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Ultrasound-Guided Radiofrequency Ablation in Tertiary Hyperparathyroidism: A Prospective Study

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Objective: To prospectively evaluate the outcomes of ultrasound (US)-guided radiofrequency ablation (RFA) in tertiary hyperparathyroidism (THPT).

Materials and Methods: Patients with THPT underwent RFA between September 2017 and January 2022. Laboratory parameters, including serum intact parathyroid hormone (iPTH) levels, were monitored for 48 months after RFA and compared with the levels at baseline. Complications related to RFA and changes in hyperparathyroidism-related clinical symptoms were recorded before and after RFA.

Results: A total of 42 patients with THPT were recruited for this study. Ultimately, 36 patients with renal failure and 2 patients who underwent successful renal transplantation (male:female, 17:21; median age, 54.5 years) were enrolled. The follow-up time was 21.5 ± 19.0 months in the 36 patients with renal failure. In these 36 patients, iPTH levels were significantly decreased to 261.1 pg/mL at 48 months compared with the baseline value of 1284.9 pg/mL ($P = 0.012$). Persistent hyperparathyroidism, defined as iPTH levels maintained at > 585.0 pg/mL for 6 months after treatment, occurred in 4.0% of patients (1/25). Recurrent hyperparathyroidism, defined as iPTH levels > 585.0 pg/mL after 6 months, were 4.0% (1/25) and 0.0% (0/9) at 6 months and 4 years after treatment, respectively. In two patients with THPT after successful renal transplantation, iPTH decreased from the baseline value of 242.5 and 115.9 pg/mL to 171.0 and 62.0 pg/mL at 6 months after treatment. All complications resolved within 6 months of ablation without medical intervention, except in 10.5% (4/38) patients with permanent hypocalcemia. The overall symptom recovery rate was 58.8% (10/17). The severity scores for bone pain, arthralgia, and itchy skin associated with hyperparathyroidism improved after treatment ($P < 0.05$).

Conclusion: US-guided RFA is an effective and safe alternative to surgery in the treatment of patients with TPTH and improves hyperparathyroidism-related clinical symptoms.

Keywords: Ultrasound; Radiofrequency ablation; Tertiary hyperparathyroidism; Efficacy; Safety

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INTRODUCTION

Secondary hyperparathyroidism (SHPT), characterized by the retention of phosphorus, decrease in calcium levels, and increase in parathyroid hormone (PTH) levels, commonly develops in individuals with chronic kidney disease (CKD) [1]. The parathyroid tissue response to calcium-PTH negative feedback progressively diminishes during the continuous stimulation of PTH secretion, which leads to tertiary hyperparathyroidism (TPHT) [2-4]. Changes from compensatory to pathological increases in PTH levels are the main differences between the SHPT and TPHT. According to previous studies, patients with renal failure have a THPT prevalence between 1.0% and 3.0%, while renal transplant recipients have a prevalence between 10.0% and 70.0% [5,6]. Increased PTH and calcium levels increase the risk of transplant kidney dysfunction, fracture, and death and are associated with worsening clinical presentations such as bone pain, arthralgia, and itchy and rough skin [7-11]. Thus, the Kidney Disease Improving Global Outcomes' (KDIGO) guidelines suggest maintaining adequate serum PTH levels in patients requiring chronic dialysis [12].

Long-term medication management for THPT is controversial and limited because hyperparathyroidism cannot be effectively controlled by pharmacotherapy. Currently, guidelines recommend parathyroidectomy (PTX) as the standard treatment in patients with THPT who fail to respond to pharmacologic therapies [13,14]. However, surgical procedures should focus on the balance between prevention of recurrence and avoidance of permanent hypoparathyroidism, which can be challenging even for experienced surgeons [13]. Effective, safe, and minimally invasive modalities are essential because of the long duration and high economic costs of conventional surgery or pharmacological therapies.

To date, no prospective studies have presented minimally invasive treatments as effective and safe alternatives in THPT [15-17], although minimally invasive modalities, including radiofrequency ablation (RFA), microwave ablation (MWA), high-intensity focused ultrasound, laser ablation, and ethanol injection, have been increasingly used as adjuncts in hyperparathyroidism at a few medical centers over the past decade [14,18].

Therefore, this prospective study aimed to assess the outcomes of US-guided RFA in patients with THPT. This study may help to further define the benefits and value of RFA in THPT management.

MATERIALS AND METHODS

Study Design and Participants

This prospective multicenter cohort study was approved by the Institutional Review Boards of all the participating hospitals (IRB No. SHSY-IEC-5.0/22K94/P02) and Chinese Clinical Trial Registry (ChiCTR-ONC-17012760). Shanghai Tenth People's Hospital, Hangzhou Hospital of Traditional Chinese Medicine, and Zhejiang Provincial People's Hospital participated in this study. THPT was defined as either 1) hyperparathyroidism (intact PTH [iPTH] > 65.0 pg/mL) with renal failure and hypercalcemia (calcium > 2.52 mmol/L) or 2) uncured hyperparathyroidism after successful renal transplantation [19]. We evaluated patients with a probable diagnosis of THPT who were referred to the medical centers. The diagnosis of THPT was confirmed based on laboratory results and imaging assessments, that is, ultrasound (US) + technetium-99m (^{99m}Tc) sestamibi scintigraphy scanning or fine-needle aspiration with a rapid PTH assay.

The inclusion criteria were as follows: 1) patients with THPT who volunteered to choose RFA treatment, 2) patients with THPT who had clinical symptoms associated with hyperparathyroidism (e.g., bone pain and severe osteoporosis), 3) at least one parathyroid lesion observed on US and confirmed by ^{99m}Tc sestamibi scintigraphy imaging or fine-needle aspiration with a rapid PTH assay, and 4) hypercalcemia and hyperparathyroidism unmanageable by pharmacological treatment. The exclusion criteria were as follows: 1) severe coagulation dysfunction, 2) unilateral or bilateral vocal cord dysfunction, 3) mental abnormalities, 4) suspicious malignant features on parathyroid imaging (e.g., irregular morphology, maximum diameter > 30 mm), and 5) retrotracheal and retrosternal parathyroid glands.

Based on THPT diagnosis and meeting the inclusion criteria, the patients were evaluated based on multidisciplinary consultations and physical conditions. Finally, patients were excluded based on the exclusion criteria. All participants were informed about the RFA procedure and study before signing an informed consent form. The flow of this study is illustrated in Figure 1.

Device Description

An iU22 US scanner (Philips Medical Systems, Bothell, WA, USA) or a LOGIQ E9 US scanner (GE Healthcare, Milwaukee, WI, USA) was equipped with high-frequency line-array probes (L9-3/L12-5/ML6-15-D) for conventional US imaging and contrast-enhanced US (CEUS). A radiofrequency system

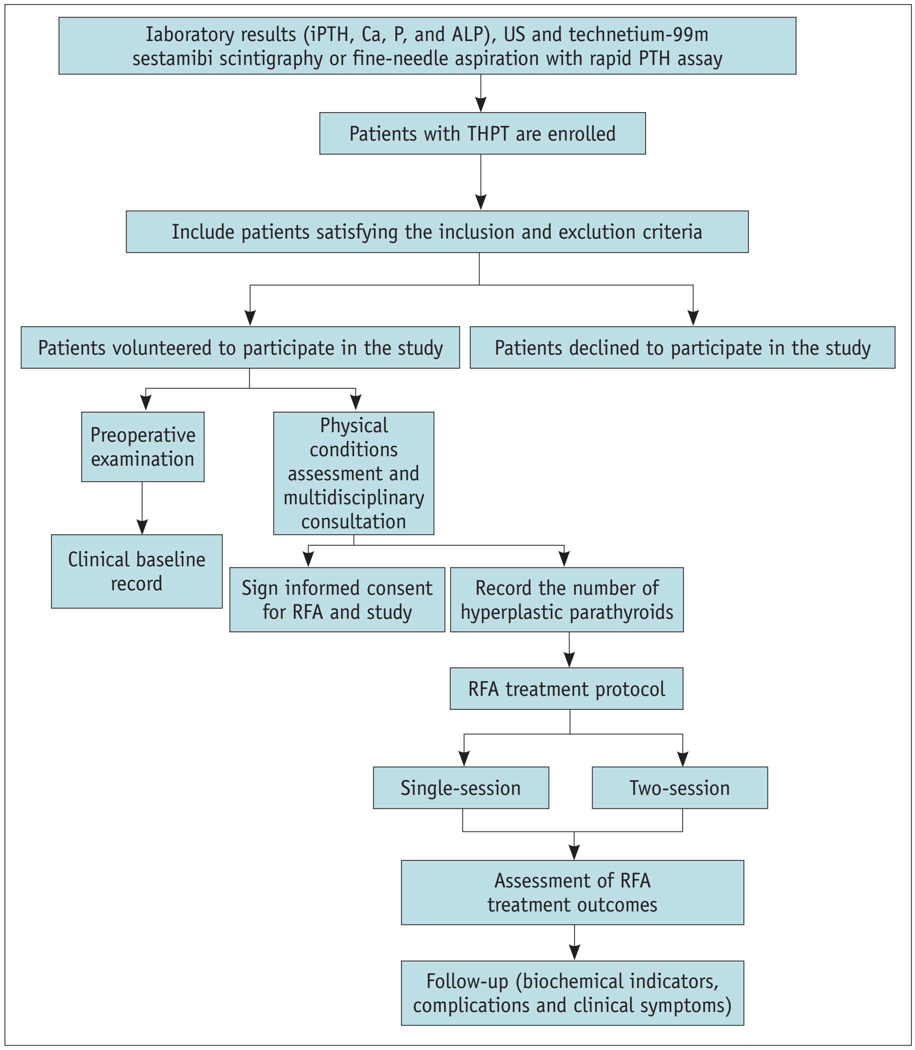

Fig. 1. The study flow. iPTH = intact parathyroid hormone, Ca = calcium, P = phosphorus, ALP = alkaline phosphatase, US = ultrasound, PTH = parathyroid hormone, THPT = tertiary hyperparathyroidism, RFA = radiofrequency ablation

(VIVA; STARmed, Goyang, South Korea) was used as the main equipment for ablation procedures.

Radiofrequency Ablation

Ablation treatments were performed by two physicians (PCZ and ZZX) with more than 10 years of US interventional experience. The ablation strategy for multiple lesions was determined based on patient tolerance and complications. If the patient was well-tolerant to the procedure and did not experience hoarseness, all lesions were treated with single-session ablation. Otherwise, two-session ablation was performed. Figure 2 is a flowchart of the study patients.

After pretreatment CEUS and skin sterilization, the subcutaneous tissue and periparathyroid area were injected with 2.0% lidocaine hydrochloride to achieve local anesthesia. A 21-gauge puncture needle was used to continuously inject a 5.0% glucose solution into high-risk areas, such as the nerves and esophagus preoperatively and intraoperatively. The 18-gauge radiofrequency electrode with an active zone length of 7 mm reached the base of the lesion via the medial approach or the lateral approach and was placed 1 mm from the lesion border for "moving-shot" ablation [20]. The output power was maintained at 35 W. At the end of the treatment, color Doppler US was used to determine the lack of a colored blood flow signal in the parathyroid nodule. CEUS was used to evaluate the local effectiveness of the ablation procedure immediately. After injecting 2.0 mL microbubble suspension (made by mixing Sonovue™ with 5 mL of sterile 0.9% sodium chloride injection) of contrast into the vein, the LOGIQ E9 US scanner selected the contrast mode to determine the range of ablation; if the target ablation zone showed residual contrast agent enhancement, an additional ablation was

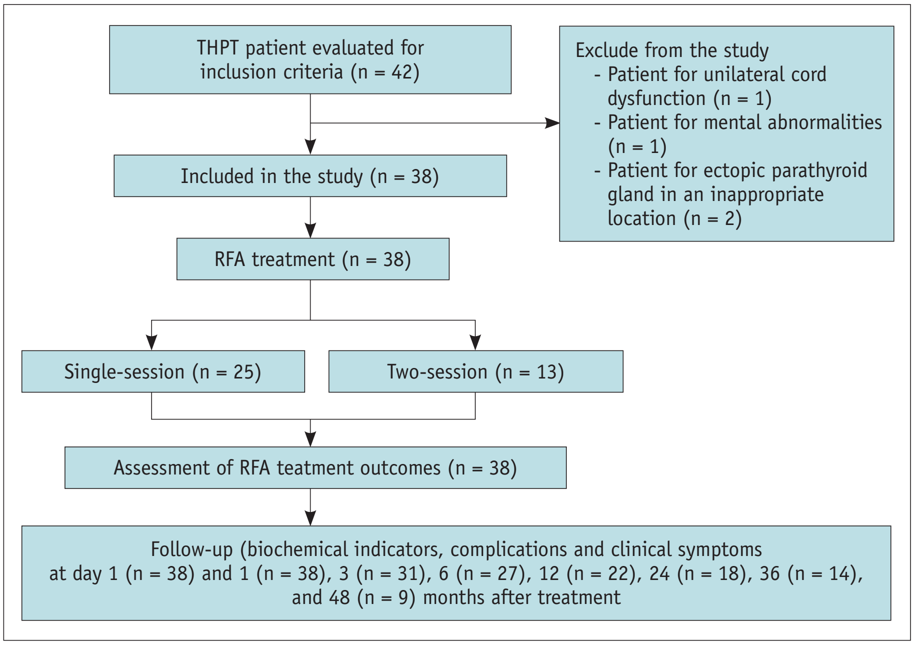

Fig. 2. Flow diagram of the study participants. THPT = teriary hyperparathyroidism, RFA = radiofrequency ablation

required. The end of the ablation was set as the edge of the nonperfused area covering the entire lesion (Fig. 3) [20].

Follow-Up

Phosphorus, calcium, and iPTH levels were carefully monitored within 1 day of treatment. One year after ablation, the follow-up intervals were set at 1, 3, 6, and 12 months. The follow-up data were collected every 12 months.

Therapeutic Effect Evaluation

Technical success was defined as at least 80% of the parathyroid lesions covered by non-perfused area [21]. Based on the KDIGO guidelines, therapeutic success in patients with renal failure, hyperparathyroidism, and hypercalcemia was defined as iPTH levels < 585.0 pg/mL (i.e., nine times the upper normal range) [12]. Therapeutic success in patients who developed hyperparathyroidism after successful renal transplantation was defined as iPTH levels < 65.0 pg/mL (i.e., the upper normal limit). iPTH levels that remained above these levels during the first 6 months after RFA were defined as persistent hyperparathyroidism. Increased iPTH levels rising above the levels after 6 months after RFA were defined as recurrent hyperparathyroidism. Temporary hypocalcemia was defined as calcium occurring for less than the lower limit (calcium < 2.11 mmol/L) within 6 months of treatment, whereas permanent hypocalcemia persisted beyond 6 months after treatment [22,23]. Temporary hypoparathyroidism was defined as iPTH levels less than the lower limit (15.0 pg/mL) within 6 months of treatment, in contrast to permanent hypoparathyroidism, which persisted longer than 6 months after treatment [19]. The clinical symptoms associated with hyperparathyroidism were graded as follows: 0, no associated symptoms; 1, mild; 2, moderate; and 3, severe.

Statistical Analysis

Baseline values are represented as median and interquartile ranges (IQR 25th–75th percentile) for skewed data and as mean and standard deviation for normally distributed data. The Wilcoxon signed-rank test was used to analyze the differences in laboratory results and clinical symptoms between pretreatment and posttreatment. The primary outcomes included changes in laboratory results, including iPTH, calcium, phosphorus, and alkaline phosphatase (ALP). Complications and assessment of clinical symptoms were the secondary outcomes. All statistical analyses were performed using SPSS software (version 20.0, IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Patient Demographics and Clinical Characteristics

Forty-two patients with THPT were initially recruited between September 2017 and January 2022. Based on the inclusion and exclusion criteria, 38 patients with THPT

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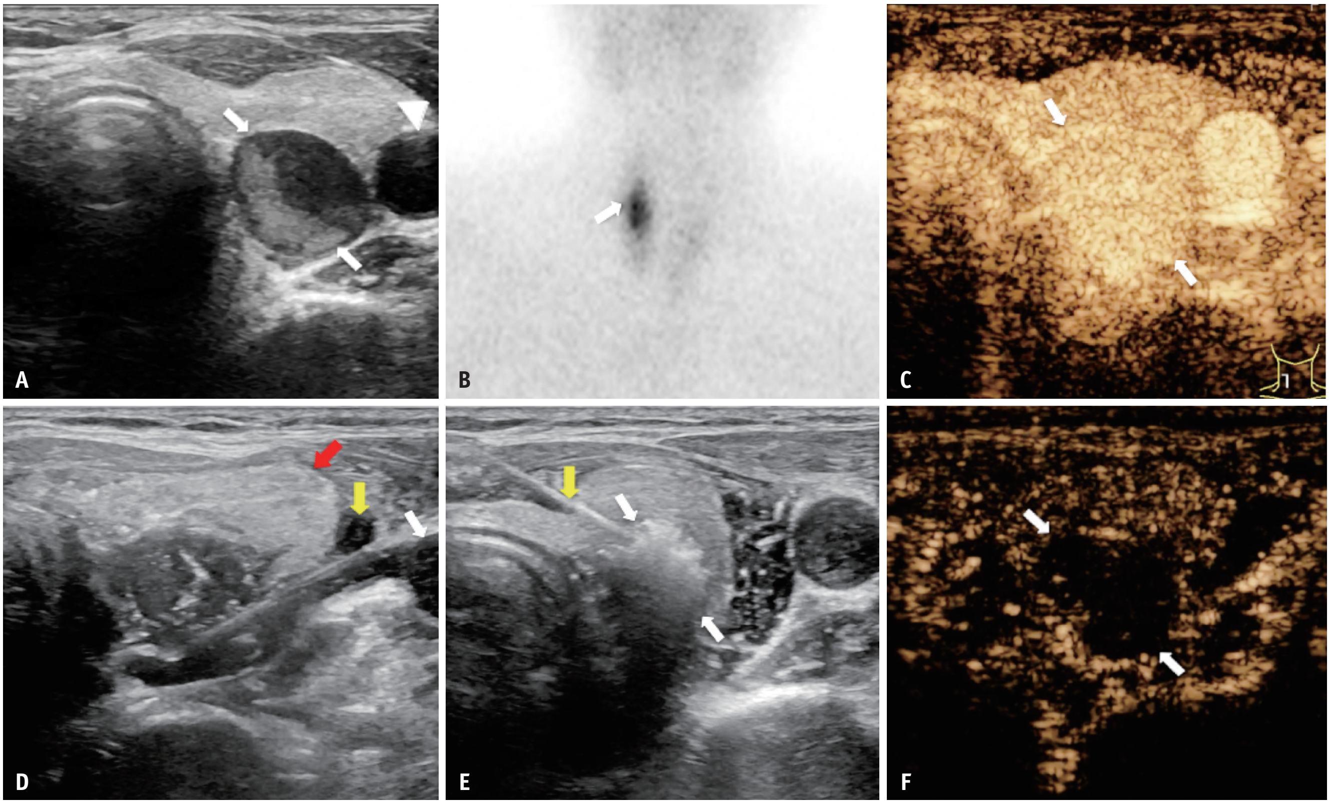

Fig. 3. A 63-year-old male who had been undergoing peritoneal dialysis for 6 years with a hyperplastic right inferior parathyroid nodule was treated with RFA. **A:** The operator performed RFA treatment at the head side of the table. The right thyroid lobe transverse ultrasound image shows a heterogeneous echogenic hyperplastic parathyroid lesion (arrows) with a volume of 3.29 mL close to the right common carotid artery (arrowhead). **B:** The posterior of the right thyroid lobe presents abnormal methoxyisobutylisonitrile metabolism (arrow), consistent with the laboratory results. **C:** The hyperplastic parathyroid lesion (arrows) presents homogeneous hyperenhancement on contrast-enhanced ultrasound. **D:** Spacer fluid comprising 5% dextrose solution (yellow arrow) is injected between the right common carotid artery (white arrow) and thyroid (red arrow) to prevent thermal damage during ablation. **E:** During ablation performed by the radiofrequency electrode (yellow arrow), a hyperechoic signal emerges inside the parathyroid lesion (white arrows). **F:** The parathyroid lesion shows a non-perfused area (arrows) on contrast-enhanced ultrasound imaging, indicating the successful treatment of the lesion. RFA = radiofrequency ablation

(male:female, 17:21; median age, 54.5 years) treated with US-guided RFA were enrolled. Among them, two patients with THPT were diagnosed after successful kidney transplantation before undergoing RFA, and the remaining 36 patients were dependent on maintenance dialysis for CKD. Table 1 shows the baseline characteristics of the 38 patients with THPT.

Primary Outcomes after RFA

Fifty-one RFA procedures were performed on 38 patients with THPT. In the 25 (65.8%) and 13 (34.2%) patients who had undergone single- and two-session ablations, respectively, 88 and 48 parathyroid lesions were treated, respectively. Thirteen additional RFA procedures were required due to intolerance or hoarseness. In the 38 patients, total procedure and total ablation times were 85.0 ± 5.0 mins and 176.3 ± 57.0 s, respectively. In the single-session ablation group, 3.6 ± 0.8 parathyroid lesions were treated. In the two-session ablation group, the average interval between ablations was 3.3 ± 2.1 days. Fifty-four parathyroid lesions underwent RFA after CEUS. The technical success rate is 100.0%.

Eleven (28.9%) of the 38 patients eventually died. Among 36 patients with renal failure, the follow-up rates at day 1 and 1, 3, 6, 12, 24, 36, and 48 months after treatment were 100.0% (36/36), 100.0% (36/36), 80.6% (29/36), 69.4% (25/36), 61.1% (22/36), 50.0% (18/36), 38.9% (14/36), and 25.0% (9/36) respectively. The status of the two patients with THPT after successful renal transplantation was followed up for 6 months.

Table 2 summarizes the changes in laboratory results of the 36 patients with THPT with renal failure during the 4-year

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Table 1. Characteristics of the patients, lesions, and RFA procedures

Variables	Value
Patients	
Age, yrs	54.5 (43.0–61.5)
Male:female	17:21
Type of dialysis	
Hemodialysis	24
Peritoneal dialysis	13
Successive hemodialysis and peritoneal dialysis	1
History of parathyroidectomy	1
Primary diseases	
Primary glomerulonephritis	29
Polycystic kidney	4
Hypertensive nephropathy	1
Diabetic nephropathy	2
Renal tumor	1
Renal injury	1
Dialysis vintage, m	102.0 (83.5–125.8)
Creatinine, μmoI/L	786.8 (561.3–969.5)
Lesions	
Total parathyroid lesions	136
No. of lesions treated per patient	
One parathyroid lesion	1
Two parathyroid lesions	4
Three parathyroid lesions	6
Four parathyroid lesions	26
Five parathyroid lesions	1
Blood flow signal of the lesion	
No blood flow signal	24
Little blood flow signal	66
Abundant blood flow signal	46
Parathyroid lesion maximum size, mm	12.3 (0.8–18.8)
Parathyroid lesions volume, mL	0.6 (0.3–1.1)
RFA procedures	
Total procedure time, min	85.0 ± 5.0
Total ablation time, s	176.3 ± 57.0

Data are presented as the median (interquartile range 25th–75th percentile), mean ± standard deviation, or number.
RFA = radiofrequency ablation

follow-up period. The mean follow-up time was 21.5 ± 19.0 months. The 4-year iPTH levels (median, 261.1 pg/mL; IQR, 144.6–366.2 pg/mL) were significantly decreased compared with those at baseline (median, 1284.9 pg/mL; IQR, 996.5–1896.2 pg/mL) (P = 0.012). Meanwhile, calcium levels decreased significantly after 1 day and remained relatively stable during the post-treatment period, which decreased from a baseline value of 2.64 (IQR, 2.58–2.72) mmol/L to 2.19 (IQR, 2.15–2.23) mmol/L at 4 years after treatment

Table 2. Primary outcomes evaluated after radiofrequency ablation in 36 tertiary hyperparathyroidism patients on renal failure with hyperparathyroidism and hypercalcemia

	iPTH (pg/mL)	*P*	Calcium (mmol/L)	*P*	Phosphorus (mmol/L)	*P*	ALP (U/L)	*P*
Before treatment								
Baseline (n = 36)	1284.9 (996.5–1896.2)		2.64 (2.58–2.72)		2.23 (1.73–2.62)		242.5 (132.8–483.4)	
After treatment								
1 d (n = 36)	62.3 (24.4–196.0)	< 0.001	2.30 (2.11–2.50)	< 0.001	1.57 (1.30–1.83)	< 0.001	-	-
1 m (n = 36)	105.2 (47.3–311.0)	< 0.001	2.15 (2.02–2.25)	< 0.001	1.22 (1.07–1.35)	< 0.001	184.6 (118.8–407.8)	0.002
3 mos (n = 29)	177.0 (65.5–383.3)	< 0.001	2.20 (2.08–2.32)	< 0.001	1.28 (1.11–1.46)	< 0.001	157.0 (98.0–269.6)	< 0.001
6 mos (n = 25)	164.2 (73.0–338.0)	< 0.001	2.24 (2.17–2.31)	< 0.001	1.35 (1.16–1.57)	< 0.001	102.0 (87.0–215.0)	< 0.001
1 yr (n = 22)	161.6 (118.0–435.5)	< 0.001	2.22 (2.10–2.34)	< 0.001	1.53 (1.32–1.67)	< 0.001	89.5 (78.3–173.6)	< 0.001
2 yrs (n = 18)	154.7 (101.0–333.0)	0.001	2.23 (2.16–2.32)	< 0.001	1.50 (1.38–1.73)	0.001	85.0 (79.5–106.5)	< 0.001
3 yrs (n = 14)	206.0 (140.0–251.7)	0.001	2.22 (2.17–2.29)	0.001	1.65 (1.58–1.77)	0.004	88.0 (64.3–124.3)	0.001
4 yrs (n = 9)	261.1 (144.6–366.2)	0.012	2.19 (2.15–2.23)	0.012	1.57 (1.45–1.83)	0.042	94.0 (70.0–115.8)	0.012

Data are presented as median (interquartile range 25th–75th percentile). P values are in comparison with baseline.
iPTH = intact parathyroid hormone, ALP = alkaline phosphatase

(P = 0.012). Additionally, phosphorus levels decreased significantly during the follow-up period, which decreased from 2.23 (IQR, 1.73–2.62) mmol/L at baseline to 1.57 (IQR, 1.45–1.83) mmol/L at 4 years after treatment (P = 0.042). In terms of ALP, its value decreased to the normal range following RFA, from a baseline value of 242.5 (IQR, 132.8–483.4) U/L to 94.0 (IQR, 70.0–115.8) U/L at 4 years after treatment (P = 0.012).

In addition, the iPTH, calcium, phosphorus, and ALP levels in two patients with THPT after successful renal transplantation decreased from 242.5 and 115.9 pg/mL, 2.70 and 2.76 mmol/L, 0.82 and 1.03 mmol/L, and 104.0 and 62.0 U/L, respectively, to 171.0 and 62.0 pg/mL, 2.49 and 2.51 mmol/L, 0.88 and 1.47 mmol/L, and 86.0 and 89.0 U/L, respectively, at 6 months after treatment.

The rate of persistent hyperparathyroidism was 4.0% (1/25) in the renal failure group. The rates of recurrent hyperparathyroidism at 6 months and 4 years after treatment were 4.0% (1/25) and 0.0% (0/9), respectively, in the renal failure group. The therapeutic success rates were 86.4% (19/22) and 100.0% (9/9) at 1 year and 4 years, respectively, following treatment in the renal failure group. After the treatment, 28.9% (11/38) of patients had discordant features as observed on the color Doppler and CEUS images.

RFA-Related Complications

Intratreatment and posttreatment complications are summarized in Table 3. No skin burns, infections, or permanent hypoparathyroidism occurred in any of the patients with THPT. In 2.6% (1/38) of the patients, a hematoma developed along the radiofrequency electrode that was passed through the sternocleidomastoid muscle to reach the left inferior parathyroid lesion. In 7.9% (3/38) of the patients, temporary hoarseness developed after RFA. RFA resulted in 34.2% (13/38), 10.5% (4/38), and 2.6% (1/38) of patients developing temporary hypocalcemia, permanent hypocalcemia, and temporary hypoparathyroidism, respectively. All other intratreatment and posttreatment complications from 1 week to 6 months of RFA were resolved without medical intervention.

Clinical Symptom Changes Associated with THPT

Table 3 summarizes the clinical symptoms (bone pain, arthralgia, itchy, restless legs syndrome, rough skin, and calcinosis cutis). In the preoperative survey, the most prevalent symptoms were "itchy" (31.6%), and "bone pain" (18.4%). All six-item clinical symptoms showed statistical differences at the end of RFA treatment follow-up in the 17 patients with positive symptoms, except for three ("restless legs syndrome," "rough skin," and "calcinosis cutis") (P < 0.05). The overall symptom recovery rate was 58.8 % (10/17).

Table 3. Complications and clinical symptoms associated with before and after radiofrequency ablation in all study patients

Variables	Before ablation	End of follow-up
Intratreatment complications		
Skin burns	-	0 (0.0)
Hematoma	-	1 (2.6)
Neck pain	-	1 (2.6)
Posttreatment complications		
Infection	-	0 (0.0)
Temporary hoarseness	-	3 (7.9)
Permanent hoarseness	-	0 (0.0)
Temporary hypocalcemia	-	13 (34.2)
Permanent hypocalcemia	-	4 (10.5)
Temporary hypoparathyroidism	-	1 (2.6)
Permanent hypoparathyroidism	-	0 (0.0)
Clinical symptoms		
Bone pain	7 (18.4)	2 (5.3)
	0.0 (0.0–1.0)	0.0 (0.0–0.0)*
Arthralgia	6 (15.8)	2 (5.3)
	0.0 (0.0–1.0)	0.0 (0.0–0.0)*
Itchy	12 (31.6)	3 (7.9)
	0.0 (1.0–1.0)	0.0 (0.0–0.0)*
Restless legs syndrome	3 (7.9)	2 (5.3)
	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Rough skin	2 (5.3)	2 (5.3)
	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Calcinosis cutis	4 (10.5)	4 (10.5)
	0.0 (0.0–0.5)	0.0 (0.0–0.5)

Data are presented as patient number with (%) or median (interquartile range 25th–75th percentile) for clinical symptom grades (0, no associated symptoms; 1, mild; 2, moderate; and 3, serious).
*P < 0.05 for the difference in symptom scores compared with preablation

DISCUSSION

Our data indicate that RFA may be particularly beneficial in patients with THPT. iPTH levels decreased compared to the preoperative levels, and calcium, phosphorus, and ALP levels were maintained within the normal range or slightly above the upper limit of normal. Owing to the normalization of calcium and ALP levels, the bone metabolism disorders were well controlled. Furthermore, clinical symptoms

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associated with hyperparathyroidism improved, except for restless legs syndrome, rough skin, and calcinosis cutis.

Importantly, few complications have been observed with RFA in patients with THPT. Complications such as hematoma, neck ache, temporary hoarseness, hypocalcemia, and hypoparathyroidism eventually resolved. A recent randomized trial showed a higher rate of temporary (41.0% vs. 18.0%) or permanent (20.5% vs. 10.3%) hypoparathyroidism in the total PTX with autologous transplantation (TPX-A) cohort than that in the subtotal PTX (STPX) cohort, respectively [19]. Our results on the incidence of hypoparathyroidism were superior, and retaining 1 mm of the parathyroid tissue at the initiation point of ablation may be essential to minimize the risk of hypoparathyroidism. In addition, in two other studies, PTX reduced calcium levels, although it was permanently below the normal range in 33.3% and 36.4% of patients [24,25]. As expected, the main complication of PTX was hypocalcemia, which was confirmed in our study. Three (7.9%) patients with temporary hoarseness recovered to a normal tone within 1 week to 6 months. This is consistent with previous studies reporting a 0.0% to 12.5% incidence of temporary hoarseness in patients undergoing PTX [17,26].

Irrespective of the treatment modality, THPT is prone to recurrence in patients with long-term renal failure. This is closely related to etiology, course, comorbidities, and other factors. The tendency of iPTH to rebound and hypocalcemia after treatment has been previously demonstrated in several patient populations with THPT [19,26-28]. The reduced renal excretion of phosphorus potentially limited the excretion of phosphorus in the dialysis fluid, affecting subsequent accumulation of phosphorus over months and years resulting in compensatory hyperplasia of the remaining parathyroid tissue. In our experience, RFA can be considered as a viable option for maintaining iPTH and normal calcium levels as its recurrence rate is lower than that of other treatment modalities [19,26,27].

Thermal ablation has unique advantages over other treatments in previous studies. It offers the advantages of a simpler procedure, fewer complications, no neck scarring, and no significant tissue adhesion. A previous study indicated that thermal ablation controls iPTH levels at < 300 pg/mL in a higher proportion than does drug therapy (46.2% vs. 14.3%) [29]. Another study performed by Diao et al. [30] concluded that MWA was better than PTX in controlling iPTH levels within the target range (100–600 pg/mL) in patients with severe SHPT undergoing hemodialysis.

Surgeons must weigh hypoparathyroidism against persistent or recurrent hyperparathyroidism after treatment, especially THPT, which is constantly stimulated to produce PTH in the background of CKD. Many patients with THPT experience treatment failure after sufficient follow-up, even if they are initially treated with STPX or TPX-A. Previous experience from other studies in patients with secondary or TPHT undergoing PTX or MWA indicated a technical success rate of 70.0%–100.0% [19,31-33]. Meanwhile, the therapeutic success rates ranged between 71.6% and 93.2% [32,34,35]. In patients with THPT with renal failure in our study, the technical success rate was 100.0%, and the therapeutic success rate was consistently maintained above 86.4%. Although these conclusions are similar to those of the present study, the definitions of technical and therapeutic successes differ. Most studies define technical or therapeutic success using laboratory results as the judgment criteria, such as calcium normalization and/or PTH decline [19]. For example, Rayes et al. [33] defined technical success as iPTH < 150 pg/mL or iPTH < 30.0% of the baseline values. Zhao et al. [35] defined therapeutic success as iPTH levels reduced by 80.0% after surgery, based on the surgical practice of SHPT for chronic renal failure. Thermal ablation requires new guidelines to harmonize terminology and avoid parameter heterogeneity, which impedes accurate comparisons among study results.

Based on the definition of THPT in this study, seven articles on PTX (in the last 5 years) and an additional representative alcohol injection article for THPT are listed in Table 4 for additional analysis [15-17,19,26-28,36]. The surgery failure rate was defined as the sum of the incidence of persistent and recurrent hyperparathyroidism after treatment. The incidences of hypocalcemia and hypoparathyroidism were determined by the summation of the temporary and permanent incidences. The range of surgery failure rates was 13.3%–39.4% [19,26,27,36]. In addition, the variable rates of hypocalcemia and hypoparathyroidism ranged from 12.8% to 100.0% and 2.1% to 45.5%, respectively [15,19,26-28,36].

This study has several limitations. First, because it was a small-sample prospective study, we lacked sufficient previous studies for controls and were unable to conduct a multivariate analysis. Second, bone mineral density was not included in this study. Based on this perspective, it is not reasonable to require regular review of this radiologically damaging examination for all patients. Third, the small final analyzable sample may have contributed to loss-to-follow-up bias. This may have led to an underestimation of the risk

Table 4. Summary of included studies on the treatment of teriary hyperparathyroidism

Study	Procedure	No. of patients	Study design	Follow-up time (m)	Therapeutic success rates	Complications	Before ablation	End of follow-up
Hu et al., 2019 [15]	MWA	23	Retrospective cohort	47.0 ± 8.4	-	Mild to moderate neck pain: 23 (100.0%) Mild headache: 2 (8.7%) Mild backache: 1 (4.4%) Local mild distension: 14 (60.9%) Transient vocal difficulty: 1 (4.4%) Hypocalcemia: 23 (100.0%)	iPTH: 3940 ± 484 pg/mL Calcium: 2.99 ± 0.25 mmol/L Phosphorus: 2.37 ± 0.21 mmol/L ALP: 1206.35 ± 230.54 U/L	iPTH: 1159.3 ± 81.3 pg/mL Calcium: 2.60 ± 0.10 mmol/L Phosphorus: 1.32 ± 0.12 mmol/L ALP: 157.91 ± 10.04 U/L
Li et al., 2019 [16]	MWA	9	Retrospective cohort	17.2 ± 1.7	-	Hematoma: 1 (11.1%)	iPTH: 780.0 pg/mL Calcium: 2.62 ± 0.32 mmol/L Phosphorus: 1.39 ± 0.61 mmol/L Blood creatinine: 88.9 ± 26.7 µmol/L Blood urea nitrogen: 5.7 ± 1.6 mmol/L	iPTH: 134.0 pg/mL Calcium: 2.27 ± 0.13 mmol/L Phosphorus: 1.17 ± 0.43 mmol/L Blood creatinine: 94.5 ± 14.7 µmol/L Blood urea nitrogen: 6.7 ± 1.4 mmol/L
Douthat et al., 2007 [17]	PEIT	8	Retrospective cohort	8.0 ± 2.8	-	Neck discomfort: 4 (50.0%) Temporary hoarseness: 1 (12.5%)	iPTH: 286.9 ± 107.2 pg/mL	iPTH: 154.6 ± 42.2 pg/mL
Choi et al., 2021 [19]	STPX vs. TPX-A	Kidney transplant group: 61 vs. 44 Dialysis group: 7 vs. 36	Retrospective cohort	> 6	Kidney transplant group STPX: 45 (73.7%) TPX-A: 37 (84.1%) Dialysis group STPX: 5 (71.4%) TPX-A: 34 (94.4%)	STPX in kidney transplant group Hypoparathyroidism: 14 (23.0%) Temporary hypocalcemia: 6 (15.4%) Permanent hypocalcemia: 4 (10.3%) TPX-A in kidney transplant group Hypoparathyroidism: 20 (45.5%) Temporary hypocalcemia: 8 (20.5%) Permanent hypocalcemia: 4 (10.3%) STPX in dialysis group Hypoparathyroidism: 2 (28.6%) Temporary hypocalcemia: 0 (0.0%) Permanent hypocalcemia: 3 (60.0%) TPX-A in dialysis group Hypoparathyroidism: 16 (44.4%) Temporary hypocalcemia: 7 (29.2%) Permanent hypocalcemia: 11 (45.8%)	Kidney transplant group iPTH: 355.1 (192–983) pg/mL Dialysis group iPTH: 1026 (698–1373) pg/mL	Kidney transplant group iPTH: 36.4 (19.3–171) pg/mL Dialysis group iPTH: 75.2 (46.86–124.98) pg/mL

Table 4. Summary of included studies on the treatment of teriary hyperparathyroidism (continued)

Study	Procedure	No. of patients	Study design	Follow-up time (m)	Therapeutic success rates	Complications	Before ablation	End of follow-up
Ramonell et al., 2022 [26]	SPTX, limited PTX	71 vs. 141	Retrospective cohort	-	-	SPTX Permanent hypocalcemia: 8 (11.3%) Transient hypocalcemia: 15 (21.1%) Temporary hoarseness: 0 (0.0%) ED visit: 1 (1.4%) Hypoparathyroidism: 4 (5.6%) Wound complication: 0 (0.0%) Readmission: 0 (0.0%) Limited PTX Permanent hypocalcemia: 2 (1.4%) Transient hypocalcemia: 16 (11.4%) Temporary hoarseness: 2 (1.4%) ED visit: 2 (1.4%) Hypoparathyroidism: 3 (2.1%) Wound complication: 0 (0.0%) Readmission: 0 (0.0%)	Mild THPT PTH: 225 (145–360) pg/mL Calcium: 9.7 (9.3–10.1) mg/dL Classic THPT PTH: 211 (149–355) pg/mL Calcium: 11.0 (10.7–11.5) mg/dL	Mild THPT PTH: 92 (45–148) pg/mL Calcium: 9.1 (8.5–9.6) mg/dL Classic THPT PTH: 73 (39–125) pg/mL Calcium: 9.5 (8.9–9.8) mg/dL
Kovács et al., 2019 [27]	PTX	19	Retrospective cohort	49	-	Hypocalcemia: 6 (31.6%) Temporary paralysis of the recurrent laryngeal nerve: 1 (5.3%)	-	-
Patecki et al., 2020 [28]	PTX	48	Retrospective cohort	36	-	Hypocalcemia: 11 (22.9%)	iPTH: 394 pg/mL Calcium: 2.63 ± 0.20 mmol/L Phosphorus: 0.89 ± 0.26 mmol/L	iPTH: 24 pg/mL Calcium: 2.23 ± 0.26 mmol/L Phosphorus: 1.16 ± 0.35 mmol/L
Meng et al., 2017 [36]	PTX	15	Retrospective cohort	49	-	-	iPTH: 229 (153–361) pg/mL Calcium: 10.8 (9.4–11.4) mg/dL Phosphorus: 2.4 (1.9–2.8) mg/dL eGFR: 62.7 (35.3–79.6) mL/m/1.73 m^2	iPTH: 77 (56–113) pg/mL Calcium: 9.4 (9.0–10.2) mg/dL Phosphorus: 2.95 (2.3–3.8) mg/dL eGFR: 60.8 (50.0–76.8) mL/m/1.73 m^2

Data are presented as subject number (percentage), mean and standard deviation or median (interquartile range 25th–75th percentile) in behind. The study by Hu et al. [15], Kovács et al. [27], and Patecki et al. [28] did not specify the type of transient or permanent hypocalcaemia.

MWA = microwave ablation, iPTH = intact parathyroid hormone, ALP = alkaline phosphatase, PEIT = percutaneous ethanol injection treatment, STPX = subtotal parathyroidectomy, TPX-A = total parathyroidectomy with autologous transplantation, PTX = parathyroidectomy, ED = emergency department, THPT = teriary hyperparathyroidism, PTH = parathyroid hormone, eGFR = estimated glomerular filtration rate of hyperparathyroidism recurrence and treatment failure.

In conclusion, this prospective study provide initial evidence that US-guided RFA is effective and safe in treating patients with TPTH. Further prospective studies with larger sample sizes and higher quality are required to elucidate the efficacy of ablation in TPTH through more conclusive results.

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

The authors have no potential conflicts of interest to disclose.

Author Contributions

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