



# Risk Factors for Malignancy in Patients with Multinodular Goiter

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## Abstract

**Introduction** The identification of thyroid cancer may be conducted through clinical detection, imaging method, and histopathological examination. Both solitary nodules and multinodular goiter are associated with malignancy.

**Objective** To assess the risk factors for malignancy among patients with multinodular goiter submitted to total thyroidectomy.

**Methods** A series of 712 consecutive patients, submitted to total thyroidectomy between 2005 and 2016 with multinodular goiter regarding clinical, ultrasound, and pathological variables, was retrospectively evaluated.

**Results** There were 408 cases of papillary carcinoma (57.3%), with the remaining being benign. Gender had no statistical significance ( $p = 0.169$ ) for malignancy, unlike the Bethesda index, higher age group ( $p = 0.005$ ), shorter clinical history time ( $p = 0.036$ ), smaller number of nodules ( $p < 0.0001$ ), and smaller nodule size ( $p < 0.0001$ ), which were related to malignancy.

**Conclusion** The Bethesda index, older age group, shorter clinical history, smaller number of nodules, and smaller size of nodule were related to the diagnosis of papillary carcinoma.

## Keywords

- ▶ thyroid cancer
- ▶ thyroidectomy
- ▶ carcinoma
- ▶ papillary

## Introduction

Thyroid nodules are a common entity in the daily practice. They are observed in ~ 8% of the adult population and are more frequent in women.<sup>1</sup> Malignant neoplasms represent ~ 1% of all malignant tumors and are the most common endocrine neoplasms. Thyroid nodules present a malignancy prevalence of 5 to 15%.<sup>2</sup> The overall incidence of papillary carcinoma is the highest among thyroid incidentalomas. The incidence is higher when, in the context of goiter, there is an

association with follicular adenoma and the total thyroidectomy must be considered as the treatment of choice, being currently practiced by most treatment centers.<sup>3</sup>

The identification of thyroid cancer can be classified into three broad situations: cancer detected clinically; detected by imaging method (without clinical suspicion); and detected by histopathological examination (without clinical suspicion and via imaging method).<sup>4</sup> Incidental carcinoma is, after surgical resection of the thyroid gland by benign pathology, the most frequent event.<sup>5</sup> In thyroidectomy

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specimens, the prevalence of incidentaloma reaches 40%.<sup>6</sup> Regarding the association of papillary thyroid carcinoma with chronic thyroiditis, thyroiditis was found in 26.8% of patients treated for the tumor, however, with no connection to cancer size.<sup>7</sup>

Due to advances in imaging techniques, the chances of detecting thyroid nodules have increased dramatically. Thus, the incidence of thyroid cancer is increasing. Patients with palpable thyroid nodules have a 20 to 57% chance of finding additional nodules on ultrasound examination.<sup>8</sup> Both solitary nodules and multinodular goiter are associated with malignancy. Solitary nodules are generally considered to have a higher risk of malignancy than multinodular goiter,<sup>2,9</sup> although some data suggest that the risk is equal.<sup>10,11</sup> A preoperative assessment of thyroid nodules, to stratify them into benign and malignant, is important to avoid unnecessary surgeries and related problems.<sup>9,12</sup> The surgical approach is indicated for suspicion of malignancy, in case of indeterminate cytopathology and high risk context, larger nodules (mainly with compressive symptoms), and in selected cases of thyrotoxicosis.<sup>13</sup>

Some risk factors for malignancy in thyroid nodules related to inflammation have been added. Erythrocyte distribution width (RDW), an inflammatory marker, was retrospectively studied in the preoperative hemogram of patients who underwent thyroidectomy, and it was significantly higher in those with cancer in comparison with those with benign nodules and in the control group.<sup>14</sup> Similarly, mean platelet volume (MPV) was retrospectively analyzed in hemograms, being significantly higher in the malignant nodule group than in the benign nodule group.<sup>15</sup> Neutrophil to lymphocyte ratio (NLR) was significantly higher in the malignant nodule group than in both the benign nodule and control groups, as well.<sup>16</sup> Thus, such factors should alert for the possibility of malignancy. Furthermore, their cost is low.

The objective is to assess patients with multinodular goiter submitted to total thyroidectomy for the presence of malignancy regarding the epidemiological, clinical, and pathological aspects.

## Methods

This study was approved by the institutional review board under the number 3.154.631.

A total of 712 consecutive patients, who underwent total thyroidectomy between 2005 and 2016, were retrospectively assessed. The inclusion criterion was patients presenting more than one nodule in preoperative radiological images, who had not previously been submitted to surgery on the gland. Our indications for surgical approach were suspicion (or confirmation) of malignancy and large goiters with compressive signs; aesthetic indication was not considered. Patients presenting malignancy findings of other cancers different from the papillary carcinoma on the histopathological examination and those with suppressed thyroid-stimulating hormone (TSH) were excluded.

In the surgical routine, the parathyroid glands and recurrent laryngeal nerves were identified, and the specimens

were sent to the pathologist for frozen intraoperative examination. A drain was placed systematically on the immediate postoperative day. All patients were discharged on the first postoperative day, with the prescription of levothyroxine adjusted according to the patient's weight.

The following items were assessed: age (in years); gender (male or female); time of clinical history (in months); the number of nodules detected on ultrasound; the size in millimeters of the dominant nodule (largest on the largest axis); and fine-needle aspiration biopsy (FNAB) result (all aspiration punctures were performed under ultrasound guidance and their results were categorized according to the Bethesda classification). Nodules with higher and intermediate risks of malignancy,<sup>17</sup> and/or all nodules presenting 2 cm or more at its largest axis, were elected to be biopsied. When more than one FNAB was performed on the same gland, we considered, for purposes of eventual surgical indication, the one with the highest Bethesda index.

The values obtained with the analysis of quantitative variables were organized and described by means, median, standard deviation, minimum, and maximum. For categorized variables, absolute and relative frequencies were used. The distributions were defined as parametric by the Kolmogorov-Smirnov test. For the comparison of quantitative variables between two sample populations, the Student *t*-test was used, and for the frequency comparisons, the chi-squared test was used. In all analyses, the statistical program IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA) was used, and a statistical significance level of 5% ( $p < 0.05$ ) was adopted.

## Results

From the 712 patients analyzed, 623 (87.5%) were female, most of whom (329–46.2%) presented two nodules on ultrasound. The non-absolute majority (275–38.6%) of the patients had a Bethesda III result on cytopathological examination. On histopathological examination, a total of 408 cases revealed papillary carcinoma (57.3%), with the remaining being benign (adenomatous goiter, follicular adenoma, and/or chronic lymphocytic thyroiditis), as shown in ► **Table 1**.

When relating the variables studied to the final finding of malignancy, the gender (male or female) was not statistically significant ( $p = 0.169$ ). High Bethesda classes were highly related to malignancy, especially V and VI, as shown in ► **Table 2**. Considering the unexpected finding of malignancy among Bethesda II cases, we can consider that 38 of 213 cases (17.8%) can be stratified as incidental papillary carcinoma. Thus, since the total series gathered 712 patients, there were 5.3% of incidental tumors. On the other hand, among those 38 cases of papillary carcinoma with previous Bethesda II, 19 nodules' sizes varied from 1 to 9 mm. They could be classified as incidentaloma due to the size criterion.

Other aspects had significance; this is to say, the cases of papillary carcinoma presented higher age range ( $p = 0.005$ ), shorter time of clinical history until the moment of surgical intervention ( $p = 0.036$ ), smaller number of nodules on

**Table 1** Epidemiological, clinical, and pathological variables

Variable	Aspect	n	%
Gender	Male	89	12.5%
	Female	623	87.5%
Number of nodules	2	329	46.2%
	3	141	18.4%
	4	93	13.1%
	5	54	7.6%
	6	35	4.9%
	7	22	3.1%
	8	14	2%
	9	8	1.1%
	11	3	0.4%
	13	2	0.3%
	15	1	0.1%
FNAB (Bethesda)	II	213	30%
	III	275	38.6%
	IV	100	14%
	V	78	10.9%
	VI	46	6.3%
Histopathological	Benign	304	42.7%
	Papillary carcinoma	408	57.3%

Abbreviation: FNAB, fine-needle aspiration biopsy.

ultrasound ( $p < 0.0001$ ), and smaller size of the largest measurement axis ( $p < 0.0001$ ), as shown in ►Table 3.

## Discussion

The papillary thyroid carcinoma is the most prevalent and the one presenting the best prognosis among all thyroid malignancies.<sup>2</sup> The reported overall incidence of thyroid carcinoma is only ~ 5%. Some studies have suggested that the incidence of malignancy may be higher for solitary nodules than for multiple nodules. Our study addressed patients submitted to multinodular goiter thyroidectomy. In a study of 265 single-node operated patients, male gender, microcalcification, and lymphadenopathy were independent

risk factors for predicting malignancy in patients with solitary thyroid nodule.<sup>9</sup>

Over the past 30 years, there has been an increase in the overall incidence of thyroid cancer.<sup>4</sup> The incidence rate of papillary carcinoma has increased more than any other malignant neoplasm.<sup>10</sup> Thus, it is important to recognize risk factors for malignancy in the context of nodular thyroid disease. Our overall occurrence of cancer was high (57.3%), compared with other similar studies.<sup>11,12</sup>

We did not find differences of malignancy risk regarding gender. This is aligned with other findings in the literature that did not show statistical difference;<sup>4,7</sup> however, there are studies in which the incidence of malignancy in male patients is higher than that found in women,<sup>2,9</sup> as shown

**Table 2** Correlation of gender and Bethesda index with malignancy

Variable	Aspect	Benign	Papillary carcinoma	$p^*$
Gender	Male	45	44	0.169
	Female	363	260	
Bethesda	II	175	38	< 0.0001
	III	168	107	
	IV	54	46	
	V	9	69	
	VI	3	43	

\* Chi-squared test.

**Table 3** Correlation of clinical aspects with malignancy

Variable	Histopathological*	Average	Standard deviation	Mean standard error	p**
Age	Benign	52.77	13.394	0.663	0.005
	Papillary ca	49.82	14.318	0.821	
History time (months)	Benign	33.05	46.213	2.288	0.036
	Papillary ca	25.37	50.760	2.921	
Number of nodules on US	Benign	3.35	2.101	0.104	< 0.0001
	Papillary ca	2.71	1.927	0.111	
Highest measurement (mm)	benign	26.46	13.141	0.651	< 0.0001
	Papillary ca	14.72	13.834	0.795	

Abbreviation: US, ultrasound.

\* benign = 408; papillary carcinoma = 304.

\*\* Student t-test.

in **Table 2**. In this study, an association of malignancy was observed in older patients, which is in accordance with the literature, with a higher prevalence in individuals around 50 to 60 years of age or older.<sup>7,9</sup>

The same situation was observed regarding the number of nodules, because as the number increased, the frequency of cancer decreased, also in accordance with the literature<sup>2,6,9</sup>, as shown in **Table 3**. However, regarding the size of the nodule, the findings differed from the literature. There was no significant relationship between nodule size and the likelihood of papillary carcinoma.<sup>2</sup> In our results, we observed that the average size of the benign lesion was bigger than the that of malignant ones.

Regarding the time of clinical history, this was higher among patients with goiter, compared with those with papillary carcinoma, as shown in **Table 3**.

The value of ultrasound and fine needle aspiration biopsy (FNAB) as a diagnostic tool for thyroid cancer in patients with endemic multinodular goiter is limited, mainly due to the high number of nodules and to the fact that thyroidectomy indications are currently not well-defined.<sup>5</sup> Although ultrasound findings suggesting malignancy include dominant hypoechoic nodules, thick or irregular halo, microcalcifications, and increased intranodular flow, the poor ultrasound accuracy disqualifies the differentiation between benign and cancerous lesions.<sup>18</sup> The indications for thyroid ultrasonography should be palpable goiter and nodules. Specialists with expertise in thyroid sonography are recommended. Thus, since the detection of early thyroid cancer does not improve survival rates, routine ultrasonographic screening should not be done, with the exception of high-risk patients.<sup>13</sup> In patients with diffuse multinodular disease, FNAB has certain limitations. Usually, nodules with less than 1 cm of diameter are usually not biopsied, and although ultrasound may guide FNAB for radiographically suspected lesions, malignancy may exist in alternate positions.<sup>5</sup> Since, by definition, a multinodular goiter contains more than one nodule, the clinician faces the difficult decision to select which nodule(s) will be used in the biopsy. One approach adopted was to perform a biopsy only in the nodules that are dominant (by size).<sup>19</sup> In our study, the FNAB

was performed on dominant nodules or on those with suspicious ultrasound morphology, and the Bethesda index of cytopathological examination showed statistical significance with the finding of malignancy. Each nodule in the context of multinodular goiter should be followed up individually.

## Conclusion

The factors related to the diagnosis of papillary carcinoma were the Bethesda index, older age group, shorter clinical history, smaller number of nodules, and smaller nodule size.

### Conflict of Interests

The authors have no conflict of interests to declare.

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