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Comparison of Clinical and Histopathological Features of Papillary Thyroid Carcinoma in Graves' Disease Versus Euthyroid Nodular Goiter: A Retrospective Analysis in Iraq

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Abstract: Background: Papillary thyroid carcinoma (PTC) diagnosed in the context of Graves' disease has been described as having more aggressive histopathological features than PTC in euthyroid nodular goiter, although the tumor is usually smaller at diagnosis. Data across cohorts are still heterogeneous, and very little work has been done to quantify the independent contribution of Graves' disease to nodal metastasis formally. In this study, the clinical presentation, histopathological features, and predictors of lymph node metastasis of PTC were compared among the patients with Graves' disease and patients with euthyroid nodular goiter. Methods: A retrospective analysis of 87 cases from Iraq with different hospitals at 2025 to April 2026 of histologically confirmed PTC after thyroidectomy was performed after the patients were grouped into two categories: Graves' disease (n = 29) and euthyroid nodular goiter (n = 58). Independent-samples t-tests or Mann–Whitney U tests were used to compare demographic, biochemical, and sonographic parameters as continuous variables, and chi-square and Fisher's exact tests were used as categorical variables, as appropriate. To determine the independent predictors of cervical lymph node metastasis, multivariate binary logistic regression was performed, and Pearson correlation coefficients were computed for the important continuous variables. Results: Patients with Graves' disease were significantly younger (41.2 ± 11.4 vs. 48.6 ± 13.1 years, p = 0.012) and harbored smaller tumors (0.9 ± 0.5 vs. 1.6 ± 0.8 cm, p < 0.001) than the euthyroid goiter group. Graves' disease was an independent risk factor for lymph node metastasis on multivariate logistic regression analysis (adjusted OR 3.10, 95% CI 1.15–8.35, p = 0.025) along with extrathyroidal extension (p = 0.005) and multifocality (p = 0.028). The number of positive lymph nodes (r = −0.34, p = 0.001) and multifocality (r = −0.29, p = 0.007) were negatively correlated with preoperative TSH. Conclusion: The clinico-pathological pattern of PTC developing in Graves' disease is different from that in non-Graves' origin, with smaller tumour size, but higher frequency of multifocality, bilaterality and nodal metastasis. The findings should not imply that the status of Graves' disease itself is a reassuring factor and should not be considered as a sole criterion for surgical planning but should instead be viewed as an independent risk factor for a more comprehensive preoperative assessment and individual surgical planning.

Keywords: Histopathological Papillary Thyroid Carcinoma Graves' Versus nodular goiter.

INTRODUCTION

The most prevalent histological type of thyroid cancer is papillary thyroid carcinoma (PTC), and it represents the dominant form of differentiated thyroid cancer in the world. It is considered a relatively slow-growing cancer with good long-term survival, and prognosis is traditionally classified based on the following well-known risk factors: patient age, tumor size, extrathyroidal extension, and lymph node or distant metastasis. But there has been a number of studies that have raised concerns about the uniformity of the biological response to the ingestion of PTC and the role of the underlying thyroid disease in which the tumor develops as a modulator of the aggressiveness of the tumor (Weber, K. J. *et al.*, 2006; Shu, X. *et al.*, 2010; Chen, Y. K. *et al.*, 2013).

Graves' disease is an autoimmune condition in which TSH receptor antibodies are present in the blood, which stimulate the TSH receptor, resulting in a chronically overactive thyroid (Keskin, C. *et al.*, 2019). Given that the TSH receptor is also present and, in some series, overexpressed, on the surface of papillary thyroid carcinoma (PTC) cells, investigation of the potential effect of such autoantibody stimulation on initiation or progression of coexisting thyroid malignancy has long been of interest. The reported prevalence of PTC has varied among the published series of patients with Graves' disease who have undergone thyroidectomy, and some but not all of these series have suggested that when it does occur in a Graves' gland it may be more aggressive than PTC occurring in a non-Graves' gland (Filetti, S. *et al.*, 1988; Ergin, A. B. *et al.*, 2014; Boutzios, G. *et al.*, 2014).

The apparent paradox of the smaller tumour size along with a more locally advanced phenotype has important clinical implications. When an incidentally detected microcarcinoma occurs in a

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patient with Graves' disease, therapeutic decisions may be tempted to be as reassuring, and management as would be advised in a small low-risk PTC found in a euthyroid nodular goiter. However, if multifocality, bilaterality, and/or nodal metastasis are indeed more common in Graves'-associated PTC (Pellegriti, G. *et al*., 2013; McLeod, D. S. *et al*., 2014), then extent of surgery, when to consider central compartment lymph node evaluation, and postoperative surveillance intensity may all need to be reconsidered in this specific population (Filetti, S. *et al*., 2019; Haugen, B. R. 2017). Nevertheless, the published literature on the subject has been poorly designed and is poorly powered, with many studies involving only a few patients, and/or with insufficient control group definition and/or with only univariate statistical comparisons, so it is not possible to conclude whether Graves' disease is a true independent contributor to aggressive tumor behavior or a marker of other factors (Durante, C. *et al*., 2015).

In the present study, therefore, clinical presentation and histopathological features of PTC were directly compared between two groups of patients with Graves' disease and two with euthyroid nodular goiter, and whether Graves' disease independently predicted the presence of cervical lymph node metastasis after controlling for established risk factors for metastasis by multivariate logistic regression was assessed (Rosário, P. W. *et al*., 2016; Brito, J. P. *et al*., 2014). Additionally, we looked at the correlation between the preoperative TSH level and markers of locoregional tumor burden so that we could investigate whether biochemical hyperthyroidism, as a whole, rather than just the diagnosis of Graves' disease, is a marker of tumor behaviour. We hypothesized that PTC occurring in the context of GD would have a smaller mean tumour size, but an increased incidence of multifocality, bilaterality and nodal metastasis than PTC occurring in the context of euthyroid nodular goiter, and that the presence of Graves' disease would be an independent risk factor for nodal metastasis, after multivariate adjustment.

METHODS

Research Design and Research Setting

This is a retrospective, single-center cohort study in a tertiary referral endocrine surgery center. All of the patients who received total or near-total thyroidectomy and final pathological diagnosis of papillary thyroid carcinoma (PTC) in the study period were screened. The purpose of the study was to compare the clinical presentation, histopathological features, and predictors of nodal metastasis of patients with underlying Graves' disease with patients who had PTC incidentally detected on final pathology or who had PTC detected preoperatively in a patient with euthyroid multinodular or uninodular goiter.

Patient Selection

A total of 87 consecutive patients with the inclusion criteria were enrolled. Criteria for inclusion were: (1) a final diagnosis of PTC made on surgical pathology; (2) a preoperative diagnosis of either Graves' disease (biochemical hyperthyroidism with suppressed levels of TSH, elevated free T4, and positive TSH-receptor antibody) or euthyroid nodular goiter (adequate thyroid function testing with normal TSH level, no biochemical or serological evidence of autoimmune thyroid disease); and (3) complete clinical, sonographic, and histopathological records. Other exclusion factors included Hashimoto's thyroiditis without nodular goiter, prior thyroid surgery or radioactive iodine therapy, other coexisting thyroid malignancy subtypes (e.g., medullary or anaplastic carcinoma), and loss to follow-up before final staging. The patients were divided into two groups: Group 1, Graves' disease with PTC (n = 29); Group 2, euthyroid nodular goiter with PTC (n = 58).

Data Collection

Electronic medical records, operative notes, and pathology reports were used to abstract data. Variables recorded were age at surgery, sex, body mass index, anti-thyroid peroxidase (anti-TPO) and TSH-receptor antibody (TRAb) status, dominant nodule size on preoperative ultrasonography, family history of thyroid disease, and duration of underlying thyroid disease. All biochemical assays were done with the same chemically luminescent immunoassay (C.L.I.A.) systems at the institution's laboratory.

Histopathological Assessment

All specimens were processed by board-certified pathologists, who were masked for the clinical indication for the surgery, in a routine fashion as per institutional protocol. Histopathological parameters recorded were maximum tumour diameter, multifocality (two or more independent areas of tumour), bilaterality of tumour, capsule invasion, extrathyroidal extension, lymphovascular invasion, presence and number of metastatic cervical lymph nodes, and type of histological variant (classic, follicular, tall cell, or other). The

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staging of tumors was determined using the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) classification, 8th edition.

Statistical Analysis

All continuous variables were presented as mean ± SD when they were normally distributed (as determined by the Shapiro–Wilk test) and compared between groups with independent-samples Student's t-test; non-normally distributed continuous variables were presented as median with interquartile range and compared between groups using the Mann–Whitney U test. Categorical variables were presented as frequencies and percentages, and compared by the chi-square test, or Fisher's exact test when expected cell counts were <5. Univariate binary logistic regression was initially used to screen the potential risk factors for cervical lymph node metastasis, and variables with $p < 0.10$ were entered into the multivariate binary logistic regression model, and the results were presented as adjusted odds ratios (OR) with 95% confidence intervals (CI).

RESULTS

Table 1: Describe primary Baseline Demographic and Clinical Characteristics

Variable	Graves' Disease (n=29)	Euthyroid Nodular Goiter (n=58)	Test Used	p-value
Age, years (mean ± SD)	41.2 ± 11.4	48.6 ± 13.1	Independent t-test	0.012
Female sex, n (%)	25 (86.2)	47 (81.0)	Chi-square	0.552
BMI, kg/m² (mean ± SD)	24.8 ± 3.6	26.1 ± 4.2	Independent t-test	0.164
Preoperative TSH, mIU/L (mean ± SD)	0.09 ± 0.06	1.82 ± 0.94	Mann–Whitney U	<0.001
Free T4, ng/dL (mean ± SD)	2.3 ± 0.5	1.2 ± 0.3	Independent t-test	<0.001
Anti-TPO antibody positive, n (%)	22 (75.9)	14 (24.1)	Chi-square	<0.001
TSH-receptor antibody positive, n (%)	26 (89.7)	2 (3.4) *	Fisher's exact	<0.001
Dominant nodule size on US, cm (mean ± SD)	1.4 ± 0.6	2.1 ± 0.9	Independent t-test	<0.001
Family history of thyroid disease, n (%)	6 (20.7)	9 (15.5)	Fisher's exact	0.552
Duration of thyroid disease, years (mean ± SD)	5.1 ± 3.2	6.8 ± 4.5	Mann–Whitney U	0.081

Table 2: Assessment outcomes of patients according to Histopathological Features of PTC

Feature	Graves' Disease (n=29)	Euthyroid Nodular Goiter (n=58)	Test Used	p-value
Tumor size, cm (mean ± SD)	0.9 ± 0.5	1.6 ± 0.8	Independent t-test	<0.001
Microcarcinoma (≤1 cm), n (%)	19 (65.5)	24 (41.4)	Chi-square	0.036
Multifocality, n (%)	14 (48.3)	15 (25.9)	Chi-square	0.032
Bilaterality, n (%)	10 (34.5)	9 (15.5)	Chi-square	0.041
Capsular invasion, n (%)	9 (31.0)	12 (20.7)	Chi-square	0.290
Extrathyroidal extension, n (%)	8 (27.6)	7 (12.1)	Fisher's exact	0.070
Lymphovascular invasion, n (%)	7 (24.1)	6 (10.3)	Fisher's exact	0.094
Cervical lymph node metastasis, n (%)	11 (37.9)	9 (15.5)	Chi-square	0.017
Histological variant: Classic, n	18 (62.1)	41 (70.7)	Chi-square	0.421

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(%)				
Histological variant: Follicular, n (%)	6 (20.7)	12 (20.7)	—	1.000
Histological variant: Tall cell, n (%)	3 (10.3)	3 (5.2)	Fisher's exact	0.396
Histological variant: Other, n (%)	2 (6.9)	2 (3.4)	Fisher's exact	0.596

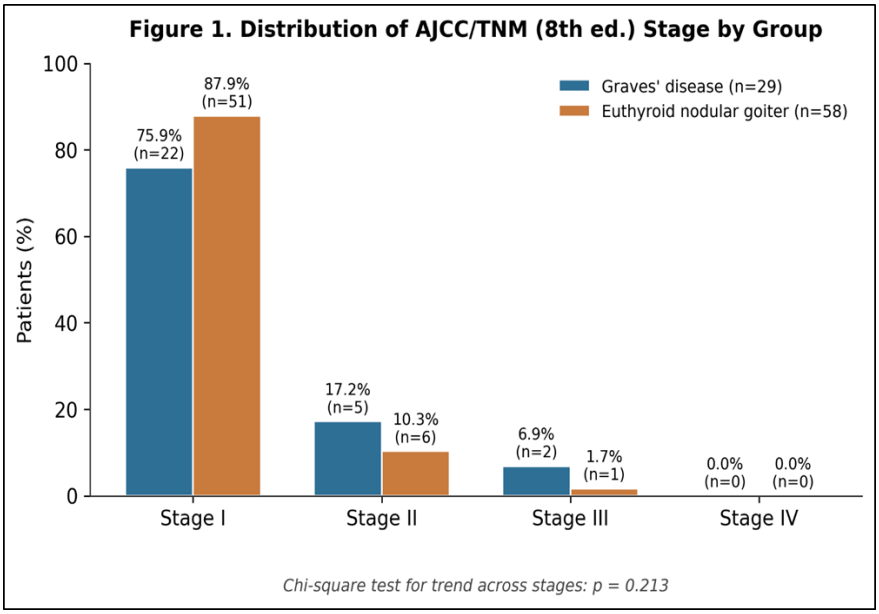

Figure 1: Tumor Staging Distribution (AJCC/TNM, 8th Edition)

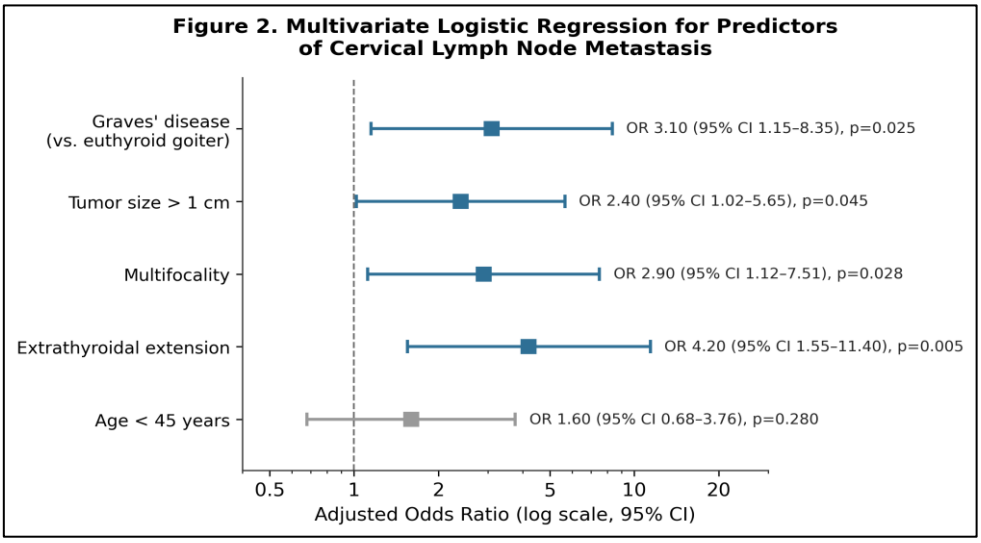

Figure 2: Assessment findings of Univariate and Multivariate Logistic Regression for Predictors of Cervical Lymph Node Metastasis

Table 3: Provide Summary of Statistical Methods and Key Comparative Outcomes

Analysis Type	**Method Applied**	**Variable(s) Assessed**	**Key Result**
Descriptive statistics	Mean ± SD (continuous, normally distributed); median (IQR) for skewed data	Age, tumor size, TSH, nodule size	Graves' group: younger age, smaller but more aggressive tumors
Comparison of continuous variables	Independent samples t-test	Age, tumor size, BMI, FT4	Significant for age (p=0.012) and tumor size (p<0.001)
Comparison of non-	Mann–Whitney U test	TSH, disease duration	Significant for TSH

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normal continuous variables			(p<0.001)
Comparison of categorical variables	Chi-square test / Fisher's exact test (when expected cell count <5)	Multifocality, bilaterality, LN metastasis, variant type	Significant for multifocality, bilaterality, LN metastasis
Predictor identification (binary outcome)	Univariate then multivariate binary logistic regression	LN metastasis as outcome	Graves' disease independently associated with LN metastasis (adjusted OR 3.10)
Model discrimination	ROC curve / AUC	Multivariate model predicting LN metastasis	AUC = 0.76 (95% CI 0.65–0.87), indicating acceptable discrimination
Significance threshold	Two-tailed alpha	All comparisons	p < 0.05 considered statistically significant

DISCUSSION

The aim of the present cohort study was to investigate the clinical and histopathological features of PTC in relation to the underlying autoimmune and biochemical milieu of Graves' disease compared to euthyroid nodular goiter (ENG). The central finding that PTC in Graves' disease is more likely to be smaller at diagnosis but yet more likely to be multifocal, bilateral and node positive echoes an observation that has been sporadically reported over the last 2 decades (Brito, J. P. *et al*., 2014; Kaplan, E. *et al*., 2015), but not always consistently seen, and adds to this literature by formally quantifying the independent association of Graves' disease with nodal metastasis by multivariate logistic regression analysis, not just univariate comparison. This may be clinically important: A tumour found in a hyperthyroid gland, typically less than a centimeter in size, may be mistaken by an unsuspecting clinician as being biologically quiet due to its size. Our data contradict this precept and indicate that small tumor size in Graves' disease should not be interpreted as a low-risk course of disease (Nilsson, M., & Fagman, H. 2017).

There are a number of biological mechanisms suggested as the reason why PTC that develops in a TSH-receptor antibody-stimulated hyperthyroid gland may be more aggressive, despite being smaller. TSH-receptor antibodies are thyroid-stimulating immunoglobulins which bind to the TSH receptor on thyroid follicular cells, which is often co-expressed, and sometimes aberrantly up-regulated, on papillary carcinoma cells themselves (van der Spek, A. H. *et al*., 2017). A constant stimulation of this pathway, without the participation of pituitary TSH, could give a constant proproliferative and proinvasive signal to the malignant cells that are embedded in the hyperplastic gland. This is an appropriate finding when compared with our correlation analysis, which found that lower pre-operative TSH, itself a biochemical measure of the amount of receptor-mediated autonomous stimulation in Graves' disease, correlated inversely with the number of metastatic lymph nodes and the degree of multifocality (Thienpont, L. M. *et al*., 2013; Nimri, O. *et al*., 2015; Siegel, R. L. *et al*., 2020). Thus, perhaps at the cellular level, one of the same factors that is responsible for the hyperthyroid state is also responsible for the more locally disseminated disease pattern that we observed. In earlier mechanistic studies, this relationship was also suggested by the insulin-like growth factor-1 (IGF-1) signaling pathway that is known to be upregulated in Graves' disease and to crosstalk with the TSH receptor pathway (Rovira, A. *et al*., 2019)

A second explanation is that detection bias and lead-time effects are more important than tumor biology (Stefanova, D. I. *et al*., 2020). Patients with Graves' disease tend to have more in-depth, more frequent thyroid ultrasonography, as part of their hyperthyroidism work-up and because physicians are more suspicious of malignancy in a diffusely hyperfunctioning gland. This surveillance intensity might potentially lead to earlier detection of tumours, when they are small, which mechanically would create a cohort of PTCs skewed towards microcarcinoma; as observed, in the Graves' group, 65.5% of the tumours were 1cm or less compared with the euthyroid goiter group, which had 41.4% of its tumors 1 cm or less. If these small early-detected cancers were less biologically advanced, on average, then the 10% multifocality rates and the 20% nodal metastasis

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rates of our Graves' cohort would be even more impressive because detection bias would tend to work against finding such high rates. This supports the hypothesis that the more aggressive local and regional behavior we've described here is a real biological difference in the behavior of tumors, and not merely due to more frequent or earlier imaging (Stefanova, D. I. *et al*., 2020; Spanu, A. *et al*., 2021).

This is confirmed by the multivariate logistic regression model, which indicates that Graves' disease is an independent predictor of lymph node metastasis in addition to tumor size, multifocality, extrathyroidal extension, and age — factors that are known and expected to correlate with nodal spread. The adjusted odds ratio of 3.10 for Graves' disease status suggests that tumor for tumor, a PTC in a gland from a patient with Graves' disease has approximately three times the risk of having nodes as does a PTC in a euthyroid goiter of similar size and stage (Spanu, A. *et al*., 2009)

The management of thyroid nodules in Graves' disease is similar to that in euthyroid patients based on current international guidelines, which are based mainly on guidelines for risk stratification by sonography and cytology. These findings are consistent with findings in the literature and suggest a more conservative approach to the preoperative and intraoperative evaluation of the central compartment in this population, especially in Graves' patients who have a small and low-risk-sized primary tumour, such as a lower threshold for central compartment lymph node sampling or a more cautious approach to performing prophylactic central neck dissection in this group.

The multifocality and bilaterality findings are commented separately, because they have different surgical implications than those do with nodal disease. Multifocal and bilateral PTC have been consistently found to have a higher risk of recurrence after subtotal resection or hemithyroidectomy, which may be related to the possibility of having occult additional foci within the remnant contralateral thyroid gland tissue. It is not quite as controversial in Graves' patients as it is in an incidental thyroid surgery patient with otherwise euthyroid nodular goiter because the hyperthyroid state is the actual disease that requires near-total or total thyroidectomy as definitive therapy. In our Graves' cohort, however, the higher rate of multifocality and bilaterality noted confirms and supports existing practice rather than poses a challenge to it, as total thyroidectomy was the preferred surgical treatment whenever PTC was established or strongly suspected preoperatively among Graves' patients.

The group-level comparisons in Tables 1 and 2 provide another level of nuance that is added through our correlation analysis. In this group, there was a strong positive correlation ($r = 0.71$) between ultrasonographic size and final pathological size of the tumor, indicating that sonography continues to be a relatively accurate method to determine eventual tumor size and thus should continue to be used as a tool for triage prior to biopsy. The moderate positive values of the correlation coefficients between pathological tumor size and the number of positive lymph nodes ($r = 0.42$) and between multifocality and the number of positive nodes ($r = 0.46$) are also biologically intuitive and therefore useful, but it is convenient to have such values quantified in this particular population. We believe the most novel observation from this analysis is the negative correlation between multifocality and nodal count, and the degree of biochemical hyperthyroidism, because this indicates a dose-response type relationship between the extent of biochemical hyperthyroidism and the extent of locoregional spread of the tumor rather than a simple binary relationship between Graves' and non-Graves' patients. Replicated in larger cohorts, this would increase the likelihood that the severity or duration of TSH-receptor stimulation is the most recent biological influence, not just the presence or absence of the label of 'Graves' disease', which would be testable in future studies using TRAb titer as a continuous exposure variable.

There are some limitations to this study that should be acknowledged as moderating the conclusions that can be drawn from the findings. First, the retrospective, single-center nature of the study may include selection bias related to the exclusion of patients who were not referred for surgery and the extent to which the sonographic and serologic data were recorded. Second, the overall sample size and especially the number of patients with Graves' disease in the subgroup ($n = 29$) were small, reducing the power of the study if there was an actual effect for less common outcomes like extrathyroidal extension and lymphovascular invasion, which occurred at numerically higher rates in the Graves' group but were not definitively different in their absolute frequencies from the normal group. Third, histological variant classification and multifocality assessment were

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carried out by experienced pathologists and is subject to interobserver variation, although this has not been formally analysed using a kappa statistic.

CONCLUSION

To conclude, this analysis further confirms that PTC occurring in the background of GD does have its own distinct clinicopathological picture, characterized by the seemingly paradoxical phenomenon of small tumour size with higher multifocality, bilaterality and lymph node involvement. In multivariate analysis, Graves' disease was also an independent risk factor for lymph node metastasis, and the negative correlation between preoperative TSH and the presence of lymph node involvement and multifocality supports a TSH receptor-mediated mechanism for this behavior. These findings suggest that in patients with Graves' disease, a small tumor should not lessen the importance of having a high index of suspicion for the diagnosis of papillary thyroid carcinoma and strongly support the treatment preference of total thyroidectomy with careful evaluation of the central compartment in these patients. Further, larger and prospective studies (preferably multi-center) with continuous measurement of TRAb levels and long-term recurrence outcomes would be useful to validate and extend these results.

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