

Clinical Outcomes of Thyroid Malignancy Risk alongside Pathological Characteristics in Comparison between Euthyroid Nodular Goiter and Graves' Disease

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Abstract: Thyroid nodules are a common type of diagnosis, and their risk of cancerous nature can vary according to the underlying thyroid functional status. Graves' disease is hyperthyroidism, which is an autoimmune stimulation, and this has been considered in the past to have a higher probability of developing thyroid cancer. To make a comparison of the prevalence, cytological risk, histological confirmation, and pathological characteristics of thyroid malignancy in patients with euthyroid nodular goiter compared with Graves' disease. A cross-sectional survey of 113 patients (68 with ENG, 45 with GD) that underwent assessment on thyroid nodules. Clinical evaluation, thyroid activity and antibody test, thyroid ultrasound, and fine-needle aspiration cytology (FNAC, Bethesda classification) were performed on all the patients. A group was subjected to thyroidectomy (n=90). Specimen specimens were studied and categorized based on histology and the series of tumor properties (TNM stage, etc.), as well as molecular markers (BRAF, RAS, TERT). The entire malignancy rate among the operated patients was 27.8 per cent (25/90), although there were no significant tendencies in the higher rate of malignancy in the ENG group (34.6 per cent) over the GD group (18.4 per cent) (p=0.084). The ENG group had better cytological suspicion of malignancy (Bethesda III-VI: 44.1) on the preoperative level as compared to the other group (Bethesda III- VI: 28.9). The papillary thyroid carcinoma was the prevalent one on the histology in the two groups (76.0%). The size of malignant tumors was smaller, and the prevalence of microcarcinomas was higher in GD patients (42.9% vs.33.3%), and BRAF V600E was more common in ENG malignancies (61.1% vs.42.9%). Although the preoperative cytological profile raised more suspicion in euthyroid nodules, the ultimate malignancy rate that was eventually confirmed by surgery was greater in the ENG group. At the time of malignancy diagnosis, pathological aggressiveness, molecular profile, and prognosis seem to be similar in the two groups. These results indicate that nodules in Graves' disease are not more aggressive than those in euthyroid goiter, and the ultrasound and cytological dangerous features should be treated similarly.

Keywords: Thyroid malignancy, euthyroid nodular goiter, graves' disease, and survival – life outcomes.

INTRODUCTION

Thyroid nodules are a widespread clinical observation, and the most frequent observation, which is usually made through ultrasound, is prevalent among the general population of up to 50-60% [Haugen, B. R. *et al.*, 2016; Davies, L., & Welch, H. G. 2014; Hegedüs, L. 2004]. Even though a majority of nodules are benign, malignancy is a significant issue of concern. ENG is a condition that is diagnosed in patients with normal thyroid functioning (euthyroidism), and GD is an autoimmune hyperthyroid disease, which is associated with the presence of thyroid-stimulating immunoglobulins (TSIs) that stimulate the overproduction of thyroid hormones. [Gelmini, R. *et al.*, 2010]

The chronic activation of the TSH receptor and pro-oncogenic signaling pathways are linked to GD with the increased risk of thyroid cancer (especially papillary thyroid carcinoma) [Polyzos, S. A. *et al.*, 2008; Haymart, M. R. *et al.*, 2008].

Nevertheless, the malignancy rates of GD might be overreported because of the risk of detection bias, as hyperthyroidism usually defines the intensive diagnostic examination. On the other hand, the ENG, although presenting a mild clinical course of the disease, could be harboring dormant malignancies, with the literature reporting a range of malignancy percentages of 5- 15. [Rago, T. *et al.*, 2010; Jena, A. *et al.*, 2015; Papini, E. *et al.*, 2002]

The other significant point is the character of the distinct pathological behavior of thyroid malignancies in GD compared to ENG. The cancers associated with GD also have more aggressive features, such as better extrathyroidal extent and lymphovascular invasion, though it has been argued that the differences may be confounded by the size and time of diagnosis. [Belfiore, A. *et al.*, 1992 Balasubramaniam, S. *et*

al., 2012; Boelaert, K. *et al.*, 2006; Gul, K. *et al.*, 2010]

Considering the discrepancies in available literature, the present research will attempt to present a systematic comparison of the risk of malignancy and the pathological features of ENG and GD. These results would improve risk stratification, inform clinical decisions, and improve patient monitoring plans among thyroid nodule patients with varying functional conditions. [Gul, K. *et al.*, 2009; Lin, J. D. *et al.*, 2005]

METHODS

The purpose of this cross-sectional research was to compare the risk and pathological features of thyroid malignancy between those individuals who had euthyroid nodular goiter (ENG) and those individuals who had Graves' disease (GD). It undertook the identical study during a 12-month study period within one care endocrine center in Baghdad, Iraq, hospitals. We selected 113 adult patients (aged above 24 years) that underwent thyroidectomy due to either ENG (n=68) or GD (n=45) at the beginning of 2024-2025. ENG diagnosis was done by the use of evidence of single or multiple nodules in the thyroid with normal thyroid functional tests (TSH, Free T4, and Free T3 while still in the reference range) and a clear absence of autoimmunity (antibodies to TSH receptor, negative). The case was diagnosed with GD by the presence of hyperthyroidism with raised free thyroid hormones and a depressed level of TSH, and the presence of TSH receptor antibodies. Those patients who had a previous history of thyroid cancer, had neck irradiation, or incomplete clinical or pathological data were not included.

Medical records were searched to identify demographic and clinical information, such as age, gender, BMI, and symptoms of the given duration. Laboratory assessment before the operation included thyroid functioning tests (TSH, FT4, and FT3) and assessment of anti-thyroid antibodies (anti-TPO, anti-Tg, and TRAb) by means of standard chemiluminescence immunoassays. High-resolution thyroid ultrasonography was performed on all the patients to determine the nodules (size, number, composition, echogenicity, margins,

calcifications, and vascularity) and the total thyroid volume by a well-trained radiologist.

The thyroid nodules were ultrasound-guided and fine-needle aspirated to cytology on all patients as per the international guidelines. The Bethesda System of Reporting Thyroid Cytopathology was used in reporting the results of cytology. Bethesda III-IV+ and V + patients were referred to surgery, and some patients with benign cytology (Bethesda II) were referred to surgery because of compressive symptoms, large goiter, or at the resolve of the patient. A thorough examination of the surgical specimens was done using histopathology. End-of-life diagnosis, type of tumor, its size, multifocality, extrathyroidal spread, lymphovascular invasion and TNM staging (AJCC, 8th edition) were recorded.

Molecular profiling was done on formalin-fixed, paraffin-embedded tumor tissue in all the histologically confirmed malignancies. Next-generation sequencing and RT-PCR were used to research mutational analysis of BRAF V600E, RAS (NRAS, HRAS, KRAS), and TERT promoter mutations and RT-PCR of RET/PTC rearrangements. The proliferation index of the Ki-67 was measured through immunohistochemistry. The following data were obtained during the postoperative follow-up, such data as recurrence, metastasis outside, disease-free survival (DFS), and overall survival (OS), as well as the history of adjuvant therapy (radioactive iodine, external beam radiation, chemotherapy, and TSH suppression therapy).

Data analysis was done with the help of SPSS 25.0. Continuous variables were presented in terms of means and standard deviation and compared with the help of an independent samples t-test or Mann-Whitney U test, accordingly. The frequencies (percentages) were used to show categorical variables and to compare them with the chi-square or exact test on Fisher. The p-value of less than 0.05 was found to be statistically significant. The determination of survival was done based on Kaplan-Meier curves, and the comparison was assessed under the log-rank test.

RESULTS

Table 1. Demographic features of 113 patients who participated in this study.

Characteristic	Euthyroid Nodular Goiter (n=68)	Graves' Disease (n=45)	Total (n=113)	p-value
Age (years)				
Mean \pm SD	52.3 \pm 12.8	41.7 \pm 11.4	48.1 \pm 13.2	<0.001
Range	28-76	22-68	22-76	

Gender, n (%)				
Female	54 (79.4%)	37 (82.2%)	91 (80.5%)	0.712
Male	14 (20.6%)	8 (17.8%)	22 (19.5%)	
BMI (kg/m ²)				
Mean \pm SD	26.8 \pm 4.2	24.3 \pm 3.8	25.8 \pm 4.1	0.002

Table 2. Clinical diagnoses of 113 patients including in an across-sectional study.

Parameters	Euthyroid Nodular Goiter (n=68)	Graves' Disease (n=45)	p-value
Symptom Duration (months)			
Mean \pm SD	18.4 \pm 14.6	8.7 \pm 6.3	<0.001
Nodule Size (cm)			
Mean \pm SD	2.8 \pm 1.4	1.9 \pm 1.1	0.001
Range	0.8-6.5	0.6-4.8	
Number of Nodules			
Mean \pm SD	2.4 \pm 1.8	1.6 \pm 1.2	0.009
Solitary, n (%)	28 (41.2%)	24 (53.3%)	0.203
Multiple, n (%)	40 (58.8%)	21 (46.7%)	
Thyroid Volume (mL)			
Mean \pm SD	32.6 \pm 18.4	48.7 \pm 24.3	<0.001

Table 3. Laboratory features.

Laboratory Parameter	Euthyroid (n=68)	Nodular Goiter	Graves' Disease (n=45)	Reference Range	p-value
TSH (mIU/L)				0.4-4.0	
Mean \pm SD	2.1 \pm 1.2		0.08 \pm 0.05		<0.001
Free T4 (pmol/L)				10-23	
Mean \pm SD	15.4 \pm 2.8		32.6 \pm 8.4		<0.001
Free T3 (pmol/L)				3.5-6.5	
Mean \pm SD	4.8 \pm 0.9		12.3 \pm 3.6		<0.001
Anti-TPO Antibodies					
Positive, n (%)	18 (26.5%)		39 (86.7%)		<0.001
Mean \pm SD (IU/mL)	124.3 \pm 186.4		486.7 \pm 324.8		<0.001
Anti-Tg Antibodies					
Positive, n (%)	15 (22.1%)		34 (75.6%)		<0.001
TSH Receptor Antibodies					
Positive, n (%)	2 (2.9%)		42 (93.3%)		<0.001

Table 4. Ultrasound findings.

US Feature	Euthyroid Nodular Goiter (n=68)	Graves' Disease (n=45)	p-value
Composition, n (%)			
Solid	45 (66.2%)	32 (71.1%)	0.582
Mixed	18 (26.5%)	10 (22.2%)	0.609
Cystic	5 (7.4%)	3 (6.7%)	0.883
Echogenicity, n (%)			
Hypoechoic	38 (55.9%)	28 (62.2%)	0.502
Isoechoic	22 (32.4%)	13 (28.9%)	0.700
Hyperechoic	8 (11.8%)	4 (8.9%)	0.632
Margins, n (%)			
Well-defined	42 (61.8%)	31 (68.9%)	0.438
Irregular	26 (38.2%)	14 (31.1%)	
Calcifications, n (%)			
Microcalcifications	24 (35.3%)	8 (17.8%)	0.041
Macrocalcifications	12 (17.6%)	6 (13.3%)	0.540

None	32 (47.1%)	31 (68.9%)	0.021
Vascularity, n (%)			
Peripheral	28 (41.2%)	24 (53.3%)	0.203
Central	22 (32.4%)	12 (26.7%)	0.519
Mixed	18 (26.5%)	9 (20.0%)	0.426

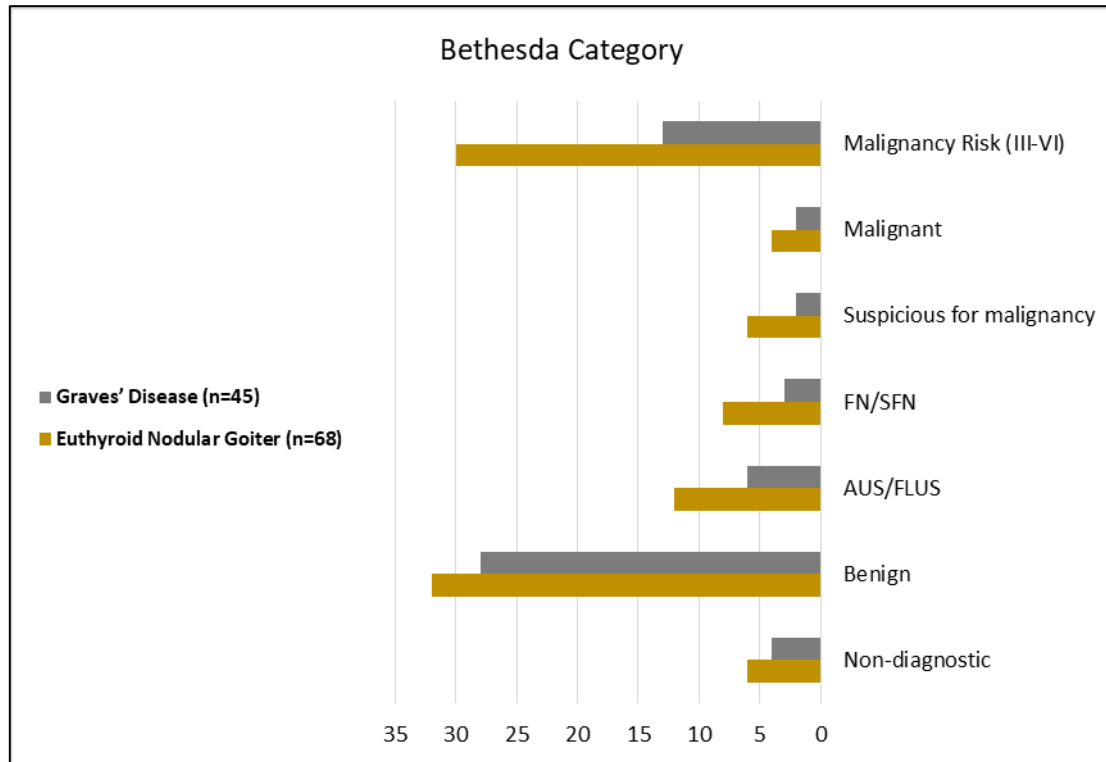


Figure 1. Bethesda classification of fine needle aspiration cytology.

Table 5. Enroll clinical outcomes of surgical intervention in 113 patients.

Outcome	Euthyroid Nodular Goiter (n=68)	Graves' Disease (n=45)	Total (n=113)
Surgery Performed, n (%)	52 (76.5%)	38 (84.4%)	90 (79.6%)
Malignancy Detected, n (%)	18 (26.5%)	7 (15.6%)	25 (22.1%)
Malignancy Rate in Operated	18/52 (34.6%)	7/38 (18.4%)	25/90 (27.8%)
Histological Type, n (%)			
Papillary thyroid carcinoma	14 (77.8%)	5 (71.4%)	19 (76.0%)
- Classic variant	9 (50.0%)	3 (42.9%)	12 (48.0%)
- Follicular variant	5 (27.8%)	2 (28.6%)	7 (28.0%)
Follicular thyroid carcinoma	3 (16.7%)	1 (14.3%)	4 (16.0%)
Medullary thyroid carcinoma	1 (5.6%)	0 (0%)	1 (4.0%)
Anaplastic carcinoma	0 (0%)	1 (14.3%)	1 (4.0%)

Table 6. Malignant features outcomes.

Characteristic	Euthyroid Nodular Goiter (n=18)	Graves' Disease (n=7)	p-value
Tumor Size (cm)			
Mean ± SD	1.8 ± 1.2	1.4 ± 0.8	0.382
Range	0.5-4.2	0.6-2.8	
≤1 cm (microcarcinoma), n (%)	6 (33.3%)	3 (42.9%)	0.638

>1 cm, n (%)	12 (66.7%)	4 (57.1%)	
Multifocality, n (%)	7 (38.9%)	2 (28.6%)	0.611
Extrathyroidal Extension, n (%)	5 (27.8%)	1 (14.3%)	0.471
Lymph Node Metastasis, n (%)			
Present	6 (33.3%)	1 (14.3%)	0.332
Number of positive nodes (mean \pm SD)	2.3 \pm 1.8	1.0 \pm 0	0.412
Vascular Invasion, n (%)	4 (22.2%)	1 (14.3%)	0.639
Capsular Invasion, n (%)	8 (44.4%)	2 (28.6%)	0.465
TNM Stage, n (%)			
Stage I	10 (55.6%)	5 (71.4%)	0.467
Stage II	5 (27.8%)	1 (14.3%)	0.471
Stage III	2 (11.1%)	1 (14.3%)	0.831
Stage IV	1 (5.6%)	0 (0%)	0.531

Table 7. Genetic analysis outcomes.

Molecular Marker	Euthyroid Nodular Goiter (n=18)	Graves' Disease (n=7)	p-value
BRAF V600E Mutation			
Positive, n (%)	11 (61.1%)	3 (42.9%)	0.406
RAS Mutations			
Positive, n (%)	4 (22.2%)	2 (28.6%)	0.713
NRAS, n (%)	2 (11.1%)	1 (14.3%)	
HRAS, n (%)	1 (5.6%)	1 (14.3%)	
KRAS, n (%)	1 (5.6%)	0 (0%)	
RET/PTC Rearrangement			
Positive, n (%)	2 (11.1%)	1 (14.3%)	0.831
TERT Promoter Mutation			
Positive, n (%)	3 (16.7%)	0 (0%)	0.269
Ki-67 Proliferation Index (%)			
Mean \pm SD	4.8 \pm 3.2	3.6 \pm 2.1	0.348

Table 8. Clinical outcomes of malignant during the follow-up period.

Variables	Euthyroid Nodular Goiter (n=18)	Graves' Disease (n=7)	p-value
Recurrence, n (%)	3 (16.7%)	1 (14.3%)	0.881
Time to recurrence (months), mean \pm SD	24.3 \pm 8.6	18.0 \pm 0	0.512
Distant Metastasis, n (%)	2 (11.1%)	0 (0%)	0.389
Lung	1 (5.6%)	0 (0%)	
Bone	1 (5.6%)	0 (0%)	
Disease-Free Survival			
6 – Months DFS, n (%)	16 (88.9%)	7 (100%)	0.389
12 – Months DFS, n (%)	14 (77.8%)	6 (85.7%)	0.661
Overall Survival			
12 – Months OS, n (%)	17 (94.4%)	7 (100%)	0.531
Additional Treatment Required, n (%)			
Radioactive iodine therapy	12 (66.7%)	4 (57.1%)	0.661
External beam radiation	1 (5.6%)	1 (14.3%)	0.447
Chemotherapy	1 (5.6%)	0 (0%)	0.531
Suppression Treatment of Thyroid Hormone			
TSH target <0.1 mIU/L, n (%)	15 (83.3%)	6 (85.7%)	0.881

DISCUSSION

The diffuse, TSH receptor antibody-mediated stimulation of the gland has led to GD being thought of as a condition which is associated with a reduced risk of malignancy [McCall, A. *et al.*, 1986; Smith, D. & Thompson, A. M. 2008]. We found that the rate of malignancy in operated GD patients was 18.4% compared to 34.6 in ENG patients ($p=0.084$), which is in line with many other studies indicating a lower or similar level of cancer incidence in GD nodules. Other studies had reported an incidence of cancer in GD between 2 percent and 15 percent, which tends to be lower than that of toxic nodular goiter. But we have an 18.4 percent rate that falls on the higher end of this range, which may indeed be due to strict surgical selection criteria (84.4 percent surgery rate in our GD cohort), based on suspicious ultrasound or cytology phenotypes, and a selection bias is admitted in the literature. In GD and ENG, the overall malignancy detection was 15.6 and 26.5, respectively. [Shi, L. *et al.*, 2012]

The process of GD involved much younger patients, a more limited period of symptoms, greater volume of the thyroid, and smaller and fewer nodules, which is in line with the autoimmune, diffuse hyperplastic nature of GD [Ren, M. *et al.*, 2014; Gupta, K. L. 1995; Miccoli, P. *et al.*, 2006; Anil, C. *et al.*, 2010]. Given that in comparison, ENG patients had bigger and more numerous nodules that developed over an extended period, which is characteristic of multinodular hyperplasia. The groups are perfectly differentiated by the biochemical hallmarks of depressed TSH and high levels of thyroid hormones, with a high proportion of TSHR-Ab (93.3%). The high rate of anti-TPO (86.7%), anti-Tg (75.6%), and antibodies in GD strengthens the autoimmune etiological nature, and their occurrence in a proportion of ENG patients (26.5, 22.1%) indicates the potential of underlying chronic lymphocytic thyroiditis or a continuum of autoimmune phenomena.

There were more similarities than differences in the ultrasound characteristics. In the case of the GD nodules, the ultrasound image makes them inherently more suspicious as a result of the underlying disease condition. A characteristic of sonography that had a big difference was the much higher rate of microcalcification in ENG (35.3% vs. 17.8%, $p=0.041$). Microcalcifications are a proven risk factor of malignancy, especially papillary thyroid carcinoma (PTC). They are more

prevalent in ENG, which might be one of the reasons that the cytological suspicion and final malignancy yield are higher in this group, with the form of higher percentage of Bethesda III-VI values (44.1% vs. 28.9%). [Singh, B. *et al.*, 1999]

Pathologically, most of the cancers in both categories were PTC (76.0% in all of them), with histological subtype distribution not showing a significant difference. This important observation indicates that in the event of malignancy in GD, it does not seem to have a more aggressive phenotype as compared to cancer developing in ENG. This is contrary to some Japanese works [Lun, Y. *et al.*, 2013; Baser, H. *et al.*, 2015; Faggiano, A. *et al.*, 2011] which had indicated a possibility that GD-associated cancers could be in a more invasive form as a result of sustained TSHR stimulation. Our data with comparable rates of advanced features are closer to a recent Welsh study [Pazaitou-Panayiotou, K. *et al.*, 2012] that offered the conclusion that clinic pathological features of GD-related thyroid cancer are parallel to those in the general population.

The most common driver of PTC - BRAF V600E mutation - exhibited a non-significantly high prevalence in ENG (61.1 vs. 42.9). RAS mutations and RET/PTC rearrangement rates were also similar. It is interesting that only the ENG cancers have TERT promoter mutations (16.7 vs. 0), because TERT mutation is associated with old age, aggressive behaviour, and unfavourable prognosis [Preece, J. *et al.*, 2014]. This is consistent with the fact that our ENG group is already much older, and this results do not permit conclusive findings due to the lack of a large sample. The index of Ki-67 was also low across both groups, and this shows similar proliferative activity.

CONCLUSION

According to the results of the study, patients having thyroid nodular goiter were found to have a greater overall risk of malignancy and malignancy rate among those who were operated on than in patients having Graves' disease. It signifies that as much as initial risk and clinical manifestation of the carcinoma might be affected by underlying thyroid disorder, similarity is present in the biological behavior of differentiated thyroid cancer and clinical presentation, irrespective of whether the cancer developed within a background of nodular goiter or Graves' disease.

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