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Original Article

Intermediate High-Frequency Ultrasound in the Differential Diagnosis of Cystic-Solid Thyroid Nodules: A Retrospective Study

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Abstract:

Background: Thyroid nodules are a common clinical problem that has a steady increase in incidence rate over the last several decades. Cystic thyroid solid nodules usually have an indolent manifestation in ultrasonography. The ultrasound with an intermediate high-frequency range of 8-15 MHz, high resolution and appropriate penetration, has been widely used for superficial tissues examination. The aim of this study is to investigate the value of intermediate high-frequency ultrasound in the differential analysis of cystic-solid papillary thyroid cancer (PTC) and cystic nodular goiter changes.

Method: Retrospective analysis of the ultrasonographic features from 41 cases of cystic solid thyroid cancer (16 males and 25 females) and 95 cases of nodular thyroid cystic changes (20 males and 75 females) was carried out.

Results: In cystic-solid PTC, the solid parts were mostly distributed eccentrically and had some microcalcifications, the cystic interface was usually irregular. In cystic-solid nodular goiter, the solid parts were distributed symmetrically without microcalcification, and the cystic interface was mainly regulated. Above all, the differences in the morphology of the solid parts, microcalcification, and cystic interface between cystic papillary thyroid carcinoma and cystic nodular goiter were statistically significant ($P<0.05$). Furthermore, multi-factorial analysis revealed that age, microcalcification in the solid section, eccentric configuration of the solid section, and irregularity of the cyst-solid interface were independent risk factors for cystic PTC.

Conclusion: Cystic-solid PTC under intermediate high-frequency ultrasonography exhibits some definitive features, and a preoperative ultrasonography is helpful for the diagnosis of cystic-solid thyroid lesions.

Key words : Intermediate high-frequency ultrasound; Cystic-solid papillary thyroid cancer; Nodular goiter

Introduction

With the advance in ultrasonographic technologies, the incidence rate of thyroid nodule-related diseases has increased steadily in recent years. Ultrasonography has become an important tool for the evaluation of thyroid nodules, especially in the discrimination between benign and malignant lesions [1]. In the past, cystic-solid thyroid nodules were mostly considered benign lesions. The majority of them were degenerating from redundant or non-redundant changes, and patients had no obvious symptoms. Thus, follow-up care and monitoring were still taken after the examination. Previous studies on the Thyroid Imaging Reporting and Data System (TI-RADS) have paid great attention to solid nodules and

reported relevant ultrasonographic features correlated with thyroid cancer (TC). Cystic or cystic-solid nodules in the thyroid gland are classified as benign nodules based on the guidelines, so that all cystic and/or cystic-solid nodules distinguishable from the inner echo are classified as TI-RADS 3 [2-4]. However, some studies have suggested that 3.3%-17.6% of cystic-solid thyroid nodules deteriorate to malignancy, whereas cystic changes can be found in 10%-28% of papillary thyroid cancer (PTC) [5-9]. Due to some controversies in the ultrasonographic presentation of benign and malignant cystic-solid nodules, there is still a misdiagnosis risk, and patients with cystic-solid nodules are frequently underestimated and mis-treated [10]. Since there are scarce cases of cystic-solid TC in previous literature, assessing the ultrasound characteristics of cystic-solid TC and cystic-solid PTC is vital for early diagnosis that can make a better outcome and identification. In this study, we re-investigated the ultrasound manifestations of cystic-solid thyroid nodules on a large scale to identify the value of preoperative ultrasonography.

Material and Methods

Study Design

This retrospective study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Ethical approval was obtained from the Institutional review board, written informed consent was provided by all participants. Permission was obtained from the hospital for the review of patient medical records.

Between June 2018 and September 2022, one hundred and thirty-six patients (age range: 21-83 years) that had been screened out by ultrasound examination with cystic-solid thyroid nodules on ultrasonography in our institution were re-analyzed. Among these patients, forty-one patients (16 males and 25 females) with cystic-solid PTC and ninety-five patients (20 males and 75 females) with nodular goiter had a clear pathological result.

Equipment and Method

A color Doppler ultrasound device (GE logiq E9, USA) with intermediate high-frequency ultrasonic probe (frequency at 8-15 MHz) was used in this study. Patients took a supine position with their shoulders padded, tilted their heads backward to expose their necks completely, and then received a multi-section scan of thyroid glands. The location (upper pole, middle pole, lower pole or isthmus), shape (regular or irregular), margin (well-circumscribed or non-circumscribed), composition (solid when more than 50% of nodule is solid-liked or cystic when more than 50% of nodule is cystic liked), morphology of the solid section (eccentric or non-eccentric), echo of the solid section (hypoechoic or isoechoic) calcification (microcalcification, macrocalcification or no calcification), cystic-solid interface (regular or irregular), aspect ratio (>1 or <1), and blood flow (peripheral, central or mixed). Two senior ultrasonographers were assigned to re-evaluate each of the nodule, and then performed a joint ultrasonographic diagnosis. The ultrasonographic diagnosis was compared with pathological result.

Statistical Analysis

Statistical tests were conducted with SPSS 25.0 software. c2-test and t-test were used for group comparisons on categorical variables and measurement data, respectively. The data were presented as mean ± standard deviation (SD). P-values of <0.05 were considered as statistically significant. Univariate and multivariate analyses were performed to calculate the risk of malignancy among independent variables. Binary logistic regression analysis (by combining age, size, cystic or solid interface and morphology to generate a multifactorial logistic protocol) was performed using the forward likelihood ratio (LR) method. Potential variables included those parameters with a statistically significant difference in the univariate analysis. Models were assessed by the Hosmer-Lemeshow (goodness-of-fit statistic), if p>0.05 indicating a better model fitting and if p<0.05 indicating differences with statistically significant. All details are shown in Table 1.

Table 1. Overall summary of the dependent and independent variables

Variable	Original value	Internal value

Dependent variable		
Nodule	Cystic nodular goiter PTC (with cystic thyroid solid nodules)	0 1
Independent variable		
Age		
Morphology of the solid section	Eccentric spread Symmetric spread	0 1
Calcification of the solid section	No calcification Microcalcification Marcocalcification	0 1 2
Interface of cystic and solid section	Regular Irregular	0 1

Results

General information

The age of cystic-solid PTC patients ranged from 23 to 83 (mean=44.98, SD=13.43) years, and the age of nodular goiter patients ranged from 21 to 80 (mean=52.94, SD=12.23) years, with a statistically significant difference (p=0.02). Lesions in cystic-solid PTC group had a maximum diameter of 0.43-3.71 (mean=1.17, SD=0.71) cm, while 0.40-5.20 (mean=1.35, SD=0.98) cm in nodular goiter patients, but no significant difference was observed (p=0.24). All details are shown in Table 2.

Ultrasonographic characteristics

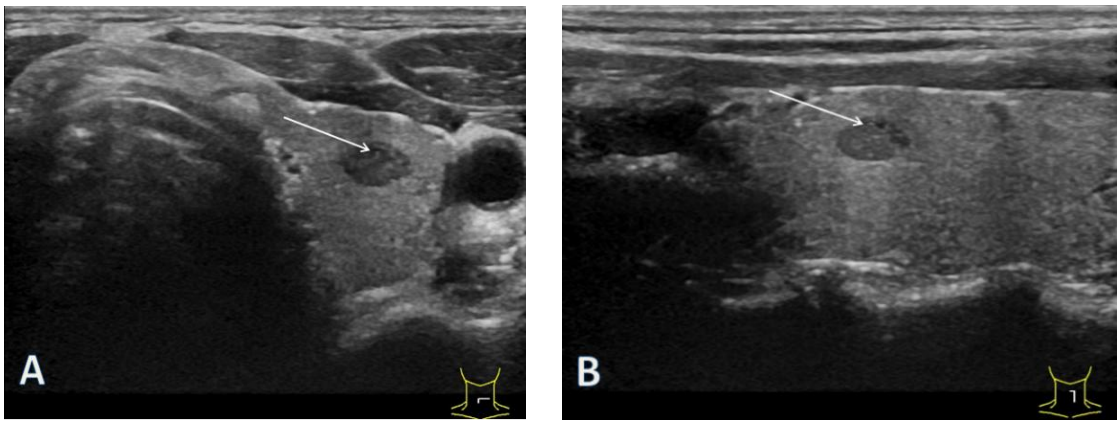
The solid part of cystic-solid PTC was mostly distributed in an eccentric manner (16/41) compared to cystic-solid goiter (10/95), accompanied with microcalcification and irregular interface (P<0.01). The solid portion of cystic-solid goiter was mostly distributed in a symmetric manner (85/95), without microcalcification (46/95), and the interface was dominantly regulated (70/95). We found that there were no significant differences in the boundary, morphology, composition, aspect ratio and blood flow of nodules between cystic-solid PTC and cystic nodular goiter. On the contrary, the differences in morphology, microcalcification and interface were statistically significant between the two types of thyroid nodules (p<0.05). All details are presented in Table 2 and Figures 1-4, which show a typical manifestation of ultrasound.

Table 2. Ultrasound findings of PTC and characteristics of cystic nodular goiter patients.

Ultrasound features	**PTC (with cystic thyroid solid nodules) （N=41）**	**Cystic nodular goiter （N=95）**	**P-value**
Age (years)	44.98±13.43 [e]	52.94±12.23[e]	0.02[*]
Median	45	52	
Range	23-83	21-80	
Sex			0.029[*]
Male	16	20	
Female	25	75	
Size (mm)	1.17±0.71 [e]	1.35±0.98 [e]	0.243
Margin			0.186
Well-circumscribed	35	88	
Non-circumscribed	6	7	
Morphology of nodules			0.492
Regular	36	87	
Irregular	5	8	

Composition			0.948
Cystic [a]	8	19	
Solid [b]	33	76	
Position of solid portion			＜0.01*
Eccentric	25	85	
Non-eccentric	16	10	
Echogenicity of solid portion			0.337
Isoechoic	10	31	
Hypoechoic	31	64	
Calcification of solid portion			＜0.01*
No calcification	3	46	
Microcalcification	37	38	
Macrocalcification	1	11	
Interface			＜0.01*
Regular	15	70	
Irregular	26	25	
A/T ratio [c]			
<1	38	91	0.452
≥1	3	4	
CDFI [d]			0.130
Peripheral vascularity	13	51	
Central vascularity	4	6	
Both	17	25	
No blood flow	7	14	

[a] Cystic, more than 50% of nodule with cystic composition.
[b] Solid, more than 50% of nodule with solid composition.
[c] A/T, the ratio of anteroposterior (A) and transverse (T) diameter.
[d] CDFI, color doppler flow imaging.
[e] Mean ± SD value.
* $p<0.05$.



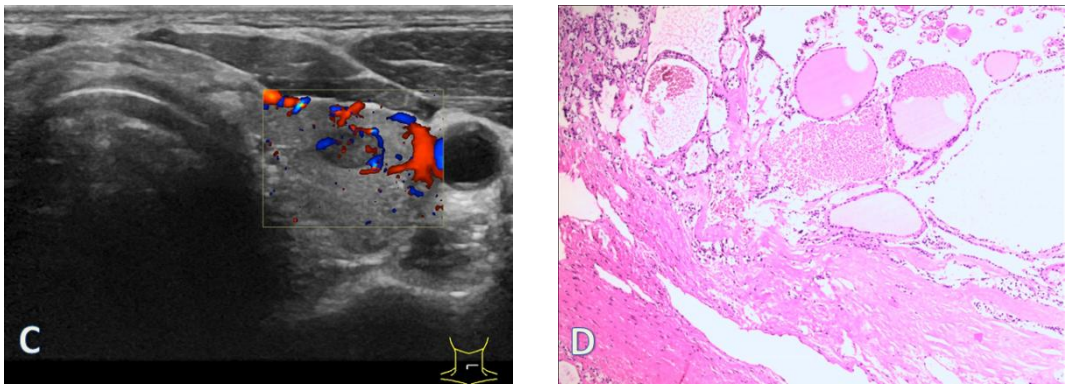


Figure 1. Ultrasonography of cystic nodular goiter in a 54-year-old male patient.
A & B: Transection (A) and vertical-section (B) of solid portion, located at the left lobe of gland. The main composition of internal structure is solid, with regular shape, isoechoic and well-circumscribed. Mass = 0.71×0.66×0.43 cm.
C: CDFI information of this cystic nodular goiter, with some central and peripheral blood flow.
D: Pathology section of cystic nodular goiter. HE-stained section, with solid follicles, colloid and degenerative cystic structure.

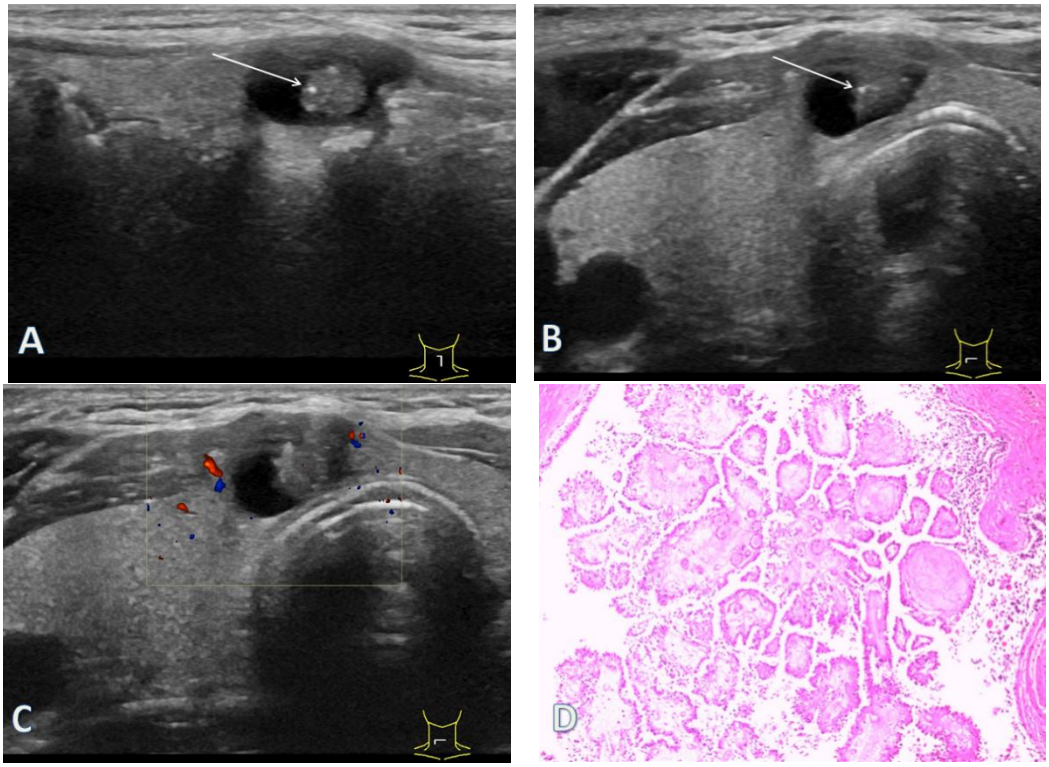


Figure 2. Ultrasonography of PTC combined with cystic degeneration in a 45-year-old male patient.
A & B: Transection (B) and vertical-section (A) of the lesion. A nodule (size = 1.35×1.24×0.68 cm) was found at the thyroid isthmus. The main composition of internal structure is solid and eccentric formation, ultrasound images featured with regular shape, isoechoic with point high-echo, and well-circumscribed. The interface was irregular.
C: CDFI of cystic PTC nodule, with peripheral blood flow information.
D: Pathology section of this PTC nodule. HE-stained section, distinctive papillary architecture and follicles.

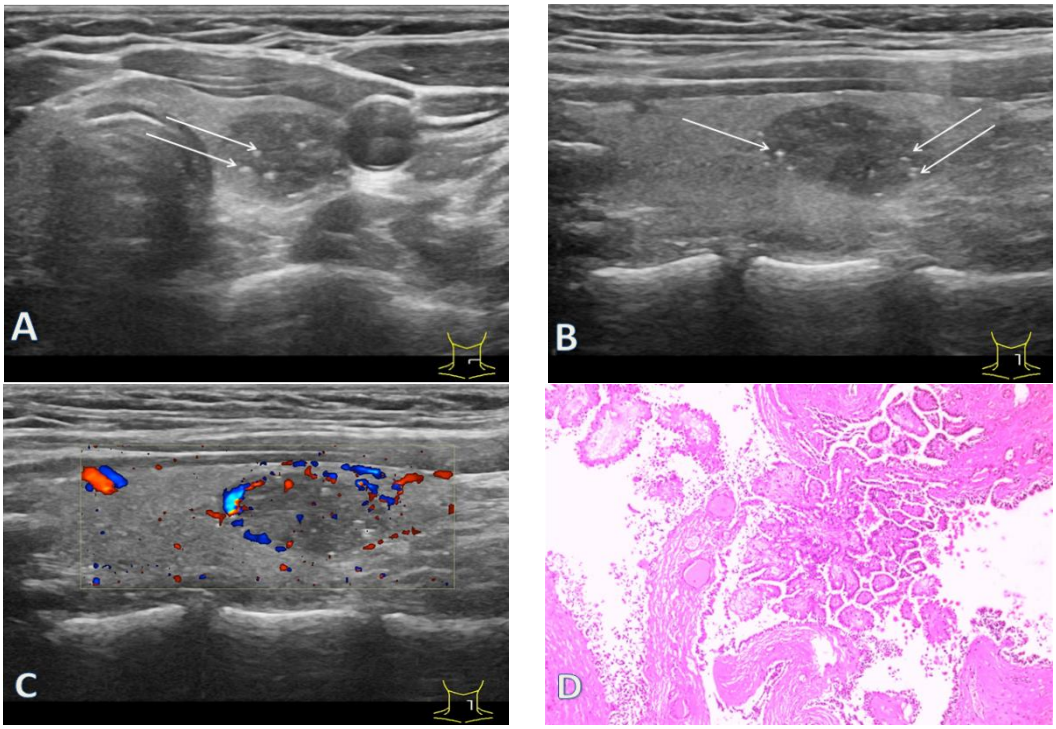


Figure 3. Ultrasonography of PTC combined with cystic degeneration in a 31-year-old female patient.

A & B: Transection (A) and vertical-section (B) of the lesion. A lesion (size = 1.70×1.52×0.96 cm) was found in the middle of the life gland. The main composition of the internal structure is solid, and the solid portion is non-eccentric, ultrasound images with a regular shape, an isoechoic and pointed high-echo, The margin is well-circumscribed, and the interface is regular.

C: CDFI of cystic PTC nodule, with some peripheral blood flow.

D: Pathology section of this PTC nodule. HE-stained section, papillary architecture and follicles.

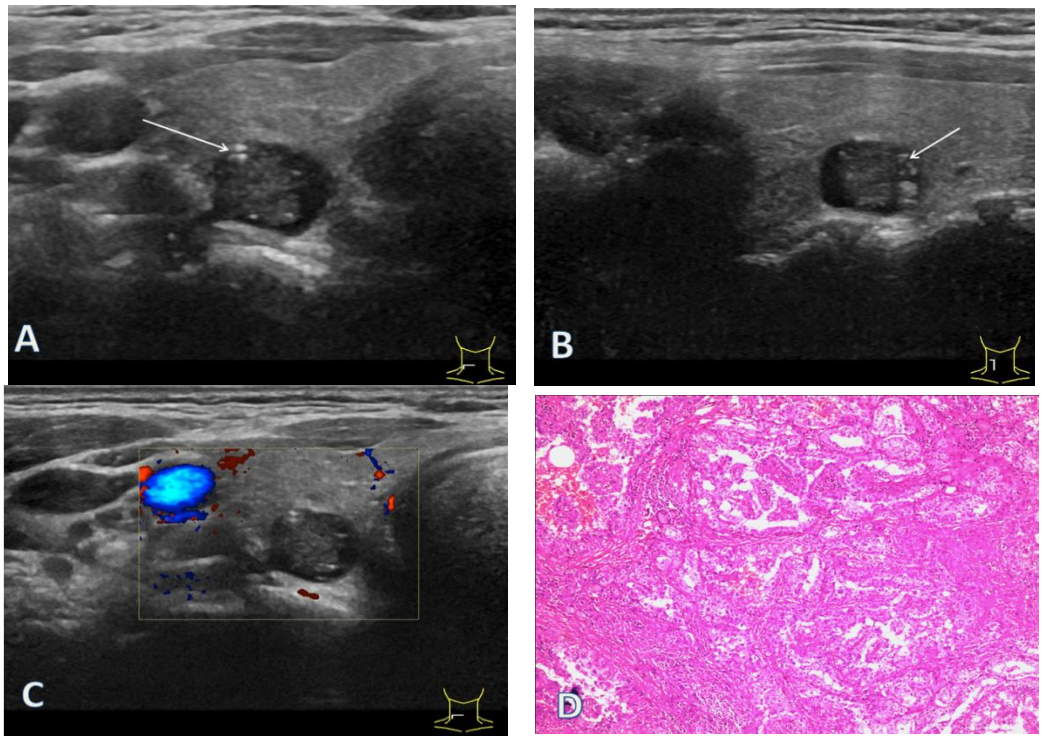


Figure 4. Ultrasonography of PTC combined with cystic changes in a 35-year-old female patient.

A & B: Transection (A) and vertical-section (B) of this lesion. A mixed-echo nodule (size = 0.99×0.98×0.65 cm) was found in the middle of the right gland, with a well-circumscribe and regular shape. The main composition of this lesion is solid, and the solid portion distributed eccentrically, Ultra-echo features are isoechoic and combined with some dotted high-echoes. The interface is irregular.
C: CDFI of this cystic PTC nodule. No blood flow was found.
D: Pathology section of this PTC nodule. HE-stained section.

Results of Logistic Regression

In logistic regression analysis, we found that age (OR=0.955, 95% CI=0.918-0.994, P=0.023), position of solid portion (OR=4.500, 95% CI=1.447-14.002, P=0.009), microcalcification (OR=13.487, 95% CI=3.479-52.286, P<0.001), and interface (OR=5.231, 95% CI=1.971-13.879, P=0.001) were statistically significant for the diagnosis of cystic-solid PTC. The risk of PTC could be evaluated when the lesions had an eccentric solid configuration, microcalcification or an irregular cyst-solid interface. All details are shown in Table 3.

Table 3. Ultrasound features of cystic PTC **by logistics regression analysis**

Variables	**Coefficient**	**SE**	**Wald x^2**	**P-value**	**Odds ratio**	**95% CI**
Age	-0.046	0.020	5.161	0.023*	0.955	0.918-0.994
Eccentric [a]	1.504	0.579	6.747	0.009*	4.500	1.447-14.002
Microcalcification	2.602	0.691	14.163	0.01*	13.487	3.479-52.286
Interface [b]	1.655	0.498	11.043	0.001*	5.231	1.971-13.879

[a] Morphology and the position of solid portion.
[b] Interface between cystic and solid portion.
* p<0.05.

Discussion

Most of the TC-associated nodules contained a solid portion and rarely exhibited a cystic appearance that represent a solid-liked nodule on ultrasound examination. Thus, cystic solid-liked PTC is a sub-type of PTC from morphology and has some ultrasound characteristics that differ from typical solid-liked PTC. The similar presentations of PTC and cystic solid-liked PTC may confuse the sonographer and result in a misdiagnosis. Indeed, the rate of misdiagnosis is high, especially among non-experienced ultrasonographers [11, 12]. Thyroid fine needle aspiration cytology (FNA) is one of the primary methods before thyroidectomy, which could facilitate the diagnosis of benign and malignant lesions [13]. Besides, the detection of cystic-liked content in thyroid nodules may weaken the efficiency of FNA, in which situation that ultrasound-guided FNA might no longer be recommended as a routine invasive examination [14, 15]. Intermediate high-frequency ultrasound is one of the most important and non-invasive diagnostic methods for thyroid diseases. With the ease and accessibility of re-examination, safe and cost-saving, quick and multi-sectional observation, ultrasound is considered to be important in the clinic compared with other morphological examination such as computed tomography. Most of the previous studies of thyroid nodules mainly focused on solid-liked thyroid nodules. Due to the cross-section of ultrasonographic manifestations in benign and malignant cystic solid-liked thyroid nodules, the features of cystic-solid thyroid nodules have received tremendous attention, which could help us to improve the accuracy of benign and malignant differentiation. This cross-section decreases and increases the accuracy rate and misdiagnosis rate of ultrasound. In this underestimated situation, the alteration of non-cancer diseases and negative follow-up strategies may harm the patients and delay the treatment progress [10, 16]. Accurate presurgical evaluation and

effective TC treatment are important for the prognosis of the patients.

Thyroid nodules with solid hypoechoic, border indistinct, microcalcification and aspect ratio >1 were considered as malignant in previous studies [2-4]. However, these ultrasound characteristics are mainly related to solid-liked thyroid nodules. For cystic solid-liked TC, only a few studies and clinical reports are accessible; therefore, there is a large margin on the deduction of sonographic features in cystic solid-liked TC nodules [10, 11].

In this study, we retrospectively evaluated the sonographic parameters of cystic-solid PTC and cystic-solid nodular goiter, and identified some potential ultrasound characteristics. First, in cystic-solid PTC, an eccentrical solid portion was considered a risk factor. The results of the logistic analysis demonstrated that an eccentric appearance of solid portion (OR=4.50) was an important characteristic for the diagnosis of PTC. The reason for the eccentric distribution of the solid portion could be attributed to the fibrosis and hyperplasia of thyroid tissue induced by thyroid cancer tissue, thus inhibiting the surrounding thyroid tissue, promoting the atrophy and degeneration of follicular cells, and eventually resulting in liquefactive necrosis [17]. Therefore, the peripheral part of thyroid cancer is prone to be cystic. As for nodular goiter disease cycle, it was composed of proliferative stage, glial storage stage and nodular stage. At specific stages, the appearances of thyroid follicular epithelium may appear different degrees of hyperplasia, regeneration or atrophy. In some cases, we can also find retention of thyroid colloid, hemorrhage, necrosis or cystic degeneration.

Second, in malignant lesions, we found that macrocalcification in the solid portion of nodules was a novel sign for the differential analysis of PTC. There were only 40.00% (38/95) of benign nodules with microcalcification in the solid portion, while 90.24% (37/41) of malignant nodules were present with some point-like hyperechoic in the same portion. The detection rate of cystic-solid PTC was much higher than that of cystic-solid nodular goiter. The definition value of microcalcification in the solid portion was reconfirmed by the results of logistic regression analysis with a statistically significant for the identification of cystic-solid PTC (OR=13.487, P<0.05). There is a correlation between the psammoma bodies and spot-liked hyperechoic of thyroid nodules [18], and microcalcification is considered as a reliable marker for the diagnosis of TC. The specificity of microcalcification for TC is 44-95%, especially for PTC, which may be found in distinctive psammoma bodies. The rapid growth of tumor cells, formation of blood vessels, and proliferation of fibrous tissues may lead to elevated calcium concentration and calcification [19]. The secretion of substances, such as glycoproteins and mucopolysaccharides, by the tumor cells may also promote calcification [20]. Dystrophic calcification in the lesions can also contribute the appearance of microcalcification in cancer tissues [21]. We found that dotted hyper-echogenicity not only located in solid portions, but also detected in cystic portions of 26.32% (25/95) patients with cystic-solid nodular goiter. It is worth noting that the hyper-echogenicity of cystic-solid nodular goiter in solid portions is a manifestation of gelatinous mass, which usually has a comet-tail sign on ultrasound.

Third, we observed that the irregular interface between the cystic and solid parts of nodules was strongly associated with malignant nodules (OR=5.231, P=0.001). The different growth patterns of cystic-solid PTC nodules possibly contributed to these findings. The majority of malignant nodules, especially PTC originating from the capsule wall, are often located at the base of the papillary part. Variations in the growth rate of tumor cells and restriction by the surrounding tissues may confer an irregular tendency of solid portion [11].

In addition, we found that age had a diagnostic value in the classification of cystic-solid PTC (OR=0.952, P=0.023), and the risk of PTC in younger patients suffered from cystic-solid lesions was lower than elder patients. As reportedly previously, age (<40 or >70) is associated with the occurrence of thyroid cancer[21], which is consistent with the

results of this study.

In conclusion, the ultrasound findings of eccentric configuration of the solid portion, spotted hyperecho in solid portion and irregular cystic-solid interface can indicate the risk of PTC malignancy. Nevertheless, this study still has some limitations. There is an inadequacy of cystic-solid PTC nodules in our study, and the ultrasound characteristics need to be confirmed in future prospective studies.

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