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Association of single and multiple thyroid nodules with a higher incidence of malignant neoplasms

Associação de nódulos tireoidianos únicos e múltiplos com maior incidência de neoplasias malignas

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ABSTRACT:
To compare the prevalence of single and multiple thyroid nodules and associate them with the presence of thyroid cancers. This was an observational, retrospective study carried out in a reference center for pathology and a private hospital in Joinville, state of Santa Catarina, Brazil. Data were collected from January 2011 to December 2021. Patients were divided into two groups: those with single and multiple thyroid nodules. The variables were age, sex, size, location, number of nodules, ultrasound findings, cytology based on needle aspiration biopsy (FNA), and histology of lesions. Multiple thyroid nodules presented higher irregularity and affected older individuals. In the adjusted odds ratio, single and multiple nodules were compared, demonstrating a higher number of cases of single nodules with BETHESDA classification 4. There were no significant differences in the association between single and multiple thyroid nodules and a higher incidence of malignant neoplasms.

Keywords: Nodule. Thyroid Neoplasms. Fine Needle Biopsy. Thyroid. Thyroidectomy.

RESUMO:
Comparar a prevalência de nódulos tireoidianos únicos e múltiplos e associá-los a presença de cânceres tireoidianos. Estudo observacional retrospectivo, realizado em um centro de referência de patologia e em um hospital privado de Joinville, Santa Catarina, Brasil. Os dados coletados foram relativos ao período de janeiro de 2011 até dezembro de 2021. Dividiu-se os pacientes em dois grupos: portadores de nódulos tireoidianos únicos e múltiplos. As variáveis analisadas foram idade, sexo, tamanho, localização e quantidade de nódulos, achados ultrassonográficos, citologia obtida pela PAAF e a histologia das lesões. Em relação às características dos nódulos tireoidianos, os múltiplos apresentaram maior irregularidade e acometeram indivíduos de maior idade. No cálculo de razão de chance ajustado, comparou-se nódulos únicos e múltiplos, demonstrando maior quantidade de casos de nódulos únicos com classificação BETHESDA 4. O presente estudo não observou diferenças significativas entre a associação de nódulos tireoidianos únicos e múltiplos com maior incidência de neoplasias malignas.

Palavras-chave: Nódulos. Neoplasias da Glândula Tireoide. Biópsia por Agulha Fina. Tireoide. Tireoidectomia.

INTRODUCTION

The thyroid gland corresponds to one of the largest endocrine glands in the human body, located inferior to the larynx and anterolateral to the trachea, just below the cricoid cartilage. The thyroxine (T4) and triiodothyronine (T3) hormones produced by this structure are essential for maintaining body homeostasis, with secretion controlled, above all, by the release of serum thyrotropin (TSH) by the adenohypophysis.[1]

According to the American Thyroid Association (ATA), thyroid nodules represent an abnormal growth of thyroid cells, forming discrete lesions within the thyroid gland, radiologically distinct from the surrounding thyroid parenchyma.[2] The various causes responsible for the development of nodules include changes in the morphological architecture of the gland, defects in the storage of hormones produced or in the availability of production substrate, exposure to radiation in childhood, and malignant and benign neoplasms.[3]

Regarding incidence, as an increasing number of patients undergo imaging exams for medical evaluations, more and more nodules are detected. Diagnostic recommendations for patients with thyroid pathology are based especially on data obtained from the analysis of nodules before the widespread use of ultrasound.[4]

Early detection of these nodules is clinically relevant to avoid thyroid dysfunction, compressive symptoms, and malignant neoplasms, resulting in the need to exclude thyroid cancer, the most common endocrine neoplasms found in the population. However, US findings still do not allow us to accurately distinguish malignant from benign lesions. However, studies have reported disparities regarding the risk of malignancy when comparing single and multiple thyroid nodules, with research suggesting a higher risk in the presence of single nodules and other studies in which this is higher in multinodular goiter.[2,6]

Given the importance of this differentiation, the exam considered the gold standard for the diagnosis and differentiation of thyroid nodules is Fine Needle Aspiration (FNA) with the study of the cytological material obtained, thus stratifying the risk of malignancy of the nodule.[5,6]

There are several retrospective observational studies and systematic reviews in the international literature addressing the topic of thyroid nodules and more appropriate management, prevalence in the population, classification, and nodular characteristics that point to a higher potential for malignancy. However, there is a lack of studies analyzing the risk of malignant thyroid cancer with the presence of single and multiple thyroid nodules.

Therefore, the present study aimed to compare the prevalence of single and multiple thyroid nodules undergoing thyroidectomy and their characteristics. In addition, to analyze the association between them and the presence of thyroid cancer, given the importance of early screening for clinical management and treatment.

METHODOLOGY

This was a retrospective observational study in a pathology reference center in a private hospital in Joinville, state of Santa Catarina, Brazil. Ultrasound findings, cytology obtained by FNA, and the histology of the lesions, considered the gold standard, were evaluated. Data were collected from the hospital's internal system from January 2011 to December 2021. Data collection began after authorization from the Research Ethics Committee. The project was approved under number CAAE 63922422.2.0000.8062 by the Research Ethics Committee (CEP) of Dona Helena Hospital, Joinville, state of Santa Catarina, Brazil.

The inclusion criteria were patients who underwent ultrasound, FNA, and surgical procedures with analysis in the pathological anatomy laboratory. Patients with incomplete medical record data were excluded.

The variables analyzed were patient age and sex, size, location, and number of nodules. Other ultrasound characteristics collected were composition (cystic, mixed, or solid), echogenic foci (none, macrocalcifications, peripheral or microcalcifications), echogenicity (anechoic, hyperechoic, isoechoic or hypoechoic), margins (smooth, ill-defined, irregular or extra-thyroidal), shape (taller or wider), TI-RADS classification and FNA indication. Cytological results using the Bethesda System and histopathological results (benign, papillary carcinoma, follicular carcinoma, or other types) were also evaluated.

The ultrasound classification of the nodules was carried out according to the ACR Thyroid Imaging Reporting and Data System classification, as follows: TR1 (zero or one point – benign), TR2 (two points – not suspicious), TR3 (three points – mild suspicion), TR4 (four to six points – moderate suspicion), and TR5 (>six points – high suspicion). Regarding the indication for FNA, nodules TR3 ≥ 2.5cm, TR4 ≥ 1.5cm, and TR5 ≥1.0cm must undergo cytological analysis (ACR TI-RADS, 2017).

The results obtained by FNA were classified according to The Bethesda System for Reporting Thyroid Cytopathology, as follows: I – unsatisfactory sample, II – benign, III – atypia of undetermined significance, IV – suspected follicular neoplasia or follicular neoplasia, V – suspected malignancy, and VI – malignant. In addition to FNA interpretation, management may depend on other factors, such as clinical, ultrasound or individual patient wishes.[2]

Concomitantly with the collection, data was entered into an electronic database. The statistical software Statistical Package for the Social Sciences (SPSS), version 21.0, was used for statistical analysis of the data. All variables were analyzed descriptively; thus, continuous (numerical) variables were studied by calculating means and standard deviations. For qualitative variables, absolute and relative frequencies were calculated. To test the hypothesis of equality between group means, the Student's *t*-test was applied when the distribution was normal, and the non-parametric Mann-Whitney test was used when the normality test was rejected. The normality test used was the Kolmogorov-Smirnov test. To prove the homogeneity of the groups concerning proportions, the Chi-square test or Fisher's exact test was adopted for frequencies below five.

Multinomial logistic regression models were constructed to compare the prevalence of single and multiple thyroid nodules, their characteristics, and their association with the presence of thyroid cancer. In this way, the relevance of the effect of variables was estimated by calculating the Odds Ratio (OR) adjusted according to confounding factors, with their respective 95% confidence intervals (95% CI). The confounding factors used were age and nodule size. Values were considered significant when $P<0.05$.

RESULTS

Among the 360 patients included in the study, given the clinical importance of evaluating the histopathological characteristics of thyroid nodules and associating them with the presence of neoplastic malignancy, the patients were divided into two groups: patients with the presence of a single nodule undergoing thyroidectomy (n = 234/65%) and multiple nodules undergoing thyroidectomy (n = 126/35%).

Among the variables analyzed, the average age of patients with a single nodule was 42.7, and patients who presented multiple nodules had an average of 45.3. Patients between 31 and 40 years old presented a significantly higher presence of single nodules in 67 (28.6) than multiple nodules (n=50/39.7%). However, patients between 41 and 50 years old demonstrated a higher prevalence of both types of nodules, with 75 patients (31.1%) having single nodules and 50 patients (39.7%) having multiple nodules. Although no statistical relevance was observed in the comparison

between the patient's sex and single nodules and multiple nodules, there was a predominance of females over males for both types of nodules in 188 (80.3%) patients with single nodules and 105 (83.3%) patients with multiple nodules.

About ultrasound findings, characteristics such as size, location, number of nodules, composition, echogenic foci, microcalcifications, echogenicity, and shape showed no statistically significant difference in patients compared to the nodule type – whether single or multiple. Finally, given the ultrasound analysis of nodule margins, multiple nodules presented greater irregularity in 29 (23%) patients and single nodules in 32 (13.7%) patients, according to Table 1.

Table 1. Characteristics of single and multiple nodules undergoing thyroidectomy*

(Continued)

	Single (n=234)	Multiple (n=126)	*P*
Age	42.7 (11.6)	45.3 (12.4)	0.037
<30 years	37 (15.8)	17 (13.5)	0.557**
31-40 years	67 (28.6)	24 (19.0)	0.046**
41-50 years	75 (32.1)	50 (39.7)	0.147**
51-60 years	36 (15.4)	22 (17.5)	0.609**
>61 years	19 (8.1)	13 (10.3)	0.485**
Gender			0.487**
Male	46 (19.7)	21 (16.7)	
Female	188 (80.3)	105 (83.3)	
Size	2.3 (1.5)	2.3 (1.4)	0.676
>1.0cm	194 (82.9)	105 (83.3)	0.918**
>1.5cm	147 (62.8)	78 (61.9)	0.864**
>2.5cm	87 (37.2)	52 (41.3)	0.447**
Location			0.082**
Right lobe	141 (60.3)	63 (50.0)	
Left lobe	78 (33.3)	57 (45.2)	
Isthmus	15 (6.4)	6 (4.8)	
Number of nodules	1.0 (0.0)	2.5 (0.7)	<0.001
Composition			0.523**
Cystic	5 (2.1)	3 (2.4)	0.574***
Misto	47 (20.1)	30 (23.8)	0.411**
Solid	179 (76.5)	93 (73.8)	0.572**
Indeterminate	3 (1.3)	0 (0.0)	0.273***
Echogenic Foci			0.579**
None	151 (64.5)	78 (61.9)	0.621**
Macrocalcifications	13 (5.6)	6 (4.8)	0.748**
Peripheral Calcifications	9 (3.8)	9 (7.1)	0.171**

(Conclusion)

	Single (n=234)	Multiple (n=126)	*P*
Microcalcifications	61 (26.1)	33 (26.2)	0.980**
Echogenicity			0.468**
Anechoic	8 (3.4)	2 (1.6)	0.313***
Hyper or Isoechoic	96 (41.0)	56 (44.4)	0.531**
Hypoechoic	122 (52.1)	65 (51.6)	0.921**
Indeterminate	4 (1.7)	0 (0.0)	0.177***
Margins			0.127**
Smooth	150 (64.1)	71 (56.3)	0.150**
Ill-defined	48 (20.5)	26 (20.6)	0.978**
Irregular	32 (13.7)	29 (23.0)	0.024**
Extrathyroidal	3 (1.3)	0 (0.0)	0.273***
Indeterminate	1 (0.4)	0 (0.0)	0.650***
Shape			0.917**
Wider-than-tall	179 (76.5)	97 (77.0)	
Indeterminate	55 (23.5)	29 (23.0)	

*Mean and standard deviation, absolute numbers and percentages; ** Chi-square test; ***Fisher's Exact Test.

The thyroid nodule classification system was used to standardize the description and classify the risk of malignancy based on ultrasound findings. The average TI-RADS score of patients with single and multiple nodules was 5.2 (2.2%) and 5.4 (2.4%). No significant difference was detected in classes TR1, TR2, TR3, TR4, and TR5 between the two types of nodules. Also, fine needle aspiration (FNA) was analyzed in conjunction with the Bethesda system for cytopathological reports of thyroid nodules, relevance in classification II (Benign), with 46 (19.7%) patients having single nodules and 37 (29.4%) with multiple nodules. Classification IV (suspected follicular neoplasia) was also of significant importance, with a higher prevalence in patients with single nodules (n=21/9%) than with multiple nodules (n=2/1.6%). The other classifications, such as I – non-diagnostic sample, III – atypia of undetermined significance, V – suspicious of malignancy, and VI – malignant, were non-significant. Regarding the histopathology of the nodule, no type showed statistical relevance, as listed in Table 2.

Table 2. TI-RADS and BETHESDA of single and multiple nodules undergoing thyroidectomy*

	Single (n=234)	Multiple (n=126)	*P*
TI-RADS score	5.2 (2.2)	5.4 (2.4)	0.418
TI-RADS			0.811**
TR1	4 (1.7)	4 (3.2)	0.368***
TR2	18 (7.7)	8 (6.3)	0.639**
TR3	38 (16.2)	21 (16.7)	0.917**
TR4	102 (43.6)	50 (39.7)	0.474**
TR5	72 (30.8)	43 (34.1)	0.515**
indicated FNA due to nodule size	135 (57.7)	68 (54.0)	0.497**
FNA (Bethesda)			0.011**
1	16 (6.8)	7 (5.6)	0.635**
2	46 (19.7)	37 (29.4)	0.037**
3	38 (16.2)	12 (9.5)	0.079**
4	21 (9.0)	2 (1.6)	0.006***
5	67 (28.6)	35 (27.8)	0.864**
6	46 (19.7)	33 (26.2)	0.153**
Histopathology			
Benign	98 (41.9)	44 (34.9)	0.197**
Papillary Carcinoma	123 (52.6)	79 (62.7)	0.065**
Follicular Carcinoma	10 (4.3)	1 (0.8)	0.058***
Other types	4 (1.7)	2 (1.6)	0.646***

*Mean and standard deviation, absolute numbers and percentages; ** Chi-square test; ***Fisher's Exact Test.

Table 3. Bethesda Crude Odds Ratio and Papillary Carcinoma compared to single nodules

	P	OR	95%CI
≥2 NODULES			
Bethesda 4	0.020	0.168	0.038-0.752
Bethesda 5	0.216	0.638	0.314-1.299
Bethesda 6	0.685	0.853	0.395-1.840
Papillary Carcinoma	0.092	1.783	0.910-3.495
≥3 NODULES			
Bethesda 4	0.622	0.680	0.147-3.140
Bethesda 5	0.283	0.561	0.195-1.611
Bethesda 6	0.712	1.216	0.432-3.423
Papillary Carcinoma	0.510	1.377	0.531-3.569
≥4 NODULES			
Bethesda 4	0.573	0.548	0.068-4.429
Bethesda 5	-	-	-
Bethesda 6	0.753	0.766	0.145-4.035
Papillary Carcinoma	0.763	0.798	0.183-3.473

Table 4. Bethesda Adjusted Odds Ratio and Papillary Carcinoma compared to single nodules

	P	OR	95%CI
≥2 NODULES			
Bethesda 4	0.023	0.175	0.039-0.788
Bethesda 5	0.325	0.686	0.324-1.453
Bethesda 6	0.939	0.969	0.431-2.175
Papillary Carcinoma	0.115	1.722	0.876-3.387
≥3 NODULES			
Bethesda 4	0.713	0.747	0.158-3.529
Bethesda 5	0.475	0.665	0.218-2.033
Bethesda 6	0.468	1.505	0.498-4.545
Papillary Carcinoma	0.553	1.332	0.516-3.437
≥4 NODULES			
Bethesda 4	0.534	0.510	0.061-4.263
Bethesda 5	-	-	-
Bethesda 6	0.744	0.747	0.130-4.298
Papillary Carcinoma	0.732	0.774	0.178-3.360

* Confounding Factors: Age and Size

In summary, according to Tables 3 and 4, after calculating the crude and adjusted odds ratio of Bethesda and papillary carcinoma for single nodules, no significant differences were detected for the association between single and multiple thyroid nodules and a higher incidence of malignant thyroid neoplasms, such as papillary cancer. However, although no such correlation was found between the characteristics of the nodule and malignancy, it must be considered that there were confounding variables in the sample, such as age and size of the nodule.

DISCUSSION

The comparative analysis of the higher incidence of malignant neoplasms between single and multiple thyroid nodules proposed here identified, in general, no significant differences between these groups. Disparities were observed in relation to the older age of the patients and irregularity of the nodules, which were shown to be higher in cases of multiple nodules. In addition to differences in the adjusted odds ratios in the BETHESDA classification 4, which is more present in single nodules.

Thyroid nodules are frequently found in clinical practice, with higher prevalence in women and with advancing age.[7] Nevertheless, our results demonstrated no significant differences between the sex of patients with the highest incidence of single or multiple nodules, and advanced ages were more related to the prevalence of multiple nodules. Furthermore, concerning the comparison of such characteristics with the malignancy of the nodule, the literature demonstrates that male sex and extremes of age (under 20 years and over 70 years) represent risk factors.[3] This comparison could not be made in the present research since both groups had similar numbers of male and female patients. Other known risk factors correspond to a history of exposure to ionizing radiation and a family history of thyroid cancer; however, this study does not provide this information, which denotes influence on the results found.[8] As for exposure to

ionizing radiation, it increases the risk of thyroid cancer, as demonstrated by several studies, and as preventive measures, the use of individual and collective protective equipment by the patient and the medical team, in addition to doctors avoiding unnecessary requests for imaging exams that use radiation.[4,6]

Thyroid cancer, in euthyroid patients, most commonly manifests as a single nodule, with the normal functioning of the gland generally small in size and asymptomatic.8 Therefore, most individuals are diagnosed accidentally. Larger nodules can be diagnosed more easily, as they lead to clinical manifestations, such as pain and tracheal and esophageal constriction due to compression of adjacent structures.[3,8] These data demonstrate the importance of palpation of the thyroid during the physical examination of the patient because the presence of a thyroid nodule is indicative of referral for an ultrasound to rule out potential malignancy.[9]

According to findings in the literature, the prevalence of malignant thyroid nodules biopsied is approximately 5%, regardless of the size and number of nodules, showing that most point to benignity.[8,9] This finding corroborates the present study since no significant differences were identified between multiple or single nodules with higher malignant potential. However, other research suggests the dominant nodule presents a greater risk of malignancy, and this risk decreases in the presence of 2 or more nodules. Thus, data indicate that the individual risk of each nodule is dependent on the others; therefore, the presence of a second suspicious nodule significantly reduces the potential for malignancy of the first.[10] In this context, the use of high-resolution US has its importance centered mainly on the need to rule out the potential malignancy of the nodule and surgical resection, and this examination should be applied to all patients who present palpable thyroid nodules.[9,11] However, as the number of diagnoses performed has increased, there has been a significant increase in their incidence.

As the need for ultrasound examination to visualize characteristics that point to the possible malignancy of the nodule becomes evident, there is a need to take measures, such as fine needle aspiration (FNA). The aspects considered malignant correspond to the presence of a solid nodule, irregular border, taller-than-wide, hypoechoic, and with echogenic foci (microcalcifications). In this study, differences in such characteristics were not correlated with a higher incidence of nodule malignancy.

Based on ultrasound findings, nodules are classified in the TI-RADS system into five categories, which aim to define the nodule as benign or suspicious in varying degrees and assist in choosing the procedure to be performed, such as the need for FNA for cytopathological analysis. TI-RADS categories 3 and 4 correspond to suspicious nodules, and the need for puncture depends on the size, whereas in TI-RADS category 5, the nodule is highly suspicious and requires FNA.[12] Therefore, the higher the classification level, the greater the probability of malignancy. In this article, according to the adjusted odds ratio, in which single and multiple nodules were compared, no significant differences were detected in the TI-RADS classification between the groups. Therefore, it was not possible to find a relationship between a higher prevalence of malignant or benign nodules and the level of classification in the TI-RADS system.

The issue regarding how many nodules should be biopsied, in cases of multiple ones, varies according to research. According to the 2015 American Thyroid Association Management Guidelines, for Thyroid FNA, all nodules larger than 1 cm carry an independent potential for malignancy, and all those presenting sufficiently concerning clinical features should be biopsied.[2,10] If none of the nodules present show considerable suspicion of malignancy, the largest one should be biopsied. In this article, no significant differences were observed in the histological classification obtained for single and multiple thyroid nodules,

expressing the same probability of benign results, papillary carcinoma, and follicular carcinoma, among other types.

Considering the results of thyroid nodules undergoing FNA biopsy, they were classified according to the BETHESDA system into 6 diagnostic categories, which guide patient management.[13,14] In the present study, in the calculation of adjusted odds ratio, there was a difference in the BETHESDA classification 4, corresponding to suspicion of follicular neoplasia, which was more present in single nodules, as demonstrated by other studies.[15] This result exposes, at the cellular level, the similarity to benign neoplasms, impairing diagnostic accuracy on the part of the pathologist.[13] Therefore, the absolute rates of malignant potential have not yet been fully established for thyroid nodules classified as BETHESDA 3 and 4.

According to our findings, it was not possible to correlate, in the adjusted odds ratio of BETHESDA and papillary carcinoma of multiple nodules compared to single nodules, considerable differences in their incidence, making it impossible to discuss the higher frequency of this carcinoma in one of the groups, independent of the number of nodules. Furthermore, there were limitations regarding the analysis, in which the number of patients in the present study sample limited the ability to find the association between some of the factors analyzed, which could influence certain results found. Thus, research data was generated from a retrospective classification.

Therefore, the present study demonstrates, based on the data presented, the impossibility of relying on the presence of single or multiple thyroid nodules to assess the increased risk of malignancy. Therefore, the number of nodules present is not a good parameter to be used when questioning whether or not to perform biopsies, and characteristics must be taken into account for this decision-making.

CONCLUSION

The results of the present study demonstrate significant differences between the association of single and multiple thyroid nodules with a higher incidence of malignant thyroid neoplasms, such as papillary cancer. Therefore, it can be concluded that we cannot use the presence of single or multiple thyroid nodules as a parameter for greater suspicion regarding their malignancy since such an association has not been evidenced.

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