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

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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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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 Hänsler 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

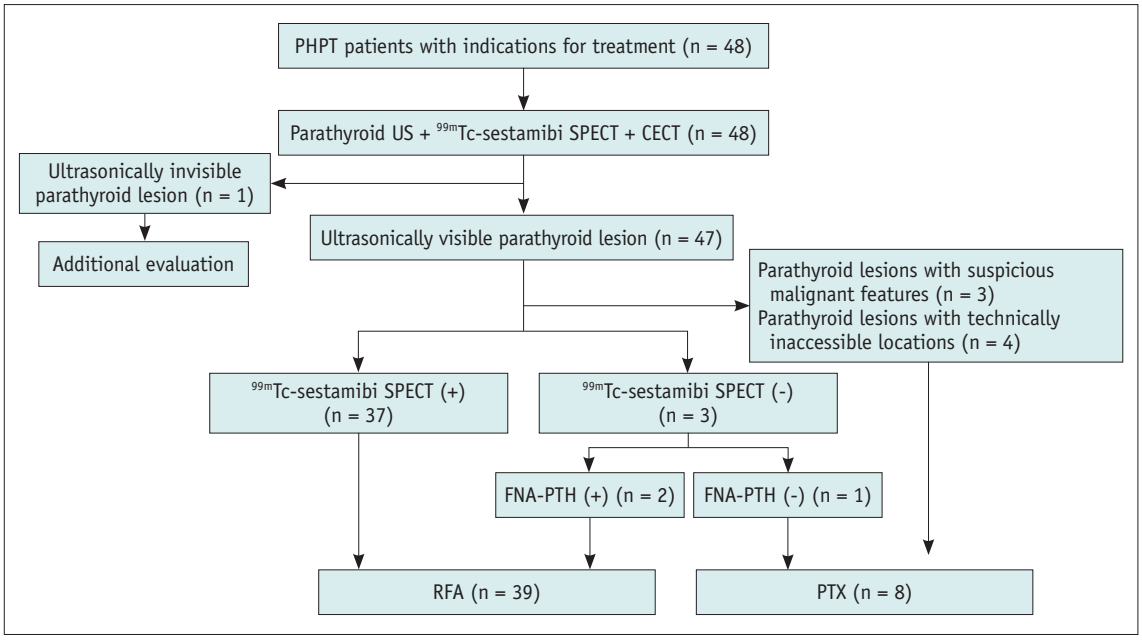

Fig. 1. Flowchart showing the patient selection process.
CECT = contrast-enhanced computed tomography, FNA = fine-needle aspiration, PHPT = primary hyperparathyroidism, PTH = parathyroid hormone, PTX = parathyroidectomy, RFA = radiofrequency ablation, US = ultrasound, ^{99m}Tc-sestamibi SPECT = technetium 99-m-labeled sestamibi single-photon emission computed tomography

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preoperative imaging (US and contrast-enhanced neck computed tomography [CECT]), and 3) positive technetium 99-m-labeled sestamibi single-photon emission computed tomography [^{99m}Tc-sestamibi SPECT] results or negative ^{99m}Tc-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

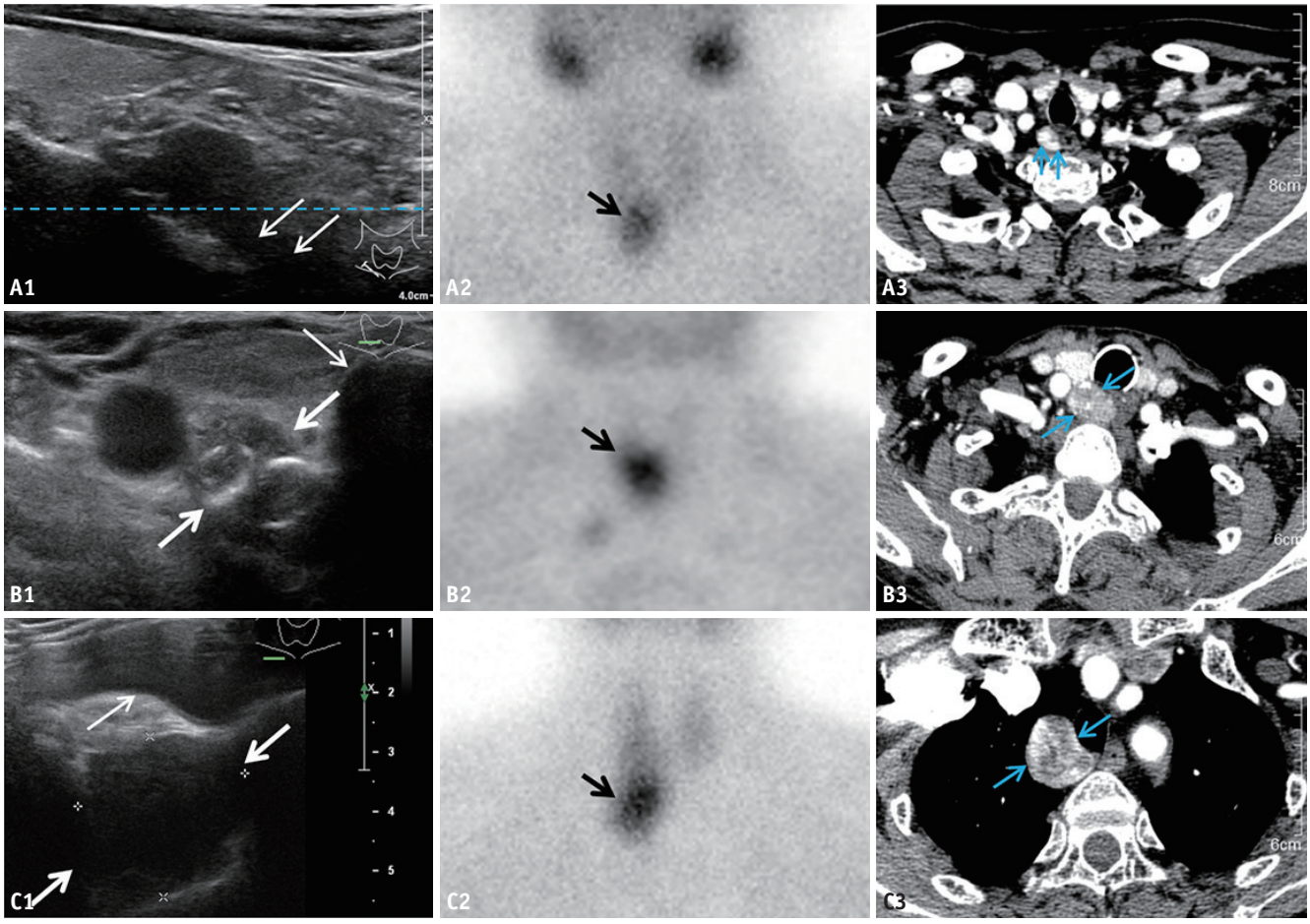

Fig. 2. Imaging features of parathyroid nodule not suited for US-guided RFA.
A1. US image reveals that the nodule's posterior margin is not clear (white arrows); the blue dotted line represents the horizontal line 30 mm from the body surface. **A2.** ^{99m}Tc-sestamibi SPECT image shows accumulation 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.** ^{99m}Tc-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.** ^{99m}Tc-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 supramediastinal mass (blue arrows) located behind the innominate artery and sternum. CECT = contrast-enhanced computed tomography, RFA = radiofrequency ablation, US = ultrasound, ^{99m}Tc-sestamibi SPECT = technetium 99-m-labeled sestamibi single-photon emission computed tomography

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(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. ^{99m}Tc-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

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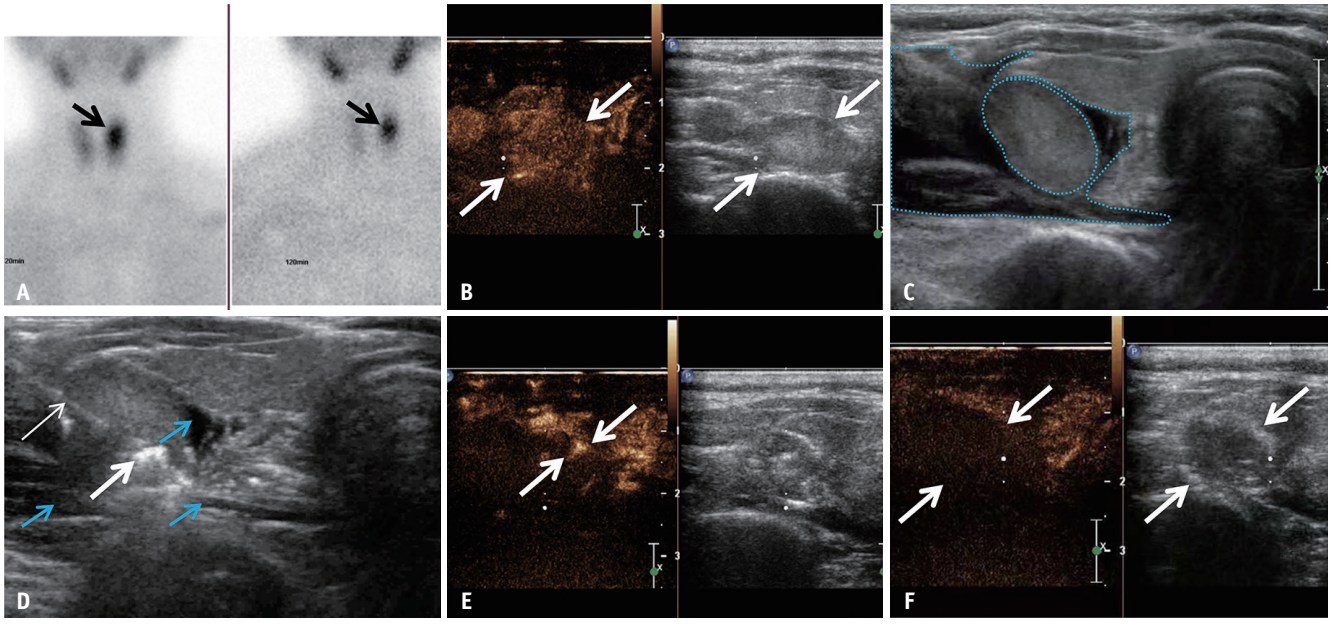

Fig. 3. Images showing the US-guided RFA procedure.
A. ^{99m}Tc-sestamibi SPECT image reveals radioactive concentration in a nodule (black arrows) in a 59-year-old female. **B.** CEUS image shows a uniformly hyperenhancing parathyroid nodule (white arrows). **C.** The hydrodissection technique involves injecting 5% dextrose in water to create a safe distance of more than 5 mm in depth (blue dotted line) between the parathyroid nodule, carotid sheath, esophagus, and trachea. **D.** The 18-G RFA electrode (thin white arrow) is inserted into the target nodule surrounded by hydrodissection (blue arrows) to ablate; US image then shows a hyperechoic area in the ablation area (thick white arrow). **E.** Immediately after RFA, CEUS image shows a small active area of enhancement (white arrows) in the ablation zone, which indicates inadequate ablation in the nodule. **F.** After additional ablation, CEUS image shows a non-enhancement area (white arrows) completely covering the nodule. CEUS = contrast-enhanced ultrasound, RFA = radiofrequency ablation, US = ultrasound, ^{99m}Tc-sestamibi SPECT = technetium 99-m-labeled sestamibi single-photon emission computed tomography

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

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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)D_3, 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)D_3: > 30 ng/mL. ALP = alkaline phosphatase, iPTH = intact parathyroid hormone, PHPT = primary hyperparathyroidism, RFA = radiofrequency ablation

outcome were 82.1% (32/39) and 84.4% (27/32) at 6 and 12 months, respectively. The 6- and 12-month biochemical cure rates were 79.4% (27/34) and 81.5% (22/27), respectively, in patients with the hypercalcemic form and 100% (5/5) and 100% (5/5), respectively, in patients with normocalcemic PHPT. The overall clinical cure rates for the secondary outcomes were 100% (39/39) and 96.9% (31/32) at 6 and 12 months after RFA, 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.

PTH After Technically Successful RFA

As shown in Table 2, the mean serum calcium levels decreased rapidly within 3 days after RFA compared with baseline (all $p < 0.001$) and stabilized within the normal range during the follow-up evaluations at 1, 3, 6, and 12 months. In contrast, we observed notable reductions in serum iPTH levels at 20 minutes and 1 day after RFA compared to baseline (all $p < 0.001$). The mean iPTH level decreased by 89.5% ± 0.10% of the initial PTH level 1 day after RFA. A significant rebound of iPTH was observed from the third day. The mean iPTH rebounded to a peak of 38.3% ± 17.1% of the initial PTH level at 1 month after RFA. Three months later, the iPTH level had gradually decreased and subsequently remained stable without additional treatment. After technically successful RFA, 44.7% (17/38), 34.3% (12/35), 15.8% (6/38), and 12.5% (4/32) of the participants had eucalcemic PTH elevation at 1, 3, 6, and 12 months, respectively. Of the six patients with eucalcemic PTH elevation at 6 months after RFA, iPTH returned to normal in two, and the remaining four still had eucalcemic PTH elevation. Follow-up CEUS showed no recurrence or new abnormal parathyroid tissue after RFA.

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

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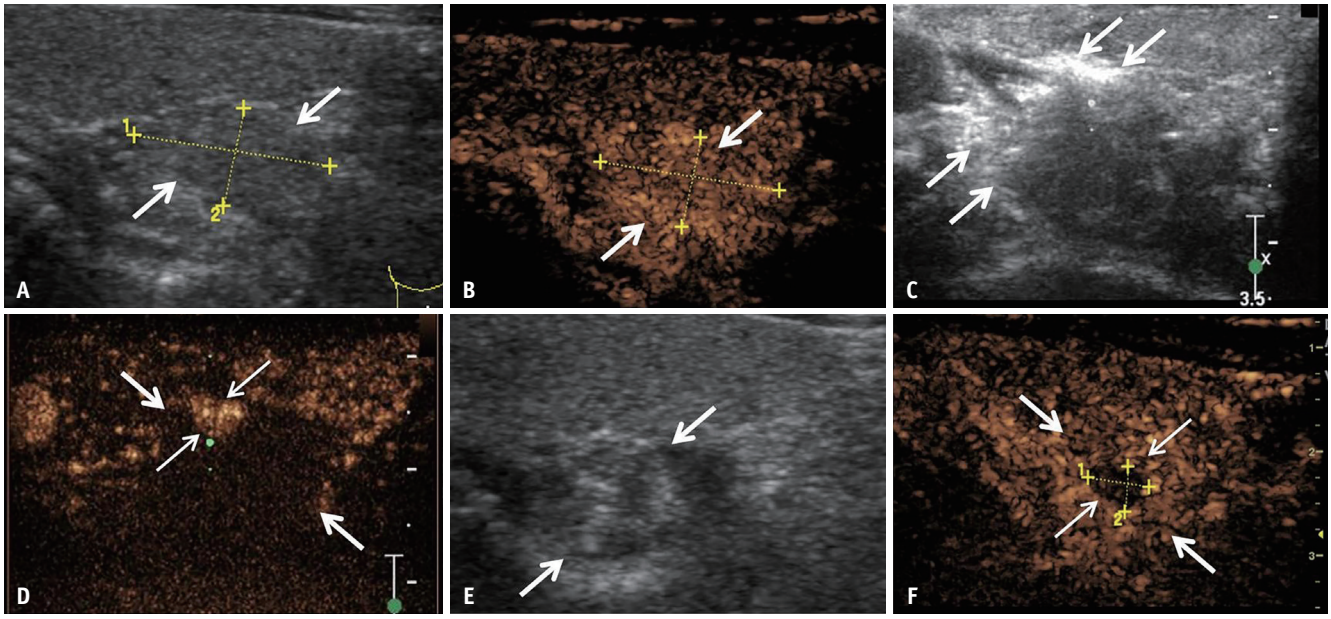

Fig. 4. Images showing a recurrent parathyroid lesion in a 58-year-old male.
A. Before RFA, US image shows an isoechoic parathyroid nodule measuring 18 x 9 x 6 mm with a sharp boundary (arrows). **B.** CEUS image shows a uniform hyperenhancement parathyroid nodule (arrows) in the posterior portion of the left thyroid gland. **C.** Immediately after RFA, US image shows the appearance of white hyperechoic marks (arrows) in the treated area. **D.** Ablative treatment was stopped because the patient developed hoarseness. CEUS image shows a non-enhancement area (thick arrows) covering most of the parathyroid nodule, but an active area of hyperenhancement (thin arrows) confined in the front indicates a small residual area on the border of the nodule. **E.** At 12 months after RFA, US image shows that the size of the mixed echoic (isoechoic and hypoechoic) parathyroid nodule (arrows) is 18 x 9 x 7 mm in the treated area. **F.** At 12 months after RFA, CEUS image shows the size of the necrotic tissue as a round non-enhancement area (thin arrows) measuring 6 x 4 x 5 mm in the treated area and an active area of hyperenhancement (thick arrows) around the necrotic tissue. CEUS = contrast-enhanced ultrasound, RFA = radiofrequency ablation, US = ultrasound

[36]. 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

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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 = 39)	3 Days (n = 37)	1 Month (n = 38)	3 Months (n = 35)	6 Months (n = 39)	12 Months (n = 32)
iPTH, pg/mL	178.0 (133.6–276.0)	10.9 (1.5–34.1)*	13.0 (7.2–32.4)*	33.4 (16.9–46.1)*‡	64.2 (54.2–107.3)*‡‖	54.4 (44.0–78.8)*‡‖	47.9 (37.3–61.9)*‡‖	44.6 (38.4–57.0)*‡¶
Calcium, mmol/L	2.76 ± 0.28	2.42 ± 0.25*	2.27 ± 0.16*‡	2.25 ± 0.13*‡	2.35 ± 0.10*¶	2.31 ± 0.32*	2.37 ± 0.07*‖	2.36 ± 0.09*‖
Phosphorus, mmol/L	0.85 ± 0.15	0.85 ± 0.21†	0.95 ± 0.25*§	1.04 ± 0.21*‡¶	1.10 ± 1.17*‡¶	1.17 ± 0.11*‡‖	1.15 ± 0.16*‡‖	1.14 ± 0.15*‡‖
Volume, mL	0.50 (0.25–1.10)	-	-	-	0.42 (0.09–0.74)*	0.12 (0.08–0.33)*	0.02 (0.00–0.10)*	0.00 (0.00–0.03)*

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 < 0.001, †p < 0.05 (compared with values before RFA), ‡p < 0.001, §p < 0.05 (compared with values 20 minutes after RFA), ‖p < 0.001, ¶p < 0.05 (compared with values 1 day after RFA). iPTH = intact parathyroid hormone, RFA = radiofrequency ablation

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.

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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.

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