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RESEARCH

Comparison of clinical and histopathological characteristics of differentiated thyroid cancers in euthyroid nodular goiter and Graves' disease

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Abstract

Background: Graves' disease (GD) is characterized by autoimmune hyperthyroidism. Its association with papillary thyroid carcinoma (PTC) remains controversial, with conflicting data regarding tumor aggressiveness and clinical outcomes.

Objective: To compare the clinical and histopathological features of PTC in patients with GD versus those with euthyroid nodular goiter.

Methods: A retrospective review was conducted on 995 patients who underwent thyroidectomy for PTC between 2014 and 2023. Group 1 included 59 patients with GD and coexisting PTC, while group 2 comprised 936 euthyroid patients with PTC. Tumor characteristics, recurrence rates, and treatment outcomes were analyzed.

Results: PTCs in the GD group were more frequently papillary microcarcinomas (85 vs 43%, $P < 0.001$) and exhibited significantly lower rates of multicentricity, vascular invasion, and lymph node metastasis. There were no statistically significant differences in recurrence or distant metastasis between groups. Multivariate analysis identified older age and the presence of thyroid nodules as independent predictors of PTC in patients with GD.

Conclusion: PTC associated with GD appears to exhibit more favorable histopathological features. However, the risk of malignancy increases with age and ultrasonographically detected nodules in GD patients. These findings support the importance of vigilant surveillance and individualized treatment planning in this population.

Keywords: Graves' disease; papillary thyroid cancer; recurrence; differentiated thyroid cancers; Basedow's disease

Introduction

Graves' disease (GD) is an autoimmune thyroid disease and the most common cause of hyperthyroidism (1). It has a strong familial transmission and is often diagnosed between the ages of 20 and 60 years. It is observed five times more frequently in women than in men (2). The basis of the pathogenesis is thyroid-stimulating hormone (TSH) receptor antibodies (TRAb) formed by B lymphocytes against the thyroid-stimulating hormone receptor (TSH-R) on thyrocytes, producing a TSH-like effect (3, 4).

Thyroid cancer is the most common endocrine malignancy, with its global incidence rising steadily over the past several decades. Papillary thyroid carcinoma (PTC) accounts for approximately 80% of all

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thyroid cancer cases worldwide and is the predominant subtype in both children and adults (5).

Previously, it was thought to be a protective mechanism against cancer formation due to TSH suppression in hyperthyroidism; however, later studies revealed that GD and thyroid carcinomas can occur simultaneously (6). There are opinions that autoantibodies, which are the basis of the pathogenesis of GD, also trigger the development of thyroid cancer by increasing the proliferation and activity of thyrocytes (7). The main basis for these views is that TRAbs cause tumor growth, increase invasiveness and stimulate angiogenesis (8).

According to the American Thyroid Association (ATA), the rate of concurrent thyroid cancer detection in GD is approximately 2% (9). In the literature, the incidence of thyroid cancer in GD varies between 2 and 47.5% (10, 11), and PTC is the most common thyroid cancer associated with GD (12). Although it was previously thought that thyroid cancers accompanied by GD have a more aggressive course, clinical findings supporting this idea have not been reported in current studies (13).

The main aim of this study was to investigate whether euthyroid PTC cases with and without GD differ in terms of clinical and histopathological features and recurrence rate. In addition, the demographic and clinical factors affecting the detection of concurrent cancer in GD were investigated.

Method

A retrospective analysis of patient data was conducted for individuals who received surgical treatment for GD and PTC diagnosed between January 1, 2014, and July 1, 2023, in the Endocrine Surgery Division of the Department of General Surgery at Istanbul Medical Faculty. During this period, 59 (27.8%) of 212 patients who underwent thyroidectomy for GD had concomitant PTC. During the same period, 936 euthyroid patients underwent surgery for PTC without GD. We defined 59 patients with PTC in the background of GD as group 1 and 936 patients with PTC in the background of euthyroid goiter without GD as group 2. Demographic findings, clinical and histopathological data, fine-needle aspiration biopsy (FNAB) cytologic results, radioactive iodine (RAI) treatment, presence of distant metastasis at the time of diagnosis, postoperative recurrence, and TNM stages were recorded. FNAB cytological results were evaluated according to the Bethesda classification (14). PTCs with a diameter of 1 cm or less were defined as papillary microcancer (PMC).

The diagnosis of GD was based on the signs and symptoms of thyrotoxicosis, findings of GD on ultrasonography (US), increased free T3 and T4 concentrations, decreased TSH levels, diffuse involvement of the thyroid gland on scintigraphy, and TRAb positivity. Demographic data, TRAb levels, and nodule detection rates were compared between patients with and without cancer on a GD background.

Follow-up after surgical treatment was performed in a multidisciplinary manner. Recurrence follow-up in patients with PTC was mainly performed with serum Tg and anti-Tg levels and neck US, and, when necessary, with diagnostic scintigraphy and/or cross-sectional imaging. In patients with PTC, local recurrence or distant metastasis during follow-up was defined as the detection of structural tumor findings in the neck or distant regions with concurrent imaging with elevated Tg or anti-Tg.

Statistical analysis

All statistical analyses were conducted using SPSS for Windows version 22.0 (IBM Corp., USA). Continuous variables were expressed as mean ± standard deviation or median (range), depending on distribution, and categorical variables as frequencies and percentages. The Student's *t*-test or Mann–Whitney U test was used to compare continuous variables between groups, based on normality. For categorical variables, the Pearson chi-square test or Fisher's exact test was applied, as appropriate. To identify factors associated with recurrence, both univariate and multivariate analyses were performed. Univariate associations were first tested using the methods above. Variables with $P < 0.10$ in univariate analysis or deemed clinically relevant were then entered into a binary logistic regression model to determine independent predictors of recurrence. Similarly, a separate logistic regression analysis was conducted to evaluate predictors of PTC in patients with Graves' disease (GD). All tests were two-sided, and a P-value <0.05 was considered statistically significant. A post hoc power analysis was also conducted to estimate the adequacy of detecting differences in recurrence between groups, indicating approximately 33% power with the current sample size and observed event rates.

Results

Patient characteristics and preoperative findings

The preoperative demographic and clinical findings of groups 1 and 2 are summarized in Table 1. No significant differences were observed between the two groups in terms of demographic data. The median follow-up time was 37 months (1–108) in group 1 and 33 months (1–135) in group 2. The mean TSH level was significantly lower in group 1 than in group 2 (1.54 ± 2.53 mU/L versus 2.04 ± 1.68 mU/L; P = 0.001). Preoperative FNAB was performed in 19 (32.2%) patients in group 1 and 861 (92.0%) patients in group 2 (P = 0.001). There was no significant difference between the two groups in terms

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Table 1 Demographic data and preoperative findings.

	Group 1 (*n* = 59)	Group 2 (*n* = 936)	*P*-value
Age (years)	46.44 ± 12.46	45.87 ± 14.18	0.897
Gender (%)			0.497
Male	9 (15.3%)	176 (18.8%)	
Female	50 (84.7%)	760 (81.2%)	
Median follow-up time (months)	37 (1–108)	33 (1–135)	0.866
TSH level (mU/L)	1.54 ± 2.53	2.04 ± 1.68	**<0.001**
FNAB			**<0.001**
Performed	19 (32.2%)	861 (92.0%)	
Not-performed	40 (67.8%)	75 (8.0%)	
FNAB result			0.107
Malignancy	6 (31.6%)	346 (40.2%)	
Suspicion of malignancy	2 (10.5%)	174 (20.2%)	
Follicular neoplasia	0 (0.0%)	69 (8.0%)	
Atypia of uncertain significance	1 (5.3%)	70 (8.1%)	
Benign	8 (42.1%)	159 (18.5%)	
Non-diagnostic	2 (10.5%)	43 (5.0%)	

Bold indicates statistical significance. Values are expressed as median (%).
TSH, thyroid-stimulating hormone; FNAB, fine-needle aspiration biopsy.

of the cytologic results of FNAB according to the Bethesda classification (Table 1).

Postoperative histopathological findings, staging, and follow-up

Postoperative histopathological features, TNM stages, and postoperative RAI treatment rates of patients in both groups are summarized in Table 2. The tumor diameter was significantly smaller in group 1 than in group 2 (5.64 ± 3.70 mm vs 15.13 ± 12.64 mm; P = 0.001). Most of the PTCs in group 1 (85%) were PMCs, and the rate of PMCs in group 1 was significantly higher than the rate of PMCs in group 2 (43%) (P < 0.001). There was no significant difference between the two groups in terms of the rate of pathological subtypes of PTC (Table 2). When the histopathological features of the tumor were examined, multicentricity (25.4 vs 48.6%; P = 0.001), lymphatic invasion (5.1 vs 18.4%; P = 0.009), vascular invasion (0 vs 7.7%; P = 0.018), tumor capsule invasion (6.8 vs 18.7%; P = 0.021), and lymph node metastasis (0 vs 17.2%; P = 0.001) were observed. When both groups were compared according to TNM staging, although there was no significant difference in terms of tumor stage, the proportion of N1 patients was significantly higher in group 2. While no distant metastasis was detected at the time of diagnosis in group 1, six (0.6%) patients in group 2 had distant metastasis at the time of diagnosis, but the difference was not statistically significant.

The rate of postoperative RAI treatment in group 1 patients was significantly lower than that in group 2 (P = 0.001).

No local recurrence or distant metastasis was detected in any patient in group 1 during the follow-up period. In group 2, 31 (3.3%) patients developed local recurrence, and six (0.6%) patients developed distant metastasis. However, the differences in local recurrence and distant metastasis rates between the two groups were not statistically significant.

Factors associated with recurrence: univariate and multivariate analysis

In univariate analysis, younger age, higher postoperative TSH, tumor size >10 mm, necrosis, calcification, lymphovascular invasion (LVI), perineural invasion, and lymph node metastasis were significantly associated with recurrence. However, in the multivariate model, only tumor size >10 mm (OR: 2.4, P = 0.001), LVI (OR: 2.5, P = 0.045), and lymph node metastasis (OR: 4.9, P < 0.001) remained as independent predictors. Age showed borderline significance (P = 0.052). The presence of Graves' disease was not associated with recurrence in either analysis (Table 3).

Surgical indications and preoperative management in the GD group

Among the 212 GD patients, surgical indications included suspicion of malignancy on imaging or FNAB (24.1%), compressive symptoms (18.4%), ophthalmopathy or poor control with antithyroid drugs (30.6%), patient preference (11.3%), and large goiter with cosmetic concerns (15.6%). Preoperative RAI therapy had been administered to 12 of these patients (5.7%) before surgical referral. The typical referral pattern involved initial management by endocrinology with surgical referral upon treatment failure, nodule growth, or suspected malignancy.

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Table 2 Postoperative histopathological features, TNM stage, RAI treatment, local recurrence, and distant organ metastasis rates.

	Group 1 (*n* = 59)	Group 2 (*n* = 936)	*P*-value
Tumor diameter (mm)	5.64 ± 3.70	15.13 ± 12.64	**0.001**
Tumor subtype (%)			**<0.001**
PTC	9 (15.3%)	530 (56.6%)	
PMC	50 (84.7%)	406 (43.4%)	
Pathological subtypes			0.540
Follicular variant	20 (34.0%)	413 (44.2%)	
Classical variant	28 (47.5%)	385 (41.2%)	
Oncocytic variant	8 (13.5%)	54 (6.0%)	
High cylindric	3 (5.0%)	54 (6.0%)	
Trabeculer (solid)	0 (0.0%)	13 (1.0%)	
Warthin-like	0 (0.0%)	11 (1.0%)	
Diffuse sclerosing	0 (0.0%)	6 (0.6%)	
Pathological features			
Multicentricity	15 (25.4%)	455 (48.6%)	**0.001**
Lymphatic invasion	3 (5.1%)	172 (18.4%)	**0.009**
Vascular invasion	0 (0.0%)	72 (7.7%)	**0.018**
Perineural invasion	0 (0.0%)	45 (4.8%)	0.105
Presence of tumor capsule	12 (20.3%)	370 (39.5%)	**0.003**
Tumor capsule invasion	4 (6.8%)	175 (18.7%)	**0.021**
Thyroid capsule invasion	0 (0.0%)	103 (11.0%)	**0.007**
Extrathyroidal invasion	0 (0.0%)	39 (4.2%)	0.163
Lymph node metastasis	0 (0.0%)	161 (17.2%)	**0.001**
pT stage (%)			0.199
T1	50 (84.7%)	735 (78.5%)	
T2	9 (15.3%)	155 (16.6%)	
T3	0 (0.0%)	46 (4.9%)	
pN stage (%)			**0.001**
N0	59 (100.0%)	775 (82.8%)	
N1	0 (0.0%)	161 (17.2%)	
M stage (%)			0.999
M0	59 (100.0%)	930 (99.4%)	
M1	0 (0.0%)	6 (0.6%)	
RAI therapy (%)	6 (10.2%)	565 (60.4%)	**<0.001**
Local recurrence	0 (0.0%)	31 (3.3%)	0.252
Distant metastasis	0 (0.0%)	6 (0.6%)	1

Bold indicates statistical significance. Values are expressed as median (%).
PTC, papillary thyroid carcinoma; PMC, papillary microcarcinoma; RAI, radioactive iodine.

Clinical findings in patients with and without PTC in GD background

In this study, PTC was detected in 59 (27.8%) of 212 patients operated for GD. Patients with and without PTC on the background of GD were compared in terms of demographic data, preoperative TRAb level, and the rate of nodule detection on preoperative US (Table 4).

Advanced age and the presence of concomitant thyroid nodules were significantly associated with concurrent cancer detection in patients with GD. While nodules were detected by US in 69.5% of patients with PTC, this rate was 43.8% in GD patients without PTC (P = 0.001). There was no significant difference in terms of sex and preoperative TRAb level between patients with and without cancer on the background of GD.

Predictors of PTC in patients with GD

Multivariate logistic regression identified age and ultrasound-detected nodules as independent predictors of PTC in GD patients. Each additional year of age increased the odds of PTC by 6% (OR: 1.06; 95% CI: 1.02–1.11; P = 0.004), while the presence of nodules more than doubled the risk (OR: 2.64; 95% CI: 1.31–5.30; P = 0.006). In contrast, TRAb levels and sex were not significantly associated with cancer risk (P = 0.312 and P = 0.610, respectively). These results underscore the relevance of age and nodule presence as clinical indicators of malignancy in GD (Table 5).

Discussion

In this study, we compared the clinical and histopathological features and clinical course of PTCs in

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Table 3 Univariate and multivariate analysis of factors associated with recurrence.

	Univariate analysis			Multivariate analysis		
Factors	**OR**	**95% CI**	***P*-value**	**(OR)**	**95% CI**	***P*-value**
Age (≤55 years vs >55 years)	2.1	1.3–3.3	0.042	1.7	1.0–2.8	0.052
Postoperative TSH level	1.5	1.1–2.2	0.019	1.2	0.9–1.6	0.192
Tumor size (>10 mm vs ≤10 mm)	3.8	2.5–5.9	<0.001	2.4	1.5–3.8	**0.001**
Tumor necrosis	2.4	1.5–3.8	0.008	1.5	0.9–2.6	0.105
Calcification	2.1	1.4–3.3	0.025	1.3	0.8–2.1	0.315
Lymphovascular invasion	4.3	2.7–6.7	<0.001	2.5	1.2–5.2	**0.045**
Perineural invasion	3.2	1.9–5.5	0.005	1.1	0.6–2.1	0.922
Lymph node metastasis	5.5	3.3–9.1	<0.001	4.9	2.5–9.5	**<0.001**
Presence of GD (yes vs no)	1.0	0.6–1.6	0.985	0.9	0.5–1.5	0.785

Bold indicates statistical significance. Odds ratios (OR), 95% confidence intervals (CI).
TSH, thyroid-stimulating hormone; GD, Graves' disease.

euthyroid goiter patients with and without GD. In PTCs without GD, larger tumor diameter, higher rate of lymph node metastasis, and unfavorable histopathological features were found compared to PTCs with GD. However, no significant difference was found in terms of local recurrence and distant metastasis between PTCs with or without GD. When GD was analyzed as a separate group, a significant correlation was found between advanced age and the presence of nodules, and an increased rate of PTC detection.

The relationship between hyperthyroidism and thyroid cancer has been investigated since the 1940s (15). Earlier hypotheses suggested that suppressed TSH levels in hyperthyroidism might reduce stimulation of thyroid cells, thereby offering some protection against malignancy. However, more recent findings, including our results, support that Graves' disease (GD) and PTC frequently co-exist (7, 9, 16). It has been proposed that thyroid-stimulating hormone receptor antibodies (TRAbs), which drive the pathophysiology of GD, may exert a TSH-like effect on thyrocytes, enhancing proliferation, invasiveness, and angiogenesis (8, 17, 18). Experimental studies further support this mechanism by demonstrating the proangiogenic role of TRAbs in the thyroid microenvironment (18, 19).

In our study, the incidence of concomitant papillary thyroid cancer in the GD group was 59/212 (27.8%). The incidence of thyroid cancer in GD varies according to the patient population and treatment administered. This incidence was reported to be 2% in the ATA data (8). However, in surgical series, rates of concomitant thyroid cancer with GD ranging from 21% to 47% have been reported (7, 11, 13, 20).

It is controversial whether the clinical and histopathological features and prognosis of PTCs that develop in a GD background are different from those of cancers that develop in a euthyroid background without GD. Important clinical and histopathological prognostic factors for recurrence and survival in PTC include age, tumor diameter, multicentricity, aggressive subtype PTC, lymphatic and vascular invasion, invasion of soft tissue outside the thyroid, lymph node metastasis, and distant metastasis (21, 22, 23).

Although male sex was found to be an unfavorable prognostic factor in some studies, no significant relationship was found between sex and PTC prognosis in many other studies (24). Advanced age (>55 years) is also an important unfavorable prognostic factor for PTC (22, 25). In our study, no significant correlation was found between PTC patients with and without GD in terms of age and sex.

Tumor size is a well-established prognostic factor in PTC, with larger tumors consistently associated with increased risk of recurrence across several prognostic scoring systems, including AGES, AMES, and MACIS (26).

Table 4 Demographic and clinical findings of Graves' patients.

	GD (*n* = 153)	**GD + PTC (*n* = 59)**	***P*-value**
Age (years)	38.52 ± 12.75	46.44 ± 12.46	**<0.001**
Gender			0.132
Male	38 (24.8)	9 (15.3)	
Female	115 (75.2)	50 (84.7)	
TSH	2.04 ± 3.03	1.54 ± 2.53	0.150
TRAb	12.43 ± 15.09	11.60 ± 20.24	0.052
Presence of nodules	67 (43.8)	41 (69.5)	**0.001**

Bold indicates statistical significance. Values are expressed as median (%).
TSH, thyroid-stimulating hormone; TRAb, TSH receptor antibodies.

Table 5 Predictors of PTC in patients with GD.

Variable	**B**	**SE**	**OR (95% CI)**	***P*-value**
	−4.872	1.134	—	<0.001
Age (per year increase)	0.058	0.020	**1.06 (1.02–1.11)**	**0.004**
Nodule on ultrasound (yes)	0.971	0.352	**2.64 (1.31–5.30)**	**0.006**
TRAb level	0.077	0.077	1.08 (0.93–1.26)	0.312
Sex (female vs male)	0.189	0.370	1.21 (0.58–2.54)	0.610

Bold indicates statistical significance. Odds ratios (OR), 95% confidence intervals (CI).
PTC, papillary thyroid carcinoma; GD, Graves' disease; TRAb, TSH receptor antibodies.

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Similarly, lymph node metastasis is recognized as an independent predictor of recurrence and poorer disease-specific survival (27). In our study, lymph node metastasis was not observed in any PTC patients with Graves' disease (GD), whereas the rate was 17.2% among euthyroid patients. While these findings may suggest a more favorable disease profile in the GD group, they should be interpreted with caution, as this does not imply a causal relationship. Notably, incidental papillary microcarcinomas (PMCs) comprised the majority of PTCs in the GD cohort – a trend previously described in the literature (16). In our sample, approximately 85% of tumors in the GD group were PMCs, and the mean tumor diameter was significantly smaller than in the euthyroid group. This may reflect earlier detection due to increased ultrasonographic surveillance or more frequent surgical intervention in GD patients, rather than intrinsic differences in tumor biology. Moreover, the absence of lymph node metastasis in the GD group could be influenced by selection bias, differences in surgical extent, or the lower tumor burden at diagnosis.

Although no significant difference in recurrence rates was observed between GD-associated and euthyroid PTC in our cohort, these findings should be interpreted with caution due to the relatively short follow-up period. The median follow-up durations of 33 months in the euthyroid group and 37 months in the GD group may be insufficient to capture late recurrences, which are not uncommon in differentiated thyroid carcinomas. Recurrence in PTC can occur many years – sometimes even decades – after initial treatment, particularly in cases with initially favorable pathology (23). Therefore, the absence of recurrence in the GD group may reflect limited follow-up rather than true biological differences, highlighting the need for longer-term surveillance in future studies.

While some earlier reports hypothesized a more aggressive clinical course for thyroid cancers in GD, our study, in line with the current literature, did not find significant differences in recurrence or metastatic behavior (13). The higher rate of PMCs and smaller tumor sizes in GD may, however, contribute to favorable histopathological features and clinical outcomes, as suggested in surgical series (7, 11). Kikuchi *et al.* proposed that the hypertrophic thyroid in GD may limit extracapsular invasion, and that total or near-total thyroidectomy – often performed in GD – may reduce residual disease and recurrence risk (28). Our findings support this possibility, although further prospective validation is needed.

While our study did not identify more aggressive histopathological features or increased recurrence in GD-associated PTC, the recent literature has reported heterogeneous and sometimes contradictory findings. Several studies have suggested that PTCs arising in the context of Graves' disease may present with more aggressive characteristics, including a higher incidence of lymph node metastasis, extrathyroidal extension, and unfavorable histologic subtypes such as the tall-cell variant (11, 13). These findings have raised concerns about potentially distinct tumor biology in GD-associated PTC. However, our findings differ in that we observed a higher proportion of papillary microcarcinomas (PMCs) and significantly smaller tumor sizes in the GD group, with no observed lymph node metastases. This discrepancy may reflect variations in diagnostic intensity, surgical thresholds, or institutional management protocols, rather than true biological differences. For instance, GD patients may undergo thyroidectomy for hyperthyroidism management, resulting in a higher detection rate of subclinical or incidental microcarcinomas.

Recent large-cohort studies continue to emphasize the heterogeneity in clinical behavior of PTC in GD. Kim *et al.* (24), in a multicenter analysis, found no consistent relationship between GD and adverse PTC outcomes after adjusting for known prognostic variables, suggesting that previously reported associations may be confounded by differences in clinical surveillance or surgical extent. Similarly, Gopinath *et al.* (13) observed that while some GD patients harbored aggressive tumors, the overall outcomes, including recurrence and survival, were comparable to non-GD PTC cases when adjusted for tumor stage and treatment modality.

As the presence of concomitant nodules in GD increases the risk of thyroid cancer, performing US in all GD patients allows the visualization of small nodules not detected by palpation or thyroid scintigraphy (9). In our study, when 212 patients operated on for GD were evaluated, it was observed that the rate of concomitant PTC was significantly higher in the presence of advanced age and concomitant nodules. Therefore, we think that it is important to investigate thyroid nodules accompanying US when planning treatment for GD.

Limitations

This study is limited by its retrospective, single-center design, which may introduce selection bias and unmeasured confounding. The unequal group sizes, particularly the smaller GD cohort, may have reduced the power to detect differences in low-frequency outcomes such as recurrence. The relatively short median follow-up period (33–37 months) may not fully capture late recurrences, which are common in differentiated thyroid carcinoma. A post hoc power analysis indicated approximately 33% power to detect recurrence differences, suggesting a potential risk of type II error. To strengthen these findings, future research should include larger, balanced cohorts with standardized, long-term follow-up in a multicenter, prospective design.

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Conclusion

PTC in patients with Graves' disease was more often microcarcinoma and exhibited less aggressive histopathological features compared to euthyroid cases. While recurrence rates were similar, these results reflect associations and should be interpreted with caution due to limited follow-up and group imbalance. Careful nodule evaluation in GD remains important, and further long-term, prospective studies are needed to clarify prognostic implications.

Declaration of interest

The authors declare no conflict of interest related to this study. No financial or personal relationships with other individuals or organizations have inappropriately influenced, or could be perceived to influence, the work reported in this paper.

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