

Microwave Ablation for Papillary Thyroid Microcarcinoma with and without US-detected Capsule Invasion: A Multicenter Prospective Cohort Study

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Conflicts of interest are listed at the end of this article.

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Background: Microwave ablation (MWA) has achieved favorable results in the treatment of papillary thyroid microcarcinoma (PTMC) confined in glandular parenchyma. However, studies on the outcome of MWA for PTMC with US-detected capsular invasion remain unclarified in the literature.

Purpose: To compare the feasibility, effectiveness, and safety of MWA in the treatment of PTMC with and without US-detected capsular invasion.

Materials and Methods: Participants from 12 hospitals with a PTMC maximal diameter of 1 cm or less without US- or CT-detected lymph node metastasis (LNM) who planned to undergo MWA were enrolled in this prospective study between December 2019 and April 2021. All tumors were evaluated with preoperative US and were divided into those with and those without capsular invasion. The participants were observed until July 1, 2022. The primary end points, including technical success and disease progression, and the secondary end points, including treatment parameters, complications, and tumor shrinkage during follow-up, were compared between the two groups, and multivariable regression was performed.

Results: After exclusion, 461 participants (mean age, 43 years $\pm$ 11 [SD]; 337 women) were included: 83 with and 378 without capsular invasion. After one participant with capsular invasion aborted MWA because of technical failure, 82 participants with and 378 participants without capsular invasion (mean tumor volume, 0.1 mL $\pm$ 0.1 vs 0.1 mL $\pm$ 0.1; $P = .07$) were analyzed with a mean follow-up period of 20 months $\pm$ 4 (range, 12–25 months) and 21 months $\pm$ 4 (range, 11–26 months), respectively. In those with and those without capsular invasion, comparable technical success rates were achieved (99% [82 of 83] vs 100% [378 of 378], $P = .18$), with one and 11 complications, respectively (1% [one of 82] vs 3% [11 of 378], $P = .38$). There was no evidence of differences in disease progression (2% [one of 82] vs 1% [four of 378]; $P = .82$) or tumor shrinkage (mean, 97% $\pm$ 8 [SD] vs 96% $\pm$ 13; $P = .58$).

Conclusion: Microwave ablation was feasible in the treatment of papillary thyroid microcarcinoma with US-detected capsular invasion and showed comparable short-term efficacy with or without the presence of capsular invasion.

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Clinical trial registration no. NCT04197960

Supplemental material is available for this article.

Papillary thyroid microcarcinomas (PTMCs), most of which are low risk and have a favorable prognosis, contributed mainly to the increased incidence of thyroid cancer (1). Current guidelines recommend surgical resection or active surveillance for PTMCs (2,3). Although PTMCs are relatively indolent, most patients prefer treatment rather than active surveillance because of anxiety about cancer (4). However, surgery may lead to more harm than benefit due to surgery-related complications, such as permanent recurrent laryngeal nerve injury, inadvertent hypoparathyroidism (5), cosmetic problems, and lifelong need

for thyroid hormone replacement (6,7), which might not be accepted by all patients.

Microwave ablation (MWA), a minimally invasive thermal ablation (TA) modality, provides an intermediate option for patients (8). Recent studies have reported promising results of TA in the treatment of PTMC, and it is considered an alternative to surgery (9–11). However, performing MWA for PTMC with clinically aggressive features remains controversial (11,12).

One previous study indicated that capsular invasion was an independent risk factor for lymph node metastasis (LNM) in papillary thyroid carcinoma (13). Another

Abbreviations

LNM = lymph node metastasis, LTR = local tumor recurrence, MWA = microwave ablation, PTMC = papillary thyroid microcarcinoma, TA = thermal ablation

Summary

Microwave ablation was a feasible and effective method with which to treat papillary thyroid microcarcinoma with and without US-detected capsular invasion.

Key Results

- In a prospective study, 461 participants with papillary thyroid microcarcinoma who planned to undergo microwave ablation were divided into those with ($n = 83$) and those without capsular invasion ($n = 378$) (mean follow-up, 20 months $\pm$ 4 [SD] and 21 months $\pm$ 4, respectively).
- No differences were observed in volume reduction rate (mean, 97% $\pm$ 8 vs 96% $\pm$ 13; $P = .58$) or disease progression (2% vs 1%; $P = .82$).
- In those with and those without capsular invasion, comparable technical success rates were achieved (99% vs 100%), with one versus 11 complications (1% vs 3%).

study indicated that shorter distance between the tumor and the thyroid capsule was associated with a higher risk of LNM (14). On the other hand, other studies have revealed no embryologic, anatomic, or histologic evidence of a continuous or homogenous fibrous capsule in the thyroid gland, with capsular invasion having no prognostic importance (15–17). In the eighth American Joint Committee on Cancer TNM staging system, the concept of minimal extrathyroid extension (including capsular invasion) has been deprecated (18).

To date, PTMC with US-detected capsular invasion has been excluded from TA over a few concerns. First, the clinical relevance of capsular invasion is controversial (17,19). Second, because of closer proximity to critical structures, such as the trachea, esophagus, and recurrent laryngeal nerve, TA for PTMC with capsular invasion may be associated with a greater risk of complications (20). Third, in the setting of capsular invasion, the space for ablation is limited, making technical success more difficult to achieve, which may lead to higher risk of local tumor recurrence (LTR) (20). Although a retrospective study has shown MWA is an effective, safe, and feasible method with which to treat PTMC close to the thyroid capsule (21), the outcomes of TA for treating PTMC with US-detected capsular invasion have not been fully explored.

We hypothesized that MWA in the treatment of PTMC might achieve similar efficacy and safety for lesions with and those without US-detected capsular invasion. This study aims to compare the feasibility, effectiveness, and safety of MWA in the treatment of PTMC with and without US-detected capsular invasion.

Materials and Methods

Participants

This prospective multicenter study (ClinicalTrials.gov identifier, NCT04197960) was approved by the institutional ethics committees of the Chinese PLA General Hospital and all other

participant centers. Written informed consent for MWA and inclusion in this study was obtained from all participants before ablation. The data of some participants with PTMC were reported in our previous multicenter studies (22), although the aims of the current study were different. In accordance with the 2017 American Thyroid Association guidelines, MWA was performed only in those participants who refused or were ineligible for surgery.

Between December 2019 and April 2021, we included participants from 12 hospitals with PTMC who planned to undergo MWA. The inclusion criteria were (a) solitary suspicious thyroid nodule diameter of 1 cm or less detected with US; (b) no US- or CT-depicted LNM or distant metastasis; (c) papillary thyroid carcinoma pathologically confirmed with fine-needle aspiration or core-needle biopsy but without histopathologically or immunohistochemically proven aggressive histologic types, according to the World Health Organization classification of thyroid tumors; and (d) no prior neck irradiation or surgery. The exclusion criteria were (a) tumors with US-apparent extrathyroid extension, multicentricity, or participants with coexisting malignancies, such as medullary carcinoma; and (b) severe conditions (Table S1) or preoperative vocal cord palsy.

We defined US-detected capsular invasion with features of capsular abutment by the nodule, subtle capsular distortion or disruption, or bulging of the normal thyroid contour but without replacement of the strap muscle or obtuse margins between the tumor and trachea, esophagus, mediastinal vessels, or carotid artery (23) (Appendix S1). The enrolled participants were then put into two groups: those with and those without capsular invasion.

Preablation Evaluations and Determination of Subgroups

Pretreatment assessment was performed as previously described (24), and details are provided in Appendix S2. For the tumor without US-detected capsular invasion, a minimum distance from the tumor edge to the thyroid capsule of 2 mm or less was defined as close to the capsule, while a minimum distance of more than 2 mm was defined as distant from the capsule. The close and distant subgroups were divided accordingly.

MWA Procedure

All procedures were performed by experienced radiologists (P.L., Z.G.C., Z.Y.H., H.W., M.A.Y., S.R.W., Y.C.) with more than 12 years of experience in diagnostic thyroid US and more than 7 years of experience in US-guided interventions (Table S1).

Tumors without Capsular Invasion

MWA was performed as previously described (9), and details are provided in Appendix S3. For tumors distant from the capsule, the target ablation zone extended at least 2 mm from the original tumor margin (Fig 1).

Tumors with Capsular Invasion

Hydrodissection was used to separate the tumor-adjacent capsule from the surrounding tissue at a safe distance. For the part of tumor with capsular invasion, the adjacent thyroid capsule was also ablated, while for the other part of the tumor that was not

adjacent to the capsule, at least 2 mm of normal thyroid tissue was ablated to achieve the safety margin. For tumors that could not be effectively separated from the trachea or blood vessels by hydrodissection, MWA was abandoned, and surgery was recommended (Fig 2).

Postablation Evaluation and Follow-Up

All participants were evaluated with thyroid US and functional examination (fT3, fT4, TSH) at the 3rd, 6th, and 12th months in the 1st year after ablation, every 6 months in the 2nd year after ablation, and every 12 months thereafter. Contrast-enhanced US was performed 6 months and 12 months after ablation to verify effectiveness of the treatment. The effectiveness of ablation was defined as the absence of enhancement in any areas of the original tumor. Biopsy was performed for imaging-suspected LTR or LNM. Additional ablation or surgical resection was performed for unsuccessfully treated or recurrent tumors based on the request of participants. CT of the neck and chest was performed annually to monitor for distant metastases.

Study End Points

The primary end points were technical success and disease progression. Technical success was defined as absence of enhancement in the tumor on contrast-enhanced US images obtained immediately after ablation. Disease progression was defined as any occurrence of LTR, new thyroid cancer, LNM, distant metastasis, or PTC-related death. LTR was defined as biopsy-confirmed papillary thyroid cancer at the edge of the ablation zone, and new thyroid cancer was defined as new recurrent malignant thyroid tumor in another area of the thyroid gland. LNM was defined as biopsy-confirmed newly detected metastatic lymph nodes in the neck. Distant metastasis was defined as metastasis outside the neck found on CT or PET images or detected with a bone scan.

The secondary end points included the treatment parameters, complications, and volume reduction rate during the follow-up period. The ablation time was calculated by starting ablation after the antenna entered the tumor and ending with the

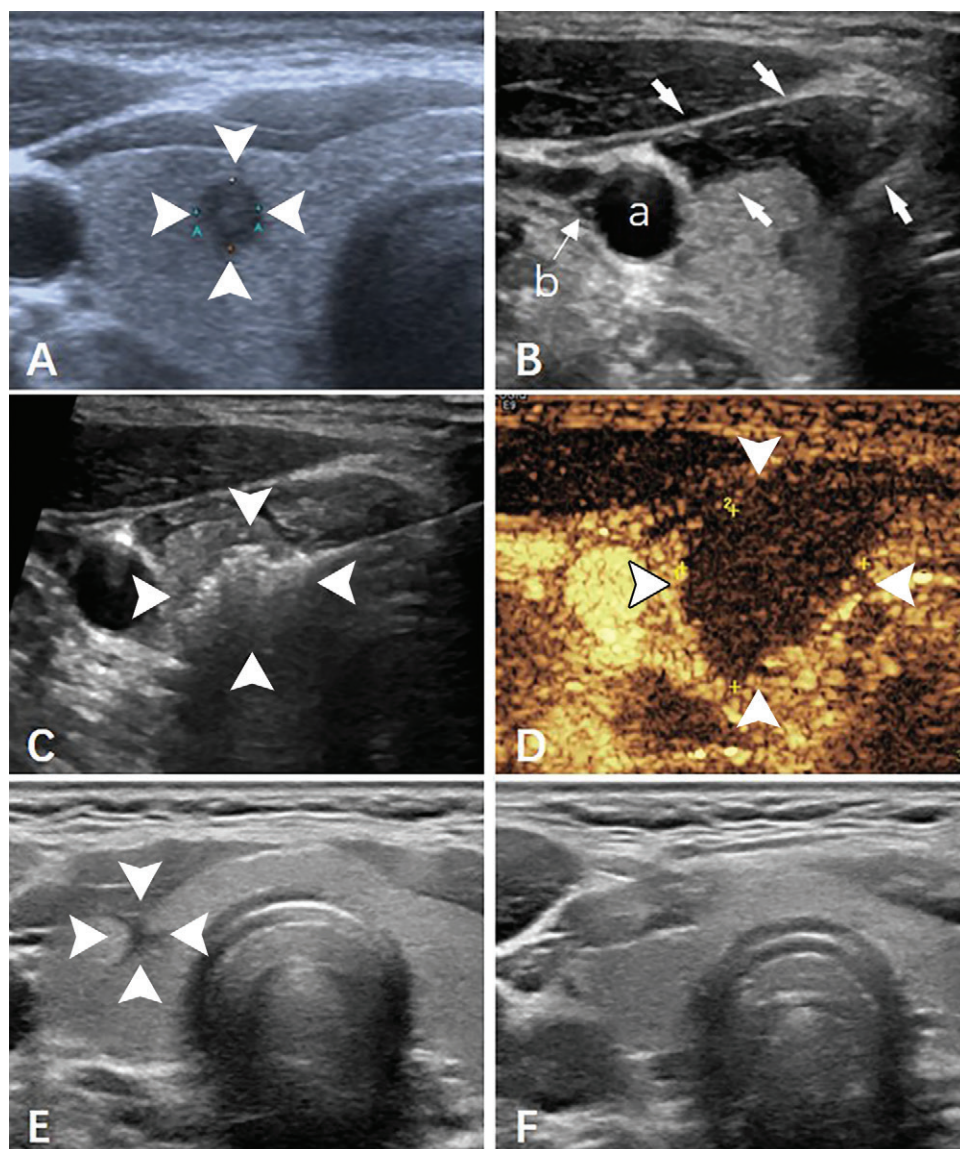


Figure 1: US images in a 36-year-old man with papillary thyroid carcinoma in the right lobe of the thyroid. **(A)** Preablation image of the tumor (arrowheads). **(B)** The hydrodissection technique (arrows) was used to protect the carotid artery (a) and vagus nerve (b). **(C)** Hyperechoic pattern in the tumor during the ablation procedure (arrowheads). **(D)** Postablation contrast-enhanced image shows no enhancement in the tumor area (arrowheads). **(E)** Image of the ablation zone 6 months after ablation (arrowheads). **(F)** The ablation area has almost disappeared 1 year after ablation.

cessation of power. Intraoperative and immediate postoperative pain scores were scaled from 0 to 10 with a visual analogue scale. Monitoring time was calculated from the completion of the ablation procedure until the participant was discharged. Major complications were defined according to the reporting standards of thyroid ablation (25); minor complications were not evaluated. Volume reduction rate, or VRR, was calculated as follows: $VRR = (T - A) \times 100 / T$, where T is initial tumor volume and A is ablation zone volume.

Statistical Analyses

Quantitative data measurements were described as the mean $\pm$ SD and the range. The Student unpaired t test was used to compare quantitative data of two groups. The χ^2 test or Fisher exact test was performed for categorical data comparisons. Re-

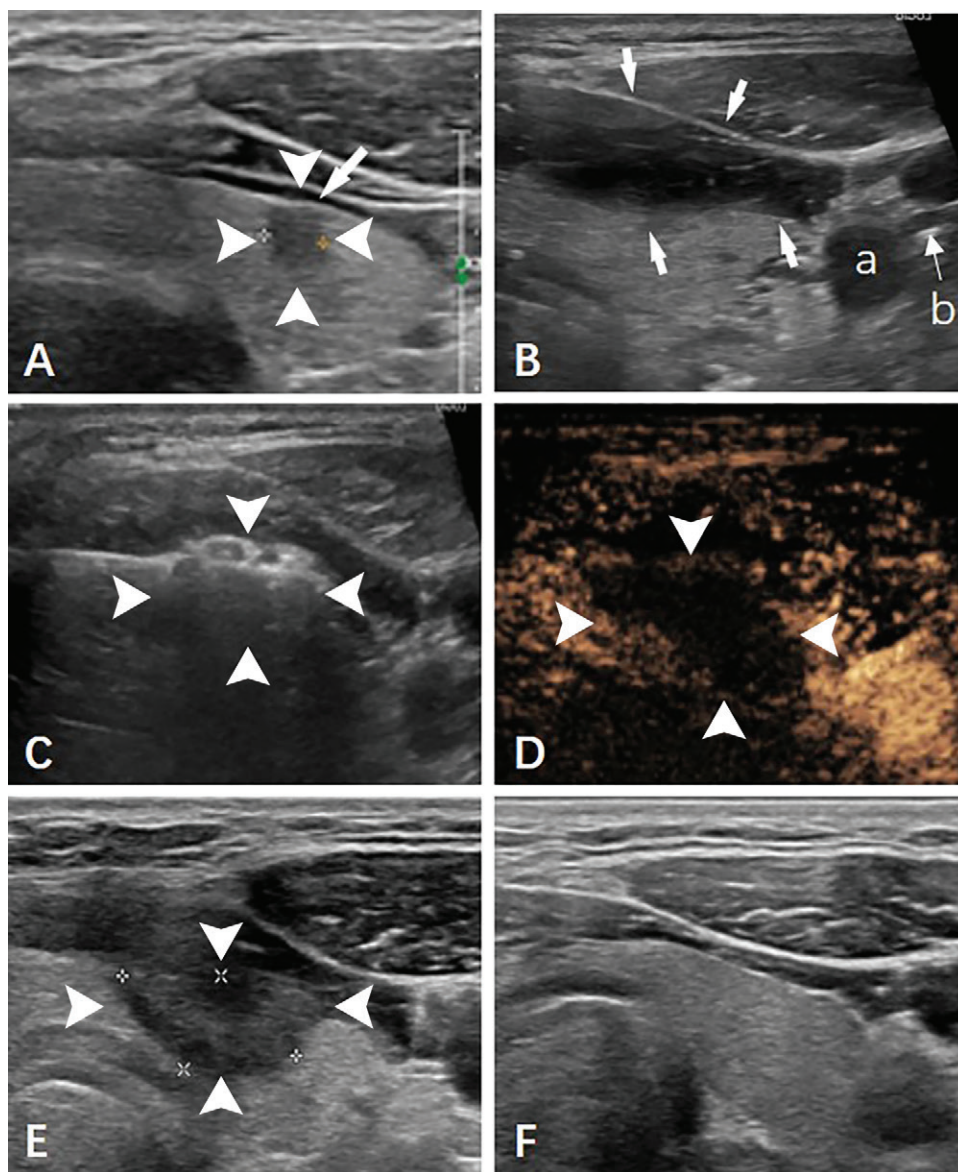


Figure 2: US images in a 30-year-old woman with papillary thyroid carcinoma show minimal invasion of the capsule in the left lobe of the thyroid. **(A)** Preablation image of the tumor (arrowheads) with capsular invasion (arrow). **(B)** The hydrodissection technique (arrows) was used to protect the carotid artery (a) and vagus nerve (b). **(C)** Hyperechoic pattern in the tumor during the ablation procedure (arrowheads). **(D)** Postablation contrast-enhanced image shows no enhancement in the tumor area (arrowheads). **(E)** Image of the ablation zone 6 months after ablation (arrowheads). **(F)** The ablation area had almost disappeared 1 year after ablation.

peated-measures analysis of variance was used for comparison of changes in the volume of each tumor before ablation and at each follow-up visit. Participants' progression-free survival curves and cumulative tumor disappearance curves were generated by using the Kaplan-Meier method, and between-group differences were assessed with the log-rank test. The effect of participant age and tumor location on the outcomes (hazard ratios and their 95% CIs) was calculated using the Cox and logistic proportional hazards regression model to control for their confounding at the primary comparison. The comparison with subgroups was post hoc. $P < .05$ indicated a significant difference. All analyses were performed with SPSS version 26 (IBM) and R Studio software (version 4.0.0; R Foundation for

Statistical Computing) by a radiologist (L.Z., with 3 years of experience in statistical analysis) with the help of a statistician with 12 years of experience in statistical analysis.

The sample size was calculated with PASS 15.0 software (NCSS): $1-\beta = 0.8$, $R = 4.5$. The disease progression rates were assumed to be 10% in the group with capsular invasion and 1% in the group without capsular invasion, and the results showed 80 and 360 participants were needed for the group with and the group without capsular invasion, respectively. The power analysis regarding disease progression in the group with and the group without capsular invasion was calculated using PASS 15.0 software (NCSS).

Results

Participants and Tumor Characteristics

Among 478 participants with PTMC who chose MWA, 461 (mean age, 43 years $\pm$ 11 [SD], 337 women) were included after exclusion of 17 participants. The numbers of tumors with and without capsular invasion were 83 and 378, respectively (Fig 3). The number of enrolled participants in the 12 participating institutions is listed in Table S2. In the group with capsule invasion, one participant aborted MWA due to hydrodissection failure (technical failure); thus, 460 participants were enrolled

for treatment effectiveness and safety analysis. The mean follow-up periods for the group with ($n = 82$) and the group without ($n = 378$) capsular invasion were 20 months $\pm$ 4 and 21 months $\pm$ 4, respectively ($P = .17$).

The demographic and clinical characteristics of enrolled participants are listed in Table 1, and tumor characteristics are shown in Table 2. The group with capsular invasion was younger (mean age, 40 years $\pm$ 11 vs 43 years $\pm$ 11; $P = .03$), with a larger proportion of tumors located in the isthmus (12% [10 of 82] vs 3% [12 of 378], $P = .002$), than the group without capsular invasion. There was no evidence of differences between the two groups in terms of sex, body mass index, Charlson comorbidity index, thyroid disease, laboratory studies, tumor size, and US tumor features.

Technical Success and Oncologic Outcomes

Hydrodissection failure occurred in one patient with capsular invasion, and the technical success rates were 99% (82 of 83) versus 100% (378 of 378), respectively, for the group with and the group without capsular invasion ($P = .18$). The oncologic outcomes of both groups are shown in Table 3. At the last follow-up, the disease progression was 1% (one of 82) versus 2% (six of 378) in the group with and the group without capsular invasion ($P = .82$). There was no evidence of difference in LTR (0% [0 of 82] vs 1% [two of 378], $P = .52$) or LNM (1% [one of 82] vs 1% [four of 378], $P = .89$). All LNMs were found in the ipsilateral cervical region. Neither new thyroid cancer nor distant metastasis was found in either group during the follow-up periods. In the close subgroup, LTR and LNM occurred in 1% (two of 156) and 3% (four of 156) of patients, while no LTR or LNM was found in the distant subgroup. There was no evidence of a difference in oncologic outcomes when comparing the group with capsular invasion with the distant or close subgroups.

Treatment Parameters and Complications

Treatment parameters and complications of both groups are shown in Table 4. All participants tolerated the MWA procedure. The total energy (mean, 4139 J $\pm$ 2958 vs 4056 J $\pm$ 3090; $P = .83$), mean ablation time (mean, 156 seconds $\pm$ 129 vs 151 seconds $\pm$ 119; $P = .71$), and volume of hydrodissection of the group with and the group without capsular invasion (mean, 23 mL $\pm$ 20 vs 24 mL $\pm$ 24; $P = .79$) did not show any differences. The intraoperative pain score (mean, 2.5 $\pm$ 1.2 vs 2.7 $\pm$ 1.3; $P = .30$), immediate postoperative pain score (mean, 1.5 $\pm$ 0.9 vs 1.6 $\pm$ 1.1; $P = .56$), and monitoring time of the group with and the group without capsular invasion (mean, 1.4 days $\pm$ 1.1 vs 1.3 days $\pm$ 0.9; $P = .67$) also had similar results.

The complication incidence in the group with and the group without capsular invasion was 1% [one of 82] and 3% [11 of 378], respectively ($P = .38$). The complication that occurred in the group with capsular invasion was hoarse voice, while the complications that occurred in the group without capsular invasion were hoarse voice (13% [10 of 378]), cough (1% [five of 378]), and Horner syndrome (0% [one of 378]). Of all the complications in the group without capsular invasion, 2% (five of 222) were in the distant subgroup and 4% (six of 156) were in the close subgroup. There was no evidence of a difference in

complications between the group with capsular invasion and the distant or close subgroups. All participants with complications reported in the two groups recovered within 3 months after ablation.

Tumor Volume Change

The mean volume of the ablation zone at each examination and mean volume reduction rate are presented in Table 5 and Figure 4. The ablation zone volume decreased significantly from 1.0 mL $\pm$ 0.7 to 0.01 mL $\pm$ 0.03 for the group with capsular invasion and from 0.9 mL $\pm$ 0.8 to 0.00 mL $\pm$ 0.01 for the group without capsular invasion ($P < .001$ for all before and after ablation). The mean volume reduction rate was 97% $\pm$ 8 versus 96% $\pm$ 13 in the group with and the group without capsular invasion at the end of the follow-up period ($P = .58$). There was no evidence of a difference in the ablation zone volume between the group with and the group without capsular invasion or between close subgroups at each follow-up period. Ablation zone volumes were larger in the group with capsular invasion than in the distant subgroup at the 1- and 3-month follow-up visits and became comparable after 6 months.

At the last follow-up, 39% (32 of 82) versus 39% (147 of 378) of tumors in the group with and the group without capsular invasion showed complete disappearance at US ($P = .98$), which included 33% (52 of 156) of the close subgroup and 43% (95 of 222) of the distant subgroup. No difference was found in the cumulative tumor disappearance during the follow-up period (Fig 5).

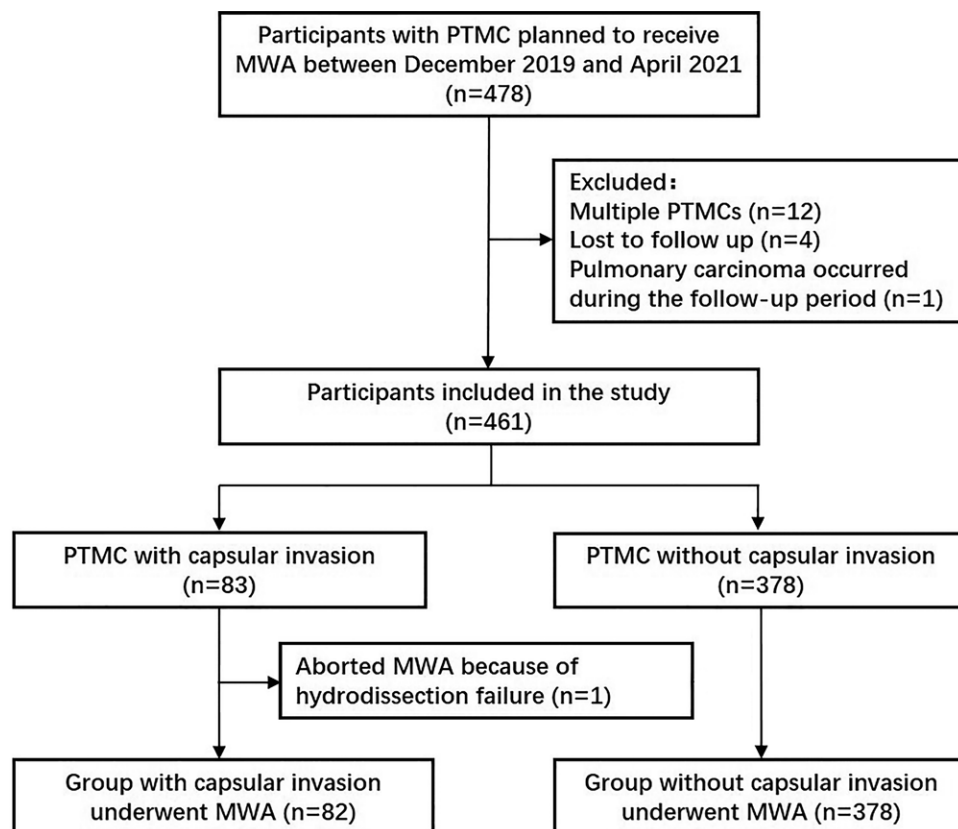


Figure 3: Research flowchart. PTMC = papillary thyroid carcinoma, MWA = microwave ablation.

Table 1: General Information of Participants in Groups with and without Capsular Invasion

Parameters	Group with Capsular Invasion (<i>n</i> = 82)	Group without Capsular Invasion (<i>n</i> = 378)	<i>P</i> Value
Sex			.81
Male	23 (28)	101 (27)	...
Female	59 (72)	277 (73)	...
Age (y)*	40 ± 11	43 ± 11	.03
BMI (kg/m ²)*	22.5 ± 3.3	23.1 ± 3.6	.19
CCI			.76
0	79 (96)	359 (95)	...
1	3 (4)	17 (5)	...
2	0	2 (0)	...
Thyroid disease			.45
Absent	71 (87)	331 (88)	...
Hashimoto thyroiditis	11 (13)	38 (10)	...
Hyperthyroidism	0	8 (2)	...
Hypothyroidism	0	1 (0)	...
Laboratory studies*			
fT3 (pmol/L)	4.7 ± 0.8	4.9 ± 1.2	.14
fT4 (pmol/L)	16.0 ± 2.5	16.6 ± 3.6	.15
TSH (mIU/L)	2.0 ± 1.1	2.2 ± 1.5	.32
Leukocyte (×10 ⁹ /L)	5.9 ± 1.8	6.2 ± 1.5	.17
Platelet (×10 ⁹ /L)	247 ± 55	251 ± 56	.57

Note.—Unless otherwise indicated, data are numbers of participants, with percentages in parentheses. BMI = body mass index, CCI = Charlson comorbidity index, fT3 = free triiodothyronine, fT4 = free thyroxine, MWA = microwave ablation, TSH = thyroid-stimulating hormone.

* Data are means ± SD.

Table 2: Tumors Characteristics of Groups with and without Capsular Invasion

Characteristic	Group with Capsular Invasion (<i>n</i> = 82)	Group without Capsular Invasion (<i>n</i> = 378)	<i>P</i> Value
Size*			
Maximal tumor diameter (cm)	0.6 ± 0.2	0.6 ± 0.2	.20
Tumor volume (mL)	0.1 ± 0.1	0.1 ± 0.1	.07
Echogenicity			.14
Hypoechoic	73 (89)	357 (94)	...
Hyperechoic	1 (1)	2 (1)	...
Isoechoic	0	2 (0)	...
Inhomogeneous	8 (10)	17 (5)	...
Vascularity			.83
Absent	52 (63)	221 (59)	...
Grade I	23 (28)	126 (33)	...
Grade II	5 (6)	22 (6)	...
Grade III	2 (3)	9 (2)	...
Calcification			.20
Absent	47 (57)	245 (65)	...
Present	35 (43)	133 (35)	...
Tumor location			.002
Left	38 (46)	172 (46)	...
Right	34 (42)	194 (51)	...
Isthmus	10 (12)	12 (3)	...

Note.—Unless otherwise indicated, data are numbers of participants, with percentages in parentheses. According to the US presentation of the internal nodule on color Doppler flow imaging, the nodular vascular scores were classified into four grades: (a) no color signal in the nodule, (b) color signals in less than 25% of the nodule (grade I), (c) color signals in 25%–50% of the nodule (grade II), and (d) color signals in more than 50% of the nodule (grade III).

* Data are means ± SD.

Table 3: Prognosis of Groups with and without Capsular Invasion

Prognosis Parameters	Group with Capsular Invasion (n = 82)	Group without Capsular Invasion (n = 378)	P Value	Subgroups of Group without Capsular Invasion		P Value*	P Value†
				Distant (n = 222)	Close (n = 156)		
Local tumor progression			.52			>.99	.31
Yes	0	2 (1)	...	0	2 (1)	...	...
No	82 (100)	377 (99)	...	222 (100)	154 (99)	...	...
New thyroid cancer			>.99			>.99	>.99
Yes	0	0	...	0	0	...	...
No	82 (100)	378 (100)	...	222 (100)	156 (100)	...	...
Lymph node metastasis			.89			.10	.50
Yes	1 (1)	4 (1)	...	0	4 (3)	...	...
No	81 (99)	374 (99)	...	222 (100)	152 (97)	...	...
Distant metastasis			>.99			>.99	>.99
Yes	0	0	...	0	0	...	...
No	82 (100)	378 (100)	...	222 (100)	156 (100)	...	...
Disease progression			.82			.10	.30
Yes	1 (1)	6 (2)	...	0	6 (4)	...	...
No	81 (99)	372 (98)	...	222 (100)	150 (96)	...	...

Note.—Unless otherwise indicated, data are number of patients, and data in parentheses are percentages.

* Comparison between the group with capsular invasion and the distant subgroup.

† Comparison between the group with capsular invasion and the close subgroup.

Table 4: Treatment Parameters and Complications of Groups with and without Capsular Invasion

Parameter	Group with Capsular Invasion (n = 82)	Group without Capsular Invasion (n = 378)	P Value	Subgroups of Group without Capsular Invasion		P Value*	P Value†
				Distant (n = 222)	Close (n = 156)		
Ablation time (sec)	156 ± 129	151 ± 119	.71	142 ± 130	164 ± 101	.38	.64
Energy (J)	4139 ± 2958	4056 ± 3090	.83	3826 ± 3523	4380 ± 2321	.44	.49
Hydrodissection (mL)	23 ± 20	24 ± 24	.79	20 ± 23	29 ± 25	.36	.08
Intraoperative pain score	2.5 ± 1.2	2.7 ± 1.3	.30	2.7 ± 1.3	2.8 ± 1.4	.37	.27
Immediate postoperative pain score	1.5 ± 0.9	1.6 ± 1.1	.56	1.7 ± 1.1	1.5 ± 1.1	.27	.84
Monitoring time (d)	1.4 ± 1.1	1.3 ± 0.9	.67	1.3 ± 1.0	1.3 ± 0.7	.78	.59
Major complications‡			.38			.57	.25
Total	1 (1)	11 (3)	...	5 (2)	6 (4)	...	...
Hoarse	1 (1)	10 (3)	...	4 (2)	6 (4)	...	...
Cough	0	5 (1)	...	2 (1)	3 (2)	...	...
Skin burn	0	0	...	0	0	...	...
Infection	0	0	...	0	0	...	...
Horner syndrome	0	1 (0)	...	1 (1)	0	...	...

Note.—Unless otherwise indicated, data are means ± SD.

* Comparison between the group with capsular invasion and the distant subgroup.

† Comparison between the group with capsular invasion and the close subgroup.

‡ Data are number of patients, and data in parentheses are percentages.

Multiple Covariates of the Potential Confounders

On the basis of the Cox and logistic proportional hazards regression model, capsular invasion was not a risk factor for disease progression, LTR, LNM, major complications, or complete tumor disappearance, and the participants' age and tumor location did not affect the outcomes according to multivariable analyses (Table 6).

Discussion

Our multicenter prospective cohort study compared the feasibility, effectiveness, and safety of microwave ablation (MWA) in the treatment of papillary thyroid microcarcinoma (PTMC) with and without US-detected capsular invasion, and our results indicated that the treatment outcomes of MWA on PTMC both with and without capsular invasion were similar. In the group

Table 5: Ablation Zone Volume after MWA in Groups with and without Capsular Invasion at Each Follow-up

Time after MWA	Group with Capsular Invasion (<i>n</i> = 82)	Group without Capsular Invasion (<i>n</i> = 378)	<i>P</i> Value	Subgroups of Group without Capsular Invasion			
				Distant (<i>n</i> = 156)	Close (<i>n</i> = 222)	<i>P</i> Value*	<i>P</i> Value†
1 month	1.0 ± 0.7	0.9 ± 0.8	0.53	0.8 ± 0.8	1.2 ± 0.8	0.04	0.20
3 months	0.5 ± 0.7	0.5 ± 0.5	0.45	0.4 ± 0.4	0.6 ± 0.5	0.04	0.60
6 months	0.2 ± 0.3	0.2 ± 0.3	0.66	0.2 ± 0.3	0.2 ± 0.3	0.38	0.76
12 months	0.1 ± 0.2	0.1 ± 0.2	0.67	0.1 ± 0.2	0.1 ± 0.1	0.60	0.86
18 months	0.03 ± 0.09	0.02 ± 0.05	0.53	0.02 ± 0.05	0.02 ± 0.04	0.46	0.53
24 months	0.01 ± 0.03	0.00 ± 0.01	0.35	0.00 ± 0.02	0.00 ± 0.01	0.48	0.40

Note.—Unless otherwise indicated, data are mean ablation zone volume (in milliliters) ± SD. MWA = microwave ablation.

* Comparison between the group with capsular invasion and the distant subgroup.

† Comparison between the group with capsular invasion and the close subgroup.

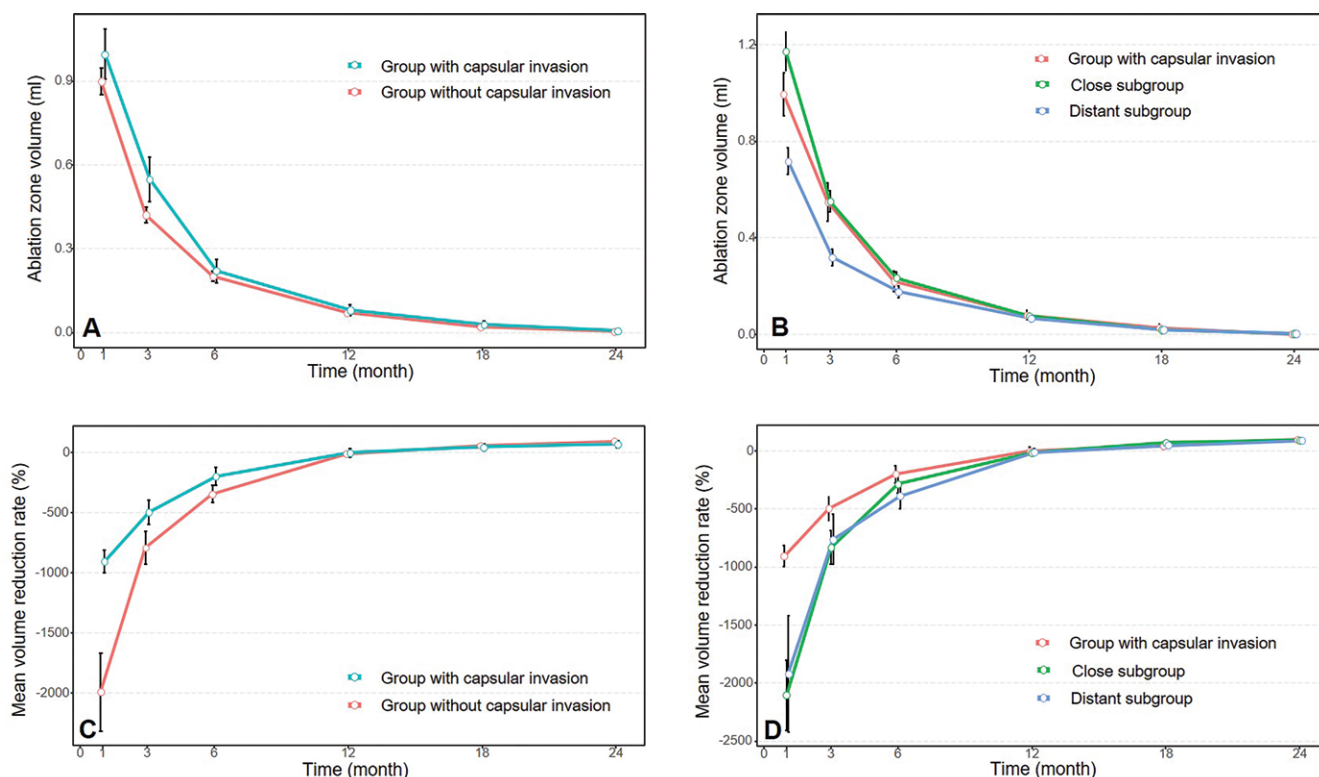


Figure 4: Tumor shrinkage during the follow-up period. (A) The mean ablation zone volume during the follow-up period in the group with and the group without capsular invasion. (B) Ablation zone volume during the follow-up period in the capsular invasion group and the distant and close subgroups. (C) Mean volume reduction rate during the follow-up period in the group with and the group without capsular invasion. (D) Mean volume reduction rate during the follow-up period in the group with capsular invasion and the distant and close subgroups. (For the tumor without US-detected capsular invasion, a minimum distance from the tumor edge to the thyroid capsule of 2 mm or less was defined as the close subgroup while a minimum distance of more than 2 mm was defined as the distant subgroup.)

with and the group without capsular invasion, comparable technical success rates were achieved (99% vs 100%, $P = .18$), with a similar incidence of complications (1% vs 3%, $P = .38$). No difference was found for disease progression during the mean follow-up periods of 20 months ± 4 and 21 months ± 4 (1% vs 2%, $P = .82$). Similar results were found in the comparison between the group with capsular invasion and the distant or close subgroups. Our study also showed an obvious shrinkage of the ablation zone in the group with and the group without capsular invasion at the end of follow-up (mean, 97% ± 8 vs 96% ± 13; $P = .58$). The 3-year age difference between the two

groups was highly unlikely to be clinically relevant, and the efficacy of MWA in treating PTMCs located in the isthmus was comparable to the efficacy of MWA in treating PTMCs located in lateral lobes (26).

Our oncologic results were consistent with those of previous studies on use of TA to treat PTMC confined to the thyroid gland (10,27). Yan et al (28) reported 3.3% LTR and 0.6% LNM approximately 4 years after TA for PTMC. Wu et al (20) reported 2.83% LNMs after TA for the treatment of papillary thyroid carcinoma close to the thyroid capsule. However, to our knowledge, there have been no reports on MWA in the

treatment of PTMC with capsular invasion or comparisons between PTMC with capsular invasion and those located in distant or close subgroups. The fact that results were similar for the two groups may be due to the indolent nature of the tumor, meaning that capsular invasion or distance from the capsule has no clinical influence on the prognosis (16,17,29). It is important to note that, based on the sample size and disease progression rates of the group with and the group without capsular invasion, we had 80% confidence to test the difference of the maximum effect size of 10% when $\alpha = 0.05$ was assumed to be the type I error. When the difference between the two groups was less than 10%, the insignificant differences may be due to the small sample size.

In a previous meta-analysis of the efficacy and safety of TA techniques in the treatment of primary PTMC, the pooled proportion of major complication was 0.7% (30), and another meta-analysis of the 5-year follow-up result of TA for low-risk PTMC reported a rate of 1.2% (31), which is in accordance with our results. In general, it is considered difficult to perform extended ablation in tumors with capsular invasion to ensure complete ablation while at the same time protecting nearby critical structures from clinical experience. In our study, the high rate of technical success and the low rate of complications in the group with capsular invasion may be attributed to the use of hydrodissection. We only encountered one hydrodissection failure, and this patient was referred for surgery instead. All participants with complications in our study recovered within 3 months during the follow-up period, and none developed permanent voice hoarseness. This indicates that thermal damage to nerves that occur during MWA is temporary and moderate.

In this study, evaluation of the relationship between the tumor and the capsule was based on US images. Previous studies reported the sensitivity of US diagnosis of capsular invasion was 87.5% (32). Most US-detected capsular invasion includes two types: neoplastic invasion of the capsule and microscopic extension of the thyroid gland, which has been proved with no prognostic

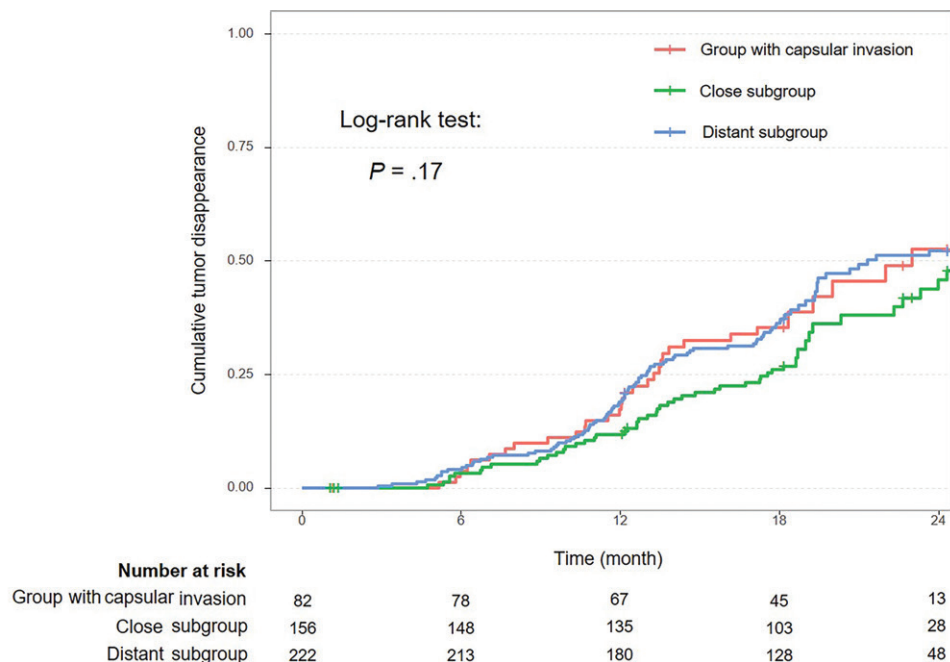


Figure 5: Cumulative tumor disappearance during the follow-up period in the group with capsular invasion and the distant and close subgroups. (For the tumor without US-detected capsular invasion, a minimum distance from the tumor edge to the thyroid capsule of 2 mm or less was defined as the close subgroup while a minimum distance of more than 2 mm was defined as the distant subgroup.)

Table 6: Factor Analyses of the Potential Confounders

End Point	P Value	Hazard Ratio
Disease progression (<i>n</i> = 7)*		
Capsular invasion	.82	0.78 (0.09, 6.48)
Capsular invasion and age	.79	0.75 (0.09, 6.30)
Capsular invasion and tumor location	.84	0.80 (0.10, 6.63)
Capsular invasion and tumor location and age	.80	0.76 (0.09, 6.37)
Local tumor progression (<i>n</i> = 2)*		
Capsular invasion	.71	0 (NA)
Capsular invasion and age	.99	0 (NA)
Capsular invasion and tumor location	.87	0 (NA)
Capsular invasion and tumor location and age	.99	0 (NA)
Lymph node metastasis (<i>n</i> = 5)*		
Capsular invasion	.72	1.50 (0.17, 13.42)
Capsular invasion and age	.75	1.44 (0.16, 12.88)
Capsular invasion and tumor location	.74	1.50 (0.14, 16.54)
Capsular invasion and tumor location and age	.75	1.48 (0.13, 16.29)
Major complications (<i>n</i> = 12)†		
Capsular invasion	.40	0.41 (0.05, 3.24)
Capsular invasion and age	.35	0.39 (0.05, 2.97)
Capsular invasion and tumor location	.41	0.42 (0.05, 3.32)
Capsular invasion and tumor location and age	.34	0.36 (0.05, 2.91)
Complete tumor disappearance (<i>n</i> = 179)†		
Capsular invasion	.61	1.11 (0.75, 1.62)
Capsular invasion and age	.56	1.12 (0.76, 1.66)
Capsular invasion and tumor location	.61	1.11 (0.75, 1.62)
Capsular invasion and tumor location and age	.56	1.12 (0.76, 1.66)

Note.—Data in parentheses are the 95% CI. NA = not applicable.

* Calculated with Cox proportional hazards regression model.

† Calculated with logistic proportional hazards regression model.

importance (17). This may contribute to the similar prognostic results between PTMC with and without capsular invasion after MWA in our study.

Our study had several limitations. First, the lack of significance might be partially due to the small number of participants and the short follow-up period; thus, the oncologic results of this study were limited. Second, assessment of the tumor and capsule depended largely on the experience of the radiologist, and therefore occult PTMCs and LNM might have been missed due to the sensitivity limitation of US. Third, the diagnosis of PTMC was based on cytologic samples only, and the relationship between aggressive histologic subtypes and prognosis was unclarified. Finally, the comparison with subgroups was performed post hoc, and there might have been selection bias.

In conclusion, microwave ablation is a feasible, effective, and safe method to treat papillary thyroid microcarcinoma (PTMC) with US-detected capsular invasion, with similar outcomes to PTMC without capsular invasion. More participants with longer follow-up will be necessary to validate these findings, and further comparison with active surveillance would be especially valuable to clarify the clinical importance of ablation therapy.

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