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ORIGINAL RESEARCH

Hepatic Arterial Infusion Chemotherapy vs Transcatheter Arterial Chemoembolization as Adjuvant Therapy Following Surgery for MVI-Positive Hepatocellular Carcinoma: A Multicenter Propensity Score Matching Analysis

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Background: Microvascular invasion (MVI) is a significant pathological feature in hepatocellular carcinoma (HCC), adjuvant hepatic arterial infusion chemotherapy (a-HAIC) and adjuvant transcatheter arterial chemoembolization (a-TACE), are commonly used for HCC patients with MVI. This study aims to evaluate the efficacies of two adjuvant therapies after surgical treatment for HCC, compare them, and identify the significant factors.

Methods: Clinical data from two randomized controlled trials involving HCC patients with MVI after surgical treatment were retrospectively reviewed. Propensity score matching (PSM) analysis was performed to balance baseline differences between patients who received a-HAIC or a-TACE, and control groups who underwent hepatectomy alone. Disease-free survival (DFS) and overall survival (OS) rates were compared.

Results: In total of 549 patients were collected from two randomized controlled trials. Using the PSM and Kaplan-Meier method, the median DFS of the a-HAIC, a-TACE, and control groups was 63.2, 21.7, and 11.2 months ($P<0.05$). The a-HAIC group show significantly better 1-, 3-, and 5-year OS rates compared to the a-TACE and control groups (96.3%, 80.0%, 72.8% vs 84.4%, 57.0%, 29.8% vs 84.5%, 62.8%, 53.4%, P<0.05). But the OS rates of a-TACE and control groups showed no significant difference ($P=0.279$). Multivariate analysis identified a-HAIC (HR=0.449, $P=0.000$) and a-TACE (HR=0.633, $P=0.007$) as independent protective factors. For OS, a-HAIC (HR=0.388, $P=0.003$) was identified as an independent protective factor, too.

Conclusion: Compared to a-TACE and the control group, a-HAIC demonstrated greater benefits in preventing tumor recurrence and improving survival in HCC patients with MVI.

Keywords: hepatocellular carcinoma, microvascular invasion, adjuvant transcatheter arterial chemoembolization, adjuvant hepatic arterial infusion chemotherapy

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignant tumors in China and ranks among the top five causes of tumor-related death in over 90 countries worldwide. It is predicted that its incidence and mortality will continue to rise in the next 20 years.[1] HCC typically arises from chronic hepatitis, regardless of the presence of cirrhosis, with common underlying factors including chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, alcohol

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consumption, exposure to aflatoxin, and non-alcoholic fatty liver disease, etc.[2–6] Currently, there are various treatment options available for HCC. Early-stage HCC can be treated with curative intent using surgical resection, local ablation therapy, or liver transplantation (LT).[6] However, liver transplantation is limited by the scarcity of donor organs, high costs, and stringent criteria for eligibility. Local ablation therapy has its limitations in terms of treatment scope, thus restricting its applicability. Surgical resection remains the primary curative treatment option.[7]

Nonetheless, the five-year recurrence rate in HCC patients after surgical resection remains unacceptably high, reaching up to 70%.[8] Important high-risk factors contributing to the high recurrence rate following surgery have been identified in numerous studies, include tumor size greater than 5 cm, narrow surgical margins (<1cm), multiple lesions, low tumor differentiation, and microvascular invasion (MVI).[9–12] Therefore, finding ways to reduce the recurrence rate after resection and effectively improve patients' prognosis has become an urgent problem. Although many guidelines do not recommend any adjuvant therapy, studies initiated by researchers have shown that certain adjuvant therapies can effectively prolong the progression-free survival (PFS) or overall survival (OS) of HCC patients who undergo curative treatment. These therapies include adjuvant autologous cytokine-induced immune killing therapy,[13] systemic chemotherapy,[14] postoperative radiotherapy,[15] etc. In our previous Phase III RCT study, we found that adjuvant transcatheter arterial chemoembolization (a-TACE) can improve the disease-free survival (DFS) and OS of HCC patients after surgical resection with a tumor diameter ≥5cm and positive microvascular invasion (MVI).[16] Wang et al also validated that a-TACE can significantly improve DFS and OS in HBV-related HCC patients with a medium-to-high risk of recurrence after surgery.[17] Although a-TACE provided survival benefits in high-risk HCC patients after surgery, complications associated with embolization limited its application.

The emergence of hepatic arterial infusion chemotherapy (HAIC) has brought a new hope for HCC patients. The EACH study confirmed the value of the FOLFOX regimen as systemic chemotherapy for advanced HCC.[18] A Phase II clinical trial initiated by Lai et al demonstrated that the combination therapy of lenvatinib, toripalimab, and HAIC improved the survival prognosis of advanced HCC patients with high-risk factors.[19] In a retrospective study by Lyu et al, HAIC was found to offer greater survival benefits to advanced HCC patients compared to sorafenib.[20] Recognizing the potential value of HAIC, we initiated a multicenter, prospective phase III RCT study to explore the significance of adjuvant HAIC (a-HAIC) in MVI-positive patients after surgery. The study verified that a-HAIC can significantly improve the DFS of MVI-positive patients after surgery while effectively managing toxicity and side effects.[21]

An article utilizing network meta-analysis (NMA) to compare the efficacy of adjuvant therapies suggested that HAIC and internal radiotherapy (IRT) were the most effective methods.[22] However, there is currently no consensus on which adjuvant therapy, a-TACE or a-HAIC, provides greater survival benefits to patients Therefore, this article utilizes real data from our own RCT study for propensity score matching (PSM) to compare the efficacy of the two adjuvant therapies and their impact on the type and timing of postoperative recurrence in patients.

Methods

Patients

This retrospectively study reviewed patients' data from two different randomized controlled trials, which were both aimed to find the optimal adjuvant therapy for HCC patients with MVI positive. The protocol and all modification have been approved by the Institutional review board and Ethics Committee of SUN YAT-SEN University Cancer Center (No. B2017-006). The study followed the Declaration of Helsinki and the Good Clinical Practice Guidelines. All participants provided written informed consents. We collected the medical record of 116 patients underwent a-TACE and 118 patients with hepatectomy alone between June, 2009 and December, 2012 (trial number: NCT02788526). And 157 patients underwent a-HAIC and 158 patients with hepatectomy alone between June, 2016 and August 2021 (trial number: NCT03192618). The eligibility criteria for inclusion of patients underwent a-TACE were as follows: 18–75 years of age; histologically confirmed HCC with MVI; Eastern Cooperative Oncology Group performance score (ECOG PS) ≤ 2; no previous treatment for HCC; solid tumor ≥ 5 cm before surgery confirmed by 2 radiological examinations (ultrasonography with computer tomography or magnetic resonance imaging); R0 resection; no evidence of recurrence at radiological follow-up (3–5 weeks after surgery); adequate hematologic, hepatic, and renal functions. The eligibility

criteria for inclusion of patients underwent a-HAIC were as follows: 18–75 years of age; histologically confirmed HCC with MVI; ECOG PS≤ 2; no previous treatment for HCC; absence of recurrence at radiological follow-up (4–6 weeks after surgery); and adequate hematologic, hepatic, and renal functions. The exclusion criteria are basically the same, included histologically positive resection margin (R1 resection); with macrovascular invasion and extrahepatic metastasis before surgery; severe functional impairment of organs (heart, brain, lung, kidney, and liver); active uncontrolled infection; allergy to related drugs or intolerance to HAIC or TACE; previous or concomitant antitumor therapy; and a history of organ transplantation, neurologic, or psychiatric diseases, human immunodeficiency virus infection, esophageal or gastric variceal bleeding, hepatic encephalopathy, or cardio-cerebrovascular events. The main differences of inclusion criteria of the two RCT studies are age, Albumin-Bilirubin Index (ALBI), tumor diameter and resection margin. The details can be seen in Table 1.

Table 1 The Baseline Characteristics of All HCC Patients with MVI Among Different Type of Treatments Before and After PSM

Variable	Before PSM				After PSM			
	HAIC	TACE	Control	P	a-HAIC	a-TACE	Control	P
n	157	116	276		86	77	163	
Gender (%)				0.167				0.536
Male	136 (86.6)	109 (94.0)	242 (87.7)		75 (87.2)	71 (92.2)	143 (87.7)	
Female	21 (13.4)	7 (6.0)	34 (12.3)		11 (12.8)	6 (7.8)	20 (12.3)	
Age (%)				0.016				0.077
≤65	141 (89.8)	112 (96.6)	243 (88.0)		76 (88.4)	74 (96.1)	142 (87.1)	
>65	16 (10.2)	4 (3.4)	33 (12.0)		10 (11.6)	3 (3.9)	21 (12.9)	
HBsAg (%)				0.835				0.537
Negative	20 (12.7)	14 (12.1)	39 (14.1)		12 (14.0)	9 (11.7)	28 (17.2)	
Positive	137 (87.3)	102 (87.9)	237 (85.9)		74 (86.0)	68 (88.3)	135 (82.8)	
ALT (%)				0.138				1.000
≤40	101 (64.3)	61 (52.6)	159 (57.6)		50 (58.1)	45 (58.4)	96 (58.9)	
>40	56 (35.7)	55 (47.4)	117 (42.4)		36 (41.9)	32 (41.6)	67 (41.1)	
Tbil (%)				0.229				0.339
≤20.5	142 (90.4)	102 (87.9)	234 (84.8)		78 (90.7)	68 (88.3)	137 (84.0)	
>20.5	15 (9.6)	14 (12.1)	42 (15.2)		8 (9.3)	9 (11.7)	26 (16.0)	
ALBI (%)				0.032				0.309
I	127 (80.9)	81 (69.8)	224 (81.2)		74 (86.0)	59 (76.6)	133 (81.6)	
II	30 (19.1)	35 (30.2)	52 (18.8)		12 (14.0)	18 (23.4)	30 (18.4)	
AFP (%)				0.354				0.354
≤400	88 (56.1)	57 (49.1)	157 (56.9)		52 (60.5)	38 (49.4)	92 (56.4)	
>400	69 (43.9)	59 (50.9)	119 (43.1)		34 (39.5)	39 (50.6)	71 (43.6)	
Tumor diameter (cm)				0.016				1.000
<10	132 (84.1)	83 (71.6)	225 (81.5)		76 (88.4)	62 (80.5)	136 (83.4)	
≥10	25 (15.9)	33 (28.4)	51 (18.5)		10 (11.6)	15 (19.5)	27 (16.6)	
Cirrhosis (%)				0.059				0.703
Absent	78 (49.7)	72 (62.1)	112 (40.6)		40 (46.5)	41 (53.2)	81 (49.7)	
Present	79 (50.3)	44 (37.9)	164 (59.4)		46 (53.5)	36 (46.8)	82 (50.3)	
Resection margin (cm)				<0.001				0.626
<1	25 (15.9)	49 (42.2)	127 (46.0)		22 (25.6)	25 (32.5)	47 (28.8)	
≥1	132 (84.1)	67 (57.8)	149 (54.0)		64 (74.4)	52 (67.5)	116 (71.2)	
Child-Pugh grade				0.513				0.498
A	155 (98.7)	116 (100.0)	272 (98.6)		85 (98.8)	76 (100.0)	163 (100.0)	
B	2 (1.3)	0 (0.0)	4 (1.4)		1 (1.2)	0 (0.0)	0 (0.0)	

(*Continued*)

Table 1 (Continued).

Variable	Before PSM				After PSM			
	HAIC	TACE	Control	P	a-HAIC	a-TACE	Control	P
Time to recurrence (months)								
≤24	63 (40.1)	65 (56.0)	165 (59.8)	<0.001	31 (36.0)	39 (50.6)	99 (60.7)	0.001
>24	6 (3.8)	21 (18.1)	15 (5.4)	<0.001	4 (4.7)	16 (20.8)	9 (5.5)	<0.001
Patterns of tumor recurrence								
Intrahepatic	55 (35.0)	75 (64.7)	148 (53.6)	<0.001	28 (32.6)	45 (58.4)	89 (54.6)	0.001
Extrahepatic	28 (17.8)	23 (19.8)	61 (22.1)	0.562	17 (19.8)	14 (18.2)	38 (23.3)	0.618

Notes: Bold values indicate statistical significance ($P < 0.05$).

Abbreviations: HCC, hepatocellular carcinoma; PSM, propensity score matching; a-HAIC, adjuvant hepatic artery infusion chemotherapy; a-TACE, adjuvant transcatheter arterial chemoembolization; HBsAg, hepatitis B surface antigen; ALT, alanine aminotransferase; TBIL, total serum bilirubin; ALBI, Albumin-Bilirubin; AFP, alpha-fetoprotein.

Preoperative Investigations and Liver Resection

All patients included in the study underwent a comprehensive evaluation within 1 week after enrollment, including demographic characteristics, medical history, physical examination, routine blood analysis (hematology, biochemistry, and tumor markers), and radiological examination (computed tomography or magnetic resonance imaging). Patients with evidence of recurrence during screening were excluded. The specific steps of HCC resection surgery have been described in detail in previous studies, and the three different groups were using the same resection way.[23] In brief, a careful routine abdominal exploration was performed to evaluate the extent of the tumor and exclude extrahepatic metastasis. After adequate mobilization of the liver, intraoperative ultrasound (ALOKA SSD-5500, Tokyo, Japan) was used to evaluate the number and size of lesions, the presence of MVI, and the extent of resection. During tumor resection, Cavitron ultrasonic surgical aspirator (Integra LifeSciences CUSA Excel, Plainsboro, NJ, USA) was used to separate liver parenchyma and ligate relevant vessels. The Pringle maneuver was also used to occlude blood inflow into the liver.

Adjuvant TACE

In the a-TACE group, conventional TACE was performed 4–6 weeks after surgery based on the patient's liver function and performance status, and the specific steps were implemented according to the previously described technique.[24] In brief, a catheter was inserted into the hepatic artery through the femoral artery using Seldinger technique for hepatic artery angiography, and 200 mg/m2 carboplatin (Carboplatin, Bristol-Myers Squibb, New York, NY, USA) and 6 mg/m2 mitomycin (Mitomycin, Hisun, Taizhou, China) were administered followed by injection of 4–5 mL of iodized oil emulsion (lipiodol, Andre Guerbet, Aulnay-sous-Bois, France) and 40 mg/m2 epirubicin hydrochloride (Epirubicin Hydrochloride, Pfizer, New York, NY, USA). These patients underwent comprehensive evaluation including physical examination, routine blood analysis and CT scan approximately one month later. The second cycle of TACE or HAIC was performed according to the decision of investigators based on the patients' conditions and the assessment results.

Adjuvant HAIC

HAIC procedure was performed as per previously reported studies[20]. After successful percutaneous femoral artery puncture and catheterization, superior mesenteric arteriography and hepatic arteriography were performed. After confirming that the patients absent of residual tumor, the hepatic artery was intubated to the predetermined position, and patients with indwelling catheter were shifted to the ward. Any implanted port system was not applied. The catheter was connected to the injection pump in the ward, and the following chemotherapeutic agents were continuously pumped: oxaliplatin, 85 mg/m2 from 0 to 3 hours once on day 1; leucovorin, 400 mg/m2 from 3 to 4.5 hours once on day 1; fluorouracil, 400 mg/m2 from 4.5 to 6.5 hours once on day 1; and fluorouracil, 2400 mg/m2 once over 46 hours from days 1 to 3. The patient was bedridden during chemotherapy. When chemotherapy ended, the catheter was pulled out, and the patient was discharged after complete hemostasis at the puncture site. The time interval between two cycles of HAIC was set at 4–5 weeks.

Postoperative Follow-Up

The follow-up interval for patients was 2–3 months. All patients diagnosed with chronic hepatitis B virus or hepatitis B surface antigen-positive need to take antiviral drugs. The tests required for follow-up include physical examination, routine blood analysis (serum levels of alpha-fetoprotein and liver function), and enhanced abdominal CT or MRI scans. Once suspicious recurrence/metastasis is found, further examinations are performed, including hepatic artery angiography or biopsy. EASL confirms recurrence or metastasis based on cytological or histological evidence, as well as non-invasive diagnostic criteria utilizing the ACR LI-RADS system for HCC.[25] The follow-up deadline for RCT studies of adjuvant TACE was March 31, 2016, and OS was not obtained for RCT studies of adjuvant HAIC, so their follow-up data was updated in this study. The median follow-up duration was 34.2 months for all patients, 30.9 months for patients who received adjuvant HAIC, 50.4 months for patients who received adjuvant TACE, and 37.0 months for the control group before and after PSM. The primary observation result is disease-free survival (DFS), which is defined as interval between random assignment and first documented diagnosis of HCC recurrence or death due to all causes depending on which occurred first. We used two years as the cutoff between early and late recurrence.[26] The secondary observation result is overall survival (OS), which refers the interval from initiation of treatment to the time when death occurs for any reason.

Statistical Analysis

Continuous variables are described as median (interquartile range, IQR) unless otherwise specified. Categorical variables are expressed as frequency and percentage. The statistical comparison of categorical variables and continuous variables was performed using chi-square test or Fisher's exact test and Mann–Whitney *U*-test, respectively. Survival estimates were calculated using the Kaplan-Meier method and compared using the Log rank test. Cox proportional hazards models were used to determine factors affecting independent prognosis of DFS and OS. Propensity score matching (PSM) was used to adjust for differences in baseline characteristics between a-TACE and a-HAIC group. Variables entered into the propensity model included age, ALBI, cirrhosis, maximum tumor diameter, tumor number, resection margin. 1:1 nearest neighbor matching method was used for matching between groups within 0.2 standard deviation range. And the same PSM method will be used to match the baseline characteristics of patients between adjuvant treatment group and hepatectomy alone group. The flow chart of PSM is shown in Figure 1. In order to determine which population of patients could benefit from a-HAIC or a-TACE and to evaluate which treatment option is superior, subgroup analysis was conducted. A quantitative risk score was assigned to each factor that showed significance in the multivariate analysis of DFS and OS (Table 2), which called TTAA score (including

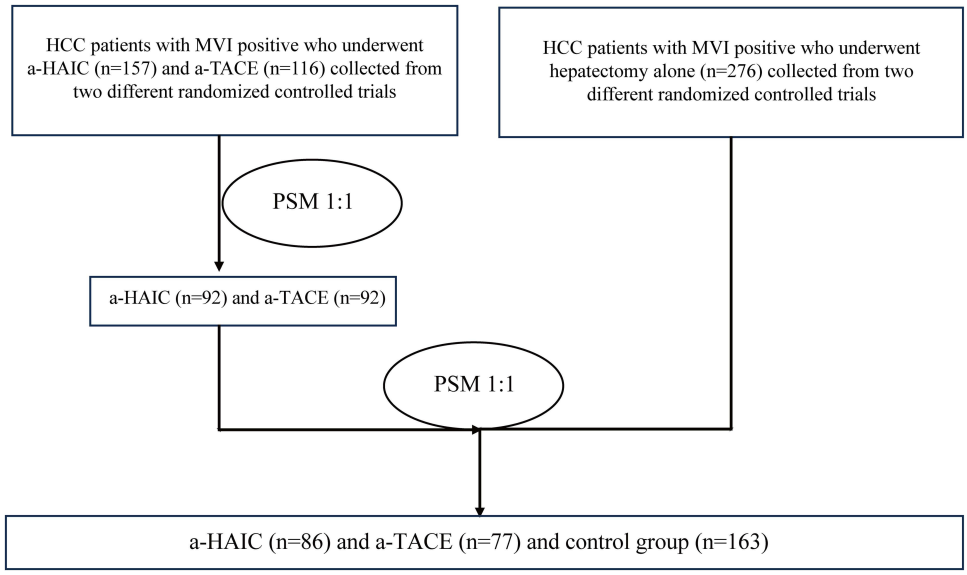

Figure 1 Flow chart of our study.
Abbreviations: HCC, hepatocellular carcinoma; a-HAIC, adjuvant hepatic artery infusion chemotherapy; a-TACE, adjuvant transcatheter arterial chemoembolization; MVI, microvascular invasion; PSM, propensity score matching.

Table 2 Univariate and Multivariate Analysis for DFS and OS in HCC Patients with MVI in Adjuvant Treatment and Control Group After PSM

Cohort	Variables	DFS						OS					
		Univariate	95% CI	P	Multivariate	95% CI	P	Univariate	95% CI	P	Multivariate	95% CI	P
		HR			HR			HR			HR		
After PSM (n=326)	Gender (Male/Female)	0.833	0.519–1.338	0.451				1.215	0.680–2.171	0.510			
	Age (>/≤ 65 years)	0.998	0.988–1.010	0.846				0.835	0.447–1.560	0.572			
	HBsAg (Absent/Present)	1.249	0.820–1.900	0.300				0.943	0.561–1.584	0.824			
	Tumor diameter (</≥10cm)	1.507	1.071–2.120	0.019	1.349	0.951–1.911	0.093	2.249	1.460–3.466	0.000	1.993	1.286–3.090	0.002
	Resection margin (>/≤ 1cm)	0.950	0.700–1.290	0.740				0.886	0.591–1.328	0.558			
	ALBI (grade I/II)	1.615	1.155–2.260	0.005	1.695	1.194–2.406	0.003	1.655	1.050–2.609	0.030	1.368	0.862–2.170	0.184
	AFP (>/≤400 ng/mL)	1.422	1.075–1.881	0.014	1.502	1.134–1.989	0.005	1.227	0.838–1.799	0.293			
	Cirrhosis (Absent/Present)	1.314	0.993–1.739	0.056				1.236	0.844–1.810	0.275			
	Type of treatment												
	Control												
	a-TACE	0.683	0.491–0.949	0.023	0.633	0.454–0.880	0.007	1.192	0.790–1.797	0.402	1.121	0.743–1.692	0.587
	a-HAIC	0.431	0.294–0.632	0.000	0.449	0.305–0.660	0.000	0.366	0.196–0.684	0.002	0.388	0.207–0.725	0.003

Notes: Bold values indicate statistical significance ($P < 0.05$).

Abbreviations: HCC, hepatocellular carcinoma; PSM, propensity score matching; a-HAIC, adjuvant hepatic artery infusion chemotherapy; a-TACE, adjuvant transcatheter arterial chemoembolization; HBsAg, hepatitis B surface antigen; ALBI, Albumin-Bilirubin; AFP, alpha-fetoprotein; DFS, disease-free survival; OS, overall survival.

Table 3 Risk Score Weight of Factors Which Were Significant in Multivariate Analysis

Variables	Score	
	1	2
Tumor diameter	<10cm	≥10cm
Tumor number	Single	Multiple
ALBI	Grade I	Grade II
AFP	≤400 ng/mL	>400 ng/mL

Abbreviations: ALBI, Albumin-Bilirubin; AFP, alpha-fetoprotein.

tumor diameter, tumor number, ALBI grade, and AFP level) (Table 3). All analyses were two-tailed, and P values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS (version 25.0, IBM, Armonk, New York, USA) and R program (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

The adjusted comparison was conducted on 273 patients, with 116 receiving a-TACE and 157 patients treated with a-HAIC. There were notable differences in baseline characteristics between the two patient groups, including tumor number, tumor diameter, age, ALBI grade, presence of liver cirrhosis, and surgical resection margin. After performing propensity score matching (PSM), there were 92 patients in the a-HAIC group and 92 patients in the a-TACE group, with no significant differences observed between the variables. The unmatched and matched comparison of baseline characteristics for these patients can be found in Supplementary Table 1. The second round of adjusted comparison was performed on 460 patients, 184 receiving adjuvant treatment, compared with 276 patients treated with hepatectomy alone. There were significant differences in baseline characteristics between the two groups of patients for age, ALBI grade, tumor diameter, tumor number and surgical resection margin. After PSM, there was no significant baseline characteristics difference between two adjuvant therapy groups and the control group. Those details are listed in Table 1.

Univariate and multivariate cox regression analyses on survival outcomes

In the entire group including the control group, the results of the univariate and multivariate analysis before PSM are shown in Supplementary Table 2. After PSM, the results of univariate and multivariate regression analysis of DFS and OS are listed in Table 2. The multiple tumor (HR=1.695, *P=0.009*), high ABLI grade (HR=1.695, *P=0.003*), AFP>400ng/mL (HR=1.502, *P=0.005*) were independent risk factors for poor DFS and independent protect factor was a-HAIC (HR=0.449, *P=0.000*) and a-TACE (HR=0.633, *P=0.007*). The independent risk factor for OS was tumor diameter ≥10cm (HR=1.933, *P=0.002*), and independent protect factor was a-HAIC (HR=0.388, *P=0.003*).

Influence of a-HAIC and a-TACE on the DFS and OS of patients before and after PSM

A total of 335 patients with tumor recurrence were identified before conducting propensity score matching (PSM), and among them, 179 patients died. The Kaplan-Meier survival analysis of disease-free survival (DFS) and overall survival (OS) before PSM is presented in Figure 2. Both the a-HAIC and a-TACE groups exhibited significantly improved DFS compared to the control group (median DFS 41.9, 15.9, and 10.0 months, *P<0.05*). The 1-, 3- and 5-year DFS rate for a-HAIC group, a-TACE group and control group were 68.8%, 52.8%, 41.7% and 57.8%, 36.1%, 25.4% and 44.6%, 24.3%, 21.0%, respectively. The 1-, 3- and 5-year OS rate for a-HAIC group, a-TACE group and control group were 95.1%, 83.5%, 78.3% and 87.0%, 52.7%, 31.6% and 81.6%, 63.0%, 45.2%, respectively.

After PSM, a total of 198 patients with tumor recurrence were identified, consisting of 35 patients in the a-HAIC group, 55 patients in the a-TACE group, and 108 patients in the control group. Among them, 107 patients died, including 12 patients in the a-HAIC group, 40 patients in the a-TACE group, and 55 patients in the control group. The Kaplan-Meier survival analysis of DFS and OS for the three groups is displayed in Figure 3. Patients in the a-HAIC group

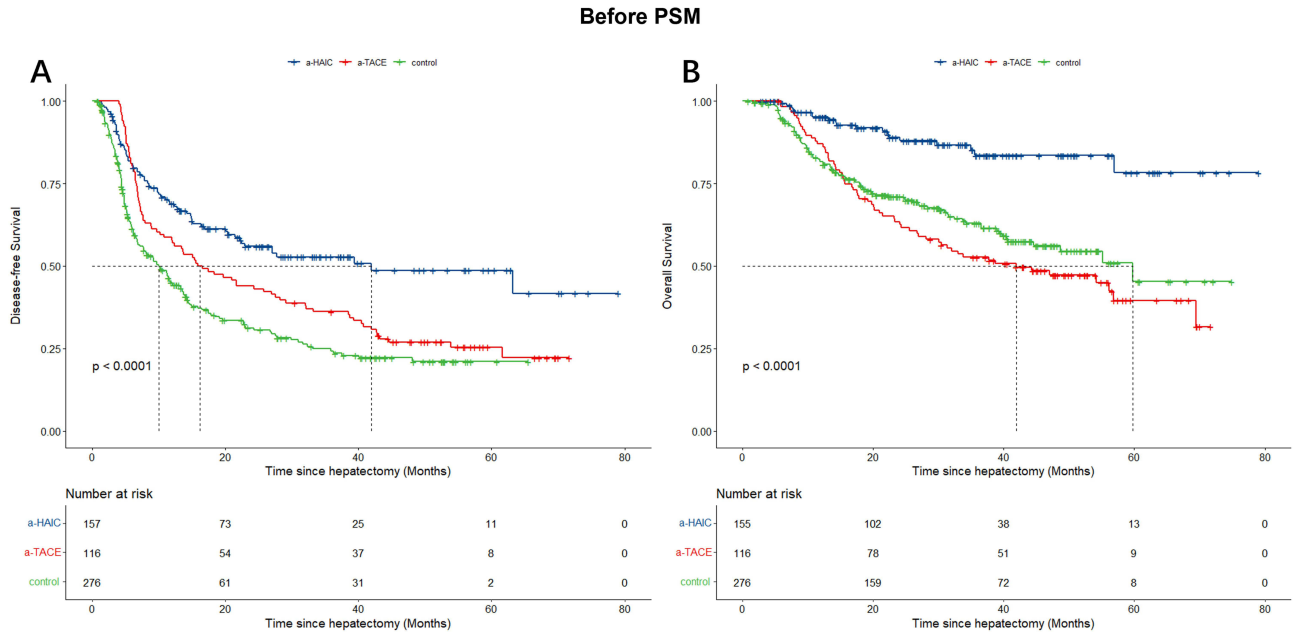

Figure 2 The Kaplan-Meier survival analysis of HCC patients DFS (**A**) and OS (**B**) before PSM between a-HAIC, a-TACE and control group.
Abbreviations: DFS, disease-free survival; OS, overall survival; HCC, hepatocellular carcinoma; a-HAIC, adjuvant hepatic artery infusion chemotherapy; a-TACE, adjuvant transcatheter arterial chemoembolization; PSM, propensity score matching.

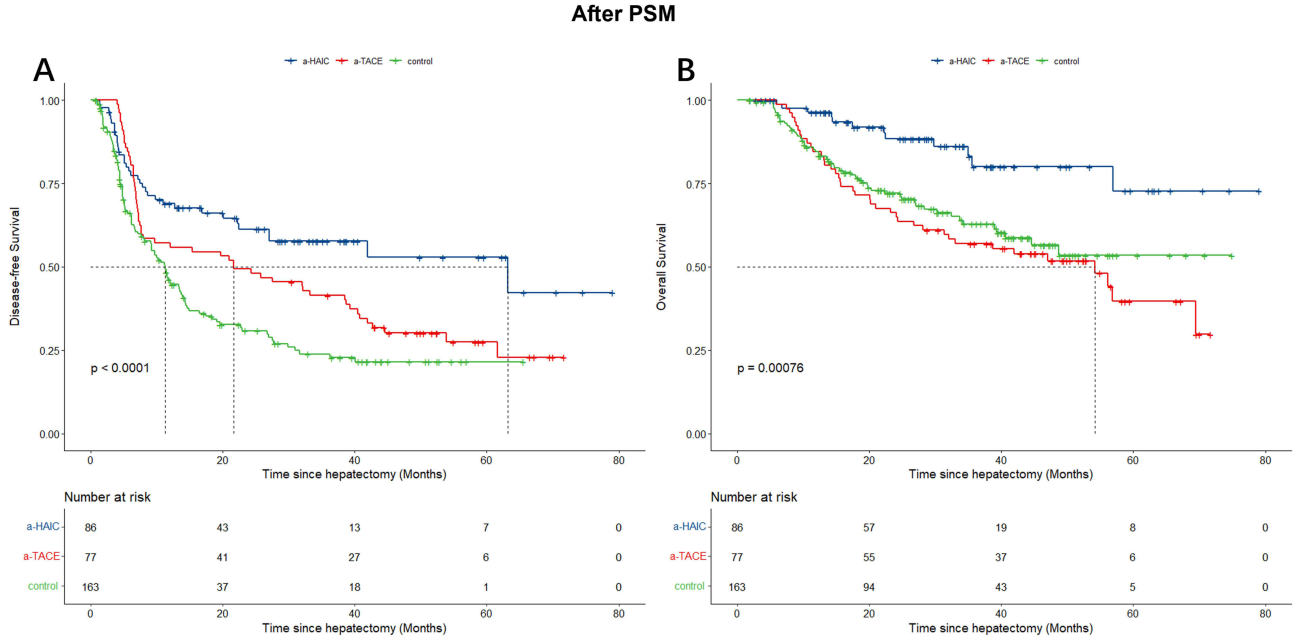

Figure 3 The Kaplan-Meier survival analysis of HCC patients DFS (**A**) and OS (**B**) after PSM between a-HAIC, a-TACE and control group.
Abbreviations: DFS, disease-free survival; OS, overall survival; HCC, hepatocellular carcinoma; a-HAIC, adjuvant hepatic artery infusion chemotherapy; a-TACE, adjuvant transcatheter arterial chemoembolization; PSM, propensity score matching.

exhibited significantly better DFS compared to those in the a-TACE group and the control group (median DFS 63.2 vs 21.7 vs 11.2 months, *P<0.05*). Furthermore, the a-TACE group also showed improved DFS compared to the control group (*P=0.019*). The 1-, 3- and 5- year DFS rate for a-HAIC group, a-TACE group and control group were 68.9%, 57.5%, 42.3% and 57.1%, 41.4%, 22.9% and 45.5%, 22.8%, 21.5%, respectively.

Regarding OS, the a-HAIC group demonstrated a superior survival rate compared to both the a-TACE group and the control group (*P<0.001*), while no significant difference was observed between the a-TACE group and the control group (*P=0.391*). The a-HAIC group exhibited significantly better 1-, 3-, and 5-year OS rates compared to the a-TACE group and the control group (96.3%, 80.0%, 72.8% vs 84.4%, 57.0%, 29.8% vs 84.5%, 62.8%, 53.4%, *P<0.05*).

Impact of a-HAIC and a-TACE on the timings and patterns of tumor recurrence before and after PSM

As shown in Table 1, before PSM, a total of 293 patients with early recurrence (replaced less than two years) were identified. The a-HAIC group demonstrated significantly lower rates of early recurrence compared to both the a-TACE group and the control group (40.1% vs 56.0%, *P=0.000*; 40.1% vs 59.8%, *P=0.000*). Moreover, patients who underwent a-HAIC treatment exhibited significantly lower rates of intrahepatic metastasis when compared to those who underwent a-TACE or hepatectomy alone (35.0% vs 64.7%, *P=0.000*; 35.0% vs 53.6%, *P=0.000*). After conducting PSM, a total of 169 patients with early recurrence were identified. Within the a-HAIC group, the rate of early recurrence was significantly lower than that in the control group (36.0% vs 60.7%, *P=0.000*), although no significant difference was observed when compared to the a-TACE group (36.0% vs 50.6%, *P=0.060*). Furthermore, patients who underwent a-HAIC treatment exhibited significantly lower rates of intrahepatic metastasis compared to those who underwent a-TACE or hepatectomy alone (32.6% vs 58.4%, *P=0.001*; 32.6% vs 54.6%, *P=0.001*).

The Results of the Subgroup Kaplan-Meier Survival Analysis of DFS and OS After PSM

The risk score, called TTAA score, was determined by factors such as tumor diameter, tumor number, ALBI grade, and AFP level. This score ranged from 4 to 7 points in the entire patient population. Based on this TTAA score, patients were categorized into two groups: high-TTAA (score > 5) and low-TTAA (score ≤ 5). Among the total population, 73 patients (22.4%) were classified as high-TTAA, while 253 patients (77.6%) fell into the low-TTAA group. The low-TTAA group consisted of 70 patients from the a-HAIC group, 55 patients from the a-TACE group, and 128 patients from the control group. On the other hand, the high-TTAA group consisted of 16 patients from the a-HAIC group, 22 patients from the a-TACE group, and 35 patients from the control group.

DFS showed significant differences between the two groups (Figure 4A, *P<0.001*). Multilevel of three type of treatments comparison in the high-TTAA and the low-TTAA groups were analyzed, and the result revealed that no difference was observed between a-HAIC, a-TACE and the control groups in the high-TTAA group (Figure 4B, *P>0.05*). However, in the low-TTAA group, there was a significant discrepancy where the a-HAIC group exhibited better DFS compared to both the a-TACE group and the control group (Figure 4C, *P<0.05*). Additionally, a significant difference was observed between the a-TACE group and the control group, with patients in the a-TACE group showing improved DFS compared to the control group (Figure 4C, *P=0.045*).

The OS was obviously different between the two groups (Figure 4D, *P<0.001*). Similar to the analysis of DFS, no significant difference was found between the a-HAIC group and either the a-TACE or control group in terms of OS within the high-risk score and low-TTAA groups (Figure 4E, *P>0.05*). However, in the low-TTAA group, the a-HAIC group displayed better OS compared to both the a-TACE group and the control group (Figure 4F, *P<0.05*). There was no significant difference between the a-TACE group and the control group in terms of OS (Figure 4F, *P=0.279*).

Discussion

In this study, we employed a standardized data collection form to gather all relevant information from two RCTs. The results showed that patients who received a-HAIC or a-TACE had better DFS outcomes compared to those who underwent hepatectomy alone. On performing multivariate analysis, both a-HAIC and a-TACE were identified as independent protective factors associated with improved DFS in patients with MVI after hepatectomy. However, when comparing the two treatment modalities, a-HAIC demonstrated greater enhancements in both DFS and OS compared to a-TACE. Furthermore, a-HAIC exhibited superior control over intrahepatic recurrence lesions when compared to both the a-TACE group and the control group.

Over the past several decades, hepatectomy remains the curative approach for HCC patients. However, long-term survival outcomes still remain unsatisfactory mainly because of the high incidence of postoperative recurrence and metastasis.[27,28] The presence of MVI is an important prognostic factor in patients with HCC. Currently, there is ongoing

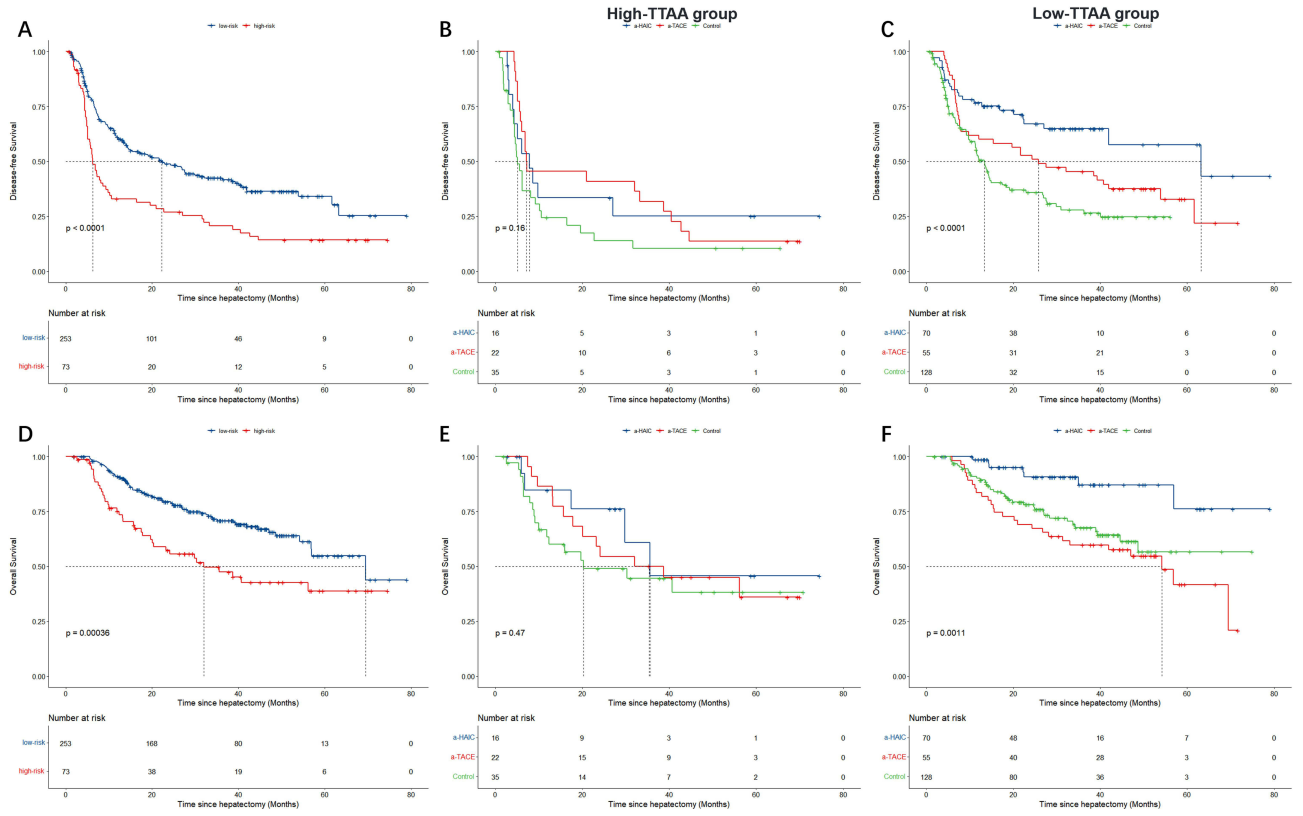

Figure 4 The Kaplan-Meier survival analysis for subgroups of HCC patients. (**A**) The Kaplan-Meier curves of DFS between high-TTAA group and low-TTAA group after PSM. (**B**) The Kaplan-Meier curves of DFS in the High-TTAA group between a-HAIC, a-TACE and control group. (**C**) The Kaplan-Meier curves of DFS in the Low-TTAA group between a-HAIC, a-TACE and control group. (**D**) The Kaplan-Meier curves of OS between high-TTAA group and low-TTAA group after PSM. (**E**) The Kaplan-Meier curves of OS in the High-TTAA group between a-HAIC, a-TACE and control group. (**F**) The Kaplan-Meier curves of OS in the Low-TTAA group between a-HAIC, a-TACE and control group.

Abbreviations: DFS, disease-free survival; OS, overall survival; HCC, hepatocellular carcinoma; a-HAIC, adjuvant hepatic artery infusion chemotherapy; a-TACE, adjuvant transcatheter arterial chemoembolization.

debate regarding the use of adjuvant therapies following radical resection. In our previous two RCTs, we have provided evidence that adjuvant therapies such as a-TACE and a-HAIC can effectively improve the DFS and OS in HCC patients with MVI positive. Although the two treatments are similar, they differ in terms of the drugs used and the administration methods employed. Therefore, it is crucial to compare the differences in survival outcomes between the a-HAIC and a-TACE groups.

One possible reason for the findings presented in this study is the concentration of medication. The anti-tumor activity of TACE is mainly caused by the retention of iodized oil embolization to induce necrosis or inhibition of residual small tumor nodules in the liver, whereas most chemotherapeutic agents will be released into systemic circulation with less than 1 hour.[29] Meanwhile, HAIC maintains a stable concentration of drugs locally by extending the infusion time, thereby reducing drug side effects. Even patients with compromised liver function show good tolerance to HAIC treatment[30] Another reason is that the non-embolized hepatic artery can more effectively deliver chemotherapy drugs repeatedly. This enables a-HAIC to achieve better control of the disease compared to a-TACE, which relies on embolization alone. Third, ischemic injury caused by a-TACE may exacerbate processes such as fibrosis of liver tissue surrounding the tumor and contribute to the deterioration of liver function.[31] Some studies have also suggested that the ischemia induced by embolization can up-regulate hypoxia-inducible factor-1a and vascular endothelial growth factor, which may promote tumor recurrence.[32,33] On the other hand, a meta-analysis has also demonstrated that the HAIC group has more significant advantages compared to the TACE group in terms of survival benefits and safety adverse events (SAEs) among unresectable HCC patients.[34] Through constant infusion by a fixed-micro catheter, the high concentration persists for longer in HAIC compared to TACE. Furthermore, prolonged chemotherapy infusion seemed to be associated with well tolerated liver toxicity. And compared with traditional cisplatin plus

fluorouracil regimen, the efficacy of FOLFOX-HAIC appears to be better.[35] These studies on treatment strategies for unresectable patients provide additional evidence supporting the potential superiority of HAIC over TACE from another perspective. In summary, the concentration of medication, the mode of drug delivery, and the potential for liver damage caused by ischemic injury may all contribute to the superior outcomes observed in patients treated with a-HAIC compared to those treated with a-TACE or no adjuvant therapy.

In the multivariate cox regression analysis after PSM, we also identified several independent risk factors that significantly affected patient survival outcomes. These risk factors included tumor diameter ≥10cm, multiple tumors, ALBI grade II, and AFP ≥400 ng/mL. Consistent with previous studies, tumor burden and liver function have been shown to be prognostic factors for HCC patients, in addition to MVI.[36–38] In our subgroup analysis, we observed that only patients with a low-TTAA score derived survival benefits from a-HAIC compared to other treatment groups. High tumor burden or impaired liver function may contribute to worse DFS and OS in MVI-positive HCC patients, thus rendering them ineligible for further benefits from adjuvant therapy. Compared with small HCC, the risk of vascular invasion and extrahepatic metastasis is significantly increased in huge HCC (≥10cm).[28,39–41] For hHCC patients, neither HAIC nor TACE as adjuvant therapy postoperatively seems to provide survival benefits (Supplementary Figure 1). According to the EASL guidelines, tumors >5 cm may benefit from surgical resection.[42] Asian countries have been broader, and so liver resection has been performed in many patients with huge HCC (≥10cm) in these countries.[43–45] Tumor recurrence is common after resection of huge HCC, but compared to primary liver malignancies, recurrent lesions after HCC resection can be managed with more modalities including repeat resection, TACE, radio frequency ablation (RFA), targeted therapy and anti-PD-1/PD-L1 therapy. Early detection and treatment of local recurrences may lead to an improvement in overall survival. These biases in patient selection for surgery also influence clinicians' perspectives on adjuvant therapy. Liu et al reported a preliminary results that the application of microparticle transcatheter arterial chemoembolization (mTACE) as a preoperative neoadjuvant method had the advantage of prolonging the overall survival time.[46] This reminds us that TACE or HAIC as neoadjuvant therapy before surgery may achieve better results for patients with hHCC. Further prospective studies are needed to determine the effectiveness and safety of each method.

The presence of MVI is strongly associated with high tumor invasiveness and has been recognized as a crucial factor in early postoperative recurrence (within 24 months) in numerous studies, typically leading to poor prognosis.[47–49] Early recurrence in HCC is often attributed to the hematogenous spread of the primary tumor, with approximately 80% of recurrences occurring within the liver.[50] Analyzing the timing of tumor recurrence, we observed that the proportion of early recurrence in the a-HAIC group was significantly lower compared to the a-TACE and control groups. Moreover, the proportion of intrahepatic recurrence in the a-HAIC group was also significantly lower than in the a-TACE and control groups. Similar to our study's conclusion, Kawabe et al demonstrated that HAIC is superior to TACE alone in reducing the incidence of intrahepatic metastasis in unresectable HCC patients.[51] These findings suggest that a-HAIC provides better control over residual, minuscule, and imperceptible lesions that could potentially become recurrent foci in the future.

However, it is important to acknowledge the limitations of this study. Firstly, the study design was retrospective, which inherently introduces biases, and the sample size was relatively small. Secondly, the majority of patients included in this study had HBV infection, and since previous studies have indicated a potential association between HBV and MVI,[52,53] it is necessary to validate these results in HCC patients with HCV infection or non-alcoholic/alcoholic fatty liver disease. Additionally, the two RCTs included patients at different times, resulting in variations in follow-up durations. With the emergence of various new treatment options for liver cancer recurrence in later stages, this has also had a certain impact on patients' survival. As an observational study conducted retrospectively using multicenter databases, the subsequent treatments administered to patients after recurrence were not recorded, which may serve as a confounding factor. These limitations suggest that multi-center, large scale prospective or randomized studies are still needed to see whether the HAIC as adjuvant treatment is better than TACE for MVI-positive HCC patients.

In conclusion, this study demonstrates that in HCC patients with MVI, a-HAIC can significantly improve DFS and OS compared to both the a-TACE and control groups.

Abbreviations

HCC, hepatocellular carcinoma; PSM, propensity score matching; Microvascular invasion (MVI); a-HAIC, adjuvant hepatic artery infusion chemotherapy; a-TACE, adjuvant transcatheter arterial chemoembolization; HBsAg, hepatitis B surface

antigen; ALT, alanine aminotransferase; TBIL, total serum bilirubin; ALBI, Albumin-Bilirubin; AFP, alpha-fetoprotein; DFS, disease-free survival; OS, overall survival.

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Disclosure

The authors declare no potential conflicts of interest.

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