Objectives—A previous 12-month study confirmed that microwave ablation (MWA) was effective for moderate secondary hyperparathyroidism (SHPT). A further analysis was performed in this study to evaluate the efficacy of MWA for moderate SHPT over an observational follow-up period of up to 60 months.

Methods—This was a retrospective cohort study of patients involved in a previous randomized controlled trial. Patients were divided into an MWA group (those who underwent MWA followed by drug therapy according to the patient’s clinical situation) and a control group (those who received drug therapy only). The primary outcome was the composite endpoint. During the efficacy assessment phase, the two groups were compared in terms of the proportion of patients with intact parathyroid hormone (iPTH) levels <300 pg/ml and the differences in iPTH levels.

Results—Twenty-seven patients were included in this study: 13 in the MWA group and 14 in the control group. The median (interquartile range) follow-up periods of the MWA and control groups were 58 (54–60) and 58 (49–60) months, respectively. The proportion of patients with iPTH levels <300 pg/ml in the MWA group was slightly higher than that in the control group (6/13 [46.2%] versus 2/14 [14.3%], respectively; \( p = .08 \)). Furthermore, iPTH levels in the MWA group were lower than in the control group during the efficacy assessment phase (411 ± 299 pg/ml versus 516 ± 369 pg/ml, respectively; \( p < .01 \)).

Conclusions—MWA helped to contain the necessary iPTH levels in patients undergoing hemodialysis for moderate SHPT in a 60-month timeframe.

Key Words—hemodialysis; long-term effect; microwave ablation (MWA); secondary hyperparathyroidism (SHPT)

Introduction

Secondary hyperparathyroidism (SHPT) is one of the most common complications in patients undergoing hemodialysis.¹ SHPT worsens patients’ bone and joint pain, muscle soreness, and overall pain² and increases the incidence of cardiovascular disease and mortality rates.
Drug therapy is the primary option for SHPT, while in cases where parathyroid hormone (PTH)-lowering therapies failed, parathyroidectomy (PTX) is the recommended treatment option per the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (2017 edition).\(^3\) Besides the two methods mentioned above, microwave ablation (MWA) is an effective therapy for SHPT,\(^4\)–\(^5\) which is most often indicated for patients whose intact PTH (iPTH) levels are higher than 800 pg/ml\(^6\) or for those not indicated for surgery.\(^7\)–\(^8\) Follow-up periods of the previous studies were approximately 6–12 months\(^5,7\); therefore, a study with a longer follow-up period is needed. A study\(^9\) followed up 34 SHPT patients who received MWA and found that their PTH levels were significantly lower 6 months after ablation than those before MWA. Bone pain in patients improved postoperatively. Ultrasound-guided percutaneous microwave thermoablation is a feasible and effective nonsurgical alternative treatment for SHPT patients. However, due to differences in invasiveness between MWA and PTX, and variable tolerance in patients, MWA may be useful for moderate SHPT. In a previous study, MWA decreased iPTH levels and prevented its progression in patients undergoing hemodialysis for mild to moderate SHPT.\(^10\) However, the follow-up time in the study was only 12 months\(^10\); therefore, the long-term effect of MWA on moderate SHPT is unclear.

In this study, we retrospectively collected data for patients involved in the previous prospective randomized trial and analyzed the long-term effect of MWA on moderate SHPT.

Methods

Study Design
This study followed up patients involved in a previous prospective randomized controlled trial.\(^10\) Patients’ clinical data were collected from the previous randomized controlled trial, from their recruitment dates to 60 months after the end of the trial. The patients were divided into an MWA group and a control group according to the type of treatment; patients in the MWA group received percutaneous MWA followed by drug therapy depending on the patient’s clinical situation. This study was approved by the Bioethics Committee of the authors’ institution (2020-P2-019-01) and was in accordance with the guidelines of the Declaration of Helsinki. We have obtained written informed consent from all patients in our previous prospective randomized controlled trial.

In this study, we retrospectively collected data for these patients. Ethical approval exempts informed consent.

Study Population
All participants who had moderate SHPT and received hemodialysis between January 1, 2015 and March 31, 2015, in the previous randomized controlled trial\(^10\) were eligible for inclusion in this study. Eligible patients’ iPTH levels had to be within 300–800 pg/ml, which is in accordance with the Kidney Disease Outcomes Quality Initiative 1 guidelines for diagnosing moderate SHPT. The additional inclusion criteria were: (1) age: 18–75 years, (2) iPTH levels: 300–800 pg/ml, (3) parathyroid nodules detectable on ultrasound, and (4) able to complete at least 12 months of follow-up. The exclusion criteria were: (1) previous parathyroid surgery, including all ablations; (2) previous treatment with a calcimimetic drug within 1 month of the current study; (3) neck surgery within 3 months of the current study; and (4) pregnancy or lactation.

Intervention
Patients in the MWA group received MWA followed by drug therapy; patients in the control group only received drug therapy that followed the clinical practice guidelines.

The MWA procedure was performed as reported previously.\(^10\) Microwave therapy was performed using a KY2000 ablation system (Nanjing Kangyou Applied Research Institute, Nanjing, China), which operates at a frequency of 2450 MHz and is equipped with a 2-mm outer diameter antenna with a 5-mm tip. The procedure is as follows (Figure 1): First, an ultrasound of parathyroid glands was used to determine the blood supply to the parathyroid nodule and the ablation path. Second, after sterilizing the neck, local anesthesia using 2% lidocaine hydrochloride was administered. Next, 5 ml of 2% lidocaine hydrochloride was diluted in 15 ml of normal saline and injected into the area around the parathyroid nodule to develop a heat insulation layer to protect the
adjacent nerves and blood vessels. Third, an ablation needle was inserted into the parathyroid tissue under ultrasound guidance. Ablation was subsequently performed. The MWA power was between 25 and 35 W according to the target nodule size. When hypoechoic signals covered the entire nodule, and no flow signal was detected, ablation was terminated.

Follow Up
In the previous trial, serum iPTH, calcium, and phosphorus levels in all patients were measured every 2 months for the first 12 months. However, in the present study, these measurements were performed every 2 months during the entire study according to the standard medical protocol of the hemodialysis center at the authors’ institute. Patients’ clinical data were collected if any of the following conditions were met: the patient was deceased, was transferred to another hemodialysis center for treatment, or underwent kidney transplant/peritoneal dialysis after December 31, 2019.

Outcomes
The primary outcome was a composite endpoint: (1) the proportion of patients with iPTH levels <300 pg/ml during the efficacy assessment phase (month 4 to the 31st of December, 2019, or until PTX, withdrawal, or death) and (2) differences in iPTH levels between the two groups during the efficacy assessment phase.

The secondary outcomes were: (1) monthly consumption of calcitriol, cinacalcet, and phosphate binders (namely, calcium carbonate, lanthanum carbonate, and sevelamer); (2) comparisons of the mean levels of serum calcium and phosphorus during the efficacy assessment phase; and (3) comparisons of the differences in the incidence of adverse events, namely, all-cause mortality, nonfatal myocardial infarction, and stroke, between the two groups.

Statistical Analysis
Data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 22.0; IBM Corp., Armonk, NY). All continuous variables with a normal distribution are reported as means and standard deviations. Variables with a nonnormal distribution are reported as medians and interquartile ranges. Categorical variables are reported as frequencies.

We used an independent t-test to compare variables with a normal distribution between the two groups, namely, age, dialysis age, baseline iPTH levels, and the size of the parathyroid nodules. The Mann–Whitney U test was used when the distribution was skewed, namely, for the mean doses of calcitriol, calcium carbonate, lanthanum carbonate, sevelamer, and cinacalcet, as well as for the follow-up periods.
The proportions of patients with iPTH levels <300 pg/ml in each group were compared using Fisher’s exact test. Because the measurement data were repeated during the efficacy assessment phase, we used a mixed linear effects model to compare iPTH, calcium, and phosphorus levels between the groups during the efficacy assessment phase.

Results

Study Population
A total of 27 patients receiving hemodialysis were enrolled in this study (Figure 2). There was no statistical difference in gender, age, dialysis age, or other patient characteristics between the MWA and control groups at baseline (Table 1). The MWA group had a slightly higher baseline iPTH level than the control group (564 ± 192 versus 530 ± 144 pg/ml, respectively; \( p = .60 \)).

Outcomes
Primary Outcome
The proportion of patients with iPTH levels <300 pg/ml during the evaluation phase was 46.2% (6/13) and 14.3% (2/14) in the MWA and control groups, respectively (\( p = .08 \)). Comparisons of the iPTH levels during the efficacy assessment phase started from month 4 and ended on December 31, 2019, or on the date of PTX, withdrawal, or death of the patient. The mean iPTH level in the MWA group was lower than that in the control group (411 ± 299 pg/ml versus 516 ± 369 pg/ml, respectively; \( p < .01 \); Figure 3A).

Secondary Outcomes
Only four patients (one in the MWA group and three in the control group) received paricalcitol, which was changed to calcitriol according to the equivalent dosage (1:4). The dosage of calcitriol in the MWA group was slightly lower than that in the control group; however, the difference was not statistically significant (\( p = .11 \)). In addition, there were no differences in the dosage of calcium carbonate (\( p = .30 \)), lanthanum carbonate (\( p = .51 \)), sevelamer (\( p = .68 \)), or cinacalcet (\( p = .73 \)) between the two groups (Table 2).

There was no difference in baseline serum calcium levels between the MWA group and the control group (2.44 ± 0.28 versus 2.58 ± 0.25 mmol/L; \( p = .18 \)). In the efficacy assessment phase, the serum...
calcium level in the MWA group was comparable to that of the control group (2.37 \pm 0.22 versus 2.41 \pm 0.23 mmol/L, respectively; \( p = .45 \); Figure 3C). There was no difference in the baseline serum phosphorus levels between the MWA and control group (1.89 \pm 0.45 versus 2.17 \pm 0.61 mmol/L, respectively; \( p = .19 \)); however, during the efficacy assessment phase, the serum phosphorus level in the MWA group was slightly lower than that in the control group (1.95 \pm 0.50 versus 2.01 \pm 0.55 mmol/L, respectively; \( p = .052 \); Figure 3D).

We also compared the differences in the rates of adverse events, namely, all-cause mortality, nonfatal myocardial infarction, and stroke, between the two groups. Because the total number of adverse events was low, we found no difference between the two groups (\( p = .42 \)). However, the incidence of adverse events was lower in the MWA group than in the control group (4 patients versus 7 patients, respectively; \( p = .42 \); Table 3 and Figure 4).

**Change in iPTH Levels in Three Patients Undergoing PTX**

Three patients in the control group underwent PTX at 8, 10, and 40 months, and these patients’ iPTH levels decreased significantly postoperatively (Table 4).

### Discussion

In this study, although no statistical difference was found for the primary outcome (the proportion of patients with iPTH levels <300 pg/ml), the proportion in the MWA group was higher than that in the control group (46.2 versus 14.3%, respectively; \( p = .08 \)) due to the small sample size. Per the results of this study, MWA cannot effectively reduce iPTH level to below 300 pg/ml. Furthermore, iPTH levels in the MWA group were lower than those in the control group (411 \pm 299 versus 516 \pm 369 pg/ml, respectively; \( p < .01 \)) during the efficacy assessment phase.

This study confirmed what was suggested in the previous trial,\(^{10}\) which stated that MWA is effective in patients who are undergoing hemodialysis for moderate SHPT. There is currently no established indication of MWA for SHPT. Clinically, MWA is generally used for patients with severe SHPT\(^{11}\) according to the indications for PTX in SHPT. However, MWA may be effective in moderate SHPT for the following

| Table 1. Study Participants’ Clinical Baseline Data |
|---------------------------------|--------------------|------------------|
| **MWA Group (N = 13)** | **Control Group (N = 14)** | **p Value** |
| Gender (Male:Female) | 5:8 | 6:8 | 1.00 |
| Age (years) | 54.23 ± 10.96 | 54.62 ± 10.41 | .93 |
| Dialysis age (years) | 9.10 ± 2.27 | 9.32 ± 2.56 | .82 |
| Cause of end-stage renal disease | | | |
| Chronic glomerulonephritis (%) | 6 (46.2) | 7 (50) | | |
| Diabetic nephropathy (%) | 2 (15.4) | 1 (71) | | |
| Hypertensive nephropathy (%) | 1 (7.7) | 3 (21.4) | | |
| Drug-induced kidney damage (%) | 2 (15.4) | 2 (14.3) | | |
| Autosomal dominant polycystic kidney disease (%) | 1 (7.7) | 1 (7.1) | | |
| Unknown (%) | 1 (7.7) | 0 | | |
| iPTH (pg/ml) | 564 ± 192 | 530 ± 144 | .60 |
| Calcium (mmol/L) | 2.44 ± 0.28 | 2.58 ± 0.25 | .18 |
| Phosphate (mmol/L) | 1.89 ± 0.45 | 2.17 ± 0.61 | .19 |
| Alkaline phosphatase (U/L) | 85.46 ± 31.61 | 79.00 ± 20.75 | .53 |
| Number of parathyroid nodules (per patient) | 2.0 (1.0–3.0) | 2.0 (1.0–2.3) | | |
| Number of parathyroid nodules ablated (per patient) | 2.0 (1.0–2.8) | NA | NA |
| Size of parathyroid nodules | | | |
| Maximum diameter (interquartile range; cm) | 1.25 (0.88–1.63) | 0.60 (0.50–0.80) | <.001 |
| Minimum diameter (interquartile range; cm) | 0.70 (0.60–0.83) | 0.50 (0.35–0.60) | <.001 |
| Follow-up period (interquartile range; months) | 58 (54–60) | 58 (49–60) | .56 |

Abbreviations: iPTH, intact parathyroid hormone; MWA, microwave ablation; N, number.
**Figure 3.** Differences in intact parathyroid hormone (iPTH), calcium, and phosphorus levels between the microwave ablation and control groups.

| Study Month | Serum iPTH, pg/mL | Control | Microwave ablation |
|-------------|------------------|---------|--------------------|
| 0           | 200              |         |                    |
| 1           | 400              |         |                    |
| 2           | 600              |         |                    |
| 3           | 800              |         |                    |
| 4           | 1000             |         |                    |
| 5           | 1200             |         |                    |
| 6           | 1400             |         |                    |
| 7           | 1600             |         |                    |
| 8           | 1800             |         |                    |
| 9           | 2000             |         |                    |

| Study Month | Serum Calcium, mmol/L | Control | Microwave ablation |
|-------------|-----------------------|---------|--------------------|
| 0           | 1.0                   |         |                    |
| 1           | 1.5                   |         |                    |
| 2           | 2.0                   |         |                    |
| 3           | 2.5                   |         |                    |
| 4           | 3.0                   |         |                    |
| 5           | 3.5                   |         |                    |
| 6           | 4.0                   |         |                    |

| Study Month | Serum Phosphorus, mmol/L | Control | Microwave ablation |
|-------------|--------------------------|---------|--------------------|
| 0           | 0                        |         |                    |
| 1           | 1                        |         |                    |
| 2           | 2                        |         |                    |
| 3           | 3                        |         |                    |
| 4           | 4                        |         |                    |
| 5           | 5                        |         |                    |
| 6           | 6                        |         |                    |

**Table 2.** Drugs for Chronic Kidney Disease-mineral and Bone Disorders During the Efficacy Assessment Phase

| Drug                                | MWA Group       | Control Group   | p Value |
|-------------------------------------|-----------------|-----------------|---------|
| Calcitriol (μg/month; interquartile range) | 5.3 (2.6–6.1)   | 7.0 (3.9–8.9)   | .11     |
| Calcium carbonate (g/month; interquartile range) | 5.0 (1.6–6.7)   | 3.6 (2.0–4.9)   | .30     |
| Lanthanum carbonate (g/month; interquartile range) | 2.6 (0.3–16.3)  | 1.4 (0–7.8)     | .51     |
| Sevelamer (g/month; interquartile range) | 0 (0–16.3)      | 0 (0–12.9)      | .68     |
| Cinacalcet (mg/month; interquartile range) | 0 (0–175.9)     | 0 (0–25.4)      | .73     |

Abbreviation: MWA, microwave ablation.
reasons. First, MWA is a minimally invasive surgery and is performed under local anesthesia without an operating room, while PTX is performed under general anesthesia in an operating room. The operative time for MWA is generally less than 10 minutes, while PTX generally requires more than 30 minutes. Second, there is still no established indication of PTX for SHPT. Most guidelines recommend that PTX be performed for severe SHPT; however, the KDIGO guidelines recently indicated that severe SHPT can be treated with PTX. However, the guidelines do not define severe SHPT. In the Kidney Disease Outcomes Quality Initiative and Chinese national guidelines, the indication for PTX is patients with severe SHPT who are drug-resistant, and the guidelines define severe SHPT as iPTH levels >800 pg/ml. In the Japanese guidelines, the indication for PTX in SHPT is more aggressive. The guidelines recommend PTX for severe SHPT refractory to medical treatment, and severe SHPT is defined as iPTH levels >500 pg/ml.

In the present study, we performed MWA in patients with moderate SHPT, and patients had at least one enlarged parathyroid gland located at a puncturable site; the observed long-term effect was encouraging.

### Table 3. Adverse Events Occurring During the Efficacy Evaluation

| Adverse Events       | MWA Group (n = 13) | Control Group (n = 14) |
|----------------------|--------------------|------------------------|
| Death, No. (%)       | 3 (23.1)           | 3 (21.4)               |
| Nonfatal stroke, No. (%) | 1 (77)         | 1 (71)                 |
| Nonfatal acute myocardial infarction, No. (%) | 0                 | 3 (21.4)               |
| Total                | 4                  | 7                      |

Abbreviation: MWA, microwave ablation.

### Table 4. iPTH Levels Before and After Parathyroidectomy

|                   | iPTH Before Parathyroidectomy (pg/ml) | iPTH After Parathyroidectomy (pg/ml) |
|-------------------|---------------------------------------|--------------------------------------|
| Case 1            | 730.3 ± 206.6                         | 50.1 ± 36.3                          |
| Case 2            | 1121.4 ± 253.3                        | 131.6 ± 83.1                         |
| Case 3            | 586.3 ± 279.1                         | 70 ± 3.6                             |

Abbreviation: iPTH, intact parathyroid hormone.

MWA has been used to treat SHPT for approximately 10 years. However, although many studies have been performed, most have reported only short-term effects, with follow-up periods of 2–26 months; therefore, the long-term effects are unclear. In the present study, we observed the long-term effects of MWA on SHPT, with a median follow-up of 58 months.

The iPTH level in the MWA group was 105 pg/ml lower than in the control group (411 ± 299 versus 516 ± 369 pg/ml, respectively). This result indicated that MWA was more effective than drug therapy in the long term. Three patients in the drug treatment group eventually developed severe SHPT and finally underwent total PTX. It was found that the iPTH levels in these three patients after PTX were significantly lower than those prior to the operation. This may be related to the strategy employed during a PTX, where the full parathyroid gland is removed (which the three patients received); other related studies have shown similar results. With respect to the effect of total PTX (TPTX) on the long-term survival rate, several studies have different points of view. A study showed that TPTX with auto transplantation (TPTX+AT) and TPTX seem to be safe and equally effective for the treatment of otherwise uncontrollable SHPT. TPTX seems to suppress iPTH more effectively and showed no recurrence after 3 years. The hypothesis that TPTX is
superior to TPTX+AT in terms of the rate of recurrent SHPT should be tested in a large-scale confirmatory trial. Nevertheless, TPTX seems to be a feasible alternative therapeutic option for the surgical treatment of SHPT. Another study31 showed that there was a higher risk of cardiovascular events in patients after TPTX compared with subtotal PTX but a lower risk of recurrent PTX. Second, the patients in this study had moderate SHPT. Drug therapy can control iPTH levels in these patients to a great extent; hence, the advantages of MWA were not noticeable.

There were several limitations to this study. First, the sample size was small. Studies with larger sample sizes are needed to confirm our conclusions. Second, a single practitioner performed the MWA procedures, and other centers may obtain different results.

In conclusion, our pilot study suggested that MWA can decrease iPTH levels in patients undergoing hemodialysis for moderate SHPT. MWA may be indicated in patients with SHPT who are undergoing hemodialysis.

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