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Efficacy analysis between ultrasound and cytology criteria in the differentiation of malignant and benign thyroid nodules: TIRADS versus BETHESDA

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ABSTRACT

Aim: Thyroid nodules (TNs) are abnormal masses of different structures and sizes to be detected promptly. The present study aimed to investigate the relationship between Bethesda and TIRADS and their diagnostic efficiency in histopathologically diagnosed malign TNs.

Material and Method: 475 patients with TNs enrolled in this cross-sectional research. Laboratory parameters and clinical thyroid history were obtained from the automation system and analyzed retrospectively. They have been staged according to TIRADS, and the neck is evaluated in suspicious lymph nodes. FNAB results are then tracked for Bethesda staging.

Results: TIRADS showed a good sensitivity at the rate of 74.5% and average specificity at 68.1% for TNs. Bethesda had a higher sensitivity at 80.1% and 95.2% specificity rates. The positive predictive (98.1 vs. 88.2) and negative predictive (13 vs. 23.6) values were higher for Bethesda than TIRADS. The diagnostic accuracy for Bethesda was 79%. According to the ROC, Bethesda had a more expansive area under curve (0.81) than TIRADS (0.63). FNAC was a better diagnostic method than ultrasonography in evaluating thyroid nodules ($p<0.001$).

Conclusion: The risk of malignancy increased parallel to the increased Bethesda and TIRADS. While both scores helped predict malignancy, Bethesda is essential to physicians in assisting the discrimination of malign and benign TNs.

Keywords: Thyroid nodule, malignancy, TIRADS, Bethesda, ultrasound

INTRODUCTION

Thyroid nodules (TN) are abnormal masses of different structures and sizes that occur within the thyroid tissue, and most of them are harmless and benign (1). The steady worldwide increase in the incidence of thyroid cancers (TCs) would be insufficient to explain it with an increase in disease frequency, as this has contributed to the lack of diagnostic methods (2). When diagnosed early and well-differentiated pathologically, the prognosis of easily treated TCs is perfect (3). Especially the long-term survival rate of most stage-1 approaches is excellent at 100% (4).

Today, evaluation with ultrasonography (USG) is accepted as the first examination together with laboratory tests and is routinely used in preoperative planning and postoperative follow-up (3,5). USG has a very flexible diagnostic power and can distinguish between solid and cystic within the framework of the user's competence (6). In addition, it supports the distinction between benign and malignant nodules based on features such as the more solid structure of the nodule, its echogenicity, border irregularity, and the presence of microcalcifications (7,8).

Guidelines for classifying cytology results and identifying USG features suspected of malignancy of nodules provide more accurate management of follow-up and treatment of TNs (9). The thyroid imaging report and data system (TIRADS), published by the American Society of Radiology for managing patients with nodules by USG, determine the cancer risk based on USG findings and nodule size (10). This defines TNs management according to USG characteristics, scored between 1 and 5 levels, and aims to help decide whether fine needle aspiration (FNAB) is necessary and thus avoid unnecessary

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procedures (11). If FNAB is performed by experienced physicians, close to 95% successful sampling can be obtained in aspirations of solid nodules. Bethesda scoring includes reporting in one of 6 diagnostic categories as the standardized cytopathology classification system for interpreting FNABs (6). The limitations and diagnostic difficulties of FNAB may cause false-negative and false-positive results. Even if the initial cytological results are benign, it has been reported that the risk of malignancy is as high in TN with suspicious USG (12,13).

Exploring the relationship between TIRADS and Bethesda will provide beneficial results for endocrinologists to increase diagnostic power and reduce the rate of misdiagnosis. The present study aimed to investigate the relationship between the Bethesda and TIRADS scores and their diagnostic efficiency in TC cases diagnosed histopathologically.

MATERIAL AND METHOD

Study Design

The study was designed as a retrospective cross-sectional clinical analysis, including patient data between September - December 2022. A total of 1148 patients who applied to outpatient clinics were screened in the hospital automation system, and 475 patients were in the current study. Of the 475 patients included in the study, 475 TIRADS and 475 Bethesda. The histopathology reported 25 (5.2%) malignant patients in all participants.

Ethical Statement

The study was carried out with the permission of Karabük University Non-interventional Clinical Researches Ethics Committee (Date: 17.01.2023, Decision No: 2023/1216). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Laboratory parameters and patient histories were obtained from the automation system.

Participant Selection

Inclusion criteria included the followings: Adult patients over 18 years, thyroid nodules on USG, and scheduled for FNAB were included in this study. Cases with autoimmune disease, systemic disease, or infection were criteria of exclusion from the study. Demographic data for the analysis were collected using the retrospective report form of the patients and were obtained from the history, clinical examination, and research reports of all.

Bethesda System

Bethesda's system scores as (B1) Non-diagnostic, (B2) Benign, (B3) Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance, (B4) Suspicious/certain Follicular Neoplasm, (B5) Malignancy Suspect, and (B6) Malignant.

TIRADS System

The American College of Radiology determines the ultrasonographic character of thyroid nodules as TIRADS (Thyroid Imaging Reporting and Data System). Based on the sonographic results on the determination of nodules, this system needs to be analyzed for potential malignancy [3]. Internal composition, echogenicity, margins, echogenic foci, and nodule shape are essential for the scoring criteria. Scoring numbers are as follows: (TR1) normal thyroid gland, (TR2) benign lesions, (TR3) probably benign, (TR4) suspicious lesion, (TR5) probably malign.

Ultrasound Assessment

High-resolution USG using Hitachi Aloka F31 Dual Dynamic Display was performed on all patients. After the patient is supine, if there are thyroid nodules due to the USG examination, they have been staged according to TIRADS, and the neck is evaluated in terms of suspicious lymph nodes. FNAB results are then tracked for Bethesda staging. All thyroid ultrasounds were performed by the same staff (His experiences in thyroid ultrasound are as follows: Since the 2nd month of the endocrine fellowship, he received ultrasound training. He has been performing thyroid ultrasounds of between 60 and 70 patients a day).

Laboratory Analysis

Routine screening, including thyroid tests, was analyzed by a spectrophotometric method in the clinical biochemistry laboratory by AU5800 Beckman Coulter. Complete Blood Count parameters were analyzed with LH780 and Sedimentation with Alifax.

Statistical Analysis

Analyses were performed using SPSS v11. The conformity of the variables to normal distribution was examined visually (histogram and probability graphs) and analytically (Kolmogorov–Smirnov/ Shapiro–Wilk). Mann evaluated laboratory parameters–Whitney U test for non-normally distributed variables and by independent samples T-test for normally distributed variables. Descriptive analyses were presented with means and standard deviations for normally distributed variables. The relationship between the measured variables was examined with Spearman correlation. Two-to-two cells were compared with Pearson Chi-Square and Fisher's Exact Tests. $P<0.05$ were considered significant.

RESULTS

Demographics

Among the 475 participants, women were the majority, with 383 against 92 ($p<0.05$). While the age distribution of the participants was 53.8±12.8, the age range was 18-89 years. While the mean BMI (kg/m²) was 29.5±5.9, the distribution range was 16.8-57.7 kg/m². In **Table 1**, some

demographic characteristics, laboratory values, and thyroid nodule sizes of the patients participating in the study are given.

Table 1. Demographic details of participants

Variables	Mean±SD	Range
Age, year	53,8±12,8	18-89
BMI, k/m²	29,5±5,9	16,8-57,7
FT3, pg/ml	3,5±3,3	1,2-71,8
FT4, ng/dl	1,3±0,3	0,5-5,95
TSH, uIU/ml	2,7±6,3	0-97,2
Thyroglobulin, IU/mL	102±199	0-1964
Nodule Diameter, mm	18,8±9,9	0-65

Abbreviations. TSH, stimulating thyroid hormone; FT3, free triiodothyronine-free thyroxine; FT4, free triiodothyronine-free thyroxine; BMI, Body Mass Index.

Diagnostic Comparison of TIRADS and Bethesda

In **Tables 2** and **3**, information about TIRADS levels and Bethesda categories of the thyroid nodules are given. Preoperative TIRADS levels and Bethesda categories of 25 malign TNs detected histopathologically are as follows: TR2: (n:2), TR3 (n:10), TR4 (n:11), T5 (n:2) and B1 (n:3), B2 (n:1), B3 (n:6), B4 (n:3), B5 (n:8), B6 (n:4).

Table 3. Distribution of parameters according to nodule types

Variables	Non-operation	Histopathology: Benign	Histopathology: Malign
TIRADS			
2	57 (13,6%)	2 (6,4 %)	2 (8%)
3	182 (43,4%)	16 (51,6%)	10 (40%)
4	163 (38,9%)	11 (35,4%)	11 (44%)
5	17 (4%)	2 (6,4%)	2 (8%)
BETHESDA			
1	76 (18,1%)	1 (3,2%)	3 (14,3%)
2	213 (50,8%)	14 (45,2%)	1 (4%)
3	130 (31%)	11 (35,5%)	6 (24%)
4	0	2 (6,5%)	3 (12%)
5	0	3 (9,7%)	8 (32%)
6	0	0	4 (16%)
Gender			
M	77 (18,3%)	8 (25,8%)	7(28%)
F	342 (81,7%)	23 (74,2%)	18 (72%)
Family history of thyroid cancer			
Yes	9 (2,1%)	0	0
No	410(97,8%)	31 (100%)	25 (100%)
Radiotherapy history			
Yes	6 (1,4%)	0	1 (4%)
No	413 (98,5%)	31 (100%)	24 (96%)

Table 2. Distribution of BETHESDA & TIRADS categories

Variables	TR2 (n:61)	TR3 (n:208)	TR4 (n:185)	TR5 (n:21)
B1 (n:80)	12 (15%)	28 (35%)	37 (46,3%)	3 (3,8%)
B2 (n:228)	38 (16,6%)	126 (55,2%)	56 (24,8%)	8 (3,5%)
B3 (n:147)	11 (7,6%)	49 (33,1%)	81 (55,2%)	6 (4,1%)
B4 (n:5)	0	3 (60%)	2 (40%)	0
B5 (n:11)	0	2 (18,2%)	7 (63,6%)	2 (18,2%)
B6 (n:4)	0	0	2 (50%)	2 (50%)

Abbreviations. TR: Tirads, B: Bethesda

Preoperative TIRADS levels and Bethesda categories of 31 benign TNs detected histopathologically are also as follows, respectively: TR2 (n:2), TR3 (n:16), TR4 (n:11), T5 (n:2) and B1 (n:1), B2 (n:14), B3 (n:11), B4 (n:2), and B5 (n:3). Comparison of malign and benign TNs with similar TIRADS levels is as follows, respectively: TR3 (n:10) and TR4 (n:11) were malign TNs, TR3 (n:16) and TR4 (n:11) were benign TNs (p=0.01); there were two benign and two malign TNs in TR5 (p>0.05). Comparison of malign and benign TNs with similar Bethesda categories is as follows: At B3 and B4 categories, nine malign TNs and 13 benign TNs (p=0.014). While there were 12 malign TNs at the B5 (n:8) and B6 (n:4), there were three malign TNs B5 (n:3) and B6 (n:0) categories (p=0.004).

TIRADS showed a good sensitivity at the rate of 74.5% and average specificity at 68.1% for TNs. However, the Bethesda system of reporting FNAC had a higher sensitivity at 80.1% and 95.2% specificity rates. The positive predictive (98.1% vs. 88.2%) and negative predictive (13% vs. 23.6%) values were higher for cytology Bethesda-scoring compared to TIRADS-scoring. The diagnostic accuracy for Bethesda was 79%.

According to the ROC curve, as shown in **Figure 1**, Bethesda-scoring had a wider area under curve (0.81) than TIRADS-scoring (0.63). FNAC was a better diagnostic method than ultrasonography in evaluating thyroid nodules (p<0.001).

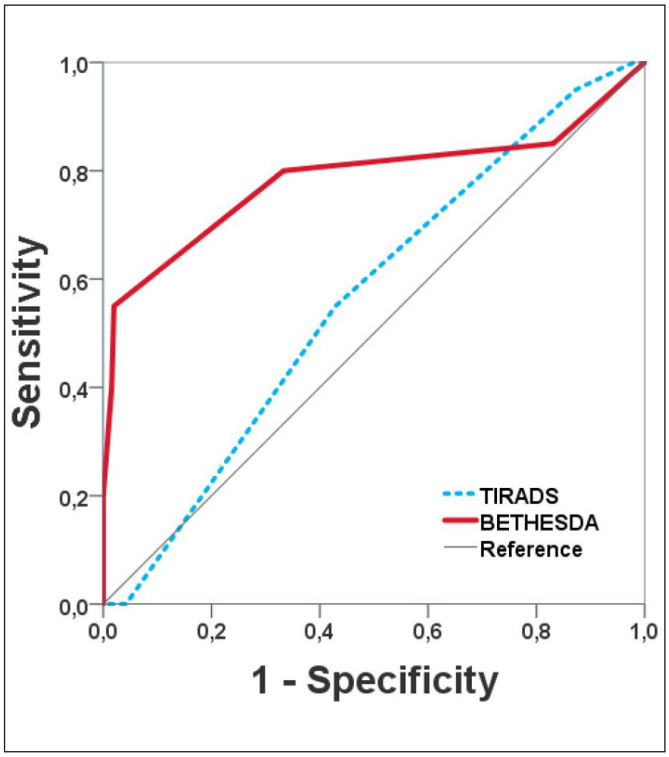

Figure 1. The ROC analysis for diagnostic accuracy of TIRADS and BETHESDA

DISCUSSION

The present analysis aimed to emphasize the importance of the correlation between Bethesda and TIRADS levels and remind that although cytopathology is superior in thyroid surgery/follow-up, TIRADS should also be considered. For scoring benign and malign TNs, the risk of malignancy increased as the Bethesda and TIRADS scores increased. With higher diagnostic accuracy, Bethesda was a better predictor of malignancy than TIRADS. While both scores helped predict malignancy, Bethesda is essential to physicians in assisting the discrimination of malign and benign TNs.

We know that the FNAB approach has a higher sensitivity and predictive value than other approaches in diagnosing TNs. It is a cost-effective, fast, and robust method in the classification of malignant TN, especially in need of reduction of unnecessary surgery or surgery. In Bethesda, numbered in 6 categories, the risk of malignancy increases for each type. While Mendes et al. (14) found TIRADS and FNAB to predict malignancy, the concordance rates with final histopathology were 75.4% and 95%, whereas Abdelkader et al. (15) showed 75.4% and 81.8%, respectively. Singaporewalla et al. (16) showed the sensitivity and specificity of TIRADS as 70.6% and 90.4%, respectively, while they were 72.3% and 66.7%, according to George et al. (17). Krzysztof et al. (18) reported that FNAB predicted thyroid carcinoma in patients with thyroid nodules as 95.8%. George et al. (17) noticed that the accuracy of FNAC in predicting malignancy with Bethesda was around 80% compared to TIRADS. According to Horvath et al. (19), thyroid malignancy was detected in 98.85% of TR5 nodules. According to Periakaruppan et al. (20), the risk of malignancy among TR5 thyroid nodules was 77.8%. In our research, TIRADS showed a good sensitivity at the rate of 74.5% and average specificity at 68.1%. However, Bethesda of reporting FNAB had a higher sensitivity at 80.1% and specificity at the rate of 95.2%. The positive and negative predictive values were higher for Bethesda-scoring compared to TIRADS-scoring. The diagnostic accuracy for Bethesda was 79%. Our results supported that FNAB was a better diagnostic method than ultrasonography in evaluating thyroid nodules.

In the analysis performed by Yılmaz and Bolukbasi (21), a similar design to our research, the nodule was reported as moderately suspicious (TR4) in 2 of 6 patients in category B1 and as highly questionable (TR5) in 1 patient. Although the risk of malignancy in the B1 category was relatively low, the TIRADS scoring was quite effective in the operation decision in 50% of the patients. According to the ultrasound findings, the nodule was reported as moderately suspicious (TR4) in 17 of 49 patients in the B3-4 category and as highly questionable (TR5) in 1 patient. While the risk of malignancy in B3 was 5-15%, it was 15-30% in B4. In 11 of 16 patients who were in the B5 category, the nodule was reported as moderately suspicious (TR4) and one highly questionable (TR5), according to ultrasound findings. While malignancy rates were 60-75% in B5, there was 75% malignancy in this patient group, according to TIRADS. 61 of 124 patients in category B6 were reported as moderately suspicious (TR4) and 13 as highly questionable (TR5), according to ultrasound findings. The malignancy rate in B6 was 90-97%. In our study, 21 malignant TNs were detected according to TR3 and TR4, while 27 were benign TNs. There were two benign and two malign TNs in TR5. According to B3 and B4, there were nine malignant TNs and 13 benign TNs. According to B5 and B6, there were 12 malignant TNs and three benign TNs.

The most substantial aspect of the present study was having a large number of participants in well-designed patient data. The main limitation of our study was its retrospective design and USG reports which were retrospectively reviewed and recategorized according to TIRADS. Finally, a lack of interpretation of the results in this study requires recognizing that more than a quarter of the subjects were female. This is probably because thyroid disease is significantly more common in women than men, and patients with autoimmune thyroid disease go to the doctor more often. This condition increases the likelihood of detecting nodules by palpation or ultrasound, defined as medical surveillance bias.

CONCLUSION

The primary purpose of using the reporting system is to determine the malignant potential of TNs and to help determine the treatment strategy in cases with benign biopsy results. Our study showed concordance between the thyroid ultrasound reported by TIRADS, FNAC reported by Bethesda, and the final histopathology report after thyroid surgery. Although the Bethesda evaluation showed superiority over TIRADS, more extensive, multicenter, randomized controlled trials are needed to confirm the role of TIRADS in the treatment of indeterminate thyroid nodules. Clinicians performing thyroid USG should associate ultrasound reports with TIRADS and follow the results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karabük University Non-interventional Clinical Researches Ethics Committee (Date: 17.01.2023, Decision No: 2023/1216).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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