Journal of Hepatocellular Carcinoma Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Transarterial Chemoembolization Combined with Microwave Ablation in Elderly Patients with Recurrent Medium or Large Hepatocellular Carcinoma

Chuxiao Zhang, Yuelan Qin, Yangguang Song, Yingying Liu, Xiaodong Zhu

Department of Radiation Oncology, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, People's Republic of China

Correspondence: Xiaodong Zhu, Department of Radiation OncologyGuangxi Medical University Cancer Hospital, No. 71 hedi Road, Nanning, Guangxi, 530021, People's Republic of China, Email xdzhu1466@hotmail.com

Purpose: There are insufficient data about the optimal treatment for older patients with recurring medium or large hepatocellular carcinoma (HCC). The study intended to assess the effect of transcatheter arterial chemoembolization combined with microwave ablation (TACE-MWA) in an elderly cohort through a retrospective analysis.

Methods: From 2011 to 2018, a cohort of individuals (age ≥70 years) with recurrent HCC tumors ranging from 3.1 cm to 7 cm underwent either a combination treatment of TACE and MWA (n = 43) or surgical intervention (n = 33). Using the Inverse Probability of Treatment Weighting (IPTW) technique, factors of disease-free survival (DFS), overall survival (OS), and rates of major adverse events were analyzed, retrospectively.

Results: The group that underwent surgery had a greater history of alcohol use before treatment (P= 0.001), as well as a higher Barcelona Clinic Liver Cancer (BCLC) stage for the primary tumor before treatment (P= 0.014) and a higher primary tumor location before treatment (P= 0.045). The TACE-MWA group had DFS rates of 86.2%, 68.8%, and 60.4% at 1, 3, and 5 years, while the surgery group had rates of 53.0%, 42.2%, and 25.8% at the same time points. In the TACE-MWA treatment group, survival rates at 1 year, 3 years, and 5 years post-treatment were recorded as 93.0%, 80.8%, and 65.7%, respectively, while in the surgery group, they were 62.7%, 46.9%, and 42.6%. In the univariate analysis using IPTW, the type of treatment was found to have a significant correlation with disease progression (hazard ratio [HR] 0.41, 95% CI 0.20–0.86, P=0.017). IPTW multivariate analysis showed that treatment modality (HR, 0.35; 95% CI, 0.17 to 0.79; P= 0.011) was the only significant prognostic factor for OS.

Conclusion: In elderly patients with recurrent 3.1 cm≤ HCC ≤ 7 cm, TACE-WMA was superior to surgery in the respects of DFS and OS.

Keywords: elderly patients, hepatocellular carcinoma, transcatheter arterial chemoembolization, microwave ablation, treatment modality

Introduction

Although surgical resection (SR) is often recommended as a curative approach for patients with extremely early or early stage HCC,[1] the recurrence of HCC after hepatectomy remains a serious challenge.[2,3] For patients who cannot undergo additional locoregional treatments, systemic therapy has become an important part of managing the disease, driven by the development of novel therapies, especially immune checkpoint inhibitors (ICIs) and targeted therapies. These treatments offer better outcomes and are more tolerable than previous options.[4–8] In contrast, locoregional therapy, such as Transcatheter Arterial Chemoembolization (TACE), microwave ablation (MWA), radiofrequency ablation (RFA), and percutaneous ethanol injection (PEI), is effective for treating localized HCC, with the exception of repeated hepatic resection. Although improvement of the dose of ethiodized oil reaching the portal veins by the superselective manner, patients still face the risk of recurrence caused by the tumor morphology or vascularity. Researchers found that the

Received: 13 April 2024
Accepted: 16 October 2024
Published: 22 October 2024

pressure within the HCC nodule is decreased from high to sluggish flow after TACE, which causes an almost complete lack of heat loss as a result of this phenomenon, and intact and perhaps even increased portal blood flow in the surrounding tissue can prevent heat diffusion outside the HCC nodule as well.[9] When ablation was performed in HCC nodules after occlusion of their arterial supply, higher tumor response and better local control could be detected in the results of histopathology. Over the course of almost a decade, multiple research studies have indicated that combining TACE with ablation, such as MWA or RFA, offers a notable increase in survival rates for individuals with recurrent HCC tumors that are 7 cm or smaller and have five or fewer lesions, in comparison to using ablation or TACE alone.[10–14] Additionally, these combined methods have shown to be equally as effective as hepatectomy.[15–17]

The number of people with age >65 years is rapidly increasing, from 461 million in 2004 to an estimated 2 billion people by 2050, which has greatly new meaning to health and social care, especially remedy for malignant tumors.[18,19] The treatment of recurrent HCC in patients over 65 years of age presents unique challenges, as these patients often have additional comorbidities and diminished physiological reserves. The combination of TACE and MWA offers effective local tumor control with relatively high maintenance quality of life, making it a suitable option for patients who are not candidates for more aggressive treatments. However, the effectiveness and adverse events of ablation combined with TACE compared to repeated hepatic have not been proven in medium or large recurrent HCCs owing to the scarcity of elderly subjects within the study sample. However, conducting prospective clinical trials in elderly patients can be difficult due to the presence of multiple comorbidities, the scarce of the patients, and organ function decline. In this case, a retrospective study can serve as an alternative approach. Therefore, a retrospective study was conducted to contrast the treatment results of TACE-MWA versus re-hepatectomy in elderly patients with medium or large recurrent HCCs (diameter span of 3.1–7.0 cm).

Methods

Patients

A tertiary academic center was the setting for our retrospective study, which passed the scrutiny and received approval from the corresponding Institutional Review Board (IRB) of the hospital (Guangxi Medical University Cancer Hospital), and that was conducted according to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from every patient prior to treatment. From 2011 to 2018, a total of 76 individuals who had a recurrence of HCC after hepatectomy were identified based on histopathological analysis or non-invasive criteria outlined by the American Association for the Study of Liver Diseases (AASLD) guidelines.[20] Of these patients, 33 patients were subjected to secondary hepatectomy, whereas 43 patients were treated with TACE-MWA (Figure 1). The eligibility requirements for this study were as follows: 1) age ≥70 years; 2) first intrahepatic recurrence following hepatectomy; 3) a solitary tumor (3.1 cm≤ and ≤7 cm in diameter in maximum extent) or up to three tumors (each 3.1 cm≤ and ≤5 cm in diameter); 4) non-invasive to vessels and no metastasis outside the liver; 5) Child-Pugh A/B classification status; 6) refused liver transplantation. These patients comprehended all the specifics of both therapeutic approaches. Surgery was recommended for the patients with a single tumor within one liver segment with adequate hepatic functional reserve, and the patients with severe portal hypertension or insufficient liver remnant avoided receiving repeated hepatic resection. Additional requirements for TACE-MWA included: 1) a clear path from the lesion to the skin surface on the ultrasound before treatment; 2) a patient declined a second hepatectomy.

TACE and MWA

A uniform medical team executed both the TACE and MWA procedures. TACE was executed with meticulous super-selectivity, subsequently followed by arterial embolization combined with chemotherapy. A 5-F catheter was utilized to conduct visceral angiography, which was inserted through the femoral artery. Subsequently, a microcatheter of 2.9-French size (manufactured by Terumo Corporation, Tokyo, Japan) was positioned within the arteries that nourished the tumor. After injecting 100 mg of oxaliplatin (made by Hengrui Medicine, Lianyungang, China) into the arteries, chemoembolization was performed with a mixture of 60 mg epirubicin (manufactured by Zhejiang Hisun Pharmaceutical, Taizhou, China) and 5–10 mL iodized oil (from Hengrui Medicine, Lianyungang, China), followed by

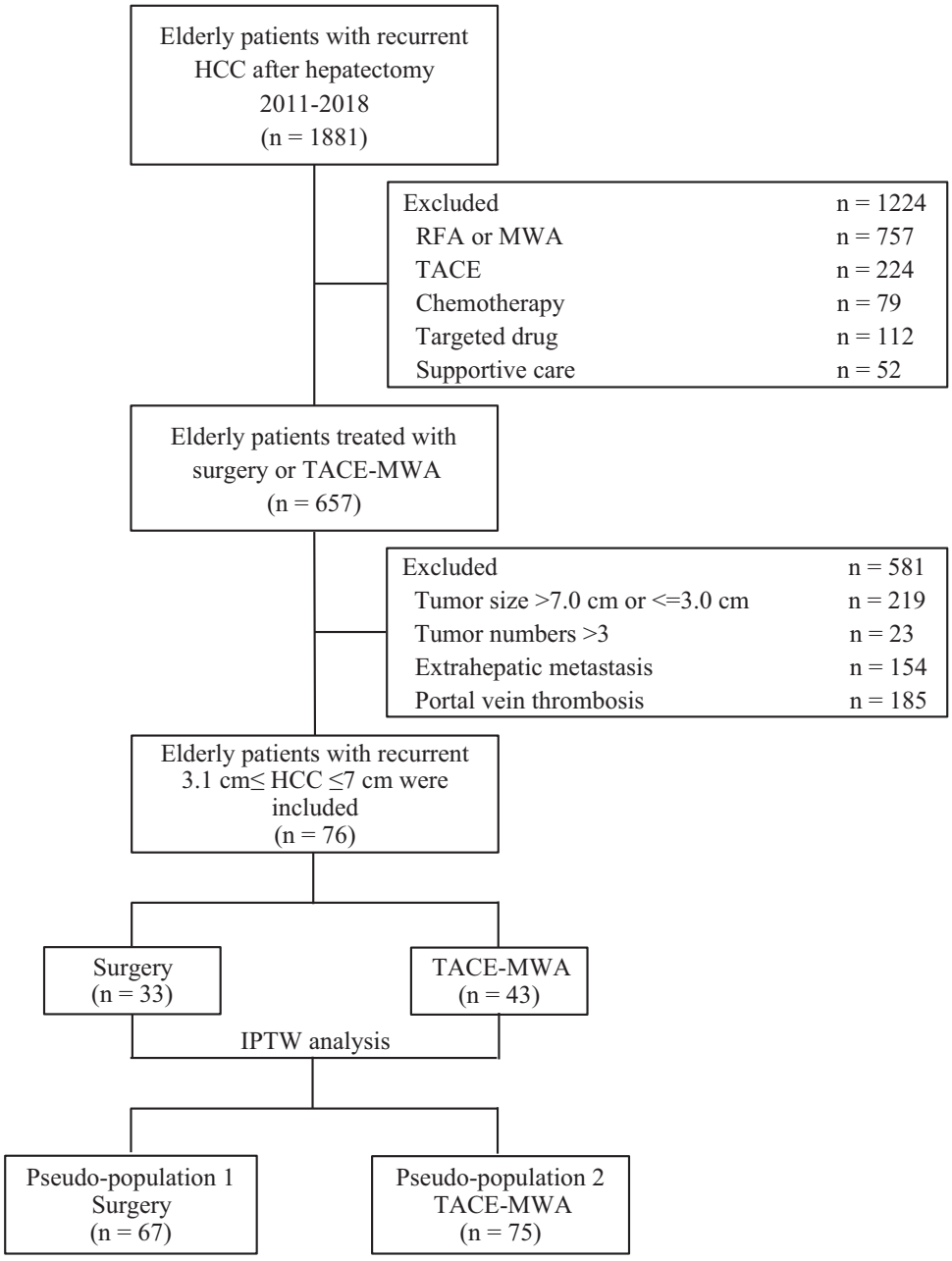

Figure 1 Flow diagram of this study.
Abbreviations: HCC, hepatocellular carcinoma; MWA, microwave ablation; TACE, transarterial chemoembolization.

the addition of gelatin sponge granules measuring 1–2 mm in diameter (Gelfoam brand; provided by Hangzhou Alc, Hangzhou, China).

Within the 4-week window subsequent to chemoembolization, microwave ablation was conducted, with a median of 15 days, and this interval varied between 10 and 28 days. Intravenous midazolam and fentanyl were given for conscious sedation, along with 1% lidocaine for local anesthesia, while using the Water-tip Microwave Ablation System (ECO-100C model, from ECO Microwave Electronic Institute in Nanjing, China) to perform ablation procedures with continuous real-time ultrasound guidance. Tumors larger than 3 cm required the use of two electrodes deployed sequentially to guarantee complete coverage of the tumor. In the course of extracting the MWA electrode, a step was taken to apply thermal ablation along the needle pathway as a measure to mitigate probabilities of bleeding and tumor metastasis. The goal was to create a boundary of ablative impact that reached a minimum of 0.5 cm into the surrounding

healthy normal tissue around the tumor, without encroaching upon the perivascular area. In instances where residual malignancy was identified through dynamic CT scans within seven days post-MWA treatment, supplementary MWA treatments were administered until the tumor was fully ablated.

Repeat hepatectomy

The resection surgery was performed under general anesthesia by a team of three surgeons, with the lead surgeon possessing 12 to 20 years of experience in hepatic resection procedures. Open re-hepatectomies were performed on 30 patients to minimize the incidence of adverse events. The suspected tumor nodule, portal vein, hepatic veins, and the liver remnant were evaluated by intraoperative ultrasound. After evaluating the size, location, patient's overall health, and underlying liver condition, a decision was made to either perform an anatomical hepatectomy or opt for a non-anatomical wedge excision. Standard safety margins were set at 2 cm, except in cases where tumors are in close proximity to primary Glissonian pedicles or major hepatic veins, where a margin of 5 mm is deemed adequate.

Follow-up

Four weeks following the conclusion of treatment, patients underwent assessments of liver function and imaging examinations using either CT scans or magnetic resonance imaging of the liver. Subsequently, patients were subjected to a series of assessments at specified intervals: they had regular physical check-ups, laboratory assessments including blood counts and liver function analyses, α-fetoprotein (AFP) level determinations, and liver dynamic contrast-enhanced CT scans on a quarterly basis throughout the initial 12-month period. From the second through fifth years, these tests occurred biannually, and from the sixth year onward, they transitioned to an annual schedule. Disease progression was assigned to describe three separate conditions: advancement of the primary tumor, appearance of new tumors at non-adjacent or distinct intrahepatic sites, and the development of recurrences outside the liver during the surveillance phase. To identify local tumor progression, we considered the emergence of heightened tumor activity within or around the area of liver necrosis for TACE patients, while for those undergoing TACE-MWA, recurrence either within the treatment zone or in close proximity was used as a determining factor. In patients experiencing recurrent HCC, other treatments like MWA, systemic chemotherapy, targeted medications, and supportive care were administered. In the evaluation of adverse events following initial treatment, the standard employed is the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 established by the National Institutes of Health (NIH).

Statistics

Frequency and percentage distributions were used to present categorical variables, while medians and interquartile ranges (IQRs) were utilized for continuous variables. In the case of categorical variables, we employed either Pearson's χ^2 test when appropriate or Fisher's exact test, whereas continuous variables were subjected to the Mann–Whitney *U*-test for assessment. The primary outcome measure was established as DFS, whereas another key metric, OS, serves as the secondary endpoint. The Kaplan–Meier method was utilized to summarize DFS and OS. In order to account for the relationship between lesions in the same patient, we utilized mixed-effects Cox models with random effects at the patient level to examine the role played by different treatments and associated factors in determining DFS.[21] In order to account for any potential bias in the initial characteristics of the two groups, we utilized propensity scores and employed the IPTW method grounded on these scores.[15] These variables encompassed multiple critical parameters, including sex, age, lesion count, tumor volume, Hepatitis B status, AFP levels, Child-Pugh liver function classification, BCLC staging, time from surgery to recurrence, alcohol history, cirrhosis status, and primary tumor site. During IPTW assessment, precise estimation of propensity scores was accomplished by employing logistic regression methods. In the IPTW approach, for patients receiving TACE-MWA therapy, individual weights were assigned as the reciprocal of their corresponding propensity scores; whereas for those opting for repeat hepatectomy, their individual weights were determined based on the reciprocal of 1- propensity scores. When the IPTW method is implemented, it generates two novel weighted pseudo-populations. The makeup of these two pseudo-populations is determined by assigning weights to individuals from the source populations, where the weights are inversely proportional to their corresponding treatment likelihoods. In the univariate Cox regression analysis, separate models were constructed to consider solely the treatment or to incorporate

both one covariate and the treatment indicator. A Multivariable Cox regression analysis was conducted to identify distinct factors associated with DFS and OS. We utilized R software (version 3.5.1, from the R Foundation for Statistical Computing in Vienna, Austria) to perform all necessary computations. A *P* value <0.05 was deemed to represent statistical significance.

Results

Baseline characteristics

Prior to IPTW adjustment, Table 1 presents the baseline characteristics of the entire patients (n = 76). Patients in the TACE-MWA group had more favorable alcohol history (*P*= 0.001), BCLC staging of the primary tumor (*P*= 0.014), and primary tumor location (*P*= 0.045) compared to the surgery group. Regarding other features, no substantial differences were detected among the two groups. Upon IPTW-adjustment, no considerable disparities in the covariates emerged between the two groups.

Table 1 Baseline Characteristics

Characteristic	Unadjusted			After IPTW		
	Surgery (n = 33)	TACE-MWA (n = 43)	*P* value	Surgery (n = 67)	TACE-MWA (n = 75)	*P* value
Gender			0.401			
Male	30 (90.9)	35 (81.4)				
Female	3 (8.1)	8 (18.6)				
Age, years			0.914			
Median	76	76				
IQR	73–79	73–79				
Alcohol history			0.001			0.454
Yes	26 (78.8)	17 (39.5)		46 (67.6)	43 (57.2)	
No	7 (21.2)	26 (60.5)		21 (32.4)	32 (42.8)	
No. of lesions			0.929			
Solitary	28 (84.8)	35 (81.4)				
Multinodular	5 (15.2)	8 (18.6)				
Tumor diameter			0.585			
≤5 cm	17 (51.5)	26 (60.5)				
>5 cm	16 (48.5)	17 (39.5)				
Hepatitis B			0.429			
Positive	30 (90.9)	42 (97.7)				
Negative	3 (9.1)	1 (2.3)				
Cirrhosis			0.429			0.556
Yes	30 (90.9)	42 (97.7)		63 (94.0)	73 (97.3)	
No	3 (9.1)	1 (2.3)		4 (6.0)	2 (2.7)	
AFP (ng/mL)			0.710			
>400	24 (72.7)	34 (79.1)				
≤400	9 (27.3)	9 (20.9)				
Child-Pugh class			0.590			
5	5 (15.1)	7 (16.3)				
6	16 (48.5)	25 (58.1)				
7	12 (36.4)	11 (25.6)				
BCLC stage of primary tumor			0.014			0.680
A	24 (72.7)	41 (95.3)		56 (83.1)	66 (87.3)	
B	9 (27.3)	2 (4.7)		11 (16.9)	9 (12.6)	

(*Continued*)

Table 1 (Continued).

Characteristic	Unadjusted			After IPTW		
	Surgery (n = 33)	TACE-MWA (n = 43)	*P* value	Surgery (n = 67)	TACE-MWA (n = 75)	*P* value
Primary tumor location			0.045			0.486
Unilobar	21 (63.6)	37 (86.0)		50 (75.2)	62 (82.6)	
Bilobar	12 (36.4)	6 (14.0)		17 (24.8)	13 (17.4)	
Interval of recurrence from initial treatment (years)			1.000			
≤1	8 (24.2)	11 (25.6)				
>1	25 (75.8)	32 (74.4)				

Abbreviations: AFP, α-fetoprotein; IQR, interquartile range; MWA, microwave ablation; TACE, transarterial chemoembolization.

DFS and OS

The TACE-MWA group's median follow-up spanned 52.4 months (varying between 4.5 and 67.1 months), while the median follow-up duration in the surgery group was 51.1 months (ranging from 3.3 to 66.6 months). Over the course of the follow-up, a total of 31 fatalities were recorded among the two groups, including 17 from tumor recurrence, seven from liver failure concurrent with non-progressing tumors, three from gastrointestinal (GI) bleeding, and four non-cancer related deaths.

The TACE-MWA group had initial, 3-year, and 5-year DFS rates of 85.7%, 68.1%, and 52.3%, while the surgery group had rates of 50.7%, 37.7%, and 22.3%. Following IPTW, 1-, 3-, and 5-year DFS rates were 86.2%, 68.8% and 60.4% after TACE-MWA and 53.0%, 42.2% and 25.8% after surgery, respectively (Figure 2A). The 1-, 3-, and 5-years OS rates without IPTW were 93.0%, 80.8%, and 65.7% in the TACE-MWA group, and 62.7%, 46.9%, and 42.6% in the surgery group, respectively. Following IPTW, the TACE-MWA group showed OS rates of 89.3%, 79.5%, and 64.9% at 1-, 3- and 5-years, while the surgery group had rates of 69.1%, 49.8%, and 28.4% at the same time points (Figure 2B).

In IPTW univariate analysis, treatment modality (HR, 0.41; 95% CI, 0.20 to 0.86; P= 0.017 for surgery vs TACE-MWA) showed a significant association with disease progression (Table 2). Meanwhile, treatment modality (HR, 0.36; 95% CI, 0.16 to 0.81; P= 0.014) and tumor number (HR, 2.03; 95% CI, 1.01 to 4.07; P= 0.047) were revealed as influential factors for overall survival. The treatment modality and tumor number were included in an IPTW multivariate analysis, which demonstrated that treatment modality (HR, 0.35; 95% CI, 0.17 to 0.79; P = 0.011) was the sole significant prognostic factor for OS (Table 3).

In subgroup analysis, eight subgroups showed that treatment modality significantly correlated with disease progression (Figure 3A), including patients with alcohol history (HR, 0.23; 95% CI, 7.76×10^{-2} to 0.69; P= 9×10^{-3}), patients with solitary tumor (HR, 0.41; 95% CI, 0.18 to 0.95; P= 0.038), patients with tumor diameter ≤5 cm (HR, 0.33; 95% CI, 0.14 to 0.78; P= 0.012), patients with alpha-fetoprotein (AFP) >400 ng/mL (HR, 0.28; 95% CI, 0.13 to 0.62; P= 0.001), patients with Child-Pugh class B (HR, 0.09; 95% CI, 0.03 to 0.31; P= 1×10^{-4}), patients with unilobar primary tumor (HR, 0.32; 95% CI, 0.14 to 0.76; P= 0.009), patients with recurrence within 1 year of initial treatment (HR, 0.28; 95% CI, 0.09 to 0.88; P= 0.029), and patients with time span since initial treatment until disease recurrence >1 year (HR, 0.43; 95% CI, 0.19 to 0.99; P= 0.048). Six subgroups showed that treatment modality significantly correlated with overall survival (Figure 3B), including patients with solitary tumor (HR, 0.34; 95% CI, 0.12 to 0.95; P= 0.039), patients with tumor diameter ≤5 cm (HR, 0.25; 95% CI, 0.10 to 0.65; P= 0.004), patients with AFP > 400 ng/mL (HR, 0.37; 95% CI, 0.16 to 0.84; P= 0.017), patients with Child-Pugh class B (HR, 0.25; 95% CI, 0.08 to 0.76; P= 0.015), patients with unilobar primary tumor (HR, 0.21; 95% CI, 0.09 to 0.54; P= 0.001), and patients with recurrence within 1 year of initial treatment (HR, 0.15; 95% CI, 0.04 to 0.53; P= 0.003).

Twenty-three patients experiencing re-recurrent HCC in the surgery group and 18 patients also grappling with re-emerging HCC in the TACE-MWA group received other therapy. Among the 23 patients, two had MWA, three received intravenous systemic chemotherapy, seven were administered targeted drug, and 11 relied on best supportive care.

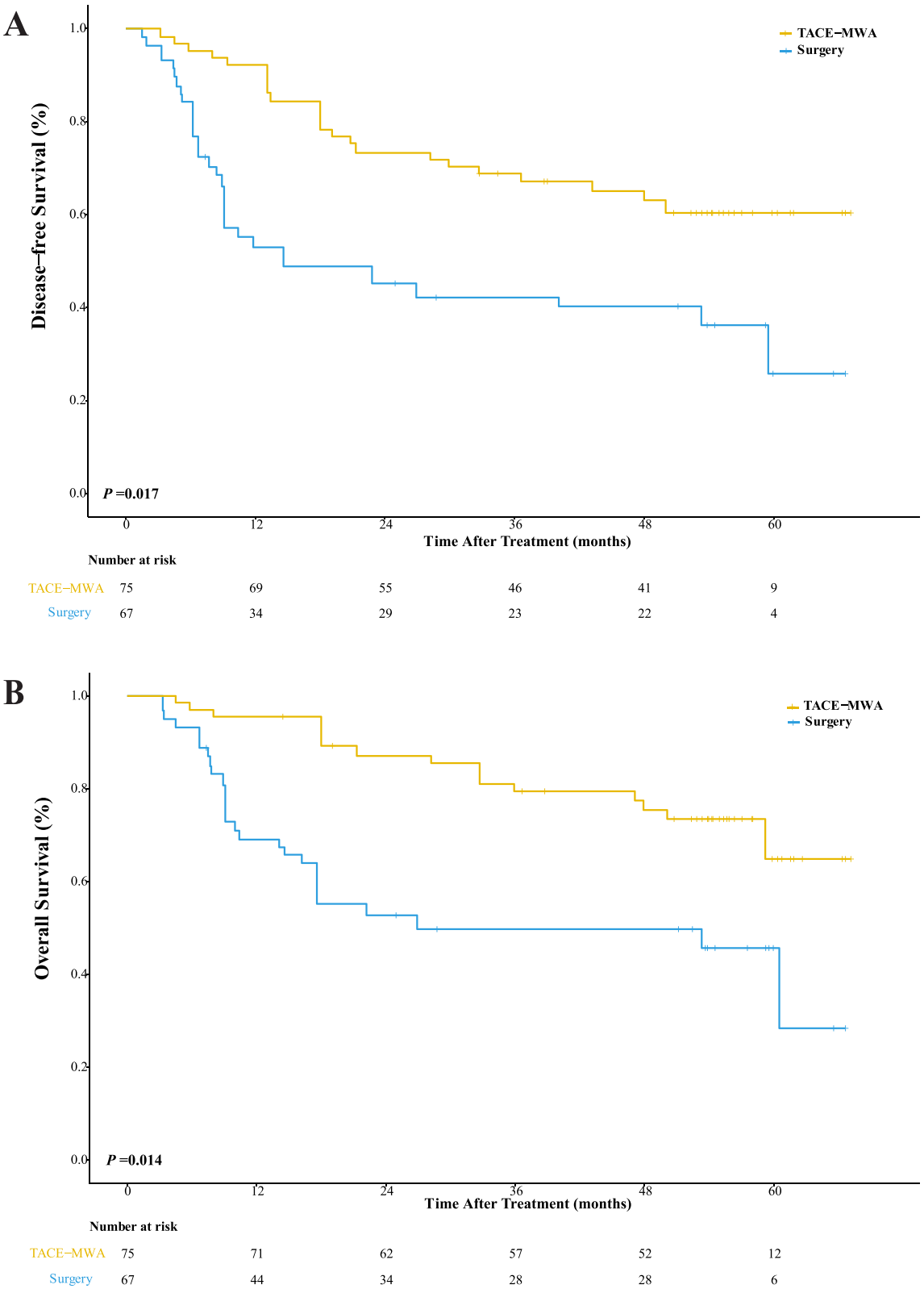

Figure 2 (**A**) Disease-free survival (DFS) for the transarterial chemoembolization (TACE) plus microwave ablation (MWA) and the surgery groups. (**B**) Overall survival (OS) for the transarterial chemoembolization (TACE) plus microwave ablation (MWA) and surgery groups.

Table 2 Univariate Analysis of Factors Associated with Disease Progression

Variable	Univariate Analysis		
	HR	95% CI	*P* value
Treatment			
Surgery vs TACE-MWA	0.41	0.20 to 0.86	0.017
Gender	3.05	0.52 to 18.0	0.219
Age	1.01	0.93 to 1.09	0.820
Alcohol history	1.64	0.73 to 3.67	0.230
Tumor size	0.77	0.37 to 1.59	0.486
Tumor number	1.73	0.85 to 3.55	0.131
Hepatitis B	1.36	0.29 to 6.36	0.700
AFP	2.30	0.80 to 6.59	0.122
Child-Pugh class	1.27	0.61 to 2.63	0.528
BCLC stage of primary tumor	1.68	0.58 to 4.87	0.340
Primary tumor location	1.71	0.84 to 3.45	0.137
Interval of recurrence from initial treatment	0.64	0.30 to 1.37	0.252

Abbreviations: AFP, α-fetoprotein; MWA, microwave ablation; TACE, transarterial chemoembolization.

Table 3 Univariate and Multivariate Analysis of Factors Associated with Overall Survival

Variable	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Treatment						
Surgery vs TACE-MWA	0.36	0.16 to 0.81	0.014	0.35	0.17 to 0.79	0.011
Gender	2.22	0.36 to 13.7	0.390			
Age	1.03	0.95 to 1.11	0.469			
Alcohol history	1.88	0.70 to 5.07	0.211			
Tumor size	0.84	0.37 to 1.90	0.680			
Tumor number	2.03	1.01 to 4.07	0.047	1.95	0.95 to 4.02	0.066
Hepatitis B	0.895	0.17 to 4.52	0.893			
AFP	2.63	0.80 to 8.57	0.110			
Child-Pugh class	1.59	0.74 to 3.43	0.197			
BCLC stage of primary tumor	2.5	0.84 to 7.43	0.099			
Primary tumor location	2.06	0.91 to 4.64	0.081			
Interval of recurrence from initial treatment	0.56	0.25 to 1.24	0.153			

Abbreviations: AFP, α-fetoprotein; MWA, microwave ablation; TACE, transarterial chemoembolization.

Among the 18 patients, two underwent further MWA therapy, five received systemic chemotherapy, five were given targeted drug, six were given best supportive care.

Adverse events

In the context of the treatment, no fatalities directly related to the therapy have occurred. In comparing the two treatment groups, no statistically discernible disparities were observed in the frequencies of all adverse events associated with therapy and the incidence of severe adverse events graded 3 to 4 (with *P*-values equating to 0.818 and 0.103, respectively). In both groups of patients, some frequently observed adverse events encompassed ascites, appetite loss, nausea, vomiting, discomfort, fever, and hepatic insufficiency (Table 4). Grade 3 to 4 pain (P= 0.046), Grade 1 to 2 pain (P = 0.032) and Grade 1 to 2 fever (P= 0.015) were more frequent adverse events in the surgery group. In the context of

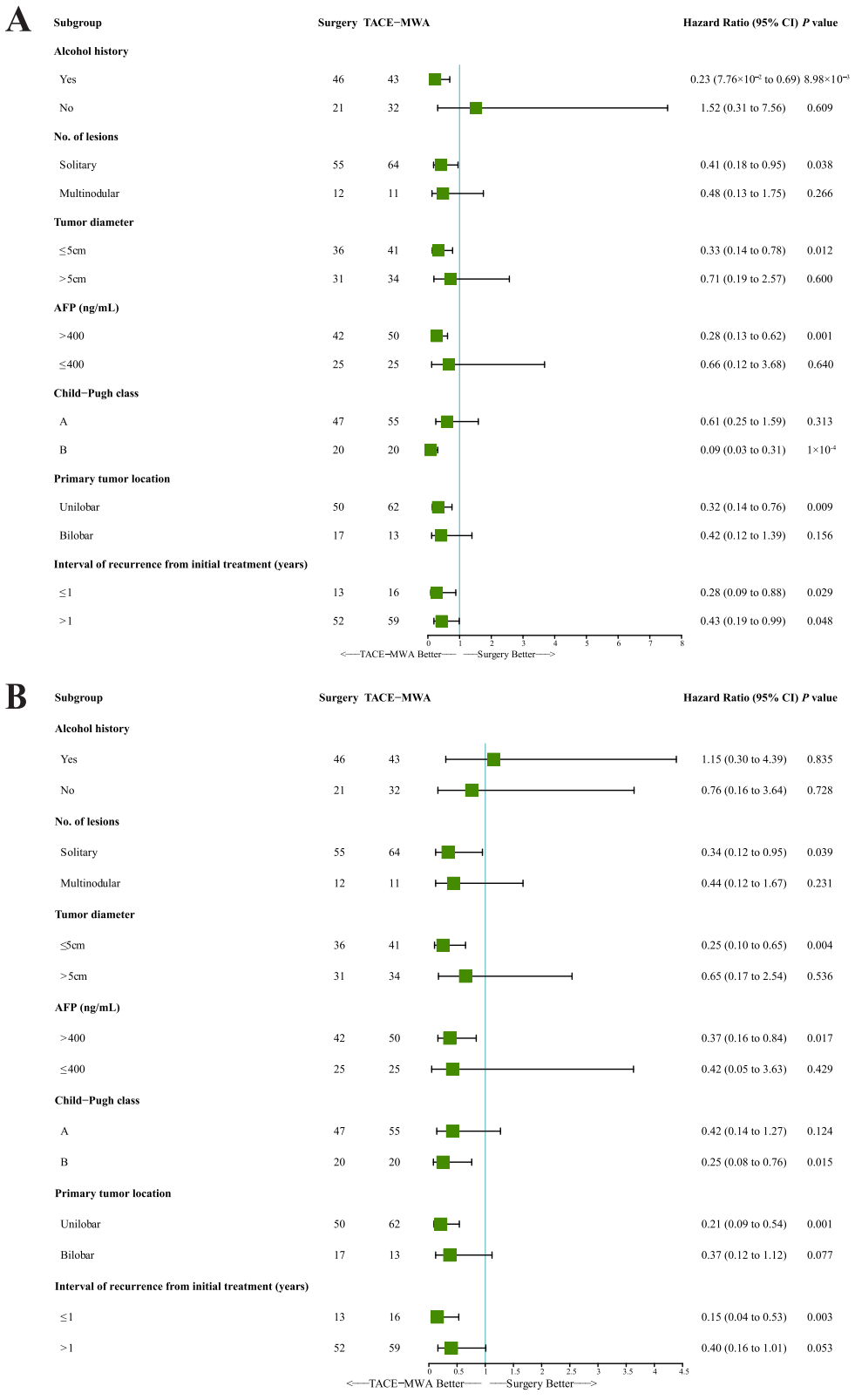

Figure 3 Subgroup analysis. (**A**) Disease-free survival (DFS) for subgroups by treatment modality. (**B**) Overall survival (OS) for subgroups by treatment modality.
Abbreviations: MWA, microwave ablation; TACE, transarterial chemoembolization.

Table 4 Adverse Events After IPTW Adjustment

Variable	Surgery (n = 67)	TACE-MWA (n = 75)	*P* value
Total	59 (88.1)	64 (85.3)	0.818
Grade 3 or 4	10 (14.9)	4 (5.3)	0.103
Ascites			
Grade 1 or 2	3 (4.5)	2 (2.7)	0.667
Grade 3 or 4	2 (3.0)	2 (2.7)	0.735
Anorexia			
Grade 1 or 2	30 (44.8)	38 (50.6)	0.594
Nausea			
Grade 1 or 2	17 (25.4)	23 (30.7)	0.608
Vomiting			
Grade 1 or 2	16 (23.8)	15 (20.0)	0.722
Pain			
Grade 1 or 2	38 (56.7)	28 (37.3)	0.032
Grade 3 or 4	8 (11.9)	2 (5.3)	0.046
Fever			
Grade 1 or 2	29 (43.3)	17 (22.7)	0.015
Liver failure	3 (4.5)	1 (1.3)	0.622
Hospital days	12 (9–22)	7 (5–10)	0.001

Abbreviations: MWA, microwave ablation; TACE, transarterial chemoembolization.

hospitalization duration, patients under the surgical group exhibited a substantially longer stay in comparison to those undergoing TACE-MWA group (P= 0.001).

Discussion

The recurrence of HCC is a critical therapeutic failure for patients undergone surgical resection.[22,23] Diverse therapeutic approaches have been utilized in addressing recurrent intrahepatic tumors, such as TACE, TACE-MWA, and targeted drug. Whereas there exists no documented comparative analysis concerning surgical intervention versus TACE-MWA for elderly patients with recurrent 3.1 cm≤ HCC ≤ 7 cm.

In our study, we discovered that the blend of TACE and MWA proved to be more effective in managing disease progression and overall survival for intrahepatic recurrent 3.1 cm≤ HCC ≤ 7 cm after hepatectomy. This result mirrored the advantages of combining TACE and MWA over surgical treatment in terms of their principal therapeutic mechanisms. Researchers have found that implementing an arterial perfusion occlusion strategy for HCC can enhance the efficacy of ablation therapy.[24] After TACE treatment, the pressure within hepatocellular carcinoma nodules is significantly reduced to a sluggish perfusion state, but this does not lead to a substantial decrease in blood flow supply to the surrounding healthy hepatic tissue. Regarding this occurrence, the amount of heat lost is almost non-existent, and the unaltered or possibly increased blood flow in the nearby healthy liver tissue can effectively block the spread of heat beyond the HCC nodule. Histopathological analysis after RFA treatment on HCC nodules subsequent to arterial blockade disclosed that nodules below 5 cm in diameter exhibited complete necrosis, whereas in a nodule of 5.2 cm diameter, necrosis levels were detected to exceed 90%.[25] Meanwhile, in clinical practice, researchers reported that TACE in conjunction with RFA could cause necrotic areas up to 7 cm in diameter in one tumor lesion.[26] Additionally, TACE facilitates the detection and management of microsatellite nodules, while thermotherapy concurrently enhances the efficacy of chemotherapeutic agents. Although RFA and MWA have comparable safety and efficacy in the treatment of HCC patients with lesions ≤3 cm,[27–29] MWA offers specific technical benefits in reducing the heat sink effect and

achieving quicker ablation.[30,31] Therefore, for 3.1 cm≤ HCC ≤ 7 cm, combination of TACE and MWA has higher DFS and OS.

The combination of TACE and MWA has been shown to be particularly advantageous in specific subgroups of patients with HCC. Patients with a history of alcohol use often have underlying liver disease (eg, alcoholic cirrhosis), which can complicate treatment and limit surgical options. Liver function preservation is key in this group, as the combination of TACE and MWA can effectively control the tumor while reducing the burden on the remaining liver tissue compared to more invasive approaches. Tumor size is a critical factor in HCC treatment. Tumors ≤5 cm are more likely to be fully ablated with MWA, while TACE enhances this by reducing the blood supply and making the ablation more effective. Some studies suggest that the outcomes for TACE+MWA in this subgroup may approach those of surgical resection. High AFP levels (>400 ng/mL) are often associated with more aggressive disease and poorer prognosis. In patients with high AFP levels, TACE+MWA can provide an advantage by offering dual therapy that targets both tumor growth (via embolization) and tumor destruction (via ablation), potentially reducing the tumor burden more effectively than either modality alone. Therefore, TACE+MWA can offer good short- to medium-term tumor control also, particularly in those who are not candidates for curative treatments like resection or transplantation.

Notably, prior studies have reported a range for the 5-year DFS (29.6–41.4%), as well as a 5-year OS (33–52%) within the TACE-RFA group.[32,33] In comparison to earlier studies, our results have proven to be superior. Potential explanations for this finding could be fewer lesions, more patients with early primary tumor stages, and unidentified factors in our treatment groups that could be linked to the biological traits of the host or tumor, ultimately decreasing the chances of recurrence and metastasis. When contrasted with TACE-MWA, surgery was connected with higher rates of Grade 3 to 4 pain after treatment. Although this complication was manageable, these adverse events might increase the risk of unplanned hospitalization, leading to a prolonged hospital day.

This study has several limitations. First, while patient demographics and tumor traits were evenly distributed between the two treatment groups in this study, it must be acknowledged the inherent flaws associated with the retrospective nature of the research. Second, this study's sample size is relatively diminutive, potentially compromising its statistical power. Third, the lack of information of elderly patients with primary medium or large the HCC, which did not reflect integrally the landscape of elderly patients with 3.1 cm≤ HCC ≤ 7 cm.

The combination of TACE and MWA holds great potential for recurrent HCC in patients over 70 years of age. In the future, we can expect this approach to become more refined, such as integrated with newer systemic therapies such as immunotherapy, by addressing several knowledge gaps through well-designed clinical trials, real-world evidence, and multidisciplinary collaboration that will significantly advance the field.

Conclusion

In summary, TACE-MWA provides excellent DFS and OS for patients with recurrent medium or large HCC. TACE-MWA and surgery can both be considered as first-line options for elderly patients with intrahepatic recurrent HCC following hepatectomy, while TACE-MWA should be preferred over surgery for elderly patients with recurrent 3.1 cm≤ HCC ≤ 7 cm.

Acknowledgments

The authors thank all the colleagues who contributed toward this work.

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.

Funding

This research received no external funding.

Disclosure

There are no conflicts of interest.

References

1. Bruix J, Sherman M. American association for the study of liver D. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53(3):1020–1022. doi:10.1002/hep.24199
2. Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg*. 2006;243(3):321–328. doi:10.1097/01.sla.0000201480.65519.b8
3. Imamura H, Matsuyama Y, Tanaka E, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol*. 2003;38(2):200–207. doi:10.1016/S0168-8278(02)00360-4
4. Rizzo A, Mollica V, Tateo V, et al. Hypertransaminasemia in cancer patients receiving immunotherapy and immune-based combinations: the MOUSEION-05 study. *Cancer Immunol Immunother*. 2023;72:1381–1394. doi:10.1007/s00262-023-03366-x
5. Dall'Olio FG, Rizzo A, Mollica V, et al. Immortal time bias in the association between toxicity and response for immune checkpoint inhibitors: a meta-analysis. *Immunotherapy*. 2021;13(3):257–270. doi:10.2217/imt-2020-0179
6. Rizzo A, Ricci AD, Brandi G. Immune-based combinations for advanced hepatocellular carcinoma: shaping the direction of first-line therapy. *Future Oncol*. 2021;17(7):755–757. doi:10.2217/fon-2020-0986
7. Guven DC, Sahin TK, Erul E, et al. The association between albumin levels and survival in patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Front Mol Biosci*. 2022;9:1039121. doi:10.3389/fmolb.2022.1039121
8. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised Phase 3 non-inferiority trial. *Lancet*. 2018;391(10126):1163–1173. doi:10.1016/S0140-6736(18)30207-1
9. Goseki N, Nosaka T, Endo M, et al. Nourishment of hepatocellular carcinoma cells through the portal blood flow with and without transcatheter arterial embolization. *Cancer*. 1995;76(5):736–742. doi:10.1002/1097-0142(19950901)76:5<736::AID-CNCR2820760505>3.0.CO;2-Q
10. Peng ZW, Zhang YJ, Liang HH, Lin XJ, Guo RP, Chen MS. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial. *Radiology*. 2012;262(2):689–700. doi:10.1148/radiol.11110637
11. Shi F, Lian S, Mai Q, et al. Microwave ablation after downstaging of hepatocellular carcinoma: outcome was similar to tumor within milan criteria. *Eur Radiol*. 2020;30(5):2454–2462. doi:10.1007/s00330-019-06604-y
12. Wang C, Liao Y, Qiu J, et al. Transcatheter arterial chemoembolization alone or combined with ablation for recurrent intermediate-stage hepatocellular carcinoma: a propensity score matching study. *J Cancer Res Clin Oncol*. 2020;146(10):2669–2680. doi:10.1007/s00432-020-03254-2
13. Koh PS, Chan AC, Cheung TT, et al. Efficacy of radiofrequency ablation compared with transarterial chemoembolization for the treatment of recurrent hepatocellular carcinoma: a comparative survival analysis. *HPB (Oxford)*. 2016;18(1):72–78. doi:10.1016/j.hpb.2015.07.005
14. Song Q, Ren W, Fan L, et al. Long-term outcomes of transarterial chemoembolization combined with radiofrequency ablation versus transarterial chemoembolization alone for recurrent hepatocellular carcinoma after surgical resection. *Dig Dis Sci*. 2020;65(4):1266–1275. doi:10.1007/s10620-019-05733-0
15. Song KD, Lim HK, Rhim H, et al. Repeated hepatic resection versus radiofrequency ablation for recurrent hepatocellular carcinoma after hepatic resection: a propensity score matching study. *Radiology*. 2015;275(2):599–608. doi:10.1148/radiol.14141568
16. Peng Z, Wei M, Chen S, et al. Combined transcatheter arterial chemoembolization and radiofrequency ablation versus hepatectomy for recurrent hepatocellular carcinoma after initial surgery: a propensity score matching study. *Eur Radiol*. 2018;28(8):3522–3531. doi:10.1007/s00330-017-5166-4
17. Zheng X, Ren Y, Hu H, Qian K. Transarterial chemoembolization combined with radiofrequency ablation versus repeat hepatectomy for recurrent hepatocellular carcinoma after curative resection: a 10-year single-center comparative study. *Front Oncol*. 2021;11:713432. doi:10.3389/fonc.2021.713432
18. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol a Biol Sci Med Sci*. 2001;56(3):M146–156. doi:10.1093/gerona/56.3.M146
19. Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. *J Am Geriatr Soc*. 2010;58(4):681–687. doi:10.1111/j.1532-5415.2010.02764.x
20. Bruix J, Sherman M. Practice guidelines committee AAftSoLD. Management of hepatocellular carcinoma. *Hepatology*. 2005;42(5):1208–1236. doi:10.1002/hep.20933
21. Ripatti S, Palmgren J. Estimation of multivariate frailty models using penalized partial likelihood. *Biometrics*. 2000;56(4):1016–1022. doi:10.1111/j.0006-341X.2000.01016.x
22. Poon RT, Fan ST, Lo CM, et al. Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. *Ann Surg*. 2001;234(1):63–70. doi:10.1097/00000658-200107000-00010
23. Minagawa M, Makuuchi M, Takayama T, Kokudo N. Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. *Ann Surg*. 2003;238(5):703–710. doi:10.1097/01.sla.0000094549.11754.e6
24. Rossi S, Buscarini E, Garbagnati F, et al. Percutaneous treatment of small hepatic tumors by an expandable RF needle electrode. *AJR Am J Roentgenol*. 1998;170(4):1015–1022. doi:10.2214/ajr.170.4.9530052
25. Goldberg SN, Solbiati L, Hahn PF, et al. Large-volume tissue ablation with radio frequency by using a clustered, internally cooled electrode technique: laboratory and clinical experience in liver metastases. *Radiology*. 1998;209(2):371–379. doi:10.1148/radiology.209.2.9807561
26. Peng ZW, Zhang YJ, Chen MS, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. *J Clin Oncol*. 2013;31(4):426–432. doi:10.1200/JCO.2012.42.9936
27. Vietti Violi N, Duran R, Guiu B, et al. Efficacy of microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma in patients with chronic liver disease: a randomised controlled Phase 2 trial. *Lancet Gastroenterol Hepatol*. 2018;3(5):317–325. doi:10.1016/S2468-1253(18)30029-3

28. Kamal A, Elmoety AAA, Rostom YAM, Shater MS, Lashen SA. Percutaneous radiofrequency versus microwave ablation for management of hepatocellular carcinoma: a randomized controlled trial. *J Gastrointest Oncol*. 2019;10(3):562–571. doi:10.21037/jgo.2019.01.34
29. Abdelaziz A, Elbaz T, Shousha HI, et al. Efficacy and survival analysis of percutaneous radiofrequency versus microwave ablation for hepatocellular carcinoma: an Egyptian multidisciplinary clinic experience. *Surg Endosc*. 2014;28(12):3429–3434. doi:10.1007/s00464-014-3617-4
30. Kalra N, Gupta P, Gorsi U, et al. Irreversible electroporation for unresectable hepatocellular carcinoma: initial experience. *Cardiovasc Intervent Radiol*. 2019;42(4):584–590. doi:10.1007/s00270-019-02164-2
31. Gupta P, Maralakunte M, Kumar MP, et al. Overall survival and local recurrence following RFA, MWA, and cryoablation of very early and early HCC: a systematic review and Bayesian network meta-analysis. *Eur Radiol*. 2021;31(7):5400–5408. doi:10.1007/s00330-020-07610-1
32. Zhang YJ, Chen MS, Chen Y, Lau WY, Peng Z. Long-term outcomes of transcatheter arterial chemoembolization combined with radiofrequency ablation as an initial treatment for early-stage hepatocellular carcinoma. *JAMA Network Open*. 2021;4(9):e2126992. doi:10.1001/jamanetworkopen.2021.26992
33. Shi F, Wu M, Lian SS, et al. Radiofrequency ablation following downstaging of hepatocellular carcinoma by using transarterial chemoembolization: long-term outcomes. *Radiology*. 2019;293(3):707–715. doi:10.1148/radiol.2019181991