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Association Between Thyroid Nodules and Thyroid Cancer Risk in Graves' Disease: A Surgical Cohort from an Iodine-deficient Region

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Abstract

Aim: The clinical relevance of thyroid nodules in Graves' disease (GD) remains controversial, particularly in iodine-deficient regions where both nodularity and thyroid cancer are more prevalent. This study aimed to compare clinical, biochemical, ultrasonographic, cytological, and pathological characteristics between nodular and non-nodular GD (non-NGD) to clarify the oncologic significance of nodularity.

Methods: This retrospective observational cohort study included 160 patients who underwent total thyroidectomy for GD between June 2020 and July 2025 at an endocrine surgery center. Patients were classified according to preoperative ultrasonography (US) as nodular or non-NGD. Demographic features, thyroid autoimmunity markers, ophthalmopathy, fine-needle aspiration biopsy (FNAB) results, and final pathology were recorded. Multivariate logistic regression analysis was performed to identify independent predictors of nodularity.

Results: Sixty-three patients (39.4%) had nodular GD (NGD), and 97 patients (60.6%) had non-NGD. Nodular patients were older and had higher body mass index (BMI) (both $p<0.05$), whereas thyroid-stimulating immunoglobulin and anti-thyroid peroxidase levels and ophthalmopathy were significantly higher in non-nodular patients. Fine-needle aspiration biopsy was more frequently performed in the nodular group (57.1% vs. 20.6%). Overall, papillary thyroid carcinoma (PTC) was diagnosed in 31.8% of the cohort, with a markedly higher prevalence in NGD (52.4% vs. 18.5%, $p<0.001$). Tumors in nodular patients were larger and more likely to exhibit lymphatic invasion. In multivariate analysis, age and BMI remained independent predictors of nodularity.

Conclusion: In this surgically treated GD cohort, nodularity identifies a structural phenotype with substantially increased PTC risk, while non-NGD reflects an autoimmune-dominant phenotype. High malignancy rates across Bethesda categories and even in non-biopsied patients indicate the need for vigilant US surveillance and a low threshold for FNAB of suspicious or dominant nodules.

Keywords: Graves disease, nodular graves disease, thyroid nodule, papillary thyroid carcinoma, biopsy, fine-needle, hyperthyroidism

Introduction

Graves' disease (GD) is the most common cause of autoimmune hyperthyroidism and remains a major global health issue with marked geographical variability in presentation, comorbidities, and treatment practices (1,2). Although GD is encountered worldwide, its clinical profile may be significantly influenced by regional iodine status, access to specialized endocrine care, and institutional preferences for therapy (3). In iodine-deficient regions such as Türkiye, nodular thyroid disease is more prevalent, underscoring the importance of careful evaluation for synchronous nodules in GD, since both nodularity and

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iodine-deficiency-related thyroid hyperplasia may influence cancer risk and clinical decision-making (4,5).

While the thyroid gland is usually diffusely enlarged in GD, nodules can also be present and detected through imaging studies (6,7). With the increased use of high-resolution ultrasonography (US), thyroid nodules are now detected in 25-50% of GD patients worldwide (2,8). In iodine-deficient regions, this prevalence may be even higher (4,5). As nodularity is a well-recognized determinant of malignancy risk in euthyroid individuals, its presence in GD has attracted considerable research interest. Over the last decade, contemporary meta-analyses have consistently demonstrated that GD patients with nodules have a 3- to 5-fold increased risk of thyroid cancer (TC) compared with nodule-free GD patients (9-11). Importantly, several regional studies from endemic goiter areas have similarly reported elevated cancer rates among nodular GD (NGD) patients, with prevalence figures exceeding those seen in iodine-sufficient countries (5).

Globally, differentiated thyroid carcinoma (DTC) incidence has risen substantially, driven partly by advances in imaging and more frequent detection of small carcinomas (12). This trend is reflected in GD cohorts, where the majority of detected malignancies are papillary thyroid carcinomas (PTC) (10,11,13). However, some iodine-deficient or endemic goiter populations have demonstrated higher rates of multifocality, tall-cell variant tumors, or other aggressive pathological characteristics among GD-associated cancers (5,14). These findings may reflect the combined effects of chronic iodine deficiency, thyrotropin receptor antibody (TRAb)-mediated proliferative stimulation, autoimmune inflammation, and oxidative DNA damage—all of which have been implicated in GD-related oncogenesis (3,12,15).

Despite the accumulating evidence, knowledge gaps persist regarding the precise clinical implications of nodularity in GD. Preoperative US characteristics, fine-needle aspiration biopsy (FNAB) accuracy, nodule size thresholds, Thyroid-stimulating immunoglobulin (TSI)/autoimmunity profiles, and the pathological behavior of cancers in nodular versus non-nodular GD (non-NGD) remain incompletely understood, and studies vary widely in methodology and patient selection (2,11,13). In the literature, various rates have been reported regarding the prevalence of thyroid nodules in GD, and the malignant potential of these nodules remains controversial (2,9).

We hypothesized that the presence of thyroid nodules in GD identifies a distinct clinical phenotype associated with a higher risk of malignancy and with specific tumor characteristics. Accordingly, this study aimed to evaluate the prevalence and oncologic significance of thyroid nodules in GD by comparing nodular and non-nodular patients in a large surgical cohort from an iodine-deficient region and to provide insights that may support more individualized and region-specific management strategies.

Materials and Methods

Compliance with Ethical Standards

This study was approved by the University of Health Sciences Türkiye, Basaksehir Cam and Sakura City Hospital Institutional Ethics Committee (approval no: 463, date: 17.12.2025) and was conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study and the use of anonymized data, the Ethics Committee waived the requirement for written informed consent.

Study Design and Setting

This retrospective observational cohort study was conducted at the Division of Endocrine Surgery, Department of General Surgery, University of Health Sciences Türkiye, Basaksehir Cam and Sakura City Hospital, Istanbul, Türkiye. The study included patients with GD who underwent total thyroidectomy at a tertiary, high-volume academic center between June 2020 and July 2025. Clinical and perioperative data were prospectively recorded during routine clinical care and retrospectively analyzed for the purposes of this study.

Patient Selection and Grouping

Eligible patients met the diagnostic criteria for GD based on clinical examination, biochemical hyperthyroidism, positive TSI, and typical findings on scintigraphy (diffuse uptake) and/or on US. Exclusion criteria included less than TT, age <18 years, prior thyroid surgery, previous headandneck malignancy, final pathological diagnosis of TC other than PTC (including 2 follicular TC, 1 medullary TC, and 1 oncocytic TC), or missing data. The flow diagram of patient selection is shown in Figure 1. Patients were categorized according to preoperative US:

- **NGD group:** Rresence of solid or mixed nodules,
- **non-NGD group*:*** Absence of synchronous thyroid nodules.

Preoperative Evaluation and Surgery

Preoperative assessment included thyroid function tests, thyroid autoantibodies, highresolution US, and selective FNAB of nodules with suspicious features. All ultrasonographic examinations and FNABs were performed by experienced radiologists specialized in thyroid imaging. Thyroid nodule cytopathology was classified according to the 2023 Bethesda System for Reporting Thyroid Cytopathology (16). Nodule characteristics and FNABhistopathology concordance were recorded. All procedures were performed by a dedicated endocrine surgery team. Euthyroidism was achieved preoperatively using antithyroid drugs (ATDs), beta-

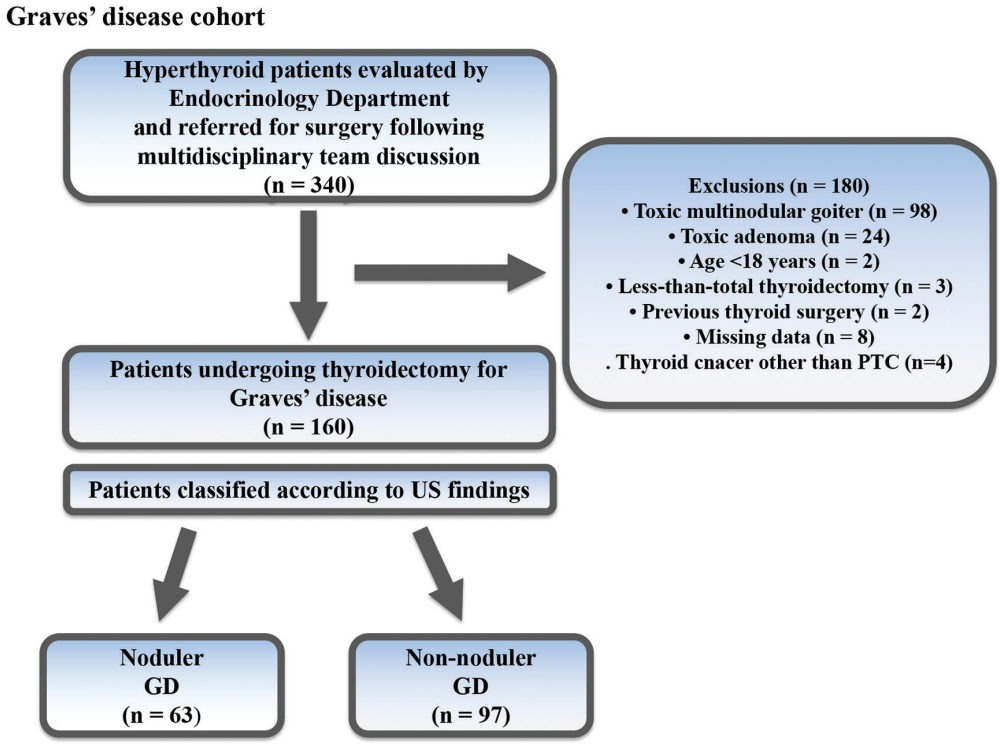

Figure 1. Flow diagram illustrating patient selection, exclusion criteria, and final study group allocation
GD: Graves' disease, US: Ultrasonography

blockers (β-blockers), and Lugol's solution when indicated. Surgical indications included relapse or intolerance to medical therapy; failure or relapse after radioactive iodine treatment (RAI); compressive symptoms; suspicion of malignancy; indeterminate cytology; planning pregnancy; contraindications to RAI; and patient preference. Central lymph node dissection was performed selectively when clinical or radiologic suspicion existed. Thyroid-stimulating hormone (TSH), FT3, FT4, and anti-thyroid peroxidase (anti-TPO) were measured in serum samples using a sandwich electrochemiluminescence immunoassay on the COBAS 8000 e801 analyzer (Roche Diagnostics, Mannheim, Germany). Thyroid-stimulating immunoglobulin levels were measured using a chemiluminescence immunoassay. The normal values for these assays are TSH 0.27-4.2 uIU/mL, FT4 0.93-1.7 ng/dL, FT3 2.6-4.4 pg/mL, anti-TPO 0-34 IU/mL, and TSI <0.1 (0.1-0.55) U/L.

Histopathological Evaluation

Surgical specimens were evaluated by the same pathology team in accordance with the World Health Organization 2022 diagnostic criteria (17). Assessed parameters included tumor size, variant, multifocality, bilaterality, lymphatic or vascular invasion, capsular invasion, extrathyroidal extension (ETE), and lymph node metastasis. Papillary microcarcinoma was defined as ≤10 mm.

Variables and Outcomes

Collected variables included demographics [age, sex, and body mass index (BMI)]; preoperative use of Graves' medications (methimazole, propylthiouracil, β-blockers steroids, Lugol solution, or potassium iodide); diagnosis of ophthalmopathy; thyroid function and autoimmunity markers; US findings; nodule characteristics; cytology results; and histopathology. Primary outcomes:

- Nodule prevalence in GD,
- Comparison of clinical, biochemical, and imaging variables between nodular and nonNGD,
- Malignancy rates and tumor behavior in relation to nodularity.

Statistical Analysis

The primary statistical objective was to identify independent predictors of nodular disease using multivariate logistic regression analysis. Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables as n (%). Normality of continuous variables was assessed using the Shapiro-Wilk test. Between-group comparisons were performed using Student's t-test, Mann-Whitney U test, or chi-square test, as appropriate. Variables with $p<0.10$ in univariate analysis or considered clinically relevant based on prior literature were included in the

multivariate logistic regression model. Odds ratios with 95% confidence intervals were reported. Statistical analyses were performed using SPSS, version 25.0 (IBM Inc., Armonk, NY, USA), and p<0.05 was considered statistically significant. Because the study objective was to compare nodular and non-NGD phenotypes within a surgical cohort, nodularity was defined as the dependent variable in the multivariate regression model. A separate multivariate model with malignancy as the dependent variable was not constructed.

Results

Comparison Between Nodular and non-NGD

A total of 160 patients who underwent TT for GD were included. Of these, 63 patients (39.4%) had at least one thyroid nodule on preoperative US, while 97 patients (60.6%) had a diffusely enlarged, non-nodular gland. Patients in the nodular group were significantly older than those without nodules (43.2±11.4 vs. 38.6±11.4 years, p=0.01). Body mass index was also higher in the nodular group (28.85±5.68 vs. 25.82±4.56 kg/m², p<0.001). In contrast, markers of autoimmune activity were more prominent in the non-nodular group: median TSI (8.27 vs. 3.41, p=0.002) and anti-TPO levels (107 vs. 31 IU/mL, p=0.03) were significantly higher. Ophthalmopathy was also more frequent in the non-nodular group (69% vs. 52.4%, p=0.04). Preoperative steroid therapy (43.3% vs. 28.6%, p=0.087) and plasmapheresis (7.2% vs. 0%, p=0.01) tended to be more frequent among non-nodular patients, while ATDs and RAI use were comparable. There was no significant difference in sex distribution between patients with and without nodules (female proportion: 31.7% vs. 30.9%; p=0.99). The duration of preoperative medical therapy was similar between groups. Mean duration was 18.19±9.95 months in the nodular group and 22.62±8.45 months in the non-nodular group (p=0.24) (Table 1).

Preoperative Cytology and FNAB Utilization

Fine-needle aspiration biopsy was performed significantly more often in patients with nodules (57.1% vs. 20.6%, p<0.001). Among FNAB-sampled nodular patients (n=36), the Bethesda II, III-IV, and V-VI categories accounted for 52.8%, 19.4%, and 27.8%, respectively. In non-NGD patients undergoing preoperative FNAB (n=20), Bethesda II cytology accounted for 80% of cases, while Bethesda III-IV and Bethesda V-VI each comprised 10% (Table 2).

FNAB-histopathology Concordance

Malignancy rates across Bethesda categories varied between groups: Bethesda II nodules showed malignancy in 42% of nodular patients vs. 12.5% of non-nodular patients; for Bethesda III-IV, 28.5% vs. 50%; and for Bethesda V-VI, 90% vs. 100%. Importantly, malignancy was also present in patients who had not undergone FNAB: 16.8% (13/77) in non-NGD and 51.9% (14/27) in NGD (Table 2).

Malignancy Rates and Tumor Pathology

Overall, 51 of 160 patients (31.8%) were diagnosed with PTC. The malignancy rate was significantly higher in the nodular group (52.4%) than in the non-nodular group (18.5%) (p<0.001). Tumor size was significantly larger

Table 1. Comparison of demographic, clinical findings between nodular and non-nodular GD

Variables	Non-nodular GD (n=97)	Nodular GD (n=63)	p-value
Age (year), mean ± SD	38.58±11.4	43.2±11.4	**0.01***
Gender, n (%) Female Male	30 (30.9) 67 (69.1)	20 (31.7) 43 (68.3)	0.99‡
Preoperative BMI, mean ± SD**	25.82±4.56	28.85±5.68	**<0.001***
Preoperative medical therapy period (month), mean ± SD	22.62±8.45	18.19±9.95	0.24*
Preoperative TSH, median (Q1-Q3)	0.05(0.02-0.82)	0.34(0.05-1.18)	0.07†
Preoperative anti-TPO, median (Q1-Q3)	107(25.4-284)	31(9-295)	**0.03†**
Preoperative TSI, median (Q1-Q3)	8.27(3.11-18.4)	3.41(1.21-7.34)	**0.002†**
Preoperative medical therapy use (n, %) ATD Steroid RAI Plasmapheresis	97 (100) 42 (43.3) 9 (9.3) 7 (7.2)	62 (98.5) 18 (28.6) 6 (9.5) 0 (0)	0.39*** 0.087‡ 1.000‡ **0.01****
Ophthalmopathy presence (n, %)	67 (69)	33 (52.4)	**0.04‡**

*Student's t-test, †Mann-Whitney U test, ‡Chi-square test, ***Fisher's exact test, bold values indicate statistically significant results (p<0.05)
**BMI: Body mass index, GD: Graves' disease, TSH: Thyroid-stimulating hormone, anti-TPO: Anti-thyroid peroxidase, TSI: Thyroid-stimulating immunoglobulin, ATD: antithyroid drug, RAI: radioactive iodine treatment, SD: Standard deviation

in nodular patients (median 7 mm vs. 3 mm, p=0.007). Lymphatic invasion was more common in nodular patients (54.5% vs. 22.2%, p=0.03), while vascular invasion, ETE, multifocality, bilaterality, and lymph-node metastasis were similar between the groups (Table 2).

Predictors of Nodule Presence

Univariate comparisons demonstrated that NGD was more common among older, higher-BMI patients and was accompanied by increased preoperative FNAB use and a greater postoperative detection rate of PTC. Ophthalmopathy was inversely associated with the presence of nodules (OR: 0.49, p=0.049). In the multivariate model, age (OR 1.04, p=0.04) and BMI (OR 1.11, p=0.01) remained independent predictors of nodular disease, whereas anti-TPO, TSI, steroid therapy, plasmapheresis, and ophthalmopathy were not independently associated with nodular disease (Table 3).

Discussion

The markedly higher prevalence of malignancy observed in NGD in our cohort supports the concept that nodularity represents a structural disease phenotype associated with thyroid carcinogenesis rather than a coincidental morphological finding. Contemporary surgical series have similarly demonstrated that TC in GD occurs predominantly in glands exhibiting nodular remodeling rather than diffuse autoimmune enlargement alone (1,5,8,11,18).

Multiple large series and meta-analyses consistently indicate that the increased TC risk observed in GD is largely confined to patients with nodular glandular architecture rather than to those with diffuse autoimmune enlargement. Both Papanastasiou et al. (9) and Huang and Chen (10) demonstrated that the excess carcinoma risk in GD is predominantly attributable to coexisting nodularity, while Palella et al. (11) further confirmed NGD as a high-risk subgroup in their umbrella analysis (9-11). This collective evidence supports the interpretation that nodularity represents a structural disease phenotype

Table 2. Comparison of histopathological findings between nodular and non-nodular GD

Variables	Non-nodular GD (n=97)	Nodular GD (n=63)	p-value
Preoperative FNAB n (%) **No** **Yes**	 77 (79.4) 20 (20.6)	 27 (42.9) 36 (57.1)	**<0.001‡**
Preoperative Bethesda category n (%) **Bethesda II** **Bethesda III and IV** **Bethesda V and VI**	 16 (80) 2 (10) 2 (10)	 19 (52.8) 7 (19.4) 10 (27.8)	0.126‡
Final malignancy rate according to FNAB n (%) **No FNAB** **Bethesda II** **Bethesda III and IV** **Bethesda V and VI**	 13 /77 (16.8) 2/16 (12.5) 1/2 (50) 2/2 (100)	 14/27 (51.9) 8/19 (42) 2/7 (28.5) 9/10 (90)	
Papillary thyroid cancer rate (n, %)	18/97 (18.5)	33/63 (52.4)	**<0.001‡**
Papillary microcarcinoma rate (n,%)	16/18 (88.9)	22/33 (66.7)	0.16‡
Tumor diameter, median (Q1-Q3)	3 (2-5.5)	7 (4.5-12)	**0.007†**
Tumor subtype, n (%) **Classic** **Foliculer** **Tallcell** **Hobnail** **Others**	 14 (77.8) 2 (11.1) 2 (11.1) 0 (0) 0 (0)	 18 (54.5) 6 (18.2) 5 (15.2) 1 (3) 3 (9.1)	0.49‡
Lymphatic invasion, n (%)	4 (22.2)	18 (54.5)	**0.03‡**
Multifocal disease, n (%)	4 (22.2)	13 (39.4)	0.21‡
Bilaterality, n (%)	2 (11.2)	10 (30.3)	0.12‡
Extrathyroidal extension, n (%)	1 (5.6)	1 (3)	0.99‡
Vascular invasion, n (%)	0 (0)	4 (12.1)	0.28‡
Lymph node metastasis, n (%)	1 (5.6)	7 (21.2)	0.23‡

†Mann-Whitney U test, ‡Chi-square test, bold values indicate statistically significant results (p<0.05)
FNAB: Fine-needle aspiration biopsy, GD: Graves' disease

Table 3. Univariate and multivariate analysis of factors associated with preoperative ultrasonographic nodularity in Graves' disease (nodular vs non-nodular GD)

	Univariate analysis†			Multivariate analysis		
Variables	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age	1.04	1.007-1.07	**0.02**	1.04	1.002-1.08	**0.04**
BMI	1.13	1.05-1.21	**0.001**	1.11	1.03-1.21	**0.01**
Preoperative TSI	0.97	0.94-1.001	0.06	0.99	0.96-1.03	0.66
Preoperative anti-TPO	0.999	0.997-1.001	0.28	1	0.99-1.001	0.81
Ophthalmopathy presence	0.49	0.25–0.95	0.049	0.78	0.37–1.63	0.51
Steroid use	0.52	0.27–1.03	0.087	0.60	0.27-1.33	0.21
Plasmapheresis	0.09	0.01–0.74	**0.01**	0.14	0.02-1.10	0.06
Preoperative FNAB situation	5.13	2.55-10.34	**<0.001**	4.97	2.17-11.35	**<0.001**
Papillary TC†	4.83	2.37-9.84	**<0.001**	3.56	1.56-8.15	**0.003**

Bold values indicate statistically significant results (p<0.05)
†Papillary thyroid carcinoma status was included as an associated pathological variable rather than a causal predictor of nodularity
GD: Graves' disease, TSI: Thyroid-stimulating immunoglobulin, anti-TPO: Anti-thyroid peroxidase, TC: Thyroid cancer, OR: Odds ration, CI: Confidence Interval, BMI: Body mass index, FNAB: Fine-needle aspiration biopsy,

associated with malignant transformation in GD rather than merely a coincidental morphological finding. In our cohort, the markedly higher cancer prevalence observed in NGD aligns with this structural risk model, suggesting that glandular remodeling and nodular transformation are key determinants of carcinogenic potential in GD.

Our malignancy rate in NGD exceeds pooled global estimates but parallels observations from endemic goiter regions, particularly Turkish surgical series in which Keskin et al. (8), Kefeli et al. (5), and Dayanan et al. (19) consistently emphasized nodularity as the principal determinant of malignancy in GD. These region-specific data suggest that in iodine-deficient settings, TC in GD is more similar to malignancy arising in nodular thyroid disease than to diffuse autoimmune goiter. Consequently, referral and selection patterns may enrich the surgical population with higher-risk disease and limit direct comparison with international series derived from iodine-sufficient cohorts or from non-surgical GD cohorts. In contrast, cohorts from iodine-sufficient populations have reported lower cancer frequencies and questioned whether GD itself—independent of nodular transformation—confers meaningful oncologic risk (20). This geographic divergence likely reflects differences in iodine status, glandular remodeling, and surgical referral patterns rather than the intrinsic biological heterogeneity of GD. In this context, our findings further support the concept that nodularity defines a high-risk structural phenotype within GD, particularly in endemic regions where both nodular transformation and carcinogenic potential are amplified. These observations reinforce the importance of meticulous ultrasonographic evaluation, maintaining a low threshold for FNAB, and considering earlier definitive surgical management in selected NGD patients.

Our findings support a two-phenotype model in GD, distinguishing an autoimmune-dominant, non-nodular form from a structurally remodeled, nodular phenotype associated with increased malignant potential. This conceptual framework is consistent with regional clinical observations in which Keskin et al. (8) and Dayanan et al. (19) emphasized that malignancy in GD is predominantly linked to nodular transformation rather than the degree of autoimmune activity alone. These data suggest that, particularly in endemic regions, glandular remodeling and nodule biology represent the principal oncogenic drivers in GD.

Beyond clinical associations, emerging molecular evidence indicates that TRAb-mediated stimulation, chronic inflammation, and oxidative stress may activate pro-carcinogenic signaling pathways within the hyperplastic Graves' thyroid. Vargas-Uricoechea (21) demonstrated that autoimmune hyperactivation is associated with increased DNA damage and enhanced proliferative signaling, supporting a mechanistic link between autoimmune stimulation and carcinogenesis. However, environmental determinants—particularly iodine status—appear to modulate this process. Pellegriti et al. highlighted that chronic iodine deficiency promotes long-standing TSH-driven hyperplasia and nodular transformation, creating a permissive environment for clonal expansion of mutated follicular cells (12). Integration of our cohort findings with these clinical and biological data suggests that non-NGD may represent an autoimmunity-dominant phenotype, whereas NGD reflects chronic structural remodeling within an iodine-deficient milieu and carries a greater carcinogenic propensity. These pathways likely interact rather than act independently, explaining the heterogeneous malignant potential observed across GD phenotypes.

In our cohort, most tumors were papillary microcarcinomas; however, NGD was associated with significantly larger PTCs and higher lymphatic invasion rates than in non-NGD, whereas multifocality, bilaterality, vascular invasion, ETE, and lymph node metastasis did not differ significantly between groups. This pattern echoes prior observations that, although many GD-associated cancers are microcarcinomas, they may still display aggressive features in a subset of patients (5,8,13). Classic reports by Belfiore et al. (22) suggested that PTCs arising in GD are more often multifocal, locally invasive, and nodal or distantly metastatic than cancers in euthyroid patients and advocated for "vigorous" treatment in this subgroup (20). Subsequent analyses have been heterogeneous, with some studies confirming more aggressive behavior and others reporting similar or even more favorable outcomes compared with non-GD controls (12,22,23). A recent systematic review and meta-analysis by Mekraksakit et al. (23) concluded that, although GD is clearly associated with an increased incidence of DTC, its independent impact on prognosis remains uncertain, with most series showing excellent long-term survival (22). Our findings are consistent with this nuanced picture: nodularity appears to mark a subgroup characterized by biologically more active tumors, while the overall profile remains dominated by low-risk PTC.

Our findings also highlight the diagnostic limitations of FNAB in GD, particularly within structurally heterogeneous and hyperfunctioning glands. Although FNAB was performed more frequently in the nodular group, malignancy rates remained high across all Bethesda classes and even among patients without biopsy, with 22-52% harboring PTC. These patterns closely parallel those reported by Wang et al. (24), in whom 53.3% of cytologically benign nodules were malignant at final pathology, emphasizing the high false-negative rate of FNAB in GD due to diffuse hypervascularity, microscopic multifocal disease, and sampling error (24). Importantly, several studies have provided mechanistic explanations for the suboptimal performance of FNAB in patients with GD. Autoimmune and hyperfunctioning glands characteristically exhibit pronounced hypervascularity, coalescent or poorly demarcated nodules, and markedly disrupted parenchymal architecture, all of which hinder accurate needle targeting and reduce specimen cellularity (25,26). These structural alterations contribute to higher false-negative rates and sampling error. This is particularly relevant when microcarcinomas are embedded within heterogeneous or inflamed tissue (27). Sampling from adjacent benign parenchyma rather than the malignant focus has been documented as a common mechanism of misdiagnosis, especially in nodules arising in a mixed autoimmune background (28). In a dedicated Graves cohort, Hang et al. (29) reported that the sensitivity of FNAB for PTC was substantially lower than expected for euthyroid nodular disease, with microcarcinomas among the lesions most frequently underdiagnosed. These findings support the concept that both the biological environment of the thyroid gland and the technical limitations of FNAB synergistically reduce the diagnostic yield. Collectively, emerging evidence, including our results, supports a more liberal FNAB strategy, careful ultrasound surveillance, and the recognition that benign cytology or the absence of FNAB does not reliably exclude PTC in patients with GD. These findings suggest that FNAB may have reduced diagnostic sensitivity in GD due to glandular hypervascularity and heterogeneous parenchymal architecture.

In our study, older age and higher BMI emerged as independent predictors of nodularity, highlighting a structural rather than an immunologic basis for nodule formation in GD. Our results are strongly supported by recent studies in Turkish endemic regions, which report that NGD patients are significantly older and more likely to harbor TC. Kefeli et al. (5) found that more than 50% of GD patients with synchronous nodules in an iodine-deficient area had PTC—many with aggressive features—and that nodular disease clustered in an older demographic. Similarly, Dayanan et al. (19) reported that age and structural thyroid enlargement, rather than autoimmune severity, predicted nodularity and were associated with higher malignancy rates in surgically treated GD patients. These studies closely mirror our findings and emphasize the combined effects of iodine deficiency and structural remodeling on nodule formation. A multicenter study by Yoon et al. (13) (15,159 GD patients; 262 cancers) also supports a structural-age effect: GD patients with coexisting nodules were significantly older (61.9±12.8 vs. 52.1±13.3 years) and more frequently female, while autoimmune activity (TBII levels, GD activity status) showed no difference between nodular and non-nodular cancers. This is consistent with our observation that TSI and anti-TPO were not independent predictors of nodularity. Yoon et al. (13) found that, although NGD patients were older, aggressive PTC variants, such as tall-cell and solid, were more common in the non-NGD group, suggesting that autoimmunity-driven and structural nodular phenotypes represent distinct biological pathways. This dual-phenotype concept of non-nodular, autoimmune-dominant GD versus nodular, structurally remodeled GD is consistent with our data and with several review studies proposing parallel mechanisms of disease expression (10,11,22). Taken together, our findings support the view that age-related glandular remodeling and BMI-associated proliferative signaling are major determinants of nodularity in GD, whereas classical autoimmune markers predict systemic

manifestations (TSI and ophthalmopathy) and do not independently contribute to nodule formation. This distinction is clinically relevant: NGD appears to represent a structurally dominant phenotype—often seen in older or metabolically at-risk individuals—and is associated with a higher prevalence of synchronous PTC, whereas non-NGD reflects an autoimmune-dominant phenotype with higher TSI levels and ophthalmopathy, but not necessarily increased structural disease.

Study Limitations

This study has several limitations. Its retrospective, single-center design and the inclusion of only surgically treated GD patients introduce selection bias, thereby limiting the generalizability to medically managed populations. The study population likely represents a selected higher-risk subgroup enriched for nodularity and/or suspicious clinical–ultrasonographic features; therefore, the observed malignancy rates cannot be generalized to all patients with GD. Ultrasonography was operator-dependent, and variability in nodule characterization or biopsy indications may have affected both nodule detection and FNAB performance. Conducting the study in an iodine-deficient/endemic goiter region may also have contributed to the high malignancy rates observed and may not reflect the situation in iodine-sufficient populations. Additionally, some subgroup analyses—particularly FNAB-based comparisons—were restricted by small sample sizes. Finally, a multivariate model with malignancy as the dependent variable was not constructed because the cohort consisted exclusively of surgically treated patients, representing a selected high-risk population enriched for nodular disease. Therefore, the association between nodularity and malignancy should be interpreted as cohort-specific rather than as an independent predictive model of TC. These limitations should be considered when interpreting the results, and causality cannot be inferred due to the observational design.

Despite these limitations, the study has several important strengths. It represents a well-characterized endocrine surgery cohort from an iodine-deficient region with systematic ultrasonographic evaluation and uniform histopathologic assessment. The direct comparison of nodular and non-NGD within the same clinical setting allowed evaluation of structural versus autoimmune determinants of malignancy risk. Furthermore, the findings provide clinically relevant support for a structural phenotype model of nodular NGD associated with increased TC risk.

Conclusion

In this large surgical cohort from an iodine-deficient region, thyroid malignancy was not uncommon in GD and was particularly pronounced in patients with NGD. These findings support the existence of two clinically relevant GD phenotypes: a nodular, structurally remodeled phenotype associated with an increased risk of cancer and an autoimmune-dominant, non-nodular phenotype. Importantly, malignancy was observed across cytological categories and even in patients without preoperative FNAB, underscoring that neither benign cytology nor the absence of biopsy reliably excludes PTC in GD. In surgically treated GD patients, nodularity may represent a high-risk structural phenotype warranting vigilant US surveillance, a low threshold for FNAB, and careful, individualized decision-making regarding surgical versus medical therapy in GD, especially in endemic goiter areas where cancer prevalence is high; however, these findings should not be extrapolated to non-surgical GD populations without further prospective data.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, Basaksehir Cam and Sakura City Hospital Institutional Ethics Committee (approval no: 463, date: 17.12.2025).

Informed Consent: Due to the retrospective nature of the study and the use of anonymized data, the ethics committee waived the requirement for written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: T.M.O., M.Y., S.A., A.C., G.Y., S.S., Concept: T.M.O., S.A., G.Y., N.Y.E., S.S., Design: T.M.O., M.Y., A.C., Data Collection or Processing: T.M.O., M.Y., G.Y., N.Y.E., Analysis or Interpretation: M.Y., S.A., A.C., G.Y., N.Y.E., S.S., Literature Search: T.M.O., S.A., A.C., N.Y.E., S.S., Writing: T.M.O.

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