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Ultrasound-Guided Radiofrequency Ablation Versus Surgery for Low-Risk Papillary Thyroid Microcarcinoma: Results of Over 5 Years' Follow-Up

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Background: Papillary thyroid microcarcinoma (PTMC) typically carries an excellent prognosis regardless of the treatment option pursued. Radiofrequency ablation (RFA) for thyroid disease has been utilized for benign lesions and in patients who are poor surgical candidates for thyroid cancers with compression symptoms, but the efficacy and limitations of RFA as first-line therapy for PTMC has not been described in adequate detail. The purpose of our study was to investigate RFA versus thyroidectomy in terms of efficacy, oncologic outcomes, quality of life, complications, and costs over a 5-year period of follow-up.

Methods: From January 2013 to November 2013, 174 consecutive patients with an isolated, solitary intrathyroidal PTMC were identified in a Chinese teaching hospital. Those with more aggressive or advanced PTMCs were not included. Ninety-four patients elected RFA and 80 patients elected surgery for treatment of these PTMC. Nodules were confirmed to be PTMC without an aggressive histological type by core needle biopsy in the RFA group and by final surgical pathology in the surgery group. The extent of surgery was decided based on patient preferences in consultation with the surgeons. Of all the patients, 58 (72.5%) underwent lobectomy, 22 (27.5%) underwent total thyroidectomy, and 53 (66.3%) underwent lymph node dissection. Pre- and post-treatment variables were compared between the two groups, including demographics, tumor characteristics, treatment, local tumor progression, lymph node metastasis, distant metastasis, local recurrence, complications, and quality-of-life findings.

Results: Patient-specific variables were similar between groups, as were oncologic outcomes after 5 years of follow-up. When compared with RFA, surgery took longer, had a longer hospitalization time, and was costlier (all $p < 0.001$). The surgery group had three complications, with 2 (2.5%) permanent recurrent laryngeal nerve injuries and 1 (1.3%) case of permanent hypoparathyroidism, while none was reported in the RFA group ($p = 0.095$). The surgery group had a lower post-treatment thyroid-related quality of life.

Conclusions: For carefully selected low-risk intrathyroidal PTMC, RFA was not oncologically inferior to open surgery, and it was associated with a higher quality of life and lower overall costs.

Keywords: thyroid, papillary, microcarcinoma, radiofrequency ablation, ultrasound

Introduction

Papillary thyroid microcarcinoma (PTMC), defined as 1 cm or less (1), is a very common subtype of thyroid carcinoma (2). It has been observed in 15.5% of 1262 autopsy cases when the entire thyroid gland was examined (3). PTMC is typically associated with a good prognosis (4–7). A study by Ito *et al.* (2) reported that very few patients developed lymph node metastasis (LNM) or clinical progression while being followed. Moreover, none of the patients had distant metastasis (DM) or died of papillary thyroid carcinoma (PTC) during observation (2). Similar results were reported by Sugitani *et al.* (8).

Although the disease is prevalent and the prognosis is good for PTMC, optimal management is controversial. According to the 2015 American Thyroid Association (ATA) guidelines, very low-risk PTMC, defined as a PTMC without clinically evident metastases or local invasion and no convincing cytologic evidence of an aggressive variant, may simply be followed with active surveillance (AS) in some situations (9). In addition, the

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ATA guidelines do not recommend biopsy for subcentimeter nodules that are highly suspicious for PTC on ultrasound (US) to avoid over-diagnosing PTMC. Despite this reluctance to over-diagnose and over-treat, it is also true that there are no clinical, imaging, molecular, or other features that can reliably differentiate the small percentage of aggressive PTMC from the majority of indolent tumors. Without the ability to identify aggressive cancers, a small percentage of patients with PTMC may ultimately develop tumor size enlargement (2,8), extrathyroidal extension, and loco-regional or DM (6,7,10). Finally, patients with PTMC may feel anxious about tumor progression if their tumors are not eliminated, and the psychological burden may last until a form of treatment is rendered.

Surgery, generally an ipsilateral thyroid lobectomy, is recommended by most professional society guidelines as definitive treatment (9,11–13). While a majority of lobectomy patients have excellent outcomes, surgery may be associated with temporary or permanent recurrent laryngeal nerve paralysis, hypothyroidism, hypoparathyroidism (14–16), and the risk of an unsightly scar (17).

US-guided radiofrequency ablation (RFA), a safe and effective technique in treating liver carcinoma (18–20), has been used with good results for benign thyroid tumors with pressure symptoms or cosmetic concerns with satisfactory reduction of volume (21–24). Our group and others have also demonstrated excellent outcomes for recurrent/persistent PTC in metastatic lymph nodes (25–28). US-guided RFA, as well as microwave ablation (MWA) and laser ablation have all been used as noninvasive treatment options in patients with low-risk PTMC (29–37). Our previous study demonstrated the technical approach of US-guided RFA for PTMC and showed a good volume reduction rate, few complications, and very few cases of recurrence or metastasis (30). Although short-term therapeutic responses have been encouraging, the role of RFA remains a topic of controversy because there is a lack of long-term data addressing efficacy. Further, there are a few comparative studies of RFA versus traditional thyroidectomy. Therefore, the purpose of our study was to investigate US-guided RFA versus thyroidectomy for PTMC in terms of technical effectiveness, oncologic outcomes, complications, and costs after more than 5 years of follow-up.

Materials and Methods

Patients

This retrospective study was approved by our institutional review board. Informed consent for treatment procedures was obtained from each patient. The medical records of all patients presenting to our department who underwent RFA or open surgery between January 2013 and November 2013 were reviewed.

For the RFA group, patients were enrolled in this study if they fulfilled the following criteria: (1) a solitary suspicious sub-centimeter thyroid nodule was detected by US; (2) no sonographic evidence of extrathyroidal invasion, LNM, or DM; (3) core needle biopsy (CNB) confirming PTMC without aggressive histological type, which was proved by histopathological or immunohistochemical results, according to the WHO classification of thyroid tumors (1). During the time of this study, U.S. and Chinese guidelines did not include options for AS. Thus, patients who met the three criteria just mentioned were offered to choose either surgery or RFA, and those who refused or were ineligible for surgery were enrolled in the RFA group.

For the surgery group, patients had undergone surgery and were included in this study retrospectively if they fulfilled the following criteria: (1) a solitary suspicious sub-centimeter thyroid nodule detected by preoperative US; (2) no sonographic evidence of extrathyroidal invasion, LNM, or DM; (3) surgical pathology confirming PTMC without aggressive histology (1).

The flow-chart illustrating the inclusion and exclusion process is shown in Figure 1A and B. The flow chart of follow-up is found in Figure 2, and no significant difference of patients' continuous follow-up was detected between the two groups ($p = 0.275$).

During the study period, 94 and 80 patients who met criteria were enrolled in the RFA and the surgery groups, respectively. All the 94 patients in the RFA group underwent CNB. Of the 80 patients who underwent surgery, 74 patients had a malignant result on CNB, and 6 patients with suspicious lesions on US were reluctant to undergo CNB and elected to undergo surgery directly.

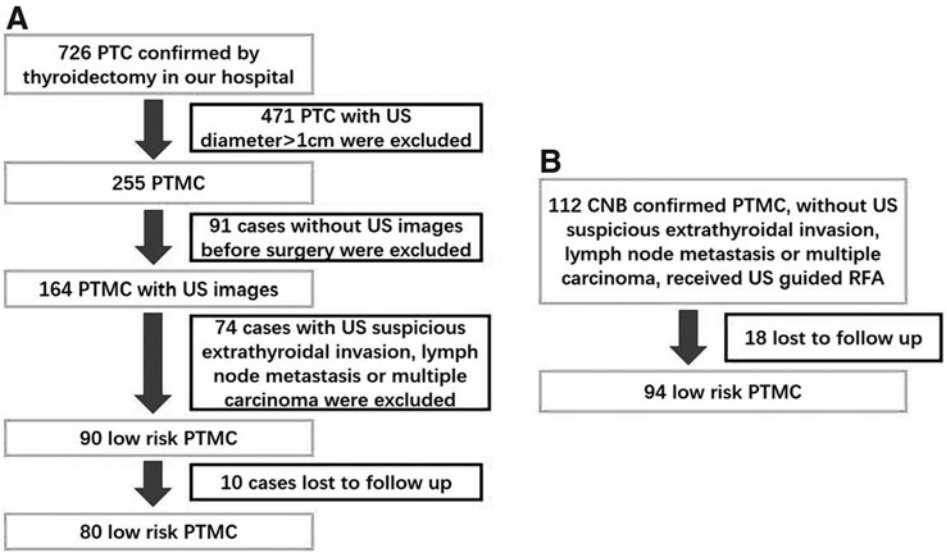

FIG. 1. (**A**) The flow chart of inclusion and exclusion of the surgical group. (**B**) The flow chart of inclusion and exclusion of the RFA group. CNB, core needle biopsy; PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma; RFA, radiofrequency ablation; US, ultrasound.

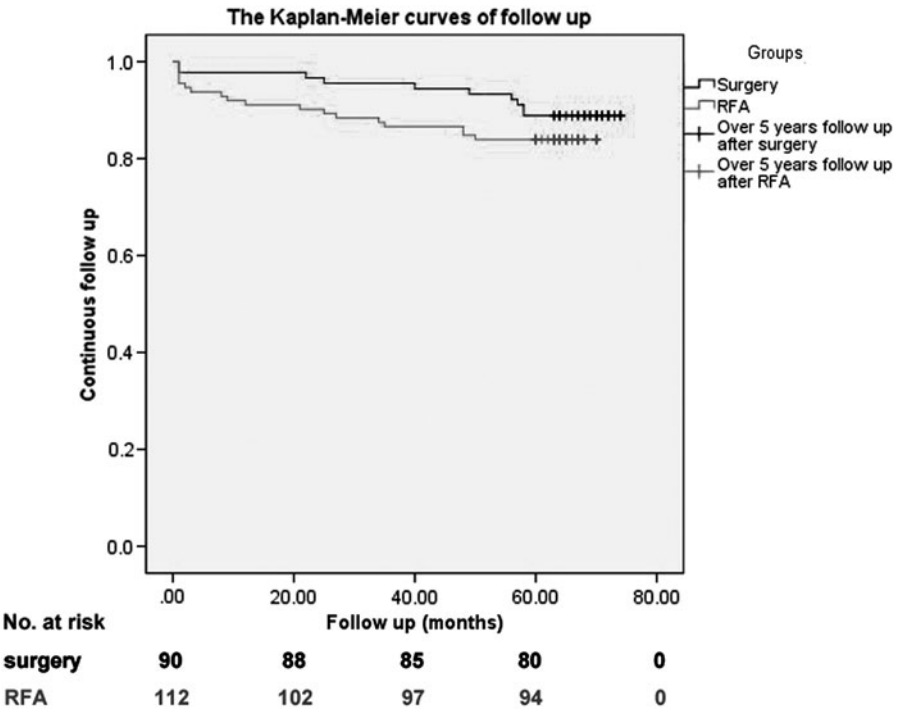

FIG. 2. The Kaplan–Meier curves of follow-up in both groups.

All patients were evaluated with laboratory tests (complete blood count, thyroid function tests), imaging studies including chest radiography, and US of the thyroid and cervical lymph nodes before treatment. When metastasis was identified or suspected based on imaging or other findings, patients were excluded from this study.

For each tumor, the dimensions, volume, and position were evaluated by US. The volume of each tumor was calculated as $V = \pi abc/6$ (where V is the volume, a is the largest dimension, and b and c are the two other perpendicular dimensions).

The diagnosis of PTMC was confirmed by surgical pathologic findings in all patients who underwent surgery. For all patients in the RFA group, PTMC was diagnosed based on pathologic findings by CNB of the lesion before RFA. No pathological diagnosis of the contralateral nodules was obtained except for those who underwent total thyroidectomy, since they had no suspicious malignant US features and no biopsy indications.

Information for each patient was obtained, including demographics, tumor characteristics, and treatment variables (including postoperative hospitalization, operation time, estimated blood loss, blood transfusion, and treatment costs). The RFA procedure time was defined as starting from disinfection of the skin before local anesthesia until the time patients left the procedure room. The time for surgery was defined as the time from incision to skin closure, and it did not include anesthesia time. The costs of RFA included the preoperative examination, operation, local anesthesia, and radiofrequency needle fees. The costs of surgery included the preoperative examination, operation (including the use of nerve monitoring, hemostatic materials, and other consumables, if any), general anesthesia, hospital bed, nursing, and postoperative medication fees. These are the charges that were billed to the patient (Amount Billed) and can be partially reimbursed according to the patient's own medical insurance.

US-guided RFA

All RFA procedures were performed by an experienced ultrasonography physician (K.Y.L.) with >20 years' experience in thyroid and interventional sonography.

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 situated supine with the neck extended during the procedure. Local anesthesia with 1% lidocaine was injected at the subcutaneous puncture site and the thyroid anterior capsule. The area close to the tracheoesophageal groove was defined as the ''danger triangle,'' which is located at the posteromedial area of the thyroid near the trachea, where the recurrent laryngeal nerve is typically located. Patients with tumors in this area are theoretically more challenging to treat fully without risk of complications due to the proximity of critical structures. Moreover, if the distance between the tumor and other critical cervical structures (including the trachea, carotid artery, internal jugular vein, and esophagus) was <5 mm, normal saline with 0.0005% adrenaline was first injected by using a 23-gauge needle to form at least a 1-cm distance between the tumor and the critical structure to reduce the risk of thermal injury. RFA was performed by using the moving-shot technique (25–26). The RFA power was 5 Watts. Contrast-enhanced ultrasound (CEUS) was used to observe the ablation area, which extended past the tumor leading edge by 3 mm.

Surgical technique

Under general anesthesia, thyroid surgery was performed by two surgeons (Z.Q. and W.T.) with >15 years of experience each in thyroid surgery. Of all the patients, 58 (72.5%) underwent lobectomy, 39 (67.2%) of whom underwent ipsilateral central lymph node dissection (CLD) and the remainder (19 patients, 32.8%) did not receive CLD. Twenty-two (27.5%) underwent total thyroidectomy because of nodules in the other lobe (patient preference despite benign sonographic features), 14 (63.6%) of whom underwent ipsilateral CLD and the remaining 8 patients (36.4%) did not receive CLD. The decision to perform total thyroidectomy or lobectomy was made by individual surgeons and patients based on patient preferences in consultation with the surgeon. All patients in the surgery group underwent thyrotropin (TSH) suppression therapy to reduce tumor recurrence risk. TSH was maintained in the mid to lower reference range (0.5–2 mU/L).

Follow-up

The follow-up included thyroid US at 1 and 3 months after treatment for the RFA group and then at 6-month intervals for both groups. In the RFA group, CEUS, which was used to evaluate the ablation range in the liver (38,39) and thyroid (40), was performed after US to verify the effectiveness of ablation. Effectiveness of RFA was defined as the absence of enhancement of any areas of the mass at a follow-up CEUS. We defined local tumor progression to include two situations: (1) new or persistent detected lesions confirmed by biopsy to be PTMC; (2) cervical LNM confirmed by biopsy. DM was detected by computed tomography, positron emission tomography, or bone scan if there were suspicious symptoms. Complications were defined according to thyroid ablation reporting standards (36).

We used the Chinese version of the Thyroid Cancer-specific Quality of Life (THYCA-QoL) questionnaire to evaluate the quality of life of the patients in February 2019, which is a specific scale for thyroid cancer patients based on the method of the European Cancer Research and Treatment Organization, consisting of seven symptom areas (neuromuscular, voice, attention, sympathetic symptoms, throat/-mouth, psychological and sensory problems) and six single items (scar, cold, hand/foot tingling, weight gain, headache, sexual interest) (41). The Chinese version of the THYCA-QoL questionnaire was developed by translation, back-translation, and cultural adaptation by Liu *et al.* (42). The items and score calculation method of THYCA-QoL questionnaire are shown in Appendix Table A1 and Appendix Table A2.

Statistical analysis

Comparison between the RFA and the surgery group was conducted by using Student *t*-test and either Pearson chi-squared test or Fisher exact test for categorical variables. All statistical analyses were performed by using SPSS 16.0 (SPSS, Chicago, IL). A p-value <0.05 was considered significant.

Results

Baseline characteristics showed no difference between the two groups, including mean age, sex, and follow-up time ($p=0.419$, 0.936, and 0.202; Table 1). The mean dimensions and volume of tumors in the two groups had no significant difference ($p=0.737$, 0.097), nor did the side of the tumors ($p=0.227$; Table 2). In the RFA group, all PTMC were ablated in one session. Eleven (11.7%) patients in the RFA group had a PTMC in the ''danger triangle.'' In the surgery group, postoperative pathology confirmed the presence of occult additional cancers in 9 patients (11.3%), which were not detected by US before surgery, and 9 patients (11.3%) with central lymph node metastases (CLM), with single node involvement in 4 patients, two lymph nodes in 4 patients, and five in 1 patient. All the CLM lesions were <2 mm. Of all the 22 patients with nodules in the contralateral lobe who underwent total thyroidectomy, pathological results showed 16 benign and 6 malignant nodules.

Table 1. General Information of Patients Undergoing Radiofrequency Ablation and Surgery

Characteristics	*RFA*	*Surgery*	p
Mean age (years) ± SD	45.4 ± 10.8	44.1 ± 9.6	0.419
Sex, *n* (%)			
Male	24 (25.5)	20 (25.0)	0.936
Female	70 (74.5)	60 (75.0)	
Median follow-up (months)	64.2 ± 2.8	63.6 ± 3.6	0.202

RFA, radiofrequency ablation; SD, standard deviation.

The surgery group had a longer operation time, more blood loss, longer hospitalization time, and higher treatment costs compared with the RFA group (all $p<0.001$; Table 3). There were significant differences of total operation time among the surgical subgroups ($p<0.001$). No significant differences were detected among subgroups in terms of blood loss, hospitalization time, and cost ($p=0.250$, 0.170, and 0.398).

One patient in the RFA group had a new lesion (1 of 94, 1.1%) arising in the remaining thyroid of the ipsilateral lobe, and one patient in the surgery group had a new lesion in the contralateral lobe (1 of 80, 1.3%, $p=0.363$; Table 4). The surgery group comprised one case with cervical LNM in an untreated central neck (1 of 80, 1.3%), and the RFA group comprised no patients with cervical LNM during follow-up (0, $p=0.460$; Table 4). No DM was identified in either group.

In the surgery group, three patients had complications while none were reported in the RFA group ($p=0.095$). Two (2.5%) patients had permanent recurrent laryngeal nerve injury (one lobectomy with CLD, and one total thyroidectomy with CLD), with persistent dysphonia and documented palsy demonstrated by flexible fiberoptic laryngoscopy >6 months after surgery. One (1.3%) patient had permanent hypoparathyroidism (total thyroidectomy with CLD), with low serum calcium and parathyroid hormone after 6 months of continuous use of calcium tablets and vitamin D. All complications occurred in patients who underwent CLD.

Table 2. Tumor Characteristics of Radiofrequency Ablation and Surgery Group

Characteristics	*RFA*	*Surgery*	p
Tumor characteristics			
Mean tumor diameter (mm) ± SD	6.14 ± 2.54	6.03 ± 1.53	0.737
Tumor volume (mm^3)	175.9 ± 228.3	132.7 ± 94.1	0.097
Side of tumor, *n* (%)			0.227
Right	49 (52.1)	49 (61.2)	
Left	45 (47.9)	31 (38.8)	

Table 3. Treatment Variables of the Radiofrequency Ablation and the Surgery Groups

Characteristics	RFA (n = 94)	Total surgery (n = 80)	Subgroups of surgery: Lobectomy (n = 19)	Lobectomy + CND (n = 39)	Total thyroidectomy (n = 8)	Total thyroidectomy + CND (n = 14)	p-Value* (RFA vs. surgery)	p-Value** (subgroups of surgery)
Total operation time (minutes) ± SD	7.99 ± 3.79	62.9 ± 15.9	52.3 ± 8.5	59.1 ± 13.9	69.9 ± 10.1	84.1 ± 10.1	<0.001	<0.001***
Estimated blood loss (mL)	0	26.1 ± 16.5	31.6 ± 23.4	22.7 ± 12.8	25.0 ± 13.1	28.6 ± 15.1	<0.001	0.250
Hospitalization (days) ± SD	0	9.35 ± 4.39	7.6 ± 2.5	9.5 ± 3.9	11.0 ± 6.3	10.4 ± 6.0	<0.001	0.170
Cost ($USD) ± SD	1832 ± 30	2355 ± 1182	2064 ± 955	2342 ± 1022	2367 ± 1150	2783 ± 1774	<0.001	0.398

*Comparison between RFA and total surgery group.
**Comparison among subgroups of surgery group.
***The *p*-values of the overall comparison and comparisons in each two subgroups were all <0.001.
CND, central lymph node dissection.

The THYCA-QoL questionnaire results of the RFA group and the surgery group demonstrated a higher score for the surgery group, which means a worse quality of life, than in the RFA group (Table 5). The interval of time between treatment and THYCA-QoL for the RFA and the surgery group was shown as ''Median follow-up months'' in Table 1, which showed no significant difference (64.2 ± 2.8 vs. 63.6 ± 3.6, $p = 0.202$). Specific domains affected included voice, sympathetic symptoms, throat/mouth problems, psychological problems, sensory problems, problems with scar, cold sensitivity, and weight gain. The total score of domains showed that the surgery group had a lower thyroid-related quality of life. Among subgroups of surgery, total thyroidectomy with ipsilateral CLD had the lowest quality of life.

Discussion

US-guided thermal ablation has been effective in treating benign thyroid nodules (21–24) and recurrent/persistent metastatic thyroid carcinoma in lymph nodes (25–28). These techniques have been used to treat primary PTMC only in recent years. Some clinical studies have shown the efficacy and safety of US-guided ablation (RFA, MWA, and laser ablation) in the treatment of low-risk PTMC (29–37). The RFA guidelines published in 2017 from South Korea recommend thermal ablation as an alternative in patients with primary thyroid cancer who refuse or cannot undergo an operation (43). Others have argued that thermal ablation may result in incomplete treatment compared with surgery, thus leading to higher recurrence rates, persistence, or even DM in long-term follow-up (44,45). This study was designed to demonstrate 5-year outcomes of RFA versus surgery in an academic medical center in China, and it has the longest follow-up of any such study to date to our knowledge. Our results demonstrate that RFA was not inferior to surgery with respect to oncologic efficacy after 5 years. This may, in part, be the indolent nature of PTMC, with very low rates of recurrent, persistent, or distant disease, regardless of treatment strategy or even AS (2,8).

Because PTMC is usually very indolent, quality of life and minimizing morbidity is important. Our study shows that the surgery group had a higher complication rate than the RFA group, findings that are similar compared with a published meta-analysis (14). Two (2.5%) patients had permanent recurrent laryngeal nerve injury. One of them was due to thermal injury caused by energy-based devices during surgery. The other injury was due to inadvertent transection of the recurrent laryngeal nerve.

In our study, we used the THYCA-QoL questionnaire, a specific scale for thyroid cancer patients, to evaluate the quality of life. Our study shows that the overall quality of life in the surgery group was lower than that of the RFA group. AS has been suggested as a viable option for PTMC. However, many patients are anxious about AS and prefer active treatment, similar to the situation with prostate cancer (46).

Table 4. Local Tumor Progression of Two Groups Over 5 Years' Follow-Up

Local tumor progression	RFA (n = 94)	Surgery (n = 80)	Subgroups of surgery: Lobectomy (n = 19)	Lobectomy + CND (n = 39)	(RFA vs. surgery)	Total thyroidectomy + CND (n = 14)	p-Value (RFA vs. surgery)	p-Value (subgroups of surgery)
New lesions, *n* (%)								
Recurrence	1 (1.1)	1 (1.3)	0 (0)	1 (2.6)	0 (0)	0 (0)	0.363	1.000
No recurrence	93 (98.9)	79 (98.7)	19 (100)	38 (97.4)	8 (100)	14 (100)		
Lymph node metastasis, *n* (%)								
Metastasis	0 (0)	1 (1.3)	0 (0)	1 (2.6)	0 (0)	0 (0)	0.460	1.000
No metastasis	94 (100)	79 (98.7)	19 (100)	38 (97.4)	8 (100)	14 (100)		

Table 5. Thyroid Cancer-Specific Quality-of-Life Scores of the Radiofrequency Ablation and the Surgery Groups

			Score-subgroups of surgery					
Domain	*Score-RFA* (n = *94*)	*Score-surgery* (n = *80*)	*Lobectomy* (n = *19*)	*Lobectomy + CND* (n = *39*)	*Total thyroidectomy* (n = *8*)	*Total thyroidectomy + CND* (n = *14*)	p-*Value** *(RFA vs. surgery)*	p-*Value*** *(subgroups of surgery)*
Neuromuscular	1	1.02 ± 0.12	1	1	1	1.33 ± 0.32	0.096	<0.001
Voice	1.02 ± 0.09	1.14 ± 0.41	1.21 ± 0.51	1.06 ± 0.26	1.93 ± 0.78	1.07 ± 0.18	0.013	<0.001
Concentration	1	1	1	1	1	1	—	—
Sympathetic symptoms	1	1.11 ± 0.31	1.13 ± 0.33	1.08 ± 0.22	1	1.32 ± 0.54	0.003	0.061
Throat/mouth problems	1.01 ± 0.08	1.07 ± 0.21	1.14 ± 0.28	1.03 ± 0.17	1	1.05 ± 0.12	0.028	0.172
Psychological problems	1.03 ± 0.09	1.16 ± 0.32	1.22 ± 0.42	1.17 ± 0.31	1	1.16 ± 0.21	0.001	0.403
Sensory problems	1.01 ± 0.06	1.25 ± 0.52	1.08 ± 0.25	1.29 ± 0.52	1.13 ± 0.35	1.93 ± 0.94	<0.001	<0.001
Problems with scar	1.02 ± 0.13	1.44 ± 0.91	1.32 ± 0.95	1.33 ± 0.62	1	1.86 ± 1.23	<0.001	0.088
Felt chilly	1.02 ± 0.13	1.13 ± 0.41	1.21 ± 0.63	1.10 ± 0.31	1	1.21 ± 0.43	0.032	0.532
Tingling hands/feet	1	1.05 ± 0.34	1.11 ± 0.46	1.05 ± 0.32	1	1	0.159	0.773
Gained weight	1.03 ± 0.25	1.23 ± 0.76	1.16 ± 0.69	1.13 ± 0.57	1	1.43 ± 0.85	0.044	0.383
Headache	1	1.06 ± 0.34	1.11 ± 0.46	1.10 ± 0.45	1.25 ± 0.71	1	0.159	0.652
Less interest in sex	1	1.01 ± 0.12	1	1.03 ± 0.16	1	1	0.341	0.795
Total score	13.1 ± 0.36	14.7 ± 2.01	14.7 ± 2.21	14.4 ± 1.43	14.3 ± 1.28	16.4 ± 3.01	<0.001	0.015

*Comparison between RFA and total surgery group.
**Comparison among subgroups of surgery group.

In our study, patients in the surgery group received TSH suppression therapy. Patients in the RFA group did not receive any treatment with levothyroxine. It is likely that this difference affects the thyroid-related quality-of-life scores to some degree, and it may even affect tumor progression or recurrence as we continue to follow this cohort in future years.

One additional concern with this study is that all patients who elected surgery chose open surgery. Remote access alternatives offer improved cosmesis and may improve health-related quality of life in some patients (47–49). While newer remote access options were not readily available in 2013, these patients would have all been excellent candidates for most remote access approaches in 2019 (50).

The cost of medical resources and the cost to patients for the treatment of PTMC should not be ignored, particularly given its high prevalence. In our study, RFA was performed in an outpatient interventional US operating room without hospitalization. Patients left without discomfort after 1 hour of observation. However, in 2013, the patients undergoing surgery underwent hospitalization before surgery and most patients completed preoperative examinations after hospitalization in our hospital, which took several days. Generally, they were discharged 2 to 3 days after the operation. While this is not representative of perioperative surgical treatment in Western countries, these practices resulted in additional costs compared with outpatient RFA. Further study will be needed to see whether RFA, indeed, is less expensive in other national health care environments.

Since PTMC is typically associated with a good prognosis, it is important to ask whether we should just perform AS without performing RFA or surgery. While this is appropriate as per the most recent ATA guidelines (9), not all patients will choose this option. In our practice, a significant majority of patients with PTMC elected intervention rather than AS. This may be due to a selection bias, in that patients often come to our clinic seeking an intervention. Nonetheless, we must enable and assist them in making an informed decision that is acceptable to them.

According to the most recent ATA guidelines, thyroid nodules <1 cm should not be biopsied routinely, but they should be observed for signs of growth or other suspicious findings. However, in China, most patients with suspected PTC undergo a biopsy and subsequent treatment even if nodules or cancer are <1 cm, according to the Chinese guidelines for the diagnosis and treatment of thyroid nodules (51). In this setting, a significant number of patients come under consideration for additional interventions.

In our hospital, CNB was the standard needle biopsy utilized for thyroid pathology in 2013, the diagnostic accuracy of which was 98% according to our data (52). In our study, we used CNB to diagnose PTMC before RFA and surgery instead of fine needle aspiration. CNB can be used for pathological characterization of PTMC, which can help to exclude invasive pathological subtypes.

The risk of recurrent or persistent disease after percutaneous treatment is real. Ma *et al.* have reported 12 ablation cases of PTC who subsequently underwent surgery and demonstrated incomplete ablation; most of these included patients with LNM (45). On closer review, only one patient included was a low-risk PTMC and the rest of the patients had multiple bilateral tumors and/or papillary carcinomas larger than 1 cm. Further, the experience of the sonographers and interventionalists was not described. As per one of the Chinese expert consensus statements, RFA should be utilized ''for PTMC in strictly intrathyroidal cases with full patient consent under the operation of qualified professionals'' (53). Our results demonstrate that RFA was not oncologically inferior to surgery for carefully selected PTMC after 5 years of follow-up, which is the longest such study to date. We also believe that RFA is probably not inferior to AS.

In our study, the PTMC lesions in the RFA group were all in the thyroid parenchyma without extrathyroidal invasion. We can, however, not exclude minimal extrathyroidal extension (mETE). However, many studies have shown that mETE has no effect on disease outcome (54–57). In the 8th edition of the American Joint Committee Cancer guidelines, the threshold for upstaging patients to triiodothyronine classification is gross extrathyroidal extension but not mETE (58).

Our study includes 9 patients with CLM and 9 patients with occult PTMC in the surgery group, which were not detected by US before surgery. We acknowledge that we may have missed occult PTMC and small central LNM when performing RFA. The clinical relevance of this is unclear. Thus, we need larger sample sizes and longer-term follow-up of patients managed with AS, RFA, and surgery. As stated previously, it is likely that oncologic outcomes will be similar for all modalities at 5 years of follow-up, thus reinforcing the need to minimize cost and complications. It is not clear which of the three strategies is associated with the best quality of life, and it is likely that this is also patient specific.

This study has several limitations. Follow-up time in this series, while longer than any such study to date, was only 5 years, and 18 (16.1%) patients were lost to follow-up before that time. Our study population is small and underpowered for such an indolent disease process. In the RFA group, we may have missed occult PTMC and small central LNM when performing RFA; of note, this also applies to AS. It remains unclear whether this is clinically relevant. Also undefined is the safety of salvage surgery. That is, if a cancer recurs or persists after RFA, will surgery be more difficult than a primary surgery would have been? Randomizing and then comparing RFA, surgical, and AS would be especially valuable. The costs of surgery are very different from what would be expected for Western patient populations. In the absence of a final pathology, any needle biopsy may inaccurately diagnose PTMC or miss areas of more aggressive cancer. Finally, the interventional sonographer who performed all cases of RFA in this series is extremely experienced. It remains to be proven whether these results, with regards to oncologic outcomes, costs, complications, or even quality of life, can be generalized to other populations or clinicians.

In conclusion, for carefully selected PTMC, RFA did not have inferior oncologic outcomes after 5 years of follow-up when compared with open surgery in this study. Complications and costs were lower, and quality of life was better. Longer follow-up and additional studies with more patients will be necessary to demonstrate whether these findings are durable or reproducible.

Author Disclosure Statement

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(*Appendix follows* →)

Appendix

Appendix Table A1. Thyroid Cancer-Specific Quality-of-Life Questionnaire

Items
1. Dry mouth
2. Problems of swallowing
3. Hoarseness
4. Weak voice
5. Lump in throat
6. Problems with scar
7. Felt chilly
8. Sensitive heat
9. Hot flushes
10. Pain joints, muscles
11. Tingling hands/feet
12. Cramp leg
13. Felt slowed down
14. Gained weight
15. Eye problems
16. Skin problems
17. Palpitations
18. Headache
19. Abrupt tiredness
20. Difficulty of thinking
21. Attentional problems
22. Restless
23. Anxious
24. Less interest in sex

Instructions: Except for ''Less interest in sex,'' which was asked based on the past 4 weeks, the rest of the items were based on last week. All entries are classified into four levels (no, a little, quite, and very) with the scores from 1 to 4 points.

Appendix Table A2. Method of Calculating Scores of the Thyroid Cancer-Specific Quality of Life

Domain no.	*Domain*	*Score calculation method*
1	Neuromuscular	(Q10 + Q12 + Q13)/3
2	Voice	(Q3 + Q4)/2
3	Concentration	(Q20 + Q21)/2
4	Sympathetic	(Q8 + Q9)/2
5	Throat/mouth problems	(Q1 + Q2 + Q5)/3
6	Psychological	(Q17 + Q19 + Q22 + Q23)/4
7	Sensory	(Q15 + Q16)/2
8	Problems with scar	Q6
9	Felt chilly	Q7
10	Tingling hands/feet	Q11
11	Gained weight	Q14
12	Headache	Q18
13	Less interest in sex	Q24
Total score = Score of Domain 1 +……+ Score of Domain 13		