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The Outcome of Patients with Thyroid Carcinoma and Graves' Disease

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Abstract: A total 847 consecutive patients with Graves' disease who underwent thyroidectomy between 1965 and 1990 were found to have a 4.3% incidence of coincident carcinoma of the thyroid. In 68.2% of these cases the tumors were less than 1 cm in diameter and were detected in only 7 patients (19.4%) prior to surgery. Dissection of the regional lymph nodes was necessary in only 11 patients. A review of the patients in 1990 revealed no carcinoma-related deaths with metastases occurring most commonly in the patients with larger tumors and in those whose cancer had been detected prior to thyroidectomy. Although the detection of potential tumors occurring with Graves' disease using preoperative echogram may be of interest, our results suggest that occult microcarcinoma occurring coincidentally with Graves' disease is not clinically significant as it did not cause any recurrence in this study. Moreover, there was no evidence to suggest that Graves' disease was associated with the increased or rapid growth of these tumors.

Key Words: thyroid carcinoma, Graves' disease, thyroid stimulating antibody (TSAb)

Introduction

The relationship of thyroid carcinoma to Graves' disease is still unclear although the coincidence of thyroid carcinoma with Graves' disease has been reported by many authors.[1–7] We report herein our experience with Graves' disease and concurrent carcinoma in a series of patients who underwent thyroidectomy for Graves' disease.

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Patients and Methods

This is a retrospective analysis of 847 consecutive patients who underwent surgical treatment for Graves' disease between 1965 and 1990 in our department. All patients had been diagnosed as having Graves' disease using standard clinical and laboratory criteria, and none had received radioactive iodine. In a previous study we reported on the clinical efficacy and postoperative results of surgically treating Graves' disease[8,9] and a follow-up survey was done in 1990.

Results

The operative procedures were performed over a period of 26 years. Thirty six of the total 847 patients, being 6 males and 30 females with ages ranging from 16 to 65 years, were found to have thyroid carcinoma. Thirty were of the papillary type and 6 of the follicular type, with an overall incidence of 4.3% (Table 1) and tumors were detected prior to surgery in only 7 of these 36 patients (19.4%).

Thirteen of the total 44 tumors were found in the right lobe, 12 in the left lobe, 4 in the isthmus, and 6 in both lobes, and 30 of the tumors (68.2%) were less than 1 cm in diameter. Of the remaining tumors larger than 1 cm, 2 were multifocal having 2 and 4 foci respectively.

Bilateral subtotal thyroidectomy was performed in 24 patients, total thyroidectomy in 5, and lobectomy with subtotal thyroidectomy of the contralateral lobe in 7. Dissection of the regional lymph nodes was necessary in only 11 patients and lymph node metastases were found in 7 of these patients (63.6%), being most often seen in those with larger tumors and those diagnosed preoperatively.

The mean follow-up period of the 28 patients with carcinoma who were reviewed in 1990 was 9.1 years,

Table 1. Data on the 36 patients with Graves' disease and concurrent thyroid carcinoma

Pt. No.	Sex	Age at operation (years)	Year of operation	Preoperative detection of nodule	Location of tumor	Pathology	Tumor size (cm)	Method of operation	Dissection of lymph node	Metastasis of lymph node	Recurrence in 1990
1	M	39	1967	N	R	P	0.5	Bil. STx	N		unknown
2	F	33	1969	Y	R	P	4.5	R. Lx and L. STx	N		unknown
3	F	17	1970	N	R	P	1.2	Bil. STx	N		N
4	F	33	1970	N	L	P	0.3	Bil. STx	N		unknown
5	F	43	1971	N	R	P	0.3	Bil. STx	N		died due to other disease
6	F	40	1971	Y	L	P	1.0	L. Lx and R. STx	N		N
7	F	58	1971	Y	R and L	P	R: 1.2 and 0.5 L: 0.5 and 0.5	Tx	N		N
8	F	29	1972	N	I	P	1.0	Bil. STx	N		N[a]
9	F	20	1975	N	unknown	P	0.3	Bil. STx	N		N
10	F	37	1975	N	L	P	0.5	Bil. STx	N		N
11	F	20	1975	N	L	P	0.3	Bil. STx	N		unknown
12	F	40	1975	N	I	P	1.2	Bil. STx	Y	N	unknown
13	F	38	1975	N	L	F	0.5	Bil. STx	N		unknown
14	F	30	1977	N	L	P	0.5	Bil. STx	N		N
15	M	29	1978	Y	R	P	5.5	R. Lx and L. STx	Y	Y	N
16	F	23	1979	N	R	F	0.5	Bil. STx	N		N
17	M	45	1979	N	L	F	0.6	Bil. STx	N		N
18	M	53	1979	N	R	P	0.5	Bil. STx	N		N
19	F	48	1979	N	R	P	0.3	Bil. STx	N		N
20	F	43	1982	N	R and L	F	R: 1.0 L: 1.0	Bil. STx	N		N
21	F	31	1982	N	L	P	0.6	Bil. STx	N		N
22	F	21	1982	N	L	P	0.8	Bil. STx	N		N
23	F	53	1982	N	R	P	1.3	R. Lx and L. STx	Y	N	N
24	F	53	1983	N	I	P	0.9	Bil. STx	Y	Y	N
25	F	48	1983	N	R and L	P	R: 3 L: 3	Tx	Y	Y	N
26	F	62	1984	Y	R and L	P	R: 1.3 L: 3.8	Tx	Y	Y	N
27	M	16	1985	N	L	P	0.5	Bil. STx	N		unknown
28	F	65	1985	N	I	P	1.0	Tx	Y	N	N
29	F	31	1986	N	L	P	0.8	Bil. STx	N		N
30	F	59	1986	N	R	F	1.0	Bil. STx	N		N
31	F	50	1986	N	R and L	F	R: 0.5 L: 2.9	R. STx and L. Lx	Y	N	N
32	M	31	1987	N	R	P	0.3	Bil. STx	N		N
33	F	18	1987	N	R	P	3.1	R. STx and L. Lx	Y	Y	Y[b]
34	F	45	1988	Y	R	P	0.9	R. Lx and L. STx	Y	Y	N
35	F	48	1988	Y	R and L	P	R: 1.4 L: 1.6	Tx	Y	Y	N
36	F	28	1990	N	L	P	0.7	Bil. STx	N		N

R, right; *L*, left; *I*, isthmus; *N*, no; *Y*, yes; *P*, papillary carcinoma; *F*, follicular carcinoma; *Bil*, bilateral; *STx*, subtotal thyroidectomy; *Tx*, total thyroidectomy; *Lx*, lobectomy

[a] Reoperation due to recurrence in remnant thyroid gland was done in 1976

[b] Multiple lung metastases were seen

with a range of 0.5–20 years. To date, 27 patients are alive and well with no sign of recurrence. However, 1 patient (no. 8) had a second exploration due to recurrence in the remnant thyroid tissue while another patient (no. 33) developed multiple lung metastases in both lung fields and received radioactive iodide therapy directed to the lung metastases 3 times over 3 years.

Discussion

Our present retrospective study provides no answers relating to the pathogenesis of carcinoma in Graves' disease. Instead, we reported the clinical analysis of a large group of patients with concurrent Graves' disease and thyroid carcinoma with respect to the size, pathology, and location of the tumor and prognosis.

The issue of the frequency of association between hyperthyroidism and thyroid cancer has been addressed by many researchers.[1–7] Shapiro et al.,[2] Hancock et al.,[3] Farbota et al.,[4] Behar et al.,[5] Pacini et al.,[6] and Belfiore et al.[7] found carcinoma in 9%, 1.5%, 5.1%, 5.2%, 6.9%, and 9.8% of cases, respectively. In our study, however, the occurrence of thyroid cancer in Graves' disease patients who underwent surgery proved to be 4.3%, although the different criteria used to select patients for surgery, as well as geographic and genetic factors, may have led to these different results. Nevertheless, our result is higher than those previously reported in the Japanese population, with Maruchi et al.[10] reporting 0.13% and Waterhouse et al.[11] reporting 0.5%–0.6% for males and 1.9%–3.0% for females in Japan.

In 68.2% of our patients, the carcinoma was less than 1 cm in diameter and only 19.4% of the affected nodules were detected preoperatively, these being almost invariably larger than 1 cm. Our results are similar to those of Olen and Klinck,[1] but different from those of Belfiore et al.[7] who reported on the aggressiveness of thyroid cancer in patients with Graves' disease. Although this discrepancy was not explained in our study, there was no evidence that the hyperthyroid status stimulated the growth of thyroid cancer.

On the other hand, Belfiore et al.[7] and Filetti et al.[12] indicated that the thyroid stimulating antibody (TSAb) plays a role in stimulating thyroid cancer growth and invasiveness. However, our patient with lung metastases has not shown any aggravation of the lesion as a result of TSAb since surgical treatment.

There was no difference in the occurrence of carcinoma between the right and left lobes. However, the frequency of papillary carcinoma was five times greater than that of follicular carcinoma after histological examination. This ratio seems in accordance with that previously observed in the histology of thyroid carcinoma in Japan.[13]

Dissection of the cervical lymph nodes was not performed in 25 cases in this series, although when a tumor was suspected of being malignant during the operation, neck dissection was carried out. Lymph node metastases were found in 7 of 11 patients (64%) suggesting that carcinoma with Graves' disease might often occur with lymph node metastases, but might also reflect a relationship between the size of the primary focus and the presence of metastases.

A follow-up survey was carried out in 1990. One patient had died of another disease, while the outcome of another seven cases was unknown. Recurrence of the tumor following initial surgery was noted in two patients. Reoperation in a patient with local recurrence was performed 4 years after primary surgery, and this patient is now well without any further evidence of recurrence. On the other hand, another patient with lung metastases has received radioactive iodide therapy three times and is still alive. Thus, no patient has succumbed to the thyroid carcinoma, although the seven patients whose outcome was unknown in 1990 must be excluded. Moreover, microcarcinomas of less than 1 cm with or without dissection of lymph nodes never caused recurrence in this series, suggesting that microcarcinomas do not have any clinical significance.

The results of our series on thyroid carcinoma occurring with Graves' disease in Japan seem to conflict those of Belfiore et al.[7] who provided evidence suggesting that circulating TSAb might play a role in inducing local recurrence or distant metastases from thyroid cancer.

It is certainly possible that some well-differentiated cellular types of thyroid carcinoma could respond to TSAb while others, including occult microcarcinoma might not and indeed, might not even be of clinical significance. However, we did not perform TSAb studies in this series, and thus could not carry out such a correlation study.

Recently, we routinely attempted to detect thyroid nodules with Graves' disease using the echogram because of the many cases of occult carcinoma found in this series and will describe the results in a future report.

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