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Microwave ablation versus radiofrequency ablation as bridge therapy in potentially transplantable patients with single HCC ≤ 3 cm: A propensity score-matched study

Xueqi Wang [a], Hongli Yu [a], Fenglin Zhao [a], Yayun Xu [a], Chunzhao Wang [a], Kaiwen Liu [b], Bo Liu [c], Hang Zheng [d], Yingnan Wei [e], Xinyu Wang [f], Qiang Zhu [a,f], Min Huang [g,*], Yuemin Feng [a,f,*]

[a] Department of Gastroenterology, Shandong Provincial Hospital, Shandong University, Jinan, Shandong Province 250012, China
[b] Department of Radiology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong Province 250021, China
[c] Department of Radiology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong Province 250012, China
[d] Department of Gastroenterology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang Province 325000, China
[e] Department of Gastroenterology, Heze Municipal Hospital, Heze, Shandong Province 274099, China
[f] Department of Gastroenterology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong Province 250021, China
[g] Department of Clinical Laboratory, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong Province 250021, China

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ABSTRACT

Objectives: The efficacy of microwave ablation (MWA) for hepatocellular carcinoma (HCC) as bridge therapy has been gradually confirmed. We aimed to compare the recurrence beyond the Milan criteria (RBM) rates in potentially transplantable patients with HCC receiving MWA or radiofrequency ablation (RFA) as bridge therapy.
Methods: In total, 307 potentially transplantable patients with single HCC ≤ 3 cm who initially received MWA (n = 82) or RFA (n = 225) were included. RBM, recurrence-free survival (RFS), and overall survival (OS) were compared between MWA and RFA groups by using propensity score matching (PSM). Competing risks Cox regression was used to identify predictors of RBM.
Results: After PSM, the 1-, 3-, and 5-year cumulative RBM rates were 6.8%, 18.3%, and 39.3% in the MWA group (n = 75), and 7.4%,18.5%, and 27.7% in the RFA group (n = 137), respectively, with no significant difference (p = 0.386). MWA and RFA were not the independent risk factors of RBM, and patients with higher alpha-fetoprotein, non-antiviral treatment, and higher MELD score were at greater risk of RBM. Neither corresponding RFS rates (66.7%, 39.2% and 21.4% vs. 70.8%, 47% and 34.7%, p = 0.310) nor OS rates (97.3%, 88.0%, and 75.4% vs. 97.8%, 85.1%, and 70.7%, p = 0.384) for 1-, 3- and 5-years were significantly different between the MWA and RFA groups. The MWA group showed more frequent major complications (21.4% vs. 7.1%, p = 0.004) and longer hospital stays (4 days vs. 2 days, p < 0.001) compared with the RFA group.
Conclusion: MWA showed comparable RBM, RFS, and OS rates to RFA in potentially transplantable patients with single HCC ≤ 3 cm. Compared to RFA, MWA might provide the same effect as bridge therapy.

1. Introduction

Liver transplantation (LT) is the best treatment option for hepatocellular carcinoma (HCC) patients with early-stage tumors [1]. Limited organ supply and increasing demand for organ transplants have prolonged transplant waiting time, resulting in increased morbidity and mortality of potentially transplantable patients on the waiting list [2]. Milan criteria is most commonly used to identify LT candidates in HCC patients [3,4]. HCC patients will have to drop out of the transplant list once recurrence beyond the Milan criteria (RBM) [1,5]. Therefore,

Abbreviations: AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; LT, liver transplantation; MWA, microwave ablation; OS, overall survival; PSM, propensity score matching; RBM, recurrence beyond the Milan criteria; RFA, radiofrequency ablation; RFS, recurrence-free survival.

* Corresponding authors at: Department of Clinical Laboratory, Shandong Provincial Hospital Affiliated to Shandong First Medical University, 324, Jing 5 Rd, Ji'nan 250021, Shandong Province, China (M. Huang). Department of Gastroenterology, Shandong Provincial Hospital, Shandong University, 324, Jing 5 Rd, Ji'nan 250021, Shandong Province, China (Y. Feng).
E-mail addresses: huangmin1983@aliyun.com (M. Huang), sdyueminfeng@163.com (Y. Feng).

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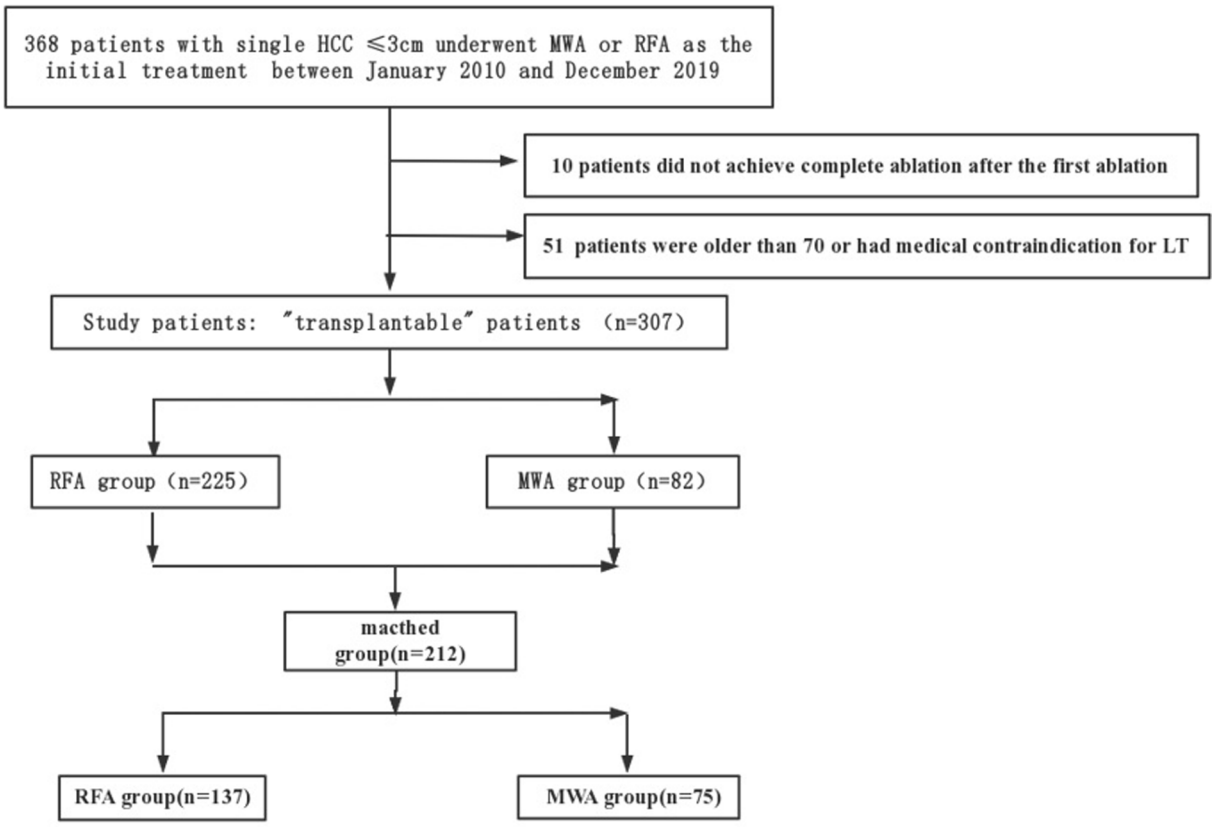

Fig. 1. Patient selection. Abbreviations: HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; MWA, microwave ablation; LT, liver transplantation.

bridge therapy is essential for potentially transplantable patients in order to prevent the progression and RBM of HCC and to confer the best chance for survival [6-9].

Microwave ablation (MWA), which utilizes thermal ablation to form a coagulated necrotic area including tumor and marginal non-tumor tissue, has been a safe and significantly effective treatment for HCC, with an ablation rate of over 95% [10-12]. There are several studies on the use of MWA as the primary or sole bridge therapy, and the efficacy of MWA for HCC within Milan criteria as bridge therapy is gradually confirmed [13,14]. Prior studies have reported that radiofrequency ablation (RFA) is deemed an effective way of bridging therapy [15,16]. RFA is an effective treatment for single HCC $\leq$ 3 cm according to American Association for the Study of Liver Diseases(AASLD) [17]. RFA achieves excellent long-term overall and tumor-specific survival, and the drop-out rate due to tumor progression is low in spite of the long wait time [8]. Compared with RFA, MWA is more effective in controlling local tumors and has fewer concerns for the heat sink effect by applying higher temperatures in a shorter time [18,19]. Some studies compared the therapeutic and safety outcomes of RFA and MWA [20]. However, there is no evidence to access RBM rates of MWA compared to RFA in these patients up to now.

Thus, we aimed to compare RBM rates in potentially transplantable patients with single HCC $\leq$ 3 cm receiving MWA or RFA as bridge therapy. Propensity score matching (PSM) was applied to reduce potential confounding bias at baseline.

2. Methods

2.1. Patients

The present study was a retrospective study conducted at two tertiary hospitals. We evaluated all adults (age $\geq$ 18 years old) newly diagnosed with single HCC $\leq$ 3 cm who received either MWA or RFA as the initial therapy between January 2010 and December 2019. All of the patients met the criteria for LT and had no transplant-related contraindications [21,22]. A total of 307 patients were included by the following inclusion criteria: (1) single HCC up to 3 cm in maximum diameter; (2) non-hepatic resection candidate or patients refused hepatic resection; (3) patients underwent RFA or MWA as the initial therapy; (4) Child-Pugh class A or B. Patients were excluded according to the following exclusion criteria: (1)Patients who did not achieve complete ablation after the initial RFA or MWA; (2) Patients disqualified from transplantability who were over 70 years of age or had contraindications to LT (vascular invasion, extrahepatic metastasis or/and complicated with other malignant tumors or noncontrollable systemic infection, etc.). The flow chart for the study of patient selection was detailed in Fig. 1. This retrospective study waived patient informed consent and was approved by institutional review.

HCC is diagnosed based on the criteria in practice guidelines of the AASLD [17]. Transplantability was defined as any patient who was younger than 70 years old, with no medical comorbidities precluding transplantation [5]. Complete ablation was defined as the first contrast-enhanced dynamic computed tomography (CT) or magnetic resonance imaging (MRI) scan approximately 1 month after ablation showed no nodules or irregular enhancement in or near the ablation area during the arterial phase [23]. At 1 month after RFA/MWA, "residual tumor" was that the treatment margin occurring irregular peripheral enhancement. If the enhancement is located near the non-ablation site, it is considered as "recurrence" [24,25]. If residual tumor was present, patients received MWA/RFA again procedure to achieve complete ablation [24]. And they were excluded in our study. First recurrence was defined as the first recurrence during the entire follow-up period.

2.2. Treatment and follow-up

Treatment options for every patient were determined by consensus

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

Variable	Total cohort n = 307				PSM cohort n = 212			
	RFA group (n = 225) +	MWA group (n = 82) +	P	SMD	RFA group (n = 137) +	MWA group (n = 75) +	p	SMD
Male※	171(76%)	62(75.6%)	0.944	0.00934	101 (73.7%)	56 (74.7%)	0.881	0.0216
Age	56(49–62)	55(48–61)	0.442	0.07134	55(48–61.5)	55(48–61)	0.735	0.0351
Etiology※			0.858				1	
HBV	205(91.1%)	74(90.2%)		0.031	123 (89.8%)	68 (90.7%)		0.0298
HCV	4(1.8%)	1(1.2%)		0.0494	2(1.5%)	1(1.3%)		0.0108
other	16(7.1%)	7(8.5%)		0.0522	12 (8.8%)	6 (8%)		0.0274
HCC size, cm	2.0(1.5–2.6)	2.0(1.675–2.5)	0.902	0.000168	2.1(1.5–2.7)	2(1.6–2.5)	0.421	0.0895
HCC size grade※			0.904	0.016			0.422	0.1155
≤2	117(52%)	42(51.2%)			67 (48.9%)	41 (54.7%)		
>2	108(48%)	40(48.8%)			70 (51.1%)	34 (45.3%)		
ALT	32(23.5–45)	31.5(22–48.25)	0.984	0.1089	32(24–44.5)	31(22–50)	0.963	0.0522
AST	35(26–47)	37.5(25–49.25)	0.932	0.08568	36(26.5–48)	38(25–51)	0.728	0.0114
AFP	9.8(3.7–89.7)	22.05(4.3–167.75)	0.056	0.03988	11.2(4.15–124.45)	21.2(4.3–134.7)	0.433	0.0322
AFP grade※			0.417				1	
0–100	172(76.4%)	57(69.5%)		0.156	98 (71.5%)	54 (72%)		0.0104
101–1,000	47(20.9%)	23(28%)		0.166	34 (24.8%)	19 (25.3%)		0.0119
>1,000	6(2.7%)	2(2.4%)		0.019	5 (3.6%)	2 (2.7%)		0.0562
antiviral treatment※	155(68.9%)	61(74.4%)	0.35	0.1223	99 (72.3%)	56 (74.7%)	0.706	0.0545
Liver cirrhosis※	187(83.1%)	71(86.6%)	0.462	0.0977	116 (84.7%)	64 (85.3%)	0.898	0.0185
Portal hypertension※	162(72%)	58(70.7%)	0.827	0.0288	103 (75.2%)	56 (74.7%)	0.934	0.0119
Child–Pugh Score※			0.453	0.0998			0.657	0.0642
A	172(76.4%)	66(80.5%)			106 (77.4%)	60 (80%)		
B	53(23.6%)	16(19.5%)			31 (22.6)	15 (20)		
MELD score	5.2(3.6–7.15)	5.45(2.6–7.025)	0.347	0.1475	5.1(3.6–7)	5.5(2.6–6.9)	0.496	0.1206

+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; RFA, radiofrequency ablation; PSM, propensity score matching; SMD, standardized mean difference.

through a multidisciplinary group meeting that included oncologists, hepatobiliary surgeons, radiologists, and radiotherapists. MWA and RFA were performed by interventional radiologists under the guidance of CT or ultrasound. The MWA therapeutic apparatus (MTC-3C, Vison-China Medical Devices R&D Center) was applied to the operation by producing 0 – 100 W of power at a frequency of 2450 ± 50 MHz. MWA was performed at each site for 4–8 min with a power of 60 – 80 W. The primary device for patients receiving RFA was Cool-tip RF Ablation (CTRF220, Covidien LLC) which produced a power of 200 W at a frequency of 480 kHz. The interventional radiologist performed RFA at each site for 8–12 min under the guidance of ultrasound which has a power of 200 W. The MWA and RFA process were detailed in our previous literature [23,26,27].

CT or MRI examination was performed 1 to 2 months after MWA or RFA in the two groups. Follow-up was performed every 3 months during the first year and every 3–6 months thereafter. Serum chemical assessments including alpha-fetoprotein (AFP) and at least one imaging examination (contrast-enhanced dynamic CT or MRI) were measured at each follow-up visit. Once the tumor recurrence was founded, subsequent treatment was conducted based on preference of patients and clinical practice of surgeons and clinicians. All patients were followed up until death, 30 June 2022, or lost to follow-up, whichever came first. Patients who received LT were followed up and the transplant date was marked as the last follow-up [28].

2.3. Survival outcomes

Recurrence beyond Milan criteria (RBM) was the primary outcome. Recurrence-free survival (RFS) and overall survival (OS) were other outcomes of interest. Time to RBM was defined between the date of MWA/RFA and the diagnosis of RBM (tumor size > 5 cm, >3 tumor nodules, > 3 cm for two or three tumors, vascular invasion, or extrahepatic disease [5]). RFS was defined between the date of ablation and the date of diagnosis of HCC recurrence or death. OS was defined as the time from the date of ablation to death or the last follow-up before June 2022.

2.4. Complications and hospital stays

We graded complications after ablation using the Clavien-Dindo Classification System [29]. Major complications included the complications of Grade ≥ 3, while minor complications included Grade ≤ 2. Hospital stays were defined as the time from the date of admission to the date of discharge or death.

2.5. Propensity score matching

In order to reduce potential bias between the two groups, a 1:2 propensity score matching (PSM) was performed to create a comparable control cohort, including sex, age, etiology, maximum tumor diameter and grade, aspartate amino-transferase level, and alanine aminotransferase level, AFP level and grade, antiviral treatment, presence of liver cirrhosis, presence of portal hypertension, Child-Pugh class, model for end-stage liver disease (MELD) score.

2.6. Statistical methods

Categorical variables were expressed as counts and percentages, continuous variables were presented as median and interquartile range. Pearson $\chi 2$ test or Fisher exact test were used for categorical variables between the two groups. Mann-Whitney test was assessed by analyzing continuous variables in both groups. Kaplan-Meier method was used to estimate the probability of recurrence exceeding Milan criteria and survival probability, and log-rank test was used to compare between groups. Predictors of post-ablation recurrence beyond Milan criteria were evaluated by Univariate and multivariate Cox regression. Duvoux et al. previously validated AFP levels which were categorized [30]. On the basis of serum AFP, patients were divided into 3 categories

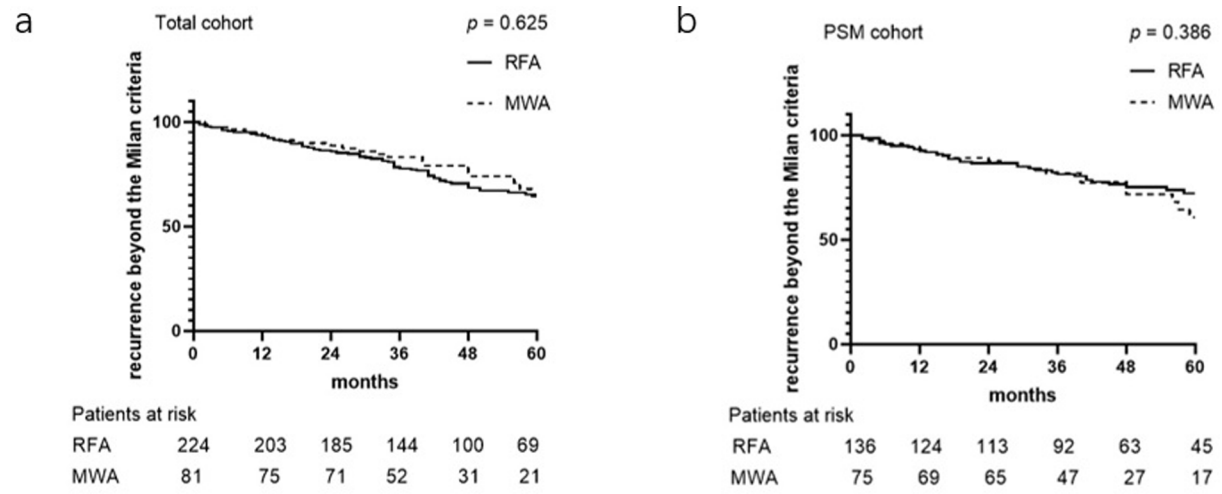

Fig. 2. Cumulative recurrence beyond Milan criteria curves in potentially transplantable patients. Cumulative RBM rates were not significantly different between the MWA and RFA groups of study patients in the total cohort (a) and PSM cohort (b). Abbreviations: MWA, microwave ablation; PSM, propensity score matching; RBM, recurrence beyond Milan criteria; RFA, radiofrequency ablation.

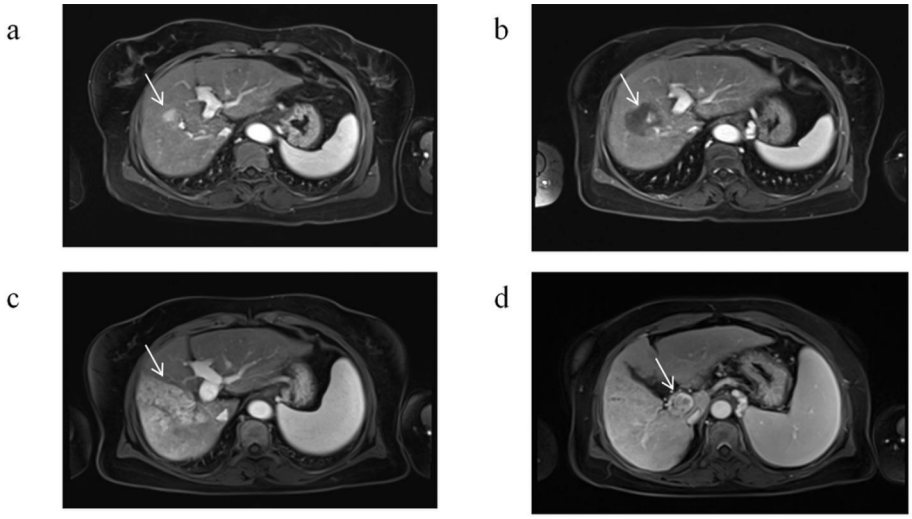

Fig. 3. One case of recurrence beyond Milan criteria with abdominal enhanced MRI images.Before MWA, the arterial phase (a) of the enhanced MRI respectively, indicated a single HCC in the right lobe of the liver. One month after MWA, the arterial phase (b) of the enhanced MRI respectively, indicated that MWA had achieved complete ablation. Fifteen months after MWA, the arterial phase (c) and venous phase (d) of the enhanced MRI, indicated that the patient occurred RBM with portal vein cancer thrombus.Abbreviations: HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; MWA, microwave ablation; RBM, recurrence beyond Milan criteria; RFA, radiofrequency ablation.

including < 100 ng/ml,100–1,000 ng/ml, and > 1,000 ng/ml. Hazard ratios (HR) with 95% confidence intervals represent the results of these analyses. SPSS 26.0 for Windows (SPSS Inc.) was used for all of the statistical analyses. All the tests were bilateral, and it is statistically significant as to $p < 0.05$.

Table 2
Recurrence patterns and recurrence beyond Milan after MWA or RFA.

Recurrence patterns	Total cohort n = 307			PSM cohort n = 212		
	RFA n = 225	MWA n = 82	p	RFA n = 137	MWA n = 75	p
Recurrence	139(61.8%)	48(58.5%)	0.607	83(60.6%)	47(62.7%)	0.766
First recurrence type						
Local	45(20%)	12(14.6%)	0.285	28(20.4%)	12(16%)	0.43
Distant intrahepatic	82(36.4%)	30(36.6%)	0.961	52(38.0%)	28(38.7%)	0.919
Distant extrahepatic	12(5.3%)	6(7.3%)	0.406	3(2.2%)	6(8.0%)	0.07
Beyond Milan criteria (%)						
At first recurrence	38(16.9%)	11(13.4%)	0.462	12(8.8%)	11(14.7%)	0.186
At any time during the follow-up	69(30.7%)	21(25.6%)	0.389	33(24.1%)	21(28%)	0.532
Reason to being classified as beyond Milan criteria						
Tumor size and/or number	44(63.8%)	10(47.6%)	0.186	22(66.7%)	10(47.6%)	0.165
Macrovascular invasion	10(14.5%)	3(14.3%)	1	4(12.1%)	3(14.3%)	1
Metastatic disease	15(21.7%)	8(38.1%)	0.132	7(21.2%)	8(38.1%)	0.177

*Chi-squared test for categorical variables and the Mann-Whitney *U* test for continuous variables.
HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; MWA, microwave ablation.

Table 3
Multivariable regression model to predict recurrence beyond Milan criteria.

Variables	total cohort			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p*	HR (95% CI)	*p*
RFA vs. MWA [ref: RFA]	1.129 (0.692–1.841)	0.626		
Sex [ref.: male]	0.929 (0.574–1.503)	0.763		
Age	1.019 (0.994–1.046)	0.137		
Etiology [ref: HBV]				
HCV	1.371 (0.556–3.381)	0.493		
Other	0.771 (0.090–6.606)	0.813		
HCC size	1.059 (0.753–1.490)	0.742		
HCC size [ref: ≤2 cm]				
>2cm	1.010 (0.667–1.530)	0.963		
ALT	1.001 (0.999–1.003)	0.318		
AST	1.001 (0.999–1.004)	0.333		
AFP	1.001 (1.000–1.001)	0.016	1.001 (1.000–1.001)	0.023
AFP (ref.: ≤100 ng/ml)				
101–1,000	0.541 (0.197–1.489)	0.234		
>1,000	0.452 (0.152–1.348)	0.154		
Antiviral treatment	0.592 (0.360–0.974)	0.039	0.589 (0.358–0.970)	0.037
Liver cirrhosis	0.942 (0.541–1.640)	0.833		
Portal hypertension	0.745 (0.464–1.197)	0.224		
Child–Pugh grade [ref.: A]				
B	0.650 (0.407–1.039)	0.072		
MELD score	1.062 (1.010–1.117)	0.020	1.063 (1.007–1.121)	0.026

AFP, alpha-fetoprotein; HBV, chronic hepatitis B; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; RFA, radiofrequency ablation.
*Stepwise backwards Cox regression.

3. Results

3.1. Study population

The study group was composed of 307 patients, 82 patients initially received MWA and 225 patients initially received RFA. After the PSM, a new cohort comprising 75 patients in the MWA group and 137 patients in the RFA group was generated. 358 patients achieved complete ablation in the first session, whereas 10 patients did not achieve complete ablation after the initial RFA or MWA. The complete ablation rate is 97.3%. In our study, 10 patients were classified as residual tumor and 26 patients were classified as recurrence at CT/MRI control at 1 month after RFA/MWA. Patient selection is shown in Fig. 1. Baseline characteristics of both the total and PSM matched group are shown in Table 1.

3.2. Recurrence beyond Milan criteria

The median follow-up period was 54 months (range, 0–144 months). Ninety (29.3%) patients had RBM within a mean time of 92.3 months, including 21 of 82 patients (25.6%) in the MWA group and 69 of 225 patients (30.7%) in the RFA group. In the total cohort, the 1-, 3-, and 5-year cumulative RBM rates were 6.3%, 16.9%, and 35.4% in the MWA group, and 6.8%, 22.2%, and 34.6% in the RFA group, respectively ($p = 0.625$) (Fig. 2**a**). After PSM, fifty-four (25.5%) patients had RBM, including 21 of 75 patients (28.0%) in the MWA group and 33 of 137 patients (24.1%) in the RFA group. the 1-, 3-, and 5-year cumulative RBM rates were 6.8%, 18.3%, and 39.3% in the MWA group, and 7.4%,18.5%, and 27.7% in the RFA group, respectively ($p = 0.386$) (Fig. 2**b**). There were no significant differences in RBM rates treated with MWA compared to RFA before and after PSM. Fig. 3 provides 1 case was recurrence beyond Milan criteria.

Notably, 49 (16.0%) patients had the RBM at first recurrence after ablation: 11(13.4%) in the MWA group and 38(16.9%) in the RFA group ($p = 0.462$) (Table 2). As for the reason to being classified as RBM, the proportion of tumor size or number, macrovascular invasion, and metastatic disease had no significant difference in total and PSM cohort between these two groups. It is the same as the specific reason for recurrence patterns (distant intrahepatic recurrence, local recurrence, and extrahepatic recurrence) in the total and PSM cohorts. The patterns of recurrence and RBM among the study groups are shown in Table 2.

3.3. Predictors of recurrence beyond Milan in the total cohort

In the univariate analysis, higher AFP (HR, 1.001; 95% CI, 1.000–1.001; $p = 0.016$), non-antiviral treatment (HR, 0.592; 95% CI, 0.360–0.974; $p = 0.039$), and higher MELD score (HR, 1.062; 95% CI, 1.010–1.117; $p = 0.02$) were significant risk factors for RBM. Uniformly, in multivariate analysis, independent predictors of RBM were higher AFP (HR, 1.001; 95% CI, 1.000–1.001; $p = 0.023$), non-antiviral treatment (HR, 0.589; 95% CI, 0.358–0.970; $p = 0.037$), and higher MELD score (HR, 1.063; 95% CI, 1.007–1.121; $p = 0.026$). Whereas MWA and RFA were not the risk factors of RBM (HR, 1.129; 95% CI, 0.692–1.841; $p = 0.626$) (Table 3).

3.4. Recurrence-free survival and predictors of recurrence-free survival

In the total cohort, 48(58.5%) HCC patients in the MWA group and 139(61.8%) patients in the RFA group were diagnosed as recurrence. The median RFS was 34 (95%CI, 27.343–40.657) months for the total cohort. The 1-, 3-, and 5-year cumulative RFS rates were 68.3%, 43.3%, and 28.6% in the MWA group vs. 71.6%,48.0%, and 33.0% in the RFA group ($p = 0.873$) (Fig. 4**a**). After PSM, the 1-, 3-, and 5-year cumulative RFS rates were 66.7%, 39.2% and 21.4% in the MWA group vs. 70.8%,47% and 34.7% in the RFA group ($p = 0.310$) (Fig. 4**b**). There were no significant differences in RFS rates between the two groups before and after PSM. In the total cohort, the multivariate analysis showed only antiviral treatment (HR 0.672; 95% CI, 0.489–0.923; $p = 0.014$) was a significant factor for RFS (Table 4).

3.5. Overall survival and predictors of overall survival

During the follow-up period, the mean OS was 98.7 months in the MWA group and 91.0 months in the RFA group. Before PSM, the 1-, 3-, and 5-year OS rates were 97.5%, 87.7%, and 76.5% in the MWA group and 97.7%, 86.3%, and 69.2% in the RFA group, respectively ($p = 0.218$) (Fig. 4**c**). After PSM, the 1-, 3-, and 5-year OS rates were 97.3%, 88.0%, and 75.4% in the MWA group and 97.8%, 85.1%, and 70.7% in the RFA group, respectively ($p = 0.384$) (Fig. 4**d**). The OS rates were not significantly different between these two groups in the total and PSM cohort. In the total cohort, the multivariate analysis showed only the Child-Pugh class (HR 0.569; 95% CI, 0.340–0.952; $p = 0.032$) was a significant factor for OS. (Table 4).

4. Treatment after MWA or RFA

The treatment after MWA or RFA is presented in Supplementary Table 1. In the total cohort, 87(38.7%) patients in the RFA group and 33 (40.2%) patients in the MWA group received curative therapies

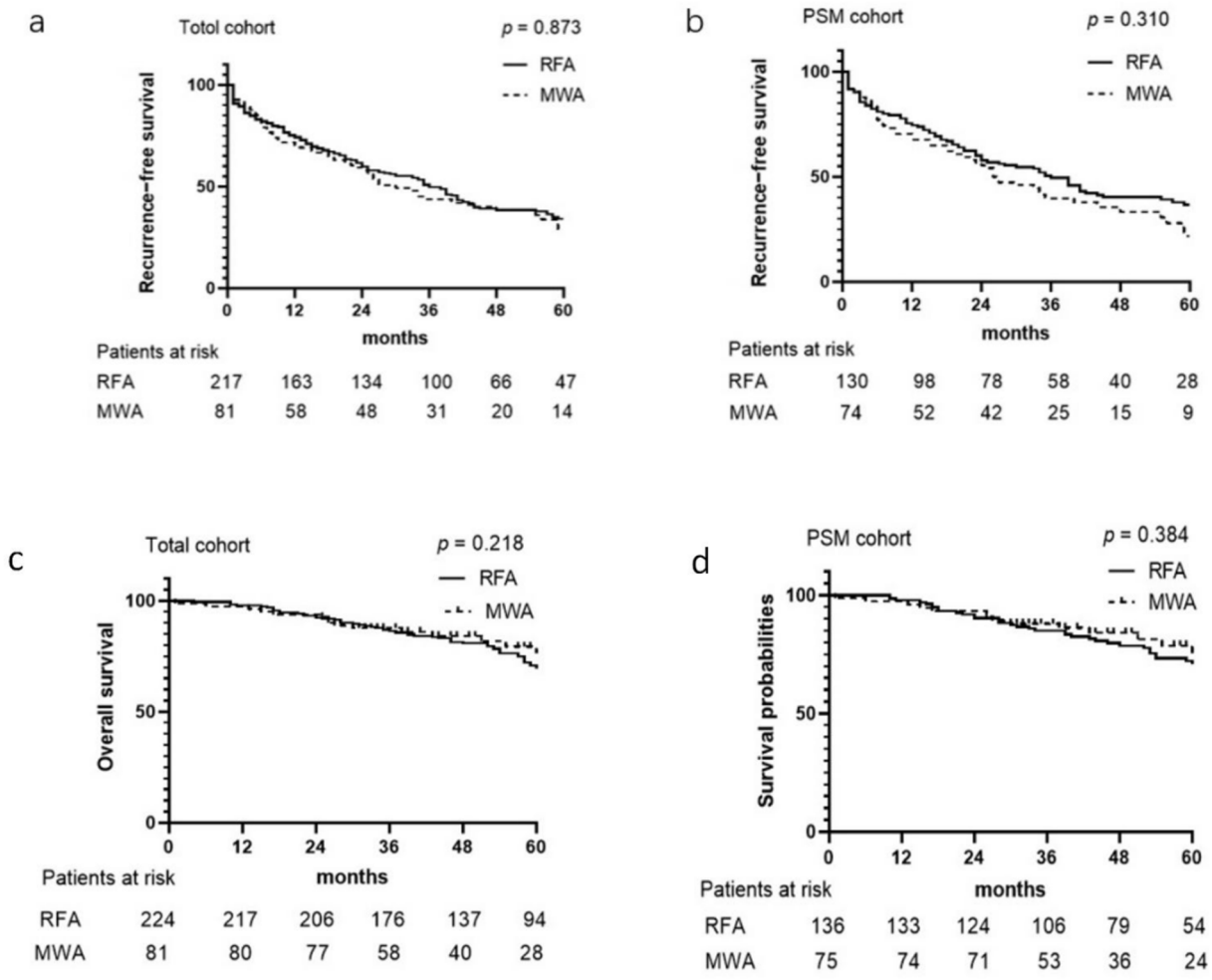

Fig. 4. Cumulative recurrence-free survival curves and overall survival curves in potentially transplantable patients. Cumulative recurrence-free survival rates were not significantly different between the MWA and RFA groups of study patients in the total cohort (a) and PSM cohort (b). Overall survival rates were not significantly different between the MWA and RFA groups of study patients in the total cohort (c) and PSM cohort (d).Abbreviations: MWA, microwave ablation; PSM, propensity score matching; RFA, radiofrequency ablation.

(ablation or liver resection) after MWA or RFA, with no significant difference ($p = 0.802$). In particular, 4 patients received LT in the RFA group while 1 patient received LT in the MWA group. Fifty-six (24.9%) patients in the RFA group and 16 (19.5%) patients in the MWA group received noncurative therapies ($p = 0.325$). As to curative and noncurative therapies, there were no differences in potentially transplantable patients in the two groups before and after PSM.

4.1. Complications and hospital stays

Complications and hospital stays of patients in the two groups were shown in Supplementary Table 2. In the PSM cohort, the MWA group showed more frequent major complications (21.4% vs. 7.1%, $p = 0.004$) and longer hospital stays (4 days vs. 2 days, $p < 0.001$) compared with the RFA group. Minor complication rates were similar in the two groups (28.6% vs. 26.5%, $p = 0.765$). Similar results were found in the total cohort.

5. Discussion

The present study demonstrated that MWA showed comparable survival outcomes to RFA in potentially transplantable patients with single HCC $\leq$ 3 cm in the total and PSM cohorts. In addition, MWA and RFA were not the risk factors of the recurrence beyond the Milan criteria.

The high RBM rate could seriously affect the prognosis in potentially transplantable patients with HCC. Once RBM, the patients will have to drop off the transplant list [1,5]. Bridge therapy has been widely used to maintain disease control, slow the progression of RBM prior to transplantation and improve long-term survival [28]. Kaoru et al. studied the cumulative RBM rates at 1, 3, and 5 years after initial locally RFA therapy which were 15.1%, 46.0%, and 61.1% [31]. Yamashiki, N. et al. suggested thermal ablation of HCC within the Milan criteria was effective in controlling the tumor progression [32]. None of above studies specifically examined the RBM outcomes of MWA as bridge treatment compared to RFA in potentially transplantable patients. In the present study, we found that MWA had similar RBM rates compared to RFA in potentially transplantable patients with single HCC $\leq$ 3 cm. This is the first study comparing the RBM between these patients who underwent RFA and MWA.

The risk factors of RBM are the non-negligible issue. Potentially transplantable patients who were at higher risk of RBM should be considered for LT earlier as soon as possible in their treatment pathway. Our study suggested that MWA and RFA were not the risk factors of RBM. Previous studies have studied risk factors for RBM after RFA in potentially transplantable patients with small HCC [5,22], but there are no relevant studies on MWA. In our study, patients with higher AFP, non-antiviral treatment, and higher MELD score are at greater risk of RBM, which is in accordance with former reports. The significant association between AFP and RBM with HCC has been confirmed in many

Table 4
Factors associated with RFS and OS in the total cohort.

Variables	RFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p*	HR (95% CI)	*p*	HR (95%CI)	*p*	HR (95%CI)	*p*
RFA vs. MWA [ref: RFA]	0.975(0.715–1.330)	0.874			1.355(0.832–2.208)	0.222		
Sex [ref.: male]	0.963(0.701–1.324)	0.817			0.851(0.549–1.321)	0.473		
Age	1.012(0.995–1.028)	0.160			1.023(0.999–1.048)	0.057		
Etiology [ref: HBV]								
HCV	1.508(0.860–2.646)	0.152			1.352(0.550–3.324)	0.512		
Other	0.290(0.038–2.219)	0.233			0.823(0.096–7.046)	0.858		
HCC size	1.016(0.813–1.269)	0.891			1.693(1.220–2.348)	0.002	1.455(0.834–2.541)	0.187
HCC size [ref: ≤2 cm]								
>2cm	1.060(0.802–1.400)	0.683			1.824(1.198–2.778)	0.005	1.342(0.665–2.709)	0.412
ALT	1.001(0.999–1.003)	0.208			1.002(1.000–1.004)	0.107		
AST	1.002(1.000–1.004)	0.116			1.002(1.000–1.005)	0.027	1.001(0.999–1.004)	0.303
AFP	1.001(1.000–1.001)	0.197			1.000(0.999–1.000)	0.719		
AFP (ref.: ≤100 ng/ml)								
101–1,000	0.905(0.399–2.052)	0.812			2.152(0.528–8.777)	0.285		
>1,000	0.813(0.347–1.905)	0.634			2.687(0.637–11.338)	0.179		
Antiviral treatment	0.635(0.466–0.866)	0.004	0.672(0.489–0.923)	0.014	0.865(0.565–1.323)	0.502		
Liver cirrhosis	0.677(0.460–0.998)	0.049	0.844(0491–1.451)	0.540	0.442(0.230–0.850)	0.014	0.664(0.271–1.629)	0.371
Portal hypertension	0.730(0.536–0.996)	0.047	0.875(0.568–1.348)	0.545	0.467(0.286–0.762)	0.002	0.590(0.295–1.177)	0.134
Child–Pugh grade [ref.: A]					0.440(0.286–0.677)	0.000	0.569(0.340–0.952)	0.032
B	0.882(0.643–1.210)	0.437						
MELD score	1.015(0.978–1.052)	0.434			1.058(1.009–1.109)	0.019	1.014(0.951–1.082)	0.670

AFP, alpha-fetoprotein; HBV, chronic hepatitis B; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; RFA, radiofrequency ablation.
*Stepwise backwards Cox regression.

studies [5,22,31]. AFP is most widely used for HCC as the diagnostic and prognostic marker [33]. The expression level of AFP is associated with the proliferation, angiogenesis, and apoptosis of HCC cancer cells [34]. The MELD score is the indicator of hepatic reserve, which has been shown to have a reliable predictive value for survival outcomes of HCC patients [26,35,36]. Another strong predictor of RBM was antiviral treatment in our results, suggesting that early antiviral therapy played an important role in delaying RBM and antiviral therapy was essential in these patients.

MWA has been shown as a powerful treatment for the early HCC. In terms of OS and RFS, previous study showed that RFA was inferior to MWA in the treatment of HCC within the Milan criteria, but it had the comparable efficacy to MWA for single HCC ≤ 3 cm [37]. Our study showed that MWA was as efficient as RFA in potentially transplantable patients, suggesting that MWA and RFA as bridge therapy for single HCC ≤ 3 cm provided excellent OS rates and efficacy of tumor control. It was consistent with the analysis of previousstudies [28,37-39]. Previous *meta*-analyses have shown that patients with early-stage HCC had been treated with LT instead of ablation, whose OS was lower than patients treated with ablation [40].

In our study, antiviral treatment was associated with RFS and the Child-Pugh class with OS. Active viral replication is associated with the higher risk of HCC. Antiviral therapy significantly reduced the incidence of HCC, demonstrating the importance of this virus in HCC development [41]. Child-Pugh class was associated with hepatic reserve, which was logically closely related to HCC prognosis [42]. Besides, major complication rates were significantly higher after MWA (21.4%) than after RFA (7.1%), ($p = 0.004$), while minor complication rates were similar in the two groups. MWA was deemed to be less safe than RFA due to the larger ablation volume and higher intratumoral temperatures [43], which seems to be confirmed in the current study.

Several limitations were presented in our study. First, in this retrospective study, only 5 patients received LT. It may be due to the limited liver source, the cost of LT, and so on. And this study might suffer from potential bias, thus our study made attempts to balance the groups and reduce the bias by using PSM. Second, we did not have enough samples of patients with HCC between 3 and 5 cm or multiple HCC tumors within Milan criteria. And HCC between 3 and 5 cm or multiple HCC tumors within Milan criteria should be the aim of future investigation. Third, since most patients in this study were chronically infected hepatitis virus, the results may not be generalizable in all potentially transplantable patients with HCC for various etiologies. Therefore, further prospective randomized controlled trials with a large sample containing more patients received LT in a multiple centers are warranted to verify our results.

In conclusion, MWA showed comparable recurrence beyond the Milan criteria, recurrence-free survival, and overall survival rates to RFA in potentially transplantable patients with single HCC ≤ 3 cm. Compared to RFA, MWA might provide the same effect as bridge therapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejrad.2023.110860.

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