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Research Article

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A SCORING INDEX FOR PREDICTING THYROID MALIGNANCIES

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Abstract

Objectives: We evaluated ultrasonography (US) features of thyroid nodules ≤ 1 cm and > 1 cm and determined the features that might predict malignancy; we also aimed to develop a new scoring system considering US features to avoid unnecessary fine-needle aspiration biopsy (FNAB), particularly for sub-centimeter nodules.

Materials and Methods: We retrospectively evaluated 2233 nodules of 1118 patients who underwent thyroidectomy. US features predictive for malignant histopathology were evaluated by multivariate logistic regression analysis. A US index score was calculated for each nodule considering these features.

Results: 337 (15.11%) nodules were ≤1 cm, and 1896 (84.89%) were > 1 cm. In total, 173 (51.33%) of the ≤1 cm nodules were histopathologically benign, and 164 (48.67%) were malignant. Anteroposterior/transverse diameter (AP/T) ≥1, microcalcifications, macrocalcifications, and hypoechoic patterns were significantly more frequent in ≤1 cm malignant compared with benign nodules. Microcalcification, macrocalcification, hypoechoic and iso-hypoechoic patterns, and solid texture were significantly higher in the malignant than the benign group in > 1 cm nodules. The best cut-off of US index scores for discrimination of benign and malignant nodules were > 2 and > 4 for ≤1 cm and > 1 cm nodules, respectively.

Conclusion: Our US scoring system may help clinicians and surgeons to select nodules for FNAB more accurately, particularly those sub-centimeter in size.

Keywords: Sub-centimeter, supra-centimeter, thyroid nodule, ultrasonography features, ultrasonography scoring.

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Introduction

Thyroid nodules are commonly seen among the adult population, especially in women.[1] The most important issue to be answered in a patient with a thyroid nodule is whether it is malignant or not because 5–13% of nodules harbor thyroid cancers.[2] Ultrasonography (US) is accepted to be a reliable and easily available diagnostic method with high sensitivity (90%) and specificity (85%) for this assessment in thyroid imaging.[3]

Several studies have made an effort to determine pathognomonic US features for malignancy, which leads to a risk stratification based on the following predictors: solid or mostly solid structure, hypoechogenicity, irregular margins, microcalcifications, a discontinuous halo, taller-than-wide (TTW) shape, intralesional flow on Doppler examinations, and a >20% size increase in 6 months.[4-6]

Furthermore, nodule size would be a predictor of malignancy.[7] In general, nodules >1 cm have the potential to be clinically significant cancers.[8] Despite all its positive qualities, diagnosis of malignancy cannot be determined solely by ultrasound features only.[9] To discriminate benign from malignant thyroid nodules, the least invasive preoperative modality is ultrasound-guided fine-needle aspiration biopsy (FNAB).[10] However, its diagnostic value in sub-centimeter thyroid nodules is controversial.

In the 2015 guidelines published by the American Thyroid Association (ATA), FNAB is not recommended for sub-centimeter nodules.[11] In contrast, other organizations and some authors have suggested that FNAB be performed on all nodules with suspicious US features independent of nodule size.[12,13] Recently, the thyroid imaging reporting and data system (TI-RADS) was developed for use in thyroid nodule risk stratification using various US features derived from the breast imaging reporting and data system.[4,14] But in some reports, it is reported that the clinical use is limited, and its practicality is challenging.[15] Therefore, it is important to determine the US features of thyroid nodules, particularly the sub-centimeter nodules. In this study, we evaluated US features in thyroid nodules ≤ 1 cm and > 1 cm and determined the features that might predict malignancy. We also aimed to develop a new scoring system considering US features to avoid or reduce unnecessary FNAB, particularly for sub-centimeter nodules.

Materials and Methods

Patients

We retrospectively evaluated patients who underwent thyroidectomy between January 2007 and December 2014 in our clinic. Patients < 16 years old and those with a history of thyroid surgery, percutaneous intervention, or radiotherapy to the head and neck were excluded from the study. Demographic data, preoperative thyroid function, thyroid autoantibodies, US findings, and histopathological features were reviewed from medical records. Local ethical committee approval was obtained in accordance with the ethical standards of the Declaration of Helsinki.

Laboratory findings

Levels of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), thyroid autoantibodies, thyroid peroxidase antibody (anti-TPO) and thyroglobulin antibody (anti-TG), and thyroglobulin were measured in all patients using a chemiluminescent method. The normal TSH, fT3, fT4, anti-Tg, and anti-TPO ranges were 0.40–4 µIU/mL, 1.57–4.71 pg/mL, 0.61–1.12 ng/dL, < 30 U/mL, and < 10 U/mL, respectively.

Conventional ultrasonography

All patients underwent preoperative US. The diameter (mm), nature, echogenicity, border regularity, microcalcifications and macrocalcifications, presence of a peripheral halo, and anteroposterior/transverse diameter ratio were evaluated. The echogenicity of the nodule was compared with that of the surrounding parenchyma and was classified as in our previous study;[16] hypoechoic, isoechoic, or iso-hypoechoic. The nature of the nodule was classified as solid (solid component > 50%), mixed (containing a cystic part), or pure cystic (almost cystic or very little solid), the same as our previous study.[16]

Ultrasonography-guided fine-needle aspiration biopsy

US-guided FNAB was performed by an experienced endocrinologist using a 23-gauge needle and 20 mL syringe. Written consent was obtained from all patients prior to FNAB. FNAB was performed for nodules > 1cm and those ≤ 1cm with suspicious US features (irregular border, hypoechoic nature, solid component, presence of microcalcifications, and taller-than-wide shape).[17]

Cytological and histopathological examinations

Material obtained by US-guided FNAB was evaluated according to the Bethesda system classification.[18] The cytology results were grouped as follows: 1) non-diagnostic, 2) benign, 3) atypia/follicular lesion of undetermined significance (AUS/FLUS), 4) follicular neoplasm/suspicious of follicular neoplasm, 5) suspicious for malignancy, and 6) malignant.[19,20]

Statistical analysis

The data analysis was performed using SPSS ver. 17.0 software (IBM Corp., Armonk, NY, USA). Continuous data are shown as means ± standard deviation or medians (range), and numbers and percentages were used for categorical variables. The χ^2 or Fisher's exact test was used to detect US differences between benign and malignant nodules, where appropriate. The diagnostic performance of the US features was evaluated by calculating the Sn, Sp, positive predictive value (PPV), negative predictive value (NPV), and accuracy.

The forward LR method of multiple binary logistic regression was used to develop the formula for recommending US-guided biopsy. Variables with a p-value < 0.25 in the univariate analysis were subjected to multivariate analysis, which included all variables of known clinical importance. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each US characteristic. The least suspicious (lowest malignancy rate) feature was used as the reference if there were more than two subgroups of features, and the ORs of the other suspicious features were analyzed and compared. The diagnostic performance of the formula was evaluated by a receiver operating characteristic curve analysis. The best cut-off point for recommending biopsy and its corresponding diagnostic values were calculated. A p-value < 0.05 was considered significant.

Results

In total, 2,233 nodules from 1,118 patients were evaluated; 884 (79.10%) patients were female, and 234 (20.90%) were male. The mean age of the patients at diagnosis was 49.51±12.11 years (range 19–84 years). The anti-TPO positive rate was 24.32%, and the anti-TG positive rate was 24%.

337 (15.11%) nodules were ≤ 1 cm, and 1,896 (84.89%) were > 1 cm. FNAB was performed on 336 (15.20%) nodules ≤ 1 cm and on 1,872 (84.80%) > 1 cm. The cytological and histopathological results are shown in Table 1. The non-diagnostic results were similar between the ≤1 cm and >1 cm nodules, whereas the suspicious malignancy and malignant nodule categories were significantly more frequent among sub-centimeter nodules compared with those > 1 cm (p<0.001). Benign FNAB results were significantly more frequent in nodules > 1 cm (p<0.001). In total, 173 (51.33%) of the ≤ 1 cm nodules were histopathologically benign, and 164 (48.67%) were malignant. A total of 1,423 (75.10%) nodules > 1 cm were benign, and 473 (24.90%) were malignant (p<0.001) (Table 1)

A comparison of US features between benign and malignant nodules ≤1 cm and the diagnostic performance of these features for predicting the histopathological results are shown in Table 2. AP/T ≥ 1, microcalcifications, macrocalcifications, and a hypoechoic pattern were significantly more frequent, and the isoechoic pattern was significantly less frequent in the ≤ 1 cm malignant nodules compared with the benign nodules (Table 2).

Table 1. Histopathology and fine-needle aspiration biopsy results of the nodules according the nodule sizes

	Nodule size		
FNAB results	**≤ 1 cm n=336 (%)**	**> 1 cm n=1872 (%)**	**p**
Non-diagnostic	88 (26.20%)	482 (25.80%)	0.864
Benign	99 (29.41%)	887 (47.42%)	**<0.001**
AUS/FLUS	40 (11.90%)	237 (12.71%)	0.712
FN/SFN	6 (1.82%)	63 (3.30%)	0.320
Suspicious for malignancy	53 (15.81%)	103 (5.47%)	**<0.001**
Malignant	50 (14.86%)	100 (5.30%)	**<0.001**
Histopathology	**≤ 1 cm n=337 (%)**	**> 1 cm n=1896 (%)**	**p**
Benign	173 (51.33%)	1423 (75.10%)	**<0.001**
Malign	164 (48.67%)	473 (24.90%)	

(FNAB; fine-needle aspiration biopsy, AUS/FLUS; atypia/follicular lesion of undetermined significance, FN/SFN; follicular neoplasm/suspicious for follicular neoplasm)

Table 2. Comparison of ultrasonographic features between benign and malignant nodules and diagnostic performance of these features in the prediction of histopathological results according to the nodule sizes

Nodule Size	**Variables**	**Benign (n=173) (%)**	**Malignant (n=164) (%)**	**p**	**Sn**	**Sp**	**PPV**	**NPV**	**Accuracy**
≤1 cm	**AP/T ratio**								
	<1	138 (79.80%)	98 (64.12%)	**0.002**					
	≥1	35 (20.20%)	55 (35.88%)		35.91%	79.82%	61.10%	58.50%	59.20%
	Border regularity								
	Regular	49 (28.29%)	42 (25.60%)	0.575					
	Irregular	124 (71.71%)	122 (74.40%)		74.42%	28.30%	49.61%	53.80%	50.71%
	Presence of halo								
	Present	30 (17.30%)	19 (11.60%)	0.134	88.40%	17.31%	50.32%	61.20%	52.90%
	Absent	143 (82.70%)	145 (88.40%)						
	Microcalcification	33 (19.12%)	71 (43.31%)	**<0.001**	43.31%	80.91%	68.30%	60.11%	62.60%
	Macrocalcification	22 (12.74%)	41 (25.00%)	**0.004**	25.01%	87.30%	65.10%	55.10%	57.01%
	Echogenicity								
	Isoechoic	66 (38.22%)	32 (19.51%)	**<0.001**					
	Hypoechoic	30 (17.33%)	54 (32.91%)	**<0.001**	32.90%	82.70%	64.30%	56.51%	58.42%
	Isohypoechoic	77 (44.45%)	78 (47.58%)	0.574	47.61%	55.52%	50.31%	52.71%	51.60%
	Nodule texture								
	Cystic	3 (1.70%)	0 (0.00%)	0.248					
	Solid	170 (98. 30%)	163 (99.40%)	0.623	99.40%	1.71%	48.92%	75.03%	49.31%
	Mixed	0 (0.00%)	1 (0.60%)	0.487					
Nodule Size	**Variables**	**Benign (n=1423) (%)**	**Malignant (n=473) (%)**	**p**	**Sn**	**Sp**	**PPV**	**NPV**	**Accuracy**
> 1 cm	**AP/T ratio**								
	<1	1160 (82.31%)	366 (79.90%)	0.257					
	≥1	250 (17.69%)	92 (20.10%)		20.10%	82.31%	26.91%	76.00%	67.00%
	Border regularity								
	Regular	598 (42.00%)	195 (41.20%)	0.761					
	Irregular	825 (58.00%)	278 (58.80%)		58.81%	42.00%	25.21%	75.42%	46.21%
	Presence of halo								
	Present	441 (31.00%)	157 (33.21%)	0.372					
	Absent	982 (69.00%)	316 (66.79%)		66.81%	31.01%	24.31%	73.72%	40.01%
	Microcalcification	495 (34.81%)	221 (46.74%)	**<0.001**	46.72%	65.23%	30.93%	78.64%	60.62%
	Macrocalcification	344 (24.23%)	176 (37.26%)	**<0.001**	37.23%	75.81%	33.80 %	78.41%	66.20%
	Echogenicity								
	Isoechoic	801 (56.31%)	197 (41.60%)	**<0.001**					
	Hypoechoic	129 (9.11%)	85 (18.00%)	**<0.001**	17.81%	91.20%	40.20%	76.91%	72.92%
	Iso-hypoechoic	493 (34.58%)	191 (40.40%)	**0.024**	40.41%	65.41%	27.92%	76.71%	59.21%
	Nodule texture								
	Cystic	60 (4.18%)	7 (%1.51)	**0.005**					
	Solid	1350 (94. 91%)	462 (97.72%)	**0.010**	97.71%	5.10%	25.51%	86.91%	28.31%
	Mixed	13 (0.91%)	4 (0.77%)	1.000					

(Sn; sensitivity, Sp; specificity, PPV; positive predictive value, NPV; negative predictive value, AP/T ratio; anteroposteriortransvers ratio)

The US features of the benign and malignant > 1 cm nodules are compared and the diagnostic performance of these features is given in Table 2. Accordingly, microcalcifications, macrocalcifications, hypoechoic and iso-hypoechoic patterns, and solid nature were significantly more frequent in the malignant than in the benign group.

US features predictive of malignancy were evaluated by multivariate logistic regression analysis. The presence of microcalcifications, nodule echogenicity, AP/T ratio ≥ 1, and macrocalcifications were independent predictors of malignancy in nodules ≤ 1 cm (Table 3). Nodule echogenicity, macrocalcification, nodule texture, and microcalcifications were independent predictors for malignancy in nodules > 1 cm (Table 3).

Table 3. Predictive factors for malignancy according to the ultrasonographic features of the nodules ≤1 cm and >1 cm.

Nodules ≤1 cm	**Odds ratio**	**95% Confidence interval**		**Wald**	**p**
		Lower limit	*Upper limit*		
AP/T ratio ≥1	1.944	1.126	3.355	5.698	**0.017**
Microcalcification	3.308	1.915	5.713	18.410	**<0.001**
Macrocalcification	2.016	1.086	3.742	4.939	**0.026**
Isoechoic	1.000	-	-	-	-
Hypoechoic	2.732	1.398	5.339	8.638	**0.003**
Isohypoechoic	1.845	1.043	3.263	4.430	**0.035**
Nodules >1 cm	**Odds ratio**	**95% Confidence interval**		**Wald**	**p**
		Lower limit	*Upper limit*		
Microcalcification	1.370	1.065	1.763	6.002	**0.014**
Macrocalcification	1.781	1.366	2.323	18,163	**<0.001**
Isoechoic	1.000	-	-	-	-
Hypoechoic	3.507	2.402	5.120	42,217	**<0.001**
Isohypoechoic	1.488	1.174	1.887	10.764	**<0.001**
Cystic nodule	1.000	-	-	-	-
Solid nodule	4.487	1.881	10.702	11.457	**<0.001**
Mixed nodule	4.881	1.172	20.332	4.741	**0.029**

(AP/T ratio; anteroposteriortransvers ratio)

A US index score was calculated for each nodule considering the factors predicting malignancy. Table 4 shows the index score for each US factor separated into nodules ≤ 1 cm and those > 1 cm.

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Table 4. Index scores related to ultrasonographic features of the nodules ≤ 1 cm and >1 cm that predict the malignancy

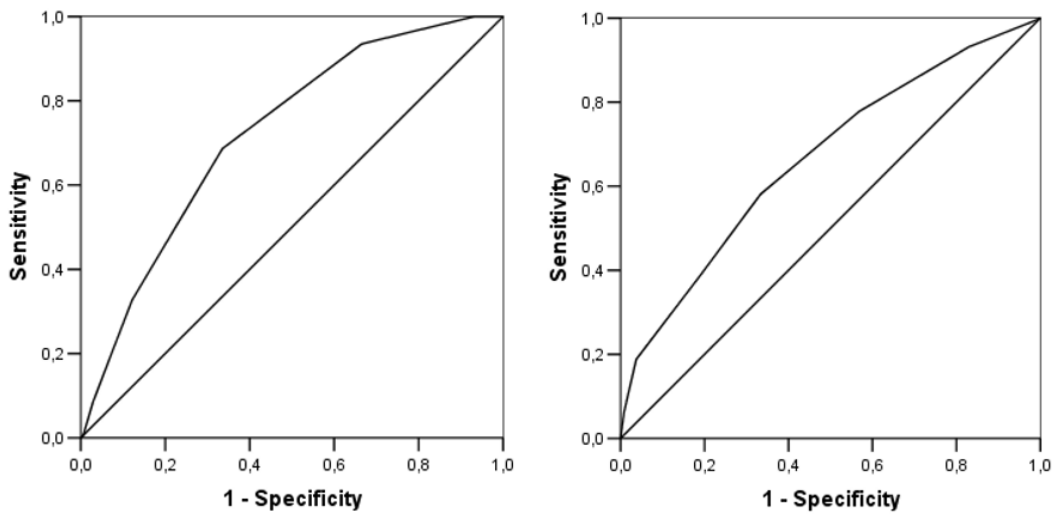
Ultrasonographic features	**Ultrasonography index scores**	
	Nodule size	
	≤1 cm	**>1 cm**
AP/T ratio		
<1	0	-
≥1	1	-
Microcalcification		
Absent	0	0
Present	1	1
Macrocalcification		
Absent	0	0
Present	1	1
Echogenicity		
Isoechoic	0	0
Isohypoechoic	1	1
Hypoechoic	2	2
Nodule texture		
Cystic	-	0
Mixed	-	1
Solid	-	2

(AP/T ratio; anteroposterior/transverse diameter ratio)

Accordingly, the mean index score for benign nodules was 2.091±1.190 and 3.041±1.060 in malignant nodules ≤1 cm (Table 5). The best cut-off value to discriminate benign and malignant nodules was > 2, with an Sn of 68.61%, Sp of 66.55%, PPV of 64.41%, and NPV of 70.61% in ≤ 1 cm nodules (Figure 1a). The mean index score for benign nodules was 3.971±1.460 and 4.951±1.701 in malignant nodules >1 cm (Table 5). The best US index score for predicting malignancy in nodules > 1 cm was > 4, with a Sn, Sp, PPV and NPV of 58.12%, 66.61%, 36.71%, and 82.71%, respectively (Figure 1b).

Table 5. Index scores related to US features that can predict malignancy in nodules ≤1 cm and >1 cm

	Nodule size	
	≤1 cm	**>1 cm**
Ultrasonographic index score		
Benign	2.091±1.190	3.971±1.460
Malignant	3.041±1.060	4.951±1.701
ROC analysis		
The area under the curve	0.722	0.665
95% Confidence interval	0.667-0.777	0.636-0.693
p-value	**<0.001**	**<0.001**
The best cut-off point	>2	>4
Sensitivity	68.612%	58.123%
Specificity	66.554%	66.610%
PPV	64.412%	36.711%
NPV	70.613%	82.712%



a) ROC curve of the nodules ≤1cm related with ultrasonographic index score *(ROC; receiver operating characteristic)*

b) ROC curve of the nodules >1cm related with ultrasonographic index score *(ROC; receiver operating characteristic)*

Figure 1. ROC curve of the nodules

Discussion

Fine needle aspiration biopsy is the primary method to define the malignancy risk of a thyroid nodule. However, it is not reasonable to perform FNAB for all thyroid nodules due to the relatively low malignancy rate. In addition, as the size of a nodule decreases, the rate of inadequate FNAB samples increases.[21]

There are conflicting reports relating to tumor size and thyroid malignancy. Retrospective studies suggested that with an increase in nodule size, there is no increase in the risk of malignancy.[7,22] It is reasonable to evaluate the malignancy risk of a thyroid nodule based on US findings or other clinical risk factors rather than size. Malignancy rates in sub-centimeter nodules were reported as 3–19% across studies.[23] Bo et al.[24] reported an overall malignancy rate of 16% in sub-centimeter thyroid nodules and 7.6% in ≥1 cm nodules based on FNAB results. The authors stated that they could not compare the two groups because FNAB was performed on supra-centimeter nodules regardless of US features, whereas it was performed only on sub-centimeter nodules with one or more suspicious US features.[24] Berker et al.[25] reported malignancy rates of 6% for sub-centimeter and 2.9% for supra-centimeter nodules. Whether FNAB is effective for sub-centimeter nodules is still controversial.[23,25] In our study, 48.67% of sub-centimeter nodules and 24.90% of supra-centimeter nodules were confirmed to be malignant by histopathology. Our higher rate of malignancy might have been due to the appropriate selection of the nodules with suspicious US features, indicating them for biopsy or surgery due to our center's experience.

An AP/T ratio ≥ 1 is a good predictor of malignancy in both supra and sub-centimeter thyroid nodules with high Sp.[23,26] Although solid nature is a weak indicator of malignancy in thyroid nodules in some studies, others have reported that it is a strong indicator.[25,27,28] Our study revealed that solid nature was significantly associated with malignancy in nodules > 1 cm but not in those ≤ 1cm. Berker et al.[25] found no significant association between solid nature and malignancy in sub-centimeter and supra-centimeter thyroid nodules.

The decrease in echogenicity indicates that the cells grow rapidly, and subsequently, follicles lose their normal alignment. This event is considered by some authors as representing an increased risk of malignancy.[9] Although some reports have revealed that a hypoechoic appearance of a thyroid nodule is significantly related to thyroid malignancy,[25] other studies did not confirm such a relationship.[29] Similar to previous studies reporting hypoechogenicity as a suspicious US feature,[25] hypoechoic patterns were significantly related to malignancy in both ≤1 cm and > 1 cm nodules in our study.

We also found a significant association between the presence of microcalcifications and macrocalcifications and malignancy in both groups. Berker et al.[25] observed a relationship between malignancy and microcalcifications only in sub-centimeter nodules and suggested that this association would have been significant in supra-centimeter nodules if their sample size had been larger.

Previous studies introduced different combinations of US features that are highly effective for differentiating benign and malignant thyroid nodules; however, different combinations of criteria were used in each study.[28] Papini et al. reported that irregular or blurred margins, intranodular vascular patterns, and microcalcifications were predictive of malignancy.[28] However, a single US feature seemed to be insufficient to differentially diagnose thyroid nodules. To define the malignancy risk, several reporting and data systems based on ultrasonographic features have been evaluated.[3] Horvath et al.[4] with a modified recommendation from Jin Kwak et al.[30] proposed the Thyroid Image Reporting and Data System (TI-RADS) in order to improve patient management and cost-effectiveness by avoiding unnecessary FNAB of thyroid nodules. However, its clinical use is limited, and it is difficult to apply in routine clinical practice.[3,15] Therefore, we developed a US scoring system based on the multivariate analysis considering US features predicting malignancy. The best cut-off score to discriminate benign and malignant nodules was > 2 for the ≤ 1 cm nodules and > 4 for > 1 cm nodules. Cheng et al. evaluated slightly different US featured predictive of malignancy in sub-centimeter thyroid nodules and revealed that irregular shape, hypoechogenicity, absence/incomplete capsule, calcifications, and AP/T ≥ 1 were strongly predictive of malignancy.[10] The mean US scores were 1.7±1.0 in the benign group and 3.4±1.1 in the malignant group. A cut-off score > 2 was predictive of malignant sub-centimeter nodules. Those authors recommended FNAB for nodules with a US index score > 2. Zhang et al.[26] reported that echogenicity, marginal irregularity, and the height-to-width ratio were the US factors that best-predicted malignancy. They calculated a formula using these features and recommended FNAB for nodules with a predicted probability of ≥ 0.284 since such nodules had a high risk of malignancy. Pompili et al,[1] evaluated the total malignancy score (TMS) of 231 nodules in 231 consecutive patients. In the multivariate analysis, hypoechogenicity, a solid structure, the presence of microcalcifications, and the number of nodules were independent predictors of the final diagnosis. They found that 47 % of the nodules had a TMS <3, 18% had a TMS 3, and 35% had a TMS >3. The authors suggested that they could asses the risk of malignancy according to the TMS category, with no risk or negligible risk for a TMS <3, low risk for a TMS of 3, and medium or high risk for higher TMS values.

In our study, non-diagnostic FNAB results were similar in > 1 cm and ≤ 1 cm nodules which were consistent with Berker et al.[25] We also found higher suspicious for malignancy and malignancy FNAB results in nodules ≤ 1 cm compared with those > 1 cm. Our higher rate may be due to the fact that several small-sized suspicious thyroid nodules were referred to our tertiary hospital and the most suspicious nodules were selected for FNAB.

The major limitation of our study was that it was retrospective and from a single center. Second, although our clinicians are experienced in US, it is inevitable to have interobserver variability when assessing US features of thyroid nodules. Another limitation of our study was that nodule vascularization had not been evaluated in a considerable number of patients; thus, we did not include it in the analysis. Additionally, fewer sub-centimeter nodules were evaluated than larger nodules in our study.

In conclusion, as the clinical significance of small thyroid cancers is controversial, it is important to evaluate these nodules using the best strategy. Although many studies have assessed the risk of thyroid cancer attributable to certain US features and formulated a combination of US features to increase their predictive value for malignancy, the diagnostic accuracy of US remains limited. Ultrasonography scoring system may help clinicians and surgeons to select nodules for FNAB more accurately and prevent unnecessary sampling, particularly those sub-centimeter in size, and help to provide cost-effectiveness.

Ethical Considerations: The study has been approved by an Ethics Committee of the Faculty of Medicine of the local University (Date: 21.10.2015, Number: 208)

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

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