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ONCOLOGY

Microwave ablation versus surgical resection for subcapsular hepatocellular carcinoma: a propensity score–matched study of long-term therapeutic outcomes

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Abstract

Objectives The therapeutic efficacy of microwave ablation (MWA) for subcapsular hepatocellular carcinoma (HCC) has not been well characterized. We aimed to compare the long-term outcomes of MWA and surgical resection (SR) in patients with subcapsular HCC.

Methods This retrospective study comprised 321 patients with subcapsular HCC meeting the Milan criteria who received MWA ($n = 99$) or SR ($n = 222$). Local tumor progression (LTP), overall survival (OS), and disease-free survival (DFS) were analyzed using propensity score matching (PSM) to compare the therapeutic efficacy.

Results In the total cohort, there were no significant differences in 5-year LTP rates (14.0% vs. 8.9%, $p = 0.12$), OS rates (70.7% vs. 73.2%, $p = 0.63$), and DFS rates (38.3% vs. 41.2%, $p = 0.22$) between the MWA and SR groups. After PSM, the cumulative LTP rates at 1, 3, and 5 years were 9.7%, 14.0%, and 16.4% in the MWA group ($n = 84$) and 7.2%, 8.6%, and 10.6% in the SR group ($n = 84$), respectively, with no significant difference ($p = 0.31$). Neither corresponding OS rates (96.4%, 84.8%, and 73.0% vs. 95.2%, 85.5%, and 72.1%, $p = 0.89$) nor DFS rates (76.0%, 52.6%, and 38.1% vs. 76.2%, 44.7%, and 32.3%, $p = 0.43$) were significantly different between the MWA and SR groups. Whereas MWA obtained fewer complications for both cohorts (both $p < 0.05$).

Conclusion MWA showed comparable long-term therapeutic outcomes to SR, and it might be an alternative curative option for subcapsular HCC within the Milan criteria.

Key Points

- *Microwave ablation showed comparable local tumor progression, overall survival, and disease-free survival to surgical resection for subcapsular hepatocellular carcinoma meeting the Milan criteria.*
- *Microwave ablation obtained fewer complications and shorter postoperative hospital stay.*

Keywords Carcinoma, hepatocellular · Microwaves · Hepatectomy

Abbreviations

ALBI	Albumin-bilirubin
DFS	Disease-free survival
HCC	Hepatocellular carcinoma
LTP	Local tumor progression
MWA	Microwave ablation
OS	Overall survival
PSM	Propensity score matching
SR	Surgical resection

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Introduction

Subcapsular location is a crucial factor for treatment selection and prognosis in patients with hepatocellular carcinoma (HCC) [1, 2]. Surgical resection (SR) is traditionally regarded as the preferred curative treatment for subcapsular HCC, considering it offers the possibility of complete tumor removal [1, 3]. But SR sacrifices more liver parenchyma and is not suitable for patients with poor liver function [4]. It is also associated with longer hospitalization and more perioperative complications, such as wound infections, blood loss, and post-hepatectomy liver failure [4, 5]. Microwave ablation (MWA) as one of the more recently developed thermal ablation modalities, has been increasingly used for treating early-stage HCC. Compared to SR, MWA provides equivalent survival outcomes for HCC patients and is associated with shorter operation time, less blood loss, and fewer complications [6, 7]. The therapeutic efficacy of thermal ablation in patients with subcapsular HCC is still controversial because subcapsular HCC has often been difficult to insert an electrode accurately and mostly too close to vulnerable key structures to achieve sufficient tumor-free margin [3, 8, 9].

Recently, ablation equipment, guiding modality, assistive technologies, and improvement in the skills of operators have improved greatly. Several studies have reported that the therapeutic efficacy of MWA as a first-line treatment yielded satisfactory results for HCC in challenging locations [9–11]. Our previous studies have also corroborated that MWA was superior to radiofrequency ablation with regard to tumor control for subcapsular HCC and perivascular HCC, due to its higher intratumoral temperature and lower susceptibility to heat sink effects than radiofrequency ablation [12, 13]. However, compared to SR, the therapeutic efficacy of MWA for subcapsular HCC within the Milan criteria has not been well characterized until now.

The purpose of this study was to compare the long-term therapeutic outcomes of MWA and SR for subcapsular HCC within the Milan criteria. Propensity score matching (PSM) was performed to reduce potential confounding bias at the baseline characteristics and to enhance intergroup comparability.

Methods

Patients

Between January 2010 and December 2020, 2542 patients with primary HCC underwent either MWA or SR as an initial treatment at Shandong Provincial Hospital Affiliated to Shandong First Medical University and Qilu Hospital Affiliated to Shandong University. Among them, 321 patients who underwent MWA (n = 99) or SR (n = 222) with subcapsular HCC were identified by the following inclusion criteria: (a) tumor meeting the Milan criteria (single tumor ≤ 5 cm or 2–3 tumors with each ≤ 3 cm in size); (b) at least one tumor meets the criteria for a subcapsular HCC; and (c) Child-Pugh class A or B. Patients were excluded based on the exclusion criteria as follows: (a) macroscopic vascular invasion or extra-hepatic metastasis on pre-treatment imaging and (b) medical comorbidities such as cardiopulmonary impairment and dysfunction or history of other organ malignancies. The detailed flow chart of the study patient selection process was presented in Fig. 1. This retrospective study was approved by the institutional reviews with a waiver of patient informed consent.

The diagnosis of HCC was based on the practice guidelines of the American Association for the Study of Liver Diseases (AASLD) [2]. Subcapsular HCC was defined when the shortest distance between the tumor margin and liver capsule (including the gallbladder fossa) was less than or equal to 3mm during either the arterial or portal phase [14, 15].

Treatment and follow-up

The treatment selections for individual patients were determined through consensus of multidisciplinary team meetings including radiologists, hepatobiliary surgeons, oncologists, and radiotherapists. MWA procedures were performed with real-time ultrasound or CT guidance by interventional radiologists who were familiar with ablation techniques. A MWA therapeutic instrument (MTC-3C, Vison Medical Devices R&D Center) was used in the procedure. Twenty-four of 99 (24.2%) patients in the MWA group received hydrodissection using artificial ascites to separate the adjacent vulnerable organs. The MWA process was described in detail in our previous literature [12]. SR procedures were performed by hepatobiliary surgeons based on per patient's tumor extent, hepatic functional reserve, and the operators' experience and preference. A total of 136 of 222 (61.3%) patients underwent open liver resection and 86 of 222 (38.7%) underwent laparoscopic liver resection. The length of postoperative hospital stay was recorded. Complications were assessed according to the Clavien-Dindo classification, and grades III and IV were classified as major complications [16, 17].

Patients were followed with clinical assessment including alpha fetoprotein level (AFP), liver function test, and using ultrasound, dynamic contrast-enhanced CT or MR imaging approximately 1–3 months after treatment, every 3 months during the first year and 3–6 months thereafter. Antiviral therapy for viral hepatitis was also persistent during the follow-up. Once the tumor recurred, the choice of re-treatment was based on a comprehensive assessment of general condition, tumor stage, and liver function. The duration of follow-up was measured from the date of initial treatment to the date of death or the last follow-up.

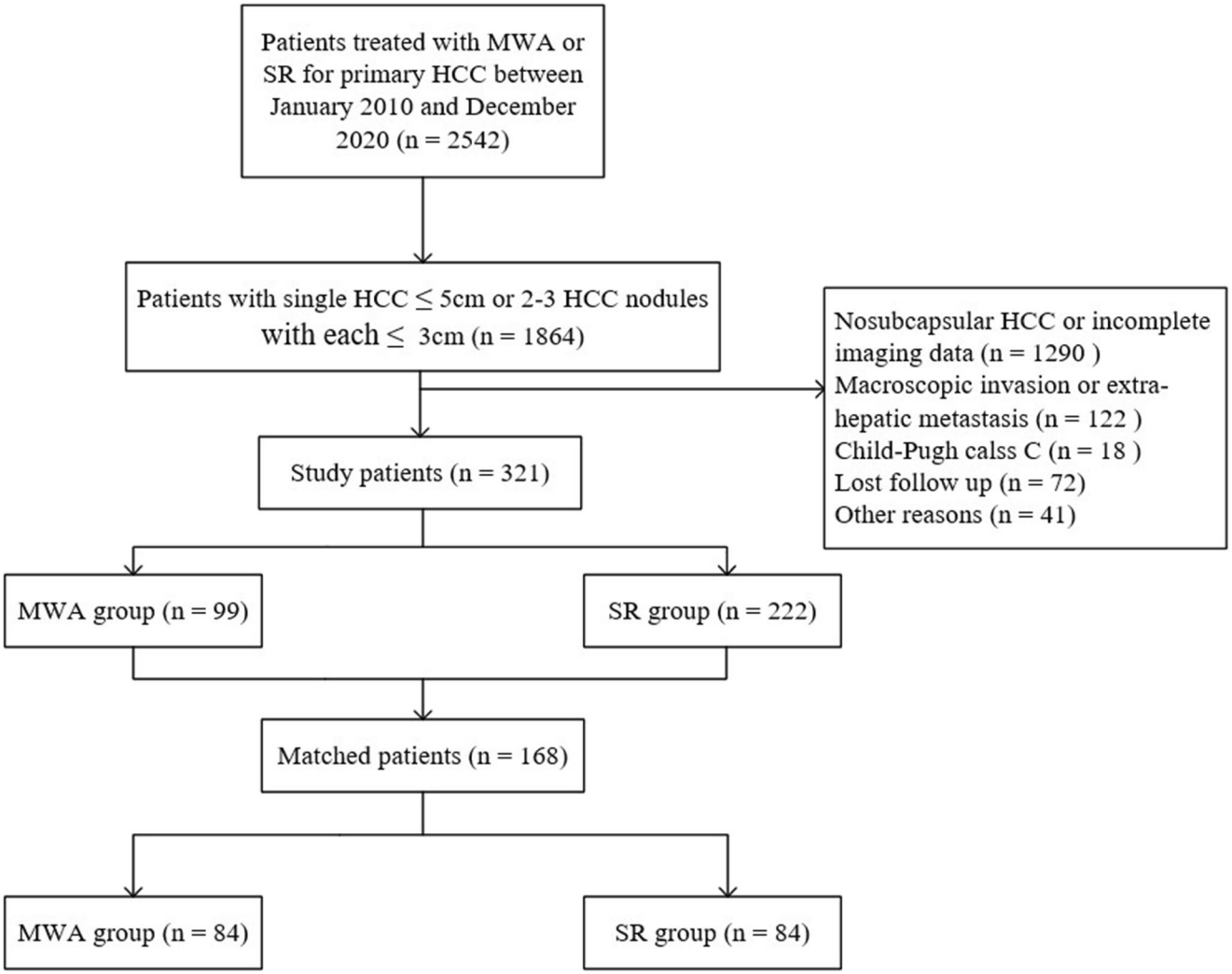

Fig. 1 Patient selection. Abbreviations: HCC, hepatocellular carcinoma; MWA, microwave ablation; SR, surgical resection

Long-term therapeutic outcomes

The long-term therapeutic outcomes were compared between the MWA and SR groups by assessing the local tumor progression (LTP), overall survival (OS), and disease-free survival (DFS). LTP was defined as the appearance of a new lesion within or at the edge of the ablated zone after complete ablation in the MWA group or around the surgical resection margin in the SR group on follow-up images [8]. OS was defined as the interval between the initial treatment of the subcapsular HCC and the time of death or the last follow-up. DFS was defined as the interval between the initial treatment of subcapsular HCC and the onset of tumor recurrence, metastasis, death, or the last follow-up.

We performed subgroup analyses of patients with solitary small HCC (≤ 3.0 cm) and solitary medium-sized HCC (3.0–5.0 cm). Since the newly developed albumin–bilirubin (ALBI) grade could classify grades clearly with different liver functions even in the Child-Pugh A patients, the therapeutic outcomes were also compared between the MWA and SR groups with the liver function of ALBI grade 1 and those with ALBI grade 2/3.

Propensity score matching

To reduce patient selection bias between the two groups, we performed 1:1 PSM using a caliper of 0.1. Variables with statistically significant differences between the MWA and SR groups at baseline characteristics ($p \leq 0.1$) or clinically important factors were selected for PSM. Finally,14 covariates were entered into PSM including gender, age, etiology of liver disease, antiviral treatment, tumor number, maximum tumor diameter, AFP level, Child-Pugh class, albumin-bilirubin grade, model for end-stage liver disease score, aspartate aminotransferase (AST), alanine aminotransferase, presence of liver cirrhosis, and presence of portal hypertension. After PSM, 84 patients from each group were selected for further analysis.

Since p value could be biased by sample size, the effect size of the covariate of balance irrelevant to the population size

was also reported by calculating standardized mean difference (SMD) before and after matching. The effect size was interpreted as follows: small, SMD = 0.2; medium, SMD = 0.5; and large, SMD = 0.8 [18].

Statistical analyses

Continuous variables are presented as medians and interquartile ranges, and categorical variables are expressed as counts and percentages. Differences in continuous variables between the two groups were compared using the Mann-Whitney test, and categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. Cumulative LTP, OS, and DFS curves were estimated using the Kaplan-Meier method, and differences between the two groups were compared using the log-rank test. Univariate and multivariate analyses were applied in determining prognostic factors associated with therapeutic outcomes using the Cox proportional hazards model. All tests were two-tailed, and p values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS 24.0 for Windows (SPSS Inc.).

Results

Patient characteristics

The total 321 patients with subcapsular HCC were divided into two groups based on the initial treatment, 99 patients with 110 subcapsular HCC nodules in the MWA group, and 222 patients with 230 subcapsular HCC nodules in the SR group. Compared to the SR group, the MWA group was significantly ($p < 0.05$) older, had more Child-Pugh class B, ALBI grade 2/3, portal hypertension, HCV infection, and higher AST level. For characteristics of tumors, smaller size and multifocality were more common in the MWA group than in the SR group (Table 1).

After PSM, a new cohort comprising 84 patients with 92 subcapsular HCC nodules in the MWA group and 84 patients with 90 subcapsular HCC nodules in the SR group was generated. All the relevant background characteristics were balanced, including age, Child-Pugh class, ALBI grade, portal hypertension, HCV infection, AST level, tumor size, and number (all $p > 0.05$) (Table 1).

Local tumor progression

The median follow-up period was 67 months (range, 3–133 months). LTP was detected in 12 of 99 patients (12.1%) in the MWA group and 16 of 222 patients (7.2%) in the SR group. For the total cohort, the cumulative LTP rates at 1, 3, and 5 years were 8.2%, 12.0%, and 14.0% in the MWA group and 4.5%, 6.7%, and 8.9% in the SR group, respectively, with no significant difference ($p = 0.12$) (Fig. 2A). After PSM, LTP was detected in 12 of 84 patients (14.3%) in the MWA group and 8 of 84 patients (9.5%) in the SR group. The cumulative LTP rates at 1, 3, and 5 years were 9.7%, 14.0%, and 16.4% in the MWA group and 7.2%, 8.6%, and 10.6% in the SR group, respectively, also with no significant difference ($p = 0.31$) (Fig. 2B).

Overall survival and disease-free survival

During the follow-up period, the mean OS was 7.9 years in the MWA group and 7.1 years in the SR group. Twenty-six of 99 (26.3%) patients in the MWA group and 49 of 222 (22.1%) patients in the SR group died. Fifty-seven of 99 (57.6%) patients in the MWA group and 111/222 (50.0%) patients in the SR group recurred. Among the patients with recurrence, 37/57 (64.9%) patients in the MWA group and 59/111 (53.2%) patients in the SR group underwent curative treatment (ablation or SR), with no significant difference ($p = 0.15$). The details were shown in Supplementary Table 1.

Before PSM, the 1-, 3-, and 5-year OS rates were 96.0%, 83.7%, and 70.7% in the MWA group and 97.7%, 84.6%, and 73.2% in the SR group, respectively ($p = 0.63$) (Fig. 3A). The corresponding DFS rates were 75.6%, 50.8%, and 38.3% in the MWA group and 81.5%, 55.8%, and 41.2% in the SR group, respectively ($p = 0.22$) (Fig. 4A). Neither the OS nor DFS rates were significantly different between the two groups in the total cohort.

After PSM, the 1-, 3-, and 5-year OS rates were 96.4%, 84.8%, and 73.0% in the MWA group and 95.2%, 85.5%, and 72.1% in the SR group, respectively ($p = 0.89$) (Fig. 3B). The corresponding DFS rates were 76.0%, 52.6%, and 38.1% in the MWA group and 76.2%, 44.7%, and 32.3% in the SR group, respectively ($p = 0.43$) (Fig. 4B). The OS and DFS rates were still not significantly different between the two groups in the PSM cohort.

Subgroup analyses

The results of subgroup analyses based on tumor diameter of patients with solitary HCC (≤ 3 cm or > 3 cm), multiple tumors, and ALBI grade (grade 1 or grade 2/3) in the total and PSM cohort are summarized in Table 2. Kaplan-Meier analyses showed that there were no differences in LTP and OS between the two groups for these subgroup analyses (all $p > 0.05$). The comparison of MWA and laparoscopic liver resection was further performed. MWA shared equivalent LTP, OS in both cohorts (all $p > 0.05$). Although the DFS rates between the two groups were different in the total cohort ($p = 0.004$), no difference was found after PSM ($p > 0.05$) (Table 3).

Prognostic factors for OS and DFS

In the total cohort, multivariate analysis confirmed that age (hazards ratio [HR], 1.04; 95% confidence interval [CI], 1.01–

Table 1 Baseline characteristics of study patients

Variables	Total cohort				PSM cohort			
	MWA group (n = 99)	SR group (n = 222)	p value	SMD	MWA group (n = 84)	SR group (n = 84)	p value	SMD
Age (years)+	61 (52–66)	56 (50–62)	0.001	0.43	62 (52–66)	59 (53–65)	0.30	0.15
Male	81 (81.8%)	199 (89.6%)	0.05	0.22	10 (11.9%)	74 (88.1%)	0.34	0.07
Etiology			0.007				0.41	
HBV	83 (83.8%)	193 (86.9%)	0.46	0.09	73 (86.9%)	75 (89.3%)	0.48	0.11
HCV	7 (7.1%)	2 (0.9%)	0.005	0.32	5 (6.0%)	2 (2.4%)	0.58	0.04
Others	9 (9.1%)	27 (12.25)	0.42	0.10	6 (7.1%)	7 (8.3%)	0.77	0.05
Antiviral treatment	67 (67.7%)	129 (58.1%)	0.10	0.20	56 (66.7%)	54 (64.3%)	0.74	0.05
Child-Pugh class B	14 (14.1%)	9 (4.1%)	0.001	0.35	6 (7.1%)	7 (8.3%)	0.77	0.05
ALBI grade 2/3	50 (50.5%)	58 (26.1%)	< 0.001	0.52	38 (45.2%)	34 (40.5%)	0.53	0.10
MELD score+	4.8 (2.6–6.6)	4.6 (2.5–6.3)	0.72	0.09	4.5 (2.5–6.1)	4.95 (3.0–6.7)	0.24	0.11
Liver cirrhosis	91 (91.9%)	189 (85.1%)	0.09	0.21	77 (91.7%)	77 (91.7%)	1.00	0.00
Portal hypertension	69 (69.7%)	119 (53.6%)	0.007	0.34	55 (65.5%)	57 (67.9%)	0.74	0.05
AFP (U/L)+	20.7 (4.2–212.6)	22.1 (4.2–200)	0.80	0.08	25.2 (4.2–234.3)	20.7 (5.9–175.0)	0.95	0.05
ALT (U/L)+	29.0 (20.0–42.0)	27.0 (20.0–46.3)	0.93	0.14	29.0 (20.5–41.5)	25.0 (19.5–45.5)	0.42	0.08
AST (U/L)+	33.0 (25.0–46.0)	28.0 (22.0–39.0)	0.024	0.10	29.5 (24.0–42.0)	28.0 (22.0–44.5)	0.23	0.003
Maximum tumor diameter (cm)+	2.6 (2.0–3.7)	3.1 (2.5–4.0)	< 0.001	0.44	2.7 (2.1–3.8)	3.0 (2.2–3.8)	0.24	0.13
Subcapsular tumor diameter (cm)+	2.5 (2.0–3.7)	3.1 (2.5–4.0)	< 0.001	0.39	2.7 (2.1–3.8)	3.0 (2.2–3.8)	0.23	0.14
Multiple tumors	16 (16.2%)	18 (8.1%)	< 0.001	0.25	14 (16.7%)	12 (14.3%)	0.67	0.07
Subcapsular tumor location (Couinaud segment)			0.73				0.78	
S1, S2, S3, and S4	22/110 (20.0%)	59/230 (25.7%)	0.25	0.14	19/92 (20.7%)	22/90 (24.4%)	0.54	0.09
S5	15/110 (13.6%)	30/230 (10.0%)	0.88	0.11	13/92 (14.1%)	9/90 (10.0%)	0.39	0.13
S6	24/110 (21.8%)	53/230 (23.0%)	0.80	0.03	21/92 (23.3%)	21/90 (23.3%)	0.94	0.00
S7	24/110 (21.8%)	47/230 (20.4%)	0.77	0.03	19/92 (20.7%)	18/90 (20.0%)	0.91	0.02
S8	25/110 (22.7%)	41/230 (17.8%)	0.29	0.12	20/92 (21.7%)	20/90 (22.2%)	0.94	0.01

Except where indicated, data are numbers of patients, with percentages in parentheses

+ Data are medians, with interquartile ranges in parentheses

Abbreviations: *AFP*, alpha fetoprotein; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *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; *SMD*, standardized mean difference; *SR*, surgical resection

1.06; p = 0.008) and ALBI grade 2/3 (HR, 1.83; 95% CI, 1.07–3.12; p = 0.027) were independent risk prognostic factors for OS. Maximum tumor diameter > 3 cm (HR, 1.42; 95% CI, 1.04–1.95; p = 0.029) and multifocality (HR, 1.71; 95% CI, 1.09–2.66; p = 0.019) were independent risk prognostic factors for DFS. Whereas primary treatment was not an independent prognostic factor for OS (HR, 0.80; 95% CI, 0.47–1.36; p = 0.41) and DFS (HR, 1.11; 95% CI, 0.80–1.55; p = 0.55) (Table 4).

Complications

Complications after treatment and postoperative hospital stay are presented in Table 5. In the MWA group, no immediate thermal injury and tumor seeding were observed. In the SR group, one patient was with intra-abdominal abscess, one with wound dehiscence, and four with liver failure. For both cohorts, the complication rates in the MWA group were statistically lower than that in the SR group (total cohort: 48.5% vs. 74.8%, p < 0.001; PSM cohort: 51.2% vs. 70.2%, p = 0.011). No significant differences were observed for major complication rates between the two groups for both cohorts (total cohort: 8.0% vs. 9.0%, p = 0.79; PSM cohort: 9.5% vs. 16.7%, p = 0.17).

Moreover, the patients in the MWA group had shorter median postoperative hospital stay than those in the SR group for the total (4 vs. 8 days, p < 0.001) and PSM (4 vs. 9 days, p < 0.001) cohorts. Fewer patients in the MWA group underwent a blood transfusion (total cohort: 3.0% vs. 9.9%, p = 0.034; PSM cohort: 2.4% vs. 17.9%, p = 0.001).

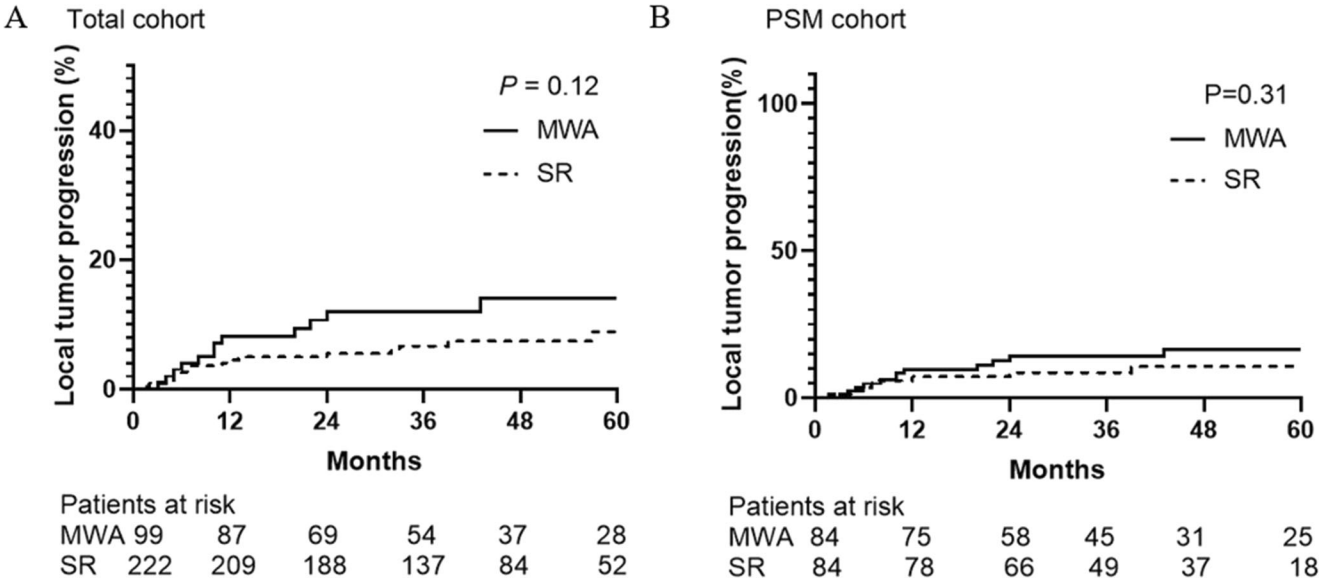

Fig. 2 Cumulative local tumor progression curves of patients with subcapsular HCC. Between the MWA and SR groups of study patients, local tumor progression rates were not significantly different in the total cohort (**A**) and PSM cohort (**B**). Abbreviations: HCC, hepatocellular carcinoma; MWA, microwave ablation; PSM, propensity score matching; SR, surgical resection

Discussion

The present study demonstrated that the long-term therapeutic outcomes of MWA were comparable to those of SR for subcapsular HCC within the Milan criteria in the total and PSM cohorts. Similar results were found in subgroup analyses, including the tumor diameter of patients with solitary HCC (≤ 3 cm or > 3 cm), multiple tumors, and ALBI grade (grade 1 or grade 2/3). In addition, MWA obtained fewer complications and shorter postoperative hospital stay than SR in the two cohorts.

MWA has been widely used for the treatment of early HCC as a more powerful ablation weapon than RFA [12, 19]. Many articles comparing the tumor control and survival outcomes between MWA and SR have been published [20–22]. Dou et al found that MWA resulted in equivalent LTP rates for HCC up to 4 cm and higher LTP rates for HCC 4.1–5.0 cm [20]. For solitary HCC 3–5 cm, MWA showed similar OS to laparoscopic liver resection [22]. Moreover, several studies reported that MWA gained a satisfactory role in tumor control for HCC located near difficult locations, such as diaphragm, gallbladder, and large vessels [23, 24].

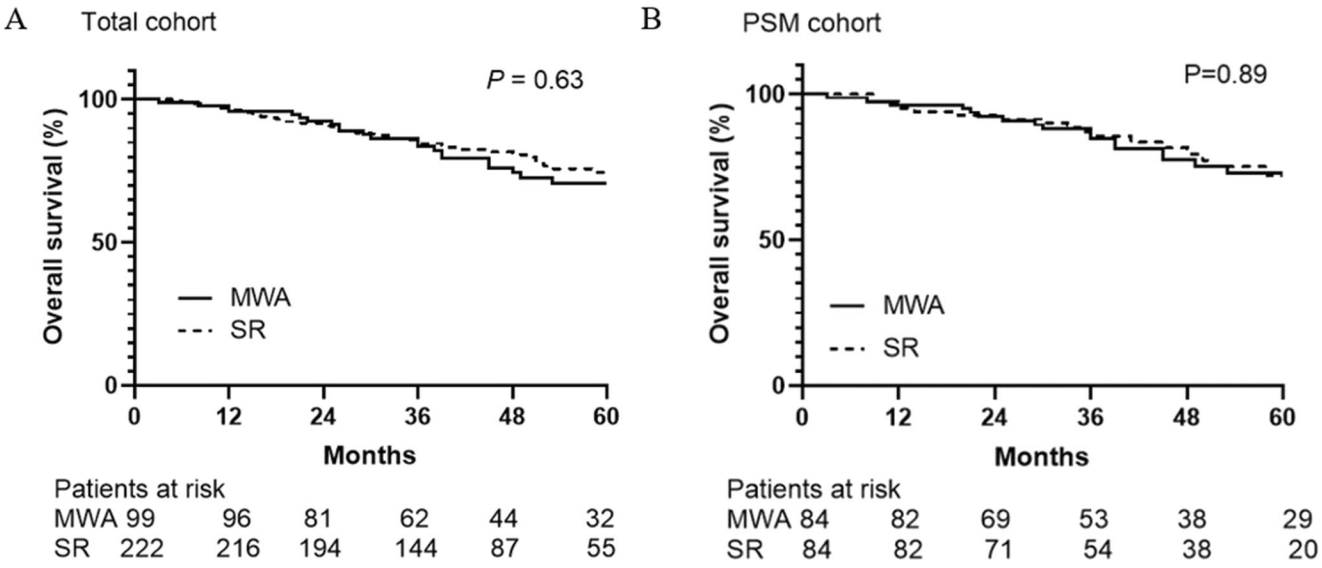

Fig. 3 Overall survival curves of patients with subcapsular HCC. Between the MWA and SR groups of study patients, overall survival rates were not significantly different in the total cohort (**A**) and PSM cohort (**B**). Abbreviations: HCC, hepatocellular carcinoma; MWA, microwave ablation; PSM, propensity score matching; SR, surgical resection

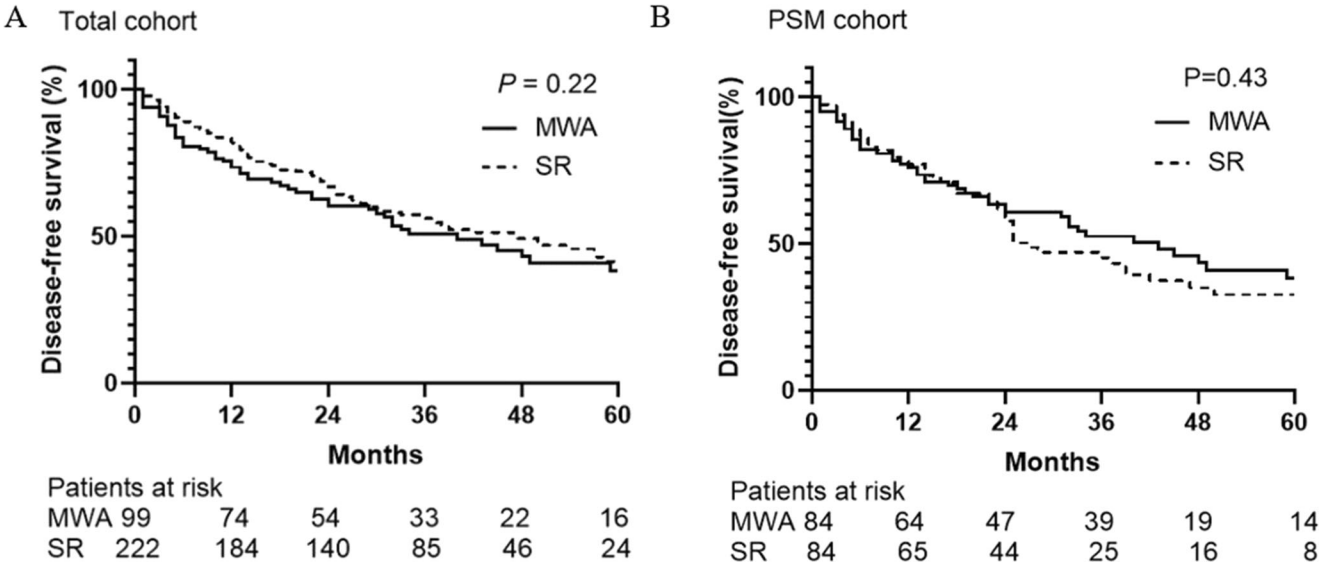

Fig. 4 Disease-free survival curves of patients with subcapsular HCC. Between the MWA and SR groups of study patients, disease-free survival rates were not significantly different in the total cohort (**A**) and PSM cohort (**B**). Abbreviations: HCC, hepatocellular carcinoma; MWA, microwave ablation; PSM, propensity score matching; SR, surgical resection

Traditionally, treatment of subcapsular HCC has been considered with caution mainly because of two concerns, local tumor control and the high risk of complications [8]. Most investigators accepted that the subcapsular location of a tumor was a risk factor for LTP after radiofrequency ablation, because of the difficulty to insert the electrode accurately and the inability to achieve enough tumor-free margin [25–27]. However, no consensus has been established on the treatment of subcapsular HCC. This is the first study comparing MWA with SR for subcapsular HCC meeting the Milan criteria, and no significant difference was observed in LTP between them. This result was mainly attributed to the advance in MWA ablation technology, which provided higher induced intratumoral temperatures in a shorter period of time, leading

Table 2 Subgroup analyses by tumor diameter and ALBI grade

	Mean LTP time (years)		5-years LTP			Mean OS time (years)		5-years OS		
Subgroup	MWA	SR	MWA	SR	*p* value	MWA	SR	MWA	SR	*p* value
Total cohort										
Tumor diameter										
Solitary, HCC ≤ 3cm (*n* = 146)	7.86	9.56	16.3%	7.3%	0.14	7.91	6.57	50.0%	86.8%	0.84
Solitary, HCC > 3 cm (*n* = 141)	7.47	8.50	14.4%	8.9%	0.48	6.52	7.12	67.7%	79.5%	0.79
Multiple HCCs (*n* = 34)	-	-	8.3%	0.0%	0.26	6.56	5.41	64.2%	77.4%	0..56
ALBI grade										
Grade 1 (*n* = 213)	8.22	8.79	15.9%	8.4%	0.18	7.45	7.53	80.4%	78.4%	0.68
Grade 2/3 (*n* = 108)	9.77	7.27	12.8%	10.2%	0.52	7.07	5.70	62.3%	59.5%	0.85
PSM cohort										
Tumor diameter										
Solitary, HCC ≤ 3 cm (*n* = 76)	9.07	6.65	21.5%	12.6%	0.35	8.20	6.02	81.2%	70.1%	0.81
Solitary, HCC > 3 cm (*n* = 66)	7.43	6.61	14.8%	12.9%	0.85	6.45	6.03	69.0%	66.1%	0.90
Multiple HCCs (*n* = 26)	-	-	10.0%	0.0%	0.34	6.73	5.18	66.7%	75.0%	0.82
ALBI grade										
Grade 1 (*n* = 96)	8.17	6.94	16.5%	8.0%	0.43	7.58	6.54	82.3%	81.6%	0.65
Grade 2/3 (*n* = 72)	9.56	6.20	16.7%	14.0%	0.53	7.00	5.27	62.8%	60.2%	0.77

Abbreviations: *ALBI*, albumin-bilirubin; *LTP*, local tumor progression; *MWA*, microwave ablation; *OS*, overall survival; *PSM*, propensity score matching; *SR*, surgical resection

Table 3 Subgroup analyses by MWA and laparoscopic liver resection

Variables	Total cohort			PSM cohort		
	MWA (n = 99)	LLR (n = 86)	p value	MWA (n = 55)	LLR (n = 55)	p value
LTP			0.33			0.27
Mean LTP time (years)	9.72	6.80		111.71	80.67	
5-year LTP	14.0%	8.3%		8.2%	10.5%	
OS			0.32			0.13
Mean OS time (years)	7.86	6.21		108.37	70.97	
5-year OS	70.7%	73.7%		84.9%	68.3%	
DFS			0.004			0.09
Mean DFS time (years)	3.72	5.25		48.22	62.08	
5-year DFS	38.3%	64.2%		44.4%	65.5%	
Postoperative hospital stay[+]	4 (3–6)	6 (5–8)	< 0.001	4 (3–6)	7 (5–9)	< 0.001
Complication	48 (48.5%)	51 (59.3%)	0.14	30 (54.5%)	29 (52.7%)	0.85
Minor (CD grade < 3)	40 (40.4%)	47 (54.7%)	0.06	24 (43.6%)	26 (47.3%)	0.70
Major (CD grade ≥ 3)	8 (8.1%)	4 (4.7%)	0.39	6 (10.9%)	3 (5.5%)	0.49

[+] Data are medians, with interquartile ranges in parentheses

Data are numbers of patients, with percentages in parentheses

Abbreviations: *ALBI*, albumin-bilirubin; *LLR*, laparoscopic liver resection; *LTP*, local tumor progression; *MWA*, microwave ablation; *OS*, overall survival; *PSM*, propensity score matching; *SR*, surgical resection

Table 4 Prognostic factors for overall survival and disease-free survival in the total cohort

Variables	OS				DFS			
	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
Primary treatment (MWA vs. SR)	1.12 (0.70–1.81)	0.63	0.80 (0.47–1.36)	0.41	1.22 (0.89–1.68)	0.23	1.11 (0.80–1.55)	0.55
Age (years)	1.04 (1.01–1.06)	0.002	1.04 (1.01–1.06)	0.008	1.00 (0.98–1.02)	0.87		
Gender (male)	0.75 (0.41–1.37)	0.35	1.06 (0.54–2.08)	0.87	1.16 (0.73–1.84)	0.52		
Etiology (ref.: HBV)		0.32		0.90		0.15		0.71
HCV	2.14 (0.78–5.91)	0.14	1.26 (0.41–3.92)	0.69	1.64 (0.77–3.51)	0.20	1.22 (0.54–2.76)	0.63
Others	1.17 (0.60–2.29)	0.64	1.11 (0.50–2.46)	0.80	0.69 (0.41–1.17)	0.17	0.82 (0.46–1.46)	0.49
Antiviral treatment	1.03 (0.65–1.64)	0.91	0.86 (0.51–1.46)	0.57	1.28 (0.93–1.75)	0.13	1.11 (0.78–1.56)	0.57
Child-Pugh class (B)	1.55 (0.71–3.38)	0.27	0.97 (0.38–2.43)	0.95	1.51 (0.90–2.56)	0.12	1.13 (0.64–1.97)	0.68
ALBI grade (2/3)	2.24 (1.42–3.53)	0.001	1.83 (1.07–3.12)	0.027	1.23 (0.90–1.68)	0.20		
MELD score	1.08 (1.00–1.17)	0.05	1.09 (0.99–1.19)	0.08	1.03 (0.98–1.09)	0.25		
Liver cirrhosis	1.92 (0.77–4.76)	0.16	1.95 (0.71–5.36)	0.20	1.89 (1.07–3.32)	0.03	1.68 (0.90–3.15)	0.10
Portal hypertension	1.32 (0.82–2.12)	0.26	1.01 (0.59–1.73)	0.98	1.37 (1.00–1.88)	0.05	1.07 (0.75–1.52)	0.72
AFP (> 200 ng/ml)	1.10 (0.66–1.82)	0.72	1.16 (0.66–2.04)	0.60	1.15 (0.82–1.63)	0.41		
ALT (> 50 U/L)	0.78 (0.44–1.40)	0.40			1.13 (0.79–1.63)	0.50		
AST (> 40 U/L)	1.3 (0.84–2.23)	0.20			1.52 (1.10–2.12)	0.01	1.33 (0.94–1.90)	0.11
Maximum tumor diameter (> 3 cm)	1.02 (0.65–1.60)	0.95	1.12 (0.69–1.81)	0.66	1.34 (0.99–1.81)	0.06	1.42 (1.04–1.95)	0.029
Multifocality	1.14 (0.57–2.30)	0.71	1.01 (0.49–2.10)	0.98	1.74 (1.13–2.68)	0.01	1.71 (1.09–2.66)	0.019

Abbreviations: *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *AFP*, alpha fetoprotein; *CI*, confidence interval; *DFS*, disease-free survival; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *HR*, hazard ratio; *LTP*, local tumor progression; *MELD*, model for end-stage liver disease; *MWA*, microwave ablation; *OS*, overall survival; *SR*, surgical resection

Table 5 Complications and postoperative hospital stay

Variables	Total cohort			PSM cohort		
	MWA	SR	*p* value	MWA	SR	*p* value
Postoperative hospital stay[+]	4 (3–6)	8 (6–11)	< 0.001	4 (3–6)	9 (7–11)	< 0.001
Complication	48 (48.5%)	166 (74.8%)	< 0.001	43 (51.2%)	59 (70.2%)	0.011
Minor (CD grade < III)	40 (40.4%)	146 (65.8%)	< 0.001	35 (41.7%)	45 (53.6%)	0.12
Major (CD grade ≥ III)	8 (8.0%)	20 (9.0%)	0.79	8 (9.5%)	14 (16.7%)	0.17
CD complication grade						
I	39 (39.3%)	142 (64.0%)		35 (41.7%)	42 (50.0%)	
II	1 (1.0%)	7 (3.2%)		0 (0.0%)	4 (4.8%)	
III	6 (6.0%)	11 (4.9%)		7 (8.3%)	9 (10.7%)	
IV	2 (2.0%)	6 (2.7%)		1 (1.2%)	4 (4.8%)	
V	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Pain requires treatment	8 (8.0%)	31 (13.9%)	0.14	8 (9.5%)	12 (14.3%)	0.34
Infection	5 (5.0%)	14 (6.3%)	0.66	4 (4.8%)	8 (9.5%)	0.23
Intra-abdominal abscess	0 (0.0%)	1 (0.5%)	1.00	0 (0.0%)	1 (1.2%)	1.00
Hydropneumothorax require drainage	6 (6.1%)	12 (5.4%)	0.81	8 (9.5%)	4 (4.8%)	0.37
Severe ascites	1 (1.0%)	7 (3.2%)	0.26	0 (0.0%)	6 (7.1%)	0.013
Wound dehiscence	0 (0.0%)	1 (0.5%)	1.00	0 (0.0%)	0 (0.0%)	1.00
Liver failure	0 (0.0%)	4 (1.8%)	0.32	0 (0.0%)	3 (3.6%)	0.25
Blood transfusion	3 (3.0%)	22 (9.9%)	0.034	2 (2.4%)	15 (17.9%)	0.001

Except where indicated, data are numbers of patients, with percentages in parentheses

[+] Data are medians, with interquartile ranges in parentheses

Abbreviations: *MWA*, microwave ablation; *PSM*, propensity score matching; *SR*, surgical resection

to enlargement of the ablation area, deepening of microwave energy penetration, and decrease of a heat-sink effect than radiofrequency ablation [19, 28]. Another possible explanation for this result was the application of assistive technologies, such as hydrodissection, contrast-enhanced ultrasound or CT guidance, and combined multimodal method, which could provide greater possibilities for radical MWA of tumor [9, 29]. Thus, MWA might be an alternative curative option to SR for subcapsular HCC within the Milan criteria.

In terms of survival outcomes, we found that MWA was as efficient as SR in patients with subcapsular HCC meeting the Milan criteria. A possible explanation for these results was that MWA remains a minimally invasive procedure, which allows preservation of functioning hepatic parenchyma and does not jeopardize the possibility of further treatment. The same results were observed in a recent study for treating HCC located in difficult locations by Qi et al They found that MWA showed similar survival outcomes to SR for HCC in the caudate lobe [29]. Our multivariate Cox analyses also confirmed that primary treatment was not an independent risk factor for OS and DFS in patients with subcapsular HCC. Indeed, initial treatment might be a small part of long-term patient care for HCC, because the incidence of intrahepatic distant recurrence, extrahepatic metastasis, or de novo carcinogenesis from the remnant liver parenchyma was estimated to be high at up to 70% at 5 years after initial treatment [30, 31].

Age and ALBI grade were independent prognostic factors for OS in our studies, in accordance with former reports in treating HCC [32–34]. In this study, the maximum tumor diameter > 3 cm and multifocality were identified as independent prognostic factors associated with poor DFS, which were the same as the previous studies in cohorts of HCC patients [21, 35]. In this retrospective study, MWA patients were significantly older and had worse clinical presentations than those in the SR group. Therefore, the results of the total cohort may have been disadvantaged by the disproportionate assignment between the two groups. Despite potential imbalances in the total cohort, the baseline characteristics were comparable between the MWA and SR groups after PSM.

In the present study, MWA obtained a lower rate of complications, shorter postoperative hospital stay, and less blood transfusion than SR. These results were consistent with the former meta-analysis in which MWA had fewer complications than SR for HCC [36] MWA is less invasive than SR and is usually applicated to patients with poorer liver function or general conditions [37]. Therefore, MWA may be a favorable treatment option, especially for patients unsuitable for SR. In addition, MWA showed similar complications and

shorter hospitalization to laparoscopic liver resection, which is in line with the report of Wang et al for 3–5 cm HCC [22].

This study had several limitations. Since this was a retrospective study, the results drawn from the analysis might be hampered by selection bias and information bias. Moreover, the characterizations of patients between the MWA and SR groups showed substantially different in the total cohort. Although we used a scientific, well-thought-out PSM method to minimize differences, uncontrolled potentially confounding factors might not have been completely avoided. Therefore, further large-sample, prospective randomized controlled trials are warranted to verify these results.

In conclusion, microwave ablation showed comparable long-term therapeutic outcomes to surgical resection, and it might be an alternative curative option for subcapsular hepatocellular carcinoma within the Milan criteria.

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Declarations

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Methodology
- retrospective
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- multicenter study

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