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Radiofrequency ablation for papillary thyroid microcarcinoma close to the thyroid capsule versus far from the thyroid capsule: a retrospective study

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Abstract

Introduction: The aim of this study was to evaluate the safety and efficacy of ultrasound-guided radiofrequency ablation (RFA) for the management of papillary thyroid microcarcinoma (PTMC) close to the thyroid capsule.

Material and methods: This was a retrospective study of 202 patients with PTMC who underwent RFA close to the thyroid capsule and 80 patients with PTMC who underwent RFA far from the thyroid capsule between June 2015 and December 2022. The follow-up time after RFA, change in size of tumour, location, thyroid function, the rates of PTMC disappearance, and complications were evaluated.

Results: A total of 202 patients with PTMC close to the thyroid capsule and 80 patients with PTMC far from the thyroid capsule successfully treated with RFA were studied. The thyroid function including free triiodothyronine (fT3), free thyroxine (fT4), triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) showed no changes after RFA for one month in both groups. The tumour size was increased at 1, 3, and 6 months after RFA compared with pre-operative RFA in both groups. The tumour size was decreased at 12 and 24 months after RFA compared with pre-operative RFA both in both group. Seventy-nine PTMC close to the thyroid capsule and 30 PTMC far from the thyroid capsule completely disappeared as assessed by ultrasound examination. Eighty-four PTMC patients close to the thyroid capsule and 34 PTMC patients far from the thyroid capsule had minor complications after RFA treatment. The complication rates between the 2 groups were similar.

Conclusion: Ultrasound-guided RFA seems to be an effective and safe method for patients with PTMC close to the thyroid capsule.

Key words: radiofrequency ablation; papillary thyroid microcarcinoma; thyroid nodule; thermal ablation

Introduction

The definition of papillary thyroid microcarcinoma (PTMC) according to the World Health Organization (WHO) is a small papillary thyroid cancer (≤ 10 mm in the largest dimension). The active surveillance (AS) was recommended for patients with low-risk PTMC according to the 2015 American Thyroid Association (ATA) guidelines, which should have no local invasion, regional lymph node, and distant metastasis, because the PTMC risk of cancer-related death is extremely low and it has an excellent prognosis [1–4]. Thyroidectomy is the main management for PTMC for patients who may feel fear. However, thyroidectomy has some complications, for example hypothyroidism, which require long-term levothyroxine sodium tablets after surgery. Therefore, a non-surgical invasive treatment method for PTMC is needed.

Thermal ablation (TA) is an option for patients wishing to treat PTMC actively in a minimally invasive

way due to patient resistance to AS and patient anxiety [5–7]. The most frequently used methods for PTMC TA are radiofrequency ablation (RFA), microwave ablation (MWA), and laser ablation (LA) [8–11]. TA has the advantage of avoiding incisions, taking shorter operative time and reducing the length of stay of inpatients compared with thyroidectomy [12–14]. RFA introduces electrodes into the lesion area, which use an alternating current to generate local thermal energy with a frequency ranging between 200 and 1200 kHz, resulting in tissue necrosis and tissue degeneration due to a high local temperature [15]. RFA is terminated when the area of the nodule becomes hyperechoic on ultrasound or when the impedance increases, or a combination of the two [15]. The 2017 Korean RFA guidelines present the potential therapeutic role of RFA in PTMC patients who refuse or are ineligible for surgery [3].

RFA has been shown to be an effective treatment method for PTMC far from the thyroid capsule.



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However, no previous studies have investigated the use of RFA in PTMC close to the thyroid capsule. The aim of the study was to assess the safety and feasibility of RFA close to the thyroid capsule compared with PTMC far from the thyroid capsule.

Material and methods

Written informed consent was received from each of the patients before RFA. The study was approved by the Institutional Review Board of Zhejiang University School of Medicine Second Affiliated Hospital.

Inclusion criteria were as follows: (1) fine-needle aspiration cytology confirmed classic variant of PTC without evidence of histological aggressiveness associated with the columnar cell variant, tall cell variant, or hobnail variant; (2) unifocal PTMC on examination; (3) maximum diameter of PTMC less than 1 cm; (4) no evidence of gross extra-thyroidal extension, lymph node metastasis, or distant metastasis on both ultrasound and enhanced computed tomography (CT); (5) co-morbidities such as stroke or myocardial infarction; and (6) adequate follow-up time after RFA. Exclusion criteria were as follows: (1) patients had undergone thyroidectomy or TA previously; (2) patients with a family history of thyroid cancer; (3) patients had prior radiation to the head and neck or environmental exposure; and (4) adolescents (patient < 18 years old).

All the patients underwent ultrasound examination performed using Mindary 7S, Aplio 500, GE LOGIQ E9, Supersonic, etc. Ultrasound can delineate the size and extent of nodules in the thyroid, determine the proximity of the nodules to the thyroid capsule, and evaluate the neck for metastatic lymph nodes. The size, location, B-mode ultrasound information, and thyroid function were recorded before fine-needle aspiration (FNA). The volume of the PTMC lesion was calculated using the formula: $V = 0.524 \times a \times b \times c$ (V: volume; a, b, c: the 3 diameters). A contrast enhanced CT scan was performed to ensure there was no lymph node metastasis or extrathyroid metastasis. FNA was performed using a 23 G puncture needle. The cytological result was read by a pathologist with 5 years' experience. Diagnoses of classic variant of PTC were made using standard criteria, by identification of areas with classic characteristics of PTC, including papillary architecture, typical PTC nuclei (enlarged, overlapping, irregular, ground-glass empty nuclei with nuclear grooves), psammoma bodies, and stromal reaction. The cytopathology from FNA revealed that the classic variant of PTC was enrolled in our study.

The RFA device used in the study was the STARmed VIVA. Contrast-enhanced ultrasound (CEUS) was performed to evaluate the PTMC boundary and extension. The shortest distance between the lesion and capsule was recorded. The capsule was divided into the anterior capsule, posterior capsule, medial capsule, and lateral capsule. One per cent lidocaine (5 mL) plus 0.75% ropivacaine (5 mL) was used for local anaesthesia before RFA. For PTMC that are close in proximity to other vital structures, hydrodissection should be applied by 0.9% normal saline in order to prevent thermal injury. The output power of the RFA was 30 W, and the total RFA time was recorded. CEUS was performed after RFA to ensure the appropriate ablation range. The ablation was considered complete when the unenhanced lesion was beyond the margin of PTMC by at least 2 mm. Otherwise, the lesion needed an additional ablation immediately. Adverse effects such as transient pain, hoarse voice, and fever after RFA were recorded by the nurse according to clinical observation or by asking patients.

Patients were followed up 1, 3, 6, 12, 24, and 48 months after RFA with CEUS examination and thyroid function test. FNA was carried out if recurrence or neck lymph node metastasis was suspected. The volume reduction rate (VRR) was measured pre- and post-RFA on ultrasound, and the formula used is as follows:

$$(\text{initial volume} - \text{final volume})/\text{initial volume}.$$

Statistical analysis

Means and standard deviations were used for continuous data; frequencies and percentages were used for categorical data. SPSS 22.0 was used for the analysis. Thyroid function and tumour volume were compared by t-test before and after RFA. P values less than 0.05 were considered to indicate statistical significance.

Results

The article selection process is illustrated in Figure 1. Finally, a total of 282 patients were enrolled in the study between June 2015 and December 2022, including 209 women and 73 men. The baseline of the 2 group was similar (Tab. 1). In total, there were 202 (71.63%) patients with PTMC close to the thyroid capsule and 80 (28.37%) patients with PTMC far from the thyroid capsule. The mean age of patients with PTMC close to the thyroid capsule was 41.52 ± 10.34 years. The mean age of patients with PTMC far from the thyroid capsule was 40.48 ± 11.77 years. The mean follow-up time after RFA was 13 (range 3–48) months. The CEUS image of preoperative and post-operative RFA close to the thyroid capsule and PTMC far from the thyroid capsule (Fig. 2 and 3).

All the patients received RFA treatment successfully according to the plan. No related deaths occurred during or after RFA. The CEUS examination within half an hour after RFA showed that all the tumour had been completely ablated beyond the margin of the tumour by at least 2 mm. The thyroid function before and after RFA is presented in Table 2. Before RFA, the mean \pm standard deviation with normal range was recorded for free triiodothyronine (fT3) (4.36 ± 0.50), free thyroxine (fT4) (12.96 ± 1.33), triiodothyronine (T3) (1.51 ± 0.23), thyroxine (T4) (98.40 ± 17.11), and thyroid-stimulating hormone (TSH) (1.77 ± 1.01) in PTMC close to thyroid capsule group and fT3 (4.43 ± 0.56), fT4 (13.17 ± 1.25), T3 (1.49 ± 0.20), T4 (98.15 ± 17.21), and TSH (1.57 ± 0.81) in PTMC far from thyroid capsule group. The thyroid function including T3, T4, fT3, fT4, and TSH were not significantly different compared with preoperative thyroid function in both groups ($p > 0.05$). After RFA, the mean \pm standard with normal range were recorded for fT3 (4.59 ± 0.58), fT4 (13.64 ± 1.47), T3 (1.53 ± 0.24), T4 (102.41 ± 16.37), and TSH (1.49 ± 0.87) in the PTMC close to thyroid capsule group and fT3 (4.64 ± 0.64), fT4 (14.17 ± 1.95), T3 (1.55 ± 0.26), T4 (104.03 ± 19.45), and TSH (1.26 ± 0.89) in the PTMC far from the thyroid capsule group. All the p-value of T3, T4, fT3, fT4, and TSH before RFA and after RFA for 1M in the PTMC close to thyroid capsule group and in the PTMC far from thyroid capsule group were > 0.05 .

The mean maximum diameter of PTMC before RFA close to thyroid capsule group and PTMC far from thyroid capsule group were 0.52 ± 0.17 cm and 0.47 ± 0.15 cm, respectively. The mean volume of

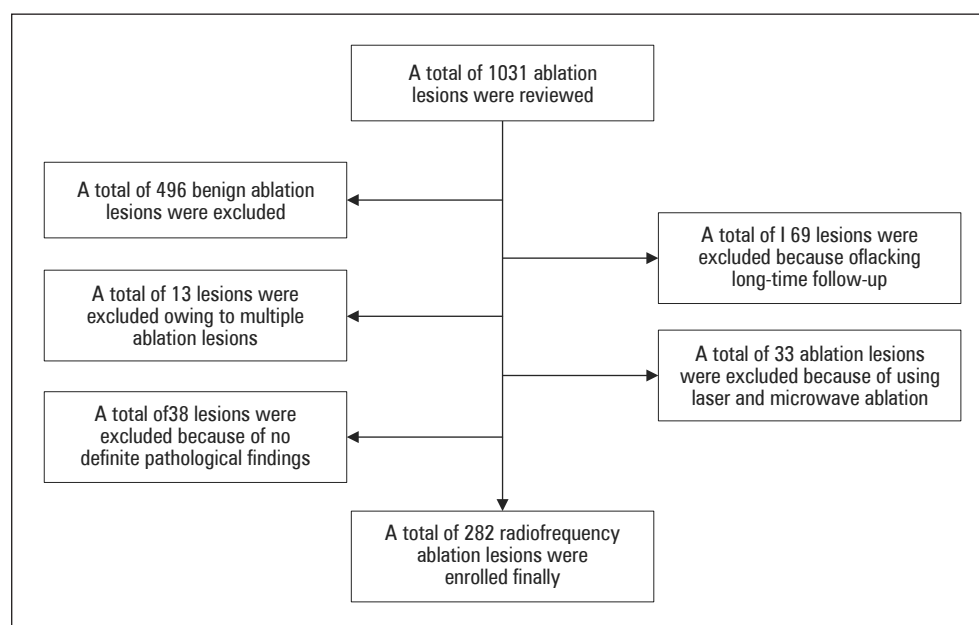


Figure 1. Flow diagram of the study

Table 1. Demographic characteristics of the papillary thyroid microcarcinoma (PTMC) close to the thyroid capsule and PTMC far from the thyroid capsule groups in the study

Variables	Close to thyroid capsule group	Far from thyroid capsule group	Total
Age [years]	41.52 ± 10.34	40.48 ± 11.77	41.22 ± 10.75
Sex			
Female	153	56	209
Male	49	24	73
Location			
Left	81	39	120
Right	94	40	134
Isthmus	27	1	28
B-mode			
Largest diameter [cm]	0.52 ± 0.17	0.47 ± 0.15	0.51 ± 0.16
Microcalcification (Yes/No)	63/139	27/53	90/192
Taller than wide (Yes/No)	160/42	69/11	229/53
Follow up (months)	13.17 (3–48)	12.75 (3–36)	13.05 (3–48)
Ablation time (s)	100.52 (28–298)	96.91 (40–201)	99.50 (28–298)

PTMC close to the thyroid capsule group and PTMC far from the thyroid capsule group were 0.067 cm³ and 0.049 cm³, respectively. The PTMC size before and after RFA is summarized in Table 3. The complete disappearance rates of PTMC were 22 (10.28%), 72 (37.70%), 96 (80.67%), 101 (94.39%), and 101 (98.06%) at the 6-month, 12-month, 24-month, 36-month, and 48-month follow-up after RFA.

No major complications appeared in both the PTMC close to thyroid capsule group and the PTMC far from thyroid capsule group. Eighty-four patients had minor complications after RFA in the close to the thyroid capsule group, including transient pain (n = 64), fever (n = 20), and hoarse voice (n = 9). Thirty-four patients had minor complications after RFA in the far from the thyroid capsule group, including transient pain (n = 30), fever

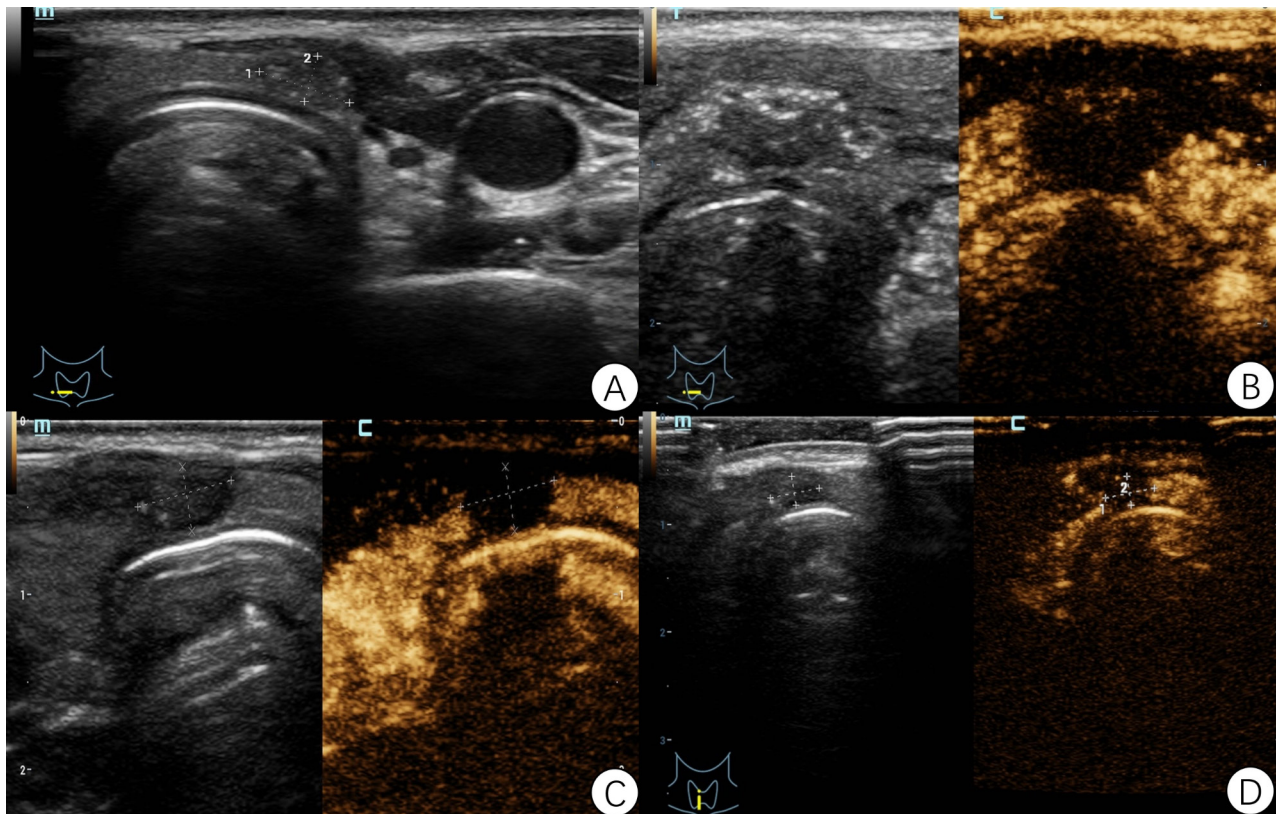


Figure 2. Radiofrequency ablation (RFA) of papillary thyroid microcarcinoma (PTMC) close to the thyroid capsule. **A.** The pre-ablation lesion was in the isthmus of the right thyroid lobe. The contrast-enhanced ultrasound (CEUS) examination was reviewed a day (**B**), 3 months later (**C**), and one year (**D**) after RFA

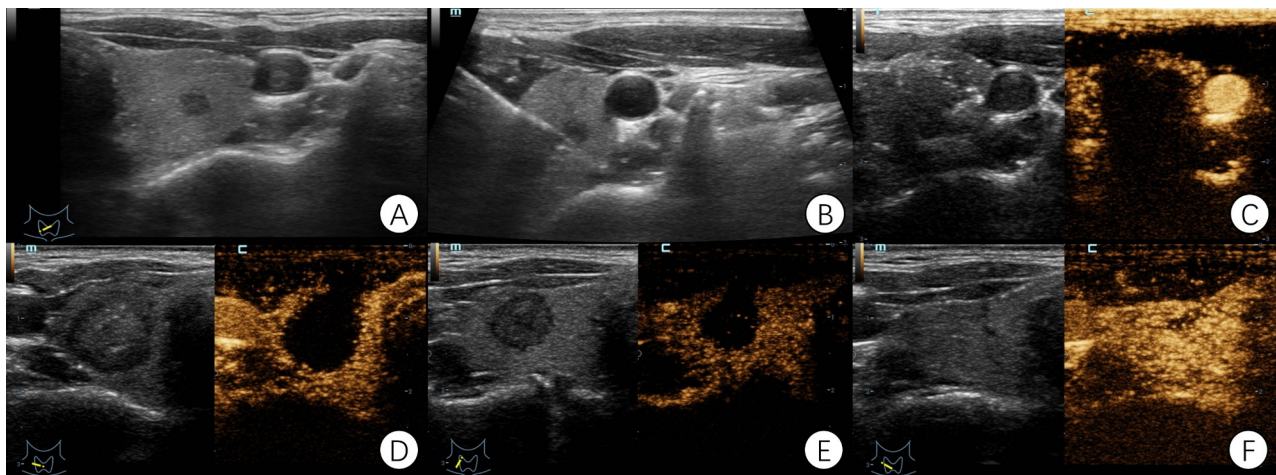


Figure 3. Radiofrequency ablation (RFA) of papillary thyroid microcarcinoma (PTMC) far from the thyroid capsule. **A.** The lesion was in the right thyroid lobe; **B.** Ablation needle was inserted into the lesion. The contrast-enhanced ultrasound (CEUS) examination was reviewed one day (**C**), one month (**D**), 6 months (**E**), and one year (**F**) after RFA

($n = 8$), and hoarse voice ($n = 7$). Transient pain was totally relieved within 3 days. Sixteen patients experienced voice changes, and they had a recovery time of approximately 10 minutes to 6 months. No patient had permanent voice change as a complication. In all the pa-

tients with fever the temperature did not exceed 38.5°C . Four patients had contralateral thyroid PTMC recurrence in the close to the thyroid capsule group, and one patient had ipsilateral thyroid PTMC recurrence in the far from the thyroid capsule group after RFA.

Table 2. The thyroid function before radiofrequency ablation (RFA) and after RFA for 1M in the close to the thyroid capsule group and the far from the thyroid capsule group

Blood test	Close to thyroid capsule group		Far from thyroid capsule group	
	Before RFA	After RFA for 1M	Before RFA	After RFA for 1M
fT3 [pmol/L]	4.36 ± 0.50	4.59 ± 0.58	4.43 ± 0.56	4.64 ± 0.64
fT4 [pmol/L]	12.96 ± 1.33	13.64 ± 1.47	13.17 ± 1.25	14.17 ± 1.95
T3 [nmol/L]	1.51 ± 0.23	1.53 ± 0.24	1.49 ± 0.20	1.55 ± 0.26
T4 [nmol/L]	98.40 ± 17.11	102.41 ± 16.37	98.15 ± 17.21	140.03 ± 19.45
TSH [mIU/L]	1.77 ± 1.01	1.49 ± 0.87	1.57 ± 0.81	1.26 ± 0.89

fT3 — including free triiodothyronine; fT4 — free thyroxine; T3 — triiodothyronine; T4 — thyroxine; TSH — thyroid-stimulating hormone

Table 3. The maximum diameter and volume of papillary thyroid microcarcinoma (PTMC) before radiofrequency ablation (RFA) and the maximum diameter and volume of ablation lesion after RFA in the close to the thyroid capsule group and the far from the thyroid capsule group

Follow-up time	Maximum diameter [cm]		Volume [cm ³]	
	Close to thyroid capsule group	Far from thyroid capsule group	Close to thyroid capsule group	Far from thyroid capsule group
Before RFA	0.52 ± 0.17	0.47 ± 0.15	0.067	0.049
After RFA				
1M	1.27 ± 0.43	1.22 ± 0.29	0.62	0.67
3M	0.87 ± 0.36	0.85 ± 0.29	0.22	0.23
6M	0.58 ± 0.33	0.57 ± 0.28	0.084	0.077
12M	0.35 ± 0.34	0.32 ± 0.28	0.042	0.022
24M	0.09	0.08	0.0053	0.0059

Discussion

RFA can be used as an effective and safe method for the treatment of PTMC close to thyroid capsule and PTMC far from thyroid capsule, as shown in our study. RFA is a minimally invasive alternative with promising outcomes and preservation of thyroid parenchyma, which that reduces the need for post-treatment replacement thyroid hormone, as reported [16–18]. Compared with surgery, patients benefit from RFA because it is associating with shorter hospitalization time, no neck scars, and lower rates of complications [19, 20]. In our study, no one needed levothyroxine after RFA in either of the groups.

Approximately 28 (9.93%) of the PTMCs were located in the isthmus in our study. Although the isthmus is close to the anterior cervical musculature and the trachea, it is not an absolute contraindication to TA. A clinical study that enrolled 21 isthmus-PTMC patients showed that TA was an effective treatment strategy [17]. No lymph node metastasis was found in the close to the thyroid capsule group and the far from the thyroid capsule group in the follow-up examination. However, 4 (1.98%) PTMC patients in

the close to the thyroid capsule group had contralateral recurrence, and one (1.25%) PTMC patient in the far from the thyroid capsule group had ipsilateral recurrence. There was no significant difference in recurrence after RFA in PTMC patients between the close to the thyroid capsule group and the far from the thyroid capsule group.

The main complications of TA in PTMC are fever, bleeding, pain, voice changes, and changes in thyroid function. Published studies report that the overall complication rate of RFA is 2.38% and the major complication is transient voice change (1.45%) [21]. In our study, 16 transient voice changes occurred due to transient damage to the recurrent laryngeal nerve. Our study reported complications besides transient voice change including pain (n = 94, 33.33%) and fever (n = 28, 9.93%). The transient pain was the most common complication in our study, treated with ice compress (n = 94, 100%) for relief. The study by Wang et al. [22] demonstrated that patients have a 100% incidence of postoperative pain after TA. The duration of pain was short and the degree of pain was light, so the criteria for assessing postoperative pain are difficult to establish. In our study, no patient pain was hard to

Table 4. The case number, volume reduction rate (VRR), and complete disappearance rate after radiofrequency ablation (RFA) in the close to the thyroid capsule group and the far from the thyroid capsule group

Follow-up time	Close to thyroid capsule group			Far from thyroid capsule group		
	Case number	VRR	Complete disappearance rate n (%)	Case number	VRR	Complete disappearance rate n (%)
After RFA						
1M	177	-17.32	0	72	-23.15	0
3M	164	-4.99	4 (2.44)	60	-7.18	1 (1.67)
6M	157	-1.42	16 (10.19)	57	-1.49	6 (10.53)
12M	137	0.43	52 (37.96)	54	0.15	20 (37.04)
24M	87	0.78	69 (79.31)	32	0.90	27 (84.38)
36M	76	0.085	73 (96.05)	31	0.97	28 (90.32)
48M	75	1.00	73 (97.33)	28	1.00	28 (100.00)

endure or widespread and long-term. Ninety-four patients had mild pain on the postoperative day and got relief within 3 days.

After RFA, the PTMC volume is likely to increase for the first 3–6 months, but it may decrease in the following 12–24 months. This is due to ablation of a margin of normal tissue around the tumour, which can give the false impression that the PTMC is progressing. The mean VRR was 17.32, 4.99, 1.42, 0.43, 0.78, 0.085, and 1.00 at 1, 3, 6, 12, 24, 36, and 48 months after RFA in the PTMC close to the thyroid capsule group, and the mean VRR was 23.15, 7.18, 1.49, 0.15, 0.90, 0.97 and 1.00 at 1, 3, 6, 12, 24, 36, and 48 months after RFA in the PTMC far from the thyroid capsule group, respectively (Tab. 4). There was no significant difference between the PTMC close to the thyroid capsule group and the PTMC far from the thyroid capsule group. The possible predictive factors related to VRR were the initial volume, applied energy, and hardness of the ablation zone. There were no clear predictors of VRR after RFA.

In our study, no patient had lymph node metastasis in the follow-up using ultrasound examination.

Our study showed that the distance of the PTC from the thyroid capsule was not associated with lymph node metastasis. Four patients had contralateral thyroid PTMC recurrence in the close to the thyroid capsule group, and one patient had ipsilateral thyroid PTMC recurrence in the far from the thyroid capsule group after RFA.

Our study has some limitations. First, we use ultrasound and enhanced CT to detect the regional lymph node and distant metastases. However, some regional lymph node metastases are difficult to detect. Second, although the mean follow-up period was 13 months, it was not long enough to completely evaluate the treatment

outcome. Third, the number of included studies was relatively small, and only one kind of TA was included in the study. Fourth, this was a single-centre study, and large-sample multicentre studies need to be done.

In conclusion, RFA was shown to be safe and effective for long-term local tumour control for low-risk PTMC, whether close to the thyroid capsule or far from the thyroid capsule, in patients ineligible for surgery or those who do not wish to undergo AS.

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Data availability

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author upon reasonable request.

Ethics statement

Written informed consent was waived by the Institutional Review Board.

Author contributions

P.H., Z.L. designed this study. T.H., P.J., Y.S., Y.C. acquired the data. J.L., T.H. wrote the main manuscript text. All authors reviewed the manuscript.

Conflict of interest

The authors confirm no conflict of interests related to this study.

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