Long-term follow-up results of PTMC treated by ultrasound-guided radiofrequency ablation: a retrospective study

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ABSTRACT

Objectives: To confirm the long-term efficacy and safety of radiofrequency ablation (RFA) for low-risk papillary thyroid microcarcinoma (PTMC).

Methods: We retrospectively reviewed data of 102 primary papillary thyroid carcinoma patients (82 women, 20 men; mean age: 43 [19] years) treated with radiofrequency ablation and thyroid-stimulating hormone (TSH) suppression therapy before December 2018. All patients were at high surgical risk or refused surgery. They were followed up at 1, 3, 6, 9, and 12 months and every 6–12 months thereafter using ultrasound and contrast-enhanced ultrasound. The volume and volume reduction ratio was calculated. Recurrence and lymph node or distant metastasis were evaluated.

Results: The mean initial tumor diameter was 0.50 (0.29) cm; the mean initial volume was 0.06 (0.09) mL. At 1, 3, 6, 9, 12, 24, 36, 48, and 60 months after RFA, complete resorption rates were 0, 0, 9.8 (10/102), 33.3 (34/102), 91.2 (93/102), 96.1 (98/102), 99 (101/102), 100, and 100%, respectively. Two patients had developed ipsilateral neck lymph node metastasis in regions IV and VI at 30- and 18-month follow-ups, respectively. After RFA, 3/102 patients (2.9%) developed hoarseness—the main side effect. No life-threatening or delayed complications occurred. The TSH value in the initial period was 0.06 (0.02) μIU/mL; the rate of reaching the TSH target was 85.7%. The TSH value at follow-up was 1.47 (0.91) μIU/mL; the compliance rate was 99.3%.

Conclusions: Ultrasound-guided RFA for PTMC is highly effective and safe. RFA can serve as a minimally invasive treatment for PTMC patients who refuse surgery or active surveillance.

Introduction

In the past 10 years, the National Cancer Institute’s Surveillance, Epidemiology, and End Results database show that differentiated thyroid cancer (DTC) accounts for 95.7% of thyroid-related cancer cases [1]. Papillary thyroid carcinoma (PTC) has shown a significant increase in the number of cases. The papillary thyroid microcarcinoma (PTMC) is the fastest-growing PTC. It accounts for 50–60% of the PTC cases. However, there is no significant growth in the PTC death rate. Currently, thyroid surgery is the standard treatment for PTMC [2]. The risks of long-term complications, scarring, and lifelong thyroxine replacement resulting from overtreatment with surgery should be minimized because of the good prognosis of low-risk PTMC and the high risks of surgery for patients who cannot tolerate it. In 2015, the American Thyroid Association (ATA) indicated that for low-risk PTMC, active surveillance can replace immediate surgery [2]. The Japan thyroid tumor diagnosis and treatment guidelines, which were published in 2018, classifies patients with T1aN0M0 tumors into the ultra-low-risk group. It also recognizes active surveillance as a treatment for these patients [2]. Oda et al. [3] and Ito et al. [4] also found that, compared with the death rate of patients treated with immediate surgeries, the death rate of those under active surveillance without surgeries was not high during the past 10 years. Therefore, active surveillance could be used to replace immediate surgery in cases of low-risk PTMC [4]. Active surveillance has been recognized as a safer and more cost-effective option for low-risk PTMC than immediate surgery [5]. However, many scholars and patients still choose immediate surgery because they have various concerns about active surveillance and anxieties about survival with cancer. There are limited clinical methods to predict the aggressiveness of PTMC. In recent years, an increasing number of scholars have gradually recognized that ultrasound-guided thermal ablation technologies, such as laser ablation (LA), microwave ablation (MWA), or radiofrequency ablation (RFA) have been successfully used to treat benign thyroid nodules as well as PTMC and metastatic lymph nodes in patients at surgical risk [3–7]. Ultrasound-guided RFA technology was first used as a treatment for PTMC in 2016. It proved effective in treating PTMC. Zhang and his colleagues studied 92 patients with PTMC who were followed up for 18 months. The average volume reduction rate (VRR) of the tumor was found to be 0%. In another study, 37 patients with PTMC were followed up for 12 months, and the VRR and recurrence rate was 99.34 ± 3.49
and 0%, respectively [8]. In recent years, several meta-analyses have confirmed that thermal ablation is an excellent method for regional tumor control in patients with low-risk PTMC [9]. The management of PTMC is a growing area of interest. In the present study, we evaluated the effectiveness and safety of RFA in patients with PTMC who were treated with RFA and thyroid-stimulating hormone (TSH) suppression after surgery. TSH suppression therapy is an important part of the post-operative treatment of DTC [10]; it aims to reduce endogenous stimulation of residual DTC cells and thus reduces tumor recurrence and metastasis. Patients were followed up for at least 3 years after the combined treatment. The recurrence rate and metastasis were studied to confirm the effectiveness and safety of RFA with TSH inhibition.

Materials and methods

The First Affiliated Hospital of Dalian Medical University’s institutional review board provided approval for this study. The protocol number is PJ-KS-KY-2020-62. Written consent was obtained from all patients before RFA treatment.

Patients

Between July 2014 and December 2018, 102 patients with PTMC with T1aN0M0 lesions were treated at our hospital using ultrasound-guided percutaneous RFA. All patients were at high surgical risk or refused surgery. They were followed up for 3–5 years after their treatment. For all patients, fine-needle aspiration (FNA) was used to confirm PTC. The inclusion criteria were a maximum diameter no larger than 10 mm and absence of capsular infiltration and extrathyroidal invasion on ultrasound (US). Tumors located within 2 mm around the capsule were defined as ‘to the capsule [11].’ Additionally, there was no cervical lymph node metastasis or distant metastasis on imaging. The exclusion criteria were thyroid cancer with severe extra thyroid metastases, lymph node (LN) metastases (imaging or cytological evidence), distant metastases, pregnancy, and severe cardiopulmonary disease. The current retrospective study includes 102 patients with T1N0M0 PTC. The results of the thyroid function test, laryngoscopy, electrocardiography, and lung computed tomography (CT) were normal.

Preoperative evaluation

Preoperative ultrasound and contrast-enhanced ultrasound were performed for all patients using the Hitachi Hivision Ultrasound system (Hitachi, Japan). Ultrasound was used to evaluate the orthogonal three-dimensional maximum diameter and size of each tumor nodule. The size of each tumor is calculated based on the formula of \( V = \pi ABC/6 \) (where \( V \) is the volume, \( A \) is the maximum diameter, and \( B \) and \( C \) are the other two vertical maximum diameters). After the evaluation of PTMC tumors, a cervical lymph node ultrasound and enhanced cervical CT were performed to assess the presence of LN metastasis. The blood supply of the nodules was assessed on contrast-enhanced ultrasound (CEUS). FNA was performed to confirm the pathology of the lesions. A puncture biopsy was performed to identify suspected LNs. Metastatic LNs were excluded. Meanwhile, routine laboratory tests including thyroid function, serum thyroglobulin, thyroglobulin antibody, blood routine, and coagulation function, and lung CT examination were also performed.

Ablation procedures

Ablation procedures were performed by a specialist with 10 years of ablation experience using the VIVA RF GENERATOR (STArmCo., Ltd., Korea) with an 18 G diameter ablation needle (STArmCo., Ltd., Korea). The 7 F or 10 F working tip was selected based on the volume of the target tumor. The procedure was performed with the patient in the supine position with his/her neck extended. The tumor’s proximity to key areas, such as nerves, the esophagus, and the trachea, was evaluated using ultrasound to prevent damage to the surrounding tissues. Adequate fluid isolation was performed immediately outside the capsule with saline or injected with 5% glucose, which was chosen based on the location of the lesion. Fluid isolation can also be performed simultaneously with regional anesthesia to avoid the nerve area.

A safe puncture route was selected to pass through some normal glands, typically the isthmus. The RFA power was 40–70 W, and the time range was 21–403 s. For a small tumor, the tip of the electrode was fixed to the center of the tumor. Large tumors were treated with unit-by-unit movement. To prevent a marginal recurrence, the ablation was expanded to 3–5 mm away from the surrounding normal tissue or to the capsule. CEUS was used to evaluate the effectiveness of RFA. If there were severe areas in the nodule, complementary ablation was performed immediately to prevent the presence of the residual tumor. Any side effects that occurred during or immediately after ablation were carefully evaluated, and all patients were observed in the hospital for 4–5 h after ablation.

Post-ablation assessment

The assessment of effectiveness mainly included the assessment of ablation range and complications. For the former, attention should be paid to the identification of the expected ablation range related to the treated lesions. The application of CEUS was used to make accurate assessments. Complete ablation was defined as no contrast agent perfusion after the injection of SonoVue into the thyroid nodule. A surgical review was conducted by a physician with more than 3 years of experience. A follow-up was performed 1 month after surgery. Then the follow-ups were completed quarterly for a year and on a semi-year basis thereafter. Follow-ups included ultrasonography to assess tumor size, volume, blood flow, and recurrence of metastasis shown in Figure 1. Information of delayed surgery (any reason for thyroid surgery during follow-up) was obtained. Thyroid function was also checked during the follow-up visits. The VRR
was calculated based on the formula of $VRR = \left(\frac{\text{initial volume} - \text{final volume}}{\text{initial volume}}\right) \times 100\%$. If the volume of a nodule decreased gradually or the volume of a nodule was not measurable, the nodule was confirmed to be inactivated. If the volume of a nodule increased, the nodule was considered to have active ingredients; in this case, another option of treatment would be used. All patients were examined using CT 6 months after ablation to detect LN metastasis, and a needle biopsy was required if abnormal lymph nodes were evident on ultrasound and CT. Side effects were the undesired events that occurred during or after a procedure, and recovery time and treatment were recorded. The main immediate (0–24 h) and peri-procedural (1–30 d) side effects are hoarse voice, bleeding, and thyroid abnormalities [12]. Thyroid function (including T3, T4, TSH, FT3, and FT4) was reexamined 1 week after surgery. According to the recommendations of China’s Guidelines for Thyroid Nodules and Differential Thyroid Carcinoma published in 2012 [13], TSH inhibition therapy was performed in compliance with the 2015 ATA dynamic dual risk assessment system [4] and the comprehensive dual risk assessment system. L-T4 was taken before any food. The dose is typically prescribed at 50 μg/d. It can be halved or started with 12.5 μg/d for patients with cardiovascular risk at an interval of 4 weeks at a dose of 12.5–25 μg. In the initial treatment period (in the first year after surgery), TSH was controlled below 0.1 mU/L. In the follow-up period (a year later after surgery), TSH was controlled below 2 mU/L.

**Statistical analysis**

The SPSS statistical software (version 23.0) was used to perform statistical analysis. Continuous data are presented as medians (interquartile range). The Wilcoxon signed-rank test was used to compare the mean volume of the tumor before RFA with the results of each after RFA at follow-up. A p-value <0.05 was considered to be statistically significant.

**Results**

The follow-up period after RFA lasted for 60 months. All tumor ablation foci disappeared during the follow-up period with the mean tumor diameter at 0.50 (0.29) cm and the mean volume at 0.06 (0.09) mL shown in Figure 2. Characteristics of the study cohort, tumors, and RFA parameters are shown in Table 1. All ablated tumors completely disappeared at the end of the follow-up period. At 1, 3, 6, 9, 12, 24, 36, 48, and 60 months after RFA, the complete resorption rate was 0, 0, 9.8 (10/102), 33.3 (34/102), 91.2 (93/102), 96.1 (98/102), 99 (101/102), 100, and 100%, respectively shown in Figure 3 and Table 2. By their 30- and 18-month post-RFA follow-ups, two patients developed ipsilateral neck lymph node metastasis in regions IV and VI, respectively. After RFA, 2.9% (3/102) of patients developed hoarseness—the main side effect. Three patients (2.9%) developed hyperthyroidism 1 week after RFA, but their thyroid functions normalized after a month shown in Table 3. One patient was diagnosed with Graves’ disease. Two patients (1.9%) developed subclinical hypothyroidism, and their thyroid functions normalized after a month. The TSH value in the initial treatment period was 0.06 (0.02) μIU/mL, and the rate at which the TSH target was achieved was 85.7%. The TSH value in the follow-up period was 1.47 (0.91) μIU/mL, and the compliance rate was 99.3%.

**Discussion**

Most PTMCs are regarded as being low risk because of their limited effect on mortality. Avoiding overtreatment of PTMC is a clinical challenge. In the study by Ito et al., 1235 patients with PTMC underwent 5- and 10-year observations and showed LN metastasis rates at 1.7 and 3.8%, respectively. Of the patients who underwent thyroid surgery for PTMC, 2–6% of them had local recurrence and 1–2% had distant metastasis. The follow-up period after RFA lasted for 60 months. All tumor ablation foci disappeared during the follow-up period with the mean tumor diameter at 0.50 (0.29) cm and the mean volume at 0.06 (0.09) mL shown in Figure 2. Characteristics of the study cohort, tumors, and RFA parameters are shown in Table 1. All ablated tumors completely disappeared at the end of the follow-up period. At 1, 3, 6, 9, 12, 24, 36, 48, and 60 months after RFA, the complete resorption rate was 0, 0, 9.8 (10/102), 33.3 (34/102), 91.2 (93/102), 96.1 (98/102), 99 (101/102), 100, and 100%, respectively shown in Figure 3 and Table 2. By their 30- and 18-month post-RFA follow-ups, two patients developed ipsilateral neck lymph node metastasis in regions IV and VI, respectively. After RFA, 2.9% (3/102) of patients developed hoarseness—the main side effect. Three patients (2.9%) developed hyperthyroidism 1 week after RFA, but their thyroid functions normalized after a month shown in Table 3. One patient was diagnosed with Graves’ disease. Two patients (1.9%) developed subclinical hypothyroidism, and their thyroid functions normalized after a month. The TSH value in the initial treatment period was 0.06 (0.02) μIU/mL, and the rate at which the TSH target was achieved was 85.7%. The TSH value in the follow-up period was 1.47 (0.91) μIU/mL, and the compliance rate was 99.3%.

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### Table 1. General conditions of patients before radiofrequency ablation.

| General conditions                  | Proportion |
|-------------------------------------|------------|
| Nodules N                           | 109        |
| Patients N                          | 102        |
| Male: female                        | 20 (19.6%); 82 (80.4%) |
| Age (years)                         | 43 (19)    |
| With or without Hashimoto’s disease | 6 (5.9%); 96 (94.1%) |
| Single: multiple                    | 91 (89.2%); 11 (10.8%) |
| Nodule size (mean diameter [cm], volume [mL]) | 0.50 (0.29) cm; 0.06 (0.09) mL |
| Diameter ≥0.5 cm; diameter <0.5 cm | 59 (54.1%); 50 (45.9%) |
| To the capsule (yes: no)            | 68 (62.4%); 41 (37.6%) |
| Left: right: isthmus                | 40 (44.9%); 57 (52.3%); 3 (2.8%) |
| Radiofrequency working tip 10 F; 7 F | 60 (10)    |
| Radiofrequency average power (W)    | 79 (65)    |

### Table 2. Changes in volume and VRR after radiofrequency ablation (RFA) at follow-up.

| Time                     | Volume (mL) | VRR (100%) | p-Value |
|--------------------------|-------------|------------|---------|
| Preoperative             | 0.06 (0.09) | NA         | <0.001  |
| After RFA                | 0.97 (0.71) | NA         | <0.001  |
| 1 month                  | 0.39 (0.62) | 0.39 (0.50) | <0.001  |
| 3 months                 | 0.26 (0.30) | 0.74 (0.29) | <0.001  |
| 6 months                 | 0.09 (0.17) | 0.90 (0.17) | <0.001  |
| 9 months                 | 0.02 (0.07) | 0.97 (0.07) | <0.001  |
| 12 months                | 0.00 (0.03) | 1.0 (0.02)  | <0.001  |
| 18 months                | 0.00 (0.00) | 1.0 (0.00)  | <0.001  |
| 24 months                | 0.00 (0.00) | 1.0 (0.00)  | <0.001  |
| 30 months                | 0.00 (0.00) | 1.0 (0.00)  | <0.001  |
| 36 months                | 0.00 (0.00) | 1.0 (0.00)  | <0.001  |
| 42 months                | 0.00 (0.00) | 1.0 (0.00)  | <0.001  |
| 48 months                | 0.00 (0.00) | 1.0 (0.00)  | <0.001  |
| 60 months                | 0.00 (0.00) | 1.0 (0.00)  | <0.001  |

VRR: volume reduction rate; NA: not applicable. Specifically, ‘preoperative’ refers to the baseline volume of the nodule. After RFA, the volumes are of the ablated area.

### Table 3. General conditions of patients after radiofrequency ablation.

| General conditions                  | Proportion |
|-------------------------------------|------------|
| TSH value (initial period [μIU/mL]) | 0.06 (0.02) |
| TSH value (follow-up period [μIU/mL]) | 1.47 (0.91) |
| Delayed surgery time (M)            | 6 (5.9%)   |
| Delayed surgery rate                | 1 (0.9%)   |
| Follow-up time (M)                  | 48 (18)    |
| Side effects (hoarseness)           | 3 (2.8%)   |
| Recurrence rate (recurrence, lymph node metastasis) | 2 (1.9%) |
| Hyperthyroidism/hypothyroidism (post-operative) | 3 (2.9%)/2 (1.9%) |
| Nodule complete absorption time (M) | 12 (12)    |
The unique feature of this paper is that TSH suppressive therapy was used with RFA. The concept of TSH suppression therapy has changed in recent years because DTC patients generally have an excellent survival rate because of the increasing prevalence of PTMC [38,39]. It is not recommended to administer TSH suppressive therapy during the period of active surveillance because the side effects of the drugs are more harmful than the disease itself. Adverse effects of TSH suppression include cardiovascular and bone loss risks [40]. TSH suppressive therapy was also not...
performed after RFA to not affect the quality of life of low-risk patients [41]. There is little evidence to guide TSH targets or the use of thyroid hormone in low-risk patients who have undergone lobectomy or RFA [2]. In this paper, we combined treatments for the following reasons: first, PTMC is defined not based on the presence of high-risk features, such as lymph node metastases and/or distant metastases but as PTC with a maximum diameter of 1 cm, no clinical lymph...

Figure 1. Ultrasound (US) image of a 33-year-old woman with a low-risk papillary thyroid microcarcinoma (PTMC). (a) Before radiofrequency ablation (RFA), US image showing a tumor (arrow) located in the right thyroid lobe; it had an initial volume of 307.13 mm³. (b) Immediately after RFA, the volume of the ablation area (arrow) was 852.82 mm³ on contrast-enhanced ultrasound. (c,d) One month after RFA, the volume of the ablation area (arrow) was 556.09 mm³. (e,f) Three months after RFA, the volume of the ablation area (arrow) was 164.12 mm³. (g,h) Six months after RFA, the volume of the ablation area (arrow) was 26.90 mm³. (i,l) Nine months after RFA, the ablation area could not be identified on the longitudinal US image. There was only a focal concavity in the capsule caused by shrinkage of the scar (arrow) on the transverse US image. (k,l) Twelve months after RFA, the ablation area completely disappeared.

Figure 2. Changes in volume at each follow-up point. After RFA, the volumes are of the ablated area.
node metastases or distant metastases, and FNA findings not indicating high-risk pathological subtypes. The 10-year recurrence rate is 30%, and the specific survival rate is 74.1% [42]. Some patients still have metastases after surgery, and post-operative recurrence is the main cause of death [31]. Second, the biological characteristics of tumors can never be evaluated by size only. So far, it remains impossible to reliably identify inert occult and high-risk cancers [43]. Related studies have confirmed that recurrence and metastasis of PTC are closely related to age, venereal disease, and tumor diameter size [40]. Recently, specific molecular profiles, such as the coexistence of BRAF with other oncogenic mutations like the TERT promoter or TP53 mutations, may serve as more specific markers of a less favorable outcome of PTC. Only active surveillance can identify if a tumor is progressive PTMC or harmless PTMC. Third, related studies and clinical data have shown that thyroid cell proliferation is dependent on TSH; a key point of DTC treatment is to reduce endogenous TSH values of low-risk patients or suppress TSH values of high-risk patients by obtaining exogenous thyroid hormones to reduce the release of TSH [44]. RFA is an in-situ treatment of tumors, and the thyroid gland and LNs are not removed. The two patients whose TSH values met the standards during TSH suppression therapy (TSH <0.1 µIU/mL at primary treatment and TSH <2 µIU/mL at follow-up) developed lymph metastases. To prevent post-operative recurrence and metastasis, it is recommended that TSH suppression therapy be used after surgery for micropapillary thyroid cancer.

There are some limitations to this study. First, it is a single-center retrospective study, and we need to conduct further prospective multicenter studies. Second, the detection of metastatic lymph nodes using ultrasound at an earlier stage cannot completely exclude the possibility of negative metastases. Third, the standards of TSH suppression we used were based on the surgical treatment of thyroid gland removal. Collaboration among different study fields and long-term follow-ups will provide high-quality evidence for TSH suppressive therapy.

Conclusion
Ultrasound-guided RFA for PTMC is highly effective and safe. RFA can serve as a minimally invasive treatment for PTMC patients who refuse surgery or active surveillance.

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Disclosure statement
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Data availability statement
The data that support the findings of this study are available on request from the corresponding author.

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