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Clinical outcomes of ultrasound-guided radiofrequency ablation for the treatment of primary papillary thyroid microcarcinoma

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AIM: To evaluate the safety, efficacy, and long-term outcomes of ultrasound-guided radiofrequency ablation (RFA) for the treatment of primary papillary thyroid microcarcinoma (PTMC).

MATERIALS AND METHODS: A total of 37 patients with 38 PTMC nodules underwent RFA at a power of 20 W between September 2014 and December 2017. The clinical data of these patients were reviewed retrospectively and analysed. Imaging studies of the nodules were conducted, and the patients' thyroid function was assessed before RFA; 1, 3, 6, and 12 months after RFA; and every 6 months thereafter. The volumes and volume reduction rate (VRR) of the nodules were also calculated.

RESULTS: RFA with a low power of 20 W was used in the treatment of 37 patients with 38 PTMC nodules. All nodules achieved complete ablation, no complications occurred, and thyroid function was not affected. During follow-up, the volume of the nodules gradually decreased. Twelve months after ablation, the mean volumes of the nodules significantly decreased to 0.01±0.03 ml with a VRR of 99.34±3.49%. At a median follow-up of 6 (range: 1–18) months, 37 of the 38 nodules were completely absorbed, and no recurrence was observed in all 37 patients.

CONCLUSIONS: Low-power RFA showed good safety and promising efficacy outcomes for the treatment of PTMC. In addition to surgery and active surveillance, RFA may be an alternative treatment option for patients with PTMC.

Introduction

Papillary thyroid carcinoma is the most common malignancy of the thyroid gland, accounting for 85% of all thyroid cancers.[1] Papillary thyroid microcarcinoma (PTMC), which is defined as a small papillary thyroid carcinoma measuring ≤10 mm in greatest dimension by the World Health Organization (WHO), accounts for approximately 50% of papillary thyroid carcinomas.[2] Currently, with the development

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of high-frequency ultrasonography (US) and physical examination, asymptomatic PTMCs can be diagnosed. Surgery has been recommended as the first-line treatment for PTMC, and a good prognosis is observed[3,4]; however, due to the satisfactory prognosis of PTMC and high complication rate of surgery, minimally invasive treatments with less complications, better quality of life, and even better cosmetic outcomes, are needed.

Thermal ablation, either radiofrequency ablation (RFA) or microwave ablation (MWA), is a safe and effective treatment for liver tumours.[5–7] In addition, in thyroid disease, thermal ablation has been used for benign thyroid nodules, and satisfactory outcomes were achieved.[8–10] Recently, researchers have considered US-guided RFA or MWA in the treatment of PTMCs[11,12]; however, its safety and efficacy, particularly the long-term efficacy of ablation for primary PTMC, still needed to be confirmed. The aim of the present study was to evaluate the safety and efficacy of US-guided low-power RFA for the treatment of primary PTMC with 1-year follow-up.

Materials and methods

Patients

The ethics committee of Renji Hospital approved this retrospective study and written informed consent was obtained from each patient before performing each procedure. From September 2014 to December 2017, 37 patients with PTMC who underwent US-guided RFA at Renji Hospital were enrolled in this study. The inclusion criteria were as follows: (1) patients with confirmed PTMC on US-guided fine-needle aspiration biopsy, (2) those without lymph node metastasis on imaging studies, (3) those with nodules that did not invade the tissues around the thyroid, (4) those without metastasis beyond the neck, (5) those with less than three tumours, (6) those who refused surgery, and (7) and those who were followed-up for at least 6 months.

Preoperative preparation

Before surgery, high-frequency US and contrast-enhanced US were performed using the Twice US system (Esaote, Italy). For each tumour, US was used to evaluate diameter, volume ($V = \pi abc/6$; V: volume; a: transverse diameter; b: vertical diameter; c: anteroposterior diameter), location, morphology, internal architecture, echo type, and microcalcifications. In addition, to evaluate the activity of the tumour, contrast-enhanced US was used to assess the blood supply to the lesion. An experienced US physician (with >20 years of experience in thyroid US) performed all the examinations. Two other investigators (both with >5 years of experience in thyroid US) independently analysed the US imaging data.

In addition, preoperative examinations, such as routine blood tests, coagulation series, thyroid function tests, an electrocardiogram, and chest radiography, were carried out. All patients received treatment while under general anaesthesia in the operating room during the daytime. For tumours located within 2 mm around the surrounding tissues, the hydrodissection technique was used before ablation to improve safety.[13]

RFA

Under guidance with US, RFA was performed in the operating room by one ultrasound intervention doctor with >5 years of thyroid RFA experience. A radiofrequency generator (MedSphere RF Generator S-500, Shanghai, China) and an 18-G (outer diameter) electrode (MEDSPHERE, Shanghai, China, Catalogue number: 10–141361) with a 0.5-cm active tip were used. The radiofrequency power was set to 20 W. The patient's blood pressure, blood O_2 saturation, heart rate, and electrical activity of the heart were monitored during the whole procedure.

Patients were placed in supine position with pillows under the shoulder and neck to extend the neck. After regular disinfection, methylprednisolone (40 mg) was administrated before ablation to prevent glandular dilatation or thyroid crisis. The trans-isthmic approach was used, and the insertion path was designed based on the location of the tumour in relation to the surrounding tissues. For tumours located within 2 mm of the surrounding tissues (including recurrent laryngeal nerve, anterior cervical muscles, trachea, oesophagus, common carotid artery, internal jugular vein, parathyroid glands, cervical sympathetic trunk, and vagus nerve), sterile water was injected using another needle to completely separate the tumour and the critical surrounding tissues.[14] After RFA commenced, vaporisation was observed around the electrode until the tumour was completely covered by a transient hyperechoic zone. The efficacy of RFA was then evaluated on contrast-enhanced US. If there were some areas of reinforcement within the nodules, timely supplemental ablation was performed to prevent residual tumour.

Postoperative evaluation and follow-up

After ablation, any discomfort or complication was observed. The patients were followed-up at 1, 3, 6, and every 6 months thereafter. The size, volume, internal echo, and colour flow of the residual thyroid tissues were evaluated on contrast-enhanced US, whereas the thyroid function indexes were also examined during each follow-up assessment. Complete ablation was defined as no contrast agent perfusion after the injection of ultrasound contrast agent (SonoVue) in the postoperative thyroid nodules at the 1-month postoperative assessment. During follow-up, the volume of ablated nodules was compared to that of the last follow-up. If the volume of a nodule was larger than that of the last follow-up, it was assumed that active tumour cells might exist, and other treatments would be recommended. If the nodules decreased in size or even absorbed, the risk of recurrence would be low, and the nodules need not to be treated. Nodules absorbed in the ablation areas leaving only a linear scar and those with volumes that could not be calculated were considered as completely absorbed nodules. Therefore, in the present study, the volume reduction

ratio (VRR) and complete absorption were used to evaluate patient outcomes.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences software version 22.0 (IBM, Armonk, NY, USA). Continuous valuables were expressed as mean and standard deviation (SD), whereas categorical variables were expressed as number and percentage. Paired-sample *t*-test was used in the statistical analysis. A *p*-value of <0.05 was considered statistically significant.

Results

Characteristics of the patients

A total of 37 patients with 38 tumours were included in the study. The mean age of the participants was 45.14±12.96 (range: 26–77) years. Among the 37 patients, 36 had a single tumour, and one patient had two tumours. The mean largest diameter was 7.36±4.13 mm. The mean volume was 0.12±0.10 (range: 0.01–0.40) ml. Detailed characteristics of the patients and tumours are summarised in Table 1.

Safety

For all tumours, RFA was performed with a power of 20 W. The ablation time ranged from 20 to 120 seconds. All patients tolerated the therapy well, and no complications, e.g., large haematomas requiring admission or monitoring, thyroid storm, or skin burns, were observed. In addition, the thyroid function of the patients was not affected by the ablation treatment. Although the mean levels of free thyroxine (FT4) significantly increased during the first day after ablation, it reduced to normal levels 1 month after ablation without any treatments. The mean free triiodothyronine (FT3) and thyroid stimulating hormone (TSH) levels were within the normal range both before and after ablation, and they were not affected by the treatment.

Table 1
General characteristics of the patients.

Characteristics	Results
Patients (*n*)	37
Age, years	
Mean±SD (range)	45.14±12.96 (26–77)
Gender (male/female)	8 (21.62%)/29 (78.38%)
History of surgery (yes/no)	3 (8.11)/34 (91.89%)
No. of tumours, *n*	
single/multiple	36 (97.30%)/1 (2.70%)
Largest diameter, mm	
Mean±SD (range)	6.77±1.92 (3–10)
Volume, ml	
Mean±SD (range)	0.12±0.10 (0.01–0.40)
Thyroid function, mean±SD (range)	
FT3 level (pmol/l)	4.92±0.44 (3.58–5.80)
FT4 level (pmol/l)	15.60±1.67 (12.82–19.76)
TSH level (mIU/l)	1.68±0.76 (0.40–3.60)
TG-AB level (IU/ml)	51.16±123.55 (0.12–649.97)
TPO-Ab level (IU/ml)	41.59±96.24 (5.21–562.03)
TRAb level (IU/l)	0.36±0.11 (0.30–0.80)

SD, standard deviation; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TG-AB, thyroid globulin antibodies; TPO-Ab, thyroid peroxidase antibody; TRAb, thyrotropin receptor antibodies.

Efficacy

After ablation, all nodules had achieved complete ablation, and no nodules required repeat RFA. Due to the significantly large ablation areas, the mean nodule volume immediately after RFA was 0.37±0.26ml, which was significantly larger than that before ablation ($p<0.001$). In addition, the nodules gradually decreased in size during follow-up. Twelve months after ablation, the mean nodule volume significantly decreased to 0.01±0.03ml ($p<0.001$) with a mean VRR of 99.34±3.49%. The changes in mean volume and VRR at each follow-up point after RFA are shown in Table 2.

Follow-up

By the end of June 2018, 37 of 38 nodules were completely absorbed (range: 1–18 months; Fig 1). The tumour disappearance time curve is presented in Fig 2. Only one nodule did not disappear during the last follow-up at 12 months. Twelve months after ablation, the nodule volume decreased to 0.17 ml with a VRR of 81.52%. In addition, no recurrent nodules and cervical lymph node metastasis were observed on US, and no distant metastasis was found on the CT or US examinations.

Discussion

With the increasing use of neck US and fine-needle aspiration biopsy, the number of individuals diagnosed with PTMC has increased in recent years. Currently,

Table 2
Mean volume and reduction rate of the tumours after RFA.

Time	Volume of the ablation area (ml)		Volume reduction rate[a] (%)
	Mean±SD	*p*-Value[b] (versus pre-ablation)	Mean±SD (versus immediately after RFA)
Pre-ablation	0.12±0.10	—	—
Immediately after RFA	0.37±0.26	<0.001	—
1 month after RFA	0.20±0.21	0.016	23.09±161.15
3 months after RFA	0.11±0.21	0.729	51.89±160.10
6 months after RFA	0.01±0.04	<0.001	97.31±6.35
12 months after RFA	0.01±0.03	<0.001	99.34±3.49

[a] VRR (%)=(initial volume (ml)-final volume (ml))/initial volume (ml)×100%.
[b] *p*-Value was calculated using paired-samples *t*-test.

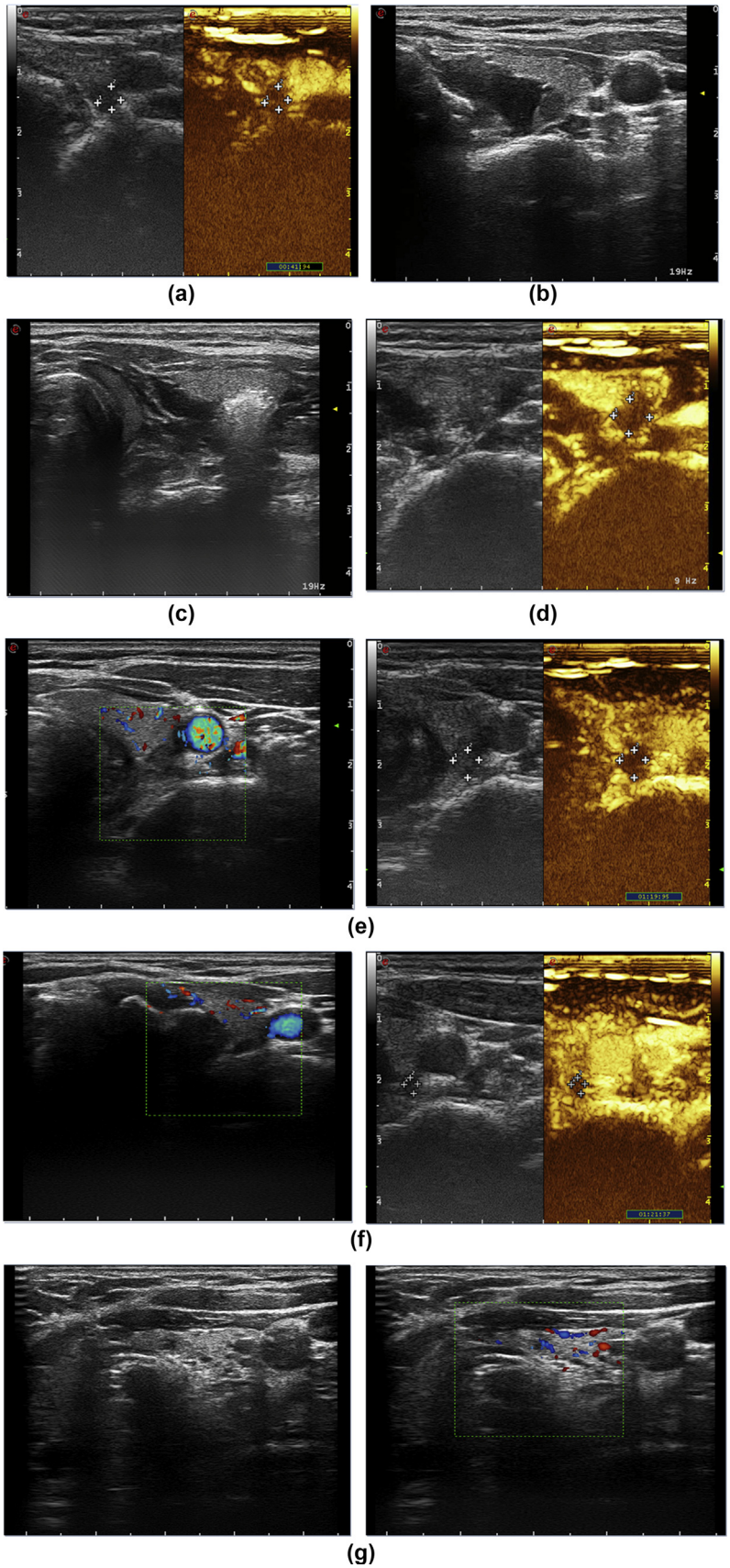

Figure 1 A patient with PTMC located close to the surrounding tissues. (a) Preoperative US. (b) Hydrodissection before ablation. (c) RFA ablation. (d) US immediately after ablation. (e) US 1 month after ablation. (f) US 3 months after ablation. (g) US 6 months after ablation.

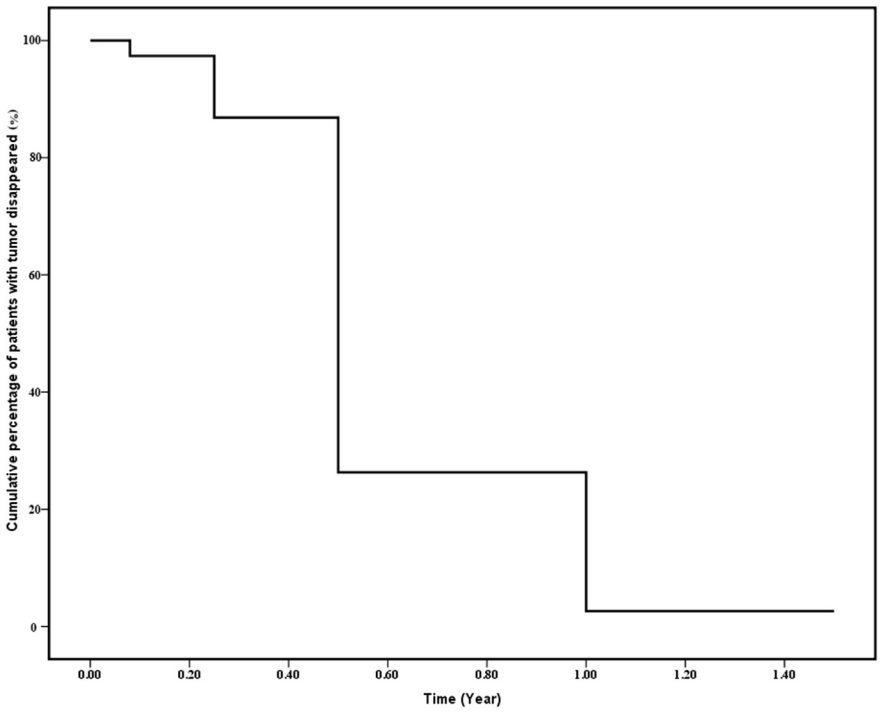

Figure 2 Tumour disappearance time curve after ablation.

surgery is considered as the primary treatment because it can completely remove the tumour and metastatic lymph nodes; however, surgery can cause complications. After surgery for PTMC, the incidence rates of hypothyroidism, recurrent laryngeal nerve injury, and permanent hypocalcaemia were 5–49%, 0.2–1.1%, and 1%, respectively.[15–18] In addition, some patients find it hard to accept the permanent scar resulting from a thyroidectomy. In fact, the management of papillary thyroid cancer is highly controversial, and there are genuine concerns regarding the overtreatment of small cancers that are unlikely to cause any harm, particularly for PTMC, which is of small size. Some researchers have confirmed that patients with PTMC had similar prognosis regardless if they underwent aggressive treatments or not, and most of these patients should be observed clinically.[19,20] In addition, Ito *et al.*[21] and Oda *et al.*[22] monitored small papillary thyroid cancers, and reported no increase in mortality in patients undergoing active surveillance compared to those who underwent immediate surgery was recorded for approximately 10 years; however, this requires the patients to have strong psychological endurance and excellent compliance.

As a minimally invasive treatment, RFA and MWA have been used in the treatment of thyroid nodules, papillary thyroid carcinoma, and recurrent thyroid cancers.[11,12,23–27] Zhang *et al.*[11] suggested that RFA could effectively treat low-risk PTMC with an extremely small complication rate, and approximately 23.5% (23/98) of nodules resolved after a mean follow-up of 7.8±2.9 months. Teng *et al.*[12] evaluated the long-term outcomes of MWA in patients with PTMC. The mean VRR was 98.78±5.61% at 6 months follow-up, and 95.2% of the nodules were completely absorbed; however, the long-term efficacy of RFA for PTMC must be confirmed. In this study, RFA with a low power of 20 W was used in the treatment of 37 patients with 38 PTMC nodules. RFA proved to be an effective treatment for PTMC. After ablation, all nodules achieved complete ablation, no complications occurred, and the thyroid function of the patients was not affected. During follow-up, the volume of the nodules decreased gradually, and the VRR 12 months after ablation was 99.34±3.49%. In June 2018, 37 of the 38 nodules were completely absorbed, and no recurrent nodule was found in all 37 patients.

This study has some limitations. First, this was a single-centre study, and only 37 patients with 38 nodules were included. Second, the follow-up data were analysed after only 12 months. Third, the cost of treatment and follow-up examinations must be considered. Currently, the optimal follow-up for patients who undergo RFA for thyroid cancer remains unknown. How often and how long patients who have undergone RFA should undergo US surveillance must be assessed. Therefore, multicentre studies with a higher number of patients and long-term follow-up must be conducted in the future to confirm the safety, efficacy, and costs of RFA for PTMC.

In conclusion, treatment with low-power RFA is safe and effective, and the intermediate-term outcomes of patients with PTMC are satisfactory. Thus, low-power RFA could be another treatment option for PTMC in addition to surgery and active monitoring.

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Disclosure statement

The authors have no conflicts of interest to declare.

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