ORIGINAL ARTICLE

Thyroid Cancer With Concurrent Hyperthyroidism

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Objective: To study the clinical manifestation, outcome, and factors predicting metastases in patients with thyroid cancer and concurrent hyperthyroidism.

Design: Retrospective study of 37 thyrotoxic patients with differentiated carcinomas of the thyroid who were operated on between 1979 and 1995. The follow-up period ranged from 562 days to 14 years 9 months (mean ± SE, 2093 ± 201 days).

Setting: University hospital with an annual performance rate of about 700 thyroid operations.

Patients: Thyroidectomy was performed in 37 patients (31 women and 6 men), including 33 papillary carcinomas and 4 follicular carcinomas. The mean ± SE age of the patients was 38.6 ± 2.2 years.

Results: The mean ± SE diameter of tumors was 13.2 ± 0.9 mm (range, 2-67 mm). The tumor size in 25 patients (68%) was 10 mm or smaller. Subtotal thyroidectomy (21 patients), total thyroidectomy (8 patients), near-total thyroidectomy (4 patients), and completion thyroidectomy (4 patients) were performed. Twenty-eight patients underwent postoperative sodium iodide I 131 (^{131}I) ablation for thyroid remnant. There was 1 local recurrence, 3 metastases to regional neck lymph nodes, and 3 distant metastases. A patient with follicular carcinoma died of metastases at 3 years 4 months after thyroidectomy. Age, sex, duration of thyrotoxic symptoms, tumor size, histopathological findings, type of goiter, extent of surgery, ^{131}I ablation, and 6-week postoperative serum concentrations of thyroglobulin or thyrotropin were not significant factors in predicting metastases. Serum levels of triiodothyronine and thyroxine before antithyroid treatment in the patients with metastases were significantly higher than in those without metastases.

Conclusion: The majority of patients with thyroid cancer and concurrent hyperthyroidism have small carcinomas.

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IT HAS been reported that thyroid cancer occurs in 0.76% to 8.7% of the glands removed for treatment of thyrotoxicosis.[1-5] Although recent reports have found higher rates of thyroid cancer associated with hyperthyroidism, earlier reports emphasize the rarity of these 2 conditions occurring simultaneously. Controversy surrounds the disease course of thyroid cancer with concurrent hyperthyroidism. Belfiore et al[6] and Ozaki et al[2] have reported that thyroid cancer associated with Graves disease had an aggressive course. In contrast, other investigators did not highlight the aggressive characteristics.[5,7,8] The discrepancies of the results are probably due to geographic, racial, or other unknown factors. To better understand the association of thyroid cancer with hyperthyroidism, we retrospectively reviewed the data of patients who had thyroid cancer with concurrent hyperthyroidism. In the present study, clinical manifestations, treatment, outcome, and factors predicting metastases are presented.

RESULTS

Goiter types of 37 patients with hyperthyroidism with thyroid cancer were toxic diffuse goiter (30 patients, 81%), toxic multinodular goiter (6 patients, 16%), and toxic adenoma (1 patient, 3%). Two of 30 patients with toxic diffuse goiter and 1 of 6 patients with toxic multinodular goiter were found to have papillary carcinoma by preoperative fine-needle aspiration cytology. The mean diameter of malignant tumors was 13.2 ± 0.9 mm (range, 2-67 mm). Twenty-five patients (68%) had a small tumor (≤10 mm) and 12 (32%) had a large tumor (>10 mm). The mean diameter of small tumors and large tumors was 6.4 ± 0.9 mm (range, 2-10 mm) and 30.0 ± 4.9 mm (range, 12-62 mm), respectively.

Thirty-one patients were women and 6 patients were men (ratio, 5.2:1). The age ranged from 20 to 82 years, with a mean ± SE age of 38.6 ± 2.2 years. The mean age of female patients was 37.5 ± 2.4 years (range, 20-82 years) and male

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PATIENTS AND METHODS

During a 17-year period from 1979 to 1995, 1013 patients with thyroid cancer were treated at the Division of General Surgery, Chang Gung Memorial Hospital, Taipei, Taiwan. There were 741 papillary carcinomas (73.1%), 168 follicular carcinomas (16.6%), 21 medullary carcinomas (2.1%), 48 anaplastic carcinomas (4.7%), and 35 carcinomas of other histological types (3.5%). During the same period, 3502 patients underwent thyroidectomy for thyrotoxicosis at our hospital. Hyperthyroidism was diagnosed on the basis of elevated triiodothyronine (T_3), elevated thyroxine (T_4), and low thyrotropin (TSH) levels in combination with hyperthyroid clinical symptoms. Of 3502 patients with hyperthyroidism, there were 2934 toxic diffuse goiters (Graves disease) (83.8%), 303 toxic multinodular goiters (8.7%), and 265 toxic adenoma (toxic autonomously functioning thyroid nodule) (7.6%). Patients were treated with carbimazole, methimazole, or propylthiouracil preoperatively. They also received Lugol iodine solution for 7 to 10 days before surgery. The indications for surgery were (1) recurrent thyrotoxicosis, (2) adverse effects of antithyroid medications, (3) patient unlikelihood or inability to take medications, (4) presence of cold nodules within toxic glands on thyroid scanning, (5) unusually large diffuse or multinodular goiters, (6) malignancy or fine-needle aspiration biopsy findings suggestive of thyroid cancer, and (7) autonomously functioning nodules.

Of 3502 patients with hyperthyroidism, 41 (1.2%) were identified to have thyroid cancer. Thirty (1.0%) of 2934 patients with toxic diffuse goiter, 6 (2.0%) of 303 patients with toxic multinodular goiter, and 1 (0.4%) of 265 patients with toxic adenoma had malignant neoplasms of the thyroid. The histopathological type of the thyroid cancer associated with hyperthyroidism included 34 papillary thyroid carcinomas (83%), 4 follicular carcinomas (10%), 2 medullary carcinomas (5%), and 1 Hürthle cell carcinoma (2%). Tumor diameter was the maximum diameter measured on pathological examination or by ultrasonography. In carcinomas with multiple foci, the maximum diameter of tumor foci was used as the diameter of tumor. Small tumor was defined as a tumor measuring 10 mm or less and a large tumor, greater than 10 mm. The patients with medullary carcinoma and Hürthle cell carcinoma and a patient who died 30 days after surgery (papillary carcinoma) were excluded from the present study. Data from the remaining 37 patients were retrospectively reviewed. Results are presented as mean ± SE.

patients was 44.5 ± 6.2 years (range, 24-69 years). Although women, on average, were 7 years younger than men, the difference was not statistically significant.

The duration of hyperthyroid clinical symptoms ranged from 30 days to 6 years (693 ± 122 days). Mean serum levels of T_3 and T_4 before administration of antithyroid medications were 5.78 ± 0.53 nmol/L (range, 2.73-12.01 nmol/L) and 232 ± 9 nmol/L (range, 172-320 nmol/L), respectively. Serum level of TSH was less than 200 µIU/L in each patient. Comparison of data between patients with small tumors and large tumors is shown in **Table 1**. There were no differences in age, sex, duration of thyrotoxic symptoms, serum levels of T_3 and T_4 before taking antithyroid medications, and 6-week postoperative serum thyroglobulin level between the 2 groups. However, 6-week postoperative serum TSH level in the group with small tumor was significantly ($P<.05$) lower than that in the group with large tumor. This difference could be attributed to the fact that most small tumors were treated with subtotal thyroidectomy (**Table 2**).

Twenty-five patients underwent technetium Tc 99m pertechnetate thyroid scanning, including those with toxic diffuse goiter (19 patients), toxic multinodular goiter (5 patients), and toxic adenoma (1 patient). Four of 19 patients with toxic diffuse goiter and 2 of 5 with toxic multinodular goiters had coexistent cold nodules on thyroid scanning. Thyroid ultrasonography with fine-needle aspiration cytology was performed in 5 patients with cold nodule on thyroid scanning and 8 patients with clinically palpable nodule. Only 3 of these patients had evidence of papillary carcinoma. Fourteen patients underwent intraoperative frozen section biopsy, including 5 with toxic diffuse goiter, 3 with toxic diffuse goiter with cold nodules on thyroid scan, 2 with toxic diffuse goiter with a solid nodule on ultrasonogram, 2 with multinodular goiter, and 2 with multinodular goiter with a cold nodule on scan. Frozen sections disclosed malignant neoplasms in 12 patients (86%). Two false-negative case results included 1 toxic diffuse goiter and 1 multinodular goiter.

Operative methods are shown in Table 2. Subtotal thyroidectomy was performed in 21 patients (57%), including 19 patients with toxic diffuse goiter and 2 with toxic multinodular goiter. Total thyroidectomy (6 patients) and near-total thyroidectomy (6 patients) were performed after confirmation of thyroid cancer by frozen section biopsy. One patient with a huge multinodular goiter was primarily treated with total thyroidectomy and postoperative pathological evaluation revealed a small papillary carcinoma. Most patients (n = 18; 49%) with small tumor underwent subtotal thyroidectomy. Three patients underwent completion total thyroidectomy after postoperative pathological confirmation of malignancy. Of these 3 patients, initial subtotal thyroidectomy was performed for toxic diffuse goiter (1 patient) and toxic multinodular goiter (2 patients). The overall postoperative complications were transient hypoparathyroidism (1 patient, 3%), permanent hypoparathyroidism (2 patients, 5%), and transient recurrent laryngeal nerve palsy (2 patients, 5%).

Whole-body scanning with 18 mBq sodium iodide I 131 (^{131}I) was performed on 29 patients 6 weeks after thyroidectomy. Of these 29 patients, 28 underwent subsequent ^{131}I ablation of thyroid remnant (13 subtotal thyroidectomies, 7 total thyroidectomies, 4 completion thyroidectomies, 4 near-total thyroidectomies) since thyroid tissue capable of ^{131}I uptake over a 24-hour period was greater than 1%. The overall mean dosage of ^{131}I radiation for ablation was 3182 ± 407 mBq (range, 1100-7400 mBq). The average ablation dosage of ^{131}I for the patients undergoing subtotal thyroidectomy was 3330 ±

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Table 1. Data of the Patients With Small and Large Thyroid Cancers*

	Small Tumors	Large Tumors	*P*
Age, y	39.4 ± 3.0 (20-82)	36.7 ± 2.7 (24-49)	.97†
Sex, F/M	22:4	9:2	1.00‡
Duration of symptoms, d	757.7 ± 141.7 (120-2196)	498.6 ± 242.6 (30-1825)	.16†
Serum T_3,§ nmol/L	5.96 ± 0.71 (2.73-12.01)	5.17 ± 0.68(3.02-7.25)	.87†
Serum T_4,§ nmol/L	238 ± 12 (178-320)	210 ± 14 (172-250)	.20†
Postoperative thyroglobulin, µg/L	20.5 ± 9.4 (1-139)	56.8 ± 48.7 (1.4-300)	.49†
Postoperative serum TSH,‖ µIU/L	6150 ± 2340 (40-35 600)	27 340 ± 13 000 (390-94 700)	.05†

*Data are expressed as mean ± SE (range) except for sex. T_3 indicates triiodothyronine; T_4, thyroxine; and TSH, thyrotropin.
†Mann-Whitney U test.
‡Fisher exact test.
§Measured before antithyroid treatment.
‖ Six-week postoperative serum TSH level was measured in 24 patients.

Table 2. Operative Methods

	No. of Patients		
Surgery	Small Tumors	Large Tumors	Total
Subtotal thyroidectomy	18	3	**21**
Near-total thyroidectomy	3	3	**6**
Total thyroidectomy	3*	4	**7**
Completion thyroidectomy	1	2	**3**

*One patient underwent total thyroidectomy for a huge toxic multinodular goiter and postoperative pathological evaluation showed a small papillary carcinoma.

407 mBq (range, 1110-3700 mBq). On the other hand, ablation dosage of ^{131}I for those with near-total or total thyroidectomy was 3219 ± 666 mBq (range, 1110-7400 mBq). These 28 patients also had thyroxine suppression treatment. Postoperative ^{131}I whole-body scanning and thyroid ablation were not performed on 8 patients with small tumors who underwent subtotal thyroidectomy. The mean tumor diameter of these 9 patients was 4.9 ± 0.7 mm (range, 2-8 mm).

The follow-up period ranged from 562 days to 14 years 9 months (2093 ± 201 days). Initial 6-week postoperative ^{131}I whole-body scan or chest x-ray films did not reveal tumor metastases. A recurrence of cancer at the thyroid bed occurred 2 years 6 months after a near-total thyroidectomy for a 3.5-cm follicular carcinoma. Distant metastases (2 papillary carcinomas and 1 follicular carcinoma) or metastases to regional neck lymph nodes (3 papillary carcinomas) occurred 20.5 ± 4.7 months (median, 17.5 months) after initial thyroidectomy (**Table 3**). The patient with follicular carcinoma died of metastases to the lungs, bone, and leptomeninges 3 years 4 months after thyroidectomy.

The patient age, tumor size, and 6-week postoperative serum levels of thyroglobulin and TSH in the patients with metastases were not different from those without metastases. However, mean serum levels of T_3 and T_4 in the patients with metastases were significantly greater than those in the patients without metastases (**Table 4**). To examine the factors capable of predicting metastases, various parameters were compared. Age, sex, duration of thyrotoxic symptoms, tumor size, histopathological tumor type, type of goiter, extent of surgery, ^{131}I ablation, 6-week postoperative serum levels of thyroglobulin or TSH were not significant factors in predicting metastases (**Table 5**). However, when patients were divided into 2 groups according to the median serum levels of T_3 (6.93 nmol/L) and T_4 (277 nmol/L) before initiation of antithyroid medications, T_3 and T_4 were significant factors in predicting metastases. Four (50%) of 8 patients with a T_4 level higher than 277 nmol/L had metastases and 4 (44.4%) of 9 patients with a T_3 level higher than 6.93 nmol/L had metastases.

COMMENT

In the present study, serum concentrations of T_3 and T_4 before antithyroid treatment were found to be significant prognostic factors in predicting metastases in patients with differentiated thyroid carcinoma with concurrent hyperthyroidism. To our knowledge, similar findings have never been reported. Serum concentrations of TSH are suppressed in patients with hyperthyroidism with elevated serum concentrations of T_3 and T_4. On the other hand, serum TSH concentrations become normal or elevated after surgery. It is not clear whether T_3 or T_4 influences the growth of normal thyroid or thyroid tumors. However, experimental data and clinical reports suggest that TSH not only stimulates normal thyroid cell growth and function[9] but also the growth of thyroid tumors.[10] Normal thyroid and benign and malignant thyroid tumors express TSH receptors on the plasma membrane.[11] Thyrotropin interacts with TSH receptors and is primarily transducted via the TSH-receptor-adenylate cyclase pathway.[9] Suppression of TSH by thyroid hormones has been used clinically to prevent the recurrence of thyroid cancer after surgery.[12-15] Therefore, elevated serum TSH concentrations in the postoperative period might stimulate the growth of residual thyroid cancer cells, eventually leading to local recurrence or metastases. However, as shown in the present study, postoperative TSH level is higher in patients with a tumor larger than 10 mm, but it is not a significant predictor of metastases in differentiated thyroid carcinoma with concurrent hyperthyroidism. This suggests that other factors may influence the prognosis of patients with thyroid cancer and concurrent hyperthyroidism. The presence of TSH receptor antibodies in the blood has been noted to be one of the causes of Graves disease.[16,17] Like TSH, TSH receptor antibodies (thyroid-stimulating immunoglobulins) interact with TSH receptors and stimulate thyroid growth and func-

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Table 3. Patient and Clinical Characteristics of Metastatic Thyroid Carcinoma

Histopathology	Patient Age, y/Sex	Tumor Size, mm	Goiter Type	Surgery*	Metastasis	Time After Surgery
Papillary carcinoma	33/F	8	Diffuse	NT	Lung	2 y
Papillary carcinoma	35/F	4	Diffuse	ST	Neck lymph nodes	11 mo
Papillary carcinoma	20/F	2, multicentric	Diffuse	ST	Neck lymph nodes	2 y 3 mo
Papillary carcinoma	49/M	20	Diffuse	NT	Neck lymph nodes	11 mo
Papillary carcinoma	26/F	67	Diffuse	CT	Lung	11 mo
Follicular carcinoma	82/F	. . .	Multinodular	ST	Lung, bone, leptomeninges	3 y 3 mo†

*NT indicates near-total thyroidectomy; ST, subtotal thyroidectomy; CT, completion thyroidectomy; and ellipses, not described in the medical chart.
†This patient died of metastases at 3 years 4 months after the initial surgery.

Table 4. Parameters in Patients With Thyroid Cancer With Metastases or Without Metastases*

	Metastases	No Metastases	P†
Age, y	40.8 ± 9.2 (20-82)	38.2 ± 2.1 (21-69)	.83
Tumor size, mm	20.2 ± 12.1 (2-67)	11.8 ± 2.4 (2-51)	.82
Serum T_3,‡ nmol/L	8.07 ± 0.75 (6.38-10.39)	5.18 ± 0.60 (2.73-12.01)	.02
Serum T_4,‡ nmol/L	272 ± 15 (226-317)	221 ± 10 (172-320)	.04
Postoperative thyroglobulin, µg/L	77.2 ± 49.6 (1-300)	11.8 ± 3.4 (1.2-57.5)	.87
Postoperative serum TSH,§ µIU/L	6300 ± 4100 (200-14 100)	13 200 ± 5000 (40-94 700)	1.00

*Data are expressed as mean ± SE (range). T_3 indicates triiodothyronine; T_4, thyroxine; and TSH, thyrotropin.
†Mann-Whitney U test.
‡Measured before antithyroid treatment.
§Six-week postoperative serum TSH level was measured in 24 patients.

tion.[18,19] Thyrotropin receptor–stimulating immunoglobulins have been found in the serum of patients with metastatic thyroid carcinomas and hyperthyroidism[18] and of patients with thyroid carcinoma and concurrent hyperthyroidism.[2,6] However, it has not yet been directly proven that TSH receptor–stimulating antibodies can stimulate the growth of thyroid carcinoma cells.

Although some authors have reported that some occult (≤1 cm) thyroid papillary carcinomas had an aggressive propensity,[20,21] the concept that small thyroid carcinomas are associated with an excellent prognosis is widely accepted.[22-25] Hay et al[25] have reported a 6% recurrence rate after 20 years in 535 patients with papillary carcinoma of 1.0 cm or less in diameter. Only 2 patients died of small papillary carcinoma in their series. As shown in the present study and the literature,[2,7] most carcinomas associated with hyperthyroidism are small and found incidentally, during pathological examination of the thyroid and during surgery. One major question is what must be done when a small carcinoma is found postoperatively on pathological examination after subtotal thyroidectomy for hyperthyroidism. Although total or near-total thyroidectomy is generally recommended for differentiated thyroid carcinoma,[26-29] many investigators believe that patients with occult papillary carcinoma or follicular carcinoma with minimal capsular invasion can be treated with limited surgery, such as lobectomy and isthmectomy.[22-24,30,31] This is based on the findings that extent of surgery did not influence the outcome of patients with small differentiated thyroid carcinomas. In the present study, extent of thyroidectomy did not influence the incidence of metastases (Table 5). Grant et al[30] have reported that there were no differences in local recurrence and survival rates of patients with thyroid cancer when subtotal thyroidectomy was compared with total thyroidectomy. Vickery et al[31] have demonstrated that no patient with a small carcinoma experienced recurrence in the resected thyroid bed or contralateral lobe after subtotal thyroidectomy or lobectomy. In a retrospective study of 867 patients with thyroid carcinomas smaller than 10 mm by Schroeder et al,[23] 416 patients (48.0%) were operated on with a preoperative diagnosis of Graves disease. The majority of patients underwent subtotal thyroidectomy, lobectomy, or partial lobectomy. The type of thyroidectomy did not affect patient survival. Therefore, thyrotoxic patients with occult differentiated thyroid cancer may be treated with limited surgery without influencing the prognosis.

In the present study, ^{131}I ablation did not influence the incidence of metastases. Ablation of thyroid remnant with ^{131}I is generally performed after total or near-total thyroidectomy for well-differentiated thyroid carcinoma.[32,33] Recent reports have shown a significant reduction in recurrence and cancer-related deaths for patients treated with ^{131}I ablative therapy.[34,35] However, most investigators would not recommend the routine administration of ^{131}I to patients with small tumor confined to the thyroid bed.[36] In the study by Schroder et al,[23] postoperative ^{131}I ablation was not administered to the patients in the absence of metastases and the recurrence-free 20-year survival rate was high. Similar findings were reported by Hay et al[25] Therefore, routine ^{131}I ablation is not indicated in the patients with small differentiated thyroid carcinoma.

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Table 5. Factors Predicting Metastases of Thyroid Cancer Associated With Hyperthyroidism*

Factor	No. (%) of Patients: Metastasis	No. (%) of Patients: No Metastasis	P†
Age, y			
≤25	1 (3)	2 (5)	.42
>25	5 (14)	29 (78)	
Sex			
Female	5 (14)	26 (70)	1.00
Male	1 (3)	5 (14)	
Duration of symptoms, y			
≥2	3 (8)	11 (30)	.65
<2	3 (8)	20 (54)	
Serum T_4 level,‡ nmol/L			
≥277	4 (11)	4 (11)	.01
<277	2 (5)	27 (73)	
Serum T_3 level,‡ nmol/L			
≥6.93	4 (11)	5 (14)	.02
<6.93	2 (5)	26 (70)	
Tumor size, mm			
≤10	4 (11)	22 (60)	1.00
>10	2 (5)	9 (24)	
Histopathology			
Papillary carcinoma	5 (14)	28 (76)	.52
Follicular carcinoma	1 (3)	3 (8)	
Hyperthyroidism§			
Diffuse goiter	5 (14)	25 (69)	1.00
Multinodular goiter	1 (3)	5 (14)	
Surgery			
Subtotal thyroidectomy	3 (8)	18 (49)	1.00
Total or near-total thyroidectomy	3 (8)	13 (35)	
Iodine 131 ablation			
Ablation	6 (16)	22 (60)	.30
No ablation	0	9 (24)	
Postoperative thyroglobulin, μg/L			
>52	2 (5)	2 (5)	.12
≤52	4 (11)	29 (78)	
Postoperative TSH,‖ μIU/L			
≥3250	2 (8)	10 (42)	1.00
<3250	1 (4)	11 (46)	

*T_4 indicates thyroxine; T_3, triiodothyronine; and TSH, thryrotropin.
†Fisher exact test.
‡Measured before antithyroid treatment.
§A toxic adenoma was not included.
‖Postoperative serum TSH level was measured in 24 patients.

In conclusion, the tumor size of the majority of patients with thyroid cancer and concurrent hyperthyroidism is 1 cm or smaller. Cold nodules on thyroid scanning might suggest the presence of thyroid carcinoma in thyrotoxic patients. Age, sex, tumor size, extent of surgery, or ^{131}I ablation do not influence the prognosis. Patients with thyroid cancer with higher serum concentrations of T_3 or T_4 before antithyroid treatment have an aggressive tumor course as compared with those with lower concentrations.

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