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Toxic nodular goiter and thyroid cancer: Is hyperthyroidism protective against thyroid cancer?

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ABSTRACT

Background: The suppressive effect of the increase in thyroid hormone in patients with toxic nodular goiter is thought to protect the extranodular thyroid tissue from thyroid malignancy. In this study, we aimed to evaluate the prevalence and features of thyroid cancer in patients with toxic nodular goiter who underwent thyroidectomy.

Methods: Medical data of patients who had solitary toxic or nontoxic nodules and underwent total thyroidectomy were reviewed retrospectively. We reviewed the clinical, laboratory, and histopathologic features of patients with toxic nodular goiter and nontoxic solitary nodules.

Results: There were 73 patients with toxic nodular goiter and 366 patients with nontoxic solitary nodules. Median age was greater in the toxic nodular goiter compared with nontoxic solitary nodules patients (50 years; range: 18–73 vs 42 years; range: 18–83, $P < .001$). Median nodule diameters were 40.9 mm (range: 11.0–98.0) and 23.3 mm (range: 4.9–99.0) in patients with toxic nodular goiter and nontoxic solitary nodules, respectively ($P < .001$). Histopathologic examination revealed thyroid cancer in 14 patients (19%) with toxic nodular goiter and 132 (36.1%) patients with nontoxic solitary nodules ($P = .008$). Median tumor diameters were 6 mm (range: 1–50) in toxic nodular goiter and 14 mm (range: 1–80) in nontoxic solitary nodules ($P = .150$). The malignant nodule was the hyperfunctioning nodule in 7 patients with toxic nodular goiter; 4 were follicular and 3 were papillary thyroid cancer. The other 7 malignant foci were located in the suppressed contralateral lobe, and all were papillary microcarcinomas. The incidence of thyroid cancer outside the main nodule was similar in 2 groups ($P = .934$).

Conclusion: Thyroid cancer in patients operated for toxic nodular goiter was 19%, which is not as rare as previously thought. A careful histopathologic examination of both the hyperfunctioning nodule and the extranodular thyroid tissue might help to disclose an unexpected tumor foci when thyroidectomy is performed in patients with toxic nodular goiter.

Introduction

Increased serum thyrotropin (TSH), even within normal ranges, was reported to be associated with an increased risk of thyroid cancer and more advanced disease in patients with nodular thyroid disease.[1] Experimental and clinical studies showed that serum TSH stimulates proliferation of both normal and well-differentiated thyroid cancer cells. As an outcome of this assumption, TSH suppression is one of the treatment approaches in most patients with differentiated thyroid cancer.

The most common causes of hyperthyroidism are Graves' disease, toxic multinodular goiter (TMNG), and toxic nodular goiter (TNG).[2] It has been suggested that decreased TSH in patients with thyroid autonomy may prevent the development of thyroid cancer by inhibiting oncogenes,[3] and therefore, patients with hyperthyroidism are less likely to develop thyroid cancer.[4] The incidence of malignancy in patients with TNG was reported to be 3% to 5% in earlier studies.[5,6] Depending on the low rate of

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malignancy in hyperfunctioning nodules, the guidelines of the American Thyroid Association have not recommended cytologic evaluation in such nodules (R2).[7] In some more recent studies, however, greater rates of thyroid cancer, as great as 12% and 18.3%, were reported in patients with TNG, suggesting that the rate of malignancy in TNG may be underestimated in such patients.[2,8]

In this study, we aimed to determine the prevalence of thyroid cancer in patients with TNG referred for surgical therapy. In addition, we tried to test the hypothesis that the suppressed extranodular thyroid tissue secondary to the hyperthyroidism is protected from malignancy in these patients.

Methods

We reviewed retrospectively the medical records of patients who had a solitary thyroid nodule and underwent total thyroidectomy in our center. Patients <18 years old and patients who had a previous history of radiotherapy to the head and neck region were excluded. Patients were defined to have TNG when serum TSH was associated with an increased or normal free triiodothyronine (fT3) or free thyroxine (fT4), a single thyroid nodule was reported in ultrasonography (US), and a hyperfunctioning nodule with suppressed uptake in the extranodular tissue was observed on Tc^{99m}pertechnetate scintigraphy.[2] Patients with preoperative normal thyroid function or hypothyroidism and single thyroid nodule on US were grouped as having a nontoxic solitary nodule (NTSN).

Demographic and clinical data of patients were recorded. Chemiluminescence methods (Immulite 2000, Diagnostic Products Corp., Los Angeles, CA, and UniCel DXI 800, Beckman Coulter, Brea, CA) were used for measurement of serum levels of TSH, fT3, and fT4, antithyroid peroxidase antibody (anti-TPO), and antithyroglobulin antibody (anti-Tg). The normal ranges for TSH, fT3, fT4, anti-TPO, and anti-Tg were 0.4 to 4 μIU/mL, 1.57 to 4.71 pg/mL, 0.85 to 1.78 ng/dL, 0 to 35 IU/mL, and 0 to 40 IU/mL, respectively. The thyroid antibody levels greater than the upper range were accepted as positive.

Preoperative US was performed with an Esaote color Doppler US (Model 796FDII; MAG Technology Co. Ltd., Yung-Ho City, Taipei, Taiwan) and a superficial probe (Model LA523 13–4, 5.5–12.5 MHz) in all patients. Tc^{99m} pertechnetate scintigraphy was performed in patients with suppressed TSH using a gamma camera equipped with a pinhole collimator. Anterior and left or right anterior oblique thyroid images were obtained 20 minutes after intravenous injection of 185 MBq of Tc^{99m} pertechnetate.

All nodules including toxic ones were evaluated by fine-needle aspiration biopsy preoperatively. The procedure was performed after achievement of euthyroidism in patients with TNG. The Bethesda classification system has been used for cytologic classification since 2010 in our center. Cytologic data of nodules evaluated according to this system were included in the analysis.

The indications for thyroidectomy were indeterminant or malignant cytology results, suspicious features on US, giant nodules that cause compression symptoms, or cosmetic concerns and patient preference. Presence of lymphocytic thyroiditis was determined histopathologically. Patients and nodules were classified as malignant and benign according to the histopathologic results. The number of tumor foci, primary tumor size, incidental malignant foci, cervical lymph node metastasis (LNM), extrathyroidal extension, and capsular and vascular invasion were recorded in patients with thyroid cancer. Data of patients with TNG and NTSN were compared. In addition, demographic, clinical, and cytologic results were compared in TNG patients with benign and malignant histopathology. The reports of the US, pathology, and scintigraphy (in toxic nodules) were matched to determine whether the malignant foci was within or outside the main nodule.

Local ethical committee approval was obtained in accordance with the ethical standards of Helsinki declaration.

Statistical analysis

The distributions of continuous variables were examined by Shapiro-Wilk's test and normality graphs. All continuous variables were summarized by median (range), whereas categorical variables were reported as frequency (%). Mann-Whitney *U* test and χ^2 test were performed to compare continuous and categorical variables, respectively. All statistical analyses were performed via IBM SPSS Statistics version 21.0. (IBM Corp, IBM SPSS Statistics for Windows, Armonk, NY).

Results

There were 73 patients with TNG and 366 patients with NTSN. The median age was 50 years (range: 18–73 years) in patients with TNG and 42 years (range: 18–83 years) in patients with NTSN ($P < .001$; Table I); 40 (54.8%) of the TNG patients and 274 (74.9%) of the NTSN patients were female ($P < .001$). Anti-TPO and anti-Tg positivity was less frequent in TNG patients than in NTSN patients ($P = .001$ and $P = .002$, respectively). The median diameter of the nodule on US in patients with TNG was greater than in patients with NTSN ($P < .001$). Cytologic evaluation according Bethesda classification system was available in 65 nodules in TNG and 325 nodules in NTSN group; the distribution of cytologic diagnoses is given in Table I. Histopathologically, lymphocytic thyroiditis was more prevalent in NTSN compared with TNG group (36.0% vs 8.3%, $P < .001$).

Histopathologic examination revealed thyroid cancer in 14 of the 73 patients (19%) with TNG and 132 (36.1%) of the 366 patients with NTSN ($P = .008$; Table II). The histopathologic type was papillary in 10 (71%) patients and follicular in 4 (29%) patients with TNG. Among patients with NTSN, tumor type was papillary in 116 (87.9%) and follicular in 5 (3.8%) patients. A follicular tumor was more frequent in TNG patients than NTSN patients ($P = .005$). In the TNG patients, the malignancy was in the hyperfunctioning nodule in 7 patients (10%) and located in the extranodular gland in 7 patients (10%). In the NTNG patients, the malignancy was in the main nodule in 101 patients (27.6%), whereas it was detected incidentally outside the main nodule in 31 patients (8.5%). The rate of malignancy in the hyperfunctioning nodule was significantly less than the nontoxic nodule (10% vs 27.6%, $P = .002$). The rates of cancer in the extranodular tissue were similar in 2 groups ($P = .934$). Median tumor diameter and the presence of LNM, vascular invasion, capsular invasion, and extrathyroidal extension did not differ between groups ($P > .05$ for each).

Demographic and clinical features of TNG patients with benign and malignant histopathology are given in Table III. The groups were similar in terms of age, sex, anti-TPO and anti-Tg positivity, and the presence of lymphocytic thyroiditis ($P > .05$ for each). There was no difference in the median diameter of the hyperfunctioning nodule in patients with benign histopathology compared with patients with malignant histopathology ($P = .413$). The cytologic reports of the hyperfunctioning nodule in benign and malignant groups are given in Table III.

The clinical, cytologic, and histopathologic features of the 7 TNG patients with malignancy in the hyperfunctioning nodule are given in Table IV. Preoperative nodule diameter in US was >20 mm in all but 1 patient. The tumor diameter was ≤10 mm in 1, 11 to 19 mm in

Table I
Demographic and clinical features of patients with toxic nodular goiter (TNG) and nontoxic solitary nodule (NTSN)

	TNG (n = 73) Median (range), n (%)	NTSN (n = 366) Median (range), n (%)	*P* value
Age (y)	50 (18–73)	42 (18–83)	<.001
Female sex	40 (54.8)	274 (74.9)	<.001
Anti-TPO positivity	3/64 (4.7)	76/325 (23.4)	.001
Anti-Tg positivity	3/66 (4.5)	63/306 (2.6)	.002
Longitudinal diameter in US* (mm)	4.9 (11.0–98.0)	23.3 (4.9–99.0)	<.001
Cytology	(*n* = 65)	(*n* = 325)	
Nondiagnostic	8 (12)	50 (15.4)	.656
Benign	51 (79)	88 (27.1)	<.001
AUS/FLUS	3 (45)	88 (27.1)	<.001
FN/SFN	2	20 (6.2)	.554
SM	0	45 (13.8)	.003
Malignant	1	34 (1.5)	.039
Lymphocytic thyroiditis	6/72 (8)	122/339 (36.0)	<.001

AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; *FN/SFN*, follicular neoplasm/suspicious for follicular neoplasm; *SM*, suspicious of malignancy.
* *n* = 72 for TNG and 355 for NTSN.

Table II
Histopathologic features of patients with TNG and NTSN

	TNG (n = 73) (%)	NTSN (n = 366) (%)	*P* value
Malignancy	14 (19.2)	132 (36.1)	.008
Papillary	10 (71.4)	116 (87.9)	.103
Follicular	4 (28.6)	5 (3.8)	.005
Medullary	0	4 (3.0)	1.000
Hurthle cell	0	3	1.000
Undifferentiated	0	1	1.000
Mixed*	0	3	1.000
Malignancy in the main nodule	7 (10)	101 (27.6)	.002
Malignancy outside the main nodule	7 (10)	31 (8.5)	.934
Tumor diameter (mm)	6 (1–50)	14 (1–80)	.154
Multifocality	1/14	21/132 (15.9)	.695
Lymph node metastasis	1/13	15/123 (12.2)	1.000
Vascular invasion	0/13	10/126 (7.9)	.598
Capsular invasion	6/13	44/129 (34.1)	.381
Extranodular extension	1/13	21/127 (16.5)	.692

* Mixed tumors: medullary and follicular, papillary and undifferentiated and papillary and Hurthle cell tumor.

Table III
Comparison of demographic and clinical features of benign and malignant patients with TNG

	Benign (n = 59) Median (range), n (%)	Malignant (n = 14) Median (range), n (%)	*P* value
Age (y)	49 (17–70)	50 (32–73)	.416
Sex (Female)	33 (56)	7 (50)	.770
Anti-TPO positivity	2/52	1/12	.470
Anti-Tg positivity	3/55 (6)	0/11	1.000
Longitudinal diameter in US* (mm)	41.5 (11.5–90.0)	35.0 (11.0–98.0)	.413
Cytology	(*n* = 56)	(*n* = 9)	
Nondiagnostic	8 (14)	0	.586
Benign	45 (80)	6/9	.392
AUS/FLUS	2	1/9	.365
FN/SFN	1	1/9	.260
SM	0	0	—
Malignancy	0	1/9	.138
Lymphocytic thyroiditis	5/58 (9)	1/14	1.000

AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; *FN/SFN*, follicular neoplasm/suspicious for follicular neoplasm; *SM*, suspicious of malignancy.
* *n* = 58 for benign nodules.

1, and ≥20 mm in 5 patients. The histopathologic type of thyroid cancer was follicular in 4 of 7 and papillary in 3 of 7 patients. Capsular invasion was observed in 4 patients.

Among the 7 TNG patients with malignancy outside the hyperfunctioning nodule, preoperative nodule diameter in US was 16 mm in 1 patient and >30 mm in the others (Table V). Tumor diameter was ≤10 mm in all patients, and all tumor foci were of the papillary type. One patient had a multifocal, bilateral tumor. LNM, capsular invasion, and extranodular extension were observed in 1, 2, and 1 patient, respectively.

Table IV
Patients with TNG and malignancy in the hyperfunctioning nodule

Patient	1	2	3	4	5	6	7
Age (y)	65	32	54	73	45	40	44
ASEx	Male	Female	Female	Female	Male	Female	Male
Anti-TPO	—	Neg	Neg	Neg	Neg	Neg	Neg
Anti-Tg	Neg	Neg	—	Neg	Neg	Neg	Neg
Longitudinal diameter in US (mm)	6	25	23	31	12	53	61.5
Cytology	ND*	Benign	Benign*	Malignant	—	SFN	Cellular atypia*
Lymphocytic thyroiditis	Neg	Neg	Neg	Pos	Neg	Neg	Neg
Tumor diameter (mm)	35	25	20	3	12	44	50
Type	Follicular	Follicular	Papillary	Papillary	Papillary	Follicular	Follicular
Multifocality	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Lymph node metastasis	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Vascular invasion	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Capsular invasion	Pos	Pos	Neg	Neg	Neg	Pos	Pos
Extranodular extension	Neg	Neg	Neg	Neg	Neg	Neg	Neg

neg, negative; *ND*, nondiagnostic; *Pos*, Positive; *SFN*, suspicious for follicular neoplasm.
* Cytologic evaluation was made before the implementation of Bethesda classification system.

Table V
The patients with toxic nodular goiter and malignancy in the extranodular thyroid tissue (incidental tumor)

Patient	1	2	3	4	5	6	7
Age (y)	72	50	50	60	43	50	58
Sex	Male	Male	Female	Female	Female	Male	Male
Anti-TPO	Neg	—	Neg	Neg	Neg	—	Neg
Anti-Tg	Neg	Pos	Neg	Neg	Neg	—	Neg
Longitudinal diameter in US (mm)	48	30.3	46.5	16.3	38.5	98	31.5
Cytology	Benign*	Benign	Benign	Benign	Benign	Benign	AUS
Lymphocytic thyroiditis	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Tumor diameter (mm)	4	3	1	8	1	4	3
Type	Papillary	Papillary	Papillary	Papillary	Papillary	Papillary	Papillary
Multifocality	Neg	Neg	Neg	Pos	Neg	Neg	Neg
Lymph node metastasis	Neg	Neg	—	Neg	Neg	Pos	Neg
Vascular invasion	Neg	Neg	—	Neg	Neg	Neg	Neg
Capsular invasion	Neg	Neg	—	Pos	Neg	Pos	Neg
Extranodular extension	Neg	Neg	—	Neg	Neg	Pos	Neg

AUS, atypia of undetermined significance; *Neg*, negative; *Pos*, positive.
* Cytologic evaluation was made before the implementation of Bethesda classification system.

Discussion

The studies concerning the association between hyperthyroidism and thyroid cancer report conflicting results. The prevalence of thyroid carcinoma in hyperthyroid patients was reported to range between 0.5% and 21.1%.[9] Differences in the cause of hyperthyroidism, patient selection for operation, type of operation (lobectomy or total thyroidectomy), and extent of histologic examination and geographic variations might be the cause for such variations in the studies.[9,10] The majority of the recent studies investigating the association between serum TSH levels and papillary thyroid cancer observed a decreased risk of malignancy associated with low serum TSH levels and an increased risk with high serum TSH levels.[11]

In the present study, we tried to test the hypothesis that low TSH is protective against thyroid cancer. For this reason, we wanted to include patients with low TSH for a relatively long time. The time between the onset of Graves' disease and the diagnosis and treatment is generally not long enough to test the potential effects of long-term TSH suppression.[12] In contrast, hyperfunctioning nodules tend to evolve gradually, and thyrotoxicosis develops in 1 to 11.8 years in patients with hyperfunctioning nodules.[13] About 20% of patients with adenomas >3 cm experience hyperthyroidism in 1 to 6 years.[14] These data suggest that patients with hyperfunctioning adenomas have low or low-to-normal TSH values long before the development of hyperthyroidism. Another cause for excluding patients with Graves' disease was to avoid the possible thyroid stimulation that can be induced by TSH receptor antibodies. We also aimed to evaluate the risk of thyroid cancer in the gland outside the hyperfunctioning nodule, particularly in the contralateral lobe. Thus, we excluded patients with TMNG and included only patients with solitary nodule to create a more unique and homogenous study group.

TNG is one of the most common causes of hyperthyroidism.[15] It has been suggested that the majority of TNG lesions are benign follicular neoplasms rarely hosting thyroid cancer.[9] Alexander et al[16] defined TNG as an almost universally benign disease in which hormonal control should be the primary objective. The incidence of thyroid cancer in TNG was reported to be 3% to 5% in historical data[5,6]; however, recent studies showed that it is not as low as thought previously.[2] The incidence of thyroid cancer in patients with TNG was 12% in the study by Giles et al[8] and 18.3% in a multicenter study in the United States.[2] It should be noted hyperfunctioning nodules in children seem to carry a greater risk of malignancy reaching to 29%.[17] We also observed a high incidence of carcinoma in patients who were operated on for TNG (19%), but it was less when compared with euthyroid patients (36.1%). The tumor focus was located in the hyperfunctioning nodule in 7 of the 14 TNG patients with thyroid cancer. The remaining 7 tumor foci were observed in the extrathyroidal tissue in the contralateral lobe. In a study of 17 patients with thyroid cancer and autonomous nodule, malignancy was within the hyperfunctioning nodule in 10 (59%) patients.[18] In the study by Mirfakhraee et al,[19] 57.1% of malignancies in the hyperfunctioning nodules was of the papillary type (18.2% with the follicular variant) and 36.4% was of the follicular type. Als

et al[20] reported that 15 of 19 (79%) malignant foci in patients with TNG were follicular cancer, and all tumor diameters were >40 mm. In accordance with these findings, we observed that the type of thyroid cancer in the hyperfunctioning nodule were follicular in 4 of the 7 patients and papillary in 3 of the 7 patients, and all but one were >10 mm. Follicular thyroid carcinoma seems to appear at a greater rate in patients with hyperfunctioning thyroid nodules compared with the overall rate in general population.[19]

The incidence of thyroid cancer in the suppressed, contralateral lobe in TNG patients was 10%, which was similar with the incidence outside the main nodule in euthyroid patients (8.5%). To our knowledge, the only study regarding the incidence of thyroid cancer in the suppressed lobe in patients with TNG included 60 patients and reported an incidence of 5%.[21] In the meta-analysis by Negro et al,[12] the risk of incidental thyroid cancer in patients with TNG and nontoxic uni-nodular goiter was similar. The authors concluded there was no association between TSH and the incidence of papillary cancer. In another study, the rates of incidental thyroid cancer were 6.4% in Graves', 6.8% in TMNG, and 5% in patients with multinodular goiter, suggesting that hyperthyroidism does not offer protection against papillary thyroid cancer in the extranodular thyroid tissue.[22] In a frequently cited study by Fiore et al[3], the prevalence of papillary thyroid cancer in patients with TSH <0.4 μU/mL was significantly less than in patients with no evidence of thyroid autonomy; this finding was interpreted because thyroid autonomy might play a protective role against the development of papillary thyroid cancer in the extranodular thyroid tissue. But when a subanalysis including patients with solitary nodule was made, there was no statistically significant difference in the rates of papillary thyroid cancer in patients with thyroid autonomy (5.3%) and normal TSH levels (7.6%). Similar rates of thyroid cancer in the extranodular tissue in patients with TNG and NTSN in our study also confirms the hypothesis that hyperthyroidism does not prevent the development of thyroid cancer in the suppressed, extranodular thyroid tissue.

Lobectomy is usually the preferred operative approach in TNG unless a suspicious lesion is present in the contralateral lobe. In case of a tumoral foci in the histopathologic examination, removal of contralateral lobe is generally not recommended if the tumor is <1 cm, unifocal, low-risk, and intrathyroidal with no LNM.[10] In our study, hyperfunctioning nodules were all histopathologically benign in patients with malignancy in the contralateral lobe. Thus, if lobectomy was performed, 7 patients (10%) with coexistent TNG and malignancy would be missed. Although all these tumors were micropapillary, 2 patients had aggressive features, such as LNM and extrathyroidal extension. None of these aggressive features were observed in patients with malignancy in the hyperfunctioning nodule.

The molecular basis of hyperfunctioning thyroid carcinoma remains unknown. Activating TSH receptor mutations were shown in malignant, hyperfunctioning nodules. A patient with hyperthyroidism owing to an angioinvasive follicular thyroid cancer bearing the TSHR-activating mutation M453T and a PAX8–PPARγ rearrangement was presented by Lado-Abeal et al.[23] In addition, an increased risk of papillary and follicular thyroid cancer was reported in patients with variants on specific loci (9q22.33 and 14q13.3), which are also associated with lesser TSH levels in the general population.[24]

It remains a challenge to differentiate malignant and benign thyroid lesions preoperatively. The true incidence of thyroid cancer in patients with TNG may be underestimated because a considerable proportion of these patients are treated with radioactive iodine. If the suggestion that hyperthyroidism is protective against thyroid cancer is accepted, clinicians will have little reason to consider operative resection in such patients.[2,18] Antithyroid drugs may be used for years, although some patients may also harbor a thyroid cancer as shown in our study. This study raises the question of how patients with TNG should be investigated extensively for coincidental thyroid cancer.

There was a discordance between nodule diameter in US and tumor diameter in the final histopathologic examination of toxic nodules. The ultrasonographically determined diameter was greater than histopathologically determined size. In a study from our center, Bilginer et al[25] reported that US diameter was greater than the measured histopathologic tumor size in 444 (73.1%) of 607 malignant nodules. In another study including 172 nodules, ultrasonographically detected nodule size was also reported to be greater than pathologic size in 88.3% of patients.[26] This discordance can be explained by interobserver variability of the US examination, differences in pathologic methods, and possible shrinkage of the lesion owing to devascularization after the operative excision. Preoperative fine-needle aspiration of the nodule might also cause decrease in size of the nodule owing to hemorrhage, infarction, and scarring.

Our study was a single center study, and more complicated patients from different regions of our country are generally referred to our center; in addition, being a series of operation is one of the most important limitations of the present study. These considerations might contribute to the greater rate of thyroid cancer in the TNG patients we managed in comparison to the literature. Studies with nonsurgical series will be helpful to define thyroid cancer risk in these patients. Functional status of nodules in patients with NTSN was not evaluated by thyroid scintigraphy. Although there might be some hyperfunctioning nodules with normal thyroid function, our study was retrospective, and there was no indication for scintigraphy examination in patients with NTSN. Among 65 patients with TNG, the cytologic diagnosis was indeterminate or malignant in only 6 patients. In contrast, among the 325 patients with NTSN, 187 (57.5%) had indeterminate or malignant cytology. A greater rate of malignancy in NTSN compared with TNG can mostly be explained by this difference.

In conclusion, the results of our study suggest that the risk of thyroid cancer in patients with TNG was not as low as has been assumed, and hyperthyroidism caused by TNG did not protect against thyroid cancer. The risk of malignancy should not be overlooked during the evaluation and management of patients with TNG, and a careful histopathologic examination might help to disclose an incidental tumor located in the hyperfunctioning nodule or in the extranodular thyroid tissue.

Conflict of Interest

There is no conflict of interest and nothing to declare in this paper.

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