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Research Article

Clinical, Laboratory and Ultrasound Evaluation and Aspirative Cytology of Benign and Malignant Thyroid Nodules

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Abstract

Thyroid nodules frequently occur in the general population. The present study was conducted in order to evaluate the occurrence of clinical (age and sex of nodule carriers, nodule numbers, size, consistency, mobility and adherence to cervical planes, and hoarseness), laboratory (TSH, FT4, FT3, thyroglobulin, anti-TPO, anti-TG, TRAB) and US findings (number and consistency of the nodules, presence of an anechoic halo, nodule limits, vascularization and presence and type of calcifications), as well as cytopathology findings (BETHESDA Classification), and to confirm suspected cases by anatomopathological (AP) exams. The study was conducted on 255 patients (236 women -92,55% ranging in age from 15 to 87 years, mean: 52.6 years, and 19 men -7,45%- ranging in age from 44 to 85 years, mean: 60.2 years). The mean age of patients classified as benign cases was 53.3 years and the mean age of malignant cases was 50.6 years. Eleven patients - 4,31% (8 women- 3,34% and 3 men-15,78%) were diagnosed as carriers of malignancy. The clinical and laboratory findings were nonspecific for malignancy. Microcalcification detected by US was correlated with malignancy in 100% of cases. Exclusively or preponderantly central vascularization showed a strong correlation with malignancy. All nodules found to be malignant by AP were solid, although 30% of them showed heterogeneity. Malignant nodules were classified as iso-or hypoechoic, with the predominance of hypoechogenicity. The partial presence or the absence of an anechoic halo in the malignant nodules was correlated with invasion of the capsule and of nearby thyroid tissue. Accessory adenomegaly suspected of malignancy by US was not diagnosed in malignant cases. Thyroid nodules continue to be a challenge in clinical practice.

Keywords: *Thyroid Nodules; Benign Thyroid Nodules; Malignant Thyroid Nodules; Clinical Thyroid Nodules; Thyroid Nodules Laboratory; Thyroid Nodules Ultrasonography; Thyroid Nodules Cytology*

Introduction

The thyroid is one of the largest endocrine organs of the human body. It weighs 15 to 20 grams in normal adults and it consists of two lobes (right and left) joined by a fine band of glandular tissue about 0.5 cm thick.

Each lobe is about 2 to 2.5 cm thick and wide in its larger axis and is 4 cm long (about 2 finger pads). When increased in side (goiter) it may present a pyramidal lobe directed upward and leftward starting from the isthmus.

The thyroid gland has a very high potential for growth, which may occur in a diffuse or nodular manner as a consequence of a continuous or repetitive hyperplastic process [1].

Thyroid enlargement may occur due to insufficient or excessive hormone production caused by enzymatic defects, iodine deficiency, inflammatory and/or autoimmune processes, or by the presence of benign or malignant tumors [2,3].

Thyroid nodules (TN) are relatively frequent in the general population, occurring in 6% of adult women and in 1% of adult men, with about 24 new cases per 1000 inhabitants per year. It is the fourth most frequent neoplasia among women [4,5].

Assessment of the thyroid gland by ultrasound (US) reveals that one third of all adult women and one fifth of adult men have small nodules [6,7]. About 90% of TN are benign; however, despite of the small possibility of its occurrence, malignancy should be considered and appropriately excluded in all patients with TN [8-10].

Most of the investigation of TN is focused on US examination accompanied or not by fine needle aspiration biopsy (FNA) for the detection of malignancy [11-17]. In some situations, even these two exams are insufficient to predict malignancy, so that it is necessary to repeat them or to use more sophisticated tests such as molecular markers and/or a genomic panel for mutations, or yet again to refer the patient to surgical exeresis of the TN for anatomopathological examination of the lesion [15,18].

Few literature studies have correlated the clinical, laboratory, US and aspiration cytology data of TN carriers in order to separate cases of suspected malignancy [19,20]. Since molecular or genomic exams are not available in our service [20], the objective of the present study was to correlate the clinical, laboratory, US and aspiration cytology data of patients with nodules in order to better predict malignancy and guide our conduct in the presence of diagnostic sensitivity.

Patients and Methods

The study was approved by the "Plataforma Brasil 6268216300005498" Ethics Committee and all patients gave written informed consent to participate.

The study was conducted on 255 patients (236 women aged 15 to 85 years and 19 men aged 44 to 85 years; mean: 52,6 for women and 60.2 years for men). The mean age was 53.3 years for patients classified as having benign nodules and 50.6 years for patients with malignant nodules.

The clinical exam was reviewed by a single examiner who evaluated the aspect of the cervical region, the number, size and consistency of palpable nodules, nodule adherence to other cervical structures, palpation of locoregional adenomegaly, and hoarseness. Nodules larger than 4 cm or presenting palpable ganglia [19] were considered to be suspicious of malignancy.

The patients were submitted to electrochemiluminescence determination of TSH (RV = 0.27 - 4.5 uIU/L); FT4 (RV = 0.9 - 1.9 ng/dl); FT3 (RV = 2.0 - 4.4 ng/ml); Tg (RV = 1.4 - 78 ng/ml); anti-TPO (RV =< 34 IU/ml); anti-Tg (RV =< 34 IU/ml) and TRAB (RV =< 1.75 IU/L).

US examination was performed in patients with palpable TN or TN diagnosed during an echographic exam of the cervical region due to other diseases. The US imaging system 8000EX (Samsung Medison Co. Seoul, Korea) was used and the lesions were classified as solid or mixed, single or multiple, with malignancy being suspected in solid nodules and being little suspected in nodules with more than 50% of their volume consisting of fluid [21,22].

Patients with 1 to 8 nodules were identified, with nodule size ranging from 3 to 40 mm. Nodules larger than 10 mm considered to be suspicious were punctured, with up to 3 nodules per patient being punctured [23].

The other parameters evaluated in this exam were: nodule delimitation (well-defined, partially defined or undefined limits), with the nodules with poorly or undefined limits being considered suspected of malignancy [19].

The nodules were classified as hypoechogenic, hyperechogenic, isoechogenic or anechoic. Hypoechoic solid nodules were considered to be suspected of malignancy [17].

The nodules were assessed by US regarding their diameters, with oval-shaped ones (height greater than width) being suspected of malignancy. Cervical ganglia were suspected when rounded in shape, with the presence of a hilus and with ill-defined limits [20,21].

Nodule vascularization was assessed and classified as: absent (I); present only at the periphery (II); present both at the periphery and in the center although predominantly at the periphery (III); present at the periphery and in the center, although predominantly in the center (IV), and exclusively central (V). Classes IV and V were considered to be suspected of malignancy [22,23].

Microcalcifications inside the nodule were considered to be suspected of malignancy and were classified as present or absent. Macrocalcifications were not considered to be suspected of malignancy [20].

The association of the nodules with Hypothyrodism (Type 1), Hyperthyroidism (Thype 2),Autoimmune Thyroiditis (Type 3) or no thyropathy associated (Type4),was determined and cases with association of them with Thyroiditis and or Hypothyroidism were considered to be suspected of malignancy (figure 2).

Ultrasound examination was also used to guide FNA of nodules larger than 10 mm and aspirated material was stained with hematoxylin-eosin, submitted to histopathology examination and classified according to the BETHESDA criteria as: I- inconclusive; II- benign; III- material with atypia and inconclusive; IV- follicular proliferation; V- suspected of malignancy, and VI- malignant. Classes 1, 3 and 4 were considered inconclusive and the nodules involved were repunctured and reclassified. If 3 repunctures continued to be inconclusive and following US showed any difference in aspects or size, the nodule in question was submitted to exeresis and to anatomopathological study. About 8 nodules fulfilled these criteria and were considered to be benign in the anatomopathological exam [24,25].

Statistical Analysis

Data were analyzed statistically by the Chi-square test (Table 1) [26].

	% Patients		Mean Age		SD Age		TSH		T4L		T3L		Thyroglob		ANTII-TPO		ANTI-TG		TRAB	
Type	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
1	5,88%	90,5%	59,56	52,82	12,72	15,39	2,07	2,46	2,26	1,25	3,22	2,95	59,47	43,22	5,80	35,73	12,87	53,67	0,53	0,46
2	1,57%	2,05%	63,67	42,80	6,51	14,24	2,99	1,52	1,51	1,28	2,85	3,27	28,05	101,9	1,00	7,17	11,50	5,66	0,30	0,30

Table 1: *Mean values according to type and sex.*

AGE = years; TSH = uIU/L; FT4 = ng/dl; FT3 = ng/ml; Thyroglobulin = ng/ml; anti-TPO = IU/ml; Anti-Tg = IU/ml; TRAB = IU/L

Figure 1 illustrates the age distribution for the benign and malignant nodules and figure 2 the associated thyropathy as determined using the GRAPH PED system (Graph 1) [27].

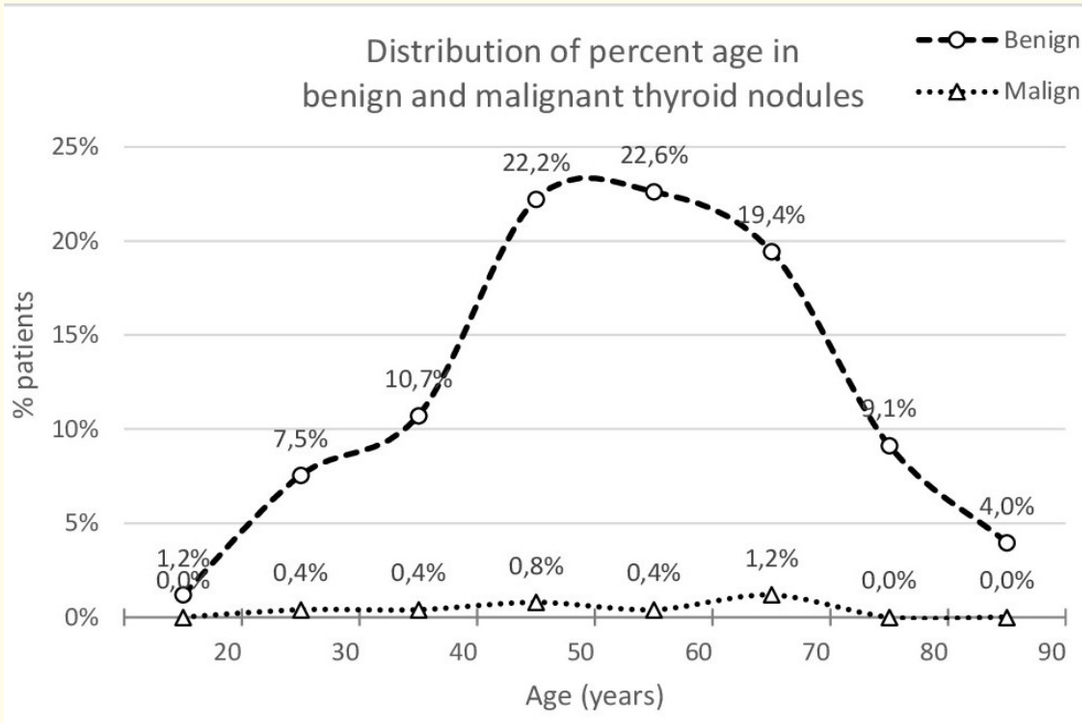

Figure 1: *Distribution of percent age (years) in benign and malignant thyroid nodules.*

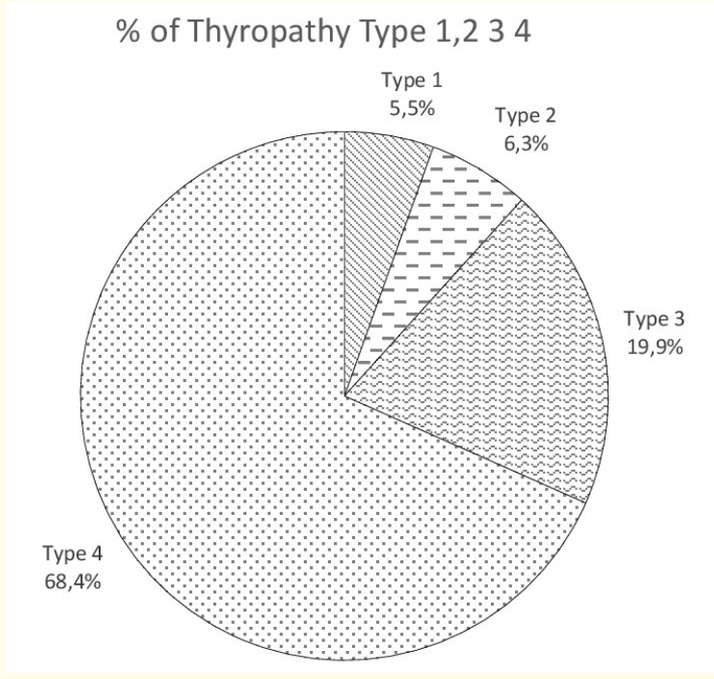

Figure 2: *Associated Thyropathy: Type 1- Hypothyroidism; Type 2- Hyperthyroidism; Type 3- Autoimmune Thyroiditis; Type 4- No Thyropathy Associated*

Results

The participation of men in the present study was reduced (n = 19) (7,45%) compared to women (n = 236) (92,55%).

The age range of patients with benign nodules was predominantly between 40 and 60 years (45% and 27.5% for women and men, respectively), followed by the 60 to 70 year age range (20% for women and 37.5% for men), while the age range for patients with malignant nodules was 60 to 70 years for both sexes (20% and 100% for women and men, respectively).

No clinical signs of malignancy were detected in patients with carcinomas such as a hardened, adherent nodule, voice changes, a larger nodule size and palpable cervical adenomegaly.

A total of 255 patients with 405 nodules were evaluated (91 X 1, 80 X 2, 17 X 3, 16 X 4, 9 X 5, 6 X 6, 0 X 7, 2 X 8) and 13 of these nodules were considered to be malignant. One woman and one man had 2 malignant nodules each.

Malignancy was diagnosed in 11 patients (4.13%), 8 of them women (3.34%) with a mean age of 42.8 years, and 3 of them men (15.78%) with a mean age of 63.7 years.

Of the 11 patients with malignancy, a single one, a woman, had hypothyroidism and concomitant autoimmune thyroiditis. Benign cases were observed in 12 patients with hypothyroidism, in 15 patients with hyperthyroidism, in 50 patients with autoimmune thyroiditis, and in 167 euthyroid patients.

Nodule size ranged from 3 to 40 mm in benign cases and from 10 to 29 mm in malignant cases.

All 255 patients were submitted to FNA of up to 3 nodules among carriers of more than 4 nodules. Eleven cases compatible with malignancy were identified and 8 cases who were left without a definitive diagnosis according to Bethesda classes 1, 3 and 4 and were re-evaluated by US and, for lack of a diagnostic conclusion, were referred to surgical exeresis, all of them being found to be benign (follicular adenoma, Hürtle adenoma, adenomatous goiter, and nodular hyperplasia) [28,29].

No patient with malignancy showed concomitant hypothyroidism or autoimmune thyroiditis. In the present study, thyroglobulin levels determined before FNA were higher among patients with malignancy ($p < 0.001$) and anti-TPO and anti-Tg levels were higher among benign cases because of the associated Hashimoto Thyroid it with them ($p < 0.001$) (Table 1).

Of the malignant nodules detected in women, 4 had well-defined limits and were surrounded by an anechoic halo (indicating benignity) and 4 had ill-defined limits or an incomplete halo and were associated with invasion of the capsule and soft parts. The 3 men with malignant lesions showed a fine halo around the nodule, 2 of them with more than one nodule, 2 with an additional benign lesion, and one with a malignant nodule and a 3 mm carcinoma focus in the contralateral lobe.

The presence of a malignant nodule occurred in pure or heterogeneous solid nodules (30% of cases) and in iso- or hypoechoic nodules, predominantly among the hypoechoic ones. Iso- or hypoechoic nodules were also identified among benign nodules, thus not representing a signal suggestive of malignancy but representing a frequent association. Heterogeneous malignant nodules were also detected by US.

The presence of microcalcifications inside the nodule occurred in 6 of the 13 malignant lesions, representing the most sensitive US signal. A 33-year-old female patient showed a single 0.6 cm isoechoice nodule with a complete halo, absent vascularization and complex annular eggshell-like calcifications, and was diagnosed by FNA as having a papilliferous carcinoma. Nodule vascularization predominantly in the center (IV) or exclusively central (V) was find in 5 of 13 malignant nodules [22,23].

A single patient had an oval-shaped nodule suggestive of malignancy and suspicious adenomegaly was not detected in any patient by US [30,31].

Discussion

Thyroid nodules are relatively common in the general population. They vary widely in size, many of them being palpable, but most are too small to be seen or palpable and asymptomatic [29]. Indeed detection of many thyroid nodules can be as incidental findings on radiological evaluation, including the neck. Every diagnosed thyroid nodule requires additional evaluation in order to diagnose and treat thyroid cancer in the earliest stage [30].

In the present study there was a predominance of women, indicating a higher incidence of endocrinopathy (TN) in this sex, as well as the fact that women seek medical care more often. However, the prevalence of malignant nodules was higher among men. Men have fewer TN, which, however, are more frequently malignant (15.78% X 3.30% for men and women, respectively, in the present study). Patients with malignant nodules also showed a larger number of nodules per thyroid gland (1 patient with 3 nodules, 2 of them malignant and another with 2 nodules, both malignant). Most of them had only one nodule [28,30].

Benign nodules predominated between 40 and 60 years of age and malignant ones predominated between 60 and 70 years, suggesting that nodular thyroid disease is associated with aging.

We did not observe an association of malignant neoplasia with autoimmunity (increased anti-TPO, anti-thyroglobulin and TRAB levels), a fact possibly explained by the small number of malignant cases and by the absence of thyroiditis among the patients studied. A positive correlation was observed between increased thyroglobulin values and malignancy. Less elevated anti-TPO and Anti-Tg titers among carriers of malignant nodules were due to the absence of autoimmune thyroiditis in this group [17].

Nodule size was not correlated with malignancy [28,29].

The presence of surrounding anechoic halo was not correlated with benign disease since it also occurred in malignant nodules, although the detection of ill-defined limits was associated with capsule and/or extra-thyroid invasion in 100% of cases, thus being considered to be a suspect signal.

The vascularization most frequently detected was predominantly central (class IV), although some of the malignant cases were correlated with vascularization exclusively or predominantly of the peripheral type. A malignant nodule was classified as poorly vascularized and another was classified as avascular and were associated with fibrosis. Few nodules considered to be benign were classified as having type IV vascularization. Thus, predominantly or exclusively central vascularization may be consider a signal suggestive of malignancy [22,23].

The absence of adenomegaly upon US and palpation did not exclude the presence of malignancy [30,31].

Intranodular microcalcification was a characteristic of malignancy and macrocalcifications were a characteristic of benign disease, suggesting a positive association when present in these studied nodules [32,33].

Conclusions

Thyroid nodules are frequent, especially among women, but malignant nodules are proportionally more frequent among men.

Benign or malignant TN occur at all ages among adult women and men, but their prevalence increases with age, especially regarding malignant nodules.

Clinical findings of a single, rigid, non-mobile nodule adhering to cervical planes and of hoarseness were infrequently present among patients with malignant nodules but, when observed, they are strongly correlated with malignancy.

Laboratory blood parameters did not show a correlation with malignancy in the present study, indicating possible etiologies other than autoimmune thyroid disease for malignant nodules.

Predominantly or exclusively central vascularization was associated with malignancy, although some malignant nodules with peripheral or even absent vascularization were detected.

The presence of microcalcifications inside a TN is suspected of malignancy, showing a correlation in 100% of cases of its occurrence in the present study.

Thyroid nodules continue to be a challenge in clinical practice.

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Conflicts of Interest

The authors declare that there were no conflicts of interest in this study.

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