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Original research

Characteristics, staging and outcomes of differentiated thyroid cancer in patients with and without Graves' disease

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ABSTRACT

Background: The incidence of thyroid cancer has increased over the last three decades with studies showing incidence of thyroid cancer is higher among patients with Graves' Disease (GD) when compared to Toxic multinodular goiter.[1] We conducted a retrospective study to further investigate characteristics and outcomes in patients with thyroid cancer and GD.

Methods: We retrospectively reviewed 62 patients with a diagnosis of Differentiated Thyroid Cancer (DTC). We compared age at diagnosis, type, size of tumor, radioactive iodine (RAI) use, and DTC recurrence amongst patients with GD, non-GD patients. We used Chi-square to test for independence among categorical variables at a nominal level of 0.05; comparison was based on *t*-test.

Results: Out of 62 patients, 29 patients had GD and DTC (47%). 94% had papillary thyroid cancer. Patients with GD were diagnosed with DTC at a younger age (mean 46 years) in comparison to patients without GD (mean 53 years). There was no difference in the type of DTC. Patients with GD had significantly smaller tumor size (mean size 1.035 cm; p value = 0.002), more Stage 1 and 2 compared to patients without GD (p-value = 0.009). Both groups of patients had similar rates of recurrence on follow up and RAI use.

Conclusion: We found patients with GD had smaller tumor size, early-stage DTC when compared to patients without GD and potentially favorable prognosis. More data is needed to understand whether this is due to pathogenesis like Graves antibodies promoting tumor formation or merely earlier detection of DTC in GD.

Introduction

Thyroid cancer is the most common endocrine malignancy and incidence of thyroid cancer in US and worldwide has increased 300% over the past three decades. [2] In the past, hyperthyroidism was thought to be protective mechanism due to suppressed TSH. Graves' disease (GD) is one of the most common causes of hyperthyroidism and is associated with elevated Thyroid Stimulating Antibodies (TSI). The coexistence of thyroid cancer with GD is well known, and the American Thyroid Association (ATA) states that thyroid cancer occurs in up to 2% of patients with GD. [3] The correlation between GD and DTC is controversial. Recent studies show that incidence of thyroid cancer is higher in patients with GD when compared to the patients with toxic nodular goiter. [1] Prior studies demonstrated thyroid cancer in patients with GD was more aggressive, and it may be due to the stimulatory effect of TSI. [1,4] However, more recent studies did not find a correlation between GD and aggressiveness of thyroid cancer. [5–6] We conducted a retrospective study to examine the characteristics and outcomes of DTC in patients with and without GD and evaluate if DTC is more aggressive in patients with GD.

Methods

This was a retrospective chart review of 62 patients with a diagnosis of DTC with or without GD. The study was reviewed and approved by the Institutional Review Board. The study was completed in accordance

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with the Declaration of Helsinki as revised in 2013. Informed consent by patients was not required. 29 patients with both DTC and GD ever seen and treated at (XXX) between 1974 and 2022 were identified from the database by using the ICD-10 codes for DTC and GD. They were compared to 33 patients with a diagnosis of DTC without GD that were randomly selected from the database. Demographic and clinical data was collected. To assess the aggressiveness of DTC we compared age at diagnosis, type and size of tumor, radioactive iodine (RAI) use, and DTC recurrence amongst patients with GD with non-GD patients. Major demographic factors have been summarized using mean with a range. We used the Chi-square to test for independence among the categorical variables at a nominal level of 0.05. The comparison of continuous variables was based on the *t*-test.

Results

The mean age of patients was 50 years (range 23 – 86 years). Out of 62 patients, 29 patients had GD and 33 patients did not have GD. 93% (58 out of 62 patients) of patients had Papillary Thyroid Cancer (PTC) and 3 patients had Follicular Thyroid Cancer (FTC). The mean tumor size was 1.8 cm (range 0.09–7.5 cm). 33 patients out of 58 patients with PTC had data about the variant of PTC. Majority of the patients had classic variant (24 patients), 1 had columnar, 1 follicular, 2 hurthle cell changes, 3 oncocytic and 2 tall cell variants. 48 patients (77 %) of the patients had Stage 1 and 2 DTC and 13 patients (21%) had Stage 3 and 4 DTC. Follow-up duration ranged from 9 months to 49 years. 11% of patients had local or distant recurrence of DTC on follow up and 29% received RAI. 4 patients had distant metastases on follow up and these patients had tall cell, oncocytic and hurthle cell variants. Patients with GD were diagnosed with DTC at a younger age (mean age 47 years) when compared to the patients without GD (mean age 53 years), but this was not statistically significant (p-value = 0.105). Patients with GD had significantly smaller tumor size (mean size 1.035 cm; p value = 0.002) and more Stage 1 and 2 DTC (27 patients) compared to patients without GD (21 patients; p-value = 0.009). There was no difference in patients with GD versus non-GD regarding the type of DTC (p value = 0.507), recurrence rate (p value = 0.610) and the need for RAI treatment (p value 0.426) (Table 1). The presence of GD in patients with DTC was associated with a significantly smaller initial tumor size (Fig. 1: P value = in 0.002).

Table 1
Results.

N = 62			
	GD	Non-GD	P-value*
Mean age (years)	47 (23–73)	53 (27–78)	0.105
Mean Tumor Size (cm)	1.03 (0.10–5.80)	2.54 (0.09–7.60)	<0.05
Tumor type			0.507
Papillary	27	31	
Follicular	1	2	
Stage of DTC			<0.05
I and II	27	21	
III and IV	2	6	
Recurrence			0.610
Yes	4	3	
No	22	25	
RAI			0.426
Yes	7	11	
No	22	22	

*P-value of < 0.05 considered significant.

Discussion

Graves' disease is the most common cause of hyperthyroidism in the United States. [3] Hyperthyroid conditions such as GD were once thought to be protective against thyroid cancer; however, recent studies suggest an increased prevalence of DTC among those with GD. [7] The incidence of thyroid carcinoma associated with GD has been reported to range from 1.8% to 6.5% in recent studies. [1,6,8] The annual incidence of thyroid cancer in GD in one study was reported as 175 per 100,000 [4]. Another longitudinal cohort study found the incidence of developing cancer in GD was 4.92 per 1000 person- years [9].The presence of solitary or multiple thyroid nodules is a common finding among those with thyroid disorders. A recent *meta*-analysis published in 2019 involving 2,582 patients treated with surgery found that the presence of at least one thyroid nodule in patients with GD was associated with higher risk for thyroid cancer (odds ratio 5.3) [10]. A subgroup analysis showed no difference in thyroid cancer risk in patients with GD according to the number of nodules (solitary versus multiple) (OR 1.4, 95% CI 0.9–2.3) [10].

Correlation of GD with DTC and the pathogenesis remains controversial. Although the pathogenesis of thyroid cancer in patients with Graves' disease is not well understood, it is postulated that the probable mechanism of increased prevalence of thyroid cancer in patients with GD is primarily the binding of Thyroid Receptor Ab to thyrotropin receptor, which promotes tumor formation, angiogenesis, and further progression of the invasiveness of cancer [11]. Chronic immune processes appear to be linked to tumorigenesis as the gland microenvironment has higher infiltrating immune competent cells, cytokines, and growth factors, that are essential components of carcinogenesis. Some thyroid carcinomas retain their TSH receptors [12] and TSH-dependent adenylate cyclase [13], therefore likely more responsive to TSI. In vitro studies done from IgG isolated from serum of patients with GD have shown that thyroid carcinoma cells respond to TSI [14]. A study of incidental thyroid cancer among 245 patients with GD found no correlation between increased incidence of TSI ab and prevalence of DTC with an AUC curve of 0.55 (95% CI: 0.46, 0.64). [15] Another study of 10 patients did not show role of TSI in growth of metastatic lesions [16].

PTC is the most common type of DTC found in patients with GD and is usually mutifocal. [1,6,17]A small study of 21 patients with non-occult DTC in GD disease found PTC in 91.4% of patients. A multicenter, retrospective study of 193 patients with GD found classic variant of PTC was most common (57.5%), tall cell variant present in 13.5%, follicular variant of PTC in 25.9% and rate of multifocality was significantly more in patients with GD compared to patients without GD[17]. Microcarcinomas have been reported to be significantly more frequent in patients with GD (60% vs 37%, p < 0.0001) [18]. In the same study, rate of recurrence/persistent disease at the end of 7.5 years was reported to be significantly higher in DTC/GD group if the tumor was ≥1 cm (24% vs. 12% in the DTC/GD − group).[18]Mean age of incidence of DTC in association with GD has been reported to occur about a decade earlier in comparison to DTC without GD in prior studies [4,15]. In our current study patients with GD were diagnosed with DTC at a younger age (mean age 47 years) when compared to patients without GD (mean age 53 years) but it was not statistically significant (p-value of 0.105).

DTC prognosis in GD is controversial with some studies showing GD affects the prognosis of DTC while others indicating that thyroid cancer in GD is not more aggressive than in euthyroid patients. [4,6,18–20] Study of 22 patients with DTC and hyperthyroidism found that patients with DTC had more locally invasive (61.5% vs 11.1%), metastatic to lymph node (61.5% vs 11.1%), metastasis to distant sites(23% vs 0%) rates compared to patients with autonomous thyroid nodules. [18] Among 21 patients with non-occult DTC in GD evaluated between 1982 and 1994 the rate of distant metastases and relapse was higher in patients with GD and the cumulative risk for recurrent or progressive distant metastases was about 3 times higher in GD compared to non-GD (odds ratio = 3.14) [4]. When followed up for a longer time, persistent/

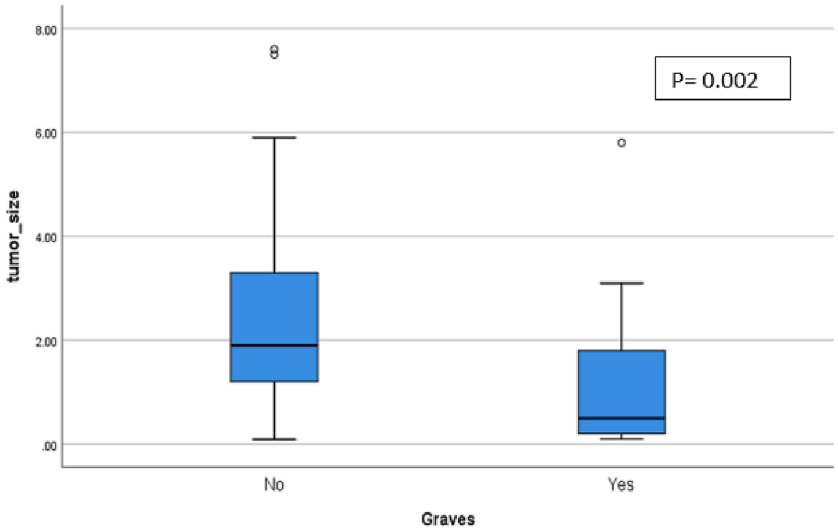

Fig. 1. Association of Graves' Disease with tumor size.

recurrent disease was more common in DCT -GD group compared to euthyroid DTC group and the DTC-GD group also had a shorter disease free survival. [19] In contrast, a retrospective study of 509 patients with GD and DTC found that disease free survival was better in patients with DTC and GD at 20 years follow up (99 vs 93%; $p < 0.001$). [20] A retrospective study of children and young adults with DTC/GD and DTC/-GD found no significant difference in disease burden or extent of metastases, long term disease outcome survival in both the groups. [6] Another analysis of incidentally discovered DTC among patients with euthyroid goiter compared with GD found that there was a trend towards increased extension to extrathyroidal tissues, central and lateral lymph node metastasis among patients with GD however this was not statistically significant. [15] A matched cohort study of surgically treated GD patients found the incidence of aggressive carcinomas in 13% patients with GD vs 20% in control with no difference in outcome. [21] In a recent South Korean study of 262 patients with GD and DTC no difference in thyroid cancer aggressiveness, clinical outcomes or prognosis was observed among those with nodular and non-nodular GD [22].

In our study, patients with GD had significantly more Stage 1 and 2 DTC compared to patients without GD (p- value 0.009) indicating favorable prognosis. The presence of GD was associated with smaller initial tumor size ($p < 0.002$). Routine US imaging with aspiration helps early diagnosis of DTC in GD. Our findings indicate that DTC is found earlier when compared to non-GD patients and that can be a result of incidental early detection of DTC due to routine ultrasound imaging. Many patients undergo total thyroidectomies for GD treatment, and we might be detecting early-stage DTC incidentally. A study to look if Thyroid Stimulating antibodies have a role to play in the pathogenesis of DTC in GD would be interesting. Pre-operative assessment and findings of nodules should consider risk of cancer in GD patients. A major limitation of the study is that it represents patients from a single center, has a small sample size and is retrospective.

Conclusion

In conclusion, we found that patients with GD had smaller tumor size and earlier stage DTC at time of diagnosis when compared to patients without GD. More data is required to understand whether the finding is due to pathogenesis like Graves antibodies promoting tumor formation or merely due to earlier detection of DTC in GD patients. Our retrospective study revealed most GD patients had an early-stage DTC, a low rate of recurrence, and potentially favorable prognosis. These patients should be treated similarly to other DTC patients.

CRediT authorship contribution statement

Chaitra Gopinath: Writing – original draft. **Hanna Crow:** Writing – original draft. **Sujata Panthi:** . **Leonidas Bantis:** Software, Methodology. **Kenneth D. Burman:** Writing – review & editing. **Chitra Choudhary:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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