

ORIGINAL ARTICLE

Efficacy and safety of hepatic arterial infusion chemotherapy combined with transarterial embolization for unresectable hepatocellular carcinoma: A propensity score-matching cohort study

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Key words

hepatic arterial infusion chemotherapy, objective response rate, progression-free survival, retrospective analysis, transarterial chemoembolization, unresectable hepatocellular carcinoma.

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Author contribution: Wenbo Guo and Jian Gao conceived and coordinated the study, designed and performed the experiments, and wrote the manuscript. Wenquan Zhuang, Zhiqiang Wu, Song Chen, and Bin Li carried out data collection and analysis and revised the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Abstract

Purpose: The aim of this study was to assess the effectiveness and safety of hepatic arterial infusion chemotherapy (HAIC) using the FOLFOX regimen combined with transarterial embolization (TAE + HAIC) in patients with unresectable hepatocellular carcinoma (HCC).

Methods: Unresectable HCC patients treated with TAE + HAIC and conventional transcatheter arterial chemoembolization (TACE), respectively, between January 2015 and October 2016 in China were retrospectively assessed. The primary outcome was progression-free survival (PFS), while secondary outcomes included the objective response rate (ORR), the disease control rate (DCR), and main complications. Propensity score matching (PSM) was estimated by multiple logistic regression using caliper matching (caliper 0.2). A Cox proportional hazards model was used to identify those factors shown to be associated with PFS.

Results: A total of 113 patients were analyzed, with 41 and 72 receiving TAE + HAIC and TACE, respectively. After PSM, 35 pairs of patients were assessed. The median PFS was 7.93 months (95% confidence interval [CI], 4.44–11.42) for the TAE + HAIC group, which was higher compared with 2.60 months (95% CI, 0.93–4.27, $P = 0.003$) for TACE. The subgroup with Barcelona clinic liver cancer (BCLC) stage C obtained more PFS benefit from TAE + HAIC ($P = 0.002$). ORRs in the TAE + HAIC and TACE groups were 37.14% (13/35) and 20.00% (7/35, $P = 0.112$), respectively; DCRs were 88.57% (31/35) and 60.00% (21/35, $P = 0.006$), respectively. Abundant blood supply (hazard ratio [HR] = 0.327, 95% CI 0.173–0.615, $P < 0.001$) and TAE + HAIC (HR = 0.332, 95% CI 0.177–0.621, $P < 0.001$) were associated with longer PFS in multivariate analysis.

Conclusions: Compared with conventional TACE, TAE + HAIC provides more PFS benefits to patients with unresectable HCC, especially in those with BCLC stage C.

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths in China.¹ A large proportion of patients with HCC is diagnosed at an intermediate or advanced stage, when curative surgery is not feasible.² Therefore, intermediate or advanced HCCs usually have poor prognosis, with a median untreated survival time of 7–9 months.³

Transarterial chemoembolization (TACE) is currently the standard treatment for intermediate stage (stage B) in the Barcelona clinic liver cancer (BCLC) system.⁴ However, cases classified as BCLC stage B according to tumor extent (i.e. number and size) and hepatic function (i.e. Child–Pugh scores of 5–9) are

quite heterogeneous. Therefore, treatment recommendations need to be individualized, especially in patients with Child–Pugh scores ≥ 8 , who are at increased risk of clinical deterioration and cannot expect long-term survival with only TACE.^{5,6}

For patients with BCLC stage C, two multicenter randomized controlled trials, SHARP and Oriental, demonstrated that sorafenib delays tumor progression in patients with advanced liver cancer, with prolonged survival.^{7,8} However, subgroup analysis in the Oriental trial suggested that Hepatitis B virus (HBV)-positive patients did not receive significant overall survival (OS) benefit.⁹ In agreement, a recent meta-analysis of randomized phase III trials found no evidence of OS improvement attributable to sorafenib in patients with HBV and negative for

Hepatitis C virus (HCV).¹⁰ HBV is the major cause of liver cancer in Chinese patients; therefore, the effectiveness of sorafenib may be limited.

Meanwhile, several chemotherapeutic regimens containing oxaliplatin extend median progression-free survival (PFS) or median time to progression (TTP), for example, in the EACH (FOLFOX4: oxaliplatin, leucovorin, and fluorouracil)^{11,12} and AGE0 (GEMOX: oxaliplatin and gemcitabine)¹³ studies and a meta-analysis.¹⁴ TACE combined with chemotherapy is a promising therapy for patients with BCLC stage B/C. However, in both the FOLFOX and GEMOX regimens, the course of treatment usually lasts 2 days, explaining why they are usually applied as intravenous systematic chemotherapies rather than intraoperative transarterial chemotherapies.

Importantly, hepatic arterial infusion chemotherapy (HAIC) can compensate for this deficiency and should be adopted for delivering chemotherapeutics continuously.¹⁵ In HAIC, a highly concentrated chemotherapeutic agent is injected into the liver via the hepatic artery; high levels of the agent at the tumor site would be expected to increase antitumor effects.¹⁶ Besides, less systematic side effects are anticipated because of the first-pass effect of the liver.¹⁷ In clinical practice, HAIC seems to provide more survival benefit in Asian patients with unresectable HCC, especially in Japan.^{15,18,19} However, HAIC is not yet a well-established treatment, and optimal protocols and chemotherapeutic regimens remain undetermined.¹⁹

Based on the above findings, patients with unresectable HCC were treated by transcatheter arterial embolization (TAE) plus HAIC using the FOLFOX regimen (TAE + HAIC), which was compared to transcatheter arterial chemoembolization (TACE) monotherapy for efficacy and safety.

Materials and methods

Study design and participants. This retrospective cohort study enrolled consecutive patients with unresectable intermediate or advanced HCC administered TAE + HAIC or TACE between January 2015 and October 2016 in the First Affiliated Hospital of Sun Yat-Sen University. This study was approved by the ethics committee of The First Affiliated Hospital of Sun Yat-Sen University. The procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. Informed consent was waived by the committee because of the retrospective nature of the study.

Eligible patients were aged 20 years or older with unresectable intermediate or advanced HCC, diagnosed according to the AASLD criteria of conclusive contrast-enhanced ultrasonography and magnetic resonance imaging without biopsy.²⁰ They were administered TAE + HAIC or TACE and had an Eastern Cooperative Oncology Group performance (ECOG) status of 0–2 and tolerant liver function (Child–Pugh class \leq B). Key exclusion criteria were: unmeasurable lesions at baseline according to modified Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) guidelines, for example, small lesions (\leq 10 mm in any dimension); diffusive lesions or tumors with obscure boundary^{21,22}; and incomplete patient data. The study flowchart is shown in Figure 1.

Procedures. The TACE group received several bolus injections in the target vessel for intraoperative chemotherapy. The bolus regimen consisted of oxaliplatin (100 mg/m²), leucovorin, (200 mg/m²), and fluorouracil (400 mg/m²), and the

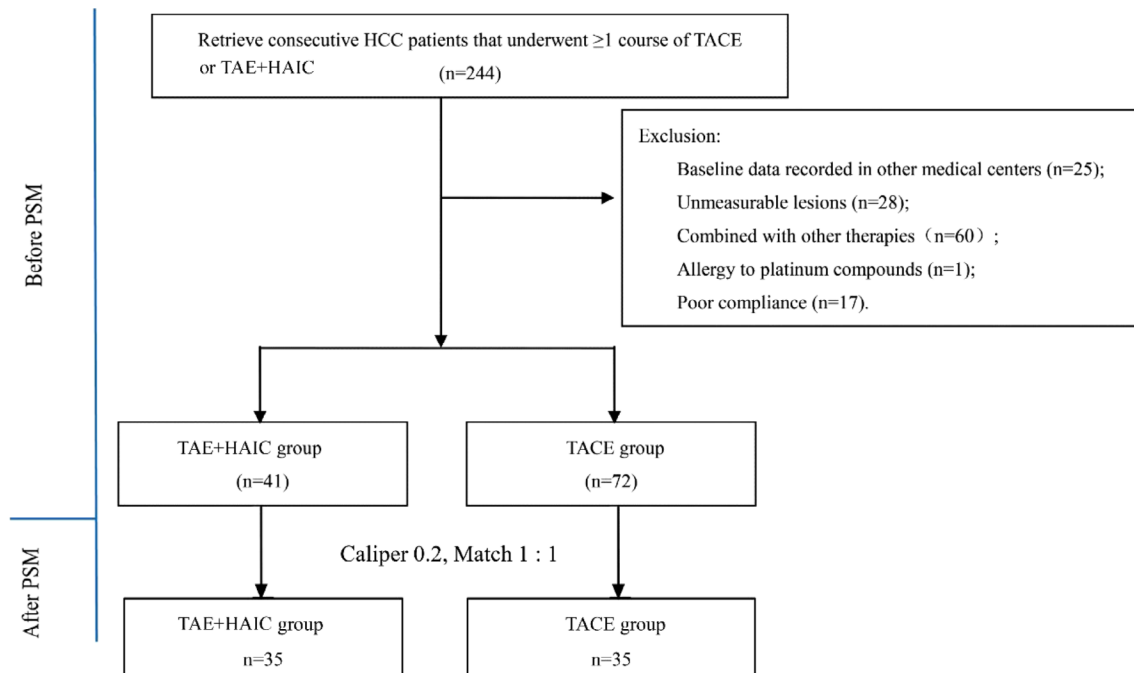


Figure 1 Screening and stratification of hepatocellular carcinoma (HCC) patients.

chemotherapeutic drugs were administered separately and orderly. Then, embolization of target tumor-feeding vessels was performed by injecting gelatin sponge or Embospheres of corresponding size according to vascular diameter. After intraoperative chemotherapy and embolization, the catheter was removed, and the puncture site was stanchied by compression and pressure dressing. Three weeks later, the effects of TACE were assessed by multiphase CT. Repeated TACE was performed until disease progression.

Patients in the TAE + HAIC group first underwent TAE. The embolization of target tumor-feeding vessels was performed by injecting gelatin sponge or Embospheres of corresponding size according to vascular diameter. After embolization, the catheter remained indwelled in the groin and was fixed. A mechanical portable infusion pump was used to administer the FOLFOX regimen (D1: oxaliplatin, 100 mg/m², 2 h; leucovorin, 200 mg/m², 2 h; fluorouracil, 400 mg/m², 15 min; fluorouracil, 600 mg/m², 22 h. D2: leucovorin, 200 mg/m², 2 h; fluorouracil, 400 mg/m², 15 min; fluorouracil, 600 mg/m², 22 h. q3w.). Multiphase CT was carried out 3 weeks later to evaluate the effectiveness of TAE + HAIC. Repeated TAE + HAIC was conducted for progression-free patients.

When progressive disease (PD) was indicated by multiphase CT during the follow up of 24 months in both groups, molecular targeted agents such as sorafenib were recommended in most cases according to the patient financial situation. Radiofrequency ablation was also sporadically performed if appropriate, basically when the new lesions were within 3 cm. Other comprehensive therapies were determined by patients.

Outcomes. The primary outcome was PFS, defined as the time from treatment completion to disease progression, assessed according to the RECIST 1.1 guidelines. Secondary outcomes included objective response rate (ORR) and disease control rate (DCR). ORR was assessed by complete response (CR) and partial response (PR). DCR was evaluated by CR, partial response (PR), and stable disease (SD). Safety was assessed by adverse events (AEs) and complications.

Statistical analysis. Because treatment procedures were not randomly assigned in this population, potential confounding and selection biases might diminish the reliability of results.²³ Therefore, we applied the propensity score-matching (PSM) method to reduce the influence of these factors. Patients were matched to receive treatment on the basis of a propensity score estimated by multivariable logistic regression models, in which the following baseline characteristics were used as covariates: age, gender, blood supply, Child–Pugh class, BCLC stage, American Joint Committee on Cancer (AJCC) staging, HBV status, HCV infection, liver cirrhosis, alpha fetal protein (AFP), and previous treatment status. A caliper of 0.2 was set to advance matching quality.²⁴ Among all covariates, previous treatment(s) was compulsively matched. Finally, 35 TAE + HAIC cases were then matched on a one-to-one basis with 35 TACE cases using the caliper propensity score (caliper = 0.2).

There is no current standard definition for blood supply of tumor. We used manifestations in enhanced CT images to help us differ hypervascular from hypovascular tumors. Compared with a plain scan, the arterial phase of the hypervascular lesion was

enhanced above 20 Hounsfield units (HU); the arterial phase of the hypovascular lesion was enhanced below 10 HU; if the lesion was enhanced between 10 and 20 HU, we titled it “hard to differ”.

Statistical analyses were processed by the SPSS 22.0 software (SPSS, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD) and analyzed by t-test. Categorical variables were analyzed by the Chi-square test or Fisher’s exact test as appropriate. PFS was estimated by the Kaplan–Meier method and compared between the two groups using the log-rank test. A Cox proportional hazards regression model was applied for univariate and multivariate analyses of PFS with the underlying prognostic factors. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the study population. A total of 113 patients were finally included in this retrospective cohort study, including 41 and 72 in the TAE + HAIC and TACE groups, respectively. Table 1 summarizes the characteristics of patients in the TAE + HAIC and TACE groups before and after the PSM method. Of the 113 enrolled patients, 106 (93.80%) had tolerant liver function with Child–Pugh stage A. A total of 100 had chronic hepatitis B as the major etiology of the underlying liver disease (88.50%). Patients with BCLC stages 0, A, B, and C were 5 (4.42%), 8 (7.08%), 40 (35.40%), and 60 (53.10%), respectively. For AJCC staging, relatively adjacent stages were combined to lessen stratifications and avoid small sample sizes in various layer. Naïve and post-treatment HCC patients were 60 (53.10%) and 53 (46.90%), respectively. Before PSM, Cancer of the Liver Italian Program scores were significantly different between the two groups ($P = 0.042$). After PSM, all characteristics were balanced between two groups. Previous treatment(s) was compulsively matched among all covariates.

Effects of TAE + HAIC and TACE. The median PFS was 7.93 months for the TAE + HAIC group (95% confidence interval [CI], 4.44–11.42), higher compared with 2.60 months observed in the TACE group (95% CI, 0.93–4.27, $P = 0.003$; Fig. 2a). Multivariate analysis indicated that TAE + HAIC (hazard ratio [HR] = 0.332; 95% CI: 0.177–0.621; $P < 0.001$) and hypervascular lesion (HR = 0.327; 95% CI: 0.173–0.615; $P = 0.0005$) were associated with longer PFS (Table 2).

After PSM, ORR showed no statistically significant differences between the TAE + HAIC and TACE groups (37.14% vs 20.00%, $P = 0.112$). DCR in patients with TAE + HAIC was significantly higher than that of the TACE group (88.57% vs 60.00%, $P = 0.003$, Table 3).

Subgroup analysis was performed for PFS rates of BCLC stages B and C patients. Patients with BCLC stage C benefited more from TAE + HAIC than TACE (Fig. 2c). Meanwhile, patients with BCLC stage B showed no statistically significant differences between the TAE + HAIC and TACE procedures (Fig. 2b).

AEs and complications. No treatment-related mortality occurred in either group. In the TAE + HAIC group after PSM, one patient (1/35) experienced grade 4 myelosuppression, requiring regime discontinuation and liver-protective therapy; three additional patients (3/35) showed grade 3 myelosuppression.

Table 1 Baseline characteristics of patients before and after PSM

Variables	Before PSM			After PSM		
	TAE + HAIC (n = 41)	TACE (n = 72)	P-value	TAE + HAIC (n = 35)	TACE (n = 35)	P-value
Age	48.0 ± 11.0	52.4 ± 12.3	0.060	47.7 ± 10.9	51.6 ± 12.9	0.178
Gender			0.666			1.000
Male	38	69		32	33	
Female	3	3		3	2	
Blood supply			0.273			0.811
Hypovascular	20	32		18	17	
Hypervascular	21	35		17	18	
Hard to differ	0	5		0	0	
CLIP score			0.042*			0.648
0	0	8		0	2	
1	28	38		23	22	
2	13	26		12	11	
HBV			0.894			0.673
Negative	4	9		2	4	
Positive	37	63		33	31	
HCV			1.000			0.493
Negative	39	72		33	35	
Positive	2	3		2	0	
Child–Pugh class			1.000			0.356
A	39	67		34	31	
B	2	5		1	4	
Liver cirrhosis			0.319			0.597
No	31	48		26	24	
Yes	10	24		9	11	
AFP			0.930			0.799
Negative	14	24		12	11	
Positive	27	48		23	24	
BCLC stage			0.273			1.000
0	0	5		0	0	
A	1	7		1	1	
B	10	30		10	10	
C	30	30		24	24	
AJCC staging			0.385			0.488
I–II	9	19		9	5	
III A–III C	18	37		15	17	
IV A–IV B	14	16		11	13	
Previous treatment			0.277			1.000
Naïve	19	41		19	19	
Posttreatment	22	31		16	16	

AFP, alpha fetal protein; AJCC, American Joint Committee on Cancer; BCLC, Barcelona Clinical Liver Cancer; CLIP, Cancer of the Liver Italian Program; HAIC, hepatic arterial infusion chemotherapy; HBV, hepatitis B virus; HCV, hepatitis C virus; PSM, propensity score matching; TACE, transcatheter arterial chemoembolization; TAE, transcatheter arterial embolization.

* $P < 0.05$.

Meanwhile, three patients (3/35) in the TACE group had grade 3 myelosuppression. Nonhematological complications in both groups included fever, nausea and vomiting, fatigue, and abdominal pain, which could be alleviated through symptomatic treatment. Detailed information and statistics after PSM are displayed in Table 4.

Discussion

According to BCLC guideline, sorafenib was the first-line treatment recommended for HCCs of BCLC stage C. Another

molecular-targeted drug, lenvatinib, was proved not to be inferior to sorafenib in a recent REFLECT trial.²⁵ Hence, the well-accepted first-line treatment has been sorafenib or lenvatinib so far. Besides, the RESORCE trial²⁶ and CELESTIAL trial²⁷ recommended regorafenib and cabozantinib as the second-line treatment, respectively. Combinations of immunotherapy and molecular-targeted drugs were spotlighted to have a bright applied prospect in HCC.²⁸ However, the high cost of treatment mentioned above was usually unacceptable in middle-class families in most of the developing countries, for example, China. Low-cost therapy such as chemotherapy, if the efficacy and

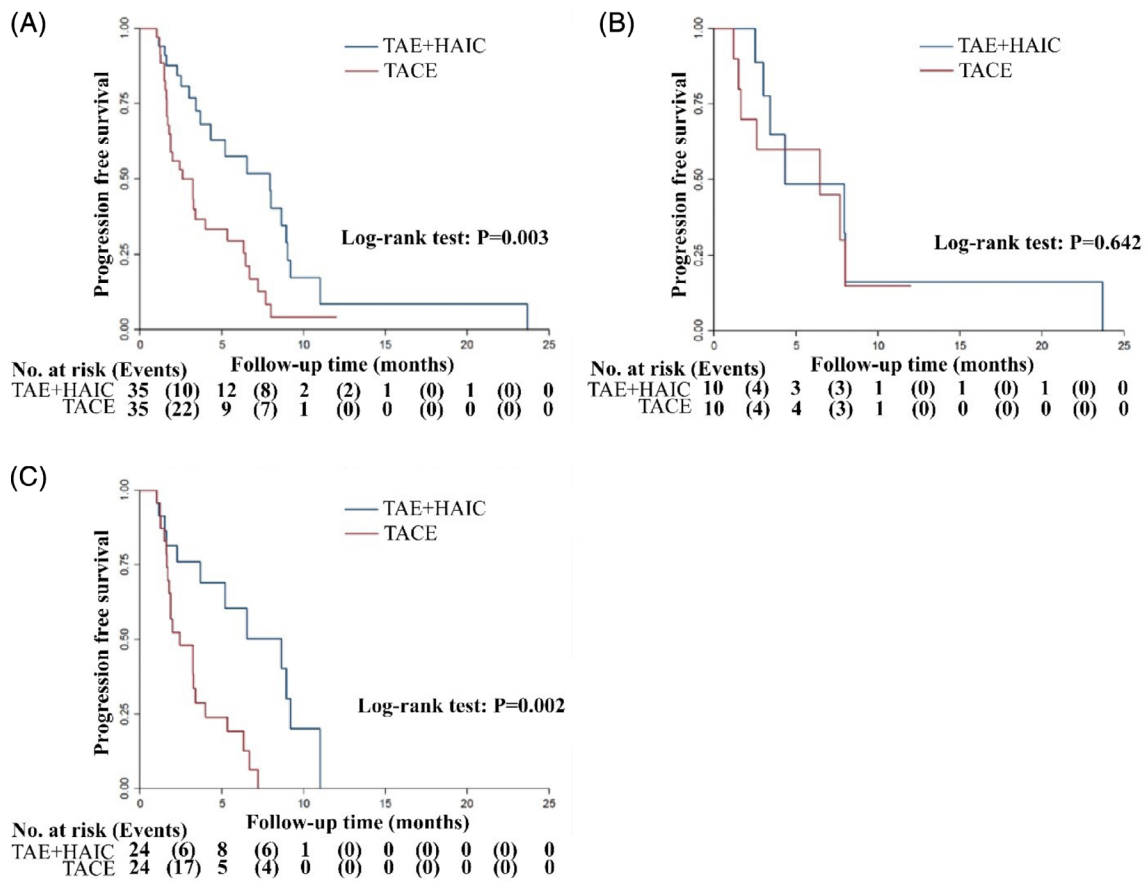


Figure 2 Progression-free survival (PFS) curves for patients after propensity score matching (a) and BCLC stages B and C subgroups (b, c).

safety are proven, would help most HCC families, especially needy ones.

This retrospective study demonstrated that TAE + HAIC resulted in longer PFS than TACE in patients with BCLC stage B/C. Specifically, patients with BCLC stage C achieved more PFS benefit in the TAE + HAIC group compared with the TACE group. Moreover, TAE + HAIC treatment and hypervascular lesion were independent protective factors of PFS in multivariate analysis.

As shown above, median PFS in patients treated with TAE + HAIC was 7.93 months, in agreement with three large trials assessing antiangiogenic drugs in combination with TAE + HAIC (169 days [median TTP] to 12 months).^{29–31} However, the above trials did not show significant benefit compared with placebo plus TACE, while the current study demonstrated an improvement of 5.33 months compared with the TACE group. The increased PFS could be explained by the additional effects of HAIC with the FOLFOX regimen used in combination with TAE. Meanwhile, most patients in this study (53.10%) were BCLC stage C and might have contributed to increase PFS as they benefited more from this treatment.

It is seemingly contradictory that HAIC was continued after TAE, in which the feeding arteries of the tumor were embolized in the same patient. We believe this combination is necessary because of the possible existence of fine-spun tumor-

feeding arteries that are hardly observed in fluoroscopy or digital subtraction angiography, let alone embolization. Besides, recent studies have shown that vessel co-option, which involves normal arteries, may be an essential mechanism contributing to tumor development and progression, as well as resistance to molecular-targeted agents, including sorafenib.^{32,33} In refractory HCC, prolonged chemotherapy (2 days of continuous hepatic arterial infusion with oxaliplatin-based chemotherapy regimen after TACE) is considered to be better than transient chemotherapy (bolus injection of oxaliplatin-based chemotherapy regimen in TACE). Nonetheless, several reports have shown PFS for FOLFOX ranging from 2.4 to 2.93 months in Asian patients,^{11,12} which is much shorter than that of TAE + HAIC. This study was a preliminary demonstration of the effect of oxaliplatin-based chemotherapy combined with HAIC and TAE.

A subgroup analysis in this study showed no treatment benefit in patients with BCLC stage B, in whom the progression pattern followed the new lesion appearance-related model,^{34–36} implying further exploration of the recurrence pattern or progression module after TAE + HAIC, which constitutes the focus of ongoing research in our laboratory. BCLC stage B constitutes a particular group of patients who should be recommended for resection when one to three tumor targets are found, with TACE preferable in those with more than three tumor targets.³⁷

Table 2 Univariate and multivariate analyses of prognostic factors of progression-free survival in HCC patients after PSM

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Female	0.970 (0.298,3.159)	0.960		
Age	0.977 (0.950,1.006)	0.121		
Hypervascular lesion	0.416 (0.229,0.755)	0.004	0.327 (0.173,0.615)	<0.001
Treatment				
TACE	Ref			
TAE + HAIC	0.412 (0.227,0.751)	0.004	0.332 (0.177,0.621)	<0.001
HBV positive	1.447 (0.566,3.699)	0.441		
HCV positive	0.954 (0.229,3.973)	0.948		
Child-Pugh class				
A	Ref			
B	0.980 (0.302,3.187)	0.974		
Liver cirrhosis	0.894 (0.472,1.693)	0.730		
AFP positive	1.186 (0.641,2.193)	0.587		
Clp score				
0	Ref			
1	0.913 (0.216,3.856)	0.902		
2	0.873 (0.198,3.840)	0.857		
BCLC stage				
A	Ref			
B	0.802 (0.178,3.620)	0.774		
C	1.260 (0.296,5.361)	0.754		
AJCC stage				
I-II	Ref			
III _A -III _C	0.684 (0.325,1.437)	0.316		
IV _A -IV _B	1.241 (0.592,2.602)	0.568		
Previous treatment				
Naive	Ref			
Posttreatment	1.725 (0.963,3.090)	0.067		

AFP, alpha fetal protein; AJCC, American Joint Committee on Cancer; CI, credibility interval; CLIP, Cancer of the Liver Italian Program; HAIC, hepatic arterial infusion chemotherapy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; PSM, propensity score matching; TAE, transcatheter arterial embolization.

** $P < 0.05$ in univariate analysis.

*** $P < 0.05$ in multivariate analysis.

Table 3 Response rate assessment after PSM, n (%)

	TAE + HAIC ($n = 35$)	TACE ($n = 35$)	P-value
Complete response (CR)	4 (11.43)	0 (0)	
Partial response (PR)	9 (25.71)	7 (20.00)	
Stable disease (SD)	18 (51.43)	14 (40.00)	
Progressive disease (PD)	4 (11.43)	14 (40.00)	
Objective response rate (ORR)	13 (37.14)	7 (20.00)	0.112
Disease control rate (DCR)	31 (88.57)	21 (60.00)	0.006

HAIC, hepatic arterial infusion chemotherapy; mRECIST, modified Response Evaluation Criteria In Solid Tumors; PSM, propensity score matching; TACE, transcatheter arterial chemoembolization; TAE, transcatheter arterial embolization.

Table 4 Adverse events and complications after PSM

Individual AEs	TAE + HAIC ($n = 35$)	TACE ($n = 35$)	P value
Hematological parameters			
Thrombocytopenia	12 (34.3%)	9 (25.7%)	0.434
Anemia	9 (25.7%)	5 (14.3%)	0.371
Leukocytopenia	6 (17.14%)	2 (5.7%)	0.133
Other parameters			
GPT elevation	18 (51.4%)	14 (40.0%)	0.472
GOT elevation	15 (42.9%)	12 (34.3%)	0.461
Bilirubin elevation	14 (40.0%)	8 (22.9%)	0.122
ALB reduction	9 (25.7%)	10 (28.6%)	0.788

AE, adverse events; ALB, Albumin; GOT, Glutamic Oxaloacetic Transaminase; GPT, Glutamic Pyruvic Transaminase; HAIC, hepatic arterial infusion chemotherapy; PSM, propensity score matching; TACE, transcatheter arterial chemoembolization; TAE, transcatheter arterial embolization.

Toxicity data in this study were consistent with the previous application of TAE + HAIC for metastatic colorectal cancer in Asian³⁸ and Western³⁹ patients. TACE-related adverse reactions occurring in this study were mild and well tolerated. Hepatic artery occlusion rarely occurred, and AEs associated with catheterization were also uncommon. Thus, TAE + HAIC in this study could be considered an acceptable procedure to treat unresectable HCC.

The loss of OS data is the greatest disappointment in our research. Over 50% patients of both groups were censored, most because the phone number changed after the patient died. We learned that timely follow up is the most essential but most difficult part for retrospective studies.

As a retrospective study, the current research may have some information biases. In addition, the sample size was small, and all patients were from the same institution; therefore, conclusions may not be easily applicable across a generalized population. Further large-scale randomized clinical trials are needed.

In conclusion, the present study showed that, compared with conventional TACE, TAE + HAIC confers PFS benefit in patients with unresectable HCCs, especially those with BCLC stage C. No treatment benefit was obtained for BCLC stage B patients. Therefore, TAE + HAIC may be a new option for Chinese unresectable HCC patients with BCLC stage C and HBV.

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