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Original Article

Analysis of contrast-enhanced ultrasound in the differential diagnosis of papillary thyroid cancer and thyroid nodules

Zheng Zhu[1*], Yongxiang Qian[2*], Fenglan Zhu[3*], Qingfeng Ni[1], Xinyan Xu[1]

Departments of [1]Ultrasound, [2]Thyroid and Breast Surgery, [3]Endocrinology, Taicang First People's Hospital, Taicang 215400, Jiangsu Province, P. R. China. [*]Equal contributors.

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Abstract: Aims: This study is to analyze the value of contrast-enhanced ultrasound in the differential diagnosis of papillary thyroid cancer and thyroid nodule. Methods: Ninety cases of papillary thyroid cancer were considered as papillary thyroid cancer group, and 90 cases of thyroid nodules in the same period were considered as thyroid nodule group. Ultrasound images were compared and differential diagnostic values of contrast-enhanced ultrasound (CEUS) were analyzed. Results: Between two groups, there were significant differences of systolic peak velocity and resistance index ($P<0.05$). In papillary thyroid cancer group, papillary thyroid cancer accounted for 74.4%, 81.2%, 62.3%, 67.8%, and 82.2% for abnormal signs of lesion's shape, border, contrast intensity, enhancement and filling defect in CEUS, respectively. Meanwhile, ROC curve was drawn for sensitivity and specificity analysis based on ultrasound images and then compared with pathology scores. The area under ROC curve (AUC) of papillary thyroid cancer and thyroid nodules was 0.924 and 0.806, respectively. The CEUS was of great diagnostic value for papillary thyroid cancer compared thyroid nodules with statistical significance ($P<0.05$). Conclusion: CEUS can distinguish between papillary thyroid cancer and thyroid nodules with satisfactory sensitivity and specificity, thus, it is of great value in clinical diagnosis and treatment.

Keywords: Papillary thyroid cancer, thyroid nodules, ultrasound imaging, pathology

Introduction

Papillary thyroid cancer and thyroid nodules are both common diseases, and thyroid papillary cancer accounts for about 74%-80% of all thyroid cancer [1]. Papillary thyroid cancer is often misdiagnosed with thyroid nodules due to its low malignancy and slow growth, thus further treatment is often delayed [2]. CT scan and MRI are limited in the diagnosis of papillary thyroid cancer. Ultrasound is the most common diagnostic tool for thyroid diseases; however, traditional ultrasound is limited in the differential diagnosis of thyroid tumors. But with the application of ultrasound with modified high-frequency probe and color Doppler, the diagnosis of thyroid diseases is greatly improved. In recent years, the application of new contrast agents and contrast-enhanced ultrasound (CEUS) significantly improves the detection of microperfusion in tissues [3], however, CEUS is still in the exploratory phase. In this study, the CEUS images of papillary thyroid cancer and thyroid nodules were analyzed and evaluated, in order to improve its diagnostic value for papillary thyroid cancer in the future.

Materials and methods

Subjects

The 180 patients from Department of Endocrinology and Department of Thyroid Surgery received CEUS from August 2013 to August 2015 were recruited. All patients had biopsy or postoperative pathology and were diagnosed by pathology. Clinical data of patients were shown in **Table 1**. Of them, 90 cases of papillary thyroid cancer were in papillary thyroid cancer group, and 90 cases of thyroid nodules were in thyroid nodule group. Meanwhile, other types of cancer were ruled out in all patients. In

Table 1. Basic demographics of two groups

Basic demographics	Papillary thyroid cancer group (n=90)	Thyroid nodule group (n=90)	*P*
Age (years)	41.29±18.36	45.82±15.36	*P>0.05*
Gender (male/female)	41/49	46/44	NS
Number of lesions	122	131	NS
Size of lesions (≤1 cm/>1 cm)	65/57	54/79	*P>0.05*
Calcifications (Yes/No)	24/66	31/59	*P>0.05*
Echo (strong/moderate/weak)	32/56/34	24/68/39	*P>0.05*
Blood CDFI) (fast/slow)	112/10	58/73	*P>0.05*

Note: CDFI: Color Doppler flow imaging. Age is presented as mean ± standard deviation. NS: no significance. $P<0.05$ was considered statistical significant.

papillary thyroid cancer group, there were 41 males and 49 females, aging from 25 to 72 years with mean age of 41.29±18.36 years. In thyroid nodule group, there were 46 males and 44 females, aging from 21 to 68 years with mean age of 45.82±15.36 years. There were no significant differences of gender, age, tumor shape, tumor border, echo, calcification, blood flow changes or lymph node metastasis between the two groups of patients ($P>0.05$). Biopsy was obtained before and after surgery. Prior written and informed consent were obtained from every patient's family and the study was approved by the ethics review board of Taicang First People's Hospital.

Equipment and material

Color Doppler ultrasound (Philips-iU22, Netherlands) was used with PM/IP imaging software and CS-2 probe (frequency of 4-9 MHZ). Mechanical index (MI), depth gain control DGC remained same during CEUS in all patients. The ultrasound host was Baishengmeili 90 with LA522 probe. The contrast agent Sono Vue (59 mg, BRACCO company, Italy) was used and diluted with 5 ml saline solution.

Operation method

All patients were in neck extension position to expose thyroid. An experienced sonographer operated ultrasound to observe the thyroid lobe, isthmus, and tumor foci to examine their location, shape, border, internal echo and CEUS. Bolus of 4.8 ml 0.9% saline diluted contrast was injected into elbow vein. With mechanical index of 0.05-0.08, single focus was placed on the edge of tumor and the gain was adjusted to inhibit the background echo of thyroid. The max section was selected and contrast mode was set to continuous monitor the perfusion peak and withdrawal of dynamic contrast agent, the enhancement level of lesions, enhanced mode and surrounding tissues. All images were stored in the hard disk and analyzed by the two independent sonographers.

HE staining

Leica TP1020 tissue dehydration machine (Leica Microsystems, Wetzlar, Germany), Germany Leica2135 slicer (Leica Microsystems, Wetzlar, Germany), Japan OlympusBX51 and BX41 microscope (Olympus optical Co., Ltd., Tokyo, Japan) was used. All surgical removed sentinel lymph nodes performed rapid frozen biopsy. The tissue was fixed with 10% neutral formalin and embedded by paraffin for routine pathology examination.

Image indicators and analysis

Ultrasound images of echo, shape, calcification, systolic peak velocity (Vmax), and resistance index (RI) were recorded and analyzed.

CEUS indicators include lesion morphology, enhanced lesion border, homogeneous enhancement, perfusion defects and enhancement degree. The enhancement degree was categorized as Grade I (the enhancement of surrounding tissues was significantly increased than that of tumor), Grade II (the enhancement of surrounding tissues was the same of tumor), and Grade III (the enhancement of tumor was significantly increased than that of surrounding tissues). Contrast-enhanced lesion diameters before and after CEUS were also recorded. The tumor lesion was analyzed by PM/IP image software for time-intensity curve and quantitative parameters.

Diagnostic value of CEUS

Presence of each of the following indications scored one point in the CEUS scoring system (0-5) [4]: irregular lesion shape, unclear lesion border, strong enhancement, heterogeneous enhancement, and perfusion defects. The

Table 2. Comparison of clinical indicators between two groups

	Gender	Shape	Echo	Calcification	V-max	RI
Papillary thyroid cancer group	1.53±0.510.51	12.53±2.512.51	18.23±7.367.36	32.41±12.6312.63	38.63±11.5211.52	2.56±0.780.78
Thyroid nodule group	1.48±0.190.19	17.53±4.654.65	19.17±8.638.63	21.34±11.2411.24	24.37±9.559.55	1.56±0.460.46
P	0.001	0.023	0.032	0.000	0.001	0.000

Table 3. CEUS characteristics of two groups (%)

CEUS characteristics		Papillary thyroid cancer group (n=90)	Thyroid nodule group (n=90)	P
Shape	Regular	23 (25.5%)	57 (63.3%)	0.00
	Irregular	67 (74.4%)	33 (36.6%)	
Border	Clear	17 (18.8%)	49 (54.4%)	0.04
	Unclear	73 (81.2%)	41 (45.6%)	
Strength	Strong	34 (37.7%)	63 (70%)	0.01
	Weak	56 (62.3%)	37 (30%)	
Enhancement	Homogeneous	29 (32.2%)	42 (46.6%)	0.00
	Heterogeneous	61 (67.8%)	48 (53.4%)	
Perfusion defects	Yes	74 (82.2%)	12 (13.3%)	0.00
	No	16 (17.7%)	78 (86.6%)	

pathology was scored as 0 (benign) or 1 (malignant). We assume CEUS score of 3-5 and pathology identified malignancy as true positive (TP); CEUS score of 1-2 and pathology identified benign as true negative (TN); CEUS score of 3-5 and pathology identified benign as false positives (FP); CEUS score of 1-2 score points and pathology identified malignant as false negative (FN). The ROC curve was drawn to determine the diagnostic value of CEUS.

Statistical analysis

SPSS17.0 software (IBM Corp, Chicago, IL,, USA) was used for data analysis. Quantitative data approximates a normal distribution and presented as means ± standard deviation. T-test was used for group comparison, with $P<0.05$ considered as statistically significant. ROC AUC was used to analyze sensitivity and specificity.

Results

Ultrasound indicator comparisons between two groups

To determine the different characteristics, ultrasound indicators were compared between groups. There were significant differences in tumor shape, border, echo, and calcification between two groups ($P<0.05$) (**Table 2**). The artery peak systolic velocity (Vmax) was 38.63± 11.52 and RI was 2.56±0.78 cm/s of patients in papillary thyroid cancer group; while the artery peak systolic velocity (Vmax) was 24.37 and RI was 1.56±0.46 cm/s of patients in thyroid nodule group. It indicated that Vmax and RI were statistically significant between the two groups ($P<0.05$).

CEUS analysis of the two groups

To determine the features of papillary thyroid cancer and thyroid nodules in CEUS, the characteristics of two groups were compared, as in **Table 3**. The CEUS of papillary thyroid showed irregular shape, strong and heterogeneous enhancement, unclear border and focal perfusion defects. Those signs were more in papillary thyroid cancer patients, accounting for 74.4% of irregular lesion shape, 81.2% of unclear lesion border, 62.3% of strong enhancement, 67.8% of heterogeneous enhancement, and 82.2% of perfusion defects, indicating the abnormal signs in CEUS were higher than that in thyroid nodule group.

CEUS and pathology results

To determine the enhancement, peak index and time to peak, two groups underwent CEUS and were diagnosed by biopsy or postoperative pathology. The representative images were shown in **Figure 1**. There were no adverse reactions or side effects during the inspection. There were 106 out of 122 cases with strong and heterogeneous enhancement, and 98 cases with perfusion defects. In thyroid nodule group, out of the 131 benign nodules there were 119 cases with homogeneous enhancement, 7 cases with annular enhancement, 4 case of heterogeneous enhancement, and 1 case of strong enhancement. There were sta-

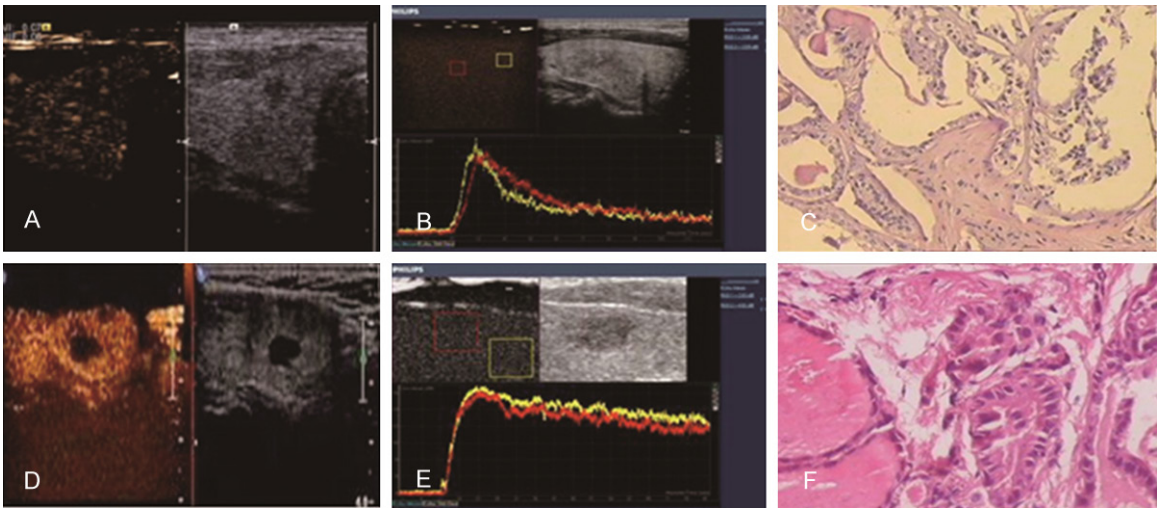

Figure 1. The time-intensity curve of CEUS for both groups. Papillary thyroid cancer group (A-C). (A) CEUS enhanced images, expressed as heterogeneous enhancement. (B) Time-intensity curve, expressed as "fast forward and fast backward" blood flow. (C) HE staining image. Thyroid nodules group (B-D). (D) CEUS enhanced images, expressed as heterogeneous enhancement. (E) Time-intensity curve, expressed as "fast forward and flow backward" blood flow. (F) HE staining image.

Table 4. ROC analysis of the two groups

	AUC	Standard error	Significance (*P* value)	95% CI	
				Lower limit	Upper limit
Papillary thyroid cancer group	0.924	0.029	0.000	0.868	0.980
Thyroid nodule group	0.809	0.050	0.0001	0.711	0.906

Note: AUC, area under ROC curve.

tistical significant differences between two groups (*P*=0.000). The peak index and time to peak (TTP) of time-intensity curve were 6.43±1.68 and 5.77±1.73 in papillary thyroid cancer group, and 5.54±1.36, 4.89±1.72 in thyroid nodule group, with no statistical significance (*P*>0.05). This result indicates that enhancement was of greater diagnostic value for thyroid cancer.

ROC curve of CEUS and pathology score for the two groups

To determine the diagnostic value of CEUS, ROC curve was drawn by SPSS17.0 software for sensitivity and specificity analysis based on ultrasound image and pathology score. It showed that CEUS was of high sensitivity and specificity for both groups. The AUC for papillary thyroid cancer group and thyroid nodule group was 0.924 and 0.806, respectively (**Table 4**). In this study, compared with AUC=0.5, CEUS was of great diagnostic value for papillary thyroid cancer (*P*=0.000), and less value for diagnosis of thyroid nodules (*P*=0.0001), with significant difference, as shown in **Figure 2**.

Discussion

Thyroid cancer is one of the most common types of cancer, and papillary thyroid cancer is the most common type for malignant thyroid cancer, accounting for about 60% to 80% of all thyroid cancers with 5-year survival rate of about 60% to 90% [5]. Therefore, early diagnosis is of great importance for patient's survival. Currently predisposing factors for papillary thyroid cancer and thyroid nodules remain unclear, and are generally believed to be associated with hormone, genes, and environment [6]. The primary symptoms for both diseases are painless mass in neck that can move up and down when swallowing. Some patients feel hoarseness, dysphagia and pressure. In ultrasonography, it showed irregular shape, unclear border and calcification. The sensitivity and specificity

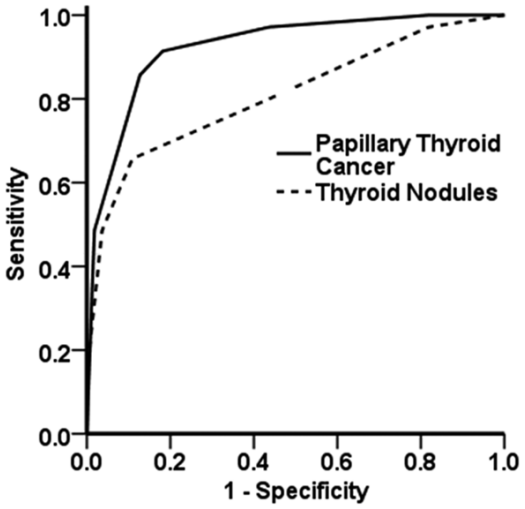

Figure 2. ROC curve of CEUS of the two groups.

of CEUS is increasing in the diagnosis of thyroid tumors, along with the increasing development of imaging, the wide application of high-frequency probe, color and spectral Doppler, and the increasingly experienced sonographer [7]. At present, CEUS is mostly used in the diagnosis of malignant nodules with controversial diagnostic value [8, 9]. Currently, thyroid blood flow is an important indicator in differentiating benign and malignant thyroid tumors, however not all blood flow can be measured by ultrasound, such as small tumor with immeasurable blood flow, thus identification of tumor malignancy can be difficult [10]. CEUS aims to increase vascular contrast when the contrast agent was injected into the vascular for more significant blood vessels and blood flow.

Ultrasound images of benign thyroid nodules showed regular shape, clear border, high echo and calcification, especially calcification of the edge, which is significant different from papillary thyroid cancer. The artery peak systolic velocity (Vmax) and RI of papillary thyroid cancer are significantly higher than that of thyroid nodules ($P<0.05$), which is consistent with many studies [6]. It is shown that CEUS of thyroid cancer present as "fast forward and fast backward" blood flow with mainly high enhancement [11, 12]. However, Xiaolong Shi et al [13] showed papillary thyroid cancer lack blood supply in CEUS. The above controversial studies may result from different pathology types of thyroid cancers. In this study, papillary thyroid cancer was chosen in order to avoid the bias of different pathology types, and compare them with thyroid nodules. It is shown that irregular lesion shape, unclear lesion border, strong enhancement, heterogeneous enhancement, and perfusion defects were significantly higher in papillary thyroid cancer that of thyroid nodule group, indicating CEUS is of great diagnostic sensitivity and specificity when compared with traditional ultrasound. Ultrasound only cannot distinguish between benign or malignant thyroid tumors, leading to non-specific diagnostic criteria.

The capillaries are rich in thyroid thus normal thyroid parenchyma can be enhanced fast and evenly after intravenous injection of contrast agent. However, papillary thyroid cancer and thyroid nodular are different from the normal parenchyma [8, 14]. It is shown [8, 14] that ultrasound contrast time - intensity curve can demonstrate vessel formation in lesion. CEUS of papillary thyroid cancer showed lack of blood supply and heterogeneous enhancement, mainly as small vessel formation, while CEUS of benign tumor showed only diffuse angiogenesis, which is consistent with other studies [5, 15]. In consistent with the above studies, in this study, papillary thyroid cancer presents as heterogeneous enhancement, and benign thyroid nodules presents as homogeneous enhancement. From analysis of ROC curve, CEUS showed great diagnostic value for papillary thyroid cancer and thyroid nodules. CEUS was of great sensitivity and specificity of papillary thyroid cancer with significant importance.

In conclusion, ultrasound is of great importance in differential diagnosis of thyroid diseases, and CEUS's application in diagnosis of thyroid disease should be standardized and further explored. In this study, CEUS is of high sensitivity and specificity in the diagnosis of thyroid papillary cancer, but its clinical application remains in exploratory stage that should be further used in the differential diagnosis of thyroid tumors.

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Disclosure of conflict of interest

None.

Address correspondence to: Zheng Zhu, Department of Ultrasound, Taicang First People's Hospital, No. 58 Changsheng South Road, Taicang 215400, Jiangsu Province, P. R. China. Tel: +86-18915778778; E-mail: cvq999@126.com

References

[1] He C, Zhang J and Xing Y. Diagnosis and treatment of thyroid papillary carcinoma. Modern Diagnosis & Treatment 2006; 17: 290-292.

[2] Shen L. The clinical importance of ultrasound diagnosis for Hashimoto's thyroiditis with diffuse nodular. Chinese Continued Medical Education 2015; 7: 187-188.

[3] Anil G, Hegde A and Chong FH. Thyroid nodules: risk stratification for malignancy with ultrasound and guided biopsy. Cancer Imaging 2011; 11: 209-223.

[4] Giusti M, Orlandi D, Melle G, Massa B, Silvestri E, Minuto F and Turtulici G. Is there a real diagnostic impact of elastosonography and contrast-enhanced ultrasonography in the management of thyroid nodules? J Zhejiang Univ Sci B 2013; 14: 195-206.

[5] Zhou Q and Du X. The diagnostic value of CEUS in papillary thyroid carcinoma. Chinese Journal of Ultrasound Medicine 2011; 27: 595-597.

[6] Liu M and Hao Y. Clinical value of ultrasound diagnosis of small papillary thyroid carcinoma and nodule. Chinese Continued Medicine 2015; 7: 39-40.

[7] Zhang D, Lu S, Wang S and Ch S. Study on CDFI and Doppler Spectra in Thyroid Lumps Compared with Pathology. Chinese Journal of Ultrasound in Medicine 2004; 20: 256-258.

[8] Bartolotta TV, Midiri M, Galia M, Runza G, Attard M, Savoia G, Lagalla R and Cardinale AE. Qualitative and quantitative evaluation of solitary thyroid nodules with contrast-enhanced ultrasound: initial results. Eur Radiol 2006; 16: 2234-2241.

[9] Song H and Wang D. CEUS analysis of solitary thyroid nodules. China Medical Imaging Technology 2008; 24: 44-47.

[10] Yang S and Qian C. Contrast ultrasound quantitative analysis of thyroid nodule perfusion. Chinese Journal of Ultrasound Imaging 2011; 20: 38-40.

[11] Gu J and Chen H. Preliminary exploration of CEUS diagnosis on thyroid tumors. China Medical Imaging Technology 2008; 24: 1018-1020.

[12] Yuan H and Wang D. Quantitative analysis of CEUS for thyroid nodules. China Clinic Medical Imaging 2008; 19: 427-428.

[13] Shi X and Zheng X. Analysis of CEUS and pathology for thyroid tumors. Zhejiang Practical Medicine 2007; 12: 87-88.

[14] Argalia G, De Bernardis S, Mariani D, Abbattista T, Taccaliti A, Ricciardelli L, Faragona S, Gusella PM and Giuseppetti GM. Ultrasonographic contrast agent: evaluation of time-intensity curves in the characterisation of solitary thyroid nodules. Radiol Med 2002; 103: 407-413.

[15] Song D and Li J. The application of CEUS in differential diagnosis of thyroid tumors. Biomedical Engineering and Clinical Medicine 2012; 16: 45-49.