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HEAD AND NECK

US-guided microwave ablation for primary hyperparathyroidism: a safety and efficacy study

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Abstract

Objectives To evaluate the safety and efficacy of microwave ablation (MWA) with the assistance of continuous cool saline injection (CCSI) in patients with primary hyperparathyroidism (PHPT).

Methods Between November 1, 2014, and February 29, 2016, 22 patients with PHPT were enrolled and treated with ultrasound-guided MWA assisted by CCSI. The levels of parathyroid hormone (PTH) and serum calcium were recorded before and after the MWA. Patients were divided into two groups (normalized and unnormalized groups) according to treatment efficacy. Fisher's exact test and the Mann-Whitney test were used to compare data between the two groups. Timing differences in serum PTH and calcium levels were analyzed with repeated measures analysis of variance.

Results Normalized outcomes for both PTH and calcium levels were achieved in 19 of 22 (86.36%) patients with PHPT. In the normalized group, PTH levels remained normal for 12 months after MWA. PTH levels in the unnormalized group were outside the reference range at six of seven follow-ups within 12 months following MWA. By contrast, serum calcium levels gradually decreased in all patients in both groups. The mean serum PTH and mean calcium levels at 6 months after therapy were significantly lower than those before MWA (both $p < 0.05$). A transient voice change developed in eight patients. One patient experienced hypocalcaemia, which was corrected by oral calcium supplementation within 2 months.

Conclusions US-guided MWA assisted by CCSI is safe and effective for destroying parathyroid gland tissue and may serve as a therapeutic alternative for patients with PHPT.

Key Points

• *Microwave ablation is a new option for patients with hypercalcemic or normocalcemic primary hyperparathyroidism.*
• *Microwave ablation can decrease PTH and calcium levels with sustained efficacy in most patients.*
• *Treatment is safe and causes only transient side effects.*

Keywords Primary hyperparathyroidism · Parathyroid glands · Parathyroid hormone

Bo-qiang Fan and Xiao-wei He contributed equally to this work.

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Abbreviations

^{99m}Tc-sestamibi SPECT	Technetium 99-m-labeled sestamibi single-photon emission computed tomography
CCSI	Continuous cool saline injection
LA	Laser ablation
MWA	Microwave ablation
PEI	Percutaneous ethanol injection
PHPT	Primary hyperparathyroidism
PTGs	Parathyroid glands
PTH	Parathyroid hormone
RFA	Radiofrequency ablation
RLN	Recurrent laryngeal nerve
US	Ultrasound

Introduction

Primary hyperparathyroidism (PHPT) is a common clinical entity typically characterized by hypercalcemia and elevated parathyroid hormone (PTH) levels [1, 2]. The estimated incidence of PHPT varies from ~0.4 to 82 cases per 100,000 persons, with a higher prevalence in females than in males; the incidence increases with age [3–5]. In addition to hypercalcemia PHPT, normocalcemic PHPT is now a well-recognized variant of PHPT [6]. Despite maintaining normocalcemia, patients continue to exhibit a high incidence of kidney stones and osteoporosis [7] and have a positive association with metabolic disturbances and cardiovascular risks, similar to patients with hypercalcemic PHPT [8].

Parathyroid surgery has been recommended for patients with symptomatic primary hyperparathyroidism in whom known target organ complications of the disease, such as renal stones, severe bone disease, fractures, or neuromuscular syndrome, are present [9]. In asymptomatic patients, management depends on serum calcium concentration, skeletal manifestations, renal manifestations, and age [2]. Despite the latest improvements in surgical techniques, there are patients who either decline surgery or are unsuitable candidates for surgery. Elderly patients with PHPT are at risk from general anesthesia and full neck exploration [1], and young females affected by PHPT are concerned about the potential for scarring on their necks [10]. In addition, possible side effects may cause certain patients to decline surgery [11, 12]. Therefore, identifying therapeutic alternatives to surgery has generated considerable interest.

At present, the rationale for alternative nonsurgical therapies for PHPT is to induce necrosis in as much of the gland as possible with either chemical substances or thermal energy. Current drugs for the treatment of PHPT can only normalize calcium levels, and PTH levels generally remain elevated [13]. Percutaneous ethanol injection (PEI) has been determined to be useful in PHPT [14]. However, its applicability is narrow because of relapse and side effects [15]. Recently, several thermal ablation modalities have been developed for use in patients with PHPT, such as laser ablation (LA), radiofrequency ablation (RFA), and high-intensity focused ultrasound treatment. However, these studies have been performed only with small numbers of patients; more studies are necessary for evaluation of their treatment outcomes.

Microwave ablation (MWA) is also a viable alternative therapeutic option for patients with PHPT. Although this procedure has been successfully applied to treat benign and malignant tumors in the body [16], clinical use of MWA in the treatment of PHPT has been reported in only a few cases [17, 18]. In particular, the use of US-guided percutaneous MWA has not been reported for patients with normocalcemic PHPT.

The purpose of this study was to evaluate the safety and efficacy of percutaneous MWA with US guidance and continuous cool saline injection (CCSI) for both hypercalcemic and normocalcemic PHPT.

Materials and methods

Patients

The retrospective study was approved by the Human Ethics Review Committee of the Jiangsu Province Hospital (a referral hospital). Written informed consent was signed by each patient prior to undergoing MWA.

Of the 70 patients with PHPT seen in the Cancer Center between November 1, 2014, and February 29, 2016, 22 patients with elevated PTH and one enlarged parathyroid gland were eligible for MWA therapy because they met all inclusion criteria: PTH levels higher than the upper limit of normal (88 pg/ml), serum calcium levels greater than 2.65 mmol/l or within normal range, normal renal function tests, positive ^{99m}Tc-sestamibi scan results (the gland could be identified with a ^{99m}Tc-sestamibi scan), positive US examination results (the gland could be identified with US), refusal of surgery, not pregnant, and older than 18 years. Patients with neck malignancies or a history of thyroid or parathyroid surgery were excluded. We excluded patients with neck malignancies based on their detailed laboratory examination as well as pathological results. Patients whose data on PTH or calcium levels were unavailable for two or more of the follow-up time points after MWA were also excluded. Figure 1 depicts the process of patient selection. In our study, nodules of all patients were prelocalized with technetium 99-m-labeled sestamibi single-photon emission computed tomography (^{99m}Tc-sestamibi SPECT) and US imaging. Thus, biopsy was not mandatory.

Equipment

The microwave platform (KY-2000; Kangyou Medical Ltd.) contains a microwave generator, a flexible coaxial cable, and a

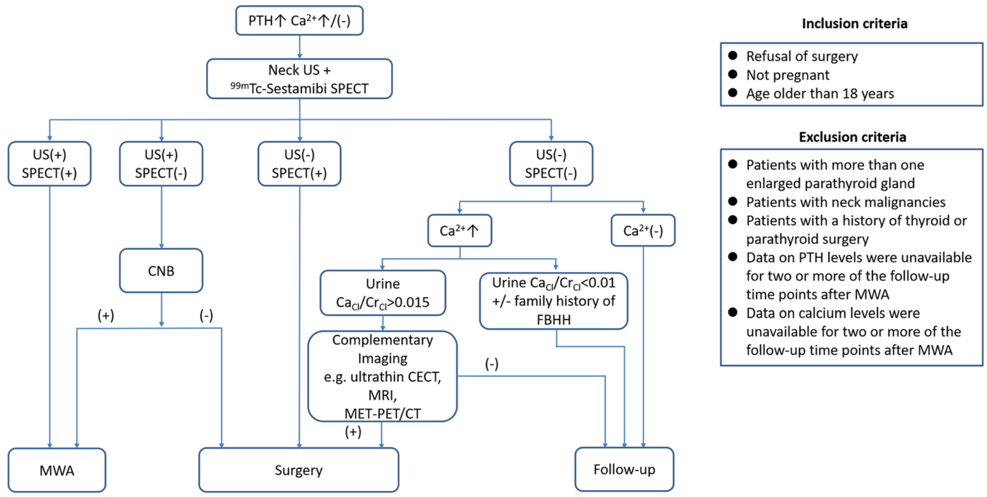

Fig. 1 Flowchart depicting the process of patient selection. Ca, calcium; ^{99m}Tc-sestamibi SPECT, technetium 99-m-labeled sestamibi single-photon emission computed tomography; US, ultrasound; CNB, core needle biopsy; Ca_{Cl}/Cr_{Cl}, calcium creatinine clearance ratio; FBHH, familial benign hypocalciuric hypercalcemia; CECT, contrast-enhanced computed tomography; MRI, magnetic resonance imaging; MET-PET/CT, 11C-methionine positron emission tomography/computed tomography; and MWA, microwave ablation

cooled-shaft antenna. The antenna is an internally cooled ablation needle (17-gauge, 11 cm in length, and a 3-mm active tip) covered with polytetrafluoroethylene to prevent adhesion. Distilled water runs through dual channels inside the antenna shaft, preventing the needle shaft from overheating. In this study, an antenna with a 3-mm active tip was used in all cases.

MWA procedure

The patient was placed in a supine position with the neck extended. Before treatment, a detailed US (MyLab 90™, Esaote S.P.A.) examination was performed to re-identify the abnormal parathyroid glands (PTGs). After sterilization, we injected 1% lidocaine (Zhaohui Pharmaceutical Ltd.) for local anesthesia (no general anesthesia or sedation before procedures was performed). Then, an 18-gauge needle (Hakko Medical Co., Ltd.) was inserted posterior-medially to the lesion, and 5 ml of cool saline (4 °C) was subsequently injected to create a hydrodissection around the lesion. Next, the ablation needle was inserted into the gland under US guidance. During the ablation process, continuous slow injection of cool saline was performed by an assistant to provide thermal insulation for the recurrent laryngeal nerve (RLN); the total injection volume was between 15 and 25 ml. For patients developing a transient voice change before ablation, the volume of saline exceeded 20 ml. During the entire procedure, patients were frequently asked if they had difficulty with phonation. For small glands, ablation was terminated when the entire lesion was covered with hyperechoic microbubbles. Large glands were divided into 2 or 3 sections for ablation. All the ablation procedures were performed by one of the authors. The complete process of MWA can be observed in the Supplementary Movie, and the effect of treatment can be found in Fig. 2. After completing the treatment, we kept the patients under observation for 2 h and applied mild compression to the neck for 20 min. Patients were discharged if no complications requiring hospitalization developed.

Data collection and follow-up

Clinical data were collected for all patients. The biochemical data collected included serum PTH (UniCel Dxl 800™, Beckman Coulter) and serum calcium (AU5800™, Beckman Coulter) levels before ablation, 10 and 20 min after ablation, and at each follow-up visit (1 day, 1 month, 3 months, 6 months, and 12 months after treatment). Neck US was performed 10 min after ablation to identify hematomas or other complications, and a US examination was performed at each follow-up visit. The volume of each gland was calculated as $V = (length \times width \times height) \times \pi/6$ (where V is the volume, *length* is the transversal diameter, *width* is the anteroposterior diameter, and *height* is the vertical diameter). Nodule vascularity was divided into 4 grades, with scores of 1, 2, 3, and 4 representing no Doppler signals, signals in < 25% of the nodule, signals in 25–50% of the nodule, and signals in > 50% of the nodule, respectively [18]. Laryngoscopic examination was performed 1 month after treatment to evaluate movement of the vocal cords. In addition, because of having osteoporosis, all patients were routinely administered one tablet of Caltrate® (Pfizer Pharmaceutical Ltd.) per day after therapy [19]. Patients with persistent hyperparathyroidism (significantly higher serum PTH than normal range) and a residue of vital gland a few months (generally 3 months) after the first session, needed to consider a second ablation [18]. Criteria for the definition of the normalized group were as follows: serum PTH and calcium levels both decreased to within normal range (12–88 pg/ml for PTH and 2.2–2.65 mmol/l for calcium) 6 months after treatment. Criteria for the definition of the unnormalized group were as follows: serum PTH levels higher than the upper limit of normal (88 pg/ml) 6 months

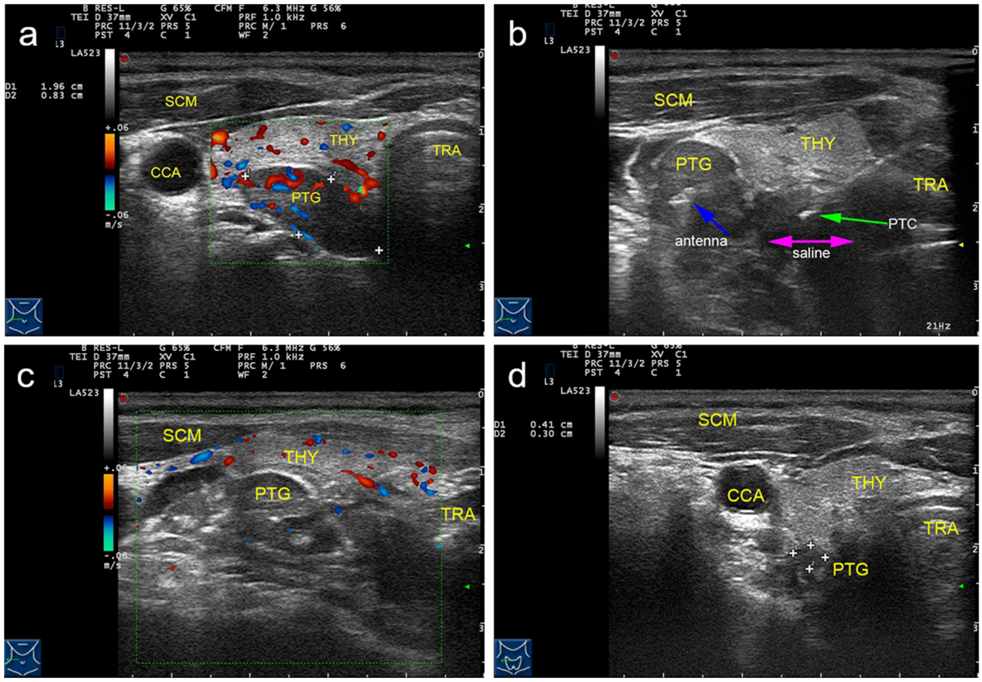

Fig. 2 Images from a 65-year-old female with a right upper parathyroid nodule (21 mm × 20 mm × 9 mm) who underwent microwave ablation therapy. **a** Before ablation, the PTG was hypervascular on the color Doppler flow image. **b** A microwave antenna (blue arrow) was inserted inside the PTG, and the PTC needle (green arrow) was placed between the PTG and trachea. Saline isolation (purple arrow) was carried out and maintained with continuous saline injection through the PTC needle. **c** No color flow was observed inside the PTG immediately after the ablation procedure. **d** Six months later, the PTG was markedly reduced in size (5 mm × 4 mm × 3 mm). PTG, parathyroid gland; CCA, common carotid artery; SCM, sternocleidomastoid muscle; THY, thyroid gland; TRA, trachea; and PTC, PTC needle

after treatment or serum calcium levels higher than the upper limit of normal (2.65 mmol/l) 6 months after treatment.

Statistical analysis

Data analysis was performed with statistical software (IBM SPSS software, version 23.0, IBM Corp.). The normality of the distribution for all continuous variables was tested using the Kolmogorov-Smirnov test of normality. Continuous variables are presented as the mean ± standard deviation (range), and categorical variables are displayed as a frequency (percentage). Fisher's exact test was used to compare categorical variables between the normalized and unnormalized groups. Continuous variables with an abnormal distribution in the two groups were compared using the Mann-Whitney test. Timing differences within individuals were analyzed with repeated measures analysis of variance. All tests were two-sided, and a p value below 0.05 was considered statistically significant.

Results

Patient demographics and clinical characteristics

The baseline clinical characteristics of the patients enrolled in the study are summarized in Table 1. In total, 22 patients (3 men, 19 women; mean age, 55.95 years; range, 31–81 years) underwent US-guided MWA assisted by CCSI between November 1, 2014, and February 29, 2016, in our hospital. Baseline serum PTH levels varied from 91.40 to 1112.50 pg/ml (mean, 251.78 ± 249.42 pg/ml), and serum calcium levels varied from 2.17 to 4.31 mmol/l (mean, 2.72 ± 0.43 mmol/l). All patients had high serum PTH levels; only half of the patients had serum calcium levels outside the normal range. Twenty-one patients had glands in normal locations, and one patient's gland was located in the suprasternal fossa. The diameter of the glands ranged from 4 to 37 mm (mean, 14.0 ± 7.8 mm), and the mean volume of the PTGs ablated varied from 0.088 to 11.51 cm^3 (mean, 2.08 ± 2.89 cm^3). The mean applied energy to the gland was 35.68 ± 3.55 W, and the duration of the procedure ranged from 24 to 566 s (mean, 129.14 ± 122.55 s).

Laboratory analysis

In this study, 10 min and 20 min were selected as check points as reported in previous surgical protocols [2, 20]. At 10 min, 20 min, and 1 day postablation, the serum PTH levels were significantly lower than those before MWA (all $p < 0.001$). The serum calcium levels 10 min, 20 min, and 1 day after MWA were decreased relative to those at baseline, but the differences were not statistically significant. Notably, the

Table 1 Clinical and treatment characteristics of the patient population treated by microwave ablation

Characteristics	Data
No. of cases	22
Gender (*n*, male/female)	3/19
Age (years)	55.95 ± 12.95 (31–81)
Baseline level of PTH (pg/ml)	251.78 ± 249.42 (91.40–1112.50)
Baseline level of calcium (mg/dl)	2.72 ± 0.43 (2.17–4.31)
Size of parathyroid nodules ablated (cm^3)	2.08 ± 2.89 (0.088–11.51)
Maximum diameter (mm)	37
Minimum diameter (mm)	4
Location of nodules	
Normal location	21 (95.45%)
Upper pole	5 (23.81%)
Lower pole	16 (76.19%)
Ectopic location	1 (4.54%)
MWA ablation	
Power used in the MWA (W)	35.68 ± 3.55 (30–45)
Ablation time (s)	129.14 ± 122.55 (24–566)
Surgical procedure	
Thyroid surgery	0
Parathyroid surgery	0
Complication or side effect	
Transient voice change	8 (36.36%)
PTC needle tract bleeding	2 (9.09%)
Hypocalcemia	1 (4.55%)

Data are presented as the mean ± standard deviation (range) or frequency (percentage)

PTH, parathyroid hormone; *MWA*, microwave ablation

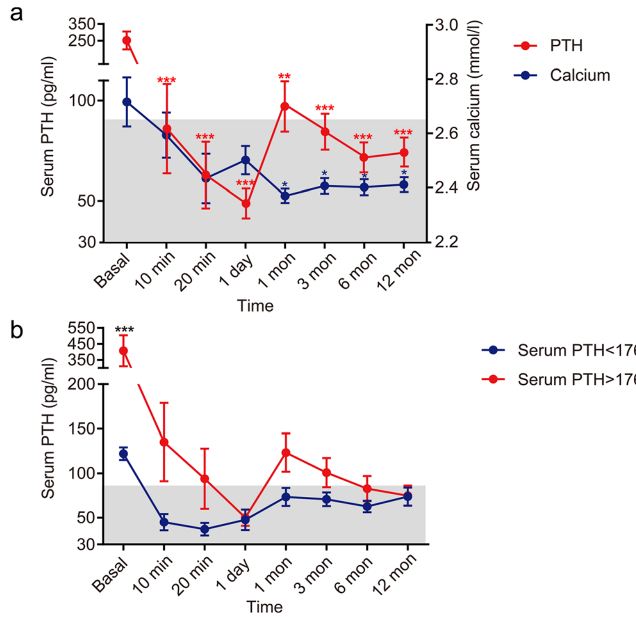

Fig. 3 Characteristics of changes in PTH and calcium levels after MWA treatment. **a** Changes in serum PTH and calcium levels. **b** Changes in serum PTH levels classified according to whether the PTH level was two times higher than the normal value. Data are presented as the mean ± standard error. The normal range is depicted in gray. $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$ compared with the baseline values before MWA treatment. PTH, parathyroid hormone; MWA, microwave ablation; min, minute; and mon, month

serum PTH levels were elevated 1 month postablation, and the difference remained statistically significant compared with baseline levels (Fig. 3a, $p = 0.003$). As shown in Fig. 3b, this rebound effect tended to occur only in the subgroup of patients with PTH levels that were two times higher than the upper limit of normal (176 pg/ml). By contrast, the mean levels of serum calcium at the 1-month follow-up were significantly lower than the initial values ($p = 0.01$). During the following 3, 6, and 12 months, the mean values of serum PTH and calcium both decreased to the normal reference ranges and tended to be stable (Fig. 3a). Eleven patients (50%) were followed up for 18 months after MWA. Their serum PTH (mean, 60.49 ± 13.15 pg/ml; range, 45.30–84.20 pg/ml) and calcium (mean, 2.42 ± 0.12 pg/ml; range, 2.24–2.59 mmol/l) levels remained within normal ranges.

In the subgroup of patients with hypercalcemia, serum PTH levels completely returned to normal in 9 of 11 patients (81.82%), and serum calcium levels completely returned to normal in all 11 patients (100%). Significant differences in PTH levels between patients with preprocedural normocalcemia and those with preprocedural hypercalcemia were observed only at baseline ($p = 0.047$), whereas significant differences in calcium levels were observed at baseline ($p = 0.001$) and 20 min after MWA ($p = 0.034$) (Fig. 4). No significant differences in serum PTH and calcium levels were observed between these two groups by the end of the follow-up period.

Treatment effect

In our study, 19 participants were included in the normalized group, and three were included in the unnormalized group. Key data on treatment outcomes are presented in Table 2. There were no significant differences in gender, age, volume, diameter, or location of the PTGs or in the baseline levels of calcium between the two groups. Similarly, no differences in the mean power of MWA or ablation time were observed. However, patients with a normalized outcome tended to have higher baseline PTH levels ($p = 0.078$).

Follow-up data from the two groups are displayed in Fig. 5. In the normalized group, PTH levels were decreased to within the reference range 10 min after MWA therapy and remained within that range for 12 months following MWA. PTH levels in the unnormalized group were outside the reference range at six of seven follow-ups within 12 months following MWA. Significant differences in PTH levels between the normalized and unnormalized groups were observed at 1 month ($p =$

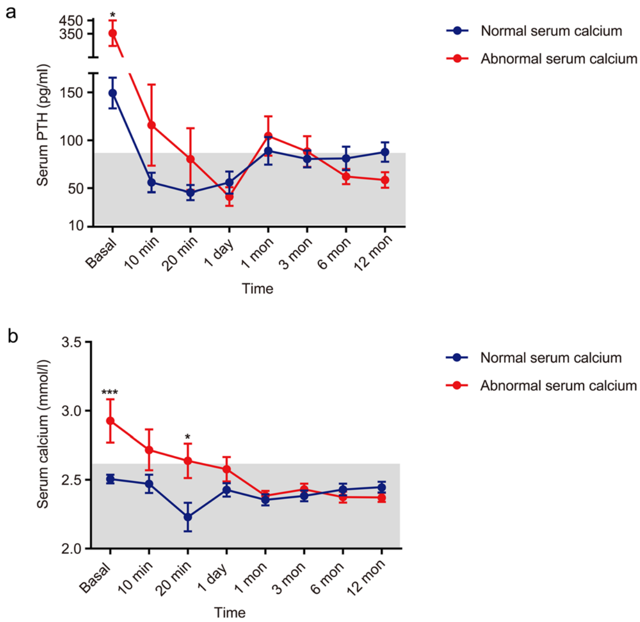

Fig. 4 Characteristics of changes in (**a**) PTH and (**b**) calcium levels according to whether the initial serum calcium level was within the normal range. Data are presented as the mean ± standard error. The normal range is depicted in gray. *$p < 0.05$ and ***$p < 0.001$ compared with the baseline values before MWA treatment. PTH, parathyroid hormone; MWA, microwave ablation; min, minute; and mon, month

0.017), 3 months ($p = 0.009$), and 6 months ($p = 0.002$) following MWA therapy. By contrast, serum calcium levels gradually decreased in all patients in both groups, although slow but continuous normalization was more pronounced in the normalized group than that in the unnormalized group.

PTG volume

Analysis of all individuals engaged in the study revealed a significant volume reduction in the PTG as soon as 1 month after WMA treatment ($p = 0.003$), and the volume of the PTGs continued to decrease during the following 3, 6, and 12 months (Fig. 6). That is, the mean percentage decrease in PTG volume progressively increased during the follow-up period from 51.48 ± 28.42% at 1 month to 76.77 ± 19.41% at 3 months, 88.93 ± 12.93% at 6 months, and finally 96.72 ± 6.38% at 12 months. Notably, the PTGs completely disappeared in 15 of the 22 patients (68.2%) at the final follow-up (mean final follow-up period was 12.55 ± 5.21 months).

Safety and tolerability of the MWA procedure

In all patients, MWA was safe, and no patients required hospitalization following treatment. Fifteen patients complained of mild-to-moderate levels of pain or discomfort during the ablation, which disappeared immediately after the energy source was turned off. A transient voice change (lowered pitch) was encountered in eight cases during the study. Specifically, before ablation, three patients experienced a transient voice change after saline injection. We think that the increase in local pressure caused by the saline injection and the accompanying tissue swelling led to the voice changes in these patients. After the absorption of saline, the local pressure decreased, and their voices recovered quickly. In addition, five patients experienced transient voice changes during ablation. This may be a result of the conduction of heat generated during the ablation to the RLN. Therefore, we inferred that heat conduction to the RLN and an increase in local pressure may be the reasons for the voice changes. The specific local anatomy between the RLN and the gland may play an important role in the voice changes. In our study, the voice change was temporary and resolved without treatment within 60 min after ablation (mean, 32.50 ± 24.64 min; range, 5 to 60 min). Laryngoscopic imaging demonstrated no vocal-cord palsy. Two patients had PTC needle tract bleeding, which was managed by manual compression. Two individuals underwent a second MWA session because of a PTH level above the normal range. Hypocalcemia occurred in one patient whose serum calcium level decreased to 1.89 mmol/l 1 month after MWA. This symptom was corrected in 2 months by adjusting the dosage of Caltrate® to 2 tablets with an additional 0.25 μg of calcitriol (Rocaltrol®, Roche Pharmaceutical Ltd.) per day. No skin burns, hematomas, infections, RLN injuries or other serious complications occurred during or after ablation.

Discussion

Our study included a one-year follow-up period and retrospectively assessed the efficacy and safety of MWA for both hypercalcemic and normocalcemic PHPT. The primary finding of this study was that MWA could significantly decrease PTH and calcium levels with sustained efficacy ($p < 0.05$). In our study, PTH levels decreased 10 min after ablation. This result may be a result of the destruction of the hyperfunctioning gland by MWA, thus reducing the total release of PTH. Furthermore, the half-life of PTH is short and may have led to its rapid decline. Previous studies have demonstrated that the mean half-life of PTH ranges from 3 min and 18 s to 3 min and 42 s [22–24]. By contrast, calcium homeostasis is a complex process involving the following four key components: serum calcium, serum phosphate, 1.25-dihydroxyvitamin D_3, and parathyroid hormone. Therefore, PTH levels rapidly returned to normal, and serum calcium levels gradually recovered.

Thermal ablation techniques such as RFA and LA have also been employed to treat PHPT although the reported literature is limited. In a study that retrospectively reviewed six cases of PHPT treated with LA, only a transient reduction in serum PTH and calcium levels was observed [12]. Therefore, the utility of LA in PHPT remains to be verified. RFA for PHPT has been reported in only three patients. In a postmenopausal woman with PHPT and osteoporosis, the serum PTH level and serum calcium

Table 2 Clinical and treatment characteristics of the patient population with respect to the treatment

Characteristics	Response ($n = 19$)	No response ($n = 3$)	p value
Gender			0.371
Male	2 (10.5%)	1 (33.3%)	
Female	17 (89.5%)	2 (66.7%)	
Age (years)			1.000
< 50	7 (36.8%)	1 (33.3%)	
≥ 50	12 (63.2%)	2 (66.7%)	
	55.47 ± 13.54	59.00 ± 9.64	0.672
Volume (cm^3)			1.000
< 1	10 (52.6%)	2 (66.7%)	
≥ 1	9 (47.4%)	1 (33.3%)	
	2.29 ± 0.74	3.06 ± 0.65	0.356
Vertical diameter (cm)	19.58 ± 9.36	14.00 ± 7.21	0.265
Transversal diameter (cm)	13.32 ± 6.33	11.33 ± 4.04	0.718
Anteroposterior diameter (cm)	10.63 ± 5.36	7.00 ± 2.00	0.265
Location of nodules			1.000
Upper pole	4 (21.1%)	1 (33.3%)	
Lower pole	14 (73.7%)	2 (66.7%)	
Suprasternal fossa	1 (5.3%)		
Solid component (%)	97.36 ± 11.47	100 ± 0	0.929
Vascularity	2.58 ± 0.84	2.67 ± 0.58	0.787
Baseline level of PTH (pg/ml)			0.078
< 176	12 (63.2%)	0 (0.0%)	
≥ 176	7 (36.8%)	3 (100.0%)	
	230.43 ± 256.02	386.97 ± 177.67	0.053
Baseline level of calcium (mg/dl)			1.000
Normal (2.2–2.65)	10 (52.8%)	1 (33.3%)	
Abnormal (< 2.2 or > 2.65)	9 (47.4%)	2 (66.7%)	
	2.70 ± 0.45	2.84 ± 0.21	0.265
Power used in the MWA (W)	35.79 ± 3.82	35.00 ± 0.00	0.929
Ablation time (s)	134.58 ± 129.19	94.67 ± 73.66	0.586

Data are presented as the mean ± standard deviation or frequency (percentage). The cutoff value for age group was based on previous studies, where age under 50 is an evidence-based guideline for surgery [2]. The cutoff value for volume group was based on previous studies, where serum biochemical function (serum calcium, carboxyl-terminal PTH, etc.) tended to be greater in larger glands (≥ 1 cm^3) [21]. In our study, the normal range for the level of PTH is 12–88 pg/ml. We used two times the upper limit to classify the preoperative PTH level. No significant differences between groups were observed

PTH, parathyroid hormone; *MWA*, microwave ablation

level were reduced to normal following treatment. An increase in bone density was observed 1 year after treatment [17]. In another study of two symptomatic patients, normocalcemia and improvement of symptoms were achieved 4 days following RFA, leaving PTH levels above the normal range [25]. Additional studies are necessary to elucidate the therapeutic effect of RFA. Kovatcheva et al validated another modern noninvasive thermal ablation method, i.e., high-intensity focused US, which has shown a potential for the treatment of PHPT [26]. Notably, complete remission was reported in three patients (23%) after 1 year, whereas ten patients (76.9%) continued to have PTH levels above the normal range.

The results of the present study suggest that MWA is feasible for patients with PHPT. MWA treatment resulted in a decrease of both serum PTH and calcium levels to a normal range in 19 of the 22 cases (86.36%). In 15 of 22 patients (68.2%), nodules disappeared completely. A recent study conducted by Liu et al also evaluated the feasibility of MWA in the management of PHPT [18]. The rate of complete nodule disappearance was 17.6%. Cao et al performed MWA in an 80-year-old man with PHPT, and serum PTH and calcium levels decreased to normal ranges 1 day and 4 days after MWA, respectively [17]. However, 6 months and 12 months after MWA, the patient's PTH level was slightly higher than the normal range.

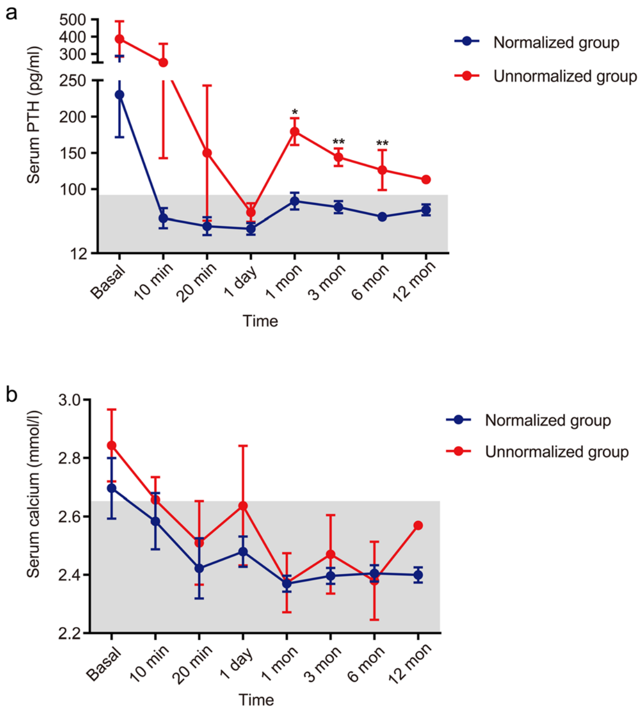

Fig. 5 Characteristics of changes in (**a**) PTH and (**b**) calcium levels by treatment group. Data are presented as the mean ± standard error. The normal range is depicted in gray. *$p < 0.05$ and **$p < 0.01$ compared with the baseline values before MWA treatment. PTH, parathyroid hormone; MWA, microwave ablation; min, minute; and mon, month

According to the literature discussed above, although LA, RFA, and MWA are all percutaneous thermal ablation techniques, their therapeutic effects on PHPT patients vary. The discrepancy between our results and the reports from the previous studies performed by the RFA, LA, or MWA may be due to divergent system performance caused by different ablation-zone shapes, times, and power combinations; different basal serum PTH and calcium levels of the patients; and different operation experiences of doctors [27].

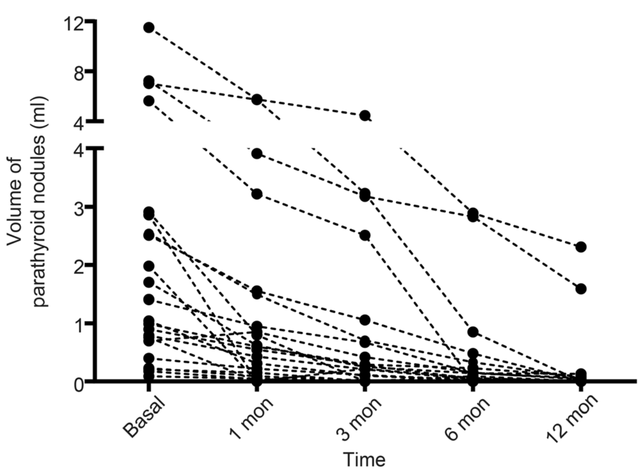

Fig. 6 Changes in parathyroid gland volume after MWA treatment ($n = 22$). The data are presented as the mean. MWA, microwave ablation and mon, month

An interesting phenomenon in our study was that the serum PTH level was distinctly elevated, with serum Ca significantly lower than their initial values 1 month postablation. The explanation for this phenomenon could be the feedback from PTH on Ca reductions [28]. When a decrease in Ca occurred after MWA treatment, synthesis and secretion of PTH increased. Three major effects further responded to help restore Ca to normal circulating levels: (1) increased Ca reabsorption at the kidney; (2) elevated synthesis of 1.25-dihydroxyvitamin D in the kidneys, which promotes Ca absorption in the gut; and (3) increased Ca resorption from osteoclasts releasing Ca from bone. These three effects were mediated by PTH works via a feedback loop on the calcium-sensing receptor, accordingly decreasing the level of PTH [1]. Three months after ablation, the serum PTH tended to be stable and normal when the Ca level remained within normal range, both significantly lower than their initial values.

To our knowledge, little is known about treatment effects in patients with normocalcemic PHPT [7]. In our study, an improvement in PTH levels and the maintenance of serum calcium levels was observed in 10 of 11 (90.90%) normocalcemic subjects. Consequently, US-guided MWA could be an option for normocalcemic patients with PHPT.

In this study, no serious complications occurred during MWA or within the follow-up period. The RLN is anatomically close to the PTG; hence, protection of the RLN is extremely important in MWA of the PTGs. Without hydrodissection, complete thermal ablation of the PTG may cause injury to the nerves, especially the RLN. In several previous ablation studies, PTH failed to reach normal levels following ablation [12, 25]. This result may be due to partial ablation of the PTGs to protect the surrounding important nerves. However, even a few residual adenomatous parathyroid cells following ablation may lead to recurrence of hyperparathyroidism [18]. With our method, thermal protection of the RLN was achieved with continuous injection of cool saline through a PTC needle. This method increases the distance between the RLN and the PTG. Sufficient space allowed us to target the entire gland with the ideal energy level. Therefore, MWA was demonstrated to be safe for patients with PHPT. In fact, both normal saline and 5% dextrose in water were used to separate surrounding structures before thermal ablation procedures [29]. With RFA, the ionic composition of the saline allows it to conduct electricity, thus potentially causing non-target tissue heating [30]. However, the mechanisms of RFA and MWA are different from one another. MWA relies on an electromagnetic field effect to rapidly rotate polarized water molecules to achieve primarily active heating, which is not associated with the electrical conductivity of the tissue [31]. Therefore, normal saline solution is safe and has been widely used in the MWA procedure [32, 33].

There were several limitations to this study. First, the number of patients enrolled in the study was relatively small, and more cases are required to draw any definitive conclusions. Second, the duration of follow-up for all of the patients was only 1 year; 11 patients (50%) were followed for 18 months after MWA. Their serum PTH and calcium levels were maintained within a normal range. Further follow-up is necessary to determine the long-term effectiveness of this treatment.

In conclusion, our study provides important evidence that MWA, with the assistance of CCSI, is an effective and safe therapy for PHPT. It may be a treatment option for PHPT patients who decline or are not able to undergo parathyroidectomy. Considering the limitations of this study, further prospective studies with large samples are necessary to test long-term efficacy.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Prof. Wei Tang.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
• retrospective
• prognostic study
• performed at one institution

References

1. Fraser WD (2009) Hyperparathyroidism. Lancet 374:145–158
2. Bilezikian JP, Brandi ML, Eastell R et al (2014) Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 99:3561–3569
3. Yeh MW, Ituarte PH, Zhou HC et al (2013) Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. J Clin Endocrinol Metab 98:1122–1129
4. Press DM, Siperstein AE, Berber E et al (2013) The prevalence of undiagnosed and unrecognized primary hyperparathyroidism: a population-based analysis from the electronic medical record. Surgery 154:1232–1237 discussion 1237–1238
5. Wermers RA, Khosla S, Atkinson EJ et al (2006) Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993–2001: an update on the changing epidemiology of the disease. J Bone Miner Res 21:171–177
6. Eastell R, Brandi ML, Costa AG, D'Amour P, Shoback DM, Thakker RV (2014) Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. J Clin Endocrinol Metab 99:3570–3579
7. Pawlowska M, Cusano NE (2015) An overview of normocalcemic primary hyperparathyroidism. Curr Opin Endocrinol Diabetes Obes 22:413–421
8. Yener Ozturk F, Erol S, Canat MM et al (2016) Patients with normocalcemic primary hyperparathyroidism may have similar metabolic profile as hypercalcemic patients. Endocr J 63:111–118
9. Bilezikian JP, Potts JT Jr, Fuleihan Gel-H et al (2002) Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Clin Endocrinol Metab 87:5353–5361
10. Barczyński M, Papier A, Kenig J, Nawrot I (2014) A retrospective case-controlled study of video-assisted versus open minimally invasive parathyroidectomy. Wideochir Inne Tech Maloinwazyjne 9: 537–547
11. Saponaro F, Faggiano A, Grimaldi F et al (2013) Cinacalcet in the management of primary hyperparathyroidism: post marketing experience of an Italian multicentre group. Clin Endocrinol (Oxf) 79: 20–26
12. Andrioli M, Riganti F, Pacella CM, Valcavi R (2012) Long-term effectiveness of ultrasound-guided laser ablation of hyperfunctioning parathyroid adenomas: present and future perspectives. AJR Am J Roentgenol 199:1164–1168
13. Marcocci C, Chanson P, Shoback D et al (2009) Cinacalcet reduces serum calcium concentrations in patients with intractable primary hyperparathyroidism. J Clin Endocrinol Metab 94:2766–2772
14. Singh Ospina N, Thompson GB, Lee RA, Reading CC, Young WF Jr (2015) Safety and efficacy of percutaneous parathyroid ethanol ablation in patients with recurrent primary hyperparathyroidism and multiple endocrine neoplasia type 1. J Clin Endocrinol Metab 100: E87–E90
15. Kovatcheva RD, Vlahov JD, Shinkov AD et al (2010) High-intensity focused ultrasound to treat primary hyperparathyroidism: a feasibility study in four patients. AJR Am J Roentgenol 195:830–835
16. Groeschl RT, Pilgrim CH, Hanna EM et al (2014) Microwave ablation for hepatic malignancies: a multiinstitutional analysis. Ann Surg 259:1195–1200
17. Cao XL, Cheng ZG, Yu XL, Han ZY, Liang P (2016) Ultrasound-guided percutaneous microwave ablation of parathyroid adenoma. J Vasc Interv Radiol 27:1929–1931
18. Liu C, Wu B, Huang P et al (2016) US-guided percutaneous microwave ablation for primary hyperparathyroidism with parathyroid nodules: feasibility and safety study. J Vasc Interv Radiol 27:867–875
19. Xia WB, Zhang ZL, Wang HF et al (2009) The efficacy and safety of calcitriol and/or Caltrate D in elderly Chinese women with low bone mass. Acta Pharmacol Sin 30:372–378
20. Barczyński M, Gołkowski F, Nawrot I (2015) The current status of intraoperative iPTH assay in surgery for primary hyperparathyroidism. Gland Surg 4:36–43
21. Saadeh G, Licata A, Esselstyn C, Gupta M (1989) Relationship of parathyroid adenoma volume and biochemical function. Horm Res 32:142–144
22. Leiker AJ, Yen TW, Eastwood DC et al (2013) Factors that influence parathyroid hormone half-life: determining if new intraoperative criteria are needed. JAMA Surg 148:602–606
23. Maier GW, Kreis ME, Renn W, Pereira PL, Häring HU, Becker HD (1998) Parathyroid hormone after adenectomy for primary

hyperparathyroidism. A study of peptide hormone elimination kinetics in humans. J Clin Endocrinol Metab 83:3852–3856
24. Bieglmayer C, Prager G, Niederle B (2002) Kinetic analyses of parathyroid hormone clearance as measured by three rapid immunoassays during parathyroidectomy. Clin Chem 48:1731–1738
25. Xu SY, Wang Y, Xie Q, Wu HY (2013) Percutaneous sonography-guided radiofrequency ablation in the management of parathyroid adenoma. Singapore Med J 54:e137–e140
26. Kovatcheva R, Vlahov J, Stoinov J, Lacoste F, Ortuno C, Zaletel K (2014) US-guided high-intensity focused ultrasound as a promising non-invasive method for treatment of primary hyperparathyroidism. Eur Radiol 24:2052–2058
27. Hinshaw JL, Lubner MG, Ziemlewicz TJ, Lee FT Jr, Brace CL (2014) Percutaneous tumor ablation tools: microwave, radiofrequency, or cryoablation–what should you use and why? Radiographics 34:1344–1362
28. Tfelt-Hansen J, Brown EM (2005) The calcium-sensing receptor in normal physiology and pathophysiology: a review. Crit Rev Clin Lab Sci 42:35–70
29. Kitchin D, Lubner M, Ziemlewicz T et al (2014) Microwave ablation of malignant hepatic tumours: intraperitoneal fluid instillation prevents collateral damage and allows more aggressive case selection. Int J Hyperthermia 30:299–305
30. Laeseke PF, Sampson LA, Brace CL, Winter TC 3rd, Fine JP, Lee FT Jr (2006) Unintended thermal injuries from radiofrequency ablation: protection with 5% dextrose in water. AJR Am J Roentgenol 186:S249–S254
31. Zhang M, Liang P, Cheng ZG, Yu XL, Han ZY, Yu J (2014) Efficacy and safety of artificial ascites in assisting percutaneous microwave ablation of hepatic tumours adjacent to the gastrointestinal tract. Int J Hyperth 30:134–141
32. Kuang M, Lu MD, Xie XY et al (2007) Liver cancer: increased microwave delivery to ablation zone with cooled-shaft antenna–experimental and clinical studies. Radiology 242:914–924
33. Ohmoto K, Tsuzuki M, Yamamoto S (1999) Percutaneous microwave coagulation therapy with intraperitoneal saline infusion for hepatocellular carcinoma in the hepatic dome. AJR Am J Roentgenol 172:65–66