CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
https://cajmns.casjournal.org/index.php/CAJMNS
Volume: 07 Issue: 02 | April 2026 ISSN: 2660-4159

Article

Incidental Papillary Thyroid Carcinoma: Clinical and Histopathological Comparison between Graves' disease and Euthyroid Nodular Goiter

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Abstract: Incidental papillary thyroid carcinoma (IPTC) is commonly to be detected during thyroidectomy in the case of benign thyroid lesions. Two of the common underlying pathologies are the disease known as Graves' disease (GD) and euthyroid nodular goiter (ENG). This purpose study aimed to determine the incidence, histopathology, and clinical outcome of IPTC in patients undergoing thyroidectomy with GD compared to those having ENG. The study based on the approach methodology was a cross-sectional study about 117 patients who had undergone a thyroidectomy, that is, 53 patients with Graves' disease and 64 patients with euthyroid nodular goiter. The groups were compared in terms of clinical, demographic, and histopathological data. Assessed parameters were tumor size, multifocality, extrathyroidal extension (ETE), tumor lymph node metastasis (LNM), histological variants, preoperative TSH level, post-operative complications, and recurrence rates, with a mean follow-up of 12 months between January 2024 and January 2025. In addition, incidental papillary thyroid carcinoma (IPTC) was found in 37.7% of the patients with Graves' disease (20/53) and 25.0% of the patients with ENG (16/64). Multifocality (30.0% vs. 18.8%), ETE (25.0% vs. 12.5%), and LNM (40.0% vs. 18.8%), which were not statistically significant (p-values 0.45, 0.29, and 0.10, respectively), exhibited numerically higher rates in GD-associated IPTC. It suppressed preoperative TSH (below 0.1 mIU/L) in 67.9% of GD patients and in 3.1% of ENG patients. There were similar rates of complications in the postoperative period, such as hypocalcemia and nerve injury. In conclusion, incidental papillary thyroid carcinoma (IPTC) is more common in Graves' disease patients than in patients with euthyroid nodular goiter. Even though GD-associated IPTC is more trended towards more aggressive histopathological features, nevertheless, both groups had shown very good disease-free survival and similar results of surgery. In addition, the results indicate that although GD could be linked to increased frequency of IPTC, clinical handling of IPTC and prognosis in GD and ENG patients are positive and comparable.

Keywords: Papillary Thyroid Carcinoma; Histopathological Outcomes; Post – Operative Complications.

Citation: Alkhirsan, Z. M. J & Gheni, M. A. Incidental Papillary Thyroid Carcinoma: Clinical and Histopathological Comparison between Graves' disease and Euthyroid Nodular Goiter. Central Asian Journal of Medical and Natural Science 2026, 7(2), 122-129

Received: 10th Nov 2025
Revised: 21th Dec 2025
Accepted: 04th Jan 2026
Published: 18th Feb 2026

1. Introduction

The most common endocrine malignancy is papillary thyroid carcinoma (PTC), which is commonly found incidentally[1]. Incidentaloma refers to a neoplasm that is identified after surgery when the thyroid tissue was removed due to an ostensibly benign provocation, and not by suspicion or screening[2]. The approach to the management of these incidentalomas has emerged as a clinical dilemma with emphasis on balancing between the risk of excessive treatment and the possibilities of aggressive malignancy [3].

Graves' disease is an autoimmune pathology, which is also typified by the presence of thyroid-stimulating immunoglobulins that result in the sustained stimulation and growth of the thyroid follicular cells[4]. This constant trophic stimulation has been supposed to be a tumorigenic catalyst, thus increasing the chances of malignant transformation and potentially enhancing a more aggressive phenotype[5]. Therefore, conventional wisdom has argued that carcinoma concomitant to the Graves' disease is a poorer prognostic agent. Conversely, euthyroid nodular goiter, which is often met by a multifactorial influence (inadequate iodine or familial predisposition), creates a more common but physiologically calm environment to the accidental discovery of carcinoma [6].

The development of papillary thyroid carcinoma when occurring in the context of Graves' disease is usually more advanced with higher frequencies of multifocality and lymphovascular invasion, which can be mediated by the TSH-activating effects of the mitogenic activity [7, 8]. However, this apparent aggressiveness could be explained by the presence of detection bias, of which is caused by increased surgical examination and comprehensive histopathologic examination of the entire diffusely hyperplastic gland in Graves, rather than the selective removal of a dominant nodule in nodular goiter [9, 10, 11]. This paper will attempt to provide a very extensive clinical and histopathologic comparison of incidental papillary thyroid carcinoma diagnosed in patients undergoing thyroidectomy to treat Graves' disease versus patients with euthyroid nodular goiter.

2. Materials and Methods

I. Study's goal:

The paper examines incidental papillary thyroid carcinoma (PTC) with regard to a comparison of its clinical and pathological characteristics in Graves' disease patients with those of euthyroid nodular goiter.

II. Study design and population:

A retrospective cohort study of 117 patients who had thyroidectomy due to Graves' disease or euthyroid nodular goiter in the period January 2024 – January 2025 in different hospitals in Iraq. The patients were separated into two groups according to pre-operative diagnosis: Group A (Graves' disease) and Group B (euthyroid nodular goiter). Incidental PTC was defined as pathological findings after surgery in patients who were not suspected of having malignancy before surgery. Inclusion they had to be: documented clinical and laboratory diagnosis of either condition, full pre-operational thyroid hormone profiles, or surgical and histopathological reports. Patients who had known pre-operative malignancy or incomplete data were excluded.

III. Data collected from patients:

Medical records were used to extract demographic and clinical data. The variables that were gathered were age, sex, duration of symptoms, and the level of thyroid hormone (TSH, free T4, and free T3) prior to the surgery. The data enabled characterization and adjustment of comparisons across groups through baseline. An evaluation of thyroid action was conducted in a period of one week before the surgery based on the standardized testing that offered information on the functioning status (hyperthyroid in Graves vs euthyroid in nodular goiter) and its impact that might affect the incidental tumor appearance.

IV. Surgical operation outcomes:

The surgery performed (total thyroidectomy) was recorded and determined depending on how the disease presented itself. Specimens were also fixed in formalin and paraffin-embedded and sectioned in order to be subjected to histological examination after excision. Pathology was aimed at the identification of incidental foci of PTC, the size of the tumor, histological variants, multifocality, extrathyroidal extension (ETE), and metastasis of the tumor to lymph nodes. The largest diameter was used to determine the size of the tumor; per the WHO guidelines, variant subtypes were documented (classical, follicular, tall cell). Multifocality was two or more PTC foci of the thyroid. On the spread

of microscopic or macroscopic outside the capsule, ETE was divided into minimal or gross. The involvement of lymph nodes was established in dissected lymph nodes to examine the metastatic spread.

V. Statistical Analysis:

Data analysis was done using SPSS 24.0 by using descriptive and inferential statistics. Continuous variables (age, tumor size, and hormone levels) were represented as means with standard deviation and compared with normality tests, t-tests, or Mann-Whitney 3 - tests. The variables (incidence of incidental PTC, histological variants, multifocality, ETE, lymph node metastasis, the type of surgery, and post-operative complications) were categorical variables and used the chi-square/ Fisher exact test. Logistic regression was used to determine the independent risk factors of the aggressive histopathological appearances (multifocality, ETE, lymph node metastasis), and the confounding factors were age and sex. The p-value of below 0.05 was taken to be significant.

3. Results

Age and sex were appropriately balanced in the study group of 117 patients with a GD (n=53) and ENG (n=64) group. There stands out the fact that IPTC is more prevalent in the GD group (37.7%, 20/53) than the ENG group (25.0%, 16/64) stands out.

Table 1. Baselines and clinical features of 117 patients.

Characteristic	Graves' Disease (GD)	Euthyroid Nodular Goiter (ENG)	Total (n=117)
Number of Patients	53	64	117
Age (mean ± SD, years)	44.7 ± 11.3	47.1 ± 10.8	46.0 ± 11.1
Female, n (%)	43 (81.1%)	50 (78.1%)	93 (79.5%)

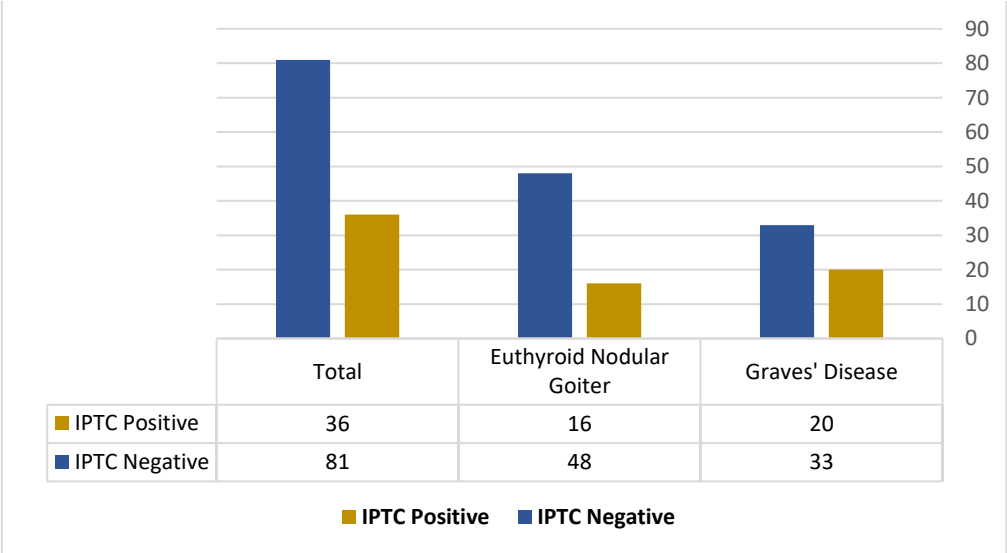
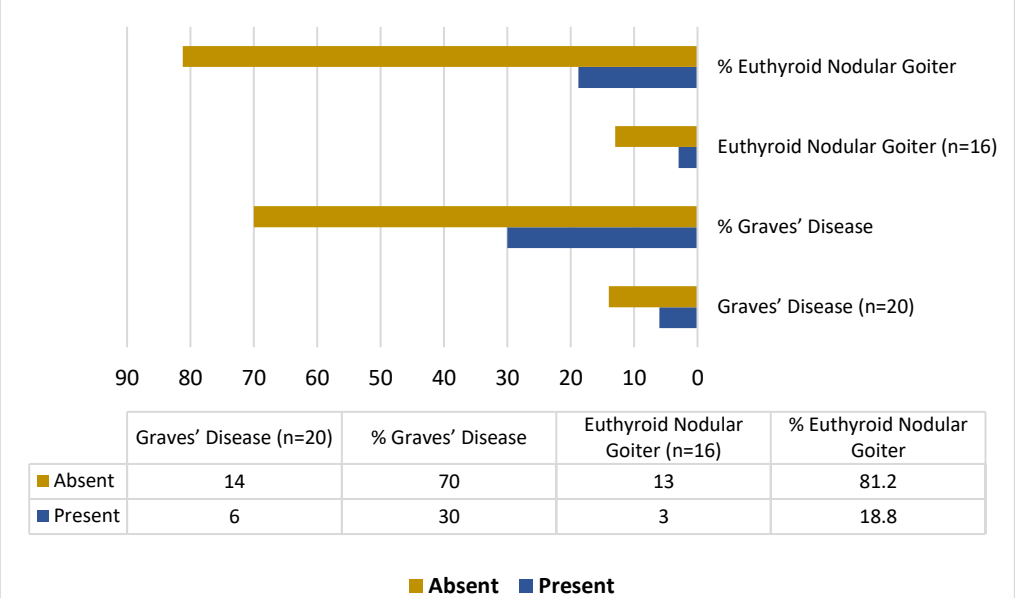


Figure 1. Distribution the incidence of incidental papillary thyroid carcinoma on the patients into both groups.

Multifocality of tumors in the disease group (30.0 vs. 18.8%), extrathyroidal extension (25.0 vs. 12.5), and lymph node metastases (40.0 vs. 18.8) were also higher in the Graves' disease group. There was also similarity in the tumor size distribution and histological pattern of variants (classic variant among them) between the cohorts.

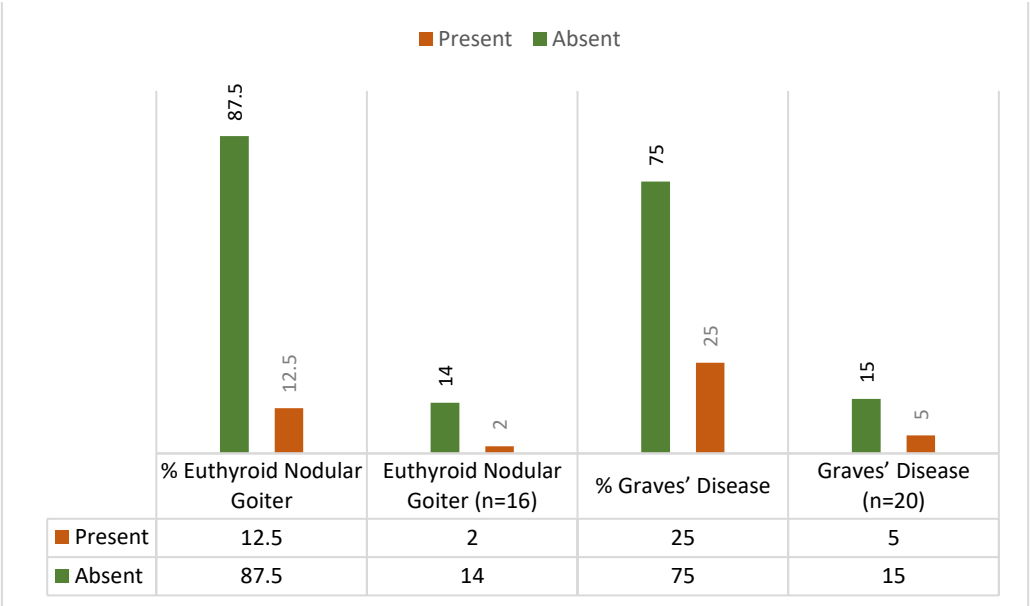
Table 2. Classification of tumor size on all patients within both groups.

Tumor Size (mm)	GD (n=20)	% within GD	ENG (n=16)
≤5	7	35.0	3
6–10	8	40.0	8
>10	5	25.0	5



	Graves' Disease (n=20)	% Graves' Disease	Euthyroid Nodular Goiter (n=16)	% Euthyroid Nodular Goiter
Absent	14	70	13	81.2
Present	6	30	3	18.8

Figure 2. Investigation of the multifocality of incidental papillary thyroid carcinoma in patients.



	% Euthyroid Nodular Goiter	Euthyroid Nodular Goiter (n=16)	% Graves' Disease	Graves' Disease (n=20)
Present	12.5	2	25	5
Absent	87.5	14	75	15

Figure 3. Identification of the extent of extra-thyroidal extension (ETE) in the patients.

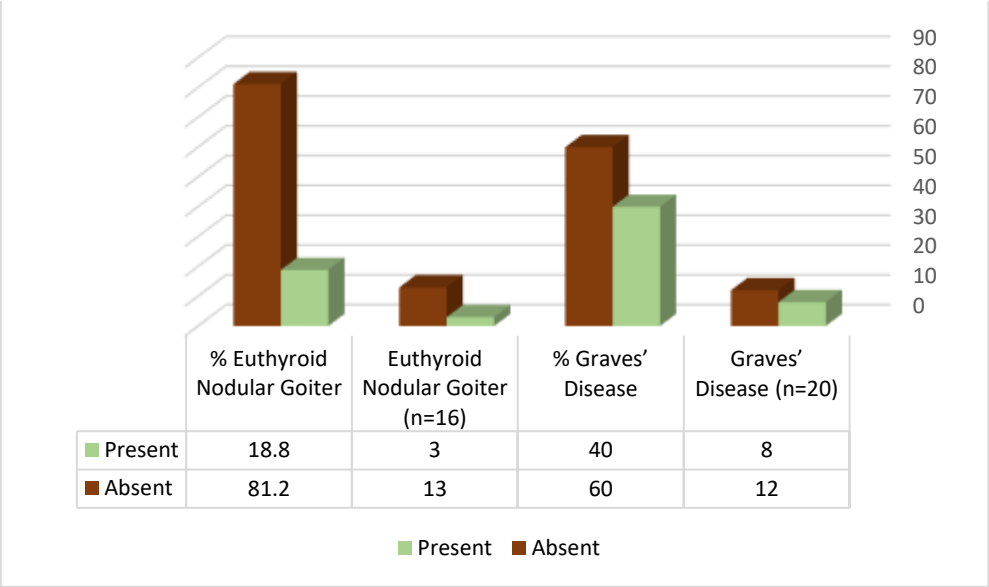


Figure 4. Distribution of lymph node metastasis (LNM) in the patients.

Table 2. Histological outcomes of incidental papillary thyroid carcinoma in the patients.

Variables	GD (n=20)	% GD	ENG (n=16)	% ENG
Classic	14	70.0	10	62.5
Follicular Variant	4	20.0	4	25.0
Tall Cell Variant	2	10.0	2	12.5

Another notable difference was seen in the level of TSH pre-surgery (67.9% of GD patients versus 3.1% of ENG patients having very low TSH levels (less than 0.1 mIU/L)). This is symptomatic of the hyperthyroidism that GD has and emphasizes the various endocrine milieus where these incidental carcinomas are found.

Table 3. Diagnosis of preoperative thyroid-stimulating hormone (TSH) levels in the patients.

TSH Range (mIU/L)	GD (n=53)	% GD	ENG (n=64)	% ENG
<0.1	36	67.9	2	3.1
0.1–0.5	12	22.6	10	15.6
0.5–4.5	5	9.5	52	81.3

Table 4. Establishing the correlation among both of Graves' disease and euthyroid nodular goiter with incidental papillary thyroid carcinoma markers.

Signs	GD (n=20)	ENG (n=16)	p-value
Multifocality (%)	30.0	18.8	0.45
Extrathyroidal Extension (%)	25.0	12.5	0.29
Lymph Node Metastasis (%)	40.0	18.8	0.10

The rate of postoperative complications (GD 18.9 versus ENG 12.5) and recurrent laryngeal nerve damage (GD 5.7 versus ENG 1.6) were lower and similar in both conditions, which is how the safety of thyroidectomy in both conditions was supported. The follow-up was low (mean: 36 months), and recurrence rates were low (GD: 10.0%, ENG: 6.3%); the disease-free survival was high (>90) in both groups. It means that

although the pathological features of the observed trends are observed, the intermediate-term prognosis of IPTC is favorable and similar.

Table 5. Assessment of post–operative clinical complications in the patients.

Complications	GD (n=53)	% GD	ENG (n=64)	% ENG
Hypocalcemia	10	18.9	8	12.5
Recurrent Laryngeal Nerve Injury	3	5.7	1	1.6

Table 6. Enroll post – operative clinical outcomes during 12 months follow-up.

Outcome	**GD IPTC (n=20)**	**% GD**	**ENG IPTC (n=16)**	**% ENG**
Recurrence	2	10.0	1	6.3
Disease-Free Survival	18	90.0	15	93.7

4. Discussion

There was increased incidences of incidental papillary thyroid carcinoma in patients with Graves' disease (GD) (37.7) as compared to euthyroid patients (ENG) (25). These facts indicate that Graves' disease could put the thyroid nodules at risk of hidden malignancy [12]. Various studies have been found in the United States which support the association between autoimmune thyroid disease and papillary thyroid carcinoma [13]. The immune stimulation that is chronic in GD can provide a microenvironment that supports carcinogenesis or cancer progression[14]

Most of the tumors were between 6 and 10 mm in size; this is the range of incidental microcarcinoma that is found when performing thyroidectomy due to benign disease. The size of tumors did not differ between the GD and ENG groups[15].

The histopathological appearances were more aggressive in the patients with Graves' disease, though the sizes of the tumors were not of proportional size. Extrathyroidal extension (ETE) was found in 25 percent of the cases of Graves' disease compared to 12.5 percent of the non-Graves group. Forty percent of patients with Graves' disease haemolymph node metastasis (LNM), was observed versus 18.8 in the control group. Multifocality also was also more prevalent in Graves' disease [16].

Even smaller (paradoxically) pre-operative TSH levels (0.1 mIU/L in 67.9% of cases with GD) were associated with phenotypically more aggressive tumors, which is in conflict with the classical theory of TSH hiking the tumor development. Taller cell variants that are more aggressive were found slightly higher in GD [17, 18].

There were no differences in post-surgery complication rate, such as transient hypocalcemia and repeated laryngeal nerve injury, suggesting that surgical tolerability is also the same when comparing GD and ENG [19, 20].

Increased proportions of aggressive tumor features in GD did not result in responses with poorer clinical outcomes in a follow-up of 12 months. The recurrence rates were low and similar (10 3 to GD to 6.3 3 to ENG), and a majority of the patients attained disease-free survival.

5. Conclusion

The correlation analysis showed that there was a tendency of increased multifocality, ETE, and LNM in GD than in ENG. Pathophysiologically, GD can affect the tumor microenvironment, including cytokine upregulation, abnormal immune surveillance, and hormone alterations, all of which might result in the development of tumors.

In conclusion, the current study showed that there was a greater occurrence of incidentally detected papillary thyroid carcinoma in patients who had been diagnosed

with Graves' disease as compared to those who had been diagnosed with euthyroid nodular goiter. This finding indicates the increased risk of occult malignancy in relation to autoimmune thyroid disease. The two cohorts had similar tumor size distribution, with most neoplasms being microcarcinomas. However, Graves' disease subjects were rather predisposed to multifacetedness, extrathyroidal expansion, and metastasis in the lymph nodes in the region, but these findings were not statistically significant.

Moreover, markers of hyperthyroidism, namely, reduced preoperative serum thyroid-stimulating hormone levels, were significantly lower in the Graves' group and could influence tumor physiology.

The morbidity in the postoperative period was rare and not significantly different between groups, and hence, it validated the safety and tolerance of surgery in the two groups. The 12-month follow-up showed low recurrence rates and positive disease-free survival regardless of the underlying thyroid pathology.

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