Clinical Study on Safety and Efficacy of Microwave Ablation for Primary Hyperparathyroidism

-CRITICAL APPRAISAL-

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Ying Wei, MD, Lili Peng, MD, Yan Li, MD, Zhen-long Zhao, MD, Ming-an Yu, MD

All authors: Department of Interventional Ultrasound, China-Japan Friendship Hospital, Beijing, China

- Recent publication
- Received on August 11, 2019; accepted on January 7, 2020; published online on March 4, 2020
- Good impact factor (3.179)
- Original article
- Title clearly describes the study

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This work was funded by Beijing Municipal Science & Technology Commission (Z181100001718135) and Beijing University of Chemical Technology-China-Japan Friendship Hospital Biomedical Transformation Joint Fund Project (PYBZ1804).
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- Authors : Name and institution were clearly written
- Single institution

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ABSTRACT

Aim of study is well and clearly written

Objective: To evaluate the safety, feasibility, and efficacy of microwave ablation (MWA) for the treatment of primary hyperparathyroidism (PHPT).

Materials and Methods: This study enrolled 67 PHPT patients (22 men, 45 women; mean age, 56.0 ± 16.3 years; range, 18–83 years) from January 2015 to December 2018. The laboratory data, including the serum intact parathyroid hormone (iPTH), calcium, phosphorus, and alkaline phosphatase (ALP) levels, were evaluated before MWA and again 2 hours, 1 day, 7 days, 1 month, 3 months, 6 months, 12 months, 18 months, and 24 months after.

Sample size, gender, age : Stated clearly
Measuring tools : Stated clearly
Study design : Not stated

Results were concisely concluded – measured variables with statistical analysis and significance

Results: Complete ablation was achieved with all 72 hyperplastic parathyroid glands found on the 67 patients enrolled, 64 of whom were treated in one session and 3 were treated over two sessions. The technical success rate was 100%. The median follow-up time was 13.6 months (range, 10.0–31.1 months). The clinical success rate was 89.4%. The volume reduction rate was 79.4% at 6 months. Compared to pre-MWA, the serum iPTH, calcium, phosphorus, and ALP levels had significantly improved 6 months post-MWA (iPTH, 157.3 pg/mL vs. 39.2 pg/mL; calcium, 2.75 ± 0.25 mmol/L vs. 2.34 ± 0.15 mmol/L; phosphorus, 0.86 ± 0.20 mmol/L vs. 1.12 ± 0.22 mmol/L; ALP, 79 U/L vs. 54 U/L, respectively; all, $p < 0.01$). Hoarseness was a major complication in 4 patients (6.0%), but it improved spontaneously within 2–3 months.

Conclusion: MWA is safe, feasible, and effective for the treatment of PHPT.

Keywords: *Microwave ablation; Primary hyperparathyroidism; Intact parathyroid hormone*

Conclusion : Clearly answer the question of interest

Keywords : Clearly written

INTRODUCTION

- Introduction clearly written
- Prevalence
- Incidence
- Background of the disease
- - symptoms
- - treatment

INTRODUCTION

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder, and its incidence increases with age (1). The prevalence of PHPT in patients over 65 years of age is 1.5%, and the incidence in postmenopausal women is 2.1–3.4% (2). Nephrolithiasis is the most common overt symptom, and although skeletal disease is rare, the incidence of osteoporosis with related fractures is increasing. Over the past 10 years in China, the percentage of asymptomatic patients with PHPT has increased from 21% to 52.5% due to the development of biochemical detection methods (3).

Surgery is the only definitive treatment for symptomatic PHPT, and it has a high cure rate of 95–98% (1, 4, 5). Early intervention in asymptomatic patients should be considered since regular surveillance and pharmacological therapies are less effective and less cost-effective than surgery (2, 4). Nevertheless, morbidity and mortality increase in advanced-age patients with comorbidities, who are contraindicated to undergo a parathyroidectomy under general anesthesia. Additionally, symptomatic hypocalcemia or hyperparathyroidism may recur during the postoperative period (6-10), and therefore, patients with few or no symptoms may decline to undergo surgery. Thus, patients who have failed surgery, have contraindications for surgery, or who refuse to undergo a parathyroidectomy should be targeted for pharmacological management of PHPT. However, it must be recognized that pharmacological management is not radical and has adverse effects (11).

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- Reference to earlier studies

- Results from previous studies were stated
- Limitations from previous studies were stated

Currently, there is considerable interest in identifying therapeutic alternatives to surgery. There have been several reports on minimally invasive treatments of PHPT, such as ethanol ablation (12), laser ablation (13), radiofrequency ablation (RFA) (14), and high-intensity focused ultrasound (US) (15, 16). As another minimally invasive treatment, microwave ablation (MWA) has also been used successfully in recent years (17-19). For PHPT management, the results of MWA and parathyroidectomy have been comparable in terms of the cure rate and the number of treatment complications (20). However, the sample sizes of that study were small, and the follow-up durations were short. Therefore, definitive evidence for the efficacy of MWA in treating PHPT has not been established. In addition, nodule size changes after ablation have not been evaluated.

Purpose of this study is clearly written

How does this study be at variance?
- Using larger sample size

Based on the promising results of MWA in the treatment of secondary hyperparathyroidism first reported by our team (21), the aim of this study was to evaluate further, the safety, feasibility, and efficacy of MWA in treating PHPT using a large sample size.

MATERIALS AND METHODS

- Study design was clearly stated
- Population and sample size were clearly stated
- Time frame of data collection was clearly stated
- Achieved approval from appropriate ethical board
- How were the subjects chosen/recruited?

Study Design

This prospective study (ChiCTR-OCN-15006163) consecutively enrolled 67 patients (72 parathyroid nodules) with PHPT who received MWA treatment at the Department of Interventional Ultrasound, China-Japan Friendship Hospital, between January 2015 and December 2018. The study protocol was approved by the Human Ethics Review Committee of the China-Japan Friendship Hospital (2015-GZR-77). Written informed consent was obtained from each patient before the ablation procedure.

Inclusion Criteria

The inclusion criteria were as follows: 1) patients with symptomatic PHPT; 2) patients who did not meet the criteria for surgery or refused surgery; 3) patients with asymptomatic PHPT with one of the following conditions: a) inability or unwillingness to comply with observation protocols; b) serum calcium level higher than the normal range; c) T-score < -2.5 at the lumbar spine, total hip, femoral neck, or distal one-third of the radius, significant reduction in bone mineral density and/or increased risk of a fragility fracture; d) reduction in creatinine clearance < 60 mL/min (4); and e) aged < 50 years; 4) at least one hyperplasic parathyroid nodule clearly shown on US; 5) increased radionuclide concentration in both the early and delayed phases on 99mTc-sestamibi (MIBI) examination.

Exclusion Criteria

The exclusion criteria were as follows: 1) abnormal coagulation function tests, such as prothrombin time > 18 seconds, prothrombin activity < 60%, or platelet count < 60 x 10^9/L; 2) underlying disease, such as cardiac insufficiency or hypertension, refractory to management with medication.

Inclusion and exclusion criteria were given

Pre-Ablation Examination and Preparation

An Aplio 500 system (Canon Medical Systems, Tokyo, Japan) with a 10.0-MHz linear probe was used for US guidance. Contrast-enhanced US (CEUS) with a contrast agent (SonoVue, Bracco, Milan, Italy) was used to evaluate the effect of the ablation. For diagnosis, an MIBI scan (SymbiaT2, Siemens Healthineers, Munich, Germany) was conducted prior to the ablation procedure. Laryngoscopy was performed to rule out recurrent laryngeal nerve (RLN) impairment in patients with voice changes.

Before MWA, the diagnosis of PHPT on US was based on the following criteria: 1) enlarged hypoechoic parathyroid glands with clearly defined margins; and 2) no suspicion of lymph node metastasis.

Vitamin D supplementation in patients with vitamin D deficiency could safely begin at a dose of 1000–2000 IU/day before MWA (22). Intravenous fluid resuscitation and pharmacological management (calcitonin, bisphosphonate, and furosemide) were used in patients with PHPT who presented with a hypercalcemic crisis (serum calcium > 3.75 mmol/L).

MWA Procedure

MWA was performed by an expert with more than 5 years of experience in MWA for hyperplastic parathyroid nodules. Before MWA, intravenous access was obtained via an antecubital vein. Electrocardiography monitoring and pulse oximetry were routinely applied. Patients were placed in a supine position with the neck extended. After the neck was sterilized, 40–60 mL of normal saline (NS) was first injected into the area around the parathyroid nodule to provide hydrodissection. Then, a lidocaine and NS mixture (1:3) was injected close to the peri-parathyroid capsule for local anesthesia. The cooled MWA antenna (17 G) with a 0.4-cm tip (Intelligent Basic Type Microwave Tumor Ablation System, Nanjing ECO Microwave System, Nanjing, China) was inserted freehand into the parathyroid gland under US guidance. A multipoint ablation strategy was adopted, where the power was 30 W and the radiation time was 15–25 seconds at each ablation point (23).

The therapy was terminated when the hyperechoic zone covered the entire nodule. A CEUS was performed 3–5 minutes later to assess the efficacy. If the ablated nodule was covered by a nonenhanced zone, complete ablation was achieved, and if there was nodular enhancement inside the nodule, further ablation was performed immediately (Fig. 1). For bilateral nodule ablation, if there were no voice changes and no abnormal vocal cord movements on US after one side was ablated, a MWA would immediately then be performed on the contralateral side. If there were any signs of RLN injury, the ablation would be stopped, and the second session would be suspended until RLN function recovered. At the end of the procedure, the puncture site was compressed for 30 minutes, and the patient remained under observation for an additional 2 hours to monitor for potential complications. Calcium and vitamin D were administered postoperatively according to the clinical symptoms and laboratory data.

Clinical Data Collection and Follow-Up

Follow-up included US examination and blood biochemistry (e.g., serum intact parathyroid hormone [iPTH], calcium, phosphate, and alkaline phosphatase [ALP]). The follow-up times were 2 hours, 1 day, 7 days, 1 month, 3

Details steps on how the study was conducted were clearly written.

Therapeutic Effect Evaluation

A technical success was defined as achievement of a complete ablation after undergoing appropriate treatment according to the protocol. For the surgical resection criteria, clinical success was defined as serum iPTH and calcium levels within the normal range 6 months after the MWA (24-26). The nodule volume was calculated according to the sphere formula (V = length x width x depth x 0.524), and the volume reduction rate was defined as (Vbefore - Vafter) / Vbefore.

Complications

Major complications were defined as events leading to substantial morbidity and disability that increased the level of care, resulted in hospital admission, or substantially lengthened the hospital stay. Permanent nerve injuries (e.g., to the RLN, cervical sympathetic ganglion, or spinal accessory nerve) and permanent hypoparathyroidism were defined as major complications. All other complications were considered minor. Therefore, hematoma, numbness, hypocalcemia, vomiting, skin burn, lidocaine toxicity, hypertension, cough, and pain were defined as minor complications (26, 27).

Statistical Analysis

All statistical analyses were performed using SPSS software (version 20.0 for Windows, IBM Corp., Armonk, NY, USA). The serum calcium, phosphate, iPTH, and ALP levels were compared at baseline and at each follow-up using paired-sample *t* tests and paired-sample Wilcoxon signed-rank tests. The relationship between the laboratory values before and after MWA was calculated using the Pearson test and Spearman rank correlation analysis. Continuous data were presented as the mean ± standard deviation or median and interquartile range. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

APPROPRIATE

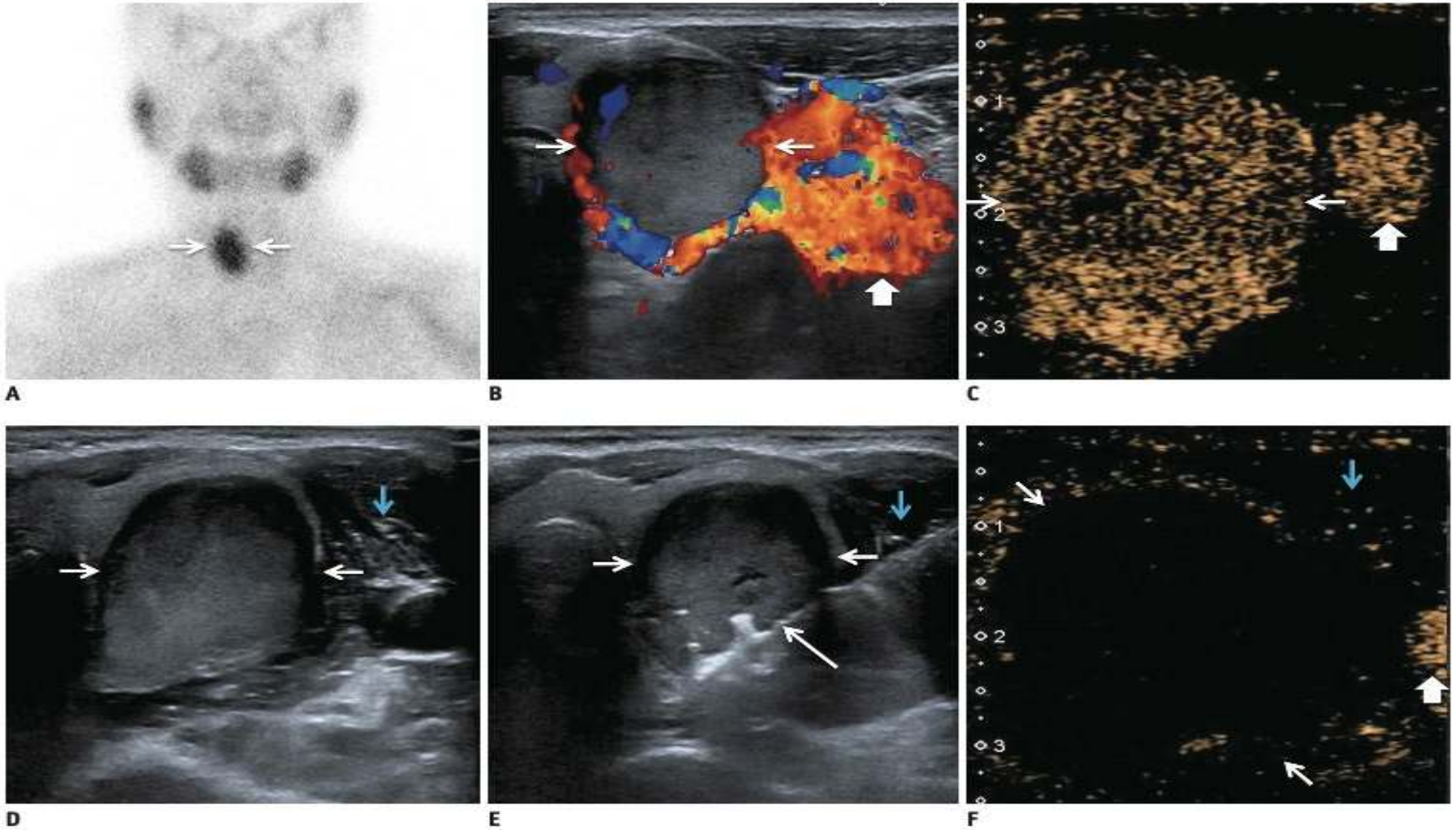

Fig. 1. Images show percutaneous MWA of PHPT nodule.

A. There was radioactive concentration in PHPT nodule (arrows) on MIBI. **B.** Isoechoic PHPT nodule with sharp boundary (arrows) behind superior left lobe of thyroid and on right side of carotid artery (thick arrow) on US. **C.** Uniform hyperenhancement of PHPT nodule (arrows) beside carotid artery (thick arrow) in arterial phase on CEUS. **D.** Injection of hydrodissection (blue arrow) around PHPT nodule (arrows) before MWA. **E.** MWA procedure of PHPT nodule: hyperechoic area emerging inside nodule (short arrows)-which surrounded by hydrodissection (blue arrow), around antenna (long arrow). **F.** After MWA, nonenhancement area covered PHPT nodule (arrows), peripheral hydrodissection (blue arrow) beside carotid artery (thick arrow) on CEUS. CEUS = contrast-enhanced US, MIBI = 99mTc-sestamibi, MWA = microwave ablation, PHPT = primary hyperparathyroidism, US = ultrasound

RESULTS

Table 1. Baseline Clinical Characteristic of Patients with PHPT (n = 67)

Characteristic	Data
Sex	
Male	22
Female	45
Mean age (years)	56.0 ± 16.3
< 50	22
> 50	45
Clinical and laboratory data	
Symptomatic	32
Nephrolithiasis	14
Ostealgia	11
Fatigue	8
Pruritus	1
Asymptomatic	35
25-hydroxyvitamin D (nmol/L)	28.7 (7.0–102.1)
Frankly deficiency	23
Insufficiency	40
Normal	4
Normocalcemic PHPT	24 (2.51 ± 0.16)
Hypercalcemic	43 (2.88 ± 0.21)
Creatinine clearance (mL/min/1.73 m^2)	91.8 (22.0–131.4)
Urinary calcium (mmol/24 h)	6.9 ± 3.1
Nodules	72
Normal location	71
Superior left	12
Inferior left	29
Superior right	11
Inferior right	19
Ectopic location	1
Within thyroid	1
Volume (mL)	0.6 (0.03–37.4)
Enhancement pattern on CEUS	
Uniform hyperenhancement	59
Nonuniform hyperenhancement	8

CEUS = contrast-enhanced ultrasound, PHPT = primary hyperparathyroidism

Well tabulated with relevant data

Table 2. Rates of Achieving Normal Level or for Serum iPTH, Calcium and Phosphorus after MWA

Follow-Up Time	iPTH (pg/mL)	Calcium (mmol/L)	Phosphorus (mmol/L)
	Rate (Normal Number/Total Number)	Rate (Normal Number/Total Number)	Rate (Normal Number/Total Number)
Post-MWA (2 H)	64.2 (43/67)	71.6 (48/67)	67.2 (45/67)
Post-MWA (1 D)	74.6 (47/63)	84.1 (53/63)	79.4 (50/63)
Post-MWA (7 D)	77.5 (31/40)	90.0 (36/40)	85.0 (34/40)
Post-MWA (1 M)	84.9 (45/53)	92.5 (49/53)	90.6 (48/53)
Post-MWA (3 M)	86.7 (39/45)	91.1 (41/45)	93.3 (42/45)
Post-MWA (6 M)	89.4 (42/47)	93.6 (44/47)	95.7 (45/47)
Post-MWA (12 M)	89.5 (34/38)	92.1 (35/38)	94.7 (36/38)
Post-MWA (18 M)	89.3 (25/28)	92.9 (26/28)	96.4 (26/28)
Post-MWA (24 M)	86.4 (19/22)	90.9 (20/22)	95.5 (21/22)

There are 42, 34, and 28 patients who received MWA more than 12 M, 18 M, and 24 M, respectively. D = day, H = hour, iPTH = intact parathyroid hormone, M = month, MWA = microwave ablation

Dropouts?

How many?

Why?

Table 3. Changes of Serum iPTH, Calcium, Phosphorus, ALP and Volume of Nodule before MWA and at Each Follow-Up

Follow-Up Time (Number)	iPTH (pg/mL)	Calcium (mmol/L)	Phosphorus (mmol/L)	ALP (U/L)	Volume (cm^3)	VRR (%)
Before MWA (n = 67)	157.3 (66.1–1577.2)	2.75 ± 0.26	0.86 ± 0.20	79 (45–1426)	0.56 (0.03–37.41)	-
2 H post-MWA (n = 63)	20.1 (1.7–348.8)*	2.63 ± 0.26*	0.85 ± 0.20	88 (41–1475)	-	-
1 D post-MWA (n = 63)	17.1 (1.7–188.2)*	2.39 ± 0.21*†	0.99 ± 0.22*†	75 (40–1360)	-	-
7 D post-MWA (n = 40)	50.5 (9.4–355.9)*†‡	2.34 ± 0.26*†	1.03 ± 0.24*†	113 (55–1246)	-	-
1 M post-MWA (n = 53)	61.4 (20.6–498.0)*†‡	2.35 ± 0.17*†	1.12 ± 0.18*†	87 (46–296)	0.51 (0.03–4.84)*	34.8 (-130.51–84.98)
3 M post-MWA (n = 45)	56.6 (16.1–4166.5)*†‡	2.39 ± 0.13*†	1.05 ± 0.18*†	60 (36–83)	0.19 (0.02–3.48)*	35.0 (-104.38–81.83)
6 M post-MWA (n = 47)	39.2 (15.1–85.6)*†‡	2.34 ± 0.15*†	1.12 ± 0.22*†	54 (37–69)*†‡	0.11 (0–2.10)*	79.4 (75.07–100)
12 M post-MWA (n = 38)	47.0 (27.7–117.4)*†‡	2.36 ± 0.13*†	1.10 ± 0.18*†‡	54 (27–104)*†‡	0 (0–1.76)*	96.4 (79.10–100)
18 M post-MWA (n = 28)	36 (22.8–96.7)*†‡	2.42 ± 0.09*†	1.13 ± 0.15*†‡	51 (27–109)*†‡	0 (0–1.62)*	100 (79.8–100)
24 M post-MWA (n = 22)	45.1 (22.8–120.4)*†‡	2.38 ± 0.17*†	1.14 ± 0.27*†‡	46 (28–94) *†‡	0 (0–0.44)*	100 (80.7–100)

Serum calcium and phosphorus were presented as mean ± standard deviation; iPTH and ALP values were medians and interquartile ranges. Normal range: iPTH, 12–88 pg/mL; calcium, 2.00–2.75 mmol/L; phosphorus, 0.81–1.78 mmol/L; ALP, 40–150 IU/L. There are 42, 34, and 28 patients who received MWA more than 12 M, 18 M, and 24 M. *$p < 0.01$ (compared with values before MWA), †$p < 0.05$ (compared with values 2 H after MWA), ‡$p < 0.05$ (compared with values 1 D after MWA). ALP = alkaline phosphatase, VRR = volume reduction rate

Appropriate

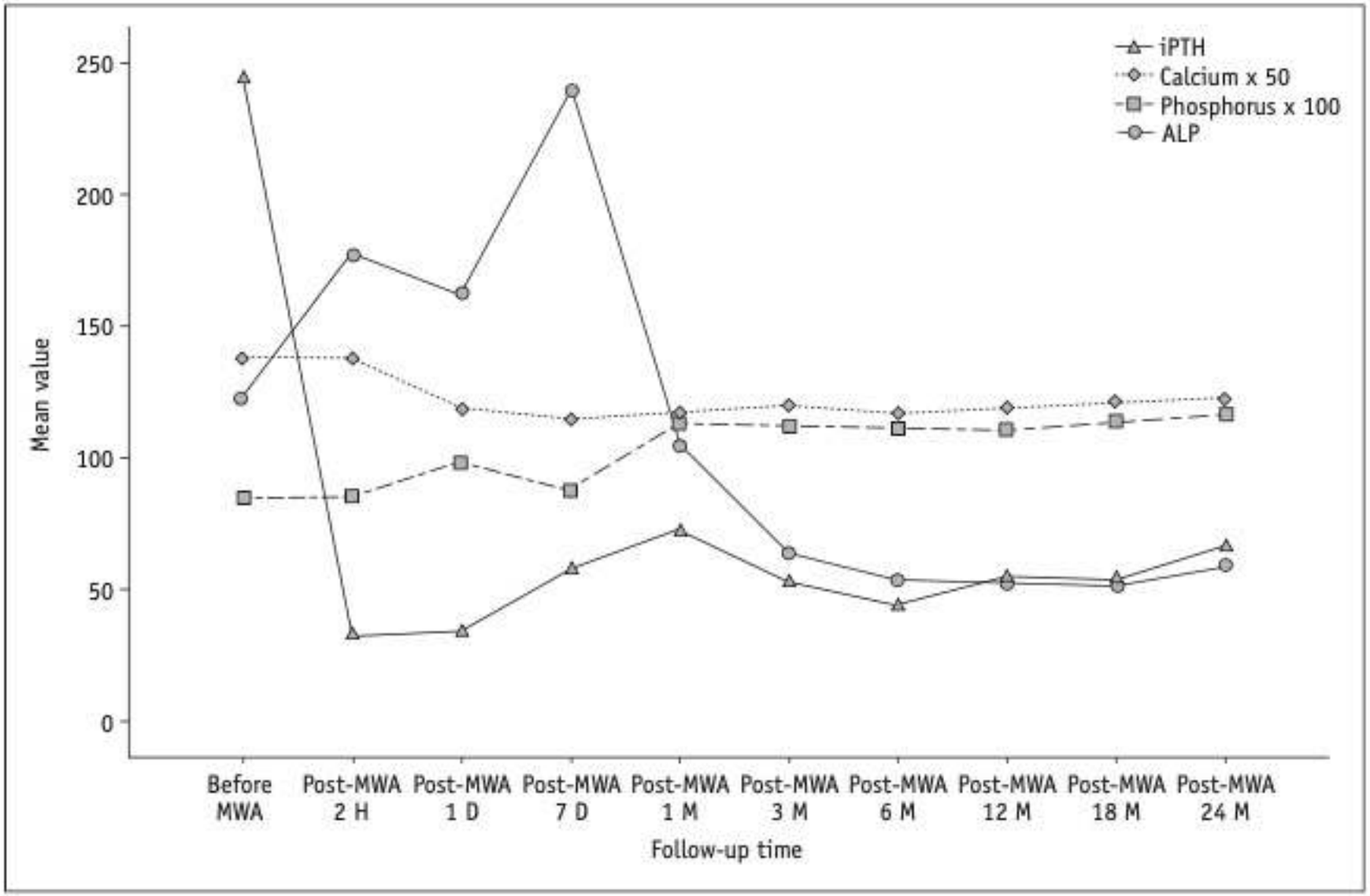

Fig. 3. Multiple comparisons among serum iPTH, calcium, phosphorus and ALP before and after ablation. ALP = alkaline phosphatase, D = day, H = hour, iPTH = intact parathyroid hormone, M = month, MWA = microwave ablation

Table 4. Complications and Side Effects of MWA in PHPT Patients

Complication or Side Effect	Number (%)	Time of Detection (Days)	Time to Recovery (Days)
Major			
Hoarseness	4 (6.0)	1–3	30–90
Minor			
Cough	2 (3.0)	1	1–3
Side effect			
Pain	11 (16.4)	1	1–3
Numbness	12 (17.9)	1–3	1–30
Hypoparathyroidism	16 (25.4)	1–7	3–14
Hypocalcaemia	2 (3.0)	1–3	3–30

Well tabulated

DISCUSSION

- Interpretations consistent with the results

- 67 PHPT treated with MWA, with technical and clinical success rates of 100% and 89.4% respectively.
- MWA could significantly decreased the iPTH and calcium levels with sustained efficacy ($p<0.05$).
- MWA could completely inactivate hyper-functional parathyroid glands with definite efficiency in most cases.

- Comparison with previous study

- Results from this study is comparable to another study, which reported a cure rate of 86.4% and iPTH that remains normal for 12 months post-ablation.
- Comparison of results with other studies on other minimally invasive techniques, such as ethanol ablation, laser ablation and RFA in treating PHPT.

- Clinical implications/applicability

- In this study, MWA was successfully used to treat PHPT, and its efficacy was confirmed.
- Hoarseness (major complication) occurred in 6% of patients – minimizing heat exposure to RLN is crucial
- Minor complications resolved spontaneously in a short time without special treatment.

LIMITATIONS

- No pathological results were obtained – biopsy was not recommended
- Follow-up period after MWA was relatively short.

CONCLUSION

- Clearly summarize the salient points of this study

In conclusion, we provide evidence that MWA can effectively reduce the serum iPTH and ALP levels and normalize the serum calcium and phosphorous levels for patients with PHPT. Therefore, for some cases, MWA could be an alternative to surgery and medication for patients with PHPT.

CONFLICT OF INTEREST

- The authors have no potential conflict of interest to disclose.

- Overall, it is a good article. Supported by other similar articles with appropriate comparison with previous study.
- Strength:

- Prospective study
- Larger sample size
- Appropriate duration of follow-up post ablation – 24 months
- Nodule size changes after ablation were evaluated

Potentially can be practiced in our department.

REFERENCE

- Al-Jundi, A., & Sakka, S. (2017). Critical Appraisal of Clinical Research. Journal of clinical and diagnostic research : JCDR, 11(5), JE01–JE05. https://doi.org/10.7860/JCDR/2017/26047.9942


Thank You!