Reliability of Fine-Needle Aspiration and Ultrasound-Based Characteristics of Thyroid Nodules for Diagnosing Malignancy in Iranian Patients

Asghar Akhavan, M.D.,[1] Seyyed Mehrdad Jafari, M.D.,[2] Mohammad Hossein Khosravi, M.D.,[2]* Hojjatollah Khajehpour, M.D.,[3] and Hamidreza Karimi-Sari, M.D.[2]

Background: *Sonography and fine-needle aspiration biopsy (FNA-B) have been approved as method of choice in diagnosis of malignant thyroid nodules. Unnecessary FNA-B not only is invasive and costly but also results in second biopsy or unnecessary surgery. So we aimed to determine the specificity and sensitivity of sonography and FNA-B, without sonography guidance, in diagnosis of malignant and benign thyroid nodules.*

Methods: *Patients with thyroid nodule referred to Baqiyatallah Hospital in 2014–2015 and candidates for surgical nodule resection were selected using simple random sampling method. Patients were evaluated by sonography and FNA. Sonographic characteristics of nodule were described. All patients underwent surgical resection and gross samples were sent for pathological evaluation, the gold standard for measuring the specificity and sensitivity of sonographic findings and FNA in diagnosis of malignant nodules.*

Results: *Ninety patients with the mean age of 45.95 ± 12.3 years were evaluated (17 male and 73 female). Comparing the patients with correct and incorrect sonography-based diagnosis showed significant differences in nodule's width, area, calcification, border, and cervical lymphadenopathy (*$P < 0.05$*). Comparing the patients with correct and incorrect FNA-based diagnosis showed significant differences in patients' age and tall-shape nodule (*$P < 0.05$*). The diagnosis of sonographist had 56.25% sensitivity and 95.9% specificity, and the FNA-based diagnosis had 81.25% sensitivity and 93.7% specificity.*

Conclusion: *Among sonography findings, width and area of nodule, calcification, and nodule border have significant effect on malignancy diagnosis. Also FNA is necessary in nodules with calcification, border irregularity, and less width and area, especially in younger patients.* Diagn. Cytopathol. 2016;44:269–273.

Key Words: ultrasonography; fine-needle aspiration; sensitivity; specificity; thyroid nodule; thyroid cancer; ultrasound characteristics

Thyroid nodules are one of the most common clinical problems of thyroid gland.[1,2] Palpable thyroid nodules have a prevalence of 4–7% (3–5) and nodules >1 cm have been found in 50–60% of autopsies of individuals without clinical thyroid disease.[4,5] Sonography, which is more sensitive than palpation, shows a prevalence of 67% for thyroid nodules in general population. Most of the thyroid nodules are symptomless and malignant transformation occurs in 5–10% of them which depends on age, gender, X-ray exposure history, and family history of thyroid cancer.[2,3,5]

Sonography and fine-needle aspiration biopsy (FNA-B) under sonography guidance have been approved as method of choice in differentiation of benign and malignant thyroid

[1]Department of Otorhinolaryngology, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran
[2]Students' Research Committee, Baqiyatallah University of Medical Sciences, Tehran, Iran
[3]Department of Radiology, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran
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*Correspondence to: Mohammad Hossein Khosravi, Baqiyatallah Hospital, Mollasadra st., Vanaq sq., Tehran, Iran. E-mail: dr.mhkhosravi@gmail.com
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nodules.[4–6] Sonography can detect nonpalpable nodules as well as central and lateral lymphadenopathies.[5] FNA-B is being used as the most reliable and gold standard diagnostic method, with 65–98% sensitivity and 72–98% specificity, for reducing unnecessary thyroid nodule surgery resection.[2,3] Unnecessary FNA-B not only is invasive and costly but also results in second biopsy or unnecessary surgery because up to one-third of the FNA-B are not diagnostic and require open biopsy.[1]

Applying an alternative method for FNA-B, which is both less expensive and more accurate, results in less use of other diagnostic methods such as CT scan and MRI and consequent lower diagnostic expenses. It can also prevent unnecessary FNA-B in patients with thyroid nodule, especially in endemic regions. Previous studies have shown that specific sonography findings can accurately differentiate benign and malignant nodules.[7] So using sonography and its specific criteria in determining malignant nodules help us refer only patients suspicious for malignancy for more accurate assessment by FNA-B.

In this study, we aimed to determine the reliability of ultrasound-based characteristics of thyroid nodules and FNA-B, without sonography guidance, in diagnosis of malignant thyroid nodules in comparison with pathology assessment as a gold standard.

Materials and Methods

This prospective study was approved by Ethics Committee of Baqiyatallah University of Medical Sciences (No: IR.BMSU.REC.1394.72). Patients with thyroid nodule referred to otorhinolaryngology clinic of Baqiyatallah Hospital (a governmental hospital in Tehran, Iran) in 2014–2015 and candidates for surgical nodule resection were considered as sampling frame. Simple random sampling method by a computer-generated randomization list was used for selecting 90 patients. Patients with known thyroid autoimmune diseases (Grave's disease, Hashimoto, and other thyroiditis), age below 15 years, and any contraindication for anesthesia, surgery, and surgical resection were excluded from the study. After signing a written informed consent, all included patients were evaluated by a unique sonographist and sonographic characteristics of nodule were described. The sonographic characteristics were length (mm), width (mm), area (mm^2), tall shape, having microcalcifications, having solid part, irregular margins, echogenicity, vascularity, and extracapsular extention. The sonographic characteristics that are associated with increased risk of malignancy are hypoechoic, microcalcifications, "Twinkling" on B-flow imaging, central vascularity, irregular margins, incomplete halo, nodule is taller than wide, and documented enlargement of a nodule.[8] The radiologist also considered the nodule benign and malignant by sonographic characteristics. Then FNA was done and reported for all patients by an expert pathologist. All FNAs were done without sonography guide and it was repeated in 13 patients because of inadequate samples.

The surgical resection was done for all patients and gross samples were sent for pathological evaluation. The gross pathology was considered as gold standard for measuring the specificity and sensitivity of sonographic findings and FNA in diagnosis of malignant nodules.

Statistical Analysis

Data were analyzed using statistical package for social sciences (SPSS) software version 21. Independent sample *t* test was used for comparing quantitative variables with normal distribution (approved by one-sample K–S test), and Mann–Whitney test for variables without normal distribution. Chi^2 and Fisher exact tests were used for comparing qualitative variables between the subgroups. Specificity and sensitivity of sonographic findings and FNA were measured compared to the gold standard (pathology). The age and sex adjusted logistic regression with forward Wald method was used for evaluating correlation of sonographic findings with malignancy.

Results

Total of 90 patients with the mean age of 45.95 ± 12.3 years were evaluated (17 male and 73 female patients). The mean nodule length, width, and area were 30.12 ± 14.7 mm, 21.93 ± 9.8 mm, and 771.9 ± 696 mm^2, respectively, with no significant differences in male and female patients. The single nodule was significantly more in male patients ($P = 0.014$). The nodule had microcalcification in 39 patients, irregular border in 9 patients, solid part in 72 patients, hypervascularity in 21 patients, tall shape in 3 patients, and cervical lymphadenopathy in 5 patients. There were no significant differences in nodule characteristics between the male and female patients (Table I).

The nodules were malignant in 12 patients and benign in 78 patients based on the diagnosis of sonographist. These nodules were malignant in 15 patients and benign in 75 patients based on the diagnosis using FNA. The final pathology report was malignant in 16 patients and benign in 74 patients. Compared to the gold standard (pathology), the diagnosis of sonographist had 56.25% sensitivity and 95.9% specificity, and the FNA-based diagnosis had 81.25% sensitivity and 93.7% specificity (Table II).

The positive predictive value and negative predictive value of sonography in diagnosis of malignancy were 75% and 91%, respectively. Also the positive predictive value and negative predictive value of FNA in diagnosis of malignancy were 86.67% and 96%, respectively.

The sonography-based diagnosis was correct in 80 patients and incorrect in 10 patients. Comparing the patients with correct and incorrect sonography-based diagnosis showed significant differences in nodule's width,

area, calcification, border, and cervical lymphadenopathy ($P < 0.05$; Table III)

The FNA-based diagnosis was correct in 85 patients and incorrect in 5 patients. Comparing the patients with correct and incorrect FNA-based diagnosis showed significant differences in patients' age and tall shape nodule ($P < 0.05$; Table III).

Comparing the patients with benign and malignant nodules showed significant differences in nodule's microcalcification, irregular border, and hypervascularity ($P < 0.05$; Table IV).

The sonographic findings had significant correlation with malignancy in the age- and sex-justified regression model ($R^2 = 0.374$, $P < 0.001$).

Table I. Comparison of Patients' Age and Sonographic Characteristics of Nodule between the Male and Female Patients

	Male (N = *17*)	*Female* (N = *73*)	P *value*	*Total* (N = *90*)
Age, year	49.8 ± 15.1	45.2 ± 12.9	0.220	45.95 ± 12.3
Nodule size				
Length, mm	27.4 ± 14.0	30.86 ± 14.9	0.385	30.12 ±14.7
Width, mm	20.2 ± 9.7	22.4 ± 9.8	0.409	21.93 ± 9.8
Area, mm^2	643.9 ± 537	805.9 ± 733	0.397	771.9 ± 696
Single nodule	3 (17.6)	38 (52.1)	0.014	41 (45.6)
Multiple nodules	14 (82.4)	35 (47.9)		49 (54.4)
Microcalcification	8 (47.1)	31 (42.5)	0.731	39 (43.3)
Irregular border	1 (5.9)	8 (11)	0.461	9 (10)
Solid	15 (88.2)	57 (78.1)	0.283	72 (80)
Hypervascularity	6 (35.3)	15 (20.5)	0.164	21 (23.3)
Tall shape	1 (5.9)	2 (2.7)	0.471	3 (3.3)
Lymphadenopathy	0 (0)	5 (6.8)	0.579	5 (5.6)

Table II. Comparing the Sonography and FNA-Based diagnosis with the Gold Standard (Final Pathology Report)

	Pathology (gold standard)		
	Malignant (N = *16*)	*Benign* (N = *74*)	*Total*
Sonography			
Malignant	9 (10)	3 (3.3)	12
Benign	7 (7.8)	71 (78.9)	78
OR (95% CI)	8.357 (3.84–18.21)		90
FNA			
Malignant	13 (14.4)	2 (2.2)	15
Benign	3 (3.3)	72 (80)	75
OR (95% CI)	21.67 (7.03–66.8)		90

Discussion

This study is the first one comparing the accuracy of sonography and FNA, based on diagnostic gold standard, in diagnosing thyroid malignancies in Iran. We found that nodule area is the most and nodule calcification is the least related factor to thyroid nodule malignancy. Also irregular border had the highest and solid view had the lowest association with correct diagnosis by sonography. Calcification, border irregularity, and hypervascularity reported by sonography were suggestive of malignancy.

In this study, prevalence of malignancy was higher in comparison with the previous studies which may be a result of simultaneous assess of patients with lymphadenopathy.[9,10]

In a retrospective study, Ucler et al. concluded that nodule size has no effect on diagnostic power of FNA which is in concordance with this study.[10] They only assessed the nodule size and suggested the consideration of all clinical and paraclinical findings for diagnosis of thyroid malignancy and reducing false-negative cases of FNA.

In another similar study by Inci et al., age, nodule heterogenicity, nodule size >3 cm, and needle size were effective factors on inadequate sample of FNA.[9] In this study, age had a significant effect on FNA result, while nodule size and echogenicity were not effective factors. Inci et al. reported 31.9% of FNA samples to be inadequate and in this study, FNA was repeated in 13 (14.4%) patients because of inadequate samples.

In agreement with this study, Samulski et al. reported that sonography findings (nodule size, echogenicity, and vascularity) have no significant effect on malignancy diagnosis.[11] Since this was a retrospective study,

Table III. Comparing the Patients with Correct and Incorrect Diagnosis Based on Sonography and FNA

	Sonography diagnosis			*FNA diagnosis*		
	Correct (N = *80*)	*Incorrect* (N = *10*)	P *value*	*Correct* (N = *85*)	*Incorrect* (N = *5*)	P *value*
Age, year	46.5 ± 12.4	41.7 ± 19.4	0.285	46.8 ± 12.9	32 ± 14.1	0.015
Male	16 (20)	1 (10)	0.397	16 (18.8)	1 (20)	0.658
Nodule size						
Length, mm	30.5 ± 15.2	27.3 ± 10.8	0.416	30.3 ± 14.8	27.8 ± 13.9	0.718
Width, mm	22.5 ± 10.1	17.9 ± 5.2	0.036	22.1 ± 9.9	19 ± 6.1	0.337
Area, mm^2	806.1 ± 703	529 ± 308	0.044	783.9 ± 712	591 ± 392	0.358
Single nodule	35 (43.8)	6 (60)	0.262	37 (43.5)	4 (80)	0.173
Multiple nodules	45 (56.3)	4 (40)		48 (56.5)	1 (20)	
Microcalcification	31 (38.8)	8 (80)	0.016	36 (42.4)	3 (60)	0.649
Irregular border	6 (7.1)	3 (30)	0.025	8 (9.4)	1 (20)	0.417
Solid	63 (78.8)	9 (90)	0.362	68 (80)	4 (80)	NS
Hyper-vascularity	18 (22.5)	3 (30)	0.426	19 (22.4)	2 (40)	0.331
Tall shape	2 (2.5)	1 (10)	0.301	2 (2.4)	1 (20)	0.033
Lymphadenopathy	5 (6.3)	0 (0)	0.031	5 (5.9)	0 (0)	0.557

Table IV. Comparison of Patients with Malignant and Benign Nodules

	Pathology		
	*Malignant (*N = *16)*	*Benign (*N = *74)*	P *value*
Age, year	38.93 ± 18.59	47.42 ± 11.55	0.024
Male	3 (18.8)	3 (18.9)	0.647
Nodule size			
Length, mm	27.63 ± 13.9	30.74 ± 14.9	0.451
Width, mm	19.69 ± 9.05	22.48 ± 9.9	0.308
Area, mm^2	640.4 ± 575	804.3 ± 724	0.403
Single nodule	8 (50)	33 (44.6)	0.694
Multiple nodules	8 (50)	41 (55.4)	
Microcalcification	12 (75)	27 (36.5)	0.005
Irregular border	4 (25)	5 (6.8)	0.027
Solid	14 (87.5)	58 (78.4)	0.408
Hypervascularity	9 (56.2)	12 (16.2)	0.002
Tall shape	1 (6.2)	2 (2.7)	0.448
Lymphadenopathy	2 (12.5)	3 (4.1)	0.215

Samulski et al. did not evaluate length, width, and area of nodule as well as calcification, border irregularity, Tall shape, and lymphadenopathy which is an indicator of better design of this study. Also in contrast with their study, all the sonographies were done by a single radiologist and in a single center in our study. Samulski et al. have reported sonography findings to be unreliable in diagnosis of thyroid nodule malignancy which is not in agreement with this study.

In accordance with this study, Tutuncu et al. have mentioned nodule width and calcification to be effective and echogenicity and solid shape not effective in diagnosis of thyroid nodule malignancy.[12] In Tutuncu et al.'s study, patients were candidates for total thyroidectomy. They recommended total thyroidectomy for hyperecho nodules and those with calcification and size >4 cm. The authors have suggested further studies for determining malignancy-predicting sonography findings.

In another retrospective study by Shin et al., nodule size, border, and microcalcification have been reported to be effective in diagnosis of malignancy which is in accordance with this study, while the results were different for solid shape and echogenicity.[13]

This study had some limitations such as low sample volume, not excluding patients with gross lymphadenopathy and not considering the effect of clinical findings on the results of this study. On the other hand, there were some strengths for this study such as the prospective design which eliminated the missing of data. Sonography, FNA, and pathology results were evaluated simultaneously in this study and pathology was considered as reference standard like Lee et al. study.[14] Since individual skills could be a confounder, all the sonographies and pathology reports were done by a single radiologist and pathologist. Also multivariate analysis was done for evaluating diagnostic power of sonography and FNA.

In conclusion, we found that sonography is able to diagnose thyroid nodule malignancy with a 56.2% sensitivity and 95.9% specificity. Among sonography findings, width and area of nodule, calcification, and nodule border have significant effect on malignancy diagnose; however, other clinical and paraclinical findings should be used because of high false-negative rates, especially in younger patients and nodules with calcification, border irregularity, and less width and area. On the other hand, sonography findings are more reliable in nodules with more width and area, those without calcification, regular borders and associated with lymphadenopathy.

Also FNA had an 81.25% sensitivity and 97.3% specificity in this study. Age and Tall shape in sonography were effective on correct diagnosis of malignancy by FNA. So because of false-negative rate (3.3%), younger patients and those with Tall shape in sonography are recommended to have more accurate diagnostic evaluations. While in older patients and those without Tall shape in sonography, FNA results are more reliable.

Regarding our results, it is recommended that nodules with low width and area, calcification, and irregular borders, especially in younger patients, to be evaluated by FNA for diagnosing malignancy. Also we suggest that FNA be done under sonography guidance in younger patients and those with Tall shape in sonography.

Further studies are suggested with a larger sample volume and prospective study design. We also recommend that future studies consider gross lymphadenopathy as an exclusion criterion.

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