ImmunoTargets and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Efficiency and Safety of HAIC Combined with Lenvatinib and PD-1 Inhibitor for Advanced Hepatocellular Carcinoma with Lung Metastasis: A Multicenter Propensity Score Matching Analysis

Song Chen[1,*], Ning Wang[2,*], Yi Xiao[3,*], Xiongying Jiang[4,*], Feng Shi[5], Hongjie Cai[1], Shuangyan Tang[6], Wenbo Guo[1], Wenquan Zhuang[1]

[1]Department of Interventional Radiology, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, People's Republic of China; [2]Department of Radiology, the Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, People's Republic of China; [3]Center of Hepato-Pancreato-Biliary Surgery, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, People's Republic of China; [4]Interventional Radiology Division, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, People's Republic of China; [5]Department of Interventional Radiology, Guangdong Provincial People's Hospital, Guangzhou, People's Republic of China; [6]Department of Radiology, the Eighth Affiliated Hospital of Sun Yat-sen University, Shenzhen, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wenbo Guo; Wenquan Zhuang, Department of Interventional Radiology, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, People's Republic of China, Email guowenbo@mail.sysu.edu.cn; zhuangwq@mail.sysu.edu.cn

Purpose: This study aimed to evaluate the clinical efficiency and safety of hepatic arterial infusion chemotherapy (HAIC) combined with lenvatinib and programmed cell death protein-1 (PD-1) inhibitor for patients with hepatocellular carcinoma (HCC) and lung metastasis.

Methods: In this multicenter retrospective study, treatment-naive patients with advanced (BCLC stage C) HCC and lung metastases who received lenvatinib and PD-1 inhibitor - with or without HAIC - between January 2019 and January 2024 were reviewed. Propensity score matching (PSM) was applied to balance baseline characteristics between the two groups. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR) according to RECIST 1.1 criteria, as well as adverse events (AEs).

Results: A total of 422 eligible patients were included, with 169 receiving HAIC (HLP group) and 253 receiving lenvatinib plus PD-1 inhibitor (LP group). After 1:1 PSM, 151 patients were matched in each group. The HLP group demonstrated significantly longer median OS compared to the LP group (26.0 *versus* 8.4 months; hazard ratio [HR]: 0.36; 95% confidence interval [CI]: 0.27–0.49; $P < 0.001$). Median PFS was also improved in the HLP group (7.6 *versus* 5.5 months; HR: 0.77; 95% CI: 0.59–1.00; $P = 0.048$). ORR and DCR were significantly higher in the HLP group (ORR: 47.7% *versus* 20.5%, $P < 0.001$; DCR: 86.1% *versus* 72.2%, $P = 0.003$). Although the HLP group experienced a higher incidence of both all-grade and grade 3/4 AEs, all were manageable, and no grade 5 events occurred.

Conclusion: HAIC combined with lenvatinib and PD-1 inhibitor shows promise as a treatment for advanced HCC with lung metastases, offering improved prognosis and a manageable safety profile.

Keywords: hepatocellular carcinoma, hepatic arterial infusion chemotherapy, lenvatinib, programmed cell death protein-1 inhibitor, propensity score matching

Introduction

According to 2022 statistics, liver cancer ranks as the sixth most common malignancy and the third leading cause of cancer-related death globally.[1] Hepatocellular carcinoma (HCC) constitutes the majority of liver cancer cases. Due to the absence of distinct early-stage symptoms and inadequate surveillance in high-risk populations, most HCC cases are

Received: 26 May 2025
Accepted: 25 August 2025
Published: 2 September 2025

diagnosed at an advanced stage, resulting in a poor prognosis—particularly in the presence of extrahepatic metastases. According to the Barcelona Clinic Liver Cancer (BCLC) staging system, advanced HCC (BCLC stage C) is defined by vascular invasion and/or extrahepatic spread.[2] The lungs are the most frequent site of extrahepatic metastasis and are associated with especially poor survival outcomes. While treatment of advanced HCC with vascular invasion has seen steady progress, optimal strategies for managing extrahepatic metastases, especially lung involvement, remain uncertain.

The presence of lung metastasis signifies advanced-stage HCC, for which systemic therapy is the standard of care. Current systemic options include tyrosine kinase inhibitors (TKIs), anti-angiogenic agents, and immune checkpoint inhibitors (ICIs). Sorafenib, the first approved TKI for advanced HCC, demonstrated a median overall survival (OS) of 10.7 months in the SHARP trial. However, subgroup analysis revealed that sorafenib conferred no significant benefit over placebo in patients with extrahepatic metastases.[3] In 2018, lenvatinib was shown to be non-inferior to sorafenib in OS and superior in terms of objective response rate (ORR) among untreated advanced HCC patients, although data specific to those with extrahepatic spread were limited.[4] In 2020, the IMbrave150 study established the superiority of atezolizumab (a PD-L1 inhibitor) combined with bevacizumab (an anti-angiogenic agent) over sorafenib, including in patients with extrahepatic disease.[5] Tislelizumab (a PD-1 inhibitor) has also demonstrated improved OS, progression-free survival (PFS), and ORR compared to sorafenib as a first-line treatment for BCLC stage B–C HCC in the RATIONALE-301 study.[6] Additionally, various clinical studies have indicated that TKIs combined with PD-1 inhibitors may further enhance outcomes in advanced HCC. However, the LEAP-002 trial showed that lenvatinib plus pembrolizumab did not significantly improve OS or PFS compared with lenvatinib alone in advanced HCC patients, including those with extrahepatic metastases,[7] suggesting that further optimization of combination regimens is warranted. Therefore, the latest guidelines emphasize a multidisciplinary approach for patients with advanced HCC, especially those with pulmonary metastases, where systemic therapies such as TKIs, ICIs, and combination regimens are increasingly being recommended. Specifically, as recommended in the 2025 EASL guideline, for patients with advanced HCC, including those with pulmonary metastasis, systemic combination therapy including at least one PD-1 or PD-L1 inhibitor should be offered,[8] consistent with the recommendation in the 2023 ASALD guideline.[9]

Although systemic therapy is the mainstay for advanced HCC with extrahepatic spread, intrahepatic tumor burden is the leading cause of death, as most patients succumb to progression of intrahepatic lesions rather than metastatic complications. Locoregional therapies such as transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) are commonly employed to control intrahepatic disease. TACE is widely used and recommended as the standard treatment for intermediate-stage HCC.[2] HAIC, particularly the FOLFOX regimen (oxaliplatin, fluorouracil, and leucovorin) developed in China, has shown efficacy in large, unresectable tumors.[10] Compared to TACE, HAIC has demonstrated improved OS and fewer severe adverse events in patients with unresectable HCC. A study showed that combining HAIC with sorafenib prolonged median OS by approximately 11 months compared to sorafenib alone in patients with lung metastases.[11] More recently, a Phase II clinical trial revealed that apatinib plus HAIC achieved a median OS of 11.3 months as a second-line treatment in advanced HCC with extrahepatic metastasis.[12] Another study suggested that HAIC might potentiate the efficacy of lenvatinib combined with PD-1 inhibitor in HCC patients with extrahepatic metastases; however, the metastatic sites varied.[13] Given the heterogeneity of metastatic patterns, it remains unclear whether adding HAIC to lenvatinib and PD-1 inhibitor offers survival benefits over dual therapy in patients specifically with lung metastases.

Therefore, this study aimed to evaluate the efficacy and safety of HAIC in combination with lenvatinib and PD-1 inhibitor versus lenvatinib plus PD-1 inhibitor alone in patients with advanced HCC and lung metastasis.

Methods

Participants

In this retrospective study, patients with HCC and lung metastasis who received lenvatinib and PD-1 inhibitor between January 2019 and January 2024 at three centers in China - the First Affiliated Hospital of Sun Yat-sen University, Guangdong Provincial People's Hospital, and the Memorial Hospital of Sun Yat-sen University - were reviewed. Based on their treatment regimen, patients were divided into two groups: the HLP group (receiving a triple combination of

HAIC, lenvatinib, and PD-1 inhibitor) and the LP group (receiving the dual combination of lenvatinib and PD-1 inhibitor). The number of patients enrolled at each center is presented in Table S1.

The inclusion criteria were as follows: (1) age between 18 and 75 years; (2) diagnosis of HCC confirmed by contrast-enhanced imaging in high-risk individuals or histopathology, according to the American Association for the Study of Liver Diseases (AASLD) guidelines; (3) lung metastasis diagnosed by computed tomography (CT) or biopsy, beyond the indications for ablation; (4) Eastern Cooperative Oncology Group Performance Status score (ECOG PS) ≤ 2 and Child-Pugh class A or B; (5) no prior treatment for HCC; (6) no history of other malignancies within the past five years; (7) receipt of at least six cycles of PD-1 inhibitor and two months of lenvatinib in both groups, and at least two cycles of HAIC in the HLP group; (8) a minimum follow-up period of 12 months from enrollment to the study cut-off; and (9) complete clinical and follow-up data. Key exclusion criteria included: (1) pathological diagnosis of fibrolamellar HCC, sarcomatous HCC, or combined hepatocellular-cholangiocarcinoma (HCC-CC); (2) signs of hepatic decompensation, such as hepatic encephalopathy or gastrointestinal variceal bleeding; and (3) discontinuation or change of therapy without a valid medical justification. Laboratory tests and imaging evaluations - including contrast-enhanced CT or magnetic resonance imaging (MRI) - were performed within one week prior to the initiation of treatment.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University.

Treatment Procedures

HAIC was performed by experienced interventional radiologists at each participating center. The procedure followed established protocols for administering the FOLFOX regimen, as described in previous studies.[14] The catheter tip was super-selectively placed into the tumor-feeding branch of the hepatic artery, based on the size, location, and vascular supply of the intrahepatic tumor. The chemotherapy regimen included oxaliplatin (130 mg/m², administered over 2 hours on day 1), leucovorin (200 mg/m², administered from hour 2 to 4 on day 1), and fluorouracil (400 mg/m² as a bolus over 15 minutes, followed by 2400 mg/m² via continuous infusion over 46 hours on days 1 and 2). This cycle was repeated every 3 weeks for a maximum of 8 cycles, depending on the physician's assessment.

Both groups received oral lenvatinib at a dose of 8 mg (for body weight ≤60 kg) or 12 mg (for body weight >60 kg), along with intravenous PD-1 inhibitor (200 mg every 3 weeks). The types of PD-1 inhibitors used are listed in Table S2. In the HLP group, lenvatinib was administered on the first day of HAIC, and PD-1 inhibitor was infused on the second day immediately following completion of HAIC. In the LP group, lenvatinib and PD-1 inhibitor were administered on the same day. If patients experienced intolerable adverse events (AEs), the dose of lenvatinib or PD-1 inhibitor was either reduced or temporarily discontinued until symptoms resolved.

Efficacy and Safety Assessment

Chest CT and abdominal contrast-enhanced CT or MRI were performed every two treatment cycles. Imaging assessments were independently conducted by two radiologists with expertise in liver diseases. In cases of disagreement, a senior radiologist reviewed the images, and a consensus was reached.

Treatment efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The primary endpoint was overall survival (OS), defined as the time from initial admission to death from any cause. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). PFS was defined as the time from admission to either radiological disease progression or death, whichever occurred first. ORR was defined as the proportion of patients who achieved a complete response (CR) or partial response (PR), while DCR was defined as the proportion of patients who achieved CR, PR, or stable disease (SD). Adverse events (AEs) occurring during treatment were documented and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Propensity Score Matching Analysis

Propensity score matching (PSM) was employed to minimize selection bias and balance baseline characteristics between the two treatment groups. Stepwise logistic regression was used to identify variables associated with treatment allocation, including age, sex, ECOG-PS, etiology, number of intrahepatic lesions, tumor size, number of lung metastases, presence

of portal vein tumor thrombosis (PVTT), alpha-fetoprotein (AFP) level, albumin-bilirubin (ALBI) grade, and Child-Pugh class. A 1:1 nearest-neighbor matching algorithm with a caliper width of 0.2 was applied.

Statistical Analysis

Statistical analyses were performed using R software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 27.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR), depending on their distribution, and were compared between groups using either the Student's *t*-test or the Mann–Whitney *U*-test. Categorical variables were presented as counts and percentages, and compared using the χ^2-test or Fisher's exact test, as appropriate. The Kaplan–Meier method was used to estimate OS and PFS, and differences between groups were assessed using the Log rank test. Univariable and multivariable Cox proportional hazards regression analyses were conducted to identify factors associated with survival outcomes. Variables with a *P*-value < 0.1 in univariate analysis were included in the multivariate model. A two-sided *P*-value < 0.05 was considered statistically significant.

Results

Participants

The patient enrollment flowchart is presented in Figure 1. A total of 422 patients with HCC and lung metastases were included in the study. Among them, 169 patients received the triple combination therapy of HAIC, lenvatinib, and PD-1 inhibitor (HLP group), while the remaining 253 patients were treated with lenvatinib and PD-1 inhibitor without HAIC (LP group). The follow-up period concluded on April 30, 2025, with median follow-up durations of 30.8 months (95% confidence interval [CI]: 16.8–51.9) in the HLP group and 32.6 months (95% CI: 17.4–50.8) in the LP group, respectively. To minimize selection bias, 1:1 PSM was performed, yielding 151 patients in each group. After PSM, baseline characteristics were well balanced between the two groups (Table 1).

Before PSM, patients in the HLP group received a median of 4 cycles of HAIC (range: 2–8), 6.8 months of lenvatinib (range: 2.5–12.2) and 12 cycles of PD-1 inhibitor (range: 6–20). In comparison, patients in the LP group received a median of 5.0 months of lenvatinib (range: 2.0–11.7) and 10 cycles of PD-1 inhibitor (range: 6–17).

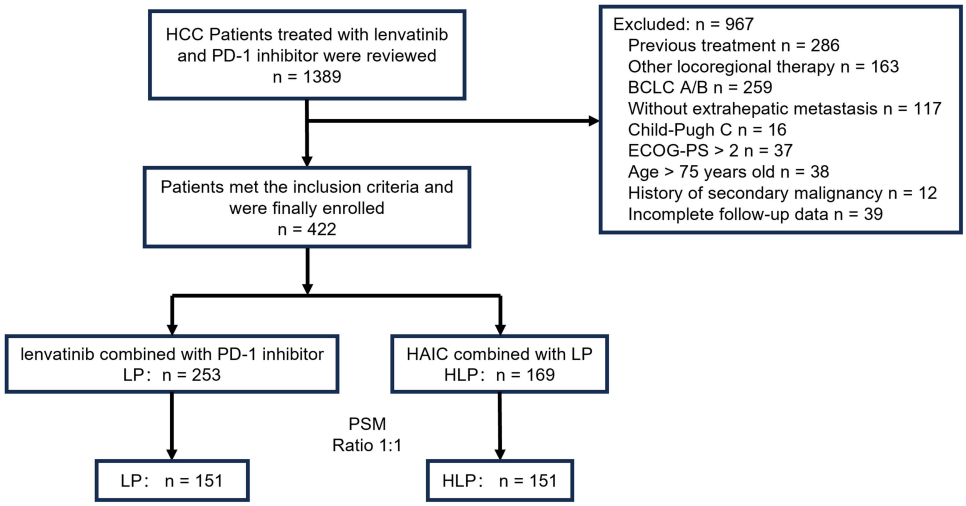


Figure 1 Patient selection flowchart. A patient might meet several exclusion criteria, but they were excluded only once from the uppermost criteria.
Abbreviations: PSM, propensity score matching; HLP, HAIC combined with lenvatinib and PD-1 inhibitor; LP, lenvatinib combined with PD-1 inhibitor; HAIC, hepatic arterial infusion chemotherapy; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance score.

Table 1 Baseline Characteristics of the Study Patients Before and After PSM

Characteristics	Before Matching			After Matching		
	LP n = 253	HLP n = 169	*P*	LP n = 151	HLP n = 151	*P*
Age (Mean ± SD, year)	49 ± 12	49 ± 12	0.661	49 ± 12	49 ± 12	0.633
Age (year)			0.510			0.644
≤ 50	140 (55.3%)	88 (52.1%)		83 (55.0%)	79 (52.3%)	
> 50	113 (44.7%)	81 (47.9%)		68 (45.0%)	72 (47.7%)	
Sex			0.086			0.729
Female	211 (83.4%)	151 (89.3%)		131 (86.8%)	133 (88.1%)	
Male	42 (16.6%)	18 (10.7%)		20 (13.2%)	18 (11.9%)	
ECOG-PS			<0.001			0.862
0	231 (91.3%)	133 (78.7%)		131 (86.8%)	133 (88.1%)	
1	20 (7.9%)	36 (21.3%)		20 (13.2%)	18 (11.9%)	
2	2 (0.8%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Etiology			0.325			0.835
HBV	237 (93.7%)	154 (91.1%)		138 (91.4%)	139 (92.1%)	
Others	16 (6.3%)	15 (8.9%)		13 (8.6%)	12 (7.9%)	
Intrahepatic lesion number			0.618			0.444
Single	78 (30.8%)	56 (33.1%)		40 (26.5%)	46 (30.5%)	
Multiple	175 (69.2%)	113 (66.9%)		111 (73.5%)	105 (69.5%)	
Size (Mean ± SD, cm)	12.3 ± 3.6	12.3 ± 3.4	0.993	12.4 ± 3.7	12.4 ± 3.4	0.943
Size (cm)			0.236			0.602
≤ 10	81 (32.0%)	45 (26.6%)		42 (27.8%)	38 (25.2%)	
> 10	172 (68.0%)	124 (73.4%)		109 (72.2%)	113 (74.8%)	
Lung metastasis number			0.797			0.764
Single	52 (20.6%)	33 (19.5%)		28 (18.5%)	26 (17.2%)	
Multiple	201 (79.4%)	136 (80.5%)		123 (81.5%)	125 (82.8%)	
PVTT			0.063			0.809
Absence	105 (41.5%)	55 (32.5%)		54 (35.8%)	52 (34.4%)	
Presence	148 (58.5%)	114 (67.5%)		97 (64.2%)	99 (65.6%)	
AFP (μg/L)			0.880			0.812
≤ 400	91 (36.0%)	62 (36.7%)		55 (36.4%)	57 (37.7%)	
> 400	162 (64.0%)	107 (63.3%)		96 (63.6%)	94 (62.3%)	
ALBI			0.826			0.946
1	85 (33.6%)	56 (33.1%)		52 (34.4%)	50 (33.1%)	
2	163 (64.4%)	108 (63.9%)		96 (63.6%)	97 (64.2%)	
3	5 (2.0%)	5 (3.0%)		3 (2.0%)	4 (2.6%)	
Child-Pugh			0.960			>0.999
A	219 (86.6%)	146 (86.4%)		132 (87.4%)	132 (87.4%)	
B	34 (13.4%)	23 (13.6%)		19 (12.6%)	19 (12.6%)	

Notes: Continuous variables are presented as mean ± SD, and categorical variables are presented as n (%).*P* values were calculated using a two-sided Welch *t*-test and Pearson's χ^2 test.

Abbreviations: PSM, propensity score matching; HLP, HAIC combined with lenvatinib and PD-1 inhibitor; LP, lenvatinib combined with PD-1 inhibitor; HAIC, hepatic arterial infusion chemotherapy; ECOG, Eastern Cooperative Oncology Group; PS, performance score; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; PVTT, portal vein tumor thrombus.

Tumor Response

Treatment responses were assessed according to RECIST 1.1 criteria before and after PSM (Table 2). Prior to PSM, the HLP group demonstrated significantly higher ORR (46.7% *versus* 22.9%, $P < 0.001$) and DCR (82.8% *versus* 69.1%, $P = 0.002$) compared to LP group. After PSM, the superiority of the HLP group remained evident, with significantly higher ORR (47.7% *versus* 20.5%, $P < 0.001$) and DCR (86.1% *versus* 72.2%, $P = 0.003$).

Table 2 Treatment Efficacy Evaluated by RECIST 1.1 Criteria Before and After PSM

Response	Before PSM			Before PSM		
	LP n = 253	HLP n = 169	*P*	LP n = 151	HLP n = 151	*P*
CR	0 (0)	0 (0)		0 (0)	0 (0)	
PR	58 (22.9%)	79 (46.7%)		31 (20.5%)	72 (47.7%)	
SD	117 (46.2%)	61 (36.1%)		78 (51.7%)	58 (38.4%)	
PD	78 (30.9%)	29 (17.2%)		42 (27.8%)	21 (13.9%)	
ORR	58 (22.9%)	79 (46.7%)	<0.001	31 (20.5%)	72 (47.7%)	<0.001
DCR	175 (69.1%)	140 (82.8%)	0.002	109 (72.2%)	130 (86.1%)	0.003

Notes: Summary of best response. Values are presented as n (%). *P* values were calculated using a two-sided χ^2 test.

Abbreviations: PSM, propensity score matching; RECIST, response evaluation criteria in solid tumors; HLP, HAIC combined with lenvatinib and PD-1 inhibitor; LP, lenvatinib combined with PD-1 inhibitor; HAIC, hepatic arterial infusion chemotherapy; CR, complete response; PR, partial response; SD, disease stable; PD, progression disease; ORR, objective response rate; DCR, disease control rate.

Survival Outcomes

Before PSM, 194 patients (76.7%) in the LP group and 68 (40.2%) patients in the HLP group had died by the end of follow-up. The median OS was significant longer in the HLP group (26.0 months, 95% CI: 18.4–NA) compared to the LP group (8.6 months, 95% CI: 7.9–10.0; HR: 0.36, 95% CI: 0.28–0.46, $P < 0.001$). Similarly, the HLP group exhibited a significantly longer median PFS than the LP group (7.7 months, 95% CI: 6.7–10.8 *versus* 5.4 months, 95% CI: 4.5–6.1; HR: 0.76, 95% CI: 0.61–0.95, $P = 0.017$). Among the 151 matched pairs after PSM, the HLP group continued to show a significantly longer median OS than the LP group (26.0 months, 95% CI: 18.6–NA *versus* 8.4 months, 95% CI: 6.7–11.8; HR: 0.36, 95% CI: 0.27–0.49, $P < 0.001$). Median PFS was also favored the HLP group (7.6 months, 95% CI: 6.3–9.0 *versus* 5.5 months, 95% CI: 3.9–6.3; HR: 0.77, 95% CI: 0.59–1.00, $P = 0.048$) (Figure 2).

Univariate and Multivariate Analysis

Univariate and multivariate analyses were conducted to identify risk factors associated with OS and PFS (Table 3). Multivariate Cox regression analysis revealed that treatment option and PVTT were independent risk factors for both OS and PFS. Additionally, the presence of multiple lung metastases was an independent risk factor for OS, but not for PFS.

Subgroup Analysis

Forest plots were generated to compare outcomes between subgroups after PSM (Figure 3). For both OS and PFS, the HLP group showed greater benefit across nearly all subgroups compared to the LP group, except in cases with small sample sizes or impaired liver function. These findings suggest that HAIC combined with lenvatinib and PD-1 inhibitor may be effective across various subgroups of HCC patients with lung metastases. However, for patients with compromised liver function - such as those classified as ALBI grade 3 or Child-Pugh class B - treatment with lenvatinib and PD-1 inhibitor may be more appropriate.

Progression Reason Analysis

Regarding the analysis of progression patterns, five modes of tumor progression were identified: intrahepatic lesion progression, development of new intrahepatic lesion(s), extrahepatic lesion progression, development of new extrahepatic lesion(s), and death. At the data cutoff, 118 patients in the HLP group and 238 in the LP group had experienced disease progression. Notably, individual patients could exhibit more than one mode of progression simultaneously. The distribution of progression modes in the HLP and LP groups was as follows: intrahepatic lesion progression (12.0% *versus* 34.1%), new intrahepatic lesion(s) (9.7% *versus* 24.7%), extrahepatic lesion progression (33.1% *versus* 17.1%), new extrahepatic lesion(s) (39.4% *versus* 16.4%), and death (5.7% *versus* 7.7%). Clearly, the proportions of intrahepatic

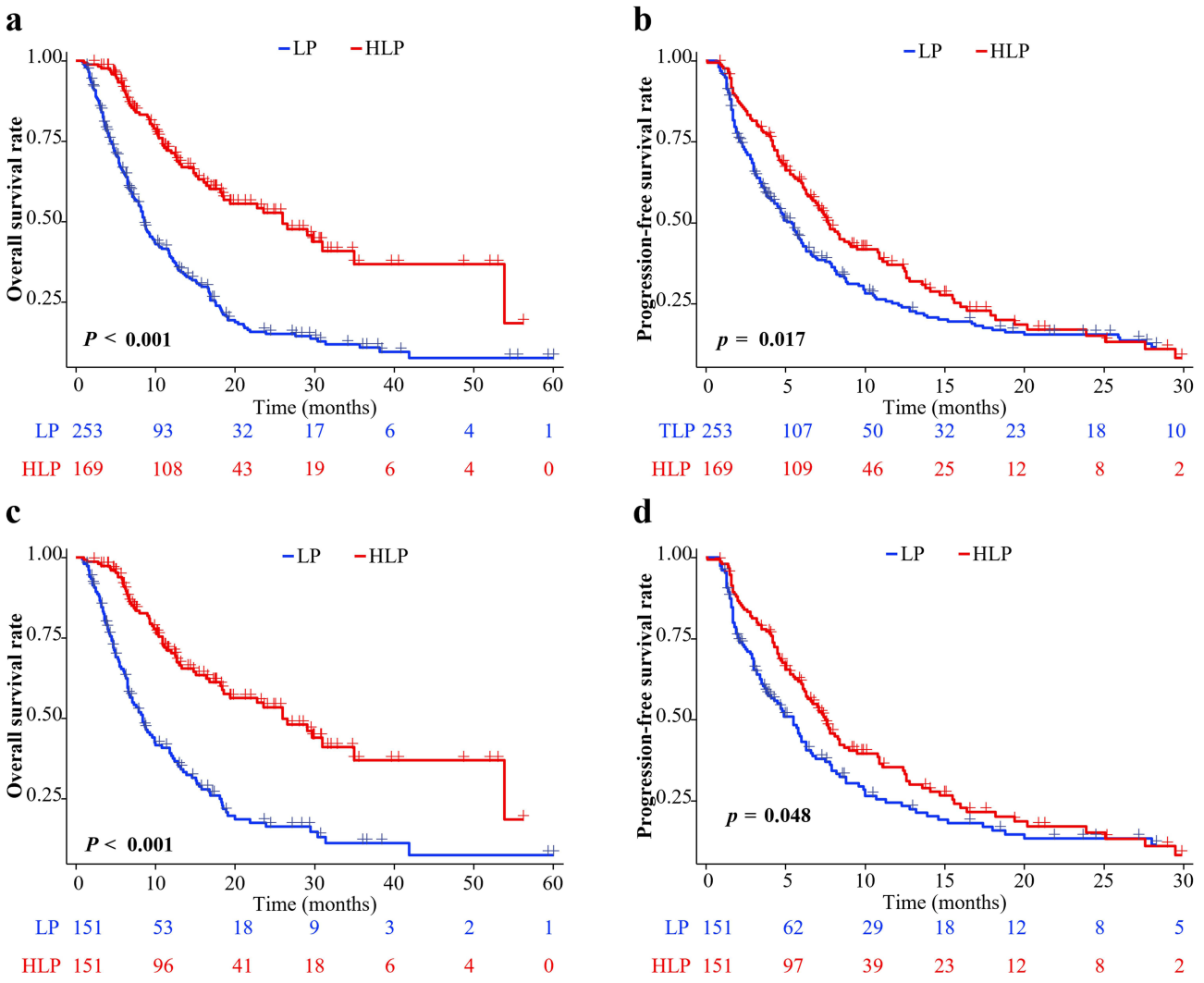


Figure 2 Kaplan-Meier curves comparing OS and PFS among patients who underwent HAIC plus lenvatinib and PD-1 inhibitor (HLP) or lenvatinib plus PD-1 inhibitor (LP) before (**a–b**) and after (**c–d**) PSM. *P* values were calculated using Log rank test.

Abbreviations: PSM, propensity score matching; HLP, HAIC combined with lenvatinib and PD-1 inhibitor; LP, lenvatinib combined with PD-1 inhibitor; HAIC, hepatic arterial infusion chemotherapy; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

lesion progression and new intrahepatic lesions were significantly lower in the HLP group compared to the LP group. (Figure S1).

Safety

As shown in Table 4, the overall incidence of adverse events (AEs) was 75.1% in the HLP group and 57.7% in the LP group. In the HLP group, the most common AEs were abdominal pain (52.7%), nausea (48.5%), decreased appetite (43.2%), and fatigue (34.9%). The most frequent grade 3–4 AEs included abdominal pain (14.2%), nausea (10.1%), and diarrhea (9.5%), most of which were associated with HAIC. In the LP group, decreased appetite (36.0%), fatigue (34.0%), hypoproteinemia (21.7%), and elevated AST (20.9%) were the most common AEs, while the most frequent grade 3–4 AEs were fatigue (6.3%), immune-related AEs (4.3%), and proteinuria (3.6%). Although the incidence of both any-grade and grade 3–4 AEs was higher in the HLP group, these events were generally manageable, and no treatment-related deaths occurred during the study period.

https://doi.org/10.2147/ITT.S542811

Table 3 Univariate and Multivariate Analyses of Predictors of Survival After Treatment

Characteristics	OS				PFS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (> 50)	0.74 (0.54, 0.99)	0.046	0.88 (0.53, 1.98)	0.342	0.85 (0.65, 1.11)	0.227		
Sex (Male)	1.13 (0.74, 1.71)	0.576			1.08 (0.74, 1.58)	0.695		
ECOG-PS (1)	1.61 (1.03, 2.50)	0.035	1.56 (1.00, 2.43)	0.052	1.30 (0.86, 1.98)	0.216		
Etiology (HBV)	0.91 (0.53, 1.58)	0.748			1.02 (0.62, 1.67)	0.938		
Intrahepatic lesion number (Multiple)	1.08 (0.77, 1.51)	0.647			1.18 (0.88, 1.59)	0.267		
Size (> 10cm)	1.22 (0.86, 1.71)	0.261			1.04 (0.77, 1.40)	0.799		
Lung metastasis number (Multiple)	1.54 (1.15, 1.81)	0.031	1.28 (1.07, 1.59)	0.042	1.12 (0.88, 1.39)	0.089		
PVTT (Presence)	1.62 (1.17, 2.24)	0.004	1.71 (1.23, 2.37)	0.002	1.31 (0.99, 1.74)	0.059	1.34 (1.01, 1.78)	0.041
AFP (> 400)	1.02 (0.75, 1.39)	0.893			1.13 (0.86, 1.50)	0.382		
ALBI (2–3)	1.13 (0.83, 1.55)	0.435			0.91 (0.69, 1.20)	0.494		
Child-Pugh (B)	1.62 (1.01, 2.59)	0.044	1.52 (0.94, 2.47)	0.087	1.38 (0.92, 2.06)	0.123		
Treatment (HLP)	0.36 (0.26, 0.49)	<0.001	0.34 (0.24, 0.46)	<0.001	0.76 (0.59, 1.00)	0.048	0.75 (0.57, 0.98)	0.033

Notes: Univariable and multivariable Cox regression analyses were performed to identify the factors associated with survival. Factors with $P < 0.1$ in univariate analysis were included in multivariate analysis. Two-sided $P < 0.05$ was defined as statistically significant.

Abbreviations: HLP, HAIC combined with lenvatinib and PD-1 inhibitor; HAIC, hepatic arterial infusion chemotherapy; ECOG, Eastern Cooperative Oncology Group; PS, performance score; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; PVTT, portal vein tumor thrombus; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

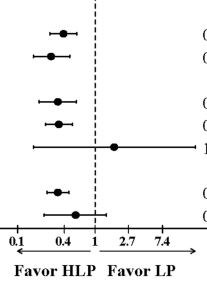
Discussion

This study is the first multicenter clinical trial to compare the efficacy of triple combination therapy—HAIC plus lenvatinib and PD-1 inhibitor—with that of the dual regimen of lenvatinib and PD-1 inhibitor in patients with advanced HCC and lung metastases. To minimize confounding variables, we applied propensity score matching (PSM), enrolled a relatively large cohort from multiple centers, and conducted long-term follow-up. In both the full and PSM-adjusted cohorts, the triple therapy significantly improved overall survival (OS), progression-free survival (PFS), and objective response rate (ORR). Notably, although the triple combination therapy was associated with a higher incidence of adverse events (AEs), all AEs were effectively managed with appropriate interventions, indicating that the regimen is both safe and tolerable.

Systemic therapy is recommended as the first-line treatment for advanced HCC, including cases with extrahepatic metastasis; however, control of intrahepatic lesions remains the most critical factor influencing patient survival.[15] This highlights the importance of combining systemic and locoregional therapies. Transarterial chemoembolization (TACE), the most commonly used locoregional approach, involves intra-arterial delivery of cytotoxic agents emulsified with lipiodol into the lesions, followed by embolization to induce both cytotoxic and ischemic effects. TACE can effectively control intrahepatic tumors, achieving an objective response rate (ORR) of approximately 24% in advanced HCC.[16] Nevertheless, its use is limited in cases with extensive intrahepatic tumor burden or severely compromised portal vein flow.[17] Furthermore, the acute hypoxia induced by embolization may stimulate vascular endothelial growth factor (VEGF) expression, potentially promoting angiogenesis, local recurrence, and distant metastasis, including to the lungs.[18] Compared with TACE, hepatic arterial infusion chemotherapy (HAIC) using the FOLFOX regimen has shown superior outcomes, with reported ORR of 46% *versus* 18% and median overall survival of 23.1 *versus* 16.2 months in patients with unresectable HCC.[10] The high-dose, continuous infusion of chemotherapeutic agents in HAIC maximizes cytotoxic effects on intrahepatic tumors. In addition, HAIC preserves hepatic arterial flow, thereby mitigating tumor hypoxia and avoiding the pro-metastatic effects associated with embolization. The gradual systemic release of chemotherapeutic agents from the liver also contributes to systemic anti-tumor effect. Notably, chemotherapy has been associated with survival benefits in HCC patients with lung metastases.[19] Moreover, the combination of FOLFOX-based HAIC with lenvatinib and toripalimab (a PD-1 inhibitor) has demonstrated promising anti-tumor efficacy in patients with HCC and extrahepatic spread.[20]

a

Subgroup	LP	HLP	OS	HR (95% CI)	*p*
Overall	112/151 (74.2)	62/151 (41.1)		0.36 (0.26, 0.49)	<0.001
Age					
> 50	46/68 (67.6)	26/72 (36.1)		0.42 (0.26, 0.69)	0.001
≤ 50	66/83 (79.5)	36/79 (45.6)		0.31 (0.20, 0.46)	<0.001
Sex					
Female	95/131 (72.5)	53/133 (39.8)		0.38 (0.27, 0.53)	<0.001
Male	17/20 (85.0)	9/18 (50.0)		0.23 (0.10, 0.55)	0.001
ECOG-PS					
0	98/131 (74.8)	53/133 (39.8)		0.35 (0.25, 0.48)	<0.001
1	14/20 (70.0)	9/18 (50.0)		0.43 (0.18, 1.03)	0.059
Etiology					
HBV	104/138 (75.4)	56/139 (40.3)		0.35 (0.25, 0.49)	<0.001
Others	8/13 (61.5)	6/12 (50.0)		0.37 (0.12, 1.15)	0.086
Intrahepatic lesion number					
Multiple	85/111 (76.6)	41/105 (39.0)		0.32 (0.22, 0.47)	<0.001
Single	27/40 (67.5)	21/46 (45.7)		0.47 (0.26, 0.83)	0.01
Size (cm)					
> 10	83/109 (76.1)	47/113 (41.6)		0.34 (0.24, 0.48)	<0.001
≤ 10	29/42 (69.0)	15/38 (39.5)		0.38 (0.20, 0.72)	0.003
Lung metastasis number					
Multiple	93/123 (76.6)	51/125 (39.0)		0.89 (0.77, 0.98)	0.048
Single	19/28(67.5)	11/26 (45.7)		0.92 (0.81, 1.23)	0.784
PVTT					
Absence	33/54 (61.1)	19/52 (36.5)		0.41 (0.24, 0.73)	0.002
Presence	79/97 (81.4)	43/99 (43.4)		0.32 (0.22, 0.46)	<0.001
AFP (μg/L)					
> 400	69/96 (71.9)	40/94 (42.6)		0.39 (0.26, 0.58)	<0.001
≤ 400	43/55 (78.2)	22/57 (38.6)		0.27 (0.16, 0.47)	<0.001
ALBI					
1	41/52 (78.8)	19/50 (38.0)		0.33 (0.19, 0.57)	<0.001
2	69/96 (71.9)	41/97 (42.3)		0.34 (0.23, 0.51)	<0.001
3	2/3 (66.7)	2/4 (50.0)		1.76 (0.16, 19.57)	0.646
Child-Pugh					
A	101/132 (76.5)	53/132 (40.2)		0.33 (0.24, 0.46)	<0.001
B	11/19 (57.9)	9/19 (47.4)		0.56 (0.22, 1.39)	0.21



b

Subgroup	LP	HLP	PFS	HR (95% CI)	*p*
Overall	111/151 (73.5)	108/151 (71.5)		0.76 (0.59, 1.00)	0.048
Age					
>50	46/68 (67.6)	49/72 (68.1)		0.94 (0.63, 1.41)	0.764
≤ 50	65/83 (78.3)	59/79 (74.7)		0.64 (0.45, 0.91)	0.013
Sex					
Female	95/131 (72.5)	93/133 (69.9)		0.79 (0.59, 1.05)	0.11
Male	16/20 (80.0)	15/18 (83.3)		0.60 (0.29, 1.23)	0.162
ECOG-PS					
0	97/131 (74.0)	97/133 (72.9)		0.80 (0.60, 1.06)	0.122
1	14/20 (70.0)	11/18 (61.1)		0.55 (0.25, 1.23)	0.144
Etiology					
HBV	104/138 (75.4)	98/139 (70.5)		0.74 (0.56, 0.97)	0.031
Others	7/13 (53.8)	10/12 (83.3)		1.07 (0.40, 2.87)	0.887
Intrahepatic lesion number					
Multiple	86/111 (77.5)	73/105 (69.5)		0.66 (0.48, 0.91)	0.01
Single	25/40 (62.5)	35/46 (76.1)		1.09 (0.65, 1.83)	0.748
Size (cm)					
> 10	78/109 (71.6)	82/113 (72.6)		0.78 (0.57, 1.07)	0.125
≤ 10	33/42 (78.6)	26/38 (68.4)		0.68 (0.41, 1.14)	0.148
Lung metastasis number					
Multiple	94/123 (76.4)	91/125 (72.8)		0.89 (0.63, 1.24)	0.789
Single	17/28 (60.7)	17/26 (65.4)		0.91 (0.75, 1.38)	0.862
PVTT					
Absence	35/54 (64.8)	38/52 (73.1)		1.03 (0.65, 1.63)	0.916
Presence	76/97 (78.4)	70/99 (70.7)		0.63 (0.46, 0.88)	0.006
AFP (μg/L)					
> 400	73/96 (76.0)	70/94 (74.5)		0.79 (0.56, 1.09)	0.151
≤ 400	38/55 (69.1)	38/57 (66.7)		0.70 (0.44, 1.10)	0.125
ALBI					
1	43/52 (82.7)	35/50 (70.0)		0.61 (0.39, 0.96)	0.032
2	67/96 (69.8)	70/97 (72.2)		0.81 (0.58, 1.13)	0.22
3	1/3 (33.3)	3/4 (75.0)		3.14 (0.32, 30.56)	0.325
Child-Pugh					
A	99/132 (75.0)	93/132 (70.5)		0.72 (0.55, 0.96)	0.026
B	12/19 (63.2)	15/19 (78.9)		1.04 (0.49, 2.23)	0.915

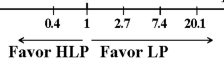


Figure 3 Forest plots based on OS (**a**) and PFS (**b**) of each subgroup. *P* values were calculated using Log rank test.

Abbreviations: PSM, propensity score matching; HLP, HAIC combined with lenvatinib and PD-1 inhibitor; LP, lenvatinib combined with PD-1 inhibitor; HAIC, hepatic arterial infusion chemotherapy; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance score; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; PVTT, portal vein tumor thrombus.

https://doi.org/10.2147/ITT.S542811

Table 4 Treatment-Related Adverse Events

Adverse events	Any grade			Grade 3/4		
	LP (n = 253)	HLP (n = 169)	*p*	LP (n = 253)	HLP (n = 169)	*p*
Overall incidence	146 (57.7%)	127 (75.1%)	< 0.001	31 (12.3%)	42 (24.9%)	< 0.001
Abdominal pain	11 (4.3%)	89 (52.7%)	< 0.001	3 (1.2%)	24 (14.2%)	< 0.001
Nausea	29 (11.5%)	82 (48.5%)	< 0.001	2 (0.8%)	17 (10.1%)	< 0.001
Diarrhea	39 (15.4%)	58 (34.3%)	< 0.001	5 (2.0%)	16 (9.5%)	< 0.001
Decreased appetite	91 (36.0%)	73 (43.2%)	0.136	2 (0.8%)	1 (0.6%)	0.812
Rash	28 (11.1%)	18 (10.7%)	0.893	6 (3.2%)	4 (2.4%)	0.998
Fatigue	86 (34.0%)	59 (34.9%)	0.846	16 (6.3%)	11 (3.0%)	0.939
Hypoproteinemia	55 (21.7%)	39 (23.1%)	0.747	5 (2.0%)	3 (1.8%)	0.882
Elevated bilirubin	20 (7.9%)	27 (16.0%)	0.010	4 (1.6%)	2 (1.2%)	0.736
Elevated ALT	49 (19.4%)	28 (16.6%)	0.466	1 (0.4%)	1 (0.6%)	0.774
Elevated AST	53 (20.9%)	25 (14.8%)	0.111	1 (0.4%)	1 (0.6%)	0.774
Hypothyroidism	10 (4.0%)	7 (4.1%)	0.923	2 (0.8%)	1 (0.6%)	0.812
Sensory neuropathy	0 (0)	41 (24.3%)	< 0.001	0 (0)	0 (0)	–
Leukopenia	19 (7.5%)	48 (28.4%)	< 0.001	3 (1.2%)	9 (5.3%)	0.012
Thrombocytopenia	42 (16.6%)	32 (18.9%)	0.537	4 (1.6%)	6 (3.6%)	0.193
Hypertension	40 (15.8%)	31 (18.3%)	0.496	7 (2.8%)	4 (2.4%)	0.801
Hand-foot skin reaction	19 (7.5%)	12 (7.1%)	0.875	1 (0.4%)	1 (0.6%)	0.774
Dysphonia	8 (3.2%)	5 (3.0%)	0.906	0 (0)	0 (0)	-
Proteinuria	45 (17.8%)	33 (19.5%)	0.652	9 (3.6%)	6 (3.6%)	0.997
Immunity-related AEs	29 (11.4%)	16 (9.5%)	0.516	11 (4.3%)	5 (3.0%)	0.465

Notes: Values are presented as n (%). *P* values were calculated using a two-sided χ^2 test.
Abbreviations: HLP, HAIC combined with lenvatinib and PD-1 inhibitor; LP, lenvatinib combined with PD-1 inhibitor; HAIC, hepatic arterial infusion chemotherapy; ALT, alanine transaminase; AST, aspartate aminotransferase; AEs, adverse events.

In our study, the triple therapy combining HAIC-FOLFOX with lenvatinib and PD-1 inhibitor significantly improved median OS (26.0 *versus* 8.4 months) and ORR (46.7% *versus* 22.9%) compared to dual systemic therapy in patients with advanced HCC and lung metastases. A prior study reported that patients with lung metastases receiving sorafenib monotherapy had a median OS of only 7.37 months, whereas those treated with sorafenib plus locoregional therapies (primarily TACE) achieved a median OS of 18.37 months.[11] Compared with this combination, our triple combination regimen demonstrated superior survival outcomes in this high-risk subgroup. In a phase II trial, patients with extrahepatic metastases received apatinib (a TKI) plus HAIC as second-line therapy, with tumor shrinkage observed in 87.2% of intrahepatic and 74.4% of extrahepatic lesions,[12] suggesting the potential of HAIC to exert systemic anti-tumor effects beyond the liver. Locoregional therapies, when combined with targeted and immunotherapeutic agents, may modulate the tumor microenvironment and inhibit the invasion and migration of cancer cells, thereby potentially limiting extrahepatic metastasis.[18]

We selected the combination of lenvatinib and PD-1 inhibitor as the control group, given the promising synergistic antitumor effects observed in unresectable or advanced HCC. However, limited studies have specifically examined its efficacy in the subset of patients with lung metastases. Lenvatinib is a multitargeted tyrosine kinase inhibitor (TKI) that suppresses VEGFR 1–3, which play key roles in pathological angiogenesis. PD-1 inhibitor is a monoclonal antibody that binds to and inhibits the PD-1 receptor expressed on activated immune cells, thereby enhancing anticancer immune responses. Lenvatinib has been shown to augment the efficacy of anti-PD-1 antibodies by normalizing tumor vasculature and promoting immune cell infiltration in HCC.[21] The combination of TKI with PD-1 inhibitor has been demonstrated to improve conversion rates in unresectable HCC.[22] In prior studies, lenvatinib plus PD-1 inhibitor therapy yielded superior outcomes compared to PD-1 inhibitor monotherapy, with higher ORR (32.7% *versus* 10.3%), longer median PFS (10.6 *versus* 4.4 months), and OS (18.4 *versus* 8.5 months).[23] Similar findings have been reported in other dual-regimen studies

compared to systemic monotherapy in advanced HCC.[24] However, in our study, the results for the dual-agent control group were less favorable, with an ORR of 18% and a median OS of 8.4 months.

Compared to the dual-agent control group, the triple combination therapy demonstrated encouraging outcomes in terms of long-term survival and tumor regression in patients with lung metastases. Similarly, a triple regimen combining TACE, lenvatinib, and camrelizumab (a PD-1 inhibitor) showed promising ORR and conversion rates in patients with unresectable HCC.[25] Another study reported that the combination of TACE, lenvatinib, and PD-1 inhibitor provided superior OS compared to TACE plus lenvatinib in patients with extrahepatic metastases, although the sample size was small.[26] A recent meta-analysis also supported the enhanced efficacy of this triple combination approach, showing that TACE combined with lenvatinib and PD-1 inhibitor significantly improved OS, PFS, and ORR compared to monotherapy, dual-agent regimens, and even the triple combination of TACE, sorafenib, and PD-1 inhibitors.[27] In a single-arm trial involving 36 patients with advanced HCC (27.8% with extrahepatic spread), treated with HAIC plus lenvatinib and toripalimab yielded a median OS of 17.9 months and an ORR of 63.9%. Moreover, increased levels of peripheral $CD8^+$ and $CD4^+$ T cells were observed following the combination therapy, indicating an enhanced systemic immune response.[28] Preclinical studies have also shown that lenvatinib combined with HAIC-FOLFOX exerts a synergistic inhibitory effect on HCC proliferation and angiogenesis by suppressing phosphorylation of multiple targets.[29]

According to clinical guidelines, for advanced HCC with lung metastases, local ablation therapy is generally recommended when the lung tumor burden is relatively low. Typically, this includes patients with no more than three metastatic lesions, each with a maximum diameter of 3 cm, and well-controlled intrahepatic disease. Studies have shown that ablation of lung metastatic lesions, especially in cases of oligometastasis, can significantly improve patient survival and may even lead to long-term outcomes comparable to those of patients without lung metastases.[30] In our study, the enrolled patients with lung metastases were initially ineligible for ablation therapy. However, following treatment, 17 (10.1%) and 9 (3.6%) patients in the HLP and LP group met the criteria for pulmonary ablation and subsequently underwent the procedure. Furthermore, both groups of patients who received pulmonary ablation showed significantly better survival outcomes compared to those who did not receive ablation. Notably, the proportion of patients who were successfully converted to ablation candidates was significantly higher in the HLP group ($P = 0.012$), indicating superior clinical efficacy. These findings further support the synergistic antitumor effect of HAIC combined with systemic therapy. This combination not only effectively controls intrahepatic disease but also contributes to the suppression of lung metastases. The possible underlying mechanisms include: (1) systemic circulation of chemotherapeutic agents used in HAIC, which exert antitumor effects on lung lesions; (2) immunomodulatory effects of chemotherapy, which may enhance both hepatic and pulmonary immune microenvironments, thereby synergizing with targeted and immunotherapeutic agents; and (3) effective intrahepatic disease control by HAIC may improve the overall immunosuppressive state, thus potentiating the efficacy of systemic treatments. Further investigations are warranted in future clinical and preclinical studies.

We also conducted subgroup analyses to evaluate factors influencing OS and PFS. The results showed that triple therapy demonstrated superior survival outcomes across the majority of subgroups. However, in subgroups with impaired liver function, including patients classified as Child-Pugh class B or ALBI grade 3, dual therapy showed a trend toward better prognosis. This suggests that patients with compromised liver function may benefit more from systemic therapy alone, and the addition of HAIC may not be appropriate. The primary reason is that HAIC, as a form of locoregional therapy, may inevitably impose additional stress on liver function. For patients with already impaired hepatic reserve, preserving liver function is often a higher priority than aggressive tumor control.[31] Therefore, in such cases, adopting a milder treatment strategy may yield greater overall benefit.

In addition to its favorable clinical outcomes, the combination of HAIC with lenvatinib and PD-1 inhibitor was associated with an increased incidence of adverse events (AEs) to some extent. A higher frequency of HAIC-related AEs was observed, which is consistent with findings from previous HAIC clinical trials. However, these AEs were generally manageable with appropriate supportive medications and did not lead to disease progression or treatment discontinuation. The incidence of AEs in the HLP group was higher compared to patients treated with either locoregional or systemic therapy in earlier studies.[4,6] This may be attributed to the poorer baseline conditions of the enrolled patients, as well as the potential additive toxicity from systemic therapy. A common HAIC-specific AE was abdominal pain caused by

arterial vasospasm during oxaliplatin infusion. Currently, there is no effective method to completely prevent this particular type of pain, other than administering analgesics and antispasmodics or reducing the infusion rate of oxaliplatin.[32] Overall, the combination of HAIC, lenvatinib, and PD-1 inhibitor was found to be safe and tolerable.

There are several potential limitations to our study. First, as a retrospective analysis, the possibility of selection bias cannot be entirely excluded. Although propensity score matching (PSM) was employed to minimize baseline differences between the two groups, residual confounding may still exist. Therefore, prospective randomized controlled trials are necessary to further validate our findings. Second, the majority of patients in our cohort had hepatitis B virus (HBV)-related HCC, which may limit the generalizability of our results to patients with other etiologies. Third, this study exclusively included patients treated with lenvatinib and PD-1 inhibitor; thus, additional research is warranted to assess whether similar outcomes can be achieved using alternative systemic agents.

In conclusion, compared to lenvatinib plus PD-1 inhibitor, the addition of HAIC to lenvatinib and PD-1 inhibitor significantly improves OS, PFS, and ORR in patients with HCC and lung metastases, while maintaining an acceptable safety profile.

Ethic Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University. Written informed consent for the treatment was obtained from all patients.

Funding

This work was supported by grants from the National Natural Science Foundation of China (82202271), Guangzhou Basic and Applied Basic Research Foundation [no. 202201011304].

Disclosure

The authors report no relevant financial or non-financial interests in this work.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74:229–263. doi:10.3322/caac.21834
2. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol*. 2022;76:681–693. doi:10.1016/j.jhep.2021.11.018
3. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359:378–390. doi:10.1056/NEJMoa0708857
4. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised Phase 3 non-inferiority trial. *Lancet*. 2018;391:1163–1173. doi:10.1016/S0140-6736(18)30207-1
5. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. 2022;76:862–873. doi:10.1016/j.jhep.2021.11.030
6. Qin S, Kudo M, Meyer T, et al. Tislelizumab vs sorafenib as first-line treatment for unresectable hepatocellular carcinoma: a phase 3 randomized clinical trial. *JAMA Oncol*. 2023;9:1651–1659. doi:10.1001/jamaoncol.2023.4003
7. Llovet JM, Kudo M, Merle P, et al. Lenvatinib plus pembrolizumab versus lenvatinib plus placebo for advanced hepatocellular carcinoma (LEAP-002): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2023;24(12):1399–1410. doi:10.1016/S1470-2045(23)00469-2
8. EASL clinical practice guidelines on the management of hepatocellular carcinoma. *J Hepatol*. 2025;82:315–374. doi:10.1016/j.jhep.2024.08.028
9. Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology*. 2023;78:1922–1965. doi:10.1097/HEP.0000000000000466
10. Li QJ, He MK, Chen HW, et al. Hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin versus transarterial chemoembolization for large hepatocellular carcinoma: a randomized phase III trial. *J Clin Oncol*. 2022;40:150–160. doi:10.1200/JCO.21.00608
11. Chen J, Lu S, Zhang Y, et al. Sorafenib monotherapy versus sorafenib combined with regional therapies for hepatocellular carcinoma patients with pulmonary oligometastases: a propensity score-matched analysis. *J Cancer*. 2018;9:1745–1753. doi:10.7150/jca.24568
12. Chen S, Wang X, Yuan B, et al. Apatinib plus hepatic arterial infusion of oxaliplatin and raltitrexed for hepatocellular carcinoma with extrahepatic metastasis: phase II trial. *Nat Commun*. 2024;15:8857. doi:10.1038/s41467-024-52700-z
13. Guan R, Zhang N, Deng M, et al. Patients with hepatocellular carcinoma extrahepatic metastases can benefit from hepatic arterial infusion chemotherapy combined with lenvatinib plus programmed Death-1 inhibitors. *Int J Surg*. 2024;110:4062–4073. doi:10.1097/JS9.0000000000001378
14. Lyu N, Wang X, Li JB, et al. Arterial chemotherapy of oxaliplatin plus fluorouracil versus sorafenib in advanced hepatocellular carcinoma: a biomolecular exploratory, randomized, phase III trial (FOHAIC-1). *J Clin Oncol*. 2022;40:468–480. doi:10.1200/JCO.21.01963

15. Lee JI, Kim JK, Kim DY, et al. Prognosis of hepatocellular carcinoma patients with extrahepatic metastasis and the controllability of intrahepatic lesions. *Clin Exp Metastasis*. 2014;31:475–482. doi:10.1007/s10585-014-9641-x
16. Pinter M, Hucke F, Graziadei I, et al. Advanced-stage hepatocellular carcinoma: transarterial chemoembolization versus sorafenib. *Radiology*. 2012;263:590–599. doi:10.1148/radiol.12111550
17. Sieghart W, Hucke F, Peck-Radosavljevic M. Transarterial chemoembolization: modalities, indication, and patient selection. *J Hepatol*. 2015;62:1187–1195. doi:10.1016/j.jhep.2015.02.010
18. Jia W, Liang S, Lin W, et al. Hypoxia-induced exosomes facilitate lung pre-metastatic niche formation in hepatocellular carcinoma through the miR-4508-RFX1-IL17A-p38 MAPK-NF-kappaB pathway. *Int J Biol Sci*. 2023;19:4744–4762. doi:10.7150/ijbs.86767
19. Wang H, Huang J, Zhang W, et al. Prognostic factors in patients with first diagnosis of hepatocellular carcinoma presenting with pulmonary metastasis and construction of a clinical prediction model. *Updates Surg*. 2024;76:71–85. doi:10.1007/s13304-023-01603-7
20. He M, Huang Y, Du Z, et al. Lenvatinib, Toripalimab plus folfox chemotherapy in hepatocellular carcinoma patients with extrahepatic metastasis: a biomolecular exploratory, phase II Trial (LTSC). *Clin Cancer Res*. 2023;29:5104–5115. doi:10.1158/1078-0432.CCR-23-0060
21. Deng H, Kan A, Lyu N, et al. Dual vascular endothelial growth factor receptor and fibroblast growth factor receptor inhibition elicits antitumor immunity and enhances programmed cell death-1 checkpoint blockade in hepatocellular carcinoma. *Liver Cancer*. 2020;9:338–357. doi:10.1159/000505695
22. Zhang W, Tong S, Hu B, et al. Lenvatinib plus anti-PD-1 antibodies as conversion therapy for patients with unresectable intermediate-advanced hepatocellular carcinoma: a single-arm, phase II trial. *J Immunother Cancer*. 2023;11.
23. Liu Q, Li R, Li L, et al. Efficacy and safety of anti-PD-1 monotherapy versus anti-PD-1 antibodies plus lenvatinib in patients with advanced hepatocellular carcinoma: a real-world experience. *Ther Adv Med Oncol*. 2023;15:17588359231206274. doi:10.1177/17588359231206274
24. Qin S, Chan SL, Gu S, et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study. *Lancet*. 2023;402:1133–1146. doi:10.1016/S0140-6736(23)00961-3
25. Wu X-K, Yang L-F, Chen Y-F, et al. Transcatheter arterial chemoembolisation combined with lenvatinib plus camrelizumab as conversion therapy for unresectable hepatocellular carcinoma: a single-arm, multicentre, prospective study. *EClinicalMedicine*. 2024;67:102367. doi:10.1016/j.eclinm.2023.102367
26. Cai M, Huang W, Huang J, et al. Transarterial chemoembolization combined with lenvatinib plus PD-1 inhibitor for advanced hepatocellular carcinoma: a retrospective cohort study. *Front Immunol*. 2022;13:848387. doi:10.3389/fimmu.2022.848387
27. Wang L, Lin L, Zhou W. Efficacy and safety of transarterial chemoembolization combined with lenvatinib and PD-1 inhibitor in the treatment of advanced hepatocellular carcinoma: a meta-analysis. *Pharmacol Ther*. 2024;257:108634. doi:10.1016/j.pharmthera.2024.108634
28. Lai Z, He M, Bu X, et al. Lenvatinib, toripalimab plus hepatic arterial infusion chemotherapy in patients with high-risk advanced hepatocellular carcinoma: a biomolecular exploratory, phase II trial. *Eur J Cancer*. 2022;174:68–77. doi:10.1016/j.ejca.2022.07.005
29. Wang M, Yao X, Bo Z, et al. Synergistic effect of lenvatinib and chemotherapy in hepatocellular carcinoma using preclinical models. *J Hepatocell Carcinoma*. 2023;10:483–495. doi:10.2147/JHC.S395474
30. Zhou Q, Li R, Wu S, et al. Metastasis-directed ablation of hepatocellular carcinoma with pulmonary oligometastases: a long-term multicenter study. *Radiol Med*. 2025;130:25–36. doi:10.1007/s11547-024-01907-7
31. Chen S, Shuangyan T, Shi F, et al. TACE plus lenvatinib and tislelizumab for intermediate-stage hepatocellular carcinoma beyond up-to-11 criteria: a multicenter cohort study. *Front Immunol*. 2024;15:1430571. doi:10.3389/fimmu.2024.1430571
32. Wu Z, Guo W, Chen S, Zhuang W. Determinants of pain in advanced HCC patients recieving hepatic artery infusion chemotherapy. *Invest New Drugs*. 2021;39:394–399. doi:10.1007/s10637-020-01009-x