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, 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. 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 Subjected 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 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 [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
Gerenova [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 10 mm 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 microcarcinoma (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 ^{131}I 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 carci-noma (capsular invasion)	49/F
M453T	n.d. 66	700 570	n.d. 103	Not studied	Papillary carcinoma	11/F
D633Y	60*	405	127	PAX8-PPARγ	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 insular, 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.

References

1 *Means JH*. The thyroid and its diseases. Philadelphia: JB Lippincott Co, 1937; 482
2 *Sokal JE*. Incidence of malignancy in toxic and non-toxic nodular goiter. JAMA 1954; 154: 1321–1325
3 *Beahrs OH*, *Pemberton J*, *Black BM*. Nodular goiter and malignant lesion of the thyroid gland. J Clin Endocrinol 1951; 11: 1157–1165
4 *Olen E*, *Klinck GH*. Hyperthyroidism and thyroid cancer. Arch Pathol 1966; 81: 531–535
5 *Shapiro SJ*, *Friedmam NB*, *Perzik SL*, *Catz B*. Incidence of thyroid carcinoma in Graves' disease. Cancer 1970; 26: 1261–1270
6 *Davies L*, *Welch HG*. Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA 2006; 295: 2164–2167
7 *Enewold L*, *Zhu K*, *Ron E*, *Marrogi AJ*, *Stojadinovic A*, *Peoples GE*, *Devesa SS*. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980–2005. Cancer Epidemiol Biomarkers Prev 2009; 18: 784–791
8 *Cappelli C*, *Braga M*, *Martino ED*, *Castellano M*, *Gandossi E*, *Agosti B*, *Cumetti D*, *Pirola I*, *Mattanza C*, *Cherubini L*, *Rosei EA*. Outcome of patients surgically treated for various forms of hyperthyroidism with differentiated thyroid cancer: Experience at an Endocrine Center in Italy. Surg Today 2006; 36: 125–130
9 *Mazzaferri EL*. Thyroid cancer and Graves's disease. J Clin Endocrinol Metab 1990; 70: 826–829
10 *Ozaki O*, *Ito K*, *Kobayashi K*, *Toshima K*, *Iwasaki H*, *Yashiro T*. Thyroid carcinoma in Graves' disease. World J Surg 1990; 14: 437–441
11 *Pazaitou-Panayiotou K*, *Perros P*, *Boudina M*, *Drimonitis A*, *Siardos G*, *Patakiouta F*, *Vainas I*. Mortality from thyroid cancer in patients with hyperthyroidism: the Theagenion Cancer Hospital experience. Eur Journal Endocrinol 2008; 159: 799–803
12 *Hayes FJ*, *Sheaham K*, *Heffernan A*, *McKenna TJ*. Aggressive thyroid cancer associated with toxic nodular goitre. Eur J Endocrinol 1996; 134: 366–370
13 *Hales IB*, McElduff *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: 886–889
14 *Pacini F*, *DiCoscio GC*, *Anelli S*, *Macchia E*, *Concetti R*, *Miccoli P*, *Arganini M*, *Pinchera A*. Thyroid carcinoma in thyrotoxicosis patients treated by surgery. J Endocrinol Invest 1988; 11: 107–112
15 *Taneri F*, *Kurukahvecioglu O*, *Ege B*, *Yilmaz U*, *Tekin EH*, *Cifter C*, *Onuk E*. Clinical presentation and treatment of hyperthyroidism associated with thyroid cancer. Endocr Regul 2005; 39: 91–96
16 *Sahin M*, *Guvener ND*, *Ozer F*, *Sengul A*, *Ertugrul D*, *Tutuncu NB*. Thyroid cancer in hyperthyroidism: incidence rates and value of ultrasound-guided fine-needle aspiration biopsy in this patient group. J Endocrinol Invest 2005; 28: 815–818
17 *Senyurek Giles Y*, *Tunka 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: 1028–1037
18 *Cakir M*, *Arici C*, *Alakus H*, *Altunbas H*, *Balci MK*, *Karayalcin U*. Incidental thyroid carcinoma in thyrotoxic patients treated by surgery. Horm Res 2007; 67: 96–99
19 *Terzioglou T*, *Tezelman S*, *Onaran Y*, *Tanakol R*. Concurrent hyperthyroidism and thyroid carcinoma. Br J Surg 1993; 80: 1301–1302
20 *Linos DA*, *Karakitsos D*, *Papademetriou J*. Should the primary treatment of hyperthyroidism be surgical? Eur J Surg 1997; 163: 651–657
21 *Vaiana R*, *Cappelli C*, *Perini P*, *Pinelli D*, *Camoni G*, *Farfaglia R*, *Balzano R*, *Braga M*. Hyperthyroidism and concurrent thyroid cancer. Tumori 1999; 85: 247–252
22 *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: 79–83
23 *Miccoli P*, *Minuto MN*, *Galleri D*, *D'Agostino J*, *Basolo F*, *Antonangeli L*, *Aghini-Lombardi F*, *Berti P*. Incidental thyroid carcinoma in a large series of consecutive patients operated on for benign thyroid disease. ANZ J Surg 2006; 76: 123–126
24 *Lin CH*, *Chiang FY*, *Wang LF*. Prevalence of thyroid cancer in hyperthyroidism treated by surgery. Kaohsiung J Med Sci 2003; 19: 379–384
25 *Zanella E*, *Rulli F*, *Muzi M*, *Sianesi M*, *Danese D*, *Sciacchitano S*, *Pontecorvi A*. Prevalence of thyroid cancer in hyperthyroid patients treated by surgery. World J Surg 1998; 22: 473–478
26 *Calò PG*, *Tatti A*, *Farris S*, *Malloci A*, *Nicolosi A*. Differentiated thyroid carcinoma and hyperthyroidism: a frequent association? Chir Ital 2005; 57: 193–197
27 *Fukunaga FH*, *Lockett LJ*. Thyroid carcinoma in the Japanese in Hawaii. Arch Pathol 1971; 92: 6–13
28 *Fukunaga FH*, *Yatani R*. Geographic pathology of occult thyroid carcinomas. Cancer 1975; 36: 1095–1099
29 *Habra MA*, *Hijazi R*, *Verstovsek G*, *Marcell M*. Medullary thyroid carcinoma associated with hyperthyroidism: a case report and review of the literature. Thyroid 2004; 14: 391–396
30 *Alagöl F*, *Tanakol R*, *Boztepe H*, *Kapran Y*, *Terzioglu T*, *Dizdaroglu F*. Anaplastic thyroid cancer with transiet thyrotoxicosis: case report and literature review. Thyroid 1999; 9: 1029–1032
31 *Belfiore A*, *Garofalo MR*, *Giuffrida D*, *Runello F*, *Filetti S*, *Fiumara A*, *Ippolito O*, *Vigneri R*. Increased aggressiveness of thyroid cancer in patients with Graves' disease. J Clin Endocrinol Metab 1990; 70: 830–835
32 *Pellegriti G*, *Belfiore A*, *Giuffrida D*, *Lupo L*. Vigneri Outcome of Differentiated Thyroid Cancer in Graves' Patients. J Clin Endocrinol Metab 1998; 83: 2805–2809
33 *Yeo PP*, *Wang KW*, *Sinniah R*, *Aw TC*, *Chang CH*, *Sethi VK*, *Tan BC*, *Lim P*. Thyrotoxicosis and thyroid cancer. Aust N Z J Med 1982; 12: 598–593
34 *Farbota LM*, *Calandra DB*, *Lawrence AM*, *Paloyan R*. Thyroid carcinoma in Graves' disease. Surgery 1985; 98: 1145–1152
35 *Lee J*, *Nam KH*, *Chung WY*, *Soh EY*, *Park CS*. Clinicopathologic features and treatment outcomes in differentiated thyroid carcinoma patients with concurrent Graves' disease. J Korean Med Sci 2008; 23: 796–801
36 *Foppiani L*, *Del Monte P*, *Marugo A*, *Arlandini A*, *Sartini G*, *Marugo M*, *Bernasconi D*. Heterogeneous malignancy in toxic thyroid nodule, letter to the Editor. J Endocrinol Invest 2005; 28: 294–295
37 *Gerenova J*, *Buysschaert M*, *de Burbure CY*, *Daumerie C*. Prevalence of thyroid cancer in Graves's disease: a retrospective study of a cohort of 103 patients treated surgically. Eur J Intern Med 2003; 14: 321–325
38 *Erbil Y*, *Barbaros U*, *Ozbey N*, *Kapran Y*, *Tükenmez M*, *Bozbora A*, *Ozarmağan S*. Graves' disease, with and without nodules, and the risk of thyroid carcinoma. J Laryngl Otol 2008; 122: 291–295
39 *Kraimps JL*, *Bouin-Pincau MH*, *Mathonnet M*, *De Calan L*, *Ronceray J*, *Visset J*, *Marechaud R*, *Barbier J*. Multicentre study of thyroid nodules in patients with Graves' disease. Br J Surg 2000; 87: 1111–1113
40 *Behar R*, *Arganini M*, *Wu TC*, *McCormick M*, *Straus FH*, *DeGroot LJ*, *Kaplan EL*. Graves' disease and thyroid cancer. Surgery 1986; 100: 1121–1127

41 *Ain KB*. Papillary thyroid carcinoma – etiology, assessment and therapy. Endocrinol Metab Clin North Am 1995; 24: 711–760
42 *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: 434–439
43 *Stocker DJ*, *Burch HB*. Thyroid cancer yield in patients with Graves' disease. Minerva Endocrinol 2003; 28: 205–212
44 *Kim WB*, *Han SM*, *Kim TY*, *Nam-Goong IS*, *Gong G*, *Lee HK*, *Hong SJ*, *Shong YK*. Ultrasonographic screening for detection of thyroid cancer in patients with Graves' disease. Clin Endocrinol (Oxf) 2004; 60: 719–725
45 *Edmonds CJ*, *Tellez M*. Hyperthyroidism and thyroid cancer. Clin Endocrinol (Oxf) 1998; 28: 253–259
46 *Yano Y*, *Shibuya H*, *Kitagawa W*, *Nagahama M*, *Sugino K*, *Ito K*, *Ito K*. Recent outcome of Graves' disease patients with papillary thyroid cancer. Eur J Endocrinol 2007; 157: 325–329
47 *Duh QY*. Thyroid cancer in Graves' disease: incidental cancer versus clinical cancer. Ann Surg Oncol 2004; 11: 356–357
48 *Phitayakorn R*, *McHenry CR*. Incidental thyroid carcinoma in patients with Graves' disease. Am J Surg 2008; 195: 292–297
49 *Chao TC*, *Lin JD*, *Chen MF*. Surgical treatment of thyroid cancers with concurrent Graves disease. Ann Surg Oncol 2004; 11: 407–412
50 *Belfiore A*, *La Rosa GL*, *La Porta GA*, *Giuffrida D*, *Milazzo G*, *Lupo L*, *Regalbuto C*, *Vigneri R*. Cancer risk in patients with cold thyroid nodules. Relevance of iodine intake, sex, age and multinodularity. Am J Med 1992; 93: 363–369
51 *Welker MJ*, *Orlov D*. Thyroid Nodules. Am Fam Phycisian 2003; 67: 3
52 *Mazzaferri EL*. Thyroid cancer in thyroid nodules: finding a needle in the haystack. Am J Med 1992; 93: 359–362
53 *Belfiore A*, *Russo D*, *Vigneri R*, *Filetti S*. Graves' disease, thyroid nodules and thyroid cancer. Clin Endocrinol 2001; 55: 711–718
54 *Stocker DJ*, *Foster SS*, *Solomon BL*, *Shriver CD*, *Burch HB*. Thyroid cancer yield in patients with Graves' disease selected for surgery on the basis of cold scintiscan defects. Thyroid 2002; 12: 305–311
55 *Gharib H*, *Papini E*, *Paschke R*, *Duick DS*, *Valcalvi R*, *Hegedüs L*, *Vitti P*; *AACE/AME/ETA Task Force on Thyroid Nodules 2010*. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules executive summary and recommendations. J Endocrinol Invest 2010; 33: 287–291; Hot Thyroidology 4: 1–88; Endocr Pract 16 (Suppl 1): 1–43
56 *Centeno BA*, *Szyfelbein WM*, *Daniels GH*, *Vickery AL Jr*. Fine needle aspiration biopsy of the thyroid gland in patients with prior Graves' disease treated with radioactive iodine. Morphologic findings and potential pitfalls. Acta Cytol 1996; 40: 1189–1197
57 *Anderson SR*, *Mandel S*, *LiVolsi VA*, *Gupta PK*, *Baloch ZW*. Can cytomorphology differentiate between benign nodules and tumors arising in Graves' disease? Diagn Cytopathol 2004; 31: 64–67
58 *Ozaki O*, *Ito K*, *Mimura T*, *Sugino K*, *Kitamura Y*, *Iwabuchi H*, *Kawano M*. Thyroid carcinoma after radioactive iodine therapy for Graves' disease. World J Surg 1994; 18: 518–521
59 *Rees Smith B*, *McLachlan SM*, *Furmaniak J*. Autoantibodies to the thyrotropin receptor. Endocr Rev 1988; 9: 106–121
60 *Filetti S*, *Belfiore A*, *Amir SM*, *Daniels GH*, *Ippolito O*, *Vigneri R*, *Ingbar SH*. The role of thyroid-stimulating antibodies of Graves' disease in differentiated thyroid cancer. N Engl J Med 1988; 318: 753–759
61 *Morshed SA*, *Latif R*, *Davies TF*. Characterization of thyrotropin receptor antibody-induced signaling cascades. Endocrinology 2009; 150: 519–529
62 *Noguchi S*, *Yamashita H*, *Murakami N*, *Nakayama I*, *Toda M*, *Kawamoto H*. Small carcinomas of the thyroid: a long-term follow-up of 867 patients. Arch Surg 1996; 131: 187–191
63 *Pacini F*, *Schlumberger M*, *Dralle H*, *Elisei R*, *Smit JWA*, *Wiersinga W and the European Thyroid cancer Taskforce*. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006; 154: 787–803
64 *Cooper DS*, *Doherty GM*, *Haugen BR*, *Kloos RT*, *Lee SL*, *Mandel SJ*, *Mazzaferri EL*, *McIver B*, *Sherman SI*, *Tuttle RM*. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006; 16: 109–142
65 *Cooper DS*, *Doherty GM*, *Haugen BR*, *Kloos RT*, *Lee SL*, *Mandel SJ*, *Mazzaferri EL*, *McIver B*, *Pacini F*, *Schlumberger M*, *Sherman SI*, *Steward DL*, *Tuttle RM*. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2009; 19: 1167–1214
66 *Stålberg P*, *Svensson A*, *Hessman O*, *Akerström G*, *Hellman P*. Surgical treatment of Graves' disease: evidence-based approach. World J Surg 2008; 32: 1269–1277
67 *Ikekubo K*, *Hino M*, *Ito H*, *Otami M*, *Yamaguchi H*, *Saiki Y*, *Ui K*, *Habuchi Y*, *Ishihsra T*, *Mori T*. Thyroid carcinoma in solitary hot thyroid lesions on Tc-99m sodium pertechnetat scans. Ann Nucl 1989; Med 3: 31–36
68 *Uludag M*, *Yetkin G*, *Citgez B*, *Isgor A*, *Basak T*. Autonomously functioning thyroid nodule treated with radioactive iodine and later diagnosed as papillary thyroid cancer. Hormones (Athens) 2008; 7: 175–179
69 *Cirillo RL Jr*, *Pozderac RV*, *Caniano DA*, *Falko JM*. Metastatic pure papillary thyroid carcinoma presenting as a toxic hot nodule. Clin Nucl Med 1998; 23: 345–349
70 *Majima T*, *Doi K*, *Komatsu Y*, *Itoh H*, *Fukao A*, *Shigemoto M*, *Takagi C*, *Corners J*, *Mizuta N*, *Kato R*, *Nakao K*. Papillary thyroid carcinoma without metastases manifesting as an autonomously functioning thyroid nodule. Endocr J 2005; 52: 309–316
71 *Low SC*, *Sinha AK*, *Sundram FX*. Detection of thyroid malignancy in a hot nodule by fluorine-18-fluorodeoxyglucose positron emission tomography. Singapore Med J 2005; 46: 304–307
72 *Ahuja S*, *Ernst H*. Hyperthyroidism and thyroid carcinoma. Acta Endocrinol (Copenh) 1991; 124: 146–151
73 *Mizukami Y*, *Michigishi T*, *Nonomura A*, *Yokoyama K*, *Noguchi M*, *Hashimoto T*, *Nakamura S*, *Ishizaki T*. Autonomously functioning (hot) nodule of the thyroid gland. A clinical and histopathologic study of 17 cases. Am J Clin Pathol 1994; 101: 29–35
74 *Hamburger JI*. Solitary autonomously functioning thyroid lesions. Diagnosis, clinical features and pathogenetic considerations. Am J Med 1975; 58: 740–748
75 *Goretzki P*, *Wahl RA*, *Branscheid D*, *Joseph K*, *Tsuchiya A*, *Roher HD*. Indication for operation of patients with autonomously functioning thyroid tissue in endemic goiter areas. World J Surg 1985; 9: 149–155
76 *Harach HR*, *Sanchez SS*, *Williams ED*. Pathology of the autonomously functioning (hot) thyroid nodule. Ann Diagn Pathol 2002; 6: 10–19
77 *Smith M*, *McHenry C*, *Jarosz H*, *Lawrence AM*, *Paloyan E*. Carcinoma of the thyroid in patients with autonomous nodules. Am Surg 1988; 54: 488–489
78 *Schröder S*, *Marthaler B*. Autonomy and malignancy of thyroid glad tumors. A critical analysis of the literature on the existence of hyperfunctioning follicular and papillary thyroid gland carcinomas. Pathologe 1996; 17: 349–357
79 *Daumerie C*, *Ayoubi S*, *Rahier J*, *Buysschaert M*, *Squifflet JP*. Prevalence of thyroid cancer in hot nodules. Ann Chir 1998; 52: 444–448
80 *Croom RD 3rd*, *Thomas CG Jr*, *Reddick RL*, *Tawil MT*. Autonomously functioning thyroid nodules in childhood and adolescence. Surgery 1987; 102: 1101–1108
81 *Niedziela M*, *Breborowicz D*, *Trejster E*, *Korman E*. Hot nodules in children and adolescents in western Poland from 1996 to 2000: clinical analysis of 31 patients. J Paediatr Endocrinol Metab 2002; 15: 823–830
82 *Als C*, *Gedeon P*, *Rosler H*, *Minder C*, *Netzer P*, *Laissue JA*. Survival analysis of 19 patients with toxic thyroid carcinoma. J Clin Endocrinol Metab 2002; 87: 4122–4127
83 *Niepomniszcze H*, *Suarez H*, *Pitoia F*, *Pignatta A*, *Danilowicz K*, *Manavela M*, *Elsner B*, *Bruno OD*. Follicular carcinoma presenting as autonomous functioning thyroid nodule and containing an activating mutation of the TSH receptor (T620I) and a mutation of Ki-RAS (G12C) genes. Thyroid 2006; 16: 497–503
84 *Spambalg D*, *Sharifi N*, *Elisei R*, *Gross JL*, *Medeiros-Neto G*, *Fagin JA*. Structural studies of the thyrotropin receptor and GSα in human thyroid cancers: low prevalence of mutations predicts infrequent involvement in malignant transformation. J Clin Endocrinol Metab 1996; 81: 3898–3901
85 *Russo D*, *Tumino S*, *Arturi F*, *Vigneri P*, *Grasso G*, *Pontecorvi A*, *Filetti S*, *Belfiore A*. Detection of an activation mutation of the thyrotropin receptor in a case of autonomously hyperfunctioning thyroid insular carcinoma. J Clin Endocrinol Metab 1997; 82: 735–738
86 *Russo D*, *Wong MG*, *Costance G*, *Chiefari E*, *Treseler PA*, *Arturi F*, *Filetti S*, *Clark OH*. A Val 677 activating mutation of the thyrotropin receptor in a Hürthle cell thyroid carcinoma associated with thyrotoxicosis. Thyroid 1999; 9: 13–17
87 *Camacho P*, *Gordon D*, *Chiefari E*, *Yong S*, *Dejong S*, *Pitale S*, *Russo D*, *Filetti S*. A Phe 486 Thyrotropin receptor mutation in an autonomously functioning folliculer carcinoma that was causing hyperthyroidism. Thyroid 2000; 10: 1009–1012

88 *Mircescu H*, *Parma J*, *Huot C*, *Deal C*, *Oligny LL*, *Vassart G*, *Van Vliet G*. Hyperfunctioning malignant thyroid nodule in an 11-year-old girl: pathologic and molecular studies. J Pediatr 2000; 137: 585–587
89 *Fuhrer D*, *Tannapfel A*, *Sabri O*, *Lamesch P*, *Paschke R*. Two somatic TSH receptor mutations in a patient with toxic metastasising follicular thyroid carcinoma and non-functional lung metastases. Endocr Relat Cancer 2003; 10: 591–600
90 *Gozu H*, *Avsar M*, *Bircan R*, *Sahin S*, *Ahiskanali R*, *Gulluoglu B*, *Deyneli O*, *Ones T*, *Narin Y*, *Akalin S*, *Cirakoglu B*. Does a Leu 512 Arg thyrotropin receptor mutation cause an autonomously functioning papillary carcinoma? Thyroid 2004; 14: 975–980
91 *Jaeschke H*, *Mueller S*, *Eszlinger M*, *Paschke R*. Lack of in vitro constitutive activity for three previously reported TSH receptor mutations identified in patients with non autoimmune hyperthyroidism and hot thyroid carcinomas. Clin Endocrinol (Oxf) 2010; 73: 815–820
92 *Cerci C*, *Cerci SS*, *Eroglu E*, *Dede M*, *Kapucuoglu N*, *Yildiz M*, *Bulbul M*. Thyroid cancer in toxic and non-toxic multinodular goiter. J Postgrad Med 2007; 53: 157–160
93 *Chigot JP*, *Ménégaux F*, *Keopadabsy K*, *Hoang C*, *Aurengo A*, *Leenhardt L*, *Turpin G*. Thyroid cancer in patients with hyperthyroidism. Presse Med 2000; 29: 1969–1972
94 *Lian X*, *Bai Y*, *Tang W*, *Dai W*, *Guo Z*. A clinical study on coincidence with hyperthyroidism and thyroid carcinoma. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2000; 22: 273–275
95 *Ruggieri M*, *Scocchera F*, *Genderini M*, *Mascaro A*, *Luongo B*, *Paolini A*. Hyperthyroidism and concurrent thyroid carcinoma. Eur Rev Med Pharmacol Sci 1999; 3: 265–268
96 *Omür O*, *Yazc B*, *Akgün A*, *Ozcan Z*, *Akyldz M*, *Argon M*, *Ozklç H*. Concomitant hyperthyroidism in patients with thyroid carcinoma and the effects of iodine supplementation in an iodine-deficient Area. Clin Nucl Med 2008; 33: 769–772
97 *Kilpatrick R*, *Blomfield GW*, *Neal FE*, *Wilson GM*. Carcinoma of the thyroid. J Med 1957; 26: 209–233
98 *Hancock BW*, *Bing RF*, *Dirmikis SM*, *Munro DS*, *Neal FE*. Thyroid carcinoma and concurrent hyperthyroidism. Cancer 1997; 39: 298–302
99 *Mazzaferri EL*, *Young RL*, *Oertel JE*, *Kemmerer WT*, *Page CP*. Papillary thyroid carcinoma: The impact of therapy in 576 patients. Medicine (Baltimore) 1977; 56: 171–196
100 *Hall R*, *Ross M*, *Teng CS*, *Smith BR*. Immunological aspects of thyroid cancer. Recent Results Cancer Res 1980; 73: 56–59
101 *Wahl RA*, *Goretzki P*, *Meybier H*, *Nitschke J*, *Linder M*, *Roher HD*. Coexistence of hyperthyroidism and thyroid cancer. World J Surg 1982; 6: 385–390
102 *Vini L*, *Hyer S*, *Pratt B*, *Harmer C*. Good prognosis in thyroid cancer found incidentally at surgery for thyrotoxicosis. Postgrad Med J 1999; 75: 169–170
103 *Bolko P*, *Lacka K*, *Manuszewska E*, *Ruchala M*, *Majewski P*, *Sowinski J*. Is hyperthyroidism often present in patients with thyroid differentiated carcinoma? Pol Arch Med Weun 2002; 107: 555–559
104 *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: 35–39
105 *Zhu XG*, *Cheng SY*. Modeling thyroid cancer in the mouse. Horm Metab Res 2009; 41: 488–499
106 *Frates MC*, *Benson CB*, *Charboneau JW*, *Cibas ES*, *Clark OH*, *Coleman BG*, *Cronan JJ*, *Doubilet PM*, *Evans DB*, *Goellner JR*, *Hay ID*, *Hertzberg BS*, *Intenzo CM*, *Jeffrey RB*, *Langer JE*, *Larsen PR*, *Mandel SJ*, *Middleton WD*, *Reading CC*, *Sherman SI*, *Tessler FN*. *Society of Radiologists in Ultrasound*. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 2005; 237: 794–800