

Thyroid Cancer in Patients with Hyperthyroidism

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Key words

- Graves' disease
- toxic multinodular goiter
- hot nodules
- hyperthyroidism
- thyroid cancer

Abstract

Thyroid cancer can be associated with thyrotoxicosis caused by Graves' disease, toxic multinodular goiter, or autonomously functioning thyroid adenoma. The objective of this study was to summarize current evidence regarding the association of thyroid cancer and hyperthyroidism, particularly with respect to the type of hyperthyroidism found in some patients, and whether this affects the outcome of the patient. A PubMed search was performed up to August 2011. Articles were identified using combinations of the following keywords/phrases: thyroid cancer, papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, ana-

plastic thyroid cancer, hyperthyroidism, Graves' disease, autonomous adenoma, toxic thyroid nodule, and toxic multinodular goiter. Original research papers, case reports, and review articles were included. We concluded that the incidence, as well as the prognosis of thyroid cancer associated with hyperthyroidism is a matter of debate. It seems that Graves' disease is associated with larger, multifocal, and potentially more aggressive thyroid cancer than single hot nodules or multinodular toxic goiter. Patients with Graves' and thyroid nodules are at higher risk to develop thyroid cancer compared to patients with diffuse goiter. Every suspicious nodule associated with hyperthyroidism should be evaluated carefully.

Introduction

In 1937 Means [1] suggested that hyperthyroidism might be protective against thyroid cancer and this initially gained some support, but was soon abandoned due to findings in the following decades. Supportive of that are reports performed in the 1950's that indicated a low incidence of thyroid cancer in patients with Graves' disease in the range of 0.15–0.5% [2, 3] or even a slightly higher incidence of 2.5% [4]. All the above data were based on patients treated with subtotal thyroidectomy. However, later studies by Shapiro et al. on patients with Graves' disease demonstrated an unsuspected thyroid cancer in 8.7% of them [5]. This increase was probably observed due to the fact that the patients were treated with total thyroidectomy; a more intense histological examination of the surgical specimen further increased the chances of diagnosing thyroid cancer [6, 7].

To further complicate the matter, discrepancies appear not only in reports on the incidence but also on the aggressiveness of thyroid cancer associated with hyperthyroidism. For instance, while

some reports describe the cancer as very aggressive [8, 9], often invasive, and metastatic to regional lymph nodes, even when the primary tumor is small [10] and possibly fatal [11, 12]; in other series the clinical course was not different from euthyroid patients [13]. Up to date the reasons for these discrepancies have not been solved and the incidence and aggressiveness of thyroid cancer remain controversial.

This review attempts to shed some light on the reasons behind these discrepancies in order to gain a better understanding in the association and the evolution of thyroid cancer in patients with hyperthyroidism, particularly with respect to the type of hyperthyroidism found in some patients and whether this co-existence affected the outcome of the patients.

Methods

This is a literature review based on articles found in PubMed up to August 2011. An electronic search of PubMed/Medline database using the MeSH (Medical Subject Headings) was performed,

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Bibliography

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Table 1 Incidence of thyroid carcinoma in hyperthyroid patients (Graves', autonomous adenoma, toxic multinodular goiter).

| Author | Hyperthyroid patients (n) | Thyroid cancer n | Thyroid cancer % |
|---------------------|---------------------------|------------------|------------------|
| Taneri [15] | 120 | 10 | 8.3 |
| Cappelli C [8] | 691 | 32 | 4.7 |
| Terzioglou [19] | 138 | 8 | 5.8 |
| Gabriele [22] | 425 | 7 | 1.6 |
| Cakir [18] | 375 | 26 | 6.9 |
| Vaiana [21] | 512 | 24 | 4.7 |
| Linos [20] | 400 | 27 | 7.0 |
| Pacini [14] | 179 | 11 | 6.1 |
| Lin [24] | 45 | 6 | 13.3 |
| Lian [94] | 394 | 12 | 3.0 |
| Senyurek Giles [17] | 817 | 53 | 6.5 |
| Calò [26] | 71 | 15 | 21.1 |
| Sahin [16] | 333 | 13 | 3.9 |
| Zanella [25] | 202 | 12 | 5.9 |

Table 2 Percentage incidence of microcarcinomas in patients with both thyroid cancer and hyperthyroidism.

| Author | Thyroid Cancer patients (n) | Type of hyperthyroidism | Tumor size n | ≤10 mm % |
|--------------------------|-----------------------------|-----------------------------|--------------|----------|
| Farbota [34] | 6 | Graves' disease | 3 | 50.0 |
| Belfiore [31] | 22 | Graves' disease, hot nodule | 11 | 50.0 |
| Ahuja [72] | 20 | All types | 7 | 35.0 |
| Vini [102] | 23 | All types | 12 | 51.2 |
| Ozaki [10] | 19 | Graves' disease | 9 | 47.4 |
| Cakir [18] | 26 | All types | 9 | 34.6 |
| Cerci [92] | 11 | Multinodular goiter | 8 | 72.7 |
| Taneri [15] | 10 | All types | 7 | 70.0 |
| Chao [49] | 61 | Graves' disease | 49 | 80.3 |
| Pazaitou-Panayiotou [11] | 60 | All types | 39 | 65.0 |
| Pellegriti [32] | 36 | Graves' disease | 15 | 41.7 |
| Lian [94] | 12 | All types | 7 | 58.3 |
| Omur [96] | 76 | All types | 50 | 65.7 |
| Gerenova [37] | 8 | Graves' | 7 | 88.0 |
| Erbil [38] | 18 | Graves' | 15 | 83.3 |
| Hales [13] | 16 | Graves' | 14 | 87.0 |

using combinations of the following keywords/phrases: thyroid cancer, papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, anaplastic thyroid cancer, hyperthyroidism, Graves' disease, autonomous adenoma, toxic thyroid nodule, and toxic multinodular goiter. Original research papers, case reports, and review articles were included in the present review.

Findings

Thyroid cancer in patients with hyperthyroidism

The prevalence of thyroid carcinomas found during surgery in hyperthyroid patients, is reported to vary widely, ranging up to 21.1% [8,14–26] (● **Table 1**). This is probably due to multiple factors, including the cause of hyperthyroidism, the different criteria for choosing surgery as the treatment modality of hyper-

thyroidism, 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 [27,28]. All histological types of thyroid cancers can be associated with all types of hyperthyroidism, although the most frequently reported type is papillary thyroid carcinoma, followed by follicular thyroid carcinoma, and rarely by anaplastic carcinoma and medullary thyroid carcinoma [11,12,29,30], in keeping with the lower incidence of these cancers in general.

It has been reported that thyroid cancer is diagnosed more frequently in patients with Graves' disease than in patients with uninodular toxic goiter or toxic multinodular goiter (TMG) [8] whereas other studies presented the same results for Graves', but slightly higher carcinoma prevalence within hot nodules and TMG [17,18]. In Graves' patients, carcinomas are found to be larger, more often multifocal, locally invasive and more often metastatic to distant sites than in patients with hot thyroid nodules [31].

Most carcinomas are small in size [10,13,32] and the majority are microcarcinomas (● **Table 2**). In many cases thyroid cancer is not known preoperatively, but is found incidentally during postoperative histologic examination of the thyroid [33]. We previously reported a study of 60 hyperthyroid patients diagnosed with thyroid cancer [11]. Among those patients, only 12 were operated for suspicion of thyroid cancer preoperatively, whereas in the remaining 48, in whom the indication for thyroidectomy was treatment for thyrotoxicosis, thyroid cancer was incidentally found after surgery. No significant differences were found in clinical characteristics at presentation between coincidentally discovered thyroid cancers and preoperatively known clinical cancers. The time of diagnosis of hyperthyroidism to thyroidectomy was not different. However, Miccoli et al. reported that, the diagnosis of incidental thyroid carcinoma in patients who were operated on for a benign disease was more frequent in euthyroid patients than in patients with hyperthyroidism [23].

Thyroid cancer in patients with Graves' disease Prevalence

The prevalence of thyroid carcinoma in Graves' hyperthyroidism has been examined over many years but the issue still remains controversial. There are significant differences in the reported incidence of thyroid cancer in patients operated for Graves' disease, ranging between 0.5 and 15.0%, [2–5,8,10,14,16–21,23,31,34–39], (● **Table 3**). Some studies suggest an association between Graves' disease and thyroid cancer [8,14,18,34,40] as the annual incidence of clinical thyroid cancer in patients with Graves' disease was reported as 175/100 000 [32], well above the incidence of 0.5–8.0/100 000 reported for the general euthyroid population [41].

Aggressiveness

It has been reported that, thyroid carcinoma concurrent to Graves' disease is usually aggressive [40] and metastatic to regional lymph nodes [8], even when the primary tumor is small [10] and that it has a worse clinical outcome compared to euthyroid patients with differentiated thyroid cancer [8,31,32,42,43]. Lymph nodes involvement was found in up to 61.5% of the patients [8,31] and the incidence of locally advanced cancers was significantly higher in older patients [44]. However, some studies report discordant results or do not highlight the aggressive characteristics of thyroid carcinomas in

Table 3 Prevalence of thyroid carcinoma in Graves' disease.

| Author | Graves' disease | Thyroid cancer | |
|---------------------|-----------------|----------------|------|
| | n | n | % |
| Beahrs [3] | 3022 | 14 | 0.5 |
| Sokal [2] | 13868 | 21 | 0.15 |
| Olen [4] | 2114 | 53 | 2.5 |
| Pacini [14] | 86 | 6 | 6.9 |
| Shapiro [5] | 172 | 15 | 8.7 |
| Farbota [34] | 117 | 6 | 5.1 |
| Belfiore [31] | 132 | 13 | 9.8 |
| Sahin M [16] | 144 | 5 | 3.5 |
| Terzioglou [19] | 33 | 4 | 6.0 |
| Vaiana [21] | 108 | 7 | 6.4 |
| Cappelli [8] | 145 | 9 | 6.5 |
| Ozaki [10] | 743 | 19 | 2.6 |
| Cakir [18] | 67 | 4 | 6.0 |
| Pellegriti [32] | 450 | 21 | 4.7 |
| Geranova [37] | 103 | 8 | 7.8 |
| Kraimps [39] | 557 | 21 | 15.0 |
| Erbil [38] | 150 | 18 | 12.0 |
| Lee [35] | 779 | 58 | 7.4 |
| Senyurek Giles [17] | 342 | 13 | 3.8 |

Graves' disease [13,37,45–47]. Hales et al. compared 16 patients with Graves' disease with concomitant thyroid cancer with a group of euthyroid patients with thyroid cancer who underwent surgery during the same time period and were matched for sex and age to the patients with Graves' disease [13]. The authors did not find increased aggressiveness of thyroid cancer in patients with Graves' disease when compared to euthyroid subjects. In this study the mean tumor diameter in the Graves' group was 1.0 cm and in the control group 2.5 cm and this is an obvious disadvantage of the study. The outcome may suggest that small carcinomas in Graves' patients have the same prognosis as larger carcinomas in euthyroid patients. Yano et al. compared the features of 154 cases of papillary thyroid cancers diagnosed in patients with Graves' disease to a euthyroid group with thyroid cancer [46] and did not find significant differences in multifocality, lymph node metastases, or distant metastases between the Graves' disease and the euthyroid group. Edmonds et al., in their study with 502 patients with thyroid cancer, reported similar mortality rates when comparing patients with Graves' disease and with multinodular goiter to that of euthyroid patients matched for age [45].

All the above mentioned studies are retrospective and explore different clinical or histological parameters and therefore are not totally comparable. Prospective studies with a large number of patients could give clear answer about the aggressiveness of thyroid cancer in GD.

Microcarcinomas – Clinically important cancers

Most carcinomas associated with Graves disease are small [10,13,32] and are found incidentally during postoperative histological examination of the thyroid [33,48]. Incidental cancers of ≤ 10 mm were found up to 88.0% of all cancers detected in Graves' disease [10,13,32,34,37,38,49]. The clinical significance of these microcarcinomas is uncertain. In a recent report, patients with microcarcinomas and concomitant Graves' disease were compared with euthyroid patients with cancers of equal size and were found to have an excellent prognosis and longer disease-free survival [42].

Pellegriti et al. evaluated the frequency and the evolution of incidentally found vs. clinically important thyroid carcinomas in 450 Graves' patients who underwent thyroidectomy, in 2 different studies in the periods 1982–1987 and 1988–1994 [32]. The overall frequency of incidentally found carcinomas in Graves' patients undergoing surgery was 3.33% (15/450) and that of clinically important thyroid carcinomas was 4.7% (21/450). All patients with microcarcinoma were disease-free except for one case that developed a local recurrence. On the contrary, patients with clinically important disease presented lymph nodes metastases, distant metastases and deaths (odd ratios=3.14 as compared with euthyroid patients). In the study of Lee et al. clinically overt thyroid carcinomas were diagnosed in 3.3% and incidental carcinoma in 4.2% of patients with Graves' disease [35]. In this study comparison of clinical findings of incidental and clinical carcinoma patients revealed no difference between the 2 groups in terms of duration of thyrotoxic symptoms, serum levels of thyroid hormones before the administration of antithyroid drugs, and postoperative serum concentration of thyroglobulin. Local recurrence was identified in 4 patients (6.9%), all of whom belonged to the clinical carcinoma group. This finding supports the conclusion that thyroid microcarcinomas in Grave's disease seldom cause metastasis.

Nodular Graves' disease

It appears that thyroid nodules in Graves' goiters have a greater risk of malignancy. Thyroid carcinoma occurs in 3–10% of palpable nodules in general, whereas the numbers for incidentally found nonpalpable nodules vary very widely, according to different studies, mostly due to differences in iodine availability [50–52]. Kraimps et al. in their multicentric study with 557 patients who underwent thyroidectomy for Graves' disease found that the incidence of thyroid carcinoma associated with Graves' disease was 3.8% [39]. This incidence was higher and – actually – 15%, if patients with a nodule were considered. Pacini et al. reported that when a thyroid nodule was present in a toxic diffuse goiter the possibility to find a carcinoma reached 22.2% of the cases, while only 2.9% with diffuse toxic goiter, without a nodule, had thyroid cancer [14]. Due to this finding the authors conclude that in patients with Graves' disease any nodule must be screened carefully to rule out malignancy. Belfiore et al. reviewed previously published data on the incidence of thyroid cancer in Graves' patients with or without thyroid nodules and found that the incidence of thyroid cancer in patients with nodules was up to 45.8% of the cases in contrast to those without nodules in whom thyroid cancer did not exceed 9.8% [53]. Thyroid scintigraphy is an important test in the evaluation of patients with Graves' disease and nodules, and the prevalence of thyroid cancer in a cold nodule provides justification for further diagnostic evaluation [54]. In the recently published medical guidelines for clinical practice for the diagnosis and management of thyroid nodules it is recommended that nodules in Graves' disease should be managed in the same way as any other thyroid nodule including follow-up and consideration of a second FNAB to reduce the number of false negative results [55]. Fine-needle aspiration cytology from nodules, which are found in patients with Graves' disease, can cause diagnostic difficulties because the cytomorphologic changes in this disease as a consequence of antithyroid drug treatment may mimic features of papillary thyroid carcinoma. Furthermore, atypia produced by the administration of radioactive iodine (RAI) may be severe, leading to an erroneous diagnosis of malignancy [56]. Provision

of the appropriate clinical history of Graves' disease treated with RAI may prevent this pitfall. In a recent study nuclear elongation, pale powdery chromatin, intranuclear grooves, and small eccentric nucleoli were found to be significant for the diagnosis of PTC arising in GD [57].

Diagnosis of thyroid cancer according to Graves' initial treatment

Thyroid cancer associated with Graves' disease is found more commonly in surgically treated patients than in patients after radioactive iodine therapy. Ozaki et al. reported a 0.17% thyroid cancer incidence in Graves' patients treated with radioactive iodine vs. 2.5% in Graves' patients treated with surgery [58]. In a study by Behar et al., 303 patients received RAI therapy for Graves' disease and only one (0.3%) subsequently developed thyroid carcinoma [40]. Of course, one could claim that patients undergoing surgery have a higher chance of a cancer being recognized, when compared to radioiodine treated patients.

Pathogenesis

The possible reasons that could explain the increased frequency and aggressiveness of clinical thyroid cancer reported by some studies for patients with Graves' disease are not clear. Thyroid stimulating hormone (TSH), by binding to the thyroid-stimulating hormone receptor (TSHR), and probably multiple other factors, affect the evolution of thyroid cancer. Neoplastic cells of differentiated thyroid cancer, like normal thyroid cells, express functional receptors for TSH.

Graves' disease is characterized by a marked decrease in TSH [59]. In Graves', antibodies (TSAbs) are produced that have strong agonistic activity to the TSHR, and this results in antibody-mediated stimulation of the receptor. Stimulation of TSHR by antibodies leads to secretion of thyroid hormone and hyperthyroidism independently of the hypothalamic-pituitary-thyroid axis. Moreover, TSABs might play a role in stimulating thyroid cancer growth, invasiveness [9,60] and angiogenesis by upregulating vascular endothelial growth factor, placenta growth factor, and their receptors. TSABs use the same signaling pathways that are used by TSH for cell activation and growth [61]. Taking into consideration that chronic TSH stimulation affects the prognosis of thyroid cancer it could be postulated that the TSH mimicking effect of TSABs could explain the increased aggressiveness of thyroid cancer in Graves' patients. Apart from that, different growth factors that probably are produced by the over stimulated, by TSABs, and hypervascularized thyroid [31] could also affect the growth and metastases of thyroid cancer in Graves' patients.

Extent of surgery

The extent of surgery for thyroid carcinoma concomitant with Graves's disease has rarely been discussed. As clinically important thyroid cancers associated with Graves's disease seems to behave more aggressively, with a tendency to lymph node metastases, total or near-total thyroidectomy plus central neck dissection are recommended [32]. In these cases surgical treatment for thyroid carcinoma is the goal and this surpasses the surgical treatment for hyperthyroidism.

Carcinomas smaller than 10mm concomitant with Graves disease could be treated by subtotal thyroidectomy with excellent outcomes [62]. 2 guidelines for the management of thyroid cancer have been published by European and American thyroid associations. Both agree that if papillary thyroid microcarci-

noma (PTM) is diagnosed preoperatively, total or near-total thyroidectomy is the treatment of choice, because it eliminates multifocal disease and decreases the recurrence rate. If PTM is found after total or near-total thyroidectomy for multinodular goiter or Graves' disease both guidelines state that no further treatment is indicated when the PTM is unifocal, well-differentiated, without lymph node metastases or extrathyroidal invasion [63,64]. Recently, the revised guideline of the American thyroid association suggests that lobectomy alone is a sufficient treatment for small (<1 cm), low-risk, unifocal, intrathyroidal papillary carcinomas in the absence of head and neck irradiation or cervical lymph nodes metastases [65]. Obviously this recommendation would not be applicable for patients with Graves' hyperthyroidism, as lobectomy is no sufficient treatment for relapsing Graves' disease. Evidence-based criteria support total thyroidectomy as the surgical technique of choice when surgery is considered for definitive management for Graves' disease [66].

Thyroid cancer in patients with autonomous adenoma

Most autonomously functioning thyroid nodules (AFTN) 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. The published data regarding the association of thyroid cancer and hot nodules are few, and are mostly limited to case reports or series with a small numbers of patients [67–71]. The reported probability of a hot nodule being associated with malignancy (i.e., a thyroid carcinoma in or outside the hot nodule) ranges between 1–10.3% [8,18,49,72–77] (● **Table 4**). An exception to that is one small series where the incidence of cancer in hot nodules was 44% [64]. Schröder and Marthaler reviewed 30 reports of warm or hot thyroid carcinomas published between 1989 and 1996 and found that only in 10 of these 30 cases the carcinoma was clearly described as located inside the hot nodule [78]. Similar findings were reported in many other studies [8,11,17,22,73,79]. However, hot nodules in children seem to carry a higher risk of malignancy of up to 29% of thyroid carcinomas within the hot nodules [80,81].

The true incidence of thyroid cancer in patients with autonomous adenomas may be underestimated because occasionally large doses of radioiodine are used to treat such cases if they do not undergo surgery, which may be sufficient not only to cure the thyrotoxicosis but also the cancer. However, in a recent report by Als et al. in 5 of 19 patients, one or more courses of ¹³¹I were preoperatively administered to the autonomously func-

Table 4 Incidence of thyroid carcinoma in patients with autonomous adenoma (inside or outside the hot nodule).

| Author | Toxic adenoma n | Thyroid cancer n | Thyroid cancer % |
|---------------------|-----------------|------------------|------------------|
| Senyurek Giles [17] | 176 | 21 | 12.0 |
| Vaiana [21] | 153 | 8 | 5.2 |
| Cappelli [8] | 207 | 10 | 4.8 |
| Gabriele [22] | 120 | 3 | 2.5 |
| Cakir [18] | 63 | 4 | 6.3 |
| Foppiani [36] | 16 | 2 | 2.5 |
| Harach [76] | 73 | 6 | 8.2 |
| Smith [77] | 30 | 2 | 6.6 |
| Hamburger [74] | 29 | 3 | 10.3 |
| Sahin [6] | 77 | 6 | 7.8 |

Table 5 All patients reported up to date with a differentiated hot thyroid carcinoma.

| Activating TSHR mutations | Cell surface expression percent of wt | cAMP accumulation (according to SSFA of GPHRs) Basal (wt = 100%) | IP accumulation (according to SSFA of GPHRs) Basal (wt = 100%) | RAS, RAF, p53, and MAPK activation | Histopathology of the tumor | Age/Sex |
|---------------------------|---------------------------------------|--|--|------------------------------------|--|---------|
| T632I | 40 50 | 420 330 | n.d. n.d. | Not studied | Follicular carcinoma | 50/M |
| D633H | 84 | 620 | 221 | No mutations | Insular thyroid carcinoma | 60/F |
| I486F | 17 20 35 | 550 400 820 | 327 n.d. 97 | Not studied | Follicular carcinoma (capsular invasion) | 49/F |
| M453T | n.d. 66 | 700 570 | n.d. 103 | Not studied | Papillary carcinoma | 11/F |
| D633Y | 60* | 405 | 127 | PAX8-PPAR γ | Follicular carcinoma | 59/M |
| F631I | n.d. | n.d. | n.d. | | | |
| L512R | 56 | 325 | 100 | Not studied | Papillary carcinoma | 52/F |

The cell surface expression determined by TSH binding

The expression levels of the respective constructs were evaluated by FACS analysis. LRA has only been reported for TSHR mutation M453T (LRA: 5.2)

TSHR: thyroid stimulating hormone receptor; GPHR: glycoprotein hormone receptor; wt: wild type; LRA: linear regression analyses; FACS: Fluorescence-activated cell sorting

Table 6 Incidence of thyroid carcinoma in patients with toxic multinodular goiter n = number of patients.

| Author | Toxic multinodular goiter n | Thyroid cancer n | Thyroid cancer % |
|---------------------|-----------------------------|------------------|------------------|
| Cerci [99] | 124 | 11 | 8.8 |
| Senyurek Giles [17] | 299 | 19 | 6.4 |
| Vaiana [21] | 251 | 10 | 3.9 |
| Cappelli [8] | 339 | 13 | 3.9 |
| Gabriele [22] | 241 | 4 | 1.6 |
| Cakir [18] | 245 | 18 | 7.3 |
| Sahin [16] | 112 | 2 | 1.8 |

Table 7 Incidence of all types of hyperthyroidism in patients with thyroid cancer.

| Author | Thyroid carcinoma n | Hyperthyroidism (all types) | |
|--------------------------|---------------------|-----------------------------|------|
| | | n | % |
| Kilpatrick [97] | 100 | 7 | 7.0 |
| Hancock [98] | 120 | 10 | 8.3 |
| Mazzaferri [99] | 576 | 19 | 3.3 |
| Hall [100] | 79 | 3 | 3.8 |
| Wahl [101] | 554 | 23 | 4.2 |
| Edmonds [45] | 502 | 22 | 4.2 |
| Ahuja [72] | 251 | 22 | 8.8 |
| Vini [102] | 986 | 23 | 2.3 |
| Bolko [103] | 217 | 20 | 9.1 |
| Pazaitou-Panayiotou [11] | 720 | 60 | 8.3 |
| Gulcelik [104] | 422 | 12 | 2.8 |
| Lian [94] | 245 | 12 | 4.9 |
| Omur [96] | 1800 | 76 | 4.2 |
| Calò [26] | 110 | 15 | 13.6 |

tioning thyroid nodule that initially had been mistaken for benign and after thyroidectomy proved to be thyroid cancer [82]. The same is reported by other authors [68].

There are reports of malignant hot nodules, in which activating mutations of the thyrotropin receptor (TSHR) gene were identified [83–90]. Among these the I486F, T620I, F631I, D633Y, T632A, and T632I activating TSHR gene mutations were identified in 5 follicular carcinomas, the D633H mutation in one insu-

lar, the M453T and L512R mutations in 2 papillary (one per one) and the L677V in one Hürthle cell carcinoma. However, functional reanalysis of these reported TSH receptor mutations revealed that only the hot thyroid carcinomas with the TSHR mutations M453T, I486F, L512R, F631I, T632A, T632I, D633H and D633Y were associated with constitutively activating TSHR mutations [91], (○ Table 5).

Thyroid cancer in patients with toxic multinodular goiter

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 hyperfunctioning multinodular goiter ranges between 1.8–8.8% [8,16–18,21,22,92–95], (○ Table 6). However, the data available in the literature regarding the incidence and the evolution of the disease are controversial. Cerci et al. found no significant difference for the incidence of thyroid cancer between toxic and nontoxic multinodular goiter [92]. In another study, lymph node involvement was found in 23% of the cases with toxic multinodular goiter and cancer [17]. In a third one, 43 toxic multinodular goiters were associated with differentiated thyroid cancer. No lymph node metastases were detected in this latter study although distant metastases were found in 3 cases [96]. The variable findings in these 3 studies are difficult to explain and to understand.

Incidence of hyperthyroidism in cancer patients

Most of the reports examined the incidence of thyroid cancer in patients with hyperthyroidism and there are only few reports looking for the incidence of hyperthyroidism in patients operated on for thyroid cancer which is reported to be up to 14% [11,17,26,45,72,94,96–104], (○ Table 7). It would be very interesting to compare the evolution of thyroid cancer in both euthyroid and hyperthyroid patients in these studies in order to really understand if thyroid cancer progresses in a different way, depending on the metabolic condition of the thyroid gland.

Conclusions

Hyperthyroidism is a benign disease. Some patients with Graves' disease are treated with antithyroid drugs for many years. This often leads to underestimation of the risk of thyroid cancer and

to a delay in performing thyroidectomy, which should be the choice of treatment in patients with Graves' disease and suspicious nodules [40]. Evaluation of the malignancy risk of a nodule in patients with Graves' disease appears to be crucial. Creation of rodent models of thyroid cancers and hyperthyroidism could elucidate molecular genetic changes underlying cancer development and progression [105].

Patients with a toxic nodule or toxic multinodular goiter usually undergo thyroid ablation soon after the diagnosis of hyperthyroidism and therefore rarely receive prolonged antithyroid treatment. These patients are at low risk for developing thyroid carcinoma in the toxic nodules based on the data reported above. It is important to perform thyroid and neck US and US-guided FNAC prior to radioiodine therapy or thyroidectomy [16], in order to detect thyroid cancer. US-FNAC should be focused on lesions, which appear suspicious by US features as stated by the Consensus of Society of Radiologists in Ultrasound [55, 106], and not on larger or clinical dominant nodules. In cases of nodules that show suspicious features and when it is not possible to exclude the possibility of malignancy by fine needle aspiration cytology, the preferred choice of treatment should be surgery. The detection of the rare truly hot thyroid carcinomas remains a clinical challenge.

Unfortunately all the reported series in the present review are retrospective. Therefore, it is impossible to know the selection criteria, which have led to choose surgery: treatment of hyperthyroidism or because a nodule was suspicious? Prospective multicenter studies based on such selection could answer if the incidence and progression of thyroid cancer is different or not.

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