Gray-scale and Doppler ultrasound: significance in predicting malignancy of thyroid nodules

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ABSTRACT

Introduction: There have been various systems for identifying risk of thyroid nodule malignancy using ultrasound (US), with the most recent being 2017 American College of Radiology proposed TI-RADS. However, this system does not take vascular patterns into account. The aim of this study is to determine the role of gray scale and color Doppler ultrasound in differentiating benign and malignant thyroid nodules

Methods: A total of 180 ultrasound images of patients with thyroid nodules were analyzed. Nodule composition, shape, margin, echogenicity, echogenic foci and vascular patterns were evaluated. The results were compared with histology findings

Results: 98 (54.4%) thyroid nodules were benign and 82 (45.5%) – malignant. Compared to malignant, more benign thyroid nodules (80.6%) were bigger than 1 cm, $p < 0.001$). Benign and malignant thyroid nodules did not significantly differ in frequency of composition or echogenicity ($p > 0.05$). Round and taller-than-wide shape, lobulated or irregular margin, microcalcifications were more common among malignant nodules ($p < 0.05$). Mean total TI-RADS score was significantly higher among malignant thyroid nodules compared to benign, $p < 0.001$. TI-RADS sensitivity in predicting the risk of malignancy was 82.9%, specificity – 69.4%, area under curve – 0.822, while vascularity had sensitivity of 40% and specificity of 36.7%. Mixed vascularity was more common among benign ($p = 0.003$) and weak perinodular vascularity was more common among malignant nodules ($p = 0.048$). Weak negative correlation was found between total amount of TI-RADS points and vascular patterns ($r_s = - 0.238$, $p = 0.001$)

Conclusions: In our study irregular or lobulated margin, taller-than-wide shape and microcalcifications were more common among malignant thyroid nodules. While thyroid US using TI-RADS had good diagnostic value in predicting malignancy, vascular patterns had low sensitivity (40.2%) and specificity (36.7%). Thyroid nodules with intranodular vascularity had a lower TI-RADS score.

Keywords: ultrasound, thyroid, malignancy.

INTRODUCTION

With the introduction of high resolution ultrasound, the prevalence of thyroid nodules became exceedingly high – reaching up to 76% in adult population [1]. Even though such high prevalence is alarming, most of the nodules are benign with only a small fraction being malignant [2]. Fine-needle aspiration (FNA) cytology is a relatively easy and cost effective test to distinguish between the two [3]. However, it is not efficient to perform FNA on every single thyroid nodule case leading to overdiagnosis which would cause more harm than good [4]. Currently, thyroid ultrasound – a reliable and noninvasive method, is used to identify the probability of malignancy and the need for FNA.

There have been various systems for identifying risk of thyroid nodule malignancy using ultrasound (US), with the most recent being 2017 American College of Radiology proposed TI-RADS (Thyroid Imaging, Reporting and Data System). Using this system thyroid nodules are awarded points for their sonographic features: composition, echogen icity, shape, margin and echogenic foci [5]. However, this system does not take vascular patterns established with color Doppler US into account.

The aim of this study is to determine the role of gray scale and color Doppler ultrasound in differentiating benign and malignant thyroid nodules.

LITERATURE REVIEW

THYROID NODULES

The thyroid is an endocrine gland in the neck which plays an important role in metabolism by producing three hormones: Triiodothyronine (T3), Tetraiodothyronine (T4), Calcitonin, and releasing them into the bloodstream. American Thyroid Association describes thyroid nodules as "discrete lesions within the thyroid gland, radiologically distinct from surrounding thyroid parenchyma." [6]. These lesions are a common finding, with prevalence reaching up to 68-76% among adults [1,7]. There was a significant leap in prevalence of thyroid nodules due to introduction of high resolution ultrasound systems. Before, thyroid nodules were palpable only in 4-7% of population [8,9]. Most of the nodules are benign, with 10-15% being malignant [10,11].

Serum thyrotropin (TSH) and thyroid US are essential in thyroid nodule evaluation, with former providing important information about nodule functionality and latter – about the presence of sonographic features that suggest malignancy. Fine-needle aspiration cytology is the test that follows thyroid US if nodules are found to be suspicious. FNA is used to effectively determine thyroid nodule malignancy or the need for histological evaluation to reach a definitive decision [3,12]. Histologically thyroid cancer can be divided into four major types: papillary, follicular, medullary and anaplastic, with the most frequent being papillary thyroid carcinoma [13].

THYROID ULTRASOUND

Thyroid sonography is an useful tool in evaluation of various thyroid disorders. According to American Association of Clinical Endocrinologists (AACE) and Associazione Medici Endocrinologi (AME) recommendations, thyroid ultrasound should be used [14,15]:

- To confirm the presence of thyroid nodules, to characterize them and to evaluate the risk of malignancy;
- To evaluate diffuse changes in thyroid parenchyma;
- To differentiate between thyroid nodules and other cervical masses;
- To detect post-operative residual or recurrent tumor in thyroid bed or metastases to neck lymph nodes;
- To screen high risk patients for thyroid malignancy (history of familial thyroid cancer, multiple endocrine neoplasia (MEN) type II and irradiated neck in childhood);
- To guide diagnostic and therapeutic interventional procedures.

As mentioned previously, thyroid ultrasound can be used to predict malignancy in thyroid nodules and to determine the need for FNA. Certain sonographic features: hypoechogenicity, taller-than-wide shape, irregular or lobulated margins, microcalcifications and increased intranodular vascularity were found to be independent risk factors suggesting malignancy [16-18]. However, 2017 American College of Radiology (ACR) TI-RADS regards solid composition of thyroid nodules as a suspicious feature and does not include vascular patterns at all [5]. Several other sources state that vascular patterns of thyroid nodules do not reflect risk of malignancy [19].

Reported diagnostic value of thyroid ultrasound in predicting malignancy varies by author. Sensitivity was reported to be as low as 41% or as high as 93%. Specificity and positive predictive value (PPV) ranged from 43 to 84% and from 34 to 74% respectively. However, reported negative predictive value (NPV) was high in most cases – ranging from 84 to 99.2% [20-22].

METHODS AND MATERIALS

A retrospective study was performed, a total of 180 patient cases with thyroid nodules from 2014 to 2017 were analyzed in Lithuanian University of Health Sciences Kaunas Clinics. In all cases the definitive diagnosis was confirmed by post-operative histologic evaluation of surgical specimen. Patients' age, gender, sonographic features of thyroid nodules and results of cytological and histological evaluation were assessed.

Thyroid ultrasound procedure was performed as follows: patients were positioned lying face-up with a pillow placed under the shoulders to extend the area to be scanned, a linear transducer was used. Thyroid nodule composition, echogenicity, shape, margin, echogenic foci were

Table 1. TI-RADS Categories

Composition	Echogenicity	Shape	Margin	Echogenic foci
Cystic or almost completely cystic – 0 pts.	Anechoic – 0 pts.	Wider-than-tall – 0 pts.	Smooth – 0 pts.	None or large comet-tail artifacts – 0 pts.
Spongiform – 0 pts.	Hyperechoic or isoechoic – 1 pts.	Taller-than-wide – 3 pts.	Ill-defined – 0 pts.	Macrocalcifications – 1 pts.
Mixed cystic or solid – 1 pts.	Hypoechoic – 2 pts.		Lobulated or irregular – 2 pts.	Peripheral (rim) calcifications – 2 pts.
Solid or almost completely solid – 2 pts.	Very hypoechoic – 2 pts.		Extra-thyroidal extension – 3 pts.	Punctate echogenic foci – 3 pts.

Points awarded for sonographic features are then added. Depending on the total amount of points, thyroid nodules are assigned to one of the TI-RADS Levels (TR): TR1, TR2, TR3, TR4 or TR5 (Table 2) [5].

Table 2. TI-RADS Levels

TI-RADS Level	Points
TR1 – Benign	0
TR2 – Not Suspicious	2
TR3 – Mildly Suspicious	3
TR4 – Moderately Suspicious	4-6
TR5 – Highly Suspicious	≥ 7

Thyroid nodule size, presence of halo and vascular patterns were assessed as well. Vascular patterns were evaluated using Color Doppler US and assigned one of the following: absent vascular flow, exclusively weak or intense perinodular, exclusively weak or intense intranodular, mixed vascular flow. As suggested in 2017 ACR TI-RADS solid composition, hypoechogenicity, taller-than-wide shape, irregular or lobulated margin, punctate echogenic foci were considered as sonographic features suggesting malignancy, intranodular vascular pattern with or without perinodular vascularity was also considered as a sign of malignancy when evaluating the diagnostic value of vascularity (Fig. 1,2).

Fig 1. Solid, very hypoechoic, taller-than-wide thyroid nodule with irregular margin, absent calcifications, weak perinodular and intranodular vascularity.

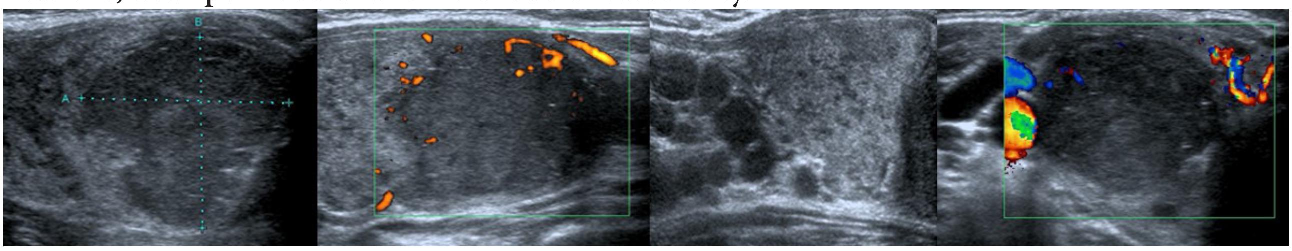


Fig 2. Solid, hypoechoic, wider-than-tall thyroid nodule with lobulated margin, punctate echogenic foci, weak perinodular and intranodular vascularity.

Statistical analysis was performed with "IBM SPSS Statistics 17.0" and "MedCalc 18.2.1". Descriptive statistics were given in form of means with standart deviation and minimum/maximum values of the variables. Student's t-test was used to compare means of two variables atleast on ordinal scale. Chi-squared test was used to compare two independant variables. Fisher's exact test was used to compare two independant variables if the sample sizes were small. Spearman correlation coefficient (rs) was used to evaluate the correlation between two variables – one on the interval and other on ordinal scale. Sensitivity, specificity and accuracy were calculated using ROC curve. Younden index (J) was used to find optimal cut-off value. Results were considered statistically significant with p values of 0.05 and lower.

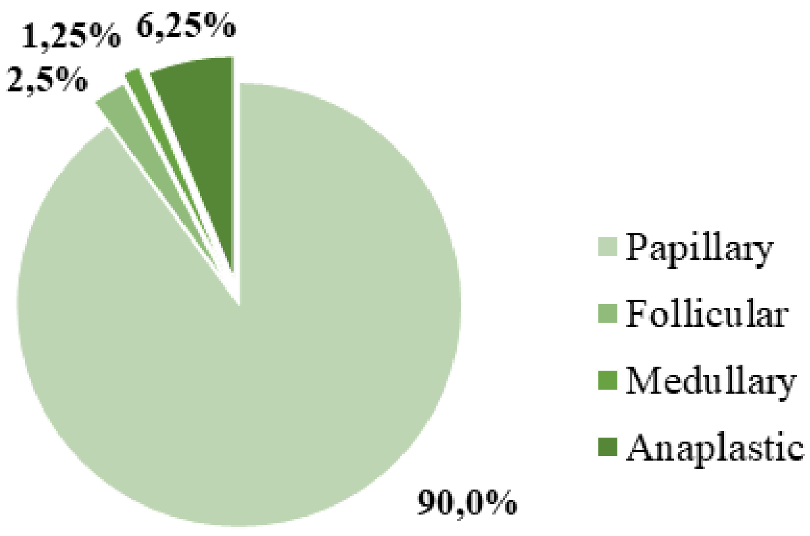
RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Out of 180 cases that were analyzed, 22 (12.2%) patients were male and 158 (87.8%) – female. Patients' mean age was 54.38 ± 18.2 years, with the youngest being 12 and the oldest – 90 years. Mean age of male patients was 58.05 ± 19.7, female – 53.87 ± 18.0 years. Mean age of patients diagnosed with thyroid cancer was 52.9 ± 17.7, with benign nodules – 55.6 ± 18.7 years – higher compared to a study by Frates et al where mean age of patients with malignant and benign thyroid nodules was 46.2 ± 0.9 and 40.1 ± 0.3 respectively [23]. No significant differences between the age of male and female patients and between age of patients with malignant and benign thyroid nodules were found ($p > 0.05$).

Out of 180 thyroid nodules, 98 (54.4%) were benign and 82 (45.5%) were malignant. Diagnoses of all cases were verified by histologic evaluation of surgical specimen. In cases of malignant thyroid nodules, papillary thyroid carcinoma was the most common (90%) and medullary thyroid carcinoma – the least common (1.25%) diagnosis. Papillary and follicular thyroid cancer combined takes up 92.5% of the cases which matches the frequency mentioned in American Thyroid Association (ATA) guidelines (> 90%) [6]. Frequency of medullary thyroid cancer was lower than the one mentioned in a study by Ball – 2-5% of all thyroid cancer cases [24]. Distribution of thyroid cancer types found during histologic evaluation is shown in Fig 3.

Fig 3. Types of thyroid cancer



THYROID ULTRASOUND

Most of the benign thyroid nodules (80.6%) measured during thyroid US procedure were bigger than 1 cm. In comparison, number of malignant nodules that were smaller than 1 cm was significantly higher (53.7%) than benign (19.4%), $p < 0.001$. These results correspond to the conclusions of a study by Cavallo et al that larger nodules have lower malignancy rate [25]. 22 (22.4%) benign and 11 (13.4%) malignant thyroid nodules had a well-defined hypoechoic halo, which is usually a sign suggesting benignity [26], however, no significant difference was found between benign and malignant nodules ($p = 0.127$). In cases of multiple thyroid nodules malignancy was found in 19 (41.3%) cases, 27 (58.7%) were benign. Some authors have found that a higher number of thyroid nodules suggest a higher risk of malignancy [27], however, no significant differences in malignancy rates in cases of multiple thyroid nodules were found ($p = 0.607$).

Benign and malignant thyroid nodules did not significantly differ in composition ($p > 0.05$). Using 2017 ACR TI-RADS, mean score awarded for composition was 0.27 ± 0.7 for benign nodules and 1.35 ± 1.45 points for malignant nodules. No significant difference between these scores was found ($p = 0.651$). Distribution of thyroid nodule composition types established during thyroid US is shown in Table 3.

Table 3. Thyroid nodules – composition

	All nodules	Benign	Malignant
Solid	87 (48.3%)	48 (48.5%)	39 (47.6%)
Mixed cystic or solid	89 (49.7%)	46 (47.4%)	43 (52.4%)
Spongiform	4 (2.2%)	4 (4.1%)	0

Most of the thyroid nodules were hypoechoic (74.4%). In ACR TI-RADS hypoechogenicity is established as sign that suggests malignancy [5], however, there were no significant difference in frequency of hypoechogenicity among benign and malignant thyroid nodules ($p > 0.05$) No difference was found in scores awarded for echogenicity as well ($p = 0.281$), mean score that benign and malignant nodules were awarded was 2.23 ± 0.76 and 2.35 ± 0.71 points respectively. Distribution of thyroid nodule echogenicity established during thyroid US is shown in Table 4.

Table 4. Thyroid nodules – echogenicity

	All nodules	Benign	Malignant
Hyperechoic	5 (2.8%)	4 (4.1%)	1 (1.2%)
Isoechoic	28 (15.6%)	15 (15.3%)	13 (15.9%)
Hypoechoic	69 (38.3%)	38 (38.8%)	31 (37.8%)
Very hypoechoic	78 (43.3%)	41 (41.84%)	37 (46.12%)

Taller-than-wide shape is said to be a highly suggestive of malignancy [5,27], which corresponds to results found in this study as well – taller-than-wide shape was significantly more frequent among malignant nodules ($p = 0.005$). Round shape was also found to be more frequent among malignant nodules compared to benign ($p < 0.001$). Mean TI-RADS score reflects this as well – average amount of points awarded for shape to benign thyroid nodules was 0.12 ± 0.6 while malignant nodules were awarded significantly more points – 0.51 ± 1.1 ($p = 0.004$). Distribution of thyroid nodule shape established during thyroid US is shown in Table 5.

Table 5. Thyroid nodules – shape

	All nodules	Benign	Malignant
Wider-than-tall	119 (66.1%)	85 (86.7%)	34 (41.5%)
Taller-than-wide	18 (10%)	4 (4.1%)	14 (17.1%)
Round	43 (23.9%)	9 (9.2%)	34 (41.5%)

Malignant thyroid nodules were found to have lobulated or irregular margins more often compared to benign nodules, p < 0.001. Also, mean score awarded to malignant nodules (0.63 ± 0.49 pts.) was significantly higher than that of benign nodules (0.04 ± 0.2 pts.), p < 0.001. Distribution of thyroid nodule margin type established during thyroid US is shown in Table 6.

Table 6. Thyroid nodules – margins

All nodules	Benign	Malignant	
Smooth	124 (68.9%)	94 (95.9%)	30 (36.6%)
Lobulated or irregular	56 (31.1%)	4 (4.1%)	52 (63.4%)

According to ACR TI-RADS, microcalcifications are associated with papillary thyroid cancer, especially when in combination with other suspicious sonographic features [5]. Similar results were found in this study as well – microcalcifications were more frequent among malignant thyroid nodules while absent echogenic foci was found more often among benign nodules, p < 0.001. Malignant thyroid nodules were awarded more points (1.35 ± 1.45 pts.) for presense of echogenic foci compared to benign nodules (0.27 ± 0.7 pts.), p < 0.001. Distribution of echogenic foci among thyroid nodules established during thyroid US is shown in Table 7.

Table 7. Thyroid nodules – echogenic foci

	All nodules	Benign	Malignant
None or colloid artifacts	123 (68.3%)	82 (83.7%)	41 (50%)
Macrocalcifications	17 (9.5%)	11 (11.2%)	6 (7.3%)
Microcalcifications	40 (22.2%)	5 (5.1%)	35 (42.7%)

Points awarded for different sonographic categories: composition, shape, echogenicity, margin and echogenic foci, were added up. Mean total TI-RADS score was significantly higher among malignant thyroid nodules (6.3 ± 2.1 pts.) compared to benign (4.1 ± 1.37 pts.), p < 0.001. Depending on total score, TI-RADS Level was determined for all thyroid nodules. Distribution of thyroid nodules‘ TI-RADS Levels and comparison with cancer risk levels presented in a study by Middleton et al [28] are shown in Table 8.

Table 8. TI-RADS Levels and malignancy risk comparison

	All nodules	Benign	Malignant	Middleton et al cancer risk levels
TR1	0	0	0	< 2%
TR2	7 (3.9%)	6 (3.3%)	1 (0.6%)	< 2%
TR3	33 (18.3%)	27 (15.0%)	6 (3.3%)	< 5%
TR4	98 (54.4%)	61 (33.9%)	37 (20.6%)	5-20%
TR5	42 (23.3%)	4 (2.2%)	38 (21.1%)	≥ 20%

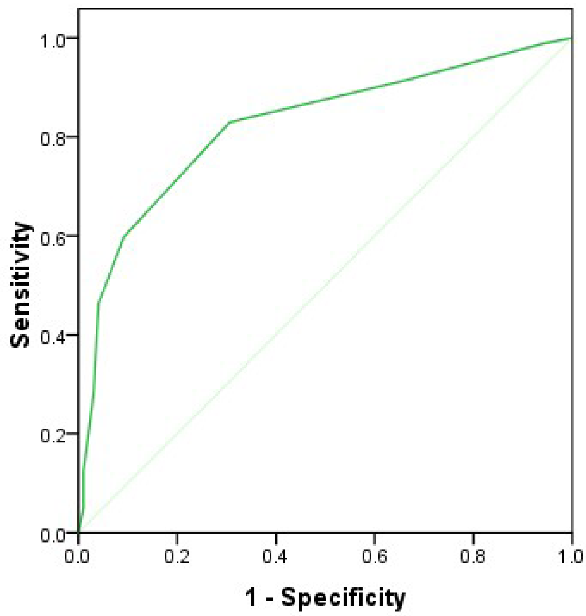
Thyroid US using 2017 ACR TI-RADS had a high sensitivity of 82.9% and a lower specificity of 69.4% in predicting the risk of malignancy of thyroid nodules. Compared to studies by Tan et al and Cappelli et al with reported sensitivity of 41-93% and specificity of 43-84%, the values found in this study are on the higher end of the interval in both sensitivity and specificity. Comparison of thyroid US sensitivity and specificity is shown in Table 9.

Table 9. Diagnostic value of thyroid US using TI-RADS

	Sensitivity (%)	Specificity (%)
Tan et al [20]	41	84
Cappelli et al [21]	93	43
Trimboli et al [29]	81	62
Horvath et al [30]	88	49
Stacul et al [22]	57	67
This study	82.9	69.4

Thyroid US using TI-RADS was found to be an useful and accurate tool in predicting the risk of malignancy. Area under curve (AUC) was 0.822, p < 0.001. Optimal cut-off value was found to be at 5 TI-RADS points (TR4) – the point where both sensitivity and specificity are the highest. ROC curve detailing sensitivity and specificity of Thyroid US using TI-RADS at multiple points is shown in Fig 4.

Fig 4. Diagnostic value of Thyroid US using TI-RADS – ROC curve



THYROID ULTRASOUND – VASCULAR PATTERNS

Mixed (both perinodular and intranodular) was the most common (52.2%) type of vascularity. Intranodular flow is generally associated with malignancy [31]. However, as mentioned in a study by Khadra et al [19], no difference in frequency of purely intranodular (weak or intense) vascularity between benign and malignant nodules was found in this study as well. Mixed vascularity was more common among benign (p = 0.003) and weak perinodular vascularity was more common among malignant nodules (p = 0.048). Distribution of vascular patterns among thyroid nodules established during thyroid Doppler US is shown in Table 10.

Thyroid nodules were awarded less TI-RADS points if the vascularity was of intranodular type – weak and negative correlation was found between total amount of TI-RADS points and vascular patterns (rs = - 0.238, p = 0.001). This correlation is shown in Fig 5.

Some authors in their studies report good diagnostic value of thyroid nodule vascular patterns in predicting the risk of malignancy: Varverakis et al – sensitivity of 70% and specificity 66% [32], Sultan et al – sensitivity of 90% and specificity 88% [33]. However, in this diagnostic value of thyroid nodule vascular patterns evaluated with Doppler US was found to be low (sensitivity of 40% and specificity of 36.7%) with more likeness to the results of a study by Lyshchik et al where sensitivity was found to be 65.2% and specificity 52.5% [33]. Diagnostic value of thyroid nodule vascular patterns is shown in Table 11.

Table 10. Thyroid nodules – vascular patterns

Vascular patterns	All nodules	Benign	Malignant
Absent	17 (9.4%)	4 (4.1%)	13 (15.9%)
Weak perinodular	63 (35%)	28 (28.57%)	35 (42.68%)
Intense perinodular	5 (2.78%)	4 (4.08%)	1 (1.21%)
Weak intranodular	1 (0.56%)	1 (1.02%)	0
Intense intranodular	0	0	0
Mixed	94 (52.2%)	61 (62.2%)	33 (40.2%)

Fig 5. Correlation between vascular patterns and TI-RADS score

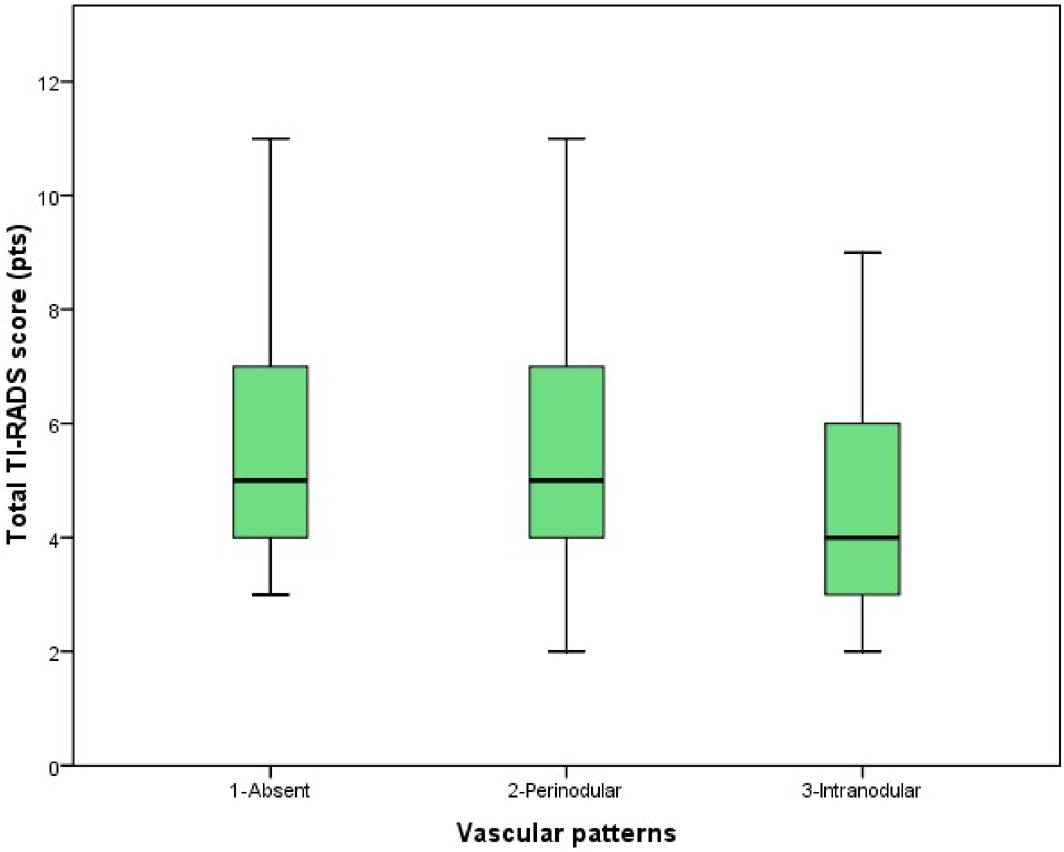


Table 11. Vascular patterns – diagnostic values in determining risk of malignancy

Sensitivity	Specificity	Positive predictive value	Negative predictive value
40.24% (95% CI 0.296-0.52)	36.73% (95% CI 0.27-0.47)	34.74% (95% CI 0.28-0.42)	42.35% (95% CI 0.35- 0.52)

CONCLUSIONS

In our study sonographic features: irregular or lobulated margin, taller-than-wide shape and microcalcifications were found to be more common among malignant thyroid nodules. While thyroid ultrasound using TI-RADS had good diagnostic value in predicting malignancy (sensitivity – 82.9%, specificity – 69.4%), vascular patterns had low sensitivity (40.2%) and specificity (36.7%). Thyroid nodules with intranodular vascularity were found to have a lower TI-RADS score.

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