Efficacy and Safety of Ultrasound-Guided Radiofrequency Ablation for Treating Low-Risk Papillary Thyroid Microcarcinoma: A Prospective Study

Mingbo Zhang, Yukun Luo, Yan Zhang, and Jie Tang

Background: Papillary thyroid microcarcinoma (PTMC) has a high incidence and a good prognosis. Surgical operation for all PTMC might be an overtreatment. The objective of this study was to evaluate the efficacy and safety of ultrasound (US)-guided radiofrequency ablation (RFA) for treating low-risk PTMC.

Methods: Ninety-eight PTMC in 92 patients were included in this study. US and contrast-enhanced ultrasound (CEUS) examinations were performed before ablation. RFA was performed using the moving-shot technique. The ablation area exceeded the tumor edge to prevent marginal residue and recurrence. Patients were followed at 1, 3, 6, and 12 months and every six months thereafter. US and CEUS examinations were used to evaluate the ablation area. At three months after ablation, US-guided core-needle biopsy (CNB) was performed in the center, at the edge of the ablation area, and in the surrounding thyroid parenchyma to exclude recurrence.

Results: The mean tumor volume was 118.8 ± 106.9 mm³. The mean volume reduction ratio (VRR) was 0.47 ± 0.27, 0.19 ± 0.16, 0.08 ± 0.11, 0.04 ± 0.10, and 0 at 1, 3, 6, 12, and 18 months after RFA, respectively. Significant differences in the VRR were found between every two follow-up times before six months (p < 0.01), and no significant differences in the VRR were found between six months and after 12 months (p = 0.42). Of all the nodules, 10 (41.7%) resolved in six months, and 23 (95.8%) resolved in 12 months. No residual or recurrent tumor tissue was detected in RFA area or in residual thyroid tissue during follow-up. No suspicious metastatic lymph nodes were detected. The histological pathology results of US-guided CNB confirmed the absence of residual or recurrent tumor. No major complications were encountered.

Conclusions: RFA can effectively eliminate low-risk PTMC with a very small complication rate. RFA may be an alternative strategy for the treatment of PTMC.

Keywords: ultrasound, radiofrequency, ablation, thyroid, microcarcinoma

Introduction

Papillary thyroid carcinoma is the most common subtype of thyroid carcinoma, and lesions ≤10 mm in diameter are defined as papillary thyroid microcarcinomas (PTMC) (1). PTMC were observed in 15.5% of 1262 autopsy cases when the entire gland was examined (2), and the prevalence of subclinical PTMC is about 1000 times higher than that of clinical thyroid carcinoma (3). PTMC is typically associated with a good prognosis (4–7). Ito et al. observed 1235 patients with low-risk PTMC for 5–15 years, and their results suggested that only 19 (1.5%) patients developed lymph node metastasis and 43 (3.5%) a progression to clinical disease, defined as a tumor size reaching ≥12 mm or the novel appearance of nodal metastasis. None of the patients had distant metastasis or died of PTC during observation (3). A study by Sugitani et al. reported similar results (8).

For PTMC, surgery is generally recommended by guidelines (9–12). However, surgery may be associated with permanent recurrent laryngeal nerve paralysis, permanent hypothyroidism, permanent hypoparathyroidism, and the risk of an unsightly scar (13–17). For such a harmless and frequent disease, surgery may be considered overtreatment. According to the recently published 2015 American Thyroid Association (ATA) guidelines, PTMC without clinically evident metastases or local invasion and no convincing cytologic evidence of aggressive disease may simply be followed with active surveillance (9). However, no clinical or imaging features can reliably differentiate the small percent of invasive PTMC, which present with regional or distal...
metastasis (9). Moreover, active surveillance may cause anxiety, which is not acceptable for many patients.

Radiofrequency ablation (RFA) is a safe and effective technique in treating liver carcinoma, and it has been used as a non-invasive treatment in patients who are poor surgical candidates (18,19). In thyroid disease, ultrasound (US)-guided RFA has been used with good results for benign thyroid tumors, including cold nodules with pressure symptoms or cosmetic concerns (20–26), as well as for autonomously functioning thyroid nodules (24,27,28). There have also been several recent reports regarding recurrent PTC treated using percutaneous US-guided RFA (29–32) with satisfactory reduction of volume and serum thyroglobulin levels. However, there are no prospective studies regarding the primary treatment of low-risk PTMC with US-guided RFA. Therefore, the purpose of this study was to validate the efficacy and safety of US-guided RFA for the therapy of low-risk PTMC.

Materials and Methods

This study was approved by the hospital’s ethics committee, and written informed consent was obtained from all patients prior to US-guided core-needle biopsy (CNB) and RFA. The RFA informed consent emphasized that surgery is the routine treatment procedure recommended by guidelines, and that RFA could not avoid recurrent PTMC and undetectable lymph node metastasis.

US and contrast-enhanced US (CEUS) examinations before and after RFA as well as during follow-up were performed using a Siemens Acuson Sequoia 512 Ultrasound System (Siemens, Mountain View, CA) with a 15L8W linear array transducer or a Philips iU22 Ultrasound System (Philips Healthcare, Bothell, WA) with a L12-5 linear array transducer or a Mindray M9 Ultrasound System (Mindray, Shenzhen, China) with a L12-4 linear array transducer. US-guided RFA and CNB were all performed using a Siemens Acuson Sequoia 512 Ultrasound System with a 6L3 linear array transducer.

Patients

Patients were enrolled in this study if they fulfilled the following criteria: (i) patients with PTMC confirmed by US-guided CNB; (ii) no extrathyroidal invasion; (iii) no lymph node metastasis on imaging studies; (iv) no metastasis beyond the neck; (v) no history of neck irradiation; and (vi) patients who had medical contraindications for surgery or refused surgery. The exclusion criteria were: (i) patients with PTMC close to the “danger triangle” (within 5 mm distance from the trachea-esophageal groove) in order to avoid injury to the recurrent laryngeal nerve; (ii) patients with aggressive histological PTMC (e.g., tall cell, insular, columnar cell carcinoma); (iii) pregnant women; (iv) patients with severe heart, respiratory, liver, or renal failure; (v) coagulation disorder with severe bleeding tendency; (vi) conscious disturbance or neck extension disorder that could not tolerate RFA; (vii) cardiac pacemaker implantation; and (viii) contralateral vocal cord paralysis.

Between September 2013 and October 2014, 98 tumors in 92 patients (23 males; $M_{age} \pm SD = 44.7 \pm 10.7$ years; range 14–69 years) were treated with US-guided RFA in the authors’ department.

Pre-ablation assessment

For each tumor, the diameters in three dimensions (transverse, anteroposterior, and longitudinal), volume, location, echogenicity, internal architecture, contour, shape (height/width), calcifications, and vascularity were evaluated by US. The volume of each tumor was calculated as $V = abc/6$ (where $V$ is the volume, $a$ is the largest diameter, and $b$ and $c$ are the two other perpendicular diameters). US appearances were evaluated and recorded according to the multidisciplinary consensus statement of thyroid nodules (33).

Contrast-enhanced US was used to describe the blood supply region of the lesion before and after ablation. Sulfur hexafluoride (SonoVueR; Bracco International, Milan, Italy) was used as ultrasound contrast agent. CEUS was performed after bolus injection of SonoVue (2.4 mL) using mechanical index from 0.19 to 0.24, followed by 5 mL of normal saline flush. In the meantime, the timer on the US machine was started, and the imaging plane was kept as stable as possible. Each contrast imaging acquisition lasted at least three minutes after bolus injection. The video clip was digitally recorded and further analyzed.

All examinations were performed by an experienced US physician (Y.L., with >20 years’ experience in thyroid US and interventional US) in order to exclude a bias introduced by different operators. The US imaging data were independently analyzed by two other off-site investigators (M.Z. and Y.Z., both with >8 years’ experience in thyroid US), who had not performed the US and CEUS examinations and who were blinded to the histological finding of CNB samples and imaging findings. When they did not reach agreement, the tumor was evaluated by another experienced investigator. Each investigator clarified the reasons for making the diagnoses, and a consensus was reached in cases of discrepancies.

Ablation procedure

All RFA procedures were performed by an experienced US physician (Y.L.) with >20 years’ experience in thyroid US and interventional US.

A bipolar RFA generator (CelonLabPOWER; Olympus Surgical Technologies Europe, Hamburg, Germany) and an 18-gauge bipolar RF applicator with a 0.9 cm active tip was used (CelonProSurge micro 100-T09; Olympus Surgical Technologies Europe) in this study. During the application of RF energy, the generator continuously measures the electric impedance of the tissue between the two electrodes at the tip of the RF applicator. The power is automatically reduced if the temperature at the electrodes reaches 100°C and causes a characteristic increase of tissue impedance.

Patients were supine with the neck extended during the procedure. An intravenous line was introduced via the ante-cubital vein. Before RFA, careful US evaluation of the relationship between tumor and cervical critical structures such as the trachea, vessels, esophagus, and recurrent laryngeal nerves was performed by the operator in order to design the best way of insertion. Local anesthesia with 1% lidocaine was injected at the subcutaneous puncture site and the thyroid anterior capsule. If the distance between the tumor and critical cervical structures (including the trachea, cervical artery,
jugular vein, esophagus, and recurrent laryngeal nerve) was <5 mm, normal saline was injected using another needle (23 gauge) to form at least 1 cm distance between the tumor and the critical structure in order to prevent thermal injury. RFA was performed using the moving-shot technique (22–23). The RFA power was 3 W. If a transient hyperechoic zone did not form at the electrode tip within 5–10 sec, the radiofrequency power was increased to 5 W. The RFA extent exceeded the tumor edge to prevent marginal residue and recurrence. The ablation was terminated when all portions of the target ablation area had changed to transient hyperechoic zones. During the procedure, special attention was given to the preservation of critical cervical structures in order to prevent significant complications such as hematoma or nerve injury. After ablation, each patient was observed for one to two hours in the hospital while any complications occurring during and immediately after ablation were carefully evaluated according to the clinical signs and symptoms.

**Post-ablation assessment**

Patients were followed using US and clinical evaluation at 1, 3, 6, and 12 months and every six months thereafter. The ablation area was evaluated by CEUS to detect the largest diameter and volume of ablation and to screen for recurrence. The development of metastatic lymph nodes was evaluated by US, and suspicious lesions were submitted to biopsy. At three months after ablation, US-guided CNB was performed in the center, at the edge of the ablation area, and in the surrounding thyroid parenchyma, respectively. Follow-up US and CEUS were performed by two physicians with more than eight years’ experience in thyroid US and CEUS (M.Z. and Y.Z.); they were blinded to the previously obtained findings. If their results were inconsistent, another physician with >15 years’ experience of thyroid US and CEUS (J.T.) was asked for consultation. CNB were performed by the US physician who performed the RFA treatment. The percentage reduction of the ablation area in volume was calculated as follows: volume reduction ratio (VRR) = [(initial volume – final volume) x 100]/initial volume. Complications during follow-up were assessed using the reporting standards of the Society of Interventional Radiology (34,35).

**Statistical analysis**

All data were analyzed using SPSS for Windows v13.0 (SPSS, Inc., Chicago, IL). Continuous data were reported as mean ± SD (range). Wilcoxon’s signed rank test was used to compare changes in the largest diameter and volume of ablation area before RFA and at each follow-up. Differences were considered statistically significant when the p-value was <0.05.

**Results**

In this study, the mean number of treated tumors per patient was 1.1 tumors (range 1–3 tumors). One tumor was treated in 87 patients, two tumors in four patients, three tumors in one patient, and four tumors in three patients.

Three tumors were located in the isthmus portion; 16 tumors were located in the medial portion. The mean distance between the tumor and trachea was 1.6 ± 0.6 mm (range 0.9–3 mm). Seventeen tumors were located in the lateral portion. The mean distance between the tumor and cervical common artery was 2.0 ± 0.9 mm (range 0.8–3 mm). The remaining 62 tumors were located in the center portion of the thyroid lobes. Among all 98 tumors, one tumor was isoechoic and 97 were hypoechoic. Three tumors were mixed solid and cystic tumors and 95 were solid tumors. Ten tumors showed a smooth and well-defined margin, 65 showed a lobulated/irregular margin, and 23 showed an indistinct margin. Twenty-three tumors showed microcalcifications and 75 showed no calcifications. Fifty tumors showed no vascularity, 36 showed only peripheral vascularity, two showed low vascularization, predominantly centrally with or without peripheral vascularization, and 10 tumors showed a high central vascularization with or without peripheral vascularization. US characteristics of all the nodules are shown in Table 1.

The mean transverse diameter, anteroposterior diameter, and longitudinal diameter of the tumors were 5.5 ± 2.0 mm (range 1.5–10 mm), 5.6 ± 1.8 mm (range 2–10 mm), and 5.8 ± 2.2 mm (range 1.9–10 mm), respectively. The mean tumor volume was 118.8 ± 106.9 mm³ (range 3.4–467.5 mm³). The mean ratio of height/width of the tumor was 0.95 ± 0.25 (range 0.47–1.7). The size of the nodules is shown in Table 2.

A power of 3 W was used in three tumors, and 5 W was used in 95 tumors. The mean RF time was 450.8 ± 230.2 sec (range 91–902 sec). The mean total energy was 1404.7 ± 822.0 J (range 260–4220 J), and the mean energy was 26,856.0 ± 40,439.2 J (range 1776.9–190,625 J).

The mean follow-up time was 7.8 ± 2.9 months (range 3–18 months). Changes in volume and VRR are shown in Table 3. The mean ablation area was initially 749.8 ± 594.4 mm³ (range 16.5–2944.1 mm³) immediately after RFA, and the volume decreased to 355.2 ± 362.7 mm³ (range 9.0–2326.9 mm³), 140.8 ± 215.1 mm³ (range 4.1–1801.9 mm³), 63.4 ± 171.6 mm³ (range 2.6–1509.3 mm³), 9.9 ± 19.0 mm³ (range 1.0–80.0 mm³), and 0 at 1, 3, 6, 12, and 18 months after

**Table 1. Ultrasound Characteristics of the Tumors**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nodules, n (%)</th>
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<tbody>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Medial portion</td>
<td>16 (16.3)</td>
</tr>
<tr>
<td>Lateral portion</td>
<td>17 (17.3)</td>
</tr>
<tr>
<td>Center portion</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>Isthmus</td>
<td>62 (63.3)</td>
</tr>
<tr>
<td>Echogenicity</td>
<td></td>
</tr>
<tr>
<td>Hypoechoic</td>
<td>97 (99.0)</td>
</tr>
<tr>
<td>Isoechoic</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Margin</td>
<td></td>
</tr>
<tr>
<td>Smooth and well defined</td>
<td>10 (10.2)</td>
</tr>
<tr>
<td>Lobulated/irregular</td>
<td>65 (66.3)</td>
</tr>
<tr>
<td>Indistinct</td>
<td>23 (23.5)</td>
</tr>
<tr>
<td>Calcification</td>
<td></td>
</tr>
<tr>
<td>Microcalcification</td>
<td>23 (23.5)</td>
</tr>
<tr>
<td>No calcification</td>
<td>75 (76.5)</td>
</tr>
<tr>
<td>Vascularity</td>
<td></td>
</tr>
<tr>
<td>No vascularity</td>
<td>50 (51.0)</td>
</tr>
<tr>
<td>Only peripheral vascularity</td>
<td>36 (36.7)</td>
</tr>
<tr>
<td>Low vascularization, predominantly centrally with or without peripheral vascularization</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>High vascularization, centrally with or without peripheral vascularization</td>
<td>10 (10.2)</td>
</tr>
</tbody>
</table>
RFA, respectively. The mean VRR was 0.47±0.27 (range 0.065–1.79), 0.19±0.16 (range 0.010–0.86), 0.08±0.11 (range 0.0037–0.73), 0.04±0.10 (range 0.00095–0.43), and 0 at 1, 3, 6, 12, and 18 months after RFA, respectively (Fig. 1). Significant differences in the VRR were found between every two follow-up times before six months (<0.01), and no significant differences in the VRR were found between six months and after 12 months (p=0.42).

Of all the tumors, 10 (10.2%) were completely resolved, and 23 (23.5%) only left needle tracks. Representative findings at RFA treatment and at follow-up of a PTMC case are shown in Figure 2.

No recurrent PTMC and no suspicious metastatic lymph nodes were detected during follow-up. The histological results of US-guided CNB suggested degeneration of follicular epithelial cell, hyaline degeneration of interstitial collagen fibers, and lymphocytic infiltration in the center and at the edge of the ablation area. No recurrent tumors were detected.

No major complications were encountered. One patient had moderate pain and received drug treatment. Four patients had transient hoarseness. Their treatment was stopped, and they were watched closely. The voice changes resolved after 10 min, 15 min, 20 min, and 3 h, respectively, and the patients continued to receive RFA with very good results. There were no skin burns, no obvious hematomas, no nodule rupture, and no brachial plexus injuries.

Discussion

The prevalence of PTMC is increasing, and most of them are incidental carcinomas discovered by US for other thyroid disorders or evaluations. The appropriate clinical treatment of these PTMC is widely debated. Usually, surgery is recommended. However, one study revealed that permanent recurrent laryngeal nerve paralysis occurred in 0.5% undergoing completion thyroidectomy, and permanent hypoparathyroidism occurred in 2.5% and 3.3% undergoing completion thyroidectomy or total thyroidectomy, respectively (17). Although the complication rate is low, these complications, which can substantially affect quality of life, appear high for a usually harmless disease. Moreover, if surgery is the therapy of choice, the costs associated with this highly prevalent disease are substantial. Of note, the recently published 2015 ATA guidelines recommend active surveillance as an alternative to immediate surgery in low-risk PTMC patients. However, there are still no means for predicting which PMTC behave more aggressively, and active surveillance can be a psychological burden for patients and hence reduce quality of life. In China, and most likely also elsewhere, many patients are very anxious about a “cancer” diagnosis and therefore wish to get rid of the lesion. Thus, RFA, a non-invasive procedure to eliminate the PTMC lesions, could be another treatment strategy.

Studies have been performed on the feasibility and reproducibility of RFA in the treatment of recurrent thyroid cancers (29–32,36). Lim et al. reported a mean volume reduction of 95% and the complete disappearance of 82% of treated tumors, which suggested that RFA can effectively control locoregional recurrent PTC without life-threatening complications and could replace “berry-picking surgery” in selected patients (36). Valcavi et al. evaluated the clinical feasibility of laser ablation on PTMC as a primary treatment (37). Three PTMC patients without extrathyroidal extension and lymph node metastasis underwent US-guided laser ablation and standard total thyroidectomy. This study demonstrated that percutaneous laser ablation is technically feasible for complete PTMC destruction and may be useful when patients refuse surgery or if they have medical contraindications for undergoing surgery. RFA has less ablation temperature, which is much safer than laser ablation. In addition, the moving-shot technique was used, which allows the ablation area to be controlled, including both the tumor and the surrounding soft tissue. If the distance between the tumor and critical cervical structures was very close (<5 mm), normal saline was injected using another needle (23 gauge) to form a distance of at least 1 cm in order to prevent thermal injury.

Table 2. Size of the Tumors

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>M ± SD</th>
<th>Range</th>
</tr>
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<tbody>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transverse diameter</td>
<td>5.5±2.0</td>
<td>1.5–10</td>
</tr>
<tr>
<td>Anteroposterior diameter</td>
<td>5.6±1.8</td>
<td>2–10</td>
</tr>
<tr>
<td>Longitudinal diameter</td>
<td>5.8±2.2</td>
<td>1.9–10</td>
</tr>
<tr>
<td>Tumor volume (mm³)</td>
<td>118.8±106.9</td>
<td>3.4–467.5</td>
</tr>
<tr>
<td>Ratio of height/width of the tumor</td>
<td>0.95±0.25</td>
<td>0.47–1.7</td>
</tr>
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</table>

Table 3. Changes in Tumor Volume and Volume Reduction Ratio After RFA and at Each Follow-Up

<table>
<thead>
<tr>
<th>Time after RFA</th>
<th>M ± SD</th>
<th>Range</th>
<th>M ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediately</td>
<td>749.8±594.4</td>
<td>16.5–2944.1</td>
<td>0.47±0.27</td>
<td>0.065–1.79</td>
</tr>
<tr>
<td>1 month</td>
<td>355.2±362.7</td>
<td>9.0–2326.9</td>
<td>0.19±0.16</td>
<td>0.010–0.86</td>
</tr>
<tr>
<td>3 months</td>
<td>140.8±215.1</td>
<td>4.1–1801.9</td>
<td>0.08±0.11</td>
<td>0.0037–0.73</td>
</tr>
<tr>
<td>6 months</td>
<td>63.4±171.6</td>
<td>2.6–1509.3</td>
<td>0.04±0.10</td>
<td>0.00095–0.43</td>
</tr>
<tr>
<td>12 months</td>
<td>9.9±19.0</td>
<td>1.0–80.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18 months</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
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</table>

RFA, radiofrequency ablation.
The results suggest that RFA can eliminate PTMC of 3 mm to 10 mm. The mean VRR was 0.08 \pm 0.11 (range 0.0037–0.73) at six months and 0.04 \pm 0.10 (range 0.00095–0.43) at 12 months after RFA. Twenty-three (23.5\%) nodules were found to have resolved during follow-up. The mean follow-up period was 7.8–2.9 months (range 3–18 months), which is not long. However, all patients underwent CNB at three months after RFA, and pathology results suggest no residual tumor in the ablation area and no recurrent tumor in the surrounding thyroid parenchyma, which confirms complete elimination of the PTMC lesions.

Baek et al. reported that the complication rate of RFA is low (38). However, various complications may occur, including voice changes, nodule rupture, hypothyroidism, brachial plexus injury, hematoma, vomiting, and skin burn, among others. Their results were based on RFA performed for benign thyroid nodules, which were usually large. In the present study, the complication rate was very low. Only one patient had pain, and four patients had transient hoarseness, which resolved within several hours. The low complication rate may be due to the fact that only small lesions were treated. The mean transverse, anteroposterior, and longitudinal diameter of the PTMC were 5.5 \pm 2.0 mm, 5.6 \pm 1.8 mm, and 5.8 \pm 2.2 mm, respectively. The mean RFA area was 749.8 \pm 594.4 mm$^3$.

This study has some limitations. First, the follow-up time is short. At this point, no recurrent PTMC was detected. But as the follow-up time becomes longer, new PTMC foci might appear, and a second RFA may be needed. Second, US cannot reliably assess the central compartment for the presence of lymph node metastasis, especially small ones. As the follow-up time becomes longer, lymph node metastasis might be
detected after RFA, even if we did not find any lymph node involvement before RFA.

To conclude, RFA can effectively eliminate PTMC with a very low complication rate. Thus, RFA could be an alternative strategy for patients with PTMC, and complement the current choices that consist of either surgery or active surveillance. For low-risk patients, RFA can eradicate the lesions with a more affordable treatment and, particularly in patients with significant anxiety, improve their quality of life.

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Author Disclosure Statement

We declare that we have no conflict of interest.

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