

## PAPER DETAILS

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# Hypoechoic nodule structure increases non-diagnostic rate of thyroid fine needle aspiration biopsy

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## ABSTRACT

**Aim:** Thyroid fine needle aspiration biopsy (FNAB) performed with ultrasonography is an effective method in diagnosing thyroid cancer. Nevertheless, some of them have non-diagnostic results. The aim is to investigate the factors that affect non-diagnostic result.

**Material and Method:** FNABs of 361 nodules of 361 patients were analyzed retrospectively. The patients were divided into two groups as fine needle aspiration biopsy result with and without non-diagnostic. The groups were compared according to demographic, clinical and sonographic data.

**Results:** Non-diagnostic rate was 14.4% in all biopsies. There was no difference in terms of age, gender, previous thyroid surgery history, smoking history, aspirin use, Hashimoto's thyroiditis, toxic nodule. Sonographic findings of the thyroid glands and nodules were similar. Only the echogenicity of the nodule was found to affect the non-diagnostic result ( $p=0.015$ ). In the post hoc analysis, the difference was found to be caused by hypoechoic nodules (32.7% versus 15.5). It was observed that the significant relationship found in univariate logistic regression analysis ( $p=0.009$ , OR: 3.227, CI: 1.334-7.803) continued in multivariate analysis ( $p=0.024$ , OR: 3.175, CI: 1.163-8.668).

**Conclusion:** Only hypoechoic echogenicity increases the risk of non-diagnostic rate. Other factors do not increase the non-diagnostic rate.

**Keywords:** Thyroid fine needle aspiration biopsy, ultrasonography, non diagnostic, hypoechoic echogenicity

## INTRODUCTION

The frequency of thyroid cancer continues to increase with each passing year. With the proliferation of ultrasonography (USG), nodular thyroid disease has been detected more frequently. The most appropriate method for making the necessary surgical decision and avoiding unnecessary surgery and related complications is fine needle aspiration biopsy (FNAB) (1,2). FNAB is an easy, inexpensive and effective diagnostic method. It is more effective when performed with USG. It has a 95% negative, 97-99% positive predictive value. FNAB indication is based on the sonographic features of the thyroid nodule. FNAB should be performed in the case of hypoechoic echogenicity, irregular edge structure, microcalcification, ratio of anterior-posterior diameter to transverse diameter  $> 1$ , and central vascularity (3).

FNAB assessment is done according to the Bethesda system and the results are given in 6 categories; benign, non-diagnostic (ND), indeterminate atypia (AUS)/

indeterminate follicular lesion (AUFL), suspicious for follicular neoplasia or follicular neoplasia (FN), suspicious cytology for malignancy and malignancy (4). In the best series, the ND rate is 2-16% (5,6). Fifty five-74% of biopsies are reported as benign, 2-5% as malignant, 2-18% as AUS/AUFL, 2-25% as FN and 1-6% as suspicious for malignancy (6).

In order to FNAB to be sufficient, there must be at least 6 groups of follicular cells containing at least 10 well-preserved epithelial cells in one area. It is reported as ND, which does not meet these criteria. It is recommended to repeat FNAB, and if ND comes again, surgery or close follow-up is recommended. While the estimated malignancy risk of the nodule with a biopsy ND is 1-4%, the actual risk of malignancy of this nodule is 9-32% (5). A nodule whose biopsy is 2 times ND has a 25% risk of being malignant (7). Therefore, surgical and medical follow-up decision should be made carefully in nodules whose biopsy is ND.

Studies investigating the factors affecting FNAB adequacy can be found in the literature. Different causes such as advanced patient age, nodule heterogeneity (8), aspirin (9), radioactive iodine therapy (10) were found to be related to ND. In this study, it was aimed to investigate the factors affecting ND biopsy results in a large sample group.

## MATERIAL AND METHOD

### Ethical Approval

The study was carried out with the permission of Amasya University Non-interventional Clinical Researchs Ethics Committee (Date: 02.05.2019, Decision No: 05-26). All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The subjects have given their written informed consent. This study does not contain animals.

### Patient Selection

Between January 1, 2018 and January 1, 2019, 361 patients who underwent FNAB were included. These biopsies were performed by an endocrinologist experienced in terms of USG and FNAB. One FNAB result of each patient was included in the study. Consent was obtained from the participants before and after the FNAB. Demographic, laboratory, ultrasound and FNAB data of the participants were obtained from the hospital information processing system. The age, gender, smoking status, aspirin usage, previous thyroid surgery was recorded. According to thyroid autoantibodies and USG, which patients had Hashimoto's thyroiditis (HT) was detected. Thyroid scanning was performed by the endocrinologist with thyroid ultrasonography device (Aloka, Mollsfeld, Meerbusch, Germany). Thyroid gland and nodule volumes were calculated according to the formula of anterior-posterior diameter x transverse diameter x longitudinal diameter x 0.52 (11). Whether the nodule is thyrotoxic in hyperthyroid patients was recorded based on thyroid scintigraphy. Biopsy Indications and Results

FNAB was performed according to the size (> 1 cm), content (solid), echogenicity (hypoechoic), edge structure (irregular), vascularity (central), calcification (microcalcification), anterior-posterior diameter/transverse diameter ratio (> 1) of the thyroid nodules (12). Local anesthesia was not applied before biopsy. FNAB was made by aspiration method by 22-gauge needle. During aspiration, the USG probe was turned from the transverse position to the longitudinal position, the needle was inserted into the nodule at a right angle to the neck, the needle was moved 5-6 times to the anterior-posterior and lateral sides. The material was spread to the

slides by the endocrinologist at the bedside. Slides were delivered to the pathology department after being dried in the air. FNAB results were categorized by experienced cytopathologists according to the Bethesda system (4).

### Statistical Analysis

Statistical analyzes were made in IBM SPSS for Windows Version 22.0. Numerical variables were summarized with mean±standard deviation. Categorical variables were indicated by number and percentage. The chi-square test or Fisher's exact test was used to determine whether there was any difference between the groups in terms of categorical variables. The Kolmogorov Smirnov test, standard deviation/mean ratio, skewness/kurtosis measures, histogram and detrended normal graphics were used to determine whether the numeric variables showed normal distribution, and the homogeneity of the variance was examined by the Levene test. Differences between two independent groups in terms of numerical variables; In the case of parametric test assumptions, t-test was used for independent groups. In the absence of parametric test assumptions, Mann Whitney U test was used. Post hoc analysis was used to compare more than 2 groups. Univariate and multivariate logistic regression analyses were applied to determinate independent predictors affecting ND result. The significance level was taken as  $p < 0.05$ .

## RESULTS

The results of the FNABs are as shown in **Table 1**. ND rate was 14.4% among all biopsies. The most reported category was benign, with a rate of 67.6% (**Table 1**).

All participants were divided into two groups according to whether the FNAB result was ND or not. Data on age, advanced age (>65), gender, previous history of thyroid surgery, smoking status, use of aspirin, presence of HT are shown in **Table 2**. No significant difference was found between the two groups (**Table 2**).

Thyroid USG features of all participants are given in **Table 3**. There was a significant difference in nodule echogenicity between the groups ( $p=0.015$ ). Post hoc analysis was performed to determine which subtype caused the difference. The difference was caused by hypoechoic subgroup by applying Bonferoni correction and adjusted residual (**Table 3**).

**Table 1.** FNAB results

Total, n	361
Non-diagnostic, n (%)	52 (14.4)
Benign, n (%)	244 (67.6)
AUS/AUFL*, n (%)	50 (13.9)
Follicular neoplasia, n (%)	4 (1.1)
Malignant, n (%)	1 (0.2)
Suspicious for malignancy, n (%)	10 (2.8)

\*: AUS/AUFL: unspecified atypia/indeterminate follicular lesion

Parameters	Total (n=361)	Non-ND <sup>a</sup> group (n=309)	ND <sup>a</sup> group (n=52)	p
Age, mean±std dev	53.03±11.78	52.66±11.96	54.79±10.35	0.227
Age >65, n (%)	58 (16)	49 (15.9)	9 (17.3)	0.792
Gender, n (%)				0.417
Male	75 (20.8)	62 (20.1)	17 (25)	
Female	286 (79.2)	247 (79.9)	39 (75)	
Previous thyroid surgery, n (%)	25 (6.9)	22 (7.1)	3 (12)	0.784
Smoking, n (%)	60 (16.6)	48 (15.5)	12 (23.1)	0.176
Aspirin, n (%)	42 (11.6)	37 (12)	5 (9.6)	0.624
HT <sup>b</sup> , n (%)	92 (25.5)	83 (26.8)	9 (17.3)	0.184
TSH, mean±std dev	1.84±7.94	1.89±8.56	1.59±1.71	0.896

<sup>a</sup>: ND: non-diagnostic, <sup>b</sup>: HT: Hashimoto's thyroiditis

Parameter	Total (n=361)	Non-ND <sup>a</sup> group (n=309)	ND <sup>a</sup> group (n=52)	P
Right thyroid volume, mL	20.403±15.016	20.429±15.272	20.250±13.525	0.697
Left thyroid volume, mL	18.580±14.020	18.381±14.290	19.760±12.354	0.202
Isthmus, mm	5.71 ± 3.99	5.64 ± 4	6.14 ± 3.95	0.348
Parenchym				0.891
Homogeneous	21 (5.8)	17 (5.5)	4 (7.7)	
Mild heter <sup>b</sup>	181 (50.1)	157 (50.8)	24 (46.2)	
Moderate heter <sup>b</sup>	113 (31.3)	96 (31.1)	17 (32.7)	
Advanced heter <sup>b</sup>	46 (12.7)	39 (12.6)	7 (13.5)	
Nodule noc, n (%)				0.950
Solitary	89 (28.1)	76 (24.6)	13 (25)	
MNGd	272 (71.9)	233 (75.4)	39 (75)	
Nodule size, n (%)				0.332
< 10 mm	15 (4.1)	11 (3.6)	4 (7.7)	
10.01-39.99 mm	312 (86.4)	270 (87.4)	42 (80.8)	
> 40 mm	37 (9.5)	28 (9)	6 (11.5)	
A-P diame/T diame				0.142
<1	345 (95.6)	293 (94.9)	52 (100)	
>1	16 (4.4)	16 (5.1)	0 (0)	
Content, n (%)				0.113
Solid	158 (43.7)	130 (42.1)	28 (53.8)	
Mixed	203 (56.3)	179 (57.9)	24 (46.2)	
Echogenity, n(%)				0.015
Isoechoic	91 (25.2)	82 (26.5)	9 (17.3)	
Hypoechoic	65 (18)	48 (15.5)	17 (32.7)	
Hyperechoic	13 (3.6)	10 (3.2)	3 (5.8)	
Spongiform	192 (53.2)	169 (54.8)	23 (53.2)	
Edge, n (%)				0.393
Smooth	270 (74.8)	230 (74.4)	40 (76.9)	
Irregular	61 (16.9)	53 (17.2)	8 (15.4)	
Undefined	30 (8.3)	26 (8.4)	4 (7.7)	
Halo, n (%)				0.284
Absent	325 (90)	275 (89)	50 (96.2)	
Present	36 (10)	34 (11)	2 (3.8)	
Calcification, n (%)				0.885
Absent	303 (83.9)	261 (84.5)	42 (80.8)	
Microcalcification	10 (2.7)	9 (2.9)	1 (1.9)	
Macrocalcification	28 (7.7)	22 (7.1)	6 (11.5)	
Micro+macrocalc	7 (1.9)	6 (1.9)	1 (1.9)	
Eggshell calc.	13 (3.8)	11 (3.6)	2 (3.8)	
Vascularity, n (%)				0.365
Absent	224 (62)	194 (62.8)	30 (57.7)	
Peripheral	108 (29.9)	89 (28.8)	19 (36.5)	
Central	3 (0.8)	2 (0.6)	1 (1.9)	
Periph+central	26 (7.3)	24 (7.8)	2 (3.8)	
Toxic nodule, n (%)	50 (13.9)	41 (13.3)	9 (17.3)	0.435

<sup>a</sup>: ND: non-diagnostic, <sup>b</sup>: heter: heterogeneity, c: no: number, calc: calcification, d:MNG: multinodular goiter, e:A-P diam: antero-posterior diameter, f:T diam: transvers diameter

**Table 4.** Univariate and multivariate regression analysis

Parameter	Univariate			Multivariate		
	P	OR <sup>a</sup>	95 % CI	P	OR	95 % CI <sup>b</sup>
Nodule echogenicity	0.009*	3.227	1.334-7.803	0.024*	3.175	1.163-8.668
Nodule size (>1-3.99)	0.037*	0.303	0.098-0.930	0.077	0.311	0.085-1.137

<sup>a</sup>:OR: odds ratio, <sup>b</sup>:CI: confidence interval, \*Univariate and multivariate analyzes were performed on other parameters, since the results were not significant, they were not shown in the Table 4.

In univariate logistic regression analysis, nodule echogenicity and size were found to have a significant effect on the ND result ( $p=0.009$  and  $p=0.037$ ). In the multivariate analysis, while the effect of echogenicity on FNAB remained ( $p=0.024$ , OR: 3.175, CI: 1.163-8.668), the effect of the nodule size was not detected ( $p=0.077$ , OR: 0.311, CI: 0.085-1.137) (**Table 4**).

## DISCUSSION

In this study, the fine needle aspiration biopsy results performed by the endocrinologist in 1 year were investigated and the factors affecting the ND result were investigated. According to the results of the analysis, it was found that only hypoechoic was increasing the likelihood of ND results.

In the study, 14.4% of total biopsies were determined as ND. This rate is similar to the literature since the probability of obtaining ND results is 2-16% (5,6). Results in other categories (except for those malignant and suspected of malignancy) are similar to the literature (6). The experience of the endocrinologist performing the biopsies provided the ND rate to be similar to the literature, and the experience is an important factor affecting the success of the biopsy (13).

Patients were divided into two groups as those with and without ND FNABs, and they were compared according to age, gender, previous history of thyroid surgery, smoking, presence of HT, thyroid USG findings.

Inci and his colleagues (8) retrospectively examined the results of FNABs performed by a radiologist (not endocrinologist) of 270 individuals in 2 years, ND rate was 31.9% and they found that advanced patient age is a factor that increases the risk of ND. Based on this study, we compared the groups in terms of age. The average age of the first study was 46 and 53 in our study. In the first study, the number of geriatric patients was not specified. In our case, there are roughly 16% geriatric patients. Contrary to the first study, we did not find a significant difference between the groups in terms of both the average age and the distribution of geriatric population, and we can say that age is not a risk factor for ND result. ND rate of the first study was markedly high, which may have led to such a conclusion about age.

The gender distribution was also similar in terms of the two groups. As in many studies, although the number

of women who underwent FNAB in our center was significantly higher than men, the effect of gender on ND outcome was not detected. For example, in the study of Ozel et al. (14), gender distribution in ND and non-ND groups is similar.

Postoperative recurrent nodular thyroid disease is seen in 2-42% in different series in patients without total thyroidectomy (15). Onal et al. (16) found that, subtotal thyroid surgery increases the risk of ND outcome by causing fibrosis and scar formation. We also considered our patients' history of thyroid surgery. The patients who had previous thyroid surgery were 6.9% and consisted of recurrent MNG cases with FNAB indication in the residual thyroid gland. There was no significant difference in the distribution of these patients into groups (7.1% versus 12%,  $p=0.784$ ). The conclusion drawn from this is that, unlike the previous study, having a previous thyroid surgery does not increase the risk of ND. However, since the number of patients with operated recurrent nodular goiter in our study was lower compared to other studies (123 patients versus 25 in total), more participatory studies are needed to support this result.

Since smoking exposure has been shown to worsen Graves' ophthalmopathy, studies have been conducted to demonstrate the relationship between smoking and thyroid. Although these studies have shown that smoking increases the risk of nodule formation and thyroid cancer (17,18), there are also studies showing that it is ineffective (19,20). In the literature, as we have determined, there are no studies investigating the effect of cigarette exposure on ND biopsy results. For this reason, we also considered the smoking history of the patients. When the distribution of the patients who ex-smokers and still smokers was compared between the two groups, no significant relationship was found ( $p=0.176$ , table 2). However, we did not elaborate on cigarette exposure (duration, amount, passive smoking, etc.). Therefore, more detailed studies to support this finding will help enlighten the issue.

HT is the most common inflammatory thyroid disease. The main diagnosis is made histopathologically, but in daily practice, HT is diagnosed according to thyroid autoantibodies and USG findings (18). According to the studies, the success of FNAB decreases in the presence of HT and it increases the diagnosis ND and AUS/AUFL

(21,22). In our study, while HT was detected in 25.5% of all patients, we could say that HT did not increase the risk of ND since there was no significant difference between the groups in terms of HT.

Toxic nodules previously thought to be protective for thyroid cancer, more FNABs are being performed today and it has been found to carry a risk of malignancy as much as non-toxic nodular goiter (23). Baser et al. (24) examined FNAB results of toxic and non-toxic nodules and showed that they had similar ND ratios. In our study, toxic nodules with FNAB were also included because they had sonographically risky features. The distribution of toxic nodules was similar between the groups, and it was determined that the toxic nodule had no effect on the ND result.

Studies investigating the efficacy/adequacy of thyroid FNAB were mostly based on sonographic findings. In our study, we compared both the general thyroid USG findings of the patients and the features of the nodules undergoing FNAB. There was no difference between the two groups in terms of thyroid gland size, parenchymal structure and number of nodules. The nodule size, the ratio of anterior-posterior diameter to transverse diameter, nodule content, echogenicity, margin arrangement, vascularity and calcification content were compared and only the nodule echogenicity was effective on the ND result. This difference was also shown by post hoc analysis that it was caused by hypoechoic echogenicity (table 3). In both univariate and multivariate logistic regression analyzes, hypoechoicity has been shown to affect the ND biopsy result. So, it was shown in our study that only hypoechoic echogenicity contributed to the ND result. Inci et al. (8) stated that heterogeneous echogenicity leads to more ND results, which may result from the hemorrhagic and necrotic content of the nodule. Ozel et al. (14) concluded that needle size is effective in ND result, and sonographic features of nodule have no effect. Moon and colleagues (25) found hypoechoicity as an independent factor for ND, as in our study. There are many other studies showing that more ND results are obtained in hypoechoic nodules (26,27). The possible reason is that due to the hypoechoic nodules being more fibrotic, sufficient material cannot be taken with fine needle aspiration (26). While cystic content increased the risk of ND in some studies (13,28), it was shown that it did not pose any risk in some (27). In our study, cystic content did not increase the risk of ND. No relation was found between size, vascularity, calcification (especially macrocalcification) and ND, as in many other studies (8,13,27).

Consequently, according to our study, the only factor that adversely affects the FNAB adequacy is the nodule hypoechoicity. Other demographic, clinical and sonographic features do not affect biopsy adequacy.

Our study provided homogeneity, covering a shorter period of time (1 year), by the same expert (1 endocrinologist), using the same USG, the same needle (22 gauge) and the same technique (aspiration). Although it covers 1 year, the number of patients (361) undergoing FNAB is quite high. We believe that this is a detailed study since it includes both demographic, clinical and USG findings.

Our study had limitations, too. We included only 1 biopsy result of 1 nodule of each patient, we did not include the results of re-biopsy. For this reason, we were unable to answer the question of whether the rate of ND will change with re-biopsy. The sample size of the study is also one of the factors limiting the study (361 biopsies performed in 1 year by 1 endocrinologist were examined.). Considering how common thyroid nodules are, analyzes with larger numbers of subjects are needed.

In some studies, the thickness of the needle used for FNAB was also investigated. The general recommendation is to make FNAB with a fine needle.<sup>12,28</sup> We performed all biopsies with a 22- gauge needle and we did not compare different needles, so we could not comment on this.

## CONCLUSION

Sonographic imaging and fine needle aspiration biopsy have an important role in the evaluation of thyroid nodules. The most important factor affecting biopsy adequacy is the echogenicity of the nodule. Performing the biopsy with USG, reduces non-diagnostic results.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Amasya University Non-interventional Clinical Researchs Ethics Committee (Date: 02.05.2019, Decision No: 05-26).

**Informed Consent:** All patients signed the free and informed consent form.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The author has no conflicts of interest to declare.

**Financial Disclosure:** The author declared that this study has received no financial support.

**Author Contributions:** The author declared (design, execution, and analysis) that all stages of the work were done by the author herself.

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