

Incidence Of Thyroid Occult Carcinoma In Patients With Graves' Disease

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Abstract

The pathogenesis of thyroid cancer is still obscure and the methods for preoperative diagnosis are not well established. According to many studies, total thyroidectomy is the treatment of choice for Graves' disease because of the relatively high incidence of concomitant minimal (occult) thyroid cancer (diameter less than 9mm).

Aim: Our aim was to prove the relatively high incidence of the combination of Graves' disease with micro-carcinoma of the thyroid gland.

Patients and Methods: During the last 15 years (1992-2006), 277 total or near total thyroidectomies were performed in our surgical department (57 men and 220 women). The pre-operative diagnoses were: 215 with multinodular goiter, 37 with diffuse toxic goiter (Basedow-Graves' disease), 11 with a single thyroid nodule and 14 with thyroid cancer.

Results: Histology examination of removed surgical specimens showed that in 4 out of 37 patients (10.8%) with Graves' disease, papillary thyroid micro-carcinoma with no invasion of the thyroid capsula was found. All these 4 patients with Graves' disease in whom occult micro-carcinoma was found accidentally, underwent CT scan of neck and thorax with no lymphadenopathy or other specific findings. No recurrence was detected in patients with Graves' disease 8-73 months after the surgical procedure.

Conclusion: In North-Western Greece, 10.8% of patients with Graves' disease had microscopical findings (less than 9-10mm of diameter) of thyroid cancer after accurate histopathological examination. Total thyroidectomy should be the treatment of choice for those patients.

INTRODUCTION

Traditionally, Graves' disease was considered a protection against thyroid cancer (1).

The natural history and optimal surgical treatment for thyroid cancer with concomitant Graves' disease are controversial. Anecdotal experience and a number of studies have suggested an increased aggressiveness of papillary and follicular thyroid cancer in patients with Graves' disease, but these findings are not universal (2). In 1937, Means et al. (3) published that 'one might almost say that thyrotoxicosis was insurance against cancer of the thyroid'. Indeed, at one time, thyroid cancer in patients with thyrotoxicosis was considered to be extremely rare, but this perception has proven to be incorrect. Several studies have demonstrated an increased incidence of thyroid micro-carcinomas in patients with Graves' disease, with a cancer rate varying from 1% to 9%

of cases (3). The rate of 10.7% is the highest found in bibliography and for that we believe that total thyroidectomy is the treatment of choice for these patients.

P. Miccoli et al. (4) state in their paper reports that there is an increased rate of well-differentiated papillary thyroid cancer in patients operated for multinodular goiter (13 out of 140, 9.3%). Only in 3 of them, preoperative diagnosis was made with FNA-C.

Finally, R. Whal et al. (5) have published that in 317 patients operated for multinodular goiter, the incidence of occult micro-carcinoma was 3.3%. The present article will summarize the existing literature pertaining to thyroid micro-carcinomas in Graves' disease, and suggest an evidence-based approach to the appropriate management for this underestimated pathology.

Aim of this study is to show the increased incidence rate of minimal occult carcinoma in patients with Graves' disease, and to indicate that total thyroidectomy is the treatment of choice for these patients.

PATIENTS AND METHODS

Two hundred seventy-seven patients, 57 men and 220 women underwent total thyroidectomy from 1992 to 2006. The age range was 18-78 yrs (mean age 47 ± 11.5 yrs). Two hundred and fifteen patients (77.9%) were operated due to multinodular goiter (39 men, 176 women, ages 18-63 yrs), 37 patients (12.7%) due to diffuse toxic goiter - Graves' disease (9 men, 28 women, ages 23-49 yrs) and 11 (4.3%) due to nodular goiter (3 men, 8 women, ages 21-57 yrs) because of suspicious positive FNA-C. Finally, fourteen patients (5.1%) had thyroid cancer (6 men and 8 women, ages 37-78 yrs). The demographic characteristics of the patients are presented in table 1.

Figure 1

Table 1: Demographic characteristics of patients

	Patients (N)	Multinodular Goiter	Graves'	Toxic Nodule	Thyroid Cancer
Patients (N)	277	215	37	11	14
Female	220	176	28	8	8
Male	57	39	9	3	6
Age	18-78 yrs	23-49 yrs	19-55 yrs	21-57 yrs	37-78 yrs

Patients with Graves' disease underwent ultrasonographic, hormonal, and scintigraphic examination of their thyroid gland pre-operatively. In those with nodular goiter, FNA-C was undertaken. CT scan of thorax and abdomen as well as cardiologic consultation was asked for in case of cancer of the thyroid.

Pre-operatively, the appropriate therapy was administered to all patients with Graves' disease for at least a year. In case of failure of therapy, patients underwent total thyroidectomy.

Intraoperatively, recurrent laryngeal nerves and parathyroid glands were always identified and protected. From 1998 to 2000, ultrasound scissors were used in all operations. From 2001, Ligasure™ diathermy was used. Ligations or clips were not used in either case since 2001.

Post-operatively, follow-up included scintigraphy with I131 (possibility to see if there remains any thyroid tissue after total thyroidectomy) and assessment of calcium concentration. Post-operative hypoparathyroidism (3-5 days after surgery) was evident as asymptomatic hypocalcemia

that was treated with calcium digluconate intravenously for the first 3-5 days post-operatively and orally over the first week after surgery. Transient hypoparathyroidism is when calcium and vitamin-D supplementation does not last over 4-6 months. Permanent hypoparathyroidism is when calcium treatment lasts over 6 months post-operatively. The patients were followed up from 8-73 months. In this study no recurrence was detected and all patients are in good condition of health.

RESULTS

In 4 of the 37 patients (10.8%) with Graves' disease, foci with characteristics of papillary micro-carcinomas of follicular type (less than 9 mm) were found. The histopathology of the specimens of the 4 patients with Graves' disease, who underwent total thyroidectomy, has not revealed invasion of the thyroid capsule or lymphadenopathy in the lymph nodes of the neck. Therefore, reoperation or radioiodine therapy was not necessary for those patients. In all those patients, total thyroidectomy was performed. Total thyroidectomy with neck lymphadenectomy was performed in the 11 patients with thyroid cancer diagnosed pre-operatively. All patients with Graves' disease have been informed pre-operatively about the possibility of coexistence of occult micro-carcinoma of the thyroid.

Patients were followed up from eight to 73 months post-operatively and no recurrence was detected.

All major intraoperative complications were described in table 2.

Figure 2

Table 2: Complications per surgical procedure

Procedure	Total	Hypocalcemia		rec. lar. nerve injury
		Transient	Permanent	
Near T. T *	81	11	1	0
T. T.	193	23	0	1
T. T. + N. L. **	3	0	0	0

T.T.: Total Thyroidectomy

N.L.: Neck Lymphadenectomy

Post-operative complications such as haemorrhage and haematoma occurred in 5 patients, 2 of which were reoperated due to dyspnoea or stridor. All postoperative complications can be seen in table 3.

Figure 3

Table 3: Postoperative complications

1. Hemorrhage:	3 patients
2. Haematoma:	2 patients
3. Transient hypocalcemia:	3 patients (2 in Graves' disease)
4. Permanent hypoparathyroidism:	1 patient
5. Laryngeal recurrent nerve injury:	1 patient
Total:	10 patients

Post-operative mortality was zero. No patient died within the first 30 postoperative days. Finally, no patient with micro-carcinoma accidentally discovered in Graves' disease received iodine post-operatively.

DISCUSSION

The incidence of occult micro-carcinomas of the thyroid in the different surgical diseases of the gland varies considerably from 0.3% to 9% (6). Occult thyroid carcinomas (< 9mm in diameter) are the rule in those situations and only a few tumors are suspected pre-operatively with ultrasonography, fine-needle aspiration or 131I scan (6).

Quan-Yang Duh (7) supports that there are two concepts for thyroid cancer: the concept of "incidental thyroid cancer" and "clinical cancer". In the first situation, Graves' disease is the only clinical diagnosis before operation, where cancer was incidentally found in the resected specimen, like in our series. These are mostly papillary thyroid cancers smaller than 9 mm and are considered as an incidental finding of minimal clinical significance. In the other situation (clinical cancer), a patient with thyroidopathy is found to have also a cancer during the pre-operative work-up. These thyroid cancers are usually larger than 15mm, surgically they must always be treated with complete resection of neck lymph nodes and post-operatively with radioiodine therapy.

Co-existence of thyrotoxicosis and 'incidental thyroid cancer' has become more common and this does not seem to be irrelevant (3,4,5, 8, 9). Graves' disease is associated with more aggressive thyroid cancer because of the action of thyroid stimulating antibodies (8).

Total thyroidectomy is gradually replacing subtotal

thyroidectomy, as many studies support, for treatment of patients with Graves' disease (7, 9). A disadvantage of total thyroidectomy is the need for post-operative hormone replacement. This is balanced against the lower risk of recurrent Graves' disease and the absence of thyroid tissue (7). On the other hand, it increases the operative complications such as injury of the recurrent laryngeal nerves and hypoparathyroidism (10, 11). In our studies, minimal occult carcinoma of diameter less than 9mm was found in 4 out of 37 patients (10.8%) with diffuse toxic goiter, the highest value found in bibliography. In all patients, histopathology revealed foci of whitish discoloration with morphological characteristics of papillary micro-carcinoma of follicular type, with no invasion of the thyroid capsule.

In a series of 250 total thyroidectomies of Perzik et al. (10), one recurrent laryngeal nerve injury (0.4%) was seen and no patient with permanent hypoparathyroidism was observed post-operatively. On the other hand, in case of total thyroidectomy due to cancer, complication rates for nerve injury and hypoparathyroidism rise to 5% and 3%, respectively. This is because of the nature of the surgical technique in case of a neoplasm (12).

In our study, we had 3 patients with transient hypoparathyroidism due to total thyroidectomy because of Graves' disease, treated with calcium supplements for no more than 6 months. We also had one patient with recurrent laryngeal nerve injury who underwent total thyroidectomy because of thyroid cancer diagnosed pre-operatively.

After a thorough review of the literature, we can assume that total thyroidectomy, when performed in specialised centres, has minimal complications (5, 12, 13). One more reason to perform total thyroidectomy, as shown also by our study, is the increased incidence of concomitant existence of minimal occult carcinoma in toxic goiter patients.

In conclusion, in hyperthyroidism and especially in its toxic form (Graves' disease), patients should be informed about the possibility of coexistent thyroid cancer. Cytologic examination through fine-needle aspiration (FNA-C) is an important preoperative examination, with low sensitivity. Suspicious clinical signs should be carefully evaluated. Most of the thyroid micro-carcinomas with concurrent Graves' disease were 9 mm or smaller. For all those reasons, we strongly believe that total thyroidectomy is the treatment of choice for these patients, with no necessity for radioiodine therapy (no invasion of the thyroid capsule in all patients

who underwent total thyroidectomy for Graves' disease).

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