

Incidence of Thyroid Cancer in Patients Operated for Hyperthyroidism: Our 10-year Experience

Yasin Tosun, Gizem Akcakoca, Cemal Hacıoğlu, Ömer Faruk İnanç,
Hasan Fehmi Küçük

Department of General Surgery,
Kartal Dr. Lütfi Kırdar City Hospital,
Istanbul, Türkiye

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Correspondence: Yasin Tosun,
Department of General Surgery,
Kartal Dr. Lütfi Kırdar City Hospital,
Istanbul, Türkiye

E-mail: yasintosun@gmail.com



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ABSTRACT

Objective: Hyperthyroidism is a clinical condition caused by inappropriate secretion of excess thyroid hormone (t4 and t3) from the thyroid gland. It is characterized by high t4, t3, and suppressed thyroid-stimulating hormone levels. In addition, studies conducted in recent years have shown that the rates of thyroid cancer with especially aggressive histology increase in patients with hyperthyroidism. The aim of this study is to determine the incidence of thyroid cancer in patients who underwent surgery for hyperthyroidism and to determine the patient groups that should be evaluated more carefully before surgery.

Methods: The study was designed as a retrospective and cohort study. A total of 301 patients who underwent surgery for hyperthyroidism between January 2012 and February 2022. The patients were divided into three groups: Graves' disease (GD), TMG, and toxic adenoma (TA). Age, gender, type of surgery, post-operative pathology results, tumor characteristics, and post-operative complications of the patients were recorded.

Results: Thyroid cancer was detected in 65 (22%) patients. The incidence of thyroid carcinoma in GD, TMNG, and TA was 16%, 24%, and 50%, respectively. The final pathology results of patients with malignancy were as follows: Classical variant of papillary thyroid carcinoma (PTC) in 23% (n=15) of patients, follicular variant of PTC in 63% (n=41) of the patients, diffuse sclerosing variant of PTC in 7% (n=4) of patients, and 7% (n=5) of patients had papillary thyroid microcarcinoma. Overall, multifocality (39%) was the most common finding, followed by lymphovascular invasion (13%) and finally extrathyroidal invasion (6%).

Conclusion: The results of our study show that the risk of thyroid cancer is not low in patients with hyperthyroidism. The risk of malignancy should not be ignored during the evaluation and management of patients with hyperthyroidism. Therefore, careful histopathological examination may help reveal an incidental tumor located in a hyperfunctional nodule or extranodular thyroid tissue.

INTRODUCTION

Hyperthyroidism is a clinical condition caused by inappropriate secretion of excess thyroid hormone (t4 and t3) from the thyroid gland. It is characterized by high t4, t3, and suppressed thyroid-stimulating hormone (TSH) levels. [1] Clinical diseases associated with hyperthyroidism are often Graves' disease (GD), toxic goiter (TMNG), and toxic adenoma (TA). [2] It is thought that hyperthyroidism will reduce the risk of cancer development with suppressed TSH level. [3,4] In addition, in recent studies, it has been determined that thyroid cancer with especially aggressive histology has an increasing tendency in patients with hy-

perthyroidism. [5-7] American Thyroid Association guidelines do not recommend biopsy in hyperfunctional nodules unless malignancy is suspected. [8] Surgery is recommended in patients with clinical signs of compression and thyroid tissue >80 g (goiter), low radioactive iodine uptake, and severe ophthalmopathy. Furthermore, in patients with graves with nodules, surgery is recommended if there is a suspicion of cancer in the biopsy. [1] The aim of our study is to determine incidence of thyroid cancer in patients who underwent surgery for hyperthyroidism and to determine the patient groups that should be evaluated more carefully before surgery.

Table 1. Distribution of incidental malignancy by fine-needle aspiration and between groups

	Total (n=301), n (%)	Graves (n=175), n (%)	TMNG (n=100), n (%)	Toxic solitary nodul (n=26), n (%)
Total malignancy	65 (22)	28 (16)	24 (24)	13 (50)
Malignancy	37	17	13	7
Incidental	28	11	11	6
No malignancy	236 (78)	147 (84)	76 (76)	13 (50)

TMNG: Toxic multinodular goiter.

MATERIALS AND METHODS

Study Design

This study is a retrospective and cohort study. A total of 301 patients who were operated on for hyperthyroidism in the Endocrine Surgery Unit of the General Surgery Clinic on January 2012 to February 2022 were included the study. The study approval number is 2022/514/234/30.

Study Cohorts and Defines

GD, TMG, and TA is study groups. Hyperthyroidism was defined as biochemical confirmation of elevated T3, T4 and suppressed TSH levels in all patients. The diagnosis of GD was established by clinical findings such as elevated serum thyroid stimulating immunoglobulin concentrations, diffuse radioactive uptake, or goiter with ophthalmopathy. Hyperthyroidism patients with nodules but without clinical and biochemical findings such as GD were defined as TMNG. Patients with a single hot nodule on scintigraphy were defined as TA.

Inclusion and Exclusion Criteria

Patients older than 18 years of age who were operated on in the general surgery clinic were included in the study. Patients younger than 18, patients who were operated in pediatric surgery or otolaryngology clinics, patients whose data could not be accessed, patients who were diagnosed with non-thyroid malignancy, and patients whose treatment could not be completed for any reason were excluded from the study.

Data

Data were obtained from patient files, surgery reports, and pathology reports. Age, gender, type of surgery,

post-operative pathology results, tumor characteristics, and post-operative complications of the patients were recorded.

Statistical Analysis

Statistical analysis of the data was performed using SPSS version 18.0 software (IBM, Chicago). Descriptive data were shown as mean±standard deviation and median minimum–maximum values. Kolmogorov–Smirnov test was used to evaluate the normality of distribution of the data. The statistical difference between categorical data was evaluated using Pearson's Chi-square test and Fisher's exact test. The quantitative data without normal distribution were compared with the Mann–Whitney U Test. $p < 0.05$ was considered statistically significant.

RESULTS

A total of 301 patients who underwent thyroidectomy were included in the study. The distribution of patients was as follows: 100 patients with TMNG (33.2%), 175 patients with GD (58.1%), and 26 patients with TA (8.6%). Of the patients, 86 (28.6%) were male and 215 (71.4%) were female. The female/male ratio was 2:5. Mean age 50.6 ± 13.4 (median: 51, range: 17–89). Thyroid cancer was detected in 65 (22%) patients. Cancer rates in the GD, TMNG, and TA groups were 16%, 24%, and 50%, respectively (Table 1).

When the fine-needle aspiration biopsy pathology results were analyzed in 100 patients due to nodule size or suspected malignancy, the results were as follows. Bethesda II (Benign) was detected in 48 patients, Bethesda III (Atypical of Indeterminate Significance/Follicular Lesion of Indeter-

Table 2. Intergroup features of malignancy

Final pathology of malignancy, n (%)	Total (n=65), n (%)	GD (n=28), n (%)	TMNG (n=24), n (%)	Toxic solitary nodul (n=13), n (%)
PTC classical variant	15 (23)	9 (31)	8 (27)	0
PTC follicular variant	41 (63)	13 (46)	15 (64)	13 (100)
PTC diffuse sclerosing variant	4 (7)	4 (15)	0	0
Incidental papillary thyroid microcarcinoma	5 (7)	2 (8)	1 (2)	0
Total PTC	65 (100)	28 (100)	24 (100)	13 (100)

TMNG: Toxic multinodular goiter; PTC: Papillary thyroid carcinoma; GD: Grave's disease.

Table 3. Tumor characteristics between groups

Tumor characteristics	Total (n=65), n (%)	GD (n=28), n (%)	TMNG (n=24), n (%)	Toxic solitary nodul (n=13), n (%)
Extrathyroidal invasion	4 (6)	2 (8)	2 (9)	0
Lymphovascular invasion	9 (13)	4 (15)	4 (18)	0
Multifocality	26 (39)	11 (38)	9 (36)	17 (67)

TMNG: Toxic multinodular goiter, GD: Grave's disease.

minate Significance) in 15 patients, Bethesda IV (suspected for follicular neoplasm) in 11 patients, Bethesda V (suspected for malignancy) in 11 patients, and Bethesda VI in 7 patients. When the post-operative pathology results were evaluated, the distribution of the total patients with malignancy is shown in Table 1.

When the pathology results of the patients with post-operative malignancy are examined, the findings are as follows: Classical variant in 23% (n=15) of patients, follicular variant in 63% (n=41) of the patients, diffuse sclerosing variant in 7% (n=4) of patients, and 7% (n=5) of patients had papillary thyroid microcarcinoma. Graves patients with malignancy are classified as follows: Classical variant in 31% (n=9) of patients, follicular variant in 46% (n=13) of patients, diffuse sclerosing variant in 15% (n=4) of patients and incidental malignancy of 8% (n=2) of patients. Classical variant was present in 27% (n=8) and follicular variant in 64% (n=15) of TMNG patients. Incidental papillary thyroid microcarcinoma was detected in 2% (n=1). All patients with TA had a follicular variant (Table 2).

When tumor characteristics were examined, multifocality (39%), lymphovascular invasion (13%), and non-thyroid invasion (6%) were the most common findings (Table 3).

DISCUSSION

In this study, we examined the incidence of cancer in patients who were operated for hyperthyroidism. Although there are studies on the relationship between thyroid cancer and hyperthyroidism in the literature, the results are still controversial. There are studies suggesting that hyperthyroidism reduces cancer formation because it suppresses the growth of thyroid tissue, or that the risk of developing aggressive thyroid cancer increases with hyperthyroidism.^[3] In recent studies, it has been revealed that the relationship between hyperthyroidism and malignancy is different. Two large-scale cross-sectional studies and a Danish study showing the association of high TSH levels with thyroid cancer found that cancer development was not low in hyperthyroid patients.^[9-11] In our study, thyroid malignancy was found in the final pathology in 22% of the patients who were operated for hyperthyroidism. Although the literature is contradictory on this subject, it can be compared with the previous studies reporting that malignancy rates range from 9% to 55%.^[6,12,13]

In our study, the most common indication for surgery in

GD was compressive effect and ophthalmopathy rather than the presence of a suspicious nodule. Carcinoma was detected in 16% of Graves' patients. In the previous studies in the literature, lower cancer association was found in patients with graves, but higher results were found in recent studies. In the study of Ergin et al., the coexistence rate of GD and thyroid cancer was reported as 26%. This ratio was determined by Wei Shuang Zheng et al. and Boutzios et al. reported in their studies as 32% and 33.7%, respectively.^[12,14-17] The presence of nodules in hyperthyroid patients increases the risk even more. In our study, TA and TMNG groups had a high risk of malignancy with 50% and 24%. Although the results are higher than the literature, the cause of hyperthyroidism, patient selection for the operation, the type of operation, the prevalence of histological examination, and geographical differences may be the reason for the differences in results between studies.^[18] Specifically, multifocal malignancy was detected in 67% of patients with toxic solitary nodules. Therefore, high malignancy rate should be considered in hyperthyroid patients with underlying structural nodular disease and surgical treatment should be considered as a priority. In our study, all patients had papillary thyroid cancer. When we looked at tumor subgroups, we found that some of them had more aggressive character. These findings suggest that surgical treatment can be extended further in nodular disease and appropriately selected patients with hyperthyroidism.

Our study had many limitations. Some of these limitations are that it is performed from a single center with a limited number of clusters, the study is retrospective and includes patients who have undergone thyroidectomy. This may have affected the high rates of malignancy. The lack of detailed information such as age, genetic predisposition, radiotherapy history, and scintigraphy results are other limitations of the study. In conclusion, in our study, we determined that thyroid cancer should be investigated in patients with hyperthyroidism and should not be missed. Careful histopathological examination may help reveal a hyperfunctional nodule or an incidental tumor in the thyroid tissue.

Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (Date: 28.09.2022, Decision No: 2022/514/234/30).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: H.F.K.; **Design:** Y.T.; **Supervision:** H.F.K.; **Materials:** G.A, C.H.; **Data:** G.A, C.H.; **Analysis:** Y.T., Ö.F.İ.; **Literature search:** .G.A., C.H.; **Writing:** Y.T., Ö.F.İ.; **Critical revision:** H.F.K.

Conflict of Interest

None declared.

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Hipertiroidi Nedeniyle Ameliyat Edilen Hastalarda Tiroid Kanseri İnsidansı: 10 Yıllık Deneyimimiz

Amaç: Hipertiroidizm, tiroid hormonunun tiroid bezi tarafından aşırı sentezlenip salgılandığı patolojik bir hastalıktır. Son yıllarda yapılan çalışmalar hipertiroidili hastalarda tiroid kanseri oranlarının arttığını ve bu hastalarda görülen malignitenin agresif histolojik özelliklere sahip olduğunu göstermiştir. Bu çalışmanın amacı, hipertiroidizm nedeniyle ameliyat edilen hastalarda tiroid kanseri görülme sıklığını belirlemek ve ameliyat öncesi daha dikkatli değerlendirilmesi gereken hasta gruplarını belirlemektir.

Gereç ve Yöntem: Çalışma retrospektif bir kohort çalışması olarak tasarlandı. Ocak 2012 ile Şubat 2022 tarihleri arasında hipertiroidizm nedeniyle ameliyat edilen toplam 301 hasta çalışmaya katıldı. Hastalar GD (graves hastalığı), TMG (toksik multinoduler guatr) ve TA (toksik adenom) olmak üzere üç gruba ayrıldı. Hastaların yaşı, cinsiyeti, cerrahi tipi, postoperatif patoloji sonuçları, tümör özellikleri ve postoperatif komplikasyonları kaydedildi.

Bulgular: Hastaların 65'inde (%22) tiroid kanseri saptandı. GD, TMNG ve TA'da tiroid karsinomu insidansı sırasıyla %16, %24 ve %50 idi. Maligniteli hastaların nihai patoloji sonuçları şöyleydi: Hastaların %23'ünde (n=15) PTC'nin klasik varyantı, %63'ünde (n=41) PTC'nin foliküler varyantı, %7'sinde (n=4) diffüz sklerozan PTC varyantı ve %7'sinde (n=5) papiller tiroid mikrokarsinomu vardı. Genel olarak, multifokalite (%39) en yaygın bulguydu, bunu lenfovasküler invazyon (%13) ve son olarak tiroid dışı invazyon (%6) izledi.

Sonuç: Çalışmamızın sonuçları hipertiroidisi olan hastalarda tiroid kanseri riskinin düşük olmadığını göstermektedir. Hipertiroidili hastaların değerlendirilmesi ve yönetimi sırasında malignite riski göz ardı edilmemelidir. Bu nedenle, dikkatli histopatolojik inceleme, hiperfonksiyonel bir nodül veya ektranodüler tiroid dokusunda yer alan rastlantısal bir tümörü ortaya çıkarmaya yardımcı olabilir.

Anahtar Sözcükler: Hipertiroidi; tiroidektomi; tiroid kanseri.