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The Effect of Thyroid Nodule Size and Characteristics on the Accuracy of Fine-Needle Aspiration Biopsy and the Risk of Malignancy

Tiroid Nodül Boyutu Ve Özelliklerinin İnce İğne Aspirasyon Biyopsisinin Doğruluğu Ve Malignite Riski Üzerine Etkisi

Mehmet Alperen Avcı[1] | Can Akgün[1] | Mustafa Gün[1] | Selim Tamam[2] | Meltem Türk[3]

[1]Samsun University, Training and Research Hospital, Department of General Surgery, Samsun, Türkiye
[2]Ankara University, Department of Oncological Surgery, Ankara, Türkiye
[3]Ordu University Training and Research Hospital, Department of Pathology, Ordu, Türkiye

Sorumlu Yazar | Correspondence Author
Mehmet Alperen Avcı
dr.maavci@gmail.com
Address for Correspondence: Kışla Mah. Barış Bulv No:199 Samsun University Training and Research Hospital, Samsun, Türkiye.

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The Effect of Thyroid Nodule Size and Characteristics on the Accuracy of Fine-Needle Aspiration Biopsy and the Risk of Malignancy

ABSTRACT

Objective: Ultrasound evaluation of nodule characteristics and FNAB is a simple, cost-effective method. However, its reliability in large nodules is controversial. This study aims to examine the impact of thyroid nodule size and characteristics on malignancy risk and FNAB accuracy as evaluated by ultrasound.

Material and Method: IThis retrospective study included 522 patients who underwent thyroidectomy between January 1, 2020, and January 1, 2024. The data included the patients' age, gender, preoperative thyroid ultrasound findings, preoperative FNAB pathology findings, operation notes, and postoperative pathology results colleected from hospital archives. Kruskal-Wallis Variance Analysis, ROC (Receiver Operating Characteristics) curve analysis, Bonferroni Corrected Mann-Whitney U Test, Chi-Square Tests, were used at statistical analysis.

Results: The median age was 49.45 years. The threshold value for nodule size in the X plane was 27 mm (*p<0.001*) when comparing preoperative FNAB with postoperative pathology. For nodules with X ≤ 27 mm, FNAB sensitivity was 0.842, the false predictive value was 0.636, and the false negative rate was 0.157. In this group, the mean age, nodule size, and two-dimensional area (X*Y) were significantly higher nodules, while isoechoic features were more common in benign nodules.

Conclusion: It was found that the risk of malignancy decreases with increasing age, nodule size, and two-dimensional area; the risk of malignancy increases with hypoechoic and microcalcification findings; and FNAB sensitivity decreases and the false negative value increases in nodules >27 mm.

Keywords: Fine-Needle aspiration biopsy, thyroid nodule, ROC analysis, ultrasound.

ÖZET

Amaç: Ultrasonografi, tiroid nodüllerinin özelliklerinin incelenmesi ve ince iğne aspirasyon biyopsisinin (İİAB) alınması noktasında kolay, avantajlı ve güvenlik-maliyet etkin bir yöntemdir. Bununla beraber, büyük nodüllerde güvenilirliği tartışmalıdır. Bu çalışmada amacımız ultrasondaki tiroid nodül boyutu ve özelliklerinin malignite riski üzerine ve ince iğne aspirasyon biyopsisinin doğruluğu üzerine etkisini incelemektir.

Gereç ve Yöntem: Çalışmaya, retrospektif olarak 01.01.2020 ile 01.01.2024 tarihleri arasında tiroidektomi operasyonu geçiren 522 hasta dahil edilmiştir. Yaş, cinsiyet, preoperatif ultrason bulguları, preoperatif İİAB sonuçları, ameliyat notları ve postoperatif patoloji bulguları arşivden araştırılmıştır. İstatistiksel analizde Kruskal-Wallis Varyans Analizi, ROC (Receiver Operating Characteristics) eğrisi analizi, Bonferroni Düzeltmeli Mann-Whitney U Testi ve Ki-Kare Testleri kullanılmıştır.

Bulgular: Medyan yaş 49,45 olarak bulundu. Preoperatif İİAB ile postoperatif patoloji uyumu incelendiğinde; nodülün X düzlemdeki boyutu için eşik değer 27 mm olarak bulundu (*p<0.001*). X ≤ 27 mm olan nodüllerde İİAB nin Sensivite 0.842, Yanlış prediktif değer 0.636 ve Yanlış Negatif Oran (FNR) 0.157 daha anlamlı bulundu. X ≤ 27 mm boyutta; yaş ortalaması, nodül X boyutu ve iki boyutlu alan (X*Y) benign grupta (*p<0.001*); X ≤ 27 mm ve X tüm boyutta hipoekoik ve mikrokalsifikasyon özelliği malign grupta, İzoekoik görünüm benign grupta anlamlı yüksek bulundu.

Sonuç: Yaş, nodül boyutu ve iki boyutlu alan artışıyla malignite riskinin azaldığı; hipoekojenite ve mikrokalsifikasyon bulgusunun malignite riskini arttırdığı; >27 mm nodüllerde İİAB nin sensivitesinin azaldığı ve false negatif değerinin arttığı görüldü.

Anahtar Sözcükler: İnce iğne aspirasyon biyopsisi, tiroid nodülü, ROC analizi, ultrasonografi.

Introduction

Thyroid nodules are a very commonly detected clinical condition (1). Before the advancement of imaging techniques, only 5-10% of patients had thyroid nodules detected by palpation (2). However, nowadays, thyroid nodules can be detected in 19-68% of randomly selected individuals via ultrasound (3). It is crucial for the clinician to accurately predict the benign or malignant nature of thyroid nodules to avoid unnecessary thyroidectomy and potential complications (4). Ultrasound is an easy method for obtaining nodule characteristics and performing fine-needle aspiration biopsy (FNAB), and it is useful in making surgical decisions for malignant or benign cases or follow up them according to the 2017 Bethesda thyroid cytopathology reporting system criteria (1-3). Although there are limited and suspicious findings depending on the radiologist; the absence of microcalcifications, the presence of regular borders and a halo, and iso-hyperechogenicity in nodule ultrasound features suggest benign nodules. FNAB is considered the gold standard diagnostic tool for thyroid nodules due to its simplicity, advantages, safety-cost effectiveness, and diagnostic specificity (5-6). Although, there are debates regarding its reliability in large (>30-40 mm) nodules. Some studies have reported that nodules larger than 40 mm have high false-negative rates of up to 30% in cytology (7-8), while other studies have suggested that nodule size does not adversely affect the reliability of FNAB (9-10). Our aim is investigate the effect of thyroid nodule size and characteristics on malignancy risk and the accuracy of fine-needle aspiration biopsy as assessed by ultrasound.

Material and Method

This retrospective study included 522 patients who underwent elective thyroid lobectomy or total thyroidectomy between January 1, 2020, and January 1, 2024, at the General Surgery Clinic of Samsun University Training and Research Hospital. Between 2018 and 2024, all patients aged 18 to 90 years who presented with thyroid compression symptoms (such as respiratory issues, swallowing difficulties, and voice problems) and were indicated for thyroidectomy based on fine-needle aspiration biopsy (FNAB) results were included in the study. Patients with a history of thyroid surgery, a history of malignancy in the neck region, those who presented with imaging and FNAB cytology results from external centers, patients with non-diagnostic FNAB pathology results, and individuals under the age of 18 were excluded from the study. Retrospective data collected included age, gender, preoperative thyroid ultrasound findings (lobe with the largest nodule, X size of the largest nodule, two-dimensional estimated nodule area (X*Y), nodule characteristics (hypoechoic, hyperechoic, isoechoic, halo finding, microcalcification, and macrocalcification findings), preoperative FNAB pathology findings, operation notes, and postoperative pathology results. The preoperative FNAB and postoperative pathology results were categorized using the Bethesda scoring system (11). The preoperative FNAB pathology results were compared with the postoperative pathology results to investigate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false positive rate (FPR), and false negative rate (FNR) of FNAB and the thyroid ultrasound nodule findings with postoperative pathology results. When examining the concordance between preoperative and postoperative pathology, preoperative FNAB pathology results were categorized as Bethesda 2 (Group 1), Bethesda 3 and 4 (Group 2), and Bethesda 5 and 6 (Group 3); postoperative pathology results were categorized as Bethesda 2 (Group 1), Bethesda 4 (Group 2), and Bethesda 6 (Group 3). The study was approved by the Ethics Committee of of Samsun University Clinical Research with the protocol number GOKAEK 2024/4/14 on February 14, 2024. The study was conducted in accordance with research and ethical principles. Descriptive statistics were performed to provide information about the general characteristics of the study groups. Quantitative data were described using mean and standard deviation (x ± sd) as well as minimum and maximum values; qualitative data were described using number (n) and percentage (%). Differences between groups for quantitative variables were assessed using the Kruskal-Wallis Variance Analysis for independent groups. Bonferroni Corrected Mann-Whitney U Test was used for pairwise comparisons. Differences between groups for qualitative variables were assessed using Chi-Square Tests. Marginal Homogeneity Test was used for dependent qualitative groups. ROC (Receiver Operating Characteristics) curve analysis was applied to determine cut-off values for nodule size based on preoperative and postoperative pathology concordance, and the area under the ROC curve (AUC) was evaluated. *P values less than 0.05* were considered statistically significant. Calculations were performed using statistical software (IBM SPSS Statistics 22, SPSS Inc., an IBM Co., Somers, NY).

Results

Between January 1, 2020, and January 1, 2024, there were 653 patients aged 18-90 who underwent thyroid lobectomy and total thyroidectomy due to thyroidectomy indication. Of these patients, 58 were excluded due to presenting with fine-needle aspiration biopsy (FNAB) and thyroid ultrasound results from different centers; 73 were excluded due to a history of previous thyroid surgery, history of neck malignancy, and nondiagnostic FNAB pathology results. Therefore, a total of 131 patients were excluded, and 522 patients were included in the study (Figure I). Among these 522 patients, 411 were female and 111 were male. The median age of the patients was found to be 49.45 years. A total thyroidectomy was performed on 430 patients, and a thyroid lobectomy was performed on 92 patients. When examining the distribution of qualitative values, the largest nodule was seen in the right lobe in 52.1% of the cases in preoperative ultrasound. In the ultrasound examination of nodule characteristics, 54% were hypoechoic in echogenicity; in the examination of calcification and halo findings, 14.4% had a halo finding, 13.8% had macrocalcification, and 12.2% had microcalcification. A total of 142 patients underwent thyroidectomy due to compression findings without preoperative fine-needle aspiration biopsy. Among the patients who underwent FNAB, the results were as follows: 116 patients (Bethesda 3) AUS/FLUS, 92 patients (Bethesda 2) Benign, 78 patients (Bethesda 4) Suspicious for Follicular Neoplasm, 39 patients (Bethesda 5) Suspicious for Malignancy, and 54 patients (Bethesda 6) Malignant. In the postoperative pathology examination, 261 patients were evaluated as Bethesda 2 Benign, 232 patients as Bethesda 6 Papillary Carcinoma, and 29 patients as Bethesda 4 Follicular Neoplasm (Table I). In the analysis of thyroid nodule sizes, the mean size in the X plane was 32.63 (3-89) mm, the mean size in the Y plane was 20.86 (0.9-79) mm, and the mean two-dimensional estimated area (X*Y) was 850.37 (6-6478) mm^2 (Table II). When examining the concordance between preoperative FNAB pathology Bethesda results and postoperative pathology Bethesda results, the ROC analysis for the nodule size in the X plane indicated a threshold value of 27 mm (*p<0.001*) (Figure II).

Table I Distribution of Qualitative Characteristics (n=522)

		n	%
Gender	Male	111	21.3
	Female	411	78.7
Preoperative Imaging	Right	272	52.1
	Left	217	41.6
	Isthmus	33	6.3
Ultrasound nodule characteristics	Hypoechoic	282	54.0
	Hyperechoic	102	19.5
	Isoechoic	138	26.4
Ultrasound nodule characteristics 2	None	297	56.9
	Halo Sign	75	14.4
	Microcalcification	63	12.1
	Macrocalcification	72	13.8
	Halo Sign- Microcalcification	7	1.3
	Halo Sign- Macrocalcification	3	0.6
	Microcalcification - Macrocalcification	5	1.0
Preoperative FNAB Pathology	None	142	27.20
	(Bethesda 2) Benign	93	17.81
	(Bethesda 3) AUS/FLUS	116	22.22
	(Bethesda 4) Suspicious for Follicular Neoplasm	78	14.95
	(Bethesda 5) Suspicious for Malignancy	39	7.48
	(Bethesda 6) Malignant	28	5.36
	(Bethesda 6) Malignant Papillary Carcinoma	26	4.98
Surgery	Thyroidectomy (Unilateral)	92	17.6
	Thyroidectomy (Bilateral)	430	82.4
Postoperative Pathology	(Bethesda 2) Benign	261	50.0
	(Bethesda 4) Follicular Neoplasm	29	5.6
	(Bethesda 6) Malignant Papillary Carcinoma	232	44.4

In the statistical analysis of the concordance between preoperative FNAB Bethesda score and postoperative pathology Bethesda score based on nodule size; no statistical difference was observed in the concordance between preoperative and postoperative pathology for nodules with X ≤ 27 mm, while a statistically significant difference was found for nodules with X > 27 mm and for all nodules (*p<0.001*) (Table III). When examining the specificity, sensitivity, predictive, and proportional values of FNAB based on nodule size; for nodules with X ≤ 27 mm, sensitivity was highest at 0.842, with a positive predictive value (PPV) of 0.888 and a negative predictive value (NPV) of 0.275. The false predictive value was 0.636, and the false negative rate (FNR) was lowest at 0.157 (Table IV).

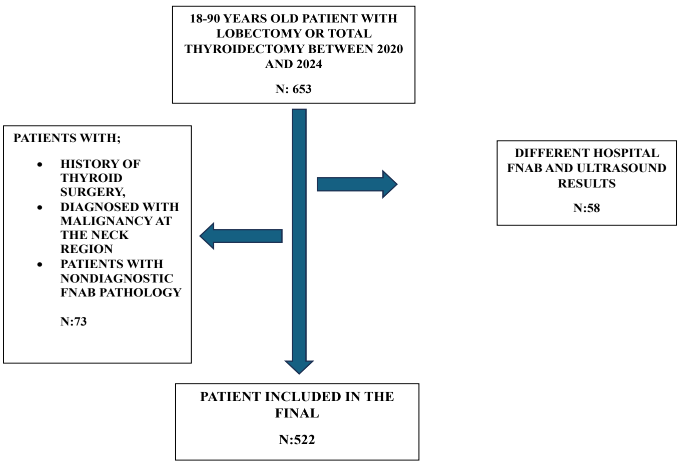


Figure I Table of included and excluded patients

Table II Distribution of Quantitative Values (n=522)

Measurement	Mean	SD	Min	Max
Age	49.45	12.54	18.00	87.00
Nodule Size X (mm)	32.63	17.72	3.00	89.00
Nodule Size Y (mm)	20.86	11.77	0.90	79.00
Nodule Two- Dimensional Area (mm^2)	850.37	864.03	6.00	6478.00

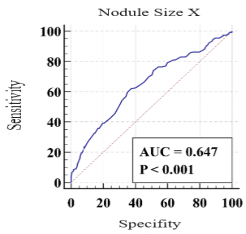
In the statistical analysis of quantitative measurements based on postoperative pathology Bethesda scoring; for patients with nodule size X ≤ 27 mm, the mean age, nodule X size, and two-dimensional estimated area (XY) in the Bethesda 2 Benign group were found to be statistically significantly higher compared to the Bethesda 6 Malignancy group (*p<0.001*). For patients with nodule size X > 27 mm, the two-dimensional area (XY) in the Bethesda 2 Benign group was statistically significantly higher compared to the Bethesda 6 Malignancy group (*p=0.006*). Across all sizes, the mean age in the Bethesda 2 Benign group was statistically significantly higher compared to the Bethesda 4 Follicular Neoplasm group (*p=0.006*). Additionally, the nodule X size and two-dimensional estimated area (X*Y) in the Bethesda 2 Benign group were statistically significantly higher compared to the Bethesda 6 Malignancy group (*p<0.001*) (Table V).

Table III Distribution of Qualitative Characteristics (n=522)

Nodule Size X ≤ 27 (n=233) (Bethesda 2)		Post Operative Pathology			*p*
		(Bethesda 4)	(Bethesda 6)		
Preop FNAB Pathology	(Bethesda 2)	21 (63.6)	-	12 (36.4)	0.226
	(Bethesda 3 ve 4)	71 (55.5)	11 (8.6)	46 (35.9)	
	(Bethesda 5 ve 6)	8 (11.1)	-	64 (88.9)	
Nodule Size X> 27 (n=289) (Bethesda 2)		Postop Pathology			*p*
		(Bethesda 4)	(Bethesda 6)		
Preop FNAB Pathology	None	84 (59.2)	12 (8.5)	46 (32.4)	**<0.001***
	(Bethesda 2)	41 (68.3)	1 (1.7)	18 (30.0)	
	(Bethesda 3 ve 4)	31 (47.0)	4 (6.1)	31 (47.0)	
	(Bethesda 5 ve 6)	5 (23.8)	1 (4.8)	15 (71.4)	
All Nodule Size X Values (n=522) (Bethesda 2)		Postop Pathology			*p*
		(Bethesda 4)	(Bethesda 6)		
Preop FNAB Pathology	None	84 (59.2)	12 (8.5)	46 (32.4)	**<0.001***
	(Bethesda 2)	62 (66.7)	1 (1.1)	30 (32.3)	
	(Bethesda 3 ve 4)	102 (52.6)	15 (7.7)	77 (39.7)	
	(Bethesda 5 ve 6)	13 (14.0)	1 (1.1)	79 (84.9)	

Marginal Homogeneity Test
p value is significant at 0.05 level.
(Bethesda 2) Benign (Bethesda 3) AUS/FLUS (Bethesda 4) Suspicious for Follicular Neoplasm (Bethesda 5) Suspicious for Malignancy (Bethesda 6) Malignant

In the statistical analysis of qualitative measurements based on postoperative pathology Bethesda scoring; no statistically significant relationship was found between gender, preoperative ultrasound nodule lobe, and postoperative pathology Bethesda groups for patients with nodule size X ≤ 27 mm, X > 27 mm, and all sizes. For patients with X ≤ 27 mm (*p=0.016*) and all sizes (p<*0.001*), the hypoechoic characteristic of the nodule was found to be statistically significantly higher in the Bethesda 6 Malignant group, while the isoechoic characteristic was found to be statistically significantly higher in the Bethesda 2 Benign group. A statistically significant relationship was found between nodule halo and calcification findings and postoperative pathology Bethesda groups for patients with nodules of all sizes. The nodule halo finding was statistically significantly higher in the Bethesda 4 Follicular Neoplasm group, microcalcification finding was statistically significantly higher in the Bethesda 6 Malignant group, and Halo-Microcalcification finding was statistically significantly higher in the Bethesda 4 Follicular Neoplasm group (*p=0.006*) (Table VI).



Area Under Curve (AUC) for ROC Curve	Value
Area Under Curve (AUC)	0.647
Standard Error	0.0270
95% Confidence Interval	0.604 to 0.688
Z-Statistic	5.437
Significance Level P (Area=0.5)	**<0.001***
Youden index	**Value**
Youden Index J	**0.2469**
Threshold Value	**≤27**
Sensitivity	**62.09**
Specificity	**62.60**

Figure II Preoperative-Postoperative Pathology Concordance Nodule X Dimension Cut-off Value

Table IV Specificity, Sensitivity, Predictive Values, and Proportional Values of Fine Needle Aspiration Biopsy (FNAB) Based on Nodule Size

	Nodule Size X ≤ 27 (n=105)	**Nodule Size X> 27 (n=79)**	**All Nodule Size X (n=184)**
Sensitivity	0.842	0.454	0.724
Specificity	0.724	0.891	0.826
Positive Predictive Value (PPV)	0.888	0.750	0.858
Negative Predictive Value (NPV)	0.636	0.694	0.673
False Positive Rate (FPR)	0.275	0.108	0.173
False Negative Rat (FNR)	0.157	0.545	0.275

Table V Distribution of Quantitative Measurements by Postoperative Pathology Status

		Nodule Size X ≤ 27 (n=233)					**Nodule Size X> 27 (n=289)**					**All Nodule Size X Values (n=522)**				
	Groups	**N**	**Mean±SD**	**Min-Max**	***p***	**Post Hoc p**	**N**	**Mean±SD**	**Min-Max**	***p***	**Post Hoc p**	**N**	**Mean±SD**	**Min-Max**	***p***	**Post Hoc p**
Age	(Bethesda 2)	100	52.99±11.40	18.00-75.00		1-2:0.006*	161	49.42±12.90	20.00-87.00			261	50.79+12.45	18.00-87.00		
	(Bethesda 4)	11	41.09±11.13	21.00-58.00	***<0.001***	1-3:0.001*	18	45.39±11.67	29.00-67.00	*0.403*		29	43.76+11.47	21.00-67.00	***0.004***	1-2:0.006*
	(Bethesda 6)	122	47.58±12.52	20.00-82.00			110	49.85±12.56	26.00-81.00			232	48.66+12.56	20.00-82.00		
Nodul Size X (mm)	(Bethesda 2)	100	19.24±5.50	4.00-27.00			161	46.81±14.34	29.00-89.00			261	36.25+17.85	4.00-89.00		
	(Bethesda 4)	11	19.09±5.34	10.00-26.00	***<0.001***	1-3:<0.001*	18	42.72±11.34	30.00-70.00	*0.190*		29	33.76+14.98	10.00-70.0	***<0.001***	1-3:<0.001*
	(Bethesda 6)	122	14.94±6.28	3.00-27.00			110	43.39±11.88	28.00-85.00			232	28.43+17.03	3.00-85.00		
Nodule Two-Dimensional Area (mm²)	(Bethesda 2)	100	270.14±146.25	12.00-675.00			161	1485.53±945.61	150.00-6478.00			261	1019.87+953.35	12.00-6478.0		
	(Bethesda 4)	11	287.27±170.46	100.00-589.00	***<0.001***	1-3:<0.001*	18	1158.39±784.56	400.00-3392.00	***0.003***	1-3:0.006*	29	827.97+754.41	100.0-3392.0	***<0.001***	1-3:<0.001*
	(Bethesda 6)	122	186.88±146.11	6.00-600.00			110	1190.00±743.28	270.00-3850.00			232	662.5+723.77	6.00-3850.0		

Kruskal Wallis Variance Analysis *p value is significant at 0.05 level.* Bonferroni Corrected Mann Whitney U Test was applied for binary comparisons. (Bethesda 2) Benign:1 (Bethesda 4) Follicular Neoplasm:2 (Bethesda 6) Papillary Carcinoma Malignant:3

Table VI Distribution of Qualitative Characteristics by Postoperative Pathology Status

Groups		Nodule Size X ≤ 27 (n=233)			Nodule Size X> 27 (n=289)			All Nodule Size X Values (n=522)		
(Bethesda 2)		Postop Pathology			Postop Pathology			Postop Pathology		
		(Bethesda 4)	(Bethesda 6)	(Bethesda 2)	(Bethesda 4)	(Bethesda 6)	(Bethesda 2)	(Bethesda 4)	(Bethesda 6)	
Gender	Male	23(23.0)	3(27.3)	15(12.3)	33(20.5)	6(33.3)	31(28.2)	56(21.5)	9(31.0)	46(19.8)
	Female	77(77.0)	8(72.7)	107(87.7)	128(79.5)	12(66.7)	79(71.8)	205(78.5)	20(69.0)	186(80.2)
		p: 0.079			*p: 0.226*			*p: 0.378*		
Preop USG Imaging Nodule Lobe	Right	48(48.0)	7(63.6)	62(50.8)	81(50.3)	10(55.6)	64(58.2)	129(49.4)	17(58.6)	126(54.3)
	Left	44(44.0)	4(36.4)	51(41.8)	75(46.6)	7(38.9)	36(32.7)	119(45.6)	11(67.9)	87(37.5)
	Isthmus	8(8.0)	-	9(7.4)	5(3.1)	1(5.6)	10(9.1)	13(5.0)	1(3.4)	19(8.2)
		p: 0.820			*p: 0.088*			*p: 0.263*		
Ultrasound	Hypoechoic	45(45.0) [a]	6(54.5) [ab]	81(66.4) [b]	75(46.6)	10(55.6)	65(59.1)	120(46.0) [a]	16(55.2) [ab]	146(62.9) [b]
	Hyperechoic	19(19.0) [a]	3(27.3) [a]	18(14.8) [a]	33(20.3)	3(16.3)	26(23.6)	52(19.9) [a]	6(20.7) [a]	44(19.0) [a]
	Isoechoic	36(36.0) [a]	2(18.2) [ab]	23(18.9) [b]	53(32.9)	5(27.8)	19(17.3)	89(34.1) [a]	7(24.1) [ab]	42(18.1) [b]
		p: 0.016			*p: 0.074*			***p<0.001***		
Ultrasound	None	57(45.2)	5(4.0)	64(50.8)	103(64.0)	8(44.4)	60(54.5)	160(61.3) [a]	13(44.8) [a]	124(53.4) [a]
	Halo Sign	13(43.3)	3(10.0)	14(46.7)	26(16.1)	6(33.3)	13(11.8)	39(14.9) [a]	9(31.0) [b]	27(11.6) [a]
	Microcalcification	12(31.6)	1(2.6)	25(65.8)	9(5.6)	2(11.1)	14(12.7)	21(8.0) [a]	3(10.3) [ab]	39(16.8) [b]
	Macrocalcification	14(48.3)	1(3.4)	14(48.3)	21(13.0)	1(5.6)	21(19.1)	35(13.4) [a]	2(6.9) [a]	35(15.1) [a]
	Halo Sign- Microcalcification	-	1(25.0)	3(75.0)	1(0.6)	1(25.0)	1(0.9)	1(0.4) [a]	2(6.9) [b]	4(1.7) [ab]
	Halo Sign- Macrocalcification	3(100.0)	-	-	1(0.6)	-	1(0.9)	3(1.1) [a]	- [a]	- [a]
	Microcalcification-Macrocalcification	1(33.3)	-	2(66.7)	-	-	-	2(0.8) [a]	- [a]	3(1.3) [a]
		p: 0.219			*p: 0.072*			***p: 0.006***		

Chi-Square Test *p value is significant at 0.05 level*. Different letters in the same row indicate statistically significant difference (*p<0.05*).

Discussion

The diagnosis and treatment of thyroid nodules remain a significant concern due to controversial outcomes. With technological advancements, the use of ultrasound-guided FNAB has increased, becoming the gold standard in diagnosis (5-6). The sensitivity of FNAB in the literature is reported to be between 65-95% and specificity between 70-100% (12). However, the reliability of FNAB concerning nodule size remains controversial. Although FNAB can accurately detect large thyroid nodules, its limitations in differentiating malignancies persist. It should be noted that the accuracy of FNAB results can be influenced by multifactorial factors such as sample volume adequacy, sampling from the correct location, and correct interpretation of results (10,13). Some studies have shown no significant difference in false negatives, false positives, positive predictive values, and negative predictive values between the groups when the cutoff value for nodule size is set at 4 cm (8,14). Other studies have indicated a high rate of false negatives in nodules larger than 4 cm (13,15-16). Some studies have demonstrated that the false-negative rates for nodules >4 cm range between 7-50% (13,16-19). These findings suggest that relying solely on FNAB results may overlook malignancies and that thyroidectomy may be considered even in cases with benign biopsy results. Some studies have taken a nodule size of 3 cm as the cutoff value and found higher false-negative rates in nodules ≥3 cm compared to those <3 cm (7-8,14,20-22), while others have found low or no differences (15,23,24). In our study, the cutoff value for the concordance of preoperative FNAB pathology results and postoperative pathology results in the ROC analysis for nodule size in the X plane was found to be 27 mm ($p<0.001$). Using this cutoff value, no statistical difference was observed in the concordance between preoperative and postoperative pathology for nodules with X ≤ 27 mm, whereas a statistically significant difference was found for nodules with X > 27 mm and for all nodules ($p<0.001$). In the examination of the specificity, sensitivity, predictive, and proportional values of FNAB based on nodule size; for nodules with X ≤ 27 mm, sensitivity was 0.842, positive predictive value (PPV) was 0.888, and false positive rate (FPR) was 0.275, all higher compared to nodules with X > 27 mm; false predictive value was 0.636, and false negative rate (FNR) was 0.157, both lower. In our study, the sensitivity, specificity, false positive, and false negative values of Fine-Needle Aspiration Biopsy (FNAB) based on nodule size were consistent with the literature. A cutoff value of 27 mm was identified as a distinct finding compared to other studies for nodule size. While the reliability of FNAB was high for nodules under 27 mm, it was demonstrated that the sensitivity of FNAB decreased for nodules larger than 27 mm.

Although fine-needle aspiration biopsy (FNAB) is the gold standard in pathological diagnosis, the ultrasound characteristics of thyroid nodules still assist clinicians in distinguishing between malignant and benign conditions. There is ongoing debate regarding nodule size as a predictive risk factor for malignancy. In the study by Albuja-Cruz et al. (7), the frequency of malignancy in nodules larger than 40 mm was found to be slightly lower compared to those smaller than 40 mm. Another study found no correlation between the size of nodules and the malignancy rate in nodules 40 mm and larger (10). Cavallo et al. (22) demonstrated that the risk increases inversely with nodule size. A meta-analysis found that the risk of malignancy is higher in nodules ≥30 mm compared to those <30 mm, but the rate decreases in nodules >60 mm (25,30). In our study, the mean size of nodules, particularly those ≤ 27 mm, was found to be statistically significantly higher in benign lesions, while no significant difference was observed in lesions > 27 mm. The mean size of all nodules was also statistically significantly higher in benign lesions. This indicates that the inverse relationship between nodule size and malignancy risk for nodules ≤ 27 mm is consistent with the literature. In the examination of all nodule sizes, particularly in nodules larger than 27 mm, we found that the risk of malignancy decreased with increasing nodule size, which contrasts with some studies in the literature. Additionally, when examining the estimated two-dimensional area of the nodule in relation to postoperative malignancy; the two-dimensional estimated area was statistically significantly higher in benign lesions for nodules ≤ 27 mm, > 27 mm, and all nodules. When reviewing the literature on the relationship between nodule ultrasound characteristics and malignancy, a study evaluating 255 patients found that nodules with combinations of hypoechoic, microcalcifications, and irregular borders had a higher rate of malignancy (26). Mandel et al. identified five features predictive of malignancy: hypoechogenicity, microcalcifications, irregular borders, absence or thick halo, and increased vascularity (27). In our study, the characteristics of thyroid nodules, specifically hypoechogenicity and microcalcifications, were found to be associated with malignancy, consistent with the literature. The presence of a halo was significantly associated with the Bethesda 4 Follicular Neoplasm group. Age and gender are important and debated risk factors for malignancy. Some authors report a higher proportional rate of malignancy in males, although there are studies that contradict this. Some studies have shown that malignant thyroid nodules are more common in females than males, with higher rates in the 20-30 decade for females and in the 30^{th} decade for males (28-30). In our study, no significant relationship was found between gender and postoperative pathology; however, a significant relationship was observed between age and postoperative pathology. For nodules ≤ 27 mm and all sizes, Bethesda 2 Benign pathology was significantly higher in older age groups.

Based on these results, although the malignancy rate decreases in nodules larger than 27 mm in clinical practice, it should be noted that the sensitivity of FNAB is low. In treatment planning, USG features should also be considered in addition to FNAB results, and options such as repeated multiple FNABs in more experienced centers or diagnostic operations should be evaluated as practical alternatives. To improve the accuracy of FNAB, it is recommended to enhance biopsy sampling techniques in experienced hands and to collaborate with more experienced pathologists.

In our study, although data were systematically collected from the hospital database, some patient data were inaccessible due to the absence of external center results in the data system. Therefore, the small patient population, single-center design, and retrospective nature of the study represent significant limitations. Future research should include multicenter, prospective studies with larger patient populations and encompass other populations.

Conclusion

In conclusion, our study demonstrated that the risk of malignancy decreases with increasing age, nodule size, and estimated two-dimensional area. The risk of malignancy increases in nodules with hypoechoic features and microcalcifications. The sensitivity of FNAB decreases in nodules larger than 27 mm, and the false-negative rate increases. While the risk of malignancy generally decreases with increasing nodule size, the reduction in the reliability of FNAB should be considered, and the presence of hypoechoic and microcalcification features in nodules should be taken into account. For nodules larger than 27 mm, repeat FNAB and diagnostic surgery may be recommended by the operator. Nonetheless, prospective studies with larger patient populations are needed to enhance the generalizability and reliability of our findings.

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