

## Thyroid cancer in hyperthyroid patients: Is it different clinical entity?

<sup>1</sup>OCAK S, <sup>2</sup>AKTEN AO, <sup>1</sup>TEZ M

<sup>1</sup>Ankara Numune Training and Research Hospital, General Surgery Clinic, Ankara, Turkey; <sup>2</sup>Aksehir State Hospital, General Surgery Clinic, Konya, Turkey,  
E-mail: mesuttez@yahoo.com

**Objective.** In this retrospective study, we aimed to analyze the frequency of thyroid cancer in patients who underwent thyroidectomy for hyperthyroidism.

**Patients and Methods.** A total number of 177 patients, who underwent surgery for hyperthyroidism between August 2005 and March 2010, were included in this study. Demographic, clinical, radiologic, and laboratory data were collected retrospectively.

**Results.** Postoperative histopathological examinations revealed thyroid malignancy in 13 (7.3%) patients. Among these 13 patients presenting thyroid malignancy, 53.9% were diagnosed with multinodular toxic goiter (MTG), 38.5% with uninodular toxic goiter (UTG) and 7.6% with Graves' disease.

**Conclusions.** Thyroid carcinoma is common in hyperthyroidism and thyroid fine-needle aspiration biopsy (TFNAB) is a reliable method in the diagnosis of the thyroid malignancy in these patients. We suggest that it is reasonable to evaluate nodules with TFNAB in hyperthyroid patients prior to surgical intervention.

**Key Words:** thyroid cancer, toxic goiter, thyroidectomy

### Patients and Methods

Thyroid cancers, which account for 1% of all cancers, are tumors that spread slowly and have a high survival rate. In the past years, it was believed that hyperthyroidism decreases the probability of the developing thyroid cancer. However, recent data suggest that uninodular toxic goiter (UTG), multinodular toxic goiter (MTG), and diffuse toxic goiter (Graves' disease) are all conditions that may be associated with the thyroid cancer (De Rosa et al. 1990; Mazzaferri 1990; Kim et al. 2007; Pazaitou-Panayiotou et al. 2012).

In this retrospective study, our attempt was to review the frequency of thyroid cancer in patients who underwent thyroidectomy for hyperthyroidism.

A total number of 177 patients, who underwent thyroidectomy for hyperthyroidism between August 2005 and March 2010, were included into this study. Data from patients including age, sex, preoperative thyroid ultrasonography, preoperative antithyroid medication usage, preoperative thyroid fine-needle aspiration biopsy (TFNAB), type of thyroidectomy, histopathologic results, and possible complications were retrospectively examined. Patients were operated after getting euthyroid with preoperative antithyroid drug treatment.

The SPSS 15.0 statistic program (SPSS Inc., Chicago, US) was used to generate statistical outputs. Because the range was non parametric, comparison between two

groups was performed using Mann-Whitney U test. Comparison between multiple groups was performed using Kruskal-Wallis and Chi-square tests, and Fisher's exact test was used for comparing nominal values.

### Results

The results of the study are summarized in Table 1. From 177 patients incorporated into the study, 134 were women and 43 were men. The average age of patients was  $45.9 \pm 14.7$  (16.0 - 75.0). None of the patients had a family history of thyroid cancer and/or neck radiation. From 177 patients with hyperthyroidism, 33 (18.6%) had Graves' disease, 112 (63.2%) had MTG, and 33 (18.6%) had UTG.

Total number of 76 patients underwent TFNAB during the preoperative period. Cytology results revealed benign lesion(s) in 44 patients, Hurthle cell lesion in five patients, malignant tumors in two patients, a probability of malignancy in 3 patients, cellular microfollicular smear in 7 patients, and insufficient material in 15 patients.

As far as the types of thyroidectomy performed, (i) 152 patients underwent bilateral total thyroidectomy,

(ii) 15 patients underwent unilateral total thyroidectomy, (iii) 5 patients underwent total thyroidectomy for one side, subtotal thyroidectomy for the other side, (iv) 4 patients underwent supplementary thyroidectomy, and (v) one patient underwent bilateral subtotal thyroidectomy.

Histopathologic classification of the patients, who had undergone thyroidectomy, revealed thyroid malignancy in 13 (7.3%) patients: 11 (84.6%) of these patients were women and 2 (15.4%) were men. The average age of these patients was  $46 \pm 14.9$ . As far as the types of thyroid malignancy, 9 (69.2%) patients presented with papillary microcarcinoma, 3 (23%) patients presented with papillary carcinoma, and one (7.8%) patient presented with minimal invasive follicular carcinoma. The average diameter of the tumor was  $0.89 \pm 1.17$  cm (0.1 - 5.0 cm). The tumor was multifocal in three patients.

From 13 patients with thyroid malignancy, 7 (53.9%) patients were diagnosed with MTG, 5 (38.5%) patients with UTG, and one (7.6%) patients with Graves's disease. The rates of malignancy were 15.1% for patients diagnosed with UTG, 6.25% for patients diagnosed with MTG, and 3.1% for patients diagnosed with Graves's dis-

**Table 1.**  
Patients with malignant cytology

Age	Gender	USG	FNAB	Operation	Pathology	Diameter (mm)	Invasion	Additional treatment	MACIS	AMES
27	F	GRAVES'		TT	PMC	0.3-0.5			Low Risk	Low Risk
58	F	MTG		TT	PMC	0.9-0.5			Low Risk	Low Risk
41	M	MTG		TT	PMC	0.9			Low Risk	Low Risk
61	F	MTG	M	TT	PMC	0.6			High Risk	Low Risk
70	F	MTG	CMFC	TT	PC	5	Vascular	RIA	High Risk	High Risk
34	F	UTG		TT	PMC	0.1			Low Risk	Low Risk
57	F	MTG	B	TT+CLND	PMC	0.4		RIA	Low Risk	Low Risk
45	F	UTG	B	TT	PMC	0.7			Low Risk	Low Risk
42	F	UTG	CMFC	LL	PC	1.1-0.2		CT+MRND+RIA	High Risk	Low Risk
75	M	UTG	M	LTRST	PC	1.2	Capsule	RIA	High Risk	High Risk
30	F	UTG	CMFC	LL	MIFC	1.5		CT+MRND+RIA	Low Risk	Low Risk
57	F	MTG		TT	PMC	0.1			Low Risk	Low Risk
46	F	MTG		TT	PMC	0.2			Low Risk	Low Risk

\*USG: ultrasonography, FNAB: fine needle aspiration biopsy, MTG: multinodular toxic goitre, UTG: uninodular toxic goiter, M: malignant, B: benign, CMFC: cellular microfollicular cytology, LL: left lobectomy, LTRST: left total right subtotal thyroidectomy, TT: total thyroidectomy, CT: completion thyroidectomy, CLND: central lymph node dissection, PC: papillary cancer, PMC: papillary microcancer, MRND: modified radical neck dissection, RIA: radioactive iodine ablation, MIFC: minimal invasive follicular carcinoma

ease. However, statistically significant differences were not found in the term of malignancy rates ( $p=0.33$ ).

When patients with thyroid cancer were compared with patients who did not have cancer in the term of age and sex, statistically significant differences were not found ( $p=0.346$  and  $p=0.444$ , respectively). When the largest nodule was considered, there were no significant differences between the diameter of the nodule and the frequency of thyroid cancer ( $p=0.448$ ).

When patients were divided into two groups, below the age of 40 and above the age of 40, no significant differences were observed between the groups in the term of rate of cancer ( $p=0.266$ ).

Seven of the patients, who had thyroid cancer, underwent TFNAB during the preoperative period. Two of these patients were diagnosed with thyroid malignancy (one patient with UTG, one patient with MTG). Three patients were recorded as a suspicion of malignancy (two patients with UTG, one patients with MTG), and two patients were recorded as benign according to TFNAB.

### Discussion

The prevalence of thyroid carcinomas found during surgery in hyperthyroid patients is reported to vary widely, ranging from 1.6% to 21.1%. This is probably due to multiple factors, including the cause of hyperthyroidism, the different criteria for choosing surgery as the treatment modality of hyperthyroidism, the extent of thyroidectomy (lobectomy or total thyroidectomy), but most likely due to the extent of histological examination of the removed thyroid tissue and possibly also the geographical variation in incidence of thyroid cancer in general (Pazaitou-Panayiotou et al. 2012). In a Turkish study, Senyurek Giles and colleagues (2008) have found that the incidence of thyroid cancer was 6.5%, who underwent surgery for hyperthyroidism.

It has been reported that thyroid cancer is diagnosed more frequently in patients with Graves' disease than in patients with UTG or MTG (Pazaitou-Panayiotou et al. 2012), whereas other studies presented the same results for Graves', but slightly higher carcinoma prevalence within hot nodules and MTG (Senyurek Giles et al. 2008). In Graves' patients, carcinomas are found to be larger, more often multifocal, locally invasive and more often metastatic to distant sites than in patients with hot thyroid nodules (Pazaitou-Panayiotou et al. 2012). In the study of Senyurek Giles et al. (2008), it has been demonstrated that the frequency of thyroid cancer was

6.4% in patients presenting with MTG, 12% in patients presenting with UTG, and 3.8% in patients presenting with Graves' disease. By comparison, in our study, the frequency of thyroid cancer was 6.25% in patients with MTG, 12.2% in patients with UTG, and 6.25% in patients with Graves' disease, thus corroborating the studies of (Senyurek Giles et al. 2008).

In contrast to the other studies in which the frequency of thyroid cancer sharply increased in patients aged 50 and above (Senyurek Giles et al. 2008; Pazaitou-Panayiotou et al. 2012), our study revealed no statistically significant associations between the age of patients and the frequency of thyroid cancer.

Iodine deficiency, deficiency in thyroid hormone synthesis, goitrogens taken with diet or as medicine, all are known to increase the risk of thyroid cancer by causing an increase in thyroid-stimulating hormone (TSH) levels (Terzioglu et al. 1993). Our country is an endemic goiter region. In another Turkish study, Terzioglu et al. (1993) have found that the incidence of thyroid cancer was 5.8%, and there were no differences between euthyroid patients and the incidence of thyroid cancer (6.2%).

At present, TFNAB procedure is extremely reliable for the evaluation of thyroid nodules: Based on various studies, the sensibility of this methodology is 65-98% and its specificity is 72-100% (Tee et al. 2007; Gul et al. 2009). In our study, preoperative TFNAB was performed on 76 patients. Papillary thyroid carcinoma was diagnosed in two patients for whom cytological findings revealed malignancy, and in 3/12 (25%) patients for whom there was no evidence to suspect malignancy. The pathological findings of 2/44 patients, whose cytology results were benign, were diagnosed as thyroid cancer. In the study of Gul et al. (2009), the rate of thyroid cancer was 5.7%, based on patients with Graves' disease without nodule or with benign state. In the same study, thyroid cancer was observed in all patients for whom the results of TFNAB revealed malignancy, and thyroid cancer was observed in 47.8% of patients for whom there was suspicion of malignancy (Gul et al. 2009).

Fine-needle aspiration cytology from nodules, which are found in patients with Graves' disease, can cause diagnostic difficulties because the cytomorphologic changes in this disease, as a consequence of antithyroid drug treatment, may mimic features of papillary thyroid carcinoma. It is important to perform thyroid and neck US and US-guided TFNAB prior to radioiodine therapy or thyroidectomy, in order to detect thyroid cancer. In cases of nodules that show suspicious features and when

it is not possible to exclude the possibility of malignancy by fine needle aspiration cytology, the preferred choice of treatment should be surgery (Pazaitou-Panayiotou et al. 2012).

Another indicator of malignancy is the size of nodule(s): The rate of cancer in patients with nodules larger than 4 cm, reaches up to 19% (McCoy et al. 2007). Nevertheless, in our study we found that there was no cor-

relation between the size of nodule(s) and the frequency of thyroid cancer. When the average tumor diameter of 0.89 cm is considered, the fact that patients with hyperthyroidism present with small sized nodule, suggests that the possibility of thyroid cancer may be predicted.

In conclusion, every suspicious nodule in hyperthyroid patients should be evaluated carefully prior to therapy of hyperthyroidism.

### References

- De Rosa G, Testa A, Maurizi M, Satta MA, Aimoni C, Artuso A, Silvestri E, Rufini V, Troncone L: Thyroid carcinoma mimicking a toxic adenoma. *Eur J Nucl Med* 17, 179-184, 1990. <http://dx.doi.org/10.1007/BF00811447>
- Gul K, Di Ri Koc A, Ki Yak G, Ersoy PE, Ugras NS, Ozdemi D, Ersoy R, Cakir B: Thyroid carcinoma risk in patients with hyperthyroidism and role of preoperative cytology in diagnosis. *Minerva Endocrinol* 34, 281-288, 2009.
- Kim TS, Asato R, Akamizu T, Harada D, Nakashima Y, Higashi T, Yamamoto N, Tamura Y, Tamaki H, Hirano S, Tanaka S, Ito J: A rare case of hyperfunctioning papillary carcinoma of the thyroid gland. *Acta Otolaryngol Suppl* 557, 55-57, 2007. <http://dx.doi.org/10.1080/03655230601066785>
- Mazzaferri EL: Thyroid cancer and Graves' disease. *J Clin Endocrinol Metab* 70, 826-829, 1990. <http://dx.doi.org/10.1210/jcem-70-4-826>
- McCoy KL, Jabbour N, Ogilvie JB, Ohori NP, Carty SE, Yim JH: The incidence of cancer and rate of false-negative cytology in thyroid nodules greater than or equal to 4 cm in size. *Surgery* 142, 837-844, 2007. <http://dx.doi.org/10.1016/j.surg.2007.08.012>
- Pazaitou-Panayiotou K, Michalakis K, Paschke R: Thyroid cancer in patients with hyperthyroidism. *Horm Metab Res* 44, 255-262, 2012. <http://dx.doi.org/10.1055/s-0031-1299741>
- Senyurek Giles Y, Tunca F, Boztepe H, Kapran Y, Terzioglu T, Tezelman S: The risk factors for malignancy in surgically treated patients for Graves' disease, toxic multinodular goiter, and toxic adenoma. *Surgery* 144, 1028-1036, 2008. <http://dx.doi.org/10.1016/j.surg.2008.08.022>
- Tee YY, Lowe AJ, Brand CA, Judson RT: Fineneedle aspiration may miss a third of all malignancy in palpable thyroid nodules: a comprehensive literature review. *Ann Surg* 246, 714-720, 2007. <http://dx.doi.org/10.1097/SLA.0b013e3180f61adc>
- Terzioglu T, Tezelman S, Onaran Y, Tanakol R: Concurrent hyperthyroidism and thyroid carcinoma. *Br J Surg* 80, 1301-1302, 1993. <http://dx.doi.org/10.1002/bjs.1800801027>