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Outcome of Differentiated Thyroid Cancer in Graves' Patients*

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ABSTRACT

The clinical behavior and outcome was evaluated in 21 nonoccult differentiated thyroid carcinomas occurring in Graves' patients during the period 1982–94 and compared with that of matched tumors occurring in euthyroid controls (n = 70). At surgery, patients with Graves' disease showed distant metastases more frequently than euthyroid patients (3/21 = 14.3% *vs*. 1/70 = 1.4%, $P = 0.0556$). Graves' patients also showed a significantly higher cumulative risk of recurrent/progressive distant metastases or total adverse events (odd ratios = 3.14 and 2.07, respectively) as compared with euthyroid patients. At the last follow-up visit, persistence of distant metastases was also more frequent in the Graves' group ($P = 0.007$), although the cumulative individual dose of radioiodine administered was higher than in the control group (median dose = 805 mCi *vs*. 350 mCi). Two patients died in the Graves' group *vs*. none in the control group. Circulating thyroid stimulating antibodies were present in all patients but one and persisted as long as signs of disease were evident. These findings indicate that differentiated thyroid carcinomas in patients with Graves' disease are more aggressive than those occurring in matched euthyroid controls and should, therefore, be managed accordingly. (*J Clin Endocrinol Metab* **83:** 2805–2809, 1998)

WE previously reported that Graves' patients with a thyroid nodule have a very high risk of thyroid cancer, and that differentiated thyroid carcinomas concomitant to Graves' hyperthyroidism are more aggressive as compared with those arising in patients with non-autoimmune hyperthyroidism or in euthyroid patients (1). Moreover, thyroid stimulating antibodies (TSAbs) present in Graves' patients are able to stimulate the function and growth of differentiated thyroid cancer metastases (2). Finally, Graves' disease may reduce the latency period of thyroid cancer developing after radiation and chemotherapy for Hodgkin's disease (3). Taken together these studies strongly suggest that Graves' disease may have a role as a favoring factor in the initiation/progression of thyroid cancer. Therefore, since 1988, we have included thyroid ultrasounds in the initial workup of Graves' patients to allow early detection of thyroid nodules. We have also avoided prolonged medical treatment and favored surgery over radioiodine for treating Graves' disease, especially in patients with thyroid nodules.

The present study was undertaken to evaluate whether this approach, aimed at the early detection and treatment of Graves' associated thyroid cancer, allowed the identification of smaller and less aggressive carcinomas. We, therefore, evaluated the frequency of occult *vs*. nonoccult thyroid carcinomas in Graves' patients, comparing the periods 1982–87 and 1988–94. In all nonoccult carcinomas observed in Graves' patients in the 1982–94 we evaluated the stage at presentation and the long-term outcome and compared these data to matched tumors in euthyroid controls.

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Patients and Methods

Graves' patients

The diagnosis of Graves' disease was based on history and signs of hyperthyroidism with increased ^{131}I thyroid uptake and the absence of hot nodules at scintiscan. The presence of ophthalmopathy and autoimmune involvement of the thyroid (circulating TSAbs, antimicrosomal and/or antithyroglobulin antibodies) confirmed the diagnosis.

In the period 1988–94, all patients with Graves' disease had a thyroid echography, and fine needle aspiration biopsy was performed whenever a thyroid nodule (either palpable or >1 cm) was detected (4). Patients with a thyroid nodule were referred to surgery unless the nodule contained abundant colloid and a scarce number of follicular cells with picnotic nuclei. In addition, Graves' patients ≤40 yr with hyperthyroidism relapsing after an 8- to 16-month treatment with metimazole were referred to surgery unless surgical treatment was contraindicated. In these patients the period between diagnosis and surgery depended on the severity of hyperthyroidism, goiter volume, patient age, compliance to therapy and achievement and persistence of remission. Graves' patients treated with metimazole were periodically examined with thyroid ultrasounds.

Radioiodine treatment was used in patients >40 yr old and without thyroid nodules or in patients with contraindications to surgery. These criteria led to 318 thyroidectomies in the 524 Graves' patients observed in the period 1988–94 (~60%) with a substantial increase in respect to 132 thyroidectomies in the period 1982–87 (33% of the 398 observed patients).

Twenty-three differentiated carcinomas were diagnosed among the 318 Graves' patients operated on in the period 1988–94. Ten of these patients were operated on because of a cytologically suspicious nodule, the remaining 13 cases were occult carcinomas incidentally found at operation and without nodal involvement.

As previously reported, in the years 1982–87 13 cancers (2 occult and 11 nonoccult) were found among the 132 Graves' patients operated on (1). In this series only one patient with an occult cancer was lost to follow-up.

Circulating TSAbs were measured as previously described (5) and were present in 35/36 Graves' patients with cancer; in the single patient with undetectable TSAbs, signs and symptoms were typical of Graves' disease.

Euthyroid control patients

For the 35 Graves' patients with cancer (21 nonoccult and 14 occult carcinomas), 86 euthyroid control patients operated on for thyroid cancer in the same period (±2 yr) and matched for sex, age (±2 yr), class of tumor size (≤1, 1.1–4.0, >4 cm), and tumor histotype were selected. This control series included patients with cancer arising as a solitary cold nodule or in an euthyroid multinodular goiter. The characteristics and follow-up period of cancer patients in the Graves' and the control group are shown in Table 1.

Surgical treatment and histopathological examination

Patients with differentiated thyroid cancer underwent total or near-total thyroidectomy plus paratracheal lymph node dissection. Latero-cervical lymph nodes were dissected when macroscopically involved or in the presence of extensive invasion of central nodes.

For each case all the histological slides were reviewed, and histopathological diagnoses were graded according to the thyroid malignancy WHO classification (6). Occult carcinomas were defined as non-palpable, unifocal carcinomas ≤1.5 cm in diameter and with no lymph node involvement or extrathyroid invasion. Tumor stage was assessed according to pTNM system (7) where T (extent of the primary tumor) and N (regional lymph node metastases) were determined on the basis of pathological data and M (evidence of distant metastases) was based on routine lung X-rays.

Postoperative patient follow-up

Postoperative evaluation was carried out as previously described (8). Residual or metastatic tumoral tissue was considered present when total body scan (TBS) with ^{131}I was positive and/or serum thyroglobulin (Tg) levels were >10 μg/L (up to 1989, as measured by RIA) or >5 μg/L (after 1989, as measured by immunoradiometric method). The presence of distant metastases at TBS was always confirmed by at least one additional imaging test [standard × rays, computerized assisted tomography (CAT) scan, nuclear magnetic resonance (NMR), bone scan]. Non-surgically removable distant metastases were treated with ^{131}I (3700–5550 MBq) every 8–12 months. Diagnosis of regional lymph node recurrence was made when ultrasound evidence of suspicious lymph nodes was confirmed by either radioiodine uptake or a finding of either neoplastic epithelial cells and/or high Tg levels in the aspirates. Local recurrences were also diagnosed by ultrasound or CAT imaging plus cytological examination. Disease progression was defined as enlargement of metastases or tumor masses in the neck (as evaluated by TBS and/or CAT imaging plus serum Tg increase) and/or appearance of new metastatic foci and/or cancer-related death.

TABLE 1. Characteristics of Graves' patients with associated thyroid cancer and matched euthyroid control patients in 1982–1994 observation period

	Graves' patients (n = 35)	Control euthyroid patients (n = 86)	*P* value
Age (y)			
Range	20.1–70.8	19.0–66.7	0.183
Median	43.0	39.9	
Gender (F/M)	30/5	74/12	0.963
Diameter (cm)			
Range	0.4–8.0	0.2–10.0	0.989
Median	1.5	1.5	
Histotype-papillary (%)	91.4	94.2	0.918
Follow-up (months)			
Range	26.6–186.1	25.2–203.0	0.451
Median	69.7	82.2	

Statistical analysis

The distribution of pathological stage and other variables in Graves' and control groups was compared with the use of contingency tables and χ-square test. Recurrence-free survival or progression-free survival in the two patient groups were calculated from date of surgery and compared using Kaplan-Meier plots. The log-rank test was used to evaluate the differences between curves. Hazard ratios and their 95% confidence intervals (C.I.) were calculated with the Cox proportional hazard regression model (9). Data analysis was performed using the SPSS (Chicago, IL) statistical package for Power Macintosh PC.

Results

Nonoccult carcinomas

Frequency. Twenty-one clinically important thyroid carcinomas were diagnosed in the 450 Graves' patients undergone thyroidectomy in the period 1982–94 (4.7%). Although patients operated on represented only part of Graves' patients observed, the frequency of nonoccult cancer in the Graves' population could be calculated as 2.76% (11/398) in 1982–87 and 1.91% (10/524) in 1988–94.

Stage. Tumor stage of nonoccult carcinomas in the Graves' group and in matched euthyroid controls is shown in Table 2. Tumor stage distribution by pTNM was very similar in the two series of Graves'-associated carcinomas (periods 1982–87 and 1988–94), but was shifted in favor of stages III and IV when compared with euthyroid controls. Accordingly, 3/21 (14.3%) patients in the Graves' group but only 1/70 (1.4%) in the control group showed nodular lung metastases at preoperative X-rays ($P = 0.0556$).

Outcome. The outcome of the 21 clinically important thyroid carcinomas in the Graves' group was compared with that of the 70 matched tumors in euthyroid controls. The follow-up period was very similar in the two groups, ranging from 34.9–186.1 months (median = 90.9) in Graves' patients and 29.2–203.0 months (median = 84.7) in the euthyroid patients.

During the follow-up period, 3 new cases of distant metastases were observed in the Graves' group and 5 in the control group with a cumulative rate of distant metastases of 6/21 = 28.6% in the Graves' group *vs.* 6/70 = 8.6% in the control group ($P = 0.0446$, χ-square test; $P = 0.0367$, log-rank test). Characteristics, mode and time of diagnosis, and outcome for individual cases with distant metastases are shown in Table 3. In the Graves' group distant metastases were cured only in 1 case and caused patient death in 2 cases. In contrast, in the control group cure was achieved in 4 cases and metastases caused no patient death ($P = 0.0071$, Table 4). The cumulative individual dose of radioiodine administered ranged from 300-1100 mCi (median = 805) in the Graves' group and 200–650 mCi (median = 350) in the control group. In the Graves' patients the hazard ratio for recurrent/progressive distant metastases *vs.* controls was 3.14 (C.I. = 1.01–9.73, $P = 0.0479$, Cox analysis).

In the Graves' group a trend for a higher frequency of lymph node metastases was also observed, both at surgery and as a cause of recurrent locoregional disease: for lymph node involvement, however, the difference between the two groups did not achieve statistical significance (Table 4). However, when recurrence/progression for any adverse event (distant metastases and/or locoregional disease) was taken

TABLE 2. Tumor stage distribution according to pTNM of nonoccult differentiated thyroid carcinomas observed in Graves' patients and in matched euthyroid controls

Tumor stage	Graves' patients			Euthyroid patients		
	1982–87 (n = 11)	1988–94 (n = 10)	1982–94 (n = 21)	1982–87 (n = 27)	1988–94 (n = 43)	1982–94 (n = 70)
I	6 (54.5)[a]	6 (60.0)	12 (57.1)	19 (70.4)	30 (69.8)	49 (70.0)
II	1 (9.1)		1 (4.8)	1 (3.7)	7 (16.3)	8 (11.4)
III	2 (18.2)	3 (30.0)	5 (23.8)	6 (22.2)	6 (13.9)	12 (17.2)
IV	2 (18.2)	1 (10.0)	3 (14.3)	1 (3.7)		1 (1.4)

[a] Numbers in parentheses are percent.
P = 0.0554, χ-square test applied to the tumor stage distribution in Graves' *vs.* euthyroid patients (period 1982–94).
P = 0.0556, χ-square test, occurrence of stage IV tumors in Graves' *vs.* euthyroid patients (period 1982–94).

TABLE 3. Characteristics of patients presenting distant metastases in Graves' and in control group (1982–94)

Age (yr)	Sex	Diameter (cm)	Histotype	pTNM stage	Distant metastases	Diagnosis	DFS (months)	Follow-up (months)	Outcome
Graves' group									
59	M	6.0	FOLL	T4N0M1	Lung	X-rays, TBS	0	165	Lung
69	F	6.0	FOLL	T4N1M1	Lung	X-rays, TBS	0	50	Dead
46	M	0.7	PAP	T4N1M0	Lung	TBS	3	35	Lung
66	F	8.0	PAP	T4N1M1	Lung, bone	X-rays, TBS	0	62	Dead
29	F	2.0	PAP	T4N1M0	Lung, Mediastinum	TBS, CAT	57	186	Mediastinum
60	M	8.0	PAP	T3N0M0	Lung	TBS, CAT	89	90	Lung
Control group									
30	F	1.5	PAP	T4N1M0	Lung	TBS	24	78	LCN
29	F	3.0	PAP	T2N1M0	Lung	TBS	6	117	DF
37	F	1.5	PAP	T2N1M0	Lung	TBS	3	30	DF
65	F	4.5	FOLL	T4N0M1	Bone	X-rays, TBS	0	53	Bone
29	F	2.0	PAP	T2N1M0	Lung	TBS	3	84	LNC
64	F	10.0	FOLL	T4N0M0	Large vessels	TBS, CAT	60	88	Large vessels

PAP, papillary; FOLL, follicular; DFS, disease-free survival; LCN, locoregional lymph nodes; DF, disease-free.

as the end point, patients in the Graves' group were significantly more affected than euthyroid control patients (11/21 = 52.4% *vs*. 20/70 = 28.6%, $P = 0.0407$, log-rank test; Fig. 1). The hazard ratio was 2.07 (C.I. = 1.01–4.26, $P = 0.0469$).

Circulating TSAbs were present in all patients who developed a recurrence with the exception of one. In those patients, circulating TSAbs persisted as long as signs of disease were evident. The only patient with a negative TSAb at recurrence also had been negative at diagnosis, although the diagnosis of Graves' disease was obvious.

Occult carcinomas

The overall frequency of occult carcinomas in Graves' patients undergoing surgery was 3.33% (15/450). The diagnosis of occult carcinoma in the Graves' patients observed at our clinic increased from 2/398 (0.5%) in 1982–87 to 13/524 (2.5%) in 1988–94 after introduction of routine ultrasounds. All patients with occult carcinomas in both the Graves' and euthyroid group (n = 16) were alive at the time of the last follow-up visit. All were disease-free except for one case in the Graves' group who developed a local recurrence.

Discussion

We observed a frequency of 4.7% clinically relevant differentiated thyroid carcinomas in the series of 450 Graves' patients operated on in the period 1982–94. If no cancer was missed in the 922 Graves' patients referred to our observation during this 13-yr period, the annual incidence of clinically relevant thyroid cancer in these patients can be calculated as 175/100,000, well above the incidence of 0.5–8.0/100,000 reported in the general population (10). These data, therefore, support previous studies suggesting an association between Graves' disease and thyroid cancer (11–14) and are at variance with other studies that have not found such association (15).

Furthermore, the present data confirm our previous report that differentiated thyroid cancers associated with Graves' disease are more aggressive than those occurring in euthyroid patients (1). Herein, we compared tumors in Graves' patients to tumors in euthyroid patients matched for age, sex, and tumor size, all factors known to affect cancer prognosis. At surgery, tumors in Graves' patients showed more frequently distant metastases than in matched euthyroid controls. Tumors in Graves' patients had also a less favorable outcome as judged by persistent disease and cancer-related deaths ($P = 0.0071$). The cumulative risk for recurrent/progressive distant metastases was approximately 3-fold higher in Graves' patients than in euthyroid patients (odds ratio = 3.14).

Although other independent studies support our conclusion that differentiated thyroid cancer concurrent to Graves' disease is usually aggressive (13), some researchers have yielded discordant results (15–18). The reason(s) for these discrepancies is not clear (19). The genetic background

TABLE 4. Occurrence and outcome of distant and locoregional metastases in Graves' patients and matched euthyroid controls with a differentiated nonoccult thyroid cancer diagnosed in period 1982–94

	Graves' patients (n = 21)	Euthyroid controls (n = 70)
Patients with distant metastases		
At surgery	3 (14.3)[a]	1 (1.4)
New cases at follow-up	3 (14.3)	5 (7.1)
Total cases[b]	6 (28.6)	6 (8.5)
Patients with locoregional metastases		
At surgery	12 (57.1)	33 (47.1)
Relapses[c]	9 (42.8)	12 (17.1)
New cases at follow-up	1 (4.8)	4 (5.7)
Total relapses/new cases[d]	10 (47.6)	16 (22.9)
Patient follow-up status		
Persistent distant metastases	3 (14.3)	2 (2.9)
Persistent lymph nodes	4 (19.0)	11 (15.7)
Deaths for cancer	2 (9.5)	0
Persistent distant metastases/deaths[e]	5 (23.8)	2 (2.9)
Total persistent disease/deaths[f]	9 (42.9)	13 (18.6)

[a] Numbers in parentheses are percent.
[b] Graves' *vs.* control patients: $P = 0.0446$.
[c] Four patients in Graves' group and four in control group had also distant metastases.
[d] Graves' *vs.* control patients: $P = 0.0276$.
[e] Graves' *vs.* control patients: $P = 0.0071$.
[f] Graves' *vs.* control patients: $P = 0.0226$.

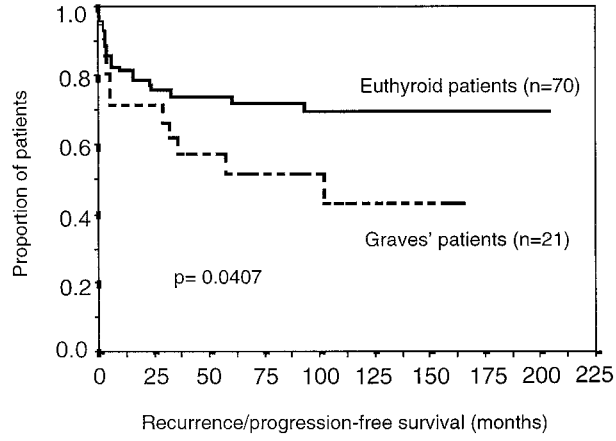

FIG. 1. Recurrence/progression-free survival (Kaplan-Meier plots) in Graves' patients or in matched euthyroid control patients with a nonoccult differentiated thyroid carcinoma observed in the 1982–94 period. *P* value is calculated according to log-rank test.

and/or unidentified environmental factors may play a role as well as patient selection. Some retrospective studies taking into account a very long period are likely to be biased by changing criteria in the preoperative selection of patients, in the thyroid pathological examination, and in the surgical and postsurgical management of the patient. One of these studies that compared Graves' patients with concomitant thyroid cancer to sex- and age-matched euthyroid controls and concluded that no difference in cancer outcome was present (15), may be interpreted in a different way. Because the mean tumor diameter was 1.0 cm in the Graves' group and 2.5 cm in the control group, the study may suggest that small carcinomas in Graves' patients have the same prognosis than larger carcinomas in euthyroid patients.

Because the molecular mechanisms underlying thyroid cancer are not entirely clarified (20, 21), the mechanism(s) leading to an increased frequency and aggressiveness of thyroid cancer in Graves' patients is also unclear. However, the possibility that TSAbs of Graves' patients play a role in thyroid cancer initiation/progression is supported by several lines of evidence. We and others have reported that thyroid cancer relapse may occur years after thyroidectomy, coincident with Graves' recurrence and circulating TSAb appearance (2, 22). *In vitro* studies have previously shown that TSAbs, like TSH, activate both the cAMP and the PIP2 (phosphatidylinositol bisphosphates) cascades, both of which are involved in thyroid cell growth regulation (23). In addition, cultured thyroid cancer cells from Graves' patients respond to the patient's own TSAbs by cAMP accumulation (2), and TSAbs effectively induce human thyroid cell growth *in vitro* (24, 25). Furthermore, TSAbs, as well as TSH, stimulate angiogenesis, a limiting step in tumor development, by upregulating vascular endothelial growth factor, placenta growth factor, and their cognate receptors (flt-1 and Flk-1/kinase domain receptor) in the thyroid (26, 27).

Like TSH, TSAbs induce specific differentiation features in thyroid cells, including gene expression of both Tg and thyroid peroxidase. Metastases from Graves'-associated thyroid carcinomas, therefore, are likely to take up iodine and respond to radioiodine therapy. Indeed, in our series, all thyroid cancer metastases in Graves' patients had a good radioiodine uptake. It should be emphasized, however, that features of differentiation and marked aggressiveness may coexist in thyroid cancer with an activated TSH receptor (28).

Finally, because TSAbs are heterogeneous with regard to serum levels, binding characteristics to the TSH receptor and biological effects on thyroid cells (29), they may variously affect thyroid cancer in different patients. In addition to the presence of TSAbs, the autoimmune process of Graves' disease *per se* may affect the clinical evolution of thyroid cancer by altering the host immune response to the tumor, an important prognostic factor (30–32).

In conclusion, we confirm previous evidence that differentiated thyroid cancer is a relatively frequent finding in patients with Graves' disease, and that nonoccult carcinomas associated to Graves' disease have a more advanced stage at presentation and a less favorable outcome than similar tumors occurring in matched euthyroid patients (1). We suggest, therefore, that Graves' patients, especially when treated with antithyroid drugs, should be screened for thyroid nodules by ultrasounds. Thyroid nodules should undergo cytological examination and prompt surgical removal when cytologically suspicious. When a cancer is found, an aggressive treatment is suggested (total thyroidectomy plus lymphadenectomy followed by radioiodine therapy) (33).

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