Diagnostic Value of Conventional Ultrasonography Combined with Contrast-Enhanced Ultrasonography in Thyroid Imaging Reporting and Data System (TI-RADS) 3 and 4 Thyroid Micronodules

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Background: The present study was conducted to investigate the diagnostic performance of conventional ultrasonography (US) combined with contrast-enhanced ultrasonography (CEUS) in thyroid micronodules with thyroid imaging reporting and data system (TI-RADS) category 3 and 4.

Material/Methods: The features of conventional US and CEUS ion 102 case of thyroid micronodule samples, which were diagnosed based on pathological and clinical examination, were retrospectively analyzed. Logistic regression analysis was used to analyze the diagnostic accuracy in malignant thyroid micronodules. Receiver operator characteristic (ROC) curve was used to assess the performance of those 2 technologies.

Results: A significant difference in age was found between the benign and malignant groups. The benign and malignant groups showed significant differences in shape, margin, aspect ratio (A/T) \(\geq 1\), microcalcification, suspicious lymph gland, enhancement time, enhancement pattern, enhancement intensity, nodule sizes, enhancement margins, and rim-like enhancement. Logistic regression analysis of conventional US showed that A/T \(\geq 1\), irregular shape, microcalcification, and suspicious lymph glands are risk factors for thyroid micronodules, while logistic regression analysis of CEUS showed that slow enhancement time and absence of rim-like enhancement are risk factors for thyroid micronodules. Logistic regression analysis of conventional US combined with CEUS demonstrated that A/T \(\geq 1\), microcalcification, suspicious lymph gland, slow enhancement time, and absence with rim-like enhancement are risk factors. The ROC curve for conventional US, CEUS, and conventional US combined with CEUS were 90.0%, 90.7%, 99.0%, respectively.

Conclusions: Our results show that conventional US combined with CEUS had superior diagnostic performance for TI-RADS 3 and 4 thyroid micronodules compared with conventional US and CEUS alone.

MeSH Keywords: Diagnosis • Microscopy, Acoustic • Thyroid Neoplasms

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Background

Micronodules may be found during neck examination for non-nodular thyroid diseases, as well as in nodular thyroid disease when a clinical thyroid nodule is found to be associated with other non-clinically detected thyroid micro-nodules [1]. Generally, most patients with thyroid nodules lacked symptoms, with 5–10% of nodules having potential for malignancy [2]. Therefore, early diagnosis and adequate treatment are urgently needed to decrease the incidence of thyroid carcinoma [3]. In 2009, the Thyroid Imaging Reporting and Data System (TI-RADS), modeled on the breast imaging reporting and data system (BI-RADS) and the initial TI-RADS scores, classified and determined the risk of thyroid nodule malignancy with ultrasound scanning [4,5]. TI-RADS scores range from 1 (normal thyroid) to 6 (proven malignancy); TI-RADS 3 and TI-RADS 4 correspond to highly probable benign nodule and high suspicion for malignancy, respectively [6,7]. The use of the standardized sonographic lexicon may help to identify malignant nodules. Multiple diagnostic tools are currently available for thyroid nodules, including ultrasonography (US), thyroid nuclear scan, and fine-needle aspiration cytology (FNAC) [8].

Conventional US is a commonly used imaging method in the detection of breast lesions. Differentiation between benign and malignant lesions is difficult in many cases because of the overlap of grey-scale and color Doppler US findings [9]. As a major improvement in ultrasound, contrast-enhanced ultrasonography (CEUS) with ultrasound contrast agents (UCAs) has achieved great improvements in clinical practice in recent decades [10]. In addition, CEUS has several advantages over traditional imaging techniques, including cost-effectiveness, portability, lack of radiation, non-invasiveness, and better patient compliance [11], which may be why CEUS performs better than US in the diagnosis of renal cystic lesions [12]. CEUS plays an important role in the identification of malignant lesions in various organs, such as colon, gallbladder, pancreas, and kidney [13–15]. Although the improvement in diagnostic performance of conventional US combined with CEUS in the differentiation capability for benign from malignant breast masses has been elucidated in previous data [9], there is limited data on conventional US combined with CEUS in differentiating solitary thyroid nodule (STN) and micronodules from normal thyroid tissue. We performed the current study to investigate the diagnostic performance of conventional US combined with CEUS in micronodules with categories of TI-RADS 3 and TI-RADS 4.

Material and Methods

Ethics statement

The study was conducted according with the protocols proposed by the Ethics Committee of Sichuan Provincial People’s Hospital. Written informed consent was obtained from each subject before the study. All procedures in this study were in compliance with the Declaration of Helsinki [16].

Subjects

From September 2012 to July 2014, patients with thyroid disease who underwent conventional US or CEUS in Sichuan Provincial People’s Hospital were considered as candidates for inclusion. The inclusion criteria were: nodules with a hypoechoic aspect, normal thyroid tissue with homogeneous echogenicity, maximum diameter for thyroid nodules ≤10 mm, and category 3 or 4 in TI-RADS [17]. The exclusion criteria were: (1) patients with neck deformity, (2) patients with cystic nodules or mixed nodules with less parenchymal nodules, (3) solid components that cannot be revealed in nodules due to macrocalcification; (4) patients with severe allergies; and (5) patients who were pregnant. After applying the inclusion and exclusion criteria, a total of 102 patients (29 males and 73 females) were included, with age range 19–80 years. The thyroid lesions collected from included subjects had maximum diameter of 2.80–9.65 mm (mean, 6.69±1.70 mm). Among the included lesions, lesions with maximum diameter <5 mm accounted for 17.6% (18/102) and ≥5 mm for 82.4% (85/102). Thyroid lesions were confirmed either by surgery or biopsy and pathological examination was considered as the criterion standard [18]. All included patients were classified into either the malignant group or the benign group.

Conventional US/CEUS examination and image analysis

The MyLab90 (MyLab GOLD Platform) color Doppler ultrasonographic diagnosis set (Esaote, Genoa, Italy) was used for conventional US measurement. Linear array transducer LA523 with a center frequency of 4–13 MHz and LA522 with a center frequency of 3–9 MHz were equipped for all conventional US. Mechanical index was fixed at 0.05. Patients were told to lie on their back with full exposure of their neck. Neck accessories such as necklaces were removed before the measurement. Routine gray scale ultrasonography was used to observe the nodule location, number, size, shape, margin, and internal echogenicity. Then color Doppler and spectrum Doppler were used to observe the characteristics of the blood supply in lesions.

After conventional US was conducted and UCAs and vein passageways were prepared, CEUS was performed within a section to fully expose lesions and the surrounding normal thyroid
tissue. After the linear array transducer was fixed, patients were told to stop swallowing and to breathe calmly. Contrast Turned Imaging (CnTI) was set with a frequency of 6~8 MHz, capacity of 3%, sound pressure of 45 KPa, gamma of 46%, and depth of 3.0~4.0 cm. The focus was located slightly below the nodules. Then patients were injected in the median cubital vein with 1.0 ml of bubble disruption, which was diluted and shaken for 30 s, followed by 5 ml of normal saline. The timer on the US machine was started and the contrast medium was injected. Each contrast imaging acquisition at 120~180 s and the process of the ultrasound contrast were preserved in the ultrasonic instrument. The measurement was performed by 3 physicians who had ultrasonic experience of more than 3 years with the same instruction standards in order to minimize the bias from different operators.

General information on thyroid nodules echogenicity, size, shape, margins, aspect ratio (A/T), microcalcification, and presence/absence of lymphadenectomy in the neck was described based on the conventional US examination. Based on the Alder classification, the blood flow signals were classified into grade 0, grade I, grade II, and grade III [19].

Dynamic contrast images underwent successive or frame-by-frame playback and were evaluated based on 7 aspects: enhanced time, enhanced uniformity, enhanced pattern, enhanced intensity, size of the enhanced nodules, margins of the enhanced nodules, and rim-like enhancement, which were regarded as indicators for qualitative analysis. The diagnostic criteria for benign thyroid nodules were based on enhanced intensity of the peaked nodules (hyper-enhancement), unchanged nodules size, clear margins of the nodules, and presence of rim-like enhancement in nodule tissues. The malignant thyroid nodules were diagnosed based on slow enhance time, enhance intensity of the peaked nodules (iso-enhancement/hypo-enhancement), nodules size changes, unclear margins of the nodules, and absence of rim-like enhancement in nodule tissues.

### Statistical analysis

Data were analyzed using SPSS21.0 software (IBM Inc., Armonk, NY, USA). Categorical data are presented with percentage or ratio, while continuous data are expressed as $\bar{x} \pm s$. Each hypothesis was tested using the $t$ test (homogeneity of variance), $\chi^2$ test, or binary logistic regression analysis (forward selection method, $\alpha=0.05$). Receiver operator characteristic (ROC) curves were used to compare the diagnostic differences among the conventional US, CEUS, and combined use of conventional US and CEUS. $P$ values of less than 0.05 were considered to indicate statistical significance.

| Pathological types | Malignant group (n=52) | Benign group (n=50) | $\chi^2$ | $P$ |
|--------------------|------------------------|---------------------|---------|-----|
| Papillary thyroid carcinoma | 52 (100.0) | 0 (0.0) |       |     |
| Nodular goiter | 0 (0.0) | 34 (68.0) |       |     |
| Adenoma | 0 (0.0) | 6 (12.0) |       |     |
| Nodular or nodular hyperplasia | 0 (0.0) | 6 (12.0) |       |     |
| Focal granulomatous inflammation | 0 (0.0) | 3 (6.0) |       |     |
| Eosinophilic changes in Follicular epithelial cells | 0 (0.0) | 1 (2.0) |       |     |

### Table 1. The comparisons on basic information between the malignant group and benign group [n (%)].

| Disease conformation | Malignant group (n=52) | Benign group (n=50) | $\chi^2$ | $P$ |
|----------------------|------------------------|---------------------|---------|-----|
| FNA | 22 (42.3) | 36 (72.0) |       |     |
| Surgery | 52 (100.0) | 14 (28.0) |       |     |

FNA – fine needle aspiration.
Results

Basic information

Among the 102 subjects, 52 patients were included in the malignant group, among which 22 patients had preoperative fine-needle aspiration (FNA) and 52 patients received surgery. The remaining 50 patients were included in the benign group, among which 36 patients received preoperative FNA and 14 patients received surgery. In the malignant group, age range was 30~50 years. A significant difference was detected in age between the 2 groups (\(P<0.05\)), but no significant difference was found for sex (\(P>0.05\)) (Table 1).

Results of conventional US and color Doppler

Conventional US showed that the micronodules in PTC had the following characteristics: irregular shape, unclear margins, aspect ratio \(\geq 1\), microcalcification in nodules, majority 0–I blood flow signals, and presence of suspicious lymph gland (Figures 1, 2). There were significant differences in the above characteristics between the malignant group and benign group (all \(P<0.05\)) (Table 2).

Results of CEUS examination

CEUS examination with PTC was often characterized by slow enhancement time, non-centrality enhanced pattern, homogeneous enhanced uniformity, hyper-enhancement at peak, no size change of the nodules, clear margins and presence of rim-like enhancement (Figures 3, 4). There were significant differences in enhancement time, enhancement pattern, enhancement intensity, size change of nodules, margins, and rim-like enhancement between the malignant group and benign group (all \(P<0.05\)). No significant difference was detected in enhancement uniformity between the 2 groups (\(P>0.05\)) (Table 3).

Logistic regression analysis

Binary logistic regression analysis was conducted with pathological diagnosis as the dependent variable and statistically different indexes in convention US, CEUS, and conventional US combined with CEUS as independent variables. Logistic regression analysis was conducted with OR >1 indicating risk factors and OR <1 protective factors. Logistic regression analysis of conventional US showed that A/T \(\geq 1\), irregular shape, microcalcification, and suspicious lymph gland are risk factors for thyroid micronodules (Table 4), whereas logistic regression analysis of CEUS showed that slow enhancement time and absence of rim-like enhancement are risk factors for thyroid micronodules (all \(P<0.05\), OR >1) (Table 5). Logistic regression analysis of conventional US combined with CEUS demonstrated that A/T \(\geq 1\), microcalcification, suspicious lymph gland, slow enhancement time, and absence of rim-like enhancement are risk factors (all \(P<0.05\), OR >1) (Table 6).
Figure 3. PTC diagnostic images by CEUS. After 1.0 ml of ultrasound contrast agents was injected for 11 s, the normal thyroid tissue was homogeneously enhanced, while the tissues in solitary thyroid nodules presented with scattered microbubbles, indicating longer enhancement time. PTC, papillary thyroid carcinoma; CEUS, contrast-enhanced ultrasound.

Figure 4. PTC diagnostic images by CEUS. After 1.0 ml of ultrasound contrast agents was injected for 16 s, the normal thyroid tissue was homogeneously enhanced, while the tissues in solitary thyroid nodules was iso-enhanced, with irregular shape and absence of rim-like enhancement. PTC, papillary thyroid carcinoma; CEUS, contrast-enhanced ultrasound.

Table 2. The examination results on thyroid nodules by two dimensional ultrasound and color Doppler [n (%)].

| Characteristics      | Malignant group (n=52) | Benign group (n=52) | χ² | P     |
|----------------------|------------------------|---------------------|----|-------|
| Shape                |                        |                     |    |       |
| Regular              | 19 (36.5)              | 34 (68.0)           | 8.887 | 0.003 |
| Irregular            | 33 (63.5)              | 16 (32.0)           |     |       |
| Margins              |                        |                     |    |       |
| Clear                | 31 (59.6)              | 41 (82.0)           | 6.152 | 0.013 |
| Unclear              | 21 (40.4)              | 9 (18.0)            |     |       |
| Aspect ratio         |                        |                     | 13.06 | 0.001 |
| <1                   | 20 (38.5)              | 37 (74.0)           |     |       |
| >1                   | 32 (61.5)              | 13 (26.0)           |     |       |
| Micorcalcification   |                        |                     | 22.39 | <0.001|
| No/gross             | 24 (46.2)              | 45 (90.0)           |     |       |
| Yes                  | 28 (53.8)              | 5 (10.0)            |     |       |
| Blood flow signal    |                        |                     | 1.050 | 0.305 |
| II–III               | 11 (21.2)              | 15 (30.0)           |     |       |
| 0–I                  | 41 (78.8)              | 35 (70.0)           |     |       |
| Suspicious lymph gland |                      |                     | 31.12 | < 0.001|
| No                   | 14 (26.9)              | 41 (82.0)           |     |       |
| Yes                  | 38 (73.1)              | 9 (18.0)            |     |       |
An ROC curve was drawn using pathological diagnosis as the criterion standard. The ROC curve showed that US had an area under the ROC curve (AUC) of 90.0% and CEUS had an AUC of 90.7%, in contrast to the AUC of 99.0% for combined use of conventional US and CEUS (Figure 5), which indicated that the combination of these 2 methods had a superior diagnostic value compared with conventional US and CEUS alone.

**Discussion**

The current study investigated the diagnostic value of conventional US combined with CEUS in TI-RADS 3 and TI-RADS
4 thyroid micronodules. We demonstrated the combination of these 2 technologies showed superior performance compared with single use of conventional US or CEUS. Our results were further enhanced by the use of both logistic regression analysis and ROC curve. Although data show that the incidence of PTC has been decreasing significantly and the prognosis for this disease has greatly improved, the early detection on this disease still needs to be emphasized because it easily spreads to the lungs and bones [20–22]. Our study investigated the diagnostic value of conventional US combined with CEUS in TI-RADS 3 and 4 thyroid micronodules.

According to the definition of TI-RADS, patients with TI-RADS 3 presented with hyper-, iso-, or hypoechoic nodules, while TI-RADS 4 has a suspicious neoplastic pattern or malignant pattern [23]. Thyroid micronodules with maximum diameter ≤10 mm were selected because nodules larger than 1 cm have high potential to develop into clinically significant cancers [24,25]. With the high sensitivity and specificity of TI-RADS, diagnosis of thyroid nodules has shown great improvement using ultrasound contrast [26]. As an important diagnostic tool in predicting thyroid malignancy and selecting thyroid nodules, conventional US has been widely used world-wide [27]. The characteristics of suspicious thyroid nodules include marked hypo-echogenicity, irregular margins, microcalcifications, and a taller than-wide shape, which contribute to better diagnostic accuracy [28]. Consistent with these features, our study, using conventional 2-dimensional and color Doppler contrast, demonstrated that the micronodules in PTC had irregular shape, unclear margins, A/T ≥1, microcalcifications, blood flow 0-1, and suspicious lymph gland. Another meta-analysis, which showed that ultrasound features are important predictors of malignancy for thyroid nodules, reported a similar result regarding the accuracy of conventional US [29].

### Table 5. The multiple factors analysis on the characteristics of the CEUS on thyroid nodules.

| Variables                  | B     | S.E.  | Wald  | df  | Sig    | Exp(B) |
|----------------------------|-------|-------|-------|-----|--------|--------|
| Aspect ratio               | 4.751 | 2.142 | 4.921 | 1   | 0.027  | 115.75 |
| Micorcalcification         | 6.078 | 2.306 | 6.944 | 1   | 0.008  | 436.038|
| Suspicious lymph gland     | 5.296 | 2.012 | 6.93  | 1   | 0.008  | 199.551|
| Enhanced time              | 9.111 | 3.411 | 7.335 | 1   | 0.008  | 9053.725|
| Rim-like enhancement       | 9.021 | 3.124 | 8.339 | 1   | 0.004  | 8271.736|

US – ultrasound; B – regression coefficient; S.E. – standard error for regression coefficient; Wald – wald chi-square value; df – free degree; Sig – significance; Exp(B) – odds ratio.

### Table 6. The multiple factors analysis on the combined use of conventional US and CEUS.

| Variables                  | B     | S.E.  | Wald  | df  | Sig    | Exp(B) |
|----------------------------|-------|-------|-------|-----|--------|--------|
| Enhanced time              | 2.215 | 0.753 | 8.648 | 1   | 0.003  | 9.159  |
| Rim-like enhancement       | 4.315 | 0.826 | 27.319| 1   | 0.000  | 74.846 |

US – ultrasound; B – regression coefficient; S.E. – standard error for regression coefficient; Wald – wald chi-square value; df – free degree; Sig – significance; Exp(B) – odds ratio.

Figure 5. The ROC curves for conventional US, CEUS, and combined use of conventional US and CEUS. The ROC curve showed that US had an area under the ROC curve (AUC) of 90.0% and CEUS had an AUC of 90.7%, in contrast to the AUC of 99.0% for combined use of conventional US and CEUS. ROC – receiver operator characteristic; US – ultrasound; CEUS – contrast-enhanced ultrasound.
In this same setting, our study revealed that CEUS had significantly better sensitivity, specificity, and accuracy than conventional US. A previous study found that real-time CEUS showed remarkably different images in benign vs. malignant thyroid nodules; therefore, CEUS has clinical value use for differential diagnosis of STN [32]. Evidence supports that CEUS has a better visualization of the microcirculation and details of stenosis compared with conventional US and power Doppler [33]. Our study demonstrated that PTC tissues had hypo-enhancement and normal thyroid tissues had hyper-enhancement using CEUS. Most malignant nodules have fibrosis, calcification, focal necrosis, and aberrant blood vessels, which may lead to hypo-echogenicity on US and hypo-enhancement on CEUS [34]. However, research also found that the differential diagnosis between benign and malignant thyroid nodules using conventional imaging methods lacks reliability, and that CEUS enhancement patterns varied between benign and malignant lesions [35]. Nevertheless, CEUS is less accurate than pathological diagnosis [36]. Therefore, the combined use of conventional US and CEUS may improve accurate diagnosis of benign and malignant lesions compared with conventional US or CEUS alone, which is reflected in the improved specificity and accuracy and higher AUC in our results. Our findings are consistent with a previous study describing the value of CEUS combined with conventional US in the diagnosis of thyroid micro-carcinoma using a logistic regression model, which found that CEUS and conventional US were very effective in thyroid nodule diagnosis [37].

Conclusions

The findings of our study suggest that the combined use of conventional US and CEUS has superior diagnostic performance in TI-RADS category 3 and 4 thyroid micronodules, compared with conventional US and CEUS alone. Early diagnosis of thyroid nodules may be helpful in treatment strategy. Therefore, the combined use of conventional US and CEUS should be advocated in thyroid micronodule diagnosis. Further testing is required to confirm the findings of the current study.

Declare of interest

None.

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