ORIGINAL ARTICLE

Diagnostic value of contrast-enhanced ultrasound in thyroid nodules with calcification

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KEYWORDS
Calcification; Contrast-enhanced ultrasound; ROC curve; Thyroid nodules

Abstract The aim of this study was to investigate the diagnostic values of conventional ultrasound and contrast-enhanced ultrasound (CEUS) in benign and malignant thyroid nodules with calcification. Conventional ultrasound and CEUS were performed in 122 patients with thyroid nodules with calcification. The thyroid nodules were characterized as benign or malignant by pathological diagnosis. The thyroid nodules were characterized as benign or malignant by pathological diagnosis. The area under the receiver operating characteristics curve (AUC) was used to assess the diagnostic values of the two imaging methods. In 122 cases of thyroid nodules with calcification, 73 benign nodules and 49 malignant nodules were verified by pathological diagnosis. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accordance rate of conventional ultrasound were 50%, 77%, 59%, 69%, and 66%, respectively, and those of CEUS were 90%, 92%, 88%, 93%, and 91%, respectively. There were significant differences between the two imaging methods. AUCs of conventional ultrasound and CEUS were 0.628 ± 0.052 and 0.908 ± 0.031, suggesting low and high diagnostic values, respectively. CEUS has high diagnostic values, being significantly greater than those of conventional ultrasound, in differential diagnosis of benign and malignant thyroid nodules with calcification.

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CEUS in calcified thyroid nodules

Introduction

In clinical practice, the incidence of thyroid nodules is high. Thyroid nodules are found in 50% of autopsy cases [1], and approximately 5% of these nodules are malignant [2]. Kuhn et al [3] reported that thyroid papillary carcinoma is the most common type of thyroid carcinoma, accounting for more than 85% of thyroid carcinomas. Ultrasound is the preferred examination method for thyroid diseases [4], and thyroid nodules with calcification are often detected with this modality. Previous studies have shown that calcification occurs in 19.8–32.1% of thyroid nodules [5,6]. As reported by Kim et al [7], the calcification rates in malignant and benign thyroid nodules are approximately 40.2% and 22.2%, respectively. In malignant thyroid nodules, the microcalcification and massive calcification rates are 42.9% and 26.7% [7]. Therefore, to avoid unnecessary surgery, a reliable method for identification of the malignant lesions in a large number of thyroid nodules with calcification is the focus of clinical attention [8].

Many researchers have attempted to distinguish benign and malignant thyroid nodules according to the calcification type [9,10]. However, because calcification may occur in both benign and malignant nodules, the application of conventional ultrasound in diagnosis of thyroid nodules has been restricted. Contrast-enhanced ultrasound (CEUS) is a new technology developed in recent years and has yielded favorable results in the examination of parenchymal organs such as abdominal organs [11–13], but its application in thyroid diseases is still in the exploratory stage. In this study, the diagnostic value of CEUS in identifying benign and malignant thyroid nodules with calcification was investigated. The objective was to assist clinicians in selecting the correct therapeutic approach for thyroid nodules.

Methods

Patients

One hundred and twenty-two patients who underwent surgery for thyroid nodules with calcification at our hospital between February 2010 and March 2012 were enrolled in this study. There were 37 male and 85 female patients, aged 18–72 years, with an average age of 46 ± 12 years. There were 122 thyroid nodules, one nodule in each patient. The nodule size was 0.35–4.2 cm, with an average of 1.5 ± 0.40 cm, and the maximum major diameter of the calcification lesions was 10 mm. According to the pathological diagnosis results, the 122 thyroid nodules were divided into a malignant group (49 nodules) and a benign group (73 nodules).

Methods

An ACUSON Sequoia 512 (Siemens Healthcare, Erlangen, Germany) ultrasound scanner was used in the present study. The scanner was equipped with a model 15Lbw high-frequency linear transducer array. The scanner has a spatial resolution of 0.1 mm. Contrast pulse sequencing (CPS) with a transmitting frequency of 7.0 MHz and a mechanical index (MI) of 0.32 was used, as recommended, for CEUS procedures [14].

The SonoVue (Bracco SpA, Milan, Italy) contrast agent was used for all patients. The agent was prepared by mixing with 5 mL saline and shaking vigorously until a milky-white microbubble suspension was obtained. A bolus injection of 2.4 mL of the SonoVue preparation was administered via the cubital vein, followed by injection of 5 mL saline to flush the syringe. Immediately thereafter, real-time harmonic gray-scale ultrasound examination of the thyroid nodule was conducted, and the dynamic images were recorded. Finally, the ultrasound images were independently evaluated by two experienced sonographers.

CEUS results were categorized as follows. (1) According to the comparison of echo intensity at peak enhancement between the thyroid nodule and the surrounding thyroid parenchyma, the enhancement degree was categorized as hypo-enhancement, iso-enhancement, or hyper-enhancement. (2) According to the uniformity of echo intensity of the lesion at peak enhancement, the enhancement uniformity was categorized as homogeneous enhancement or inhomogeneous enhancement (including local nonenhancement). Quantitative parameters of CEUS, including time to enhancement, time to peak, and peak intensity, were obtained using 2D Cardiac Performance Analysis (CPA) magnetic resonance (MR) quantification software (TomTec Imaging Systems, Unterschleissheim, Germany) [15]. According to Zhou et al [16], inhomogeneous hypo-enhancement was defined as the diagnostic standard for malignant thyroid nodules.

Statistical analysis

Data were expressed as mean ± SD. Statistical analysis was performed using SPSS 18.0 statistical software (SPSS Inc., Chicago, IL, USA). The t test and Chi-square test were performed for analyzing the measurement data and enumeration data, respectively. A p value <0.05 was considered statistically significant. The pathologically diagnosed malignant thyroid nodules were used as standards, and the receiver operating characteristics (ROC) curves of multivariate observations were drawn, with the sensitivity of the malignant nodule imaging diagnosis as ordinate and 1-specificity as abscissa.

Results

CEUS findings in benign and malignant thyroid nodules

In the malignant group, all 49 thyroid nodules were papillary carcinomas, including 44 nodules with microcalcification and five nodules with coarse calcification. After the injection of contrast agent, 29 nodules with microcalcification and two nodules with coarse calcification were categorized as inhomogeneous hypo-enhancement (Fig. 1). Thirteen nodules with microcalcification displayed inhomogeneous hypo-enhancement with penetration of contrast agent into the surrounding thyroid parenchyma and point-like appearance of contrast agent in the center of the nodule. Two nodules with microcalcification and two nodules with coarse
calcification were categorized as iso-enhancement, and one nodule with coarse calcification as hyper-enhancement.

In the benign group, there were 11 cases of thyroid adenoma and 62 cases of nodular goiter. In the 11 cases of thyroid adenoma, there were 10 cases with coarse calcification and 1 case with microcalcification. In the 62 cases of nodular goiter, 46 and 16 cases had coarse calcification and microcalcification, respectively. All 11 cases of thyroid adenoma were categorized as homogeneous hyper-enhancement, and the enhancement degree was higher than that of the surrounding thyroid parenchyma (Fig. 2). In the 46 cases of nodular goiter with coarse calcification, 37, seven, and two cases were categorized as homogeneous iso-enhancement (Fig. 3), homogeneous hyper-enhancement, and inhomogeneous hypo-enhancement, respectively. In the 16 cases of nodular goiter with microcalcification, nine, three, and four cases were categorized as homogeneous iso-enhancement, homogeneous hyper-enhancement, and inhomogeneous hypo-enhancement, respectively. The Chi-square test results ($\chi^2 = 80.75, p < 0.001$) showed that there was a
significant difference in enhancement degree in CEUS between benign and malignant thyroid nodules (Table 1).

Comparisons of quantitative parameters in CEUS between benign and malignant thyroid nodules

Results of CEUS quantitative parameters showed that there was no significant difference in time to enhancement and time to peak between benign and malignant nodules. The peak intensities between benign and malignant nodules were statistically different ($p < 0.05$) (Table 2).

Indexes of conventional ultrasound and CEUS in diagnosis of thyroid nodules

The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accordance rate of conventional ultrasound were 50%, 77%, 59%, 69%, and 66%, respectively, and those of CEUS were 90%, 92%, 88%, 93%, and 91%, respectively. There were significant differences between the two imaging methods ($p < 0.05$) (Table 3).

ROC curves of conventional ultrasound and CEUS in the diagnosis of thyroid nodules

In conventional ultrasound, the area under the ROC curve (AUC), standard error, 95% confidence interval, and $p$ value were 0.628, 0.052, 0.526—0.731, and 0.016, respectively. In CEUS, the AUC, standard error, 95% confidence interval, and $p$ value were 0.908, 0.031, 0.847—0.969, and $< 0.001$, respectively (Fig. 4).

Discussion

Thyroid calcification is divided into coarse calcification and microcalcification. On CEUS of thyroid nodules with calcification, malignant nodules are characterized by inhomogeneous hypo-enhancement, and benign nodules by homogeneous hyper-enhancement and iso-enhancement.

![Figure 3. Contrast-enhanced ultrasound of nodular goiter with coarse calcification.](image)

**Table 1** Comparison of enhancement degree in contrast-enhanced ultrasound between benign and malignant thyroid nodules.

<table>
<thead>
<tr>
<th>Pathological type</th>
<th>Coarse calcification</th>
<th>Microcalcification</th>
<th>Enhancement degree *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhomogeneous hypo-enhancement</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>5</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>Adenoma</td>
<td>10</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nodular goiter</td>
<td>46</td>
<td>16</td>
<td>6</td>
</tr>
</tbody>
</table>

* There was a significant difference of enhancement degree in CEUS between benign and malignant thyroid nodules ($\chi^2 = 80.75$, $p < 0.001$).
In this study, there were 49 nodules in the malignant group, which were all diagnosed as papillary carcinoma on pathological examination. Of these, 44 cases had microcalcification, of which 42 were categorized as inhomogeneous hypo-enhancement on CEUS. This finding concurs with the results of Bartolotta et al. [17], who reported that eight of 15 malignant nodules showed no or weak enhancement and were categorized as inhomogeneous.

One reason for this finding may be that the calcified bodies (psammoma bodies) with hard texture in papillary carcinoma affect tumor angiogenesis [7]. Thus, the absolute tumor microvessel density is decreased, leading to poor blood supply. Another reason is that, although there are numerous new vessels in tumor tissue, the tortuosity and irregularity of new vessels and malignant growth of the tumor destroys many tissue structures including blood vessels. The degree of vascular necrosis exceeds angiogenesis; thus, the enhancement degree of malignant nodules is significantly reduced, with manifestation of inhomogeneous hypo-enhancement on CEUS. In addition, interstitial fibrosis often occurs in thyroid papillary carcinoma, further reducing the number of vessels in the nodule [18]. In the benign group, there were 62 cases of nodular goiter and 11 cases of adenoma, suggesting that benign thyroid nodules with calcification are mainly nodular goiters (62/73). This is consistent with the observations reported by Seiberting et al. [19] and Khoo et al. [20] that angiographic manifestations are related to the pathological type of nodules. The nodular goiter is characterized by homogeneous iso-enhancement. The reason is that the nodular goiter has no fibrous capsule, and there is no obvious difference in vascular distribution between the nodule and the surrounding thyroid tissue. The internal blood flow status and perfusion of nodular goiters are close to those in normal thyroid tissue [18]. In this study, six cases of nodular goiter were categorized as inhomogeneous hypo-enhancement. The finding of inhomogeneous hypo-enhancement in this benign tumor type is related to the lesion development pattern of nodular goiter. At the late hyperplasia stage of nodular goiter, liquefaction, necrosis, and hemorrhage in parts of the thyroid gland and long-term compression of nodules lead to the above manifestations. The results of this study show that thyroid adenoma is characterized mainly by homogeneous hyper-enhancement. The main reason is that the adenoma has a complete capsule, with surrounding rich and thick vessels, resulting in relatively abundant blood supply and perfusion compared with normal thyroid tissue. This study also found that, in thyroid nodules with calcification, the malignant nodules are characterized mainly by inhomogeneous hypo-enhancement. Zhang et al. [21] found that inhomogeneous enhancement is strongly suggestive of a malignant nodule, which was also evident in this study. The angiographic characteristics of benign and malignant nodules are obviously different, with significant differences in peak intensity in CEUS between them.

Calcification is very common in thyroid nodular disease, and the occurrence of microcalcification in malignant thyroid nodules is high. It is generally believed that microcalcification with a maximum diameter of 2 mm is one of the morphological features of thyroid papillary carcinoma [22,23]. However, calcium oxalate crystals can form in nodular goiters and thyroid adenomas, and manifest as microcalcification on imaging studies. In this study, 16 cases of nodular goiter and one case of thyroid adenoma had microcalcification. In 49 cases of papillary carcinoma, 44 cases had microcalcification. This indicates that microcalcification may occur both in benign and malignant thyroid nodules. So differentiation of benign and malignant nodules with conventional ultrasound is restricted. CEUS technology has provided a new way of identifying benign and malignant thyroid nodules. However, image interpretation in CEUS is affected by visual resolution and subjective factors. In CEUS quantitative analysis technology, the

<table>
<thead>
<tr>
<th>Group</th>
<th>Time of enhancement beginning (s)</th>
<th>Time to peak (s)</th>
<th>Peak intensity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>12.20 ± 3.46</td>
<td>18.30 ± 4.87</td>
<td>85.58 ± 10.76</td>
</tr>
<tr>
<td>Malignant</td>
<td>13.13 ± 4.32</td>
<td>21.37 ± 5.11</td>
<td>41.40 ± 14.10</td>
</tr>
<tr>
<td>t</td>
<td>1.852</td>
<td>1.866</td>
<td>27.516</td>
</tr>
<tr>
<td>p</td>
<td>0.065</td>
<td>0.063</td>
<td>0.000</td>
</tr>
</tbody>
</table>

### Table 2
Comparison of quantitative parameters in contrast-enhanced ultrasound between benign and malignant thyroid nodules [mean ± standard deviation (SD)].

<table>
<thead>
<tr>
<th>Imaging method</th>
<th>Examination result</th>
<th>Pathological findings</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
<th>Diagnostic accuracy rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional ultrasound</td>
<td>Malignant</td>
<td>48.98</td>
<td>76.71</td>
<td>58.54</td>
<td>69.14</td>
<td>65.57</td>
<td></td>
</tr>
<tr>
<td>CEUS</td>
<td>Benign</td>
<td>89.80 *</td>
<td>91.78 *</td>
<td>88.00 *</td>
<td>93.06 *</td>
<td>90.98 *</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malignant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benign</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* p < 0.05 compared with conventional ultrasound.
changes in contrast agent perfusion with time can be visualized using a time–intensity curve [24,25], and the quantitative parameters including time to enhancement, time to peak, and peak intensity can be obtained. Compared with the conventional differential diagnosis method dependent on nodular morphological and blood flow observation, CEUS quantitative analysis provides additional valuable information [26,27]. In this study, the CEUS data of thyroid nodules were analyzed using TomTec 2D CPA MR quantification software. The results showed that the time to enhancement and time to peak were greater in malignant nodules than in benign nodules, and that the peak intensity of malignant nodules was lower than that of benign nodules (p < 0.05). While the time to enhancement and time to peak had no statistical significance (p > 0.05) in the benign and malignant thyroid nodules, the peak intensity played an important role in the diagnosis of thyroid nodules in this study.

Thyroid fine needle aspiration (FNA) is usually recommended prior to thyroid nodule resection, and in many institutions, it is always recommended for solitary nodules, regardless of the ultrasound findings of these nodules. However, approximately 2–3% of suspected malignant nodules are pathologically proven benign by FNA [28], and 7–10% cannot be diagnosed by FNA. Even repeated puncture fails to obtain diagnostic cytological results in 5–7% of cases [29]. CEUS provides a basis for determining which thyroid nodules should undergo FNA. It also aids in judging whether the nodules with suspected cytological results need repeated biopsy.

This study had several limitations. The malignant nodules were all papillary carcinomas, with no medullary carcinomas or undifferentiated carcinomas. Further, nodular goiters were the main type of benign nodule. This study therefore does not represent all pathological types of thyroid nodule. In further research, all pathological types of thyroid nodule with a large sample size should be collected for analyzing the CEUS features.

In conclusion, in the diagnosis of thyroid nodules with calcification, inhomogeneous hypo-enhancement in CEUS indicates malignant thyroid nodules, and homogeneous hyper-enhancement and iso-enhancement suggest benign nodules. CEUS is a valuable diagnostic tool in distinguishing benign and malignant thyroid nodules with calcification.

References


