Original Article

Approaching Indeterminate Thyroid Nodules in the Absence of Molecular Markers: "The BETH-TR Score"

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Abstract

Context: Given the lack of easy access to molecular markers for indeterminate thyroid nodules (Bethesda (BETH) category III, IV), the clinician can either decide to get a second opinion from an expert high-volume thyroid cytopathologist, redo the FNAC after a period of 3–6 months, or send the patient for a diagnostic hemithyroidectomy. Reviewing the sonographic risk features is also one way of triaging these nodules. The ACR-TIRADS (TR) is an objective method of sonographic risk assessment and is superior to other forms of sonographic classification. **Aim:** We propose combining the scoring of the TR category and BETH category (both expressed as a numerical value and summated) and look at the score which could potentially guide the clinician in deciding whom to send for surgery. **Settings and Design:** Observational prospective collection of consecutive patient data from the thyroid FNAC clinic. **Statistical Analysis Used:** The BETH categories were represented numerically and summated with the TR category. The categorical outcome variables of benign and malignant nodules and the summated score was analyzed using the Kruskal-Wallis test. **Results:** We analyzed 450 FNAC data, out of which 403 were thyroid nodule aspirates. Out of these nodules, 96 of them underwent surgery and 64% of these nodules were malignant on final histopathology (malignant = 62 and benign = 34). The mean size of the benign nodules was 3.6 ± 2.2 cm compared to 2.8 ± 1.8 cm of the malignant nodules. After excluding those with BETH 1 (n = 4), the mean BETH-TR score for benign nodules was 6 ± 1.4 and malignant nodules 9.4 ± 2.1 ($P < 0.0001$). The BETH-TR score progressively increased from 7.3 ± 0.92 in follicular thyroid cancers (FTC) to 8.6 ± 1.4 in follicular variant papillary thyroid cancer (FVPTC) to 10 ± 1.3 in classic papillary thyroid cancers (PTC). Among the indeterminate nodules (BETH III and IV; n = 40), the BETH-TR score of benign nodules was 6.75 ± 1 and malignant nodules was 7.5 ± 0.72 (P value = 0.01). A BETH-TR score ≥7 gave a sensitivity of 92% specificity of 74% and correctly identified malignant nodules in 86% of cases (likelihood ratio 3.5; ROC area: 0.8841; CI 0.79–0.94). **Conclusion:** A combined sonocytological BETH-TR score is one way to triage the management of indeterminate thyroid nodules. A BETH-TR score ≥7 gave a sensitivity of 92% specificity of 74% and correctly identified malignant nodules in 86% of cases.

Keywords: ACR-TIRADS, Bethesda, indeterminate thyroid nodules

Introduction

The Bethesda System for the Reporting of Thyroid Cytology (BETH) recognizes six diagnostic categories of thyroid nodule cytology with an incremental risk of malignancy [Table 1].[1] Although the BETH system created a much-needed handhold by standardizing the cytological diagnosis and management of thyroid nodules worldwide, clearly helping with the decision to observe or operate. However, the system does not provide a clear answer to the heterogeneous group of nodules with indeterminate cytology.[2] The BETH category III of "atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)," could be either "architectural atypia,' or "nuclear atypia," or "preparatory artifacts related atypia."

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DOI: 10.4103/ijem.IJEM_620_19

In the BETH category IV (follicular neoplasm [FN]), cytology does not show the capsular and/or vascular invasion that distinguishes a follicular thyroid cancer from a benign follicular adenoma. The clinician must discuss with the pathologist to ascertain the reason for the categorization of the cytology in the indeterminate category if it is not

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Submitted: 01-Dec-2019 **Revised:** 26-Dec-2019
Accepted: 13-Feb-2020 **Published:** 30-Apr-2020

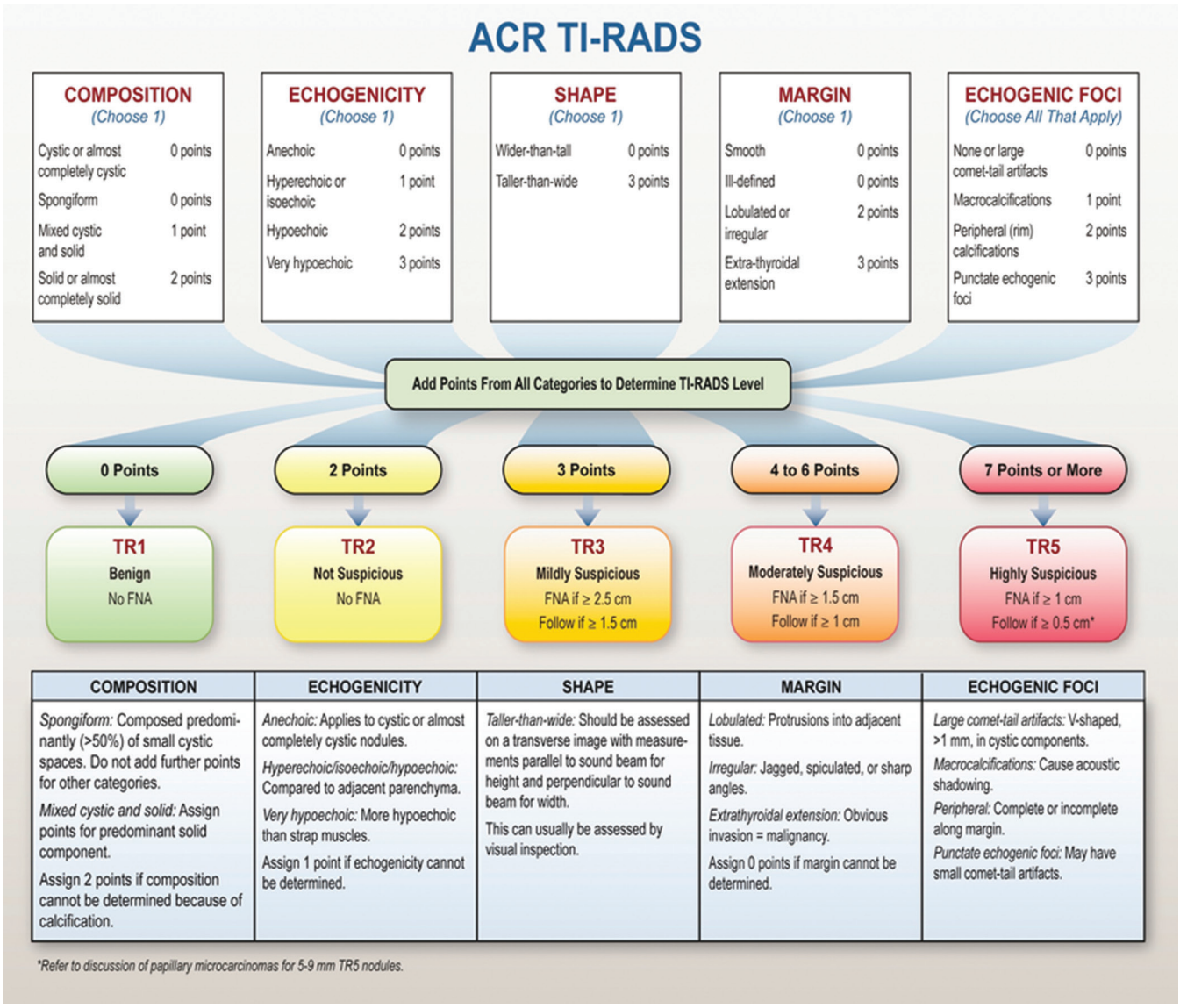
How to cite this article: Mehta S, Kannan S. Approaching indeterminate thyroid nodules in the absence of molecular markers: "The BETH-TR score". Indian J Endocr Metab 2020;24:170-5.

explicitly indicated. Improvement in the assessment of indeterminate fine-needle aspiration (FNA) results with molecular testing that allows better risk stratification and reduces the need for diagnostic thyroid surgery. However, their current availability and utility in the Indian scenario are quite limited. This leaves the clinician to fall back on three options, the clinician can either decide to get a second opinion from an expert high-volume thyroid cytopathologist, redo the FNAC after a period of 3–6 months, or send the patient for a diagnostic hemithyroidectomy.[3] Traditionally, thyroid sonography has been used to decide on which nodules need further investigation including FNAC. The ACR-TIRADS

Table 1: The Bethesda System for Reporting Thyroid Cytopathology and their Management

Bethesda Class	Diagnostic Criteria	Risk of malignancy (%)	Usual management
I	Non-diagnostic		Repeat FNAC with Ultrasound guidance
II	Benign	0-3	Clinical Follow up
III	Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)	5-15	Repeat FNAC
IV	Follicular Neoplasm (Specify if Hurthle cell type)	15-30%	Surgical Lobectomy
V	Suspicious for Malignancy	60-79	Near-total thyroidectomy or Surgical Lobectomy
VI	Malignant	97-99%	Near-total thyroidectomy

Table 2: ACR TI-RADS reporting system for sonographic classification of thyroid nodules and their management



scoring (TR) [Table 2] has higher performance for selecting thyroid nodules for FNAC compared to the rest of the TIRADs and ATA risk stratification.[4,5] However, sonography can also be used for triaging indeterminate nodules and improve the predictive value of Bethesda scoring and improve the risk assessment.[6-9] The prevalence of suspicious sonographic features among studies of AUS/FLUS cytology nodules ranged from 18% to 50%. From the four Korean studies (overall malignancy rate 40%–55%), the reported cancer risk in AUS/FLUS nodules with the high suspicion sonographic pattern is 90%–100%,[6-8] and the presence of even one suspicious sonographic feature (irregular margins, taller than wide shape, marked hypoechogenicity, or microcalcifications) increases the cancer risk to 60%–90%. Thus having decided to FNAC a thyroid nodule based on sonographic features, it may a good idea to "look back" at the sonographic features once we have indeterminate cytology to effectively triage these nodules either for observation or surgery.

Aim and Objective

We propose combining the scoring of TR and BETH (both expressed as a numerical value and summated) and look at the score of indeterminate nodules which could potentially guide the clinician in deciding whom to send for surgery.

Subjects and Methods

We prospectively collected the data of patients attending the Thyroid Nodule Clinic of the Endocrinology Department of Narayana Hrudhalaya Hospitals, Bangalore from July 2018 to December 2019. All patients had a sonographic stratification of the nodule intended for FNAC using the ACR-TI-RADS scoring (TR) by a single observer. In patients referred for surgery, the TR score was confirmed and detailed mapping of the neck was done preoperatively. The ultrasound-guided FNAC was performed using 23G needles and wet slides were sent to the pathology department in Koplik jars while dry slides were sent on trays and cell blocks in plastic containers.

Table 3: BETHESDA and TIRADS category distribution in the nodules that were operated and excluding Beth I category (*n*=92)

	TR2	TR3	TR4	TR5
BETH II	*n*=3 (All Benign)	*n*=10 (All Benign)	*n*=3 (All Benign)	-
BETH III	*n*=1 (Benign)	*n*=8 (Benign=7) FTC (MI)=1	*n*=15 (Benign=4) (Malignant=11)*	*n*=10 (Benign=3) (Malignant=7)**
BETH IV	-	*n*=1; FTC (MI)=1	*n*=2 FVPTC=2	*n*=3 FTC (WI) = 2; Benign=1
BETH V	-	-	-	*n*=7 (PTC=6; FVPTC=1)
BETH VI	-	-	*n*=3 (PTC=2; Lymphocytic thyroiditis=1)	*n*=26 (PTC=23; MTC=2; FVPTC=1)

FTC (MI): Follicular thyroid cancer (minimally invasive) FTC (WI) = Follicular thyroid cancer (widely invasive). PTC=papillary thyroid cancer; MTC=medullary thyroid cancer. *Malignant category included FTC (MI) = 5, PTC=3, FVPTC=1; FTC (widely invasive) = 1; ATC=1. **Malignant category included PTC=4; FTC (WI) = 1; FVPTC=2

Table 4: Studies in the literature assessing the role of sonographic scores in indeterminate thyroid nodules

Study	Number of surgically operated Indeterminate nodules	Sonographic Classification used	Prevalence of Malignancy on final histology	Sensitivity and Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)
Grani *et al*.[10]	49	ATA TIRADS (Korean)	39%		TIRADS 4c: 71% TIRADS 4a: 42% ATA Int Risk: 63% ATA Low Risk: 44%	ATA Extremely low risk 91-100% TIRADS 2-3: 74-100%
He *et al*.[13]	453	TIRADS (Korean)	29% (Beth III) 44% (Beth IV)	Sensitivity 99.6% Specificity 14%	PPV 60% and Accuracy 62.3%	NPV 96.6%
Maia *et al*.[14]	136	TIRADS (Korean)	8.7% (Beth III) 51.3% (Beth IV)		TI-RADS 4B and 5, combined with Bethesda IV resulted in a PPV of 75% for malignancy	TI-RADS 3 and 4A and Bethesda III combined to an NPV of 90%
Baser *et al*.[11]	179	TIRADS (Korean)			TIRADS categories of 4c and 5 were more frequent in malignant nodules (P<0·05) under AUS category	In FLUS categories, TIRADS categories were not associated with malignant nodules (P>0.05)
Lee *et al*.[12]	133	ATA			ATA risk stratification helped discriminate malignant nodules in the AUS group (P=0.032) but not the FLUS group (P=0.168).	Malignancy rate in the very low suspicion group was 0% in AUS/FLUS nodules

The cytology was reported by four different cytopathologists. Ethics approval was obtained from the ethics committee of Narayana Hrudhalaya Hospitals.

Statistical analysis

The data was analyzed using a Stata Software version 15 (StataCorp). Continuous variables were represented using mean and standard deviation. The BETH categories were represented numerically and summated with the TR category. The categorical outcome variables of benign and malignant nodules and the summated score was analyzed using the Kruskal-Wallis test.

Results

We analyzed 450 FNAC data, out of which 403 were thyroid nodule aspirates. Out of these nodules, 96 of them underwent surgery and 64% of these nodules were malignant on final histopathology (malignant = 62 and benign = 34) [Figure 1]. The mean size of the benign nodules was 3.6 ± 2.2 cm compared to 2.8 ± 1.8 cm of the malignant nodules. After excluding those with BETH 1 (n = 4), the mean BETH-TR score for benign nodules was 6 ± 1.4 and malignant nodules 9.4 ± 2.1 ($P < 0.0001$). The BETH-TR score progressively increased from 7.3 ± 0.92 in follicular thyroid cancers (FTC) to 8.6 ± 1.4 in follicular variant papillary thyroid cancer (FVPTC)

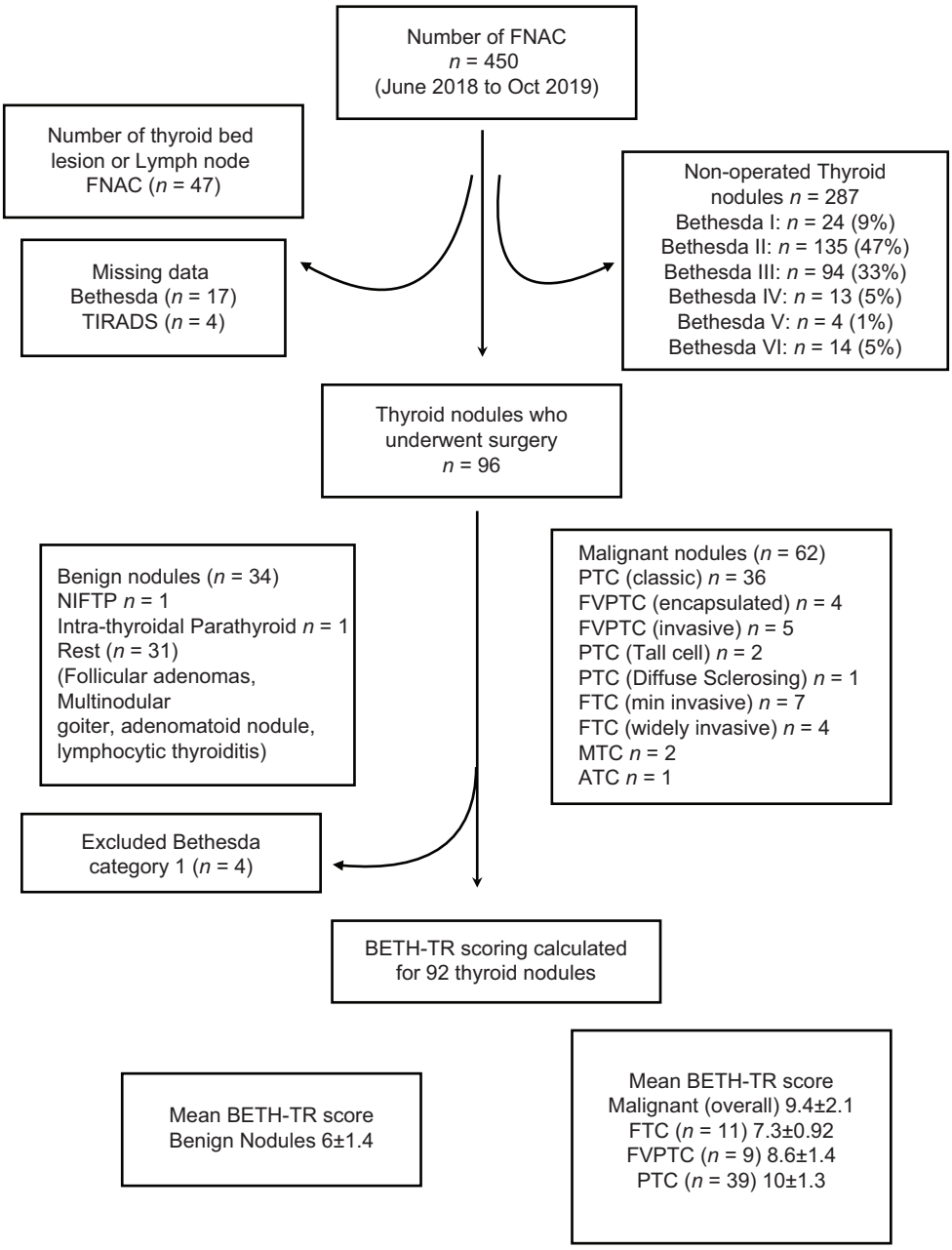


Figure 1: Summary of the thyroid nodules underwent FNAC and those that underwent surgery and their BETH-TR scores

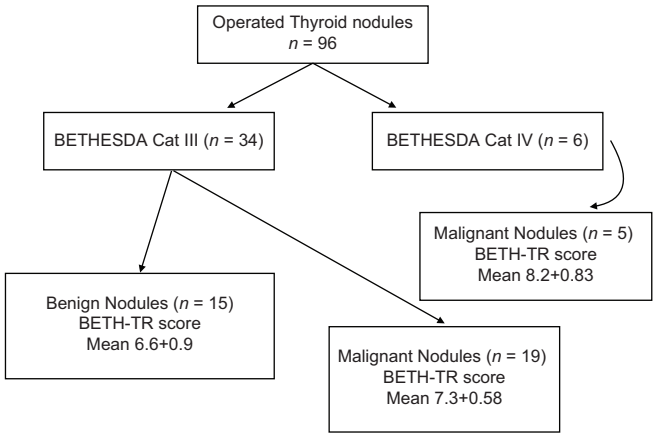


Figure 2: BETH-TR scoring in indeterminate thyroid nodules

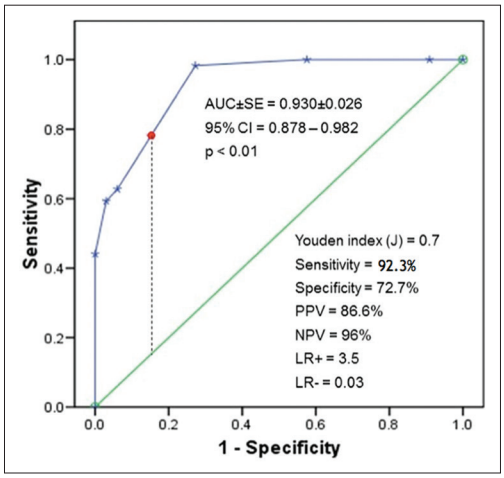


Figure 3: ROC curve generated for a combined BETH-TR score >7

to 10 ± 1.3 in classic papillary thyroid cancers (PTC). A table of the BETH and TR scoring is shown in Table 1. None of the BETH II nodules had a TR5 sonographic phenotype, similarly, none of the BETH V or VI nodules had a TR2 or TR3 phenotype. Among the indeterminate nodules, there is a progressive increase in the number of malignant nodules as the TIRADS phenotype progresses from TR2 to TR5 [Table 3]. Among the indeterminate nodules (BETH III and IV; $n = 40$), the BETH-TR score of benign nodules was 6.75 ± 1 and malignant nodules was 7.5 ± 0.72 (P value = 0.01) [Figure 2]. A BETH-TR score ≥7 had a sensitivity of 92% specificity of 74% and correctly identified malignant nodules in 86% of cases (likelihood ratio 3.5; ROC area: 0.8841; CI 0.79–0.94) [Figure 3].

Discussion

ACR-TIRADS sonographic phenotyping has a lot of advantages. While it was primarily developed to triage nodules for FNAC, and avoid unnecessary FNACs of benign nodules, it is clear that it can also help identify malignant nodules effectively, particularly when combined with the Bethesda scoring. We found that our combined BETH-TR score was lowest in the benign nodules and progressively increased in FTC, FVPTC, and was the highest in PTCs. Among the malignant nodules, PTC has highly specific sonographic features while sonography is less discriminative of FTC and FVPTC. However, when combined with cytological features the discriminatory power of ACR-TIRADS could improve. Few studies have addressed the role of sonographic scores in indeterminate thyroid nodules [Table 4].[10-14] The presence of marked hypoechogenicity, taller-than-wide, punctate echogenic foci and extra-thyroidal extension each carry three points and likely to push the sonographic phenotype into a TR4 or TR5 nodules. Maia *et al*. studied the combination of the TI-RADS score with the Bethesda system to stratify malignancy risk in 136 indeterminate thyroid nodules, showing a negative predictive value of 90% in nodules classified as Bethesda III and TI-RADS 3 and 4a scores, and a higher risk of malignancy (75–77%) in nodules scored as TI-RADS 4b and 5 with Bethesda IV and V.[14] While individual risk stratification of BETH scoring and TR scoring has been studied in indeterminate thyroid nodules, there is not much literature in combining these two risk scores. The advantage of doing this is because of the high concordance between the two scoring systems in the extreme cases of benign and malignant thyroid nodules. In the indeterminate categories (BETH categories III and IV), adding the TR score may help risk-stratify nodules better. Hence, sonographic scoring could not only select the nodule for biopsy but also triage cytologically indeterminate thyroid nodules for management (sonographic follow-up, repeat FNAC, or surgery). The limitations of our study include the clinical (circular) bias in referring a patient for surgery one of the factors being sonographic characteristics and a smaller number of surgically resected indeterminate nodules.

Conclusion

A combined sonocytological BETH-TR score is one way to triage the management of indeterminate thyroid nodules. A BETH-TR score ≥7 gave a sensitivity of 92% specificity of 74% and correctly identified malignant nodules in 86% of cases.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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