Comparison of ultrasound-guided percutaneous microwave ablation and parathyroidectomy for primary hyperparathyroidism

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ABSTRACT

Purpose: To compare the clinical efficacy of ultrasound-guided percutaneous microwave ablation (MWA) and parathyroidectomy for primary hyperparathyroidism.

Methods: In an observational retrospective study, we compared the outcomes in patients with primary hyperparathyroidism who underwent ultrasound-guided MWA with the outcomes in those who underwent surgical resection (SR). The primary outcome was cure rate. Secondary outcomes were the rate of complications, and the difference of the treatment parameters of two treatment methods. Propensity-score matching was used to assemble a cohort of patients with similar baseline characteristics.

Results: Among 108 patients who met inclusion criteria, 28 patients who underwent ultrasound-guided MWA (MWA group) and 28 who underwent SR (SR group) had similar propensity scores and were included in the analyses. There was no significant difference in the cure rate between MWA group and SR group (82.1% vs. 89.3%, \( p = 0.705 \)). Patients who underwent MWA had significantly less estimated blood loss and shorter surgical time than those who underwent SR (\( p < 0.001 \)). The incidence of side effects and complications was comparable between MWA group and SR group (21.4% vs. 25%, \( p = 0.752 \)).

Conclusions: MWA and SR provided comparable short-term results in terms of cure rate and complications in treatment of primary hyperparathyroidism. Ultrasound-guided percutaneous MWA is a promising and minimally invasive method for primary hyperparathyroidism.

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Introduction

Primary hyperparathyroidism is a common endocrine disorder of calcium metabolism characterized by hypercalcaemia and elevated or inappropriately normal concentrations of parathyroid hormone (PTH). Primary hyperparathyroidism is most commonly due to a single benign parathyroid adenoma (approximately 80% of patients), with multiglandular disease seen in approximately 15–20% of patients [1]. Parathyroid cancer is rare and accounts for well under 1% of all cases of primary hyperparathyroidism [2]. Primary hyperparathyroidism is generally discovered when asymptomatic but the disease always has the potential to become symptomatic, resulting in bone loss and kidney stones. Surgery remains the only definitive treatment for hyperparathyroidism according to the guidelines from the 4th International Workshop [3]. However, the morbidity and mortality associated with parathyroid surgery are increased in elderly patients [4]. Although minimally invasive parathyroidectomy relies on localization technology and intraoperative adjuvant measures to reduce the risk to some extent, it is still challenging for patients with mild hypercalcemia and multiple glands [5].

In recent years, with the development of thermal ablation technology, microwave ablation (MWA) and other thermal ablation techniques, such as radiofrequency ablation and laser ablation (LA), have been used in the treatment of hyperparathyroidism and become a safe and effective treatment for primary hyperparathyroidism patients who do not meet surgery criteria or decline surgery [6–8]. However, can MWA achieve the same therapeutic effect as surgical resection (SR) in the treatment of hyperparathyroidism that meets the surgical criteria? As far as we know, there is no relevant report yet. Therefore, the purpose of our study is to compare the clinical efficacy of ultrasound-guided percutaneous MWA and SR for treatment of primary hyperparathyroidism caused by parathyroid hyperplasia or adenoma.

Materials and methods

Study design

This retrospective study was approved by our institutional review board. Informed consent for treatment procedures was obtained from each patient. The medical records of all...
patients with primary hyperparathyroidism who underwent ultrasound-guided MWA or SR between May 2013 and December 2018 in our hospital were reviewed. Information for each patient was obtained that included demographics, comorbidities, longest diameter of lesions, lesion numbers, pathologic type of lesion, location of lesion and treatment variables (including hospitalization, surgical time, estimated blood loss, complications, and pre- and postoperative serum PTH level, serum calcium and serum phosphorus levels).

The diagnosis of primary hyperparathyroidism was based on the basis of recommendations proposed by the International Workshop on Primary Hyperparathyroidism [3]. Parathyroid lesions were localized by ultrasound and 99mTc sestamibi (MIBI), and dynamic computed tomography (CT) or magnetic resonance were used if necessary. Although the incidence of parathyroid adenocarcinoma is very low, differentiation between benign and malignant is very important. Therefore, in the preoperative evaluation process, if the patient’s clinical symptoms or imaging examination suspect malignancy, especially when ultrasound suspects malignancy, such as unclear boundary, irregular shape, lobulated, microcalcification, enlarged lymph nodes around the tumor, and unclear boundary between the lesion and surrounding tissue, surgical resection is recommended instead of fine needle aspiration (FNA) or core needle biopsy (CNB). Only those patients with hyperparathyroidism who are not suspected of malignant will undergo CNB at the same time as MWA, providing more clues to further exclude the possibility of malignant tumors. All enrolled patients were considered as benign parathyroid adenoma or hyperplasia according to clinical symptoms, imaging findings and pathological findings in our study. The inclusion criteria, based on the guidelines established on the basis of the Fourth International Workshop on the Management of Primary Hyperparathyroidism, were as follows: patients with symptomatic primary hyperparathyroidism; patients with asymptomatic primary hyperparathyroidism whose serum calcium concentration is more than 0.25 mmol/L above the upper limit of normal range; patients with asymptomatic primary hyperparathyroidism who have skeletal involvement: (a) reduced bone mineral density as a T score of less than –2.5 at any site (lumbar spine, hip or distal one-third radius), (b) vertebral fracture by radiography, CT or vertebral fracture assessment; or patients who have renal involvement: (a) creatinine clearance less than 60 ml/min, (b) kidney stone or nephrocalcinosis by ultrasound, CT or abdominal radiography; patients with asymptomatic primary hyperparathyroidism who have hypercalciuria (>400 mg per day) accompanied by a biochemical stone risk profile that places the patient at risk of kidney stones or patients whose age less than 50 years [3,9].

**Microwave equipment and ablation technique**

The MW unit (KY-2000; Kangyou Medical, Nanjing, China) consists of an MW generator, a flexible low-loss coaxial cable, and a cooled-shaft antenna. The generator is capable of producing 1–100 W of power at 2450 MHz in pulse or continuous form. The MW antenna is a 16-gauge needle (1.9 mm in diameter and 3 mm or 5 mm in length) coated with polytetrafluoroethylene to prevent adhesion. To prevent shaft overheating, distilled water is circulated through dual channels inside the antenna shaft, continuously cooling the shaft. The patients were in the supine position with the neck extended. MWA was performed under local anesthesia with 2% lidocaine (Synera, Salt Lake City, UT) at the puncture site. The hydrodissection technique was performed which was used in thyroid and parathyroid ablation [6–8]. With US guidance, normal saline solution was injected into the region between the parathyroid nodule and vital structures of the neck (carotid artery, trachea, esophagus, nerve and thyroid) to achieve a 5 mm liquid-isolating region. The antenna was inserted freehand into the parathyroid gland under US guidance with an 8.4–9 MHz linear probe for glands in the neck and the supra-ternal fossa or supra-anterior mediastinum (LOGIQ E9; GE, USA). The approach was lateral for glands in the neck and supra-ternal fossa and cranio-caudal for glands in the supra-anterior mediastinum to avoid the clavicle [10]. Before each ablation, the needle tip location in the gland was confirmed by means of US, followed by ablation using the ‘moving-shot’ technique. The power for ablation was 20–30 W for each microwave application. Ablation was terminated when transient hyperechoic echotexture was seen throughout the gland. After ablation, contrast-enhanced US (SonoVue; Bracco, Milan, Italy) was used to evaluate the extent of ablation of the parathyroid gland [11]. If the non-enhanced zone at contrast-enhanced US covered the ablated gland, the ablation was considered complete. If there was nodular enhancement inside a gland, an additional ablation was performed immediately. At the end of the procedure, mild compression was applied to the site of the needle insertion for 20 min.

**Surgical technique**

Parathyroidectomy was performed under general anesthesia. After successful general anesthesia, the patient took a supine position, shoulder pillow, head back, routine disinfection and sterile sheet, and cloth was placed on both sides of the neck to fix. The upper two transverse fingers of sternal notch were taken and the collar transverse incision along the dermatoglyphic direction was about 5–8 cm. The skin, subcutaneous, latissimus cervicalis and superficial layer of deep cervical fascia were incised, and the incision was pulled up. The skin flaps were free between the loose connective tissue plane of latissimus cervicalis and deep cervical fascia, from the upper margin of thyroid cartilage to the sternal notch to fully expose the outer layer of deep cervical fascia. Lift the fascia on both sides of the median line, cut the white line of the neck and separate the gap between the subhyoid muscle group and the thyroid capsule with the finger to the front of the sternocleidomastoid muscle. The bilateral sternohyoid and thyroidal muscles were pulled apart to explore parathyroid tumors and to perform parathyroidectomy. The ipsilateral recurrent laryngeal nerve (RLN) was explored by nerve monitor to protect it intraoperatively. Hemostasis was fully achieved and the incision was sutured layer by layer.
Outcomes
The primary outcome of the study was cure rate. Various secondary outcomes were also assessed, including the rate of complications, and the difference of the treatment parameters of two treatment methods. Cure was defined as normal PTH and calcium levels six months after parathyroidectomy or MWA.

Statistical analysis
All baseline data are presented as percentages for categorical data and for continuous as means ± standard deviation (SD) where data followed a normal distribution, or medians and interquartile range where they did not. Given the differences in the baseline characteristics between eligible participants in the two groups (Table 1), propensity-score matching was used to identify a cohort of patients with similar baseline characteristics. The propensity score is a conditional probability of having a particular exposure (MWA vs. SR) given a set of baseline measured covariates. The propensity score was estimated with the use of a nonparsimonious multivariable logistic-regression model, with MWA as the dependent variable and all the baseline characteristics outlined in Table 1 as covariates. Matching was performed with the use of a 1:1 matching protocol without replacement (greedy-matching algorithm), with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score.

In the matched cohort, comparison of general characteristics and various ratios between the two groups were conducted by using student t test, Wilcoxon signed rank test for continuous variables and either Pearson χ² test or Fisher exact test for categorical variables. p Values <.05 were considered as statistical significance. All analyses were performed using Empower (R) (www.empowerstats.com, X&Y solutions, Inc., Boston, MA) and R (http://www.R-project.org).

Results
Patient characteristics
We identified 108 patients with primary hyperparathyroidism who met our inclusion criteria, of whom 36 patients underwent ultrasound-guided MWA (MWA group) and 72 patients underwent SR (SR group). Before propensity-score matching, there were differences between the two groups in mean age of the baseline variables. With the use of propensity-score matching, 28 patients who underwent ultrasound-guided MWA were matched with 28 patients who underwent SR. After matching, baseline characteristics of patients were comparable between the two groups (p > .05) (Table 1).

Treatment parameter
The surgical time for the MWA group was significantly shorter than that for the SR group (p < .001). There was less estimated blood loss in the MWA group (p < .001). The mean incision length was 5.5 cm for the SR group, but only one 1 mm pinhole for the MWA group. There was no significant difference in hospitalization time between the two groups (p = .797) (Table 2).

Clinical outcome
Twenty-three patients in MWA group had normal PTH and serum calcium levels in six months after treatment, and the cure rate was 82.1%. In the SR group, 25 patients had normal levels of PTH and serum calcium in six months after operation, with a cure rate of 89.3%. There was no significant difference in the cure rate between MWA group and SR group (p = .705).

In the MWA group, the levels of PTH and serum calcium increased in two of the five patients who did not reach the

Table 1. Baseline characteristics of patients undergoing MWA and SR before and after propensity-score matching.

| Characteristic               | Before matching | p Value | After matching | p Value |
|------------------------------|-----------------|---------|----------------|---------|
|                              | MWA (n = 36)    | SR (n = 72) |                 |         |
| Gender (male/female)         | 12/24           | 15/72   | .157           | .629    |
| Mean age (year) (range)      | 60.1 ± 12.5     | 52.2 ± 12.0 | .002           | .979    |
| BMI*                         | 24.3 ± 2.9      | 24.2 ± 3.0 | .829           | .947    |
| CCR (%)                      | 87.1 ± 40.0     | 97.7 ± 31.6 | .136           | .337    |
| Diabetes mellitus (yes/no)   | 6/30            | 6/66    | .194           | .095    |
| Hypertension (yes/no)        | 16/20           | 19/53   | .059           | .787    |
| symptomatic PHP (yes/no)     | 26/10           | 45/27   | .316           | .517    |
| PTH level (pg/ml)            | 228.0 ± 187.5   | 421.2 ± 760.4 | .137          | .451    |
| Serum calcium(mmol/L)        | 2.7 ± 0.3       | 2.8 ± 0.3 | .583           | .840    |
| Phosphorus(mmol/L)           | 0.8 ± 0.2       | 0.8 ± 0.2 | .406           | .451    |
| 25(OH)D3(pg/ml)              | 10.3 ± 3.1      | 10.4 ± 4.8 | .936           | .729    |
| No. of nodules               |                |         |                |         |
| Single nodule                | 34              | 68      | .741           | .451    |
| Two nodules                  | 2               | 3       | .311           | .289    |
| Three nodules                | 0               | 1       | .83 ± 0.94     | .311    |
| Nodule’s diameter (cm)       | 1.9 ± 1.0       | 2.1 ± 1.0 |                |         |

*BMI: Body mass index; CCR: creatinine clearance rate.

Table 2. Comparison of treatment parameter and clinical efficacy between MWA and SR group after propensity-score matching.

| Parameters                  | MWA (n = 28) | SR (n = 28) | p Value |
|-----------------------------|--------------|-------------|---------|
| Surgical time (min)         | 22.0 ± 6.3   | 77.8 ± 50.6 | <.001   |
| Hospitalization time (days) | 8.8 ± 3.4    | 9.1 ± 5.6   | .797    |
| Blood loss (ml)             | 1.7 ± 0.4    | 20.0 ± 21.3 | <.001   |
| Incision length (cm)        | None         | 5.5 ± 1.0   | .979    |
| Cure rate                   | 23/28        | 25/28       | .705    |
| Complications               | 6/28         | 7/28        | .752    |
| Voice change                | 2            | 0           | .491    |
| Headache                    | 0            | 1           |         |
| Perioral and limb numbness  | 4            | 6           | .727    |
Table 3. The rates of achieving the normal level for PTH, serum calcium and phosphorus in MWA group and SR group after treatment.

| Variable | SR (n = 28) | MWA (n = 28) | p     |
|----------|-------------|--------------|-------|
| PTH (pg/ml) |             |              |       |
| 1st day   | 22/28 (78.6%) | 22/28 (78.6%) | 1     |
| 3rd day   | 23/28 (82.1%) | 21/28 (75%)  | .515  |
| 30th day  | 27/28 (96.4%) | 22/28 (78.6%) | .101  |
| 90th day  | 25/28 (89.3%) | 24/28 (85.7%) | 1     |
| 180th day | 25/28 (89.3%) | 23/28 (82.1%) | .705  |
| Ca (mmol/L) |             |              |       |
| 1st day   | 22/28 (78.6%) | 21/28 (75%)  | .752  |
| 3rd day   | 26/28 (92.9%) | 26/28 (92.9%) | 1     |
| 30th day  | 28/28 (100%) | 26/28 (92.9%) | .491  |
| 90th day  | 27/28 (96.4%) | 25/28 (89.3%) | .611  |
| 180th day | 28/28 (100%) | 26/28 (92.9%) | .491  |
| P (mmol/L) |             |              |       |
| 1st day   | 14/28 (50%)  | 17/28 (60.7%) | .42   |
| 3rd day   | 23/28 (82.1%) | 27/28 (96.4%) | .193  |
| 30th day  | 27/28 (96.4%) | 26/28 (92.9%) | 1     |
| 90th day  | 26/28 (92.9%) | 25/28 (89.3%) | 1     |
| 180th day | 28/28 (100%) | 24/28 (85.7%) | .111  |

Table 4. Changes of PTH, serum calcium and phosphorus in MWA group and SR group before and after treatment.

| Variable | SR (n = 28) | MWA (n = 28) | p     |
|----------|-------------|--------------|-------|
| PTH(pg/ml) |             |              |       |
| Preoperation | 223.7 ± 175.7 | 197.7 ± 129.0 | .532  |
| 1st day   | 15.0 ± 8.8  | 42.6 ± 31.3  | <.001 |
| 3rd day   | 23.0 ± 10.6 | 58.4 ± 25.9  | <.001 |
| 30th day  | 39.3 ± 16.2 | 65.3 ± 18.9  | <.001 |
| 90th day  | 50.6 ± 24.0 | 64.8 ± 15.2  | .034  |
| 180th day | 53.4 ± 15.2 | 61.3 ± 19.6  | .254  |
| Ca(mmol/L) |             |              |       |
| Preoperation | 2.8 ± 0.3  | 2.7 ± 0.3  | .284  |
| 1st day   | 2.4 ± 0.3  | 2.4 ± 0.2  | .465  |
| 3rd day   | 2.3 ± 0.2  | 2.2 ± 0.2  | .619  |
| 30th day  | 2.2 ± 0.1  | 2.3 ± 0.1  | .055  |
| 90th day  | 2.2 ± 0.1  | 2.3 ± 0.2  | .199  |
| 180th day | 2.3 ± 0.1  | 2.4 ± 0.2  | .241  |
| P(mmol/L) |             |              |       |
| Preoperation | 0.8 ± 0.2  | 0.8 ± 0.2  | .84   |
| 1st day   | 0.8 ± 0.3  | 1.0 ± 0.2  | .050  |
| 3rd day   | 1.0 ± 0.2  | 1.1 ± 0.2  | .282  |
| 30th day  | 1.0 ± 0.2  | 1.0 ± 0.2  | .923  |
| 90th day  | 1.0 ± 0.1  | 1.0 ± 0.1  | .205  |
| 180th day | 1.0 ± 0.1  | 1.0 ± 0.2  | .692  |

Normal range: PTH:15–65 pg/ml, Ca:2.09–2.54 mmol/L, P:0.89–1.6 mmol/L.

Side effects and complications

Voice change occurred in two patients and recovered three months after operation in MWA group. Headache occurred in one patient and recovered one week after operation in SR group. Postoperative mild transient hypocalcemia accompanied by perioral and limb numbness occurred in four cases of MWA group and in six cases of SR group. The symptoms were gradually relieved by the appropriate use of calcitriol and supplemental calcium. The incidence of side effects and complications was comparable between the two groups (MWA, 21.4% vs. SR, 25%; p = .752).

Discussion

Surgery remains the only definitive treatment for primary hyperparathyroidism according to guidelines from the 4th International Workshop [3,9], while as one of the thermal ablation techniques, MWA is a safe and effective technique for the treatment of primary hyperparathyroidism [6,12].

In our study, the cure rates of MWA group and SR group were 82.1% and 89.3% as evidenced by normalization of both serum PTH and calcium levels in six months after operation, respectively. There was no significant difference in the cure rate between two groups (p = .705). Moreover, there were no significant differences in the rates of achieving the normal level for serum PTH, calcium and phosphorus between MWA group and SR group at any of the follow-up time points within six months. Therefore, MWA and surgical resection have achieved similar clinical efficacy in the treatment of primary hyperparathyroidism in our study. Literatures reported that cure rates are above 95% in centers with expertise in parathyroid surgery, which was slightly higher than the cure rate in our study [13,14]. The main factor of low cure rate is the low rate of PTH reaching normal level after treatment in our study, while the rates of serum calcium reaching normal level were 92.9% and 100% in six months after treatment. The rebound of PTH was only caused by residual lesions in two cases of MWA group, and no definite residual lesions were found in the rest of patients during the follow-up. Lack of vitamin D levels in Chinese patients may be one of the factors contributing to this outcome [15]. The preoperative 25-hydroxyvitamin D3 level in both groups is obviously insufficient, and there is no cure level, while in the other three patients only PTH increased and serum calcium was normal. The follow-up of imaging examination after operation indicated the local residual abnormal parathyroid tissue in ablation area of two patients with hypercalcemia. One of the two patients with elevated serum calcium was the patient with the largest lesion diameter (4.8cm in diameter) and the other was the patient with hoarseness during MWA. Of the three patients who had not been cured in the SR group, only PTH level was elevated and serum calcium level was normal. No residual and new abnormal parathyroid tissues were found in the follow-up of imaging examination after operation.

The rates of achieving the normal level for PTH were comparable between the MWA group and SR group at the following follow-up time points: 78.6% vs. 78.6% at the 1st day (p = 1), 75% vs. 82.1% at the 3rd day (p = .515), 78.6% vs. 96.4% at the 1st month (p = .101), 85.7% vs. 89.3% at the 3rd month (p = 1.0), 82.1% vs. 89.3% at the 6th month (p = .705), respectively. There were no significant differences in the rates of achieving the normal level for calcium (p > .05) between MWA group and SR group at any of the follow-up time points within six months. The rates of achieving the normal level for phosphorus were also comparable between the MWA group and SR group (p > .05) (Table 3).

The mean levels of PTH for SR group decreased much lower than that for MWA group on the 1st, 3rd day, 1st, and 3rd month after treatment (p < .05), while its were comparable between two groups at the 6th month after treatment (p > .05) (Table 4). There were no significant differences in the mean levels of serum calcium and phosphorus between MWA group and SR group on the 1st, 3rd day, 1st, 3rd and 6th month after treatment (Table 4).
effective supplement after treatment in our study. The low vitamin D level after operation stimulates the rebound of PTH, which is also a problem that has not been paid attention by most Chinese doctors after parathyroid surgery. Therefore, vitamin D supplementation after parathyroid surgery for vitamin D deficiency patients is an important factor in the cure rate [16]. A study from China also reported that the cure rate of laser ablation for primary hyperparathyroidism was 81%, which was similar to that of MWA in our study [7].

There were significantly less estimated blood loss and shorter surgical time in the MWA group than the SR group (p < .001) in our study. Surgical excision requires a 5–8 cm incision, whereas MWA requires only a 1 mm pinhole and does not leave scars on the neck of the patient. In addition, MWA only needs to be operated under local anesthesia. Therefore, MWA provides an effective and minimally invasive treatment for patients who cannot tolerate general anesthesia or surgical resection. At the same time, it also meets the aesthetic needs of patients without scar on neck, especially for female patients.

Because of the anatomical location of the parathyroid gland, postoperative voice changes are one of the most feared complications of parathyroid surgery or MWA, and RLN injury is one of the most common causes of postoperative voice change. The frequency of RLN injury during thyroid and parathyroid surgery has been reported to be up to 3.9% for transient nerve palsy and 3.6% for permanent palsy [17,18]. Therefore, how to avoid the injury of RLN is the key. In our study, there were two cases of hoarseness in MWA group and none in SR group. Because the RLN is invisible on ultrasound image, ultrasound-guided MWA can only avoid the injury of the RLN by water isolation according to the anatomical structure of the parathyroid gland and the RLN, which has achieved satisfactory results, but water isolation may be difficult to achieve satisfactory results in the presence of RLN variation or parathyroid lesions adhering to RLN, although this rarely happens [6–8,19,20]. By contrast, the application of visualization and nerve monitoring technology of the RLN during surgery may reduce the occurrence of RLN injury when there is a RLN variation [18,21]. Nevertheless, there was no significant difference in the incidence of voice change between the two methods in our study.

There were several limitations to this study. First, this was a nonrandomized, observational study and hence suffers from potential selection and ascertainment bias despite robust propensity-score matching. Second, relatively few patients were enrolled, limited sample size might have reduced statistical power in comparative analysis and more patients are needed for a confident conclusion. Third, the comparison of clinical effects is mainly short-term within six months, and the long-term results need further study. Fourth, pathologically differentiating parathyroid adenoma from adenocarcinoma requires complete excision of the lesion. Parathyroid adenocarcinoma can be diagnosed only when there is invasion of blood vessels, capsule and adjacent tissues or distant metastasis and recurrence [22]. In the MWA group, the possibility of excepting adenocarcinoma was based on clinical symptoms, imaging and CNB. FNA and CNB are limited in differentiating parathyroid adenoma from adenocarcinoma [23].

In conclusion, MWA and SR provided comparable short-term results in terms of cure rate and complications. These results are promising and serve as a useful framework for future prospective and randomized trials that compare MWA and SR for the treatment of primary hyperparathyroidism caused by parathyroid hyperplasia or adenoma.

Disclosure statement
No potential conflict of interest was reported by the authors.

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