Efficacy and Safety of Ultrasound-Guided Radiofrequency Ablation for Primary Hyperparathyroidism: A Prospective Study

Hui-hui Chai1, 2, Yu Zhao3, 4, Zeng Zeng2, Rui-zhong Ye2, Qiao-hong Hu2, Hong-feng He2, Jung Hwan Baek5, Cheng-zhong Peng1, 6, 7, 8

1Department of Graduate, Bengbu Medical College, Bengbu, China; 2Department of Ultrasound, Zhejiang Provincial People’s Hospital, Affiliated People’s Hospital, Hangzhou Medical College, Hangzhou, China; 3Health Management Center, Department of Endocrinology, Zhejiang Provincial People’s Hospital, Affiliated People’s Hospital, Hangzhou Medical College, Hangzhou, China; 4Key Laboratory of Endocrine Gland Diseases of Zhejiang Province, Hangzhou, China; 5Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; 6Department of Medical Ultrasound, Shanghai Tenth People’s Hospital, Shanghai, China; 7Ultrasound Research and Education Institute, Clinical Research Center for Interventional Medicine, Tongji University School of Medicine, Shanghai, China; 8Shanghai Engineering Research Center of Ultrasound Diagnosis and Treatment, Shanghai, China

Objective: To assess the efficacy and safety of ultrasound (US)-guided radiofrequency ablation (RFA) in patients with primary hyperparathyroidism (PHPT).

Materials and Methods: This prospective study enrolled 39 participants (14 male, 25 female; mean age, 59.5 ± 15.3 [range, 18–87] years) between September 1, 2018, and January 31, 2021. All participants had parathyroid lesions causing PHPT, proven biochemically and through imaging. The imaging features of the PHPT nodules, including the shape, margin, size, composition, and location, were evaluated before treatment. Serum intact parathyroid hormone, calcium, and phosphorus levels; parathyroid nodule volume; and PHPT-related symptoms were recorded before and after treatment. We calculated the technical success, biochemical cure, and clinical cure rates for these patients. Complications were evaluated during and after the ablation.

Results: Complete ablation was achieved in 38 of the 39 nodules in the 39 enrolled participants. All the patients were treated in one session. The technical success rate was 97.4% (38/39). The mean follow-up duration was 13.2 ± 4.6 (range, 6.0–24.9) months. At 6 and 12 months post-RFA, the biochemical cure rates were 82.1% (32/39) and 84.4% (27/32), respectively, and the clinical cure rates were 100% (39/39) and 96.9% (31/32), respectively. Only 2.6% (1/39) of the patients had recurrent PHPT. At 1, 3, 6, and 12 months after technically successful RFA, 44.7% (17/38), 34.3% (12/35), 15.8% (6/38), and 12.5% (4/32) of participants, respectively, had elevated eucalcemic parathyroid hormone levels. Recurrent laryngeal nerve paralysis occurred in 5.1% (2/39) of the patients, who recovered spontaneously within 1–3 months.

Conclusion: US-guided RFA was effective and safe for PHPT patients. RFA may be an alternative treatment tool for patients who cannot tolerate or refuse to undergo surgery.

Keywords: Radiofrequency ablation; Primary hyperparathyroidism; Intact parathyroid hormone; Parathyroid glands; Interventional ultrasound

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Corresponding author: Cheng-zhong Peng, MD, Department of Medical Ultrasound, Shanghai Tenth People’s Hospital; Ultrasound Research and Education Institute, Clinical Research Center for Interventional Medicine, Tongji University School of Medicine; Shanghai Engineering Research Center of Ultrasound Diagnosis and Treatment, 301 Yanchang Zhong Road, Shanghai 200072, China.
• E-mail: pcz001@126.com; and
Jung Hwan Baek, MD, PhD, Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
• E-mail: radbaek@naver.com

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common disorder of calcium, phosphate, and bone metabolism caused by increased release of parathyroid hormone (PTH) by the parathyroid glands [1]. It is traditionally characterized by elevated PTH and hypercalcemia [1]. The incidence of PHPT varies from 0.4–82.0 per 100000 population [2,3]. Clinical manifestations of symptomatic PHPT mainly involve bones and kidneys, resulting in severe bone disease, renal stones, and fractures [4,5]. Asymptomatic PHPT often presents with mild hypercalcemia, reduced bone mineral density, increased risk of fracture, and clinically asymptomatic kidney stones [5]. Normocalcemic PHPT is a recognized variant of PHPT [6] with complications similar to those of hypercalcemic PHPT. This is thought to be an early form of PHPT [7]. Parathyroidectomy is the first-line therapy in patients with PHPT, with a clinical cure rate of approximately 95.0%–99.0% [1,5,8,9]. However, parathyroidectomy is an extensive and complex procedure associated with a high risk of complications [10,11]. Some patients cannot tolerate or refuse to undergo the procedure [12]. Recently, thermal ablation, including laser ablation [13], microwave ablation [14], high-intensity focused ultrasound (US) [15], and radiofrequency ablation (RFA) [16], has been used in patients with PHPT. Since US-guided RFA was first used successfully in 2002 by Hächsl et al. [17], as a treatment for single parathyroid adenoma in humans, RFA has emerged as a novel method for managing PHPT [16,18,19]. However, to the best of our knowledge, no prospective studies have reported on patients who underwent RFA for PHPT. This prospective study aimed to gather more evidence on the efficacy and safety of US-guided RFA in patients with PHPT.

MATERIALS AND METHODS

Participants

From September 1, 2018, to January 31, 2021, 48 patients with biochemically proven PHPT from the inpatient department of Zhejiang Provincial People’s Hospital were prospectively evaluated for RFA treatment. Thirty-nine patients (39 parathyroid nodules) were eligible for RFA because they fulfilled all the inclusion criteria and were subsequently enrolled in this prospective study (Approval No. ChiCTR-ONC-17012760). Figure 1 shows the flowchart of the patient selection process. The study protocol was approved by the Human Ethics Review Committee of the Zhejiang Provincial People’s Hospital. Written informed consent was obtained from all participants before ablation.

Patients were included in this study if they met all the following criteria: 1) symptomatic or asymptomatic PHPT, 2) a single enlarged parathyroid gland detected by

![Flowchart showing the patient selection process.](https://example.com/flowchart.png)

CECT = contrast-enhanced computed tomography, FNA = fine-needle aspiration, PHPT = primary hyperparathyroidism, PTH = parathyroid hormone, PTX = parathyroidectomy, RFA = radiofrequency ablation, US = ultrasound, $^{99m}$Tc-sestamibi SPECT = technetium 99-m-labeled sestamibi single-photon emission computed tomography
preoperative imaging (US and contrast-enhanced neck computed tomography [CECT]), and 3) positive technetium 99-m-labeled sestamibi single-photon emission computed tomography [99mTc-sestamibi SPECT] results or negative 99mTc-sestamibi SPECT results but the gland confirmed as parathyroid tissue by fine-needle aspiration biopsy with tissue fluid PTH analysis [20]. Patients with asymptomatic PHPT were included if at least one of the following conditions was met [9]: 1) blood calcium > 0.25 mmol/L above the upper limit of normal, 2) T-score < -2.5 at the lumbar spine, total hip, femoral neck, or distal third of the radius, significantly reduced bone density, and/or increased risk of vertebral fracture, 3) reduction in creatinine clearance to < 60 mL/min, 4) biochemical stone risk analysis suggesting an increased risk of kidney stones or 24-hour urinary calcium > 400 mg/day with calcium-containing stones, or 5) age < 50 years.

Patients were excluded from this study if they met at least one of the following criteria: 1) secondary or tertiary hyperparathyroidism, 2) history of parathyroidectomy or ablation for hyperparathyroidism, 3) hoarseness or any vocal cord movement abnormalities, 4) no parathyroid nodule found on US or a nodule with suspicious malignant features such as irregular shape, intra-nodular calcifications, infiltrative border, or maximum diameter > 30 mm [21-23] or a technically inaccessible location.

Fig. 2. Imaging features of parathyroid nodule not suited for US-guided RFA.
A1. US image reveals that the nodule’s posterior margin is not clear (white arrows); the blue dotted line represents the horizontal line 30 mm from the body surface. A2. 99mTc-sestamibi SPECT image shows accumulation of the radiotracer (black arrow) in the neck in the late phase. A3. CECT images confirm a depth of more than 30 mm between the posterior margin (blue arrows) of the nodule and body surface. B1. US images show that a parathyroid nodule (thick white arrows) has internal calcifications, and the medial margin is not clearly delineated due to posterior shadowing of the trachea (thin white arrow) and retrotracheal location. B2. 99mTc-sestamibi SPECT image shows that the nodule had radioactive concentration (black arrow) in the late phase. B3. CECT image showing a nodule (blue arrows) located behind the trachea. C1. US image shows an enlarged parathyroid gland (thick white arrows) located behind the innominate artery (thin white arrow). C2. 99mTc-sestamibi SPECT image shows that the nodule had radioactive concentration in the superior mediastinum (black arrow) in the late phase. C3. CECT image showing an enhanced supamediastinal mass (blue arrows) located behind the innominate artery and sternum. CECT = contrast-enhanced computed tomography, RFA = radiofrequency ablation, US = ultrasound, 99mTc-sestamibi SPECT = technetium 99-m-labeled sestamibi single-photon emission computed tomography.
(Fig. 2) such as a depth > 30 mm between the posterior margin of the nodule and surface of the body [15,24,25], retrotracheal parathyroid, or substernal parathyroid [26], 5) prothrombin time > 18 seconds, prothrombin activity < 60%, or a platelet count < 60 x 10^9/L, or 6) cardiac insufficiency or refractory hypertension that could not be controlled with medication [14].

Pre-Ablation Assessment

An iU22 US system (Philips Healthcare) and high-frequency linear probe (L12-5) were used for US guidance. A radiofrequency generator (VIVA RF generator; STARmed) with an 18-gauge monopolar internally cooled electrode (VIVA; STARmed) was used. The radiofrequency electrode had a 7-cm length shaft with a 0.7-cm active tip and was cooled by a water circulation pump (VIVA pump; STARmed). CEUS with a contrast agent (SonoVue; Bracco) and high-frequency linear probe (L9-3) were used to evaluate the effect of RFA. 99mTc-sestamibi SPECT (Infinia; GE Healthcare) and CECT (Definition AS; Siemens Healthcare) were routinely performed before RFA. Nodule volume was calculated using the sphere formula (V = π x length x width x depth/6).

Demographic, clinical, and biochemical data (such as patient age, sex, symptoms, size of the enlarged parathyroid gland, and intact PTH [iPTH], calcium, and phosphorus levels) were collected from all participants before ablation.

RFA Procedures

Before RFA, the participant was placed in a supine position with the neck hyperextended. CEUS was routinely performed to assess the blood supply to the parathyroid nodule. After disinfection of the skin, 1% lidocaine was administered to the subcutaneous layer and perilesional tissue for local anesthesia. Next, 10–100 mL of 5% dextrose in water was slowly injected to create a “hydrodissection” with a width of at least 5 mm to separate the nodule from neighboring structures such as the esophagus, trachea, or the recurrent laryngeal nerve (RLN). The RFA electrode was then placed near the deepest portion of the target nodule from the medial to lateral aspect. The lateral approach was used if the vessels appeared prominent in the medial approach. The nodule was ablated unit by unit using the “moving-shot” technique until the hyperechoic regions completely covered the parathyroid margin [27]. CEUS was performed immediately after RFA to assess ablation effects [28]. If the non-enhanced zone covered the entire target nodule, ablation was terminated and additional ablation was performed for residual enhancement areas. CEUS was repeated until the non-enhanced zone completely covered the entire parathyroid nodule (Fig. 3). If there were any voice changes, ablation was stopped immediately.

Data Collection and Follow-Up

Follow-up times were 20 minutes, 1 and 3 days, and 1, 3, 6, and 12 months after RFA. Procedure-related complications and symptomatic improvement were noted during the follow-up period. Serum iPTH, calcium, and phosphorus levels were evaluated during each follow-up period. US was performed 1, 3, 6, and 12 months after RFA. CEUS was performed if there were elevated serum iPTH or calcium levels or if conventional US identified nodules suspected of being undertreated in the parathyroid region. The normal ranges were as follows: iPTH, 15–65 pg/mL; calcium, 2.11–2.52 mmol/L; phosphorus, 0.85–1.51 mmol/L.

Evaluation of Therapeutic Effect

Technical success was defined as complete ablation (CEUS showing no enhancement of the target nodule after RFA) [29]. Biochemical cure was defined as calcium and iPTH levels within the normal range for at least 6 months after RFA, which served as the primary outcome of this study [30-32]. Clinical cure was the secondary outcome and was defined as serum calcium normalization for the hypercalcemic form and normalization of iPTH for patients with normocalcemic PHPT more than 6 months after RFA (according to the criteria for parathyroidectomy) [8,33]. Recurrent PHPT was defined as the recurrence of hypercalcemia after a normocalcemic interval of > 6 months after RFA. Persistent PHPT was defined as failure to achieve normocalcemia within 6 months after ablation. Eucalcemic PTH elevation was defined as an iPTH level exceeding the normal range but with serum calcium levels within the reference range after technically successful RFA [8].

Complications

Complications include hoarseness, hypocalcemia, perioral and limb numbness, convulsions, subcutaneous edema, various degrees of pain, cough, skin burns, hematoma, infection, and life-threatening complications during or after RFA [18,34,35].

Statistical Analysis

All statistical analyses were performed using SPSS software (version 26.0; IBM Corp.). Continuous data are
presented as mean ± standard deviation or as median and interquartile range (IQR, Q25–Q75). Categorical data are displayed as frequency or percentage. Serum iPTH, calcium, and phosphate levels and nodule volumes were compared at baseline and at each follow-up using paired-sample t-tests or paired-sample Wilcoxon signed-rank tests. All tests were two-sided, and the significance level was set at \( p < 0.05 \).

**RESULTS**

The clinical and treatment characteristics of patients who underwent RFA are summarized in Table 1. Thirty-nine parathyroid nodules from 39 participants, including 34 patients with hypercalcemic PHPT and five patients with normocalcemic PHPT, were evaluated in this study. The mean follow-up duration was 13.2 ± 4.6 (range, 6.0–24.9) months. All 39 parathyroid nodules were treated with RFA in a single session. The median ablation time was 80 (IQR, 48–124) seconds. The median ablation energy was 35 W (IQR: 35–40 W) for a single gland. CEUS examinations were performed 86 times, including 39 preoperatively and 47 immediately after the ablation. Thirty-eight nodules were completely ablated. The technical success rate was 97.4\% (38/39). One nodule was not completely ablated, as the patient developed hoarseness during RFA; CEUS showed residual hyperenhancement in the nodule. Hypercalcemia reappeared in this case at 7 months after RFA, and at 12 months after RFA, CEUS showed that the original ablated area was basically absorbed, and the original residual portion had enlarged further (Fig. 4).

**Effect of Treatment**

Table 2 shows the changes in iPTH, calcium, and phosphorus values and nodule volume before and after RFA in patients with PHPT. By 12 months post-RFA, the serum iPTH, calcium, and phosphorus levels had significantly improved (iPTH, 178.0 [IQR, 134.0–276.0] vs. 44.6 [IQR, 38.4–57.0] pg/mL; calcium, 2.76 ± 0.28 vs. 2.36 ± 0.09 mmol/L; phosphorus, 0.84 ± 0.15 vs. 1.14 ± 0.15 mmol/L, respectively; all \( p < 0.001 \)). Significant reductions in the volume of the nodules were noted (0.50 [IQR, 0.25–1.10]) vs. 0.00 [IQR, 0.00–0.03] mL; \( p < 0.001 \) at 12 months after RFA.

The overall biochemical cure rates for the primary
outcome were 82.1% (32/39) and 84.4% (27/32) at 6 and 12 months, respectively. The 6- and 12-month clinical cure rates were 100% (34/34) and 96.3% (26/27), respectively, in patients with the hypercalcemic form and 100% (5/5) at both time points in patients with normocalcemic PHPT.

In terms of symptomatic improvement, dizziness occurred in two participants pre-RFA but disappeared rapidly within 1 day post-RFA, and 11 participants who had complained of fatigue reported resolution within 1–3 months post-RFA. Ostealgia occurred in eight participants, which disappeared by 1 month after RFA in seven participants (7/8, 87.5%) and was markedly relieved within 1–3 days post-RFA in one participant. No new fragility fractures occurred in the three participants with pre-RFA fractures. Other than the 18 participants with nephrolithiasis before RFA, no other participants reported nephrolithiasis.

**Table 1. Clinical and Treatment Characteristics of Patients Who Underwent RFA**

| Characteristic | Data |
|---------------|------|
| **Demographics** | |
| Age, years | 59.5 ± 15.3 |
| Female:male | 25:14 |
| Body mass index | 23.1 ± 3.0 |
| Hypercalcemic PHPT | 34 |
| Normocalcemic PHPT | 5 |
| **Biochemical data** | |
| Blood urea nitrogen, mmol/L | 5.28 (4.02–6.38) |
| Serum creatinine, μmol/L | 65.90 (61.70–79.90) |
| Hemoglobin, g/L | 137.45 ± 15.74 |
| Serum iPTH, pg/mL | 178.0 (133.6–276.0) |
| Serum calcium, mmol/L | 2.74 (2.56–2.82) |
| Serum phosphorus, mmol/L | 0.85 ± 0.15 |
| Serum ALP, U/L | 124.0 (90.0–148.0) |
| Serum 25(OH)D3, ng/mL | 16.14 ± 6.32 |
| **Location** | |
| Superior left | 7 |
| Inferior left | 14 |
| Superior right | 5 |
| Inferior right | 13 |
| Maximum diameter, mm | 16.23 ± 6.04 |
| Volume, mL | 0.50 (0.25–1.10) |
| **Clinical presentation** | |
| Nephrolithiasis | 18 |
| Fatigue | 11 |
| Ostealgia | 8 |
| Fragility fractures | 3 |
| Dizziness | 2 |
| **RFA procedure** | |
| Power used in the RFA, W | 35 (35–40) |
| Ablation time, seconds | 80 (48–124) |

Data are presented as the mean ± standard deviation, median (interquartile range), or number of patients. The normal ranges were blood urea nitrogen: 3.10–8.0 mmol/L; creatinine: 45.0–84.0 μmol/L; hemoglobin: 115–150 g/L; iPTH: 15.0–65.0 pg/mL; calcium: 2.11–2.52 mmol/L; phosphate: 0.85–1.51 mmol/L; ALP: 35–100 U/L; 25(OH)D3: > 30 ng/mL. ALP = alkaline phosphatase, iPTH = intact parathyroid hormone, PHPT = primary hyperparathyroidism, RFA = radiofrequency ablation.

**Complications**

Two patients developed hoarseness. One patient developed hoarseness during the procedure, and the other developed hoarseness immediately after the procedure. When hoarseness was found, cold 5% dextrose in water was immediately injected into the RLN area; however, no immediate improvement was observed. Both patients recovered within 3 months without medical treatment.
Seven patients had hypocalcemia, five had perioral and limb numbness, and one had convulsions. All patients recovered completely without sequelae within 1–3 days with vitamin D and calcium supplementation; vitamin D and calcium supplementation was stopped when the hypocalcemia was corrected. Moderate subcutaneous edema was observed in four patients but resolved within 1–3 days without specific treatment. Cough occurred in eight patients during or after ablation but resolved spontaneously within 1 day in all cases without additional medication. Permanent consequences were not observed. Pain of varying severity occurred in 32 patients but spontaneously remitted within 1–2 days. No skin burns, infections, esophageal perforation, tracheal injury, permanent RLN injury, permanent hypocalcemia, or life-threatening complications occurred during or after RFA.

**DISCUSSION**

Our pilot study included 39 patients with PHPT who were treated with RFA. Treatment was well tolerated by all patients. The volume of ablated nodules gradually decreased after RFA. At the 12-month follow-up, the ablated area was essentially absorbed in all cases, except one. Symptomatic improvement was apparent within 3 months of ablation. The biochemical and clinical cure rates were 84.4% (27/32) and 96.9% (31/32), respectively, 12 months after RFA, which is consistent with the results of other reports on US-guided thermal ablation and parathyroidectomy for PHPT [1,8,37]. Only one of the 39 patients developed recurrent PHPT. CEUS confirmed enlargement of the original residual active lesion in situ. PHPT did not recur in the other patients in whom the nodule had been completely ablated.

In our study, although the iPTH level decreased rapidly to or below the normal level within 20 minutes or 1 day after RFA in all cases, eucalcemic PTH elevation was observed in some cases during the follow-up period. The frequency of eucalcemic PTH elevation was the highest 1 month after ablation. Subsequently, the frequency of eucalcemic PTH elevation gradually decreased. Similar to patients with surgically treated PHPT, the incidence of eucalcemic PTH elevation has been reported in 12%–43% of cases during the postoperative period, and the prevalence of this isolated elevation of PTH typically decreases as the time...
interval from surgery increases [38]. An explanation for this phenomenon could be the feedback from serum iPTH on calcium reduction [12]. In this study, CEUS revealed no new abnormal parathyroid tissue after treatment in patients with eucalcemic PTH elevation. However, a longer follow-up period among patients with eucalcemic PTH elevation is necessary to determine the presence of residual parathyroid tissue that might have been difficult to detect with current imaging.

In previous studies, the indications for ablation in PHPT were mainly based on surgical criteria, that is, PTH level combined with calcium level, bone mineral density, renal function, age, and other biochemical data or symptoms that occur in patients with PHPT [9]. However, because the entire ablation process is conducted under US guidance, parathyroid nodules with suspected malignant features or technically inaccessible locations should be excluded and surgical excision recommended [39-41]. Known ultrasonographic features, including an irregular shape, intranodular calcifications, infiltrative border, or large size (> 30–33 mm) of the parathyroid lesion, may increase the malignancy risk [21-23]. Owing to the interference of air or bone, it is difficult to clearly display retrotracheal or substernal lesions. Regarding the depth of the lesion, lesions within 30 mm of the skin surface can be clearly displayed using a 10 MHz high-frequency linear array probe [24]. Thus, if the penetration depth is > 30 mm, the total attenuation of the ultrasonic intensity in soft tissues is > 30 dB, which inevitably introduces interference in the monitoring of the lesion boundary, ablation process, and ablation zone [25].

In our series, the most common major complication was hoarseness, which occurred in 5.1% of patients. Previous studies have reported RLN injury rates of 2.9%–7.0% during thyroid and parathyroid surgery [42-44] and 6.0%–38.0% during thermal ablation [12,14,18,35]. The incidence rate in this study was equal to that of parathyroidectomy but lower than that of thermal ablation, as reported in most studies. Other complications such as hypocalcemia, pain, subcutaneous edema, and cough improved within a short time. Subcutaneous edema may have been caused by the absorption of the hydrodissection fluid by some loose tissues that persisted for less than 3 days and quickly disappeared without the need for treatment. Cough may be related to thermal propagation or edema compression of the peritracheal tissue to the trachea. The low complication rate may be because we selected parathyroid nodules with a small diameter and oval/round shape for ablation.

### Table 2: Changes in Serum iPTH, Calcium, Phosphate Levels and Volume of Ablated Parathyroid Nodules Before RFA and During Each Follow-Up Period

| Laboratory Tests | Baseline (n = 39) | 20 Minutes (n = 39) | 1 Day (n = 38) | 3 Days (n = 37) | 1 Month (n = 38) | 3 Months (n = 35) | 6 Months (n = 39) | 12 Months (n = 32) |
|------------------|------------------|------------------|---------------|---------------|----------------|----------------|----------------|-----------------|
| iPTH, pg/mL      | 178 ± 32        | 10.9 ± 21       | 9.5 ± 25†     | 8.5 ± 15      | 0.50 (0.25–1.30) | 0.50 (0.25–1.30) | 0.50 (0.25–1.30) | 0.50 (0.25–1.30) |
| Calcium, mmol/L  | 2.76 ± 0.28     | 2.42 ± 0.25*    | 2.27 ± 0.16   | 2.25 ± 0.13*  | 2.33 ± 0.25*    | 2.37 ± 0.26*     | 2.37 ± 0.26*     | 2.37 ± 0.26*     |
| Phosphorus, mmol/L | 0.85 ± 0.15  | 0.85 ± 0.15  | 0.85 ± 0.15  | 0.85 ± 0.15  | 0.85 ± 0.15  | 0.85 ± 0.15  | 0.85 ± 0.15  | 0.85 ± 0.15  |
| Volume, mL       | 0.50 (0.25–1.30) | 0.50 (0.25–1.30) | 0.50 (0.25–1.30) | 0.50 (0.25–1.30) | 0.50 (0.25–1.30) | 0.50 (0.25–1.30) | 0.50 (0.25–1.30) | 0.50 (0.25–1.30) |

Data are mean ± standard deviation or median (interquartile range). The normal ranges were iPTH: 15.0–65.0 pg/mL; calcium: 2.11–2.52 mmol/L; phosphate: 0.85–1.51 mmol/L. *p < 0.05 (compared with baseline), †p < 0.01 (compared with values before RFA), ‡p < 0.001 (compared with values 20 minutes after RFA), ¶p < 0.001 (compared with values 1 day after RFA). iPTH = intact parathyroid hormone, RFA = radiofrequency ablation.
Such nodules are easy to separate from the neighboring structures, but much larger or deeper target nodules, especially in dangerous locations, increase the risk of damage to the adjacent structures [45].

This study has several limitations. First, it was preliminarily conducted at a single center. Multicenter, prospective studies are required to confirm our results. Second, the follow-up period was relatively short. Studies with longer follow-up duration are needed to assess the long-term efficacy and safety of RFA in PHPT management. Third, the number of patients enrolled in this study was relatively small, and more samples should be included in future studies. Fourth, owing to technical difficulties, we did not use RFA to treat relatively high-risk nodules, such as those that were too deep or located in the carotid sheath. Future studies should use improved techniques and prophylactic measures to ablate these nodules.

In conclusion, RFA is an effective and safe treatment for patients with PHPT and may be an alternative treatment modality for patients who cannot tolerate or refuse to undergo surgery.

Availability of Data and Material
The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest
Jung Hwan Baek who is on the editorial board of the Korean Journal of Radiology was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions
Conceptualization: Cheng-zhong Peng, Jung Hwan Baek. Data curation: all authors. Formal analysis: all authors. Funding acquisition: Yu Zhao. Investigation: all authors. Methodology: Cheng-zhong Peng, Hui-hui Chai, Rui-zhong Ye. Project administration: Cheng-zhong Peng. Resources: Yu Zhao and Cheng-zhong Peng. Supervision: Cheng-zhong Peng. Validation: Cheng-zhong Peng, Jung Hwan Baek. Writing—original draft: Hui-hui Chai, Cheng-zhong Peng, Jung Hwan Baek, Yu Zhao, Zeng Zeng. Writing—review & editing: Hui-hui Chai, Jung Hwan Baek, Cheng-zhong Peng, Yu Zhao.

ORCID iDs
Hui-hui Chai  https://orcid.org/0000-0003-3704-2805
Yu Zhao  https://orcid.org/0000-0002-3904-4276
Zeng Zeng  https://orcid.org/0000-0002-8944-2950
Rui-zhong Ye  https://orcid.org/0000-0002-3644-2455
Qiao-hong Hu  https://orcid.org/0000-0001-7934-3660
Hong-feng He  https://orcid.org/0000-0003-0645-9106
Jung Hwan Baek  https://orcid.org/0000-0003-0480-4754
Cheng-zhong Peng  https://orcid.org/0000-0003-4886-7466

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REFERENCES
1. Bilezikian JP, Bandeira L, Khan A, Cusano NE. Hyperparathyroidism. Lancet 2018;391:168-178
2. Werners RA, Khosla S, Atkinson EJ, Achenbach SJ, Oberg AL, Grant CS, et al. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993-2001: an update on the changing epidemiology of the disease. J Bone Miner Res 2006;21:171-177
3. Yeh MW, Ituarte PH, Zhou HC, Nishimoto S, Liu IL, Harari A, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. J Clin Endocrinol Metab 2013;98:1122-1129
4. Walker MD, Silverberg SJ. Primary hyperparathyroidism. Nat Rev Endocrinol 2018;14:115-125
5. Insogna KL. Primary hyperparathyroidism. N Engl J Med 2018;379:1050-1059
6. Pierreux J, Bravenboer B. Normocalcemic primary hyperparathyroidism: a comparison with the hypercalcemic form in a tertiary referral population. Horm Metab Res 2018;50:797-802
7. Schini M, Jacques RM, Oakes E, Peel NFA, Walsh JS, Eastell R. Normocalcemic hyperparathyroidism: study of its prevalence and natural history. J Clin Endocrinol Metab
20. Kwak JY, Kim EK, Moon HJ, Kim MJ, Ahn SS, Son EJ, et al. Parathyroid incidentalomas detected on routine ultrasound-directed fine-needle aspiration biopsy in patients referred for thyroid nodules and the role of parathyroid hormone analysis in the samples. Thyroid 2009;19:743-748
21. Fang C, Konstantatou E, Mulholland NJ, Barocinì S, Husainy MA, Schulte KM, et al. A retrospective review of the role of B-mode and color Doppler ultrasonography in the investigation of primary hyperparathyroidism: features that differentiate benign from malignant lesions. Ultrasound 2018;26:110-117
22. Bae JH, Choi HJ, Lee Y, Moon MK, Park YJ, Shin CS, et al. Preoperative predictive factors for parathyroid carcinoma in patients with primary hyperparathyroidism. J Korean Med Sci 2012;27:890-895
23. Hundahl SA, Fleming ID, Fremgen AM, Mencik HR. Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985-1995: a National Cancer Data Base Report. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer 1999;86:538-544
24. Ng A, Swanevelder J. Resolution in ultrasound imaging. Cont Educ Anaesth Crit Care Pain 2011;11:186-192
25. Hendee WR, Ritenour ER. Chapter 19. Ultrasound waves. In: Hendee WR, Ritenour ER, eds. Medical imaging physics. 4th ed. New York: Wiley, 2002:303-316
26. Wang R, Jiang T, Chen Z, Chen J. Regression of calcinosis following treatment with radiofrequency thermoablation for severe secondary hyperparathyroidism in a hemodialysis patient. Intern Med 2013;52:583-587
27. Jeong WK, Baek JH, Rhim H, Kim YS, Kwak MS, Jeong HJ, et al. Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. Eur Radiol 2008:12:1365-1250
28. Zhuo L, Peng LL, Zhang YM, Xu ZH, Zou GM, Wang X, et al. US-guided microwave ablation of hyperplastic parathyroid glands: safety and efficacy in patients with end-stage renal disease-a pilot study. Radiology 2017;282:576-584
29. Ahmed M, Solbiati L, Brace CL, Breen DJ, Callstrom MR, Charboneau JW, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria--a 10-year update. Radiology 2014;273:241-260
30. Mauri G, Pacella CM, Papini E, Solbiati L, Goldberg SN, Ahmed M, et al. Image-guided thyroid ablation: proposal for standardization of terminology and reporting criteria. Thyroid 2019;29:611-618
31. Krawitz R, Glover A, Koneru S, Jiang J, Di Marco A, Gill AJ, et al. The significance of histologically “large normal” parathyroid glands in primary hyperparathyroidism. World J Surg 2020;44:1149-1155
32. Pal R, Arya AK, Aggarwal A, Singh P, Dahiya D, Sood A, et al. Weight gain after curative parathyroidectomy predicts increase in bone mineral density in patients with symptomatic primary hyperparathyroidism. Clin Endocrinol (Oxf) 2020;93:28-35
33. Trébouet E, Bannani S, Wargny M, Leux C, Caillard C, Kraeber-Bodéré F, et al. Mild sporadic primary hyperparathyroidism: high rate of multiglandular disease is associated with lower surgical cure rate. Langenbecks Arch Surg 2019;404:431-438
34. Ye J, Huang W, Huang G, Qiu Y, Peng W, Lan N, et al. Efficacy and safety of US-guided thermal ablation for primary hyperparathyroidism: a systematic review and meta-analysis.
US-Guided RFA for Primary Hyperparathyroidism

Int J Hyperthermia 2020;37:245-253
35. Liu F, Yu X, Liu Z, Qiao Z, Dou J, Cheng Z, et al. Comparison of ultrasound-guided percutaneous microwave ablation and parathyroidectomy for primary hyperparathyroidism. Int J Hyperthermia 2019;36:835-840
36. Baek JH, Lee JH, Sung JY, Bae JI, Kim KT, Sim J, et al. Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: a multicenter study. Radiology 2012;262:335-342
37. Fraser WD. Hyperparathyroidism. Lancet 2009;374:145-158
38. Oltmann SC, Maalouf NM, Holt S. Significance of elevated parathyroid hormone after parathyroidectomy for primary hyperparathyroidism. Endocr Pract 2011;17 Suppl 1:57-62
39. Kovatcheva R, Vlahov J, Stoinov J, Lacoste F, Ortuno C, Zaletel K. US-guided high-intensity focused ultrasound as a promising non-invasive method for treatment of primary hyperparathyroidism. Eur Radiol 2014;24:2052-2058
40. Zini M, Attanasio R, Cesareo R, Emmolo I, Frasoldati A, Gianotti L, et al. AME position statement: primary hyperparathyroidism in clinical practice. J Endocrinol Invest 2012;35(7 Suppl):2-21
41. Kim JH, Baek JH, Lim HK, Ahn HS, Baek SM, Choi YJ, et al. 2017 thyroid radiofrequency ablation guideline: Korean Society of Thyroid Radiology. Korean J Radiol 2018;19:632-655
42. Dhillon VK, Rettig E, Noureldine SI, Genther DJ, Hassoon A, Al Khadem MG, et al. The incidence of vocal fold motion impairment after primary thyroid and parathyroid surgery for a single high-volume academic surgeon determined by pre- and immediate post-operative fiberoptic laryngoscopy. Int J Surg 2018;56:73-78
43. Schneider M, Dahm V, Passler C, Sterrer E, Mancusi G, Repasi R, et al. Complete and incomplete recurrent laryngeal nerve injury after thyroid and parathyroid surgery: characterizing paralysis and paresis. Surgery 2019;166:369-374
44. Joliat GR, Guarnero V, Demartines N, Schweizer V, Matter M. Recurrent laryngeal nerve injury after thyroid and parathyroid surgery: incidence and postoperative evolution assessment. Medicine (Baltimore) 2017;96:e6674
45. Xiaoyin T, Ping L, Dan C, Min D, Jiachang C, Tao W, et al. Risk assessment and hydrodissection technique for radiofrequency ablation of thyroid benign nodules. J Cancer 2018;9:3058-3066