

Research Article

The sonographic pattern of nodule and thyroid fine needle aspiration cytology in the evaluation of thyroid malignancy risk

Tiroid malignitesi riskinin değerlendirilmesinde nodülün sonografik paterni ve tiroid ince iğne aspirasyon sitolojileri

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Abstract

Introduction: Thyroid fine-needle aspiration biopsy (TFNAB), which is basically planned according to the ultrasonographic features is of clinical importance; since it helps early diagnosis of malignancy, facilitates the selection of patients who will undergo thyroid surgery and prevents unnecessary surgical procedures. In our study, we aimed to evaluate the adequacy of TFNAB as well as the retrospective investigation of the link between the estimated malignancy risk and the descriptive features, radiologic findings and biopsy cytology of patients who underwent ultrasonography guided TFNAB.

Methods: In this study, the ultrasonographic characteristics of 659 thyroid nodules belonging to 523 patients who underwent TFNAB between 2018 and 2021 were evaluated. The correlation between the risk of malignancy and demographic data, thyroid hormone levels, and ultrasonographic characteristics of nodules was examined. The diagnostic accuracy performances of European thyroid imaging reporting and data system (EU-TIRADS) classification prepared by the European Thyroid Association (ETA), the risk classification systems recommended by the American Thyroid Association (ATA) and the Society of Endocrinology and Metabolism of Turkey (TEMMD) were compared with The Bethesda System for Reporting Thyroid Cytopathology (Bethesda). The adequacy of biopsy was also evaluated. The data which is obtained from the study was statistically analyzed by means of SPSS 20.0 (Statistical Package for the Social Sciences; SPSS Inc. Chicago, IL, USA) program.

Results: In this study, the biopsies of 41 (6.2%) among 659 thyroid nodules appeared to be malignant. A statistically significant correlation was detected between malignancy and hypoechogenicity ($p=0.011$), microcalcification ($p=0.005$), irregular margins ($p=0.028$), and accompanying pathological lymph node ($p=0.002$). Compared to the surgical pathology results, the accuracy that was closest to that of Bethesda System (AUC: 0.778) (Area Under Curve) was found in EU-TIRADS (AUC:0.715). In the biopsies performed in our own endocrinology clinic (43.7% of the total biopsies), the ratio of non-diagnostic results was found to be 8.3%, whereas it was 29.1% in the biopsies performed in other clinics (56.3% of the total biopsies).

Conclusion: It should always be kept in mind that, in the cytologic evaluation, the ultrasonographic nodule pattern recommended by the guidelines is very important in the management of patients, because cytology may show false negative and false positive results as well as unclear or non-diagnostic pathological findings. However, clinicians should also understand that classification systems may have strengths and weaknesses. Our study also emphasizes the importance of how experienced a clinic performing biopsy is as well as the role of cytopathologist in obtaining diagnostic results in biopsy.

Keywords: Thyroid nodule, neoplasia, ultrasonography, biopsy fine-needle

Öz


Giriş: Temel olarak ultrasonografik özelliklere göre planlanan tiroid ince iğne aspirasyon biyopsisi (TİİAB); malignitenin erken tanısının yanında, tiroid cerrahisi yapılacak hastaların seçimini kolaylaştırmak ve gereksiz cerrahi işlemleri önlemek için de klinik önem arz etmektedir. Çalışmamızda, ultrasonografi (US) eşliğinde TİİAB uygulanan hastaların tanımlayıcı özelliklerinin, radyolojik bulgularının ve biyopsi sitolojilerinin hastalarda malignite riskinin tahmini ile ilişkisinin retrospektif araştırılmasını ve TİİAB yeterliliğini değerlendirmeyi amaçladık.

Yöntem: Çalışmamız kapsamında, 2018-2021 yılları arasında TİİAB yapılmış olan 523 hastaya ait toplam 659 tiroid nodülünün ultrason özellikleri değerlendirilmiştir. Hastaların demografik verileri, tiroid hormonu düzeyleri ve nodüllerin ultrasonografik özelliklerinin malignite riski ile korelasyonu incelendi. Avrupa Tiroid Derneği'nin (ETA) hazırladığı EU-TIRADS sınıflandırmasının yanında Amerikan Tiroid Derneği (ATA) ve Türkiye Endokrinoloji ve Metabolizma Derneği'nin (TEMMD) önermiş olduğu risk sınıflandırma sistemleri ile sitopatoloji tanısal sınıflandırma (Bethesda) sisteminin tanısal doğruluk performansları karşılaştırıldı. Ayrıca biyopsi yeterliliği değerlendirildi. Elde edilen veriler istatistiksel olarak SPSS 20.0 (Statistical Package for the Social Sciences; SPSS Inc. Chicago, IL, USA) programı yardımıyla analiz edildi.

Bulgular: Çalışmada, biyopsi yapılan 659 tiroid nodülünün 41'i (%6,2) malign idi. Hipoekojenite ($p=0,011$), mikrokalsifikasyon ($p=0,005$), kenar düzensizliği ($p=0,028$) ve tiroid nodülüne patolojik lenf nodunun eşlik etmesi ($p=0,002$) ile malignite arasında istatistiksel anlamlı ilişki saptandı. Cerrahi patoloji sonuçları ile kıyaslandığında, Bethesda Sistemine (AUC:0,778) (Area Under Curve) en yakın doğruluğun EU-TIRADS'ta (AUC:0,715) olduğu görülmüştür. Merkezimizde endokrinoloji kliniğince yapılan biyopsilerde (toplam biyopsilerin %43,7'si) tanısal olmayan sonuçların oranının %8,3 olduğu görülmüştür. Diğer kliniklerde yapılan biyopsilerde ise (toplam biyopsilerin %56,3'si) tanısal olmayan sonuçların oranının %29,1 olduğu görülmüştür.

Sonuç: Sitolojik değerlendirmede, yanlış negatif ve yanlış pozitif sonuçların yanında belirsiz veya tanısal olmayan patolojik bulgular gösterebilen sitolojiler nedeniyle, hastaların yönetiminde kılavuzların önerdiği ultrasonografik nodül paterninin önemli olduğu unutulmamalıdır. Ancak sınıflandırma sistemlerinin zayıf ve güçlü yanlarının olabileceği klinisyenlerce göz önüne alınmalıdır. Ayrıca çalışmamız biyopside tanısal sonuçların alınmasında, sitopatolog rolü olduğu kadar biyopsiyi yapan kliniğin deneyiminin önemine de işaret etmektedir.

Anahtar kelimeler: Tiroid nodülü, neoplazi, ultrasonografi, ince-iğne biyopsisi

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Key Points

1. Fine-needle aspiration biopsy of thyroid nodules should be performed according to the guideline recommendations assessing the risk of malignancy.
2. Fine-needle aspiration biopsy of thyroid nodules should be performed by experienced physicians.

Introduction

The diseases related to the thyroid gland are quite common today. The most frequently seen endocrine pathology of the thyroid gland is thyroid nodules, undoubtedly. It is observed that the incidences of both thyroid nodules and cancer (which is approximately 5% of all nodules), ascend with the increase in the clinical use of ultrasonography (US) [1].

Thyroid fine-needle aspiration biopsy (TFNAB), which is basically planned according to the ultrasonographic features, is of clinical importance; since it helps early diagnosis of malignancy, facilitates the selection of the nodules to be operated and prevents unnecessary surgery. Apart from continuously following the up to date data from the literature, it is also underlined that centers should periodically review and control their own TFNAB diagnoses [2].

In our study, we planned to create an archive about the patients who registered to Balikesir University Faculty of Medicine and underwent US guided TFNAB, to reveal the radiological pattern of the nodules, to show the pathological distribution of the fine needle aspiration biopsy (FNAB) results, to review the biopsy adequacy and to retrospectively investigate the correlation between the cytology and histopathology results after thyroidectomy. It was aimed to reveal the data belonging our hospital and to contribute to the literature. The relationship between the descriptive characteristics, the radiological and pathological findings of the patients and the estimated malignancy risk were investigated. Additionally, the risk classification systems created according to ultrasonographic features and performance of the Bethesda System used in cytopathology reporting following FNAB were evaluated comparatively.

Methods

In our study, the data of patients who registered to Balikesir University Faculty of Medicine Hospital and underwent TFNAB between September 2018 and September 2021 were retrospectively analyzed. The biopsy characteristics of a total of 659 thyroid nodules belonging to 523 patients who were over 18 years old with sufficient data were evaluated.

The demographic data of the patients, such as age and gender, were recorded. Thyroid hormone levels in the last 6 months before performing TFNAB were noted. Thyroid stimulant hormone (TSH) levels were measured with a Beckman Coulter UniCel DxI 800 device. The hormone profile was classified in line with NHANES-III TSH upper limits according to the ages of patients. The total number of nodules biopsied in a patient, the distribution of repeated biopsy results (if any), whether the biopsy was performed by the endocrinology clinic or others, whether the biopsied gland was multinodular, the location of the thyroid nodule that was biopsied, the section lengths and the longest diameter of nodule in all three dimensions (if any), the composition of biopsied nodules, the echogenicity and the shape were noted. The calcification and vascularity status were categorized. The presence or absence of sonographic features such as halo in nodules, irregular margins, extrathyroidal spread, pathological lymphadenopathy, whether sonographic features such as having a height greater than width on transverse section (AP>T) existence were recorded.

The category classification that the nodules, whose malignancy risk is defined in accordance with their ultrasonographic features, was determined by means of the different risk classification systems. The category of cytology results reported after TFNAB according to the Bethesda System, the presence of surgical intervention for the nodule after biopsy and the distribution of pathological diagnoses of those who underwent surgery were investigated. The relationship between the descriptive characteristics, laboratory, radiological, pathological findings of the patients and the estimated malignancy risk was analyzed. In the meantime, three risk scoring systems that were created according to the ultrasonographic features; the classifications in European thyroid imaging reporting and data system (EU-TIRADS), Society of Endocrinology and Metabolism of Turkey (TEMED) and American Thyroid Association (ATA) guidelines were compared with the performances of the Bethesda System used in cytopathology reporting after TFNAB, according to the results of surgical pathology.

Ethical approval

Local Ethics Committee Approval for this study was obtained from Balikesir University Clinical Research Ethics Committee (Decision no: 2021/227, decision date: 06.10.2021).

Statistical analysis

The obtained data were statistically analyzed with the help of SPSS 20.0 (Statistical Package for the Social Sciences; SPSS Inc. Chicago, IL, USA) program. Numerical variables were expressed as mean and standard deviation, while categorical variables were expressed as n and %. In the analysis of parameters; Chi-Square, Fisher's Exact and Mann Whitney-U tests were used. The relationship between scoring and surgical pathology results was evaluated by ROC analysis. The P value smaller than 0.05 ($p < 0.05$) was accepted as statistically significant value.

Results

As defining characteristics, 409 (78%) of the 523 patients included in the study were female and 114 (22%) were male. Of the 659 thyroid nodules underwent biopsy, 514 (78%) were female and 145 (22%) were male. The median age was 56 (45-64) years. The number of patients who had multinodular glands was 537 (81.5%) and the number of biopsied nodules from the glands that had 1, 2, 3, 4 and 5 nodules were 411 (62.4%), 190 (28.8%), 45 (6.8%), 8 (1.2%) and 5 (0.8%), respectively. When it comes to the hormone profiles of the patients, the mean serum TSH level was

1.32 mU/L (for the median 25th-75th percentile 0.65-2.18), with 516 patients (78.3%) being euthyroid, 59 (9.8%) hypothyroid and 84 (12.7%) hyperthyroid.

The results of the ultrasonographic evaluation of a total of 659 nodules which underwent biopsy are shown in Table 1. The condition of the tissues around the thyroid was also examined. Accordingly, while no extrathyroidal spread was observed in 652 nodules (98.9%), it was apparent in 7 (1.1%). Furthermore, there were no pathological lymph nodes in 639 (97%) nodules, whereas they were clearly observed in 20 (3%).

Table 1. The results of the ultrasonographic measurements of the sample

Ultrasonographic parameters	Number(n)	Percent (%)
Localization	Nodule maximum diameter (mm)	20.00*
	Right lobe	49.3%
	Left lobe	44.5%
	Isthmus	6.2%
Nodule structure	Solid	52.7%
	Mix	44.8%
	Cystic	2.6%
Nodule echogenicity	Isoechoic	54.8%
	Hypoechoic	36.6%
	Hyperechoic	3.6%
	Anechoic	2.9%
	Pronounced hypoechoic	2.1%
Halo	No	90.7%
	Yes	9.3%
Calcification	No	73.7%
	Microcalcification	13.5%
	Macrocalcification	11.2%
	ESC	1.5%
Irregular margins	No	91.4%
	Yes	8.6%
AP>T presence	No	94.5%
	Yes	5.5%
Vascularity	Type 1 (none)	77.7%
	Type 2 (peripheral)	8.3%
	Type 3 (intra-nodule)	14.0%

* Median (25th-75th percentiles) AP: Anteroposterior diameter. T: Transverse diameter. ESC: Eggshell calcifications

Based on the ultrasonographic evaluations, the patients were categorized regarding the classifications given in EU-TIRADS, TEMD and ATA guidelines which were improved by the European Thyroid Association (ETA) (Table 2).

Table 2. The distributions of ultrasonographic malignancy classifications

Classification	Number(n)	Percent (%)
EU-TIRADS	2 (benign)	2.6%
	3 (low risk)	46.7%
	4 (moderate risk)	25.8%
	5 (high risk)	24.9%
TEMD	Benign	2.6%
	Low risk	45.5%
	Moderate risk	25.6%
	High risk	26.3%
ATA	Benign	2.6%
	Very low suspect	8.0%
	Low suspect	46.3%
	Moderate suspect	18.4%
	High suspect	12.3%
	Unclassifiable	12.4%

EU-TIRADS: European thyroid imaging reporting and data system. TEMD: Society of Endocrinology and Metabolism of Turkey. ATA: American Thyroid Association.

The number of nodules that were performed TFNAB in the endocrinology clinic was 288 (43.7%), while 371 (56.3%) were performed by other clinics. In the entire biopsies, the proportion of inadequate cytology for the first biopsy was 20%, while it was 8.3% for the biopsies performed by the endocrinology clinic and 29.1% for those done in other clinics. For 584 (88.61%) patients TFNAB was applied only once, for 75 (11.38%) patients twice, for 19 (2.88%) patients thrice and for 1 patient it was performed 4 times (0.15%). The results of the biopsy materials obtained by TFNAB are presented in Table 3 with Bethesda classification.

Table 3. The distribution of biopsy results

Bethesda Classification	1. Biopsy	2. Biopsy	3. Biopsy	4. Biopsy
Non-diagnostic (I)	132 (20.00%)	33 (34.7%)	6 (30.00%)	-
Benign (II)	344 (52.2%)	36 (37.9%)	10 (50.00%)	1 (100%)
AUS/FLUS (III)	86 (13.1%)	17 (17.9%)	2 (10.00%)	-
Follicular neoplasia or suspected (IV)	47 (7.1%)	3 (3.2%)	1 (5.00%)	-
Suspicion of malignancy (V)	34 (5.2%)	6 (6.3%)	1 (5.00%)	-
Malignant (VI)	16 (2.4%)	-	-	-
Total	659	95	20	1

AUS: Atypia of undetermined significance. FLUS follicular lesion of undetermined significance

The population sent to surgery according to the biopsy results and the distribution of surgical biopsy results are shown in Figure 1. The ratio of nodules that were found to be malignant in surgical pathology to those that were biopsied was 6.2%. It was noticed that the malignancy percentages of nodules belonging to male and female genders was also both 6.2%. When analyzed based on total biopsy patients, this rate was 7.7% in general, while it was 7.6% and 7.9% in women and men, respectively.

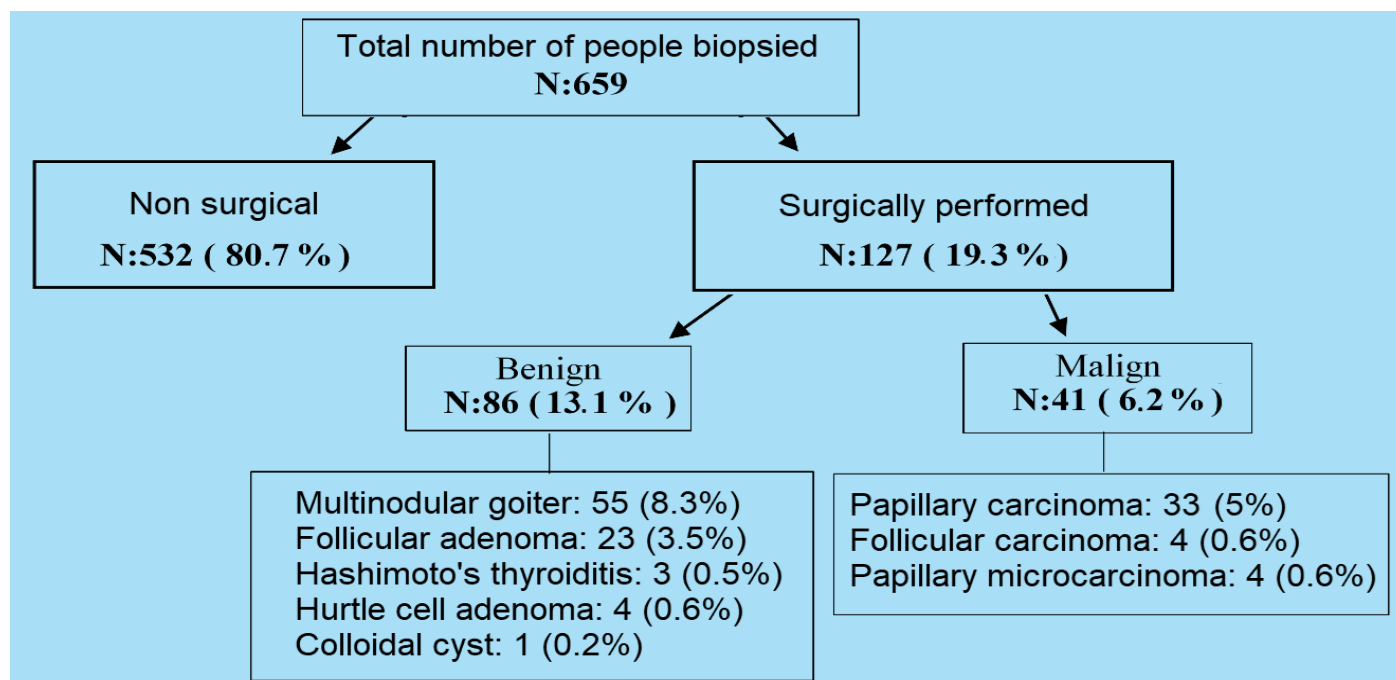


Figure 1. The distribution of surgical cases

When the relationship between the surgical pathology results and the descriptive characteristics of the patient was examined, no statistically significant correlation was observed between those results and the age of the patients, the longest diameter of the nodule that underwent biopsy and the initial serum TSH levels of the patient. When the genders of the patients were compared, most of the cases (79.5%) were women. Nonetheless, the rates of benign or malignant surgical pathology were found to be similar in both genders. The rate of malignancy in men was 34.6%, whereas it was 31.7% in women. When analyzed, it was concluded that there was no statistically significant difference between them. Moreover, on first evaluation, no statistically significant difference was observed when the presence of multinodular glands, hormone profiles and the localization of the nodule were evaluated (Table 4).

Table 4. The analysis of the relationship between the surgical pathology result and the descriptive parameters

	Surgical Pathology Result		p
	Benign	Malignant	
Age	55.0 (44.0-61.0) *	54.00(39.5-64.0) *	0.583**
Nodule maximum diameter (mm)	23.0 (15.0-36.25) *	19.0 (12.0-35.0) *	0.142**
Serum TSH level (µIU/mL)	1.48 (0.6-2.28) *	1.57 (0.69-1.80) *	0.648**
Gender	Male	17 (19.8%)	9 (22.0%)
	Female	69 (80.2%)	32 (78.0%)
			0.776***
Presence of multinodular glands	76 (88.4%)	31 (75.6%)	0.065***
Localization	Right lobe	38 (44.2%)	22 (53.7%)
	Left lobe	44 (51.2%)	15 (36.6%)
	Isthmus	4 (4.7%)	4 (9.8%)
			0.229***
Hormone Level	Euthyroid	70 (81.4%)	31 (75.6%)
	Hypothyroidism	3 (3.5%)	2 (4.9%)
	Hyperthyroidism	13 (15.1%)	8 (19.5%)
			0.681****

*Median (25-75. Percentile) **Mann Whitney-U test *** Chi-Square test ****Fisher's Exact test TSH: Thyroid stimulant hormone

The correlation analyzes between the ultrasonographic characteristics of the patients and the surgical pathology results are presented in Table 5. Accordingly, no statistically significant correlation was found between the surgical pathology results and the structure of nodule, the presence of AP greater than T (AP>T), extrathyroidal extension and vascularity parameters. However, when evaluated in terms of echogenicity, it was observed that the hypoechogenicity was significantly higher in surgical pathologies ($p=0.011$) that were resulted as malignant. Surgical pathology was statistically appeared to be more malignant in patients who exhibited microcalcification, marginal irregularity or pathological lymph node ($p=0.005$).

Table 5. The relationship between US evaluation and surgical pathology result

Ultrasonographic parameters		Surgical Pathology Result		P
		Benign	Malignant	
Nodule structure	Solid	56 (65.1%)	32 (78.0%)	0.317*
	Mix	29 (33.7%)	9 (22.0%)	
	Cystic	1 (1.2%)	-	
Echogenicity	Isoechoic	53 (61.6%)	17 (41.5%)	0.009*
	Hypoechoic	27 (31.4%)	17 (41.5%)	
	Hyperechoic	4 (4.7%)	1 (2.4%)	
	Anechoic	1 (1.2%)	-	
Microcalcification	Pronounced hypoechoic	1 (1.2%)	6 (14.6%)	0.005
	Yes	7 (8.1%)	11 (26.8%)	
Irregular margins	No	79 (91.9%)	30 (73.2%)	0.028
	Yes	7 (8.1%)	9 (22.0%)	
AP>T presence	No	79 (91.9%)	32 (78.0%)	0.680*
	Yes	4 (4.7%)	3 (7.3%)	
Extrathyroidal spread	Yes	1 (1.2%)	1 (2.4%)	0.543*
	No	85 (98.8%)	40 (97.6%)	
Pathological lymph node	Yes	1 (1.2%)	7 (17.1%)	0.002*
	No	85 (98.8%)	34 (82.9%)	
Vascularity	Type 1 (none)	68 (79.1%)	28 (68.3%)	0.116
	Type 2 (peripheral)	9 (10.5%)	3 (7.3%)	
	Type 3 (intra-nodule)	9 (10.5%)	10 (24.4%)	

*Fisher's exact test. AP: Anteroposterior diameter. T: Transvers diameter.

The descriptive and chi-square analyzes between surgical pathology results and the EU-TIRAD system developed by ETA, the scoring in the TEMD, ATA guidelines, the biopsy material scoring (Bethesda) analyzed by TFNAB are presented in Table 6. Accordingly, a statistical difference was observed between the subgroups of all scorings and the surgical pathology result. When the TFNAB categories (I, II, III, IV, V, VI) in biopsies are examined within themselves, the Bethesda classification rates of malignancy are 16.7% - 14.3% - 17.7% - 22.2% - 54.2% - 100%, respectively.

Table 6. The relationship analysis between scoring models and surgical pathology results

Parameters		Surgical Pathology Result		P
		Benign	Malignant	
EU-TIRADS	2 (benign)	1 (1.2%)	-	0.001
	3 (low risk)	50 (58.1%)	10 (24.4%)	
	4 (moderate risk)	19 (22.1%)	9 (22.0%)	
	5 (high risk)	16 (18.6%)	22 (53.7%)	
TEMD	Benign	1 (1.2%)	-	0.002
	Low risk	48 (55.8%)	10 (24.4%)	
	Moderate risk	19 (22.1%)	11 (26.8%)	
ATA	High risk	18 (20.9%)	20 (48.8%)	0.002
	Benign	1 (1.2%)	-	
	Very low suspect	2 (2.3%)	-	
	Low suspect	49 (57.0%)	10 (24.4%)	
	Moderate suspect	17 (19.8%)	11 (26.8%)	
	High suspect	9 (10.5%)	12 (29.3%)	
Bethesda category	Unclassifiable	8 (9.3%)	8 (19.5%)	<0.001
	I.	10 (11.6%)	2 (4.9%)	
	II.	30 (34.9%)	5 (12.2%)	
	III.	14 (16.3%)	3 (7.3%)	
	IV.	21 (24.4%)	6 (14.6%)	
	V.	11 (12.8%)	13 (31.7%)	
VI.	-	12 (29.3%)		

EU-TIRADS: European thyroid imaging reporting and data system. TEMD: Society of Endocrinology and Metabolism of Turkey. ATA: American Thyroid Association.

The ability of the scorings to demonstrate malignancy was analyzed by ROC analysis and summarized in Table 7. According to this, while the AUC value was found to be the highest in the Bethesda System, the value closest to it was observed in the EU-TIRADS scoring. (Figure 2)

Table 7. ROC analyzes between scores and surgical pathology results.

	AUC	Standard error	p	95% Confidence Interval	
				Lower	Upper
Bethesda	0.778	0.049	<0.001	0.682	0.873
TEMED	0.690	0.050	0.001	0.592	0.789
EUTIRADS	0.715	0.050	<0.001	0.617	0.812
ATA	0.703	0.049	<0.001	0.607	0.799

AUC: Area under curve. EUTIRADS: European thyroid imaging reporting and data system. TEMED: Society of Endocrinology and Metabolism of Turkey. ATA: American Thyroid Association.

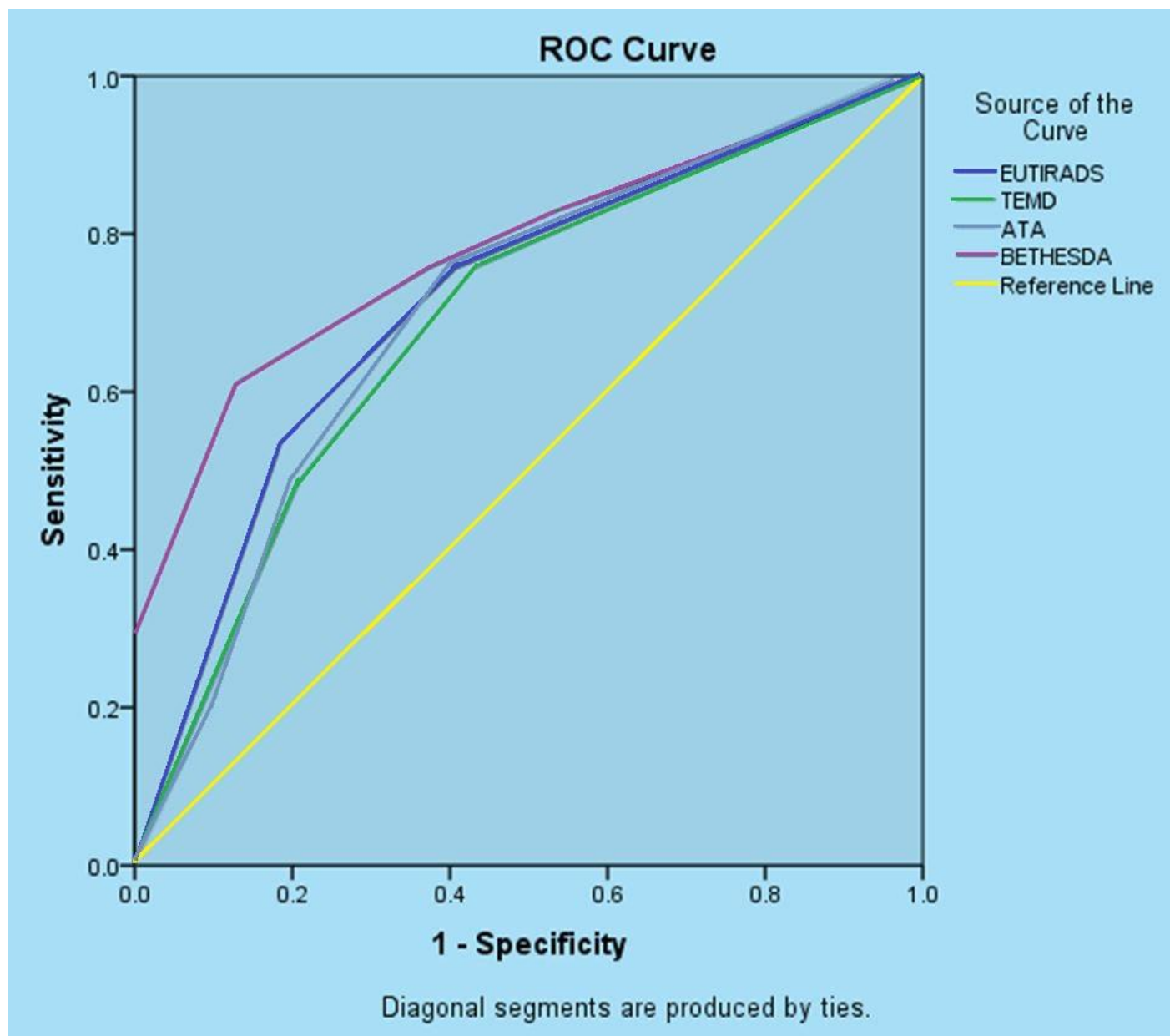


Figure 2. Investigation of the ROC Curve Between Scorings

EUTIRADS: European thyroid imaging reporting and data system. TEMED: Society of Endocrinology and Metabolism of Turkey. ATA: American Thyroid Association.

Discussion

Thyroid nodules are more common in women than men [3]. In a large-scale population study held by Vander et al. which lasted for 15 years, nodules were found to be 4.3 times more common in women [4]. In our study, among the patients who underwent biopsy, female gender accounted for the majority with an amount 3.6 times more than that of male, which is consistent with the prevalence data reported in the literature. There are some studies showing that there is a difference between the sexes in terms of the malignancy risk. Belfiore et al. reported that the rate of cancer is twice as high in men as in women [5]. However, due to the high incidence of thyroid nodules in women both in Türkiye and worldwide, thyroid malignancies are more common in women [1]. In our study, malignancy rates were found to be similar in both genders and there was no statistically

significant difference between them. At the same time, the median age of the patients who underwent biopsy was found to be 56 (45-64), and there was no statistically significant correlation between the age factor and the risk of malignancy.

The risk of malignancy in a nodule given in different studies is inconstant due to bias. Miller et al. found the malignancy rate in nodules after surgery to be 6.5% [6]. In a study by Belfiore et al., 5% of the total biopsy nodules were found to be malignant. The incidence of cancer in nodules was found to be 28% in the surgical specimens of patients who were recommended surgery soon after the results of biopsies were out [7]. In our study, the rate of malignancy in nodule pathologies was found to be 32.3% in patients referred for the operation. The ratio of nodules whose surgical pathologies were malignant to the nodules that were biopsied was 6.2%. When evaluated separately by gender, the malignancy ratio of nodules was also 6.2%, for both male and female.

There is no direct relationship between nodule size and malignancy. There are many studies with different results on this matter. Shin et al. reported that malignancy was more common in nodules larger than 2 cm compared to those smaller than that [8]. Kamran et al., on the other hand, stated that the risk increased gradually in nodules up to 4 cm, while the frequency of malignancy did not continue to increase for sizes greater than that [9]. In our study, which was carried out by taking the maximum sizes into account, no statistically significant relationship was found between size and malignancy. Yet, the evidence suggesting that larger nodule sizes may be associated with a greater risk of thyroid cancer and poor prognosis of malignancy is stronger [10].

In our study, when the nodule structures were examined, the most common nodule was occurred to be solid natured ones (52.7%) in patients who underwent biopsy. The most common US findings that could indicate benignancy for a nodule were stratified nodules which were defined as spongy nodules formed by cystic spaces observed throughout the nodule structure [11]. In line with the opinions that nodules with little or no solid component might more likely be benign, solid structure had been noted while describing nodule pattern [12]. In our study, it was found that most of the malignant nodules were in solid nature (78%), but no statistically significant link was found with malignancy. This may have been due to the fact that we didn't perform the biopsy in accordance with the guidelines (number of samples), from patients with little or no solid component.

TSH levels are accepted as an independent risk factor in predicting malignancy. In a study by Haymart et al., higher TSH levels were reported to be associated with advanced stages of cancer [13]. In our study, most of the patients who underwent biopsy (78.3%) were euthyroid and no statistically significant correlation was found between malignancy risk and TSH levels, as well as hormonal profile that was categorized by age.

The shape of the nodule in US is of importance. In a study by Cappelli et al., it was shown that having an AP/T ratio greater than and equal to 1 ($AP/T \geq 1$) might be more useful than other malignancy features such as microcalcification or marginal irregularity in detecting cancer [14]. In our study, unlike the general literature, no statistically significant correlation was found between the shape of the nodule (height > width in the transverse section) and the risk of malignancy. This may be because the finding of $AP/T \geq 1$ was found only in 5.5% of the nodules and some errors in reporting might have occurred in our study.

In the light of current information, studies on the reliable differentiation of benign and malignant pathology by doppler US vascularization are contradictory. Papini et al detected the Type 3 pattern in approximately 74% of malignant nodules [15]. In a study by Yang et al., intranodular blood supply was not detected in most of the thyroid malignancies [16]. In our study, Type 3 pattern was observed in approximately 24.4% of the malignant nodules and there was no statistically significant correlation with malignancy.

Malignant thyroid nodules are generally observed as hypoechoic. It was shown by Solbiati et al. that 62% of thyroid cancers was hypoechoic [17]. Moon et al. found the sensitivity of a hypoechoic appearance as 53% and the specificity as 73% [11]. When nodule echogenicity was examined in our study, it was observed that most of the malignant nodules were hypoechoic (56.1%), and a statistically significant correlation was found between this appearance and malignancy ($p=0.011$). Surgical pathology was found to be malignant in most (85.7%) patients with significant hypoechoic nodules in subgroups. It can be said that the more prominent the hypoechoic echogenicity of the nodule is, the higher the specificity of malignancy is [12]. The association of hypoechoic echogenicity with malignancy was found to be consistent with the literature.

Nodules containing microcalcifications are associated with a high risk of malignancy. They have been observed in approximately 1/3 of malignancy cases [12]. In our study, microcalcification was observed in 26.8% of malignant nodules, and a statistically significant relationship was found with malignancy ($p=0.005$). At the same time, there was a statistically significant correlation between the presence of irregularity at the margins of nodules, which is one of the malignant US features for a nodule, and malignancy ($p=0.028$). Almost all guidelines recommend the biopsy of the thyroid nodule in the presence of suspicious lymph nodes, regardless of the pattern of the thyroid nodule [12]. In our study, a statistically significant correlation was found between the pathological lymph node accompanying the thyroid nodule and malignancy ($p=0.002$).

The incidence of Bethesda category I cytology results (inadequate due to non-diagnostic pathological findings) in the initial biopsy varies between 3% and 10% in experienced centers [18]. In our study, the failure rate was found to be 20% for all biopsied nodules. In our hospital, 43.7% of the nodules were performed FNAB in the endocrinology clinic. The failure rate was 8.3% for biopsies performed by the endocrinology clinic, while it was 29.1% for those performed in other clinics. Two facts may have contributed to this notable difference; first one is that US and fine needle aspiration biopsy cytology (FNABs) were performed by a single clinician in the endocrinology clinic and second one is that from each nodule 2-4 biopsies were taken. Additionally, this situation indicates the importance of wide experience in performing biopsy as well as the role of cytopathologist in obtaining diagnostic results in biopsy.

The risk of malignancy in Bethesda I cytology is between 5% and 10% [2]. In our study, the incidence of malignancy was found to be 16.7%, which was higher than the literature. The risk of malignancy in Bethesda II cytology was found to be between 0% and 3% [2]. The false negative of FNABs was approximately 1.7% [1]. In our study, the incidence of malignancy was 14.3%, which is higher than the literature. The risk of

malignancy in Bethesda III cytology is between 10% and 30% [2]. In our study, the incidence of malignancy was found to be 17.7%, which was similar to the literature. The risk of malignancy in Bethesda IV cytology has been found to be between 25% and 40% [2]. Although it was lower than the literature, it was observed at similar rates and was found to be 22.2% in our study. The risk of malignancy in Bethesda V cytology is between 50% and 75% [2]. In our study, the incidence of malignancy was found to be 54.2%, which also aligned with the literature. The risk of malignancy in Bethesda VI cytology has been found to be between 97% and 99% [2]. In our study, the incidence of malignancy was found to be 100%, almost the same as literature. In this study, papillary microcarcinoma was found in 4 (0.6%) of the surgical pathology results of the nodule biopsies. When the cytology categories of these nodules were examined, it was seen that two of them were in the Bethesda I category and the other two were in the Bethesda II category. The median value of the longest diameters of 41 nodules that were found to be malignant in surgical pathology was 19 mm. The insufficient sampling from the entire nodule due to the oversizedness and also the inclusion of cytology diagnosed as papillary microcarcinoma into these categories may have contributed to the higher percentages of malignancy in the Bethesda I and Bethesda II cytology reports compared to the literature.

In our study, risk classification systems created according to the ultrasonographic features and the performances of the Bethesda System which was used in cytopathology reporting following FNAB were evaluated comparatively. In a study done by Grani et al. which includes 477 patients and 502 nodules, an AUC value of 0.6 (0.51-0.69) was calculated in the classification system recommended in the ATA guideline, and an AUC value of 0.59 (0.5-0.68) in EUTIRADS [19]. In another study by Koc et al. that included 540 patients and 597 nodules, an AUC value of 0.74 (0.70-0.78) was found in the classification system recommended in the ATA guideline, and 0.73 (0.69-0.77) in EU-TIRADS [20]. In our study, where 523 patients and 659 nodules were examined, the scorings existing in EU-TIRADS and TEMD, ATA guidelines which were included in our study, were compared with the Bethesda System. The AUC value was calculated as of 0.778 (0.682-0.873) in the Bethesda System. The closest values to the FNAB biopsy classification system were found to be; EU-TIRADS with AUC value of 0.715 (0.617-0.812), scoring system specified in ATA guideline with AUC value of 0.703 (0.607-0.799), classification system specified in TEMD guideline with AUC value of 0.690 (0.592-0.789), respectively.

Limitations

Inadequate patient recordings due to the retrospective nature of our study, the fact that US-FNAB procedures were not performed by a single clinician in other clinics and the narrow scale of patient diversity which might not reflect the general population might be considered as the main limitations of the study.

Conclusion

In the light of these findings, our study shows that EU-TIRADS might be relatively more effective in evaluating the risk of malignancy and determining the nodules to be biopsied compared to other noninvasive ultrasonographic scoring methods. It can be said that the level of experience of the endocrinology clinic is also important in obtaining diagnostic results in biopsy. Clinicians should remember that ultrasonographic nodule features are also important in the management of patients because of the possibility that cytology may show ambiguous or non-diagnostic pathological findings as well as false-negative results. It should always be taken into account that classification systems may have strengths and weaknesses.

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	Author Contributions	Author Contributions
SCD	Study Conception and Design	BK, ME
AD	Acquisition of Data	BK, ME
AID	Analysis and Interpretation of Data	BK, ME
DM	Drafting of Manuscript	BK
CR	Critical Revision	ME

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