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INTERVENTIONAL

Microwave ablation versus radiofrequency ablation for subcapsular hepatocellular carcinoma: a propensity score–matched study

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Abstract

Objectives Thermal ablation is now accepted as one of the curative treatments for patients with early-stage hepatocellular carcinoma (HCC), but the efficacy of this treatment for subcapsular HCC is not well characterized. Therefore, we aimed to compare the outcomes of microwave ablation (MWA) and radiofrequency ablation (RFA) for patients with subcapsular HCC.

Methods In total, 195 patients with subcapsular HCC who met the Milan criteria and underwent MWA or RFA were included. Local tumor progression (LTP), overall survival (OS), recurrence beyond the Milan criteria (RBM), and complications of these patients were compared.

Results After propensity score matching, the 1-, 3-, and 5-year cumulative LTP rates were 6.7%, 9.6%, and 11.4% in the MWA group, and 13.4%, 24.6%, and 29.1% in the RFA group, respectively ($p = 0.006$). The cumulative rates of RBM were lower in patients treated with MWA than in those treated with RFA (4.4% versus 12% at 1 year; 14.5% versus 23.0% at 3 years; and 37.4% versus 53.9% at 5 years; $p = 0.03$). The OS rates at 1, 3, and 5 years were 97.1%, 85.9%, and 73.4% in the MWA group, and 95.6%, 80.4%, and 61.4% in the RFA group, respectively ($p = 0.36$). The rate of major complications showed no significant difference between the MWA group and the RFA group (17.4% vs. 11.6%, $p = 0.33$).

Conclusion Compared to RFA, MWA showed better tumor control for subcapsular HCC within the Milan criteria. There was no difference in the incidence of major complications between the two groups.

Key Points

- *Compared to radiofrequency ablation, microwave ablation showed better local tumor control for patients with subcapsular hepatocellular carcinoma.*
- *Microwave ablation showed similar major complication rates for patients with subcapsular hepatocellular carcinoma.*
- *Microwave ablation may be preferred for patients with subcapsular hepatocellular carcinoma when they need to receive thermal ablation.*

Keywords Carcinoma · Hepatocellular · Microwaves · Radiofrequency ablation

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Abbreviations

HCC	Subcapsular hepatocellular carcinoma
LTP	Local tumor progression
MELD	Model for end-stage liver disease
MWA	Microwave ablation
OS	Overall survival
PSM	Propensity score matching
RFA	Radiofrequency ablation
RMB	Recurrence beyond the Milan criteria

Introduction

The location of the tumor is an important factor for prognosis and treatment selection in patients with hepatocellular carcinoma (HCC) [1, 2]. With regard to subcapsular tumors, surgical resection (SR) is now considered an effective treatment, because it provides optimal survival outcomes [2]. However, SR is often limited by clinically portal hypertension or insufficient postoperative hepatic reserve. Thermal ablation, representing a less invasive procedure, may be recommended as an alternative therapeutic option for these patients.

Prior studies have reported that thermal ablation, such as radiofrequency ablation (RFA) and microwave ablation (MWA), is effective and safe for subcapsular HCC [3–5]. However, the literature does not provide sufficient data for the comparison of thermal ablation for subcapsular and non-subcapsular HCCs. Therefore, RFA is still a controversial therapy in subcapsular HCC, because a higher local tumor recurrence rate has been documented in multiple studies [6–8], and it may increase the incidence of complications [2, 9]. A recent study has compared the efficacy between RFA and surgical resection in subcapsular HCC and found a significant increase in local tumor recurrence in the RFA group [7]. The American Association for the Study of Liver Diseases has suggested that investigation of other types of ablation for these specifically located HCCs may be a better choice [1]. Recently, MWA has been used more frequently as it has advantages over RFA in terms of higher temperature and shorter operation time. Furthermore, MWA is not limited by tissue conductance and is less susceptible to the heat sink effect [10–12]. Several studies have reported that MWA shows a decrease in local tumor recurrence for HCC compared to RFA [13, 14].

However, to our knowledge, there is currently no study comparing the efficacy and safety of MWA to those of RFA in the treatment of patients with subcapsular HCC. To clarify these issues, we performed a retrospective analysis of patients with subcapsular HCC within the Milan criteria, using propensity score matching (PSM) to minimize potential selection and confounding bias.

Methods

Patients

The present study was a retrospective study conducted at two hospitals in China. From January 2010 to June 2018, 1284 HCC patients underwent initial RFA or MWA at Shandong Provincial Hospital Affiliated to Shandong First Medical University or Qilu Hospital Affiliated to Shandong University. Among them, 195 patients were identified by the following inclusion criteria: (1) older than 18 years; (2) patients with subcapsular HCC (subcapsular HCC was defined as the closest distance from the tumor margin to the liver capsule being ≤ 3 mm [15, 16]); (3) tumor within Milan criteria [2] (single tumor up to 5 cm or 2–3 tumor nodules up to 3 cm in size, without vascular invasion); (4) no extrahepatic metastasis; and (5) Child–Pugh class A or B. Patients were excluded based on the following exclusion criteria: (1) Patients received transcatheter arterial chemoembolization (TACE) or other treatments due to failure to achieve a complete ablation after RFA or MWA (complete ablation was defined as the first dynamic contrast-enhanced CT or MRI scan approximately 1 month after ablation, in which the ablation area during the arterial phase had no enhancement); or (2) other significant comorbidities, such as cardiopulmonary compromise. The diagnosis of HCC was based on criteria in the practice guidelines of AASLD [1]. The flow chart of study patient selection is detailed in Fig. 1. The present study was approved by the Institutional Review Board and the informed consent requirement was waived.

Treatment and patient follow-up

In general, patients with subcapsular HCC received SR as the first-line treatment, and thermal ablation was recommended as an alternative therapeutic option for patients who were unsuitable for SR.

The MWA and RFA procedures were performed by interventional radiologists under the guidance of CT or ultrasound at Shandong Provincial Hospital or Qilu Hospital. In the MWA group, the procedures were performed with patients under the guidance of CT (47.5% in the total group, 44.9% in matched group) or ultrasound. A microwave ablation therapeutic instrument (MTC-3C, Vison-China Medical Devices R&D Center) was used with a power of 40–80 W at a frequency of 2450 ± 50 MHz for 4–10 min at each site. One microwave antenna was used for tumors ≤ 3 cm in maximum diameter, and 2 microwave antennae were simultaneously used for tumors > 3 cm.

The main equipment for patients who underwent RFA was Cool-tip RF Ablation (CTRF220, Covidien LLC)

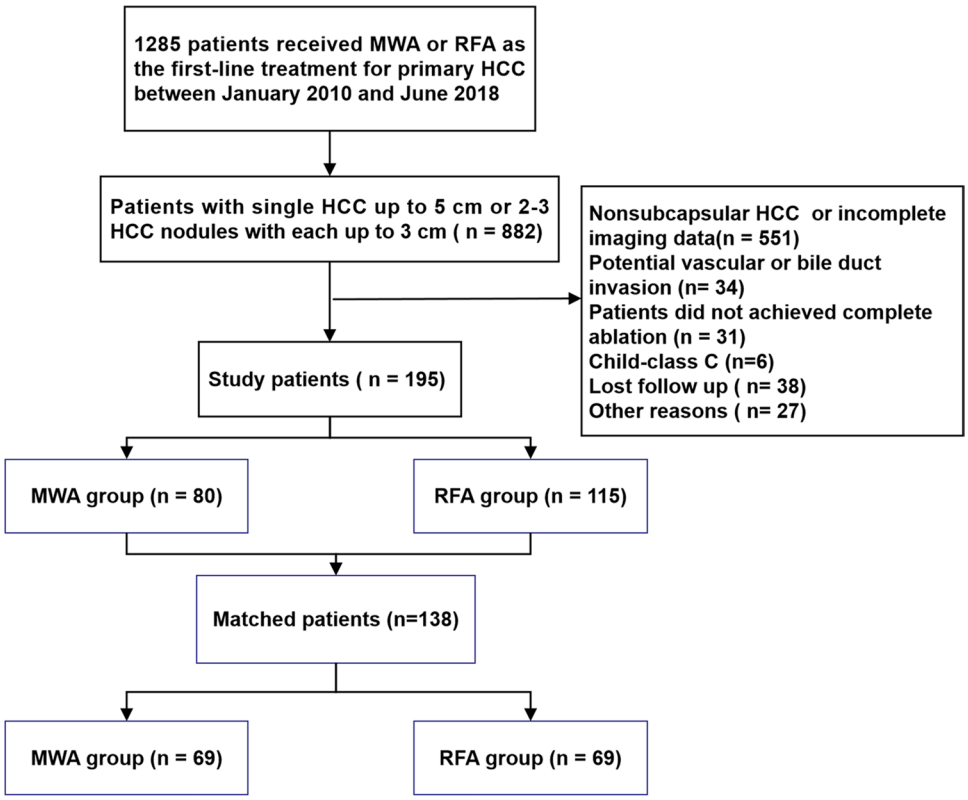

Fig. 1 Patient selection. *HCC,* hepatocellular carcinoma; *RFA*, radiofrequency ablation; *MWA*, microwave ablation

which produces 0–200 W of power at a frequency of 480 kHz. The interventional radiologists performed RFA under the guidance of ultrasound with a power of 200 W for 8–12 min at each site. For large tumors, multiple overlapping ablations were performed based on the clinical practice of interventional radiologists.

Antenna track ablation was routinely performed during needle removal. Ablation performers attempted to achieve complete tumor ablation with a 1 cm margin, except for the subcapsular portions in both groups. For subcapsular HCC adjacent to the gastrointestinal system or diaphragm, an introducer sheath was inserted under the guidance of CT or US. A sufficient volume of 0.9% saline was injected through the sheath to separate the tumors from the risk organs by 0.5–1.0 cm.

Patients generally underwent contrast-enhanced CT or MRI 1–2 months postoperatively to assess complete ablation. Primary technical success was defined as the first ablation that achieved complete ablation. Patients were followed every 3 months at the first year and 3–6 months thereafter. Once the tumor recurred, the therapy selection was based on the preference of patients and the clinical practice of clinicians, and the treatments for initial tumor recurrence were also analyzed. All patients were followed up until death, March 15, 2021, or were lost to follow-up, whichever came first.

Survival outcomes

The primary endpoint of the study was local tumor progression (LTP) of subcapsular HCC nodules. Recurrence beyond the Milan criteria (RBM) and overall survival (OS) were also investigated. LTP was defined as the appearance of a tumor at the edge of the ablation zone [17]. RBM was defined as recurrence with tumor size > 5 cm, more than 3 tumor nodules, > 3 cm for two or three tumors, vascular invasion, or extrahepatic disease [18]. OS was defined as the time from the date of operation to death or the last follow-up before March 15, 2021.

Complications

The criteria for complications were in accordance with the definitions of the Society of Interventional Radiology [19]. Major complications were defined as events that led to additional therapy, prolonged hospitalization, disability, or death that was associated with ablation procedures. Because there has been a debate on complications of subcapsular HCC, that is, ablation may increase the risk of tumor seeding and thermal injury of perihepatic structures [3, 4, 9]; these complications were also investigated during follow-up.

Propensity score matching

To decrease the selection bias between the two study groups, we performed 1:1 propensity score matching (PSM) to create a comparable control cohort, including age, sex, Child–Pugh class, presence of liver cirrhosis, model for end-stage liver disease (MELD) score, antiviral treatment, serum α fetoprotein, alanine aminotransferase level, aspartate aminotransferase level, presence of portal hypertension, tumor number, and maximum tumor diameter.

Statistical analysis

Categorical variables are presented as counts and percentages, and continuous variables are expressed as medians and interquartile ranges. Differences in categorical variables between the two groups were analyzed using Pearson's χ^2 test or Fisher's exact test, and continuous variables were compared using the Mann–Whitney test. OS, cumulative LTP, and cumulative RBM curves were constructed by the Kaplan–Meier method and estimated by the log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to analyze prognostic factors related to OS and LTP. All statistical analyses were performed using SPSS 24.0 for Windows (SPSS Inc.). All tests were two-tailed, and differences of $p < 0.05$ were considered statistically significant.

Results

Patient characteristics

Among the 195 patients with subcapsular HCC enrolled in this study, 80 patients with 90 subcapsular HCC nodules initially received MWA, and 115 patients with 123 subcapsular HCC nodules initially received RFA. Twenty-one (26.3%) patients who underwent biopsies prior to thermal ablation received MWA and 20 (17.3%) patients received RFA ($p = 0.14$). In the total cohort, the median age for the MWA group was 61 (interquartile range, 51–66) years, and the median age for the RFA group was 59 (49–63) years ($p = 0.04$). For the MELD score, the median MELD score was 4.71 (2.53–7.15) in the MWA group and 5.71 (4.18–7.83) in the RFA group ($p < 0.001$). After PSM, a new cohort comprising 69 patients with 79 subcapsular HCC nodules in the MWA group and 69 patients with 75 subcapsular HCC nodules in the RFA group was generated. In the PSM cohort, 18 (26.1%) patients in the MWA group and 14 (20.3%) patients in the RFA group underwent biopsies prior to thermal ablation ($p = 0.42$). All the relevant background characteristics were balanced (Table 1).

Local tumor control

Of these 195 patients, the median follow-up period was 58 months (range, 1–113 months). In the MWA group, 81 of 90 (90%) subcapsular HCC nodules achieved primary technical success. Similarly, 106 of 123 (86.2%) subcapsular HCC nodules in the RFA group achieved primary technical success ($p = 0.40$). LTP was detected in 9 of 90 (10%) subcapsular HCC nodules (9 of 80 patients) in the MWA group and in 30 of 123 (24.4%) subcapsular HCC nodules (30 of 115 patients) in the RFA group during the follow-up periods. The 1-, 3-, and 5-year cumulative LTP rates were 6.7%, 9.6%, and 11.4% in the MWA group, and 13.4%, 24.6%, and 29.1% in the RFA group, respectively ($p = 0.006$) (Fig. 2a).

In the PSM cohort, LTP was detected in 6 of 79 (7.6%) subcapsular HCC nodules (6 of 69 patients) in the MWA group and in 14 of 75 (18.7%) subcapsular HCC nodules (14 of 69 patients) in the RFA group during the follow-up periods. The 1-, 3-, and 5-year cumulative LTP rates were 3.6%, 7.0%, and 9.1% in the MWA group, and 9.7%, 18.2%, and 24.9% in the RFA group, respectively ($p = 0.03$) (Fig. 2b).

Recurrence beyond Milan criteria

During follow-up, 22 of 80 patients (27.5%) in the MWA group and 43 of 115 patients (37.4%) in the RFA group eventually had RBM. The 1-, 3-, and 5-year cumulative RBM rates were 6.4%, 17.9%, and 39.4% in the MWA group, and 11.6%, 26.1%, and 47.0% in the RFA group, respectively ($p = 0.11$) (Fig. 3a). After PSM, the cumulative rates of RBM were lower after MWA than after RFA (4.4% versus 12% at 1 year; 14.5% versus 23.0% at 3 years; and, 37.4% versus 53.9% at 5 years) for patients with subcapsular HCC ($p = 0.03$) (Fig. 3b).

Overall survival

In the total cohort, the mean OS time for patients with MWA was 7.07 years, and the mean OS time for patients with RFA was 6.39 years. The OS rates at 1, 3, and 5 years were 96.2%, 85.3%, and 72.6% in the MWA group and 97.3%, 79.4%, and 60.3% in the RFA group, respectively ($p = 0.27$) (Fig. 4a). In the PSM cohort, the mean OS time for patients with MWA was 7.06 years, and the mean OS time for patients with RFA was 6.18 years. The OS rates at 1, 3, and 5 years were 97.1%, 85.9%, and 73.4% in the MWA group, and 95.6%, 80.4%, and 61.4% in the RFA group, respectively ($p = 0.36$) (Fig. 4b).

Table 1 Baseline characteristics of the total cohort and the PSM cohort

Variables	Total cohort				PSM cohort			
	MWA group ($n=80$)[+]	RFA group ($n=115$)[+]	p value	SMD	MWA group ($n=69$)[+]	RFA group ($n=69$)[+]	p-value	SMD
Age	61 (51–66)	59 (49–63)	0.04	0.31	60.00 (50.00–65.50)	60 (55.50–65.50)	0.60	0.1
Male[※]	64 (80.0%)	90 (78.3%)	0.77	0.04	56 (81.2%)	53 (76.8%)	0.53	0.10
Antiviral treatment[※]	52 (65.0%)	88 (76.5%)	0.08	0.26	48 (69.6%)	51 (73.9%)	0.57	0.09
Child–Pugh class A[※]	61 (78.2%)	293 (77.8%)	0.96	0.001	53 (76.8%)	53 (76.8%)	> 0.99	0
Liver cirrhosis[※]	75 (93.8%)	101(87.8%)	0.17	0.20	65 (94.2%)	64 (92.8%)	0.73	0.06
Portal hypertension[※]	59 (73.8%)	88 (76.5%)	0.66	0.07	53(76.8%)	53(76.8%)	> 0.99	0
MELD score	4.71 (2.53–7.15)	5.71 (4.18–7.83)	0.01	0.39	5.05 (2.69–7.32)	5.40 (3.59–7.39)	0.58	0.09
ALT (U/L)	21.0 (30.0–50.0)	29.0 (22.0–46.0)	0.37	0.21	30.0 (21.0–50.0)	29.0 (22.0–44.5)	0.64	0.15
AST (U/L)	35 (26.0–64.25)	37.0 (27.5–49.0)	0.95	0.20	35.0 (26.0–64.5)	37 (29.0–51.5)	0.64	0.12
AFP (U/L)	19.64 (4.21–199.45)	14.33 (4.53–65.47)	0.46	0.16	13.16 (3.96–149.35)	12.57 (5.12–63.45)	0.89	0.07
Maximum tumor diameter (cm)	2.5 (2.0–3.58)	2.5 (1.8–3.0)	0.58	0.01	2.5 (2.0–3.55)	2.5 (1.7–3.0)	0.61	0.07
Subcapsular tumor diameter (cm)	2.2 (1.7–3.4)	2.5 (1.7–3.0)	0.98	0.03	2.2 (1.6–3.4)	2.4 (1.7–3.0)	0.95	0
exophytic subcapsular HCC[※]	13 (14.4%)	13 (10.6%)	0.39	0.12	10 (12.7%)	11 (14.6%)	0.72	0.056
Subcapsular tumor location[※] (couinaud segment)			0.39				0.44	
S2, S3, and S4	20/90 (22.2%)	31/123 (25.2%)	0.62	0.07	20/79 (25.3%)	20/75 (26.7%)	0.85	0.03
S5	13/90 (14.4%)	13/123 (10.6%)	0.39	0.12	10/79 (12.7%)	6/75 (8.0%)	0.34	0.15
S6	20/90 (22.2%)	17/123 (13.8%)	0.11	0.22	17/79 (21.5%)	10/75 (13.3%)	0.18	0.22
S7	19/90 (21.1%)	29/123 (23.6%)	0.67	0.06	17/79 (21.5%)	18/75 (24.0%)	0.71	0.06
S8	18/90 (20.0%)	33/123 (26.8%)	0.25	0.16	15/79 (19.0%)	21/75 (28.0%)	0.19	0.17
Etiology[※]			0.45				0.90	
HBV	67 (83.8%)	100 (87.0%)	0.53	0.09	58 (84.1%)	58 (84.1%)	> 0.99	0
HCV	5 (6.2%)	3 (2.6%)	0.37	0.18	4 (5.8%)	3 (7.2%)	> 0.99	0.05
Others	8 (10.0%)	12 (10.4%)	0.92	0.01	7 (10.1%)	8 (8.7%)	0.78	0.05
Tumor number[※]			0.81	0.03			0.83	0.04
Single	65 (81.3%)	95 (82.6%)			56 (81.2%)	55 (79.7%)		
Multiple	15 (18.8%)	20 (17.4%)			13 (18.8%)	14 (20.3%)		

[+]Except where indicated, data are medians, with interquartile ranges in parentheses

[※]Data are numbers of patients, with percentages in parentheses

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *AFP*, alpha fetoprotein; *HBV*, hepatitis B virus; *HCC*, hepatocellular carcinoma; *HCV*, hepatitis C virus; *MELD*, model for end-stage liver disease; *MWA*, microwave ablation; *PSM*, propensity score matching; RFA, radiofrequency ablation; *SMD*, standardized mean difference

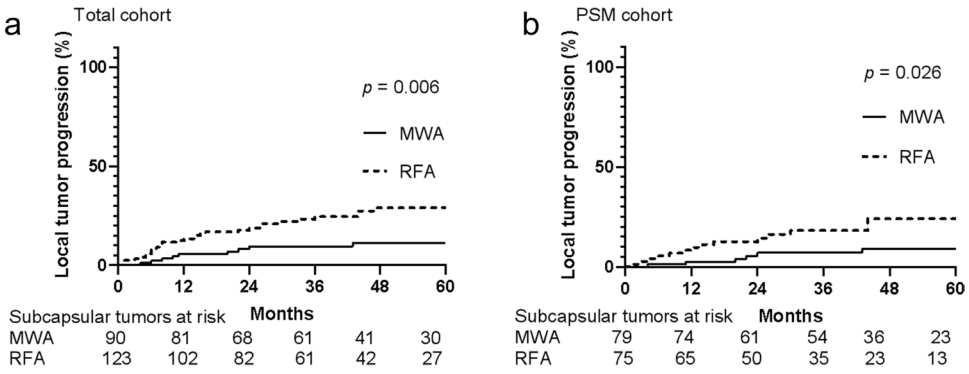

Fig. 2 Cumulative local tumor progression curves of patients with subcapsular hepatocellular carcinoma within the Milan criteria. MWA had a lower cumulative local tumor progression rate than RFA in the total cohort (**a**) and PSM cohort (**b**) for subcapsular hepatocellular carcinoma within the Milan criteria ($p=0.006$, $p=0.03$)

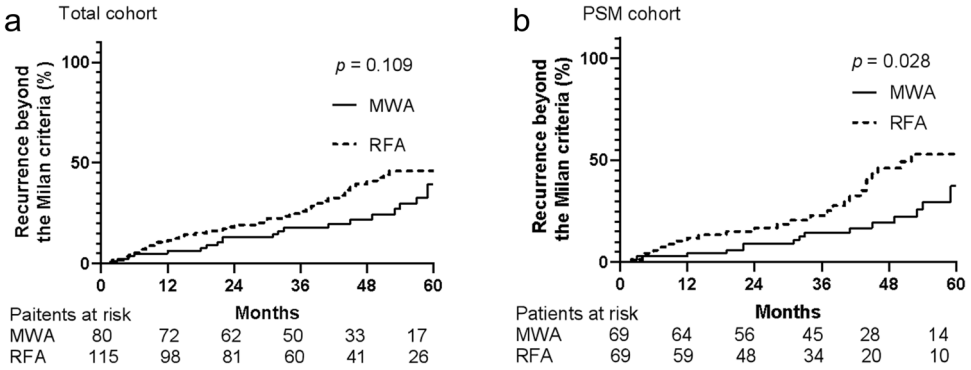

Fig. 3 Cumulative recurrence beyond the Milan criteria curves of patients with subcapsular hepatocellular carcinoma within the Milan criteria. There were no significant differences in cumulative recurrence beyond the Milan criteria rate between the MWA group and RFA group in the total cohort (**a**) for subcapsular hepatocellular carcinoma within the Milan criteria ($p=0.11$). After propensity score matching, MWA had a lower cumulative recurrence beyond the Milan criteria rate than RFA (**b**) ($p=0.03$)

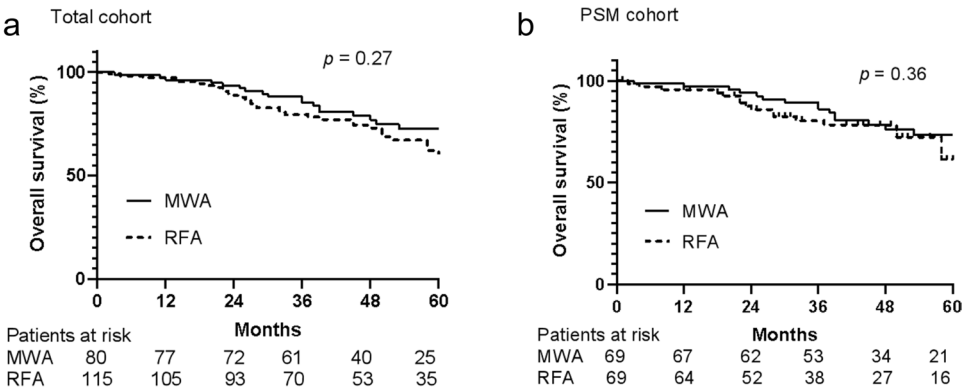

Fig. 4 Overall survival curves of patients with subcapsular hepatocellular carcinoma within the Milan criteria. There were no significant differences in overall survival curves between the MWA group and RFA group in the total cohort and PSM cohort for subcapsular hepatocellular carcinoma within the Milan criteria ($p=0.27$, $p=0.36$)

Factors associated with LTP and OS in the total cohort

The univariate analysis showed that MWA (compared to RFA) (hazard ratio [HR], 0.387; 95% confidence interval [CI], 0.184–0.816; $p=0.01$) was a significant factor for LTP. In multivariate analysis, MWA (compared to RFA) (HR, 0.288; 95% CI, 0.087–0.953; $p=0.04$) was an independent significant risk factor for LTP. In the univariate analysis for OS, cirrhosis (HR, 4.291; 95% CI, 1.044–17.630; $p=0.04$), portal hypertension (HR, 2.529; 95% CI, 1.198–5.337; $p=0.02$), and MELD score (HR, 1.097; 95% CI, 1.021–1.177; $p=0.01$) were significant factors. In multivariate analysis, multiple tumor nodules (HR, 2.514; 95% CI, 1.281–4.934; $p=0.007$) were an independent significant risk factor for OS (Table 2).

First recurrence type and subsequent treatment

After the PSM, 39 (56.5%) patients in the MWA group and 46 (66.7%) patients in the RFA group experienced HCC recurrence during the follow-up ($p=0.22$). The first recurrence types are shown in Table 3. As for treatment, 23 (33.3%) patients in the MWA group and 30 (43.5%) patients in the RFA group received curative therapies ($p=0.221$). The treatments for initial HCC recurrence are summarized in Supplementary Table 1.

Complications

The complications of patients after ablation are listed in Table 4. In the total cohort, 18 (22.5%) patients in the MWA group compared to 27 (23.4%) in the RFA group received hydrodissection during ablation ($p=0.87$). A higher rate of overall procedure-related complications was observed in the MWA group than in the RFA group (51.25% vs. 33.9% $p=0.02$), but the rate of major complications did not show a significant difference (16.3% vs. 10.4% $p=0.23$). There were no immediate complications related to thermal injury of perihepatic structures, and no tumor-seeding was observed during the follow-up. In the PSM cohort, 14 (20.2%) patients in the MWA group compared to 12 (17.3%) patients in the RFA group received hydrodissection during ablation ($p=0.66$). The complications of the PSM cohort showed similar results to those in the total cohort.

Table 2 Factors associated with OS and LTP of the total cohort

Variables	LTP				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value
MWA vs RFA	0.387 (0.184–0.816)	0.01	0.288 (0.087–0.953)	0.04	0.742 (0.434–1.267)	0.27	0.788 (0.438–1.421)	0.43
Age (per year)	1.011 (0.98–1.043)	0.49			1.006 (0.980–1.033)	0.64		
Gender (male)	1.105 (0.466–2.209)	0.97			1.361 (0.744–2.488)	0.32		
Maximum tumor diameter (per cm)	1.107 (0.815–1.503)	0.51	1.074 (0.754–1.529)	0.69	1.109 (0.866–1.421)	0.41	1.103 (0.839–1.449)	0.48
Cirrhosis	0.541 (0.238–1.227)	0.14	0.48 (0.193–1.192)	0.11	4.291 (1.044–17.630)	0.04	2.582 (0.498–13.387)	0.26
Portal hypertension	1.097 (0.534–2.254)	0.80			2.529 (1.198–5.337)	0.02	1.79 (0.718–4.463)	0.21
Child–Pugh class B VS A	1.335 (0.632–2.882)	0.45			1.433 (0.771–2.663)	0.26	1.079 (0.518–2.249)	0.84
MELD score	1.076 (0.987–1.173)	0.10	1.081 (0.985–1.187)	0.10	1.097 (1.021–1.177)	0.01	1.06 (0.972–1.156)	0.19
Antiviral treatment	1.577 (0.725–3.431)	0.25			1.161 (0.645–2.093)	0.62		
Multiple tumor nodules	0.928 (0.389–2.216)	0.87			1.643 (0.884–3.054)	0.12	2.514 (1.281–4.934)	0.007
AFP (> 200 ng/mL)	1.35 (0.639–2.853)	0.43	1.475 (0.673–3.235)	0.33	1.123 (0.581–2.173)	0.73		
ALT (> 50U/L)	1.026 (0.535–1.966)	0.94			0.529 (0.259–1.081)	0.08	0.993 (0.982–1.005)	0.25
AST (> 40U/L)	0.971 (0.445–2.121)	0.94			0.979 (0.577–1.662)	0.94		
Etiology of liver disease (ref.: HBV)		0.42				0.80		
HCV	2.004 (0.641–6.541)	0.25			0.841 (0.204–3.464)	0.81		
Others	0.721 (0.221–2.35)	0.59			1.282 (0.580–2.834)	0.53		
Subcapsular tumor location (couinaud segment) (ref: S2, S3, and S4)		0.77				0.3		0.95
S5	1.04 (0.312–3.454)	0.95			0.51 (0.188–1.38)	0.17	0.87 (0.389–2.311)	0.78
S6	0.775 (0.254–0.372)	0.66			0.426 (0.168–1.076)	0.07	0.71 (0.273–1.851)	0.48
S7	1.438 (0.577–3.581)	0.44			0.929 (0.467–1.848)	0.61	1.053 (0.514–2.157)	0.89
S8	1.367 (0.55–3.40)	0.50			0.639 (0.317–1.289)	0.17	0.974 (0.453–2.091)	0.95
Exophytic subcapsular HCC	2.006 (0.922–4.366)	0.08	1.938 (0.771–4.869)	0.16	0.717 (0.285–1.80)	0.48		
CT guidance vs US guidance	0.499 (0.195–1.277)	0.15	1.465 (0.347–6.188)	0.6	0.916 (0.474–1.773)	0.80		

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *AFP*, alpha fetoprotein; *CI*, confidence interval; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *HR*, hazard ratio; *MELD*, model for end-stage liver disease; *MWA*, microwave ablation; *OS*, overall survival; *PSM*, propensity score matching; *RFA*, radiofrequency ablation

Table 3 The patterns of first recurrence for patients in the PSM cohort

First recurrence type	MWA ($n=69$)	RFA ($n=69$)	p value
Overall	39 (56.5%)	46 (66.7%)	0.22
Local	5 (7.2%)	12 (17.4%)	0.07
Intrahepatic (non-local)	30 (43.5%)	32 (46.4%)	0.73
Distant	4 (5.8%)	5 (7.2%)	> 0.99

MWA, microwave ablation; *RFA*, radiofrequency ablation

Discussion

After using 1:1 PSM, the present study showed that MWA provided better local tumor control and a similar major complication rate for subcapsular HCC within the Milan criteria compared to RFA. Additionally, a higher rate of recurrence exceeding the Milan criteria occurred in patients treated with RFA than in those treated with MWA.

Currently, thermal ablation such as RFA is recommended as the standard treatment for early-stage HCC, which is not suitable for surgery [2]. However, considering that tumors located on the liver surface may be a risk factor for RFA in the local tumor recurrence rate [6–8] and the incidence of complications for patients [2, 9] with subcapsular HCC, the clinical application of RFA in these patients is still under debate [2].

Severe complications associated with thermal injury of adjacent structures or tumor seeding along the tract were not observed in the present study, which was consistent with previous results [3, 20]. Some researchers have reported that the use of biopsy in patients with subcapsular HCC may increase the incidence of tumor seeding [20–22]. As the non-invasive diagnostic criteria of HCC were applied in patients with cirrhosis, there was a low rate of patients undergoing biopsy in the current study. Moreover, antenna track ablation was routinely performed during needle removal to avoid tumor seeding and bleeding. For thermal injury, application of hydrodissection using artificial ascites may reduce thermal injury to adjacent organs for patients with subcapsular HCC [23], which may explain why no tumor seeding or thermal injury of adjacent structures was observed in the present study. In addition, more major pain in MWA group were observed in the present study, which may be linked to the higher intratumoral temperatures and more back energy in the abdominal wall with microwaves.

In terms of efficacy, previous studies have shown a comparable efficiency between RFA and MWA for patients with HCC up to 3 cm [24, 25]. Compared to RFA, however, MWA generates a higher temperature in a shorter period of time leading to a larger ablation area and fewer concerns for the heat sink effect [13, 24, 26]. Several studies have suggested that MWA is superior to RFA for local tumor control and long-term survival in larger neoplasms [24, 26–28]. Moreover, previous studies have compared the results of MWA with RFA for perivascular HCC, showing better outcomes in the MWA group [10, 27, 29]. As a supplement, the present study showed that MWA had better tumor control than RFA for patients with subcapsular HCC within the Milan criteria.

The main reason why RFA may increase the incidence of LTP for subcapsular HCC could be linked to the inability to sufficient enough safety margin along the hepatic capsule [3, 4]. The primary goal of observation in ablation of HCC is to obtain complete tumor necrosis and a 1.0-cm disease-free margin, and obtaining this goal for surgical resection could improve the rate of R0 resection [27, 30]. For RFA, a high-frequency alternating current is used to induce tumor destruction. The frequency energy is converted into heat around the needle electrode [24, 31]. Thus, the ablation zone is affected by electrical conductivity, thermal conductivity, and heat capacity, resulting in an irregular ablation shape in RFA [24, 27]. A certain tumor-free margin could assist the operator in assessing whether the tumor is covered by the

Table 4 Complications between MWA group and RFA group for subcapsular HCC

	Total cohort			PSM cohort		
	MWA	RFA	p value	MWA	RFA	p value
Complication	41 (51.25%)	39 (33.9%)	0.015	36 (52.2%)	24 (34.8%)	0.039
Minor complication	28 (35.0%)	27 (23.5%)	0.09	24 (34.7%)	16 (23.2%)	0.13
Major complication	13 (16.3%)	12 (10.4%)	0.23	12 (17.4%)	8 (11.6%)	0.33
Pain require treatment	8	3		7	2	
Infection	5	6		4	5	
Hydropneumothorax Require drainage	4	2		3	2	
Hepatic encephalopathy	0	2		0	0	
Post procedure ascites	1	1		1	0	
Death	0	0		0	0	

HCC, hepatocellular carcinoma; *MWA*, microwave ablation; *RFA*, radiofrequency ablation

irregular ablation zone during the operation. Such an intraoperative assessment would be difficult in subcapsular HCC. Additionally, the ablation area of RFA in HCC has two zones as follows: a direct and active heating zone within a small area around the needle electrode; and an indirect heating zone far from the ablation needle with a low intensity of energy [27]. Thus, the indirect heating zone in HCC ablation may increase the uncertainty of intraoperative assessment caused by insufficient margins and increase the risk of remnant tumors, thereby leading to LTP in the future. However, a previous study has compared MWA and RFA in ex vivo and in vivo porcine livers and reported that MWA shows a significantly faster and a higher rate of temperature increase to 54 °C (when complete necrosis can be obtained) than RFA at the same distance from needle electrode [32]. As the shortcomings of ablation in the irregular ablation shape and passive heating zone are amplified with insufficient ablation margin, the advantages of MWA in higher ablation temperature and more predictable ablation shape would make MWA superior to RFA in tumor control for subcapsular HCC.

Moreover, the present study showed that MWA provides better RBM than RFA for subcapsular HCC. Many patients who receive thermal ablation as the first-line therapy may have the potential to receive live transplantation or salvage liver transplantation in the future [18]. Prior studies have suggested that salvage live transplantation has a better survival benefit than re-resection and re-ablation [33, 34]. A lower rate of recurrence exceeding the Milan criteria would allow patients to have more choices in future treatment.

The current study showed no difference in OS between the MWA group and RFA group, which may be partly attributed to the relatively insufficient follow-up period. Additionally, the present study showed that the RFA group had a higher rate of patients receiving curative treatments after tumor recurrence. This positive treatment strategy for recurrent HCC may be another reason why the OS was similar in the MWA group and RFA group. Although the OS was similar in the MWA group and RFA group, poorer tumor control of patients treated with RFA may require more retreatments and additional medical costs.

The present study had several limitations. First, due to the retrospective nature of this study, potential bias may have occurred, even with a PSM method to balance the group and minimize the bias. Second, few subcapsular tumors with exophytic growth or close to the gallbladder were included in the present study due to the difficulty in treating these tumors with percutaneous thermal ablation. Third, most of the patients in the present study had hepatitis B virus infection and the performance of RFA and MWA may be different in HCC with other etiologies. Therefore, the results may not be generalizable to all patients with subcapsular HCC.

In conclusion, MWA has a better tumor control than RFA for subcapsular HCC within the Milan criteria. Regarding complications, MWA has a high overall complication rate than RFA but the major complications rates do not significantly differ.

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Declarations

Guarantor The scientific guarantor of this publication is Qiang Zhu.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Forty-nine patients have been previously reported in Microwave ablation shows similar survival outcomes compared with surgical resection for hepatocellular carcinoma between 3 and 5 cm.

Methodology
- retrospective
- case–control study
- multi-center study

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