

Diagnostic Approach to Thyroid Carcinoma in Graves' Disease

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Among 545 surgically treated Graves' disease patients, 17 were found to have coexisting thyroid neoplasms. Of these 17 patients, 11 turned out to have thyroid carcinomas. These patients could be divided into 2 groups; Group I with a diffusely enlarged gland with a clinically palpable nodule (n=6) and Group II without a palpable nodule (n=5). In Group I, 4 patients were diagnosed by preoperative fine needle aspiration cytology, and the remaining 2 by intraoperative frozen-section examination. In Group II, none of the patients were suspected of any concurrent thyroid carcinoma preoperatively, and only 2 were identified by intraoperative frozen-section examination. Thus, 8 of the 11 patients were diagnosed preoperatively or intraoperatively. These observations suggest that in all patients with Graves' disease and concurrent thyroid nodules, the suspicion of associated malignancy may be raised. And also, fine needle aspiration cytology in every case of Graves' disease with a palpable nodule and intraoperative frozen-section examination of the suspicious lobe in the cases of non-palpable nodules appear worthwhile in detecting a concurrent thyroid carcinoma.

Key Words: Thyroid carcinoma, Graves' disease

The incidence of thyroid carcinoma in Graves' disease varies from 0.15% to 9% and seems to be an increasing trend by years (Behar *et al.* 1986; Farbota *et al.* 1985; Shapiro *et al.* 1970).

In general, diagnosis of the thyroid carcinoma in Graves' disease is not always easy unless a nodule is palpated in the thyroid gland, and methods for the preoperative diagnosis have not yet been fully established.

This study was undertaken to review our experience with thyroid carcinoma in Graves' disease and to discuss the diagnostic approach for such cases.

MATERIALS AND METHODS

Of 545 patients with Graves' disease operated on between 1982 and 1990, 17 were found to have coexisting thyroid neoplasms. Of these 17 patients, 11 turned out to have thyroid carcinomas. The medical records and thyroid histology of the 11 patients have been reviewed and relevant details are summarized in Table 1. There were 9 female and 2 male patients. Their ages ranged from 20 to 68 years with a mean of 39 years. These 11 patients were divided into 2 groups depending on presence or absence of a palpable nodule in the thyroid glands; Group I with a palpable nodule (n=6) and Group II without a palpable nodule (n=5). Our standard surgical procedure for Graves' disease is a bilateral subtotal thyroidectomy, leaving 3-4 gm of remnant tissue on each side.

In Group I, the histological diagnosis was obtained by fine needle aspiration cytology

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Table 1. Clinical characteristics of patients with thyroid carcinoma in Graves' disease

Sex/ Age	Pathology	Preoperative T3 (ng/dl) T4 (μ g/dl)	Tumor Size (cm)	Site	Mass on P/E	Cold Nodule on scan	Diagnosis	Surgery	Extent of Tumor
M/34	P.C.	307/14	1.0	Rt. upper	Yes	Yes	FNAC: Malignancy	Total Rt. CCND	
F/48	P.C.	670/21	2.5	Lt. upper	Yes	Yes	FNAC: Malignancy	Lt. total Rt. subtotal Lt. CCND	Pericapsular invasion
F/43	P.C.	335/19	2.0	Rt. mid	Yes	Yes	FNAC: Malignancy	Total Lt. CCND	Lymph node+
F/68	P.C.	390/20	3.0	Lt. mid	Yes	Yes			Muscle invasion
F/68	P.C.	438/20	1.2	Rt. upper	Yes	Yes	F/S: Malignancy	Total Rt. CCND	Intrathyroidal metastasis
F/68	F.C.	438/20	2.5	Rt. mid	Yes	Yes	F/S: Malignancy	Rt. total Lt. subtotal Rt. CCND	Pericapsular invasion
M/20	P.C.	527/21	3.0	Rt. upper	Yes	Yes	FNAC: Malignancy	Rt. total Lt. subtotal	Pericapsular invasion
F/43	P.C.	330/16	0.2	Rt. upper	No	No	F/S: Malignancy	Rt. CCND Lt. subtotal	No
F/36	P.C.	527/19	0.4	Rt. upper	No	No	F/S: Benign	Rt. total Lt. subtotal	No
F/35	P.C.	505/24	0.5	Rt. mid	No	No	F/S: Benign	Bilateral subtotal	No
F/34	P.C.	265/19	0.5	Rt. mid	No	No	F/S: Not found	Bilateral subtotal	No
F/21	P.C.	252/14	0.2	Rt. upper & mid	No	No	Lt. subtotal Rt. CCND	Rt. total Lt. subtotal Rt. CCND	No

P.C.: Papillary carcinoma

F.C.: Follicular carcinoma

F/S: Frozen section

FNAC: Fine needle aspiration cytology

CCND: Central compartment node dissection

P/E: Physical examination

(FNAC) preoperatively and more detailed information by intraoperative frozen-section examination. In Group II, a resected unilateral thyroid lobe was sent for frozen-section examination while the contralateral lobe was being operated on.

Near-total or total thyroidectomy was performed when thyroid carcinoma was identified incidentally in frozen-section examination. For statistical analysis of these data, unpaired Student's t-test was used.

RESULTS

All of the concurrent thyroid carcinomas

were located in the upper two thirds of the gland; 9 in the right, 1 in the left and 1 in both lobes of the gland. Thus, 10 cancer foci were located in the upper two thirds of the right gland. The mean age of the 11 patients (39 years) was significantly higher than that of the 534 patients with Graves' disease without thyroid carcinoma (29.8 years; range 16-62 years) based on Student's t-test ($P < 0.05$). Group I showed a higher mean age (44 years) than Group II (34 years) (Table 2). The female: male ratio was higher in the 11 patients (4.5:1) than in the patients with Graves' disease without thyroid carcinoma (3.7:1). Histologically, papillary carcinoma was present in 10 patients and follicular carcinoma in 1. The average diameter of the thyroid carcino-

ma in Group I and Group II were 27 mm and 2.7 mm, respectively.

In Group I, all of the patients showed a cold nodule on ^{99m}Tc thyroid scan, but none of the patients in Group II. In Group I, 4 patients were diagnosed by FNAC before surgery and 2 were confirmed by frozen-section examination intraoperatively. Whereas for Group II, none of the patients were suspected of any concurrent carcinoma preoperatively, and only 2 patients were identified by intraoperative frozen-section examination, and the remaining 3 were reported as benign ($n=2$) or unrecognized ($n=1$) by frozen-section examination.

Thus, 8 of the 11 patients were diagnosed preoperatively or intraoperatively and these patients underwent a near-total or total thyroidectomy with or without regional lymph node dissection. The remaining 3 patients whose diagnoses were established by permanent histological section received bilateral

subtotal thyroidectomy only, because of their early tumor staging and favorable histologic findings (well differentiated papillary carcinoma).

All of the 11 patients are still alive without evidence of cancer recurrence for 2 to 11 years postoperatively.

DISCUSSION

It has been believed that thyroid carcinoma and Graves' disease rarely coexist and that the thyroid nodule in Graves' disease is usually a benign lesion (Dobyns *et al.* 1974; Livadas *et al.* 1976). As shown in Table 3 however, recent reports showed a higher incidence of this association, and the coexistence of these two disorders has now become well established.

Our results demonstrate that 2.2% of Graves' disease has a thyroid carcinoma and 50% of Graves' disease with a clinically palpable nodule has a concurrent thyroid carcinoma. However, the preoperative diagnostic modalities for such cases have not yet been fully established.

Ozaki *et al.* (1990) suggested that the minute calcification in the thyroid on the X-ray may serve as a part of the diagnostic clues for the thyroid carcinoma in Graves' disease. In general, the size of the thyroid nodule must be approximately 1 cm or more in diameter in order to be palpated on physical examination or seen on thyroid scan (Thomp-

Table 2. Age of patients with Graves' diseases

	Age (Year)	p-value
Graves' disease alone (N=534)	29.8±9.05	
Graves' disease with thyroid cancer (N=11)	39.1±12.7	p<0.05
Group I (N=6)	44	
Group II (N=5)	34	

Values are mean ± SD

Table 3. Incidence of the thyroid carcinoma in Graves' disease from a review of published series

Author	Year	No. of Graves' disease	No. of Carcinoma	%
Shapiro <i>et al.</i>	1970	172	15	8.7%
Behar <i>et al.</i>	1986	194	10	5.2%
Farbota <i>et al.</i>	1985	117	6	5.1%
Olen & Klinck	1966	2114	53	2.5%
Ozaki <i>et al.</i>	1990	743	19	2.6%
Wahl <i>et al.</i>	1982	385	8	2.1%
Beahr <i>et al.</i>	1951	3029	14	0.5%
Dobyns <i>et al.</i>	1974	10013	41	0.4%
Sokal	1954	13868	21	0.15%
Present series	1992	545	11	2.2%

son *et al.* 1978). Behar *et al.* (1986) reported that the concurrent thyroid carcinoma was not suspected preoperatively in 11 out of 20 Graves' disease with concurrent thyroid carcinoma patients. Using the thyroid scan, Farbota *et al.* (1985) suspected thyroid carcinoma foci in 2 out of 6 patients (size 4.2 cm and 4.5 cm) and Sarda *et al.* (1989) recognized 1 out of 4 patients preoperatively.

In our present series, the thyroid carcinoma of all 5 patients in Group II, of which tumor size was 1 cm or less, was not detected by palpation or preoperative thyroid scanning, whereas all the lesions in Group I, which were more than 1 cm in diameter, were recognized preoperatively.

Therefore, the thyroid scan did not seem to be helpful in the diagnosis of thyroid carcinoma and only served to supplement the clinical findings. Although the ultrasonography has not been used in Graves' disease patients, our results suggest that it seems useful to detect a nodule in old aged female patients, especially those more than 40 years. The mean age of the patients with thyroid carcinoma in Graves' disease (39 years) was significantly higher than those with Graves' disease without a concurrent thyroid carcinoma (29.8 years), and the former was noted more frequently in female patients than was those of the latter. In the present study, 4 of the 6 patients in Group I were diagnosed by means of FNAC, and the remaining 2 by frozen-section examination during operation. Conversely, in Group II, only 2 were identified by intraoperative frozen-section examination. Some reports suggest that most of the incidentally discovered thyroid carcinomas in Graves' disease usually are confirmed by postoperative histologic section (Farbota *et al.* 1985; Wahl *et al.* 1982; Hancock *et al.* 1977).

However, in our series, the majority of the concurrent thyroid carcinomas (8/11) were identified preoperatively or intraoperatively.

This high detection rate appears to result from our liberal use of the FNAC and intraoperative frozen-section examination. In conclusion, we recognize that old aged female patients with Graves' disease or patients with Graves' disease and a concurrent thyroid nodule are at risk for an associated thyroid carcinoma, and the FNAC in the cases of a

palpable nodule and the intraoperative frozen-section of the suspicious lobe in the cases of a non-palpable nodule seem to be the best chance for identifying a coexistent thyroid carcinoma.

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