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Keywords

Thyroid; Nodule; EU-TIRADS; Bethesda; Pathological anatomy

Abbreviation's

FNA: Fine Needle Aspiration; PA: Pathological Anatomy; TSH: Thyroid-Stimulating Hormone; ATA: American Thyroid Association; SD: Standard Deviations; NPV: Negative Predictive Value; PPV: Positive Predictive Value

Research Article

Correlation between Ultrasound, Cytology and Anatomo Pathology in Thyroid Nodules

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Abstract

Introduction: Surgical pathologies of the thyroid are frequent; essential tools for its assessment constitute ultrasound, Fine Needle Aspiration (FNA), and Pathological Anatomy (PA) of the resected sample.

Objective: To determine the correlation between sonographic, cytological and pathological findings of thyroid nodules in years.

Materials and methods: Observational, descriptive and retrospective study of thyroidectomized patients between 2010 and 2014 at Clinical's Hospital-Uruguay.

Results: Sixty-seven patients, 59 women and 8 men, with a mean age of 45 ± 16 years. According to ultrasound findings, the majority corresponded to EU-TIRADS 3 (43%), followed by EU-TIRADS 4 (27%). According to Bethesda classification, the most frequent was indeterminate (48%), followed by benign (32%) and malignant (19%). 54% had benign PA and 46% malignant, papillary carcinoma was the most frequent (61%).

Discussion: A significant association between EU-TIRADS 4-5 and the Bethesda classification was demonstrated. The finding of a probably benign (EU-TIRADS 3) or suspicious (EU-TIRADS 4) nodule, whose risk described in the literature of 2-4% and 6-17%, can hide a malignant tumor in up to 1/4 or 6 /10 cases respectively. Sensitivity of ultrasound was 74% and specificity 66%. The ultrasound elements significantly related to malignancy were the solid variant, hypoechoic and the presence of microcalcifications. Bethesda classification categories clearly associated with malignancy were IV, V, and VI.

Conclusions: An adequate correlation was demonstrated to differentiate benignity from malignancy when comparing ultrasound findings of thyroid nodules with FNA and PA.

Introduction

Surgical pathologies of the thyroid are frequent worldwide; Essential tools for its assessment are ultrasound, Fine Needle Aspiration (FNA), and Pathological Anatomy (PA) of the resected sample. Thyroid nodules correspond sonographically to a lesion within the thyroid gland, which radiologically differs from the parenchyma that surrounds it. The prevalence of palpable lesions is estimated at 5% in women and 1% in men in areas with sufficient iodine. This increases up to 19-68% with image techniques. The clinical importance of evaluating a thyroid nodule lies in the need to exclude thyroid malignancy, which occurs in 5 to 10% of the cases [1-3]. The initial evaluation of thyroid nodular pathology consists of dosing Thyroid-Stimulating Hormone (TSH) to determine function, and performing a thyroid ultrasound to assess glandular structure [4]. Thyroid ultrasound is an imaging technique that provides general morphological information such as integrity, position, size, shape, contours, borders; and specific morphological information such as echogenicity and echostructure of the gland and nodules if present. The use of Doppler adds information on the vascularization of normal and pathological tissue [5-7]. It is the first-line tool for evaluation for malignancy risk of thyroid nodules. However, reliability is affected by the variability that exists between operators. Sonographic risk factors for malignancy include thyroid nodules with presence of microcalcifications, irregular margins, taller than wide shape, and hypo echogenicity. The first three characteristics present greater specificity, close to 90% [8, 9]. EU-TIRADS system allows the analysis, classification and follow-up of thyroid nodules in a reliable and reproducible way. It allows a quantitative stratification of malignancy risk and aims to rationalize the indications for punctures and surgery. It is a simple tool, however, it is operator dependent [10]. Nodules are classified into five classes, from 1 (no nodules) to 5 (high risk) (Figure 1). Following this approach, the experts of the European Thyroid Association (ETA) have estimated a risk of malignancy close to zero in EU-TIRADS 2; 2 to 4% in EU-TIRADS 3; 6 to 17% in EU-TIRADS 4 and range between 26 and 87% in EU-TIRADS 52.

FNA was established in 1980, is the test of choice to assess the benignity or malignancy of a thyroid nodule [11]. It is a low-complexity and low-risk method, which consists of extracting a cytological sample through a direct puncture of the nodule. A reliable technique, guided by ultrasound, approximate sensitivity of 80% and specificity of 90%, however, it depends on the experience of both the cytologist and the person in charge of taking the sample [12-14]. In 2015, the American Thyroid Association (ATA) published its recommendations for FNA, based on the risk of malignancy defined by ultrasound characteristics. For the cytopathological diagnosis, Bethesda System, described in 2007, is currently used. This system recognizes six diagnostic categories and provides an estimate risk of cancer within each category, according to literature review and expert opinion8 (Figure 2). Finally, the pathologist is in charge of making the definitive diagnosis of the thyroidectomy specimen and its nodules, through the issuance of a pathology report. It can be a benign lesion such as lymphocytic thyroiditis, multinodular goiter, colloid cysts, or malignant lesions such as papillary, follicular, medullary, or anaplastic carcinoma [16-18]. The objective of this study was to determine the correlation between the ultrasound, cytological and pathological findings of thyroid nodules in 5 years.

Category	US features	Malignancy risk, %
EU-TIRADS 1: normal	No nodules	None
EU-TIRADS 2: benign	Pure cyst Entirely spongiform	≅0
EU-TIRADS 3: low risk	Ovoid, smooth isoechoic/hyperechoic No features of high suspicion	2–4
EU-TIRADS 4: intermediate risk	Ovoid, smooth, mildly hypoechoic No features of high suspicion	6–17
EU-TIRADS 5: high risk	At least 1 of the following features of high suspicion: – Irregular shape – Irregular margins – Microcalcifications – Marked hypoechogenicity (and solid)	26–87

EU-TIRADS, European Thyroid Imaging Reporting and Data System; US, ultrasound.

Figure 1: Categories and risk of malignancy according to EU-TIRADS.

Diagnostic category	*Estimated/predicted risk of malignancy by the Bethesda system, %*[a]
Nondiagnostic or unsatisfactory	1–4
Benign	0–3
Atypia of undetermined significance or follicular lesion of undetermined significance	5–15
Follicular neoplasm or suspicious for a follicular neoplasm	15–30
Suspicious for malignancy	60–75
Malignant	97–99

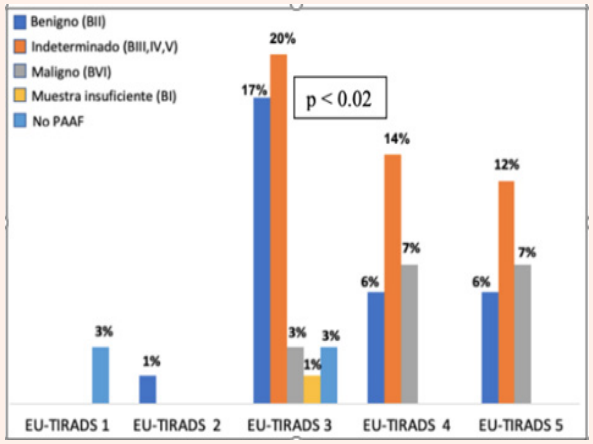
Figure 2: Categories of the Bethesda System and risk of malignancy.

Materials and Methods

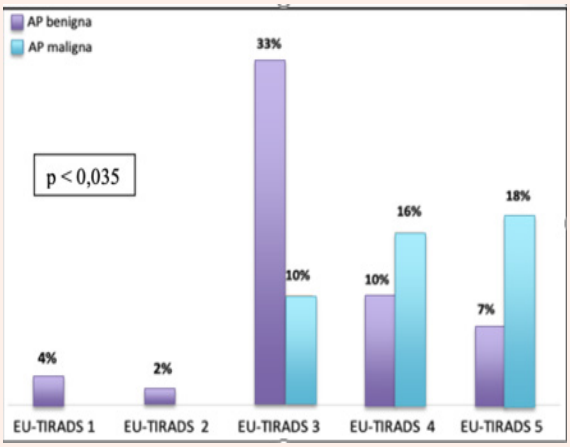
This is an observational, descriptive, retrospective study. A data collection sheet was used during the design of this study with variables taken into account. Clinical records of patients with a diagnosis of nodular thyroid pathology, who underwent surgery at de Clinical's Hospital during January 1st, 2010 to December 31st, 2014. Indirect observation technique was used to collect the data. All the principles of bioethics in research were taken into account while conducting the study, with approval of the hospital ethics committee.

Results

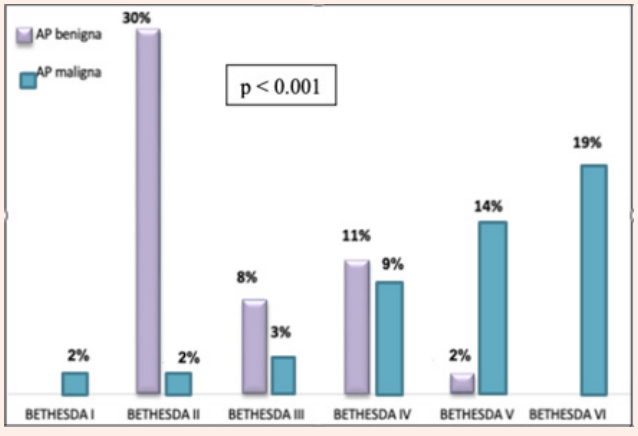
67 patients underwent ultrasound, thyroid surgery and pathological anatomy in that period of time, which represents the entire sample. There were 4 patients who did not undergo FNA, so some results were tabulated over the remaining 63. Of the total, 58% came from Montevideo; 88% were women. The age range varies from 14 to 76 years, with a mean range of 46.6 ± 16 years Standard Deviations (SD) for the sample. 30% were under treatment for thyroid hypo- or hyperfunction, 12 were receiving levothyroxine, while 8 were receiving antithyroid drugs. According to the ultrasound findings, 43% had EU-TIRADS category 3; 27% EU-TIRADS 4; 26% EU-TIRADS 5; 3% EU-TIRADS 1 and 1% EU-TIRADS 2. According to Bethesda classification (B), the most frequent was indeterminate category-BIII-IV and V (48%), followed by benign-BII (32%) and malignant-BVI (19%). Regarding PA, 54% were benign and 46% malignant, papillary carcinoma was the most frequent (61%), followed by micropapillary (32%). EU-TIRADS criteria correlated with Bethesda and PA classification, and finally Bethesda with PA. (Graph 1-3). It was observed that 2 patients in EU-TIRADS 1 did not undergo FNA (they did not have criteria given the absence of thyroid nodular pathology). The only patient in EU-TIRADS 2 had a nodule punctured for size that was Bethesda II.



Graph 1: EU-TIRADS correlation with Bethesda.

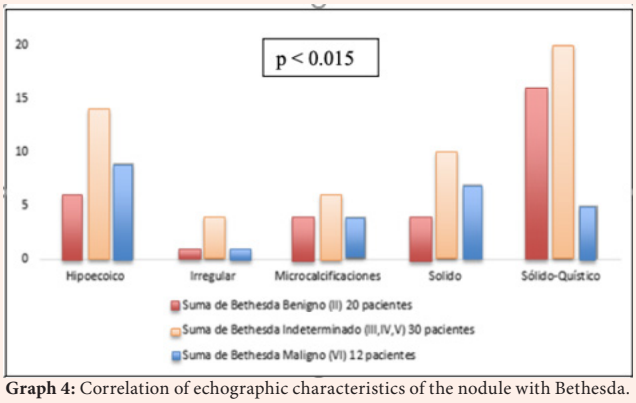


Graph 2: EU-TIRADS correlation with AP.

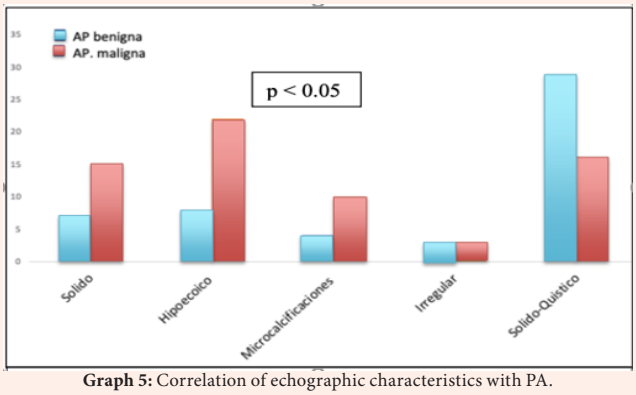


Graph 3: Bethesda correlation with PA.

Of a total of 67 nodules, they were divided into 2 groups, the first group of 32 nodules (48%) classified by ultrasound as low risk of malignancy (EU-TIRADS I, II and III) and the second group included 35 nodules (42%) classified sonographically as high risk of malignancy (EU-TIRADS IV and V). This distribution was based on the results found in the literature to determine the potential risk of malignancy. The percentage of malignancy corresponding to each group was 22% for group 1 and 66% for group 2. Next, ultrasound characteristics mostly associated with malignancy are determined, both for Bethesda and for anatomophatology. The variables that were taken into account were: solid, hypoechoic, microcalcifications, irregular margin and cystic component (Graphs 4 and 5).



Graph 4: Correlation of echographic characteristics of the nodule with Bethesda.



Graph 5: Correlation of echographic characteristics with PA.

Finally, the Sensitivity (S), Specificity (s), Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of ultrasound vs PA, and FNA vs PA are calculated, taking the latter as the gold standard technique for detecting malignancy. For ultrasound, the population is arbitrarily separated into two groups, according to EU-TIRADS 1,2 and 3 as suggestive of benignity, while 4 and 5 as suggestive of malignancy (Table 1, 2).

Table 1: Calculation of sensitivity, specificity, PPV and NPV for ultrasound vs PA.

ECO vs. AP	Benigno AP	Maligno AP
Benigno Eco	24	8
Maligno Eco	12	23

S: 74%; s: 66%; PPV: 65%;NPV: 75%

Table 2: Calculation of sensitivity, specificity, PPV, NPV for FNA vs PA (excluding undetermined).

PAAF VS. AP	Benigno AP	Maligno AP
B2 (Benigno)	12	0
B6 (Maligno)	1	19

S: 100%; s: 92%; PPV: 95%; NPV: 100%

Discussion

Thyroid pathology is more frequent in females and our study represents it, with a tendency to decrease as age increases. This could be explained by the frequency of thyroid nodules, which most commonly occur during the third, fourth and fifth decades of life, and their incidence decreasing as age increases of the ultrasound reports according to EU-TIRADS, we found percentages similar to those described in the literature (Table 3).

Table 3: EU-TIRADS comparison among different studies.

	Nuestro estudio	Laukiene et al[19]	Hasnaoui et al[10]
EU-TIRADS 1	3%	-	-
EU-TIRADS 2	1%	1%	12%
EU-TIRADS 3	43%	62%	44%
EU-TIRADS 4	27%	22%	38%
EU-TIRADS 5	26%	15%	6%

When Bethesda system is grouped as proposed by ATA15, we find that almost half (48%) are indeterminate, this can be explained because there are three categories. 32% were classified as benign in this system and almost 2 of 10 as malignant. Concerning anatomopathology, 46% of the nodules were malignant, similar to what was found by [20]. with 51% of malignancy. This figure is higher than that found by Mora et al16 where 35% of the nodules were malignant; the vast majority were papillary carcinomas (84%), when we had 61%; but they considered papillary microcarcinomas within the total number of papillary and we separated them (if we add our microcarcinomas to the papillary ones, we found a similar number). When analyzing the EU-TIRADS association with Bethesda pooled, it is highlighted that the scarce presence of patients with EU-TIRADS 1 and 2 results is explained by the bias of the sample due to the inclusion criteria for this study, additionally generally they do not require puncture or surgery and only require vigilance. In the cases of EU-TIRADS 3, 4 and 5, the preponderant Bethesda is the indeterminate group, which may be due to the fact that includes 3 subtypes (Bethesda III, IV and V). Subtype IV was the most frequent (62%, n=8) in EU-TIRADS 3. In EU-TIRADS 4 there are no significant differences between the three subtypes and in EU-TIRADS 5 the majority corresponds to subtype V (63% - n=5). This is what the literature reports where EU-TIRADS 5 category is considered to have a high risk of malignancy (between 26-87%) and the Bethesda V category is suspicious for malignancy with a risk of 60-75% in it. Regarding EU-TIRADS relationship with PA, a statistically significant association was demonstrated, malignancy by category was 0% for EU-TIRADS 1, 0% for EU-TIRADS 2, 23% for EU-TIRADS 3, 62% for EU-TIRADS 4, and 72% for EU-TIRADS 5. In another studies we observe the following (Table 4).

Table 4: Comparison with other studies of the EU-TIRADS vs PA correlation.

EU- TIRADS	AP maligna (nuestro estudio)	AP maligna estudio de Kraus G et al[20]	AP maligna Estudio Hasnaoui et al[10]	European Thyroid Association (Riesgo de malignidad)
EU-TIRADS 3	23%	31%	7,2%	2-4%
EU-TIRADS 4	62%	41%	7,4%	6-17%
EU-TIRADS 5	72%	93%	30,4%	26-87%

In our study we have shown how the finding of a probably benign (EU-TIRADS 3) or suspicious (EU-TIRADS 4) nodule, whose risk described in the literature is 2-4% and 6-17%, can hide a malignant tumor up to 1/4 or 6/10 cases respectively. When analyzing the sensitivity of ultrasound compared to pathology, we observed that of 32 patients characterized as benign EU-TIRADS, 24 were truly benign according to PA. In contrast, 35 patients were placed in the malignant EU-TIRADS group, of which 23 were truly malignant according to PA. Therefore, the sensitivity was 74% and the specificity 66%, PPV 65% and NPV 75%, practically the same as that described by Hasnaoui et al10 who had a sensitivity of 76% and specificity 62%, with PPV 26% and NPV of 93%. Our work indicates that thyroid ultrasound has a better NPV (75%) to discriminate benignity, but not enough specificity and PPV (66%) to determine malignancy compared to PA as the gold standard technique, which makes it ideal as a screening study. On the other hand, the clear correlation that exists between Bethesda classification and pathological anatomy is interesting. A frank benignity

is demonstrated for the Bethesda II category with 30% vs 2%, statistically significant (94% for benignity). For categories BIII and IV, the rate of benignity decreases significantly, while the rates of malignancy rise significantly for BV (14% vs 2%) (88% for malignancy) and reach 100% for BVI. We also highlight the absolute certainty of Bethesda VI to confirm malignancy and the coincidence in percentage of malignancy of Bethesda V, as indicated by the classification system itself, between 60-75%. All the patients who underwent surgery with a cytological suggestion of malignancy had this result. As for the indeterminate group, the sensitivity drops markedly (43%), which translates into low detection of malignancy when compared to the standard test, which is PA. Regarding the ultrasound characteristics of the nodules, to avoid confounding factors, the variable taller than width was excluded, since a significant number of ultrasounds did not have an adequate description of the dimensions. For Bethesda, the variable most frequently associated with malignancy was solid and hypoechoic. The indeterminate group is the one that appears most frequently in all the variables studied, due to the grouping of three subtypes. For PA, a different scenario is shown, where the solid variable is statistically significant to discriminate malignancy (n=15 vs n=7); for hypoechoic the relationship is even more marked (n=22 vs n=8) and this trend is maintained with respect to microcalcifications (n=10 vs n=4). This aspect correlates with what is described in the literature, Chala33 found hypoechogenicity and microcalcifications to be associated with malignancy.

Conclusions

a) The EU-TIRADS malignancy risk categories have a good correspondence with the Bethesda cytological categories in our hospital.

b) The analysis of EU-TIRADS with FNA and EU-TIRADS with PA shows a significant correlation to discriminate malignancy.

c) The level of ultrasound accuracy was higher than the cytological level when compared to the final pathological anatomy to discriminate malignancy; nodules with indeterminate cytology are a poor predictor of the final result.

d) The ultrasound elements that were significantly related to malignancy were the solid variant, hypoechoic, and the presence of microcalcifications, and the categories of the Bethesda classification clearly associated with malignancy were IV, V, and VI.

e) When comparing the ultrasound findings with FNA and PA, an adequate correlation is demonstrated to differentiate between benign and malignant thyroid nodules.

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