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Research Article

Prognosis of well Differentiated Thyroid Carcinoma Associated with Hyperthyroidism

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Abstract

Backgrounds: This paper aim to report prognosis 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 retrospectively reviewed with regard to patient demographics, clinical presentation, preoperative biological and imaging findings, surgery, pathology and follow-up records.

Results: 11% presented hyperthyroidism with well differentiated thyroid carcinoma. Papillary thyroid carcinoma being the most common histological type. Papillary microcarcinoma, multifocality, bilaterality, and recurrence was more associated with Grave's disease. Extrathyroid extension, and positive lymph nodes were more showed in toxic multinodualr goiter. We noted 3 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 Grave's disease. We did not show any statistically significance difference of well differentiated thyroid carcinoma in euthyroid patients compared to hyperthyroid patients.

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

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. Although all histological types of thyroid carcinomas can be associated with hyperthyroidism, the most frequently reported type 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 the prognosis of these associations.

Methods

Patients

From January 2000 to June 2022, all consecutive patients who underwent primary thyroid surgery were included in the study. The medical records of these patients were retrospectively reviewed with regard to patient demographics, clinical presentation, preoperative biological and imaging findings,

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surgical procedures, final pathology and follow-up records. 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.

Variables

After reviewing the included patients' files, 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 was 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.

Surgical Management

Iodine-free solutions (chlorehexidine) 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. Inadvertently removed or unequivocally devascularized parathyroid glands were removed routinely for immediate auto transplantation into a pocket fashioned in the ipsilateral sternocleidomastoid muscle. The transplantation site was closed with permanent silk suture. Lymph node exploration was systematically performed centrally and bilaterally in cases of papillary thyroid carcinoma. Macroscopically enlarged lymph nodes and adenopathies detected on preoperative imaging studies were all removed for pathologic study. No prophylactic lymph node dissection and no picking procedure were undertaken. We performed Lateral neck dissection (Level II, III, IV, V, and VII) 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.

Perioperative Care

Monitoring of the cervical wound was assessed closely in the postoperative period. The following parameters were queried: volume of the resected thyroid gland, presence of local complications (hemorrhage, hematoma, seroma) and time to hospital discharge. Postoperative complications (vocal cord paralysis and hypocalcaemia) were recorded. The patients were discharged from the hospital when they were asymptomatic or when the serum calcium level rose above 2 mmol/l. The patients were also instructed to contact their physician if symptoms of hypocalcemia developed.

Post-operative variables and Follow-up includes pathologic results of the thyroid specimen, and histological types of thyroid cancer. All data on surgery, postoperative complications and clinical outcomes were analyzed. 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 on Microsoft excel 2017 and analyzed with descriptive statistics using SPSS version 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

Preoperative Variables

From January 2000 to June 2022, 6123 patients underwent thyroidectomy by one surgeon (BA). All the medical records of 642 who underwent surgery for hyperthyroidism in our department 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, 173.3–800 ng/dL), and that of T4 was 18.7 ng/dL (range, 14.1–39 ng/dL). Serum TSH concentration was less than 0.1 mIU/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.

Intraoperative Variables

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 ± 2.09 cm, 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.

Bleeding and or seroma: A total of 4 patients (6%) developed postoperative hematoma and/or seroma. There were no major bleeding, that is, the patient had minor bleeding or seroma not requiring surgical intervention and resolved spontaneously in 3 weeks. None developed a wound infection. Airway compromise did not occurred in this series.

Postoperative length of stay: the postoperative length of stay 1 day in 68 patients (93%), 2 days in 5 patients (7%). Asymptomatic hypocalcemic patients were discharged from the hospital the next day after operation. During follow-up, 15 patients required Calcium and Vitamin D supplementation with no clinical symptoms of hypocalcaemia at 12 months postoperatively. The incidence of permanent hypoparathyroidism was 1%. Unilateral transient vocal cord paralysis was observed in one patient and completely recovered within 4 weeks.

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).

Postoperative Management and Follow-up

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.

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

Patients	GD	TMG	TUG	P value
Number n=73	46(63%)	24(33%)	3(4%)	<.001
Gender(F/M)	35/11	17/7	2/1	NS
Age	16-67	27-81	22-79	.11
Tumor size(cm)	0.3-4	0.5-6	2-4	.72
Bilateral thyroidectomy	100%	100%	67%	.13
PTC n=50 (69%)	29(63%)	19(79%)	2(67%)	.08
FTC n=2 (2%)	1(2%)	0(0%)	1(13%)	<.0002
Microcaner n=21 (29%)	16(35%)	5(21%)	0(0%)	<.001
Positive Lymph node n=8(11%)	5(11%)	3(13%)	0(0%)	<.001
Mulifocality n=17(23%)	12(26%)	5(20%)	0(0%)	<.001
Bilaterality n=13(18%)	9(20%)	4(17%)	0(0%)	<.001
Extra thyroid extension n=2(3%)	1(2%)	1(4%)	0(0%)	.49
Recurrence n=1(1%)	1(2%)	0(0%)	0(0%)	.77
Metastases n=0(0%)	0(0%)	0(0%)	0(0%)	.99

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

Patients	WDTC with euthyroidism	WDTC with hyperthyroidism	P value
Gender(F/M) %	78/22	74/26	NS
Age	6-83	16-81	.43
Tumor size(cm)	0.5-13	0.3-6	.01
Bilateral thyroidectomy %	98	99	.99
PTC %	67	69	.87
FTC %	3	2	.76
Microcaner %	30	29	.93
Positive Lymph node %	14	11	.31
Mulifocality %	26	23	.57
Bilaterality %	20	18	.28
Extra thyroid extension %	5	3	.19
Recurrence %	3	1	.03
Metastases %	2	0	.02

Comparison of WDTC associated with GD, TMG, and TUG

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.

Comparison of WDTC in euthyoid patients and hyperthyroid patients:

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).

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 loboisthmusectomy. 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 seris 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.

Conclusions

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. Extra thyroid 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.

References

1. Yoon JH, Jin M, Kim M, Hong AR, Kim HK, Kim BH, et al. Clinical cha racteristics and prognosis of coexisting thyroid cancer in patients with Graves' disease: A retrospective multicenter study. Endocrinol Metab (Seoul). 2021; 36: 1268-76.
2. Bonati E, Bettoni S, Loderer T, Del Rio P. Can we still consider thyroid hyperfunction a protective condition for the onset of thyroid cancer? Gland Surg. 2021; 10: 1359-67.
3. More Y, Khalil AB, Mustafa H, Gupte M, Al-Abbadi M, Elamin D, et al. Incidental thyroid cancer in patients undergoing surgery for hyperthyroidism. Am J Otolaryngol. 2020; 41: 102187.
4. Alvarez AL, Mulder M, Handelsman RS, Lew JI, Farra JC. High rates of underlying thyroid cancer in patients undergoing thyroidectomy for hyperthyroidism. J Surg Res. 2020; 245: 523-8.
5. Liang L, Zheng XC, Hu MJ, Zhang Q, Wang SY, Huang F. Association of benign thyroid diseases with thyroid cancer risk: a meta-analysis of prospective observational studies. J Endocrinol Invest. 2019; 42: 673-85.
6. Fu H, Cheng L, Jin Y, Chen L. Thyrotoxicosis with concomitant thyroid cancer. Endocr Relat Cancer. 2019; 26: R395-413.
7. Mohamed TZ, Sultan AAEA, Tag El-Din M, Mostafa AAE, Nafea MA, Kalmoush AE, et al. Incidence and risk factors of thyroid malignancy in patients with toxic nodular goiter. Int J Surg Oncol. 2022; 2022: 1054297.

8. Lau LW, Ghaznavi S, Frolkis AD, Stephenson A, Robertson HL, Rabi DM, et al. Malignancy risk of hyperfunctioning thyroid nodules compared with non-toxic nodules: systematic review and a meta-analysis. Thyroid Res. 2021; 14: 3.

9. Chigot JP, Ménégaux F, Keopadabsy K, Hoang C, Aurengo A, Leenhardt L, et al. Thyroid cancer in patients with hyperthyroidism. Presse Med. 2000; 29: 1969-72.

10. Kitahara CM, Farkas DKR, Jorgensen JOL, Cronin-Fenton D, Sorensen HT. Benign thyroid diseases and risk of thyroid Cancer: a Nationwide cohort study. J Clin Endocrinol Metab. 2018; 23: 23.

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

12. Kwon H, Moon BI. Prognosis of papillary thyroid cancer in patients with Graves' disease: a propensity score-matched analysis. World J Surg Oncol. 2020; 18: 266.

13. Tam AA, Ozdemir D, Alkan A, Yazicioglu O, Yildirim N, Kilicyazgan A, et al. Toxic nodular goiter and thyroid cancer: is hyperthyroidism protective against thyroid cancer? Surgery. 2019; 166: 356-61.

14. Yeh NC, Chou CW, Weng SF, Yang CY, Yen FC, Lee SY, et al. Hyperthyroidism and thyroid cancer risk: a population-based cohort study. Exp Clin Endocrinol Diabetes. 2013; 121: 402-6.

15. Mekraksakit P, Rattanawong P, Karnchanasorn R, Kanitsoraphan C, Leelaviwat N, Poonsombudlert K, et al. Prognosis of differentiated thyroid carcinoma in patients with Graves disease: a systematic review and meta-analysis. Endocr Pract. 2019; 25: 1323-37.

16. Song YS, Kim KS, Kim SK, Cho YW, Choi HG. Screening leads to overestimated associations of thyroid dysfunction and thyroiditis with thyroid cancer risk. Cancers (Basel). 2021; 13: 5385.

17. Gulcelik MA, Gulcelik NE, Dinc S, Kuru B, Camlibel M, Alagol H. The incidence of hyperthyroidism in patients with thyroid cancer in an area of iodine deficiency. J Surg Oncol. 2006; 94: 35-9.

18. Medas F, Erdas E, Canu GL, Longheu A, Pisano G, Tuveri M, et al. Does hyperthyroidism worsen prognosis of thyroid carcinoma? a retrospective analysis on 2820 consecutive thyroidectomies. J Otolaryngol Head Neck Surg. 2018; 47: 6.

19. Kadia BM, Dimala CA, Bechem NN, Aroke D. Concurrent hyperthyroidism and papillary thyroid cancer: a fortuitous and ambiguous case report from a resource-poor setting. BMC Res Notes. 2016; 9: 369.

20. Rees DO, Anthony VA, Jones K, Stephens JW. Follicular variant of papillary thyroid carcinoma: an unusual cause of thyrotoxicosis. BMJ Case Rep. 2015; 2015: bcr2014207091.

21. Ibrahim A, Loseva V, Rodriguez R. A case of t3 thyrotoxicosis with concomitant follicular thyroid carcinoma. J Endocr Soc. 2021; 5: A878.

22. Wong CP, AuYong TK, Tong CM. Thyrotoxicosis: a rare presenting symptom of Hurthle cell carcinoma of the thyroid. Clin Nucl Med. 2003; 28: 803-6.

23. Habra MA, Hijazi R, Verstovsek G, Marcelli M. Medullary thyroid carcinoma associated with hyperthyroidism: a case report and review of the literature. Thyroid. 2004; 14: 391-6.

24. Berker D, Isik S, Ozuguz U, Tutuncu YA, Kucukler K, Akbaba G, et al. Prevalence of incidental thyroid cancer and its ultrasonographic features in subcentimeter thyroid nodules of patients with hyperthyroidism. Endocrine. 2011; 39: 13-20.

25. Kovatch KJ, Bauer AJ, Isaacoff EJ, Prickett KK, Adzick NS, Kazahaya K, et al. Pediatric thyroid carcinoma in patients with Graves' disease: the role of ultrasound in selecting patients for definitive therapy. Horm Res Paediatr. 2015; 83: 408-13.

26. 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 Otolaryngol. 2014; 35: 784-90.

27. Miccoli P, Minuto MN, Galleri D, D'Agostino J, Basolo F, Antonangeli L, 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.

28. Kikuchi S, Noguchi S, Yamashita H, Uchino S, Kawamoto H. Prognosis of small thyroid cancer in patients with Graves' disease. Br J Surg. 2006; 93: 434-9.

29. Boutzios G, Vasileiadis I, Zapanti E, Charitoudis G, Karakostas E, Ieromonachou P, et al. Higher incidence of tall cell variant of papillary thyroid carcinoma in Graves' disease. Thyroid. 2014; 24: 347-54.

30. Canales N, Nieves YR, Ortega NIB, Castellano JMC, Cordero NH, Santini AJG, et al. Incidental diffuse sclerosing variant papillary thyroid cancer in Grave's disease. J Endocr Soc. 2021; 5: A891-2.

31. MacFarland SP, Bauer AJ, Adzick NS, Surrey LF, Noyes J, Kazahaya K, et al. Disease burden and outcome in children and young adults with concurrent Graves disease and differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2018; 103: 2918-25.

32. Shu X, Ji J, Li X, Sundquist J, Sundquist K, Hemminki K. Cancer risk in patients hospitalised for Graves' disease: a population-based cohort study in Sweden. Br J Cancer. 2010; 102: 1397-9.

33. Chen YK, Lin CL, Chang YJ, Cheng FT, Peng CL, Sung FC, et al. Cancer risk in patients with Graves' disease: a nationwide cohort study. Thyroid. 2013; 23: 879-84.

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

35. Pellegriti G, Mannarino C, Russo M, Terranova R, Marturano I, Vigneri R, et al. Increased mortality in patients with differentiated thyroid cancer associated with Graves' disease. J Clin Endocrinol Metab. 2013; 98: 1014-21.

36. Kwon Hyungju, Moon BI. Prognosis of papillary thyroid cancer in patients with Graves' disease: a propensity score-matched analysis. World J Surg Oncol. 2020; 18: 266.

37. Kraimps JL, Bouin-Pineau MH, Mathonnet M, De Calan L, Ronceray J, Visset J, et al. Multicentre study of thyroid nodules in patients with Graves' disease. Br J Surg. 2000; 87: 1111-3.

38. Papanastasiou A, Sapalidis K, Goulis DG, Michalopoulos N, Mareti E, Mantalovas S, et al. Thyroid nodules as a risk factor for thyroid cancer in patients with Graves' disease: A systematic review and meta-analysis of observational studies in surgically treated patients. Clin Endocrinol (Oxf). 2019; 91: 571-7.

39. Zhang L-L, Liu B, Sun FF, Li H-Y, Li S, Zhao L-R. Papillary thyroid carcinoma with hyperthyroidism and multiple metastases: A case report. Med (Baltim). 2020; 99: e21346.

40. Bommireddipalli S, Goel S, Gadiraju R, Paniz-MondolFi A, DePuey EG. Follicular variant of papillary thyroid carcinoma presenting as a toxic nodule by I-123 scintigraphy. Clin Nucl Med. 2010;35(10):770-5.

41. Bitterman A, Uri O, Levanon A, Baron E, Lefel O, Cohen O. Thyroid carcinoma presenting as a hot nodule. Otolaryngol Head Neck Surg. 2006; 134: 888-9.

42. Ruggeri RM, Campennì A, Giovinazzo S, Saraceno G, Vicchio TM, Carlotta D, et al. Follicular variant of papillary thyroid carcinoma presenting as toxic nodule in an adolescent: coexistent polymorphism of the TSHR and Gsα genes. Thyroid. 2013; 23: 239-42.

43. Mirfakhraee S, Mathews D, Peng L, Woodruff S, Zigman JM. A solitary hyperfunctioning thyroid nodule harboring thyroid carcinoma: review of the literature. Thyroid Res. 2013; 6: 7.

44. Fortuna GMG, Rios P, Rivero A, Zuniga G, Dvir K, Pagacz MM, et al. Papillary thyroid carcinoma with cystic changes in a patient with prior history of toxic nodule. J Investig Med High Impact Case Rep. 2020; 8: 2324709620942672.

45. Van Vlaenderen J, Logghe K, Schiettecatte E, Vermeersch H, Huvenne W, De Waele K, et al. A synchronous papillary and follicular thyroid carcinoma presenting as a large toxic nodule in a female adolescent. Int J Pediatr Endocrinol. 2020; 2020: 14.

46. Hu L, Wu Y. Papillary thyroid carcinoma presenting as a functioning thyroid nodule: report of 2 rare cases. Int J Clin Exp Pathol. 2020; 13: 2895-906.

47. Shinkai S, Ohba K, Kakudo K, Iwaki T, Mimura Y, Matsushita A, et al. Hyperfunctioning papillary thyroid carcinoma with a braf mutation: the first case report and a literature review. Eur Thyroid J. 2021; 10: 262-7.

48. Calimon MAP, Lim-Uy SW. Papillary thyroid carcinoma in an autonomous hyperfunctioning thyroid nodule. Endocr Rev. 2014; 35.

49. Camacho P, Gordon D, Chiefari E, Yong S, DeJong S, Pitale S, et al. A Phe 486 thyrotropin receptor mutation in an autonomously functioning follicular carcinoma that was causing hyperthyroidism. Thyroid. 2000; 10: 1009-12.

50. Uchida T, Yamaguchi H, Kawabata T, Tanaka H, Kawano F, Shimoda K. Longitudinal changes in an autonomously functioning thyroid nodule with coexisting follicular thyroid carcinoma over 14 years. Oxf Med Case Rep. 2022; 2022: omac041.

51. Majima T, Doi K, Komatsu Y, Itoh H, Fukao A, Shigemoto M, et al. Papillary thyroid carcinoma without metastases manifesting as an autonomously functioning thyroid nodule. Endocr J. 2005; 52: 309-16.

52. Cunningham K, Antonetti J, Wood B. Oncocytic papillary carcinoma in an autonomous thyroid nodule. Am J Case Rep. 2021; 22: e931757.

53. Senyurek Giles Y, Tunca F, Boztepe H, Kapran Y, Terzioglu T, Tezelman S. The risk factors for malignancy in surgically treated patients for Graves' disease, toxic multinodular goiter, and toxic adenoma. Surgery. 2008; 144: 1028-36.

54. Verburg FA, Reiners C. The association between multinodular goiter and thyroid cancer. Minerva Endocrinol. 2010; 35: 187-92.

55. Pascual Corrales E, Príncipe RM, Laguna Muro S, Martínez Regueira F, Alcalde Navarrete JM, Guillén Grima F et al. Incidental differentiated thyroid carcinoma is less prevalent in Graves' disease than in multinodular goiter. Endocrinol Nutr. 2012; 59: 169-73.

56. Shaikh IA, Muthukumarsamy G, Vidyadharan R, Abraham SJ. High incidence of thyroid cancer in toxic multinodular goiters. Asia-Pac J Clin Oncol. 2007; 3: 119-24.