CLINICAL STUDY

Mortality from thyroid cancer in patients with hyperthyroidism: the Theagenion Cancer Hospital experience

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Abstract

Background: Thyroid carcinoma has been reported in patients operated for different types of hyperthyroidism and the probability of a hot nodule being malignant seems to be low. The aim of the present study was to explore the relationship between thyroid cancer, hyperthyroidism and outcome in a large cohort of patients who presented to a tertiary cancer centre in Northern Greece.

Patients: Among 720 patients treated for thyroid cancer, 60 had a concomitant diagnosis of hyperthyroidism due to Graves' disease ($n=14$), solitary autonomous adenoma ($n=17$), or multinodular goiter ($n=29$). Adverse prognostic factors were common in patients with a previous history of hyperthyroidism at the time of diagnosis of thyroid cancer, including cases where the cancer was discovered coincidentally after thyroid surgery for hyperthyroidism and cases where tumor size was more than 10 mm.

Results: In 10 out of 17 patients with hyperthyroidism due to solitary autonomous adenomas, the tumor was located within the hot nodule and two of these patients developed local and distant metastases and died from the disease 4 and 15 years after thyroidectomy.

Conclusion: Clinicians managing patients with hyperthyroidism need to be aware of the possible increased risk of thyroid cancer in this patient group.

European Journal of Endocrinology 159 799–803

Introduction

The coexistence of thyroid cancer and hyperthyroidism in patients presenting with the latter is well described, although the nature of this relationship is controversial (1, 2). The reported incidence of thyroid cancer found at surgery for hyperthyroidism ranges from 0.21 to 9.0% (1, 3, 4). The incidence of thyroid cancer may be increased in patients with Graves' disease presenting with a palpable nodule (5), while the probability of a hot nodule being malignant is low, ranging from 1 to 6% (6–8), but may be as high as 11% in children (9). Occasionally, some advanced thyroid cancers can cause hyperthyroidism due to autonomously functioning metastases (10, 11). Conversely, a history of hyperthyroidism in thyroid cancer patients is reported as 2.3–19% (8, 12–16).

Some studies suggest that thyroid cancer is not only commoner than expected in patients with Graves' disease, but may also be more aggressive (8, 17–19), although these findings are not universal (20, 21). The published data on thyroid cancer in autonomously functioning nodules (solitary or within multinodular goiters), are scanty and mostly anecdotal.

The aim of the present study was to explore the relationship between thyroid cancer, hyperthyroidism, and outcome in a large cohort of patients who presented to a thyroid cancer centre.

Patients and methods

The case records of patients treated for thyroid cancer at Theagenion Cancer Hospital between 1988 and 2005 were reviewed. Patients with a diagnosis of both thyroid cancer and hyperthyroidism were identified and their characteristics were further analyzed. Hyperthyroidism was diagnosed on the basis of a low serum TSH ($\text{TSH}=0.094\pm0.090$, minimum 0.03 and maximum 0.3 U/l, normal range 0.3–4.0 mU/l), elevated thyroid hormone concentrations ($\text{FT4}=34.8\pm3.39$ normal range 9–26 pmol/l, $\text{FT3}=9.25\pm1.46$, normal range 3–8 pmol/l) and concordant clinical features. Hyperthyroidism was classified according to the underlying etiology as solitary autonomous adenoma ($n=17$), Graves' disease ($n=14$), and multinodular goiter ($n=29$). The diagnosis of Graves' disease was based on clinical features of ophthalmopathy and/or positive thyrotropin receptor

antibodies. All patients with solitary autonomous adenoma had ⁹⁹Tc-pertechnetate and ¹³¹I scans, which showed a hot area corresponding to the nodule with lower or no uptake in the remaining thyroid tissue. The diagnosis of multinodular goiter was based on clinical features, scintigraphy, and ultrasonography. Staging was assigned in accordance with the 5th edition of the TNM classification (22). All patients had the diagnosis of hyperthyroidism established 1–6 years (median 3.5 years) before the diagnosis of thyroid cancer and 55 of them received antithyroid drugs for the same period of time for the treatment of thyrotoxicosis. Five patients (three with autonomous adenoma and two with toxic multinodular goiter), received only β blockers as the hyperthyroidism was deemed to be mild.

Pathology

All thyroid tissue samples were oriented, cut in parallel longitudinal slices each 5 mm thick and fixed in 10% neutral buffered formalin for 24 h. After fixation the samples were finely cut and paraffin embedded. For solitary encapsulated nodules measuring up to 5 cm, an additional section was taken for each additional centimeter in diameter, including the tumor capsule and adjacent thyroid tissue. For multinodular goiters, one section of each nodule (up to five nodules) was taken and more than one section for larger nodules (23). Samples were routinely processed after paraffin embedding. Normal tissue adjacent to neoplastic areas was also evaluated. All samples were retrospectively examined by one pathologist (FP). Pathologists were consistent in looking for coincidental microcarcinomas.

Statistical analysis

Summary statistics for continuous variables were expressed as mean ± s.d. Cross-tabulation and Pearson’s chi-square test, as well as one-way ANOVA were used for examining the relationship between two categorical variables, as tests of independence and measures of association. Variables analyzed were age, sex, tumor size, number of tumor foci, lymph node metastases and invasion of thyroid parenchyma, thyroid capsule, extrathyroidal invasion, or vessels invasion. A second data analysis was done with the same parameters excluding microcarcinomas. Calculations were carried out using SPSS version 12.0. Results were considered statistically significant when *p* value was less than 0.05.

Results

Between 1988 and 2005, 720 consecutive patients with thyroid cancer were treated at Theagenion Cancer Hospital, a tertiary referral center for patients with thyroid cancer in Northern Greece. Review of the case records identified 60 patients with a previous diagnosis

of hyperthyroidism and thyroid cancer, who comprised the study group. Their clinical characteristics are shown in Table 1. None of the patients had received previous radioiodine treatment or external beam irradiation. The indication for surgery was suspicion of thyroid cancer in 12 patients (cervical lymphadenopathy with positive fine-needle aspiration cytology (FNAC) in two patients with Graves’ disease and two with solitary autonomous adenoma, positive FNAC of a clinically suspicious nodule in three patients with toxic multinodular goiter and one cold nodule in a patient with Graves’ disease, and suspicious ultrasonographic findings in three patients with multinodular goiter and one with Graves’ disease). In the remaining 48 patients the indication for thyroidectomy was treatment for thyrotoxicosis. Among this group of thyrotoxic patients with no preoperative suspicion of thyroid cancer, a surprisingly high proportion 17/48 (35.40%) had advanced disease, including 11/48 (22.9%) with extrathyroidal soft tissue invasion. No significant correlations were found between type of hyperthyroidism, sex or age, and disease stage at diagnosis. All patients with preoperative suspicion or diagnosis of thyroid cancer had stage II–IVA disease. There were no significant differences in clinical characteristics at presentation between coincidentally discovered thyroid cancers and those with preoperative suspicion or diagnosis of thyroid cancer.

All but 5 out of the 60 patients had total/near total or completion thyroidectomy. The remaining five patients had lobectomies/subtotal thyroidectomies (all of these cases had tumors less than 1 cm, without evidence of residual disease). Ablation therapy with 100mCi of ¹³¹I was administered in 35/57 patients with follicular cell thyroid cancers. Patients with unifocal microcarcinoma without lymph nodes metastases or extrathyroid invasion were not ablated (24). All patients received levothyroxine therapy in a dose of 1.5–2 µg/kg per day after surgery/¹³¹I ablation aiming to suppress the serum TSH to less than 0.1 mU/l.

Table 1 Clinical characteristics of patients with hyperthyroidism and thyroid cancer.

	Carcinomas ≤ 10 mm	Carcinomas > 10 mm ^a
<i>n</i>	39	21
Male/female	3/36	8/13
Mean age at the diagnosis of cancer	50.36 ± 13.81	51.62 ± 14.45
Time from diagnosis of hyperthyroidism to thyroidectomy (median)	3.5 years (range 1–6)	3.3 years (range 1–6)
Carcinomas located within hot nodules	4/10	6/10

^aNo significant difference was found between the mean age of the patients and tumor size.

Pathology

Three medullary and 57 differentiated thyroid cancers were identified. The size of tumors was 1–10 mm in 39 (65%) and more than 10 mm in 21 patients (Table 2). The proportion of microcarcinomas (tumor size ≤ 10 mm) in the different types of hyperthyroidism were: 64.7% in patients with solitary autonomous adenomas, 50.0% in patients with Graves' disease, and 72.4% in patients with toxic multinodular goiter. These differences were not significant ($\chi^2=2.086$, $P=0.36$). No correlation was found between tumor size and age of the patient ($t=-0.332$, $P=0.7$; Table 1). Seven out of 39 patients with tumor ≤ 10 mm in diameter displayed features of aggressive behavior: two patients had lymph nodes metastases, in two patients there was tumor invasion of thyroid parenchyma, and in three patients there was extrathyroidal extension. In 18/39 patients with microcarcinomas multiple tumor foci were present and in 14/39 patients the tumor had the characteristics of the so-called 'occult papillary thyroid carcinoma'. In 10 out of the 17 (58.79%) patients with solitary autonomous adenomas, the tumor was located within the hot nodule (in seven, the entire nodule was malignant with tumor size more than 10 mm in 6 and 10 mm in one patient, and in three there was an area of microcarcinoma within the nodule) and was of papillary type in eight cases and follicular in two. In the other seven patients with solitary autonomous adenomas, a microcarcinoma was located outside the hot nodule and was papillary in all cases (one follicular variant, one tall cell variant). No correlation was found between tumor size, number of tumor foci, or invasion in different forms of hyperthyroidism. There was a trend for a higher prevalence of lymph node metastases at the time of diagnosis of thyroid cancer in patients with Graves' disease and autonomous adenoma than in patients with

multinodular goiter ($P=0.05$). This trend disappeared when microcarcinomas were excluded. For tumors more than 10 mm a trend was noted of an association between tumor size and the invasion of thyroid parenchyma and extrathyroidal invasion in all types of hyperthyroid patients, though this failed to reach statistical significance ($\chi^2=8.2$, $P=0.06$); however, such an association was significant for patients with multinodular goiter ($\chi^2=7.4$, $P=0.045$). Nineteen out of 54 papillary carcinomas were multifocal. There was no significant difference in incidence of multifocality between the different types of hyperthyroidism ($\chi^2=0.861$, $P=0.66$).

Follow-up

The median duration of follow-up was 54 months (range 14–205 months). All patients were followed up at six monthly intervals with clinical examination and high resolution neck ultrasonography. Thyroid stimulating hormone, serum thyroid hormones and thyroglobulin were measured annually. A patient was considered to be free of disease if all of the above assessments were negative including undetectable serum thyroglobulin after levothyroxine withdrawal and a negative whole body scan. At 18 months after the initial treatment, two patients (one with a history of solitary autonomous adenoma and one with toxic multinodular goiter) received additional therapy with 200 and 150 mCi of ^{131}I to treat residual local disease. Two patients with solitary autonomous adenoma represented, one with bone metastases and multiple s.c. nodular metastases in the neck 2 years after thyroidectomy, and the other with cervical lymph node recurrence 10 years and lung metastases 12 years after diagnosis respectively. The first of these cases had a 6 cm follicular thyroid cancer located inside the

Table 2 Staging and outcome in patients with hyperthyroidism and thyroid cancer > 10 mm.

<i>n</i> =21	Type of hyperthyroidism		
	Solitary autonomous adenoma (cancer within the hot nodule)	Graves' disease	Toxic multinodular goiter
Mean age $\pm$ s.d. (years)	55.33 $\pm$ 14.29	41.57 $\pm$ 16.96	60.63 $\pm$ 8.16
Cancer incidentally found after thyroidectomy	3	4	4
Preoperatively suspicious cancer	3	3	4
Stage at presentation			
I	2	1	2
II	2	3	4
III	1	3	1
IVA	1		1
Tumor size ≥ 10 mm	6 (35.3%)	7 (30.8%)	8 (29.6%)
Histology			
Papillary (including follicular variant)	4	6	6
Follicular	2	1	–
Medullary	–	–	2
Recurrences/metastases	2	No	No
Duration of follow-up (months)			
Median	52	50	60
Range	25–150	14–168	20–205
Disease specific mortality	Yes	No	No

hot nodule with thyroid capsular and vascular invasion at the time of diagnosis (Stage III). The second one had a 2.5 cm papillary thyroid cancer, columnar cell variant, also located inside the hot nodule, with extrathyroidal spread and multiple cervical lymph node metastases at the time of diagnosis (stage III). Both patients died due to metastatic thyroid cancer. Patients with medullary cancer were followed by neck ultrasound and by measuring serum calcitonin. During follow-up, one patient developed bone metastases and died from an unrelated cause 5 years after thyroidectomy.

Discussion

Thyroid carcinoma can be associated with various types of hyperthyroidism. Hyperthyroidism apparently does not ‘protect’ patients from thyroid cancer as it was believed years ago. Careful evaluation of hyperthyroid patients is always necessary to exclude the presence of associated malignancy and to determine the most appropriate therapeutic plan.

The size of malignant tumor was ≤10 mm in the majority of our patients. Although small in size, some of them presented lymph nodes metastases, invasion of thyroid parenchyma, extrathyroidal extension of the cancer, or had more than one foci with unilateral or bilateral location. Tumors more than 10 mm were found in 21/60 (35%) of our patients. The incidence of tumors more than 10 mm in hyperthyroid patients has previously been reported to be between 27.3 and 65.4% (Table 3).

The reported prevalence of local invasion at diagnosis in patients with differentiated thyroid cancer ranges between 5 to 12% in large series (29–31). Our study has revealed a high prevalence of locally advanced thyroid cancer in patients with hyperthyroidism, including cases where no preoperative suspicion of cancer was present. The reasons for this are unclear and probably complex. It is possible that this observation may represent referral patterns to a tertiary centre, with low-risk coincidental cancers being managed locally. A change in the true incidence of thyroid cancer among patients with thyrotoxicosis is also a possibility, though no conclusions can be drawn from the available data. The true incidence

of thyroid cancer in patients with autonomous adenomas may be underestimated when large doses of radioiodine are used to treat such cases (as opposed to surgery), which may be sufficient not only to cure the thyrotoxicosis but also the cancer. As hyperthyroidism is considered a benign disease, physicians may continue to treat patients (some of whom may happen to also harbor a thyroid cancer) with antithyroid drugs for years. Under such circumstances, the risk of thyroid cancer is probably underestimated and the decision about surgery is therefore delayed. Routine thyroid US scans and US-guided FNAB should be considered for complete evaluation of hyperthyroid patients, since this pathology frequently implies the development of thyroid nodules that are not always detectable on clinical or radionuclide examination. Surgery is mandatory when nodules with suspicious ultrasonographic features are found and if malignancy cannot be excluded with FNAC. Multinodularity of goiter should no longer be considered an indicator of probable benign disease. Since thyroid cancer may be present in hyperthyroid patients and may be invasive or metastatic, long-term therapy with antithyroid drugs should be carefully monitored, especially if a thyroid nodule is present. It is, therefore, preferable to avoid prolonged medical treatment and favor surgery over radioiodine for treating hyperthyroid patients, with suspicious nodules.

Our data show an aggressive behavior of autonomous solitary adenomas associated with thyroid cancer, compared with other causes of hyperthyroidism associated with cancer. In 58.8% of solitary autonomous adenomas associated with thyroid cancer, the tumor was located within the hot area observed on the isotope scan, including the two autonomous solitary adenomas that led to death. Thyroid cancer (either papillary or follicular) has been described in association with autonomously functioning adenomas (32, 33). Whether the two neoplasms (papillary thyroid cancer and follicular adenoma) arise independently of each other, or their coincidence is linked, is unknown.

The disease-specific mortality in the cohort of patients studied (with thyroid cancer and hyperthyroidism) was 3.3% over 4.5 years of mean follow-up. In comparison, 5-year mortality of patients with thyroid cancer in Greece has been reported at 2% (papillary) to 8%

Table 3 Incidence of carcinomas > 10 mm in the different types of hyperthyroidism and carcinomas located in the hot nodules.

Patients		Type of hyperthyroidism	Tumor size > 10 mm	Tumor inside the hot nodule
Farbota (2)	6	Graves' disease	3 (50%)	
Belfiore (5)	22	Graves' disease, hot nodule	9 (40.9%)	9/9
Ahuja (7)	20	All types	13 (65%)	2/2
Vini (16)	23	All types	11 (47.8%)	4/4
Ozaki (17)	19	Graves' disease	8 (42.1%)	
Cakir (25)	26	All types	17 (65.4%)	4/4
Cerci (26)	11	Multinodular goiter	3 (27.3%)	
Tanerli (27)	10	All types	3 (30%)	2/2
Ikekubo (29)	7	Hot nodule	Not reported	7/7
Chao (28)	61	Graves' disease	12 (19.7%)	
Our data	60	All types	21 (35%)	10/17

(follicular) (29). It appears therefore that patients with thyroid cancer and thyrotoxicosis have as aggressive course to their cancer as those without thyrotoxicosis.

The data presented here raise questions as to how intensively patients presenting with hyperthyroidism should be investigated for the presence of coincidental thyroid cancer. Although there is insufficient evidence to base recommendations for any change in practice, clinicians managing patients with hyperthyroidism need to be aware of the possible increased risk of thyroid cancer in this patient group. In particular, the proposition that hot nodules are associated with exceedingly low probability of malignancy (6–8), needs to be re-evaluated in prospective studies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 2 September 2008

Accepted 2 September 2008