



Research

Relationship Between Non-diagnostic Result and Nodule Size in Thyroid Fine Needle Aspiration Biopsies

Tiroid İnce İğne Aspirasyon Biyopsilerinde Non-diagnostik Tanı ile Nodül Boyutları Arasındaki İlişki

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ABSTRACT

Objective: Twenty-one percent of total thyroid fine needle aspiration biopsies (FNABs) result non-diagnostic (ND). It is a major problem in management of thyroid nodules. The aim of this study is to investigate the relationship among ND result, nodule size, ultrasonographic features and laboratory findings in patients whose cytopathologic examination of thyroid FNABs resulted in ND.

Methods: Retrospectively, 520 patients aged 18-85 years, whose thyroid FNABs were performed between the years 2012-2016 and whose cytopathology was ND, were evaluated with laboratory, ultrasonography, and final pathologic results.

Results: There was no significant relationship among ND result, nodule size, and final pathology result. It was determined that no macrocalcifications were found in any of the ultrasonographic examinations of the nodules evaluated to be pathologically malignant. There was a significant relationship between the free triiodothyronine (fT₃) level and the total number of biopsies taken from the same nodule. Significant relationship was observed between the anti-thyroid peroxidase (anti-TPO) level and the number of biopsies taken, which resulted in ND. In patients with high anti-TPO levels, an ND biopsy is one of the follow-up biopsies taken from the nodule.

Conclusion: We concluded there is no distinct correlation between the ND result and nodule dimensions in the FNAB. Ultrasonographic features still cannot provide a prediction of whether the nodule is benign or malignant. Laboratory findings like fT₃ and anti-TPO, may provide guidance to the clinical approach.

Keywords: Nodule size, non-diagnostic, thyroid fine needle aspiration biopsy, ultrasonographic characteristics

ÖZ

Amaç: Toplam tiroid ince iğne aspirasyon biyopsisinin (İİAB) yüzde 21'i sonucu non-diagnostiktir (ND). Bu, tiroid nodüllerinin tedavisinde önemli bir sorundur. Bu çalışmanın amacı tiroid İİAB sitopatolojik incelemesi ND olan hastalarda ND sonuç, nodül boyutu, ultrasonografik (USG) özellikler ve laboratuvar bulguları arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler: 2012-2016 yılları arasında tiroid İİAB'si yapılan ve sitopatolojisi ND 18-85 yaş arası 520 hasta retrospektif olarak laboratuvar, USG ve patoloji sonuçlarıyla değerlendirildi.

Bulgular: ND sonuç, nodül boyutu ve nihai patoloji sonucu arasında anlamlı bir ilişki yoktu. Patolojik olarak malign olarak değerlendirilen nodüllerin USG incelemelerinin hiçbirinde makrokalsifikasyona rastlanmadığı belirlendi. Serbest triiyodotironin (fT₃) düzeyi ile aynı nodülden alınan toplam biyopsi sayısı arasında da anlamlı bir ilişki vardı. Ayrıca ND olarak değerlendirilen biyopsinin, hastanın bu nodülünden alınan kaçınıcı biyopsisi olduğu ile anti-tiroid peroksidaz (anti-TPO) değeri arasında anlamlı ilişki görülmektedir. Anti-TPO değeri yüksek olan hastalarda ND çıkan biyopsinin, hastanın bu nodülünden alınan daha sonraki biyopsilerinden biri olduğu görülmektedir.

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ÖZ

Sonuç: ND sonuç ile İİAB'deki nodül boyutları arasında belirgin bir korelasyon olmadığı sonucuna vardık. USG özellikleri hala nodülün benign mi olduğuna dair kesin bir tahmin sağlayamamaktadır. fT3 ve anti-TPO gibi laboratuvar bulguları, klinik yaklaşımda yol gösterici olabilir.

Anahtar Kelimeler: Nodül boyutu, non-diagnostik, tiroid ince iğne aspirasyon biyopsisi, ultrasonografik özellikler

INTRODUCTION

Approximately 60% of adults have thyroid nodules detected by ultrasound, but most are clinically insignificant. Thyroid nodules are more common in women than in men and in areas where iodine intake is limited. The frequency of nodules increases with age, and the vast majority, 95%, are benign (1).

Ultrasonography and fine needle aspiration are of great importance in the diagnosis and follow-up of thyroid nodules. Clinicians, surgeons, pathologists, and oncologists work together in the management of thyroid nodules. There was a need for standardization of the cytopathological examination of thyroid aspiration sampling using a common language to increase the sensitivity and specificity of sampling in managing the patient's thyroid disease.

This problem was largely resolved with the "Bethesda Thyroid Cytopathology Reporting System" (TBSRTC). Compared to previous systems, TBSRTC has allowed for a significant reduction in the rate of ND/undetermined cases, making the results of fine needle aspiration biopsies (FNABs) more clinically useful. TBSRTC improves communication between cytopathologists, reduces the number of unnecessary operations in benign lesions, and makes it possible to perform timely surgical interventions and predict the risk of thyroid cancer in patients with malignant lesions. It provides simple and reliable data exchange not only among various laboratories, but also institutions all around the world (2).

There are classifications based on nodule size and ultrasonographic (USG) features, such as the American College of Radiology Thyroid Imaging Reporting and Data System and the American Thyroid Association (ATA) guide. In recent years, studies have been carried out on AI-based classification.

Additionally, molecular testing has emerged as a powerful tool with the potential to improve diagnostic evaluation of indeterminate nodules preoperatively (3).

FNAB has an indispensable role in revealing the risk of malignancy, even though it is possible to obtain valuable findings about the thyroid nodule non-invasively with detailed USG examination and laboratory findings. However, due to the insufficiency of the material or the

incompatibility of the sample taken during the biopsy, non-diagnostic (ND) pathology samples constitute a dilemma in the clinical approach (4).

Our goal in this study was to investigate the relationship among ND result, nodule size, USG features and laboratory findings in patients who had cytopathologic examination of thyroid FNABs resulting in ND.

METHODS

After obtaining the approval of the Ethics Committee of University of Health Sciences of Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no: 2017-01-02, date: 17.04.2017), the reports of 12,219 patients who underwent pathological examination from the archive files between 2012 and 2016 were reviewed. As the study had a retrospective design, informed consent was not required from the patients. The patients were divided into two groups based on findings from thyroid FNAB (n=10,718) and thyroidectomy specimens (n=1,501). Afterwards, the results of FNAB of 10,718 patients were investigated, and it revealed that the pathology reports of 838 patients were evaluated as ND. USG reports of the patients evaluated as ND were obtained from hospital archives. 318 patients, whose USG results could not be obtained from the archives, were excluded from the study as planned. The study was performed on 520 patients between the ages of 18 and 85 who were evaluated as ND as a result of FNAB. Their USG results were obtained from the archives (Figure 1).

The records of these patients were evaluated retrospectively. The final pathology diagnoses, based on the nodule size and USG features, if any, were established from biopsies made from this nodule. In addition to the demographic information of the patients, in terms of USG features, the length of the nodule in 2 dimensions, whether the nodule was cystic or solitary, whether it was calcified, border irregularity, vascularization, whether it gave a halo, and echogenicity features were examined.

As laboratory analysis; serum thyroid stimulating hormone (TSH), free triiodothyronine (fT₃), free tetraiodothyronine (fT₄), anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) levels were screened.

Statistical Analysis

Normality tests were performed for each variable considered in the study, and Kolmogorov-Smirnov and Shapiro-Wilk tests were applied. Since the variables had $p < 0.05$, it was determined that they were not normally distributed and non-parametric methods were preferred in the analysis. The data considered have both categorical and continuous data structures. Chi-square analysis was used to determine the relationship between two categorical variables, and Kendall's tau-b correlation coefficient was used to analyze two continuous variables. In the analysis of group differences, the Mann-Whitney U test was applied for two groups and the Kruskal-Wallis test was applied for three or more groups. Since the normal distribution is not used to describe the statistics, median and range (minimum-maximum) values are given for continuous data. Frequency distribution tables were interpreted for categorical data. Analyses were made with SPSS version 22.0, and significance was evaluated at $p < 0.01$ and $p < 0.05$ levels.

RESULTS

In our study, all patients aged between 18-85 years who were evaluated as ND as a result of FNAB performed in our hospital between 2012 and 2016 and whose USG results could be obtained from hospital archives were included. There were 520 patients who met these criteria.

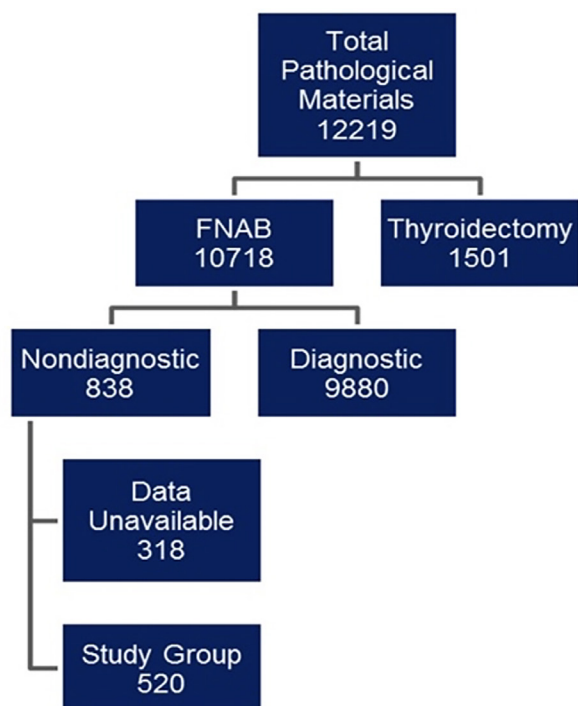


Figure 1. The distribution of the ND patient group in all examinations. FNAB: Fine needle aspiration biopsy, ND: Non-diagnostic

85.2% of all patients ($n=443$) were women, 14.8% ($n=77$) were men, and the average age was 52 years.

In the 2-dimensional evaluation of the nodule diameters, the larger 1st diameter was found to be 15 mm on average, and the smaller 2nd diameter was 10 mm.

Upon inspection of the largest first diameter of nodule sizes in patients, 16.5% ($n=86$) had nodules between 1-10 mm, 47.9% ($n=249$) between 11-20 mm, 19.8% ($n=103$) between 21-30 mm, 9.8% ($n=51$) between 31-40 mm, and 6% ($n=31$) had nodules greater than 40 mm.

When inspecting the smaller 2nd diameter of the nodule size of patients, 43.7% ($n=227$) is between 1-10 mm, 41.5% ($n=216$) is between 11-20 mm, 11.3% ($n=59$) is between 21-30 mm, 2.3% ($n=12$) is between 31-40 mm, and 1.2% ($n=6$) is greater than 40 mm.

When the USG properties of the biopsies were evaluated in terms of the presence of cystic components, it was observed that there was an approximately equal distribution. Microcalcification was detected in 15.8% ($n=82$) of the patients and macrocalcification in 10.6% ($n=55$). It was observed that only 1.7% of the patients ($n=9$) had vascularity. Borders were regular in 91% ($n=473$) of the nodules taken, and in 9% ($n=47$), borders were irregular. The presence of halo around the nodule was observed in 25.6% ($n=133$) of all patients. A classification of nodules according to their echogenicity revealed that 37.9% ($n=197$) are hypoechogenic, 25.2% ($n=131$) hypo-isoechogenic, 28.1% ($n=146$) isoechogenic, 3.1% ($n=16$) iso-hyperechogenic, 3.8% ($n=20$) hyperechogenic, and 1.9% ($n=10$) of them are mixed. 31.2% of 520 biopsies were reported as ND due to material insufficiency.

The median value for serum TSH level was 1.09, the minimum value was 0.01, and the maximum value was 76.12. Serum TSH levels were high in 11% of patients ($n=57$), low in 13.8% ($n=72$), and within the normal range in 75.2% ($n=391$) [normal values (N)=0.27-4.2 mIU/mL].

For the fT_3 level, the median value was 2.91, the minimum value 0.41, and the maximum value 6.84. Serum fT_3 level was found to be high in 18.5% ($n=96$) patients, low in 3.65% ($n=19$), and in 77.9% ($n=405$) was within normal limits ($N=2-4.4$ pg/mL).

The median value for the fT_4 level was 0.98, the minimum value 0.05, and the maximum value 9.03. Serum fT_4 level was found to be high in 2.31% ($n=12$), low in 30.8% ($n=160$), and within normal limits in 66.9% ($n=348$) of patients ($N=0.93-1.7$ ng/dL).

In serum anti-TPO level measurements, the median value was 13.23, the minimum value 1.45, and the maximum value

3,000. Serum anti-TPO levels were within normal limits (0-40 IU/mL) in 79.81% (n=415) of patients, while they were high in 20.19% (n=105).

The median value for serum anti-Tg level was 20, the minimum value was 10, and the maximum value was 3,000. Serum anti-Tg levels were found to be within normal limits in 79.23% (n=412) of patients, while they were high in 20.77% (n=108) (N=0-35 IU/mL).

While the total number of FNABs performed in the nodules diagnosed with ND was investigated in the study, 51.9% (n=270) of the patients had no other biopsy. 40.8% (n=212) had a total of 2 biopsies; 4.8% (n=25) had a total of 3 biopsies; 2.3% (n=12) had a total of 4 biopsies; and 2% (n=1) had a total of 5 biopsies.

When the group of 250 patients, excluding the 270 patients without any other biopsy, was examined, the number of ND results obtained from FNAB biopsies were as follows: 1st biopsy resulting in ND; 40.2% (n=209) were 1st biopsies resulting in ND 7.5% (n=39) were 2nd biopsy; 2nd 0.2% (n=1) were 3rd biopsies; 3rd 0.2% (n=1) were 4th biopsies.

Of 250 patients who underwent repeat biopsy, 24.4% (61 patients) were ND again, 70.8% (177 patients) were diagnosed as Bethesda 2, 1.6% (4 patients) as Bethesda 3, 0.8% (2 patients) as Bethesda 4, 1.2% (3 patients) as Bethesda 5, and 1.2% (3 patients) as Bethesda 6 (Table 1).

In the group of 250 patients whose final Bethesda results were obtained from the archives, there was no significant relationship between the large diameter or the small diameter values of the nodule diameter sizes and the Bethesda result ($p>0.05$) (Table 2).

It was concluded that there was no statistically significant difference between the nodule sizes and the number of biopsies taken that resulted in ND in the same group of 250 patients ($p>0.05$) (Table 3).

In the comparison made in terms of TSH levels in the group of 250 patients whose final Bethesda results were obtained from the archives, further analysis revealed significant trends. There was a significant difference between the nodule

diameters, including large and small diameter values, and the presence of cystic components. While patients with low TSH levels had the largest diameters, patients with high TSH levels had the smallest diameters. the cystic component was statistically significantly more common in patients with low TSH levels and was observed less commonly in those with high TSH levels.

When the population of 250 patients whose final Bethesda results were obtained was analyzed according to the level of fT_3 , it was seen that the FNAB performed with the same nodule was mostly applied in patients with high fT_3 level, and least in patients with normal fT_3 level ($p<0.05$) (Table 4). In other features, there was no statistically significant difference among groups.

In our study, patients were divided into two groups, normal and high, in terms of anti-TPO levels. A significant

Table 2. Bethesda results by nodule dimensions

	Result	N	Average rank	p-value
Nodule size greater diameter	Bethesda 1	61	127.86	0.432
	Bethesda 2	177	124.05	
	Bethesda 3	4	98.63	
	Bethesda 4	2	223.75	
	Bethesda 5	3	109.33	
	Bethesda 6	3	149.67	
	Total	250		
Nodule size smaller diameter	Bethesda 1	61	128.16	0.327
	Bethesda 2	177	123.81	
	Bethesda 3	4	106.13	
	Bethesda 4	2	233.25	
	Bethesda 5	3	97.67	
	Bethesda 6	3	152.67	
	Total	250		

Kruskal-Wallis test was used as statistical method

Table 3. Relationship of nodule diameters with ND FNAB

	Which FNAB resulted ND	N	Average rank	p-value
Nodule size greater diameter	1. Biopsy	209	123.97	0.446
	2. Biopsy	39	132.32	
	3. Biopsy	1	223.50	
	4. Biopsy	1	80.50	
Nodule size smaller diameter	1. Biopsy	209	124.95	0.298
	2. Biopsy	39	127.95	
	3. Biopsy	1	232.00	
	4. Biopsy	1	38.50	

Kruskal-Wallis test was used as statistical method

FNAB: Fine needle aspiration biopsy, ND: Non-diagnostic

Table 1. Distribution of final Bethesda results after repeat biopsies

	N	Percentage
Bethesda 1	61	24.4%
Bethesda 2	177	70.8%
Bethesda 3	4	1.6%
Bethesda 4	2	0.8%
Bethesda 5	3	1.2%
Bethesda 6	3	1.2%
Total	250	100%

relationship was observed between anti-TPO level and the biopsy number resulting in ND ($p < 0.05$) (Table 5). In patients with high anti-TPO levels, the ND biopsy appears to be one of the subsequent biopsies taken from the nodule. Although there was no significant difference in the total number of biopsies performed or the final Bethesda results ($p > 0.05$), further analysis is needed to understand the underlying factors.

DISCUSSION

Woo et al. (5) reported that in their study group of 1,203 patients, 84 patients (6.98%) had ND cytological results. In our study, 7.82% ($n=838$ patients) of 10,718 FNABs performed within a 5-year period were evaluated as ND.

Ziemianska et al. (6), reported that they examined 159 ND nodules and found a 20.8% ND result in repeated FNAB. In our study, ND results were obtained in 61 (24.4%) of 250 patients with repeated FNAB.

In the study of Glynn et al. (7) investigating 413 nodules, it was observed that 89% of the patients were women, the average age of the patients was, and the nodule diameter was 25 mm. In our study where ND nodules were examined, it was noteworthy that 85% of the patients were women, the average age of the patients was 52, and the average largest diameter of the nodules was 15. In our study, we evaluated

only ND nodules; but Glynn et al. (7) included all nodules in their study; their nodule median size was 25 mm, while our median size was 15 mm. This suggesting that biopsy of smaller nodules probably results in increased ND results.

In one of the studies, on the relationship between nodule depth and ND diagnosis, nodule size was also investigated. Asakly et al. (8) have reported in their study, no significant relationship was found between nodule size and ND result. Xia et al. (9) reported nodule diameters between 5 and 10 mm that have macrocalcification were more likely to be ND in cytological results compared to those with a maximum diameter greater than 10 mm. This suggests that small nodules may be more likely to result in ND. Another study showed that nodules 1 cm or less were associated with ND and Bethesda system categories that are suspicious for malignancy compared to nodules greater than 1 cm (10). The reason for this association may be the difficulty of performing FNAB on small nodules.

Eun et al. (11) worked with nodules that had ND results after a second FNABs. Malignancy rates, patient characteristics, and USG features were compared in 297 nodules with an average patient age of 52 and an average diameter of 9.8 mm. The tumors were classified as benign or malignant through surgical resection or repeated FNAB. One hundred fifty-three patients were evaluated as benign based on a repeat biopsy result. In the 12-month follow-up, the nodules

Table 4. Relationship of ft_3 with ND FNAB

	ft_3 level	N	Average rank	Kruskal-Wallis test	p-value
ND FNAB biopsy number*	Low	47	129.17	1.866	0.393
	Normal	193	123.74		
	High	10	142.2		
Total number of FNABs taken	Low	47	136.6	6.194	0.035
	Normal	193	121.75		
	High	10	145.75		

*: Number of biopsy taken (1st biopsy, 2nd biopsy, 3rd biopsy, etc.) which resulted ND

Kruskal-Wallis test was used as statistical method

FNAB: Fine needle aspiration biopsy, ND: Non-diagnostic

Table 5. Relationship of anti-TPO with ND FNAB

	Anti-TPO level	N	Average rank	Kruskal-Wallis' test	p-value
Total Number of FNABs taken	Low	207	123.51	4.038	0.126
	Normal	43	135.07		
	High	250			
ND FNAB biopsy number*	Low	207	121.87	3.966	0.007
	Normal	43	142.98		
	High	250			

*: Number of biopsy taken (1st biopsy, 2nd biopsy, 3rd biopsy etc.) which resulted ND

Kruskal-Wallis test was used as statistical method

FNAB: Fine needle aspiration biopsy, ND: Non-diagnostic, anti-TPO: Anti-thyroid peroxidase

of 7 patients shrank; no change was observed in the nodules of 74 patients, and therefore, they were evaluated as benign; 63 patients were subsequently operated on. Of 297 ND nodules, 44 (14.8%) were evaluated as malignant, and 253 (85.2%) nodules were benign. In our study, ND results were obtained in 7.8% of all FNABs and unfortunately 24.4% of these FNABs were ND again. The mean diameter of these ND nodules was 18.6 mm. In the follow-up, while the benign cytology rate was 70.8% in cytopathological results, the control FNAB results for Bethesda categories 3, 4, 5, and 6 among 250 patients were 1.6%, 0.8%, 1.2%, and 1.2% respectively, with a total of 4.8%.

Recurrent ND FNABs have high ND rates and malignancy rates. Surgical resection, follow-up by USG, or the decision to repeat FNAB poses an important challenge in clinical management for clinicians and radiologists. There are up-to-date guidelines and management recommendations on this subject. In the ATA guideline, the risk of malignancy group is determined according to cutoff values for nodule sizes and USG features. In addition, the risk of malignancy in completely cystic nodules is evaluated as less than 1% and biopsy is not recommended (12). Yoon et al. (13) state that it is more appropriate to follow up nodules that have no suspicious USG findings especially completely cystic nodules. Eun et al. (11) also stated in their study that no tumor with more than 50% cystic sections was malignant. In our study, macrocalcification, which is one of the findings suggesting that the nodule is benign, was not observed in any of our 12 patients, all of whom were classified as Bethesda 3, 4, 5, or 6.

Woo et al. (5) also stated that the detection of hypoechogenicity in USG findings in recurrent ND FNABs was identified as a significant risk for malignancy. Kim et al. (14) classified nodules containing at least one of the USG features: microcalcification, irregular or microlobular nodule boundaries, pronounced hypoechogenicity, and a longer-than-width sign as positive. They classified nodules without any of these features as negative. Malignancy was detected in 46 of 82 positive nodules and only in 3 of 73 negative nodules. According to these numbers, sensitivity was calculated as 93.8%, specificity as 56.1%, positive predictive value as 56.1%, negative predictive value as 95.9%, and accuracy as 74.8%. In our study, the feature of nodules being longer than wide in the USG image was not collected; therefore, after excluding this feature and continuing with the classification, malignancy was detected in 9 of our 196 positive nodules and only 3 of 54 negative nodules. In our study, the negative predictive value was similarly 94%.

Woo et al. (5) stated that 51 patients who had ND results, in the second FNAB in a 1,203 patient study group, had 36 (70.6%) malignant nodules. Nodule diameter, hypoechogenicity, and microcalcification were important risks for malignancy. In the detailed examination, it was concluded that only hypoechogenicity is an independent risk factor for the ND result. In a study conducted by Çetin (15), an endocrinologist examined FNABs performed by 1 year, and investigated the factors affecting the ND result. It was determined that only hypoechogenicity increased the probability of an ND result (15). In our study, when both malignant and benign USG findings were examined in relation to ND results and Bethesda results, no statistically significant relationship was found.

In our study, when the patients were divided into three groups low, normal, and high according to TSH values, no significant differences were found in the number of FNABs performed on the patient's ND nodule, the number of biopsies obtained from the ND nodule, and the final Bethesda results. However, the differences in TSH levels are observed especially between ND nodules containing a cystic component and ND nodule sizes. Larger nodules are seen in patients with low TSH levels and smaller nodules in patients with higher TSH levels.

When the patients were divided into 3 groups as low, normal, and high according to fT_3 level, no significant difference was found between the number of FNABs performed on the patients' ND nodule and the final Bethesda result. However, the only relationship was observed between the fT_3 level and the total number of FNABs performed on the patient's ND nodule. It is seen that the number of FNABs applied to the patient is the highest with high fT_3 levels, while the lowest in normal fT_3 levels. Although the synchronicity of hyperthyroidism and malignancy is rare, there are many studies demonstrating this association (16-20). As this association becomes more known, more FNABs are being performed in patients with hyperthyroidism due to the risk of thyroid malignancy.

Current studies are being conducted on the management of thyroid nodules using AI. The most important report from research conducted in recent years is that the evaluation of AI can be successfully used as a computer-aided diagnosis system to assist clinicians in making further diagnostic and treatment decisions (21-23).

CONCLUSION

We concluded there is no distinct correlation between the ND result and nodule dimensions in the FNAB. Even

if some USG findings (macrocalcification and completely cystic nodules tend to be more likely benign but irregular bordered, hypoechogenic and microcalcified nodules more likely malignant) can assist clinicians in determining the malignancy risk of ND nodules, USG features still cannot provide a definitive prediction of whether the nodule is benign or malignant. As studies show the association of hyperthyroidism and thyroid malignancies, laboratory findings like fT_3 and anti-TPO, can provide guidance to the clinical approach in making decisions for follow-up, possible biopsy repeat or surgical resection.

ETHICS

Ethics Committee Approval: Approval was obtained from the Ethics Committee of University of Health Sciences of Türkiye, Bakırköy Sadi Konuk Training and Research Hospital (approval no: 2017-01-02, date: 17.04.2017).

Informed Consent: As the study had a retrospective design, informed consent was not required from the patients.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: Ö.P., F.K.Ç., H.P., M.M., Concept: B.Ö.D., Ö.P., M.Ş., H.Y.A., M.M., Design: B.Ö.D., E.D., H.P., M.M., Data Collection or Processing: B.Ö.D., F.K.Ç., M.Ş., H.Y.A., Analysis or Interpretation: B.Ö.D., Ö.P., F.K.Ç., E.D., H.P., M.M., Literature Search: B.Ö.D., E.D., M.Ş., H.Y.A., Writing: B.Ö.D., Ö.P., E.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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