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Differentiation of benign thyroid nodules from malignant ones using European thyroid imaging reporting and data system (EU-TIRADS)

Avrupa tiroid görüntüleme raporlama ve veri sistemi (EU-TIRADS) kullanılarak benign ve malign tiroid nodüllerinin ayırımı

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Abstract

Purpose: It is essential to predict the malignancy risk in thyroid nodules. For this purpose, thyroid imaging reporting and data system (TIRADS) classification system can be used to evaluate malignancy risk and plan the treatment strategy. The aim of this study is to evaluate the clinical feasibility and reliability of European-TIRADS (EU-TIRADS) classification.

Materials and methods: In all, 156 patients who underwent ultrasound-guided FNAB of thyroid between May 2013 and May 2016 were included in this retrospective study. Ultrasound images were reviewed, and ultrasound-guided FNAB results were obtained. With the use of EU-TIRADS classification, each nodule was categorized as TIRADS from 1 to 5 according to its ultrasound features.

Results: FNAB was performed in 196 nodules. Twenty-seven (14%) nodules were histopathologically diagnosed as malignant. The risk of malignancy of TIRADS 2, 3, 4, and 5 was 0%, 2.2%, 5.1%, 59,5%, respectively. Considering TIRADS 2, 3, and 4 as probable benign and TIRADS 5 as probable malignant, the sensitivity, specificity, positive predictive value, and negative predictive value were found to be as 0.82, 0.91, 0.60, and 0.97, respectively. The overall accuracy of ultrasound was determined as 0.90.

Conclusion: EU-TIRADS is an easy tool to apply and it is reliable in prediction of malignancy risk of thyroid nodules.

Key Words: TIRADS, fine needle aspiration biopsy, thyroid nodule, ultrasound.

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Özet

Amaç: Tiroid nodüllerinde malignite riskini tahmin etmek esastır. Bu amaçla, TIRADS sınıflandırma sistemi malignite riskini değerlendirmek ve tedavi stratejisini planlamak için kullanılabilir. Bu çalışmanın amacı, EU-TIRADS sınıflamasının klinik uygulanabilirliğini ve güvenilirliğini değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif çalışmaya Mayıs 2013 ile Mayıs 2016 tarihleri arasında ultrason eşliğinde tiroid İİAB yapılan 156 hasta dahil edildi. Ultrason görüntüleri incelendi ve ultrason rehberliğinde İİAB sonuçları elde edildi. EU-TIRADS sistemi kullanılarak her bir nodül, ultrason özelliklerine göre TIRADS 1 ile 5 arasında sınıflandırılmıştır.

Bulgular: Yüz doksan altı nodüle İİAB yapıldı. Yirmi yedi (%14) nodül histopatolojik olarak malign teşhis edildi. TIRADS 2, 3, 4 ve 5 malignite riski sırasıyla %0, %2,2, %5,1, %59,5 idi. TIRADS 2, 3 ve 4'ün muhtemel benign ve TIRADS 5'in muhtemel malign olduğu düşünüldüğünde; duyarlılık, özgüllük, pozitif prediktif değer ve negatif prediktif değer, sırasıyla 0,82, 0,91, 0,60 ve 0,97 bulundu. Ultrasonun genel tanısal doğruluğu 0,90 olarak belirlenmiştir.

Sonuç: EU-TIRADS uygulaması kolay bir yöntemdir ve tiroid nodüllerinin malignite riskini tahmin etmede güvenilirdir.

Anahtar Kelimeler: TIRADS, ince iğne aspirasyon biyopsisi, tiroid nodülü, ultrasonografi.

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Introduction

Thyroid nodules have been diagnosed with the aid of radiological studies, following routine screenings or upon suspicion in physical examination. Radiological studies such as ultrasonography (US), computerized tomography (CT), and magnetic resonance imaging (MRI) have been increasing the number of incidentally diagnosed thyroid nodules, which can not be palpated [1]. Thyroid nodules are diagnosed by palpation in 10% in women and 2% in men. With the use of US, these rates reach approximately 50% [1, 2]. In several autopsy studies, the rate of the patients diagnosed with thyroid nodules were reported as 8-65% [3, 4]. Annual incidence rate of thyroid cancer is 3.2 in every 100.000 women and 1.3 in every 100.000 men. Even though thyroid nodules are very common, thyroid malignancies are relatively rare and they count for 1% of total malignant neoplasms [2, 5].

Thyroid nodules are clinically important due to the local symptoms, possible hyperthyroidism, and the risk of thyroid cancer counts for about 4-6.5% of all thyroid nodules [6, 7]. Most thyroid malignancies are slow in growth, and most patients are expected to have a long life span following initial diagnosis.

Fine needle aspiration biopsy (FNAB) is the most used diagnosis method in thyroid nodules. Today, this method is considered as one of the most effective methods in distinguishment of benign thyroid nodules from malignant ones with a 95% success rate [7, 8]. According to the study of Griffin, FNAB increased the diagnosis rates of annual preoperative thyroid carcinoma from 24% to 56% [9]. Hawkins et al. reported that FNAB decreased surgical operation rates in all thyroid diseases from 61% to 14% and increased diagnosis rates of preoperative thyroid carcinoma from 8.3% to 37.3% [10]. In this situation, the approach to an incidentally diagnosed single nodule and nodule choice for FNAB in multinodular goiter should be well evaluated. Several studies have reported US findings, such as solid structure, microcalcification, hypoechogenicity, irregular borders, microlobulation, absence of peripheral halo, and taller than wider shape in differentiating benign and malign thyroid nodules. The presence of more than one of these US parameters increases the diagnostic accuracy rate [11-23].

Materials and methods

In all, 156 patients who underwent US-guided thyroid FNAB between May 2013 and May 2016 were included in this retrospective study. US-guided FNAB was performed in a total of 196 thyroid nodules. FNAB results and US images were evaluated. Ethics committee approval was received from local ethical committee.

TIRADS

Even though there are some useful guidelines, there is not a consensus on this issue [11, 12]. When different strategies were applied to some types of nodules, different diagnoses and treatment results can be achieved. “Thyroid Imaging Reporting and Data System” (TIRADS) terminology is first used by Horvath et al. [12]. TIRADS terminology is partially inspired by “Breast Imaging and Data System” (BIRADS) [24]. The use of standard US findings in diagnosis of nodules is important for the physician in understanding nodule characteristics as well as predicting the risk for malignancy. Horvath et al. defined 10 US patterns that can help to assess the malignancy risk [12]. However, these US patterns can not be used in every nodule and they may cause some difficulties in routine clinical usage. Park et al. [13] reported 12 US findings to assess the malignancy risk in thyroid nodules. Although these approaches allow us to categorize the nodules, it is occasionally hard to apply these in every nodule. The positive feedback of users showed us that TIRADS classification is a reliable, repeatable, and practical method in daily clinical usage.

Recently, various TIRADS guidelines have been reported from several institutions and societies [25-28]. To increase the success rate in thyroid nodule analysis and the accordance between the physician and radiologist, Russ et al. presented TIRADS classification [17] that was laterly named French-TIRADS [28]. Shortly after, the European Thyroid Association (ETA) developed a new and useful reporting system (European Thyroid Imaging and Reporting Data System; EU-TIRADS), which classifies the risk of malignancy of thyroid nodules to the following categories; benign, low-risk, intermediate-risk,

and high-risk nodules [29]. The aim of this study is to evaluate the clinical usability and reliability of EU-TIRADS classification.

Imaging and image analysis

All neck and thyroid gland US studies were performed using Philips HD15 US System (Philips, Bothell, WA, USA) with 12 to 5 MHz surface probe. All examinations were performed by a radiologist with more than 5 years' experience in this field. All features of nodules, such as internal components (solid, mixed, cystic), echogenicity, calcification, and shape were noted. The margins were classified as regular, lobulated, or irregular. The echogenicity was classified as hyperechogenic, isoechogenic, hypoechogenic, and marked hypoechogenic. The isoechoic nodule was defined as a nodule consisting of the same echogenicity with surrounding normal thyroid tissue. It was classified as marked hypoechogenic when it is less echogenic than surrounding superficial neck muscles. The calcifications less than 1 mm were defined as microcalcification, while calcifications greater than 1 mm with acoustic shadows were defined as macrocalcification. The shape of the nodule was categorized as "taller-than-wide" shape (greater in its antero-posterior dimension than in its transverse dimension) or "wider-than-tall" shape.

Considering the EU-TIRADS classification, each nodule is categorized as TIRADS 1, 2, 3, 4, and 5 according to its US features (Table 1). The sample images of a nodule according to the EU-TIRADS classification are shown (Figures 1-6).

Table 1. EU-TIRADS Classification System.

Category	US features
EU-TIRADS 1: normal	No nodules
EU-TIRADS 2: benign	Pure cyst Entirely spongiform
EU-TIRADS 3: low-risk	Ovoid, smooth isoechoic/hyperechoic No features of high suspicion
EU-TIRADS 4: intermediate-risk	Ovoid, smooth, mildly hypoechoic No features of high suspicion
EU-TIRADS 5: high-risk	At least 1 of the following features of high suspicion: – Irregular shape – Irregular margins – Microcalcifications – Marked hypoechogenicity (and solid)

EU-TIRADS, European Thyroid Imaging Reporting and Data System; US, ultrasound

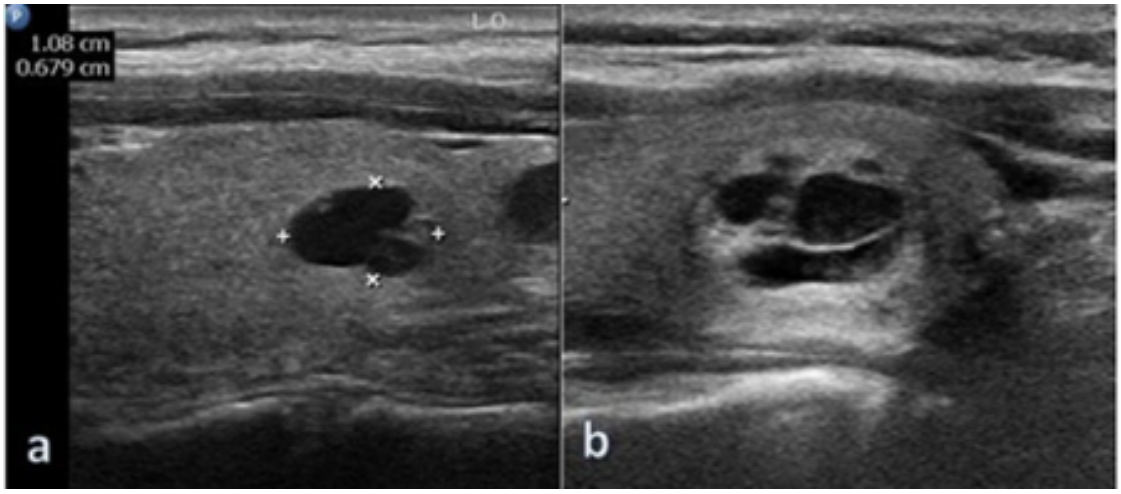

Figure 1. EU-TIRADS 2 A: US image of typical colloid cysts: anechoic areas with minimal isoechoic debris. B: US image of a semicystic nodule, the internal component is classified as solid portion less than 50%, and the solid portion is hyperechoic.

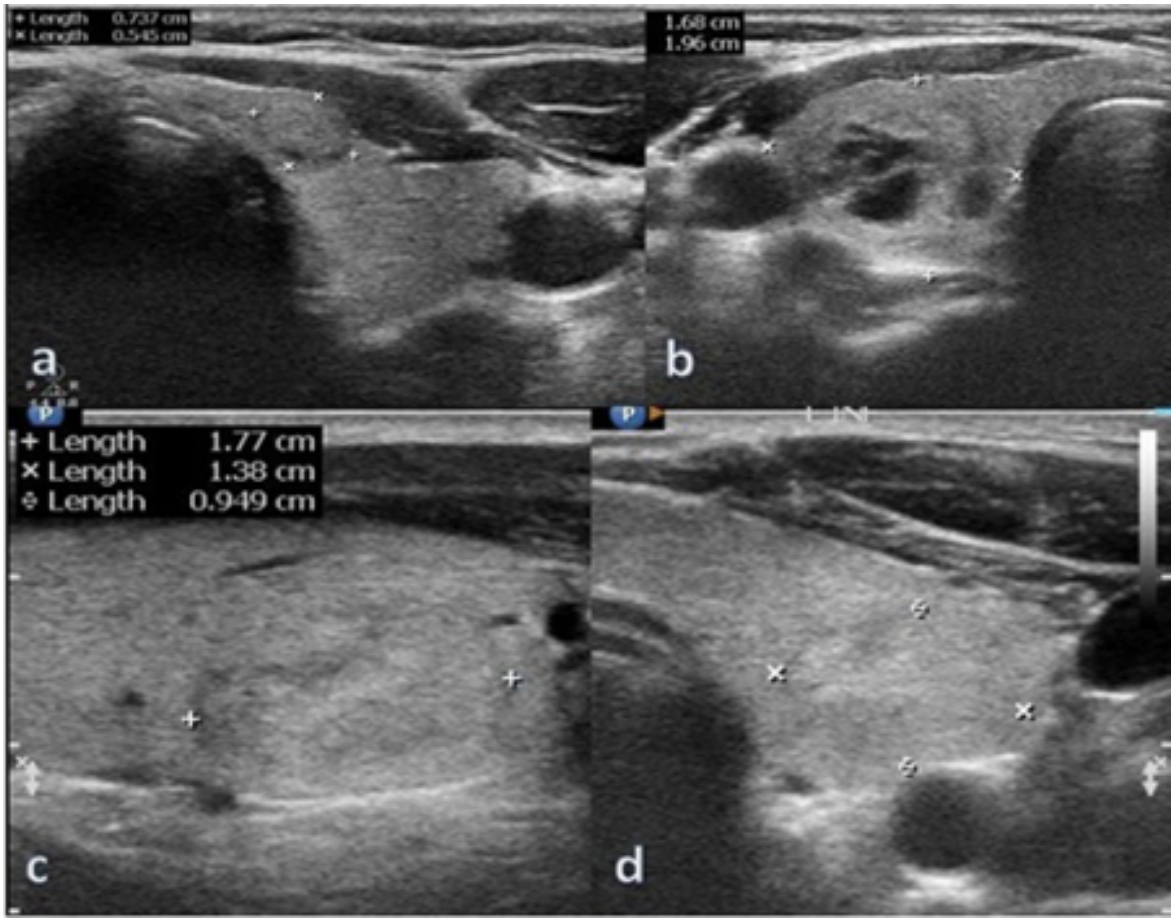

Figure 2. EU-TIRADS 3; A: Solid isoechoic nodule surrounded by a thin capsule with well-defined border and without calcifications. B: On ultrasound image of a semisolid nodule, the internal component is classified as solid portion greater than 50%, the solid portion is isoechoic and the nodule is well-defined. C, D: A macrolobulated solid isoechoic nodule surrounded by a thin capsule, without calcifications or irregular margins.

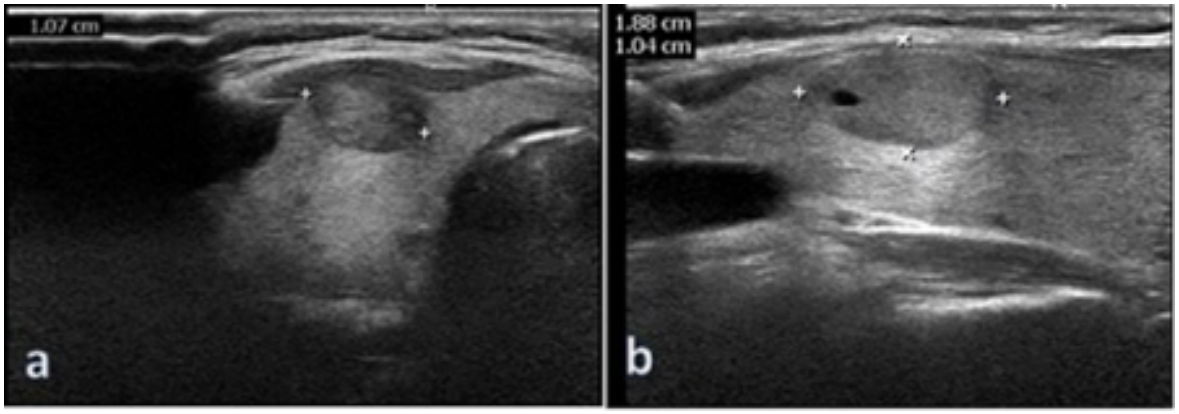

Figure 3. EU-TIRADS 4; A: Moderately heterogenous nodule with isoechoic and mildly hypoechoic regions, regular shape and borders. B: Mildly hypoechoic nodule is defined as more hypoechoic than the surrounding gland but less than strap muscles, regular shape and borders.

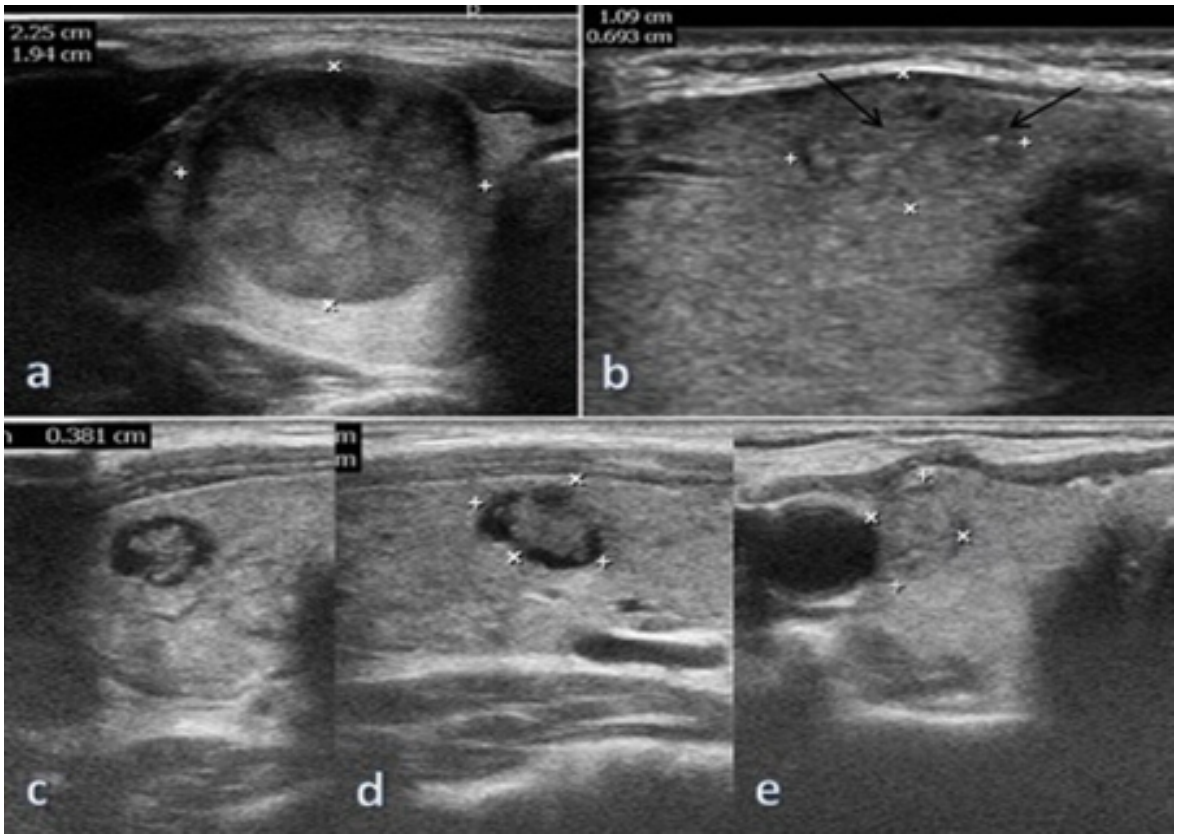

Figure 4. EU-TIRADS 5; A: Markedly hypoechoic nodule with regular borders. B: Solid isoechoic or mildly hypoechoic nodule with microcalcifications (arrows). C, D: Heterogenous nodule with microlobulated borders and surrounded by a thick capsule. E: Isoechoic nodule with taller-than-wide shape. There is only one major US finding in these cases.

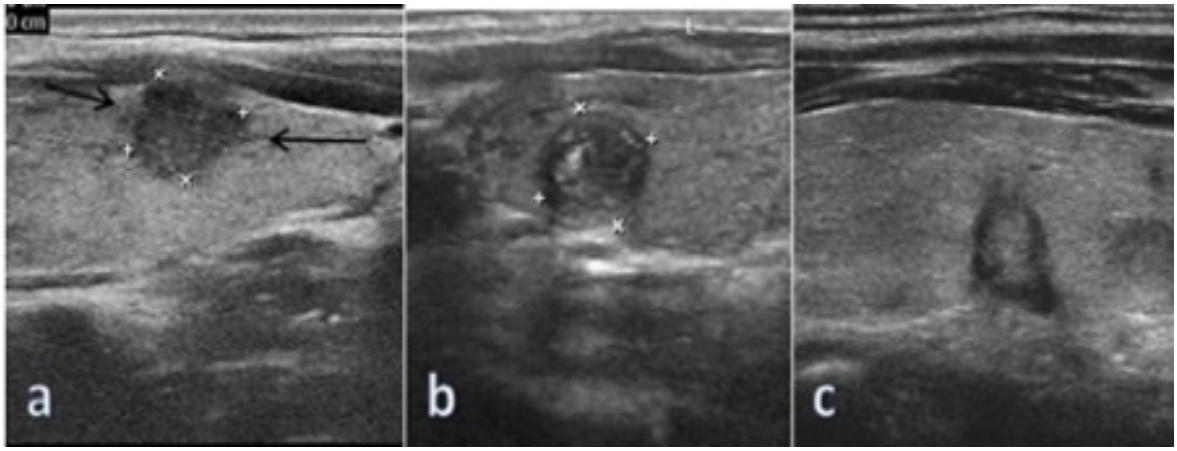

Figure 5. EU-TIRADS 5; A: Solid markedly hypoechoic nodule with irregular margins (arrows) without taller-than-wide shape and microcalcifications. B: Solid markedly hypoechoic nodule with microcalcifications without taller-than-wide shape. C: Moderately heterogenous nodule with taller-than-wide shape and microlobulated borders without microcalcifications. There are two major US findings in these cases.

US guided FNAB

After the thyroid US examination, FNAB was performed in the biopsy recommended patients. Before the biopsies, the patients were asked for contraindications (anticoagulant usage or high anxiety level that do not allow FNAB to be performed). Patients' consents were obtained. The biopsy region was sterilized and locally anesthetized. A sterile cover was used to cover 12 to 5 MHz surface probe with Philips HD15 US System (Philips, Bothell, WA, USA). Aspiration was performed using 22-gauge 10 cc disposable plastic injectors. The specimens were carefully obtained in solid and semisolid nodules. FNAB was repeated 2-4 times to collect enough materials. Hemostasis was achieved following FNAB, and bleeding was checked using repeated US. Patients were discharged after an appropriate follow-up period.

Aspirated materials were sent to the pathology department for a histopathological analysis. Thyroid cytologies were classified as follows; benign, indeterminate, suspicious for malignancy, malignant, or inadequate. Since January 2010, the Bethesda system was used to classify cytologic results in our hospital [30]. In patients with cytological results as indeterminate or suspicious for carcinoma, tru-cut biopsy was performed. Twelve patients with inadequate materials were excluded from the study.

Data analysis

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each of the "major" ultrasound imaging features that highly suggest malignancy (irregular borders, taller-than-wide feature, presence of microcalcifications, and marked hypoechogenicity) according to previous studies [18, 20]. Risk prediction (odds ratio) was calculated and specified using 95% confidence interval (CI). The malignancy risk of each TIRADS category was evaluated. P value less than 0.05 was considered as statistically significiant. Statistical analysis was performed using the IBM SPSS Statistics 24.0 (Armonk, NY: IBM, United States)

Results

FNAB was performed in 156 patients and 196 nodules. Twenty-seven nodules (14%) were histopathologically diagnosed as malignant nodules. Patients' demographics and features of nodules are presented in Table 2.

The different TIRADS categories were confronted with the results of pathology, and the risk of malignancy was evaluated (Table 3).

Considering TIRADS 2, 3, and 4 as probable benign and TIRADS 5 as probable malignant (Table 4), the sensitivity, specificity, PPV, and NPV of US were 0.82, 0.91, 0.60, and 0.97, respectively. The overall accuracy of US was determined as 0.90.

The "major" US features suggestive for malignancy were analyzed according to TIRADS categories. The sensitivity, specificity, PPV, and NPV were calculated for each US feature. The results are presented in Table 5.

Seven of 27 (26%) malignant patients had two major findings, and nine of them (33%) had three or more major findings. Six of them (22%) had only one major finding, while five of them (19%) had no major findings at all. When major US findings were reviewed, one major finding had a sensitivity of 0.32 and accuracy of 0.83, two major findings had a sensitivity of 0.88 and accuracy of 0.89, and more than 3 findings had a sensitivity of 0.90 and accuracy of 0.90 (p<0.05). Seventeen (10%) of 169 benign nodules had a single major finding (5 with marked hypoechogenicity, 6 with microcalcification, 4 with irregular margins, and 2 with taller-than-wider shape). Two (1.2%) nodules were diagnosed with 2 or more major findings with benign cytological diagnosis (p<0.05).

Discussion

Some US findings were defined as findings for suspected malignancy in the previous studies [11-23]. Malignancy criteria on US include microcalcification, solid or predominantly solid structure, irregular margins or microlobulation, marked hypoechogenicity, and taller-than-wide shape [11-23]. The nodules with marked hypoechogenicity, microcalcification, irregular borders, and taller-than-wide shape were defined as high malignancy risk in our study. In 27 malignant patients, 15 patients (56%) had nodules with marked hypoechogenicity, 16 patients (59%) had nodules with

Table 2. Demographics of the patients and features of nodules.

		Benign	Malign	Total	Malignany Rate(%)
Sex	Male	25	6	31	19.4
	Female	144	21	165	12.7
Age	30 <	13	6	19	31.6
	30-60	136	21	157	13.4
	> 60	20	0	20	0
Shape	Taller-than-wide shape	3	7	10	70
	Regular shape and borders	166	20	186	10.8
Borders	Regular	165	15	180	8.3
	Irregular	4	12	16	75
Calcification	None	150	11	161	6.8
	Micro	6	16	22	72.7
	Macro	13	0	13	0
Echogenicity	Hypoechogenicity	55	10	65	15.4
	Isoechogenicity	87	2	89	2.2
	Hyperechogenicity	21	0	21	0
	Marked hypoechogenicity	6	15	21	71.4
Nodular - MNG	Nodular	16	5	21	23.8
	Multinodular	153	22	175	12.6
Cystic Changes	Cystic Degeneration	112	8	120	6.7
	None	57	19	76	25
Peripheral Halo	None	137	25	162	15.4
	Thin Halo	29	1	30	3.3
	Thick Halo	3	1	4	25
Dimension (mm)	1-10	18	5	23	21.7
	11-20	97	13	110	11.8
	20 >	54	9	63	14.3

Table 3. TIRADS categories.

TIRADS category	Pathology			Risk of malignancy (%)
	Benign	Malign	Total	
TIRADS 2	11	0	11	0
TIRADS 3	87	2	89	2.2
TIRADS 4	56	3	59	5.1
TIRADS 5	15	22	37	59.5
Total	169	27	196	

TIRADS, Thyroid Imaging Reporting and Data System.

Table 4. Diagnostic value of US in TIRADS categories.

TIRADS category	Pathology		Total
	Malignant	Benign	
TIRADS 2, 3, 4	5	154	159
TIRADS 5	22	15	37
Total	27	169	196

TIRADS, Thyroid Imaging Reporting and Data System; US, ultrasound.
The sensitivity, specificity, positive predictive value and negative predictive value of ultrasound were 0.82, 0.91, 0.60 and 0.97, respectively. The overall accuracy of ultrasound was 0.90 (p<0.05).

Table 5. Major US findings and pathology results.

		Pathology		Total	SE (%)	SP (%)	PPV (%)	NPV (%)	O.R	*p*	Correct %
		Benign	Malign								
Shape	Regular shape and borders	166	20	186	25.9%	98.2%	70.0%	89.2%	19.367 (4.635 – 80.916)	0.0001*	88.30%
	Taller-than-wide shape	3	7	10							
Border	Regular	165	15	180	44.4%	97.6%	75.0%	91.7%	33 (9.465 – 115.06)	0.0001*	90.30%
	Irregüler	4	12	16							
Calcification	Others	163	11	174	59.3%	96.4%	72.7%	93.7%	39.515 (12.9- 121.039)	0.0001*	91.30%
	Micro	6	16	22							
Echogenicity	Others	163	12	175	55.6%	96.4%	71.4%	93.1%	33.958 (11.151 – 103.41)	0.0001*	90.80%
	Marked hypoechogenicity	6	15	21							
Total		169	27	196							

Se=Sensitivity; Sp=Specificity; PPV=Positive Predictive Value; NPV=Negative Predictive Value; OR=Odd Ratio. *p<0.05 statistically significant.

microcalcification. The nodules of 12 patients (44%) had irregular margins and the nodules of 7 patients (26%) had taller-than-wide shape. According to our study, the novel EU-TIRADS classification system created recently by the European Thyroid Association is both practical and reliable for predicting thyroid malignancies.

Hong et al. [19] reported that the presence of microcalcification, marked hypoechogenicity, and taller-than-wide shape were 3 significant findings for malignancy. In a multicentric and retrospective study, risk factors for malignancy were defined as hypo-echogenicity, marked hypo-echogenicity, non-parallel orientation, microlobulated or spiculated margin, ill-defined margins, and the presence of microcalcification [20]. In their study, 7.3% of malignant nodules didn't have suspicious malignant features on US. In our study, 27 (17%) of 156 FNAB performed patients were diagnosed with thyroid malignancy. Five (2.6%) malignant nodules didn't have suspicious malignant features on US.

Microcalcification within nodules, which is a specific US finding for thyroid malignancies, was demonstrated in 29-59% of primary thyroid carcinomas, especially in papillary type [5, 23]. In our study, this type was the most presented carcinoma type (70.3%). Microcalcification was present in 15 of 19 papillary carcinoma cases (79%).

Papini et al. reported that malignancy risk increased in hypoechoic nodules with irregular margins and microcalcification [11]. In our study, major US findings presented together increases significantly the malignancy risk. We found that 7 of 27 (26%) malignant patients had 2 major findings, and 9 of them (33%) had 3 or more major findings. Six of them (22%) had only one major finding, while five of them (18.5%) had no major findings at all (2 patients were diagnosed as TIRADS 3 and 3 patients were diagnosed as TIRADS 4). On the other hand, 17 (10%) of 169 benign nodules had single major finding (5 with marked hypoechogenicity, 6 with microcalcification, 4 with irregular margins, and 2 with taller-than-wider shape). Only 2 (1.2%) nodules with 2 or more major findings were diagnosed as having benign cytological changes. This points that the nodules with 2 or more major findings tend to be malignant.

TIRADS classification system should be easily applicable, repeatable, and quite reliable so that it can be routinely used in clinical practice. EU-TIRADS system used by Russ et al. seemed to be easily performed, and we achieved reliable results with the use of it [29]. We detected that malignancy risk significantly increases from TIRADS 3 to 5. In addition, this risk was found to be as 0 in TIRADS 2 pointing that TIRADS 2 can be considered as a benign lesion. Similar to our study, Horvarth et al. stated that malignancy risk was smaller than 5% in TIRADS 3, 5-10% in TIRADS 4, and 10-80% in TIRADS 5 [12].

Most cancers were found to be as TIRADS 4 and 5, thus FNAB should be definitely performed in nodules within these groups. Coming to the other categories, TIRADS 2 (benign) and TIRADS 3 (possibly benign) nodules should be followed, risk factors should be assessed, and FNAB should be performed if necessary.

This study has several limitations. First, this study has a retrospective design with small sample size. Second, the lack of US elastography made our study limited in terms of nodule elasticity.

In conclusion, EU-TIRADS classification is a reliable classification system for predicting thyroid malignancies. TIRADS classification system may improve the accordance between the physician and radiologist. It may also help to evaluate the thyroid malignancy risk in centers where FNAB is not possible and to avoid unnecessary FNAB interventions in low-risk groups. Further studies are required to show more evidence in this field and increase the compliance between physician and radiologist.

Conflict of Interest: The authors report no conflict of interest.

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