Association of the Thyroid Nodules' Sonographic Features With Fine Needle Aspiration (FNA) Cytology Results

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Abstract- Thyroid nodules are a common finding in clinical practice. Although ultrasonography is an accepted method for evaluating these nodules, Fine Needle Aspiration (FNA) is the procedure of choice for assessing the risk of malignancy. This study aims to determine the association between sonographic features of thyroid nodules based on Thyroid Imaging Reporting and Data System classification and the cytology results. In this prospective cohort study, 147 patients from Tehran Medical Imaging Center who had thyroid nodules underwent ultrasonography-guided FNA, and their sonographic features were recorded. The pathologic findings were also obtained according to the Bethesda system. Finally, the association between sonographic features and cytological results was analyzed. Eighteen (12.3%) nodules were malignant, and 129 nodules (87.7%) were benign. The association of TIRADS categories with the risk of malignancy is as follows: TIRADS 1 (n=0, 0%), TIRADS 2 (n=10, 16.9%), TIRADS 3 (n=6, 10.5%), TIRADS 4 (n=2, 16.7%), and TIRADS 5 (n=0, 0%). The bloody lamellae of thyroid nodules were significantly correlated with the risk of malignancy ($P<0.05$). However, there was no statistically significant association between the risk of malignancy and gender ($P=0.47$), calcification ($P=0.9$), firmness ($P=0.19$), halo sign ($P=0.95$), location of nodules ($P=0.35$), and nodules' echogenicity ($P=0.058$). Although there are trusted classifications such as TIRADS for categorizing thyroid nodules, there is still uncertainty in utilizing them, especially in the management of nodules classified as TIRADS 2, in which various sonographic features are shared between benign and malignant nodules.

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Keywords: Cytology; Fine needle aspiration; Sonographic features; Thyroid nodule; Thyroid imaging reporting and data systems (TIRADS)

Introduction

Thyroid nodules are a frequent clinical finding revealed during a precise physical exam or a variety of imaging procedures (1). According to epidemiological documents, in iodine-sufficient regions of the world, nearly 5% of the females and 1% of the males are detected with palpable thyroid nodules (2). Thyroid nodules can be discovered in 10-41% of adults by ultrasonography (US), and the diagnosis rate is progressively increasing with the recently growing use of this imaging procedure (3). It is stated that most of these nodules are benign (4). Despite an increasing incidence of thyroid nodules due to improved healthcare access of the population (5), the effort to diagnose them at the lowest cost and least possible time is still a priority.

Ultrasonography (US) is one of the most common first-line modalities of evaluating palpable thyroid nodules or detecting them incidentally (6). However, most of these nodules should undergo Fine Needle Aspiration (FNA), which is the keystone of assessing nodular thyroid disease, to increase the accuracy of

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predicting their potential cancer risk. There has also been a substantial controversy over assessing clinically asymptomatic nodules by FNA biopsy or close observation (7).

Thyroid Imaging Reporting and Data System (TIRADS) classification, which was first established in 2009, is a model for evaluating the thyroid nodules based on specific patterns of US that enhances the selection of nodules for further evaluation by FNA biopsy (8). Although several sonographic features are suggestive of malignancy of the thyroid nodules, there is extreme variability in the reported sensitivity and specificity of these findings in correlation with final cytology results from study to study (3).

Our study aimed to compare the cytology reports of thyroid nodules' FNA biopsy with their specific sonographic features and to assess the ability of each sonographic feature in predicting the risk of thyroid malignancy. We hypothesized that some US characteristics might be the independent predictor of malignant or benign cytology reports.

Materials and Methods

In this prospective cohort study, a total of 147 consecutive patients with thyroid nodules from December 2018 to September 2019 were identified. All patients were referred for FNA biopsy to our institute in Tehran Medical Imaging Center, Tehran, Iran. After obtaining informed consent, patients underwent US imaging and cytological study, respectively. We included any patient who was referred for further evaluation of his/her suspicious thyroid. Those who had a history of benign cytology results and previous thyroid malignancy were excluded from the study. Sample size (n=89) was calculated based on this formula;

$$n = \frac{z^2_{1-\propto/_2} \times Spec. \times (1-Spec.)}{d^2 \times (1 - Prevalence)}$$

Neck US was performed for each patient by our experienced radiologist using a high-resolution US apparatus (Medison Accuvix V10, Korea) with a 7 MHz linear transducer. Every thyroid nodule was assessed based on ACR TIRADS criteria such as composition, echogenicity, shape, margin, and echogenic foci (9). The TIRADS model categorizes the nodules into 5 groups ranging from 1 (benign) to 5 (highly suspicious), as summarized in Table 1. All 147 patients underwent FNA, regardless of the nodules' TIRADS grade, to determine the accuracy of the ACR-TIRADS classification system.

Table 1. ACR TI-RADS categories and criteria for FNA and follow-up sonography

ACR TI-RADS	Definition	Indicated management
1	Benign	No FNA
2	Not suspicious	No FNA
3	Mildly suspicious	FNA if ≥ 2.5 cm Follow if ≥ 1.5 cm
4	Moderately suspicious	FNA if ≥ 1.5 cm Follow if ≥ 1 cm
5	Highly suspicious	FNA if ≥ 1 cm Follow if ≥ 0.5 cm

FNA biopsy was performed by our qualified interventional radiologist for every thyroid nodule under the guidance of US in a supine position with a mid-extended neck position under standard sterilized conditions. Lidocaine was used as the local anesthesia. Target nodules were aspirated with a 21-gauge needle attached to a 20cc syringe, using the aspiration technique; the obtained samples were fixed with alcohol on glass slides. Thereafter, a pathologist reported cytology based on the Bethesda system. The pathologists were blind regarding the sonographic findings of the evaluated nodules.

Finally, the cytology results and TIRAD scoring of these nodules were recorded and analyzed using SPSS software. The statistical tests used included Chi-square and Fisher and Kappa for comparison of categorical variables. A *P* less than 0.05 was considered statistically significant. In addition, the sensitivity, specificity, positive predictive value, and negative predictive value of TIRADS were determined.

Ethics approval and consent to participate

The study protocol was approved by the medical Ethics Committee of our institute (Ethics ID: IR.TUMS.VCR.REC.1398.686)

Results

One hundred forty-seven nodules of 147 patients were assessed. The patients' mean±SD age was 49.8±13.7 and

126 (85.7%) patients were female. The age ranges of patients were from 20 to 80 years. In histopathologic assessment, absolutely 18 (12.3%) nodules were malignant, of which 15 (83.3%) were Papillary Thyroid Carcinoma (PTC), and 3 were Hurthle cell neoplasm (Table 2).

Table 2. Description of malignant thyroid nodules size

Malignant thyroid nodules	Transverse (T) size (mm)	Antero posterior (AP) size (mm)	TI-RADS score
Nodule 1	9.00	4.00	2.00
Nodule 2	18.00	10.00	3.00
Nodule 3	10.00	16.00	4.00
Nodule 4	8.00	8.00	2.00
Nodule 5	9.00	9.00	3.00
Nodule 6	4.00	8.00	2.00
Nodule 7	5.00	5.00	2.00
Nodule 8	10.00	10.00	3.00
Nodule 9	18.00	18.00	2.00
Nodule 10	16.00	14.00	4.00
Nodule 11	20.00	20.00	3.00
Nodule 12	9.00	7.00	3.00
Nodule 13	7.00	5.00	2.00
Nodule 14	20.00	11.00	3.00
Nodule 15	21.00	21.00	2.00
Nodule 16	10.00	10.00	2.00
Nodule 17	11.00	13.00	2.00
Nodule 18	40.00	35.00	2.00

Hence, benign lesions were seen in 129 (87.7%) nodules, in which the most common lesion was follicular nodules (86, 66.7%). Table 3 summarizes the different histological findings of these nodules.

Table 3. Distribution of different histopathological findings among the nodules

Malignancy	Finding	Number (%)/ *n=147*
Benign lesions	Benign Follicular Nodule	86 (58.5)
	Hashimoto disease	9 (6.1)
	Non-Diagnostic	2 (1.3)
	Cystic fluid only	21 (14.3)
	Atypia of Undetermined Significance	11 (7.5)
Malignant lesions	PTC	15 (10.2)
	Hurthle Cell Neoplasm	3 (2.1)

The mean suction time for each nodule was 13.7±4.8. The mean lamellae provided for patients was 3.7±1. The mean anteroposterior diameter was 14.2±7.3 mm, the mean transverse diameter was 15±8.5 (1-50) and the mean score of vacuum force was 9.5±1.7, of which none of them was significantly associated with malignancy of the thyroid nodules.

According to our results, TIRADS categories were associated with the risk of malignancy as follows: TIRADS 1 (0%), TIRADS 2 (16.9%), TIRADS 3 (10.5%), TIRADS 4 (16.7%), and TIRADS 5 (0%). The most common location of the nodules was in the right lobe (77, 52.4%), of which 67 were benign. The cystic transformation was seen in 69 nodules (46.9%) and calcification was seen in 88 nodules (59.9%). Table 4 summarizes the ultrasonographic features of all evaluated nodules in our study.

The diagnostic predictability of different variables was assessed, and ROC curves were made for each variable. The Area Under Curve (AUC) of the variables is demonstrated in Table 5. Based on our results, echogenicity had the highest AUC (0.65) among all sonographic features in predicting malignant nodules (Figure 1). Moreover, Table 6 summarizes the diagnostic indices of echogenicity in predicting malignant nodules.

Table 4. Demographic and sonographic features of the thyroid nodules

Variable		Thyroid nodule Benign n=129 No (%)	Thyroid nodule Malignant n=18 No (%)	*P*
Gender	Male	20 (95.2)	1 (4.8)	0.47
	Female	109 (86.5)	17 (13.5)	
TIRADS	1	14 (100)	0 (0)	0.45
	2	49 (83.1)	10 (16.9)	
	3	51 (89.5)	6 (10.5)	
	4	10 (83.3)	2 (16.7)	
	5	3 (100)	0 (0)	
Cystic formation	Yes	61 (88.4)	8 (11.6)	0.82
	No	68 (87.2)	10 (12.8)	
Location	Right	67 (87)	10 (13)	0.35
	Left	60 (89.5)	7 (10.5)	
	Isthmus	2 (66.7)	1 (33.3)	
Calcification	Yes	77 (87.5)	11 (12.5)	0.9
	No	52 (88.1)	7 (11.9)	
Bloody lamellae	Tiny	36 (97.3)	1 (2.7)	0.047*
	Somehow	71 (83.5)	14 (16.5)	
	Intermediate	15 (93.8)	1 (6.3)	
	High	5 (71.4)	2 (28.6)	
Angle	Equal to 75º	126 (88.1)	17 (11.9)	0.41
	Other than 75º	3 (75)	1 (25)	
Hardness	No	107 (89.9)	12 (10.1)	0.19
	Mild	15 (78.9)	4 (21.1)	
	Moderate	5 (83.3)	1 (16.7)	
	Completely	2 (66.7)	1 (33.3)	
Halo sign	Yes	67 (89.3)	8 (10.7)	0.95
	No	52 (89.7)	6 (10.3)	
Echogenicity	Hyperecho	27 (87.1)	4 (12.9)	0.058
	Hypoecho	32 (80)	8 (20)	
	Isoecho	37 (97.4)	1 (2.6)	
	Heterogenous	23 (95.8)	1 (4.2)	

* Indicator of significant correlation

Table 5. AUC of the thyroid nodule characteristics

variable	AUC	*P*	95% CI of AUC
AP size	0.6	0.16	0.46-0.75
Transverse size	0.6	0.22	0.44-0.74
TIRADS	0.51	0.95	0.37-0.64
Cystic Feature	0.49	0.85	0.34-0.63
Location	0.52	0.79	0.36-0.68
Calcification	0.51	0.92	0.37-0.65
Bloody lamellae	0.61	0.13	0.49-0.73
angle	0.52	0.83	0.37-0.66
hardness	0.58	0.26	0.43-0.73
Halo sign	0.5	0.96	0.34-0.66
echogenicity	0.65	0.065	0.49-0.81

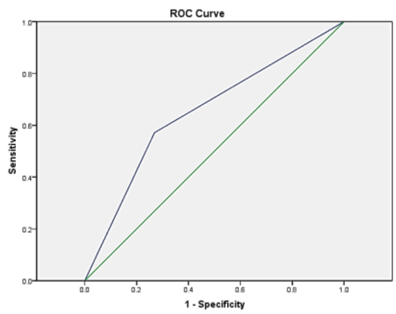

Figure 1. ROC curve of Echogenicity in the diagnosis of malignancy when the hypoechogenic's nodules are considered malignant

Table 6. Diagnostic efficacy indices of echogenicity in the diagnosis of malignant nodules

Index	Estimate	Lower 95% CI	Upper 95% CI
Sensitivity	0.57	0.29	0.82
Specificity	0.73	0.64	0.81
Efficiency	0.71	0.63	0.79
Predictive value of positive test	0.20	0.09	0.36
Predictive value of negative test	0.96	0.86	0.98
Likelihood ratio of positive test	2.13	1.24	3.65
Likelihood ratio of negative test	1.71	0.92	3.15
Cohen's Kappa	0.17	0.01	0.33

Discussion

Fine Needle Aspiration Biopsy (FNAB) is accepted as a precise, safe, and cost-effective diagnostic tool for thyroid nodules, especially in the setting of preoperative decision-making (10). Sonography-guided FNAB has been also improved remarkably in terms of diagnostic accuracy recently (11). US is usually the most common diagnostic modality of the incidental or purposeful finding of a thyroid nodule (12). Therefore, further evaluation of these nodules is based on these nodules' sonographic features. However, most of these sonographic characteristics are shared between benign and malignant lesions (13). In this study, we tried to compare these sonographic features based on the ACR TIRADS model with final cytology reports of the thyroid nodules and evaluate how these features could help physicians in predicting the malignancy of these nodules.

Despite an increased rate of thyroid nodule diagnosis following a growing variety of modalities, most of the nodules are benign (14). As in our study, 89.1% of the nodules were benign lesions, including benign follicular nodules, cystic fluid only, Colloid nodules, etc. However, different factors affect this prevalence, such as iodine deficiency, post-radiation therapy, and even patients' level of health service accessibility in different societies (14,15).

According to our experience, like some other studies (16,17), the size of the nodules is not a good indicator of the risk of malignancy of thyroid nodules. However, some researchers claim that there is a strong association between these two factors as the larger size of the nodules correlates with a higher malignancy rate with a threshold of 2.0 cm (18,19). Generally, the nodules' size is not an important predictive indicator of thyroid malignancy unless accompanied by other malignant features (16).

In this study, we found no significant correlation between the TIRADS model and the risk of malignancy. This is in contrast with what Singaporewalla *et al*., (20) claimed in their research. They showed that there was an accuracy of 83% in predicting the risk of malignancy based on using TIRADS. However, the maximum correlation that we found was in TIRADS 2, with a 16.9% of malignancy association. Other studies by Horvath *et al*., (8), Park *et al*., (21), and Kwak *et al.,* (22) reported the highest association of TIRADS with the risk of malignancy as 89.6%, 100%, and 87.5%, respectively. This may be due to our limited sample size. Nonetheless, the TIRADS model is somehow operator dependent, as some studies suggest using this model by two radiologists at the same institution.

Based on our results, TIRADS 2 had the most correlation with the risk of malignancy. This increases the uncertainty of using this scoring system as an indicator of thyroid nodules' FNA requirement. We believe that this discrepancy may cause the misdiagnosis of patients who present with thyroid nodules with TIRADS 2 and will not be further assessed according to ACR-TIRADS.

Our study showed that the location of the thyroid nodules was significantly associated with the risk of their malignancy, and most of our cytologically malignant nodules were located in the right lobe. Although 67 out of all 77 nodules of the right lobe were benign, 10(13%) were malignant compared to 7 (10.5%) out of 67 nodules of the left thyroid lobe. Most studies claim that there is no relationship between the location of the thyroid nodules and malignancy and despite the absence of association, the isthmus, and mid-lobar nodules were the most sites of the thyroid correlated with the risk of malignancy (23,24).

In accordance with a retrospective observational cohort study conducted by Frates *et al*., (25), one of the sonographic characteristics which correlate with malignancy is the existence of microcalcifications. This is in contrast with our study's findings, in which there was no association between the nature of calcification and the risk of malignancy (P=0.9). In another study by Rago *et al*., (26), only a combination of the presence of microcalcification plus the absence of a halo sign had a significant relationship with the possibility of malignancy, which was associated with high specificity (93.0%) but low sensitivity (36.0%). Our research did not differentiate the subtypes of calcifications (such as micro, macro, coarse, and peripheral) and this may affect the results as some studies showed that although malignant thyroid nodules might correlate with microcalcifications, benign lesions are even associated with macro-calcification (27,28).

Several studies have tried to determine if Fine Needle Capillary (FNC) sampling is superior to Fine Needle Aspiration due to a higher amount of cellular material. However, they did not find any statistically significant difference (29,30). Although FNA sampling provides a more specific field and more diagnostic parameters than the FNC technique (30), our experience revealed that the samples accompanied by blood were significantly associated with a higher risk of malignancy.

In this study, we evaluated a relatively new variable to determine if the angle of the needle entry to thyroid nodules during FNA sampling affects the risk of malignancy. According to the results, there was no significant association between the group of patients in whom the needle was induced at the angle of 75º and the other group who underwent this procedure at any other angle of needle entry.

Based on our experience in this research, hypoechogenicity is somehow associated with malignancy with a p-value of 0.058, which was statistically insignificant. However, Nabahati *et al*., revealed that there was a considerable positive correlation between malignancy and hypoechogenicity [odds ratio (OR) 3.577, 95% confidence interval (CI) 2.045-6.256] as their 29 nodules out of all 221 hypoechoic nodules were malignant (P<0.001). In our study, 26% of the thyroid nodules were hypoechogenic, of which 20% were malignant. Overall, echogenicity is one of the criteria of ACR-TIRADS, and as in our study, the more hypoechogenic the thyroid nodule, the higher the risk of malignancy is expected.

There were some limitations in our study. First, it is a single-center study. Hence, further investigations, including more patients and multiple health centers, are needed to prove the results and conclusion of this paper. The second and most important limitation lies in the fact that although FNA is a reliable and cost-benefit diagnostic intervention, it has some false-positive and false-negative results. FNA is not routinely an effective tool in diagnosis of follicular lesions of undetermined significance (FLUS) or follicular neoplasm and suspected lymphoma. However, none of our patients were diagnosed with these conditions, which minimizes the effect of this limitation on our study.

Thyroid nodules are a common finding of clinical practice worldwide. The clinical approach to this clinical finding is based on the first sonographic features and the FNA biopsy results. Although there are accepted models such as TIRADS to distinguish malignant lesions with high sensitivity and specificity, our study demonstrates that even these relatively well-known scoring systems may not be trustworthy enough, and most of these sonographic features are mutual between malignant and benign lesions.

Although current guidelines do not recommend meticulous and intensive surveillance for nodules classified as TIRADS 2, we suggest a more precise investigation of this nodule classification, as they might carry a higher risk of malignancy than expected before. However, confirmation would be necessary in future studies with a larger sample size. We recommend re-evaluating the TIRADS guidelines by multi-center prospective studies.

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