Effectiveness and Safety of Thermal Ablation in the Treatment of Primary Hyperparathyroidism: A Multicenter Study

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Abstract

Purpose: To evaluate the effectiveness and safety of thermal ablation for primary hyperparathyroidism (pHPT).

Materials and Methods: From January 2015 to March 2020, data pertaining to patients who received thermal ablation for pHPT at 4 centers were retrospectively analyzed. The median follow-up duration was 18.1 months (IQR: 6.5-42.2 months). A cure referred to the reestablishment of normal values of serum calcium and intact parathyroid hormone (iPTH) throughout the entire follow-up period, at least more than 6 months. The technical success, effectiveness, and safety of treatment were analyzed.

Results: 119 patients (mean age, 57.2 ± 16.3 years; 81 female) with 134 parathyroid nodules were enrolled. The mean maximum diameter of the parathyroid glands was 1.6 ± 0.9 cm. Ninety-six patients underwent microwave ablation (MWA), and 23 patients underwent radiofrequency ablation (RFA). The technical success rate was 98.3% and the cure rate was 89.9%. Significant differences were found in the maximum diameter between the cured patients and the patients who did not undergo ablation of the target lesions. Except the cases with pHPT nodules <0.6 cm in diameter, the cure rate was 95%. There were no difference in cure rates at 6 months between the MWA and RFA (MWA vs. RFA, 90.6% vs. 87.0%; χ²=0.275, p = 0.699). The volume reduction rate of the ablation zone was 94.6% at 12
months. The complication rate was 6.7% (8/119). Except one patient with persistent voice impairment, other symptoms were spontaneously resolved within six months.

**Conclusion:** Thermal ablation was effective and safe for pHPT.

**Keywords:**

Primary Hyperparathyroidism; Intact Parathyroid Hormone; Microwave Ablation; Radiofrequency Ablation.
Introduction

Primary hyperparathyroidism (pHPT) is a common endocrine disorder characterized by elevated serum parathyroid hormone (PTH) and/or hypercalcemia. Patients with pHPT often suffer from renal stones, bone loss, fractures, neurocognitive impairment syndrome or even hypercalcemic crisis. Therefore, patients with symptomatic hyperparathyroidism require treatment. In addition, nearly 30% asymptomatic pHPT patients take the risk of disease progression; therefore, treatment is also considered necessary for asymptomatic patients with skeletal and/or renal involvement. Recently, a newest variant of PHPT, normocalcemic PHPT (NHPT) was recognized. Some researchers suggested that NHPT may represent the early stage of PHPT, and sometimes it can progress to frank hypercalcemia. However, optimal management strategies in NHPT have not yet been established.

Parathyroidectomy is recommended as the standard treatment method for pHPT. It can be used to completely remove the pHPT nodules and provide a definitive and durable cure. However, in elderly patients, the mortality and morbidity related to parathyroidectomy are increased. Some patients who have few or no clinical symptoms are reluctant to undergo parathyroidectomy or are not suitable for parathyroidectomy. In recent years, thermal ablation, such as microwave ablation (MWA) and radiofrequency ablation (RFA), has been effective in inactivating parathyroid nodules and normalizing serum PTH as well as calcium. A recent prospective study reported that MWA and surgical resection had similar cure rates in pHPT. However, although promising outcomes of thermal ablation in treating pHPT have been demonstrated, definitive evidence for the effectiveness is difficult to obtain, mainly due to the small sample size and short-term follow-up in most studies. The aim of the present multicenter study was to assess the effectiveness and safety of thermal ablation for pHPT, enrolling a large number of patients from four centers and using a relatively long-term follow-up.
Materials and Methods

This retrospective study was approved by the institutional review board of all hospitals which participated in this study. All patients signed informed consent for each procedure before the procedure; informed consent for participation in current study was waived.

The inclusion criteria were: 1) symptomatic pHPT; or 2) asymptomatic pHPT patients meet one of the following conditions: a) serum calcium higher than 0.25 mmol/L above the normal upper limit; b) T-score < -2.5 at total hip, lumbar spine, femoral neck or distal one-third of the radius, remarkable osteopenia and/or increasing risk of fragility fractures; and c) age < 50 years; 3) patients with renal involvement: a) kidney stone or nephrocalcinosis found by imageological examination (eg. ultrasound, CT or X-ray examination); b) creatinine clearance < 60 ml/min, 4) pHPT patients who refused parathyroidectomy or were not suitable for parathyroidectomy ; 5) pHPT patients unwilling to comply with the observation protocols; and 6) patients with pHPT with no history of parathyroidectomy. The exclusion criteria were: 1) patients with severely abnormal coagulation function tests (e.g., prothrombin activity < 60%, prothrombin time > 18 seconds, or platelet count < 60 x 10^9/L; 2) patients with a severe comorbidities (e.g., hypertension or cardiac insufficiency that refractory to management by medication); and 3) patients with suspected parathyroid carcinoma on imaging examinations and laboratory tests (e.g., enlarged inhomogeneous hypechoic parathyroid glands with unclear margins, lymph node metastasis, markedly elevated iPTH levels and severe hypercalcemia). The flowchart of patient selection is displayed in Figure 1. Between January 2015 and March 2020, a total of 131 pHPT patients who underwent thermal ablation at four centers were reviewed.
Ablation Procedure

In patients with vitamin D deficiency, supplementation could safely begin at a dose of 1000 - 2000 IU/d before ablation. The parathyroid nodules were pre-localized with technetium 99m-labeled sestamibi single-photon emission computed tomography (99mTc-sestamibi SPECT), routine ultrasound (US) and contrast enhanced ultrasound (CEUS) (a LOGIQ E9 US system with a 6-15 MHz linear probe [GE Healthcare] and an iU22 US system [Philips] with a 5-12 MHz linear probe). The patients take a supine position. 1% lidocaine was injected at the designated ablation site for local anesthesia. To avoid thermal injury, under the guidance of US, 30-40 mL normal saline was first injected through a 18G PTC needle as isolation fluid around the parathyroid nodule to separate the parathyroid gland from adjacent important structures (e.g., esophagus, trachea, carotid artery and recurrent laryngeal nerve). The distance of liquid isolation was generally more than 0.5cm between the parathyroid nodule and the adjacent structures. Then, a mixture of 2% lidocaine and normal saline (1:3) was administered near the periparathyroid capsule for local anesthesia. For the ablation, the cooled MWA antenna (16G or 17G) with a 3-mm active tip (Intelligent Basic Type Microwave Tumor Ablation System, KY-2000, Kangyou Medical; or Nanjing ECO Microwave System) or a 17G radiofrequency electrode with 7-mm active tip (Cooltip Radiofrequency Ablation System, Covidien) was used. To provide thermal insulation, a continuous slow injection of NS was performed through the PTC needle by an assistant during the ablation process. The moving-shot or multipoint ablation technique was adopted. In MWA, the power was maintained at 30W; in RFA, ablation was performed with 35-40 W of radiofrequency power according to the size of the treated pHPT nodule. At each point, the radiation time was 15-25 seconds in MWA or when the impedance reduced in the RFA. The treatment was terminated when the entire pHPT nodule was covered by the hyperechoic ablation zone. Three-five minutes later, CEUS (SonoVue; Bracco,) was
performed to assess the ablation effectiveness (Figure 2). If the pHPT nodule was covered by the non-enhanced area, complete ablation was achieved. Further ablation was performed immediately if there was enhancement inside the ablation zone. For patients with bilateral pHPT nodules, the contralateral side ablation was only performed when vocal cord movement was normal on US and no voice change after one side was ablated; otherwise, the procedure was terminated and the second session was suspended until the recurrent laryngeal nerve (RLN) function recovered.\textsuperscript{21-23}

**Therapeutic Effect Evaluation and Outcome**

A technical success was defined as achievement of a complete ablation after undergoing appropriate treatment according to the protocol. The cure rate was analyzed as the primary outcome, while the secondary outcome was the rate of complications. A cure referred to the reestablishment of normal values of serum calcium and iPTH throughout the entire follow-up period, at least more than 6 months. Adverse events were classified into 2 categories: persistent pHPT and recurrent pHPT. Persistent pHPT referred to a failure to achieve normocalcemia/iPTH within 6 months and recurrent pHPT referred to the recurrence of hypercalcemia and/or an elevated iPTH level 6 months after ablation.\textsuperscript{3}

**Follow-Up**

All patients’ demographic and clinical symptoms were recorded. Serum iPTH, phosphorus, calcium and alkaline phosphatase (ALP) were conducted 24 hours before ablation and at 2 hours, 1 day, 7 days, 1 month, 3 months, 6 months, and then at 6-month intervals after ablation. Sphere volume formula was used to calculate nodule volume.

\[ V = \frac{\pi abc}{6} \]
(V, the volume; a, the largest diameter; b and c are the other two perpendicular diameters.
The following equation: \((V_{\text{before}} - V_{\text{after}}) / V_{\text{before}}\) was used to calculate the volume reduction rate (VRR).

**Statistical analysis**

The SPSS software package (version 20.0; IBM) was used to make the statistical analysis. Continuous data are presented as the mean ± standard deviation or the median and 25-75% interquartile range (IQR) if the data did not fit a normal distribution. Paired t test was used to analyze continuous variables, while chi-square test was used to analyze categorical ones. Cure curves were plotted by the Kaplan-Meier method. P values < 0.05 were considered indicative of statistical significance.

**Results**

The demographic characteristics of enrolled patients are listed in Table 1. Of the 131 patients reviewed, 12 were lost to follow-up. Finally, 119 pHPT patients (38 male and 81 female), with 134 parathyroid nodules (a single nodule in 106 patients, two nodules in 11 patients and three nodules in 2 patients) were enrolled in the study. Their mean age was 57.2 ± 16.3 years (range from 17 to 86 years). The mean maximum diameter of the nodules was 1.6 ± 0.9 cm (range from 0.4 cm to 5.8 cm). Ninety-six patients underwent MWA, and 23 patients underwent RFA. No significant difference was found in the baseline characteristics of the pHPT patients between the MWA and RFA groups (Table 2).

At the time of consultation, of the 119 enrolled patients, 27 (27/119, 22.7%) had severe vitamin D insufficiency (<25nmol/L), 81(81/119, 68.1%) had vitamin D insufficiency (25-74nmol/L) and 11(11/119, 9.2%) had normal (>75nmol/L) of vitamin D values. All patients
with vitamin D insufficiency received vitamin D supplementation. The results of the vitamin D test of the week before RFA/MWA showed that 74 patients still had vitamin D deficiency. During the follow-up duration, there were no newly developed nephroliths in the 28 patients (28/28, 100%) who had a history of urolithiasis before ablation. Lumbago, backache and knee discomfort disappeared in 16 patients (16/24, 66.7%) and considerably improved in 8 patients (8/24, 33.3%).

**Thermal Ablation**

Complete ablation was achieved in 117 patients (1 session in 115 patients, 2 sessions in 2 patients). The median ablation time was 129 seconds (IQR 49-364 seconds). The technical success rate was 98.3%. The median follow-up time was 18.1 months (IQR: 6.5-42.2 months). One patient had myocardial infarction 8 months after MWA and died. Serum iPTH and calcium in two patients elevated three months after the first ablation. Residual lesions displaying hyperenhancement were showed on CEUS. They underwent additional ablations. Two older pHPT patients with large hyperplastic parathyroid nodules (volume: 37.4 cm$^3$, 40.5 cm$^3$, respectively), high serum ALP levels (patient 1: 447 IU/L, patient 2: 589 IU/L) and elevated serum iPTH levels (patient 1: 572 pg/mL, patient 2: 478 pg/mL) presented with a hypercalcemic crisis before ablation. They received two-session ablation within 3 months according to the preoperative planning to i) avoid the severe hypocalcemia generally induced by a sudden decrease of iPTH; ii) protect important adjacent structures; and (iii) guarantee complete ablation based on an obvious shrinkage of pHPT nodule after first ablation.
Therapeutic Effect

One hundred and seven patients had normal serum iPTH and calcium levels in the follow-up period more than 6 months post ablation, and the cure rate was 89.9%. The cure curve of the thermal ablation is shown in Figure 3; the cure rates were 86.0% and 82.3% at 12 and 18 months respectively, and there were no differences in the cure rates at 6 months between the MWA group and RFA group (MWA vs. RFA, 90.6% vs. 87.0%; $\chi^2=0.275$, $p = 0.699$).

Figure 4a shows the changes of serum biochemical data before and after ablation. Figure 4b shows the volume of the ablation zone began to decrease significantly 3-6 months after ablation, and the VRR was 94.6% at 12 months. There was no difference in VRR between the MWA and RFA groups at 6 months (MWA vs. RFA, 75.7% vs. 64%, p=0.152) and 12 months (MWA vs. RFA, 94.7% vs. 83.1%, p=0.057). The changes of serum iPTH, calcium, phosphorus, ALP and volume of nodule before ablation and at each follow-up were listed in Table 3.

Of the 12 patients who did not achieve a cure at 6 months, 9 (9/12, 75.0%) patients had persistent pHPT, and 3 (3/12, 25.0%) had recurrent pHPT. Seven patients with persistent pHPT did not undergo ablation of the affected parathyroid nodule: i) the ablation zone covered the soft tissue other than the pHPT nodule in 5 cases; ii) adjacent lymph nodes rather than the pHPT nodules were ablated in 2 cases with Hashimoto's thyroiditis; and iii) 2 patients with persistent pHPT had local residual parathyroid nodules on follow-up imaging. In the other 3 patients with recurrent pHPT, there were no new parathyroid nodules in imaging examination during follow-up. In these three patients, the vitamin D values were 29.4nmol/L, 36.2nmol/L and 63.6 nmol/L, respectively.

There were significant differences in the maximum diameter between the cured patients and patients who did not undergo ablation of the target lesions (1.4 cm vs. 0.5 cm, $p < 0.001$).
According to the ROC analysis, a maximum diameter less than 0.6 cm resulted in the highest Youden index values of missed ablation (AUC=0.705). Among the 9 patients with nodules smaller than 0.6 cm, 77.8% (7/9) of the patients were uncured. Except 7 cases with small pHPT nodules those were not cured, the cure rate of thermal ablation was 95% (105/110). The comparison of relevant clinical parameters between the cured cases and the cases those did not undergo ablation of the target lesions was showed in Table 4.

Complications and Side Effects

The overall complication rate in current study was 6.7% (8/119). The incidence of complications in the MWA group and the RFA group was comparable (MWA vs. RFA, 7.3% vs. 4.3%; χ²=0.256, p = 1.000). Major complication - hoarseness encountered in 6 patients (5.0%). Five patients’ voices recovered completely within 6 months after ablation. The other patient had persistent voice impairment throughout the follow-up period. As a minor complication, hematomas occurred in 2 (1.7%) patients, one in the sternocleidomastoid (range, 1.8 cm x 1.0 cm) and one in the anterior superior mediastinum (range, 3.0 cm x 1.7 cm). The hematomas were successfully treated by applying pressure. Side effects included fever (1/119, 0.8%), headache (1/119, 0.8%), hand numbness (18/119, 15.1%), hypocalcemia (2/119, 1.7%) and transient hypoparathyroidism (36/119, 30.3%). Those cases all rapidly improved within 1 month without any specific therapy (Table 5).

Discussion

The present large population multicenter study enrolled 119 patients with 134 parathyroid nodules and had a median follow-up of 18.1 months. The cure rate was 89.9% and was maintained above 80% to 18 months. The ablation zone was disappeared in most patients at the 12th month of follow-up.
In contrast with surgical resections with a cure rate of 95% reported in the literature, the cure rate of thermal ablation is slightly lower, which is mainly attributed to false puncture or incomplete ablation\(^{24,25}\). When establishing hydrodissection, the liquid can diffuse unevenly and cause nodular-like changes in the surrounding tissues. In cases with a target lesion less than 0.6 cm, the echogenicity of the liquid is similar to that of the parathyroid nodules - both are hypoechoic, which can easily misguide the operator to false targets. In fact, some small parathyroid nodules might be missed even during open surgery\(^{26}\). In the present study, if the 7 uncured cases with small pHPT nodules were excluded, the cure rate of thermal ablation could reach 95% (105/110), which is comparable to surgery. In addition, according to the literature\(^{17}\), thermal ablation owned less estimated blood loss (MWA vs. surgery, 1.7ml vs. 20ml), shorter treatment time (MWA vs. surgery, 22min vs. 78min), no scars on neck (MWA vs. surgery, 0cm vs. 5.5cm) and only needs to be operated under local anesthesia. The hospitalization time was 3-5 days in the present study, which was shorter than 9 days that reported in surgery resection. Therefore, thermal ablation provides an effective and minimally invasive treatment for pHPT patients.

For patients with Hashimoto's thyroiditis, the perithyroidal central compartment lymph nodes can commonly be misdiagnosed as parathyroid nodules\(^{27}\). CEUS might be helpful in making a differential diagnosis because the higher-functioning pHPT nodules are generally hyperenhanced in the arterial phase\(^{28}\). Partial remission of hyperparathyroidism caused by incomplete ablation has also been described in previous studies\(^{13,29}\). According to the results of current study, it is suggested that: i) a complete ablation should ablate both the hypoechoic hyperplastic nodules and the surrounding normal parathyroid tissue, which often appears as a hyperechoic structure around the hypoechoic hyperplastic nodules on routine US and becomes clearer after the establishment of hydrodissection; and (ii) intraoperative iPTH monitoring could be applied as one of many adjuncts to achieve a complete ablation\(^{30}\). In
addition, obviously insufficient preoperative vitamin D levels and less effective supplementation after ablation may be one of the factors contributing to uncured patients. Therefore, mastery of the puncture technique details, a complete ablation, and adequate vitamin D supplementation are the key factors to achieve a cure.

In the management of pHPT, thermal ablation has been recommended as an alternative in recent ten years. RFA was only reported in a few of patients, and there was no exact cure rate reported. The researches of MWA had relatively larger sample size and a longer follow-up duration; the cure rate was approximately 82.1%-89.4%. Although the mechanisms of RFA and MWA are different, the cure and complication rates between the MWA and RFA groups were comparable in this study. At present, there were no definite criteria for choosing RFA or MWA in the treatment of pHPT. The selection criteria mainly depended on the operator's habits. A previous study comparing MWA and RFA in benign thyroid nodules demonstrated that a larger VRR can be achieved in the RFA group than those in the MWA group at 6 months and later follow-up. However, in the present study, there was no difference in VRR between the MWA and RFA groups at 6 and 12 months. This might be attributed to the relatively small size of the pHPT nodule (median maximum diameter: 1.6-1.8 cm). Other thermal ablation techniques such as high-intensity focused ultrasound (HIFU) and laser ablation (LA) have also been used to treat pHPT. However, only a transient decrease of serum iPTH and calcium was observed. Thus, the application of LA and HIFU in the treatment of pHPT remains to be further verified.

Transient hoarseness was reported in previous studies of thermal ablation of pHPT, with a variable rate of 6%-38%. In the present study, transient hoarseness occurred in 5 patients (4.2%). This rate was higher than that reported for parathyroidectomies (3.9%) and thermal ablation of thyroid nodules (1.5%). However, compared with the incidence of permanent RLN injury in thyroidectomy or parathyroidectomy, the rate of permanent nerve
palsy hoarseness was lower (0.8% vs. 3.9%)\textsuperscript{17}. The reason for this might attributed to the anatomic sites of parathyroid glands. Some parathyroid nodules were too close to the RLN which was very sensitive to thermal stimulation. Efficient hydrodissection technology could effectively reduce thermal stimulation to the RLN. Additionally, accurate puncture and ablation monitored by US could help protect the RLN against thermal injury.

There are still a few limitations. First, as a retrospective study, there may be selection bias in the present study, and thus additional prospective studies are needed to establish more definitive results. Second, a comparative study between thermal ablation and surgery is still necessary. Third, both MWA and RFA therapy were included, but the number of RFA cases was relatively small, so there may be bias between the therapies. Fourth, since biopsy was not recommended, no pathological results were obtained.

**Conclusion**

The results of this multicenter study indicated that thermal ablation was an effective and safe treatment option for pHPT. Microwave ablation and radiofrequency ablation had comparable medium-term results in cure rates. For pHPT nodules larger than 0.6 cm, thermal ablation could be an alternative to surgery.
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Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.
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Figure Legend

Figure 1 The patient selection process was showed flowchart.

Figure 2 Ablation procedure of pHPT nodule in a 56-year male.

a. MIBI scan showed radioactive concentration in a pHPT nodule (arrows). b. US showed a hypoechoic pHPT nodule (white arrows) on the left side of carotid artery (yellow arrow). c. CEUS showed a hyperenhanced pHPT nodule (white arrows) on the left side of carotid artery (yellow arrow) in arterial phase. d. Establishment of hydrodissection (black arrowheads) around pHPT nodule (white arrows). e. Ablation procedure: hyperechoic zone around antenna (white arrowheads) was emerging inside pHPT nodule (white arrows) – that surrounded by hydrodissection (black arrowheads). f. CEUS showed nonenhancement zone covered the pHPT nodule (white arrows).

pHPT = primary hyperparathyroidism, US = ultrasound, CEUS = contrast-enhanced ultrasound, MIBI = 99mTc-sestamibi

Figure 3. Cure curve of pHPT patients in total group, MWA group and RFA group, respectively.

MWA = microwave ablation, pHPT = primary hyperparathyroidism, RFA = radiofrequency ablation.

Figure 4. a. Changes of serum biochemical parameters before and after ablation. b. Line chart of volume reduction rate over time.

iPTH = intact parathyroid hormone, ALP = alkaline phosphatase, M = month, D = day, H = hour.
Table 1: Clinical and treatment characteristics of patients with pHPT (n=119).

| Characteristic                          | Data                      |
|-----------------------------------------|---------------------------|
| Sex (Male/Female)                       | 38/81                     |
| Mean age (years)                        | 57.2 ± 16.3 (17 - 86)     |
| Symptomatic                             | 70                        |
| Nephrolithiasis                         | 28                        |
| Lumbago, backache, knee discomfort      | 24                        |
| Fatigue                                 | 23                        |
| Asymptomatic                            | 49                        |
| iPTH (pg/ml)                            | 145.9 (91.6 - 660.7)      |
| Serum calcium (mmol/L)                  | 2.73 ± 0.27 (2.13 - 3.67) |
| Serum phosphorus (mmol/L)               | 0.86 ± 0.18 (0.46 - 1.39) |
| ALP (U/L)                               | 88 (52 - 389)             |
| 25-hydroxyvitamin D (nmol/L)            | 28.1 (10.00 - 80.9)       |
| Creatinine clearance (mL/min/1.73m²)    | 96.5 ± 22.5 (22.4 - 152.5) |
| Serum creatinine (umol/L)               | 63.2 (44.8 - 109.6)       |
| Urinary calcium (mmol/24 h)             | 6.9 ± 2.7 (0.3 - 12.3)    |
| Number of nodules                       | 134                       |
| Normal location                         | 132                       |
| Upper pole                              | 34                        |
| Lower pole                              | 98                        |
| Ectopic location                        | 2                         |
| Volume (ml)                             | 0.404 (0.063 - 4.669)     |
| Maximum diameter (cm)                   | 1.6 ± 0.9 (0.4 - 5.8)     |
| Treatment Method (MWA/RFA)              | 96/23                     |
| Ablation time (s)                       | 129 (49-364)              |

pHPT = primary hyperparathyroidism
Table 2 Baseline characteristics of patients underwent MWA and RFA. MWA = microwave ablation, RFA = radiofrequency ablation, iPTH=intact parathyroid hormone; ALP=alkaline phosphatase

| Variables                        | MWA (96)                          | RFA (23)                          | P     |
|----------------------------------|-----------------------------------|-----------------------------------|-------|
| **Baseline**                     |                                   |                                   |       |
| Female(n)                        | 65                                | 16                                | 1.000 |
| Age (years)                      | 56.8 ± 16.2                       | 59.1 ± 16.6                       | 0.530 |
| Symptomatic                      | 64                                | 14                                | 0.630 |
| **Laboratory examination**       |                                   |                                   |       |
| iPTH (pg/ml)                     | 141(90.9 - 583.2)                 | 174(86.0 - 806.1)                 | 0.078 |
| Serum calcium (mmol/L)           | 2.72 ± 0.26                       | 2.77 ± 0.30                       | 0.500 |
| Serum phosphorus (mmol/L)        | 0.85 ± 0.19                       | 0.86 ± 0.16                       | 0.844 |
| ALP (U/L)                        | 79(51 - 203)                      | 83(55 - 257)                      | 0.741 |
| 25-hydroxyvitamin D (nmol/L)     | 31.6(14.1 - 81.2)                 | 33.8(15.8 - 93.2)                 | 0.289 |
| Creatinine clearance (mL/min/1.73m²) | 92.1 ± 22.5                      | 101.4 ± 28.1                     | 0.765 |
| Serum creatinine (umol/L)        | 60.2(43.0 - 108.3)                | 66.2(48.0 - 132.1)                | 0.071 |
| Urinary calcium (mmol/24 h)      | 7.00 ± 2.80                       | 5.72 ± 1.70                       | 0.279 |
| Total protein (g/L)              | 67.8 ± 6.6                        | 68.1 ± 6.7                        | 0.823 |
| Hemoglobin (g/L)                 | 130.6 ± 17.8                      | 127.9 ± 19.0                     | 0.517 |
| **Parathyroid nodules**          |                                   |                                   |       |
| Volume (ml)                      | 0.415(0.070 - 4.205)              | 0.490(0.087 - 33.591)             | 0.280 |
| Maximum diameter (cm)            | 1.6 ± 0.9                         | 1.8 ± 1.1                         | 0.367 |
Table 3 Changes of serum iPTH, calcium, phosphorus, ALP and volume of nodule before ablation and at each follow-up.

| Follow-up Time | iPTH(pg/mL) | Calcium (mmol/L) | Phosphorus (mmol/L) | ALP (U/L) | Volume (cm³) | VRR (%) |
|----------------|-------------|------------------|---------------------|-----------|--------------|---------|
| Before Ablation (n=119) | 145.9 (91.6 - 660.7) | 2.73 ± 0.27 | 0.86 ± 0.18 | 88 (52 - 389) | 0.404 (0.063- 4.669) | - |
| 2H Post ablation (n=113) | 19.0 (1.6-101.5)* | 2.60 ± 0.27 | 0.86 ± 0.22 | 88(41-1125) | - | - |
| 1D Post ablation (n=112) | 17.9 (2.4-98.9)* | 2.37 ± 0.19 | 1.01 ± 0.23 | 88(43-804)* | 0.565(0.101-5.639)* | -14.1(-897.7-63.6) |
| 7D Post ablation (n=85) | 42.3 (9.4-113.7)* | 2.31 ± 0.21 | 1.08 ± 0.24 | 99(46-1136) | - | - |
| 1M Post ablation (n=109) | 59.0 (19.9-143.8)* | 2.35 ± 0.14 | 1.11 ± 0.18 | 87(51-144)* | 0.435(0.039-3.916)* | 0.0 (-444.8-84.1) |
| 3M Post ablation (n=96) | 54.9 (17.0-124.8)* | 2.40 ± 0.17 | 1.09 ± 0.20 | 70(43-172)* | 0.209(0.028-1.170)* | 2.0(-280.3-93.1) |
| 6M Post ablation (n=119) | 59.4 (21.8-110.8)* | 2.39 ± 0.21 | 1.06 ± 0.16 | 70(42-112)* | 0.092(0.1-5.90)* | 71.3(22.0-100) |
| 12M Post ablation (n=87) | 47.7 (20.7-102.1)* | 2.35 ± 0.15 | 1.11 ± 0.16 | 68(40-90)* | 0.025(0-0.840)* | 94.6(0-100) |
| 18M Post ablation (n=60) | 47.7 (23.8-106.5)* | 2.36 ± 0.19 | 1.12 ± 0.16 | 68(35-94)* | 0(0-0.856)* | 100(79.8-100) |
| 24M Post ablation (n=39) | 52.3 (22.8-154.3)* | 2.37 ± 0.24 | 1.08 ± 0.24 | 70(44-99)* | 0(0-0.444)* | 100(80.7-100) |
| 30M Post ablation (n=22) | 50.6 (27.3-85.8)* | 2.39 ± 0.10 | 1.12 ± 0.18 | 70(38-88)* | 0(0-0.264)* | 100(81.2-100) |
| 36M Post ablation (n=15) | 45.7 (26.5-80.3)* | 2.35 ± 0.33 | 1.12 ± 0.13 | 76(40-88)* | 0(0-0.046)* | 100(81.8-100) |
| 42M Post ablation (n=6) | 51.2 (46.4-88.1)* | 2.39 ± 0.11 | 1.12 ± 0.12 | 70(60-90)* | 0(0-0.015)* | 100(84.7-100) |

P value: post-ablation vs. pre-ablation, respectively. *p < 0.05.

iPTH=intact parathyroid hormone; ALP=alkaline phosphatase; VRR=volume reduction rate

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 94, 68, 44, 26, 19 and 11 patients who received thermal ablation more than 12, 18, 24, 30, 36 and 42 months, respectively.
Table 4 Comparison of relevant clinical parameters between the cured cases and the cases those did not undergo ablation of the target lesions.

| Variables                      | Operative failure (7) | Cured (107) | P    |
|--------------------------------|-----------------------|-------------|------|
| Female (n)                     | 3                     | 74          | 0.211|
| Age (years)                    | 44.1±10.8             | 55.3±16.8   | 0.055|
| Pre-MWA iPTH (pg/ml)           | 119.7(103.4-128.1)    | 154.9(89.9-666.8) | 0.035|
| Serum calcium (mmol/L)         | 2.53±0.30             | 2.74±0.27   | 0.044|
| Serum phosphorus (mmol/L)      | 0.93±0.17             | 0.85±0.18   | 0.279|
| ALP (U/L)                      | 70(54-90)             | 88(51-115)  | 0.062|
| 25(OH)D3(nmol/L)               | 42.1(30.7-54)         | 32.7(14.6-80.9) | 0.080|
| GFR(mL/min)                    | 103.3(83.1-116.8)     | 97.6(50.3-128.9) | 0.377|
| CCR(umol/L)                    | 76.9(57.1-87.2)       | 60.1(43.1-108.3) | 0.428|
| Max Diameter (cm)              | 0.5(0.4-0.9)          | 1.4(0.8-3.6) | <0.001|
| Volume (ml)                    | 0.042 (0.024-0.157)   | 0.484(0.084-5.951) | 0.001|
Table 5 Complications and side effects after thermal ablation

| Complication or Side Effect | Number (%) | Time of Detection (D) | Time to Recovery (D) |
|-----------------------------|------------|----------------------|---------------------|
| Major Hoarseness            | 6(5.0)     | 5(5.2)               | 1(4.3)              | 1-3                   | 30-180(6) |
| Minor Hematoma              | 2(1.7)     | 2(2.0)               | 0(0)                | 1                     | 1         |
| Side effect                 | 55(46.2)   | 43(44.8)             | 12(52.2)            |                       |           |
| Fever                       | 1(0.8)     | 0(0)                 | 1(4.3)              | 2                     | 5         |
| Headache                    | 1(0.8)     | 1(1.0)               | 0(0)                | 1                     | 7         |
| Numbness                    | 15(15.1)   | 12(12.5)             | 3(13.0)             | 1-3                   | 2-54      |
| Hypocalcaemia               | 2(1.7)     | 2(2.0)               | 0(0)                | 1-3                   | 3-30      |
| Hypoparathyroidism          | 36(30.3)   | 28(29.2)             | 8(34.7)             | 1-7                   | 3-30      |

MWA=microwave ablation; RFA=radiofrequency ablation; D=day
Figure 1

Patients with pHTP (n=306)

Recurrent pHTP (n=4)
Mislabeled dHTP (n=9)
History of parathyroidectomy (n=4)

Symptomatic Patient (n=99)

Asymptomatic Patients with Medical Therapy (n=196)

Effectiveness (n=48)

(Ineffectiveness with one of the following, n=142)

a) Serum calcium >0.25 mmol/L above the normal upper limit
b) T-score <−2.5; Frailty fracture
c) Age < 50 years
d) Creatinine clearance < 60ml/min
e) Clinical development of a kidney stone

Negative result (n=11)

Ultrasound examination (n=241)

Enlarged HPT glands (n=230)

Surgical Resection (n=77)

The glands with radionuclide concentration (n=216)

Ineligible for Surgery or Declined Surgery (n=139)

Refuse ablation (n=5)

Coagulation Function Test
Concurrent Disease Correction

Underwent Ablation (n=131)

Enrolled in the study (n=119)
Figure 3

Strata: MWA, RFA, Total

Number at risk: n

| Strata   | 0  | 10 | 20 | 30 | 40 | 50 | 60 |
|----------|----|----|----|----|----|----|----|
|          |    |    |    |    |    |    |    |
| 96 (100)|    |    |    |    |    |    |    |
| 23 (100)|    |    |    |    |    |    |    |
| 119 (100)|   |    |    |    |    |    |    |

Cure probability

Time

p = 1
Figure 4

(a) Graph showing mean values over follow-up time.

(b) Graph showing another set of data over follow-up time.