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ORIGINAL RESEARCH

TACE-HAIC versus TACE as Initial Regional Therapy for Unresectable Huge Hepatocellular Carcinoma (>10 cm): A Propensity Score-Matched Study

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Purpose: Hepatocellular carcinoma (HCC) remains challenges in treatment, particularly when tumors are unresectable and huge. This study aimed to assess the safety and efficacy of combining transarterial chemoembolization (TACE) with hepatic arterial infusion chemotherapy (HAIC) for this patient population.

Patients and Methods: A retrospective review was conducted on patients with unresectable huge HCC (>10 cm) who received either TACE-HAIC or TACE as initial regional treatment from January 2020 to December 2023. Tumor response, progression-free survival (PFS), overall survival (OS), and adverse events were evaluated by propensity score matching (PSM).

Results: Among the 242 patients included, 132 received TACE-HAIC and 110 received TACE. After PSM, 77 matched pairs were analyzed. The TACE-HAIC group had significantly higher objective response (74.0% vs 58.4%, $P = 0.040$) and disease control rates (93.5% vs 72.7%, $P = 0.001$) than the TACE group. TACE-HAIC therapy also led to longer PFS (median: 12.3 vs 7.4 months, $P < 0.001$) and prolonged OS (median: 26.8 vs 20.4 months, $P = 0.006$). Stratified analysis showed that patients in Barcelona Clinical Liver Cancer stage C had longer survival benefits in the TACE-HAIC group (median PFS: 10.5 vs 5.6 months, $P < 0.001$; median OS: 24.5 vs 19.8 months, $P = 0.013$). Among grade 3/4 adverse events, liver abscesses ($P = 0.018$) were more common in the TACE group.

Conclusion: Compared to TACE alone, TACE-HAIC therapy presented an acceptable safety profile, and offered improved local efficacy and prolonged survival benefits in patients with unresectable huge HCC (> 10 cm).

Keywords: liver cancer, chemoembolization, huge HCC, combination therapy

Introduction

Hepatocellular carcinoma (HCC) is one of the most common and deadly cancers worldwide,[1] representing a significant health burden. Huge HCC (>10 cm) present unique challenges due to their size, major hepatic vascular invasion or microsatellite or limited volume of remanent liver, making surgical resection infeasible in many cases.[2] Currently, transarterial chemoembolization (TACE) is an important treatment for unresectable large HCC.[3] However, TACE's effectiveness is limited by the tumor's extensive blood supply and potential for incomplete embolization.[4]

Hepatic arterial infusion chemotherapy (HAIC) with the FOLFOX regimen (leucovorin, oxaliplatin, fluorouracil) has shown promise in improving overall survival in patients with unresectable large HCC.[5–8] HAIC works by delivering high local drug concentration and prolonging tumor exposure to the drugs through catheter placement in the hepatic artery[9] but depends heavily on drug sensitivity.[10]

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Combining TACE with HAIC may offer a synergistic effect, enhancing local tumor control and improving patient outcomes.[11,12] TACE can induce rapid tumor necrosis by blocking tumor blood flow, while HAIC can enhance drug delivery and prolong exposure to chemotherapy agents throughout the residual tumor. We hypothesized that this combination could overcome the limitations of each modality alone.

There is limited evidence specifically evaluating TACE followed by HAIC for huge unresectable HCC. Huang et al[13] compared drug-eluting-beads-TACE (DEB-TACE) plus HAIC versus DEB-TACE alone in patients with large or huge unresectable HCC, and reported significantly improved median progression-free survival (PFS) (9.3 vs 6.3 months, $P = 0.005$) and overall survival (OS) (19.0 vs 14.0 months, $P = 0.008$) in the combination group. However, only about half of the tumors exceeded 10 cm, and the small sample size limited the applicability of the findings to huge HCC. Despite this, the study offers preliminary support for the potential benefit of TACE-HAIC in this population. This study aims to retrospectively analyze the safety and efficacy of combining TACE with HAIC in treating unresectable huge HCC (> 10 cm), comparing outcomes with those who received TACE. The findings of this study could provide valuable insights into optimizing treatment strategies for huge unresectable HCC, potentially improving patient survival and life quality.

Materials and Methods

Patients

This retrospective, single-center study was approved by the Ethics Committee of Henan Cancer Hospital (Approval No: 2024–380-002) and conducted in accordance with the Declaration of Helsinki (1975). All patient data were handled with strict confidentiality. We retrospectively reviewed and analyzed the data from patients with huge (>10cm) unresectable HCC treated with TACE-HAIC or TACE in our interventional department from January 2020 to December 2023. Written informed consent was obtained from each patient before the clinical interventional operation.

Inclusion Criteria

(a) Aged 18-75 years; (b) patients diagnosed with unresectable huge HCC (> 10cm) based on pathological biopsy or clinical guidelines[14] and (c) received at least one cycles of regional treatment (TACE-HAIC or TACE) as initial treatment; (d) Child-Pugh A or B liver function; (e) Eastern Cooperative Oncology Group performance status of 0 or 1; and (f) adequate hematologic blood counts (white blood cell count $>3.0 \times 10^9$/L, absolute neutrophil count $> 1.5 \times 10^9$/L, platelet count $> 60 \times 10^9$/L, hemoglobin concentration > 85 g/L). The extent of portal vein invasion was classified into four types, namely, Vp1-Vp4, according to the Liver Cancer Study Group of Japan's criteria.[15] Systemic therapy was subsequently applied on the first day after TACE or TACE-HAIC procedures, in accordance with the Barcelona Clinic Liver Cancer (BCLC) guidelines.[16] Treatment regimens used in this study included sorafenib,[17] lenvatinib,[18] or sintilimab combined with bevacizumab,[19] or apatinib combined with camrelizumab.[20]

Exclusion Criteria

(a) Severe cardiac, pulmonary, or renal disease; (b) history of a second primary- malignancy; (c) arterioportal shunts, (d) incomplete clinical data and (e) patients lost to follow-up.

Treatment Protocol

TACE procedures included conventional TACE (C-TACE) and DEB-TACE, and were performed by three interventional radiologists licensed with Certificate of Added Qualification, having 6, 8, and 12 years of experience, respectively. A femoral artery puncture approach using the Seldinger technique[21] was employed to obtain intraoperative digital subtraction angiography images of the celiac trunk, hepatic artery, or superior mesenteric artery. After identifying the arteries supplying the tumors, a microcatheter was coaxially inserted into the tumor-feeding arteries to perform super-selective embolization. This involved using either a water-in-oil emulsion of lipiodol (5–15 mL) and epirubicin (20–40 mg) for C-TACE or drug-eluting-beads (100–400 μm) loaded with 40 mg epirubicin for DEB-TACE, followed by the administration of a gelatin sponge slurry under fluoroscopic guidance until either portal vein visualization near the tumor or stasis was achieved. The embolization principle prioritizes blocking smaller tumor feeders first, then larger

ones, starting with those outside the liver, then moving to those within it, and targeting distant vessels before nearby ones, all to reduce vascularization as much as possible.[22]

For patients undergoing TACE-HAIC, tumors received HAIC therapy following TACE, using the same procedure as described above. The placement of the catheter varies based on the tumor's extent within the liver. For example, for tumors localized to a specific liver lobe (such as the left lateral section, left medial section, right anterior section, right posterior section, or caudate lobe), the catheter was positioned in the corresponding lobar artery. In cases where tumors affect the left lobe (left lateral section plus left medial section) or right lobe (right anterior section plus right posterior section), it was placed in the main left or right hepatic artery. For tumors involving multiple liver lobes or presenting with portal vein tumor thrombus (PVTT), the catheter was inserted into the proper hepatic artery to ensure comprehensive tumor coverage. Upon the patient's return to the ward, the catheter was externally connected to an artery infusion pump for the administration of FOLFOX-based chemotherapy: 85 mg/m^2 of oxaliplatin infusion for 2 h via artery, 400 mg/m^2 of leucovorin infusion for 2 h via vein, 400 mg/m^2 of 5-FU bolus via artery, and 2400 mg/m^2 of continuous 5-FU infusion for 46 h via artery.

Hemostasis was achieved with manual compression after embolization or arterial infusion, marking the completion of the treatment session. Repeated TACE-HAIC or TACE sessions were conducted at intervals of 3–4 weeks and continued until the intrahepatic lesions progressed or toxicity became unacceptable or patient refused.

Assessment of Tumor Response and Survival

Radiological responses of the tumors were assessed by two radiologists with 11 and 15 years of experience, respectively, using the modified response evaluation criteria in solid tumors (mRECIST).[23] Tumor responses were categorized as follows: complete response, partial response, stable disease, progressive disease, objective response rate (ORR) and disease control rate (DCR). The best response before progression during follow-up was recorded. PFS was defined as the period from treatment initiation to tumor progression, and OS was defined as the period from treatment initiation to death or the last follow-up assessment.

Follow-up

Tumor response was evaluated 3–4 weeks after treatment using intravenous dynamic contrast-enhanced computed tomography or/and dynamic contrast-enhanced magnetic resonance imaging. As the disease progressed, individualized treatments such as repeated TACE therapy, systemic therapy, and best supportive therapy were implemented in accordance with clinical guidelines. Blood tests, including serum alpha-fetoprotein, liver function, renal function, complete blood count, and coagulation parameters, were performed before each procedure. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria version 5.0.

Statistical Analysis

Propensity score matching (PSM) analysis was used to reduce selection bias and balance the patient characteristics. The propensity score model included age, sex, alpha-fetoprotein (AFP), BCLC stage, Child-Pugh class, systemic therapy, PVTT classification, hepatic vein invasion, extrahepatic spread, intrahepatic major tumor size, tumor location, tumor margin, and tumor number as covariates. Matched pairs were generated in a 1:1 ratio without replacement. Following Austin's (2011)[24] recommendation, a caliper width of 0.2 times the standard deviation of the logit of the propensity score was applied. Considering the standardized mean differences (SMD) balance, a final caliper of 0.02 was used.

Quantitative data were presented as mean ± standard deviations or median with range, and count data were expressed as frequency. Continuous variables were compared using independent-sample Student's *t*-test. Categorical variables were compared using the χ^2 test or Fisher exact test. Confirmed response rates were compared between treatment groups. OS and PFS were presented with the use of Kaplan-Meier curves. *P* value and hazard ratios (HR) for disease progression or death were estimated using multivariate Cox proportional hazards model. A stratified analysis was conducted to further evaluate the survival outcomes of TACE-HAIC across different disease stages (BCLC A–B and C) and systemic therapy subgroups. Multivariate analyses were also performed to identify parameters for predicting survivals. All analyses were two-sided, and *P* values less than 0.05 were considered statistically significant. All statistical analyses and PSM were

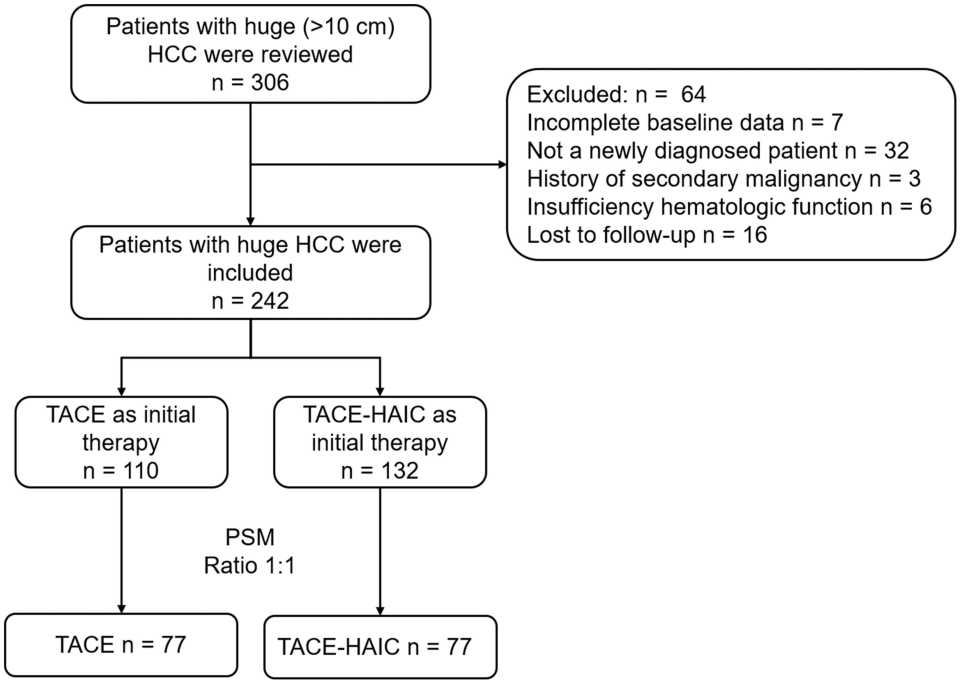

Figure 1 Flowchart of patient selection with unresectable huge HCC (>10 cm).
Abbreviations: HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; PSM, propensity score matching.

performed using SPSS version 25.0 software (IBM, Armonk, New York), while SMD calculations and Love plot generation were performed using Stata version 15.0 (StataCorp, College Station, TX).

Result

Patient Characteristics

A total of 306 patients with unresectable huge HCC who underwent TACE-HAIC or TACE were assessed for eligibility during the study period. Sixty-four patients were excluded for not meeting the inclusion criteria or meeting the exclusion criteria (Figure 1). Ultimately, 242 patients were included in the analysis, with 110 in the TACE group (median follow-up : 24.2 months; 95% CI: 21.4–27.1 months) and 132 in the TACE-HAIC group (median follow-up: 18.3 months; 95% CI: 15.6–21.0 months). BCLC stage, systemic therapy, tumor number, tumor location, margin, PVTT and extrahepatic spread were significantly different between the two groups (Table 1). After PSM, the baseline characteristics between the two

Table 1 Patient and tumor characteristics before and after PSM

Variables	Before Matching			After Matching		
	TACE (n=110)	TACE-HAIC (n= 132)	*P*	TACE (n = 77)	TACE-HAIC (n= 77)	*P*
Patient characteristics						
Age (years)	56.7±11.6	54.6±11.3	0.472	55.9±12.2	54.7±12.0	0.506
Sex (male)	98 (89.1)	111 (84.1)	0.259	70 (90.9)	69 (89.6)	0.786
ALT (U/L)			0.582			0.738
> 50	68 (61.8)	77 (58.3)		50 (64.9)	48 (62.3)	
≤ 50	42 (38.2)	55 (41.7)		27 (35.1)	29 (37.7)	

(*Continued*)

Table 1 (Continued).

Variables	Before Matching			After Matching		
	TACE (n=110)	TACE-HAIC (n= 132)	*P*	TACE (n = 77)	TACE-HAIC (n= 77)	*P*
AST (U/L)			0.621			0.628
> 40	61 (55.5)	69 (52.3)		42 (54.5)	39 (50.6)	
≤ 40	49 (44.5)	63 (47.7)		35 (45.5)	38 (49.4)	
Child-Pugh class			0.705			0.476
class A	81 (73.6)	100 (75.8)		57 (74.0)	53 (68.8)	
class B	29 (26.4)	32 (24.2)		20 (26.0)	24 (31.2)	
Imaging cirrhosis (Y)	64 (58.2)	82 (62.1)	0.533	46 (59.7)	50 (64.9)	0.506
Virus hepatitis			0.166			0.232
none	14 (12.7)	9 (6.8)		8 (10.4)	7 (9.1)	
HBV	91 (82.7)	120 (90.9)		64 (83.1)	69 (89.6)	
HCV	5 (4.5)	3 (2.3)		5 (6.5)	1 (1.3)	
AFP (ng/ml)			0.248			0.506
≤ 400	46 (41.8)	65 (49.2)		27 (35.1)	31 (40.3)	
> 400	64(58.2)	67 (50.8)		50 (64.9)	46 (59.7)	
BCLC stage			0.002			0.168
A	25 (22.7)	12 (9.1)		10 (13.0)	10 (13.0)	
B	26 (23.6)	22 (16.7)		19 (24.7)	10 (13.0)	
C	59 (53.6)	98 (74.2)		48 (62.3)	57 (74.0)	
Systemic therapy (Y)	85 (77.3)	120 (90.9)	0.003	67 (87.0)	67 (87.0)	1.000
Tumor characteristics						
Tumor number			0.001			0.864
<10	58 (52.7)	29 (22.0)		26 (33.8)	25 (32.5)	
≥10	52 (47.3)	103 (78.0)		51 (66.2)	52 (67.5)	
Tumor size (cm)	11.9±2.2	12.3±2.9	0.268	12.1±2.2	12.3±2.8	0.534
Tumor location			0.007			0.912
one lobe	31 (28.2)	22 (16.7)		15 (19.5)	17 (22.1)	
left/right lobe	48 (43.6)	48 (36.4)		35 (45.5)	33 (42.9)	
multiple liver lobes	31 (28.2)	62 (47.0)		27 (35.1)	27 (35.1)	
Margin			0.024			0.498
continuous capsule	20 (18.2)	11 (8.4)		13 (16.9)	10 (13.0)	
non-continuous capsule	90 (81.8)	120 (91.6)		64 (83.1)	67 (87.0)	
PVTT			0.001			0.12
none	68 (61.8)	47 (35.6)		41 (53.2)	28 (36.4)	
vp1-2	15 (13.6)	16 (12.1)		12 (15.6)	9 (11.7)	
vp3	17 (15.5)	39 (29.5)		15 (19.5)	22 (28.6)	
vp4	10 (9.1)	30 (22.7)		9 (11.7)	18 (23.4)	
Hepatic vein invasion (Y)	13 (11.8)	18 (13.6)	0.673	8 (10.4)	8 (10.4)	1.000
Extrahepatic spread (Y)	22 (20.0)	45 (34.1)	0.015	18 (23.4)	24 (31.2)	0.278

Note: results are expressed as mean ± SD, or number of patients or tumors and (percentages).
Abbreviations: PSM, propensity score matching; TACE, transcatheter arterial chemoembolization; HAIC, hepatic arterial infusion chemnotherapy; ALT, alanine transaminase; AST, aspartate transaminase; HBV, Hepatitis B virus; HCV, Hepatitis B virus; AFP, alpha-fetoprotein; BCLC, Barcelona clinical liver cancer staging system; Vp classification: The Liver Cancer Study Group of Japan ranks portal vein tumor thrombosis (PVTT) into five types, from Vp0 to Vp4.

groups were well balanced, with most SMDs reduced to below 0.1 (Supplementary Table 1). The matching quality was further illustrated in the Love plot (Supplementary Figure 1).

Before PSM, the median treatment cycle was 2 (range: 1–8) in the TACE group and 3 (range: 1–10) in the TACE-HAIC group. Among all TACE procedures, 45.4% were C-TACE and 54.6% were DEB-TACE.

Table 2 Treatment Response Before and After PSM

Tumor Response	Before Matching			After Matching		
	TACE	TACE-HAIC	*P*	TACE	TACE-HAIC	*P*
CR	13	22		9	15	
PR	59	71		36	42	
SD	14	28		11	15	
PD	24	11		21	5	
ORR (%)	72 (65.5)	93 (70.5)	0.406	45 (58.4)	57 (74.0)	0.040
DCR (%)	86 (78.2)	121 (91.7)	0.003	56 (72.7)	72 (93.5)	0.001

Abbreviations: PSM, propensity score matching; CR, complete response; PR, partial response; SD, stable disease, PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Tumor Responses

Table 2 summarizes the tumor response outcomes. Prior to PSM, the ORR was 70.5% in the TACE-HAIC group and 65.5% in the TACE group ($P = 0.406$), whereas the DCR was significantly higher in the TACE-HAIC group (91.7% vs 78.2%, $P = 0.003$). After matching, the ORR increased to 74.0% in the TACE-HAIC group compared to 58.4% in the TACE group ($P = 0.040$), and the TACE-HAIC group continued to demonstrate a superior DCR (93.5% vs 72.7%, $P = 0.001$; Figure 2). Additionally, AFP elevation > 50% after treatment occurred more frequently in the TACE group (20.3% vs 5.2%, $P = 0.003$; Supplementary Table 2), further indicating a less favorable tumor response.

Survival Outcomes

Before PSM, disease progression was observed in 58 of 132 patients (43.9%) in the TACE-HAIC group and 70 of 110 patients (63.6%) in the TACE group. The median PFS for TACE-HAIC and TACE groups was 12.9 and 8.0 months, respectively (HR = 0.577, 95% CI: 0.393–0.848, $P = 0.005$; Figure 3A). After PSM, the median PFS remained significantly longer in the TACE-HAIC group (12.3 months) versus the TACE group (7.4 months) (HR = 0.407, 95%

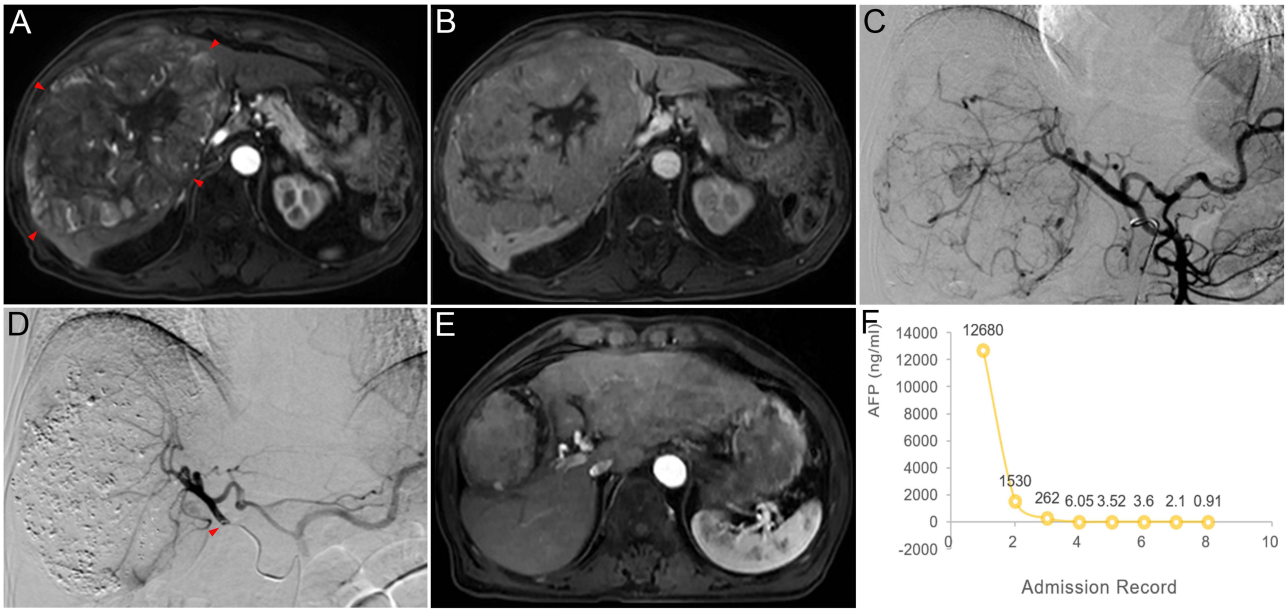

Figure 2 A 67-year-old man with huge hepatocellular carcinoma received conventional transarterial chemoembolization (C-TACE) and hepatic arterial infusion chemotherapy (HAIC). (**A**) Preoperative dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) revealed a 16.8-cm giant mass occupying the right hepatic lobe, demonstrating arterial phase hyperenhancement (arrowhead). (**B**) with subsequent washout during the portal venous phase. (**C**) Digital subtraction angiography (DSA) performed before embolization revealed tumor-feeding vessels originating from the right hepatic artery. (**D**) DSA after the first C-TACE showed residual tumor blush and the microcatheter was reserved at the proper hepatic artery for HAIC (arrowhead). (**E**) DCE-MRI after three cycles of C-TACE-HAIC showed significant tumor shrinkage with no enhancement. (**F**) Alpha-fetoprotein (AFP) levels normalized after three TACE-HAIC sessions.

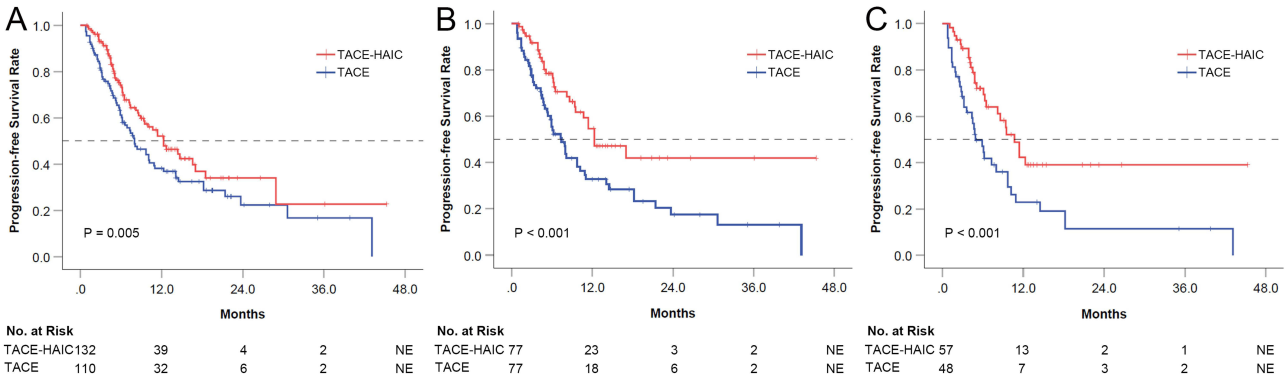

Figure 3 Kaplan-Meier survival curves comparing progression-free survival among patients treated with TACE-HAIC therapy or TACE. (**A**) Primary cohort. (**B**) Matched cohort. (**C**) Matched cohort in BCLC stage C.

Abbreviations: TACE, transcatheter arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; PSM, propensity score matching. BCLC, Barcelona Clinical Liver Cancer staging system; NE, could not be evaluated.

CI: 0.256–0.648, $P < 0.001$; Figure 3B). Multivariate analysis identified BCLC stage C as an independent risk factor for PFS (HR = 3.141, 95% CI: 1.108–8.905, $P = 0.031$; Supplemental Table 3). Notably, among patients with BCLC stage C, TACE-HAIC therapy was associated with significantly longer PFS than TACE therapy (median: 10.5 vs 5.6 months; HR = 0.381, 95% CI: 0.223–0.648, $P < 0.001$; Figure 3C). In contrast, no significant difference in PFS was observed between the two groups among patients with BCLC stage A-B (HR = 0.424, 95% CI: 0.130–1.384, $P = 0.155$).

During follow-up, 104 of 242 patients died before PSM (TACE-HAIC: 50/132; TACE: 54/110). The median OS for the TACE-HAIC and TACE groups was 26.9 and 21.8 months, respectively (HR = 0.630, 95% CI: 0.428–0.928, $P = 0.019$; Figure 4A). After PSM, the median OS remained significantly longer in the TACE-HAIC group (26.8 months) versus the TACE group (20.4 months) (HR = 0.519, 95% CI: 0.325–0.829, $P = 0.006$; Figure 4B). The 1-year and 2-year OS rates were 81.5% and 57.6% in the TACE-HAIC group, compared to 72.4% and 42.0% in the TACE group, respectively. Multivariate analysis identified Child-Pugh class B (HR = 1.863, 95% CI: 1.176–2.953, $P = 0.008$) and tumors with a non-continuous capsule (HR = 1.841, 95% CI: 1.281–2.645, $P = 0.001$) as independent risk factors for OS (Supplemental Table 4). Furthermore, stratified analysis demonstrated that TACE-HAIC therapy provided significantly longer OS than TACE therapy in BCLC stage C (median: 24.5 vs 19.8 months; HR = 0.511, 95% CI: 0.300–0.869, $P = 0.013$; Figure 4C) but not in BCLC stage A-B (HR = 0.453, 95% CI: 0.144-0.428, $P = 0.177$).

To further evaluate the impact of different systemic therapies on survival outcomes, we conducted subgroup analyses based on the most commonly used regimens: (1) no systemic treatment, (2) sintilimab plus bevacizumab, and (3) camrelizumab plus apatinib (Supplemental Table 5). In the original cohort, patients who did not receive systemic therapy

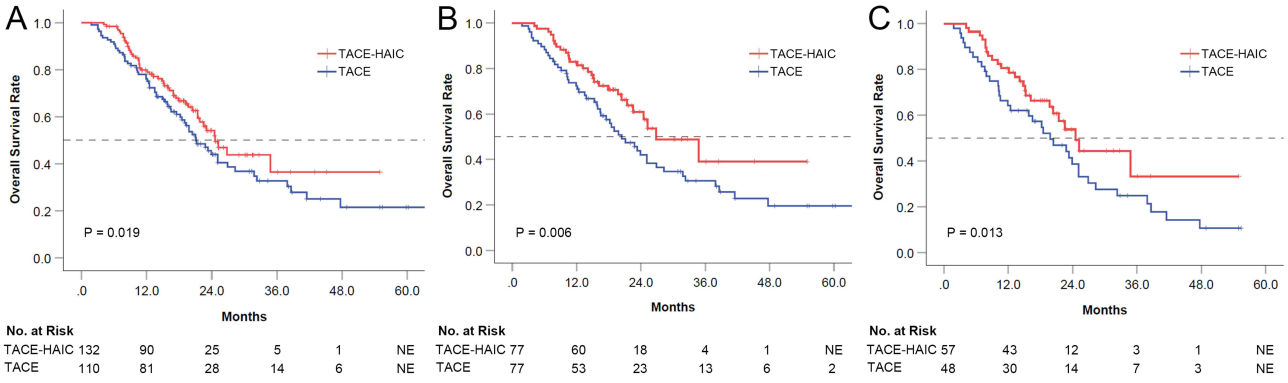

Figure 4 Kaplan-Meier survival curves comparing overall survival among patients treated with TACE-HAIC therapy or TACE. (**A**) Primary cohort. (**B**) Matched cohort. (**C**) Matched cohort in BCLC stage C.

Abbreviations: TACE, transcatheter arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; PSM, propensity score matching. BCLC, Barcelona Clinical Liver Cancer staging system; NE, could not be evaluated.

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Table 3 Related Adverse Events in the Primary Cohorts

Adverse Events	Any Grade			Grade 3–4		
	TACE-HAIC (n=132)	TACE (n=110)	*P*	TACE-HAIC (n=132)	TACE (n=110)	*P*
Nausea/vomiting	63 (47.1)	30 (27.3)	0.001	8 (6.1)	6 (5.5)	0.841
Abdominal pain	38 (28.8)	43 (42.7)	0.024	21 (15.9)	18 (16.4)	0.924
Diarrhea	13 (9.8)	8 (7.3)	0.478	3 (2.3)	1 (0.9)	0.628
Transaminase						
ALT elevation	92 (69.7)	81 (73.6)	0.499	20 (15.2)	18 (16.4)	0.796
AST elevation	102 (77.3)	90 (81.8)	0.385	23 (17.4)	20 (18.2)	0.878
Leukopenia	46 (34.8)	24 (21.8)	0.026	7 (5.3)	4 (3.6)	0.758
Thrombocytopenia	44 (33.3)	22 (20.0)	0.020	8 (6.1)	4 (3.6)	0.554
Hand–foot skin reaction	35 (26.5)	23 (20.9)	0.309	6 (4.5)	3 (2.7)	0.449
Hypertension	13 (9.8)	8 (7.3)	0.478	3 (2.3)	1 (0.9)	0.628
Hypothyroidism	12 (9.1)	9 (8.2)	0.802	2 (1.5)	2 (1.8)	1.000
Immune hepatitis	3 (2.3)	1 (0.9)	0.628	2	—	—
Liver abscess	0	5 (4.5)	0.018	0	5 (4.5)	0.018
Groin hematoma	4 (3.0)	5 (4.5)	0.735	0	0	—

Notes: values are presented as n (%).
Abbreviations: TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; AST, aspartate transaminase; ALT, alanine transaminase.

showed no significant differences in PFS (P = 0.279; Supplemental Figure 2A) or OS (P = 0.614; Supplemental Figure 3A) between the TACE-HAIC and TACE groups. Among patients treated with sintilimab plus bevacizumab, the TACE-HAIC group exhibited significantly longer PFS (median: 12.7 vs 7.3 months, P = 0.007; Supplemental Figure 2B), while the difference in OS (median: 26.8 vs 21.7 months, P = 0.171; Supplemental Figure 3B) was not statistically significant. In the camrelizumab plus apatinib subgroup, the TACE-HAIC group demonstrated significantly longer PFS (median: 11.4 vs 8.1 months, P = 0.002; Supplemental Figure 2C) and OS (median: 25.2 vs 19.8 months, P = 0.022; Supplemental Figure 3C). After PSM, similar trends were observed. In patients without systemic therapy, no significant differences were found in either PFS (P = 0.136; Supplemental Figure 2D) or OS (P = 0.159; Supplemental Figure 3D) between groups. In the sintilimab plus bevacizumab subgroup, the TACE-HAIC group achieved significantly longer PFS (median: 11.7 vs 7.3 months, P = 0.033; Supplemental Figure 2E) and OS (median: 26.8 vs 21.7 months, P = 0.023; Supplemental Figure 3E). Likewise, in the camrelizumab plus apatinib subgroup, the TACE-HAIC group showed significantly longer PFS (median: 11.4 vs 6.2 months, P = 0.004; Supplemental Figure 2F) and OS (median: 25.2 vs 18.5 months, P = 0.020; Supplemental Figure 3F).

Treatment Safety

Treatment-related adverse events in the primary cohort are summarized in Table 3. No treatment-related deaths occurred. The overall incidence of adverse events was similar between the two groups. The TACE-HAIC group had significantly higher rates of nausea/vomiting (47.1% vs 27.3%, P = 0.001), leukopenia (34.8% vs 21.8%, P = 0.026), and thrombocytopenia (33.3% vs 20.0%, P = 0.020) compared to the TACE group. In contrast, the TACE group exhibited a significantly higher incidence of abdominal pain (42.7% vs 28.8%, P = 0.024) and liver abscess (4.5% vs 0.0%, P = 0.018). However, the incidence of grade 3/4 adverse events did not differ significantly between groups, except for liver abscess, which led to treatment delays in two patients and interruptions in three patients in the TACE group. After PSM, no statistically significant differences in grade 3/4 events were observed (Supplementary Table 6).

Supportive care measures were implemented to manage adverse events. In the TACE-HAIC group, prophylactic antiemetics, hematopoietic growth factors, and dose adjustments were used to mitigate gastrointestinal and hematologic toxicities. In the TACE group, abdominal pain was managed with analgesics, and liver abscesses were treated promptly with antibiotics and, when necessary, percutaneous drainage. These interventions helped ensure treatment continuity.

Discussion

The study's findings showed that TACE-HAIC therapy conferred significantly long PFS and OS compared to TACE in the treatment of unresectable huge HCC, especially in patients with BCLC stage C. The TACE-HAIC group also presented an improved ORR and DCR among unresectable huge HCC. Moreover, the overall incidence of adverse events is similar between the two groups. These results indicated that TACE-HAIC therapy is superior to TACE for patients with unresectable huge HCC.

Previous studies have explored various locoregional strategies for unresectable large HCC, including TACE or HAIC alone and in combination with systemic treatment.[5,12,13,25] Yang et al[5] compared TACE-HAIC with HAIC alone for unresectable large HCC, reporting a lower ORR (65.6%) and a higher median PFS (16.5 months) in the TACE-HAIC group, which differs from our findings. Their TACE-HAIC group received a lower fluorouracil dosage (1500 mg/m² over 22 hours) and included a small sample size (32 cases), potentially reducing local efficacy and limiting the reliability of the PFS results. Yuan et al.[25] retrospectively compared TACE-HAIC combined with targeted therapy and immunotherapy with TACE alone in HCC patients with PVTT, reporting significantly longer survival in the combination group (median OS: not reached vs 10.4 months; median PFS: 14.8 vs 2.3 months), highlighting the advantage of multimodal therapy. Nonetheless, only around 50% of their patients had tumors > 10 cm, and TACE monotherapy is no longer considered standard of care for HCC with PVTT. A recent multicenter retrospective study[12] further demonstrated that adding HAIC to lenvatinib plus DEB-TACE significantly improved ORR (61.2%), time to progression (median 9.8 months), and OS (median 16.7 months) in large HCC (> 7 cm) patient with PVTT, reinforcing the survival benefits of incorporating HAIC into TACE-based regimens. Distinct from previous work, our study exclusively included patients who received either TACE-HAIC or TACE as initial regional therapy, utilized propensity score matching to reduce baseline bias, focused on HCC > 10 cm to assess the added value of HAIC in local tumor control, and permitted systemic therapy in accordance with clinical guidelines—thus offering relevant insight into real-world clinical practice.

TACE induces rapid tumor necrosis by blocking tumor-feeding arteries. However, massive HCC often has a rich blood supply and multiple collateral circulations, making complete embolization challenging.[26] Given the efficacy of FOLFOX-HAIC in unresectable large HCC, adding continuous arterial infusion chemotherapy after TACE offers several theoretical advantages. It enables chemotherapeutic agents to cover a wider tumor area, particularly targeting regions that may have escaped adequate embolization during TACE- such as residual tumor cells at the periphery of necrotic zones. Moreover, TACE-induced ischemia may sensitize tumor cells to subsequent chemotherapy[27,28] and improve the overall drug efficacy. Additionally, post-embolization hepatic blood flow redistribution may enhance the exposure of chemotherapeutic to previously un-embolized tumor areas, further increasing the cytotoxic effect of HAIC on residual lesions. Importantly, any viable tumor tissue remaining after HAIC can be re-targeted during the next TACE session, forming a complementary and potentially synergistic treatment cycle that may contribute to improved tumor control and prolonged survival. However, in this study, the embolization strategy involved relatively extensive tumor coverage in a single session, which may have led to greater liver function impairment and adverse events. Considering both the underlying mechanisms and safety concerns, a more quantitative and standardized approach—such as cone-beam computed tomography (CBCT) -guided staged embolization followed by HAIC—may improve treatment precision, enhance efficacy, and better preserve liver function. This strategy merits further investigation in future studies.

Stratified analysis further revealed that TACE-HAIC offered superior clinical benefits for BCLC stage C patients in terms of both PFS and OS. There are several possible explanations for these benefits. First, TACE is more effective in unresectable early and intermediate-stage HCC,[29] partially diminishing the added advantage of HAIC in these patients. Second, patients with BCLC stage C often receive tyrosine kinase inhibitor (TKI), which enhance chemotherapeutic drug delivery by promoting vascular normalization.[30] Third, the effectiveness of TACE is frequently impaired in BCLC stage C patients due to compromised liver function. Finally, HAIC has shown promising therapeutic outcomes in HCC patients with PVTT.[31]

To assess the potential influence of systemic therapy on the treatment benefits of TACE-HAIC, we performed subgroup analyses based on different systemic treatment regimens. Among patients receiving systemic therapy—either sintilimab plus bevacizumab or camrelizumab plus apatinib—TACE-HAIC consistently yielded better PFS and OS than

TACE alone after PSM. However, this benefit was not observed in the subgroup without systemic therapy, likely due to their earlier disease stage. This finding aligns with our stage-based subgroup analysis and further supports the efficacy of TACE-HAIC in advanced massive HCC.

In our study, no treatment-related deaths occurred. Patients treated with TACE-HAIC experienced significantly higher frequencies of chemotherapy-related adverse events, including nausea/vomiting, leukopenia and thrombocytopenia of any grade. However, these adverse events were expected and manageable through treatment interruption or dose modification. In contrast, the incidence of abdominal pain and liver abscess was significantly higher in the TACE group. We considered this is due to the high tumor burden in the included patients. To achieve the most complete embolization possible, the embolization area often needed be expanded for better tumor control. Overall, TACE-HAIC was well tolerable and safe for treating huge HCC, with systemic therapy administered as needed.

Our study had several limitations. Firstly, the retrospective nature of the study introduced inherent selection bias, which PSM analysis could not entirely eliminate. Second, the median follow-up duration was differed between the two groups, and subsequent treatments after progression varied, making their potential impact on OS a concern. Third, as a single-center study, the generalizability of the findings may be limited. Nevertheless, the promising outcomes of TACE-HAIC offer valuable insights for future research.

Conclusion

In conclusion, our study demonstrated that TACE-HAIC is a safe and more effective treatment than TACE alone for patients with unresectable huge HCC (>10 cm), offering improved tumor response and survival outcomes. These benefits were consistently observed across key subgroups, including patients with BCLC stage C and those receiving different systemic therapy regimens. Given the high tumor burden in this population, TACE-HAIC represents a promising therapeutic strategy. Nonetheless, potential confounding from follow-up duration and post-progression treatments should be taken into account when interpreting the OS benefit. Further validation through large-scale randomized studies is warranted.

Institutional Review Board

Ethics Committee of Henan Cancer Hospital (No: 2024-380-002).

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Disclosure

The authors declare that they have no interests in this work.

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