Application value of contrast-enhanced ultrasound in preoperative localization of microwave ablation for primary hyperparathyroidism

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Funding information
National Scientific Foundation Committee of China, Grant/Award Number: 81871375

Abstract

Background: Ultrasonography (US) and 99mTechnetium-sestamibi scintigraphy (99mTc-MIBI) are currently first-line imaging modalities to localize parathyroid adenomas with sensitivities of 80% and 84%, respectively. Therefore, finding other modalities to further improve the diagnostic accuracy for preoperative localization is critically needed.

Purpose: To evaluate the application value of contrast-enhanced ultrasound (CEUS) in the preoperative localization of microwave ablation (MWA) for primary hyperparathyroidism (PHPT).

Methods: Between December 2012 and May 2021, 100 PHPT patients (34 males and 66 females; mean age, 56.31 ± 13.43 years; age range, 25–85 years) with 130 suspected parathyroid nodules were enrolled. US, CEUS, and 99mTc-MIBI were performed for the localization of pathological parathyroid glands. All patients were performed MWA under ultrasound guidance. All the suspected parathyroid nodules underwent core needle biopsy under ultrasound guidance during MWA to confirm the pathology. The diagnostic performance of all the imaging tests was analyzed in comparison with the pathological results.

Results: A total of 130 nodules suspected to be of parathyroid origin from preoperative localization images were confirmed by pathological results, of which 116 were of parathyroid origin, and 14 were not of parathyroid origin. The sensitivities, specificities, accuracy, and the area under receiver operating characteristic curve of CEUS in the localization of pathological parathyroid glands were 100%, 92.86%, 99.23%, and 0.964, which were significantly higher than those of US (93.10%, 42.86%, 87.69%, and 0.680) and 99mTc-MIBI (81.90%, 42.86%, 77.69%, and 0.624) (p < 0.05). The sensitivity and accuracy of CEUS were 100% and 97.22%, which were higher than those of 99mTc-MIBI (65.62% and 63.89%) or US (75.00% and 72.22%) in patients with multiple parathyroid glands (p < 0.05). For smaller parathyroid adenomas (≤2 cm in diameter), the sensitivities of CEUS in locating hyperfunctioning parathyroid glands were 100%, which was significantly higher than that of 99mTc-MIBI (73.68% and 84.31%, p < 0.05).

Conclusions: CEUS is a valuable preoperative localization method for PHPT patients performed MWA, especially for the patients with smaller pathological parathyroid gland and multiple glandular lesions.
1 | INTRODUCTION

Primary hyperparathyroidism (PHPT) is known as a common endocrine disorder, and hypercalcemia is the main biochemical indicator of the disease.1,2 Severe PHPT may lead to serious clinical symptoms, such as pathological fracture, peptic ulcer, hypertension, myasthenia, and other related diseases.3,4 Because PHPT is mainly due to a solitary benign parathyroid adenoma, surgical resection is currently the main treatment in PHPT patients.4,5 Minimally invasive treatment, including minimally invasive surgical resection and thermal ablation, has become possible and achieved a similar cure rate to traditional surgical resection.6–9 Imaging of parathyroid glands plays an important role in the localization of parathyroid adenomas prior to minimally invasive treatment.6,10 Ultrasonography (US) and 99mTechnetium-sestamibi scintigraphy (99mTc-MIBI) are currently first-line imaging modalities to localize parathyroid adenomas with sensitivities of 80% and 84%, respectively.11,12 However, these are related to the operator’s experience and the patient’s thyroid disease and surgical history.13–15 Four-dimensional parathyroid computed tomography remains a problem-solving technique in challenging cases and after failed neck exploration, but it has radiation.16,17 Therefore, finding other modalities to further improve the diagnostic accuracy for preoperative localization is critically needed.

In recent years, contrast-enhanced ultrasound (CEUS) has aroused great interest as an imaging modality to improve the sensitivity and specificity of detecting and localizing abnormal parathyroid tissue.18,19 In the setting of hyperparathyroidism, the glands are usually rich in blood supply. Typical peripheral blood supply or polar blood supply from the branch of the inferior thyroid artery can be seen.20 CEUS can dynamically detect microvascular perfusion, and microvascularization can be regarded as a reliable symptom to localize parathyroid gland adenomas in the preoperative period.21 In addition, the research and development of perfusion analysis software can provide a quantitative information about tissue perfusion and then benefit the localization of hyperfunctional parathyroid glands.22 Recent studies have shown CEUS can elevate the accuracy of preoperative localization of glands, especially in detecting double adenomas.18,21 However, to our knowledge, the localization effect of CEUS in thermal ablation of PHPT is lacking. Therefore, the focus of this study was to clinically assess the value of CEUS in preoperative localization for PHPT patients performed microwave ablation (MWA) compared with conventional US and 99mTc-MIBI.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

From December 2012 through May 2021, patients with hyperparathyroidism who underwent MWA under ultrasound guidance at our department were enrolled. Exclusion criteria were secondary or tertiary hyperparathyroidism as well as allergy to contrast agent (SonoVue, Bracco, Italy). The diagnosis of PHPT was based on recommendations proposed by the International Workshop on PHPT.3 Parathyroid lesions were localized by US, CEUS, and 99mTc-MIBI before ablation in all patients. Outcomes from the imaging modalities were reported as uniglandular disease, multiglandular disease, or negative. The ablated nodule was determined by the doctor who performed MWA based on the findings of all the localization imaging modalities. Ultrasound-guided core needle biopsy was performed for all the suspected parathyroid nodules on any of the localization imaging modalities during ablation to confirm the pathology. All imaging outcomes were compared with pathological results. Cure was defined as a patient whose blood calcium level remained normal more than half a year after MWA. This study was approved by our institutional human research review committee. Written informed consent was obtained from all patients.

2.2 | Preoperative localization imaging

All US examinations of the thyroid and the parathyroid gland region were accomplished by ultrasound experts with more than 15 years of experience in neck ultrasound using a multifrequency linear probe. During the examination, we placed the patient in a supine position with their necks hyperextended and tried to fully expose the front of the neck. B-scan US was used to examine the both sides of thyroid and parathyroid in the axial and longitudinal plane. Store the digital imaging for at least 30 s. Parathyroid lesion features, such as size, internal echo, margin, and texture were evaluated. Color-coded Doppler sonography and power Doppler imaging were used for assessment of microvascularization.

CEUS was accomplished by an ultrasound expert with more than 15 years’ experience in CEUS using a multifrequency linear probe (6–9 MHz/LOGIQ E9/GE)—who are blinded to MIBI results. After the B-scan US and Doppler assessment of the suspected lesion, we selected the largest section of the lesion as the
CEUS observation section and switched to CEUS mode. Dynamic CEUS was performed with a low mechanical index between 0.08 and 0.16. It is necessary to advise patients to avoid swallowing and speaking during imaging process. Each patient was given a rapid bolus injection of 2.4 ml sulfur hexafluoride microbubbles (SonoVue, Bracco, Italy) followed by 5 ml saline solution via a cubital venous cannula. The dynamic imaging sequences were documented from injection of contrast agent continuing to wash out. Imaging observation and acquisition time were no less than 3 min. Positive findings for CEUS in suspected parathyroid adenomas were early arterial hypervascularization from the margin to the center plus washout in the late phase.

Dual-phase $^{99m}$Tc-MIBI planar imaging was composed of early imaging and delayed imaging, which were obtained 30 min and 2 h after injection of 740 MBq $^{99m}$Tc-MIBI intravenously, respectively. Planar images from the neck to the front chest were performed in a $128 \times 128$ matrix, 140 keV photo-peak, and low-energy high-resolution parallel collimator. The typical finding of parathyroidism appeared as an area with increased $^{99m}$Tc-MIBI uptake near the thyroid tissue in the early phase and become predominant with thyroid uptake and washout in the late phase. All imaging analyses were independently performed by two nuclear medicine specialists.

### 2.3 Statistical analysis

Data analysis was performed using SPSS17.0 for windows (SPSS Inc., Chicago, IL, USA) and the continuous data were expressed as mean $\pm$ standard deviation where data followed a normal distribution, or medians, and interquartile range where they did not. Based on the pathological results as the gold standard, the sensitivity (defined as the ratio of true-positive tests to the sum of true-positive and false-negative tests), specificity, accuracy, positive predictive value, and negative predictive value of each of three localization imaging modalities were calculated. The McNemar test was used to compare the ratios of different imaging modalities. $p$ Values of $<0.05$ were regarded as statistically significant.

### 3 RESULTS

#### 3.1 Characteristics of population

A total of 110 patients met the inclusion criteria, whereas 10 were excluded because that were diagnosed as secondary hyperparathyroidism. Of the 100 patients with PHPT (34 males and 66 females; mean age, $56.31 \pm 13.43$ years; age range, 25–85 years) who underwent MWA, all patients received preoperative localization using US, CEUS, and $^{99m}$Tc-MIBI (Figure 1).

![Figure 1](image1.png)

**Figure 1** A 49-year-old female patient with HPHT. (a) Ultrasonography (US) shows a hypoechoic nodule behind the left thyroid lobe and contrast-enhanced ultrasound (CEUS) shows high enhancement in the arterial phase (white arrow); (b) $^{99m}$Technetium-sestamibi scintigraphy ($^{99m}$Tc-MIBI) scintigraphy shows a positive nodule in the left lobe of the thyroid (black arrow).

The flowchart of this study shown in Figure S1. In all 100 patients, a total of 130 nodules suspected of parathyroid origin in preoperative localization images were confirmed by pathological results, of which 116 were of parathyroid origin and 14 were of non-parathyroid origin. A total of 116 parathyroid gland lesions confirmed by pathology were found in 98 patients. No parathyroid gland lesions were found in two patients. One was thyroid adenoma and the other was sympathetic ganglion (Horner syndrome after biopsy and MWA). In addition, the remaining 12 non-parathyroid nodules were lymph nodes. The comparison among US, MIBI, and CEUS regarding pathological results (parathyroid hormone (pg/ml), calcium (mmol/L), phosphorus (mmol/L), and ALP (IU/L)) was shown in Tables S1–S4. Details regarding participation are presented in Table 1. The blood calcium of 96 patients remained normal for more than 6 months after MWA. The cure rate was 96%.

#### 3.2 Localization results of US, CEUS, and $^{99m}$Tc-MIBI

CEUS correctly localized all abnormal parathyroid glands, whereas only 95 parathyroid lesions were
TABLE 1  Patient characteristics and preoperative laboratory findings

| Characteristics                          | Value                |
|------------------------------------------|----------------------|
| Patients (n)                             | 100                  |
| Age (years)                              | 56.31 ± 13.43        |
| Gender (male/female)                     | 34/66                |
| Body mass index                          | 23.57 ± 3.03         |
| Preoperative parathyroid hormone (pg/ml) | 132.85 (101.38, 214.13) |
| Preoperative serum calcium (mmol/L)      | 2.64 (2.48, 2.84)    |
| ALP (IU/L)                               | 86.05 (62.40, 111.25) |
| Phosphorus (mmol/L)                      | 0.89 ± 0.22          |
| 25(OH)D3 (ng/ml)                         | 12.76 ± 5.97         |
| Patients with unigland/multigland        | 84/14                |
| Pathological findings                    | 116                  |
| Parathyroid nodules                      | 59                   |
| Location                                 | 57                   |
| Right                                    | 1                    |
| Left                                     | 1                    |
| Thyroid adenoma                          | 12                   |
| Sympathetic ganglion                     |                      |
| Lymph nodes                              |                      |

Note: Data are means ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables. Normal range: iPTH 15–65 pg/ml, calcium 2.09–2.54 mmol/L, phosphorus: 0.89–1.6 mmol/L, ALP: 0–130 IU/L; 25(OH)D3: 20–32 ng/ml.

TABLE 2  Comparison among contrast-enhanced ultrasound (CEUS), ultrasonography (US), and MIBI in all patients

| Parameters           | US (%) | CEUS (%) | MIBI (%) | p Value | US vs. CEUS | US vs. MIBI | CEUS vs. MIBI |
|----------------------|--------|----------|----------|---------|-------------|-------------|---------------|
| Sensitivity          | 93.10  | 100      | 81.90    | 0.008   | 0.011       | <0.001      |               |
| Specificity          | 42.86  | 92.86    | 42.86    | 0.039   | 1.000       | 0.039       |               |
| Accuracy             | 87.69  | 99.23    | 77.69    | <0.001  | 0.035       | <0.001      |               |
| Positive predict value| 93.10  | 99.15    | 92.23    |         |             |             |               |
| Negative predict value| 42.86  | 100.00   | 22.22    |         |             |             |               |

FIGURE 2  The receiver operating characteristic (ROC) curves for MIBI, ultrasonography (US), and contrast-enhanced ultrasound (CEUS) imaging modalities in the localization of parathyroid glands. The green curve represents the area under receiver operating characteristic curve (AUC) of MIBI imaging and the AUC value is 0.624. The orange curve represents the AUC of US imaging and the AUC value is 0.680. The blue curve represents the AUC of CEUS imaging and the AUC value is 0.964.

detected by MIBI and 108 by US. The sensitivity, specificity, accuracy, and the area under receiver operating characteristic curve (AUC) of CEUS in the localization of pathological parathyroid glands were 100%, 92.86%, 99.23%, and 0.964, which were significantly higher than those of US (93.10%, 42.86%, 87.69%, and 0.680, p < 0.05) and 99mTc-MIBI (81.90%, 42.86%, 77.69%, and 0.624, p < 0.05) (Table 2 and Figure 2). Using conventional US, pathological parathyroid glands in eight cases were not correctly detected. In addition, among the parathyroid nodules diagnosed by ultrasound, there were six lymph nodes, one thyroid nodule, and one sympathetic ganglion. In addition, 21 pathologically confirmed abnormal parathyroid gland lesions were not detected by 99mTc-MIBI. The characteristics of nodules with false-negative and false-positive diagnoses on ultrasound and MIBI were shown in Table S5. We found the median diameters of misdiagnosis nodules by US imaging and MIBI imaging were small (US 0.85 and 0.95 cm; MIBI 1.1 and 1.1 cm, respectively). Moreover, nodules are more likely to be misdiagnosed if they are in the lower left. Among the lesions diagnosed as parathyroid adenoma by MIBI and US, there were six cases of misdiagnosis, respectively, which were verified to be lymph nodes (Figure 3). For the diagnosis of lymph nodes, CEUS has higher diagnostic sensitivity (91.7%), specificity (100%), and accuracy (99.2%) than conventional US (sensitivity, 50.0%, p = 0.125; specificity, 93.1%, p = 0.008; accuracy, 89.0%, p = 0.001, respectively).

The diagnostic sensitivity of three imaging methods for different sizes of parathyroid nodules was analyzed (Table 3). The sensitivity of CEUS was all 100% in three groups (d ≤ 1; 1 < d ≤ 2; d > 2). For nodules larger than 2 cm in diameter, there was no difference in sensitivity among the three imaging methods. For parathyroid nodules less than 2 cm in diameter, especially parathyroid
A 51-year-old-female patient with HPHT. Pathology showed that the left lower pole lesion was lymph node and the right lower pole lesion was parathyroid adenoma. (a) Ultrasonography (US) shows a hypoechoic nodule behind each of the right thyroid lobe ((i) cross section, (ii) longitudinal section, white arrows) and the left thyroid lobe ((iii) cross section, (iv) longitudinal section, white arrows), considering parathyroid adenoma; (b) the hypoechoic nodule at the right lower pole showed overall high enhancement in arterial phase (white arrows), considering parathyroid adenoma, and (c) contrast-enhanced ultrasound (CEUS) showed that the lesions in the arterial phase of the left lower very hypoechoic nodule showed enhancement of hilus like structure (white arrows), considering lymph nodes.

TABLE 3 Comparison among contrast-enhanced ultrasound (CEUS), ultrasonography (US), and MIBI sensitivity in patients with different lesion sizes

| Lesion diameter (cm) | US (%) | CEUS (%) | MIBI (%) | p Value |
|----------------------|-------|--------|--------|--------|
|                      | US vs. CEUS | US vs. MIBI | CEUS vs. MIBI |
| ≤ 1                  | 86.84   | 100    | 73.68  | 0.063  | 0.267 | 0.002 |
| 1 < d ≤ 2           | 96.07   | 100    | 84.31  | 0.500  | 0.031 | 0.008 |
| > 2                 | 96.29   | 100    | 88.88  | 1.000  | 0.625 | 0.250 |

nodules less than 1 cm in diameter, the sensitivity of CEUS was significantly higher than that of $^{99m}$Tc-MIBI ($p < 0.05$), although there was no significant difference between US and CEUS.

The diagnostic ability of three imaging methods for patients with single and multiple gland diseases was analyzed (Table 4). Out of the 116 pathological parathyroid glands in 98 patients, 84 patients had unigland disease, and 14 patients had multigland disease. The sensitivity and accuracy of CEUS were significantly higher than that of $^{99m}$Tc-MIBI in patients with unigland disease or multigland disease ($p < 0.05$). Especially in patients with multigland disease, the sensitivity and accuracy of CEUS were 100% and 97.22%, which were higher than those of US or $^{99m}$Tc-MIBI ($p < 0.05$).
### TABLE 4
Comparison among contrast-enhanced ultrasound (CEUS), ultrasonography (US), and MIBI in patients with single and multiple gland disease

| Parameters         | US (%) | CEUS (%) | MIBI (%) | p Value US vs. CEUS | p Value US vs. MIBI | p Value CEUS vs. MIBI |
|--------------------|--------|----------|----------|---------------------|--------------------|-----------------------|
| **Unigland**       |        |          |          |                     |                    |                       |
| Sensitivity        | 100    | 100      | 88.09    | 1.000               | 0.002              | 0.02                  |
| Specificity        | 50.00  | 100      | 50.00    | 0.125               | 1.000              | 0.125                 |
| Accuracy           | 95.65  | 100      | 84.78    | 0.125               | 0.031              | <0.001                |
| Positive predict value | 95.45  | 100      | 94.87    |                     |                    |                       |
| Negative predict value | 91.30  | 100      | 28.57    |                     |                    |                       |
| **Multigland**     |        |          |          |                     |                    |                       |
| Sensitivity        | 75.00  | 100      | 65.62    | 0.008               | 0.581              | 0.001                 |
| Specificity        | 50.00  | 75.00    | 50.00    | 1.000               | 1.000              | 1.000                 |
| Accuracy           | 72.22  | 97.22    | 63.89    | 0.012               | 0.607              | 0.002                 |
| Positive predict value | 92.31  | 96.97    | 91.30    |                     |                    |                       |
| Negative predict value | 20.00  | 100      | 15.38    |                     |                    |                       |

4 | DISCUSSION

Parathyroid minimally invasive surgical resection or thermal ablation can effectively relieve the symptoms of bone and joint pain, and muscle weakness and reduce the risk of fracture and cardiovascular calcification. Therefore, the success rate of this operation and the recurrence rate after operation, to a certain degree, depend on an accurate preoperative localization of the abnormal parathyroid glands. Parathyroid adenomas usually get their blood supply from branches of the inferior thyroid artery. CEUS has an advantage in dynamically detecting microcirculation. Therefore, CEUS has potential significance in the localization of parathyroid gland lesions, and it is of great significance to define its role in localization of pathological parathyroid glands. This study successfully demonstrated the feasibility of CEUS in the preoperative localization of MWA of PHPT for the first time.

In our study, the sensitivity, specificity, and accuracy of CEUS in the localization of pathological parathyroid glands were 100%, 92.86%, and 99.23%, which were significantly higher than those of US (93.10%, 42.86%, and 87.69%) and 99mTc-MIBI (81.90%, 42.86%, and 77.69%) (p < 0.05). 99mTc-MIBI and US are commonly used in clinical preoperative localization of abnormal parathyroid glands. Korwar et al. reported that US (80.80%, 92.35%, and 75.73%) was superior to 99mTc-MIBI (71.82%, 94.61%, and 69.00%) and SPECT (70.21%, 97.78%, and 69.11%) in terms of sensitivity, positive predictive value, and accuracy. With its clinical application, CEUS gradually shows a unique diagnostic value compared with conventional US and 99mTc-MIBI. Uller et al. compared the results of B-scan US and CEUS and showed that CEUS could accurately evaluate microcirculation of the parathyroid with both sensitivity and specificity of 98.4%. Our study showed similar results to these previous studies. As to the hyperfunctioning parathyroid gland, we can see hypoechoic structure with uniform echogenicity and hypervascular on color Doppler around the capsule and centrally in ultrasound and rapid contrast enhancement from the margin in the CEUS arterial phase compared to the thyroid. In addition, CEUS can effectively distinguish between parathyroid glands and lymph nodes according to the enhancement characteristics. Parathyroid adenoma and parathyroid hyperplasia presented with early and homogeneous hyperenhancement, with central washout in the later phases. But benign lymph nodes were observed centrifugal and homogeneous enhancement, and a complete bright ring in the subcapsule of the lymph nodes.

The three imaging methods had different abilities in the localization diagnosis of parathyroid adenomas of different sizes. For nodules larger than 2 cm in diameter, there were no difference in sensitivity among the three imaging modes in our study. However, for parathyroid adenomas with a diameter of less than 2 cm, especially those with a diameter of less than 1 cm, the sensitivity of CEUS was significantly higher than that of MIBI (p < 0.05), although there was no difference between US and CEUS, due to the limitation of sample size. Similar to what reports by other authors, Carral et al. reported size of removed adenoma ≤1 cm was an independent association between negative 99mTc-MIBI scanning. 99mTc-MIBI results are also affected by patient’s thyroid disease, body mass index, and surgical history. Besides, gland weight could also affect the 99mTc-MIBI result, and the smaller the gland nodule, the more likely it is to be negative.

In our study, the sensitivity and accuracy of CEUS were significantly higher than that of 99mTc-MIBI in patients with single gland disease or multigland disease (p < 0.05). Especially in patients with multigland disease, the sensitivity and accuracy of CEUS are higher than US or 99mTc-MIBI (p < 0.05). Bhansali et al. in their reports described that the sensitivity and positive predictive value of single gland abnormality detected by
US were 73% and 100%, respectively, whereas those of radionuclide imaging were 98%. Among the patients with multigland disease, of the 10 abnormal parathyroid lesions detected by surgical exploration, 3 were missed by US and 6 were missed by radionuclide scan. In our study, the sensitivity of US to detect a single adenoma was 98.1%, similar to other relevant experience using US. Patients with multigland disease have a higher false negative rate of $^{99m}$Tc-MIBI, which may be concerned with different functional activities of various abnormal glands, making the tracer less available for poorly functioning glands. Compared with $^{99m}$Tc-MIBI and US, CEUS is a better method of preoperative localization for patients with multigland PHPT. However, CEUS also has some limitations, especially in ectopic glands, so alternative imaging techniques will still be required. Moreover, sufficient medical equipment and skilled examiners are the prerequisite for accurate preoperative localization.

There are some limitations in our study. First, the number of non-parathyroid gland nodules was less. Studies with a larger sample size are needed. Second, the gold standard in this study is based on the pathological results of biopsy, not the pathology after bilateral exploration and resection of the parathyroid gland, and there is the possibility that location is missing on all imaging modalities, although this situation is rare.

5 CONCLUSION

CEUS is a valuable preoperative localization method for patients with PHPT, especially for those with smaller pathological parathyroid glands or and multiple glandular lesions.

ACKNOWLEDGMENTS

We thank all the participants in this study. We thank all the clinical staff who made sample collection possible.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTION

Study conception or design: Ping Liang, Fangyi Liu; analysis, or interpretation of data: Yunlin Li, Yang Liu; drafting the work or revising: Fangyi Liu; contributing patients and collecting data: Li Zang, Zhiwei Guan, Xiaoling Yu, Zhiyu Han; all authors read, revised, and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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**How to cite this article:** Liu F, Zang L, Li Y, et al. Application value of contrast-enhanced ultrasound in preoperative localization of microwave ablation for primary hyperparathyroidism. J Appl Clin Med Phys. 2022;23:e13802. https://doi.org/10.1002/acm2.13802