



Prevalence of thyroid cancer in hyperthyroidism: Identifying risk factors for malignancy

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Abstract

Aim: Contrary to the previously held belief that hyperthyroidism may be protective against the development of cancer, a growing number of studies suggest a link between hyperthyroidism and thyroid cancer. The purpose of this study is to investigate the incidence of malignancy in patients undergoing total thyroidectomy for hyperthyroidism with toxic adenoma (TA), toxic multinodular goiter (TMNG), and/or Graves' disease (GD), and to identify factors predictive of malignancy.

Materials and Methods: This is a retrospective study of patients aged 18 years and older who underwent total thyroidectomy for toxic adenoma and toxic multinodular goiter associated with hyperthyroidism and Graves' disease. Thyroidectomies were performed by a single surgeon at a tertiary teaching hospital between January 2014 and December 2020. Our cohort was divided into two separate groups based on whether the pathology results were malignant or benign.

Results: Between January 2014 and December 2020, 199 patients were included, 66.3% were female and the average age was 44.6 years. Hyperthyroidism cases included 52.7% toxic multinodular goiter (TMNG), 9.1% toxic adenoma (TA), and 38.2% Graves' disease (GD). The cohort revealed a 32.6% thyroid cancer incidence in hyperthyroid patients. The leading malignancy was papillary carcinoma. Hyperthyroidism causes significantly predicted malignancy; TMNG had a 42.8% malignancy rate, compared to 22.4% for GD and 16.3% for TA ($p=0.005$). Fine needle aspiration biopsy (FNAB) findings were significant for malignancy prediction ($p=0.001$), with 62.9% malignancy after non-diagnostic FNAB results.

Conclusion: The study emphasizes the need for careful consideration of malignancy risk in hyperthyroidism cases. Factors such as FNAB results and the type of hyperthyroidism condition significantly influenced malignancy prediction. The results underscore the necessity for a thorough evaluation of hyperthyroid patients at risk of malignancy.

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Introduction

Hyperthyroidism is a clinical condition characterized by abnormally elevated synthesis and secretion of thyroid hormones by the thyroid. Hyperthyroidism may occur due to autoimmune causes in Graves' disease or as a result of autonomic secretion in multinodular goiter or toxic adenoma [1,2]. It was believed that the suppressive effect caused by the increase in thyroid hormones in patients with toxic nodular disease protected the goiter's extranodular thyroid tissue from thyroid cancer [3]. Nonetheless, the relationship between hyperthyroidism and thyroid cancer, which has been reported more often in recent years, is remark-

able. There are reports that increased thyrotropin levels, even within the normal range, increase the risk of nodular thyroid disease and thyroid cancer. In parallel with this opinion, TSH suppression is still the treatment of choice for well-differentiated thyroid cancers [4,5]. It has been suggested that even in patients with euthyroidism, a reduction in TSH may prevent the development of thyroid cancer by inhibiting oncogenes. It is therefore known that patients with hyperthyroidism have a lower risk of developing thyroid cancer [6]. The incidence of malignancy in toxic nodular goiter has been reported to be 3% to 5% in previous studies. However, some recent studies have reported a higher incidence of thyroid cancer by 12-21% [5,7,8]. The aim of our study was to investigate the incidence of malignancy in patients undergoing total thy-

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roidectomy for hyperthyroidism with toxic adenoma (TA), toxic multinodular goiter (TMNG) and/or Graves' disease (GD), and to determine the predictive factors associated with malignancy by comparing patients with benign and malignant pathologies.

Materials and Methods

This is a retrospective study of patients aged 18 years and older who underwent total thyroidectomy for toxic adenoma and toxic multinodular goiter associated with hyperthyroidism and Graves' disease. Thyroidectomies were performed by a single surgeon at a tertiary teaching hospital between January 2014 and December 2020. Ethical approval was given by the Clinical Research Ethics Committee of University of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital (date: 29.08.2022 number: 145/26). Informed consent was waived due to the retrospective nature of the study. Patients under 18 years of age and those with other causes of thyroidectomy, including benign goiter and thyroid malignancy, were excluded from the study. All nodules were assessed by fine needle aspiration biopsy (FNAB) prior to surgery. The Bethesda classification system was used to categorize the cytological evaluation. The indications for thyroidectomy in hyperthyroidism were nodules suspicious for malignancy based on FNAB findings, gigantic goiters causing compression symptoms, and the indications for thyroidectomy for Graves' disease. In patients with thyroid cancer, the diameter of the tumor, the presence of tumor foci in terms of unifocal and multifocal, the size of the primary tumor, and the pathological type of the tumor were evaluated. Our cohort was divided into two separate groups based on whether the pathology results were malignant or benign. To identify reliable predictors of malignancy in hyperthyroidism, demographics, FNAB results, and postoperative pathology results were used to compare the two groups.

Statistical analysis

For quantitative variables, mean, standard deviation and median (minimum to maximum) were used as descriptors, while for qualitative variables; the number of patients (percentage) was used. Numbers and percentages were used for categorical variables. The Kolmogorov-Smirnov test was used to test the normal distribution of numerical variables. The Mann-Whitney U or Student's t-test was used to compare two independent groups. The Chi-square test was used to compare differences between categorical variables. Version 22.0 of the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL) for Windows was used for all analyses. A p-value of 0.05 was considered statistically significant.

Results

One hundred and ninety-nine patients were included into study January 2014 and December 2020. There were 132 female patients (66.3%) and 67 male patients (33.7%). The average age of patients was 44.6 years. Of the patients with hyperthyroidism, 105 had toxic multinodular goiter (52.7%), 18 had toxic adenoma (9.1%), and 76 had Graves'

disease (38.2%). Table 1 presents the demographic characteristics, FNAB and the pathological findings. The cohort was divided into benign and malign categories. In our cohort of hyperthyroid patients, the incidence of thyroid cancer was 32.6% (65/199). The most malignant pathology (n = 63) was papillary carcinoma. The average weight of the thyroid specimen was 48 grams, and the average diameter of the tumor, as determined by pathological measurements, ranged from 1 to 40 millimeters. Fortunately, 96.9% (193/199) of patients had no complications after thyroidectomy. Only one patient had unilateral vocal cord paralysis (0.5%), and one patient had persistent hypoparathyroidism (0.5%).

The mean age of patients in the benign group was 43.8 years, while the mean age of patients in the malignant group was 46.1 years (Table 2). Age, gender, and development of complications did not differ between benign and malignant pathology ($p > 0.05$). The causes of hyperthyroidism were statistically significant in predicting malignancy. The rate of malignancy was 42.8% (n = 45/105) in toxic multinodular goiter, compared to 22.4% in Graves' disease and 16.3% in toxic adenoma ($p = 0.005$). FNAB findings were statistically significant regarding to malignancy ($p = 0.001$). Benign FNABs were significantly more likely to result in benign pathologies (79.4% vs. 20%). The majority of non-diagnostic or inadequate FNABs were malignant in permanent total thyroidectomy specimens (62.9% vs. 37.9%). Thus, non-diagnostic or inadequate FNAB results were indicative of malignancy in our series. All FNABs suspicious for malignancy were evaluated as malignant based on permanent pathological evaluation (n=3).

Discussion

To our knowledge, this is the first study to identify a 32.6% risk of malignancy associated with hyperthyroidism. Despite the exclusion of micropapillary carcinoma, the presence of 11.1% invasive thyroid carcinoma requires a cautious evaluation of nodular disease in hyperthyroidism. Furthermore, the presence of malignancy in 22.4% of Graves' disease cases suggests that hyperthyroidism is not as benign as previously thought. The detection of malignancy in 62.9% of thyroidectomy specimens after non-diagnostic FNAB requires further evaluation of suspicious nodules in the presence of hyperthyroidism.

Hyperthyroidism affects approximately 1.2% of the population. The most common cause of hyperthyroidism, Graves' disease (GD), is an autoimmune disorder in which antibodies to the thyrotropin receptor stimulate the TSH receptor [1]. The co-occurrence of Graves' disease (GD) and thyroid cancer (TC) is increasing, but the underlying mechanisms remain unclear. Iodine uptake and oxidation, as well as the proliferative effect of triiodothyronine, are thought to be responsible for the development of cancer [9]. You and colleagues found that about fifty percent of patients with GD who underwent thyroidectomy had thyroid cancer [10]. In our series, we found that 22.4% of GD patients had thyroid malignancy. Multicentricity and distant metastasis were significantly higher in GD and thyroid cancer according to a meta-analysis. In all malignant thyroidectomy specimens, 55.4% showed multifocality. The

Table 1. Demographic characteristics, fine needle aspiration biopsies according to the Bethesda System, and pathological findings.

		Number, %
Sex	Female	132, 66.3
	Male	67, 33.7
Median age (years)		44.6 (18-84)
Distribution of patients with hyperthyroidism by diagnosis	Toxic adenoma	18, 9.1
	Toxic multinodular goiter	105, 52.7
	Graves' disease	76, 38.2
Fine needle aspiration biopsies according to the Bethesda System	Nondiagnostic or unsatisfactory	27, 13.5
	Benign	136, 68.4
	Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance	28, 14.1
	Follicular neoplasm or suspicious for a follicular neoplasm	5, 2.5
	Suspicious for malignancy	3, 1.5
	Malignant	0
Pathologic findings	Benign	134, 67.4
	Malign	65, 32.6
The histopathologic type of tumour, n, %	Papillary cancer	63, 96.9
	Micropapillary	48, 73.8
	Follicular	2, 3.1
Presence of malignant foci in tumour	Unifocal	29, 44.6
	Multifocal	36, 55.4
The mean weight of thyroid specimen (gram)		48 (10-386)
The mean diameter of malign nodules according to pathologic examinations (mm)		5.7 (1-40)
Complications n, %	None	193, 96.9
	Present	6, 3.1
	Unilateral vocal cord paralysis	1, 0.5
	Transient hypocalcemia	4, 2.1
	Persistent hypoparathyroidism	1, 0.5

Table 2. Comparison of demographics and FNAB diagnoses of patients with benign and malignant pathologies.

		Benign	Malign	p
Median age (years)		43.8±14.2	46.1±13.3	0.29
Sex	Female	90 (68.1)	42 (31.9)	0.72
	Male	44 (57.1)	23 (29.9)	
Distribution of patients with hyperthyroidism by diagnosis (n, %)	Toxic adenoma	15 (83.7)	3 (16.3)	0.005
	Toxic multinodular goiter	60 (57.2)	45 (42.8)	
	Graves' disease	59 (77.6)	17 (22.4)	
Fine needle aspiration biopsies according to the Bethesda System (n, %)	Nondiagnostic or unsatisfactory	10 (37.1)	17 (62.9)	0.001
	Benign	108 (79.4)	28 (20.6)	
	Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance	13 (46.4)	15 (53.6)	
	Follicular neoplasm or suspicious for a follicular neoplasm	3 (60)	2 (40)	
	Suspicious for malignancy	0	3 (100)	
	Malignant	0	0	
Weight of thyroid specimen (gram)		97.4	105.21	0.37
Presence of complications		5 (3.7)	1 (2.5)	0.39

reported incidence of incidental thyroid cancer in GD is 8%, and this is multiplied by five if at least one nodule is palpated [11,12]. Patients with GD should therefore be evaluated with caution due to the higher prevalence of PTC in this population.

Toxic multinodular goiter (TMNG) and toxic adenoma (TA) are the other common causes of hyperthyroidism. In nodular thyroid disease, hormone stimulation causes existing nodules to grow or new nodules to form over time. The 2016 American Thyroid Association (ATA) guidelines recommend radioactive iodine (RAI) and surgery for the treatment of TA and TMNG. However, RAI treatment is preferred for older patients, those with comorbidities, and those with surgical contraindications. Surgical treatment of hyperthyroidism offers almost 100% cure rates and detection of incidental malignancies. In one study, the causes of hyperthyroidism that underwent thyroidectomy were statistically significant in predicting malignancy. The malignancy rate was reported to be 21.43%, and TMNG showed a statistically higher prevalence in the malignant group [13]. In our series, the malignancy rate was also higher in toxic multinodular goiter (42.8%), compared to GD and TA (16.3%). The malignancy rate of TMNG has been reported to be as low as 2.7% and as high as 21.43% [5,9-14]. Interestingly, a malignancy rate of 29% has been reported for TMNG in the pediatric population [14]. Our findings of a high co-occurrence of hyperthyroidism and malignancy suggest that hyperfunctioning nodules are not innocent in the development of malignancy, despite differences between studies.

In the presence of hyperthyroidism and thyroid malignancy, the preoperative choice of medical or surgical treatment and the need for neck dissection if surgery is chosen must be determined. Preoperative fine needle aspiration biopsies guide the surgeon [6]. Gul et al. recommended FNAB as a reliable method for the diagnosis of thyroid malignancy in patients with hyperthyroidism and suggested FNAB evaluation of nodules in hyperthyroid patients prior to radioactive iodine therapy or surgery to rule out the possibility of high malignancy. The authors reported that 44.4% of inadequate cytology from FNABs resulted in thyroid cancer [15]. Similarly, in our series, 62.9% of non-diagnostic cytology resulted in thyroid malignancy and FNAB findings were statistically significant for malignancy. Therefore, inadequate cytology in FNABs should be highlighted and repeat FNAB should not be delayed due to the high likelihood of malignancy.

In the hands of high-volume thyroid surgeons, the incidence of permanent hypoparathyroidism after thyroidectomy for hyperthyroidism is less than 2%, and the incidence of permanent RLN injury is less than 1% [16]. According to the data, the clinical outcomes for patients of surgeons who perform more than 25 thyroid operations per year are superior [17]. Our results are analogous to those reported in recent publications, with a low incidence of complications for an experienced single surgeon in thyroid surgery. There was no relationship between benign and malignant groups and the incidence of complications.

Conclusion

Contrary to the previously held belief that hyperthyroidism may be protective against the development of cancer, this research presents a 32.6% incidence of thyroid cancer observed among hyperthyroid patients undergoing total thyroidectomy for toxic adenoma (TA), toxic multinodular goiter (TMNG), and Graves' disease (GD). The findings underscore the importance of comprehensive evaluation and individualized management strategies for hyperthyroid patients. Factors such as fine needle aspiration biopsy (FNAB) results and the specific type of hyperthyroidism condition play pivotal roles in predicting malignancy. Notably, the presence of malignancy in 22.4% of Graves' disease cases raises concerns about the perceived benign nature of this condition.

Ethical approval

Ethical approval was given by the Clinical Research Ethics Committee of University of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital (date: 29.08.2022 number: 145/26).

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