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

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**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.

**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*

# INTRODUCTION

- Primary hyperthyroidism (PHPT) is 3rd most common endocrine disorder and increasing with age.
- Symptoms: nephrolithiasis, skeletal disease, osteoporosis with fracture.
- Nowadays, majority become asymptomatic as biochemical test pick up early.

- Treatment:

a) Symtopmatic – surgery (high cure rate 95-98%).

b) Asymptomatic – pharmacological therapy but less cost-effective compared to surgery.

Issues regarding treatment:

-As ages increased, patient has more comorbidities and contraindicated for surgery under general anaesthesia.
-Besides that, some patient may have recur hypocalcaemia or hyperparathyroidism during postoperation period.

*So these group patients are targeted for pharmacology therapy. But pharmacological theraphy is not radical and has adverse effect.

*There are studies of alternative treaments.

- Alternative:

1. Ethanol ablation
2. Laser ablation
3. Radiofrequency ablation (RFA)
4. High intensity focused ultrasound
5. Microwave ablation (MWA)

-MVA VS parathyroidectomy results are compared based on:

a) Cure rate

b) Number of treatment complication

- But these study sample size are small and short follow up duration. Also no evaluation on post ablation nodule changes.

***This study suing larger sample size and duration up to 24 months.

# MATERIAL AND METHODS

STUDY DESIGN
-Prospective
-67 patient enrolled (72 parathyroid nodules)
-Jan 2018 to Dec 2018.
-Written consent prior to MVA

INCLUSION CRITERIA
1. Symptomatic
2. Do not meet surgery criteria / refuse surgery
3. Asymptomatic but;
    - Unable to compliant to observation
    - High serum calcium
    - T-score < -2.5 at lumbar spine, total hip, femoral neck, distal 1/3 radius, significant reduce bone mineral density/ increase risk of fracture.
    - EGFR <60ml/min.
    - Aged <50
4. At least 1 hypoplasic parathyroid nodule clearly shown on US.
5. Increased radionuclide concentration in both early and delayed phases on 99mTc-sestamibi (MIBI)

EXCLUSION CRITERIA
1. Abnormal coagulation test;
    - prothrombin time >18sec
    - prothrombin activity <60%
    - platelet $<60x10^9$ /L
2. Underlying:
    - Cardiac insufficiency
    - Hyperntension.

# PRE-ABLATION EXAMINATION &PREPARATION

- For diagnosis PHPT:

  -MIBI scan

  -Laryngoscopy to rule out recurrent laryngeal nerve impairment in patient with voice changes.

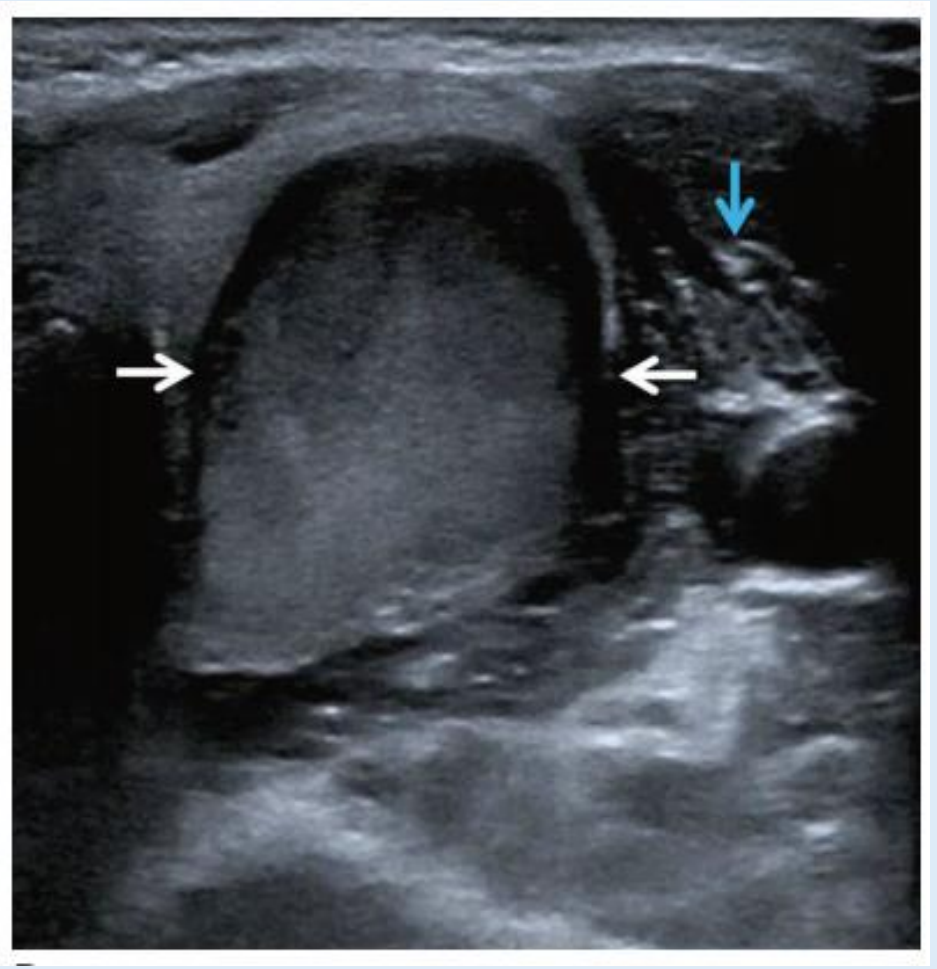
  -US criteria:
  a)enlarged hypoechoic parathyroid glands with clear defined margin.

  b)No suspicious node metastasis.
- Vit D supplement in patient Vit D deficiency.
- IV fluid
- Pharmacological – calcitonin, biphosphate, furosemide for patient with hypercalcemic crisis (serum calcium >3.75 nmol/L).
- Cotrast enhanced US (CEUS) with contrast agent (Sonovue, Bracco, Milan , Italy) used to evaluate effect of ablation.

# MWA PROCEDURE

- Performed by expert with >5 years experience in MVA for hyperplastic parathyroid nodules.

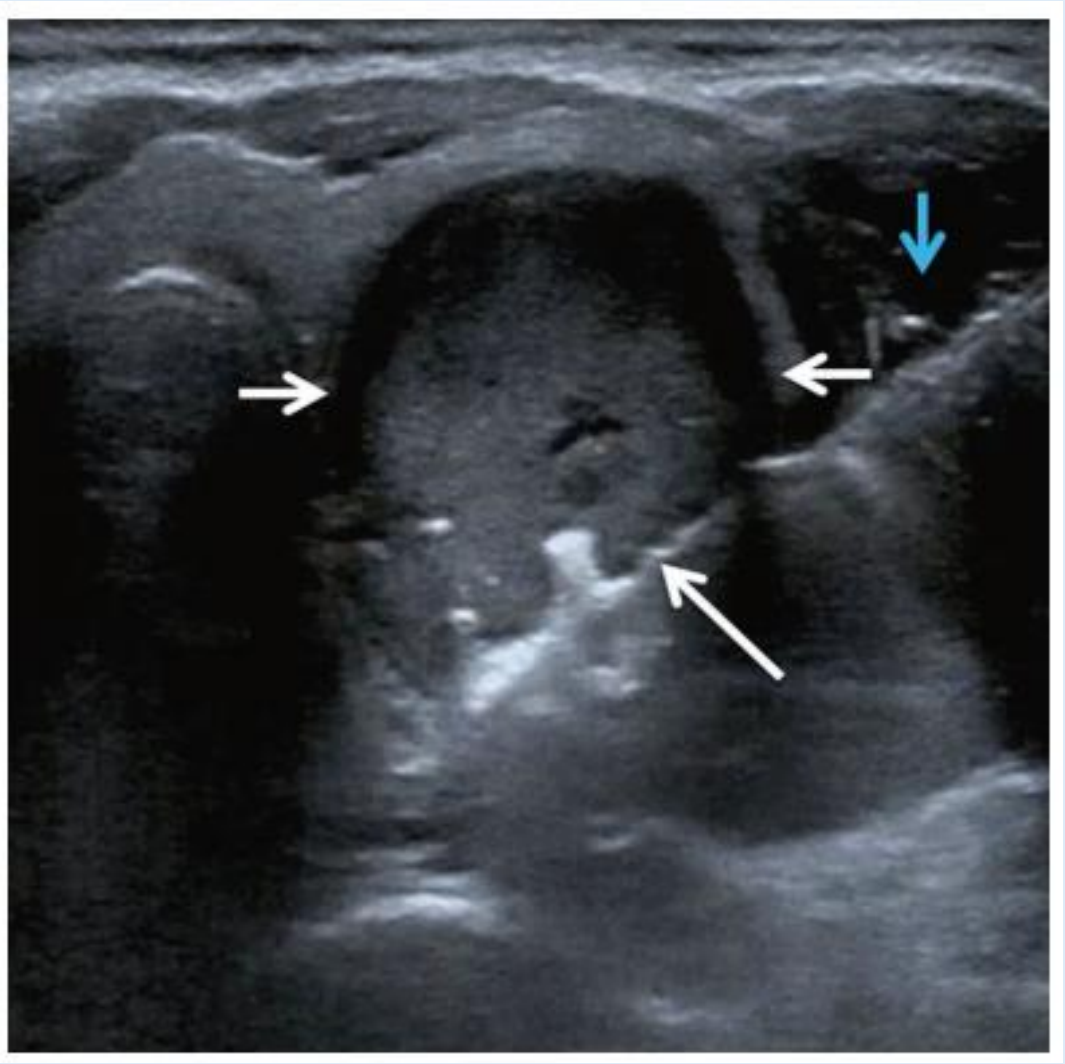
1) IV access
2) ECG monitoring & pulse oximetry.
3) Patient in supine position with neck extended.
4) Neck is sterilized, 40-60ml of normal saline 1st injected into area around parathyroid nodule to provide hydrodissection.
5) Then lignocaine and NS mixture (1:3) injected closed to peri-parathyroid capsule for LA.



Injection of hydrodissection (blue arrow) around PHPT nodule before MWA

# MWA PROCEDURE

6) Cooled MWA antenna (17G) with a 0.4cm tip (Intelligent Basic type Microwave Tumour Ablation system) inserted freehand into parathyroid gland under US guidance.
7) Multipoint ablation strategy was adopted, where power 30W and radiation time 15 – 25 sec at each ablation point.
8) Therapy terminate when hyperechoic zone covered the entired nodule.



MWA procedure of PHPT nodule: hyperechoic area emerging inside nodule (short arrows)-which surrounded by hydrodissection (blue arrow), around antenna (long arrow)

# MWA PROCEDURE

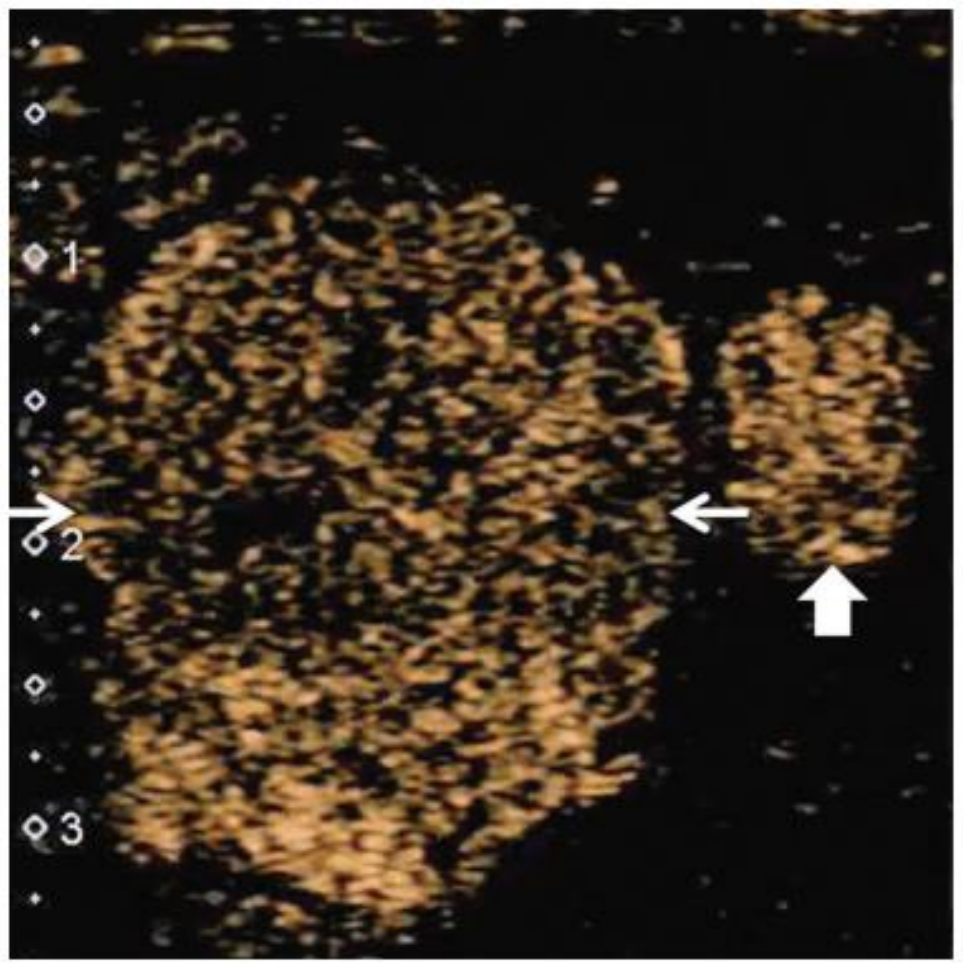
9) CEUS performed 3-5 min to assess efficacy.

- If ablated nodule, was covered by a nonenhanced zone, complete ablation was achieved.
  - If there was nodular enhancement inside the nodule, further ablation was performed immediately.

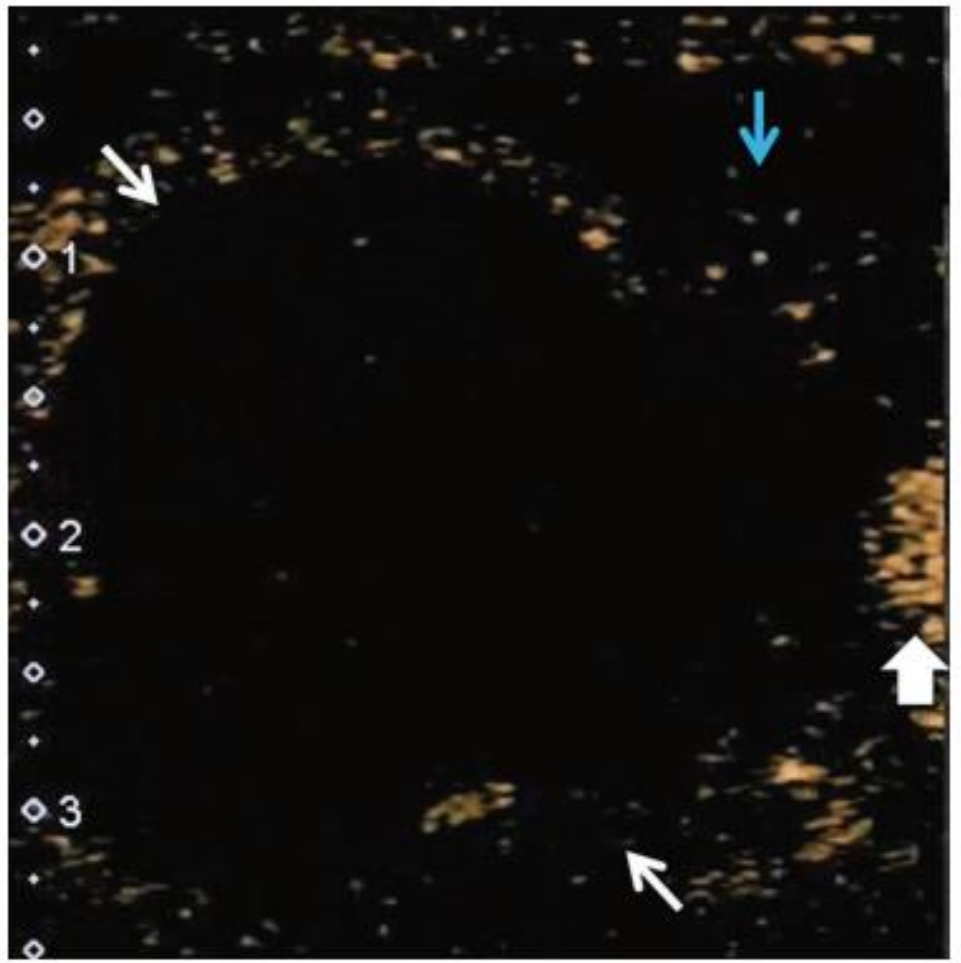
10) For bilateral nodule ablation, if there were no voice changes and no abnormal vocal cord movements on US after one side was ablated, a MWA would immediately then be performed on the contralateral side. If there were any signs of RLN injury, the ablation would be stopped, and the second session would be suspended until RLN function recovered.

11) 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.

12) Calcium and vitamin D were administered postoperatively according to the clinical symptoms and laboratory data




Uniform hyperenhancement of PHPT nodule (arrows) beside carotid artery (thick arrow) in arterial phase on CEUS




After MWA, nonenhancement area covered PHPT nodule (arrows), peripheral hydrodissection (blue arrow) beside carotid artery (thick arrow) on CEUS

## CLINICAL DATA COLLECTION & FOLLOW-UP

- Follow-up times: 2 hours, 1 day, 7 days, 1 month, 3months, 6 months, 18 months and 24 months after MWA.
  - -US.
  - -Blood biochemistry (serum intact parathyroid hormone iPTH, calcium, phosphate, alkaline phosphatase).
- CEUS only done if serum iPTH and calcium level elevated or US showed suspicious nodules in parathyroid region.
- The 14-item Chalder Fatigue Scale was used to assess symptoms of fatigue before and after MWA

## 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.
- 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

# 14-item Chalder Fatigue Scale

1. Do you have problems with tiredness?
2. Do you need to rest more?
3. Do you feel sleepy or drowsy?
4. Do you have problems starting things?
5. Do you lack energy?
6. Do you have less strength in your muscles?
7. Do you feel weak?
8. Do you have difficulties concentrating?
9. Do you make slips of the tongue when speaking?
10. Do you find it more difficult to find the right word?
11. How is your memory?
12. Do you start things without difficulty but get weak as you go on?
13. Do you think as clearly as usual?
14. Are you still interested in the things you used to do?

| Scoring schemes for the Chalder Fatigue Scale | | |
|---|---|---|
| | Bimodal score | Likert score |
| Less than usual | 0 | 0 |
| No more than usual | 0 | 1 |
| More than usual | 1 | 2 |
| Much more than usual | 1 | 3 |

*This scale can be scored "bimodally" with columns representing 0, 0, 1 & 1 and a range from 0 to 11 with a total of 4 or more qualifying for "caseness". Alternatively it can be scored in "Likert" style 0, 1, 2 & 3 with a range from 0 to 33. Mean "bimodal" score for CFS sufferers was 9.14 (SD 2.73) and for a community sample 3.27 (SD 3.21). Mean "Likert" score was 24.4 (SD 5.8) and 14.2 (SD 4.6).*

Cella, M. and T. Chalder (2010). *"Measuring fatigue in clinical and community settings."* J Psychosom Res 69(1): 17-22. This study involved 361 CFS sufferers and 1615 individuals from the community. Average age was in the 30's. Fatigue levels were similar for males and females. A score of 29 discriminated between CFS sufferers and the community sample in 96% of cases and a score in the 30's discriminated in 100% of cases. The CFS sufferers also scored a mean of 26.99 on the Work & Social Adjustment Scale (W&SAS) with a SD of 8.6 (i.e. about 70% scoring between 18.4 and 35.6).

## COMPLICATION

- 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).
- Permanent hypoparathyroidism were defined as major complications.
- All other complications were considered minor - hematoma, numbness, hypocalcemia, vomiting, skin burn, lidocaine toxicity, hypertension, cough, and pain.

## STATISTICAL ANALYSIS

- All statistical analyses were performed using SPSS software version 20.0.
- 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 signedrank 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.

# 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 |

Total patient: 67
Total nodule: 72 (63patient 1 nodule, 3 patient 2 nodules and 1 patient 3 nodules.
Initial PHPT: 65 patient
Recurrent PHPT: 2 patient

# MWA

| | |
|---|---|
| **Complete ablation** | Total: 67 patient (1 session: 64, 2 sessions: 3) |
| **Median ablation time** | 170 sec (80-950 sec) |
| **Median follow up duration** | 13.6 months (10-31.1 months) |
| **Increase iPTH + residual lesion on CEUS** | 2 patients (so underwent 2nd ablation) |
| **Hypercalcemic crisis prior mwa** | 1 patient (she received 2nd ablation after 4 months) |

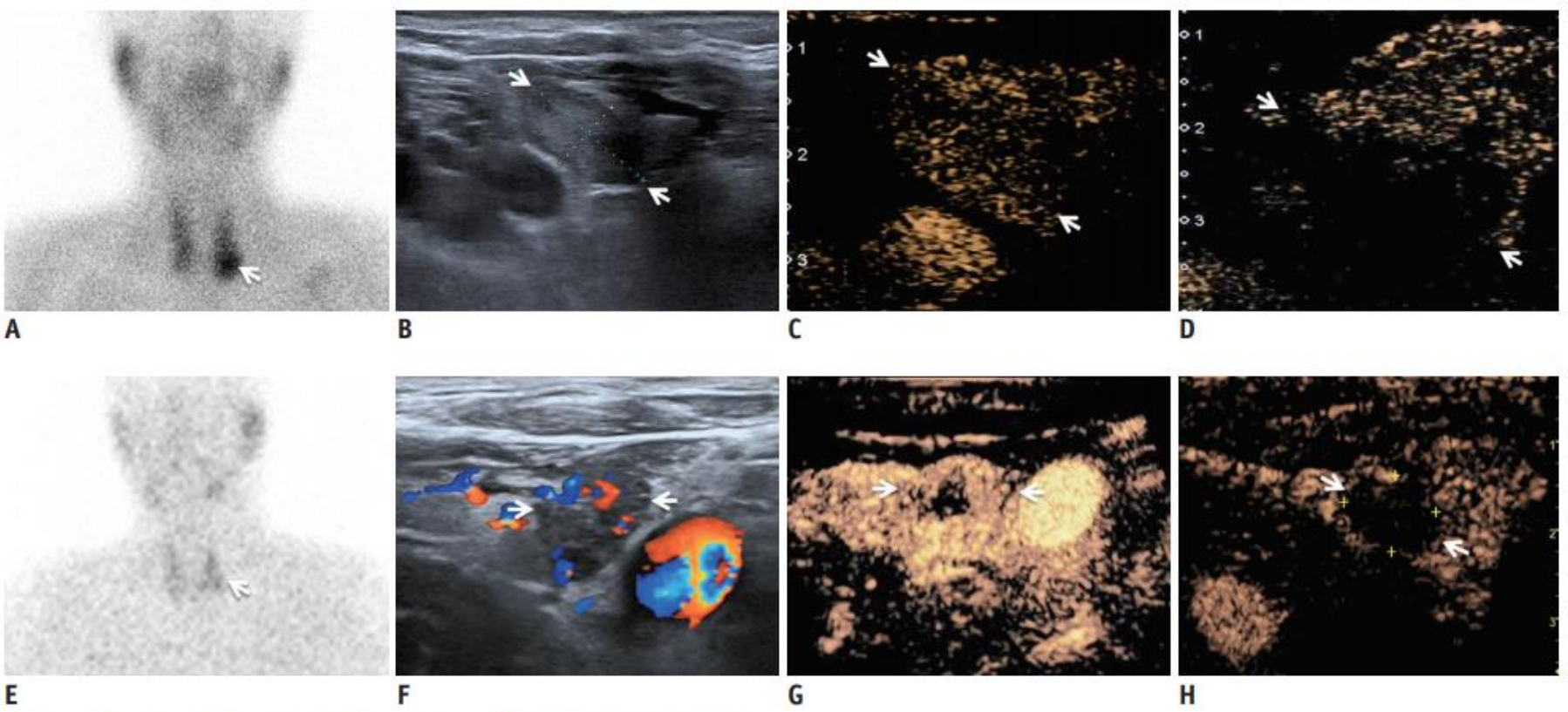



**Fig. 2. Images show additional ablation of residual PHPT lesion.**
**A.** There was radioactive concentration in PHPT nodule (arrow). **B.** Before MWA, inhomogeneous isoechoic PHPT nodule on US (arrows). **C.** There was nonuniform hyperenhancement PHPT nodule (arrows) on CEUS. **D.** After MWA, nonenhancement area (arrows) covered PHPT nodule on CEUS. **E.** Three months after MWA, there was radioactive concentration in PHPT nodule (arrow). **F.** Hypoechoic PHPT nodule with abundant blood flow signals (arrows) around ablation zone was shown on US. **G.** There was active area-hyperenhancement (arrows) around ablation zone on CEUS. **H.** After additional ablation, non-enhancement (arrows) was shown on CEUS.

# LABORATORY ANALYSIS

**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

Serum IPTH, calcium, phosporus and ALP level significant improved after 6 months post MWA.

**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

Serum IPTH, calcium, phosporus and ALP level significant improved after 6 months post MWA

The volume reduction rate was 79.4% at 6 months and 96.4% at 12 months.

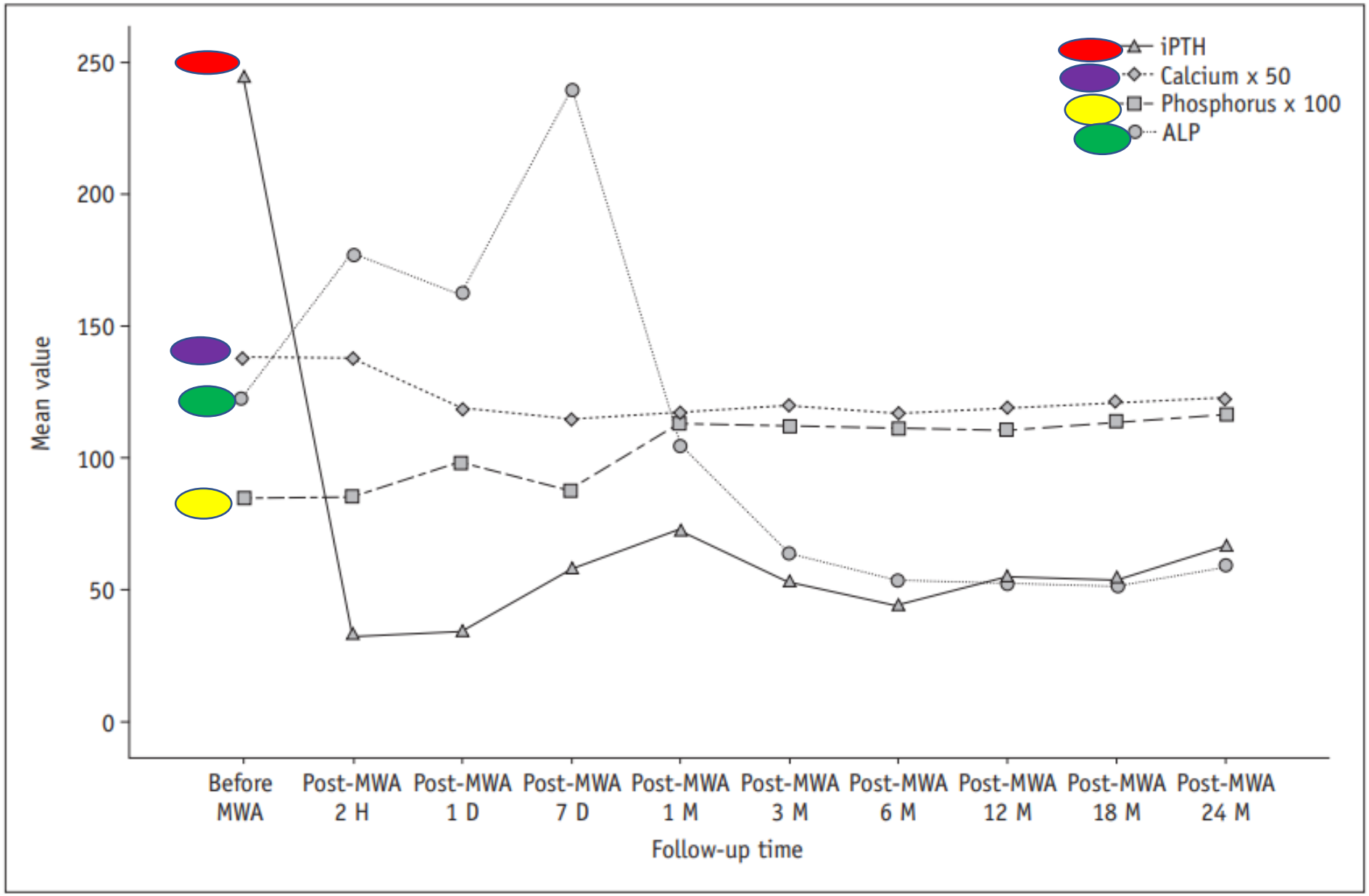



**Fig. 3. Multiple comparisons among serum iPTH, calcium, phosphorus and ALP before and after ablation.** ALP = alkaline phosphatase, D = day, H = hour, iPTH = intact parathyroid hormone, M = month, MWA = microwave ablation

# COMPLICATIONS AND SIDE EFFECTS

**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 |

# DISCUSSION

- Parathyroidectomy:
  - ✓1st line therapy for symptomatic PHPT.
  - ✓Also consider appropriate treatment for asymptomatic PHPT patient who are at high risk disease progression, hypercalcemia, even normocalcemic PHPT can develop kidney and bone involvement).

*However, some patient refused or not candidate of surgery.

*Surgery problems:

- ✓Difficult to identified all lesion esp ectopic (44.3%) and small lesion.
- ✓Those with ectopic /small lesion likely need bilateral neck exploration.
- ✓May need reoperation.
- ✓Risk of surgery.

MWA:

- Technical success rate: 100%
- Clinic success rate: 89.4%
- Significantly decrease iPTH and calcium level.
- Completely inactive hyperfunctional parathyroid gland with definite efficiency.
- Short term cure rate for MWA PHPT: 82.1% vs surgical resection 89.3% (another study finding).

- iPTH and calcium level were maintained during follow up period in most cases. Only 5 cases did not archieve curative treatment in 6 months – 4 of them had no new abnormal lesion during followup period. *possible reason cloud be the presence of some mildly hyperplastic glands that were not show in US or MIBI.
- Complete ablation usually achieved after 1 session because most PHPT cases, the adenoma or hyperplasia affected only 1 single gland.
- Patient with secondary hyperparathyroidism require more sessions to achieve complete ablation because of multiple hyperplastic parathyroid gland underlying long term stimulation of high serum phophorus and low serum calcium.

- Complication:
  - ✓Major: hoarseness – in 4 patient MWA (6%) vs parathyroidectomy (3.6%). Recurrence laryngeal nerve sensitive to thermal stimulation. So minimized heat exposure and effective hydrodissection can prevent nerve injury.
    - However, all patient hoarseness in this study recovered.
    - In this study, NS is use for hydrodissection instead of 5% distilled water. NS is ionic fluid conduct electricity. But in MWA, tissue heating is caused by oscillation of polar water molecule. So nerve injury by NS is unknown.
  - ✓Minor: resolved spontaneously in short time without special treatment.

*Parathyroidectomy- persistent hypoparathyroidism, neck hematoma, pneumothorax also reported.

Limitation

- No pathological result – because no biopsy recommended.
  - Follow up after MWA was relatively short.

Conflicts of interest.

- No potential conflict of interest.

Overall conclusion:

MWA can effectively reduce serum iPTH and ALP level and normalised serum calcium and phosphorus level in PHPT patient.  So it is alternative to surgery and medication therapy.

# THANK YOU