

Diagnostic Specificity of Sonography in Describing Thyroid Nodules Correlated With Histopathological Report

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Abstract: **Background:** The first line investigation in evaluation of thyroid nodules is sonography. An USG-based risk stratification system for classifying thyroid nodules is Thyroid imaging reporting and data system (TIRADS). Bethesda classification of Fine needle aspiration cytology (FNAC) aids in appropriate surgical intervention for highly suspicious nodules. To reduce the number of unnecessary aspirations and biopsy procedures, it is crucial that we develop a comprehensive system of stratifying thyroid nodules. Therefore, this study is aimed to say the diagnostic specificity of sonography in describing thyroid nodules using the TIRADS score correlated with the histopathological diagnosis. **Material and methods:** This is a prospective study conducted on 104 patients with palpable thyroid nodules and diffuse thyroid disease. All subjects underwent FNAC after initial sonography assessment were included in the study. Histopathological report was used as the gold standard. USG results were compared with histopathological report sensitivity, specificity, PPV, NPV and the nodule types were compared using Fisher's exact test. **Results:** Out of 104 subjects, 49 were benign and 33 were malignant. The specificity, sensitivity, positive-predictive value and negative-predictive value of sonography in determining the benign and malignant was 56.1%, 56.3%, 23.7% and 84.1% respectively. The USG and histopathology report were strongly associated with, Hypoechoogenicity ($P=0.01$), Taller than wider shape ($P=0.01$), Irregular margin ($P=0.02$) and Peripheral calcification & punctate echogenic foci ($P<0.001$). **Conclusion:** Sonography can be used as a reliable modality in classifying thyroid nodules and can assist in decision making for to avoid unnecessary biopsy and surgical intervention.

Keywords: thyroid nodules, TIRADS, histopathology, specificity.

INTRODUCTION

Globally, thyroid nodules are 4-8% prevalent by palpation alone and 19-67% prevalent by ultrasonography. About 8.5% of the Indian population has thyroid nodules. (1) The majority of thyroid nodules are derived from thyroid follicular cells. Benign follicular nodules are the most common mass lesions, either solitary or as part of a multinodular goiter. About 7.15% of recognized thyroid nodules are malignant. (2) Factors that predict the risk of malignancy include history (age, sex, family history, history of radiation exposure, rapid growth of nodule), examination (cervical lymphadenopathy, hard craggy and fixed nodule, hoarseness of voice), and thorough investigations. (3) Thyroid nodules are more common in females than males, and females are less aggressive in the histological subtypes of thyroid cancer. (4)

Detailed history and imaging are crucial in the examination of the thyroid nodules. The first line of investigation is sonography in clinically detected thyroid nodules. With the advancement of ultrasound technology, even a small thyroid lesion of a few millimeters can be detected while fine needle aspiration cytology (FNAC) still remains the standard technique for the diagnosis of thyroid nodules. (5) Thyroid imaging recording and data system (TI-RADS), a risk stratification system for classifying thyroid nodules into

5 categories based on 5 features of the nodule – composition, echogenicity, shape, margin and echogenic foci. (6) By adding all the points given by each category provides a numerical value of the TI-RADS score.

FNAC is the standard diagnostic procedure for early diagnosis and treatment of various thyroid lesions as it is a highly sensitive test. It aids in appropriate surgical intervention for highly suspicious nodules using the Bethesda classification. (7,8) However the procedure can result in substandard samples (8), has its own risk, and often involves unnecessary costs.

To reduce the number of unnecessary aspirations and biopsy procedures, it is crucial that we develop a comprehensive system of stratifying thyroid nodules and describing them confidently. For nodules that can be safely monitored with interval USG, USG can be considered as a reliable tool for the early detection of thyroid lesions and for ruling out malignancy, minimizing the need for expensive procedures. Therefore, this study is aimed to say the diagnostic specificity of sonography in describing thyroid nodules using the TI-RADS score correlated with the histopathological diagnosis.

MATERIALS AND METHODS

This is a prospective study conducted on 104 patients with palpable thyroid nodules and diffuse thyroid disease referred for an ultrasound of the neck to the Department of Radiology, Saveetha Medical College and Hospital. The exclusion criteria are neck swelling other than thyroid, non-cooperative patients, and Post-operative and post-radiotherapy cases. The demographic details of the patient, onset, duration and symptoms of the present illness were recorded. Examination of the neck and signs relating to thyroid swelling were examined and the thyroid profile of all the patients was performed.

Ultrasound examination:

USG had been performed using GE Voluson S8 fitted with 9 – 14 MHz high-frequency linear array transducer and Doppler evaluation of thyroid nodules was carried out. The ultrasound examination was performed by two well-experienced radiologists from Saveetha Medical College and Hospital. The nodule dimensions, shape and number, internal composition of the nodules, heterogeneity, echogenicity and calcifications were the characteristics examined. Qualitative measures were used for assessing the echogenicity and margins. Only the dominant nodule in terms of suspicious sonographic features was analyzed in patients with multiple nodules. Each nodule was categorized as TR1 – benign, TR2 – not suspicious, TR3 – mildly suspicious, TR4 – moderately suspicious, and TR5 – highly suspicious based on ACR TIRADS (6).

Fine needle aspiration procedure:

Informed written consent was obtained from the patients after explaining the purpose and steps involved in the procedure. The patient was placed in the supine position with a slightly extended neck supported by the pillow. The neck was painted with betadine (10% povidone-iodine) solution and lidocaine, a topical anesthetic agent

applied to the skin overlying the nodule. A high resolution (7.5 – 15 MHz) linear-array sonographic transducer with its headpiece covered with a sterile cover was used for the ultrasound. A non-aspiration capillary action technique using a 23/25-gauge hypodermic needle was used for performing FNAC in the nodule. The needle was withdrawn once the desired amount of material is seen in the syringe and smears were prepared for cytological examination. Then post-surgery the resected thyroid nodules are sent for histopathological (HPE) examination. The HPE results were assessed by two pathologists blinded to ultrasound findings. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was employed to categorize benign, atypia and malignant nodule (9).

The categorization (benign or malignant) of the nodule was made by correlating the final FNAC reports and the Ultrasonography features of the nodule.

Statistical analysis:

All collected data has been compiled and entered in MS Office Excel and were analyzed using SPSS, version 22. Frequency, Pearson's Chi-square for categorical variables, Fisher exact test were performed to compare the types of nodules and the Kappa test was used. The malignancy risk of TIRADS and BETHESDA system with respect to histopathological reports was determined. Ultrasound features suggestive of malignancy (solid or almost solid, hypoechoogenicity, taller than wider nodules, irregular margin and microcalcifications) were used to calculate Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Odds ratio with a 95% confidence interval (CI) were calculated. The statistically significant P value was considered as < 0.05.

RESULTS AND OBSERVATIONS:

Out of 104 subjects, 83 (79.8%) were females and 21 (20.2%) were males with a female preponderance. The age range was found between 14 to 67 years. The mean age was found to be 40.07 ± 13.60 years. Solitary and multiple thyroid nodules distributions in various age groups were 6.8% (5) cases in the age group between 11 – 20 years, 20.3% (15) cases in the age group between 21 – 30 years, 25.7% (19) cases between 31 – 40 years, 19% (14) cases between 41 – 50 years, 22% (16) cases between 51 – 60 years and 6.8% (5) cases in the age group between 61 – 70 years. The number of patients with solitary nodules included in this study was 84 (80.8%) and multiple nodules were 20 (19.2%). The incidence of malignancy in solitary thyroid nodules is found to be higher in females.

Table 1 displays the frequency of different ultrasonography features/characteristics of solitary and multiple thyroid nodules. Table 2 shows the frequency of patients with different TIRADS score, the frequency of patients with different BETHESDA category as per FNAC findings and the number of benign (n=49) and malignant (n=33) nodules according to the post-surgical histopathological report (n=82). The incidence of malignancy was more in females since 27 out of 33 malignant thyroid nodule/s were females and 8 were males.

Subjects of TIRADS 1 and 2 were not subjected to FNAC but TIRADS 3,4 & 5 underwent FNAC under USG guidance. The most common category was TIRADS 3. With the TIRADS 3 – 5, the risk of malignancy increased according to Table 3. Our study showed the risk of malignancy TIRADS 3, TIRADS 4 and TIRADS 5 were 15.9%, 66.6% and 85.7% respectively.

A comparison of TIRADS with risk of malignancy (preoperative score of TIRADS with histopathology report) is shown in Table 4 ($P = <0.0001$) by taking TIRADS 3 as probably benign USG findings, and TIRADS 4 and 5 (moderately and highly suspicious of malignancy) as probably malignant USG findings. The Sensitivity, Specificity, Positive predictive value (PPV) and Negative predictive value (NPV) of TIRADS with histopathological reports are 56.3%, 56.1%, 23.7% and 84.1% respectively. The diagnostic accuracy of ultrasonography is 56%. Table 6 depicts the specificity (USG features suggestive of malignancy) of Solid or almost solid composition, Hypoechoic or very hypoechoic, Taller than wider, Irregular margin and Peripheral calcification and punctate echogenic foci were 57.6%, 69.7%, 66.7%, 75.8% and 78.8% respectively. The overall accuracy of ultrasonography is 56%.

Table 5 shows the USG features suggestive of malignancy with histopathological findings. The USG features significantly associated with malignancy are hypoechoic or very hypoechoic ($P = 0.01$), taller than wider shape ($P = 0.01$), nodules with irregular margin ($P = 0.02$) and peripheral calcification and punctate echogenic foci ($P = <0.0001$) specifying that ultrasonography aids in the identification of thyroid nodules. Kappa statistics were performed for TIRADS and there was moderate agreement of 0.6 was appreciated.

Table 1: Ultrasonography features of subjects with thyroid nodules

PARAMETERS	CHARACTERISTICS	N	%
COMPOSITION	spongiform	1	0.96
	mixed cystic and solid	38	36.54
	solid or almost solid	65	62.50
ECHOGENECITY	anechoic	12	11.54
	hyperechoic or isoechoic	69	66.35
	hypoechoic	18	17.31
	very hypoechoic	5	4.81
SHAPE	wider than taller	96	92.31
	taller than wider	8	7.96
MARGIN	smooth	69	66.99
	ill defined	15	14.56
	lobulated or irregular	18	17.48
	extra thyroidal extension	1	0.97
ECHOGENIC FOCI	none or large comet - tail artifacts	70	67.31
	macro calcifications	19	18.27
	peripheral (rim) calcifications	13	12.50
	punctate echogenic foci	2	1.92

Table 2: Frequency of radiological, cytological and histopathological findings

SCORING SYSTEM	CATEGORIES		N	%
TIRADS	TIRADS 1	Benign	No FNAC	No FNAC
	TIRADS 2	Not suspicious	No FNAC	No FNAC
	TIRADS 3	Mildly suspicious	44	42.31
	TIRADS 4	Moderately suspicious	24	23.08
	TIRADS 5	Highly suspicious	14	13.46
BETHESDA	BETHESDA 1	Non-diagnostic	8	7.69
	BETHESDA 2	Benign	27	25.96
	BETHESDA 3	AUS/FLUS	5	4.81
	BETHESDA 4	Follicular neoplasm	13	12.50
	BETHESDA 5	Suspicious for malignancy	18	17.31
	BETHESDA 6	Malignant	11	10.58
HISTOPATHOLOGICAL FINDING (n=82)	Benign		49	47.12
	Malignant		33	31.73

Fig 1: Gender distribution of thyroid nodules according to ACR-TIRADS 2017

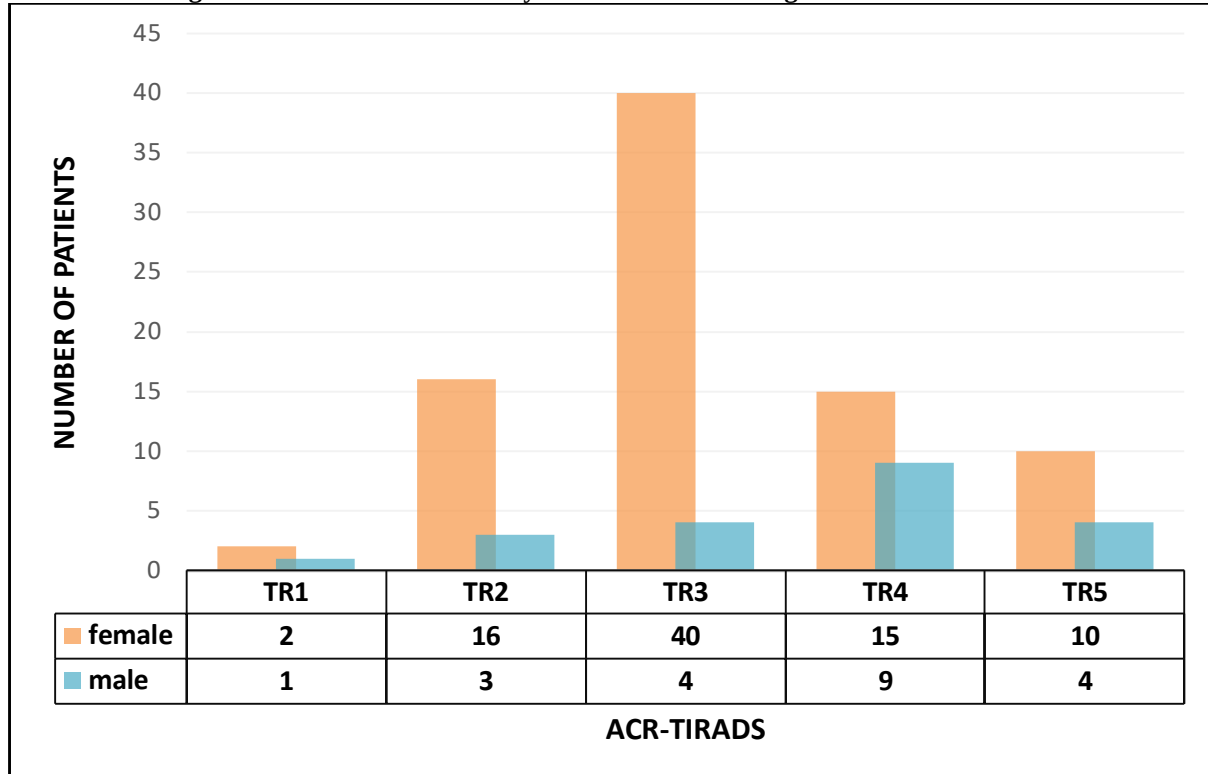


Table 3: Malignancy proportions as per TIRADS score

TIRADS Score	Histopathology		Total	Risk of malignancy (%)
	Malignant	Benign		
3	7	37	44	15.9
4	16	8	24	66.6
5	12	2	14	85.7

Table 4: Association of TIRADS with risk of malignancy

pre-operative investigation	Histopathology			P
Ultrasound	Malignant	Benign	Total	<0.001
TIRADS 3	7 (16%)	37 (84%)	44 (53.7%)	
TIRADS 4,5	28 (73.6%)	10 (26.3%)	38 (46.3%)	
Total	35 (42.7%)	47 (57.3%)	82 (100%)	

Table 5: Correlation between USG features suggestive of malignancy and histopathology results

USG features		Histopathology			P
		Malignant (n=47)	Benign (n=35)	Total (n=82)	
Solid or almost solid	Present	31	34	65	0.09
	Absent	4	13	17	
Hypoechoic or very hypoechoic	Present	15	8	23	0.01
	Absent	20	39	59	
Taller than wider	Present	7	1	8	0.01
	Absent	28	46	74	
Irregular margin	Present	12	6	18	0.02
	Absent	22	41	63	
Peripheral calcification and punctate echogenic foci (microcalcification)	Present	13	2	15	<0.001
	Absent	20	47	67	

Table 6: Diagnostic attributes of ACR-TIRADS in malignancy

Features	sensitivity	specificity	PPV	NPV	OR (95%CI)	Likelihood Ratio
Solid or almost solid	37.5%	57.6%	17.6%	79.2%	2.44 (0.78,7.65)	2.03
Hypoechoic or very hypoechoic	43.8%	69.7%	25.9%	83.6%	3.39 (1.23,9.31)	1.41
Taller than wider	50%	66.7%	26.7%	84.6%	10.86 (1.27,92.93)	1.21
Irregular margin	25%	75.8%	20%	80.6%	4.63 (1.46,14.65)	1.39
Peripheral calcification and punctate echogenic foci (microcalcification)	56.8%	78.8%	39.1%	88.1%	3.98 (1.40,11.28)	1.45

DISCUSSION

It is of immense clinical significance to classify the benign and malignant thyroid nodules. Although ultrasound remains the initial mode of assessment of thyroid nodules, fine needle aspiration cytology aids in the diagnosis of thyroid nodules by categorizing it as benign, atypia and malignant nodule. Histopathological examination (HPE) is considered to be the gold standard for diagnosing thyroid nodules by differentiating the benign and malignant nodules. It is crucial that we develop a comprehensive system of stratifying thyroid nodules and describing them confidently, to avoid unnecessary aspiration and biopsy techniques.

This study found that 83 (79.8%) of the 104 participants were female, which is in accordance with the other study performed on the sex difference among the thyroid nodules. (10) This study showed the highest number of cases (n = 19, 26%) were reported in the 31 – 40 years age group followed by 51 – 60 years (n= 15, 22%) and the mean age was 40.07 years. This is consistent with the previous studies. (10,11) This study showed the incidence of malignancy in solitary thyroid nodules was more in females correlating to Anitha, et.al (11). Fluctuation of women's sex hormones during menstruation and pregnancy and skewing of X-chromosome inactivation, are the two potential causes (12,13,14).

The risk of malignancy in our study for TIRADS 3, TIRADS 4 and TIRADS 5 were 15.9%, 66.6% and 85.7% respectively. The risk stratification of malignancy for TIRADS 3, 4, and 5 is 2.2%, 5.9-57.9%, and 100%, respectively, according to research done in France (15) and according to Kwak et.al 1.7%, 3.3-72.4% and 87.5% for TIRADS 3, 4 and 5 respectively (16). According to a study conducted in India by Srinivas et.al (17), the risk of malignancy for TIRADS 3, TIRADS 4 and TIRADS 5 was correspondingly 0.64%, 4.76-83.33% and 100% and another study from India (18) concluded 0.5%, 3.85-84.22% and 100% for TIRADS 3,4 and 5 respectively. Our results are in accordance with these previously

conducted studies. The P value of risk of malignancy is <0.001.

In accordance with a study by Al-Ghanimi et al. (19), our research revealed a significant P value of USG findings indicative of malignancy for hypoechoic (0.01), taller than wider shape (0.01), irregular margin (0.02), and microcalcification (0.001) in comparison to those results (0.001). Srinivas et.al (17) depicted a significant P value of <0.001 for the solid composition while our study exhibited an insignificant P value of 0.09 which could be attributed to the composition's being purely solid or predominantly solid with a cystic component. (20)

The intriguing malignancy rate found in our study for TIRADS 3 is 15.9% which is associated with a study conducted in Chennai (21) which showed 13.3% malignancy rate for TIRADS 3. Barbosa et.al (22) which showed a higher rate of malignancy than our study of 23.3%, used the same latest ACR-TIRADS criteria 2017. There are four possible types in which TIRADS 3 can be classified into solid and hyperechoic, solid and isoechoic, mixed solid and hyperechoic with macrocalcification and mixed solid cystic and hypoechoic which might explain the higher malignancy rate in TIRADS 3. One of the disadvantages of the ACR-TIRADS criteria 2017 as it does not include individual features like macrocalcification or hyperechogenicity of the nodule to predict the rate of malignancy in previous systems. (1)

Hekimsoy et al. (24) reported a higher specificity of ACR-TIRADS of 75%, compared to our study's specificity of 56.1% for the ACR-TIRADS score by ultrasonography. The specificity was found to be 59% in a research of a similar kind from Italy (23), which is in accordance with our investigation.

CONCLUSION

This study's results indicate that several sonographic features under the TIRADS scoring system, including solid composition, hypoechogenicity, taller than wider shape, irregular margin and microcalcification (peripheral calcification and punctate echogenic foci)

can be used to identify the potential risk of malignancy in thyroid nodules. Microcalcification was the most specific (78.8%) of all individual sonography characteristics, followed by irregular margin (75.8%). ACR-TIRADS can provide substantial guidance pertaining to the requirement of FNAC or histopathology analysis according to this study. A benign nodule under TIRADS 5 (USG) does not rule out the risk of malignancy, and the patient has to undergo surgical biopsy or resection for further conformation. Although specific for malignancy, sonography characteristics including microcalcification and irregular margin have poor sensitivity. Surgical biopsy and resection have the potential to resolve the suspicious indeterminate results, which appear to be an area of uncertainty.

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