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Research Article

Characteristics of Well Differentiated Thyroid Carcinoma Associated with Hyperthyroidism

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Abstract

Objectives: This paper aim to report characteristics of well differentiated thyroid carcinoma associated with hyperthyroidism: Grave's disease, toxic multinodualr goiter, and toxic uninodular goiter.

Methods: The medical records of all consecutive patients who underwent surgery for hyperthyroidism were reviewed with regard to patient demographics, clinical presentation, preoperative biological and imaging findings, surgery, pathology and follow-up records.

Results: 11% presented hyperthyroidism associated with well differentiated thyroid carcinoma. Papillary thyroid carcinoma being the most common histological type. Papillary microcarcinoma, multifocality, bilaterality, and recurrence were more associated with Grave's disease. Extrathyroid extension, and positive lymph nodes were more showed in toxic multinodualr goiter. We noted three differences (size of the nodules, recurrence, and presence of distant metastases) without reaching statistically significance in the characteristics and prognosis of well differentiated thyroid carcinoma in euthyroid patients compared to hyperthyroid patients.

Conclusion: Well differentiated thyroid carcinoma was more associated with Grave's disease. We did not show any statistically significance difference in characteristics of well differentiated thyroid carcinoma in euthyroid patients compared to hyperthyroid patients.

Keywords: Euthyroidism; Hyperthyroidism; Prognosis; Surgery; Thyroid carcinoma

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Introduction

The prevalence of thyroid carcinomas found during surgery in hyperthyroid patients is reported to vary widely, ranging up to 21.1% [1-17]. Thyroid cancer is typically present with euthyroid or clinical/subclinical hypothyroidism. Thyrotoxicosis with suppressed TSH should lead to a lower incidence of thyroid cancer than that observed in euthyroid patients. The most frequently reported type associated with hyperthyroidism is Papillary Thyroid Carcinoma (PTC) [1,6,18-32]. Some studies reported that thyroid cancer is diagnosed more frequently in patients with Graves' Disease(GD) [28-39], than in patients with Toxic Uninodular Goiter (TUG) [40-52] or toxic multinodular goiter (TMG) [7,8,13,53-56], whereas other studies presented the same results for GD, but slightly higher carcinoma prevalence within hot nodules and TMG. In many cases thyroid cancer is not known preoperatively, but is found incidentally during postoperative histologic examination of the thyroid. Most carcinomas are small in size and the majority is microcarcinomas [3,26-31]. Some reports describe the thyroid cancer associated with hyperthyroidism as very aggressive, often invasive, and metastatic to regional lymph nodes, even when the primary tumor is small and possibly fatal; in other series the clinical course was not different from euthyroid patient [1,2,6-13,14-20]. The aim of this paper was to report our series of patients operated for Well Differentiated Thyroid Carcinoma (WDTC) associated with hyperthyroidism and evaluate characteristics of these associations.

Patients and Methods

Patients

From January 2000 to June 2022, the medical records of all consecutive patients who underwent primary thyroid surgery were retrospectively reviewed. Of these patients, those who presented with hyperthyroidism prior to the thyroidectomy were selected. This study was approved by the Institutional Review Board. Access permit to the included patients' files was obtained from hospital ethical committees. Exclusion criteria: familial history of thyroid cancer, previous exposure to ionizing radiation or external head-and-neck radiotherapy, previous thyroid or neck surgery. Multiple variables were collected: Clinical data: age, gender, symptoms of hyperthyroidism, presence of goiter; Biological data: preoperative serum concentrations of Triiodothyronine (T3), Thyroxine (T4), Thyroid-Stimulating Hormone (TSH), Thyroid-Stimulating Hormone Receptor Antibody (TRAb), Thyroglobulin (Tg), Thyroglobulin Antibody (TgAb) and Thyroperoxidase Antibody (TPOAb) concentrations were assessed at baseline; Radiological and histologic data: type of imaging done to aid the diagnosis of the thyroid pathology, the etiology of hyperthyroidism were reviewed, results of perioperative pathologic examinations including Fine Needle Aspiration Cytology (FNAC), frozen section, and permanent pathology were also reviewed. Indications for surgery included clinical findings such as severe disease with recurrence after medical treatment, side effects of medication, large goiter size causing locally compressive symptoms, clinical and /or FNAC suspicion of malignancy, or patient preference. Iodine-free solutions

were used to swab the operative field. All surgeries were done under general anaesthesia using horizontal cervical incision. The thyroidectomies were all performed in a similar fashion with careful dissection attempting to identify and preserve the parathyroid glands with their vascular supply, as well as the recurrent laryngeal nerves. We performed central and/or lateral neck dissection when there were pre or intraoperative evidence of enlarged lymph nodes in these areas. Valsalva maneuver was performed at the end of thyroidectomy in all patients to detect hemorrhage. Cervical wound was closed without drain tubes in all cases. Monitoring of the cervical wound was assessed closely in the postoperative period. The presence of local complications (hemorrhage, hematoma, seroma) and time to hospital discharge were noted. Postoperative complications (vocal cord paralysis and hypocalcaemia) were recorded. Post-operative variables and Follow-up includes pathologic results of the thyroid specimen, and histological types of thyroid cancer. In this retrospective series, patients were treated after surgery with RAI ablation after thyroid hormone withdrawal or in euthyroidism after administration of recombinant human TSH (rhTSH) when indicated. Post-surgical staging was assessed according to pTNM staging system. During follow-up, ranged from 12 to 240 months, (every 6-12 months), serum FT4, TSH, TRAb (in Graves' patients), thyroglobulin (Tg) and TgAb were measured. US were repeated every 6-12 months to detect persistent or recurrent regional disease. If US pattern was suspicious for recurrence, FNAB (with Tg measurement in the needle washout fluid) was performed.

Statistical Analysis

The data were plotted in Microsoft excel 2017 and analysed with descriptive statistics using SPDD 22. Continuous variables are reported as mean ± standard deviation, and categorical variables are reported as number and percentage. Discrepancy was evaluated by comparing outcomes between the groups using 2x2 Fisher's exact test; statistical significance for comparison between nominal variables was set at $p<0.05$.

Results

From January 2000 to June 2022, 6123 patients underwent thyroidectomy. All the medical records of 642 who underwent surgery for hyperthyroidism during this period were analyzed retrospectively. Of these, 73 patients (11%) presented hyperthyroidism with WDTC (54 females and 19 males; mean age at diagnosis, 32.4 years; range, 16-81 years), satisfied inclusion criteria were included in this study. Hyperthyroidism was diagnosed on the basis of elevated T3, elevated T4, and low TSH concentrations in combination with hyperthyroid clinical symptoms and signs. Before administration of antithyroid medications, mean serum T3 concentration was 350.8 ng/dL (range, 173.3-800ng/dL), and that of T4 was 18.7ng/dL (range, 14.1-39ng/dL). Serum TSH concentration was less than 0.1mIU/mL in each patient. The 73 patients could be classified into three major groups: 46(63%) had GD, 24(33%) had TMG, and 3(4%) had TUG. Methimazole treatment was typically used prior to surgery to achieve a euthyroid state. Three patients had received both antithyroid drugs and radioiodine. The duration of symptoms before hospital visits ranged from 3 months to 11 years. 11 patients presented with large goiter. All the patients 100% had undergone a cervical ultrasound, while 67% (n=49), 7% (n=5), and 5% (n=4) had undergone a thyroid scan, CT scan and MRI of the neck respectively. Thyroid ultrasound revealed calcification in 6 patients with GD. FNAC under US was performed in 17 patients before thyroidectomy. 4 patients had benign results, seven malignant result, 4 indeterminate results, and the results from 2 patients were inconclusive because of scanty cellularity in the cytology specimen. Total or near total thyroidectomy was the surgical procedure performed on 63 and 9 patients respectively. 1 patient with TUG underwent unilateral thyroidectomy. Tumor specimens from 9 patients in whom frozen-section analysis was performed had readings malignant in 6 cases. The number of identified parathyroid glands were 4 in 62 patients (83%), three in 8 patients (11%), and two in 4 patients (6%). Recurrent laryngeal nerves were identified and preserved in all the patients. The mean of the size of the largest nodule was 3.5cm±2.09cm, 61% of the included cases had a size of the largest nodule below 3.5 cm. 17 patients (23%) underwent lymph node dissection. 8 patients (8/73=11%) were positive for lymph node metastases. The pathological diagnoses of the resected tumors showed papillary carcinomas n=50; 69%-Follicular Carcinoma (FTC) n=2; 2%-microcarcinoma n=21; 29%%. Multifocality and bilaterality were showed in 23% and 18% respectively. Extrathyroidal extension and recurrence were seen in 3% and 1% respectively. Weight of the thyroid tissue averaged 83g (53g-644g). All patients underwent thyroid-stimulating hormone suppression therapy. Radioactive iodine treatment was considered in patients with high risk for recurrence and when indicated. None of the patients underwent postoperative external radiation therapy. Follow-up evaluations, including physical examination, neck ultrasound, serum thyroglobulin, and thyroglobulin antibodies, were performed at intervals of 6-12 months. There was no peri- or postoperative mortality among our patients. Mean follow-up was 78.3 months (range, 12-240 months). 71 patients were alive and apparently free of residual disease at the time of writing. Two patients had persistence or recurrence of biochemical disease only. In our series, WDTC was more associated and in statistically significant way with GD then TMG and TUG (63%, 33%, and 4% respectively). The classic variant of PTC being the most common histological type (69%) and showed with GD, TMG, and TUG in 63%, 79%, and 67% respectively (differences statistically significant). Papillary microcarcinoma was associated with GD, TMG, and TUG in 35%, 21%, and 0% respectively (differences statistically significant). FTC was associated more with TUG (13%), than GD (2%), and TMG (0%). Positive lymph nodes were present with GD, TMG, and TUG in 11%, 13%, and 0% respectively (differences statistically significant). Multifocality and bilaterality were associated with GD, TMG, and TUG in 26%, 20%, and 0% respectively, 20%, 17%, and 0% respectively (differences statistically significant). Extrathyroid extension showed with GD, TMG, and TUG in 2%, 4%, and 0% respectively. Locoregional recurrence and distal metastases were seen with GD, TMG, and TUG in 2%, 0%, and 0% respectively, 0%, 0%, and 0% respectively. In our series, we noted 3 differences (size of the nodules, recurrence, and presence of distant metastases) without reaching statistically significance in the characteristics and prognosis of WDTC in euthyroid patients compared to hyperthyroid patients (Tables 1 & 2).

Patients	GD	TMG	TUG	P value
Number n=73	46(63%)	24(33%)	3(4%)	<0.001
Gender(F/M)	35/11	17/7	2/1	NS
Age	16-67	27-81	22-79	0.11
Tumor size(cm)	0.3-4	0.5-6	2-4	0.72
Bilateral thyroidectomy	100%	100%	67%	0.13
PTC n=50 (69%)	29(63%)	19(79%)	2(67%)	0.08
FTC n=2 (2%)	1(2%)	0(0%)	1(13%)	<0.0002

Microcaner n=21 (29%)	16(35%)	5(21%)	0(0%)	<0.001
Positive Lymph node n=8(11%)	5(11%)	3(13%)	0(0%)	<0.001
Mulifocality n=17(23%)	12(26%)	5(20%)	0(0%)	<0.001
Bilaterality n=13(18%)	9(20%)	4(17%)	0(0%)	<0.001
Extra thyroid extension n=2(3%)	1(2%)	1(4%)	0(0%)	0.49
Recurrence n=1(1%)	1(2%)	0(0%)	0(0%)	0.77
Metastases n=0(0%)	0(0%)	0(0%)	0(0%)	0.99

Table 1: Characteristics of patients with WDTC associated with Hyperthyroidism.

Patients	WDTC with euthyroidism	WDTC with hyperthyroidism	P value
Gender(F/M) %	78/22	74/26	NS
Age	6-83	16-81	0.43
Tumor size(cm)	0.5-13	0.3-6	0.01
Bilateral thyroidectomy %	98	99	0.99
PTC %	67	69	0.87
FTC %	3	2	0.76
Microcaner %	30	29	0.93
Positive Lymph node %	14	11	0.31
Mulifocality %	26	23	0.57
Bilaterality %	20	18	0.28
Extra thyroid extension %	5	3	0.19
Recurrence %	3	1	0.03
Metastases %	2	0	0.02

Table 2: Comparaison of WDTC in euthyroid patients and in hyperthyroid patients.

Discussion

In our series, 11% (73/642) of patients operated for hyperthyroidism had thyroid carcinoma. GD, TMG, and TUG represented 63%, 33%, and 4% of hyperthyroid patients with thyroid cancer. 72 patients underwent bilateral thyroidectomy and 1 patient underwent unilateral thyroidectomy. 17 patients (23%) underwent lymph node dissection, of which 8 patients (47%) had lymph node metastases. 98% of patients in our series had the classic variant of papillary thyroid carcinoma, of which 29% had a papillary microcancer. Follicular variant represented 2% of these cases. Lymph node involvement, extrathyroid extension, and recurrence were seen in 11%, 3%, and 1% respectively. In our series, we noted 3 differences (size of the nodules, recurrence, and presence of distant metastases) without reaching statistically significance in the characteristics and prognosis of WDTC in euthyroid patients compared to hyperthyroid patients (Table 2). In recent years, reports have appeared on the growing prevalence of thyroid cancer in hyperthyroid patients. This increase is probably due to multiple factors, including the cause of hyperthyroidism, the different criteria for choosing surgery as the treatment modality of hyperthyroidism, the extent of thyroidectomy (lobectomy or total thyroidectomy), but most likely due to the extent of histological examination of the removed thyroid tissue and possibly also the geographical variation in incidence of thyroid cancer in general [2-6,11,13-18]. The prevalence of concomitant thyroid cancer occurring in patients with GD reaches up to 17% [3,6,14,26,33-39]. The incidence of thyroid carcinoma associated with GD varied from 0.5 and 15.0%. This incidence varied from 15% to 45.8% if patients with a nodule were considered [6,13,28,37,38]. Although PTC is the most frequently reported histologic type occuring in GD, MTC with concomitant GD has also been reported [26]. Most carcinomas associated with GD are small and are found incidentally during postoperative histological examination of the thyroid (up to 88.0%). The overall frequency of incidentally found carcinomas in Graves' patients undergoing surgery varied from 3.33% to 4.2% and that of clinically important thyroid carcinomas varied from 3.3 % to 4.7% [27,28]. The incidence of microcarcinomas in our series was 29%. Patients with microcarcinomas and concomitant GD and euthyroid patients with cancers of equal size have an excellent prognosis and longer disease-free survival. In Graves' patients, carcinomas are found to be larger, usually aggressive, more often multifocal, locally invasive and more often metastatic to lymph nodes and distant sites than in patients with hot thyroid nodules. In our study, no signs of metastases or extrathyroidal invasion were observed in our patients. All were alive with no evidence of malignancy at the time of writing. However, some studies report discordant results or do not highlight the aggressive characteristics of thyroid carcinomas in GD [28,32-34]. Surgery is the most appropriate treatment for GD with concomitant DTC. Near-total or total thyroidectomy is now well established as the choice in patients undergoing surgery for GD. In addition, cervical lymph nodes are dissected when macroscopically involved [1,6,7,12,13]. Some authors reported that typical fine calcification was seen in 60% of patients with thyroid cancer in Graves' goiters, and in most of these, the calcification pattern was considered to be diagnostic of carcinoma [15]. Whereas carcinomas, largely of the papillary type, occur in nontoxic nodular goiters with a reported frequency of 4-17 % of cases, the reported incidence of thyroid cancer in patients with TMG ranges between 1.8-8.8% [7,8,11,13,54-56]. Some authors found no significant difference for the incidence of thyroid cancer between toxic and nontoxic multinodular goiter. In another study, lymph node involvement was found in 23% of the cases with TMG and cancer. In a third one, no lymph node metastases were detected although distant metastases were found in some cases [24-26]. Surgery is the first choice because it can resect the primary tumor and resolves compression and thyrotoxicosis symptoms [6-8,11,13,53,54]. The reported probability of a hot nodule being associated with malignancy ranges between 1 and 44%. However, hot nodules in children seem to carry a higher risk of malignancy of up to 29% of thyroid carcinomas [40-52]. There are reports of malignant hot nodules, in which activating mutations of The Thyrotropin Receptor (TSHR) gene were identify ed. Most autonomously functioning thyroid nodules are benign follicular neoplasms but rarely patients with toxic adenoma may harbor thyroid cancer in the autonomously functioning nodule. These mainly involve papillary and less often follicular or Hurthle histological types [6,13]. In our series, WDTC was more associated and in statistically significant way with GD then TMG and TUG (63%, 33%, and 4% respectively). The classic variant of PTC being the most common histological type. Papillary microcarcinoma, multifocality, bilaterality, and recurrence were more associated and in statistically significant way with GD then TMG and TUG. Extrathyroid extension, and positive lymph nodes were more showed in TMG than GD, and TUG. In our series, we noted 3 differences (size of the nodules, recurrence, and presence of distant metastases) without reaching statistically significance in the characteristics and prognosis of WDTC in euthyroid patients compared to hyperthyroid patients (Table 2).

There are some limitations of this study. One limitation is that by design, the study is retrospective. The subgroup analysis is also limited by the small sample sizes. Larger multi-institutional studies are needed to better identify risk factors and prognosis of these associations.

Conclusion

In our series, WDTC was more associated and in statistically significant way with GD then TMG and TUG. The classic variant of PTC being the most common histological type. Papillary microcarcinoma, multifocality, bilaterality, and recurrence were more associated and in statistically significant way with GD then TMG and TUG. Extrathyroid extension, and positive lymph nodes were more showed in TMG than GD, and TUG. We noted 3 differences (size of the nodules, recurrence, and presence of distant metastases) without reaching statistically significance in the characteristics and prognosis of WDTC in euthyroid patients compared to hyperthyroid patients.

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