Endocr (2011) 39:13–20
DOI 10.1007/s12020-010-9405-6

ORIGINAL ARTICLE

Prevalence of incidental thyroid cancer and its ultrasonographic features in subcentimeter thyroid nodules of patients with hyperthyroidism

Dilek Berker · Serhat Isik · Ufuk Ozuguz · Yasemin Ates Tutuncu · Kerim Kucukler · Gulhan Akbaba · Yusuf Aydin · Serdar Guler

Received: 15 March 2010 / Accepted: 7 September 2010 / Published online: 9 November 2010

Abstract In patients, who undergo surgery for hyperthyroidism, many cases of incidental thyroid cancer (ITC) have been detected. In the literature, there is no study about ITC in subcentimeter nodules in these patients. We performed this study to determine the frequency of ITC in subcentimeter nodules and ultrasonographic features that can predict malignancy in the patients with hyperthyroidism. We retrospectively reviewed our database about 3114 patients, who underwent thyroidectomy in our hospital. Among 869 patients (27.9%), who were operated because of hyperthyroidism, we enrolled 337 patients, who underwent total thyroidectomy and had subcentimeter nodule [59 Graves' disease (GD) 98 subcentimeter nodule; 278 toxic multinodular goitre (TMNG), 359 subcentimeter nodule], in this study. Twenty-five nodules with ITC and 432 benign nodules have been detected and compared for ultrasonographic (US) features. Incidental thyroid cancer detection ratio was 5.4% [10.2% (10/98) in subcentimeter thyroid nodules in individuals with GD, and 4.1% (15/359) in individuals with TMNG, $P = 0.018$)]. Significant differences have been observed between the groups in terms of microcalcification in US examination of malign and benign subcentimeter thyroid nodules and the ratio of anterioposterior diameter to transverse diameter (A/T) ≥ 1 [(OR = 5.172; 95% CI: 1.495–17.886, $P = 0.015$), and (OR = 5.930; 95% CI: 1.531–22.971, $P = 0.007$), respectively]. We detected a higher incidence of ITC in subcentimeter thyroid nodules in GD compared to TMNG. US examination of subcentimeter nodules in hyperthyroid individuals has indicated that microcalcification and ratio of A/T ≥ 1 are the parameters that predict malignancy.

Keywords Thyroid nodules · Thyroid cancer · Ultrasonography · Hyperthyroidism

D. Berker (✉)
Department of Endocrinology and Metabolism, Ministry of Health, Ankara Numune Research and Training Hospital, 23.cad Simkent Sitesi No:8/11 Kirkkonaklar, Ankara, Turkey
e-mail: dberker6@yahoo.com

S. Isik · U. Ozuguz · Y. A. Tutuncu · K. Kucukler · G. Akbaba · Y. Aydin · S. Guler
Department of Endocrinology and Metabolism, Ministry of Health, Ankara Numune Research and Training Hospital, Ulku Mahallesi Talatpasa Bulvari, No: 5, 06100 Altindag, Ankara, Turkey
e-mail: isik_serhat@yahoo.com

U. Ozuguz
e-mail: uozoguz@yahoo.com.tr

Y. A. Tutuncu
e-mail: kardelendr@yahoo.com

K. Kucukler
e-mail: kerimkucukler@yahoo.com

G. Akbaba
e-mail: gakcil@yahoo.com.tr

Y. Aydin
e-mail: dryusufaydin@yahoo.com

S. Guler
e-mail: sgulers@yahoo.com

Introduction

In the past, it was believed that hyperthyroidism protected patients against thyroid malignancy [1, 2]. Some reports stress that hyperthyroidism and cancer rarely occur simultaneously [3–5]. However, many recent studies show that finding an incidental thyroid cancer (ITC) among

patients operated for a benign thyroid disease is not infrequent. The prevalence of thyroid carcinoma in patients with Graves' disease (GD) has been reported to range from 0 to 16.6%, 2.5–12% in patients with toxic adenoma (TA) and 1.6–8.2% in patients with toxic multinodular goitre (TMNG) [6–8].

Studies, which evaluate the features of thyroid nodules for prediction of thyroid cancer, indicate that solid, hypoechoic appearance, irregular or blurred margins, and microcalcifications are significant for predicting malignancy [9]. There are a few studies on the relation between US features of thyroid nodules and malignancy in patients with hyperthyroidism. In individuals with GD, a relation between thyroid cancer and ultrasonographic features such as microcalcification, hypoechoic feature, blurred margins and A/T $\geq$1 is found [10, 11].

In English literature, we seem to have no data on malignancy rate in subcentimeter thyroid nodules in patients with hyperthyroidism. Therefore, this study will provide useful information for preoperative assessment of the patients that will undergo surgery as a permanent treatment option as it aims to determine the prevalence and clinical outcome of the ITC identified in patients with subcentimeter nodules, who undergo thyroidectomy for hyperthyroidism, and to identify the ultrasonographic features that are predictive of malignancy in patients with hyperthyroidism.

Methods

Study design and patients

3114 patients, who were subjected to thyroidectomy for any reason between January 2004 and January 2009, have been retrospectively scanned from the database of our hospital. Eight hundred and sixty-nine (27.9%) of these patients have been diagnosed with overt or subclinical hyper-thyroidism. Of 869 patients (2237 nodules), 342 had GD, 477 had TMNG, and 50 had TA. First of all, we evaluated the patients, who were operated because of hyperthyroidism (869 patients), as specified in Table 1. Among these patients, who were operated because of hyperthyroidism, 337 patients, who were subjected to total thyroidectomy and had <1 cm nodule in terms of ultrasonographic aspects, have been included in the study. Ultrasonographic features of the subcentimeter nodules have been compared according to the histopathology results.

Diagnostic approach and exclusion criteria

Diagnosis of GD has been established by the presence of signs and symptoms of thyrotoxicosis accompanied by a diffuse goitre, an increased radioiodine uptake, and biochemical evidence of hyperthyroidism and high circulating

Table 1 Characteristics of the patients with hyperthyroidism

	GD ($n = 342$)	TMNG ($n = 477$)	TA ($n = 50$)
Age (year)$^{\alpha}$	40.6 ± 13.9	52.3 ± 14.0	47.2 ± 14.4
Gender, no. (%)$^{\beta}$			
Male	82 (24.0)	137 (28.7)	10 (20)
Female	260 (76.0)	340 (71.3)	40 (80)
Rate of malignancy, no. (%)$^{\gamma}$			
In patients	24/342 (7.0)	38/477 (8.0)	3/50 (6.0)
In all nodules	19/568 (3.4)	32/1517 (2.1)	2/152 (1.3)
Method of surgical treatment, no. (%)			
Lobectomy	0	0	41 (82.0)
Subtotal thyroidectomy	0	99 (20.8)	9 (18.0)
Near-total thyroidectomy	76 (22.2)	66 (13.8)	0
Total thyroidectomy	266 (77.8)	312 (65.4)	0
Tumour localization, no. (%)			
Parenchymal	6[a] (24)	9[b] (22.0)	1 (33.3)
Nodal	19[a] (76)	32[b] (78.0)	2 (66.7)
Subcentimeter	10 (40)	15 (36.5)	0
Supracentimeter	9 (36)	17 (41.5)	2 (100)

GD Graves' disease, *TMNG* toxic multinodular goitre, *TA* toxic adenoma

$^{\alpha}$ $P < 0.001$, $^{\beta}$ P = no significant difference, $^{\gamma}$ P = no significant difference

[a] Number of the patients with GD with identified thyroid cancer is 24, yet bilateral thyroid cancer has been identified in 1 patient and it is parenchymally localized in one side and nodally localized in the other

[b] Thyroid cancer is detected in 38 patients with TMNG, but, since multifocal cancer is found in 3 patients, tumour tissue is detected in 41 foci

TSH receptor antibodies. Thyroid scintigraphy or radioactive iodine uptake has been performed for the relevant patients following the detailed thyroid ultrasonography applied to the patients with hyperthyroidism. As a result, TMNG and TA separation has been made.

- Patients with a history of thyroid cancer in family, patients who received radiation to the neck area, and the patients with another diagnosed malignancy have been excluded.
- Patients with >1 cm nodule except for active nodule have been excluded.
- Patients have been excluded if a lymph node with a pathological appearance is observed in cervical examination by ultasonography.
- As we think that thyroid cancer, which is histopathologically identified in the patients with abnormal results in fine needle aspiration biopsy (FNAB) that is performed in the pre-operative period, cannot be accepted as ITC, all patients with abnormal FNAB results have been excluded. FNAB has been applied on only 105 (23.0%) of subcentimeter nodules.
- As the existence of ITC cannot be certainly known in the remaining thyroid tissue in the surgical procedures except for total thyroidectomy, the patients, who were subjected to a surgical procedure other than total thyroidectomy, have been excluded.

Indications of surgery and surgery procedures

All patients with toxic thyroid diseases were treated with antithyroidal drugs and were euthyroid at the time of surgery.

For patients with GD, the indications for surgery have been classified into several groups including the following categories: preference of patients (128 patients, 37.4%), clinical ophthalmopathy (17 patients, 5.0%), patients with serious suspicion of malignancy in US (3 patients, who have microcalcification through US, shape irregularity and hypoechogenicity characteristics, 0.9%), compressive symptoms due to large goitre or large thyroid volume (9 patients, 2.6%), failure of antithyroid drugs or relapse after antithyroid treatment (178, 52.0%), and/or serious side effects of antithyroid drugs including agranulocytosis and hepatotoxicity (7 patients, 2.1%).

In patients with GD, total thyroidectomy is indicated in patients with a coexisting malignancy, severe ophthalmopathy, or in patients unwilling to undergo reoperation or radioactive iodine therapy.

The main reason for performing a near-total thyroidectomy is to preserve the blood supply of at least one healthy parathyroid gland. Rarely, when a total resection is intended, but the entire gland cannot be safely dissected from the surrounding nerves, a little part of thyroid is left near the nerve.

Surgery indications for TMNG have been the presence of an active nodule for which radioiodine treatment would be inefficient (nodule size is more than 4 cm), preference of patients and findings of compression.

Table 1 presents the distribution of surgical procedures performed on all patients operated for reasons of hyperthyroidism. Although the preferred surgical method was lobectomy in TA patients, subtotal thyroidectomy was performed in 9 patients because of compression (Table 1).

Confirmation of ultrasonographic findings of thyroid with histopathology

Histopathology reports of patients treated with total thyroidectomy have been macroscopically evaluated in US in terms of specified/unspecified nodules. Specimens for light microscopy were fixed in 10% buffered formalin and embedded in paraffin. Sections of 4 μm thickness were cut and were stained with haematoxylin and eosin.

No thyroid nodule, which was followed up in the pathology specimen, was apparent, but could not be detected by US. If the tumour tissue is not defined within a nodule formation in histopathology and if it is integrally specified in a parenchyma, it has been accepted as "parenchymal tumour tissue"; irrespective of detection of a nodule through US, if the tumour tissue is located within a nodule formation in histopathology, it has been accepted as "nodular tumour tissue".

Thyroid US, FNAB, and cytological examinations

Ultrasonographic examinations and FNABs of the patients have been performed by endocrinologists (DB, YA, SG) in our clinic using the LOGIQ 3 (General Electric Healthcare, Waukesha, WI, USA) US equipment and the 11 MHz linear probe. Fine needle aspiration biopsies have been performed with either a 22-gauge needle attached to a 10-ml disposable plastic syringe or an aspirator. Freehand biopsies have been performed for all FNABs. Samples have been stained with haematoxylin and eosin and Giemsa and evaluated by the pathology department of our institution. The cytological diagnoses have been as follows: malignant, benign, suspicious, or inadequate.

Laboratory assays

Serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT_3), free thyroxin (FT_4), anti-TSH receptor antibody (TR-Ab), anti-thyroperoxidase antibody (TPO-Ab), and anti-thyroglobulin antibody (Tg-Ab) levels have been analyzed. Serum TSH, FT_3, and FT_4 levels have been evaluated by using the Abbott Architect 2000 device and Chemiluminescence Microparticle Immunoassay (CMIA)

method. Serum Tg-Ab and TPO-Ab values have been evaluated by immunoradiometric assay (IRMA) methods (ICN Pharmaceuticals, USA). Anti-TSH receptor antibodies have been measured in patients with the use of a radioreceptor assay (Radim, Italy). Patients with TSH levels lower than 0.35 μIU/ml and with normal FT3 and FT4 levels (subclinical) or above normal FT3 and FT4 levels (overt) (>3.71 pg/ml and >1.48 ng/dl; respectively) have been accepted as hyperthyroidism. Normal levels for thyroid autoantibodies in our laboratory are as follows: Tg-Ab < 50 IU/ml; TPO-Ab < 10 IU/ml, and TR-Ab < 9 U/l (9–14 U/l border line, >14 U/l positive).

Statistical analysis

Data analysis has been performed by using Statistical Package for Social Sciences (SPSS) version 11.5 software (SPSS Inc., Chicago, IL, United States). The metric discrete variables are shown as mean ± standard deviation, and percentages are used for categorical variables. Chi-square tests have been used to assess the statistical significance of differences between groups in the frequency distribution of categorical variables, unless the expected cell size is less than five when Fisher's exact test is used. Medians have been compared by using Mann–Whitney *U* test when the number of independent groups is two. Differences between the medians of more than two groups have been evaluated by using Kruskal–Wallis test. Sensitivity, specificity, positive, and negative predictive values have been calculated for evaluation of diagnostic performance of each US property. A *P* value less than 0.05 has been considered to be statistically significant.

Results

Prevalence and clinical features

All patients with hyperthyroidism

Of 869 patients with hyperthyroidism, 640 are female (73.6%) and 229 are male (26.4%); mean age is 48.2 ± 14.8 (19–78) years. Of these patients, 342 had GD (39.4%), 477 had TMNG (54.9%), and 50 had TA (5.7%).

Thyroid carcinoma has been found in 7.5% ($n = 65$) of all patients with hyperthyroidism. Thirty-eight (8.0%) of the patients with TMNG, 3 (6.0%) of the patients with TA, and 24 (7.0%) of the patients with GD had thyroid carcinoma (Table 1). A total of 69 tumour tissues have been detected in 65 patients while 4 patients have multifocal thyroid cancer.

Sixteen of those patients have been diagnosed with parenchyma (6 patients with GD, 1 patient with TA, and 9 patients with TMNG) and nodules have been diagnosed in 53 patients (Table 1). Ratio of thyroid cancer detected in nodules of all patients with hyperthyroidism is 2.3% for all nodules (if 16 parenchymal tissues were excluded, it would be 53/2237). Of 53 nodules, in which thyroid carcinoma has been detected, 25 are subcentimeter (47.2%) and 28 are supracentimeter (52.8%) nodules. In toxic adenoma patients, no thyroid cancer has been detected in the subcentimeter nodules.

Histological examination has revealed 63 papillary (61 microcarcinoma), 5 follicular carcinoma (one microcarcinoma), and 1 anaplastic carcinoma. Histopathological type is papillary cancer in all Graves' patients with identified thyroid cancer and in toxic adenoma patients. Yet, follicular cancer has been identified in 5 patients with TMNG and 1 patient has anaplastic cancer.

In the patients with toxic adenoma and TMNG, malignity ratio of functional nodules is 1.3% (7/527). Five of these are patients with TMNG and 2 are patients with TA (Table 2). Of the thyroid cancers identified in these functional nodules, 5 are PTMC and 1 is follicular carcinoma. In the patient diagnosed with anaplastic cancer, a larger anaplastic cancer tissue has been observed with a differential thyroid cancer tissue with a size of 9 mm in terms of histopathology in the nodule, which has scintigraphically functional parts (Fig. 1a, b).

Extracapsular invasion and vascular invasion have been found in 7 patients (10.8%) (in 5 papillary cancer and 2 follicular cancer patients) and 5 patients (7.7%) (in 2 papillary cancer and 3 follicular cancer patients), respectively.

Table 2 Characteristics of the patients with tumour identified from functional nodule

Patients no	Gender	Diagnosis	Tumour type	Tumour size (cm)	Nodule size (cm)
1	Female	TMNG	Anaplastic cancer	2.8 cm	3.7
			Differential cancer	0.9 cm	
2	Female	TA	PTMC	0.2	1.8
3	Female	TMNG	Follicular carcinoma	0.9	3
4	Female	TMNG	PTMC	0.9	2.5
5	Female	TMNG	PTMC	0.5	1.5
6	Male	TMNG	PTMC	0.6	1.5
7	Female	TA	PTMC	0.6	5.5

PTMC papillary thyroid microcarcinoma, *TA* toxic adenoma, *TMNG* toxic multinodular goitre

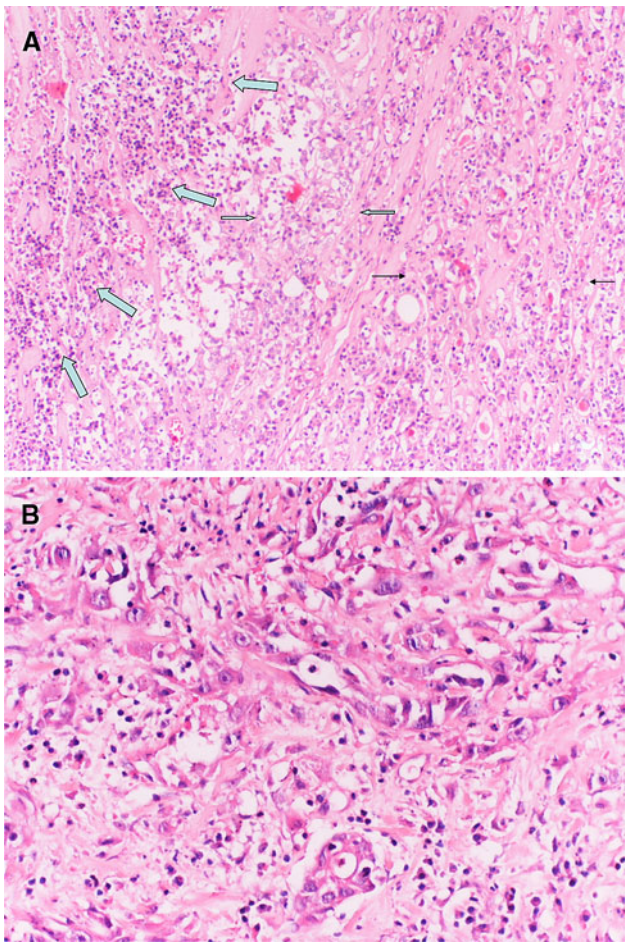

Fig. 1 **a** The transition from well differentiated follicular carcinoma (between *thin arrows*) to a higher grade tumour and necrosis (*thick arrows*) (H/E ×100). **b** Anaplastic tumour component composed of pleomorphic cells with hyperchromatic nuclei, prominent and multiple nucleoli, and bizarre tumour cells. An inflammatory response to the tumour including lymphocytes, plasma cells, and neutrophilic leucocytes is present

Multiple lesions have been noted in four cases (6.1%). There is no vascular or capsular invasion in the case with anaplastic cancer. In supracentimeter nodules, none of the patients with PTMC has lymph node metastasis. In the patients with subcentimeter nodules, LN metastasis has not been taken into consideration as routine LN excision cannot be performed.

Study population

Incidental thyroid cancer rates in subcentimeter nodules in patients with GD and patients with TMNG are 10.2% (10/98) and 4.1% (15/359), respectively. Significant differences have been observed between the patients with GD and with TMNG ($P = 0.018$). Rate of malignancy is 5.4% (25/457) among all evaluated subcentimeter nodules. Tumours have a mean diameter size of 0.61 ± 0.28 cm (range, 0.1–0.9) in ITC identified in subcentimeter nodules. The diameter of the tumour tissues found in the nodule is larger than that of the tumour tissues found in the parenchyma (0.64 ± 0.35 vs 0.46 ± 0.17, respectively, $P = 0.026$).

Graves' disease

In 59 patients with GD, there are 98 subcentimeter nodules [mean age is 41.4 ± 13.4; 44 are female (74.6%) and 15 are male (25.4%)]. Rate of malignancy in subcentimeter nodules is 10.2% (10/98) depending on the number of nodules, 16.9% depending on the number of patients (10/59). Tumour type is papillary thyroid microcarcinoma in all cases. Average tumour size is 0.5 ± 0.2 cm in patients with ITC. In 1 out of 10 cases with subcentimeter ITC, there is capsular invasion, and none of them has vascular invasion.

Toxic multinodular goitre

In 278 patients with TMNG, there are 359 subcentimeter nodules. Mean age of these patients is 50.3 ± 13.2; 197 are female (70.9%) and 81 are male (29.1%). In TMNG patients, rate of malignancy in subcentimeter nodules is 4.1% in nodules (15/359), 5.3% in patients (15/278). Tumour type is papillary thyroid microcancer in all cases. Average diameter of thyroid cancer is 0.72 ± 0.2 cm in patients with TMNG, whose ITC has been identified in a subcentimeter nodule. In 1 out of 15 cases with subcentimeter ITC, there is capsular invasion, and none of them has vascular invasion.

Ultrasonographic characteristics of subcentimeter nodules and associations with malignancy

98 (21.4%) of the subcentimeter nodules in patients with GD and 359 (78.6%) of the subcentimeter nodules in patients with TMNG have been included in the study. 25 malign subcentimeter nodules (10 patients with GD and 15 patients with TMNG) and 432 benign subcentimeter nodules (88 patients with GD and 344 patients with TMNG) have been compared in terms of ultrasonographic features.

Mean age of the patients diagnosed with malignity is higher than that of the patients with benign pathology; however, that is not statistically significant (52.6 ± 11.8 vs 47.0 ± 15.1, $P = 0.059$). Prevalence of malignancy in relation to subcentimeter nodules in GD patients is statistically significantly higher than that of TMNG group (16.9 and 5.3%, respectively, $P < 0.001$).

US features of benign and malign thyroid nodules of patients included in the study are shown in Table 3 and sensitivity, specificity, negative predictive value (NPV),

Table 3 Comparison of ultrasonographic features of histopathologically malign and benign subcentimeter thyroid nodules

	Malign ($n = 25$)	Benign ($n = 432$)	P
Structure			
Solid	21 (84.0)	406 (94.0)	1.000
Cystic	0	4 (0.9)	
Solid + cystic	4 (16.0)	22 (5.1)	
Echogeneity			
Hypoechoic	8 (32.0)	139 (32.2)	0.755
Isoechoic	3 (12.0)	99 (22.9)	
Hyperechoic	0	25 (5.8)	
Mixed	14 (56.0)	169 (39.1)	
Microcalcification	12 (48.0)	60 (13.9)	0.015
Halo absence	20 (80.0)	378 (87.5)	0.383
Shape irregularity	8 (32.0)	26 (6.0)	0.692
AT ≥1	18 (72.0)	133 (30.8)	0.007

AT anteroposterior diameter to transverse diameter ratio

and positive predictive value (PPV) of certain US features in prediction of malignancy are presented in Table 4. No significant correlation has been observed between malignancy and nodule structure for predicting malignancy ($P = 1.000$). When compared to cystic structure, solid structure does not significantly increase the risk of malignancy (since there is no nodule of either cystic or malignant nature, or it could not be calculated).

There is no statistically significant correlation between nodule echogenicity and malignancy ($P = 0.755$) (Table 3). No statistically significant correlation is present between hypoechoic structure and malignancy [OR and %95 CI for hypoechoic structure is 1.201 and (0.341–4.222), respectively] ($P = 0.751$).

A statistically significant correlation has been found between malignancy and anteroposterior to transverse diameter ratio (AT ratio) (OR = 5.930; 95% CI: 1.531–22.971) ($P = 0.007$). For predicting malignancy, AT ratio ≥1.0 has 72.7% sensitivity, 69.0% specificity, 9.5% positive predictive value, and 98.3% negative predictive value.

Microcalcification has a statistically significant value in predicting malignancy [OR and %95 CI for microcalcification is 5.172 (1.495–17.886), respectively] ($P = 0.015$). Sensitivity is 45.5%, specificity is 86.1%, positive predictive value is 12.8%, and negative predictive value is 97.2% for microcalcification.

Halo absence does not have a statistically significant value in predicting malignancy ($P = 1.000$). Irregularity of the margins does not have a statistical significance in predicting malignancy, either ($P = 1.000$).

There is no difference in distribution of diagnoses between malign and benign cases following surgery ($P = 0.965$). A statistically significant difference is not found between GD and TMNG groups when all parameters of the nodule features are evaluated ($P > 0.05$).

Discussion

In our series, patients with GD, TMNG, and TA have 7.0, 7.9, and 6.0% prevalence of incidental thyroid carcinoma, respectively. However, in GD and TMNG, malignancy frequencies in subcentimeter nodules are 16.9 and 5.3% in cases and 10.2 and 4.1% in nodules, respectively. Rate of incidental malignancy is similar in all groups, but nodular disease because of an increased number of nodules in each patient shows lower malignancy per nodule. The evaluation of correlation between US features of preoperative thyroid nodules and malignancy reveals that AT ratio and presence of microcalcification has a predictive value.

Thyroid carcinoma has been found in 7.5% ($n = 65$) of all patients with hyperthyroidism. ITC ratio detected in nodules of all hyperthyroid patients is 2.3% for all nodules, but ITC ratio in subcentimeter nodules is 5.4% in all patients with hyperthyroidism.

In general, the risk of malignancy for subcentimeter thyroid nodules has been reported to be similar to the rates in supracentimeter nodules [9, 12]. However, there are studies reporting a higher rate of thyroid cancer in subcentimeter nodules than supracentimeter nodules [13].

The prevalence of incidental thyroid carcinoma in Graves' disease has been reported to be between 0.3 and 10.0% [6–8]. In our study, in GD patients, the rate of malignancy is 7.0%, which is similar to the rates in previous studies. It is suggested that the wide variation in incidence could be due to the differences in the extent of resection as well as in the number of histological sections examined per specimen [3]. Although different mechanisms are suggested to explain Graves' disease and pathogenesis of thyroid cancer, they seem to be contradictory and inefficient [14–18]. Especially, TSH receptor antibodies are closely linked to angiogenesis, which plays a crucial role in tumour growth and development [16, 18]. Therefore, GD patients with differentiated thyroid cancer (DTC) have been found to have a worse clinical outcome than euthyroid patients with DTC [14, 19, 20]. In contrast, other investigators suggest that GD is not related to the aggressiveness of coexisting thyroid carcinoma [21]. All patients with GD and a concomitant ITC in this series have papillary cancer. Papillary thyroid cancer is the most common histological subtype accounting for 85% of all thyroid cancer cases [22]. Papillary microcarcinoma is a distinct subtype of papillary thyroid cancer which is usually non-aggressive in its clinical behaviour [23].

Table 4 Sensitivity and specificity of selected ultrasonographic characteristics for prediction of malignancy in subcentimeter thyroid nodules coexisting with hyperthyroidism

	Halo absence	Hypoechogenicity	Microcalcification	Solid structure	AT ≥1	Shape irregularity
Sensitivity (%)	80.0	32.0	48.0	84.0	28.0	32.0
Specificity (%)	12.5	67.8	86.1	6.0	69.2	94.0
PPV (%)	5.0	5.4	16.6	4.9	11.9	23.6
NPV (%)	91.5	94.5	96.6	86.6	97.7	96.0

Sensitivity number of true positives divided by the number of true positives plus the number of false positives, *Specificity* number of true negatives divided by the number of true negatives plus the number of false positives, *PPV (positive predictive value)* number of true positives divided by the number of true positives plus the number of false positives, *NPV (negative predictive value)* number of true negatives divided by the number of true negatives plus the number of false negatives

The incidence of ITC in patients with TA (6.0%) and TMNG (8.0%) is higher in this series than in previous series. In our study, we have included only the patients that have undergone total thyroidectomy, and therefore, ITC rate may be high. There are studies, which also include surgical procedures other than total thyroidectomy. We are aware that ITC may be left in the residual tissue. Our country is located in an iodine deficiency region. Although iodine deficiency is not very severe in general, it may rise to a significant level depending on the area [24]. Iodine status of our country has improved thanks to iodine prophylaxis program initiated in 1999 [25]. We assume that the high incidence of TA and TMNG is related to the introduction of iodine salt supplementation in our iodine-deficient areas, as already reported [26–28].

When we identify a thyroid nodule, we perform a thyroid FNAB for all ultrasonographically suspicious nodules. In a previous study, we state that the rates of malignancy in >1 cm thyroid nodules and <1 cm thyroid nodules are similar [12]. In this study, the rates of malignancy in subcentimeter thyroid nodules of hyperthyroid patients are similar to euthyroid subcentimeter thyroid nodules. But, the rate of malignancy for subcentimeter nodules in GD patients is higher than that of TMNG patients. We know that lymph node metastasis may accompany microcarcinomas in diagnosis [29, 30]. Thyroid microcarcinoma with a very aggressive course has also been reported. But in our study, we have not detected lymph node metastasis in any of our patients.

In the previous studies investigating subcentimeter thyroid nodules of euthyroid patients, solid structure, microcalcifications, and hypoechogenicity show a correlation with malignancy [12]. Besides, in individuals with GD, there is a relation between thyroid cancer and US features such as microcalcification, hypoechoic feature, blurred margins and A/T ≥1 [10, 11]. However, there is no study evaluating the features of subcentimeter thyroid nodules regarding the risk of malignancy in patients with hyperthyroidism.

Our study has identified no significant difference in the rate of a solid structure nodule between hyperthyroid malign and benign groups. In addition to studies reporting solid structure as a weak indicator of malignity in thyroid nodules as most of benign nodules are of solid structure, there are some other publications reporting it as a strong indicator of malignity [9, 12, 31, 32].

We have not established a statistically significant association between nodular echogenicity and malignity. In previous studies, hypoechoic US appearance in thyroid nodules is significantly associated with malignancy [12, 33]. However, there are studies, which do not establish a relationship between malignity and hypoechoic US appearance [32].

It is reported that AT rate ≥1.0 is a very good predictor for the risk of thyroid cancer in thyroid nodules [34]. Also, in individuals with Graves' disease, similar results are observed [10]. In our study, AT ratio OR = 5.930 (95% CI: 1.531–22.971) is a good predictor with 72.7% sensitivity and 69.0% specificity. Besides, in our study, microcalcification is found to be a predictor of malignancy with 5.172 OR (95% CI: 1.495–17.886), 45.5% sensitivity, and 86.1% specificity.

Study limitations

In patients with hyperthyroidism, it is necessary to operate all patients with hyperthyroidism and to evaluate histopathology data regardless of nodule in order to report the prevalence of ITC. However, it is not easy to carry out a prospective study designed in this way. We, in this retrospective analysis, have tried to present the actual ITC ratios by excluding the patients that have not undergone total thyroidectomy and have a suspicious FNAB result in evaluating the subcentimeter thyroid nodules.

Ultrasonographic nodule vascularization has not been evaluated in all patients; this feature has not been used in comparison of malignant and benign subcentimeter nodules. Further studies are needed on various geographical

regions and societies to determine which ultrasonographic characteristics of thyroid nodules accompanying hyperthyroidism indicate the risk of malignancy.

Conclusion

In this study, we have observed that incidence of ITC *n* subcentimeter thyroid nodules is higher in GD than in TMNG. In US evaluation of subcentimeter thyroid nodules of individuals with hyperthyroidism, microcalcification, and anteroposterior diameter to transverse diameter ratio ≥ 1 are found to be parameters that predict malignancy. It seems that the surgical method should be preferred to perform FNAB in preoperative preparation phase as in euthyroid nodular goitre patients since the rates of malignancy are similar in subcentimeter and supracentimeter nodules of patients with hyperthyroidism. It is important that, in hyperthyroid patients, subcentimeter nodules should be treated in a way similar to the supracentimeter nodules.

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