

Correlation between ultrasonographic and cytologic features of thyroid nodules: a single-center cross-sectional study

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ABSTRACT

A thyroid nodule is managed according to the clinical context, ultrasound (US) findings, and fine needle aspiration (FNA) results. Most thyroid nodules are benign; however, nodule classification is crucial to avoid unnecessary thyroid surgery. We conducted this study to compare the findings of fine-needle aspiration cytology (FNAC) expressed using the Bethesda system with the features of thyroid US classified using the EU-TIRADS classification to assess the risk of malignancy. A descriptive and analytical study involving 99 patients with thyroid nodules followed up in the Department of Endocrinology-Diabetology and Nutrition. Data were collected from medical records and analyzed using SPSS software V21. FNA was performed on 121 nodules using the BETHESDA system. These nodules were classified as malignant, suspicious for follicular neoplasm, and suspicious for malignancy in 5.8%, 5%, and 1.7% of cases, respectively. As for the EU-TIRADS 2017 classification, 59.5% of benign nodules were classified as EU-TIRADS III, whereas 66.7% of malignant nodules were classified as EU-TIRADS V and significantly related to malignant prediction ($P = 0.000$). The size of nodules was significantly correlated to the risk of malignancy ($P = 0.013$). Seventy-five percent of nodules with central vascularity were malignant ($P = 0.012$). Irregularity of nodule contours was significantly associated with the risk of malignancy, as 30% of nodules with irregular contours were Bethesda VI ($P = 0.003$). Hypoechoogenicity was found in 77.8% of malignant nodules ($P = 0.004$). Additionally, only 9.2% of the nodules were taller than wide, of which 37.5% were malignant ($P = 0.012$). For a safe management strategy, US-guided FNAC should be performed on each suspicious thyroid nodule, given the correlation between EU-TIRADS classification features and the risk of malignancy.

KEYWORDS: EU-TIRADS, fine-needle aspiration, malignancy, thyroid nodule, ultrasound

ABBREVIATIONS: ATA, American Thyroid Association; CI, Confidence Interval; EU-TIRADS, European Thyroid Imaging Reporting and Data System; FNA, Fine Needle Aspiration; FNAC, Fine-Needle Aspiration Cytology; FT4, Tetraiodothyronine; OR, Odds Ratio; TBSRTC, The Bethesda System for Reporting Thyroid Cytopathology; TSH, Thyroid-Stimulating Hormone; TPOAb, Thyroid Peroxidase Antibody; TTW, Taller-Than-Wide; US, Ultrasound

INTRODUCTION

A thyroid nodule, as defined by the American Thyroid Association (ATA), is a “discrete lesion within the thyroid gland that is radiologically distinct from surrounding thyroid parenchyma” [1]. Thyroid nodules are a frequently encountered reason for consultation. It is a common clinical finding, with a prevalence ranging from 2 to 6% for palpable nodules and 19 to 35% for ultrasound-detectable nodules [2]. The malignancy risk of thyroid

nodules can be predicted by various clinical practice elements. They are managed based on the clinical context, ultrasound findings, and fine needle aspiration. When dealing with a thyroid nodule, the major issue is discerning its benign or malignant nature. Fortunately, 95% of thyroid nodules are benign, but 5% are malignant. Therefore, a treatment protocol needs to be established [3].

Ultrasound (US) is the reference imaging method for thyroid nodules. It has the advantage of being non-invasive and easily

accessible. It is widely used in current practice for identifying and stratifying thyroid nodules, using multiple risk stratification systems, including the European Thyroid Imaging Reporting and Data System (EU-TIRADS) [4]. This EU-TIRADS is a scoring system that defines the risk of malignancy, thus determining whether the nodule requires a fine needle aspiration (FNA).

The FNA is a complementary technique to ultrasound that allows the cytological classification of thyroid nodules with a sensitivity of 95%[5]. They are mostly performed to diagnose and exclude malignant thyroid nodules. FNA findings are standardized by the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) [6]. This system reduces the rate of unnecessary thyroidectomies and helps plan the surgical modalities.

This study examined the diagnostic utility of thyroid ultrasound (US) in characterizing thyroid nodules and determining the necessity for FNA. It also aimed to study and compare ultrasound findings of thyroid nodules with cytological results and, more specifically, to describe and analyze the different ultrasound features predictive of malignancy (hypoechoic echogenicity, central and mixed vascularity, nodule size, irregular borders, and shape) and their correlation with cytological aspects.

MATERIAL AND METHODS

Study design and patients

This study was a retrospective, descriptive, and analytical cross-sectional analysis conducted at the Endocrinology-Diabetology and Nutrition Department of Mohammed VI University Hospital in Oujda, Morocco, over a three-year period. We included patients who presented with thyroid nodules, identified either incidentally, through self-examination, clinical examination, or due to thyroid-related symptoms, and who underwent a thyroid ultrasound

and a fine needle aspiration with complete medical records. Data were collected from 143 patients diagnosed with thyroid nodules. Of these, 99 patients underwent an ultrasound-guided FNA (Figure 1).

Study protocol

Demographic evaluation

For each patient, we collected the following data: age, sex, associated pathologies, circumstances of nodule discovery, dysthyroid symptoms, and personal or family history of thyroid nodule or carcinoma.

Biological evaluation

After detecting a thyroid nodule, the thyroid stimulating hormone (TSH) and serum-free tetraiodothyronine (FT4) were measured using a radioimmunoassay. Anti-thyroperoxidase antibodies, anti-thyroglobulin antibodies, and calcitonin were measured using an automated immunochemiluminescent assay.

Sonographic evaluation

Thyroid ultrasound is the standard imaging modality for thyroid nodules. It enables the establishment of a diagnosis and description of their features. Thyroid ultrasonography was performed by an experienced practitioner using a HITACHI ARIETTA V70 machine. We recorded the ultrasound features of the thyroid nodules such as size (measured in three dimensions: length, width, and height), composition (solid, cystic proportion, or spongiform), echogenicity compared to the surrounding strap muscle or thyroid parenchyma (hyperechoic, isoechoic, hypoechoic, or

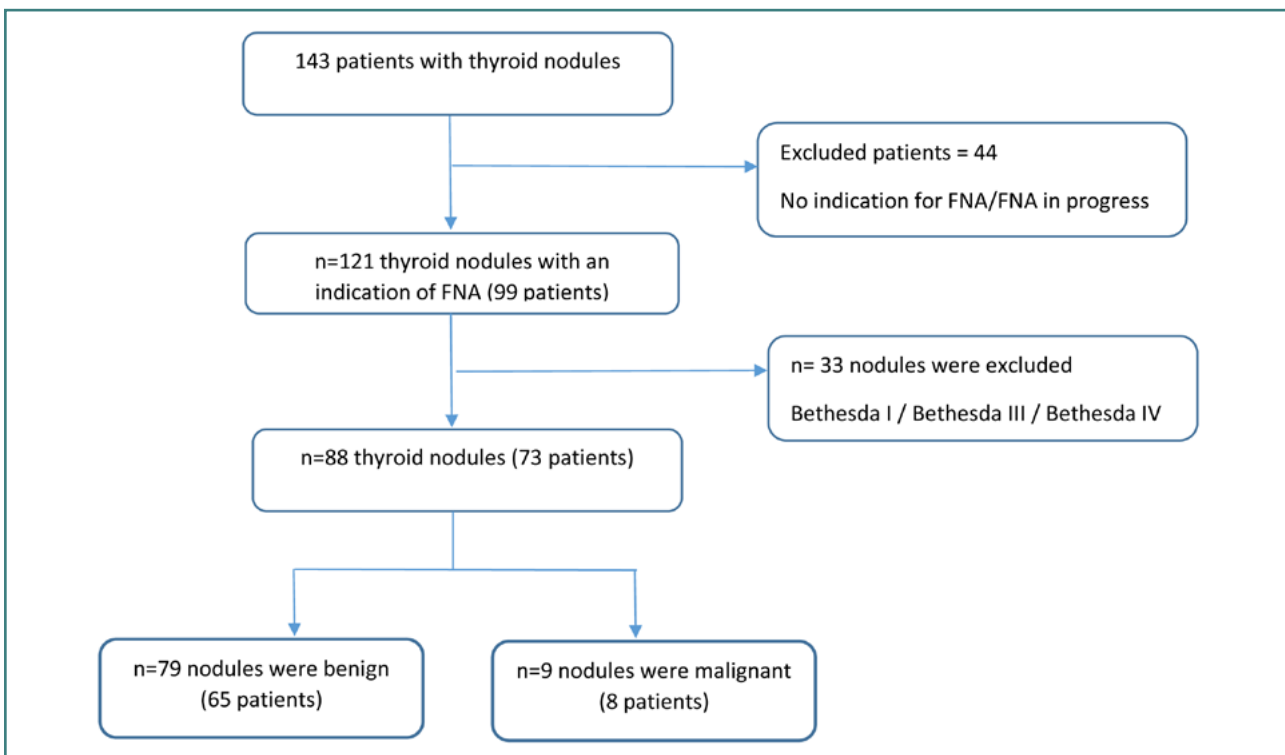


Figure 1. Flow chart showing the number (%) of patients with thyroid nodules in benign and malign categories (Bethesda V and Bethesda VI)

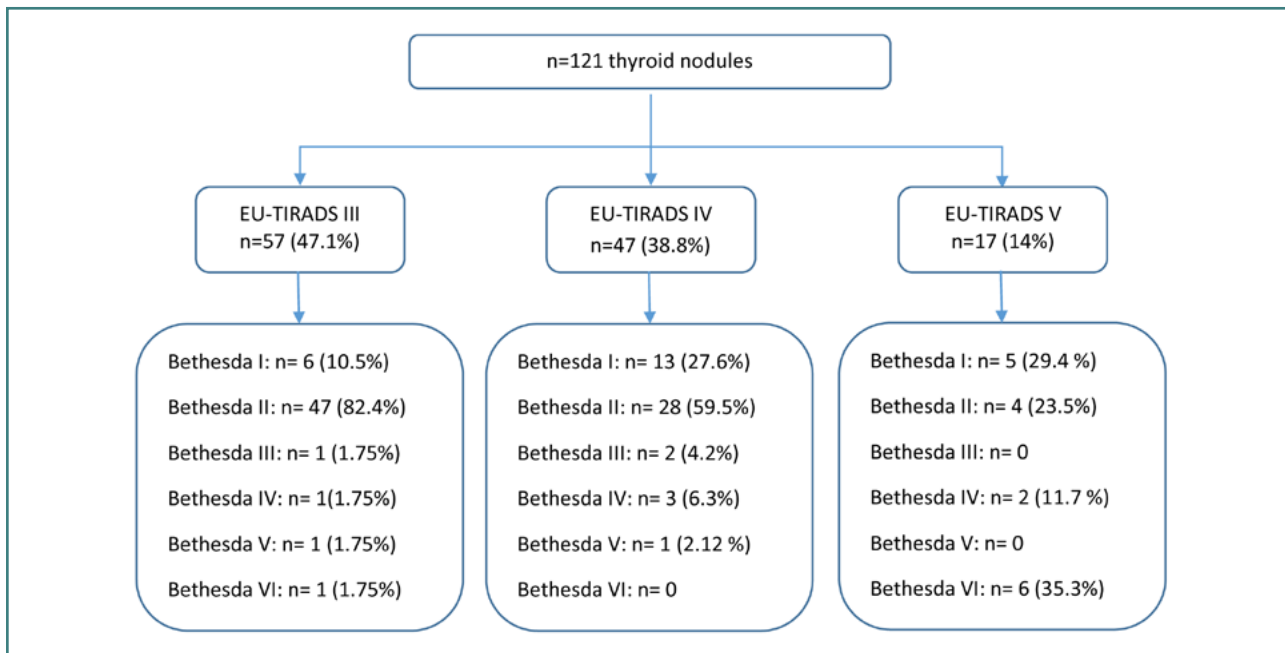


Figure 2. Flow chart showing the distribution of thyroid nodules according to EU-TIRADS score on thyroid ultrasound and corresponding Bethesda classification after FNA

mixed), nodules margins, presence and type of calcifications, shape (if taller than wide), vascularity, and lymph node.

Thyroid imaging reporting and data systems by the European Thyroid Association (EU-TIRADS) were used to provide a score to stratify the thyroid nodules and select them for fine needle aspiration. EU-TIRADS includes five categories [4]:

- EU-TIRADS 1: Normal thyroid gland
- EU-TIRADS 2: Benign
- EU-TIRADS 3: Low risk of malignancy
- EU-TIRADS 4: Intermediate risk of malignancy
- EU-TIRADS 5: High risk of malignancy.

EU-TIRADS 1 and 2 were excluded since there were no indications of fine needle aspiration.

FNA cytology procedure and evaluation

FNA was performed by an experienced senior endocrinologist. Patients were placed in a supine position with a slightly extended neck. Once the lesion was localized, the neck was prepared in a sterile, draped environment. A 25-gauge needle mounted on a 5-ml syringe with support was positioned just above the transducer. The cytological diagnosis was made by an experienced pathologist. The patient should avoid swallowing, talking, or moving during the procedure. It is recommended that the aspirates be taken sequentially from the peripheral areas and from different parts of the nodule to ensure representative sampling [7].

Results were analyzed according to the 2017 Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), which classifies thyroid nodules into six categories [8]:

- Bethesda I: Non-diagnostic or unsatisfactory
- Bethesda II: Benign
- Bethesda III: Atypia of undetermined significance or follicular lesion of undetermined significance
- Bethesda IV: Follicular neoplasm or suspicious for a follicular neoplasm

- Bethesda V: Suspicious for malignancy
- Bethesda VI: Malignant.

For US-guided FNA, the criteria included nodules [4,9]:

- ≥ 1 cm classified EU-TIRADS 5
- ≥ 1.5 cm classified EU-TIRADS 4
- ≥ 2 cm classified EU-TIRADS 3
- If there were suspicious lymph nodes or extra-thyroidal expansion for thyroid nodules ≤ 1 cm

Additionally, FNA was indicated under the following specialized conditions:

- A suspected lymph node or distant metastasis
- High-risk features: Size increase, juxta-capsular nodule (≤ 2 mm), superior polar nodule, multifocality suspicion, and age under 40 years.

In our study, cases reported as 'suspicious' by cytology were included in the malignant category for statistical analysis, as both suspicious and confirmed lead to surgical management. Vice versa, cases represented in the benign category include only thyroid nodules with a BETHESDA II classification.

Outcomes

The primary outcome of our study was to describe the various ultrasound parameters predictive of malignancy (size, echogenicity, microcalcifications, vascularization, and presence or absence of lymph nodes). The secondary outcome was to correlate US features and the clinical and biological characteristics of patients with thyroid nodules with the results of FNA.

Statistical analysis

The collected data were analyzed using SPSS IBM Statistics, version 21. The results were presented as frequencies and percentages, given that all variables were categorical. In order to assess the association between ultrasound features and the risk of malignancy, the chi-square test and Fisher's exact test were

employed. Variables significantly associated with the risk of malignancy were then selected for univariate analysis using a logistic regression model (crude odds ratios). A *P* value < 0.05 was considered statistically significant. Multivariate analysis via a logistic regression model was not employed due to the limited number of malignant nodules. Additionally, sensitivity, specificity, and positive and negative predictive values were calculated to evaluate diagnostic performance.

RESULTS

We collected the data from 143 patients with thyroid nodules, of whom 99 underwent an ultrasound-guided FNA, i.e., in 69% of the cases, FNA was performed on 121 nodules in 99 patients (Figure 1). Cytopathology found 79 benign nodules (65.3%), 24 were inadequate for cytological diagnosis (19.8%), seven nodules were malignant (5.8%), six were suspicious for follicular neoplasm (5%), three were indeterminate (2.5%), and two were suspicious for malignancy (1.7%). Figure 2 illustrates the distribution of the 121 thyroid nodules according to the EU-TIRADS score and their corresponding Bethesda classification after the FNA procedure.

To compare the clinical, biological, and US features of malignant and benign nodules, we singled out Bethesda II nodules (benign nodules) and compared them to Bethesda V and VI

nodules (Table 1). The general characteristics of the 73 patients with these selected nodules and those who underwent FNA are detailed in Table 1. The age of the patients varied between 10 and 79 years, with an average age of 45.05 ± 14.34 and a female predominance (87.9%). The highest number of cases was seen in the age group ≥ 45 years (54.5%).

In our series, self-palpation was the most common circumstance of discovery (37.5% of cases). Most patients (84.9%) did not exhibit thyroid abnormalities. The levels of calcitonin were mildly elevated in two patients, and thyroid peroxidase antibodies (Anti-TPO Ab) were positive in 6% of cases. Nodules were mostly solitary in 60.2% of cases and multiple in 39.8%.

The ultrasound characteristics of the 121 nodules evaluated in this study are detailed in Table 2, together with the description of the nodules according to the Bethesda classification. The average size of the nodules was 3.04 ± 1.58 cm. Hypoechoogenicity was found in 37.2% of nodules. Most nodules (92.6%) had well-defined margins, and the majority (91.7%) had regular contours. Among the nodules with irregular contours (*n* = 10), 20% were classified as benign and 30% as malignant. The presence of microcalcifications was noted in 4.1% of the nodules. Regarding vascularization, it was predominantly peripheral, occurring in 65.83% of all nodules and 67.5% of those classified as benign (Table 2).

Concerning the EU-TIRADS classification, most of the benign nodules were classified as EU-TIRADS III (59.5%), where-

Table 1. Comparative characteristics of patients undergoing FNA (overall sample and subgroups with benign and malignant nodules)

| Variables | All patients <i>n</i> = 99 (121 nodules) | Patients with benign or malignant nodules on cytology <i>n</i> = 73 (88 nodules) | | <i>P</i> value* |
|--------------------------------|--|---|-----------------------------------|-----------------|
| | | Benign nodules (<i>n</i> = 65) | Malignant nodules (<i>n</i> = 8) | |
| Age (years) | | | | 1 |
| <45 years | 45 (45.5%) | 30 (46.1%) | 4 (50%) | |
| ≥ 45 years | 54 (54.5%) | 35 (53.9%) | 4 (50%) | |
| Mean ±SD | 45.05 ±14.34 | 44.12 ±13.98 | 46.62 ±16.37 | |
| Range | 10-79 years | 10-79 years | 27-75 years | |
| Gender | | | | 0.300 |
| Women | 87 (87.9%) | 57 (87.7%) | 6 (75%) | |
| Men | 12 (12.1%) | 8 (12.3%) | 2 (25%) | |
| Solitary nodules | 59 (60.2%) | 41 (64.1%) | 2 (25 %) | 0.054 |
| Multiples nodules | 39 (39.8%) | 23 (35.9%) | 6 (75 %) | |
| Self-examination | 36 (37.5%) | 23 (36.5%) | 3 (37.5%) | 0.159 |
| Thyroid symptoms | 25 (26%) | 14 (12.2%) | 4 (50%) | |
| Clinical examination | 11 (11.5%) | 7 (11.1%) | 1 (12.5%) | |
| Incidentally discovered | 24 (25%) | 19 (30.2 %) | 0 (0%) | |
| Thyroid function | | | | 0.078 |
| Euthyroid | 84 (84.9%) | 58 (89.2%) | 5 (62.5%) | |
| Hyperthyroid | 2 (2%) | 1 (1.5%) | 1 (12.5%) | |
| Hypothyroid | 13 (13.1%) | 6 (9.2%) | 2 (25%) | |
| Calcitonin | | | | 0.113 |
| Positive | 2 (2.1%) | 0 (0%) | 1 (12.5%) | |
| Negative | 95 (97.9%) | 63 (100%) | 7 (87.5%) | |
| Anti-TPO Ab | | | | 0.382 |
| Positive | 6 (6.1%) | 3 (4.7%) | 1 (12.5%) | |
| Negative | 92 (93.9%) | 61 (95.3%) | 7 (87.5%) | |

Anti-TPO Ab, Anti Thyroid Peroxidase Antibody

*significance level from the chi-square test comparing characteristics between patients with benign and malignant nodules

Table 2. Ultrasound findings according to the FNAC results (n = 121)

| Parameters | All nodules n = 121 | Bethesda I n = 24 | Bethesda II n = 79 | Bethesda III n = 3 | Bethesda IV n = 6 | Bethesda V n = 2 | Bethesda VI n = 7 | P value |
|-------------------------------------|------------------------|----------------------|-----------------------|-----------------------|----------------------|---------------------|----------------------|---------|
| Nodules size | | | | | | | | |
| <2cm | 36 (29.7%) | 14 (58.3%) | 13 (16.5%) | 2 (66.7%) | 1 (16.7%) | 1 (50%) | 5 (71.4%) | 0.000 |
| 2-4cm | 52 (43%) | 6 (25%) | 42 (53.2%) | 1 (33.3%) | 2 (33.3%) | 0 (0%) | 1 (14.3%) | |
| >4 cm | 33 (27.3%) | 4 (16.7%) | 24 (30.4%) | 0 (0%) | 3 (50%) | 1 (50%) | 1 (14.3%) | |
| Average size | 3.04±1.58 | | | | | | | |
| Taller-than-wide¹ | | | | | | | | |
| Yes | 12 (9.9%) | 3 (12.5%) | 5 (6.3%) | 0 (0%) | 1 (16.7%) | 0 (0%) | 3 (50%) | 0.049 |
| No | 109 (90.1%) | 21 (87.5%) | 74 (93.7%) | 3 (100%) | 5 (83.3%) | 3 (100%) | 3 (50%) | |
| Hypochoic | | | | | | | | |
| Yes | 45 (37.2%) | 15 (62.5%) | 19 (24.1%) | 1 (33.3%) | 3 (50%) | 1 (50%) | 6 (85.7%) | 0.000 |
| No | 76 (62.2%) | 9 (37.5%) | 60 (75.9%) | 2 (66.7%) | 3 (50%) | 1 (50%) | 1 (14.3%) | |
| Margin | | | | | | | | |
| Well-defined | 112 (92.6%) | 21 (87.5%) | 76 (96.2%) | 3 (100%) | 4 (66.7%) | 2 (100%) | 6 (85.7%) | 0.071 |
| Ill-defined | 09 (7.4%) | 3 (12.5%) | 3 (3.8%) | 0 (0%) | 2 (33.3%) | 0 (0%) | 1 (14.3%) | |
| Irregular borders | | | | | | | | |
| Yes | 10 (8.3%) | 3 (12.5%) | 2 (2.5%) | 0 (0%) | 2 (33.3%) | 0 (0%) | 3 (42.9%) | 0.003 |
| No | 111 (91.7%) | 21 (87.5%) | 77 (97.5%) | 3 (100%) | 4 (66.7%) | 2 (100%) | 4 (57.1%) | |
| Microcalcifications | | | | | | | | |
| Yes | 5 (4.1%) | 0 (0) | 3 (3.8%) | 0 (0%) | 1 (16.7%) | 0 (0%) | 2 (28.6%) | 0.062 |
| No | 115 (95.8%) | 24 (100%) | 76 (96.2%) | 3 (100%) | 5 (83.3%) | 2 (100%) | 5 (71.4%) | |
| Vascularity | | | | | | | | |
| None | 12 (10%) | 7 (12.5%) | 5 (6.5%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0.015 |
| Peripheral | 79 (65.83%) | 17 (79.2%) | 52 (67.5%) | 3 (100%) | 5 (83.3%) | 1 (50%) | 1 (16.7%) | |
| Central | 4 (3.33%) | 0 (0%) | 1 (1.3%) | 0 (0%) | 0 (0%) | 0 (0%) | 3 (50%) | |
| Mixed | 25 (20.83%) | 2 (8.3%) | 19 (24.7%) | 0 (0%) | 1 (16.7%) | 1 (50%) | 2 (33.3%) | |
| EU-TIRADS² | | | | | | | | |
| III | 57 (47.1%) | 6 (25%) | 47 (59.5%) | 1 (33.3%) | 1 (16.7%) | 1 (50%) | 1 (14.3%) | 0.000 |
| IV | 47 (38.8%) | 13 (54.2%) | 28 (35.4%) | 2 (66.7%) | 3 (50%) | 1 (50%) | 0 (0%) | |
| V | 17 (14.1%) | 5 (20.8%) | 4 (5.1%) | 0 (0%) | 2 (33.3%) | 0 (0%) | 6 (85.7%) | |

¹ A taller-than-wide thyroid nodule is characterized by an anteroposterior diameter greater than its transverse diameter

² EU-TIRADS: European Thyroid Imaging Reporting and Data System

as 85.7% of malignant nodules were classified as EU-TIRADS V (Table 2).

Of 121 thyroid nodules that underwent FNA, 88 were classified as benign (Bethesda II) or malignant (Bethesda V and VI). Table 3 summarizes the US findings of each group and presents the factors associated with malignancy. The results of our statistical analysis revealed a correlation between specific critical ultrasound features and the risk of malignancy. These findings are presented in Table 4, while Table 5 provides a detailed summary of the performance of various ultrasound features.

The mean size of malignant nodules was 2.7 ± 1.6 cm, while the majority had a size less than 2 cm (with a sensitivity of 66.7%). In contrast, benign nodules typically ranged from 2 to 4 cm, comprising 53.2% of this group). Statistical analysis revealed a significant association between nodule size and malignancy risk (P = 0.003). Additionally, only eight nodules (9.2%) were taller-than-wide, of which 3 (37.5%) were malignant (P = 0.023) with a specificity of 93.7% and a sensitivity of 37.5%. Most of the malignant nodules were hypochoic (77.8%) (P = 0.002), whereas 76% of the benign nodules were not hypochoic, the specificity and sensitivity values being 75.9% and 77.8%, respectively. The positive and negative predictive values for hypochoic nodules in predicting malignancy were 26.9% and 96.7%, respectively.

Well-defined margins were observed in 96.2% of the benign nodules, and the ill-defined margin was not associated with malignancy (P = 0.356). However, irregular margins were significantly associated with an increased risk of malignancy (P = 0.007), with a high specificity of 97.5% and a sensitivity of 33.3%. Microcalcifications were noted in 28.6% of malignant nodules and were not significantly associated with malignancy (P = 0.080). Color Doppler imaging revealed central and mixed vascularization in 75% of the malignant nodules (P = 0.009) with a negative predictive value of 96% (Tables 3-5).

DISCUSSION

In our study, out of all 121 thyroid nodules, 65.5% were benign. There were no statistically significant differences between the two categories (benign and malignant) regarding sex, age, thyroid function, and solitary or multiple nodules (P > 0.05). The risk of malignancy was determined by the presence of hypochoic echogenicity, vascularity, nodule size, irregular border, and shape (diameter taller than wide).

The mean age of 45 years observed in our study aligns with findings from other research [10,11], although we found no

Table 3. Ultrasound characteristics associated with malignancy in thyroid nodules (n = 88)

| Parameters | Benign n = 79 (%) | Malignant n = 9 (%) | P |
|-------------------------------------|----------------------|------------------------|-------|
| Nodules size | | | |
| <2cm | 13 (16.4 %) | 6 (66.7%) | 0.003 |
| 2-4cm | 42 (53.2 %) | 1 (11.1 %) | |
| >4 cm | 24 (30.4 %) | 2 (22.2%) | |
| Mean±SD | 3.3±1.5 cm | 2.7±1.6 cm | |
| Taller-than-wide¹ | | | |
| Yes | 5 (6.3%) | 3 (37.5%) | 0.023 |
| No | 74 (93.6%) | 5 (62.5%) | |
| Hypoechoic | | | |
| Yes | 19 (24 %) | 7 (77.8%) | 0.002 |
| No | 60 (76 %) | 2 (22.2%) | |
| Marked hypoechoogenicity | | | |
| No | 17 (94.4%) | 5 (71.4%) | 0.006 |
| Yes | 1 (5.6%) | 2 (28.6%) | |
| Ill-defined margins | | | |
| No | 76 (96.2%) | 8 (88.8%) | 0.356 |
| Yes | 3 (3.8 %) | 1 (11.2%) | |
| Irregular borders | | | |
| Yes | 2 (2.5%) | 3 (33.4%) | 0.007 |
| No | 77 (97.5%) | 6 (66.6%) | |
| Microcalcifications | | | |
| Yes | 3 (3.8%) | 2 (22.2%) | 0.080 |
| No | 76 (96.2%) | 7 (77.8%) | |
| Vascularity | | | |
| None and peripheral | 57 (74%) | 2 (25%) | 0.009 |
| Central and mixed | 20 (26%) | 6 (75%) | |
| Central | 1(1.3%) | 3 (37.5%) | |
| Mixed | 19 (24.7%) | 3 (37.5%) | |
| EU-TIRADS² | | | |
| III | 47 (59.5%) | 2 (22.2%) | 0.000 |
| IV | 28 (35.4%) | 1 (11.1 %) | |
| V | 4 (5.1%) | 6 (66.7%) | |

¹A taller-than-wide thyroid nodule is characterized by an anteroposterior diameter greater than its transverse diameter

²EU-TIRADS: European Thyroid Imaging Reporting and Data System.

significant association between age and the risk of malignancy. Contrasting evidence from the literature shows that the risk of malignancy increases in individuals aged 45 years and older in some studies [12], while other reports suggest a higher risk in younger individuals under 45 years [13]. Our study included approximately 87.9% of women, which is in line with previous studies that demonstrate a higher prevalence of thyroid nodules in women [14]. Women seem more prone to developing thyroid nodules, while men are more likely to develop a malignant nodule [10,15]. Nevertheless, our study did not show significant differences in malignancy rates between genders, which could be attributed to the relatively smaller sample size compared to other studies. The initial evaluation of patients with thyroid nodules typically includes measuring TSH levels. Globert *et al.* [16] reported that higher serum TSH levels are associated with an increased risk of thyroid cancer in patients with nodules. How-

Table 4. Ultrasound features of thyroid nodules according to the risk of malignancy

| Parameters | Univariate analysis | |
|-------------------------------------|---------------------|---------|
| | OR* (95% CI**) | P value |
| Nodules size | | |
| >4 cm (Ref) | 1 (Reference) | 0.013 |
| 2-4 cm | 5.53 (0.97-31.45) | 0.53 |
| <2 cm | 0.28 (0.025-3.31) | 0.317 |
| Taller-than-wide¹ | | |
| Yes | 8.88 (1.62-48.30) | 0.012 |
| No | | |
| Hypoechoic | | |
| Yes | 11.05 (2.11-57.78) | 0.004 |
| No | | |
| Marked hypoechoogenicity | | |
| No | 0.147 (0.011-1.979) | 0.148 |
| Yes | | |
| Vascularity² | | |
| None and peripheral | 8.55 (1.59-45.8) | 0.012 |
| Central and mixed | | |
| Irregular borders | | |
| Yes | 19.25 (2.67-138.4) | 0.003 |
| No | | |
| EU-TIRADS³ | | |
| III | 1 (Reference) | 0.000 |
| IV | 0.839(0.073-9.68) | 0.888 |
| V | 35.25(5.28-23.24) | 0.000 |

¹A taller-than-wide thyroid nodule characterized by an anteroposterior diameter greater than its transverse diameter

²Vascularity: devised in two groups: none and peripheral/central and mixed

³EU-TIRADS: European Thyroid Imaging Reporting and Data System

*OR: Odds Ratio, **CI: Confidence Interval

Table 5. Diagnostic performance of ultrasound features in thyroid nodule assessment

| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|-------------------------------------|-----------------|-----------------|---------|---------|
| Nodules size (< 2cm) | 66.7 | 82.2 | 30 | 95 |
| Taller-than-wide¹ | 37.5 | 93.7 | 37.5 | 93.6 |
| Hypoechoic | 77.8 | 75.9 | 26.9 | 96.7 |
| Irregular borders | 33.3 | 97.5 | 16 | 93.5 |
| Vascularity² | 75 | 74 | 23 | 96 |

¹A taller-than-wide thyroid nodule is defined by having an anteroposterior diameter greater than its transverse diameter

²Vascularity: devised in two groups: the first one; None and Peripheral / the second; Central and mixed

ever, in the current study, TSH levels were not associated with malignancy.

Although nodule size is routinely measured, its impact on the risk of thyroid cancer is still under discussion. Some studies highlight that the size of the nodule plays an important role in determining the risk of malignancy [17], while others find no significant link between nodule size (greater than 4 cm) and malignancy risk [18-20]. In our study, 66% of malignant nodules were less than 2 cm in diameter. When combined with other malignant features, nodule size may be a useful predictor of malignancy.

Studies by Boelaert *et al.* [21] and Kim *et al.* [22] suggest that single nodules are more likely to be malignant, contrary to other research, which argues that multiple nodules carry a higher risk [12]. The present study found no significant correlation between nodule multiplicity and malignancy risk.

Several recent studies have shown that a round appearance, a taller-than-wide (TTW), or round nodules can suggest malignancy [23,24]. Ren J. *et al.* [25] found that TTW > 1, along with other ultrasound risk factors, has great diagnostic performance for the diagnosis of papillary thyroid carcinomas, especially in small-sized nodules, with high specificity (96.8%) and sensitivity (81.4%). In our study, this characteristic was observed in 37.5% of malignant nodules ($P = 0.012$).

Consistent with literature [14,26], hypoechogenicity is commonly observed in malignant thyroid nodules. Our study reinforces this association, showing that 66.7% of severely hypoechoic nodules were malignant ($P = 0.148$). Our observations regarding irregular borders as an indicator of malignancy were consistent with those reported in the literature [9].

Intranodular vascularity appeared to be associated with malignant lesions, which is consistent with the findings of Lyschik *et al.* [27]. This association was statistically significant in the current study ($P = 0.012$). Some reports suggest that Doppler color does not aid in differentiating between malignant and benign nodules [28, 29]. In addition, the presence of microcalcifications is a well-known risk factor for malignancy in thyroid nodules, as identified in a comprehensive meta-analysis conducted by Campanella *et al.* [30]. This finding was not confirmed in our study.

The study results highlight the diagnostic value of thyroid US and the importance of the EU-TIRADS score in characterizing thyroid nodules and indicating FNA. Although the EU-TIRADS III score was more common in benign nodules, our study found one patient with EU-TIRADS III who had a BETHESDA VI cytology result, indicating the need to consider the risk of malignancy with EU-TIRADS III.

FNA is a crucial tool in guiding thyroid nodule management and is considered the gold standard for determining whether nodules are benign or malignant [31]. It is recommended that a second FNA be performed on nodules classified as Bethesda I and III. Generally, the percentage of thyroid cytology classified as Bethesda III should not exceed 7 to 10%, while Bethesda I cytology rates are ideal at less than 10% [32, 33]. In our study, these percentages were 2.5% and up to 19%, respectively.

The disparities in ultrasound features between our study and others can be attributed to differences in inclusion and exclusion criteria and the basis for distributing control groups.

Our study's strengths lie in being the first of its kind conducted in our country. Our study highlights the significance of adhering to the guidelines for managing thyroid nodules and how the use of ultrasound and FNA in combination can enhance the diagnostic accuracy of thyroid nodules.

Our study has several limitations. Its retrospective design restricted our ability to assess some factors comprehensively, which may have influenced the results. Additionally, some clinical information was missing from the medical records during data collection, which could have contributed to gaps in data analysis. Additionally, the sample size of our study was relatively small, and the number of malignant thyroid nodules was also limited. This has a significant impact on the accuracy of the other statistical analyses.

CONCLUSION

The identification of benign and malignant thyroid nodules is a crucial aspect of clinical practice. Our findings confirm that the EU-TIRADS score and the fine needle aspiration remain valuable and straightforward methods for assessing the risk of malignancy in thyroid nodules, determining patients who require surgery, and avoiding unnecessary procedures.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

The ethical review committee at the Faculty of Medicine, Mohamed the First University of Oujda (CERBO), approved the study design and protocol (22/11.11.2020).

Consent to participate

We provided patients with written information regarding the aim and objective of the study, and they gave their consent to access their medical records.

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Authorship

IZ, the first author, primarily wrote the manuscript. AJ contributed to the writing and participated in manuscript revisions. IA also contributed to the manuscript writing, supervised the process, and provided revisions. IK was responsible for data collection. Both SR and HL provided supervision and critically revised the final manuscript. All authors have read and approved the final draft of the manuscript.

REFERENCES

1. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer; Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, *et al.* Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2009 Nov;19(11):1167-214. doi: 10.1089/thy.2009.0110
2. Rehman AU, Ehsan M, Javed H, Ameer MZ, Mohsin A, Aemaz Ur Rehman M, *et al.* Solitary and multiple thyroid nodules as predictors of malignancy: a systematic review and meta-analysis. *Thyroid Res*. 2022 Dec 5;15(1):22. doi: 10.1186/s13044-022-00140-6
3. La Vecchia C, Malvezzi M, Bosetti C, Garavello W, Bertuccio P, Levi F, *et al.* Thyroid cancer mortality and incidence: a global overview. *Int J Cancer*. 2015 May 1;136(9):2187-95. doi: 10.1002/ijc.29251
4. Durante C, Hegedüs L, Czarniecka A, Paschke R, Russ G, Schmitt F, *et al.* 2023 European Thyroid Association Clinical Practice Guidelines for thyroid nodule management. *Eur Thyroid J*. 2023 Aug 14;12(5):e230067. doi: 10.1530/ETJ-23-0067
5. Fadda G, Basolo F, Bondi A, Bussolati G, Crescenzi A, Nappi O, *et al.* Cytological classification of thyroid nodules. Proposal of the SIAPEC-IAP Italian Consensus Working Group. *Pathologica*. 2010 Oct;102(5):405-8.

6. Ali SZ, Baloch ZW, Cochand-Priollet B, Schmitt FC, Vielh P, VanderLaan PA. The 2023 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid*. 2023 Sep;33(9):1039-1044. doi: 10.1089/thy.2023.0141.
7. Goellner JR, Gharib H, Grant CS, Johnson DA. Fine needle aspiration cytology of the thyroid, 1980 to 1986. *Acta Cytol*. 1987 Sep-Oct;31(5):587-90
8. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. *J Am Soc Cytopathol*. 2017 Nov-Dec;6(6):217-222. doi: 10.1016/j.jasc.2017.09.002
9. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults: The EU-TIRADS. *Eur Thyroid J*. 2017 Sep;6(5):225-237. doi: 10.1159/000478927
10. Bukasa-Kakamba J, Bayauli P, Sabbah N, Bidingija J, Atoot A, Mbunga B, *et al*. Ultrasound performance using the EU-TIRADS score in the diagnosis of thyroid cancer in Congolese hospitals. *Sci Rep*. 2022 Nov 2;12(1):18442. doi: 10.1038/s41598-022-22954-y
11. Bouaity B, Darouassi Y, Chihani M, Touati MM, Ammar H. Analyse des facteurs prédictifs de malignité des goitres nodulaires : à propos de 500 cas [Analysis of predictors of malignancy of nodular goiters: about 500 cases]. *Pan Afr Med J*. 2016 Mar 15;23:88. French. doi: 10.11604/panj.2016.23.88.8405
12. El-Gammal A, E-Balshy M, Zahran K. Relationship between thyroid nodule size and incidence of thyroid cancer. *Menoufia Med J*. 2019; 32: 1142.
13. Bessey IJ, Lai NB, Coorrough NE, Chen H, Sippel RS. The incidence of thyroid cancer by fine needle aspiration varies by age and gender. *J Surg Res*. 2013 Oct;184(2):761-5. doi: 10.1016/j.jss.2013.03.086
14. Joseph-Auguste J, Lin L, Demar M, Duffas O, Molinie V, Sulpicy C, *et al*. Epidemiologic, Clinical, Ultrasonographic, and Cytological Features of Thyroid Nodules in Predicting Malignancy Risk: A Retrospective Study of 442 French Afro-Caribbean Patients. *Int J Endocrinol*. 2020 Mar 31;2020:4039290. doi: 10.1155/2020/4039290
15. Paul P, Ali KA, Jasir M. Predictors of malignancy in solitary nodule thyroid. *Int Surg J*. 2017; 4: 703.
16. [16] Golbert L, de Cristo AP, Faccin CS, Farenzena M, Folgieriini H, Graudenz MS, *et al*. Serum TSH levels as a predictor of malignancy in thyroid nodules: A prospective study. *PLoS One*. 2017 Nov 16;12(11):e0188123. doi: 10.1371/journal.pone.0188123
17. Yim Y, Na DG, Ha EJ, Baek JH, Sung JY, Kim JH, *et al*. Concordance of Three International Guidelines for Thyroid Nodules Classified by Ultrasonography and Diagnostic Performance of Biopsy Criteria. *Korean J Radiol*. 2020 Jan;21(1):108-116. doi: 10.3348/kjr.2019.0215
18. Megwalu UC. Risk of Malignancy in Thyroid Nodules 4 cm or Larger. *Endocrinol Metab (Seoul)*. 2017 Mar;32(1):77-82. doi: 10.3803/EnM.2017.32.1.77
19. Kamran SC, Marqusee E, Kim MI, Frates MC, Ritner J, Peters H, *et al*. Thyroid nodule size and prediction of cancer. *J Clin Endocrinol Metab*. 2013 Feb;98(2):564-70. doi: 10.1210/jc.2012-2968
20. Kuru B, Gulcelik NE, Gulcelik MA, Dincer H. Predictive index for carcinoma of thyroid nodules and its integration with fine-needle aspiration cytology. *Head Neck*. 2009 Jul;31(7):856-66. doi: 10.1002/hed.21049
21. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. *J Clin Endocrinol Metab*. 2006 Nov;91(11):4295-301. doi: 10.1210/jc.2006-0527
22. Kim ES, Lim DJ, Baek KH, Lee JM, Kim MK, Kwon HS, *et al*. Thyroglobulin antibody is associated with increased cancer risk in thyroid nodules. *Thyroid*. 2010 Aug;20(8):885-91. doi: 10.1089/thy.2009.0384.
23. Huang K, Gao N, Zhai Q, Bian D, Wang D, Wang X. The anteroposterior diameter of nodules in the risk assessment of papillary thyroid microcarcinoma. *Medicine (Baltimore)*. 2018 Mar;97(10):e9712. doi: 10.1097/MD.00000000000009712
24. Liu J, Zheng D, Li Q, Tang X, Luo Z, Yuan Z, *et al*. A predictive model of thyroid malignancy using clinical, biochemical and sonographic parameters for patients in a multi-center setting. *BMC Endocr Disord*. 2018 Mar 7;18(1):17. doi: 10.1186/s12902-018-0241-7
25. Ren J, Liu B, Zhang LL, Li HY, Zhang F, Li S, *et al*. A taller-than-wide shape is a good predictor of papillary thyroid carcinoma in small solid nodules. *J Ultrasound Med*. 2015 Jan;34(1):19-26. doi: 10.7863/ultra.34.1.19
26. Nicolaou MA, Jacobs K, Bhana S, Naidu K, Nicolaou V. A retrospective study correlating sonographic features of thyroid nodules with fine-needle aspiration cytology in a South African setting. *SA J Radiol*. 2019 Jun 26;23(1):1749. doi: 10.4102/sajrv.23i1.1749
27. Lyshchik A, Moses R, Barnes SL, Higashi T, Asato R, Miga MI, *et al*. Quantitative analysis of tumor vascularity in benign and malignant solid thyroid nodules. *J Ultrasound Med*. 2007 Jun;26(6):837-46. doi: 10.7863/jum.2007.26.6.837
28. Moon HJ, Kwak JY, Kim MJ, Son EJ, Kim EK. Can vascularity at power Doppler US help predict thyroid malignancy? *Radiology*. 2010 Apr;255(1):260-9. doi: 10.1148/radiol.09091284
29. Wienke JR, Chong WK, Fielding JR, Zou KH, Mittelstaedt CA. Sonographic Features of Benign Thyroid Nodules. *J Ultrasound Med*. 2003; 22: 1027–1031.
30. Campanella P, Ianni F, Rota CA, Corsello SM, Pontecorvi A. Quantification of cancer risk of each clinical and ultrasonographic suspicious feature of thyroid nodules: a systematic review and meta-analysis. *Eur J Endocrinol*. 2014 Apr 10;170(5):R203-11. doi: 10.1530/EJE-13-0995
31. Tamhane S, Gharib H. Thyroid nodule update on diagnosis and management. *Clin Diabetes Endocrinol*. 2016 Oct 3;2:17. doi: 10.1186/s40842-016-0035-7
32. Castro MR, Gharib H. Thyroid fine-needle aspiration biopsy. *Endocr Pract*. 2003; 9:128–136.
33. Jeffrey PB, Miller TR. Fine-needle aspiration cytology of the thyroid. *Pathology (Phila)*. 1996;4(2):319-35.