0 cm | 30 | 20 (66.7%) | 10 (33.3%) | | 1 | 1 | |
| size 1.1-2.0 cm | 91 | 69 (75.8%) | 22 (24.2%) | 0.292 | 0.557 | 0.638 | 0.260- 1.565 |
| size \geq 2.1 cm | 96 | 65 (67.7%) | 31 (32.3%) | 0.626 | 0.764 | 0.954 | 0.399- 2.280 |
| Age 20-29 | 11 | 10 (90.9%) | 1 (9.1%) | | 1 | 1 | |
| Age 30-39 | 51 | | 7 (13.7%) | 0.744 | 1.484 | 1.591 | 0.175- 14.429 |
| Age 40-49 | 47 | 33 (70.2%) | 14 (29.8%) | 0.218 | 4.246 | 4.242 | 0.495- 36.369 |
| Age 50-59 | 44 | 26 (59.1%) | 18 (40.9%) | 0.086 | 7.658 | 6.923 | 0.813- 58.941 |
| Age 60-69 | 44 | 29 (65.9%) | 15 (34.1%) | 0.056 | 9.953 | 5.172 | 0.604- 44.318 |
| Age 70-79 | 17 | 10 (58.8%) | 7 (41.2%) | 0.052 | 12.028 | 7.000 | 0.722- 67.840 |
| Age 80-89 | 3 | 2 (66.7%) | 1 (33.3%) | 0.080 | 20.994 | 5.000 | 0.212- 117.894 |
| Number | | | | 0.374 | 0.686 | 0.531 | 0.281- 1.001 |
| Gender | | | | 0.53 | 0.289 | 0.286 | 0.101- 0.805 |

cystic portion should be done to evacuate fluid. Then FNAC of the residual solid portion may be performed. In case of simple cysts, aspiration of the fluid content is inevitably done and satisfactory cytology is not expected. Insufficient cellular material does not reflect poor aspiration skill in the simple cyst aspiration. Most thyroid cysts are benign but a small number of papillary carcinoma are cystic so it is reasonable to perform FNAC in thyroid cysts. About 50-70% of benign cysts do not recur, in contrast, all cystic papillary carcinoma recur¹⁰. Repeated FNA is suggested if cyst recurs or shows progressive growth on follow-up.

In an ideal settings, slides are immediately reviewed by an on-site cytopathologist. This allows immediate feedback regarding specimen adequacy to the interventional radiologist performing the aspiration. In less ideal environment, the radiologist may require skill and training to produce high quality slides.

Any residual specimen can be dispersed into an appropriate rinse solution by flushing the needle to extract all of the specimen for cytologic examination as liquid-based technique. In the cytopathology laboratory this material will be spun in a centrifuge, and the resulting precipitant will be used to produce smears. Liquid-based technique appears to produce more satisfactory slides than the conventional smear¹¹.

In our study, we prepared specimens only with conventional smear technique which had some limitations related to the low cellularity and bloody background. No on-site cytopathologist was available during the procedure.

Besides insufficient cellular materials, air-drying artifact is one of the causes of unsatisfactory FNAC. This problem can be easily avoided with immediate fixation of the smears in 95% ethyl alcohol.

Blood contamination may limit the cytopathologist to evaluate the smears, resulting in unsatisfactory result. In our study, we used a 21-gauge needle for aspiration with suction technique. Some have suggested the use of 23-, 25- or 27 gauge needle and non-suction technique for FNA of markedly hypervascular nodules to produce specimens that are less bloody⁹. However conventional suction technique sometimes yields more material¹⁰. Liquid-based smear may also show cleaner background¹¹.

Not only FNA technique but also specimen preparation has influenced the diagnostic or non-diagnostic cytology. The interventional radiologist who performs the procedure should produce high quality specimens by improving his skill and technique for FNA and specimen preparation. Liquid-based smear may increase diagnostic result from increasing cellular material, particularly in case of predominant cystic nodule so liquid-based technique should be implemented.

Conclusion

To optimize the usefulness of FNAC, we should realize that solid-cystic composition of the thyroid nodules influence the non-diagnostic and diagnostic cytology. The appropriate technique of US guided FNAC and specimen preparation should be tailored especially in case of the predominant cystic nodule which has a high possibility of unsatisfactory cytology.

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