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

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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 (χ² = 1.170, P = .279; χ² = 0.796, P = .372). The aspect ratio, microcalcification, internal echo, borderline, Vmax, 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 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, which is subject to the subjective judgment factors.[5] 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.[6] 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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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, \( R_I \) 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 demonstrated that CEUS can further improve the detection rate.

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**Table 1**

| Description | Malignant nodules (n = 42) | Benign nodules (n = 82) | \( \chi^2 \) | \( P \) |
|-------------|---------------------------|-------------------------|-------------|-------|
| Male/female | 18/24                     | 37/45                   | 0.058       | .910  |
| 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  |
| \( V_{\text{max}} \) | 33.6 ± 8.3 | 16.5 ± 7.4 | 21.632 | <.001 |
| \( R_I \)    | 24.3 ± 8.5 | 16.2 ± 6.6 | 13.625 | <.001 |
| Total score | 6.2 ± 1.6 | 3.5 ± 1.1 | 5.865 | .011  |

\( R_I = \) resistance index.

**Table 2**

| Description | Malignant nodules (n = 45) | Benign nodules (n = 79) | \( \chi^2 \) | \( P \) |
|-------------|---------------------------|-------------------------|-------------|-------|
| 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 | 16.5 ± 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 |
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, $V_{\text{max}}$, 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 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. 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. 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, 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. 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.

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.

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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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