Thyroid cancer in toxic and non-toxic multinodular goiter

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ABSTRACT

Background: Many authors have claimed that hyperthyroidism protects against thyroid cancer and believed that the incidence of malignancy is lower in patients with toxic multinodular goiter (TMG) than in those with non-toxic multinodular goiter. But in recent studies, it was reported that the incidence of malignancy with TMG is not as low as previously thought. **Aim:** To compare the thyroid cancer incidence in patients with toxic and non-toxic multinodular goiter. **Settings and Design:** Histology reports of patients treated surgically with a preoperative diagnosis of toxic and non-toxic multinodular goiter were reviewed to identify the thyroid cancer incidence. Patients having a history of neck irradiation or radioactive iodine therapy were excluded from the study. **Materials and Methods:** We reviewed 294 patients operated between 2001-2005 from toxic and non-toxic multinodular goiter. One hundred and twenty-four of them were toxic and 170 were non-toxic. Hyperthyroidism was diagnosed by elevated tri-iodothyroinine / thyroxine ratios and low thyroid-stimulating hormone with clinical signs and symptoms. All patients were evaluated with ultrasonography and scintigraphy and fine needle aspiration biopsy. **Statistical Analysis Used:** Significance of the various parameters was calculated by using ANOVA test. **Results:** The incidence of malignancy was 9% in the toxic and 10.58% in the non-toxic multinodular goiter group. Any significant difference in the incidence of cancer and tumor size between the two groups could not be detected. **Conclusions:** The incidence of malignancy in toxic multinodular goiter is not very low as thought earlier and is nearly the same in non-toxic multinodular goiter.

KEY WORDS: Non-toxic multinodular goiter, thyroid cancer, toxic multinodular goiter

Hyperthyroidism is the condition resulting from the effect of excessive circulating thyroid hormones. Graves' disease is the most common form of the hyperthyroidism and toxic multinodular goiter (TMG) is seen rarely. Many authors have claimed that hyperthyroidism protects against thyroid cancer and believed that the incidence of malignancy is lower in patients with TMG than in those with non-toxic multinodular goiter (NMG). On the other hand, it was reported in different studies that the incidence of malignancy with TMG was not as low as previously thought and especially in macrocarcinomas, vascular, capsular and lymphatic invasion were often found.[1-3] In the present study, we compared the incidence of thyroid cancer in patients with toxic and non-toxic multinodular goiter.

Materials and Methods

For retrospective analysis, we reviewed 294 patients operated between 2001-2005 for toxic and non-toxic multinodular goiter. One hundred and twenty-four of them were toxic and 170 were non-toxic. None of the patients had a history of neck irradiation or radioactive iodine therapy.

In the TMG group (32 male, 92 female), recurrent hyperthyroidism after medical treatment, enlarging nodule, persistent drug side-effects, cytological evidence of malignancy and symptoms of tracheal or esophageal compression were the criteria of surgery and the surgery was performed only after euthyroidism was achieved by propylthiouracil or methimazole. Hyperthyroidism was diagnosed by elevated tri-iodothyroinine / thyroxine ratios and low thyroid-stimulating hormone with clinical signs and symptoms. All patients were evaluated with ultrasonography (USG) and scintigraphy. All nodules greater than 10 mm in diameter and nodules 5-10 mm in diameter having calcification were fine-needle biopsied under USG guided. All scintigraphic cold nodules were also evaluated with fine needle aspiration biopsy (FNAB). Twelve of 124 patients were operated for cytological suspicion in toxic group. Total or near total thyroidectomy was the choice of the surgery .

In the NMG group (49 male, 121 female) indications for surgery were cosmetic or pressure effects, a dominant nodule increasing in size or showing cytological features raising the possibility of malignancy or retrosternal extension. All patients were evaluated with USG and scintigraphy. Fine needle biopsy was performed on nodules greater than 10 mm or nodules 5-10 mm in size having calcification. Forty-three of 170 patients had malignancy or suspicion of malignancy on cytopathologic examination. Total thyroidectomy, bilateral subtotal thyroidectomy, near

total thyroidectomy, lobectomy + subtotal or near total thyroidectomy were the procedures performed in the NMG group. All patients received suppression therapy and adjuvant radioactive iodine therapy performed to all patients with papillary and follicular cancer.

Statistical analyses

Significance of the various parameters was calculated by using ANOVA test.

Results

Eight papillary, one follicular, one medullary and one Hurthle cell, carcinomas were found in 124 patients operated for TMG. The incidence of malignancy was 9% in this group. The prevalence was 10.86% (10/92) in female, 3.1% (1/32) in male patients. Tumor sizes ranged from 2 mm to 3 cm and eight of them were less than 1 cm in diameter. Multifocality was detected in two patients [Table 1].

In the NMG group histological examination revealed thyroid cancer in 18 of the 170 patients (10.58%). The cancer prevalence was 12.2% (6/49) in male and 10% (12/121) in female patients. Following thyroidectomy, histology revealed papillary (11), Hurthle cell (4) and follicular (2) carcinomas, and angiosarcoma (1). Tumor sizes ranged from 2 mm to 9 cm and six of them were less than 1 cm I diameter. Multifocality was detected in four patients [Table 2].

The average tumor size was 9.63 ± 10.38 mm in the toxic and 24.76 ± 24.14 mm in the non-toxic group and was not significantly different (P=0.072 with ANOVA). On the other hand, any significant difference in the incidence of cancer between toxic and non-toxic MG could not be detected (P=0.627 with ANOVA).

In the toxic group only in one patient the frozen section revealed malignancy, but any malignancy in FNAB results could not be detected preoperatively in this group.

In the non-toxic group there were three malignancies in FNAB results and all of their tumor sizes were greater than 1.8 cm in diameter.

Vascular and capsular invasion were seen in two patients in the TMG group. In the NMG group four vascular and six capsular invasions were detected.

The preoperative ultrasound examination of patients with thyroid carcinoma showed hypoechoic nodules in all TMG and NMG patients.

Discussion

The incidence of cancer in our series was 9% in TMG and 10.6% in NMG. In the past, it was believed that hyperthyroidism excluded thyroid malignancy and very few cases reported .[4,5] It was believed that hyperthyroidism was a protector against thyroid cancer and the risk of thyroid cancer in hyperthyroidism was reported to be as low as 1-2%.[6] While the frequency of carcinoma in TMG was reported to be less than 1%,[2] some investigators found the incidence of carcinoma as high as 21%.[7] In a recent study, the incidence of malignancy in TMG was found to be 7% and most of them were papillary microcarcinomas.[3] On the other hand, the incidence of cancer in NMG was reported between 6.2-9.7% in several studies.[8,9] It has been suggested that upward incidence trends in thyroid cancer have also been associated with increased diagnostic activity because of more sensitive diagnostic tests.[10] In our study, any significant difference in the incidence of cancer between toxic and non-toxic MG could not be detected.

All benign thyroid disorders showed predominance in women. From epidemiological studies it appears that the gender factor

Table 1: Cancer patients in toxic multinodular goiter group

	Size (cm)	Number of foci	Vascular invasion	Capsular invasion	Ultrasonography	Scintigraphy	FNAB	Gender
Hurthle cell carcinoma	1.1	1	+	+	Hypoechoic nodules	Hyper and hypoactive nodules	Hurthle cell	F
Medullary carcinoma	0.5 and 0.3	2	-	-	Multiple hypo and isoechoic nodules	Hyperactive nodule	Benign	F
Papillary carcinoma	0.4	3	-	-	Multiple hypoechoic nodules	Hyper and hypoactive nodules	Colloidal nodule	F
Papillary carcinoma	0.3	1	-	-	Hypo and isoechoic nodules	Hyper and hypoactive nodules	Benign	F
Papillary carcinoma	3	1	-	-	Multiple hypoechoic nodules	Hyper and hypoactive nodules	Suspicious	M
Papillary carcinoma	0.2	1	-	-	Multiple hypoechoic nodules	Hyperactive nodules	Benign	F
Papillary carcinoma	0.8	1	-	-	hypo and hyperechoic nodules	Hyper and hypoactive nodules	Non-diagnostic	F
Papillary carcinoma	0.3	1	-	-	Hypoechoic nodule	Hyper and hypoactive nodules	Benign and non-diagnostic	F
Papillary carcinoma	0.5	1	-	-	Hypoechoic nodules	Hypoactive nodules	Benign	F
Papillary carcinoma	3	1	-	-	Hypoechoic nodules	Hyperactive nodule	Non-diagnostic	F
Follicular carcinoma	0.6	1	+	+	Multiple hypoechoic nodules	Hyper and hypoactive nodules	Non-diagnostic	F

Table 2: Cancer patients in multinodular goiter group

	Size (cm)	Number of foci	Vascular invasion	Capsular invasion	Ultrasonography	Scintigraphy	FNAB	Gender
Angiosarcoma	Diffuse				Hypoechoic nodules	Nonhomogene uptake	Suspicious	M
Follicular carcinoma	3	1	+	+	Hyperechoic nodules	Hyper and hypoactive nodules	Suspicious	M
Follicular carcinoma	1.7	1	+	+	Hypoechoic nodules	Nonhomogene uptake	Suspicious	F
Hurthle cell carcinoma	1	1	-	+	Hypoechoic nodules	Nonhomogen activity	Benign	M
Hurthle cell carcinoma	2.5	1	+	+	Hypoechoic nodules	Hypoactive nodules	Suspicious	F
Hurthle cell carcinoma	7	1	?	?	Hypoechoic nodules	Hypoactive nodules	Suspicious	F
Hurthle cell carcinoma	4.5	1	-	+	Hypo and isoechoic nodules	Hypoactive nodules	Suspicious	F
Papillary carcinoma	0.5	1	-	-	Hypoechoic nodules	Nonhomogen activity	Benign	F
Papillary carcinoma	<0.5	3	-	-	Hypo and isoechoic nodules	Nonhomogen activity	Benign	F
Papillary carcinoma	1.8	1	-	+	hypo and hyperechoic nodules	Hypoactive nodules	Papillary ca	M
Papillary carcinoma	0.2	1	-	No capsule	Hypo and hyperechoic nodules	Nonhomogen activity	Benign	M
Papillary carcinoma	9	1	+	No capsule	Hypo and hyperechoic nodules	Hyper and hypoactive nodules	Papillary ca	M
Papillary carcinoma	1.6	4	-	+	Hypo and isoechoic nodules	Hypoactive nodules	Suspicious	F
	0.5							
	0.4							
	0.3							
Papillary carcinoma	0.6	2	-	-	Hypo and isoechoic nodules	Nonhomogen activity	Benign	F
	0.3							
Papillary carcinoma	1.8	1		No capsule	Hypo and hyperechoic nodules	Nonhomogen activity	Suspicious	F
Papillary carcinoma	0.3	2	-	-	Hypoechoic nodules	Hyper and hypoactive nodules	Benign	F
	0.2							
Papillary carcinoma	0.2	1	-	-	Hyper and hypoechoic nodules	Hyperactive nodules	Benign	F
Papillary carcinoma	2.5	1	+	No capsule	Hypo and hyperechoic nodules	Hypoactive nodules	Papillary ca	F

may influence the risk of benign thyroid diseases and thyroid cancer in women.[11,12] On the other hand, some studies pointed out that the incidence of thyroid cancer showed male/female parity in patients from endemic areas compared with patients from non-endemic areas.[13,14] Male/female ratio was 1/10 (10%) in the TMG group and 6/12 (50%) in the NMG group in our study. We also found a significant difference in the incidence of malignancy in male patients between the two groups and the incidence of malignancy was found to be higher in the non-toxic male patients.

In the TMG group in eight of 11 patients, tumor size was smaller than 0.5 cm and in all of these patients FNAB was either non-diagnostic or benign. It was reported that in patients with hyperthyroidism US-guided FNAB was useful for detecting thyroid cancer in nodules greater than 5 mm in diameter.[15] It seems that US-guided FNAB is not effective in the detection of cancer smaller than 0.5 cm. In the toxic group we did not have any cancer diagnosed with FNAB. The results of FNAB in NMG were also similar with TMGs in tumors smaller than 0.5 cm. But in tumors bigger than 1cm in diameter 11 patients had a biopsy diagnosis of malignant or suspicious.

In the toxic group six of 11 patients and in the non-toxic group six of 18 patients had micropapillary carcinoma and two of the group's showed multifocality. Papillary microcarcinoma of the thyroid is defined by the World Health Organization as a papillary thyroid carcinoma measuring ≤ 10 mm in the greatest dimension.

However, many autopsy series[16-18] showed that papillary microcarcinoma was a very frequent incidental finding, corroborating the idea that small papillary cancer was 'quite the normality' and that most of these tumors did not progress to clinical cancer. There were also some reports of clinical evidence of massive lymph node metastases in some papillary microcarcinoma which further indicated the potential aggressiveness of some small cancers.[18-21]

The literature provides us with conflicting information, telling us that, on the one hand, papillary microcarcinoma could be a normal finding with a low growth tendency and, on the other hand, microcarcinoma should need treatment because it can be associated with local spread and that, moreover, treatment should be advocated because microcarcinoma has an excellent prognosis.[22-24]

In recent studies it has been suggested that microcarcinomas and cancers of major size appear to be 'the same disease', with a classical progression from microcarcinoma to clinically evident disease.[25] The treatment of patients with papillary microcarcinoma should be no different from the treatment of patients with papillary thyroid cancer and thyroidectomy followed by radioiodine therapy may be a possible option for treatment of papillary microcarcinoma.[26]

On the other hand, incidental thyroid carcinoma was found in 6.9% of subjects with all types of thyrotoxicosis and papillary thyroid microcarcinomas constituted 34.6% of these thyroid carcinomas.[27] It was reported that tumors discovered incidentally at thyroidectomy in patients with thyrotoxicosis generally had a good prognosis.[28] In our series no recurrence and death were observed in patients with TMG. In the NMG group, in three patients lymph node recurrence occurred and block dissection of lymph nodes was performed. One of them died eight months later after lymph node dissection, probably

due to brain metastasis. In another patient with Hurthle cell carcinoma, local recurrence occurred 16 months after the surgery and the patient was re-operated.

Conclusion

The incidence of malignancy in TMG is not very low as thought before and is nearly the same as in NMG. Our findings, in accordance with those of the few other studies published to date, remind physicians to consider the possible association between hyperthyroidism and cancer, especially micropapillary cancer. The increasing incidence of cancer in toxic multinodular goiter in recent years could be attributed to better nodule detection, differences in the extent of thyroid resection and the number of histological sections examined per specimen. It is still very difficult to reveal micro size malignancy preoperatively so the aim of the surgery should not be only to maintain euthyroidism but also to prevent the risk of cancer in TMG patients.

References

1. Mittendorf EA, McHenry CR. Thyroidectomy for selected patients with thyrotoxicosis. Arch Otolaryngol Head Neck Surg 2001;127:61-5.
2. Vaiana R, Cappelli C, Perini P, Pinelli D, Camoni G, Farfaglia R, *et al*. Hyperthyroidism and concurrent thyroid cancer. Tumori 1999;85:247-52.
3. Rios A, Rodriguez JM, Balsalobre MD, Torregrosa NM, Tebar FJ, Parrilla P. Results of surgery for toxic multinodular goiter. Surg Today 2005;35:901-6.
4. Leiter L, Seidlin S, Marinelli M, Baumann E. Adenocarcinoma of the thyroid with thyroid with hyperthryoidism and functional metastasis. Studies with thiouracil and radioiodine. J Clin Endocrinol 1948;6:247-52.
5. McLaughlin RP, Scholz DA, McConahey WM, Childs DS. Metastatic thyroid carcinoma with hyperthyroidism: Two cases with functioning metastatic follicular thyroid carcinoma. Mayo Clin Proc 1970;45:328-35.
6. Gittoes NJ, Franklyn JA. Hyperthyroidism, current treatment guidelines. Drugs 1998;55:543-53.
7. Livadas D, Psarras A, Koutras DA. Malignant cold thyroid nodules in hyperthroidism. Br J Surg 1976;63:726-8.
8. Pelizzo MR, Bernante P, Toniato A, Fassina A. Frequency of thyroid carcinoma in a recent series of 539 consecutive thyroidectomies for multinodular goiter. Tumori 1997;83:653-5.
9. Sachmechi I, Miller E, Varatharajah R, Chernys A, Carroll Z, Kissin E, *et al*. Thyroid carcinoma in single cold nodules and in cold nodules of multinodular goiters. Endocr Pract 2000;6:5-7.
10. Verkooijen HM, Fioretta G, Pache JC, Franceschi S, Raymond L, Schubert H, *et al*. Diagnostic changes as a reason for the increase in papillary thyroid cancer incidence in Geneva, Switzerland. Cancer Causes Control 2003;14:13-7.
11. Negri E, Dal Maso L, Ron E, La Vecchia C, Mark SD, Preston-Martin S, *et al*. A pooled analysis of case-control studies of thyroid cancer II. Menstrual and reproductive factors. Cancer Causes Control 1999;10:143-55.
12. Memon A, Bernington A, Lugmani Y. Family history of benign thyroid disease and cancer risk of thyroid cancer. Eur J Cancer 2004;40:754-60.
13. Riccabona G. Thyroid cancer and endemic goiter: *In*: Stanbury JB, Hetzel BS, editors. Endemic goiter and endemic cretinism. Wiley Eastern Ltd: New Delhi; 1985. p. 33-5.
14. Sarda AK, Kapur MM. Thyroid surgery in an area of iodine deficiency. Head Neck 2005;27:383-389.
15. Sahin M, Guvener ND, Ozer F, Sengul A, Ertugrul D, Tutuncu NB. Thyroid cancer in hyperthyroidism: Incidence rates and value of ultrasound-guided fine-needle aspiration biopsy in this patient group. J Endocrinol Invest 2005;28:815-8.
16. Harach HR, Franssila KO, Wasenium VM. Occult papillary carcinoma of the thyroid. A “normal” finding in Finland. A systematic autopsy study. Cancer 1985;56:531-8.
17. Bondeson L, Ljungberg O. Occult papillary thyroid carcinoma in the young and aged. Cancer 1984;53:1790-2.
18. Franssila KO, Harach HR. Occult papillary carcinoma of the thyroid in children and young adults. A systemic autopsy study in Finland. Cancer 1986;58:715-9.
19. Ansari-Lari MA, Westra WH. The prevalence and significance of clinically unsuspected neoplasms in cervical lymph nodes. Head Neck 2003;25:841-7.
20. Verge J, Guixa J, Alejo M, Basas C, Quer X, De Castro J, *et al*. Cervical cystic lymph node metastasis as a first manifestation of occult papillary thyroid carcinoma: Report of seven cases. Head Neck 1999;21:370-4.
21. Wada N, Duh QY, Sugino K, Iwasaki H, Kameyama K, Mimura T, *et al*. Lymph node metastasis from 259 papillary thyroid microcarcinoma: Frequency, pattern of occurrence and recurrence and optimal strategy for neck dissection. Ann Surg 2003;237:399-407.
22. Mazzaferri EL, Jhiang SM. Long term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418-28.
23. Baudin E, Travagli JP, Ropers J, Mancusi F, Bruno-Bossio G, Caillou B, *et al*. Microcarcinoma of the thyroid gland: The Gustave-Roussy Institute experience. Cancer 1998;83:553-9.
24. Appetecchia M, Scarcello G, Pucci E, Procaccini A. Outcome after treatment of papillary thyroid microcarcinoma. J Exp Clin Cancer Res 2002;21:159-64.
25. Barbaro D, Simi U, Meucci G, Lapi P, Orsini P, Pasquini C. Thyroid papillary cancers: Microcarcinoma and carcinoma, incidental cancers and non-incidental cancers - are they different diseases? Clin Endocrinol Oxf 2005;63:577-81.
26. Kucuk NO, Tari P, Tokmak E, Aras G. Treatment for microcarcinoma of the thyroid--clinical experience. Clin Nucl Med 2007;32:279-81.
27. Cakir M, Arici C, Alakus H, Altunbas H, Balci MK, Karayalcin U. Incidental thyroid carcinoma in thyrotoxic patients treated by surgery. Horm Res 2007;67:96-9.
28. Vini L, Hyer S, Pratt B, Harmer C. Good prognosis in thyroid cancer found incidentally at surgery for thyrotoxicosis. Postgrad Med J 1999;75:169-70.

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