A Practical Score Model for Detecting Malignant Thyroid Nodules by Using Ultrasonographic Findings

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Abstract- About 10% of thyroid nodule Fine Needle Aspirations (FNAs) are reported indeterminate, and this number is much higher in Iran. All of these patients undergo thyroid surgery, whereas, only about 20% of them are malignant and they did not need surgery. Therefore, we decided to evaluate the ultrasonographic features of malignant thyroid nodules to find a predictive scoring model for thyroid nodules and consequently reduce the unnecessary thyroid surgeries. This prospective cross-sectional study was conducted on 114 patients with thyroid nodule who were candidate for thyroid surgery. All the patients were assessed by ultrasonography of thyroid before surgery, and after surgery by the gold standard of permanent pathology, the sensitivity, specificity, positive predictive value, and negative predictive value of each parameter of ultrasonography were determined. Finally, by using the logistic regression analysis, a predictive scoring model was suggested. A total of 114 patients with mean age of 43.13±13 years (90 females (78.9%) were studied. Prevalence of malignancy in final pathology was 75.9%, 39.0%, and 15.9% in FNA biopsies which were malignant, undetermined and benign, respectively. FNA correctly verified 48.9% of the malignant pathologies. In all, smaller nodules, hypoechogenicity, metastatic lymphadenopathy, oval shape, thick or incomplete halo, ill margins, microcalcification, and heterogenicity are associated with malignancy (All, $P<0.05$). We recommend that complementary tools upon ultrasonographic data along with FNA can be helpful for more accuracy and early diagnosis of malignant thyroid nodules.

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Keywords: Malignant thyroid nodule; Ultrasonographic factures; Practical model

Introduction

Solitary thyroid nodule (STN) arise in about 4% of general population. Nevertheless, the prevalence of thyroid malignancies is far less than this. According to literature, about 5 to 20% of thyroid nodules are malignant (1-4). Therefore, in confronting with thyroid nodules, we should investigate the malignancy by FNA (fine needle aspiration) and ultrasonography (US), and after confirming the malignancy, thyroid surgery, either lobectomy or total thyroidectomy is performed for the patient. Thyroid surgery has cost, cosmetic, and medical problems for patient and some probable complications including injury to recurrent laryngeal nerve, voice change, temporary or permanent parathyroid damage and the resulting hypocalcemia and hematoma, it is reasonable and necessary to diagnose a malignancy with high accuracy to reduce the number of unnecessary operations and the related complication (5).

Diagnosing malignant thyroid nodules by FNA was associated with sensitivity of 54-90% and specificity of 60-100% (6,7). However, even by the guide of ultrasonography (US) still, a substantial portion of FNAs are reported as non-diagnostic or indeterminate. Previous studies have shown 8.6 to 36 percent of FNAs to remain inconclusive (8,9). The frequency of inconclusive FNAs would be higher when it's not guided by US (9). Moreover, follicular neoplasms account for around 12% of the reported FNAs, from which, almost 20% are malignant (10,11). Practically, clinical suspicion may

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lead many of the patients with FNA report of the follicular neoplasm to undergo surgery. This may result in more benign pathologies and more unnecessary thyroidectomies (11).

US is proposed to increase the diagnostic accuracy of FNA in detecting malignant STNs. US can indicate non-palpable thyroid nodules as well. Most of the malignant STNs are hypoechoic and may have irregular shapes and margins. Hypoechogenicity, punctuate microcalcification, adjacent lymphadenopathy, incomplete halo, and elongated shape of nodules are features of a malignant STNs (12-15). Number of studies has evaluated the diagnostic accuracy of US in the detection of malignant STNs. They reported sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 93.8%, 68%, 56%, and 95%, respectively (12,16). Other studies investigated the association of US features of an STN with malignant pathology. Microcalcification, lymphadenopathy, elongated shape and irregular margins were consistent with increased likelihood of malignancy (17-19). Association of nodule size, echogenicity, and presence of a solid component were of debate (17,20). Assessment of central blood flow is a promising determinant of malignancy (21). However, its absence in the majority of malignant nodules confines its clinical usefulness (3). We decided to investigate the ultrasonographic features such as the shape of nodule, margins, solid or cystic, concurrent lymphadenopathy and microcalcification and central blood in patients with STN who are candidate for surgery and determine the sensitivity, specificity, positive predictive value, and negative predictive value of each feature by comparison with the gold standard of the permanent pathology report after surgery. Finally, by using advanced statistical analysis, our main objective was to develop a simple scoring system, by using the ultrasonographic findings to predict malignancy in thyroid nodules. By inspiration of Alvarado scoring system in predicting acute appendicitis and AGES, MACIS system for predicting the prognosis of thyroid malignancy, an accurate ultrasound-based scoring system which is available, can aid us in clinical decision making, especially in indeterminate and follicular neoplasm, in FNA report. Therefore, reducing the unnecessary operations and the consequent likely complications.

Materials and Methods

In a prospective cross-sectional study, all patients consecutively referred to Endocrine Surgery Clinic of Tehran University of Medical Sciences (TUMS), Shariati hospital, during 2011 and 2012 were included. All patients were referred from a General Endocrinology Clinic for thyroidectomy after being diagnosed with a cold thyroid nodule. A written informed consent was obtained. The study was approved by the ethical committee of TUMS.

Data collection

Demographic data including age, sex, and family history of thyroid neoplasm (if positive, whether in father, mother or siblings) were recorded. Patients underwent diagnostic US evaluation of thyroid and neck by a single expert head and neck radiologist, the author (AP.H) prior to surgery. The US was performed with a 5-7.5 MHz linear transducer, in a supine position with the neck in extension and a small pad under the shoulders to facilitate the procedure. Nodule size, shape (round vs oval), echogenicity (Hyperecho, Isoecho, Hypoechoic or Anecho), halo (thin or complete vs thick or incomplete), margin (well defined vs ill-defined), pattern (homogenous vs heterogeneous), presence of lymphadenopathy (reactive vs metastatic) and calcification (coarse vs micro) were recorded. All patients underwent FNA of the suspected nodule. Results of the FNA biopsy were categorized as benign, malignant or undetermined. Laboratory examination for serum levels of TSH, T4, and T3 was obtained. Results of the surgical pathology were set as the outcome in a binary variable as malignant or benign. Pathology results were categorized as Multi Nodular Goiter (MNG), Thyroiditis, Papillary Thyroid Carcinoma (PTC), and Follicular Thyroid Carcinoma (FTC), Follicular adenoma, Medullary Thyroid Carcinoma (MTC), Anaplastic Thyroid Carcinoma (ATC) or Hurthle cell adenoma. The dominant location of the lesion was recorded as the left, right or the isthmus lobe of thyroid.

Statistical analysis

Univariate analysis of the association of pathology results to clinical and demographic variables was done by using Student's t-test and the Mann-Whitney U-test for continuous variables and Pearson's chi-squared test and Fisher's exact test for categorical variables. To define a scoring system, we used logistic regression modeling. In the first step, all demographic factors (including age, sex and family history) and potential predictors (except for the FNA) including US features and TSH levels were included in a logistic regression model. This model was defined as "Full model." Next, by using the backward method, factors with *P* of more than 0.2 were excluded from the Full model. To do so, we excluded the variable

with the highest *P* in each attempt and ran the model again. This procedure was repeated until there was no factor with a *P* greater than 0.2. The final model was defined as the "Reduced model." Receiver Operating Curve (ROC) analysis showed the corresponding Area under the Curve (AUC) for these two models. Using the variables remained in the model and the coefficients derived from the logistic regression, we conducted a scoring system to predict the malignant cases. ROC analysis revealed Sensitivity (Sen), Specificity (Spe), PPV, NPV, Accuracy, Positive and Negative Likelihood for each of the predictors as well as the whole scoring system. For the scoring system, the optimal cut-off was selected as the point on the ROC curve, having the smallest distance between the ROC curve and the upper left-hand corner of the plot. All analysis was performed using SPSS (Chicago, v 19) and a *P* of less than 0.05 was considered significant.

Results

In all, 114 consecutive patients with mean age of 43.13±13-year-old consisting of 90(78.9%) females and 51(44.7%) subjects with a positive family history of thyroid neoplasm were studied. All were referred for having a nodule and underwent laboratory assessment of TSH, thyroid US, FNA and excisional biopsy using thyroidectomy. Total of 45(39.5%) patients had malignant pathologies. The most common pathology was MNG (42%), and the most common malignancy was PTC (31.3%). There was no statistical difference in age, gender, family history or the location of the lesion between groups with or without malignant pathologies. Table 1 shows the demographics and the pathology type categories of the study population in groups with and without malignant pathologies.

Table 1. Demographic data of patients

Parameter	Level	Total	Pathology		*P*
			Benign	Malignant	
Age	**Mean±SD**	43.13±13.0	44.09±12.23	41.67±14.12	0.334†
		42.5 (7 to 70)	45 (18 to 70)	42 (7 to 66)	
Sex	**Male**	24 (21.1%)	16 (66.7%)	8 (33.3%)	0.489*
	Female	90 (78.9%)	53 (58.9%)	37 (41.1%)	
Family history	**Negative**	63 (55.3%)	38 (60.3%)	25 (39.7%)	0.960*
	Positive	51 (44.7%)	31 (60.8%)	20 (39.2%)	
	Mother	18 (15.8%)	8 (44.4%)	10 (55.6%)	
	Father	19 (16.7%)	14 (73.7%)	5 (26.3%)	0.194
	Sibling	17 (14.9%)	10 (58.8%)	7 (41.2%)	
Pathology type	**MNG**	47 (42.0%)	47 (100.0%)	0 (0.0%)	<0.001**
	Thyroiditis	16 (14.3%)	15 (93.8%)	1 (6.2%)	
	PTC	35 (31.3%)	0 (0.0%)	35 (100.0%)	
	FTC	5 (4.5%)	0 (0.0%)	5 (100.0%)	
	Follicular adenoma	5 (4.5%)	5 (100.0%)	0 (0.0%)	
	MTC	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	ATC	2 (1.8%)	0 (0.0%)	2 (100.0%)	
	Hurthle-cell adenoma	2 (1.8%)	2 (100.0%)	0 (0.0%)	
Lobe	**Right**	56 (49.6%)	34 (60.7%)	22 (39.3%)	>0.99**
	Left	54 (47.8%)	32 (59.3%)	22 (40.7%)	
	Bismuth	3 (2.7%)	2 (66.7%)	1 (33.3%)	

† Based on t-test.
** Based on Chi-square test.

Neither TSH (1.22±1.35 vs. 1.82±1.38), T4 (10.68±12.85 vs. 8.21±2.95) nor T3 (133.07±26.61 vs. 133.81±36.02) levels were statistically different in groups with or without malignant pathologies. Prevalence of malignancy in final pathology was 75.9%, 39.0% and 15.9% in FNA biopsies which were malignant, undetermined and benign, respectively. In all, FNA verified 48.9% of the malignant pathologies. Table 2 shows the distribution of the predictors across groups with and without malignancy.

Table 2. Distribution of the predictors by the results of the pathology

Parameter	Level	Total[α]	Pathology[β]		*P*
			Benign	Malignant	
TSH	**Mean±SD**	1.89±1.38 1.70 (0.2 to 8.9)	1.82±1.38 1.9 (0.2 to 7.1)	1.22±1.35 1.7 (0.2 to 8.9)	0.327‡
T3	**Mean±SD**	133.52±32.51 125.00 (90 to 290)	133.81±36.02 123 (90 to 290)	133.07±26.61 131 (90 to 200)	0.624
T4	**Mean±SD**	9.18±8.43 8.40 (0.42 to 92.40)	8.21±2.95 8.1 (0.42 to 13.19)	10.68±12.85 9 (1.2 to 92.40)	0.179
FNA	**Benign**	44 (38.6%)	37 (84.1%)	7 (15.9%)	<0.001*
	Malignant	29 (25.4.1%)	7 (24.1%)	22 (75.9%)	
	Undetermined	21 (36.0 %)	25 (61.0%)	16 (39.0%)	
Nodule shape	**Round**	43 (38.1%)	31 (72.1%)	12 (27.9%)	0.043*
	Oval	70 (61.9%)	37 (52.9%)	33 (47.1%)	
Nodule size	**Mean±SD**	30.34±17.57 28 (3 to 88)	34.13±19.11 33 (3 to 88)	24.62±13.21 23 (7 to 55)	0.002‡
Echogenicity	**ISO**	40 (35.1%)	35 (87.5%)	5 (12.5%)	<0.001*
	Hypo	65 (57.0%)	26 (40.0%)	39 (60.0%)	
	Hyper	9 (7.9%)	8 (88.9%)	1 (11.1%)	
	An	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Lymphadenopathy	**Negative**	76 (66.7%)	55 (72.4%)	21 (27.6%)	<0.001*
	Positive	38 (33.3%)	14 (36.8%)	24 (63.2%)	
Calcification	**Negative**	77(67.5%)	58 (75.3%)	19 (24.7%)	<0.001*
	Positive	37 (32.5%)	11 (29.7%)	26 (70.3%)	
Margin	**well defined**	77 (67.5%)	55 (71.4%)	22 (28.6%)	0.001*
	ill defined	37 (32.5%)	14 (37.8%)	23 (62.2%)	
Pattern	**Homogenous**	36 (31.6%)	28 (77.8%)	8 (22.2%)	0.010*
	Heterogeneous	78 (68.4%)	41 (52.6%)	37 (47.4%)	

‡ Based on Mann-Whitney test.
* Based on Chi-square test
α Percent is calculated within column
β percent is calculated within rows

Table 3. Diagnostic accuracy criteria of TSH and US features.

Variable	Indicator	Sen [95% CI]	Spe [95% CI]	PPV [95% CI]	NPV [95% CI]	Accuracy
TSH	**≥ 1.26**	68.9% [0.543 to 0.805]	50.7% [0.392 to 0.622]	47.7% [0.36 to 0.596]	71.4% [0.576 to 0.822]	57.9%
Nodule size	**≤ 36**	82.2% [0.687 to 0.907]	47.1% [0.357 to 0.588]	50.7% [0.395 to 0.618]	80.0% [0.652 to 0.895]	61.1%
Nodule shape	**Oval**	73.3% [0.59 to 0.84]	45.6% [0.343 to 0.573]	47.1% [0.359 to 0.587]	72.1% [0.573 to 0.833]	56.6%
Echogenicity	**Hypo**	86.7% [0.738 to 0.937]	62.3% [0.505 to 0.728]	60.0% [0.479 to 0.71]	87.8% [0.758 to 0.943]	71.9%
Lymphadenopathy	**Positive**	53.3% [0.391 to 0.671]	79.7% [0.688 to 0.875]	63.2% [0.473 to 0.766]	72.4% [0.614 to 0.812]	69.3%
Calcification	**Positive**	57.8% [0.433 to 0.71]	84.1% [0.737 to 0.909]	70.3% [0.542 to 0.825]	75.3% [0.646 to 0.836]	73.7%
Halo	**Thick or incomplete**	79.5% [0.655 to 0.888]	75.4% [0.64 to 0.84]	67.3% [0.538 to 0.785]	85.2% [0.743 to 0.92]	77.0%
Margin	**ill defined**	51.1% [0.37 to 0.65]	79.7% [0.688 to 0.875]	62.2% [0.461 to 0.759]	71.4% [0.605 to 0.803]	68.4%
Pattern	**Heterogenic**	82.2% [0.687 to 0.907]	40.6% [0.298 to 0.524]	47.4% [0.367 to 0.584]	77.8% [0.619 to 0.883]	57.0%

Sen=sensitivity, ppv=positive predictive value
Spe=specificity, Npv=negative predictive value
D accuracy=Diagnostic accuracy, CI=Confidence Interval

We compared the US features in groups with and without malignancy. Nodules which were smaller in size (24.62±13.21 vs 34.13±19.11), oval in shape (47.1% vs 27.9% in round), Hypocho (60.0% vs 12.5% in Isoecho and 11.1% in hyperecho), microcalcified (80.0% vs 30.0% in coarse and 24.7% in non-calcified) and had thick halo (67.3% vs 14.8% in thin halo), ill margins (62.2% vs 28.6% in well-defined margins) and heterogeneous pattern (47.4% vs 22.2% in homogenous) were more likely to be malignant. Metastatic lymphadenopathy was also accompanied with malignancy in almost every case (93.8% vs. 40.9% in reactive lymphadenopathy and 27.6% in those without lymphadenopathy). Table 3 presents the diagnostic accuracy of TSH and each US feature, in details. The full model consisting of age, sex, family history, TSH levels and 8 US features (Table 4) had an AUC (area under the curve) of 0.909 (0.858-0.960, P<0.001) and successfully predicted the presence of malignancy. The reduced model consisting of gender, nodule size, nodule shape, echogenicity, lymphadenopathy, calcification and halo characteristics was also successful in prediction of outcome with statistically insignificant reduction in AUC in comparison to the full model (AUC=0.902; 0.849-0.956,by confidence interval 95%, P<0.001) (Figure 1). Therefore, we used coefficients of the reduced model to derive a simple scoring system. The diagnostic criteria are presented in Table 5. A cut-off of 4.7 was shown to best optimize both the sensitivity and the specificity of the scoring system in the prediction of malignancy with confidence interval=95%. The last row on table 5 demonstrates the diagnostic accuracy of the simple scoring system. The P for the likelihood ratio test comparing the full model to the reduced model was <0.02.

Table 4. The area under the curve

	Area	*P*	95% CI	
			Lower	Upper Bound
Full model	0.909	<0.001	0.858	0.96
Reduced model	0.902	<0.001	0.849	0.956

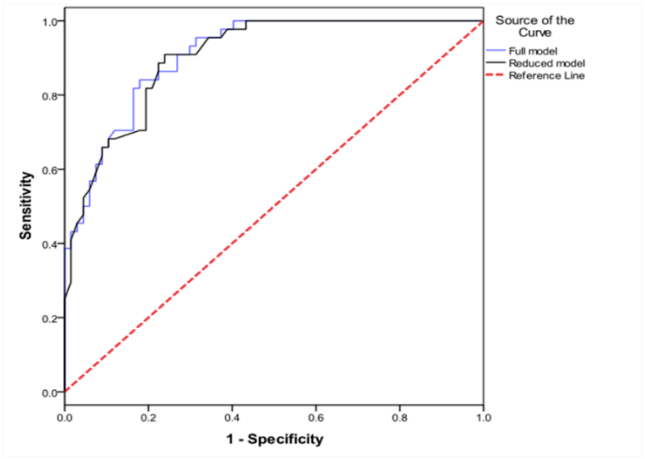

Figure 1. ROC analysis demonstrating minimal loss of information when reducing the full model for a simple risk score was done.

Table 5. Scoring system to predict the malignant cases

Variables	Criteria	Score*	Odds ratio	95% CI		*P*
				Lower	Upper	
Sex	Female	1.1	2.9	0.7	11.9	.131
Nodule size	≤ 36	0.9	2.5	0.7	9.2	.159
Nodule shape	Oval	0.9	2.4	0.8	7.8	.136
Echogenicity	Hypo	1.8	5.9	1.7	20.8	.006
Lymphadenopathy	Positive	1.1	3.0	0.8	11.8	.120
Calcification	Positive	1.1	3.0	0.8	11.7	.115
Halo	Thick or incomplete	1.5	4.3	1.4	13.6	.013

*Whenever a subject got a score more than 4.7 we could consider it as a malignant case.

Table 6. With mentioned cut-off, the score test has the following characteristics

	Indicator	TP	TN	FP	FN	Sen	Spe	PPV	NPV	D Accuracy	DO	LR+	LR-
Score	> 4.7	40	51	16	4	90.9%	76.1%	71.4%	92.7%	82.0%	4.6	3.81	0.12

TP: True positive, FP: False Positive, Sen: Sensitivity, PPV: Positive Predictive Value
TN: True Negative, FN: False Negative, Spe: Specificity, NPV: Negative Predictive Value
D Accuracy: Diagnostic Accuracy / DO: Diagnostic Odds Ratio / LR: Likelihood Ratio

Discussion

Using logistic regression analysis, we developed a simple scoring system to predict malignant thyroid nodules by six US features of the nodule. The scoring system had an accuracy of 82.0% and is shown to be 90.0% sensitive and 76.1% specific. Hypoechogenicity has the largest effect size (OR=5.9) and receives the highest score on our sheet. To pass the cut-off (achieving 4.7 points out of 8.4) one must fulfill at least 4 criteria, and it's not likely for a patient having 3 features to come up with a malignant nodule. In the other hand, everyone who fulfills five of the criteria should be considered to have a malignant thyroid nodule. This simple scoring system has an easy and intuitive implication for rapid triage of patients according to their US features.

In our study group, 45 out of 114 (39.5%) patients had malignant pathologies. This relative frequency of the malignant thyroid nodules should be explained by the fact that our Endocrine Surgery center is one of the core units

of Iran's endocrine surgery and has nation-wide referral patients. The mean age of our referred patients was 43.13±13.0 years. Like previous reports, there was no significant difference between the ages of the groups with or without malignant pathologies (3,4). Even though 78.9% of our patients were women, the frequency of malignant pathologies was similar among both genders. Previous studies had also admitted higher prevalence of thyroid nodules in women despite similar overall rates of malignancies (3-5). Regarding the FNA results, 38.6% were benign, 25.4% were malignant, and 36% were indeterminate. Among indeterminate FNA biopsies, 39.0% were malignant. Other studies have reported an around 20% frequency of malignancy among indeterminate cases (3,4), present results indicated an almost twice (39.0%) risk of malignancy in indeterminate FNA biopsies. One possible explanation can be the fact that the patients with higher clinical suspicion are usually referred to a tertiary center like our Endocrine Surgery center. In the other hand, low accuracy of FNA biopsies in Iran can take part as well. Without utilization of US guided FNA, the accuracy of FNA can be as low as 70.0% in Iranian studies (22).

It is proposed that TSH level can be associated with nodule size, which is in correlation with the risk of malignancy (3). Our study failed to show such relationship. Possible confounders of the TSH levels may take part in this association. Like previous studies, Oval and elongated nodules were associated with higher risk of malignancies in our patients (13,17). In general, correlation of US features was in concordance with other studies (17,18,20). Reports have shown larger nodules to bear a higher risk of malignancy, especially when larger than 40mm (4, 23-29). However, our results have shown an inverse relation of size to the risk of malignancy. In our model, the nodule size was selected as lower than 36 mm. The number 36 was the median in our data, and it seems a good choice. Also, TSH more than or equal to 1.26 was an indicator of malignancy. The number 1.26 was also the median and more than this cut off shows the relative hypothyroidism (Table 5). We observed that hypoechogenicity was the most important feature in predicting the malignancy of a nodule and after that, the thick or incomplete halo was important especially in females.

We state that the AUC values may be biased high because they are computed on the same data used to construct the model. Resampling methods can be used to yield estimates with less bias. The diagnostic performance metrics based on the optimal cut-off also suffer from an optimistic bias because they are computed on the same data used to select the cut-off. These are the limitation of our study, and the results need to be validated on a large independent dataset. One important finding in our study was the low sensitivity of FNA for thyroid nodule (48.9). This may be due to multiple reasons. First, this study was performed in the endocrine surgery center in Iran, and the cases may be a bit more difficult to diagnose completely before the operation, and this was the cause for referring to our center. Secondly, which seems more important, is that in Iran, FNA is not routinely performed under the guide of ultrasonography. We suggest conducting another study for determining the exact and correct sensitivity and specificity of FNA for thyroid nodules in Iran. The radiologist should be encouraged to transfer their knowledge in FNA of thyroid nodule to endocrinologist.

Differentiating malignant STNs was the goal of many recent studies. Various additional methods including Doppler US and elastography have been evaluated for this purpose (28-30). STNs are frequent in general population, and the random US of them may declare nothing more than a benign nodule (31,32). A clinical decision bears an interdisciplinary collaboration (5). Considering low rates of malignancy even in inadequate FNAs (33,34), US can play an important role in clarifying the clinical decision (34,35). This is the first US based simple scoring system which can predict the chance of malignancy in a thyroid nodule. Our scoring system has shown the high sensitivity of 90.9%. The clinical implication of such sensitive models can possibly reduce unnecessary surgery (35); knowing that reports indicate high prevalence of adverse outcomes including laryngeal nerve injury especially in total thyroidectomy (4). Moreover, a sensitive model can also be used for early detection of the malignant lesions as well (31). Further studies are needed to determine whether utilizing such scoring system would enhance early detection of malignant nodules and improve the outcome or not. Finally, we recommend using this simple scoring system, which we called it Hedayat model, especially in settings with lower accuracy of FNA biopsies. In conclusion, the two important findings of this study are: 1) thyroid FNA biopsies in Iran should be done under ultrasonography guide and 2) if a result of ultrasonography of thyroid is a Hypoechoic nodule, there is high suspicion for malignancy.

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