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Stratifying Indeterminate Cytology Thyroid Nodules by Combining Thyroid Imaging Reporting and Data Systems (TI-RADS) and The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)

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ABSTRACT

Objective: To determine the risk of malignancy of Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) indeterminate Thyroid Nodules (Bethesda III, IV and V) by combining cytologic (TSBRTC) and Thyroid Imaging Reporting and Data Systems (TI-RADS) ultrasonographic features based on final histopathology.

Methods:

Design: Retrospective review of records
Setting: Tertiary Private Training Hospital
Participants: 551 records

Results: Among 81 eligible participants, 59 out of 84 nodules (70.24%) were malignant on histopathology. The malignancy risk of Bethesda classification was 60.87% (28 out of 46) for Bethesda III, 57.14% (8 out of 14) for Bethesda IV and 95.83% for Bethesda V. The malignancy risk for TI-RADS categories was 0 % (0/1) for TI-RADS 2, 50% (10 out of 20) for TI-RADS 3, 71.05 % for TI-RADS 4 and 91.67 % for TI-RADS 5. The highest risk of malignancy (100%) was associated with [Bethesda IV/TI-RADS 1, 2, and 3], [Bethesda V/TI-RADS 1, 2 and 3], [Bethesda IV and V/TI-RADS 1, 2 and 3] and [Bethesda IV/TI-RADS 5]. The lowest risk of malignancy (33.33%) was associated with [Bethesda III/TI-RADS1, 2 and 3]. A high Bethesda classification (Bethesda V) was almost 5x more likely to have a malignant anatomorphology compared with Bethesda III (p = .05) while a TI-RADS 4 or 5 category was almost 5x more likely to have a malignant anatomorphology compared to TI-RADS 1, 2 or 3 (p = .026).

Conclusion: This study showed that TI-RADS scoring is a sensitive diagnostic classification in recognizing patients with thyroid cancer and combining Bethesda classification and TI-RADS scoring increases the sensitivity in the diagnosis of malignant thyroid nodules. A higher likelihood of malignancy is associated with higher Bethesda classification and TI-RADS scoring.

Keywords: *Cytologically Indeterminate Thyroid nodule; ACR TI-RADS; Bethesda Classification; thyroid malignancy; thyroid ultrasonography; Ultrasound Guided- Fine Needle aspiration biopsy; thyroidectomy*

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Ultrasonography plays a vital role in the evaluation of thyroid nodules for fine needle aspiration biopsy (FNAB).[1] In 2017, the American College of Radiology (ACR) recommended a point system for the assessment of imaging of thyroid nodules (TNs). Points are assigned based on 5 ultrasound features and the sum determines the ACR TI-RADS classification of the nodule.[2] The point total determines the nodule's ACR TI-RADS level, which ranges from TR1 (benign) to TR5 (high suspicion of malignancy). The ACR TI-RADS is consistent with most other guidelines in recommending FNAB for highly suspicious nodules 1 cm or larger. However, their thresholds for mildly suspicious (TR3) and moderately suspicious (TR4) nodules (2.5 and 1.5 cm, respectively) are higher.

Cytologically indeterminate thyroid nodules currently present a challenge for clinical decision-making. In 2007, a conference to standardize the diagnostic terminology for the reporting of thyroid cytopathology results was held in Bethesda, leading to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC).[3] The 6 diagnostic categories (DC) used in the TBSRTC are: DC I = nondiagnostic, DC II = benign, DC III = atypia/follicular lesion of undetermined significance (AUS/FLUS), DC IV = follicular neoplasm/ suspicion for a follicular neoplasm (FN/SFN), DC V = suspicious for malignancy and DC VI = malignant.[3] According to the 2015 American Thyroid Association (ATA) guidelines, if the nodule has benign cytology, further immediate diagnostic studies or treatment are not required and if a cytology result is diagnostic for primary thyroid malignancy, surgery is generally recommended.[4] If the results are indeterminate (DC III, IV, V) management can be either a repeat FNAB, molecular testing or surgical excision depending on the clinical risk factors, sonographic features, patient preference.

In current practice, the Bethesda scoring system is utilized as the sole tool in treatment decision making. This study aims to increase awareness of the use of the TI-RADS scoring system in treatment decision making in the future. By incorporating both ultrasonographic and cytologic scoring systems in pre-operative planning, treatment plans may be more objective and precise in selecting patients for surgery. To the best of our knowledge, based on a search of HERDIN Plus, the ASEAN Citation Index (ACI), the WHO Western Pacific Region Index Medicus (WPRIM), the Directory of Open Access Journals (DOAJ), MEDLINE (PubMed and PubMed Central), and Google Scholar using the search terms " thyroid nodule," "BETHESDA,""TIRADS,","thyroid cytology" and "Thyroidectomy", there are no local studies to date that evaluated the benefit of a combination of 2017 ACR TI-RADS with TBSRTC on the approach to indeterminate TNs.

Hypothesizing that Indeterminate Thyroid nodules with Higher TI-RADS scoring have an increased risk of malignancy, this study aims to determine the risk of malignancy of indeterminate Thyroid Nodules (Bethesda III, IV and V) by combining cytologic and ultrasonographic features using Thyroid Imaging Reporting and Data Systems (TI-RADS) based on final histopathology.

METHODS

With St. Luke's Medical Center Institutional Ethics Review Committee approval (EC Reference No.: SL-21027) this retrospective study screened hospital records of all patients who underwent thyroid surgeries from January 1, 2017 to December 31, 2020 for possible inclusion in the study. Inclusion criteria were indeterminate cytology results on fine needle aspiration biopsy; thyroid ultrasound performed in our institution with image availability; and final histopathology reports of the thyroid surgery specimen. Excluded were records with incomplete data and those with any data obtained from another hospital.

Sample Size Computation

A minimum of 78 subjects were required for this study based on a level of significance of 5%, a prevalence of 4%, sensitivity of 72.7%, specificity of 95.3%. The values for the prevalence of malignant nodules and sensitivity of the Bethesda were based on the study by Reddy *et al.*, Evaluation of Bethesda system for reporting thyroid cytology with histopathological correlation.[5]

Demographic data such as the age and sex were obtained from the hospital database. Thyroid ultrasound (US) results were retrieved from the Institute of Radiology. From static grayscale US images recorded during the original examination, the following categories were evaluated by a board-certified radiologist (KTGM): composition, echogenicity, shape, margins and echogenic foci. Composition was classified as spongiform, mixed or solid. Echogenicity was classified as hyper-, iso- or hypoechoic to the surrounding thyroid parenchyma or as showing marked hypoechogenicity when compared with the adjacent strap muscle. Shape was classified as wider-than-tall or taller-than-wide (greater in the anteroposterior dimension than in the transverse dimension). Margins were classified as smooth, lobulated or irregular and if there were extrathyroidal extension. Echogenic foci, if present, was classified as macrocalcifications, peripheral/rim calcifications and microcalcifications. For the ACR TI-RADS classification, each ultrasound feature received point(s) according to the 2017 ACR TI-RADS publication,[6] being classified as TR1 (0 points), TR2 (2 points); TR3 (3 points); TR4 (4–6 points) and TR5 (≥ 7 points). Radiologists referred to

the lexicon white paper for detailed descriptions of all categories and features, which also contains images illustrating these features.[7]

The FNAB results were retrieved from the Institute of Pathology. Official readings had been previously signed out by a board-certified pathologist. Only FNAB results reported as Bethesda III, IV or V were included in data analysis. The final histopathology reports of patients who underwent thyroid surgery were also retrieved from the Institute of Pathology. Each report included in the study was classified as either benign or malignant. A malignant diagnosis was considered the control for comparison of cytologic and ultrasonographic diagnoses in this study. The FNAB and final histopathologic results were reviewed by at least 1 board-certified pathologist if results were benign and at least 2 board-certified pathologists if results were malignant.

Outcome Measures and Data Analysis

The primary outcome in this study was the distribution of malignant histopathologic diagnosis among Bethesda categories III, IV and V, calculated according to risk of malignancy. The distribution of malignant histopathologic diagnosis among ACR TI-RADS scores were also calculated according to risk of malignancy. This study combined FNAB results with 2017 ACR TI-RADS and the distribution of malignancy of the ACR TI-RADS score combined with Bethesda III, Bethesda IV and Bethesda V were likewise calculated using risk of malignancy. The diagnostic performance of Bethesda with ACR TI-RADS when considering Bethesda III and category TR1, 2 and 3 as negative and Bethesda IV and V and TR4 and 5 as positive were calculated in terms of sensitivity, specificity, positive predictive value, negative predictive value and accuracy.[7]

The likelihood of malignant anatomorphology (AP) were estimated according to the ACR TI- RADS [1, 2, 3, 4 and 5] and Bethesda system (III, IV and V) by logistic regression model and Wald Chi-Square test statistical analysis.[7] Crude and adjusted odds ratios and their corresponding 95% confidence intervals were determined. Null hypotheses were rejected at 0.05 alpha level of significance. SPSS software version 1.0.0.1508 (IBM Corp., Armonk, NY, USA) was used for data analysis.

RESULTS

Out of records of 551 patients who underwent thyroid surgeries from 2017-2020, only 392 patients had available FNAB results. Three hundred eleven (311) patients were excluded from the study due to the following reasons: 189 had FNAB results that were not classified as indeterminate while six lacked FNAB results data; 108 had ultrasonograms that were not performed in our hospital while another eight lacked ultrasound data.

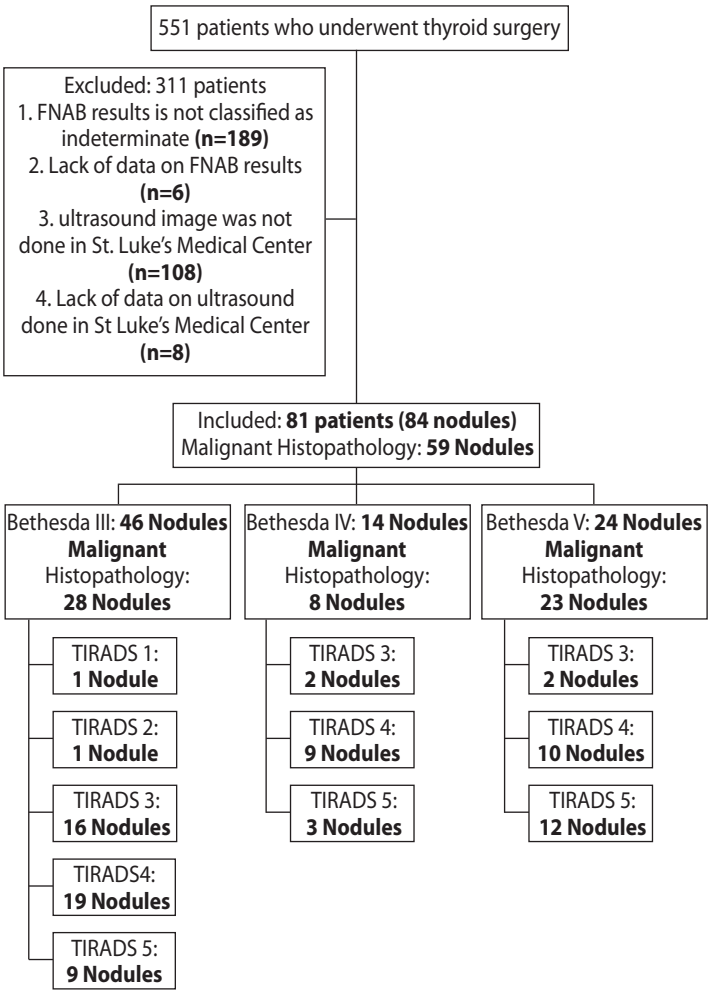

Figure 1. Summary of study population

The remaining 81 patients (84 nodules) were finally included in our study. Most (N=76, 90.48%) were female and in their 40s (N=27, 32%) and the mean age was 48 years old. There were 84 nodules, of which 59 nodules (70.24%) were confirmed to be malignant via histopathology. There were 46 (54.76%) Bethesda III, 14 (16.67%) Bethesda IV and 24 (28.57%) Bethesda V nodules and 20 (23.81%) were classified TI-RADS 3, 38 (45.23%) TI-RADS 4, and 24 (28.57%) TI-RADS 5. *(Figure 1)*

The malignancy risk for Bethesda classifications was 60.87% (28/46) for Bethesda III, 57.14% (8/14) for Bethesda IV and (23/24) 95.83% for Bethesda V. The malignancy risk for TI-RADS categories was 0 % (0/1) for TI-RADS 2, 50% (10/20) for TI-RADS 3, 71.05 % (27/38) for TI-RADS 4 and 91.67 % (22/24) for TI-RADS 5. *(Table 1)*

The malignancy risk of combined Bethesda classification and TI-RADS categories was also computed. The highest risk of malignancy (100%) was [Bethesda IV/TI-RADS 1, 2, and 3], [Bethesda V/TI-RADS 1, 2

Table 1. Risk of malignancy for Bethesda classification and TIRADS categories

		Histopathology		Risk of Malignancy (%)	p value*	df	C.I	Wald
	All (%) n=84	Benign n= 25	Malignant n=59					
Bethesda Classification								
Bethesda III	46	18	28	**60.87**	.79 (reference)	2		5.089
Bethesda IV	14	6	8	**57.14**	.451	1	.161-2.252	.569
Bethesda V	24	1	23	**95.83**	**.05**	1	**1.001-72.434**	**3.844**
TIRADS Category								
1	1	1	0	**0**	.28 (reference)			
2	1	1	0	**0**	1.00	1	.000	.000
3	20	10	10	**50**	1.00	1	.000	.000
4	38	11	27	**71.05**	1.00	1	.000	.000
5	24	2	22	**91.67**	1.00	1	.000	.000
4 and 5	62	13	49	**79.03**	**.03**	1	**1.237-86.555**	**4.649**

**Logistic regression and Wald test*

Table 2. Accuracy of TIRADS classification

			Histopathologic Results		
			Malignant	Benign	TOTAL
	TIRADS	TR 4 and 5 (Unfavorable)	49	13	62
		TR1/TR2/ TR3 (Favorable)	10	12	22
	TOTAL		59	25	84
	Sensitivity (%)				**83.05**
	Specificity (%)				**21.31**
	Positive Predictive Value (%)				**79.03**
	Negative Predictive Value (%)				**54.55**
	Accuracy (%)				**72.62**

Table 3. Accuracy of Bethesda classification

			Histopathologic Results		
			Malignant	Benign	TOTAL
	TBSRTC	Bethesda IV/V	31	7	38
		Bethesda III	28	18	46
	TOTAL		59	25	84
	Sensitivity (%)				**52.54**
	Specificity (%)				**14.29**
	Positive Predictive Value (%)				**81.58**
	Negative Predictive Value (%)				**39.13**
	Accuracy (%)				**58.33**

and 3], Bethesda [IV and V/TI-RADS 1, 2 and 3] and [Bethesda IV/TIRADS 5]. The lowest risk of malignancy (33.33% was [Bethesda III/TI-RADS 1, 2 and 3].

The diagnostic value of Bethesda classification, TI-RADS scoring, and Bethesda combined with TI-RADS when compared with histopathology [malignant vs benign] was calculated. Comparing histopathology with TI-RADS only [TR4/5 vs TR1,2,3] had a sensitivity of 83.05%, specificity of 21.31%, positive predictive value (PPV) of 79.03%, negative predictive value of 54.55% and accuracy of 72.62%. *(Table 2)* Comparing histopathology with Bethesda classification only (Bethesda III vs Bethesda IV/V) had a sensitivity of 52.54%, specificity of 14.29%, positive predictive value (PPV) of 81.58%, negative predictive value of 39.13% and accuracy of 58.33%. *(Table 3)*

Comparing histopathology and Bethesda III combined with TI-RADS [TR4/5 vs TR1/2/3] had a sensitivity of 78.57%, specificity of 17.65%, positive predictive value (PPV) of 78.57%, negative predictive value of 66.67% and accuracy of 73.91%. Comparing histopathology and Bethesda IV/V combined with TI-RADS [TR4/5 vs TR1/2/3] had a sensitivity of 93.10%, specificity of 25.93%, positive predictive value (PPV) of 79.41%, negative predictive value of 0% and accuracy of 75%. *(Table 4)*

Combining the Bethesda IV/V with TIRADS 4 and 5 had a sensitivity of 93.10% and accuracy of 75% which gives the highest sensitivity and accuracy in predicting the risk of malignancy comparing it with only TIRADS or Bethesda alone and from the combination of Bethesda III with TIRADS 4 and 5. *(Table 5)*

We conducted a stepwise logistic regression to determine predictors of malignant anatomorphology. *(Table 1)* We found that in our study, predictors of malignancy are the following: (1) High Bethesda classification (Bethesda V) and High TI-RADS Score (TI-RADS 4 or 5). A high Bethesda classification (Bethesda V) is almost 4x more likely to have a malignant anatomorphology compared with having Bethesda III (p = .03 ; CI: 1.24 – 86.56) while having TI-RADS 4 or 5 is almost 5x more likely to have a malignant anatomorphology compared to having TI-RADS 1, 2 or 3 (p = .03; CI 1.24 - 86.55).

DISCUSSION

The diagnosis of a benign or malignant lesion in the indeterminate thyroid nodule really presents a challenge for clinicians. Careful and judicious use and analysis of preoperative work-ups of thyroid nodules can help decrease the number of unnecessary diagnostic surgeries or avoid undiagnosed malignant thyroid nodules. The primary outcome of the study showed that in sample of indeterminate thyroid nodules having a high BETHESDA or TIRADS scores showed an increased risk for malignancy.

There have been a number of studies conducted through the years regarding indeterminate thyroid nodules. In 2009, Horvath *et al.* first published a study on the use of TIRADS classification which aims to improve the ultrasound characterization of nodules and establish risk groups for patients who will undergo FNAB.[8] In their study, 10

Table 4. Accuracy of using TIRADS scoring in Bethesda III Cytology patients

			Histopathologic Results		
TBSRTC		**TIRADS**	**Malignant**	**Benign**	**TOTAL**
Bethesda III	ACR-TIRADS score	TR 4 and 5 (Unfavorable)	22	6	28
		TR1/TR2/ TR3 (Favorable)	6	12	18
	TOTAL		28	18	46
	Sensitivity (%)				**78.57**
	Specificity (%)				**17.65**
	Positive Predictive Value (%)				**78.57**
	Negative Predictive Value (%)				**66.67**
	Accuracy (%)				**73.91**

Table 5. Accuracy of using TIRADS scoring in Bethesda IV and V Cytology patients

			Histopathologic Results		
TBSRTC		**TIRADS**	**Malignant**	**Benign**	**TOTAL**
Bethesda IV/V	ACR-TIRADS score	TR 4 and 5 (Unfavorable)	27	7	4
		TR1/TR2/ TR3 (Favorable)	2	0	34
	TOTAL		31	7	38
	Sensitivity (%)				**93.10**
	Specificity (%)				**25.93**
	Positive Predictive Value (%)				**79.41**
	Negative Predictive Value (%)				**-**
	Accuracy (%)				**75**

ultrasound patterns of thyroid nodules with related risk of malignancy were described.[8] In the same year, a study by Park *et al.* proposed an equation for predicting the probability of malignancy on the basis of 12 ultrasound features.[9] In 2011, Kwak *et al.* researched a practical TIRADS classification for the management of thyroid nodules.[6] Sonographic characteristics predictive of malignancy such as: solid echogenicity, hypoechogenicity or marked hypoechogenicity, microcalcifications, microlobulated or irregular border and taller than wide shape was used to classify TIRADS from 1 to 5.[6] They categorized the TIRADS to 1: normal thyroid gland, 2: benign nodules, 3: probably benign nodules, 4a: one ultrasound features suggestive of malignancy, 4b: two ultrasound features suggestive of malignancy, 4c: three or four features suggestive of malignancy and 5: five ultrasound features suggestive of malignancy. The 2016 study by Srinivas *et al.* used the TIRADS classification suggested by Kwak *et al.* and showed that the classification is a reliable modality in differentiating benign nodules from malignant nodules.[10]

In our study, the risk of malignancy increases as TI-RADS scoring for ultrasound increases with the risk of malignancy from TI-RADS 1, 2, 3, 4 and 5 were 0%, 0%, 50%, 71.05%, 91.67% respectively. The increasing pattern was not seen with the risk of malignancy for Bethesda classification with 60.87%, 57.14%, and 95.83% for Bethesda III, IV and V respectively; although not significant, this can be explained by the low number of cases having a Bethesda IV (14 cases) compared to Bethesda III (46 cases) and Bethesda V (24 cases).

Also in our study when TIRADS or BETHESDA scoring system is used as a diagnostic tool, the accuracy of TI-RADS scoring is 72.62% (sensitivity of 83.05% and specificity of 21.31%) compared with the Bethesda classification accuracy of only 58.33% (sensitivity of 52.54% and specificity of 14.29%). The combination of ultrasound features using TI-RADS scoring and cytology reading using the Bethesda classification can be a useful tool (especially preoperatively) in diagnosing malignant nodules classified Bethesda IV/V with a sensitivity of 93.1%. In addition, a low risk nodule (Bethesda III/TI-RADS ½/3) in our study has a malignancy risk of only 33%, in contrast, the risk of malignancy of a high risk nodule (Bethesda IV and V/TI-RADS 5) has a risk of malignancy of 93.33% which can be a useful tool in stratifying patients pre-operatively.

Comparing the results of our study with a local study published in 2017 by Dy *et al.,* the malignancy risk of TI-RADS categories are the following: category 3, 4 and 5 are 12.5%, 33% and 66.67%, respectively; also in their study, the accuracy of TI-RADS was only 53%.[11] In our study, the malignancy risk of TIRADS category is 50%, 71% and 92%, respectively with an accuracy of 72.62%.

A 2019 study by Barbosa *et al.* attempted to stratify indeterminate lesions according to the risk of malignancy by combining cytology with 2017 ACR TI-RADS and 2015 ATA guidelines.[5] In their study, patients classified as Bethesda III and presenting a favorable ultrasound appearance (TI-RADS 2, 3 or 4a / ATA very low, low or intermediate), only 5.9 and 5.7% (TI-RADS and ATA, respectively) had malignant histological results.[7] In contrast, 81.6 and 87.2% (TI-RADS and ATA, respectively) classified as Bethesda IV or V, which presented an ultrasound considered unfavorable (TI-RADS 4 and 5) had malignant histological results.[7] The results of our study showed 33.33% for low risk nodule (Bethesda III and TIRADS 1,2 and 3) for thyroid nodules with high risk features showed 68.42% and 93.33% for nodules with [Bethesda IV and V with TIRADS 4] and [Bethesda IV and V with TIRADS 5], respectively.

Our study showed that a high Bethesda score (Bethesda V) and high TI-RADS score (TI-RADS 4 and 5) are associated with having a malignant histopathology upon surgical intervention and is statistically significant. Having those findings suggested it was almost 5 times more likely to have a malignant histopathology compared to having a low risk nodule. This can be helpful in stratifying patients for surgery and giving the clinician other ways to explain it to their patients.

There are several limitations to our study. The main limitation is sample attrition bias, due to the stringent selection criteria. Specifically, sample attrition was due to the following reason: 1) some results lacked ultrasound images that were used in characterizing nodules using TI-RADS; and 2) there were a number of patients with indeterminate thyroid nodules on cytology who lacked ultrasound results or where the ultrasonogram was acquired in another institution; and 3) there was a significant number of patients that did not have histopathology results. Sampling cases only from our institution add another limitation, as our results might not be reflective of the larger population. Our study suggested an increased risk for malignancy of thyroid nodules compared with the study of Barbosa *et al.*[7] The differences in results can be attributed to institutional differences in terms of population, specialists reading the FNAB results, general practice of the clinician (ultrasound guided FNAB or not) as well as differences in timeline in which the study was done.

In conclusion, our study showed that TI-RADS scoring is a sensitive classification in recognizing patients with thyroid cancer and can be used as a guide in deciding the need for fine needle aspiration biopsy. Combining Bethesda classification and TIRADS scoring increases the sensitivity in the diagnosis of malignant thyroid nodules. This study also showed that having a higher Bethesda classification and TIRADS scoring is associated with a high likelihood of thyroid malignancy.

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