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Effect of Hashimoto's thyroiditis on the extent of the ablation zone in early stages of ultrasound-guided radiofrequency ablation for papillary thyroid microcarcinoma: a large cohort study of 772 patients

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ABSTRACT

Purpose: To evaluate the effect of Hashimoto's thyroiditis (HT) on the extent of ablation zone in ultrasound (US)-guided radiofrequency ablation (RFA) for early stages of papillary thyroid microcarcinoma (PTMC).

Method: We selected 772 patients with 797 PTMCs who underwent with RFA from August 2017 to August 2020. They were subdivided into two groups as follows: (i) 216 patients (224 PTMCs) with HT in the 'HT + PTMC' group and (ii) 556 patients (573 PTMCs) with healthy thyroid in the 'PTMC' group. We assessed the extent (maximum diameter and volume) of the ablation zone by contrast-enhanced ultrasound (CEUS) immediately, one day, and 1 week following RFA.

Results: The ablation zone of the 'HT + PTMC' group was smaller than that of the 'PTMC' group at 1 week of RFA (maximum diameter: 14.6 ± 3.1 mm vs. 15.2 ± 3.2 mm and volume: 0.932 ± 0.498 mL vs. 1.028 ± 0.540 mL, respectively, $p < .05$). However, there were no differences before, immediately, and one day post-RFA ($p > .05$). Life-threatening complications did not develop in any of the patients.

Conclusion: RFA-treated PTMCs were smaller in size in patients with HT than in those with a healthy thyroid at 1 week of RFA. However, the exact mechanism underlying this phenomenon and its clinical significance warrant further investigation.

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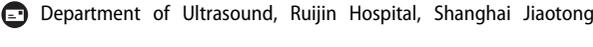
Radiofrequency ablation; Hashimoto's thyroiditis; papillary thyroid microcarcinoma; contrast-enhanced ultrasound; ablation zone

Introduction

The widespread use of high-frequency ultrasound (US) has rapidly increased the incidence of thyroid cancer (TC). In the United States, the incidence increased by 211% between 1975 and 2013 [1], whereas it revealed a trend of rapid growth during 2005–2015 in China [2]. The primary reason for this phenomenon is the increasing incidence of papillary thyroid microcarcinoma (PTMC) [3]. Papillary thyroid carcinoma (PTC) is the most common and inert histological subtype of TC [4]. PTMC is defined as PTC with a maximum diameter ≤ 10 mm [5]. Thyroidectomy is the standard treatment for PTMC; however, active surveillance (AS) may be used for low-risk PTMC [6,7]. Moreover, the 2015 American Thyroid Association (ATA) recommended AS for low-risk PTMC [8]. AS prevents the risks of surgery in some patients; however, anxiety over possible metastasis by clinicians and patients hinders its implementation [9]. The aforementioned strategies also cause a dilemma for clinicians and patients during treatment selection. However, US-guided thermal ablation (TA), including radiofrequency ablation (RFA), laser ablation (LA), and microwave ablation (MWA), has demonstrated satisfactory efficacy and safety in PTMC treatment [10].

Hashimoto's thyroiditis (HT) is closely related to PTC [11,12], and approximately 1/3 cases of PTC are concurrent with HT [13,14]. HT is known as chronic autoimmune thyroiditis and chronic lymphocytic thyroiditis (CLT), caused by the destruction of thyroid cells by antibodies or immune cell-mediated cytotoxicity. This results in morphological and microscopic changes in the thyroid gland, including pathophysiologic changes, such as enlarged thyroid morphology, inflammatory cell infiltration, fibrous tissue hyperplasia, calcification, and vascular hyperplasia [15].

Researchers have extensively investigated the use of RFA in solid tumors of the liver [16]. Low thermal conductivity of the background tissue is conducive to achieving a higher temperature within a defined ablation target [17,18], termed 'the oven effect.' For example, low thermal conductivity of cirrhosis would benefit the efficacy of RFA for liver tumors [19]. Similarly, the efficiency of RFA may increase in patients with extrarenal renal cell carcinoma surrounding the perirenal fat and bone tumor around the cortical bone [20]. There are reports on differences in the ablation size of RFA between liver cirrhosis and normal liver background [21]. Considering the differences between HT and normal thyroid parenchyma, we assume that variations in the range of

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ablation zone of RFA for PTMC exist between patients with HT and those with a healthy thyroid.

We aimed to evaluate the effect of HT on the extent of the ablation zone in early stage in US-guided RFA for PTMC.

Materials and methods

Patients

This prospective study was approved by medical ethics committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China (protocol number: KY2017-125). All patients provided written informed consent for the TA of PTMC before RFA. The inclusion criteria were as follows: (1) nodules confirmed as PTC on cytology by US-guided fine-needle aspiration; (2) the maximum diameter of the nodule ≤ 1 cm; (3) less than two PTC tumors; (4) no capsular infiltration and extrathyroidal invasion; (5) no sign of lymph node metastasis on clinical examination; and (6) inability or the refusal of surgery. The exclusion criteria were as follows: (1) severe coagulation disorders; (2) respiratory failure, myocardial infarction, or other serious systemic diseases; (3) impaired neck extension; (4) contralateral vocal cord paralysis; (5) the fusion of two ablation regions following ablation; and (6) re-ablation owing to suspicious residuals following the initial ablation.

Figure 1 depicts the selection procedure for this study. A total of 788 patients with PTMC were treated with US-guided RFA from August 2017 to August 2020. Of the 16 patients excluded from the study, six were lost to follow-up (did not participate in the follow-up within 1 week after RFA), three had two lesions and the fusion of the two ablation foci occurred after RFA, and seven were re-ablated because of

suspicious residuals following the first ablation. Eventually, we analyzed 772 patients with 797 PTMCs treated with RFA. There were 621 women and 151 men, with an average age of 40.8 ± 11.0 years (range 19–74 years). Patients were divided into two groups as follows: (i) 216 patients (224 PTMCs) with HT in the 'HT + PTMC' group and (ii) 556 patients (573 PTMCs) with healthy thyroid in the 'PTMC' group.

HT was diagnosed by combining high-frequency US with serological examinations. High-frequency US of the thyroid revealed diffuse hypoechoic thyroid parenchyma. Serum examination displayed positive thyroid peroxidase antibody (TPOAb) or thyroglobulin antibody (TgAb) [15].

Pre-ablation assessment

All patients completed preoperative examinations, including thyroid US, laboratory examinations, electrocardiography (ECG), and laryngoscopy. All US scans were obtained with commercial US scanners (Mindray Resona 7 and 8, Shenzhen, China) equipped with 9–14 MHz linear array transducer probes. During US examinations, two radiologists (J.Q.Z. and Y.J.D.) with >15 years of experience in thyroid US carefully evaluated the position, size, and volume of the nodules.

Laboratory examinations consisted of serum thyroid stimulating hormone, triiodothyronine (T3), thyroxine (T4), free T3, free T4, TPOAb (negative <5.61 IU/mL), TgAb (negative <4.11 IU/mL), and blood coagulation test platelet count (including prothrombin time and activated partial thromboplastin time).

RF ablation procedures

One operator (J.Q.Z.) performed all RFA procedures in the outpatient department. The patients were placed in a supine

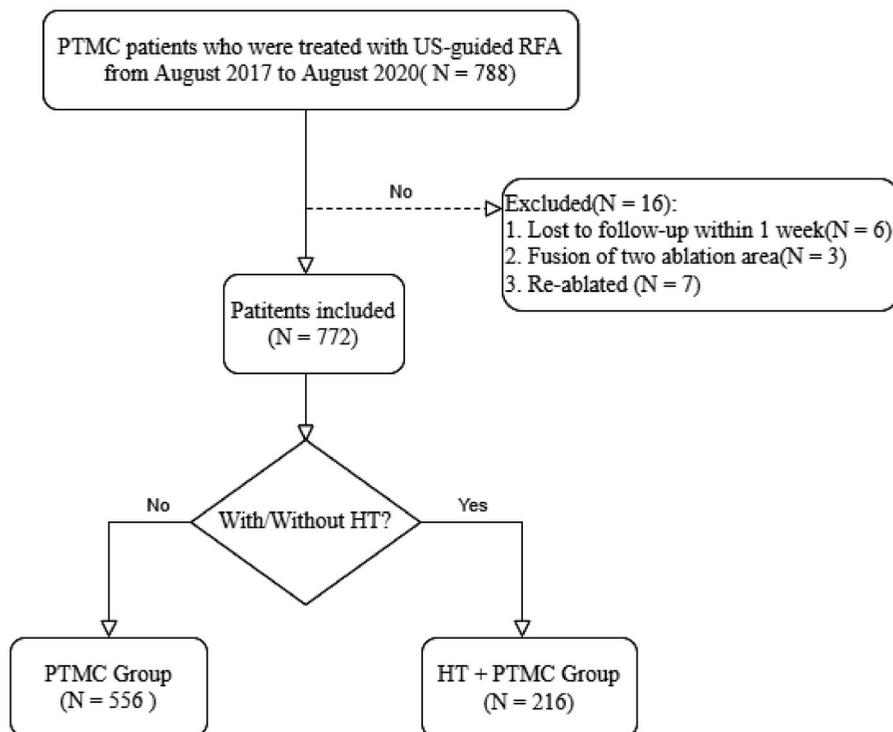


Figure 1. Flow diagram of the study selection procedure.

position with their neck extended. A multi-parameter device was connected to continuously monitor their ECG, noninvasive blood pressure, oxygen saturation, and pulse. An intravenous catheter was inserted into the superficial vein of the upper limb. We used a radiofrequency generator (VIVA RF generator, STARmed, Goyang, South Korea, and VRS01; RF Medical, Seoul, South Korea) and an 18-gauge thyroid-dedicated internally cooled electrode with a 10-mm exposure tip (Star RF Electrode_Fixed, STARmed; VIVA RF System, Goyang, South Korea).

Following local anesthesia with 2% lidocaine, 0.9% sodium chloride solution was injected around the thyroid gland to preserve important structures surrounding the ablation, such as the trachea, esophagus, recurrent laryngeal nerves, and carotid artery. Under real-time US guidance, an 18-gauge ablation needle was inserted into the target tumor and the ablation power was set to 65 W according to the literature [22].

In this study, single- or multi-point fixed ablation technology was used. Multi-point ablation was sometimes used in order to completely cover the tumor in three-dimensional space with the hyperechoic zone produced by ablation. The ablation process can be stopped only after the lesion was completely covered with a hyperechoic zone caused by vaporization in three-dimensional space on gray-scale US [23]. Simultaneously, the needle track was ablated to avoid the metastasis of tumor cells along the needle channel. The ablation energy of each nodule was subsequently recorded.

Conventional ultrasound and contrast-enhanced ultrasound (CEUS)

We used B-mode US, Color Doppler US, and CEUS to evaluate the ablation zone immediately, one day, and 1 week following ablation. B-mode US and Color Doppler US principally focused on morphological changes and complications, such as hematoma, in the ablation area. We used CEUS to assess the extent of the ablation area. All CEUS were performed using sulfur hexafluoride-filled microbubbles (SonoVue, Bracco, Milan, Italy). All dynamic and static US images were digitally stored on the hard disk of the US scanner and uploaded to the picture archiving and communication systems for subsequent analysis.

All nodules were measured with three orthogonal diameters (length, width, and thickness) in CEUS graphs. Their volumes were evaluated using the following formula: $V = \pi ABC/6$ (where V is the volume, A is the length, and B and C are the remaining two vertical diameters). The post-ablation follow-up was performed by our team, each of whom had undergone standardized training to minimize inter-operator variation.

Statistical analysis

We used SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL) to analyze the results. All data are expressed as the mean \pm standard deviation. We analyzed categorical variables, such as sex and continuous variables, such as the age, ablation

Table 1. The demographic and ablation data of the selected patients and lesions.

| | Total | PTMC | HT + PTMC | <i>p</i> Value |
|------------------------|-------------------|-------------------|-------------------|----------------|
| Patients | 772 | 556 | 216 | |
| Lesions | 797 | 573 | 224 | |
| Age (years) | 40.8 \pm 11.0 | 41.5 \pm 11.1 | 38.8 \pm 10.5 | .001 |
| Gender | | | | .000 |
| Male | 151 (19.56%) | 132 (23.74%) | 19 (8.8%) | |
| Female | 621 (80.44%) | 424 (76.26%) | 197 (91.2%) | |
| Maximum diameters (mm) | 5.6 \pm 1.8 | 5.5 \pm 1.8 | 5.6 \pm 1.8 | .466 |
| Volumes (mL) | 0.078 \pm 0.078 | 0.078 \pm 0.079 | 0.078 \pm 0.073 | .775 |
| Ablation time (s) | 62.6 \pm 42.7 | 61.1 \pm 42.7 | 66.2 \pm 55.5 | .714 |
| Ablation energy (kJ) | 1.904 \pm 1.576 | 1.880 \pm 1.485 | 1.966 \pm 1.792 | .735 |

PTMC: papillary thyroid micro-carcinoma; HT: Hashimoto's thyroiditis.

energy, maximum diameter, and volume, using the chi-square test and two independent samples nonparametric tests (Mann-Whitney's U test), respectively. Differences were considered statistically significant at p values $<.05$.

Results

Patients and ablation data

Table 1 summarizes the demographic and ablation data of the selected patients and their lesions. There were significant differences in sex and age ($p < .05$) between the 'PTMC' group and 'HT + PTMC' group. Patients in the 'HT + PTMC' group were younger than those in the 'PTMC' group (38.8 \pm 10.5 years vs. 41.5 \pm 11.1 years, $p = .001$). The proportion of women was higher in the 'HT + PTMC' group than that in the 'PTMC' group (91.2%, 197/216 $>$ 76.26%, 424/556, $p = .000$). The ablation energies and ablation time of the 'PTMC' and 'HT + PTMC' groups were 1.880 \pm 1.485 kJ and 1.966 \pm 1.792 kJ and 61.1 \pm 42.7 s and 66.2 \pm 55.5 s, respectively (both $p > .05$). The initial maximum tumor diameters and tumor volumes in the 'PTMC' and 'HT + PTMC' groups were 5.5 \pm 1.8 mm and 5.6 \pm 1.8 mm and 0.078 \pm 0.079 mL and 0.078 \pm 0.073 mL, respectively, without significant differences ($p > .05$).

Maximum diameter and lesion volume

In all cases, the tumor nodules were completely covered by the ablation areas. The maximum diameters and volumes of the ablation zone 1 week following RFA were significantly larger than those before ablation. The maximum diameters and volumes of the ablation zone reached the peak one day post-RFA (Figures 2–4). There were no significant differences between the 'PTMC' and 'HT + PTMC' groups in the maximum diameter immediately and one day post-RFA (14.0 \pm 2.6 vs. 14.0 \pm 2.5 mm, 16.1 \pm 3.1 vs. 15.8 \pm 3.2 mm, respectively, $p > .05$ for both). However, the maximum diameter 1 week post-RFA in the 'HT + PTMC' group was significantly smaller than that in the 'PTMC' group (14.6 \pm 3.1 vs. 15.2 \pm 3.2 mm, respectively, $p = .005$) (Table 2, Figure 2).

Similarly, there were no significant differences in the ablation volume between the 'PTMC' and 'HT + PTMC' groups immediately and one day post-RFA (0.838 \pm 0.426 vs. 0.841 \pm 0.434 mL, 1.259 \pm 0.624 vs. 1.214 \pm 0.629 mL,

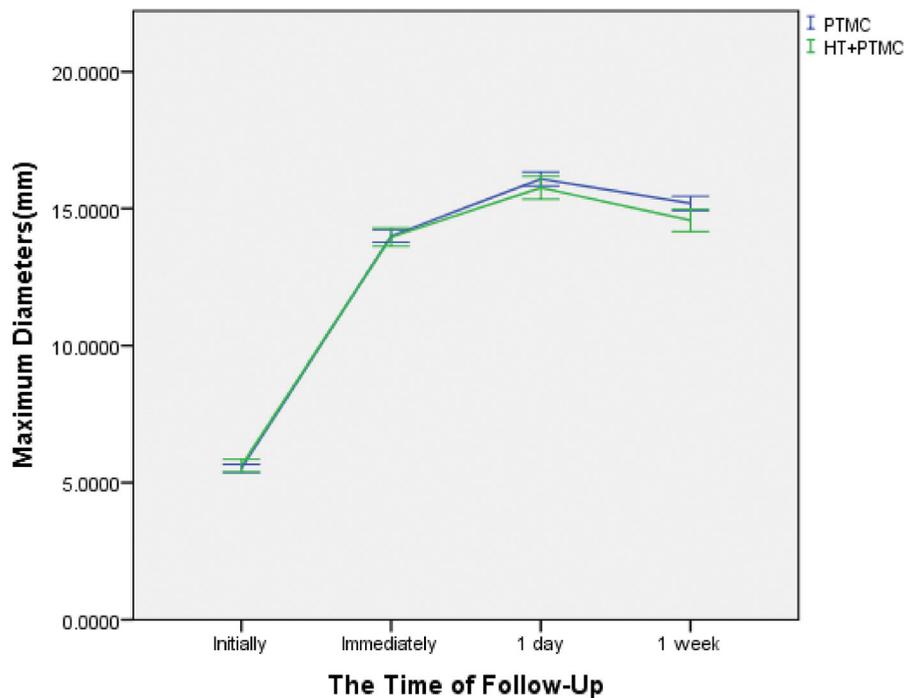


Figure 2. Changes in maximum diameters in PTMC cases with/without HT. Error bar: 95% confidence interval; PTMC: papillary thyroid microcarcinoma; HT: Hashimoto's thyroiditis.

Table 2. The maximum diameters of the lesion before and after RFA (mm).

| Time | PTMC | | HT + PTMC | | <i>p</i> Value |
|-------------|-------------|----------|-------------|----------|----------------|
| | Mean ± SD | Range | Mean ± SD | Range | |
| Initially | 5.5 ± 1.8 | 1.8–10.0 | 5.6 ± 1.8 | 2.1–10.0 | .466 |
| Immediately | 14.0 ± 2.6* | 7.6–24.3 | 14.0 ± 2.5* | 7.6–24.3 | .890 |
| One day | 16.1 ± 3.1* | 8.9–30.4 | 15.8 ± 3.2* | 7.6–28.9 | .076 |
| One week | 15.2 ± 3.2* | 5.9–28.4 | 14.6 ± 3.1* | 4.7–27.9 | .005 |

*Means *p* value <.05 (compared with the initial maximum diameters).

Table 3. The volumes of the lesion before and after RFA (mL).

| Time | PTMC | | HT + PTMC | | <i>p</i> Value |
|-------------|----------------|------------|----------------|-----------|----------------|
| | Mean ± SD | Range | Mean ± SD | Range | |
| Initially | 0.078 ± 0.079 | 0.003–0.99 | 0.078 ± 0.073 | 0.01–0.34 | .775 |
| Immediately | 0.838 ± 0.426* | 0.05–4.72 | 0.841 ± 0.434* | 0.14–2.63 | .633 |
| One day | 1.259 ± 0.624* | 0.23–4.84 | 1.214 ± 0.629* | 0.14–4.02 | .189 |
| One week | 1.028 ± 0.540* | 0.05–4.12 | 0.932 ± 0.498* | 0.03–3.29 | .007 |

*Means *p* value <.05 (compared with the initial volumes).

respectively, $p > .05$ for both). However, the volume at 1 week post-RFA in the 'HT + PTMC' group was significantly smaller than that in the 'PTMC' group (1.028 ± 0.540 vs. 0.932 ± 0.498 mL, respectively, $p = .007$) (Table 3, Figure 3).

Complications

Life-threatening complications did not occur in any patient. Seventeen patients experienced hoarseness following RFA. Of these patients, 16 recovered after 1 week to 3 months without any special treatment, whereas one did not recover after 6 months. Laryngoscopy examinations revealed fixation of one vocal cord. In addition, two patients had postoperative hematomas, fixed hemostasis was used, and absorption was recovered naturally. Rashes and pain occurred in one patient

each. There was no evidence for the recurrence of ablated areas within 1 week of the follow-up.

Discussion

TA uses extremely high or low temperatures to cause protein denaturation, irreversible cell damage, and coagulative necrosis of the tumor cells [20,24]. TA has become a promising treatment for several types of tumors [25], such as liver [26], kidney [27,28], bone [29], and lung tumors [30]. RFA, MWA, and LA are the most common techniques used in clinical practice.

Rossi et al. and McGahan et al. [31,32] first reported on a study on RFA for liver tumors in animal models in 1990. In 1994, Seki et al. [33] reported on a preliminary study on US-guided percutaneous microwaves for human liver cancer (≤ 2 cm maximum diameter). In 1985, Ohyama et al. [34] developed the contact Nd-YAG laser system with ceramic rods and applied it to head and neck tumors. In 1995, Anzai et al. [35] published the first report on RFA in humans for the treatment of cerebral tumors. Pacella et al. [36] first reported on the use of percutaneous LA for human untreatable recurrent TC in 2000, whereas Dupuy et al. [37] reported on the use of RFA for locally recurrent lesions of well-differentiated TC in 2001. In 2006, Kim et al. [38] used RFA to treat 35 cold benign thyroid nodules, which relieved mass-related symptoms without damaging thyroid function and severe complications.

RFA is a safe, cost-effective, and minimally invasive procedure for treating benign and/or malignant thyroid nodules [39]. TA significantly reduces the volume of benign thyroid tumor or eliminates it by avoiding thyroidectomy and hypothyroidism [40–42]. Numerous studies on TC treatment have

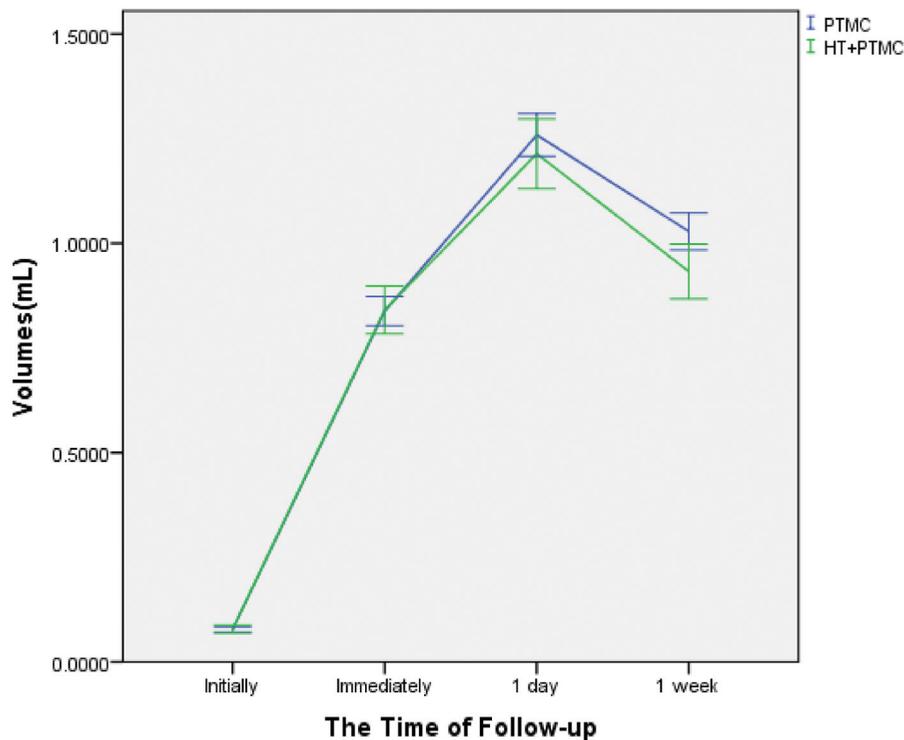


Figure 3. Changes in volumes in PTMC cases with/without HT. Error bar: 95% confidence interval; PTMC: papillary thyroid microcarcinoma; HT: Hashimoto's thyroiditis.

verified the safety and feasibility of US-guided TA for low-risk PTMC [43–46]. In a recent multicenter study, Cao et al. [47] reported on the efficacy and safety of TA in patients with isolated T1bN0M0 PTC. Moreover, a recent meta-analysis reported that TA for PTC was as effective, secure, and economical as conventional surgery [48].

CEUS is considered a valuable tool for assessing ablation zones. It facilitates identifying tumor sites that are not adequately covered by ablation. Therefore, early ablation can be supplemented in time to reduce the risk of recurrence [49–51]. CEUS is useful to assess the efficacy of ablation by displaying the parenchyma microvasculature and assessing angiogenesis and tissue perfusion using contrast agents [52]. Therefore, we used CEUS to accurately measure the extent of ablation lesions.

PTC is associated with HT [11,12], which is the most common inflammatory thyroid disease. It is principally characterized by lymphocyte infiltration, fibrosis, and atrophy of the thyroid parenchyma [15]. The blood supply characteristics and histology of the thyroid parenchyma in HT differ from those of the normal thyroid, which may affect the efficacy of RFA for PTC. However, few studies have been conducted to understand this further. Zhang et al. [23] compared the effects of RFA for PTMC with/without HT using 60 cases of PTMC, and concluded that the recovery of patients with PTMC in combination with HT following ablation was similar to those with PTMC alone. However, their sample size was considerably small ($n=60$) and data were compared during 1–18 months follow-up. Moreover, there is limited research on differences in the early stage. However, we used a higher sample size to study the effects of HT on the extent of RFA of PTMC in the early stage (within 1 week).

Previous studies have found that the ablation zone could be differentiated macro- and micro-morphologically into central zone with coagulation necrosis and peripheral zone with dilated sinusoid and congestion of erythrocytes, perhaps with inflammation or edema, adjacent to the unaffected tissue [53,54]. Low thermal conductivity of the thyroid fibrous tissue in HT may exert an effect similar to 'the oven effect,' [16] which accumulated heat in the lesions, thus limiting the degree of inflammation or edema in the peripheral zone. Moreover, the increase of thyroid blood supply in HT may accelerate the absorption of inflammation and edema, as well as the regression of dilated sinusoid and congestion of erythrocytes in peripheral zone. This may explain that the maximum diameters and volumes of the ablation zone in the 'HT + PTMC' group were smaller than those in the 'PTMC' group at 1 week post-RFA, while there were no differences immediately, and one day following the RFA.

The present study had some limitations. First, this was a single-center, prospective study. Second, the maximum diameter and volume of the ablation zone were smaller in the 'HT + PTMC' group than that in the 'PTMC' group; however, our follow-up time was insufficient to determine if the smaller ablation zone increased the recurrence rate of HT + PTMC. Third, we did not collect information on the volume of the treatment lobe, which may be affected by diffuse diseases, such as HT. Patients with HT often have smaller thyroid glands; therefore, nodules near the thyroid capsule are more likely to be present. In these nodules, the ablation zone may be smaller for purely geometric reasons. Our results should be confirmed by more multicenter and prospective studies with larger sample size. In addition, a relatively high ablation power, i.e., 65 W, was used in this study.

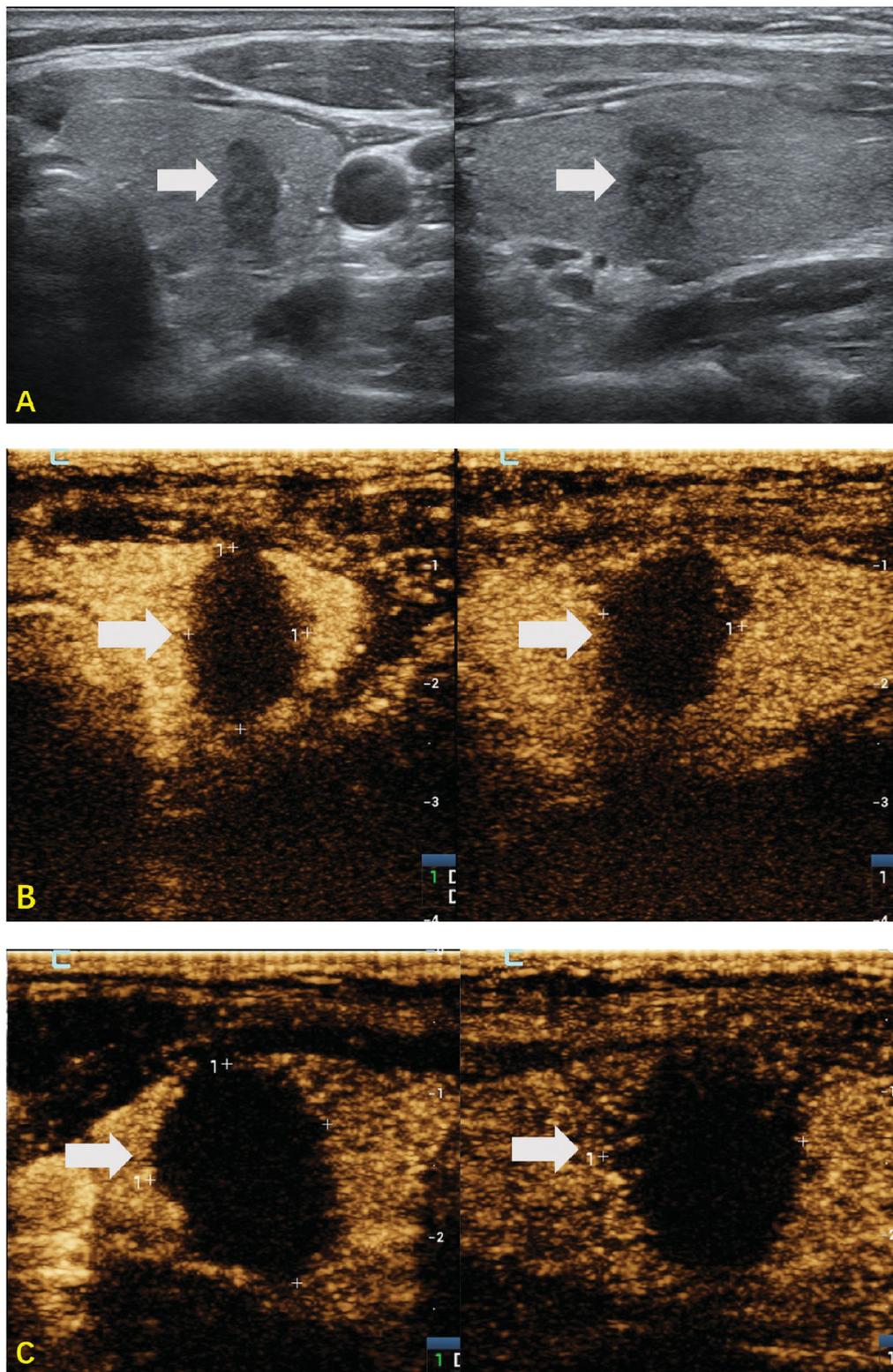


Figure 4. Representative case of RFA-treated PTMC with HT within 1 week in a 29-year-old woman. High-frequency US of the thyroid revealed diffuse hypoechoic thyroid parenchyma and a nodule in the middle of the right thyroid. The nodule was confirmed as PTC on cytology by US-guided fine-needle aspiration. (A) The sonograms of the nodule before RFA, including transverse section and longitudinal section (size: $5.0 \times 9.5 \times 6.7$ mm, the volume about 0.17 mL); (B) the sonograms immediately after RFA (including the gray-scale US and CEUS of transverse and longitudinal sections), showed that no contrast was filling in the ablation area (size: $10.1 \times 15.3 \times 11.8$ mm, the volume about 0.69 mL); (C) the sonograms at one day of RFA (including the gray-scale US and CEUS of transverse and longitudinal sections), showed that there was no contrast filling in the ablation area (size: $13.0 \times 16.0 \times 14.1$ mm, the volume about 1.54 mL); (D) the sonograms at 1 week of RFA (including the gray-scale US and CEUS of transverse and longitudinal sections), showed that there was no contrast filling in the ablation area (size: $10.9 \times 14.5 \times 13.4$ mm, the volume about 1.11 mL).

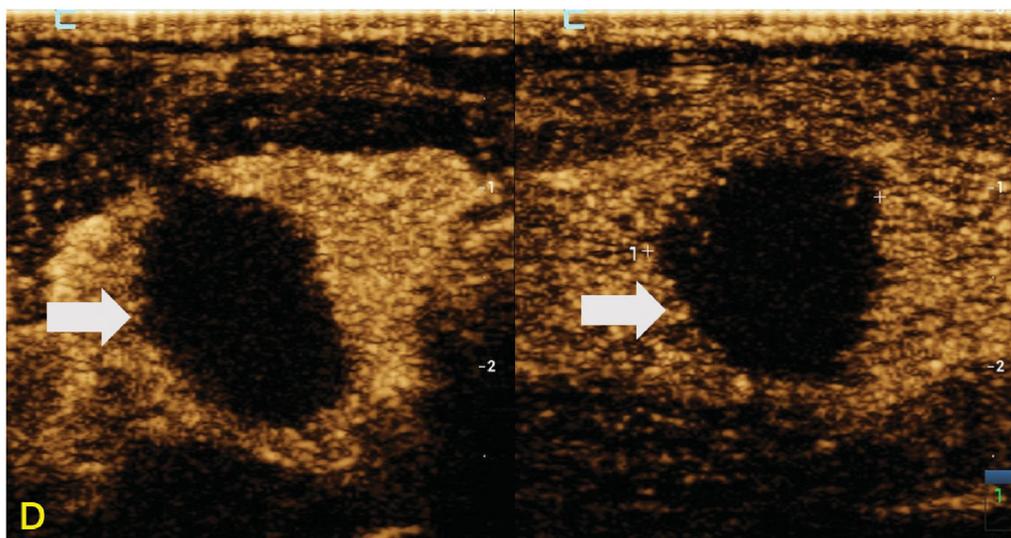


Figure 4. Continued.

Considering that different ablation powers may lead to differences in the degree of carbonation, which can lead to differences in ablation volume, future studies on the effectiveness of high-power ablation and low-power ablation in the treatment of PTMC can be conducted.

Conclusion

RFA-treated PTMCs were smaller in size in patients with HT than in those with a healthy thyroid at 1 week of RFA. Therefore, HT exerts an influence on the ablation extent of PTMCs treated with RFA. However, the exact mechanism underlying this phenomenon and its clinical significance warrant further investigation.

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Disclosure statement

The authors report there are no competing interests to declare.

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