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High resolution ultrasonography of thyroid nodules: can ultrasonographic assessment obviate the need for invasive aspiration cytology in ultrasonographically benign lesions?

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ABSTRACT

The use of high-resolution ultrasound (HRUS) thyroid imaging has resulted in a significant revolution in the treatment of thyroid nodules. The enigma of thyroid nodules has been a blind spot for radiologists for a long period. Reporting a thyroid nodule as benign or malignant is quite difficult and many times not accurate. The American Collage of Radiology-Thyroid Imaging Reporting and Data System (ACR-TIRADS) 2017 classification has solved this problem to a large extent. However, the classification needed pathological confirmation for it to be highly accurate. We compared our HRUS-based TIRADS labeling of thyroid nodules with thyroid cytopathology using revised Bethesda classification system. Patients detected with thyroid nodules by HRUS were categorized using ACR-TIRADS and further were taken for fine needle aspiration cytology (FNAC) in our department. The pathological results were compared with the initial TIRADS category of the nodule and the effectiveness of the TIRADS classification in categorizing nodules into benign and malignant was assessed using various statistical variables. The initial USG and the FNAC were performed by a single radiologist with over 10 years of experience. A total of 201 patients underwent HRUS followed by FNAC after obtaining written consent in our department. The thyroid nodules labeled as true benign on ACR-TIRADS (TIRADS 2) were all true benign on Bethesda cytopathology (less than Bethesda III), confirming the high accuracy of HRUS. The diagnostic accuracy of HRUS in cases of ACR-TIRADS 3 nodules was approximately 90.6% with an error rate of 9.4%. Nodules labeled as ACR-TIRADS 4 and 5 had error rates of 47% and 10% in labeling nodules as malignant. The ultrasound-based ACR-TIRADS system can accurately predict the likelihood of specific nodules being benign. There is a strong concordance between Bethesda cytology and ACR-TIRADS classification, particularly for benign nodules. In resource-constrained system like ours, patients with TIRADS 2 and 3 nodules can be safely followed obviating the need for an invasive procedure like FNAC.

Keywords:
thyroid imaging reporting & data system (TIRADS);
ultrasonography (USG);
Bethesda;
fine needle aspiration cytology (FNAC);
high resolution ultrasonography (HRUS)

INTRODUCTION

Thyroid nodules are quite common and often detected incidentally. The method used to diagnose them has a significant impact on their prevalence rates.[1] Imaging techniques like high-resolution ultrasound (HRUS) show the prevalence rate in the adult population ranging from 20 to 76% as opposed to just 4 to 7% when determined solely by palpation method.[2] Most thyroid nodules are benign but to categorize a nodule as benign or malignant based

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on imaging has been traditionally difficult. The ability to diagnose a nodule as malignant is the ultimate goal of all imaging modalities so that appropriate treatments can be started at the earliest. The incidence of malignancy among thyroid nodules varies based on clinical and radiological assessment.[3] Histopathological assessment, which in the case of thyroid nodules took the form of fine needle aspiration cytology (FNAC), has historically been the solution to clinical and radiological uncertainty. Nevertheless, FNAC only detects malignancy in 4-6% of thyroid nodules.[4] The frequency of incidental diagnoses of thyroid nodules (thyroid incidentalomas) is rising as a result of the frequent use of HRUS and the improved accessibility to cytological analysis through Ultrasound guided FNAC.[5] Therefore the question of their benignity or malignant nature is a big question that needs to be answered. This question has been partially answered by the introduction of the ACR TIRADS system of classification of thyroid nodules.[6] Incidence of these thyroid nodules is more among women and is almost four times than that of men of same age group. This gender difference is thought to be secondary to hormonal effect (both progesterone and estrogen).[7]

Nodules are grouped into their respective TIRADS category based on shape (S), echogenicity (E), margin (M), and echogenic foci (F). The final ACR-TIRADS categories are based on the sum of the scores for each of these categories, which range from 0 to 3.[8,9] The histopathological results of thyroid nodules are classified based on the Bethesda system for reporting thyroid cytopathology (2017) which categorizes the specimens into 6 categories.[10]

Our study was aimed at reaffirming the role of the ACR TIRADS classification in the management of thyroid nodules, especially with regard to benign nodules, so that a large number of invasive procedures (FNAC, biopsies) can be avoided in a resource constrained system like ours. We also sought to put to test the accuracy of TIRADS system to suggest a diagnosis of malignant thyroid nodule and thereby direct early management of these nodules.

MATERIALS AND METHOD

Patients

This study was conducted in the Department of Radio-diagnosis and Imaging Sheri Kashmir Institute of Medical Sciences, Srinagar in collaboration with The Department of Endocrinology and Department of Pathology over a period for 2 years (September 2020 to October 2022) and included patients who had thyroid nodules on high resolution ultrasound imaging. Informed consent was obtained from all participants in this study. Normal thyroid scan (TIRADS 1) and histopathologically documented cases of thyroid malignancies (TIRADS 6) were excluded. The study was approved by the Institutional ethical committee-vide approval no IEC/ SKIMS Protocol # RP 159/2022. A total of 201 patients were included in the final study who underwent USG based TIRADS categorization followed by FNAC at our department. Loco regional lymphadenopathy was also evaluated and recorded. All USG's were done using 12-14 Hz Ultrasound probe of Logic P5 GE Machine by a radiologist with over 10 years of experience. All patients in our study group underwent FNAC as we wanted a complete evaluation of the TIRADS classification including benign appearing nodules.

Protocol of study

A final TIRADS grade was given to the nodule after consideration of the nodule's nature, its morphology, the

presence or absence of calcifications, and any additional thyroidal expansion. All patients with TIRADS 2-5 then underwent FNAC in our department. The patient's coagulation profile and serology were assessed before any intervention. Informed consent was taken from all patients and all patients were cannulated before the procedure. After cleaning the neck with an antiseptic, sterile drapes were placed over the patient. FNAC was done by using 22G or 25G needles based on the nodular characteristic and operator preference. The procedure was done using real time guidance via USG and the aspirate was then flushed onto multiple slides using a 5mL syringe. Slide preparation, fixation and staining were done by an experienced pathologist with over 10 years of experience.

The slides were then evaluated for classification into BETHESDA system based on various characteristics. The pathologist evaluating the slides was kept blinded to the TIRADS grading of the nodule. The histopathological grade of the thyroid nodule was one of the six grades based on BETHSEDA system with the percentages in brackets indicating the likelihood of malignancy: grade I non diagnostic (1-4%), grade II benign (0-3%), grade III atypia of undetermined significance (5-15%), grade IV follicular neoplasm (15-30%), grade V suspicious for malignancy (60-75%) and grade VI malignant (97-99%).

Statistically analysis

The data was collected and evaluated using SPSS 21.0. Descriptive data was analyzed by frequencies and categorical data by percentages and continuous variables by means and standard deviations. Finally the TIRADS grading of the nodule was correlated with the BETHESDA grading and statistically significant concordances were sought with a p value of <0.05 considered statistically significant.

RESULTS

A total of 201 patients were included in this study with proportion of females versus male equal to 4:1. The mean age of the patients included in our study was 45 years. TIRADS3 and TIRADS4 made up the majority of the nodules on ultrasonography in 77.61% (156/201) of the cases. Using HRUS, thyroid nodules were stratified and TIRADS scoring was labeled for each patient. Out of the 201 nodules, 14(6.9%) nodules were categorized under TIRADS2, 85(42%) nodules were classified under TIRADS3, 71(35%) nodules were labeled as TIRADS 4, and 31(15%) were documented as TIRADS 5 (FIGURE 1). The nodules labeled as Bethesda I, II and III pathologically were considered benign while as those with Bethesda IV, V, and VI categorization were labeled as malignant. 120/201 (approximately 59%) were labeled as Bethesda I and II and III with US guided FNAC results. Further 40% (81/201) nodules proved to be malignant (TABLE 1). Out of the 14 TIRADS 2 nodules, all were benign on FNAC results. Among the 85 TIRADS 3 nodules, 62 nodules (72%) were Bethesda II (FIGURE 2) proving efficacy of HRUS for benignity, 7 nodules (8.2%) were Bethesda 1, 8 nodules (9%) were Bethesda III, 2 nodules (2.3%) were Bethesda IV, 3 nodules (2.3%) were Bethesda V, and 3 nodules (2.3%) were Bethesda VI. A total of 102 nodules were classified as TIRADS4 (FIGURE 3) and TIRADS5 (FIGURE 4) on USG and among them 11 turned out to be Bethesda II and 10 turned as Bethesda III. HRUS had approximately drop rate of 1.8% as in classifying the nodules as malignant (TABLE 1).

TABLE 1. Distribution of Bethesda grading of study subjects.

Bethesda grading	Frequency	Percentage (%)
Bethesda 1	14	6.97
Bethesda 2	85	42.29
Bethesda 3	21	10.45
Bethesda 4	24	11.94
Bethesda 5	17	8.46
Bethesda 6	40	19.90
Total	201	100.00

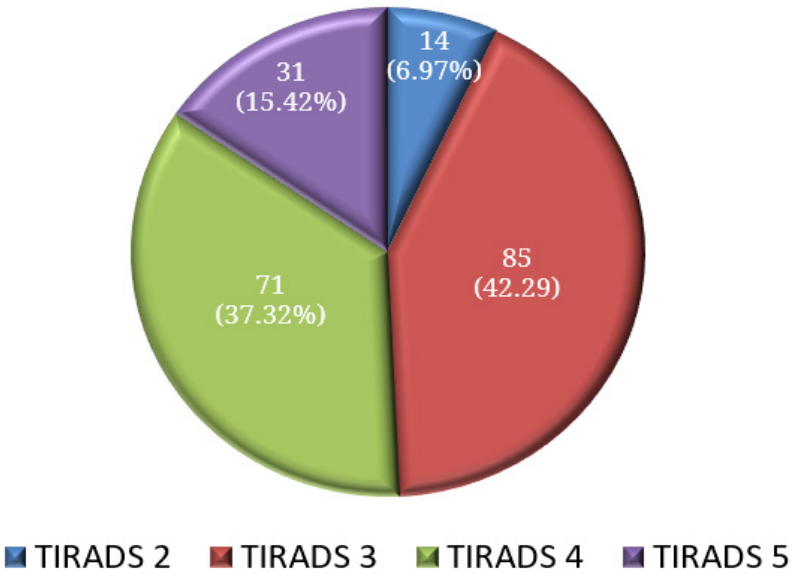

FIGURE 1. Pie chart showing the percentage distribution of thyroid nodules based on the TIRADS categorization on HRUS.

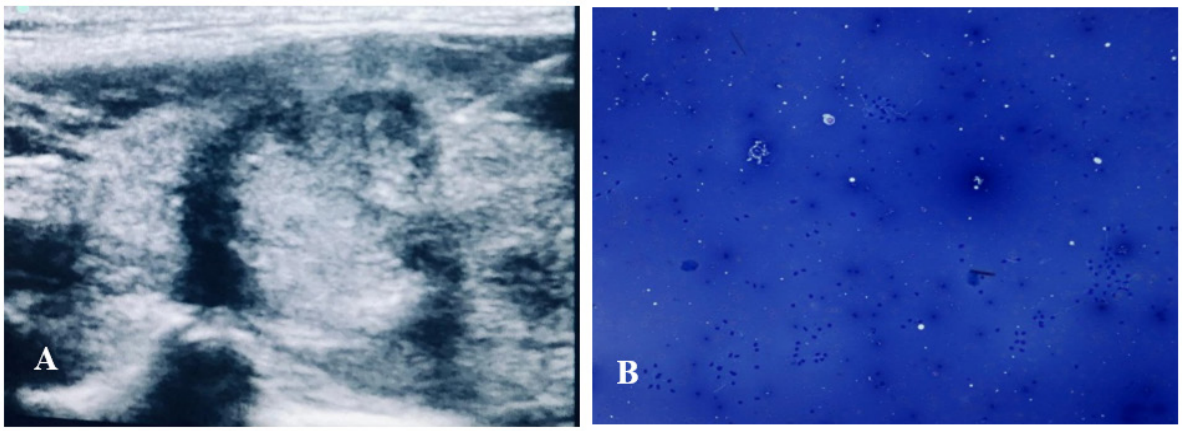

FIGURE 2. Transverse USG scan (A) of left thyroid lobe showing a well defined iso-hyperechoic, solid lesion with no calcifications labeled as TIRADS 3 which on FNAC. (B) came out to be colloid nodule (Bethesda II).

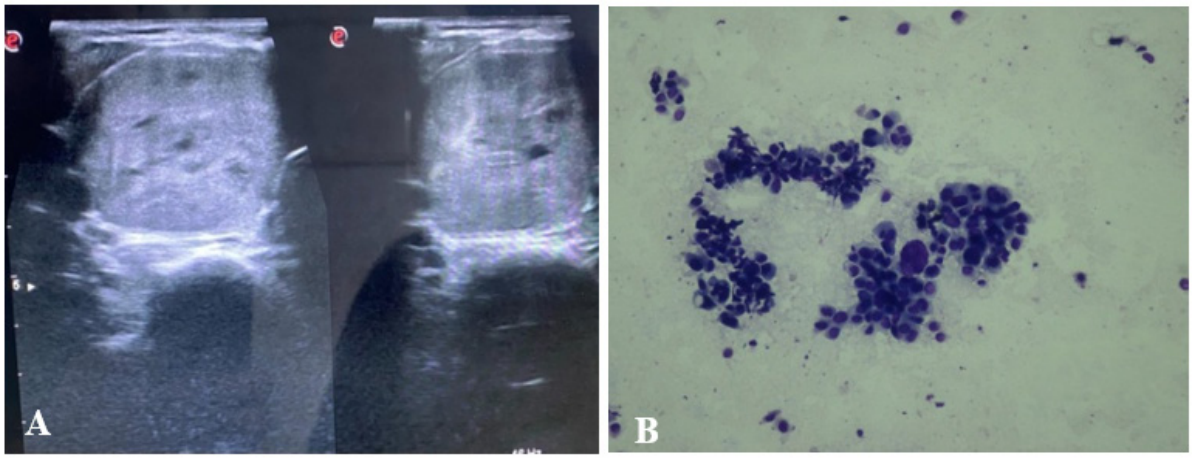

FIGURE 3. Transverse USG images (A) of right thyroid lobe in a 40-year-old female shows well defined, solid, hypoechoic nodule with no calcifications, wider than taller labeled as TIRADS -4 which on FNAC. (B) came out to be medullary carcinoma Thyroid [Bethesda VI].

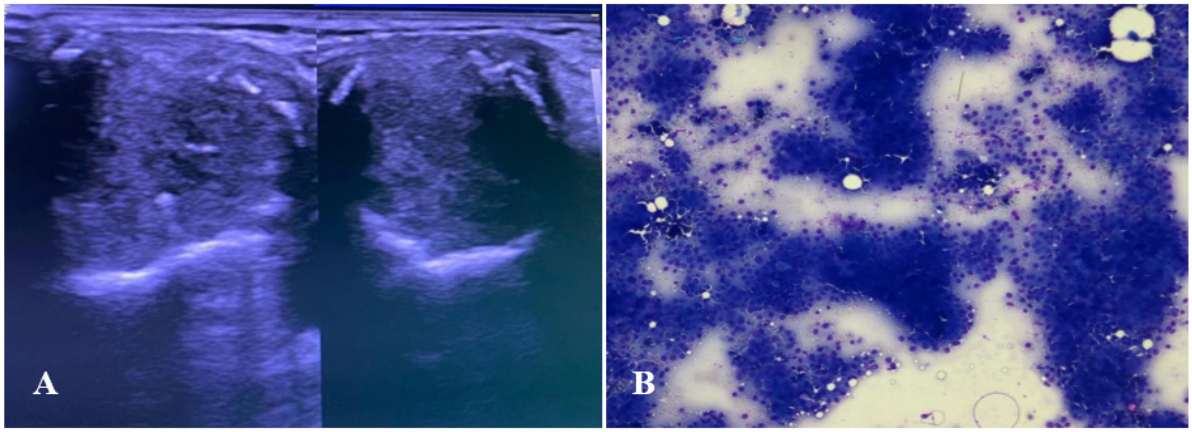

FIGURE 4. (A). Transverse USG images of right thyroid lobe in a 27-year-old female showing well defined, solid, hypoechoic, wider that taller lesion with peripheral calcification labeled as TIRADS 5. (B) came out to be papillary thyroid Carcinoma (Bethesda 6) on FNAC.

Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy were also calculated based on FNAC results. TIRADS4 and 5 were considered positive for malignancy, while TIRADS scores of 1–3 were considered negative for malignancy. Our study showed 86% sensitivity, 84.16% specificity, 84.3% PPV, and 85.9% NPV in labeling thyroid nodules as benign/malignant based on US findings. Significant correlation was seen between ACR-TIRADS and Bethesda system classification with $p<0.001$ (TABLE 2).

TABLE 2. Association of TIRADS classification of thyroid nodules with Bethesda grading

TIRADS	Bethesda grading (n or %)						Total	p
	1 (n=14)	2 (n=85)	3 (n=21)	4 (n=24)	5 (n=17)	6 (n=40)		
TIRADS2	2 (14.29)	12 (14.12)	0 (0)	0 (0)	0 (0)	0 (0)	14 (6.97)	<0.001
TIRADS3	7 (50)	62 (72.94)	8 (38.10)	2 (8.33)	3 (17.65)	3 (7.50)	85 (42.29)	
TIRADS4	5 (35.71)	11 (12.94)	10 (47.62)	22 (91.67)	12 (70.59)	11 (27.50)	71 (35.32)	
TIRADS5	0 (0)	0 (0)	3 (14.29)	0 (0)	2 (11.76)	26 (65)	31 (15.42)	
Total	14 (100)	85 (100)	21 (100)	24 (100)	17 (100)	40 (100)	201 (100)	

The efficacy of ultrasound in labeling benign nodule as for TIRADS2, TIRADS3 was 100 and 90.6%. Labeling TIRADS4 and TIRADS5 as malignant were 63.5 and 90% respectively. The risk of malignancy for patients classified as ACR-TIRADS5, ACR-TIRADS4 and ACR-TIRADS3 were in ratio of 10:7:1.

DISCUSSION

Ultrasound should be utilized while assessing the thyroid gland and nodule for the first time. Although guidelines have been put forth for the management and need of FNAC in thyroid nodules, an institutional guideline may differ from the international guidelines based on the availability of resources and the nature of the patients being treated. It is a minimally invasive procedure, but FNAC is an effective and affordable approach for finding thyroid cancer. It is crucial to choose the cases based on their risk of malignancy because it is not cost-effective, nor advisable to do such a test on all thyroid nodules. In an effort to aid in this selection, several classifications based on monographic traits have recently been put forth.[10] The TIRADS system of categorization seeks to correlate cytological classification to sonographic properties. Recent investigations found that 7.3% of malignant nodules lacked ultrasonography evidence of malignancy. The USG characteristics of the thyroid nodule that we considered in classification of nodules as suspicious for malignancy were hypoechogenicity, solid-composition, micro calcifications, taller than wide morphology and irregular margins. It is important to note that the malignancy of the nodule was not correlated with the presence or absence of any one specific ultrasonography characteristic. It is important to always keep in mind that combining at least two ultrasonographic markers will help distinguish between benign nodules and high-risk nodule.

At the end of our study, we have derived the following results after using several ultrasonographic factors to decide the TIRADS scoring of the nodules. The efficacy of ultrasound in labeling benign nodules for TIRADS2, TIRADS3 was 100 and 90.6% and labeling TIRADS4, and TIRADS5 as malignant were 63.5 and 90% respectively. Horvath *et al.*,[9] proposed ten ultrasound features to be seen during the ultrasound examination and nodule classification from TIRADS2–6.[11] They estimated a risk of malignancy of 0% for TIRADS2, 3.4% for TIRADS3, 10–80% for TIRADS4, and 87% for TIRADS5. Kwak *et al.*,[12] gave TIRADS classification used five ultrasound criteria's for thyroid evaluation.[13] The malignant risk of 0% for TIRADS2, 1.7% for TIRADS3, 72.4% for TIRADS4, and 87.5% for TIRADS 5.[14] Similar studies by Indian writers like Srinivas *et al.*,[15] came to the conclusion

that the probability of malignancy for TIRADS categories 1, 2, 3, 4A, 4B, 4C, and 5 was 0, 0, 64, 4.76, 66.67, 83.33, and 100%, respectively. Our study is well correlating with these studies.

CONCLUSION

The need for FNAC in nodules labeled as TIRADS1, 2 and 3 can be obviated considering the high accuracy of HRUS in detecting nodules that are benign especially in a resource constrained system and in patients who are apprehensive of an invasive procedure. With regard to TIRADS4 and 5, the correlation between TIRADS and pathological BETHESDA system is not that strong, so we suggest that FNAC should be performed in all such patients.

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