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Application of Ultrasonography in Stratifying Malignancy Risk for Indeterminate Thyroid Nodules as per TBSRTC 2023

Sofia Guerreiro [1,*], Mariana Mourão [1], Isabel Loureiro [2], Rosário Eusébio [3], Sule Canberk [4,5] and Hugo Pinto Marques [1]

[1] Serviço de Cirurgia Geral, Centro Hospitalar Universitário Lisboa Central, Hospital Curry Cabral, 1069-166 Lisboa, Portugal; marianamourao8@gmail.com (M.M.); hugo.marques3@ulssjose.min-saude.pt (H.P.M.)
[2] Escola Nacional de Saúde Pública, Universidade NOVA de Lisboa, 1099-085 Lisboa, Portugal; isalou@ensp.unl.pt
[3] Serviço de Cirurgia Geral, Centro Hospitalar de Setúbal, 2910-446 Setúbal, Portugal; rosarioeusebio@gmail.com
[4] IPATIMUP, Institute of Molecular Pathology and Immunology of University of Porto, 4200-135 Porto, Portugal; sulecanberk@gmail.com
[5] I3S, Instituto de Investigação e Inovação em Saúde, University of Porto, 4099-002 Porto, Portugal
* Correspondence: sofiacuco@gmail.com; Tel.: +351-912782550

Abstract: Introduction: Thyroid nodules are extremely common and require complex management to prevent unnecessary surgical intervention and ensure that no malignant disease is overlooked. Several diagnostic tools and scoring systems are available to evaluate the risk of malignancy (ROM). The goal is to assess variables that can aid and support the clinical recommendations suggested by the updated Bethesda System for Reporting Thyroid Cytopathology (TBSRTC-2023), such as the ultrasonographic features of thyroid nodules, particularly for the indeterminate categories III (atypia of undetermined significance) and IV (follicular neoplasm). Methods: We retrospectively analysed the correlation of the demographic and ultrasonographic characteristics of thyroid nodules with the cytopathological and histopathological diagnoses of TBSRTC categories III (atypia of undetermined significance), IV (follicular neoplasm), V (suspicious for malignancy), and VI (malignant) in patients who underwent surgery in a single Portuguese centre over a 10-year period. Results: In total, 360 nodules were evaluated in 341 patients, and 57% were histopathologically malignant or borderline. The majority were included in the TBSRTC indeterminate categories III and IV, with ROMs of 44% and 43%, respectively. The ultrasonographic characteristics associated with a higher TBSRTC category and a greater ROM value were hypoechogenicity, the presence of microcalcifications, irregular margins, and the presence of cervical adenopathy. When correlating with a malignant histology, only adenopathy and the presence of microcalcifications were observed to be statistically significant. Discussion: The indeterminate categories of the TBSRTC have been the most challenging ones to manage. The new TBSRTC (2023) guidelines, as well as the ultrasonographic characteristics of a patient's nodule, can be helpful in assessing the ROM and deciding on an appropriate course of treatment. Other resources, such as molecular tests, are also playing a more important role in the clinical decision process and may become crucial in the future. Conclusions: The worrisome ultrasound features that this study found to statistically correlate with a malignant histology were the presence of microcalcifications and adenopathy. The clinical management of thyroid nodules requires a careful analysis of clinical history and an evaluation of demographic details, personal and family history, ultrasonographic features, and the results of cytopathology, thyroid function, and molecular/genetic tests.

Keywords: The Bethesda System for Reporting Thyroid Cytopathology; thyroid nodules; risk of malignancy; grey area; indeterminate thyroid nodules; ultrasonographic characteristics

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1. Introduction

Thyroid nodules are extremely common and are present in 19–68% of randomly selected individuals subjected to thyroid ultrasonography. However, only a small percentage of these (7–15%) constitute thyroid cancer [1–3]. Ultrasonography is the most widely used imaging modality for the assessment of thyroid diseases. It is an easily available, inexpensive, and radiation-free diagnostic tool that allows for the evaluation of the thyroid parenchyma; measurement of size, location, and characterization of nodules; and evaluation of cervical lymph nodes. Thyroid nodules are evaluated based on their size, their echogenicity, the presence of calcifications, their shape (taller-than-wide), their vascularity, their halos, and their margins [4–6]. Since none of these yield results that are 100% predictive of thyroid cancer and ultrasonography has poor reproducibility with significant inter- and intra-operator variability, several classification systems have been proposed by medical researchers to support the decision to perform ultrasound-guided fine-needle aspiration cytology (FNAC), estimating the risk of thyroid cancer. One such cancer risk assessment system is the Thyroid Imaging Reporting and Data System (TI-RADS), and it is named after the widely accepted Breast Imaging Reporting and Data System used for breast imaging. Several versions of TI-RADS, such as the European Thyroid Association (EU TI-RADS), the American College of Radiology TI-RADS, the Chinese TI-RADS, and the Korean Society of Thyroid Radiology TI-RADS, have been validated and have demonstrated diagnostic value in predicting thyroid malignancy [7–10]. However, the studies conducted for these validations were mostly retrospective and showed poor reproducibility owing to the variability in operators and equipment. For EU TI-RADS category 5 (high-risk, with at least one of the following features: irregular shape, irregular margins, microcalcifications, or marked hypoechogenicity), the estimated malignancy risk according to the European Thyroid Association guidelines is 26–87% [7].

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was created to report thyroid cytopathology after FNAC, categorize the risk of malignancy (ROM), and standardize the management of thyroid nodules [11]. There are six TBSRTC categories: I—non-diagnostic (ND); II—benign (B); III—atypia of undetermined significance (AUS); IV—follicular neoplasm (FN); V—suspicious for malignancy (SM); and VI—malignant (M); each is associated with clinical recommendations. The TBSRTC categories III (AUS) and IV (FN) are termed the indeterminate categories, with ROMs that vary greatly in the literature, and present the most challenging clinical management decisions [11,12]. Current guidelines suggest repeating FNAC, molecular testing, or lobectomy for AUS and molecular testing or lobectomy for FN [13]. Even with the updated third version of the TBSRTC published in 2023 that further scrutinizes these categories, the management of these nodules remains challenging [13].

Combining the ultrasonography-based overdiagnosis of thyroid nodules with the lack of a clear course of action associated with TBSRTC categories III (AUS) and IV (FN) may result in the unnecessary surgical excision of benign nodules, thereby exposing patients to the potential risks of a surgical procedure and its complications.

This study aimed to assess variables (such as clinical, demographic, and ultrasonographic characteristics) that can aid in deciding between a surgical or active surveillance approach for the indeterminate TBSRTC categories, supporting and complementing the recommendations provided by the updated TBSRTC and its new ROMs.

2. Methods

2.1. Study Design and Participants

A retrospective review was carried out of all adult patients (>18 years old) who underwent FNAC; whose cytopathology corresponded to TBSRTC categories AUS—III, FN—IV, suspicious for malignancy—V, and malignant—VI; and who underwent partial or total thyroidectomy in the Endocrine Surgery Section, Department of General Surgery, of a single Portuguese hospital over a 10-year period (between January 2009 and January 2019).

Only patients who underwent all cytological examinations, surgery, and histopathological analyses at the hospital were included in the study sample. Data were accessed from the hospital records for research purposes in 2019 (June to December). A fine-needle aspiration procedure was used.

All FNACs were performed using 22-gauge needles. Two direct smears were prepared for each aspiration. Air-dried Diff-Quik stained smears were used for rapid on-site evaluation, and one slide was fixed in 95% alcohol for Papanicolaou staining. Cells blocks were made from the remaining material in the syringe.

2.2. Measurements

Patient age, sex, comorbidities, the type of surgery, the number of nodules evaluated, ultrasonographic characteristics, and cytological and histological diagnoses of the nodules were recorded, and the ROM was calculated.

The results of ultrasonography and the FNAC findings were reviewed by a single endocrine surgeon.

3. Statistical Analysis

The statistical analysis was performed using the SPSS PASW Statistics 18 software package, release version 18.0.0, by employing a Pearson chi-square independence test. This test uncovers the relationship between two categorical variables, where each variable can have two or more categories. It considers a crosstabulation table, with cases classified according to the categories in each variable. This work considered two crosstabulation tables: (1) between the ultrasonography characteristics and the cytopathological classification and (2) between the ultrasonography characteristics and the histological classification.

The null hypothesis states there is no association between the two variables, while the alternative hypothesis states there is an association. To obtain the conclusion of this test and assess its statistical significance, the *p*-value is evaluated and compared with the threshold defined for the significance level (5%). For a *p*-value higher than this threshold, there is no statistical evidence to reject the null hypothesis, indicating that the variables do not have any association between them. For a *p*-value lower than the threshold, there is statistical evidence to reject the null hypothesis, which means there is statistical evidence of an association between the variables tested.

The Pearson chi-square test is used when the population distribution is unknown, making it ideal for testing independence between two attributes with nominal or ordinal scales.

Ethical Statement

This study was approved by the ethics committee of our hospital, and written informed consent was obtained from all patients (Ethical Approval Number: 001/2019F).

4. Results

A total of 341 patients were included in this study, of whom 88% were women and 56% were older than 55 years old. Among the women in the study sample, 56% had a malignant disease, while this percentage increased to 66% in the male patients. Regarding the variable of age, the ROM values were similar between individuals below and above 55 years of age (58% and 56%, respectively). The age cutoff was based on the American Joint Committee on Cancer Tumor, Node, and Metastasis staging system classification (5).

The most prevalent comorbidity was hypertension (46%), followed by dyslipidaemia (23%) and diabetes (15%). Previous radiation exposure was present in 4% of patients, with an ROM of 72%.

The majority of the nodules had sizes ranging from 10 to 40 mm (71%), followed by nodules larger than 40 mm (9%), with the remainder being smaller than 10 mm.

The surgical procedure was total thyroidectomy in 94% of the patients and lobectomy with isthmectomy in the remaining patients.

FNAC was performed in one nodule in 322 patients and in two nodules in 19 patients (n = 360 index nodules). Hereafter, all data are referred to in terms of nodules from a total of 360 nodules.

Regarding histopathological diagnoses, the majority (55%) were diagnosed with malignant tumours, of which the largest proportion was made up by Papillary Thyroid Cancer (PTC) (180/197). In this patient cohort, 43% had a benign diagnosis and 2.1% were borderline (Table 1). The new TBSRTC guidelines were taken into consideration, and the AUS and FN categories were divided into two subcategories: AUS with nuclear atypia versus AUS-other (architectural atypia, oncocytic atypia, nuclear changes not suggestive of PTC, psammoma bodies, and atypical lymphoid cells) and FN with and without oncocytic features.

Table 1. The number of histopathological and cytological diagnoses.

	Characteristics	n	% (n/360)
Histopathological diagnoses	Benign histology/tumours	155	43
	Borderline tumours	8	2
	NIFTP	6	2
	WDT-UMP	2	1
	Malignant tumours	197	55
	Sub-cm	10	3
	PTC	180	50
	FTC	2	1
	MTC	1	0
	OCA	4	1
Cytological diagnoses	AUS *	79	22
	AUS-nuclear atypia	(11)	(3)
	AUS-other	(68)	(19)
	FN *	173	48
	FN without oncocytic cells	(95)	(26)
	FN with oncocytic cells	(78)	(22)
	SM	44	12
	M	64	18

NIFT-P, non-invasive follicular tumour with papillary-like nucleus; WDT-UMP, well-differentiated tumour of uncertain malignant potential; Sub-cm, subcentimeter papillary thyroid carcinoma; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; OCA, oncocytic carcinoma; AUS, atypia of undetermined significance; FN, follicular neoplasm; SM, suspicious for malignancy; M, malignant. * According to the Third TBSRTC guidelines, the AUS and FN categories are each split into two subcategories. The number of nodules in these subcategories are given in parentheses.

In the cytological diagnoses, FN dominated (48%), with the majority being "without oncocytic cells", followed by AUS (22%) (Table 1).

Malignant histology was more prevalent in the malignant cytology category (TBSRTC VI) (97%), followed by the suspicious for malignancy category (TBSRTC V) (77%). For AUS (TBSRTC III) and FN (TBSRTC IV), the percentages of malignant tumours were 44% and 43%, respectively (Table 2).

The malignancy rates among unilateral and bilateral nodules were 60% and 67%, respectively. Regarding focality, the ROMs were 57% and 69% for unifocal and multifocal nodules, respectively. Adenopathy (without assessment of the ultrasonographic features of each adenopathy) was present in only 7% of the malignant cases; however, when present, 94% were malignant.

Various ultrasonographic characteristics, namely echogenicity, calcification, margins, shape (taller-than-wide), halo, and vascularization, were evaluated. The results were correlated with the cytological (Table 3) and histopathological classifications (Table 4).

Table 2. Histopathological results following FNAC diagnoses.

	Benign Histology	Malignant (or Borderline) Histology	Total Number	Risk of Malignancy * (%)
AUS	44	35	79	44
AUS-nuclear atypia	(5)	(6)	(11)	(55)
AUS-other	(39)	(29)	(68)	(43)
FN	99	74	173	43
FN without oncocytic cells	(45)	(50)	(95)	(53)
FN with oncocytic cells	(54)	(24)	(78)	(31)
SM	10	34	44	77
M	2	62	64	97

AUS, atypia of undetermined significance; FN, follicular neoplasm; SM, suspicious for malignancy; M, malignant; NIFT-P, non-invasive follicular tumour with papillary-like nucleus; WDT-UMP, well-differentiated tumour of uncertain malignant potential. * The risk of malignancy (ROM) was calculated, including borderline (WDT-UMP and NIFT-P) tumours.

Table 3. Crosstabulation tables between ultrasonographic characteristics and cytopathological classification.

Ultrasonographic Characteristics	AUS n (%)	SFN n (%)	SM n (%)	M n (%)	*p*-Value (for Pearson Chi-Square Independence Test)
Echogenicity					
Cystic	-	2 (1.4)	-	2 (3.8)	<0.001
Hypoechoic	16 (21.9)	49 (33.8)	14 (35)	32 (61.5)	
Isoechoic	55 (75.3)	94 (64.8)	26 (65)	18 (34.6)	
Hyperechoic	2 (2.7)	-	-	-	
Calcification					
No calcification	52 (75.4)	105(73.9)	27 (73)	19 (39.6)	<0.001
Macrocalcification	8 (11.6)	14 (9.9)	7 (18.9)	13 (27.1)	
Microcalcification	9 (13)	23 (16.2)	3 (8.1)	16 (33.3)	
Margins					
Regular	54 (79.4)	114(80.9)	29 (74,4)	23 (52.3)	0.001
Irregular	14 (20.6)	27 (19.1)	10 (25.6)	21 (47.7)	
Shape					
Wider-than-tall	68 (94.4)	137(91.3)	34 (87.2)	42 (79.2)	0.036
Taller-than-wide	4 (5.6)	13 (8.7)	5 (12.8)	11 (20.8)	
Halo					
No halo	36 (49.3)	88 (57.9)	29 (69)	41 (69.5)	0.135
Complete hypoechoic	33 (45.2)	56 (36.8)	11 (26.2)	12 (20.3)	
Incomplete hypoechoic	3 (4.1)	7 (4.6)	2 (4.8)	4 (6.8)	
Hyperechoic	1 (1.4)	1 (0.7)	-	2 (3.4)	
Adenopathy					
Absent	77 (97.5)	169(97.7)	43 (97.7)	55 (85.9)	0.001
Present	2 (2.5)	4 (2.3)	1 (2.3)	9 (14.1)	
TOTAL	65	135	36	38	

AUS, atypia of undetermined significance; FN/SFN, follicular neoplasm/suspicion of follicular neoplasm; SM, suspicious for malignancy; M, malignant. A total of 274 nodules have the following radiological features: echogenicity, calcification, halo, irregular shape, margins, and adenopathy. Vascularization is excluded because of the high number of "not applicable (N/A)" cases and a very high *p*-value.

Table 4. Crosstabulation tables between ultrasonographic findings and histological characteristics (malignant includes low-risk tumours).

Ultrasonographic Characteristics:	Benign n (%)	Malignant n (%)	*p*-Value (for Pearson Chi-Square Independence Test)
Echogenicity			
Cystic	1 (0.7)	3 (1.8)	0.093
Hypoechoic	40 (28.8)	71 (41.5)	
Isoechoic	97 (69.8)	96 (56.1)	
Hyperechoic	1 (0.7)	1 (0.6)	
Calcification			
No calcification	112 (81.2)	91 (57.6)	<0.001
Macrocalcification	13 (9.4)	29 (18.4)	
Microcalcification	13 (9.4)	38 (24.1)	
Margins			
Regular	109 (80.7)	111 (70.7)	0.047
Irregular	26 (19.3)	46 (29.3)	
Shape			
Wider-than-tall	135 (94.4)	146 (85.4)	0.009
Taller-than-wide	8 (5.6)	25 (14.6)	
Halo			
No halo	82 (56.2)	112 (62.2)	0.142
Complete hypoechoic	57 (39)	55 (30.6)	
Incomplete hypoechoic	7 (4.8)	9 (5)	
Hyperechoic	-	4 (2.2)	
Adenopathies			
Absent	154 (99.4)	190 (92.7)	0.002
Present	1 (0.6)	15 (7.3)	

5. Discussion

All patients (TBSRTC categories III, IV, V, and VI) underwent surgical intervention, with the majority undergoing total thyroidectomy. However, 43% of the cases proved to be benign tumours. This raises the question of how surgeons may limit unnecessary surgical interventions while ensuring that no malignant cases are overlooked.

While evaluating a patient and deciding how to manage thyroid nodule disease, multiple factors should be considered, including patient demographics, personal and family histories, and the results of the diagnostic tools available.

Historically, women have been associated with a greater presence of thyroid nodules and men with higher malignancy rates. Nevertheless, the meta-analysis of autopsy studies for subclinical thyroid cancer conducted by LeClair et al. led to the belief that this is an oversimplification, and that sex disparity is mostly confined to the detection of small subclinical PTCs that are equally common in both sexes in autopsy studies but are identified much more often in women. According to their findings, as cancer lethality increases, the ratio of detection by sex approaches 1:1. This data trend may be associated with sex differences in healthcare utilization and may pose a danger for both sexes, with over- and under-detection in women and men, respectively [14,15]. Other retrospective studies continue to confirm the higher prevalence in women, but with a tendency to fade in older age groups, and with poorer prognoses in men, along with poorer survival and more aggressive disease at presentation. However, no clear reasons have been reported for these disparities [16–18].

Hypertension was the most common comorbidity in patients with thyroid nodules. Although this aligns with the findings reported in the literature, no direct correlation between these two diseases has been demonstrated [16,19,20]. However, previous radiation

exposure has been shown to have a positive correlation with the occurrence of thyroid nodules, especially if exposure occurs at an early age, with the most notable studies being the ones focused on survivors of the atomic bomb attacks in Japan and the reactor disaster in Chernobyl [21,22]. Although our present study sample has a limited number of cases of radiation exposure, the ROM was still high in this subgroup (72%).

Several diagnostic instruments guide surgeons in selecting the optimal course of action. The TI-RADS scoring system and some of its variations based on ultrasonographic characteristics indicate the need for FNAC [8]. In this study, this decision was based on the Portuguese Direção Geral de Saúde guidelines.

The cytopathology report, especially if it follows the TBSRTC guidelines, will further guide the course of treatment based on the ROM for each category.

The indeterminate categories (TBSRTC III and IV) remain problematic, without a clear consensus on treatment options. The calculated ROM was observed to be similar between both categories: 44% and 43% for categories III and IV, respectively. These values are considerably higher than those reported in the literature, including the ROM values for malignancies like non-invasive follicular tumours with papillary-like nucleus and well-differentiated tumours of uncertain malignant potential. The literature reports a 10–30% ROM for TBSRTC III and 25–40% for TBSRTC IV categories [11]. A possible reason for this disparity is that only nodules that underwent surgery were evaluated, suggesting that other factors could have been considered. For the suspicious for malignancy (V) and malignant (VI) TBSRTC categories, the ROM was in agreement with that reported in the literature [1,23–25].

To improve the discriminatory power of the cytopathological classification, the TBSRTC 2023 guidelines (that separate each of the two indeterminate categories into two subcategories) make it possible to further scrutinize the risk of malignancy. The TBSRTC category III (ROM 13–30%) is now divided into atypia of undetermined significance with nuclear atypia and other atypia of undetermined significance. The calculated ROM was 55% for AUS nuclear atypia and 43% for AUS other, and this agrees with the original purpose of this subdivision, as it emphasizes a relatively higher ROM in the presence of nuclear atypia. Regarding TBSRTC Category IV (23–34%) that is now divided into Follicular Neoplasm with and without oncocytic cells to further align with the 2022 World Health Organization Classification of Thyroid Neoplasms, the calculated ROMs were 31% and 53%, respectively [26].

Most published studies correlate the ultrasonographic features with the cytological results, given their relevance in the scoring systems that guide the decision to perform FNAC. Similarly, we have correlated the individual ultrasonographic characteristics with the cytological results in the present study. The ultrasonographic characteristics that were statistically significant for pre-surgery characterization in the higher TBSRTC categories were the presence of hypoechoic nodules ($p < 0.001$), microcalcifications (p-0.001), irregular margins (p-0.001) and the presence of adenopathy (p-0.001).

In Alyusuf et al.'s work, they concluded that hypoechogenicity and calcifications in the ultrasonographic morphologies of Bethesda III and IV thyroid nodules were independent predictors of malignancy [27]. Li et al. found that hypoechogenicity and microcalcification, as well as irregular borders and a taller-than-wide shape, increased the risk of thyroid cancer in Bethesda III and IV nodules [28].

Hypoechogenicity is known to be highly specific for malignancy (92–94%) [29]. Microcalcifications have a specificity for malignancy of 86–95% in the literature [29]. The evaluation of margins also plays an important role in assessing malignancy, with previous studies reporting that spiculated or micro-lobulated margins (92% specificity) and poorly defined margins suggest malignancy [29]. Only the regularity of the margins was evaluated, with irregular margins being associated with a higher TBSRTC classification score. In future, further division into regular, spiculated, and ill-defined margins may enhance nodule description and provide information about the ROM.

Although not helpful on its own, the size of the nodule should be monitored over time, because malignant nodules usually grow more quickly [2,30]. The progression of nodule growth was not evaluated in this study.

Characteristics such as a taller-than-wide shape and the halo sign, although usually associated with an increased ROM [31,32], showed no statistical significance in this study. The significance of central vascularity was not assessed because it was not reported in the ultrasonographic results for the majority of this patient cohort.

To further test the possible role of ultrasonographic features as a deciding factor between surgery and surveillance, they were correlated with the final histopathological results. In this analysis, only the presence of microcalcifications and adenopathies were observed to be significantly associated with a higher ROM. These results agree with a systematic review conducted by Remonti et al., where only the presence of microcalcifications was significantly correlated with the histopathological diagnosis of indeterminate cytology nodules [33]. Sgro' D. et al. reported that the presence of microcalcifications, hypoechogenic patterns, and irregular margins correlated with malignancy and were typical of classic variant PTC, whereas the association between hypoechogenic pattern, irregular margins, and no microcalcifications was more frequent in tall-cell subtype PTC than in classic subtype PTC [34].

The assessment of microcalcifications can be particularly challenging because they are often similar to colloids. Considering its importance, it is essential that professionals performing ultrasonography are highly trained and that they correctly document the presence of microcalcifications and/or colloids. The authors recognize the variability associated with performing ultrasound. To minimize this problem, the examination was performed by the endocrine surgery team according to standardized training and the results were reviewed by a single researcher.

The presence of adenopathy is also associated with malignancy; thus, ultrasonographic examination of cervical lymph nodules and reporting their location and characteristics are essential for all ultrasonographic thyroid evaluations. According to the American Thyroid Association guidelines, a comprehensive cervical lymph node survey is advisable for all thyroid cancer cases, and a preoperative map highlighting possible adenopathies should be prepared [1].

Ultrasonographic characteristics should be reported in a standardized manner to ensure that every relevant parameter is evaluated, easily understandable, and useful in the decision-making process. This would decrease inter-operator variability in the data, facilitate surveillance strategies, be helpful for research purposes, and simplify the processing and sharing of data.

Moving forward, other diagnostic tools such as molecular and genetic tests should be considered to help evaluate the ROM and prevent unnecessary surgical interventions [35–37]. Molecular tests are an emerging tool; however, they are not available in our centre nor in most centres in our region, as is currently the case in most countries.

Elastosonography also has an important role to play and should be employed and evaluated, with "stiffness" or hard consistency being reported to have a sensitivity for malignancy of up to 97% [29,33].

When deciding on the best clinical and surgical approach for thyroid nodules, patient demographics, symptoms, comorbidities, personal and family histories, and the results of ultrasonography, cytopathology, thyroid function, and molecular/genetic tests should be considered to provide the best possible care. The present study highlights the essential role that ultrasonography can play not only when deciding the diagnostic approach but also when managing treatment options, and this is especially important in the TBSRTC indeterminate categories.

Regarding the limitations of this study, this was a retrospective study that excluded patients in the non-diagnostic and benign TBSRTC categories (TBSRTC categories I and II). This sampling strategy precluded the calculation of other parameters, such as specificity and predictive values. Regarding the relative prevalence of each TBSRTC category in our

study sample, there was an increase in the prevalence of the remaining categories because of the exclusions mentioned above. In a normal setting, to ensure the reliability of the cytological results, TBSRTC III should account for no more than 10% of all specimens, whereas it amounts to 22% of the present study sample [25]. Although not evaluated, family history should not be overlooked, as it is important in malignant disease diagnoses.

In the present investigation, setbacks occurred, namely the difficulty in effectively controlling all variables in the sample patients operated on, so there is some variability in the results obtained. On the other hand, after applying Pearson's chi-square test, the degree of association between the variables under study should have been studied in order to characterize it more completely. Finally, no international grading system, such as the TI-RADS system, was used.

6. Conclusions

Selecting the best intervention strategy for indeterminate-category thyroid nodules remains challenging, even after the release of the 2023 TBSRTC classification. This study found a statistically significant relationship between the presence of hypoechoic nodules, microcalcifications, irregular margins and adenopathy in ultrasound, and characterization in a higher TBSRTC category, as well as a correlation between the presence of microcalcifications and adenopathy and a final malignant histology diagnosis.

This highlights the importance of the ultrasound examination, providing information that should be considered when deciding the clinical management of thyroid nodules.

This study contributes data for the evaluation of the new TBSRTC guidelines, in addition to ultrasonographic factors that can influence the ROM.

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Abbreviations

Histopathological diagnoses of nodules:	
Benign:	
CLT	Chronic lymphocytic thyroiditis
FA	Follicular adenoma
PA	Papillary adenoma
OA	Oncocytic adenoma
Borderline:	
NIFT-P	Non-invasive follicular tumour with papillary nucleus

WDT-UMP	Well-differentiated tumour of uncertain malignant potential
Malignant:	
PTC	Papillary thyroid carcinoma
Sub-cm	Subcentimeter Papillary thyroid carcinoma
FTC	Follicular thyroid carcinoma
MTC	Medullary thyroid carcinoma
OCA	Oncocytic carcinoma
Cytological categorization of nodules according to Bethesda:	
ND	Non-diagnostic (Category 1)
B	Benign (Category 2)
AUS	Atypia of undetermined significance (Category 3)
FN/SFN	Follicular neoplasm or Suspicious for follicular neoplasm (Category 4)
SM	Suspicious for malignancy (Category 5)
M	Malignant (Category 6)

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