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Original Article

Diagnostic accuracy of ultrasonographic features for benign and malignant thyroid nodules smaller than 10 mm

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Abstract: Objectives: To evaluate benign and malignant thyroid nodules ≤ 1 cm according to ultrasonographic (US) features before surgery. Methods: Thyroid nodules 1-10 mm were evaluated in 600 patients. The US features in benign and malignant nodules were compared, and the odds ratios of the suspicious US features were determined with univariate and multivariate analyses. Diagnostic specifications such as sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and the area under the receiver operating characteristic curve value were calculated to evaluate the value of these US features. Results: Echogenicity, composition, height and width, margin, shape, capsule, calcification, and number were significantly different between benign and malignant nodules, whereas vascularity was not significantly different. Multivariate logistic regression analysis showed that solidity, taller than wide, irregularity, microcalcification, and multifocality were independent features in predicting malignant thyroid lesions. Irregularity had the highest sensitivity in all the independent features and solid composition was the most specific, although still at a low rate (only 69.1%). The sensitivity improved when two features were combined. Conclusions: Our study recommended that US features of solidity, taller than wide, irregular, microcalcification, and multifocality were useful sonographic criteria for differentiating malignant thyroid nodules ≤ 1 cm from benign ones. A combination of at least two of these characteristics can increase the diagnostic value for thyroid nodules.

Keywords: Ultrasonographic features, subcentimeter thyroid nodules, diagnostic accuracy

Introduction

Papillary thyroid carcinoma (PTC), the most common malignant thyroid neoplasm, accounts for 80% of all thyroid cancers [1, 2]. Papillary thyroid microcarcinoma (PTMC) is defined as a thyroid cancer measuring ≤ 1.0 cm in its greatest dimension, according to the World Health Organization classification system. The proportion of PTMCs was reportedly approximately 30% of all papillary thyroid cancer [3-5]. PTMC cases are often treated differently, as many of their characteristics are different from those of large PTCs. The treatment aspects such as surgical approach, risk of recurrence, and prognosis differ among both types.

With the increasing detection of thyroid nodules by using high-resolution ultrasound, the rate of detection of asymptomatic thyroid cancers, especially papillary thyroid cancer and PTMCs, has increased. Various recent studies have focused on ultrasonographic (US) features in the diagnosis of benign and malignant thyroid nodules. However, few studies exist regarding the US characteristics of thyroid nodules ≤ 1 cm. As mentioned previously, there are many differences between PTMCs and PTC ≥ 1 cm, so it is vital to independently evaluate the US features in the diagnosis of benign and malignant thyroid nodules ≤ 1 cm.

Table 1. The basic characteristics and ultrasound features for the thyroid nodules

Characteristics and Features	Malignant (n = 356)	Benign (n = 244)	P
Age (years)			0.351
≥ 45	192	141	
< 45	164	103	
Sex			0.210
Female	296	193	
Male	60	51	
Body mass index			0.740
BMI < 18.5	19	17	
18.5 ≤ BMI < 25	249	172	
25 ≤ BMI < 30	81	52	
BMI ≥ 30	7	3	
Echogenicity			< 0.001
Hypoechoic	339	172	
Isoechoic	11	60	
Hyperechoic	6	12	
Composition			< 0.001
Cystic > 50%	1	16	
Predominantly solid	54	102	
Solid	301	121	
Spongiform	0	5	
Taller and wide			< 0.001
Oval to round	201	220	
Taller than wide	155	24	
Boundary			< 0.001
Well defined	143	193	
Poorly defined	213	51	
Shape			< 0.001
Regular	169	218	
Irregular	187	26	
Capsule			< 0.001
Complete	302	237	
Incomplete	54	7	
Vascularity			0.371
Negative	71	60	
Peripheral	52	36	
Central	190	114	
Both	43	34	
Calcication			< 0.001
No calcification	123	112	
Macrocalcification	11	53	
Microcalcication	222	79	
Number			< 0.001
Solitary	232	218	
Multifocality	124	26	

Additionally, fine-needle aspiration biopsy (FNAB) is considered to be one of the best approaches to achieve diagnostic accuracy for thyroid nodules; however, its efficacy in diagnosing thyroid nodules ≤ 1 cm is still speculated [6-8]. Based on these two reasons, our study focused on the diagnostic accuracy of US features for thyroid nodules ≤ 1 cm to detect PTMCs effectively.

Methods and materials

Patients

Our study included thyroid nodules ≤ 10 mm in maximum diameter in 600 patients who underwent conventional ultrasonography examinations of the thyroid gland before surgery in Union hospital from January 2012 to July 2015. Our study was approved by the Ethics Committee of our hospital and written informed consent was obtained from each patient before the US examination.

All patients evaluated in the study underwent thyroid surgery for nodules. Patients who had nodules ≥ 10 mm were excluded. If a patient had multiple nodules, each nodule was evaluated.

Ultrasonography evaluation

All conventional US examinations were performed by two independent ultrasound physicians with an Acuson S2000 diagnostic ultrasound system (Siemens Medical Solutions). Patients were examined in the supine position with a fully exposed neck.

Statistical analysis

Initial clinical and pathological data were collected by using EpiData Software v3.1 (EpiData Association, Odense, Denmark). All statistical analyses were performed by SPSS software, version 13.0 (SPSS, Chicago, IL), and a two-tailed *P*-value of less than 0.05 was considered as statistically significant.

Comparisons of frequency distributions were performed with a χ^2 test. Multivariate logistic regression analysis was performed to determine independent sonographic predictors malignant from the US characteristics that showed

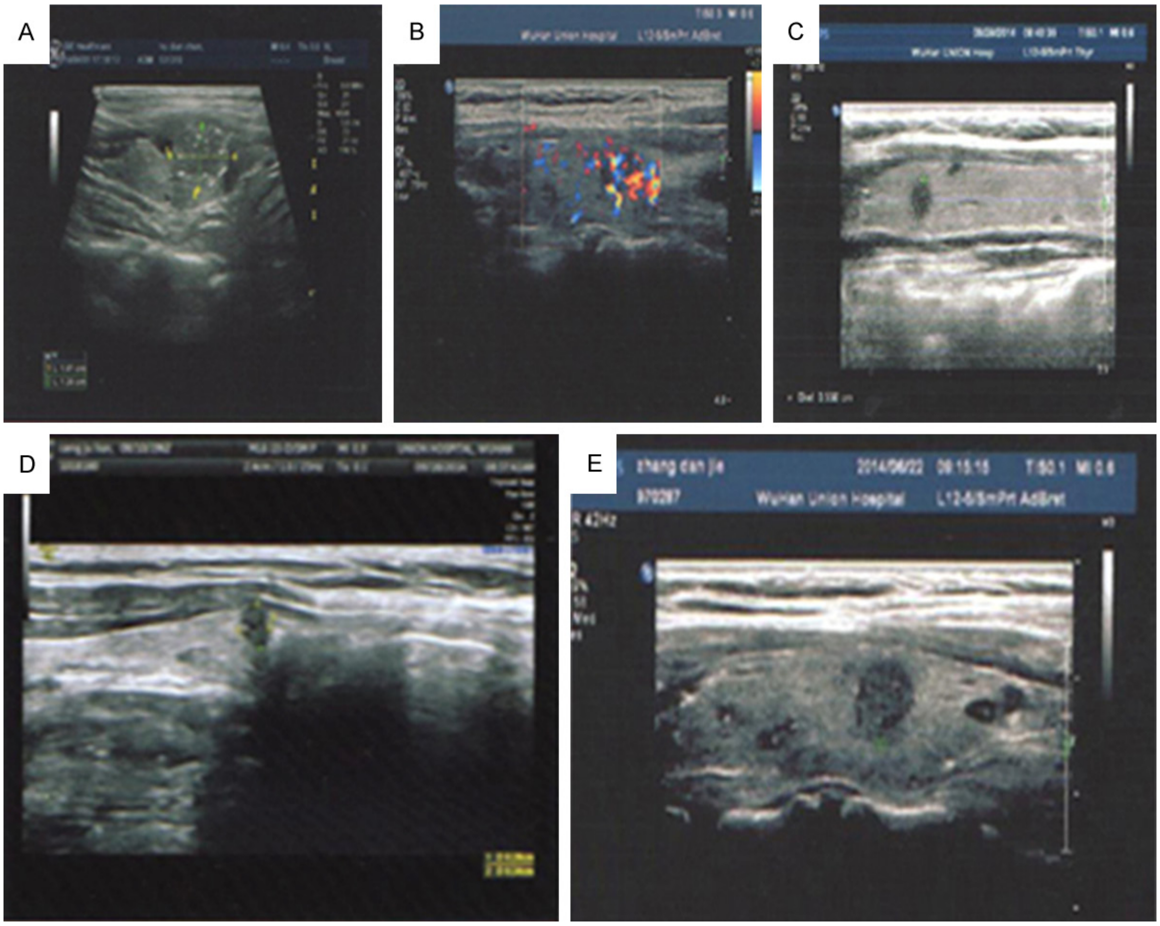

Figure 1. Ultrasonographic features of thyroid nodules. A. Ultrasonography showed thyroid nodule with microcalcication inside. B. Ultrasonography showed thyroid nodule with central vascularity. C. Ultrasonography showed thyroid nodule with solid composition, hypoechoic echogenicity, Taller than wide, poorly defined boundary and irregular shape. D. Ultrasonography showed thyroid nodule with incomplete capsule. E. Ultrasonography showed thyroid nodule with multifocality.

Table 2. Multivariate analysis of the features suggestive of malignant thyroid nodules

Pathological category	Multivariate analysis		
	P	HR	95% CI
Hypoechoic	0.123	2.382	0.790-7.183
Solid	< 0.001	3.059	1.861-5.029
Taller than wide	0.021	1.958	1.106-3.465
Poorly defined boundary	0.150	1.440	0.877-2.364
Irregular	< 0.001	3.769	2.192-6.481
Incomplete capsule	0.148	1.998	0.783-5.103
Microcalcication	< 0.001	6.882	3.097-15.292
Multifocality	0.005	2.299	1.290-4.096

statistical significance. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for each US characteristic suspicious for malignancy were calculated. The diagnostic accuracy of predictions of malignancy was calculated with receiver operating characteristic (ROC) analysis.

Results

According to histopathologic examination after thyroid surgery or FNAB, out of the 600 patients, 244 were benign, and 356 were malignant.

The sonographic characteristics of these thyroid nodules are shown in **Table 1** and **Figure 1**. Echogenicity, composition, height and width, margins, shape, capsule, calcification, and number were significantly different between benign and malignant nodules. Vascularity was not significantly different between benign and malignant nodules. Compared with benign nodules, malignant nodules were more frequently

Table 3. Predictive value of US features in thyroid lesions

US features	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %	AUC	Youden index
Solid	71.3	69.1	84.6	50.4	70.7	0.542	0.404
Taller than wide	86.6	52.3	43.5	90.2	62.5	0.709	0.389
Irregular	87.8	52.3	52.5	89.3	67.5	0.650	0.401
Microcalcication	73.8	55.2	62.4	67.6	64.5	0.669	0.290
Multifocality	82.7	48.4	34.8	89.3	57.0	0.621	0.311

hypoechoic (95.2% vs. 70.5%), solid (84.6% vs. 49.6%), had taller than wide (43.5% vs. 9.8%), were poorly defined boundaries (59.8% vs. 20.9%), irregular (52.5% vs. 10.7%), incomplete capsule (15.2% vs. 2.9%), and showed microcalcification (62.4% vs. 32.4%) and multifocality (34.8% vs. 10.7%; $P < 0.001$). In the color Doppler sonographic features, the frequency of central Vascularity had no significant difference between benign and malignant nodules (65.4% vs. 60.7%; $P = 0.371$).

The results of multivariate logistic regression analysis of the features suggestive of malignant thyroid nodules are shown in **Table 2**. Five criteria (solidity, taller than wide, irregularity, microcalcification, multifocality) showed a significant association with malignant nodules ($P < 0.05$).

And other three features (Hypoechoic, poorly defined boundary and incomplete capsule) were turn out to not be independent factors to detect malignant thyroid nodules (P = 0.123, 0.150, 0.148; respectively).

The sensitivity, specificity, PPV, NPV, and diagnostic accuracy of the useful sonographic features are shown in **Table 3**. We see that irregularity showed the highest sensitivity in all the independent features, and solid composition was the most specific, although still at a low rate (69.1%). Conversely, solid composition was the most accurate feature, with 70.7% accuracy. The sensitivity, specificity, PPV, NPV, and diagnostic accuracy of two useful US features are shown in **Table 4**. The sensitivity was mostly improved when two features were combined. For example, when taller than wide was combined with irregular shape, the sensitivity reached 91.2%. The receiver operating characteristic curve for the irregularity feature is seen in **Figure 2**, optimal cut-off value (sensitivity, 0.878; 1-specificity, 0.437).

Discussion

The detection of thyroid nodules has increased with the use of high-resolution ultrasound. FNAB, although an excellent diagnostic tool for thyroid nodules, has limited application in nodules ≤ 1 cm. Therefore, the use of US features to detect the properties of thyroid nodules is necessary to evaluate the risk of thyroid foci before surgery.

In our current study, we evaluated the US features such as echogenicity, composition, height and width, boundary, shape, capsule, vascularity, calcification, and number of foci. We found that hypoechoicity, solidity, taller than wide, poorly defined boundaries, irregularity, incomplete capsule, microcalcification, and multifocality enabled differential diagnosis between benign and malignant thyroid nodules with maximum diameters ≤ 1 cm, whereas vascularity did not enable differentiation. The above mentioned characteristics are therefore independent factors implying malignant lesions for subcentimeter thyroid nodules.

Low degree of differentiation in cancer cells, fewer interstitial components, and good sound transmission in the tumor may be correlated with the hypoechoic nature of nodules. However, echogenicity may change with nodule growth as blood vessels and fibrous tissue undergo hyperplasia [9]. In the current study, echogenicity was significantly different between benign and malignant nodules, which is similar to the results seen in most current studies [10].

Frantes et al. reported that predominantly solid composition of nodules was associated with an increased risk of thyroid carcinoma [11]. Zhang et al. demonstrated that solid composition did not cause significant differences in benign and malignant nodules; however, cystic or spongiform composition was always seen in benign thyroid nodules [12]. In our study, however, solid composition was an independent characteristic for diagnosing malignant lesions.

Taller than wide was suggested as a significant US characteristic to distinguish benign and

Table 4. Predictive value of two US features in thyroid nodules

US features	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %	AUC	Youden index
Solid* Taller than wide	87.3	51.4	40.7	91.4	61.7	0.656	0.387
Solid* Irregular	89.1	54.8	48.3	91.4	65.8	0.698	0.439
Solid* Microcalcication	82.8	56.1	55.3	83.2	66.7	0.693	0.389
Solid* Multifocality	86.4	47.3	28.7	93.4	55.0	0.611	0.337
Taller than wide* Irregular	91.2	60.5	40.2	95.5	56.2	0.681	0.517
Taller than wide* Microcalcication	89.5	47.1	36.7	95.5	54.5	0.611	0.366
Taller than wide* Multifocality	88.3	44.9	19.1	96.3	50.5	0.577	0.332
Irregular* Microcalcication	88.5	49.5	34.5	93.4	58.5	0.640	0.380
Irregular* Multifocality	86.1	44.3	17.4	95.5	49.3	0.567	0.304
Microcalcication* Multifocality	88.4	49.5	34.6	93.4	58.5	0.640	0.379

*: with.

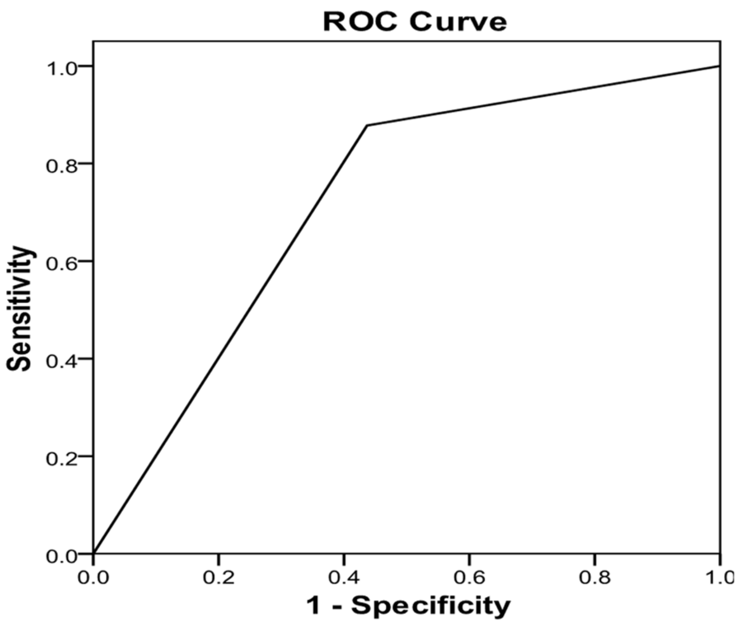

Figure 2. Receiver operating characteristic curve for the Irregular features.

malignant thyroid lesions by Popowicz et al. [13]. A height-to-width ratio ≥ 1 was a very sensitive factor for differential diagnosis in lesions < 1.5 cm than in nodules > 1.5 cm. Taller than wide represents a typical growth pattern of malignant thyroid lesions that often grow longitudinally. In our study, taller than wide was the second most sensitive feature (86.6%) for diagnosing malignant thyroid nodules. Therefore, taller than wide is a very useful US feature for clinicians to decide whether patients need radical management, such as thyroidectomy, when they are evaluated.

Irregular margins and incomplete capsule have been poor features for thyroid carcinoma in histopathology; they predict a poor prognosis [14, 15]; they are typical US characteristics seen in most studies [16-19]. In our study, irregular margin and incomplete capsule were both significantly different in benign and malignant thyroid nodules, although only irregular margin was an independent factor in multivariate analysis.

Microcalcifications reportedly result from growth of autocrine tumor cells [20]; in ultrasound images, they may reflect psammoma bodies [21]. Coarse calcification, known as dystrophic calcification, may occur due to rapid growth of cancer cells, degeneration, tissue hyperplasia, and calcium deposition [10, 11, 22]. In our study, microcalcifications were observed in 62.6% of the PTMCs and 32.4% of the benign thyroid nodules. No calcification only accounted for 34.6% in PTMCs. On further analysis, microcalcifications combined with taller than wide was the most sensitive value for PTMCs.

Multiple nodules can occur in both benign nodules and thyroid microcarcinoma. When multiple foci are present in thyroid ultrasound, each focus should be evaluated independently. Especially, atypical nodules should not be ignored, since thyroid cancer foci may have polyclonal or monoclonal origin. Additionally, thyroid cancer foci may also merge with other benign thyroid lesions such as nodular goiter, Hashimoto's thyroiditis, and adenoma [15]. Interestingly, in our study, multifocality was not only a dependent US predicting factor for prognosis of malignant nodules, but also very sensitive when combined with microcalcifications.

We observed contradictory views regarding the value of vascularity for differentiating malignant and benign thyroid nodules [10]. Many current studies suggest that abundant vascularity, especially central vascularization, is more likely to indicate malignant lesions [10, 23]. However, in our study, central vascularization was seen to be a negative characteristic for diagnosis of subcentimeter thyroid carcinoma.

Our study has certain limitations. First, the sample size was not large enough, and only typical nodules, even among multiple nodules, were included. Second, nodules > 10 mm were not included for more analysis, as only subcentimeter lesions were analyzed. In addition, our current study only had qualitative analysis, whereas quantitative analysis should be used in future studies.

Conclusion

In conclusion, US features of solidity, taller than wide, irregularity, microcalcification, and multifocality were useful US criteria for differentiating malignant thyroid nodules ≤ 1 cm from benign ones. A combined analysis with two of these characteristics can increase their value for diagnosing thyroid nodules. Information about the probability of each US feature's association with malignancy would enable surgeons to reach a clinical decision of performing FNAB or surgery.

Disclosure of conflict of interest

None.

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