Hyperthyroidism with thyroid cancer: more common than expected?

Ann Ital Chir, 2020 91, 1: 16-22
pii: S0003469X20030250
free reading: www.annitalchir.com

Süleyman Özkan Aksoy*, Ali İbrahim Sevinç*, Merih Güray Durak**

**Dokuz Eylül University Faculty of Medicine, Department of Surgery, Izmir, Turkey*
***Dokuz Eylül University Faculty of Medicine, Department of Pathology, Izmir, Turkey*

Hyperthyroidism with thyroid cancer: more common than expected?

OBJECTIVE: *Hyperthyroidism is a group of diseases with many different etiologies and clinical manifestations. The most common causes include toxic multi-nodular goiter, Graves' disease and toxic adenoma. The prevalence of thyroid cancer developing in patients with hyperthyroidism has gradually increased in recent years. The aim of this study is to detect the incidental thyroid cancer rates in patients who have undergone a surgical operation due to hyperthyroidism, and to specify the patient groups in whom surgical treatment should come into the foreground.*
METHODS: *A total of 591 patients, who had surgical excision of the thyroid due to hyperthyroidism between January 2007 and June 2017, were retrospectively analyzed.*
RESULTS: *Of all the patients included in the study, 377 (63.7%) had multi-nodular goiter, 132 (22.3%) had Graves' disease, 55 (9.4%) had nodular Graves' disease, and 27 (4.6%) had toxic adenoma. Thyroid cancer was determined in 131 out of 591 patients (22.6%) who were operated. The most common histologic type was thyroid micropapillary carcinoma (65/131; 49.6%). The accompanying pathologies to thyroid cancer were as follows: Toxic multi-nodular goiter (89/131; 67.9%), nodular Graves' disease (24/131; 18.3%), Graves' disease (13/131; 9.9%) and toxic adenoma (5/131; 2.8%).*
DISCUSSION: *Prevalence of cancer on a background of hyperthyroidism has gradually increased in recent years. It is not realistic to determine thyroid cancer prevalence only based on autopsy examinations. This rate significantly increases in the presence of nodule in clinical studies. Most of the carcinomas are microcarcinomas that do not have lymphovascular invasion and have very low lymph node metastasis. Thus, their treatment is still under debate.*

KEY WORDS: Hyperthyroidism Micropapillary Cancer, Thyroid cancer

Introduction

Hyperthyroidism (HT) has many different etiologies, clinical course and treatments. While its prevalence varies among different countries, it is seen at a rate of 1.2% (0.5% clinical and 0.7% subclinical) in the adult population. Graves' disease (GD), toxic multi-nodular goiter (TMNG) and toxic adenoma (TA) are the most common causes [1,2].

The increase in thyroid hormone levels affects many organs and tissues. The symptoms manifest as increased thermogenic effect, increased basal metabolic rate, elevated cholesterol levels and increased systemic vascular resistance. Surgical indications include compression-related symptoms, irresponsiveness to medical treatment, ophthalmopathy and risk of malignancy. Co-existence of hyperthyroidism and thyroid cancer is an important issue. Thyroid cancer mostly coexists with GD, TMNG or TA.

Graves' disease is an autoimmune disease and accounts for 60%-80% of all hyperthyroidism cases [1]. Although its etiology is still controversial, post-partum conditions, excessive iodine, lithium treatment, and bacterial and

Pervenuto in Redazione Gennaio 2019. Accettato per la pubblicazione Febbraio 2019
Correspondence to: Süleyman Özkan Aksoy, Dokuz Eylül, University Faculty of Medicine, Department of Surgery, Mithatpasa Street, no:1606, Inciraltı, Balçova, Izmir, Turkey, 35340 (e-mail: suleyman.aksoy @yahoo.com)

viral infections are the potential triggering factors. The prevalence of development of a thyroid nodule in this disease is higher than that in the normal population. Increased prevalence of nodule varies between 22% and 45% in the literature [3]. The prevalence of malignancy varies between 0.4% and 9.8% in these nodules.

Hyperthyroidism cases are composed of TMNG (10-15%) and TA (5%). Signs and symptoms of TMNG are similar to Graves' disease; however, extra-thyroidal findings are usually not present. The diagnosis is based on history, physical examination, as well as elevated thyroid hormone levels in contrast to suppressed serum thyroid stimulating hormone (TSH) levels, negative anti-thyroid antibodies, elevated radioactive iodine (RAI) uptake and detection of multiple nodules with increased uptake and suppression in the remaining tissue.

Hyperthyroidism related to a single hyperfunctioning nodule is seen in toxic adenoma (TA). It is mostly observed in young adults. TSH-R gene and G-protein stimulating gene (gsp) mutations may be observed in these patients.

Thyroid cancers are the most frequent endocrine cancers that develop from thyroid epithelial cells. Papillary cancer originating from follicular epithelial cells is responsible for 80% of the cases. The incidence of follicular cancer that also arises from epithelial cells, and medullary cancer which originates from parafollicular (C cells) are 14% and 4%, respectively. Approximately 3% of follicular carcinomas are oncocytic type cancers.

Thyroid cancer is the 9th leading type of cancer worldwide and the mortality rate from thyroid cancer is about 0.5/100000 [4]. Papillar thyroid microcarcinomas (PMCs), defined by WHO as lesions which are smaller than 1.0 cm, are more commonly observed. Majority of the patients with PMCs have excellent prognosis, however in some sub-groups PMCs are as agressive as large solid tumors [5]. Until recently, it was believed that thyroid cancers rarely developed in patients with hyperthyroidism, and even more hyperthyroidism did protect from cancer [6]. However, recent studies have revealed that the prevalence of undifferentiated thyroid cancer is much more in patients with hyperthyroidism than in the normal population [7]. Current hypothesis of carcinogenesis includes thyroid stimulating antibodies as inducing insulin-like growth factors and promoting invasion and angiogenesis [8].

The aim of this study isto determine the incidental thyroid cancer rates in patients undergoing operation due to hyperthyroidism, and to specify patient groups in whomsurgical treatment should come into the foreground.

Methods

A total of 591 patients who had undergone an operation due to hyperthyroidism at the Endocrine Surgery Unit of General Surgery Department of Dokuz Eylul University between January 2007 and June 2017 were retrospectively included in the study. Patients whose data could not be reached, those diagnosed with a non-thyroid malignancy, and those whose treatment could not be completed due to any reason, were not included in the study. Data management system of the hospital was used for the data collection. The approval of Dokuz Eylul University Medical Faculty Ethical Committee for was obtained (101018-593).

The cause of hyperthyroidism was defined according to positive Thyroid stimulating antibody (TRAb)

ho developed thyroid cancer was 57±12 years (range 25-84). Eighty-six patienand/or nuclear thyroid scintigraphy, together with clinical and biochemical characteristics. The indications for surgery were as follows: medical therapy failure, presence of a pregnancy plan within 4-6 months , compression-related symptoms, suspicious for malignancy, patient preference, ophthalmopathy, and RIA inconsistency. None of the patients had received radioactive therapy or radiotherapy to the cervical region prior to the operation.

All patients were examined with thyroid ultrasonography (US) (with 5-7 MHz probe) before the operation. TSH, free tri-iodothyronine (fT3), free thyroxine (fT4) levels, TRAb, AntiTPO, AntiTg and thyroid scintigraphy results for some patients were also evaluated. Patients were divided into 4 groups according to the pre-operative assessment as GD without nodule, nodular GD (NG), TMNG and TA. Some patients who were suspicious for malignancy underwent fine needle aspiration biopsy (FNAB).(Fine needle aspiration biopsy becomes the gold standard in the diagnosis of particularly solitary nodules bigger than 1 cm and/or nodules which have malignancy criteria in ultrasound imaging [9]. Five patients underwent complementary thyroidectomy following lobectomy, whereas all the remaining patients underwent total or subtotal thyroidectomy. AJCC/UICC Staging system (8th edition) was used to determine the stage of the cancer in patients who developed thyroid cancer.

Statistical analysis was performed using the SPSS software (SPSS Inc., Chicago, IL). The frequency distribution of categorical variables between subgroups was compared by the continuity corrected chi square test, Fisher's exact test, or the Kruskal–Wallis test. Numerical variables between subgroups were compared by unpaired t tests. The continuous data were expressed as mean values ± standard deviation. A p value less than 0.05 was considered statistically significant.

Results

A total of 591 patients who had undergone thyroidectomy due to hyperthyroidism were included in the study. Of all the patients, 377 (63.7%) had TMNG, 132

(22.3%) had GD, 55 (9.4%) had NG, and 27 (4.6%) had TA. Most of the patients were female (434/591 (73.5%), whereas 157 (26.5%) were male. The female/male ratio was 2.77:1 (Table I).

The mean age of the patients with HT wts who developed cancer were female (65.6%) and 45 were male (34.4%). The causes of HT were TMNG (89/131, 67.9%), NG (24/131, 18.3%), GD (13/131, 9.9%) and TA (5/131, 2.8%). The duration between diagnosis of HT and surgery was in the range of 1 month and 138 months (mean 20.4±24 months). The patients weretreated with either Propylthiouracil (PTU) (53/131, 48.1%) or Methimazol (43/131, 32.8%) until the operation. Pre-operative imaging methods revealed a thyroid nodule in 118 patients (118/131, 90%). FNAB was performed in 42 out of 118 patients who were determined to have a nodule (42/118, 32.1%) (Table II).

Total or subtotal thyroidectomy was performed in all of our patients, except 27 patients with TA and 1 patient with TMNG, in whom all the nodules were collected in one lobe (563/591 95.2%). Complementary thyroidectomy was performed in 6 patients in whom papillary cancer was detected after the surgery pathologically (5 of them had TA and 1 patient had TMNG).

Central and/or neck dissection was not performed in the patients, as no lymph nodes with suspicious for metastasis were detected on the imaging methods and intraoperatively. There was no post-operative morbidity or mortality. The mean duration of follow-up was 104 months (± 32months).

Tumor pathology was analyzed in 8 subgroups, with the micropapillary histologic type as the most common (Table III).

The mean ages of the patients with GD and TMNG

Table I - *Operated HT cases*

	TMNG (N=377)	GD (N=132)	NG (N=55)	TA (N=27)	Total (N=591)
GENDER					
famele	301(79.8%)	85(64.3%)	31(56.3%)	17(62.9%)	434(73.5%)
male	76(20.2%)	47(35.7%)	24(43.7%)	10(37.1%)	157(26.5%)
AGE (MEAN) (min-max±SD)	58(33-79±10)	54(24-65±11)	59(39-84±13)	55(34-70±12)	56(24-84±12)
With TC	89(23.6%)	13(9.8%)	24(43.6%)	5(18.5%)	131(22.2%)

Table II - *Preoperative characteristic of HT with TC*

	N	Mean	±SD	Min	Max
Age	131	57.5	12.7	25	84
TSH (□IU/m)	131	0.44	0.53	0.004	1.9
Free T3 (pg/mL)	131	3.891	2.794	0.59	29.2
Free T4 (ng/dL)	131	1.48	1.18	0.31	11.6
AntiTPO (IU/mL)	103	88.6	232.5	0	1000
AntiTG (IU/mL)	103	69	278.1	0	2500
TRAB (U/L)	65	7.7	24.01	0.1	150
Size of Thyroid (cm)	131	6.7	1.79	4	15
Size of nodule (cm)	118	2.8	0.51	1	3

Normal ranges :TSH 0.38-5.33 □IU/mL; fT3 2.5-3.9 pg/mL; fT4 0.5-1.51 ng/dL; AntiTPO 0-35 IU/mL; AntiTG 0-40 IU/mL; TRAB 0-1 U/L negative, 1.1-1.5 U/L Borderline, >1.5 U/L Positive.

Table III - *Patient pathological characteristic*

	N	%	Microcarsinoma (tm size <1cm)	Carsinoma (tm size ≥1cm)	Multifocal cancer
Thyroid papillary cancer (TPC)	6	4.6%	2	4	2
Thyroid papillary cancer follicular variant (TPCFV)	37	28.2%	12	25	22
Micropapillary thyroid cancer (MPTC)	35	26.7%	35	0	3
Thyroid papillary cancer oncositic variant (TPCOV)	12	9.2 %	6	6	7
Micropapillary thyroid cancer follicular variant (MPTCFV)	30	22.9 %	28	2	5
Thyroid follicular cancer (TFC)	7	5.3%	1	6	2
Microinvazive follicular cancer (MİFC)	3	2.3%	2	1	2
Thyroid follicular cancer oncositic variant	1	0.8%	0	1	0

TABLE IV - *Thyroid Cancer with Graves disease (GD+NG) and TMNG*

Factor	Total (N= 126)	TMNG(N=89)	GD+NG(N=37)	p-value
Age (mean-year)	57[25-84]	58[33-79]	55[24-84]	0,578b
Gender				0,167 c
Famale	84 (66.7%)	56 (62.9%)	28(75.7%)	
Male	42 (33.3%)	33 (37.1%)	9 (24.3%)	
Reason for surgery rerferral				0,00d
Suspicious cancer	41 (32.5%)	30 (33.7%)	11 (29.7%)	
Medical therapy failure	51 (40.5%)	36 (40.4%)	15 (40.5%)	
Patient preference	14 (11.1%)	13 (14.6%)	1 (2.7%)	
Pressure symptoms	10 (7.9%)	9 (10.1%)	1 (2.7%)	
Ophtalmopathy	10 (7.9%)	1 (1.1%)	9 (24.3%)	
FNAB	42 (33.3%)	30 (33.7)	12 (32.4%)	0,415d
FNAB result				0,918d
Benign	32 (76.2%)	23 (76.7%)	9 (75%)	
Malign	6 (14.3%)	4 (13.3%)	2 (16.7%)	
Atypia	3 (7.1%)	2 (6.7%)	1 (8.3%)	
Nondiagnostic	1 (2.4)	1 (3.3%)	0 (0%)	
Ophthalmopathy	13 (10.3)	2 (2.2 %)	11 (29.7%)	<0,001b
TSH (mean±SD)	0,442 (±1.16)	0,456(±1.2)	0,407(±1.08)	0,210b
Free T3 (mean±SD)	3.88 (±2.7)	3.71 (±2.8)	4.33 (±2.5)	0,222b
Free T4(mean±SD)	1.51 (±1.01)	1.43 (±1.26)	1.58 (±0.9)	0,656b
Usg Suspicion	40 (31.7%)	33 (37.1%)	7 (18.9%)	0,046c
Size of nodüle				0,035c
0.5-1 cm	15 (13.3%)	8 (9.1%)	7 (28.0%)	
1-2 cm	39 (34.5%)	29 (33%)	10 (40%)	
2-3 cm	28 (24.8%)	23 (26.1%)	5 (20%)	
>3	31 (27.4%)	28 (31.8%)	3 (12%)	
Nuclear Thyroid Scan	62 (49.2%)	41 (46.1%)	21 (56.8%)	0,185d
Nuclear feature nodule				<0,001c
Hot	41 (66.1%)	41 (100%)	0 (0.0%)	
Cold	39 (62.9%)	23 (56 %)	16 (76.1)	
Holt+Cold	21 (32.3%)	18 (40.9%)	3 (14.3%)	
Not done	5 (7.7%)	5 (23.8%)	0 (0.0%)	
Multi-focality	83 (65.9%)	55 (61.8%)	28 (75.7%)	0,097d
T Stage				
T1a	86 (67.4%)	59 (66.2%)	27 (72.9%)	0,532b
T1b	23 (18,2%)	15 (16.8%)	8 (21.6%)	
T2	15 (12.3%)	13 (14.6%)	2 (5.4%)	
T3	2 (1.6%)	2 (2.2%)	0 (0.0%)	
Vasculer invasion	6 (4.8%)	6 (6.7%)	0	0,118d
Thyroid capsule invasion	12 (9.5%)	9 (10.1%)	3 (8.1%)	0,509 d
Extrathyroid invasion	3 (2.4%)	2 (2.2%)	1 (2.7%)	0,881 d
Postoperative RAI	61 (48.4%)	45 (50.6%)	16 (43.2%)	0,454 c

Values presented as Median [P25, P75] or N (column %). p-values: b = Kruskal–Wallis test, c = Pearson's chi-square test, d = Fisher's Exact test.

who developed thyroid cancer were 55 years and 58 years (p=0.578), respectively. No significant difference was determined between the groups with regard to gender (p=0.167). When the laboratory results of the same patient groups were evaluated, the mean TSH, fT3, fT4 levels were similar in both groups. A difference was detected in Nuclear Thyroid Scan (NTS) images of 62 patients in both groups (p<0.001). No difference was determined between the groups with regard to tumor size, multi-focality, vascular invasion, thyroid capsule invasion, and extra-thyroid invasion rates (Table IV). Five out of 27 patients (18.5%) who had undergone surgery due to toxic adenoma had thyroid cancer. Pathologic examination of these 5 patients revealed that instead of a toxic adenoma nodule, the patients had a tumor, the size of which ranges between 3 cm and 5 cm (T2), and all were found to be of follicular type. The patients were evaluated by a multi-disciplinary team and 61 (48.4%) of them received RAI treatment (p=0.454).

Discussion

Thyroid cancer was determined in 131 out of 591 HT cases (22.2%) who had undergone an operation, and the

vast majority was of micropapillary type (n=65; 49.6%). It is not realistic to determine thyroid cancer prevalence only based on autopsy examinations. In an autopsy study, the micropapillary type thyroid cancer prevalence was reported to be less than 2% in patients under 40 years [10]; the rate was reported to rise to 12% in advanced age [11]. In another study investigating all age groups, the rate was determined as 7% [12] supporting the previous study. Phitayakorn et al. (2008) investigated the prevalence of papillary thyroid cancer and GD, MNG and TMNG in a retrospective analysis of 507 patients, and reported GD with thyroid cancer as 2.2%, and TMNG with thyroid cancer as 6.2% [13]. However, higher rates have also been reported in the literature supporting our study. The total number of GD was 187 (132 GD and 55 NG). The thyroid cancer rate was determined as 9.8% and NG was determined as 43.6% in GD. Thyroid cancer prevalence was found as 19.7% when all Graves' patients were evaluated (GD and NG) and this rate was quite higher than that reported in previous studies. Coexistence of GD and thyroid cancer was reported as 5.1% in the study of Farbota et al. in 1985, 2.6% in the study of Ozaki et al. in 1990 (19 out of 743 cases), and this rate varies between 2% and 10% in many studies [14-17]. We consider that the limited surgical procedure or insufficient histological examinations in previous studies have led to this difference. In the recent studies in the literature, the rate of coexistence of GD and thyroid cancer was reported as 26% in the study of Ergin et al. [18]. This rate was reported as 32% and 33.7% in the studies of Wei Shuanzeng et al. and Boutzios et al., respectively [16,17]. The high thyroid cancer ratio in NG patients in our study (43.6%) emphasizes that the operation selection was made more carefully, and that the follow-up of a nodule in the disease setting is significant. This coexistence has been emphasized in recent studies in the literature and is prominent when non-surgical treatments are applied. The mean age of the GD patients who were determined to have thyroid cancer was 55(24-84), the mean age of the TMNG patients who were determined to have thyroid cancer was 58(33-79), and the difference was not significant (p=0.578). The mean ages in the studies of Shuanzeng et al. and Preece were 41 years and 43 years, respectively [19,21]. These ages were younger than that found in our study The mean ages in the studies of Ergin [18] and Abbas 22 were determined as 53 years and 54 years, respectively, similar to our study. Suspicious for malignancy, failure of medical therapy, failure and/or inappropriate uptake of RAI, ophthalmopathy, and compression-related symptoms are indications for thyroidectomy in hyperthyroid patients. A statistically significant difference was determined between the patients with GDand TMNG patients with thyroid cancer. While compression-related symptoms and patient preference were greater in the TMNG group, ophthalmopathy was more common among patients with GD (p=0.00). The rates (p=0.415) and results (p=0.918) of FNAB procedure performed to 42 (33%) patients who were determined to have a nodule prior to the operation were similar in both groups. The nodule sizes were significantly different in both groups with thyroid cancer (p=0.035), and the rate of suspicious for malignancy was higher in the TMNG group (p=0.046).

Five thyroid cancers were determined in 27 patients who had undergone an operation due to toxic adenoma. Despite the small number of cases, all of these 5 patients had follicular cancer with T2 tumor (tumor size ranging between 2 cm and 5 cm), two had vascular and lymphatic invasion. In the literature, thyroid cancerrate was reported between 2.5% and 12% among patients with TA [23]. Higher cancer rates among patients with TA in our study may be associated with the small number of patients, acting selectively for the operation criteria.

Treatment of nodules when evaluating hyperthyroidism is still of debate. Even the presence of a nodule in GD severely increases the rate of thyroid carcinoma. Cancer was determined at a rate of 46% in NG patients in our study group. Early thyroidectomy is recommended in endemic areas, as reported in many papers [24-26].

The mean follow-up of the patients was 104 months. The vast majority of carcinomas developing in a background of hyperthyroidism are microcarcinomas and their treatment is still of debate. These tumors are usually determined incidentally during surgery, which is performed for treatment of hyperthyroidism. However, it is well-known that microcarcinomas may lead to metastasis and even death [27-30]. Althoughsome researchers have reported that carcinoma is more aggressive in patients with hyperthyroidism, there is opposite data in the literature as well [8,31].

Limitations of the Study

Although some data could not be accessed due to the retrospective design of the study, this did not affect the results of our study. Thyroid US, which is used for detection of a nodule in the pre-operative period, may be useful for selecting total thyroidectomy; all patients were evaluated by the endocrine surgery team and additional imaging methods were performed as required.

In conclusion, the rate of carcinoma in hyperthyroidism has gradually increased in recent years as the indications for surgery and pathological examination are carried out more meticulously. The rate of detecting carcinoma in the pre-operative period is still insufficient. Our study has revealed that despite the absence of a significant association between the size of a nodule and development of cancer, the risk is significantly high in the presence of a nodule. Although most cancers are micropapillary type without lympho-vascular invasion and very low lymph node metastasis ratios, the rate of 46% of thyroid cancer development cannot be neglected, and surgical intervention should be primarily considered in patients with nodular Graves Disease.

Riassunto

L'ipertiroidismo ha diverse eziologie e differenti manifestazioni cliniche. Le cause più comuni sono il gozzo multi-nodulare tossico, la malattia di Graves e l'adenoma tossico. La prevalenza del cancro alla tiroide che si sviluppa in pazienti con ipertiroidismo è gradualmente aumentata negli ultimi anni. Lo scopo di questo studio è di rilevare i tassi incidentali di cancro alla tiroide in pazienti che hanno subito un intervento chirurgico a causa di ipertiroidismo e di specificare i gruppi di pazienti in cui il trattamento chirurgico dovrebbe essere di primo approccio.

La casistica studiata retrospettivamente riguarda 591 pazienti sottoposti ad escissione chirurgica della tiroide a causa di ipertiroidismo tra gennaio 2007 e giugno 2017. Di tutti i pazienti inclusi nello studio, 377 (63,7%) avevano gozzo multi-nodulare, 132 (22,3%) avevano la malattia di Graves, 55 (9,4%) avevano la malattia di Graves nodulare e 27 (4,6%) avevano un adenoma tossico. Il cancro della tiroide è stato individuato 131 sul totale dei pazienti analizzati (22,6%). Il tipo istologico più comune era il carcinoma micropapillare tiroideo (65/131, 49.6%) e le patologie associate al carcinoma tiroideo erano rispettivamente un gozzo multinodulare tossico (89/131; 67,9%), la malattia di Graves nodulare (24/131; 18,3%), la malattia di Graves (13/131; 9,9%) e l'adenoma tossico (5/131; 2,8%).

La presenza del cancro su uno sfondo di ipertiroidismo è gradualmente aumentata negli ultimi anni, e non è realistico determinare l'incidenza del cancro tiroideo solo sulla base di esami di autopsia. Questo tasso aumenta significativamente in presenza di noduli negli studi clinici, e la maggior parte dei carcinomi sono microcarcinomi che non presentano invasione linfovascolare e con bassa incidenza di metastasi linfonodali.

Pertanto, il loro trattamento è ancora in discussione.

Referances

1. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, Walter MA: *2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis*. Thyroid, 2016; 26:1343-421.

2. Bahn RS, Hurch HB, Cooper DS, Garber JR, Greenlee C, Klein I, et al.: *Hyperthyroidism and other causes of thyrotox- icosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocri-nologists*. Endocr Pract, 2011; 17:1-53.

3. Mishra A, Mishra S: *Thyroid nodules in Graves' disease: Implications in an endemically iodine deficient area*. J Postgrad Med, 2001; 47:244-47.

4. L.M. Farbota DB, Calandra AM, Paloyan LE: *Thyroid carcinoma in Graves' disease*. Surgery, 1985; 98 (6):1148e1153.

5. Ardito G, Avenia N, Giustozzi E, Salvatori M, Fadda G, Ardito F, Revelli L: *Papillary thyroid microcarcinoma: Proposal of treatment based on histological prognostic factors evaluation*. Ann Ital Chir, 2014; 85(1):1-5.

6. Gelmini R, Franzoni C, Pavesi E, Cabry F, Saviano M: *Incidental thyroid carcinoma (ITC): A retrospective study in a series of 737 patients treated for benign disease*. Ann Ital Chir. 2010; 81(6):421-27.

7. Gabriele R, Letizia C, Borghese M, De Toma G, Celi M, Izzo L, Cavallaro A: *Thyroid cancer in patients with hyperthyroidism*. Horm Res, 2003; 60:79e83.

8. Hales IB, McElduf A, Crummer P, Clifton-Bligh P, Delbridge L, Hoschl R, Poole A, Reeve TS, Wilmshurst E, Wiseman J: *Does Graves' disease or thyrotoxicosis affect the prognosis of thyroid cancer?* J Clin Endocrinol Metab, 1992; 75 (3):886e889.

9. Wilson SD: *Thyroid gland morphology in young adults: Normal subjects versus those with prior low-dose neck irradiation in childhood.* Thyroid, 1983; 94:984-88.

10. Nishiyama RH, Ludwig GK, Thompson NW: *The prevalence of small papillary thyroid carcinomas in 100 consecutive necropsies in an American population.* In *Radiation-Associated Thyroid Carcinoma* In Eds pp. 123-35. Eds. De Groot LJ Frohman LA Kaplan EL Refetoff S, New YorkGrune & Stratton 1977.

11. Pezzolla A, Lattarulo S, Madaro A, Docimo G, Lacalendola E, Prete F, Marzaioli R: *What really is an indeterminate FNA thyroid nodule?* Ann Ital Chir, 2017; 88:275-81.

12. Bondeson L, Ljungberg O: *Occult papillary thyroid carcinoma in the young and the aged.* Cancer, 1984; 53:1790-92.

13. Phitayakorn R, McHenry CR: *Incidental thyroid carcinoma in patients with Graves' disease.* Am J Surg, 2008; 195:292-97.

14. Ozaki O, Ito K, Kobayashi K, et al.: *Thyroid carcinoma in Graves' disease.* World J Surg, 1990; 14:437-40 [discussion 440-1; May-Jun].

15. Pellegriti G, Belfiore A, Giuffrida D, et al.: *Outcome of differentiated thyroid cancer in Graves' patients.* J Clin Endocrinol Metab 1998;83:2805-9.

16. Miccoli P, Minuto MN, Galleri D, et al.: *Incidental thyroid carcinoma in a large series of consecutive patients operated on for benign thyroid disease.* ANZ J Surg, 2006; 76:123-6.

17. Behar R, Arganini M, WuTC, et al.: *Graves'disease and thyroid cancer.* Surgery, 1986; 100:1121-27.

18. Ergin AB, Saralaya S, Olansky L: *Incidental papillary thyroid carcinoma: clinical characteristics and prognostic factors among patients with Graves' disease and euthyroid goiter, Cleveland Clinic experience.* Am J Otolanryngol Head Neck Med Surg, 2014; 784-90.

19. Wei S, Baloch ZW, LiVolsi VA: *Thyroid carcinoma in patients with Graves' disease: an institutional experience.* Endocr Pathol, 2015; 26:48-53.

20. Boutzios G, Vasileiadis I, Zapanti E, Charitoudis G, Karakostas E, Ieromonachou P, Karatzas T: *Higher ıncidence of tall cell variant of papillary thyroid carcinoma in graves' disease.* Thyroid 2014, 24(2):347-54.

21. Preece J, Grodski S, Yeung M, Bailey M, Serpell J: *Thyrotoxicosis does not protect against incidental papillary thyroid cancer.* Surgery; 2014; 1153-56.

22. Tam AA, Kaya C, Kılıç FBM, et al.: *Thyroid nodules and thyroid cancer in Graves' disease.* Arq Bras Endocrinol Metabol, 2014; 58:933-38.

23. Pazaitou-Panayiotou K, Michalakis K, Paschke R: *Thyroid cancer in patients with hyperthyroidism.* Horm Metab Res, 2012; 44: 255-62.

24. Erbil Y, Barbaros U, Özbey N, Kapran Y, Tükenmez M, Bozbora A, Özarmağan S: *Graves' disease, with and without nodules, and the risk of thyroid carcinoma.* The Journal of Laryngology & Otology, 2008; 122(3), 291-295. doi:10.1017/ S0022215107000448

25. Belfiore A, Russo D, Vigneri R, Filetti S: *Graves' disease, thyroid nodules and thyroid carcinoma.* Clin Endocrinol, 2001; 55:711-18

26. Kraimps JL, Bouin-Pineau MH, Mathonnet M, DeCalan L, Ronceray J, Visset J et al: *Multicentre study of thyroid nodules in patients with Graves' disease.* Br J Surg, 2000; 87:1111-13.

27. Lee J, Nam KH, Chung WY, et al.: *Clinicopathologic features and treatment outcomes in differentiated thyroid carcinoma patients with concurrent Graves' disease.* J Korean Med Sci, 2008; 23:796–801.

28. Okamoto T, Iihara M, Obara T: *Management of hyperthyroidism due to Graves' and nodular diseases.* World J Surg, 2000; 24:957-61.

29. Ringel MD, Ladenson PW: *Controversies in the follow-up and management of well-differentiated thyroid carcinoma.* Endocrine-Related Carcinoma, 2004; 11:97-116.

30. Pellegriti G, Scollo C, Lumera G, Regalbuto C, Vigneri R, Belfiore A: *Clinical behavior and outcome of papillary thyroid carcinomas smaller than 1.5 cm in diameter: study of 299 cases.* J Clin Endocrinol Metab, 2004; 89:3713-20.

31. Carnell NE, Valente WA: *Thyroid nodules in Graves' disease: classification, characterization, and response to treatment.* Thyroid, 1988; 8:571–76