

Comparison of the Efficacy and Safety of Transarterial Chemoembolization Plus Microwave Ablation versus Surgical Resection in Patients with Solitary Large Hepatocellular Carcinoma: A Propensity Score-Matched Analysis

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Background: The liver resection for solitary large hepatocellular carcinoma (SLHCC) remains controversial due to the high risk of complications and recurrence after resection. This study aimed to compare the efficacy and safety of transcatheter arterial chemoembolization (TACE) plus microwave ablation (MWA) with resection for SLHCC.

Methods: We retrospectively analyzed a total of 148 patients who were treated with either TACE-MWA (n = 94) or resection (n = 54) for SLHCC (≥ 5 cm). A matched cohort composed of 86 patients was included after propensity score matching (PSM). The primary endpoint was overall survival (OS), and the secondary endpoints were progression-free survival (PFS) and safety.

Results: The TACE-MWA group was older with higher ALT and AST (all $P < 0.05$). After PSM, the 1-, 3-, and 5-year OS were 100%, 80.3%, and 51.0% in the TACE-MWA group, and 88.3%, 66.7%, and 39.4% in the liver resection group, respectively. The 1-, 3-, and 5-year PFS were 76.7%, 48.8%, and 19.6% in the TACE-MWA group, and 72%, 40.2%, and 22.6% in the liver resection group, respectively. There was no significant difference in OS and PFS between the two groups (all $P > 0.05$). For SLHCC patients with tumor size ≥ 7 cm, TACE-MWA showed favorable OS than liver resection. The TACE-MWA group exhibited a lower rate of major complications and shorter hospital stay than the resection group.

Conclusion: TACE-MWA showed comparable efficacy to liver resection in patients with SLHCC, but better safety and shorter hospital stay. TACE-MWA might provide a longer OS than liver resection for SLHCC patients with tumor size ≥ 7 cm.

Keywords: transarterial embolization, microwave ablation, hepatocellular carcinoma, liver resection

Introduction

Worldwide, hepatocellular carcinoma (HCC) is the sixth most common malignancies, with nearly 906,000 new cases and 830,000 deaths in 2020.¹ China is responsible for nearly half of the global morbidity and mortality, where solitary large HCC (SLHCC) (maximal diameter > 5 cm) has a higher incidence compared with other countries.² This is potentially explained by the different aetiology of HCC, no obvious symptoms in the early stage, limited awareness of early screening, and poor economic conditions.³ As per the Barcelona Clinic Liver Cancer (BCLC) staging system, although SLHCC without macrovascular invasion and/or extrahepatic spread is classified in the early stage where patients can benefit from curative therapies such as liver resection, liver transplantation or thermal ablation, the optimal therapies for SLHCC remain controversial.⁴⁻⁷

Liver resection is the preferred option for patients with early-stage HCC, but SLHCC occupying more space may compromise liver function seriously and often invade the surrounding tissues, which amplifies the risk of surgery.^{3,8} Furthermore, postoperative complications and long-term risk of recurrence are still the main challenges in patients with SLHCC.⁹ Liver transplantation has worse outcomes in SLHCC patients compared with those with small HCC due to tumor size beyond Milan criteria (single tumor ≤ 5 cm or ≤ 3 tumors each ≤ 3 cm).¹⁰ Ablation, mainly radiofrequency ablation (RFA) and microwave ablation (MWA), is recommended in patients who are not candidates for resection, with a higher local recurrence than the resection, especially in patients with large tumor.^{11,12} Transcatheter arterial chemoembolization (TACE) has been widely used in large HCC. However, due to TACE as a palliative treatment, complete tumor necrosis is rarely achieved in one session and residual tumors often exist in large HCC.¹³

Currently, the combination of TACE with ablation has shown better efficacy as compared to either alone.^{14–16} TACE can decrease the heat-sink effect, which may compromise the efficacy of ablation by reducing the arterial blood flow to the tumor, and combined therapy provides a larger ablation area than ablation alone.¹⁷ Therefore, TACE combined with ablation has been widely used in the management of HCC. Recently, a meta-analysis showed no significant differences in terms of overall survival (OS) and progression between the TACE plus RFA groups and liver resection group when only the propensity-matched data were evaluated.¹⁸

MWA, theoretically, can achieve larger ablation zones with higher temperatures than RFA.¹⁹ Furthermore, a meta-analysis comparing TACE combined with RFA or MWA demonstrated that the superiority of TACE plus MWA was mainly reflected in patients with larger tumors (≥ 3 cm).²⁰ Given TACE plus MWA seems to be a more effective therapy than TACE plus RFA for large HCC, with better survival outcomes and similar safety, we thus performed this study to compare the survival and safety outcomes between TACE-MWA and liver resection for the treatment of SLHCC.

Materials and Methods

Patients

This study was conducted in line with the Declaration of Helsinki, and written informed consent was obtained from all the eligible patients before treatment. Clinical research protocol and clinical data were approved by the Ethics Committee of Beijing Ditan Hospital (KY2020-030).

The medical records of HCC patients treated with TACE with MWA and liver resection between September 2008 and December 2019 were retrospectively examined. The following eligibility criteria were included (i) patients with HCC confirmed by pathological or radiological examination, (ii) age ranges >18 years, (iii) solitary HCC tumor >5 cm in diameter, (iv) liver function indicated by Child-Pugh grade A or B, with $<25\%$ retention of indocyanine green 15 min after injection (v) treatment by surgical resection or TACE-MWA, and suitability for the other therapies in a re-evaluation by our multidisciplinary teams; (vi) no history of other malignancies, (vii) Eastern Cooperative Oncology Group performance status 0. The criteria of exclusion included (i) macrovascular invasion or extrahepatic metastasis, (ii) severe chronic condition (eg, heart failure), (iii) insufficient residual liver volume, (iv) esophageal or gastric variceal bleeding, (v) hepatic encephalopathy, (vi) severe coagulation disorders, (vii) prior history of any treatment except TACE.

Clinical information including age, sex, date of diagnosis, tumor size, date of death, etiology of HCC, cirrhosis, antiviral treatment, pre-TACE, alpha-fetoprotein (AFP), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), Child-Pugh grade, neutrophil counts, lymphocyte counts platelet (PLT) counts, international normalized ratio (INR) and follow-up results were collected.

Neutrophil to lymphocyte (NLR) was calculated by dividing the neutrophil count by the lymphocyte count. Its cutoff value was determined by the maximally selected rank statistics in all patients.²¹ ALBI score = $(\log_{10} \text{bilirubin } [\mu\text{mol/L}] \times 0.66) + (\text{albumin } [\text{g/L}] \times -0.0852)$. ALBI grades were stratified as follows: ALBI score ≤ -2.60 (ALBI grade 1), > -2.60 to ≤ -1.39 (ALBI grade 2), and > -1.39 (ALBI grade 3).²²

Treatment Strategies

The decision to whether perform surgical resection or TACE+MWA for individual patients was determined by multidisciplinary team (MDT) meetings and each patient's preference.

TACE Plus MWA Procedure

TACE was performed by two radiologists in our cancer center, with more than 10 years of experience in interventional radiology. Patients were under local anesthesia with 1% lidocaine. A 5-F catheter was introduced through the femoral artery, and the survey of tumor feeding arteries was performed. Distal superselective 5-F catheterization of tumor-feeding hepatic arteries with Embosphere microspheres (300–500 μ m; Biosphere Medical Inc., Rockland, MA), lipiodol (5–20 mL) (Lipiodol Ultra-Fluide; André Guerbet Laboratories, AulnaySous-Bois, France), and epirubicin (50 mg) (Pharmorubicin; Pfizer, Wuxi, China). Repeated TACE was performed if the viable tumor or intrahepatic recurrences were detected by CT/MRI. MWA was performed 3–14 days after TACE. Two cooled-shaft microwave systems (KY-2000, Kangyou Medical, Nanjing, China) with frequencies of 2450 MHz and 915 MHz were used with two generators, both capable of producing 1–100 W of power. The antennae were percutaneously inserted into the tumor and placed at a designated location under CT guidance. A power output of 50–60 W was routinely used during MWA. Completed ablation was considered as the heat-generated hyperechoic water vapor completely encompassing the entire tumor with no enhancement in the CT image. The tumor response was assessed one month later using CT and/or MRI.

Liver Resection Procedure

All included patients in the liver resection group were performed by experienced surgeons under general anesthesia. Preoperative CT/MRI was routinely used to evaluate the tumor extent, the liver remnant, and the resection margin. The detailed surgical protocol was according to tumor location, hepatic functional reserve, and residual liver content. All procedures of liver resection are according to the standard procedures recommended by the guidelines.⁵

Follow-Up and Outcomes

Routine radiological examinations and laboratory tests were performed at 1 month, 3 months, and then every 6 months after treatment. The primary endpoint of this study was overall survival (OS), which was calculated from the date of HCC treatment to death from any cause or the time of the last follow-up by December 31, 2021. The secondary endpoint was progression-free survival (PFS), which was defined from the date of treatment until tumor progression, death from any cause, or the last visit by December 31, 2021. Other outcomes included the major complications (major complications were defined as an event that resulted in disability or morbidity and caused a hospital admission or prolonged the length of hospital stay). If tumor recurrence is identified, subsequent treatments will include resection, MWA, TACE, targeted therapies, and immunotherapies after discussion by MDT.

Statistical Analysis

Categorical variables were presented as a frequency (%) and analyzed by Chi-square or Fisher exact tests. Continuous variables were represented as mean \pm standard deviation (SD) or median (interquartile range [IQR]) and analyzed by Student's *t*-test or Mann–Whitney *U*-test. Moreover, we perform propensity score-matching analyses (PSM) using logistic regression to reduce the potential selection bias and the influence of confounding factors, with covariates including sex, age, etiology, cirrhosis, ALT, AST, TBIL, tumor size, pre-TACE, and platelet counts. TACE-MWA group and surgical resection group were matched 1:1 using the nearest neighbor matching method (caliper = 0.1). Kaplan–Meier analysis was used to compare the OS and PFS between groups and the difference was compared by Log rank test. Univariate and multivariate Cox regression analyses were used to identify independent prognostic factors of OS and PFS. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using R Software version 4.1.1 (R Package for Statistical Computing; www.r-project.org).

Results

Patient Characteristics

Finally, 148 patients with SLHCC treated by TACE-MWA or liver resection were included in this study (Figure 1). Patients in the TACE-MWA group were older and had higher ALT and AST than those in the liver resection group. There were no significant differences in baseline characteristics between the TACE-MWA group and the liver resection group

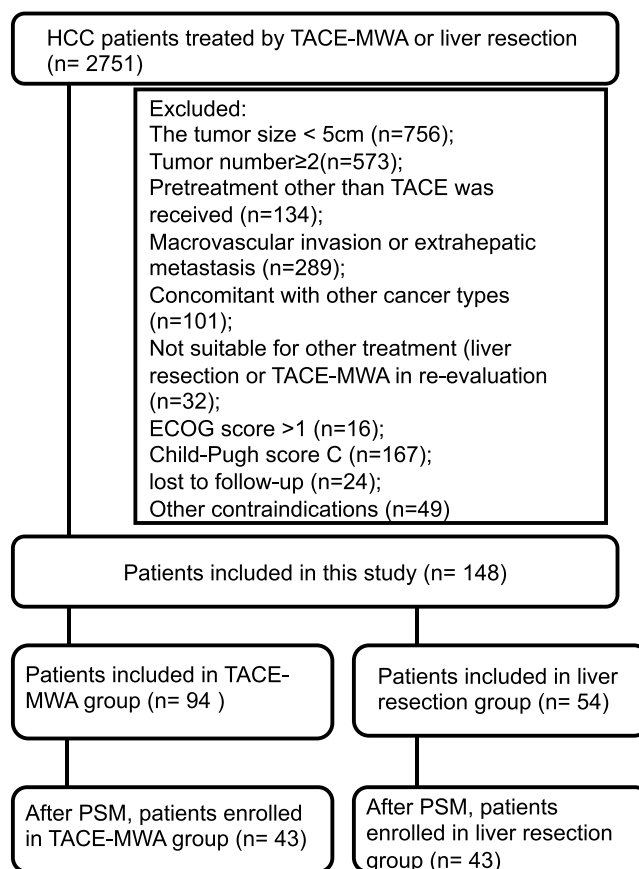


Figure 1 Flow chart of patient selection criteria.

except for age, ALT, and AST. In the TACE-MWA group, a total of TACE treatment was used 329 times (average: 3.5 times/case) and a total of ablations were conducted 196 times (average: 2.08 times/case).

After PSM, a total of 86 patients were matched, including 43 patients in the TACE-MWA group and 43 patients in the liver resection group, respectively. The differences in the baseline characteristics between the two groups were balanced after PSM. The detailed characteristics of the patients before and after PSM are summarized in [Table 1](#).

Overall Survival

The median follow-up period was 80.7 months (95% CI, 69.7–104.6 months) in all patients. During the follow-up period, 76 patients (80.8%) in the TACE-MWA group and 42 patients (87.5%) in the liver resection group died. The median OS was 50.2 months in the TACE-MWA group and 54.1 months in the liver resection group. The cumulative survival rates at 1, 3, and 5 years were 92.5%, 69.1%, and 37.5% in the TACE-MWA group and 90.7%, 71.4%, and 40.5% in the liver resection group, respectively. The survival benefits were comparable between the two groups ($P = 0.93$, [Figure 2A](#)).

After employing PSM, the median OS was 61.2 months in the TACE-MWA group and 54.3 months in the liver resection group. The cumulative survival rates at 1, 3, and 5 years were 100%, 80.3%, and 51.0% in the TACE-MWA group and 88.3%, 66.7%, and 39.4% in the liver resection group, respectively. The TACE-MWA group still showed comparable OS to the resection group even after PSM ($P = 0.3$, [Figure 2B](#)). Subgroup analyses were then conducted according to potentially important factors, including age, gender, etiology, tumor size (<7cm vs ≥ 7 cm), AFP (AFP <400ng/mL vs AFP ≥ 400 ng/mL), and ALBI grade. No significant differences were observed in most of the subgroups apart from the patients with tumor size ≥ 7 cm. Patients with tumor size ≥ 7 cm in the TACE-MWA group had significantly prolonged OS compared to patients in the liver resection group ($P < 0.001$) ([Figure 3](#)).

Table I The Detailed Characteristics of the Patients Before and After PSM

Characteristic	Before PSM (N=148)		P	After PSM (N=86)		P
	TACE+MWA N=94	Liver Resection N=54		TACE+MWA N=43	Liver Resection N=43	
Age	61.1±9.56	53.8±10.3	<0.001	56.9±8.71	57.2±7.34	0.831
Sex			0.734			0.406
Male	73 (77.7%)	44 (81.5%)		37 (86.0%)	33 (76.7%)	
Female	21 (22.3%)	10 (18.5%)		6 (14.0%)	10 (23.3%)	
Etiology			0.920			1.000
HBV	77 (81.9%)	43 (79.6%)		34 (79.1%)	34 (79.1%)	
HCV	2 (2.13%)	1 (1.85%)		1 (2.33%)	1 (2.33%)	
Other	15 (16.0%)	10 (18.5%)		8 (18.6%)	8 (18.6%)	
Tumor size, cm	6.47±1.26	6.33±1.53	0.569	6.27±1.20	6.38±1.53	0.808
Pre-TACE			1.000			1.000
No	83 (88.3%)	48 (88.9%)		39 (90.7%)	39 (90.7%)	
Yes	11 (11.7%)	6 (11.1%)		4 (9.30%)	4 (9.30%)	
Cirrhosis			1.000			1.000
No	34 (36.2%)	19 (35.2%)		14 (32.6%)	14 (32.6%)	
Yes	60 (63.8%)	35 (64.8%)		29 (67.4%)	29 (67.4%)	
Antiviral therapy			0.454			0.369
No	20 (21.3%)	8 (14.8%)		30 (69.8%)	25 (58.1%)	
Yes	74 (78.7%)	46 (85.2%)		13 (30.2%)	18 (41.9%)	
AFP:			0.833			0.736
< 400 ng/mL	57 (60.6%)	31 (57.4%)		4 (9.52%)	6 (14.3%)	
≥ 400 ng/mL	37 (39.4%)	23 (42.6%)		38 (90.5%)	36 (85.7%)	
ALT (IU/L):	31.8 [24.5–46.1]	27.2 [19.4–34.6]	0.041	28.0 [22.2–43.0]	26.9 [21.2–34.8]	0.671
AST (IU/L):	35.0 [25.3–52.7]	28.5 [21.9–39.6]	0.018	30.1 [25.0–47.3]	27.5 [23.2–34.5]	0.254
TBIL (mg/dL)	12.2 [8.48–19.1]	11.9 [8.83–15.3]	0.541	11.4 [8.10–19.1]	11.4 [8.83–14.6]	0.651
Album (g/L)	39.7±4.58	40.0±4.14	0.668	40.1±4.83	40.0±4.01	0.860
Child-Pugh			0.5			1.000
A	84 (89.4%)	50 (92.6%)		41 (95.4%)	41 (95.4%)	
B	10 (10.6%)	4 (7.4%)		2 (4.6%)	2 (4.6%)	
ALBI grade			0.154			1.000
I	50 (53.2%)	36 (66.7%)		26 (60.5%)	27 (62.8%)	
II or III	44 (46.8%)	18 (33.3%)		17 (39.5%)	16 (37.2%)	
Neutrophil (10⁹/L)	4.06±7.81	3.33±1.18	0.374	3.03±1.20	3.36±1.17	0.201
Lymphocyte (10⁹/L)	1.64±1.99	1.47±0.58	0.439	1.60±1.88	1.49 ±0.60	0.721
PLT(10⁹/L)	153±75.0	147±57.5	0.643	145±77.7	149±60.2	0.822
INR	1.04 ±0.07	1.04±0.15	0.940	1.08±0.09	1.05±0.16	0.654

Note: Data are exhibited in N (%) or median (interquartile range).

Abbreviations: TACE, transcatheter arterial chemoembolization; MWA, microwave ablation; HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; NLR, neutrophil to lymphocyte.

Univariate and multivariate regression results are shown in [Table 2](#). In the univariate analysis, the significant prognostic factors were antiviral treatment (HR = 0.25; 95% CI: 0.13–0.52; $P = 0.002$), tumor size ≥ 7 cm (HR = 2.27; 95% CI: 1.30–3.95; $P = 0.004$) and NLR ≥ 2.81 (HR = 3.34; 95% CI: 1.97–5.68; $P < 0.001$). Similarly, antiviral treatment (HR = 0.57; 95% CI: 0.34–0.97; $P = 0.037$), tumor size ≥ 7 cm (HR = 1.88; 95% CI: 1.07–3.31; $P = 0.029$) and NLR ≥ 2.81 (HR = 3.49; 95% CI: 1.79–6.83; $P < 0.001$) remained significantly associated with OS in the multivariate analysis.

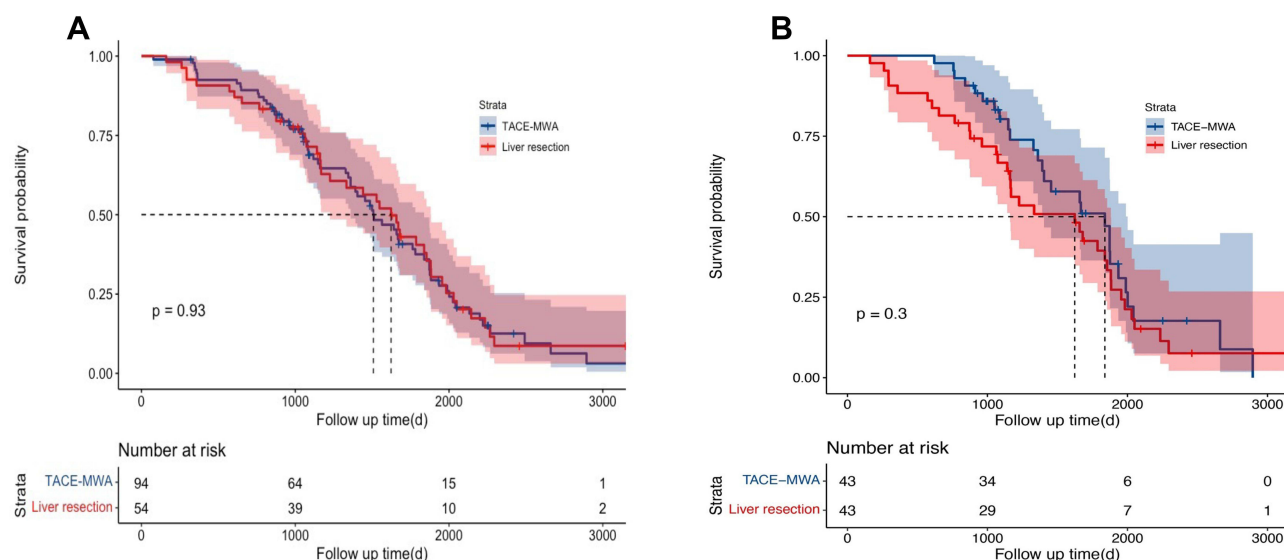


Figure 2 Overall survival (OS) of patients before or after propensity score matching. **(A)** There is no significant difference in terms of OS in the TACE-MWA group and liver resection group. ($P = 0.93$). **(B)** In the propensity score-matched cohort, TACE-MWA showed comparable efficacy to liver resection ($P = 0.3$).

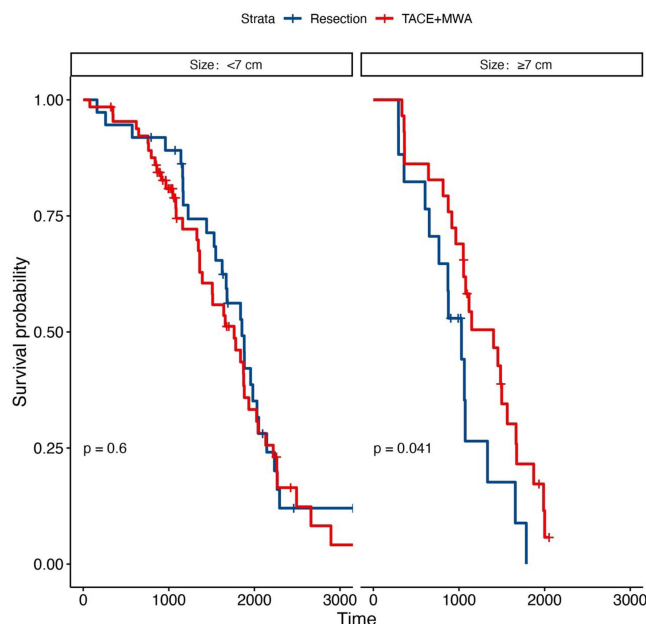


Figure 3 Subgroup analysis between patients with tumor size <7cm and ≥7cm. There was no significant difference in the OS in patients with HCC patients with tumor size <7cm. ($P = 0.6$) between the two groups. In patients with HCC ≥7cm, the OS of patients in the TACE-MWA group showed better efficacy in the liver resection group ($P = 0.041$).

Progression Survival

During the follow-up period, 84 (89.3%) patients in the TACE-MWA group and 42 (77.7%) patients in the liver resection group had tumor progression. The median PFS, 1-, 3-, and 5-year PFS rates were 24.4 months, 74.2%, 37.5%, and 15.2% in the TACE-MWA group and 32.5 months, 75.9%, 45.1%, and 28.2% in the liver resection group, respectively. PFS did not significantly differ between the two groups ($P = 0.12$, Figure 4A).

In the PSM adjusted population, the median PFS was 35.3 months in the TACE-MWA group and 31.3 months in the liver resection group. The 1-, 3-, and 5-year PFS rates were 76.7%, 48.8%, and 19.6% in the TACE plus MWA group and 72%, 40.2%, and 22.6% in the liver resection group, respectively. Similarly, there was still no significant difference in

Table 2 Univariate and Multivariate Analyses of Prognostic Factors for Overall Survival in Patients with Solitary Large HCC and in the Propensity Score-Matched Cohort

Variable	Univariate	P	Multivariate	P
	HR (95% CI)		HR (95% CI)	
Sex:				
Female vs Male	0.91 (0.47–1.75)	0.773		
Age:				
≥ 60 vs < 60	1.04 (0.59–1.83)	0.884		
Treatment:				
Liver Resection vs TACE-MWA	1.30 (0.79–2.16)	0.304		
Pre-TACE:				
Yes vs No	0.81 (0.32–2.02)	0.648		
ALBI Grade:				
II or III vs I	1.25 (0.75–2.09)	0.384		
Cirrhosis:				
Yes vs No	1.06 (0.60–1.86)	0.845		
Antiviral treatment				
Yes vs No	0.25 (0.13–0.52)	0.002	0.57 (0.34–0.97)	0.037
Tumor Size				
≥7cm vs <7cm	2.27 (1.30–3.95)	0.004	1.88 (1.07–3.31)	0.029
AST (IU/L):				
≥40 vs <40	0.86 (0.47–1.56)	0.614		
ALT (IU/L):				
≥40 vs <40	0.67 (0.36–1.25)	0.211		
AFP (ng/mL):				
≥400 vs <400	0.92 (0.54–1.56)	0.752		
TBIL (mg/dL):				
≥17.1 vs <17.1	1.19 (0.67–2.11)	0.558		
ALB (g/L):				
≥35 vs <35	0.83 (0.50–1.38)	0.473		
NLR:				
≥2.81 vs <2.81	3.34 (1.97–5.68)	<0.001	3.49 (1.79–6.83)	<0.001

Abbreviations: TACE, transcatheter arterial chemoembolization; MWA, microwave ablation; HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; NLR, neutrophil to lymphocyte.

PFS between the two groups after PSM ($P=0.66$; Figure 4B). Subgroup analyses showed that no significant difference was obtained.

Univariate and multivariate analyses are shown in Table 3. In the univariate analysis, the significant prognostic factors were antiviral treatment (HR = 0.55; 95% CI: 0.43–0.71; $P = 0.001$), tumor size ≥ 7 cm (HR = 2.15; 95% CI: 1.31–3.54; $P = 0.003$) and NLR ≥ 2.81 (HR = 2.07; 95% CI: 1.28–3.35; $P = 0.003$). Similarly, antiviral treatment (HR = 0.47; 95% CI: 0.34–0.65; $P = 0.002$), tumor size ≥ 7 cm (HR = 2.04; 95% CI: 1.24–3.37; $P = 0.005$) and NLR ≥ 2.81 (HR = 1.97; 95% CI: 1.22–3.20; $P = 0.006$) remained significantly associated with PFS in the multivariate analysis.

Complications and Length of Hospital Stay

No treatment-related deaths were observed in the TACE-MWA group and the liver resection group. Minor complications in both groups included fever, nausea, vomiting, abdominal pain, transient abnormal liver function, and pleural effusion, which could be relieved by symptomatic treatments. Major complications in the TACE-MWA group included liver abscess, bile leakage, and bleeding, while these in the liver resection group were liver failure, biliary leakage, ascites,

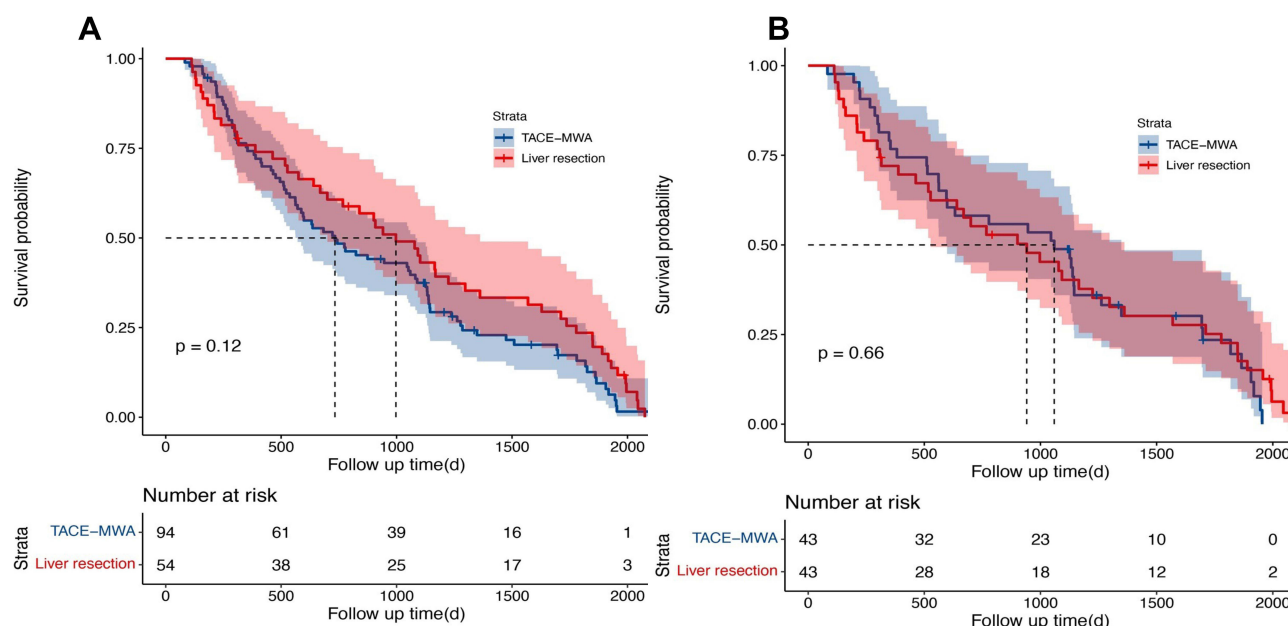


Figure 4 Progression-free survival (PFS) of patients before or after propensity score matching. **(A)** There is no significant difference in terms of PFS in the TACE-MWA group and liver resection group. ($P = 0.12$). **(B)** In the propensity score-matched cohort, TACE-MWA showed comparable PFS to liver resection ($P = 0.66$).

liver abscess, hemorrhage, pulmonary infection, and abdominal infection. Major complications were reported more frequently in the resection group than in the TACE-MWA group either before or after PSM (before: $P = 0.001$; after: $P = 0.029$) (Table 4). Also, the length of hospital stay was significantly shorter in the TACE-MWA group (before: 14.4 ± 7.62 ; after: 13.2 ± 6.78 days) than in the resection group (before: 26.2 ± 14.0 ; after: 23.1 ± 12.2 days) either before or after PSM (before: $P < 0.001$; after: $P < 0.01$).

Table 3 Univariate and Multivariate Analyses of Prognostic Factors for Progression Free Survival in Patients with Solitary Large HCC and in the Propensity Score-Matched Cohort

Variable	Univariate	P	Multivariate	P
	HR (95% CI)		HR (95% CI)	
Sex:				
Female vs Male	0.86 (0.47–1.58)	0.629		
Age:				
≥ 60 vs < 60	1.23 (0.73–2.07)	0.427		
Treatment:				
Liver Resection vs TACE-MWA	0.95 (0.60–1.52)	0.829		
Pre-TACE:				
Yes vs No	1.14 (0.52–2.49)	0.747		
ALBI Grade:				
II or III vs I	0.97 (0.61–1.55)	0.893		
Cirrhosis:				
Yes vs No	1.53 (0.92–2.55)	0.101		
Antiviral treatment				
Yes vs No	0.55 (0.43–0.71)	0.001	0.47 (0.34–0.65)	<0.001
Tumor Size				
$\geq 7\text{cm}$ vs $< 7\text{cm}$	2.15 (1.31–3.54)	0.003	2.04 (1.24–3.37)	0.005
AST (IU/L):				
≥ 40 vs < 40	1.05 (0.62–1.77)	0.861		

(Continued)

Table 3 (Continued).

Variable	Univariate	P	Multivariate	P
	HR (95% CI)		HR (95% CI)	
ALT (IU/L): ≥40 vs <40	0.90 (0.53–1.54)	0.701		
AFP (ng/mL): ≥400 vs <400	1.27 (0.79–2.04)	0.333		
TBIL (mg/dL): ≥17.1 vs <17.1	1.11 (0.65–1.90)	0.700		
ALB (g/L): ≥35 vs <35	1.09 (0.69–1.73)	0.719		
NLR: ≥2.81 vs <2.81	2.07 (1.28–3.35)	0.003	1.97 (1.22–3.20)	0.006

Abbreviations: TACE, transcatheter arterial chemoembolization; MWA, microwave ablation; HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein.

Table 4 Safety in Patients with Solitary Large HCC Before and After PSM

Characteristic	Before PSM (N=148)		P	After PSM (N=86)		P
	TACE+MWA N=94	Liver Resection N=54		TACE+MWA N=43	Liver Resection N=43	
Major complications	15 (27.8%)	6 (6.32%)	0.001	10 (23.3%)	2 (4.65%)	0.029
Liver failure	2 (3.70%)	0 (0.00%)	0.132	2 (4.60%)	0 (0.00%)	0.494
Biliary leakage	1 (1.85%)	2 (2.13%)	1.000	0 (0.00%)	1 (2.33%)	1.000
Ascites	2 (3.70%)	0 (0.00%)	0.132	0 (0.00%)	0 (0.00%)	1.000
Liver abscess	2 (3.70%)	2 (2.13%)	0.623	1 (2.33%)	0 (0.00%)	1.000
Hemorrhage	3 (5.56%)	2 (2.13%)	0.355	2 (4.65%)	1 (2.33%)	1.000
Pulmonary infection	5 (9.26%)	0 (0.00%)	0.006	2 (4.65%)	0 (0.00%)	0.006
Abdominal infection	2 (3.70%)	0 (0.00%)	0.132	2 (4.65%)	0 (0.00%)	0.132

Discussion

In our study, TACE-MWA showed comparable efficacy in terms of OS and PFS to liver resection in patients with SLHCC. Of note, TACE plus MWA showed longer OS than liver resection for HCC patients with tumor size ≥ 7 cm. Moreover, the TACE-MWA group had a lower rate of major complications and shorter length of hospital stay. To our knowledge, this is the first study to compare TACE plus MWA with surgical resection in patients with SLHCC.

SLHCC is a special subgroup of HCC, for which the best treatment option remains to be addressed. According to the BCLC staging system, solitary tumor irrespective of their size, along with good clinical conditions and preserved liver function without macrovascular invasion and extrahepatic spread, is defined as early stage. Liver resection is the first-line option for patients at the early stage.^{4,5} Nevertheless, some authors considered that SLHCC should be classified as BCLC B stage or BCLC AB stage, due primarily to its significantly worse prognosis when resected as compared to a small tumor, creating an urgent need to optimize treatments for these patients.^{3,23,24} Ablation therapies are considered comparable to resection in patients with HCC ≤ 3 cm, but their efficacy decreases with the tumor burden increasing. Livraghi et al reported that the complete ablation rate was 75% after RFA in patients with a medium tumor (3–5 cm), while the rate was only 23–25% in patients with a large tumor (≥ 5 cm).¹¹ Although MWA achieves more tumor necrosis rate than RFA, its survival benefits remain limited in large tumor.¹⁹ TACE has been regarded as the first-line treatment for unresectable HCC, which is difficult to achieve complete necrosis in one session, especially in large HCC. TACE is usually used repeatedly. The repeated TACE not only increases the cumulative dose of chemotherapeutic drugs, thereby worsening liver function, but also may result in “TACE refractory” and reduce the efficacy.²⁵ Several studies have shown

that TACE alone in the treatment of SLHCC is inferior to surgical resection. Jin et al reported the 1-, 3-, and 5-year survival rates of SLHCC were 83.2%, 75.7%, and 65.0% in the resection group, and 68.5%, 45.0%, and 17.5% in the TACE group ($P < 0.01$).²⁶ Liu et al also reported that 1-, 3- and 5-year survival rates of SLHCC were 87%, 76%, and 61% in the resection group, and 79%, 46%, and 36% in TACE alone group, respectively ($p < 0.001$). These results showed that ablation or TACE was insufficient to improve the prognosis of SLHCC.

TACE plus ablation is a promising therapy for large HCC in clinical scenario.^{27,28} The rationale of the combination includes (1) a large tumor has richer blood supply than a small one. The thermal energy generated by the ablation is more easily carried away by the blood flow (heat-sink effect), which reduces the efficacy of ablation. This phenomenon can be improved by TACE via a reduction in blood supply. (2) Post-TACE lipiodol deposition provides help for tumor localization and guidance for subsequent ablation and the achievement of precise ablation. (3) For large tumor burden, the tumor volume can be significantly reduced by TACE, thereby decreasing the ablation zone and time. (4) The chemotherapy drugs used in TACE have immunosuppressive side effects, while some studies have demonstrated that ablation can enhance immune response.^{29,30}

Previous studies compared TACE combined with RFA versus surgical resection in HCC. Kagawa et al³¹ in 2010 reported that the 1-, 3-, and 5-year OS in the TACE+RFA group were 100%, 94.8%, and 64.6%, while those in the surgical resection group were 92.5%, 82.7%, and 76.9% within the Milan Criteria, respectively ($P > 0.05$). Kim et al³² published a study in 2013 comparing TACE plus RFA versus surgical resection for single 2–5 cm HCC. The 1-, 2-, 3-, and 4-year OS in the TACE+RFA group were 97.3%, 86.5%, 78.4% and 78.4%, and 95.7%, 89.4%, 84.3% and 80.3% in the surgical resection group ($P = 0.6321$). Since the patients included in our study had larger tumor size compared with the above studies, the OS and PFS were lower. Pan et al³³ compared TACE-RFA and liver resection in patients with HCC who met the up-to-seven criteria (the sum of the size of the largest tumor (cm) and the number of tumors equals seven). After PSM, the median OS was 56.0 months and 58.0 months in the TACE plus RFA group and surgical resection, respectively. The 1-, 3-, and 5-year survival rates were 96.1%, 76.7%, and 41.3% and 96.1%, 86.4% and 46.2%, respectively. No significant difference was obtained in the two groups ($P = 0.261$). Tumor size >5 cm was not an independent prognostic factor ($P=0.0163$). This conclusion was consistent with our study. Subsequently, Yuan et al³⁴ published a study in 2018 comparing the efficacy of TACE plus RFA and liver resection in patients with liver cancer beyond Milan criteria. The 1-, 2-, 3-, and 5-year OS rates and median survival time in the TACE combined with the RFA group were 98.5%, 83.1%, 66.2%, and 37.1% and 46 months, and 89.6%, 69.4%, 53.7%, 30.3%, and 38 months in the surgical resection group, respectively ($P = 0.017$). The better OS in our study may be due to the larger tumor diameter, and 100 patients (37.1%) were multiple tumors in Yuan et al's study.

In our study, tumor diameter ≥ 7 cm was an independent risk factor for OS and PFS. The larger the liver tissue ablated or resected, the worse liver function compromised. Besides, the invasiveness of the tumor enhances with the tumor size increasing.³⁵ A great number of studies suggested that tumor diameter was associated with microvascular invasion in HCC, which significantly affected postoperative recurrence and survival.³⁶ The study by Zhuang et al³⁷ showed that tumor diameter >7.1 cm was an independent risk factor for surgical resection of large solitary HCC (HR: 2.21, 95% CI: 1.3–3.75, $P = 0.003$). Yuan et al's study comparing surgical resection and TACE combined with RFA in patients beyond Milan criteria also showed that tumor diameter >7 cm was an independent risk factor for OS and PFS.³⁴

In addition, this study found that higher NLR was an independent risk factor for OS and PFS. In HCC patients, previous studies demonstrated the prognostic value of NLR in multiple treatment modalities, including TACE, ablation, targeted, and immunotherapy.^{38,39} Numerous studies have shown that systemic inflammatory response plays a crucial role in the development and progression in various cancers. Neutrophils promote cancer progression by suppressing the cytolytic activity of immune cells and the secretion of various inflammatory cytokines and therefore probably lead to a stimulating tumor microenvironment.^{40,41} Moreover, lymphocytes have long been considered one of the primary effector cells in anti-tumor response, and previous researches showed that increasing infiltration of tumors with lymphocytes was associated with better response to cytotoxic treatment and prognosis in cancer patients.^{42,43}

Antiviral treatment plays a critical role in the management of HCC. The predominant etiology of HCC in China is HBV, which is higher than other etiology.⁴⁴ HBV reactivation may be influenced by operations such as resection or TACE, which activates HBV-DNA replication, thereby influencing prognosis.^{45,46}

This study has several limitations. First, the main concern of our study is its retrospective nature, which makes selection and confounding biases inevitable, thus limiting the power of conclusions. Although PSM and multivariate regression may adjust for some of the imbalanced covariates, unknown confounders that cannot be adjusted for may exist. Second, this study is a single-center study, and the results of this study may be affected by the experience of doctors and the patients who come to our hospital. Third, the sample size is small especially after PSM, with only 43 patients in each group. Fourth, most patients in this study were viral hepatitis, especially hepatitis B. Therefore, the results need to be further verified in large-scale cohorts or randomized clinical trials.

Conclusions

In conclusion, TACE plus MWA provides comparable efficacy, better safety, and shorter hospital stay. For HCC patients with tumor diameters greater than 7 cm, TACE plus MWA may be superior to surgical resection. Large-scale randomized clinical trials are warranted to validate these results in the future.

Ethics Approval and Informed Consent

This study was conducted in line with the Declaration of Helsinki, and written informed consent was obtained from all the eligible patients before treatment. Clinical research protocol and clinical data were approved by the Ethics Committee of Beijing Ditan Hospital (KY2020-030).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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

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