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Incidental thyroid carcinoma in a population with goiter: A retrospective cohort study

Carcinoma Tiroideo Incidental en una Población con Bocio: Estudio de Cohorte Retrospectivo

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Abstract

Introduction: Incidental thyroid carcinoma is the unexpected discovery of malignancy in patients undergoing thyroid surgery initially intended for preoperatively considered benign diseases. **Objective:** This study aims to describe a cohort of patients with Incidental thyroid carcinoma and identify the primary risk factors for malignancy. **Methods:** A retrospective cohort study was conducted on patients with goiter and Bethesda II cytology nodules who underwent thyroidectomy over a four-year period. The analysis included descriptive statistics, bivariate, and multivariate analyses, with Incidental thyroid carcinoma as the primary outcome. **Results:** Among the 299 patients meeting the inclusion criteria, multinodular goiter affected 49.49% of patients. Incidental thyroid carcinoma was diagnosed in 38 patients (12.7%). Papillary carcinoma was the most frequent malignant histology, comprising 83.7% of cases, with the classic variant being the most common (43.2%). In both bivariate and multivariate statistical analyses, multinodular goiter was identified as an independent risk factor for presenting malignant thyroid pathology (OR, 2.461; 95% CI, 1.654-3.659; p = 0.023). **Conclusion:** Incidental thyroid carcinoma is not an uncommon occurrence, and multinodular goiter has been established as an independent risk factor. Micropapillary thyroid carcinomas were the most prevalent among patients presented with incidental thyroid carcinoma.
Keywords: thyroid carcinoma, incidental carcinoma, microcarcinoma, goiter, thyroid gland.

Resumen

Introducción: *El carcinoma tiroideo incidental es el hallazgo inesperado de malignidad en pacientes sometidos a tiroidectomía, inicialmente destinada para enfermedades consideradas benignas antes de la cirugía.* ***Objetivo:*** *Este estudio tiene como objetivo describir una cohorte de pacientes con carcinoma tiroideo incidental e identificar los principales factores de riesgo para la malignidad.* ***Métodos:*** *Se llevó a cabo un estudio de cohorte retrospectivo en pacientes con bocio y nódulos de citología Bethesda II que se sometieron a tiroidectomía, durante un período de cuatro años. El análisis incluyó estadísticas descriptivas, análisis bivariados y multivariados, siendo el carcinoma tiroideo incidental el resultado principal.* ***Resultados:*** *De los 299 pacientes que cumplían con los criterios de inclusión, el bocio multinodular afectó al 49,49% de los pacientes. Se diagnosticó carcinoma tiroideo incidental en 38 pacientes (12,7%). El carcinoma papilar fue la histología maligna más frecuente, comprendiendo el 83,7% de los casos, siendo la variante clásica la más común (43,2%). En los análisis estadísticos bivariados y multivariados, el bocio multinodular fue identificado como un factor de riesgo independiente para presentar patología tiroidea maligna (OR, 2.461; IC del 95%, 1.654-3.659; p = 0,023).* ***Conclusión:*** *El carcinoma tiroideo incidental no es una ocurrencia poco común, y el bocio multinodular se ha establecido como un factor de riesgo independiente. Los carcinomas tiroideos micro papilares fueron los más prevalentes entre los pacientes que presentaron carcinoma tiroideo incidental.*
Palabras Clave: *Carcinoma tiroideo, Carcinoma incidental, microcarcinoma, Bocio, Glándula tiroidea.*

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Introduction

Incidental thyroid carcinoma (ITC) is the pathological discovery of malignancy in a previously suspected benign thyroid disease during preoperative imaging and cytologic evaluation. Despite advancements in diagnostic techniques leading to improved early detection of thyroid carcinomas, ITC remains a frequent occurrence, with an incidence ranging from 2% to 40%[1-6].

Goiter is a semiotic description, defined as the abnormal enlargement of the thyroid gland, which becomes evident upon physical examination and is confirmed through diagnostic imaging when a volume exceeding 18 ml for women and 25 ml for men is documented[7]. Goiter is typically asymptomatic and manifests mainly when it attains a substantial size, resulting in symptoms such as globus pharyngeus, dysphagia, and dysphonia in advanced stages. Importantly, it does not necessarily indicate a functional alteration of the thyroid gland and can be found in euthyroid, hypothyroid, or hyperthyroid patients[7-9]. Iodine deficiency, once a common cause of goiter, has become increasingly rare in societies that have implemented iodine supplementation plans in foods like salt[10]. Other frequent etiologies include thyroiditis, both autoimmune and non-autoimmune, thyroid cysts, benign thyroid nodules, acromegaly, and conditions induced by drugs or TSH-producing tumors[9]. Goiter may manifest as uninodular, diffuse, or multinodular[1], with thyroid carcinoma being a primary consideration in the differential diagnosis. According to the 2022 WHO Classification of Thyroid Neoplasms, diffuse and multinodular goiter are categorized as thyroid follicular nodular disease in definitive pathology, and single nodules must undergo further histopathological classification[11].

The initial approach to a patient with clinical goiter should include TSH measurement and a neck ultrasound (US). **Figure 1** illustrates the diagnosis and management algorithm for goiter employed by our group based on the ATA 2015 guidelines[12].

The existing literature has described age, nodular disease, size and symptoms of goiter with malignant disease, but these are not consistent among the authors[13-15]. We hypothesize that certain variables could heighten suspicion of malignancy before surgery. The aim of this study is to characterize the incidence of ITC in a cohort of individuals with goiter who are candidates for surgery and to identify if there are preoperative risk factors associated with ITC.

Materials and Methods

A retrospective cohort study was conducted at the National University Hospital of Colombia from January 2017 to December 2020. We included patients aged 18 and older who underwent either total or partial thyroidectomy for goiter and had a Bethesda II pre-surgical fine needle aspirate (FNA) (See Figure 1). Patients treated at different facilities were excluded from the study. We also ensured the exclusion of patients with missing data or those who did not provide their consent to participate in any research. The surgical procedures and pathology evaluations were carried out by professionals who were not part of the research team.

The outcome of ITC was defined as the presence of the following final diagnoses in the pathology evaluation:

- Papillary thyroid carcinoma.
- Follicular thyroid carcinoma.
- Oncocytic carcinoma.
- Medullary thyroid carcinoma.
- Anaplastic thyroid carcinoma.
- Primary thyroid lymphoma.
- Other types of malignancies.

We established a database on the RedCap platform to collect all data, ensuring adequate data protection. Two researchers (DFB and DL) collected the variables, which were subsequently verified by a third team member (SZP). These variables included:

- Age.
- Sex.
- Ultrasonographic tumor size (pre-procedure).
- TIRADS classification (pre-procedure).
- Type of goiter: diffuse, single nodule or multinodular.
- Presence of thyroiditis.

Tumor size was considered a potential

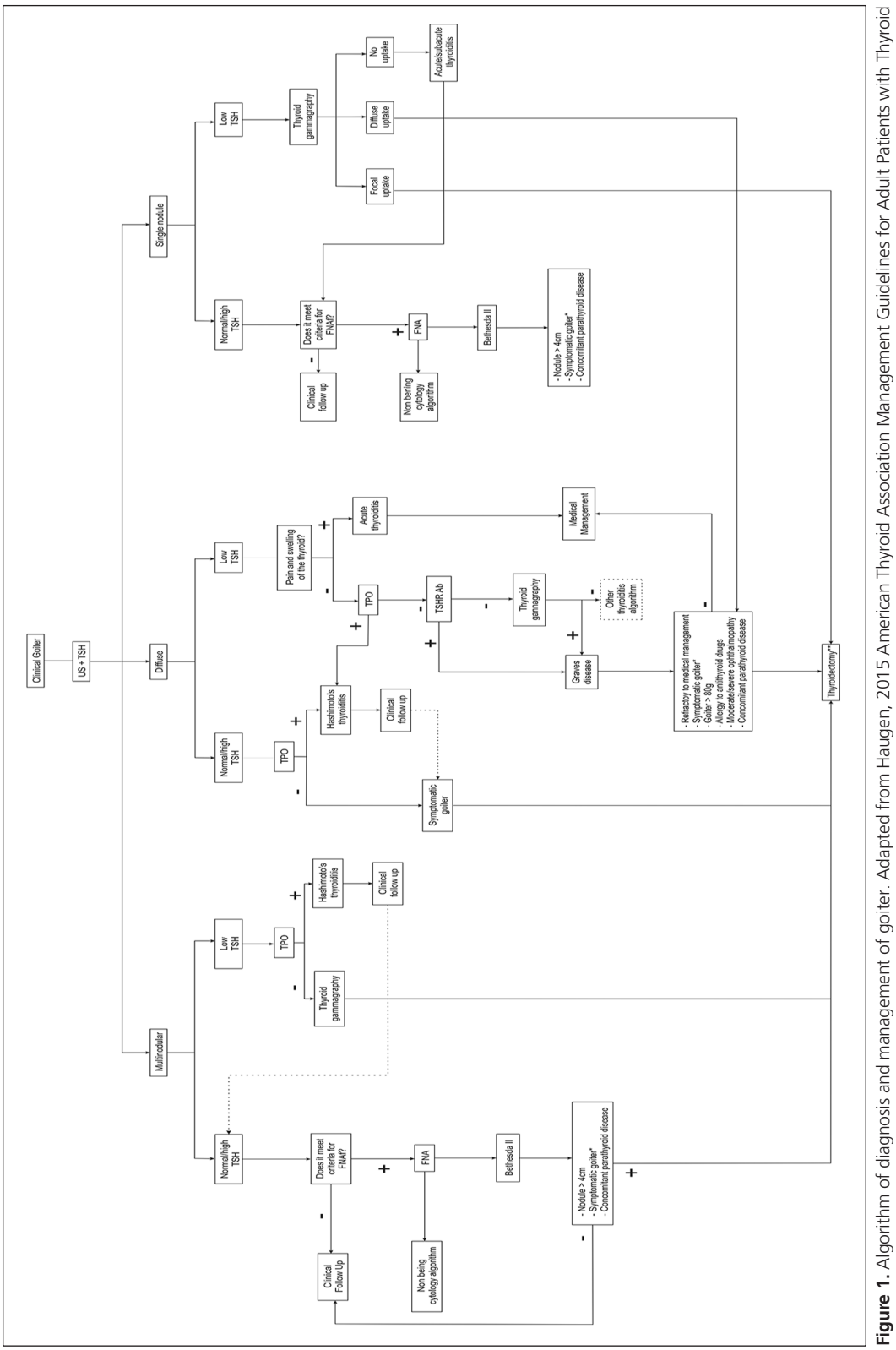

Figure 1. Algorithm of diagnosis and management of goiter. Adapted from Haugen, 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1), 1–133. https://doi.org/10.1089/thy.2015.0020. *Symptomatic goiter: Tracheal compression, Esophageal compression, Vascular compression, Cervical sympathetic chain compression, hoarseness (uncommon). **Thyroidectomy: The extent of the thyroidectomy depends on whether there were bilateral nodules or not. For diffuse and multinodular goiter total thyroidectomy is recommended. Single nodule goiter or toxic adenoma might be managed with partial thyroidectomy. TPO: Thyroid peroxidase antibody test.

confounder due to its impact on the diagnostic performance of FNA, and this was controlled for in the multivariable analysis. We also considered other potential biases, with information bias being controlled by directly collecting data from the Head and Neck Registry. This registry is meticulously maintained for research purposes, minimizing the likelihood of systematic errors. The research protocol was submitted and approved by the ethical and institutional review board (ID: CEI-2021-05-06).

All analyses were conducted using R and R Studio (Version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria). For descriptive purposes, the normality distribution of quantitative variables was assessed using the Shapiro-Wilks test, and results were presented in terms of means and standard deviations. Qualitative variables were presented as absolute and relative frequencies. Bivariate and multivariate analyses were performed to explore the association between potential factors and the outcome of ITC, as indicated in the literature. A 95% confidence interval was employed, and statistical significance was defined as a p-value less than 0.05.

The extent of thyroidectomy depended on the presence of bilateral nodules. Patients with Graves' disease were managed with total thyroidectomy. Those with a single nodule or multinodular goiter underwent FNA with Bethesda II results. FNA was not performed on patients with diffuse goiter lacking suspicious nodules. Patients with preoperative cytology results other than Bethesda II, those with a history of previous surgical intervention at a different hospital, and individuals with intraoperative findings suggestive of malignancy altering the surgical approach were excluded from the study.

Results

Over the course of the four-year analysis, a total of 1,889 patients underwent various forms of thyroidectomy at the National University Hospital of Colombia. Among these, 315 patients presented with goiter as an initial diagnosis of presumed benign disease, either diffuse goiter or nodules exhibiting Bethesda II cytology. Seven patients had previously undergone partial thyroidectomy for unrelated reasons at other institutions, and nine patients had undergone total thyroidectomy with central node dissection due to intraoperative suspicious findings; consequently, these nine patients were excluded from the study. A total of 299 patients met the inclusion criteria, with 274 of them being women (91.6%), as detailed in **Table 1**. The most common symptom

Table 1. Characteristics of the population, stratified by the final pathology result

Variables	Benign (%)	Malignant (%)	*p* value
n	261 (87.2)	38 (12.8)	
Age (mean (SD))	50.17 (13.98)	48.42 (14.31)	0.473
Sex			0.407
Female	241 (92.3)	33 (86.8)	
Male	20 (7.6)	5 (13.1)	
Size			0.478
≤ 10 mm	13 (5.0)	2 (5.3)	
11-20 mm	25 (9.6)	6 (15.8)	
21-30 mm	57 (21.8)	10 (26.3)	
31-40 mm	64 (24.5)	4 (10.5)	
41-50 mm	43 (16.5)	8 (21.1)	
51-60 mm	35 (13.4)	6 (15.8)	
≥ 61 mm	24 (9.2)	2 (5.3)	
Type of goiter			0.044
Multinodular	127 (48.7)	11 (28.9)	
Single	122 (46.7)	26 (68.4)	
Diffuse	12 (4.6)	1 (2.6)	
TIRADS			0.897
1	108 (41.4)	18 (47.4)	
2	27 (10.3)	3 (7.9)	
3	31 (11.9)	3 (7.9)	
4	37 (14.2)	4 (10.5)	
5	38 (14.6)	6 (15.8)	
6	20 (7.7)	4 (10.5)	
Comorbidity			0.863
No	164 (62.8)	25 (65.7)	
Yes	97 (37.2)	13 (34.2)	

n: absolute values. SD: standard deviation.

Table 2. Absolute and relative frequencies of malignant pathologies found in the records of patients operated at the National University Hospital of Colombia, from 2017 to 2020

Predictor	RR	SE	95% Confidence limits	*p* value
Age	0.99	0.01166	0.98 – 1.00	0.501
Sex				
Male				
Female	0.60	0.5799	0.34-1.08	0.291
Size				
≤ 10 mm				
11-20 mm	1.45	0.81650	0.64 – 3.28	0.648
21-30 mm	1.12	0.77460	0.52 – 2.43	0.884
31-40 mm	0.44	0.86603	0.19 – 1.05	0.344
41-50 mm	1.18	0.79057	0.53 – 2.59	0.837
51-60 mm	1.10	0.81650	0.49 – 2.48	0.909
≥ 61 mm	0.58	1.00000	0.21 – 1.57	0.582
Type of goiter				
Single				
Multinodular	2.20	0.35968	1.54 – 3.16	0.028*
Diffuse	0.97	1.04447	0.34 – 2.74	0.973
TIRADS				
1				
2	0.70	0.62361	0.38 – 1.31	0.567
3	0.62	0.62361	0.33 – 1.15	0.440
4	0.68	0.55277	0.39 – 1.19	0.490
5	0.95	0.47140	0.60 – 1.53	0.921
6	1.17	0.55277	0.67 – 2.03	0.780
Comorbidity				
No				
Yes	0.89	0.34190	0.98 – 1.00	0.742

*Statistical significance.

for consultation was the sensation of a neck mass reported by 198 patients (66.4%). Other symptoms, such as dysphagia or dysphonia, were reported by 24 (8%) and 12 patients (4%), respectively. Additionally, 22.1% of patients were considered asymptomatic. Of the total, 44.1% underwent total or near-total thyroidectomy, while the remaining 55.9% underwent hemithyroidectomy on the affected side, including the isthmus. It's worth noting that frozen section analysis was not routinely performed for thyroid pathology at our institution. Among the study population, benign thyroid conditions were confirmed in 261 patients, accounting for 87.3% of cases, while 38 patients (12.7%) were diagnosed with ITC. The mean age of the ITC group was 48.42 years (+/-14.30), and for the benign pathology group, it was 50.16 (+/-13.97), as shown in **Table 1**. The most prevalent type of goiter among those

Table 3. Bivariable analysis

Predictor	RR	SE	95% Confidence limits	*p* value
Age	0.99	0.01241	0.98 – 1.00	0.38250
Sex				
Male				
Female	0.51	0.72544	0.25-1.06	0.20220
Size				
≤ 10 mm				
11-20 mm	1.42	0.83246	0.62 – 3.26	0.67570
21-30 mm	1.11	0.79355	0.50 – 2.45	0.89910
31-40 mm	0.45	0.89127	0.18 – 1.09	0.36680
41-50 mm	1.20	0.81472	0.53 – 2.70	0.82530
51-60 mm	0.98	0.85208	0.42 – 2.29	0.97860
≥ 61 mm	0.61	1.02185	0.22 – 1.69	0.62850
Type of goiter				
Single				
Multinodular	2.28	0.37373	1.57 – 3.31	0.02750*
Diffuse	1.21	1.06795	0.41 – 3.51	0.86090
TIRADS				
1				
2	0.62	0.64386	0.33 – 1.18	0.46110
3	0.62	0.64739	0.33 – 1.19	0.15340
4	0.60	0.55987	0.34 – 1.04	0.35400
5	0.82	0.48072	0.51 – 1.33	0.68650
6	0.86	0.56666	0.49 – 1.51	0.78810
Comorbidity				
No				
Yes	0.94	0.36258	0.65 – 1.34	0.8535

* Statistical significance.

operated on was multinodular, representing 49.5% of cases, closely followed by uninodular. Among patients with benign pathology, the most frequent histology was colloid goiter, found in 124 patients (47.5%), followed by adenomatous nodules in 119 patients (45.6%), with the follicular type being the most common. In the ITC group, 60.52% had microcarcinomas, defined as tumors smaller or equal to 1 cm. The most common malignant histology was papillary carcinoma, with the classical variant being observed in 42.1% of cases. Additionally, one case of medullary carcinoma and one of primary thyroid lymphoma were documented (**Table 2**). Bivariate and multivariate statistical analyses revealed multinodular goiter to be an independent risk factor for the presence of malignant thyroid pathology (RR, 2.13; 95% CI, 1.47-3.07; p = 0.034), as detailed in **Tables 3** and **4**.

Table 4. Clinically-relevant multivariable model

Predictor	RR	SE	95% Confidence limits	*p* value
Size				
≤ 10 mm				
11-20 mm	1.33	0.82429	0.58 – 3.03	0.73141
21-30 mm	1.03	0.78439	0.47 – 2.25	0.97113
31-40 mm	0.43	0.87865	0.18 – 1.04	0.33933
41-50 mm	1.17	0.80046	0.53 – 2.61	0.84108
51-60 mm	1.11	0.82725	0.48 –2.53	0.90178
≥ 61 mm	0.59	1.01442	0.21 – 1.62	0.59970
Type of goiter				
Single				
Multinodular	2.13	0.36586	1.47 – 3.07	0.03922*
Diffuse	1.04	1.05202	0.36 – 2.97	0.97288
TIRADS				
1				
2	0.70	0.63254	0.37 – 1.31	0.56591
3	0.45	0.6354	0.24 – 0.84	0.20473
4	0.61	0.558	0.35 – 1.06	0.37101
5	0.86	0.47642	0.54 – 1.39	0.75689
6	0.83	0.56331	0.47 – 1.47	0.74768

* Statistical significance.

Discussion

The management of goiter hinges on factors such as thyroid hormone levels, the degree of malignancy suspicion based on imaging and cytological findings, and the size of the goiter. According to the American Thyroid Association (ATA) 2015 guidelines, patients with no imaging findings suggestive of malignancy and a benign cytology result for the nodule, or dominant nodules, are only recommended for surgical intervention if the dominant nodule exceeds 4 cm in size or if it causes compressive symptoms like dysphagia, dyspnea, aesthetic concerns, or significant growth in follow-up with a control FNA once again confirming Bethesda II[12,16]. Additionally, patients initially considered for iodine therapy aimed at thyroid ablation, but with an estimated gland weight exceeding 80 grams, are also candidates for surgical management, as I-131 therapy is less effective for larger glands[17,18].

The cut-off size value for asymptomatic benign nodules warranting surgery, according to ATA guidelines, is 4 cm[16,19]. However, this recommendation is considered weak, backed by low-quality evidence. Some studies have reported a higher incidence of false-negative FNAs in thyroid nodules larger than 3 cm compared to smaller ones[20,21]. The impact and cost-effectiveness of operating on smaller single or multiple benign nodules remain uncertain.

In our practice, surgical resection is considered for patients with apparent benign thyroid nodules exceeding 2 cm in size, especially if the nodule is visible at sight, causing symptoms, or showing signs of growth. Had we

strictly adhered to the cut-off value suggested by the American Thyroid Association of 4 cm or greater nodules alone, 60.5% of the patients with ITC would not have been diagnosed[12]. Although the clinical significance of this is debated, we believe that the larger the goiter, the greater the risk of trans and postoperative complications, in line with findings from other authors, albeit still a topic of debate[22,23].

When a patient initially diagnosed with a benign goiter undergoes surgery, and the pathology reveals ITC, the first step is to inform the patient about the diagnosis's implications. These may include the need for clinical and imaging follow-up, occasional surgical reinterventions, changes in prognosis, impacting the quality of life, and increasing treatment costs. The prognosis following an incidental diagnosis of thyroid carcinoma varies and is associated with specific pathological findings. However, whether these findings result from mostly low-risk tumors or promptly treated tumors with improved prognosis remains a matter of debate[24,25].

In this study, the incidence of ITC in patients with goiter was 12.7%, aligning with other reports and highlighting the persistence of this entity despite advances in imaging and cytopathology. This is partially attributed to subcentimeter tumor foci within large goiters, which accounted for 60.52% of cases in our cohort[5,6]. Although the ITC rate was slightly higher in men than in women (20% vs. 12%), this difference was not statistically significant (RR, 0.60; 95% CI, 0.34-1.08; p = 0.291).

In a prior study, published in 2021, involving 816 patients with well-differentiated thyroid carcinoma at this same institution and during the same period, papillary neoplasm was the most frequent histology, detected in 98.8% of cases, with the classic variant being predominant in 74.7%[19]. Conversely, in the current study, the incidence of papillary carcinoma decreased among patients with ITC, accounting for 84.2%, accompanied by an increase in the rate of follicular carcinomas, which reached 10.5%. Furthermore, the rate of the follicular variant of papillary thyroid carcinoma was higher in the ITC group in this study, comprising 37.5% of papillary malignancies, compared to 23.85% as previously reported[19]. Notably, one case of medullary carcinoma and one primary thyroid lymphoma were identified, representing an incidence of 2.6% for each histological type. Although the sample size is small, these findings underscore the importance of considering these histologies when operating on rapidly growing goiters.

Regarding pre-surgical variables, no associations were found between the pathologic diagnosis of ITC and age, sex, ultrasound nodule classification, patient comorbidities, or dominant nodule size. However, a significant association with ITC was observed in patients with multinodular goiters (RR, 2.13; 95% CI, 1.47-3.07; p = 0.034). These findings align with those reported by Miccoli P, et al[1], although they are not consistently described in the literature. We believe this result may be due in part to the majority of ITCs diagnosed being microcarcinomas, which, due to their size, are not typically subjected to FNA. Moreover, it is possible that in large multinodular thyroids, some malignancy-carrying nodules may not be thoroughly evaluated.

The predictive risk factors associated with malignancy in patients undergoing thyroidectomy for goiter have been diverse and inconsistent in the literature. An Iraqi study found a relationship between smoking and a history of head and neck radiation, which increased the risk of malignancy in a retrospective cohort of 120 patients[3]. However, none of the patients in our population had previously received head and neck radiation, so this variable was not analyzed. The history of smoking was not consistently reported in medical records, preventing its inclusion as a study variable. The role of TSH levels in the pathogenesis of differentiated thyroid carcinoma remains a topic of debate. Some studies have suggested that long-term TSH suppression reduces the risk of papillary thyroid carcinoma[26,27], but a recent systematic review and meta-analysis found no difference in malignancy or ITC risk in patients with Graves' disease[28]. Additionally, a study conducted in the United Kingdom found that men and patients with thyroiditis had a statistically significant higher risk of ITC[29]. Unfortunately, thyroid hormone levels were not consistently reported in all medical records, precluding their inclusion in the study analysis.

Limitations

This study was based on data from a single center and involves a limited number of patients. Furthermore, the retrospective methodology restricts the available variables for analysis. In future research, we plan to enhance this registry to provide a more comprehensive dataset.

Conclusions

ITC is a condition that exhibits a significant incidence among patients who undergo thyroid surgery with an initial diagnostic suspicion of benign pathology. A statistically significant difference was observed, indicating that patients with multinodular goiters have a greater likelihood of being diagnosed with ITC when compared to those with uninodular goiters or diffuse goiters.

Furthermore, the rate of follicular carcinomas and the follicular subtype of papillary carcinomas appears to be higher in the goiter population in comparison to a previous research effort conducted by our group, which encompassed all patients with differentiated thyroid carcinoma.

To solidify these findings and assess the potential relevance of reducing the threshold for thyroid nodule size, beyond which surgical resection would be recommended, it is imperative to undertake multicenter studies with larger sample sizes.

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