

State of the Art of Thyroid Pathology: Fine-Needle Aspiration Diagnostic Accuracy in an Intermediate Center in Ibagué – Colombia

Estado del arte de la patología tiroidea: ACAF, precisión diagnóstica en un centro intermedio de Ibagué (Colombia)

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ABSTRACT

Background: In Colombia, thyroid cancer is the seventh cancer in incidence and mortality for both sexes. Currently, fine-needle aspiration (FNA) is the most used method for studying nodular lesions of the thyroid. **Objective:** To describe the characteristics of a sample of surgical specimens in a histopathological diagnostic center located in an intermediate city, correlate characteristics of PTC variants, and calculate diagnostic accuracy for FNA. **Materials and methods:** In this retrospective study, pathology report data was gathered from a diagnosis center; information was included from patients who underwent thyroid biopsy or resection between 2015 and 2022, with a total of 495 cases; information was gathered; and a statistical analysis was performed. **Results:** higher frequency for all thyroid pathologies in patients younger than 55 years of age. Papillary thyroid carcinoma (PTC) was the most frequent diagnosis (42.7%) in men, while in hyperplasia was the most frequent in women (39.1%). Of all PTC diagnoses (n = 233), 77.6% had an additional diagnosis. Of previous FNA cases, 65.3% had a Bethesda score of II to IV, and 30.5% of those had a definitive carcinoma diagnosis. **Conclusions:** There is coexistence of benign thyroid diseases and PTC. FNA is essential for the initial histopathological study of thyroid lesions, but multiple factors may affect its diagnostic accuracy.

Keywords

thyroid papillary cancer; biopsy; fine-needle aspiration; thyroiditis; hyperplasia; sensibility and specificity.

RESUMEN

Introducción: En Colombia, el cáncer de tiroides ocupa el séptimo puesto en incidencia y mortalidad en ambos sexos. El método diagnóstico más usado para lesiones nodulares de la tiroides es el aspirado con aguja fina (ACAF). **Objetivo:** Describir las características de una muestra de especímenes quirúrgicos de un centro de diagnóstico patológico en una ciudad intermedia de Colombia y correlacionar las características de las variedades del carcinoma papilar de tiroides para calcular la precisión diagnóstica del ACAF para este centro. **Metodología:** En este estudio retrospectivo, se obtuvieron datos de reporte de patología de la base de datos de un centro de diagnóstico de la ciudad de Ibagué, se incluyó información de pacientes que se sometieron a biopsia de tiroides entre 2015 y 2022, con un total de 495 casos, se recogieron datos y se realizó el análisis estadístico. **Resultados:** Se encontró mayor frecuencia para todas las enfermedades tiroideas benignas y malignas en menores de 55 años. En hombres, el carcinoma papilar fue el diagnóstico más común (42,7%) y en mujeres fue la hiperplasia (39,1%). Además, del total de diagnósticos de carcinoma papilar (n = 233), el 77,6% tenía un diagnóstico adicional. De los casos con ACAF previo, el 65,3% presentaron Bethesda II a IV, de los cuales el 30,5% tuvieron como diagnóstico definitivo carcinoma. **Conclusión:** Hay coexistencia de enfermedades tiroideas benignas con el carcinoma papilar de tiroides. El ACAF es fundamental para el estudio histopatológico inicial de las lesiones tiroideas; sin embargo, presentan múltiples factores que inciden sobre su precisión diagnóstica.

Palabras clave

aspirado con aguja fina; cáncer papilar de tiroides; hiperplasia; tiroiditis; sensibilidad y especificidad.

Introduction

Thyroid cancer is one of the neoplasms with higher prevalence worldwide and also the most common malignant endocrine neoplasm (1,2). According to the World Health Organization's data, in 2020, thyroid cancer incidence in Colombia was 9.1 per 100 000, and mortality rate was 0.43 per 100 000. In Colombia, thyroid cancer ranks seventh in incidence and mortality in the general population; in women, it is the fourth cancer in incidence and mortality, while in men it ranks 20th (3). For 2022, the American Cancer Society estimates that, in the United States, the record of new cases of thyroid cancer in women will be much higher than in men(4).

The most common histological subtype of thyroid carcinoma is the papillary subtype (80–90%), followed by follicular and medullary carcinoma (1,2,5). Despite the high incidence of papillary thyroid carcinoma (PTC), when diagnosed and treated early, the patient's 10-year survival rate is of about 90% and less when diagnosed in advance stages (1). Only 15–20% of patients have recurrence and metastasis (6). Some studies have shown that BRAF and TERT mutations in PTC are associated with aggressive characteristics (larger tumor size, extrathyroidal extension, vascular invasion, nodal metastasis); therefore, these mutations are considered prognostic markers (5,7). Thirty percent (30%) of PTCs are papillary microcarcinomas (PMC), defined as carcinomas smaller than 10 mm, which are regularly indolent (with low risk of recurrence, metastasis, and mortality); however, when BRAF V600E mutation is present, it is treated as a normal PTC, independent of the tumor size (1,8).

Among the risk factors associated with PTC, there are benign pathologies of the thyroid gland, such as chronic lymphocytic thyroiditis (CLT) (9,10) and nodular hyperplasia (NH) (11,12). CLT is an autoimmune disease against follicular thyroid cells settling generalized thyroid inflammation (10,13), which also has an incidence of 0.1-5% in adults, being more frequent between 45 and 65 years old and in women with a 10:1 ratio (9,13). Some hypotheses suggest that chronic inflammation, along with cell damage and high TSH as a consequence of CLT, promote development of PTC (9,10). NH has a 7% prevalence worldwide (14), and some studies have shown the incidental finding of PTC in patients with NH.

Currently, the most used method for diagnosing nodular thyroid lesions is Fine-Needle Aspiration (FNA), a diagnostic method in which thyroid cells are obtained through a minimally invasive procedure guided by ultrasound (15,16); the FNA is later analyzed by a pathologist to establish if these cells belong to a benign or malignant lesion and, using the Bethesda classification system, a score between I to VI is assigned, where I is considered to include non-

diagnostic or unsatisfactory samples, II to IV are non-malignant findings, and V and VI represent high risk of malignancy or malignancy (16). In any case, FNA has a number of factors that can alter its results, which, on occasion, can give false positives and false negatives (15).

The goal of this study is to describe the characteristics of a sample of surgical specimens in a center of pathologic studies located in an intermediate city, correlate characteristics between the histological varieties of PTC, and find the diagnostic accuracy of FNA for this center.

Materials and methods

The “Genetic analysis of human diseases” research program of the research group in cytogenetics, phylogeny, and population evolution received the ethical approval of the bioethics committee of Universidad del Tolima. In this retrospective study, data was gathered from pathology reports of a diagnostic center in Ibagué, Tolima, an intermediate city; information from patients who had undergone thyroid biopsy or thyroidectomy between the years 2016 and 2022 was included, gathering a total of 495 cases. The data gathered from the sample was: age, sex, presence of malignancy, histopathological diagnostic, FNA results; for cases with malignancy, further information was collected, including bilaterality, tumor size (T), and histological subtype.

The included diagnosis were: papillary carcinoma, hyperplasia/goiter, thyroiditis, and adenoma. The “uncertain” and “other” classifications of the ICD-10 were used; “uncertain” was used for specimens which had no conclusive diagnostic and needed further study with immunohistochemistry, and “other” was used for infrequent pathologies of the thyroid gland, such as unique nodular cyst, leiomyosarcoma, medullary carcinoma, and follicular carcinoma. All of the diagnoses were independently analyzed by at least two pathologists and subject to double-blind peer

review using routine staining (i.e., hematoxylin and eosin stain).

The obtained data was registered in a spreadsheet, in which they were filtered in order to classify and quantify the variables in frequencies and percentages, which were then included in contingency tables. The statistical analysis of significance was calculated by the χ^2 method, establishing a $p < 0.05$ as significant; the correlation between variables were analyzed in papillary carcinoma through univariate analysis, obtaining the Odds Ratio (OR) for bilaterality, tumor size in relation to the follicular, and classic variants; Sensibility (Sen), Specificity (Sp), Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were calculated for FNA, wherein a Bethesda score of V or VI was a positive result and a score from II to IV was negative. Statistical analysis was performed using VassarStat’s online software.

Results

In 495 cases, 780 (100%) different thyroid pathologies were diagnosed: 38.2% (298) were hyperplasia; 29.9% (233) were thyroid carcinoma; 19.1% (149) were thyroiditis; 10.6% (83) were adenoma; and 2.2% (17) were uncertain and other. Most of the sample was under 55 years of age at 58.4% (289), and the predominant sex was female at 90.1% (446) (Table 1).

Table 1
Sample characteristics

Histopathological diagnosis	n (%)
Papillary carcinoma	233 (29.9)
Nodular hyperplasia	298 (38.2)
Adenoma	83 (10.6)
Lymphocytic thyroiditis	149 (19.1)
Uncertain and others	17 (2.2)
Total	780 (100)
Sex	
Female	446 (90.1)
Male	49 (9.9)
Total	495 (100)
Age	
<55 years	289 (58.4)
>55 years	206 (41.6)
Total	495 (100)

Source: Own elaboration.

In men, papillary carcinoma was the most common diagnosis (42.7%), while for women it was hyperplasia (39.1%). Adenomas were diagnosed in 73 (10.4%) women and 10 (13.3%) men. Thyroiditis was more frequent in 193 (19.7%) women. In total, there were 11 “uncertain” diagnoses, all of which were female; the diagnoses cataloged as “others” correspond to three unique non-neoplastic cysts, one leiomyosarcoma, one follicular carcinoma, and one medullary carcinoma. The diagnoses classified as “other” and “uncertain” were those of lower frequency and, together, they represent 2.2% of the total diagnoses ($p = 0.0502$).

More thyroid diseases — both benign and malignant — were found in people under 55 years of age, the most common being hyperplasia, followed by papillary carcinoma, adenoma, uncertain, and others. No significant differences were found between the two groups on the order of frequency of the diseases mentioned above ($p = 0.533$).

Of the total cases (495), 130 (26.3%) had previous FNA, and 85 (65.3%) had a Bethesda score of II to IV, the definitive diagnosis of which was carcinoma in 26 (30.5%). On the other hand, 27 (20.8%) of the 130 cases described a malignant pathology with a Bethesda score of V and VI, only 1 case of which was a benign pathology in the definitive diagnosis (Table 2).

Table 2
Diagnostic accuracy of FNA

Bethesda	Malignant	Benign	n (%)
	n (%)	n (%)	
I	4 (6.9)	14 (18.9)	18 (13.6)
II	1 (1.7)	14 (18.9)	15 (11.4)
III	4 (6.9)	2 (2.7)	6 (4.5)
IV	21 (36.2)	43 (58.1)	64 (48.5)
V	24 (41.4)	1 (1.4)	25 (18.9)
VI	2 (3.4)	0 (0)	2 (1.5)
Total	56 (42.4)	74 (56.1)	130 (26.3)
<i>p</i>	<0.0001		

Source: Own elaboration.

For these cases, the FNA for malignancy showed a specificity of 98.3%, a sensitivity of 50.0%, a positive predictive value (PPV) of 96.3%, and a negative predictive value (NPV) of 69.4%.

Unilateral PTCs were the most frequent in both classical papillary carcinoma (81.1%) and

follicular papillary carcinoma (74.6%); there was a correlation of follicular PTC with bilaterality (OR = 1.46) but without statistical significance ($p = 0.3032$). Eighty-six point eight percent ($n = 200$) had a size greater than 10 mm, and 14.2% ($n = 33$) had a size smaller than 10 mm; the classical PTC was correlated with a tumor size smaller than 10 mm with statistical significance (OR = 3.45; $p = 0.0035$) (Table 3).

Table 3
Variable analysis for CPT

	Classical CPT (n = 111)	Follicular CPT (n = 122)
	n (%)	n (%)
Laterality		
Bilateral	21 (18.9)	31 (25.4)
Unilateral	90 (81.1)	91 (74.6)
OR	0.684	1.460
<i>p</i>	0.3032	
Size		
<10 mm	24 (21.7)	9 (7.4)
>10 mm	87 (78.3%)	113 (92.6)
OR	3.455	0.290
<i>p</i>	0.0035	

Source: Own elaboration.

Of the total papillary carcinoma ($n = 233$) diagnoses, it was found that 77.6% ($n = 181$) had an additional diagnosis. Thus, 96 cases of papillary carcinoma were registered in which the residual thyroid tissue also had hyperplasia, 75 had lymphocytic thyroiditis, and 10 with adenoma. Of the 233 CPT cases, 111 (47.6%) were PTC of classical variant; 41 of these cases had hyperplasia, 34 had thyroiditis, and 7 had adenoma. One hundred and twenty-two (52.4%) were PTC of follicular variant, 55 cases of which had hyperplasia, 41 had thyroiditis, and 3 had adenoma. A correlation was identified between hyperplasia and classical PTC (OR = 1.41) and between thyroiditis and classical CPT (OR = 1.26) (Table 4).

Table 4
Thyroid pathologies associated with CPT

	Classical CPT	Follicular CPT	OR	<i>p</i>
	n	n		
No association	41	39	0.78	0.322
Hyperplasia	41	55	1.41	
Thyroiditis	34	41	1.26	
Adenoma	7	3	0.45	

Source: Own elaboration.

It was found that 80 of all malignancies did not have an associated benign pathology, while 98 were associated with hyperplasia, 77 with thyroiditis, and 12 with adenoma.

Discussion

More thyroid diseases — both benign and malignant — were found in women, which aligns with previous studies, in which PTC, nodular hyperplasia, and lymphocytic thyroiditis were more common in women than in men (1,5,7–14,17), with women being seven times more likely to suffer from thyroid disease (14). It is important to be on the lookout for clinical manifestations of thyroid pathologies in women in order to achieve an early diagnosis. There is also more frequency of thyroid pathologies in subjects younger than 55 years of age, which is important for PTC because it is an indicative of its prognosis, as the tumor size and node invasion in people younger than 55 are not directly related to prognosis because, in these patients, metastasis defined two stages: stage 1 (non-metastatic) and stage 2 (metastatic), while tumor size, node invasion and metastasis in patients older than 55 years are all important in PTC staging (18,19). It has also been demonstrated that the presence of the BRAF V600E mutation increases with aging, which may contribute to poor prognosis in people older than 55, related to bigger tumors, nodal invasion, and recurrence, given that it is also associated with histopathological characteristics of aggressiveness (5–8,20). Therefore, it is recommended to check BRAF V600E expression

status in cases older than 55 years and, from there, take therapeutic choices accordingly to the tumor's molecular profile (Table 5).

Table 5
Thyroid pathologies associated with malignancy

	Malignancy	No malignancy	<i>p</i>
	n	n	
No association	80	0	<0.001
Hyperplasia	98	200	
Thyroiditis	77	72	
Adenoma	12	71	

Source: Own elaboration.

In both this study and the consulted literature, PTC is more prevalent in women (1,5,7–10,14,17). However, some authors have attributed this difference to reproductive and hormonal factors, suggesting a sensibility of thyroid tissue to estrogens and similar compounds, but further revisions have not been able to establish a consistent association with risk of developing thyroid cancer (17). Even though more women than men showed thyroid pathologies, men were more likely to have PTC, according to another study, which found that, even though there was a higher frequency in women, the percentage in men was higher (21). This suggests that, even though all the thyroid diseases mainly affect women, men suffer more frequently from malignancy, which is important in clinical practice when a thyroid pathology is suspected in men.

In this study, only 33 (14.2%) cases of PMC were detected within the 233 cases of PTC; it has been documented that this low frequency of PMC is partly due to its difficult preoperative diagnosis, being undetectable before surgery; oftentimes, its coexistence with hyperplasia, its small size, its location deep within the gland, its slow growth rate, and the absence of specific symptoms further complicate early detection, which tends to be incidental (1,7). However, this diagnostic trend may be due to

the characteristics of the population; studies have shown a higher frequency related to greater tumor size in Colombian patients with PTC, as is the case of a study conducted in Colombia, where 141 patients were examined and compared with clinical data from the John Hopkins Hospital cohort, revealing that Colombians had a higher prevalence of large tumors; this could be explained by late diagnoses (7). The majority of PMC cases occurred in women, due to the fact that women are more likely to have clinically small cancers detected, which could be attributed to greater participation in health care and undergoing ultrasound more frequently (17). However, so far there is no consensus on how to accurately predict the prognosis of PMC; many authors agree that PMC can be considered as an early stage of PTC, rather than an indolent cancer, supported in part by its good prognosis, low mortality, and invasion rates; although some cases present with aggressive histological variants, its classification is usually in low stages (1,8).

Unlike other studies where the frequency of the classic variant of PTC was predominant (7,8), most cases in this study corresponded to the follicular variant (Classical Variant PTC [47.6%] and Follicular Variant PTC [52.4%]), which is clinically relevant considering that the follicular variant is considered more aggressive, due to its association with extra thyroid extension and regional lymphadenopathy (22). In this study, the adenomas showed a correlation with classic PTC, while hyperplasia was correlated with follicular PTC; no other studies were found that report the presence of benign pathologies with the PTC variants, probably because, in some centers, only cancer is placed in the definitive diagnosis, and not the associated diagnoses.

In this study, the most common thyroid pathology was nodular hyperplasia (NH), as in the global literature (11,12,14). However, taking into account that the main cause of NH is iodine insufficiency in their diet (13,14) it is striking that the population from which the sample was taken does not have this dietary limitation (23,24); therefore, and in agreement with other studies, a sporadic NH is suggested, related to

the consumption of goitrogenic substances that interfere with the synthesis of thyroid hormone (13); however, we recommend that specific studies be carried out on the possible causes of goiter in non-endemic areas of iodine deficiency.

It was observed that 77.6% of people with PTC had an additional diagnosis, the most common being hyperplasia, followed by thyroiditis and adenoma. Regarding studies where an association between thyroid cancer in diseases such as hyperthyroidism, hypothyroidism and goiter was identified (11,12,14), it suggests and supports the fact that these diseases are considered risk factors for cancer. However, it was not consistent with a meta-analysis conducted by Liang, in which twelve articles were selected from the databases (PubMed, Cochrane, Web of Science) between the years 1985–2018, without specifying the countries or cases where they found no association of thyroiditis and adenoma with risk of thyroid cancer (2). Even though there was no association in this meta-analysis, the relationship between benign diseases and the progression of PTC cannot be denied. The frequency of cases in which benign and malignant pathologies coexist suggests and supports the different hypotheses that link these diseases with the development of PTC.

Although there was no association in the latter, this cannot be separated from the relationship that the different benign diseases have in the progression to PTC, including adenoma and thyroiditis; the frequency of cases in which benign and malignant pathologies coexist suggests and supports the different hypotheses that link these diseases with the development of PTC.

For this reason, strict clinical follow-up in people with benign thyroid diseases is important in order to detect PTC in early stages, and it is recommended that, for future studies in the Colombian population, their sample sizes be increased in order to establish the relationship between PTC and benign pathologies.

In this sample, the second most frequent benign thyroid pathology associated with PTC was lymphocytic thyroiditis. Currently, the literature postulates two hypotheses about the

relationship between these two pathologies: the first one proposes that inflammation of the thyroid generates cell damage (2,9,10), leading to rearrangement of the *RET/PTC* oncogene, which may promote the formation of PTC (2), based on Virchow's studies on the relationship between pro-inflammatory states with the origin and progress of the cancer (9,25), thyroiditis should be treated as a risk factor for PTC; the second hypothesis states that it is PTC that leads to thyroiditis, as the patient's immune response to cancer; however, thyroiditis caused by PTC tends to be localized and perilesional (2,10). Regarding the adenoma, molecular studies have shown that they may contain mutations in the *RAS* and *RET* genes that are often found in thyroid cancers (2).

The low frequency of medullary carcinoma and leiomyosarcoma was evidenced, both of which have little information available in the consulted databases. However, it is important to highlight that, although they are referred to as neoplasms with an incidence less than or equal to 0.11 per 100,000 (26) in the literature, only one patient in this sample of 495 people was found for each of these pathologies; this could have been attributed to the difficulty of accurate diagnosis of medullary carcinoma and leiomyosarcoma when only FNA is used and, therefore, discrepancies in the diagnosis usually appear (26–28). The frequency of follicular carcinoma is closely related to iodine deficiency, so it is lower in countries where iodine supplementation is available (14). In addition, it is difficult to diagnose follicular carcinoma through FNA because it does not usually present cellular atypia or pathognomonic nuclei; as a result, surgical resection of the tumor is necessary to evaluate the tumor capsule and identify the invasion of the vascular bed, in order to differentiate it from a benign tumor such as a follicular adenoma (20,26).

Although follicular carcinoma is less frequent, it is important to consider them as a differential diagnosis, especially in regions with endemic iodine deficiency (14,29). It is also important to know the patient's history, such as the family history of multiple endocrine neoplasia type 2 (MEN-2) and medullary carcinoma. Also, a

known history of extra thyroidal cancer in the patient, such as leiomyosarcoma, can lead to suspecting the possibility of metastatic disease in the thyroid gland (29).

In this study, FNA showed a specificity of 98.6% for malignancy but a low sensitivity 46.4%; this correlates with other studies with similar results, having high specificity (72–100%) but lower sensitivity (65–98%) (30,31). The causes of low sensitivity may be associated with thick or hemorrhagic smears; it may also be due to sampling, in which cells with atypia are not captured, or to specific cytological characteristics in cell morphology that cause discrepancies in diagnoses (16). However, high specificity can be attributed to the fact that cells with atypical appearance or cell accumulations that allow identifying a clear morphology provide an accurate diagnosis of malignancy (15,31). In this study, the most frequent diagnosis by FNA was Bethesda IV, while in other studies, Bethesda III has been reported as the most frequent; this difference can be attributed to the fact that, in this study, only patients who subsequently underwent surgery for partial or total resection of the thyroid were taken into account (32). Bethesda III, which is “atypia of indeterminate significance,” both in other studies and in this one, have been shown to be more frequently benign than malignant (32).

Conclusions

Coexistence of benign thyroid disease and PTC was identified — an association that might be partially explained by tissular conditions generated from these benign diseases that turn into a favorable environment for carcinogenesis, and follow-up is recommended in patients with benign pathologies in order to promote detection of PMC, which is often found incidentally during the analysis of benign diseases.

It is important to keep in mind that, even though thyroid pathologies are more frequent in women, when it does present in men, it is more likely to be malignant.

Regarding FNA and the Bethesda classification system, they are essential for the initial histopathological study of thyroid lesions. However, there are multiple factors that influence its diagnostic accuracy, having an impact mainly in its sensitivity for detecting malignant lesions; this low sensitivity can be complemented with an appropriate correlation with clinical manifestations and radiologic criteria (TIRADS), which allow differentiation of cases in high risk of malignancy or need for surgical intervention. FNA, however, has an exceptionally high specificity when it comes to malignancy diagnosis, making it a valid method for the study of thyroid pathologies.

Conflict of Interest

None declared by the authors.

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