

Rate of Malignancy in Exophytic Thyroid Nodules

Fatma Dilek Dellal,^{1*} Husniye Baser,¹ Dilek Arpaci,² Abbas Ali Tam,³ Didem Ozdemir,³ Aydan

Kilcarslan,⁴ Ersin Gurkan Dumlu,⁵ Reyhan Ersoy,³ and Bekir Cakir³

¹Department of Endocrinology and Metabolism, Ataturk Training and Research Hospital, Ankara, Turkey

²Department of Endocrinology and Metabolism, Bulent Ecevit University, Zonguldak, Turkey

³Department of Endocrinology and Metabolism, Faculty of Medicine, Yildirim Beyazit University, Ankara, Turkey

⁴Department of Pathology, Faculty of Medicine, Yildirim Beyazit University, Ankara, Turkey

⁵Department of Surgery, Faculty of Medicine, Yildirim Beyazit University, Ankara, Turkey

*Corresponding author: Fatma Dilek Dellal, Department of Endocrinology and Metabolism, Ankara Training and Research Hospital, Ankara, Turkey. Tel: +90-3122203052, Fax: +90-3122912525, E-mail: drdellal@yahoo.com

Received 2016 August 03; Revised 2016 November 28; Accepted 2017 January 25.

Abstract

Background: There are ultrasonography (US) features suggested to be associated with a higher risk of malignancy in thyroid nodules. However, exophytic appearance of thyroid nodules has not been studied previously.

Objectives: To evaluate US features, and cytological and histopathological findings in exophytic thyroid nodules.

Patients and Methods: Patients with an exophytic thyroid nodule who underwent fine needle aspiration biopsy (FNAB) between January and July 2015 were evaluated prospectively. Demographical data, US features, and cytology results were noted and histopathological findings were determined in operated patients. The results were compared with non-exophytic nodules of age and sex matched patients.

Results: Data of 253 exophytic nodules in 247 patients and 529 non-exophytic nodules in 357 patients were analyzed. Hypoechoogenicity, mixed texture, and absence of peripheral halo were significantly higher in exophytic nodules ($P < 0.001$, $P < 0.001$, and $P = 0.018$, respectively). Nondiagnostic, atypia of undetermined significance/follicular lesion of undetermined significance and suspicious for malignancy cytology results were significantly higher in exophytic nodules ($P = 0.002$, $P < 0.001$ and $P < 0.001$ respectively). 6.7% of exophytic nodules and 1.9% of non-exophytic nodules had malignant cytology ($P = 0.001$). Histopathologically, 35 (47.9%) of 73 exophytic nodules and 18 (24.3%) of 74 non-exophytic nodules were malignant ($P < 0.01$). Capsular invasion was higher in the malignant exophytic group (53.5% vs 14.3%, $P = 0.027$). US features other than hypoechoic pattern which was higher in the malignant group were similar in benign and malignant exophytic nodules.

Conclusions: Exophytic nodules seem to carry a higher rate of malignancy both cytologically and histopathologically. Suspicious US features except hypoechoic pattern were not higher in malignant compared to benign exophytic nodules.

Keywords: Exophytic Appearance, Thyroid Nodule, Cytology, Histopathology, Thyroid Ultrasonography

1. Background

The prevalence of thyroid nodules is very high in population reaching 19-68% of randomly selected individuals when high-resolution ultrasonography (US) is used. Although the majority of nodules are benign and the malignancy rate is relatively low (7% - 15%), it is important to differentiate malignant and benign thyroid lesions (1).

Fine needle aspiration biopsy (FNAB) of the thyroid is the gold standard diagnostic technique for determination of malignancy in thyroid nodules. It helps to avoid unnecessary surgery; however, this procedure is invasive. US is a non-invasive, cheap, easy and sensitive method for detection of thyroid nodules. Although the diagnostic value of US to differentiate between benign and malignant nodules is limited, some US features were reported to be associated with a higher risk of malignancy (2). These features are hypoechoic pattern, solid texture, presence of micro-

calcification, absence of peripheral halo, marginal irregularity, ratio of anterior-posterior to transvers diameter > 1 , increased vascularity, and high strain index in elastosonography (3).

There are different definitions for the term "exophytic" in the literature. By the most commonly used definition, exophytic tissue is defined as a tissue growing outside towards the surface epithelium of an organ or structure in which it is originating from (4). For thyroid tissue, exophytic nodule refers to a nodule that sticks out of the normal thyroid boundary/outline. According to another definition, a nodule that makes an acute angle with the adjacent thyroid capsule could be called as exophytic nodule (5). Exophytic feature is often evaluated in many tumors. However, to our current knowledge, there is no study evaluating the exophytic feature of thyroid nodules in the literature. In this study, we aimed to determine US features,

cytological findings, and the malignancy rate in exophytic thyroid nodules and compared our findings with non-exophytic ones.

2. Objectives

To evaluate US features, and cytological and histopathological findings in exophytic thyroid nodules.

3. Patients and Methods

3.1. Subjects

Adult patients with an exophytic thyroid nodule who underwent FNAB procedure between January 2015 and July 2015 in our clinic were recruited for this prospective study. Exophytic nodule was defined when a nodule was localized at the anterior surface of the thyroid beyond the gland borders making an acute angle with the adjacent thyroid capsule (Figure 1). Nodules larger than their originating lobe or region and nodules that overflowed outside the gland were defined as expansive nodules and excluded from the study (Figure 2). Additionally, nodules that were directly adjacent to the rigid structures such as the trachea (eg. nodules in the isthmus junction) or macrocalcific nodules/lesions which could show expansive features were excluded from the study as these nodules may falsely be considered as exophytic (Figure 3). Patients with a previous history of thyroidectomy and radiotherapy to the head and neck region were also excluded from the study. Age and sex-matched patients who had a non-exophytic thyroid nodule and underwent US guided FNAB during the same period were chosen as the control group. A total of 280 exophytic nodules in 273 patients were detected and due to exclusion criteria, data of 253 exophytic nodules in 247 patients were analyzed. Serum thyrotrophin (TSH) and thyroid hormones were measured in the last 3 months before FNAB in all patients. Antithyroid peroxidase antibody (anti-TPO) and anti-thyroglobulin antibody (anti-TGAb) were measured. US features and cytological findings of nodules were evaluated. Final histopathological diagnosis and malignancy rates of nodules were determined. Local ethical committee approved the study. All patients and control group gave written informed consent to participate in the study.

3.2. Laboratory

Chemiluminescent immunoassay was used for TSH, free triiodothyronine (fT3), free thyroxine (fT4), antithyroid peroxidase antibody (anti-TPO), and anti-thyroglobulin antibody (anti-TGAb). (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA,

and the UniCel Dxl 800, Beckman Coulter, CA, USA). Normal ranges for TSH, fT3 and fT4 were 0.4 - 4.0 uIU/mL, 1.57 - 4.71 pg/mL, and 0.61 - 1.12 ng/dL, respectively. Anti-TPO higher than 10 U/mL and anti-Tg higher than 30 U/mL were accepted to be positive. Thyroid functional status (euthyroid/hypothyroid/hyperthyroid) and antibody positivity were compared in patients with exophytic and non-exophytic nodules.

3.3. Ultrasonography

Thyroid US was performed by an Esaote color Doppler US (Taipei, Taiwan) and compatible superficial probe (5.5 - 12.5 MHz). Parenchymal heterogeneity, fibrous bands, border regularity of thyroid gland, presence of thyroiditis and parenchymal color doppler flow were evaluated. Ultrasonographically chronic thyroiditis was diagnosed when thyroid gland had a coarse, heterogeneous and hypoechoic echo pattern and/or micronodules scattered throughout the parenchyma and/or when it was permeated by fibrous echogenic layers, giving the gland a pseudolobular appearance (6, 7). Number of the nodules, localization (right or left lobe), diameters (millimeters), presence of halo, echogenicity (hypoechoic/isoechoic/hyperechoic), marginal regularity (regular or irregular), presence of microcalcification and macrocalcification, and vascularization (peripheral and/or santral) were determined. US features of exophytic and non-exophytic nodules were compared. In addition, clinical and US features of histopathologically benign and malignant exophytic nodules were compared.

3.4. Fine Needle Aspiration Biopsy and Cytopathology

US-guided FNAB was carried out by an experienced clinician with a 27-gauge needle and 10 mL syringe using a Logic Pro 200 GE US machine and 7.5 MHz probe. During FNAB procedure, aspiration was performed for at least 2 - 4 times, 4 - 6 air-dried slides were prepared and sent for cytological assessment. Informed consent was taken from all patients and control group before FNAB procedure.

Bethesda classification system was used for the cytological diagnoses. The categories were nondiagnostic, benign, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for follicular neoplasm, (FN), suspicious for malignancy and malignant (8). In case of nondiagnostic cytology result, FNAB was repeated at least 3 months after and a nodule was considered nondiagnostic when the result was same at least for 2 times. Cytological diagnosis was compared between exophytic and non-exophytic nodules.

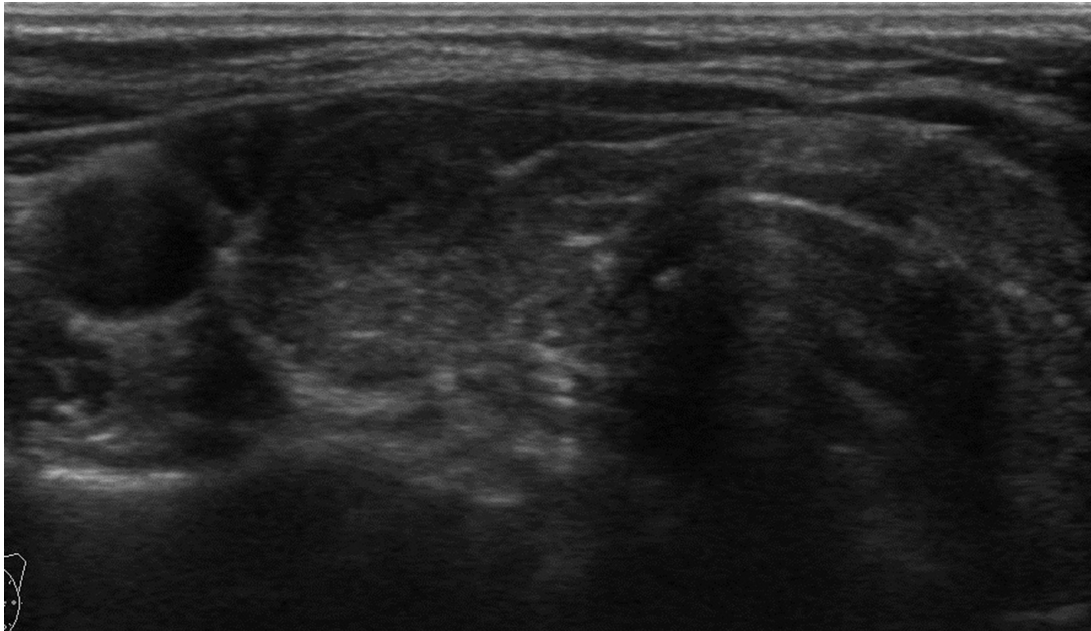


Figure 1. Exophytic nodule is located on the anterior surface of the right lobe of the thyroid gland in the neighborhood of carotid.

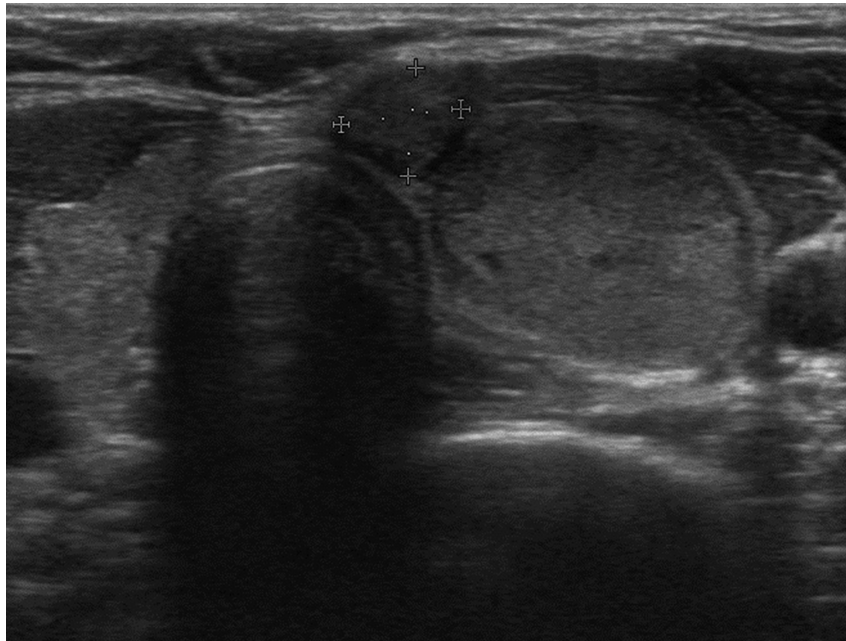


Figure 2. Expansile nodule is located in the left lobe of thyroid gland. Istmic nodule is seen in medial neighborhood of expansile nodule.

3.5. Histopathology

Total/near total thyroidectomy or lobectomy was performed depending on the size and/or US features and/or cytopathological result of the nodule. Postoperative

histopathologic findings were classified as benign and malignant. In malignant nodules, tumor type, size and histopathological features such as multicentricity, vascular invasion, capsular invasion, extracapsular extension

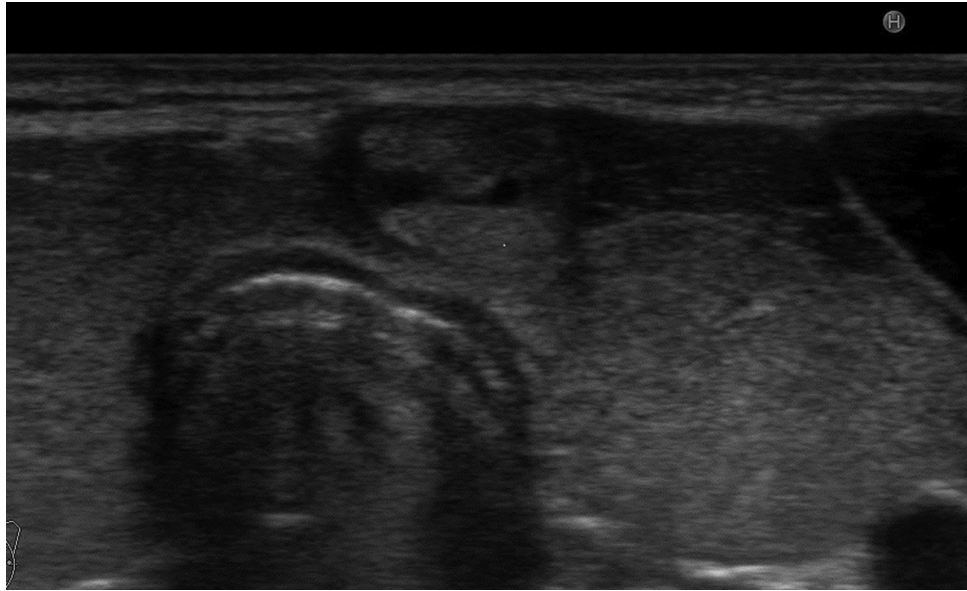


Figure 3. Isthmic nodule

and lymph node metastasis were noted. Rates of malignancy were determined in exophytic and non-exophytic nodules. In addition, histopathological features of malignant exophytic and non-exophytic thyroid nodules were compared.

3.6. Statistical Analysis

All data were analyzed with SPSS Statistics for Windows, version 21.0 (Armonk, NY: IBM Corp, 2012). Descriptive analysis were presented as mean \pm standard deviation for non-categorical and as number of cases and percentage for categorical variables. Noncategorical variables were compared by Student's t test and categorical variables were compared by Chi-square test. The effect of the clinically related factors with malignancy were examined by the univariate binary logistic regression analysis. The multivariate model was constructed by using significant factors determined by the univariate analysis. The odds ratio (OR) and the 95% confidence of the OR were determined. Forward likelihood ratio was used as the variable selection method. A P value < 0.05 was accepted to indicate statistical significance.

4. Results

4.1. Clinical Features and Hormonal Status

A total of 5250 patients were evaluated by US during the study period in our clinic. Exophytic nodule was detected in 273 patients and seven patients had multiple exo-

phytic nodules. Twenty-five patients with a history of thyroidectomy and one with a history of radiotherapy to the head and neck region were excluded from the study. Data of 247 patients with exophytic and 357 patients with non-exophytic thyroid nodules were included in the analysis. Mean age and sex were similar in the two groups ($P = 0.826$ and $P = 0.508$, respectively). There were no differences in terms of thyroid functional status, anti-TPO and anti-Ig positivity between groups (Table 1).

4.2. Ultrasonography Features

There were 253 exophytic nodules in 247 patients and 529 non-exophytic nodules in 357 patients (Table 2). Mean nodule number and incidence of ultrasonographically detected chronic thyroiditis were significantly higher in the exophytic group compared to controls ($P < 0.001$ for each). Mean nodule diameter and rate of taller than wide nodules were similar in two groups ($P = 0.603$ and $P = 0.164$, respectively). Absence of peripheral halo was observed with a significantly higher rate in exophytic nodules compared to non-exophytic ones ($P = 0.018$). Microcalcification, marginal regularity and vascularity did not differ between groups ($P = 0.085$, $P = 0.280$ and $P = 0.265$, respectively). Macrocalcification was present in 30 (11.9%) of exophytic and 121 (22.9%) of non-exophytic nodules ($P < 0.001$). Hundred twenty four (49.4%) of exophytic and 192 (36.7%) of non-exophytic nodules were hypoechoic ($P < 0.001$). Solid texture was found with a lower and mixed texture was

Table 1. Clinical Features of Patients with Exophytic and Non-Exophytic Nodules^a

	Exophytic (n = 247)	Non-Exophytic (n = 357)	P Value
Age	48.21 ± 12.1	48.43 ± 12.18	0.826
Gender			0.508
Female	211 (85.4)	297 (83.4)	
Male	36 (14.6)	59 (16.6)	
Function			0.325
Euthyroid	195 (78.9)	263 (73.7)	
Hypothyroid	29 (11.7)	51 (14.3)	
Hyperthyroid	23 (9.3)	43 (12.0)	
Anti-TPO positivity	68 (27.5)	113 (31.6)	0.308
Anti-TG positivity	68 (27.5)	115 (32.2)	0.587
Ultrasonographically chronic thyroiditis	151 (61.1)	147 (41.2)	< 0.001
Nodule number	4.98 ± 3.71	3.75 ± 2.57	< 0.001

Abbreviations: anti-TG, anti-thyroglobulin antibody; anti-TPO, anti-thyroid peroxidase antibody.

^aValues are expressed as mean ± SD or No (%).

found with a higher rate in exophytic nodules compared to nonexophytic ones ($P = 0.001$).

4.3. Cytological Results

There was statistically significant difference in cytology results between exophytic and non-exophytic nodules ($P < 0.001$) (Table 2). Benign cytology was observed in 156 (61.7%) of exophytic and 468 (88.5%) of non-exophytic nodules ($P < 0.001$). Nondiagnostic, AUS/FLUS and suspicious for malignancy cytologies were higher in exophytic nodules ($P = 0.002$, $P < 0.001$ and $P < 0.001$ respectively). Seventeen (6.7%) of exophytic and 10 (1.9%) of non-exophytic nodules were cytologically malignant ($P = 0.001$).

4.4. Histopathological Results

Seventy three (28.9%) exophytic nodules in 73 patients and 74 (13.9%) non-exophytic nodules in 47 controls were operated. Rate of thyroidectomy was significantly higher in the exophytic group ($P < 0.001$) (Table 2). Histopathologically, there was no significant difference in the presence of chronic thyroiditis between exophytic and non-exophytic nodules ($P = 0.429$). 35 (47.9%) of 73 exophytic nodules and 18 (24.3%) of 74 non-exophytic nodules were malignant ($P < 0.01$) (Table 2).

Histopathological features were available in 28 exophytic and 14 non-exophytic malignant nodules. The most common type of thyroid cancer in the two groups was papillary thyroid cancer (PTC). All malignant non-exophytic nodules were PTC, while among 28 malignant exophytic nodules, 23 were PTC, two were follicular thyroid cancer (FTC) and three were thyroid tumors of uncertain malignant potential (TT-UMP). There were no statistically significant differences between the two groups in terms of can-

cer type ($P = 0.242$). Capsular invasion was higher in exophytic group compared to non-exophytic group (53.5%, vs 14.3%, $P = 0.027$). There were no significant differences in terms of tumor size, vascular invasion, multicentricity, extracapsular extension, lymph node metastasis and presence of histopathological thyroiditis between two groups (Table 3).

4.5. Univariate and Multivariate Analysis of Ultrasonography Features

Univariate logistic regression analysis was made including all nodules with histopathological diagnosis. Exophytic appearance increased the likelihood of malignancy by 5.10 times (95% CI: 2.287 - 11.371; $P < 0.001$). Thyroid malignancy was significantly associated with microcalcification (OR = 2.598, 95% CI: 1.160 - 5.823), taller than wider shape (OR = 3.602, 95% CI: 1.624 - 7.999), hypoechoogenicity (OR = 6.303, 95% CI: 2.506 - 15.855), solid texture (OR = 3.045, 95% CI: 1.133 - 8.183), and irregular margins (OR = 2.750, 95% CI: 1.028 - 7.359) (Table 4).

Multivariate logistic regression analysis was performed with the significant predictors in the univariate analysis. Exophytic appearance (OR = 6.853, 95% CI: 2.843 - 16.518), microcalcification (OR = 3.759, 95% CI: 1.497 - 9.439), taller than wider shape (OR = 4.629, 95% CI: 1.815 - 11.809), hypoechoogenicity (OR = 5.670, 95% CI: 2.156 - 14.915), solid texture (OR = 4.886, 95% CI: 1.667 - 14.316) and irregular margins (OR = 3.445, 95% CI: 1.164 - 10.19316) were still associated with malignancy (Table 4).

4.6. Clinical and Ultrasonography Features of Benign and Malignant Exophytic Nodules

We compared clinical and US features of histopathologically confirmed benign and malignant exophytic nod-

Table 2. Ultrasonography Features, Fine Needle Aspiration Biopsy and Histopathology Results in Exophytic and Non-Exophytic Nodules^a

	Exophytic (n = 253)	Non-Exophytic (n = 529)	P Value
Diameter, mm, (mean ± SD)	15.56 ± 7.00	15.90 ± 8.95	0.603
Localization			0.517
Right	133 (52.6)	265 (50.9)	
Left	120 (47.4)	264 (49.1)	
Taller than Wider shape	50 (19.8)	82 (15.5)	0.164
Absence of peripheral halo	180 (71.1)	331 (62.6)	0.018
Microcalcification	200 (79.1)	432 (81.7)	0.085
Macrocalcification	30 (11.9)	121 (22.9)	< 0.001
Echogenity			< 0.001
Hypochoic	124 (49.4)	192 (36.7)	
Isochoic	127 (50.6)	319 (61)	
Hyperechoic	0	12 (2.3)	
Texture			0.001
Solid	122 (48.2)	326 (61.6)	
Cystic	13 (5.2)	16 (3.1)	
Mixed	118 (46.6)	187 (35.3)	
Irregular margins	153 (60.5)	341 (64.5)	0.280
Vascularity			0.265
Peripheral	107 (42.2)	220 (41.6)	
Central	6 (2.4)	5 (0.9)	
Peripheral and central	46 (18.2)	54 (10.3)	
Absent	94 (37.2)	250 (47.2)	
Cytology			< 0.001
Nondiagnostic	34 (13.4)	36 (6.8)	
Benign	156 (61.7)	468 (88.5)	
AUS/FLUS	30 (11.9)	8 (1.5)	
FN/suspicious of FN	0	1 (0.2)	
Suspicious for malignancy	16 (6.3)	6 (1.1)	
Malignant	17 (6.7)	10 (1.9)	
Surgery	73 (28.9)	74 (14.0)	< 0.001
Histopathology	N = 73	N = 74	0.01
Benign	38 (52.1)	56 (75.7)	
Malignant	35 (47.9)	18 (24.3)	
Histopathologically chronic thyroiditis	N = 73	N = 74	0.429
	26 (35.6)	21 (28.4)	

Abbreviations: AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN, follicular neoplasm.

^aValues are expressed as No (%).

ules (Table 5). There were 38 (52.1%) benign and 35 (47.9%) malignant exophytic nodule. Thyroid functional status and anti-TPO positivity were similar and anti-Tg positivity was significantly higher in malignant exophytic nodules ($p = 0.071$, $p = 0.876$ and $P = 0.045$, respectively). Ultrasonographically, mean nodule diameter was 19.00 ± 8.46 mm in benign and 14.67 ± 6.95 mm in malignant exophytic nodules ($P = 0.020$). Hypochoic pattern was ob-

served with a significantly higher rate in malignant nodules compared to benign ones (74.3% vs 47.4%, $P = 0.019$). There were no significant differences in terms of taller than wide appearance, absence of peripheral halo, texture and marginal irregularity between benign and malignant exophytic nodules.

Table 3. Histopathological Features of Malignant Exophytic and Non-Exophytic Thyroid Nodules^a

	Exophytic (n = 28)	Non-Exophytic (n = 14)	P Value
Tumor diameter, mm, (mean ± SD)	10.31 ± 6.25	10.75 ± 5.88	0.810
Microcarcinoma	11 (39.3)	7 (50.0)	0.555
Variant and type			0.242
PTC	23 (82.1)	14 (100)	
FTC	2 (7.1)	0	
TT-UMP	3 (10.8)	0	
Vascular invasion	6 (21.5)	0	0.076
Capsular invasion	15 (53.5)	2 (14.3)	0.027
Extracapsular extension	8 (28.6)	2 (14.3)	0.426
Multicentricity	12 (42.9)	8 (57.1)	0.382
Lymph node metastasis	1 (3.6)	0	0.499
Thyroiditis	8 (28.5)	2 (14.2)	0.189

Abbreviations: FTC, Follicular thyroid cancer; PTC, Papillary thyroid cancer; TT-UMP, Thyroid tumors of uncertain malignant potential.

^aValues are expressed as No (%).

Table 4. Univariate and Multivariate Logistic Regression Analyses of Ultrasonography Features in Prediction of Malignancy in Thyroid Nodules

Factors	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	% 95 CI	P Value	Odds Ratio	% 95 CI	P Value
Exophytic	5.100	2.287 - 11.371	< 0.001	6.853	2.843 - 16.518	< 0.001
Taller than Wider shape	3.602	1.624 - 7.999	0.002	4.629	1.815 - 11.809	0.001
Absence of peripheral halo	2.569	0.960 - 6.875	0.060	-	-	-
Microcalcification	2.598	1.160 - 5.823	0.020	3.759	1.497 - 9.439	0.005
Echogenity (Hypo vs.Isoec)	6.303	2.506 - 15.855	< 0.001	5.670	2.156 - 14.915	< 0.001
Texture						
Mixed. Vs. Solid	3.045	1.133 - 8.183	0.027	4.886	1.667 - 14.316	0.004
Cystic vs. Mixed	0.435	0.049 - 3.888	0.456	0.321	0.031 - 3.346	0.342
Irregular Margins	2.750	1.028 - 7.359	0.044	3.445	1.164 - 10.193	0.025
Vascularity	-	-	0.311	-	-	-

5. Discussion

We found both cytologically and histopathologically higher rates of malignancy in exophytic nodules compared to non-exophytic ones. In addition, benign cytology was obtained only in 61.7% of exophytic nodules and nearly one third revealed indeterminate (nondiagnostic or AUS/FLUS or suspicious for malignancy) cytology. There are some US features of thyroid nodules well-known to be predictive for malignancy. These are presence of microcalcification, hypoechogenity, enhanced nodular vascularization, irregular borders, anteroposterior diameter greater than transverse diameter and elastosonographi-

cally increased strain index (3, 9). Although these features were extensively studied previously, exophytic configuration was rarely assessed as an US feature in studies of thyroid nodules. With univariate and multivariate analysis, we showed that in addition to taller than wider shape, microcalcification, hypoechogenity, solid texture and irregular margins, exophytic appearance was also associated with malignancy. To the best of our knowledge, this is the first study to evaluate clinical and US features and malignancy rate in exophytic thyroid nodules.

Although it is rare for thyroid, studies assessing exophytic growth pattern in non-thyroidal tumors are available in the literature. Only one study evaluated exophytic

Table 5. Clinical and Ultrasonography Features of Benign and Malignant Exophytic Nodules^a

	Benign (n = 38)	Malignant (n = 35)	P Value
Function			0.071
Euthyroid	23 (60.5)	29 (82.9)	
Hypothyroid	6 (15.8)	1 (2.9)	
Hyperthyroid	9 (23.7)	5 (14.3)	
Anti-TPO positivity	11 (28.9)	11 (31.4)	0.876
Anti-TG positivity	6 (15.8)	13 (37.1)	0.045
Nodule diameter, mm, (mean ± SD)	19.00 ± 8.46	14.67 ± 6.95	0.020
Ultrasonographically chronic thyroiditis	21 (55.3)	18 (51.4)	0.743
Localization			0.472
Right	22 (57.9)	19 (54.3)	
Left	16 (42.1)	16 (45.7)	
Taller than Wider shape	10 (26.3)	11 (31.4)	0.630
Absence of peripheral halo	30 (78.9)	29 (82.9)	0.672
Microcalcification	13 (34.2)	8 (22.9)	0.284
Macrocalcification	6 (15.8)	3 (8.6)	0.349
Echogenity			0.019
Hypochoic	18 (47.4)	26 (74.3)	
Isochoic	20 (52.6)	9 (25.7)	
Texture			0.991
Solid	17 (44.7)	16 (45.7)	
Cystic	19 (50.0)	17 (48.6)	
Mixed	2 (5.3)	2 (5.7)	
Irregular margins	25 (65.8)	28 (80.0)	0.174

Abbreviations: anti-TG, anti-thyroglobulin antibody; anti-TPO, anti-thyroid peroxidase antibody.

^aValues are expressed as No (%).

feature of thyroid nodules (5). Computerized tomography of the neck was used as the imaging method in that study and exophytic feature was observed in 6.0% of malignant and 2.2% of benign nodules. Although exophytic feature was three times more often in malignant nodules the difference did not reach statistical significance. In our study, malignancy rate was cytologically nearly 3.5 times and histopathologically nearly two times higher in exophytic nodules and the differences were statistically significant. Rate of nondiagnostic cytology was also higher in exophytic nodules. This may be related with technical difficulties due to localization and protrusion of these nodules from thyroid capsule. Additionally, AUS/FLUS and suspicious for malignancy cytologies which carry 5% - 15% and 60% - 75% risk of malignancy, respectively, were observed with significantly higher rates in exophytic group than non-exophytic group.

Hypoechoicity and absence of halo which are known to be associated with malignancy were seen with higher rates in exophytic nodules in our study. Since we showed higher rates of cytologically and histopathologically malignancy in exophytic nodules, this result was not surprising. Additionally, lower rate of macrocalcification in exophytic group which is suggested to be in favor of benign histopathology supports this finding. However, microcalcification and marginal irregularity which are associated with malignancy were similar in exophytic and non-exophytic groups. Solid consistency is more common in malignant thyroid nodules and the vast majority (82% - 91%) of thyroid cancers are solid (10-12). In a study including 360 consecutively surgically removed thyroid cancers, 88% were reported to be solid or minimally cystic (13). It is suggested that malignancy rate is higher in predominantly solid than mixed solid/cystic nodules, while cystic

or spongiform ones have the lowest rate among all nodules (14). There was significant difference in texture of exophytic and non-exophytic nodules in our study and mixed texture was higher in exophytic nodules (46.6% vs 35.3%).

Prognosis and aggressiveness in exophytic configuration of different non-thyroidal tumors are controversial. Association of exophytic appearance and prognostic histopathological features has not been evaluated in thyroid malignancies previously. In our study, capsular invasion was seen with a significantly higher rate in exophytic compared to non-exophytic thyroid cancer, however there were no differences in terms of vascular invasion, extracapsular extension and lymph node metastasis. Hypothetically, exophytic nodules might have a more aggressive behaviour and exophytic appearance in US might represent capsular invasion of tumor microscopically. Gkountouvas et al. reported a case with an exophytic and ulcerated recurrence of papillary thyroid carcinoma infiltrating adjacent vital organs and skin (15).

When we compared histopathologically benign and malignant exophytic nodules, we found higher rate of anti-Tg positivity in malignant nodules, however anti-TPO positivity was similar in both. This finding was concordant with the literature which reported higher anti-TG positivity in patients with PTC compared to the general population suggesting that it is associated with increased risk for malignancy (16-18). Also, anti-TPO positivity was presented to have a protective role against thyroid cancer (19). In a recent study, TPO expression was detected to be increased in benign lesions compared to malignant ones (20). Hypoechoicogeny which is a feature known to be associated with malignancy was observed with higher rate in malignant than benign exophytic nodules also in our study. However, taller than wide appearance, absence of peripheral halo, microcalcification, solid texture and marginal irregularity which are believed to be suggestive for malignancy were similar in malignant and benign exophytic nodules. These features seem to lose their predictive role for malignancy in exophytic nodules. However, it is difficult to come to such a conclusion with this preliminary study.

We evaluated a large number of exophytic thyroid nodules in our study, however a limited number of patients were operated and malignancy was detected in 35 (47.9%) of them. Low number of malignant cases might be considered as a limitation. Another limitation of the present study was lack of data on prognosis, overall survival and follow-up in patients with thyroid cancer. However, our aim was to determine malignancy rate in exophytic nodules and further studies can be conducted to find out whether exophytic feature is associated with poor prognosis or not.

In conclusion, cytologically and histopathologically

malignancy rates were significantly higher in exophytic nodules compared to non-exophytic ones. Although positive anti-Tg antibodies and hypoechoic appearance seem to be associated with malignancy in exophytic nodules, many other US features known to be predictive for malignancy were not higher in malignant compared to benign exophytic nodules.

Footnotes

Authors' Contributions: Study concept and design, and collection of data: Fatma Dilek Dellal, Didem Ozdemir, and Dilek Arpaci; acquisition of data: Fatma Dilek Dellal, Dilek Arpaci, Husniye Baser, and Abbas Ali Tam; writing of the manuscript: Fatma Dilek Dellal, and Didem Ozdemir; revision for content and English language: Didem Ozdemir, Reyhan Ersoy, and Bekir Cakir; statistical analysis: Fatma Dilek Dellal, and Didem Ozdemir; administrative, technical, and material support: Husniye Baser, Dilek Arpaci, Abbas Ali Tam, Aydan Kilicarslan, and Ersin Gurkan Dumlu; study supervision: Reyhan Ersoy, and Bekir Cakir

Financial Disclosure: The authors declare that they have no financial interests related to the material in the manuscript.

Funding/Support: This study was not supported by any grant.

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