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Significance of contrast-enhanced ultrasonography in differential diagnosis of thyroid nodules

Qing Tian, MM, Haohui Zhu, MD*, Hui Li, MB

Abstract

The present study was aimed to compare the application values between 2-dimensional color Doppler ultrasonography (2DUS) and contrast-enhanced ultrasonography (CEUS) in the differential diagnosis of thyroid malignant nodules.

A total of 124 patients suspectedly diagnosed with malignant thyroid nodules under conventional gray-scale ultrasonography were recruited in this study. All enrolled patients were examined by both 2DUS and CEUS.

A total of 153 nodules (94.44%) and 45 cases (90.00%) with malignant nodules were detected by the CEUS. No significant differences were noted in nodule detection rates between 2DUS and CEUS ($\chi^2=1.170$, $P=.279$; $\chi^2=0.796$, $P=.372$). The aspect ratio, microcalcification, internal echo, borderline, V_{max}, resistance index, and total scores of malignant nodules were higher than those of benign nodules (all $P<.05$) when diagnosed by 2DUS. The peripheral/internal enhancement time, peak intensity, local enhancement, ring enhancement, and total scores of malignant nodules were significantly higher compared with those of benign nodules (all $P<.05$) by CEUS. Total score of malignant nodules diagnosed by 2DUS was approximately 3.5 and 2.3 points for CEUS. The diagnostic accuracy of 2DUS as observed by area under the curve was 0.821 with the cut-off value of 3.9, the sensitivity was 82.5%, and the specificity was 85.6%. The diagnostic accuracy of CEUS was 0.862 with the cut-off value of 2.8, the sensitivity was 86.7%, and the specificity was 91.3%.

Both 2DUS and CEUS are worthy of application values in the differential diagnosis from benign to malignant thyroid nodules.

Abbreviations: 2DUS = 2-dimensional color Doppler ultrasonography, CEUS = contrast-enhanced ultrasonography, CI = confidence interval, RI = resistance index, ROC = receiver operating characteristic, USI = Universal Salt Iodization.

Keywords: color Doppler ultrasound, contrast-enhanced ultrasound, ROC curve, thyroid malignant nodule

1. Introduction

In 1996, China launched the Universal Salt Iodization (USI) program. The USI program aims to reduce the prevalence of goiter and thyroid nodules, whereas the median urinary iodine concentration in school-age children has simultaneously rose sharply. Consequently, in 2002, national standards for iodized salt were revised to reduce the iodine concentration at the production level. In 2012, global data identified China as a region with more than adequate iodine intake. Meanwhile, a growing number of Chinese clinical endocrinologists have reported an increasing incidence of thyroid diseases since the implementation of the USI program in recent years.[1]

The superficial tissue resolution of high-frequency ultrasound is high, which has become the optimal method to screen and identify the thyroid malignant nodules.[2] Currently, the detection rate of thyroid nodules is 10% to 30%, 3% to 5% for the malignant nodules and follow-up nodular malignant transformation rate is approximately 0.6% to 1.5%.[3] Thyroid cancer can occur in all age groups. Younger individuals are often diagnosed with microcarcinoma. The accuracy rate of conventional 2-dimensional color Doppler ultrasonography (2DUS) in the diagnosis of microcarcinoma is approximately 60% to 80% with a sensitivity of 70% to 85% and a specificity of merely 50% to 66%.[4] These studies have demonstrated that the ultrasound performance of microcarcinoma largely overlaps with that of benign nodules,[5] which is subject to the subjective judgment factors.[6] The diagnostic accuracy can be improved by using the quantitative ultrasound indexes and standard results judgment criteria. The contrast-enhanced ultrasonography (CEUS) can achieve real-time observation on the perfusion and enhancement of blood flow in the lesions and adjacent tissues and has a good application value in identifying benign from malignant tumors in the hepatic tissues.[7] However, it has been rarely applied in the diagnosis of thyroid lesions because no unified standards on the enhancement mode of CEUS in the diagnosis of thyroid cancer has been achieved, which severely limits its clinical application. Consequently, the aim of this study is to statistically compare the application values between 2DUS and CEUS in the differential diagnosis of thyroid malignant nodules, as well as to explore

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The study received approval from the relevant ethical standards of the Committee. Informed consent was obtained.

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Department of Ultrasonography, Henan Provincial People's Hospital, Zhengzhou City, Henan Province, China.

** Correspondence: Haohui Zhu, Department of Ultrasonography, Henan Provincial People's Hospital, No. 7, Weiwu Road, Jinshui District, Zhengzhou City, Henan Province 450003, China (e-mail: haohuizh@yeah.net).*

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quantitative analysis indexes and establish assessment standards and criteria for thyroid carcinoma in order to provide references for clinical application.

2. Materials and methods

2.1. Sample selection

A total of 124 cases of patients with highly suspected malignant thyroid nodules that were admitted to our hospital from June 2014 to June 2016 and treated with routine gray-scale ultrasound for the first time were for this study. In terms of the thyroid stimulating hormone (TSH) levels, the mean TSH concentration in the benign nodules was detected as 1.35 ± 1.02 mU/L, significantly lower compared with 2.25 ± 1.14 mU/L in their counterparts diagnosed with malignant nodular lesions. Inclusion criteria: Those aged 18 to 60 years old; those who received gray-scale ultrasound, color Doppler, and CEUS examinations simultaneously and received a review at a 1-month interval; and those with complete clinical data. Exclusion criteria: Those with a medical history of neck trauma, surgery, and receiving radiation; and those who suffer from severe endocrine disorders, autoimmune diseases, or having taken steroid hormones. The criteria of gray-scale ultrasound examination on malignant thyroid nodules were as follows: belonging to the solitary nodules, the maximum diameter >10 mm, the aspect ratio ≥1, hypoechoic, ill-defined, in irregular shapes and associated with calcification. In this cohort study, 55 male and 69 female patients were recruited, aged 42.5 ± 13.6 years on average.

2.2. Research methods

The 2DUS and CEUS were performed to deliver imaging examinations. Surgical resection or fine-needle aspiration pathology diagnosis were used to confirm the imaging outcomes. The iU22 ultrasonic diagnostic apparatus was adopted (Philips). The L12-5 probe was used for conventional ultrasound examination, and the L9-3 probe was used for CEUS. The frequency was from 8 to 12 MHz and mechanical index was from 0.09 to 0.12. The contrast agents were purchased from SonoVue of Bracco Company (Italy). A portion of 24.98 mg of dry powder was dissolved in 5 mL of normal saline and then intensively mixed, 1.5 mL of the mixed liquor was extracted each time and then the injection was administered by using an intravenous bolus injection method via the peripheral elbow veins. Meanwhile, CEUS was performed and the focus point was adjusted to the middle-lower part of the thyroid nodules. Subsequently, double-contrast examination mode was adopted. The probe was in parallel with the long axis of the thyroid and fixed at the maximum section of the nodules. The dynamic data obtained within at least 2 minutes were collected and analyzed. Patients did not conduct deglutition when the contrast was performed.

The 2DUS observation indexes included the quantity of nodules, the maximum diameter and the aspect ratio (longitudinal diameter/transverse diameter), shape, microcalcification, internal echo, border, blood flow velocity, and resistance index (RI) with each assigned 0 to 1 point, 0 to 9 points in total, among which 0 point for multiple nodules and 1 point for solitary nodules. 0 point was defined as the maximum diameter ≤10 mm and 1 point for the maximum diameter >10 mm. 0 point for the aspect ratio <1 and 1 point for ≥1. 0 point for round or oval nodules and 1 point for irregular shape nodules or the growth direction not in parallel with the long thyroid axis. 0 point for no calcification in nodules and 1 point for nodules accompanied by microcalcification (diameter ≤2 mm). 0 point was defined as the signs of equal echoes or hyperechoes in nodules and 1 point for appearing hypoechoes in nodules. 0 point clear borders or complete dark rings or no dark rings and 1 point for obscure borders or incomplete dark rings. 0 point for the peak systolic velocity of blood flow (V_{max}) <40.00 cm/s and 1 point for ≥40.00 cm/s. 0 point for RI <0.50 and 1 point for RI ≥0.50.

CEUS indexes included nodule peripheral and internal enhancement time, peak intensity, local enhancement, and ring enhancement with each assigned 0 to 1 point, 0 to 6 points in total, among which 0 point was defined as the nodule peripheral normal thyroid reference area was enhanced and 1 point for nodules being enhanced at first. 0 point for the nodule internal area being enhanced at first and 1 point assigned for non-enhancement at first. 0 point for the nodule peripheral enhancement reaching its peak intensity at first (equal echoes or hyperechoes) and 1 point for it did not reach its peak intensity at first (hypoechoes). 0 point for the nodule internal enhancement reaching peak intensity at first and 1 point was assigned for it did not reach peak intensity at first. 0 point for the nodule enhancement area ≥50% and 1 point for <50% (local enhancement). 0 point for relatively uniform ring enhancement zones in the peripheral areas of lesions (ring enhancement) and 1 point for incomplete ring enhancement in the same area.

The quality control of examinations was as follows. The 2DUS examination was conducted by 2 professional ultrasound physicians for each patient and CEUS examination was conducted by another 2 professional ultrasound physicians. The results of 2DUS and CEUS did not keep the cross-reference. The results obtained each time were determined after negotiation by 2 professional physicians and the mean value was calculated. Each patient completed 2DUS and CEUS examinations for 3 times, which were conducted by the same physician. Obvious outliers were excluded or taken as data errors by rigorous statistical analyses. The average value was used as the final result.

2.3. Observation indexes

The accuracy of the 2 methods was compared; the sensitivity and specificity were compared by the receiver operating characteristic (ROC) curve.

2.4. Statistical methods

The SPSS 20.0 software was used for statistical analysis. The measurement data were expressed as mean ± standard deviation. Independent samples t test were used for comparisons between groups. The count data were expressed as the number of cases or (%). The normality test was performed. The diagnostic accuracy, sensitivity, and specificity were included for statistical analysis. The chi-squared test was used for intergroup comparisons; and $P < .05$ represented that the differences were statistically significant.

3. Results

3.1. Diagnostic accuracy analyses of DUS

A total of 162 nodules were detected in 124 patients. Fifty cases (40.32%) with malignant nodules were confirmed pathologically as having 58 nodules (35.80%), all of which were papillary carcinomas. There were 74 cases with a total of 104 benign nodules, which were nodular goiters. A total of 148 nodules were detected by 2DUS with a detection rate of 91.36% and a total of

Table 1

Analyses of characteristics of 2-dimensional color Doppler ultrasonography in the diagnosis of benign and malignant thyroid nodules.

	Malignant nodules (n = 42)	Benign nodules (n = 82)	t/χ^2	P
Male/female	18/24	37/45	0.058	.810
Age, y	43.6 ± 15.9	41.9 ± 14.7	0.236	.754
The number of nodules	19.6 ± 5.7	18.5 ± 4.6	0.152	.923
Maximum diameter	22.3 ± 6.7	21.8 ± 6.3	0.163	.905
Aspect ratio	25.5 ± 5.7	13.3 ± 4.6	12.632	<.001
Shape	15.7 ± 4.6	15.3 ± 4.4	0.066	.867
Microcalcification	31.2 ± 6.9	13.4 ± 5.6	16.954	<.001
Internal echo	19.3 ± 4.7	12.4 ± 4.2	6.532	.009
Border	16.7 ± 5.3	11.3 ± 5.2	5.432	.013
V_{max}	33.6 ± 8.3	16.5 ± 7.4	21.632	<.001
RI	24.3 ± 8.5	16.2 ± 6.6	13.625	<.001
Total score	6.2 ± 1.6	3.5 ± 1.1	5.865	.011

RI = resistance index.

42 cases with malignant nodules were detected with an accuracy rate of 84.00% (42/50).

Diagnosed by 2DUS, there were no significant differences in the gender, age, the quantity of nodules, diameter, and the shape score between patients with benign and malignant thyroid nodules (all $P > .05$). The aspect ratio, microcalcification, internal echo, border, V_{max}, RI score, and the total score of malignant nodules were significantly higher than those of benign nodules (all $P < .05$), as illustrated Table 1.

3.2. Diagnostic accuracy analyses of CEUS

A total of 153 nodules (94.44%) and 45 cases (90.00%) with malignant nodules were detected by CEUS. There were no differences in the nodule detection rate and the accuracy rate of malignant nodule diagnosis when compared to 2DUS ($\chi^2 = 1.170$, $P = .279$; $\chi^2 = 0.796$, $P = .372$).

Diagnosed by CEUS, there were no significant differences in gender, age, the number of nodules, diameter, and the shape score of patients with benign thyroid nodules and those with malignant thyroid nodules (all $P > .05$). The peripheral and internal enhancement time, peak intensity, local enhancement, ring enhancement score, and total score of malignant nodules were significantly higher than those of benign nodules (all $P < .05$), as demonstrated in Table 2.

3.3. Comparison of the sensitivity and specificity of diagnosis by ROC

The total score of malignant nodules diagnosed by 2DUS was > 3.5 points and >2.3 points for CEUS used as the diagnostic criteria and concluded into the ROC analysis, from which it could be found that the 2DUS diagnostic accuracy (area under the curve was 0.821, 95% confidence interval [CI] = 0.799–0.867, $P = .012$; the cut-off value was 3.9, the sensitivity was 82.5%, and the specificity was 85.6%). The diagnostic accuracy of CEUS was 0.862, 95% CI = 0.813 to 0.924 ($P < .001$). The cut-off value was 2.8, the sensitivity was 86.7%, and the specificity was 91.3%, as shown in Fig. 1.

4. Discussion

The innovative highlights of this study were as follows. First, common indexes of 2DUS in the diagnosis of thyroid malignant nodules were properly quantified, thus not only avoiding a misdiagnosis and missed diagnosis due to the relatively low diagnostic sensitivity and specificity of a single index, but also reducing the phenomenon that incomplete analysis indexes affect the results of diagnosis. Second, the diagnostic indexes of CEUS were properly quantified and the nodule peripheral and internal enhancement conditions were comprehensively assessed. Third, the accuracy of result evaluation was strictly controlled and the 2DUS and CEUS independent analyses were conducted independently and the results did not keep cross-reference. Meantime, 2DUS and CEUS were completed by the same examiner, thus reducing bias. The data were collected from each patient 3 times successively and then the mean value was calculated, which improved the accuracy. Through this study, it can be concluded that there were no differences in the detection rate of nodules and the diagnostic accuracy rate between the malignant nodules between the 2 methods after comparison. Another study[8] demonstrated that CEUS can further improve the detection rate

Table 2

Analyses of characteristics of contrast-enhanced ultrasonography in the diagnosis of benign and malignant thyroid nodules.

	Malignant nodules (n = 45)	Benign nodules (n = 79)	t/χ^2	P
Male/female	20/25	35/44	0.000	.988
Age, y	44.2 ± 17.8	41.3 ± 16.6	0.312	.724
Nodule peripheral enhancement time	26.7 ± 5.9	15.3 ± 5.3	9.635	<.001
Nodule internal enhancement time	25.4 ± 5.3	13.2 ± 4.8	12.534	<.001
Nodule peripheral peak intensity	28.5 ± 6.4	16.4 ± 5.6	16.527	<.001
Nodule internal peak intensity	26.9 ± 6.2	17.2 ± 6.7	20.321	<.001
Local enhancement	31.2 ± 7.8	16.8 ± 5.9	26.534	<.001
Ring enhancement	33.5 ± 7.5	18.5 ± 7.3	27.854	<.001
Total score	4.2 ± 1.3	2.3 ± 0.9	8.532	<.001

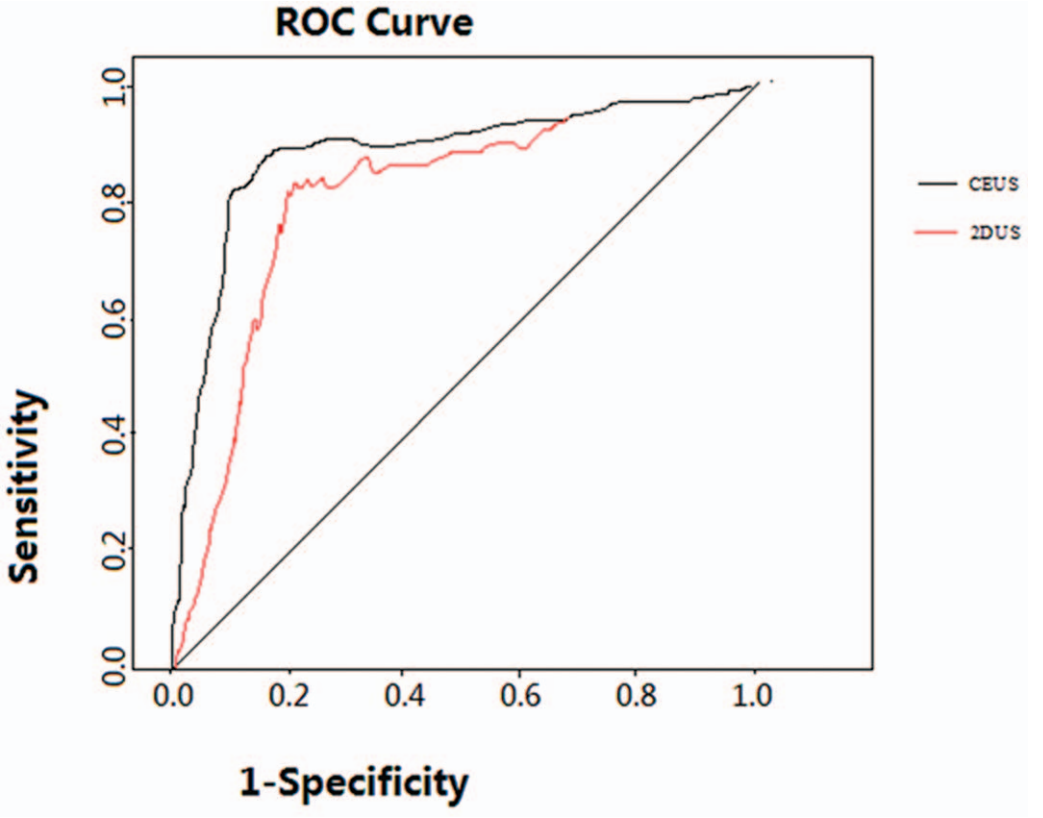

Figure 1. Comparison of ROC analysis between 2DUS and CEUS in the quantitative diagnosis of thyroid malignant nodules. 2DUS = 2-dimensional color Doppler ultrasonography, CEUS = contrast-enhanced ultrasonography, ROC = receiver operating characteristic.

of thyroid nodules. The reason for this was related to the differences in subjects, the sample sizes, and the examination techniques. In particular, the 2 examination techniques were quantified, which significantly improved the diagnostic accuracy of the nodules.

Diagnosed by 2DUS, the aspect ratio, microcalcification, internal echo, border, V_{max}, RI score, and the total score of malignant thyroid nodules were all higher than those of the benign thyroid nodules, but there were no differences in the number of nodules, the maximum diameter, and the shape score between them. A large population-based retrospective study concluded[9] that the sensitivity and specificity of a single index of 2DUS in the diagnosis of thyroid cancer were only approximately 50% to 60%, but multiple indexes could be increased to 65% to 80%. Although microcalcification is significantly correlated with thyroid cancer, the incidence rate is low approximately 10% to 30%. In addition, other indexes have similar problems. Their relatively low appearance rate or many similarities to benign nodules make them important factors in reducing diagnosis results.[10,11] Diagnosed by CEUS, the peripheral and internal enhancement time, peak intensity, local enhancement, ring enhancement score, and the total score of malignant nodules were significantly higher than those of benign nodules. A study by Zhang et al[12] demonstrated that the sensitivity of ring enhancement in CEUS in the determination of benign nodules is 85% and the specificity is 95%, whereas the sensitivity of heterogeneous enhancement in the diagnosis of malignant nodules is 90% and the specificity is 95%. The CEUS enhancement modes of thyroid nodules were related to pathological types. The vascular density of micropapillary carcinoma is relatively large, and therefore, it tends to be enhanced anterior to peripheral normal tissues,[13] but the mesenchyme is often accompanied by interstitial fibrosis and the formation of psammoma bodies. The internal blood flow is obstructed significantly, and the entrance of contrast microbubbles is relatively slow, therefore, it manifests an internal enhancement happens later than peripheral enhancement of nodules, and the enhancements are uneven.[14] In addition, the papillary carcinoma may be accompanied by follicular structures to various degrees and enhancement peak delay, manifesting as local enhancement, incomplete ring enhancement, and diversified enhancement.[15,16]

ROC was used for further analyses, from which the cut-off value, sensitivity, specificity, and accuracy of 2DUS and CEUS were concluded. Quantitatively 2DUS and CEUS are of significant application values in the differential diagnosis from benign to malignant nodules, which provides significant reference basis for quantitatively analyzing thyroid cancer and judgment criteria.

This study has certain limitations. The age of patients with malignant nodules was elder compared with their benign counterparts, and the risk of benign nodules is elevated over aging. Thus, the results and conclusions in this study remain to be further confirmed.

Author contributions

Conceptualization: Qing Tian.
Data curation: Qing Tian, Haohui Zhu, Hui Li.
Formal analysis: Qing Tian.

Investigation: Qing Tian, Haohui Zhu, Hui Li.
Methodology: Qing Tian, Haohui Zhu.
Project administration: Haohui Zhu.
Writing – original draft: Qing Tian.
Writing – review & editing: Haohui Zhu.

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