Journal of Hepatocellular Carcinoma

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ORIGINAL RESEARCH

HAIC Combined with Lenvatinib and Pembrolizumab for Unresectable Hepatocellular Carcinoma: A Retrospective Study

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Background & Aims: The optimal treatment strategy for unresectable hepatocellular carcinoma (uHCC) remains under active investigation. Hepatic arterial infusion chemotherapy (HAIC) has shown promising outcomes, particularly among patients with high intrahepatic tumor burden. We assessed outcomes and tolerability of HAIC combined with lenvatinib and pembrolizumab (HAIC+L+P) as initial treatment for uHCC.

Methods: We retrospectively identified consecutive, treatment-naïve patients with uHCC (BCLC stage B/C) treated with HAIC+L+P at a single center from January 2019 to January 2024. Tumor responses were evaluated using RECIST 1.1 and mRECIST. Overall survival (OS), progression-free survival (PFS), and treatment-related adverse events (AEs) were analyzed.

Results: Sixty-six patients were analyzed, of whom 81.8% had BCLC stage C disease, 68.2% had vascular invasion, and 45.5% had extrahepatic metastasis. The median PFS was 9.63 months (95% CI, 6.59–12.68), and the median OS was 27.50 months (95% CI, 18.17–36.83). The ORR was 47.0% according to RECIST 1.1 and 66.7% according to mRECIST, with a DCR of 90.9% by both criteria. Six patients (9.1%) underwent curative-intent surgical resection during treatment. All AEs were controllable and no treatment-related deaths were recorded.

Conclusion: HAIC combined with lenvatinib and pembrolizumab was associated with encouraging antitumor activity and a manageable safety profile in this real-world cohort. These findings should be considered hypothesis-generating and warrant validation in prospective controlled studies.

Keywords: hepatocellular carcinoma, hepatic arterial infusion chemotherapy, lenvatinib, pembrolizumab

Introduction

In 2022, primary liver cancer ranked as the sixth most frequently diagnosed malignancy and the third leading cause of cancer-related mortality worldwide, with hepatocellular carcinoma (HCC) accounting for approximately 75–85% of cases.[1] Owing to the often asymptomatic early course, diagnosis for patients often occurs at intermediate or advanced stages, when curative surgery is usually not feasible.[2,3] Consequently, systemic and local therapies have become the backbone of management for many patients.

Combination therapies, integrating both systemic and local approaches, have shown promising results in improving treatment outcomes for HCC. Multiple studies have demonstrated that combining systemic and locoregional treatments can significantly enhance survival.[4–7] The LEAP-012 trial provides one example: in patients with unresectable hepatocellular carcinoma (uHCC) without extrahepatic metastasis, adding lenvatinib plus pembrolizumab to transarterial

https://doi.org/10.2147/JHC.S600557
Received: 1 February 2026
Accepted: 20 May 2026
Published: 26 May 2026

chemoembolization (TACE) resulted in a clear prolongation of PFS versus TACE with placebo, alongside favorable OS signals. In parallel, EMERALD-1 showed that incorporating durvalumab and bevacizumab into a TACE-based strategy substantially extended PFS compared with TACE alone, while no unexpected safety concerns emerged in a clinically diverse uHCC population.[8,9]

In terms of systemic therapy, targeted therapy and immunotherapy are the most commonly utilized strategies. In the REFLECT study, lenvatinib achieved OS outcomes comparable to sorafenib, meeting the trial's prespecified non-inferiority criterion in uHCC.[10] In addition, the KEYNOTE-394 study reported that pembrolizumab, administered as second-line therapy, significantly prolonged both OS and PFS in previously treated Asian patients with advanced HCC, and produced a higher ORR than placebo.[11]

Local treatments also play a critical role in HCC management. HAIC is a well-established modality for intermediate and advanced HCC, wherein chemotherapy is delivered via the hepatic artery, ensuring high intrahepatic exposure while minimizing systemic toxicity.[12,13] Several studies suggest that HAIC may be more effective than TACE, particularly for large HCCs or those with portal vein thrombosis.[14–18] Moreover, a prior report associated the addition of HAIC to lenvatinib plus PD-1 inhibition with longer OS and PFS than systemic therapy alone.[19]

Despite these advances, the most effective treatment sequence for advanced HCC still remains a subject of ongoing research. Early data indicate that combination of HAIC+L+P may overcome resistance to monotherapy and improve patient outcomes.[20] However, evidence specifically evaluating HAIC combined with lenvatinib and pembrolizumab in treatment-naive uHCC remains limited. Therefore, this study aimed to evaluate the efficacy and safety of this combination in a real-world cohort.

Methods

Patient Selection

We retrospectively screened consecutive patients with uHCC treated at Sun Yat-sen University Cancer Center who received HAIC+L+P between January 2019 and January 2024. The Institutional Review Board of Sun Yat-sen University Cancer Center approved the study (Approval number: B2023-673-01). The study adhered to the Declaration of Helsinki, and the requirement for written informed consent was waived due to the retrospective design. Patient confidentiality was strictly maintained, and all data were anonymized.

Eligible patients met all of the following criteria: (a) HCC diagnosis established by imaging and/or pathology according to the American Association for the Study of Liver Diseases (AASLD) guidance; (b) BCLC stage B or C; (c) ECOG performance status 0–1; (d) at least one measurable lesion; (e) receipt of HAIC+L+P as first-line treatment, with at least one cycle completed; (f) complete baseline and follow-up records. Patients were excluded if they had incomplete follow-up information, a history of other malignancies, inability to continue treatment for non-medical reasons, or severe hepatic/renal/cardiopulmonary dysfunction.

Treatment Procedure

HAIC was performed according to institutional standard procedures. Catheter placement was determined based on tumor-feeding arteries and angiographic findings.[15,21] After arterial access via the Seldinger technique, angiography was performed to delineate tumor-feeding vessels, and a microcatheter was positioned within the target hepatic arterial branch. To reduce catheter-related thrombosis, heparinized saline was infused after catheter placement. Chemotherapy was then administered through the hepatic artery using a FOLFOX-based regimen: oxaliplatin 85–130 mg/m^2 over 2 hours, calcium folinate 400 mg/m^2 over 2 hours, and 5-fluorouracil 400 mg/m^2 as a 1-hour bolus, followed by continuous 5-fluorouracil 2400 mg/m^2 over 23 hours. Treatment cycles were repeated every 3 weeks, accompanied by standard supportive measures (antiemetics, hydration, and hepatoprotective care) during the chemotherapy infusion.[22,23]

Lenvatinib and pembrolizumab were initiated within 1 week before or after HAIC. Lenvatinib was given orally once daily at 8 mg/day for body weight <60 kg and 12 mg/day for ≥60 kg. Pembrolizumab was given intravenously at 200 mg every 3 weeks.[24] Dose modifications of lenvatinib and pembrolizumab were performed based on toxicity, liver function, and clinical judgment according to institutional practice.

The number of HAIC cycles and systemic therapy cycles varied depending on treatment response and tolerance. Subsequent treatments after disease progression were heterogeneous and included systemic therapy, locoregional interventions, or best supportive care.

Efficacy and Safety Evaluation

Patients were followed through 1 October 2025. Clinical assessment was performed at least every 2 months after treatment initiation, together with laboratory tests and contrast-enhanced imaging. Abdominal CT/MRI was routinely obtained, and additional sites (eg, chest, bone, brain) were evaluated when clinically indicated. Up to two target lesions per organ were selected. Lesions were considered measurable when the longest diameter exceeded 1 cm. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and the modified Response Evaluation Criteria in Solid Tumors (mRECIST) and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The objective response rate (ORR) was defined as the proportion of patients achieving CR or PR, and the disease control rate (DCR) as the proportion achieving CR, PR, or SD.

Overall survival (OS) was calculated from treatment start to death from any cause or last follow-up. Progression-free survival (PFS) was calculated from treatment start to radiographic progression or death, whichever occurred first. Treatment-related adverse events(AEs) were recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analysis

Statistical analyses were performed using SPSS (version 25.0) and R (version 4.4.1). Continuous variables are presented as mean ± standard deviation when approximately normally distributed and as median (IQR) otherwise. Kaplan–Meier curves and waterfall plots were generated in R software. Cox proportional hazards models were used to evaluate associations with OS and PFS; variables with $P < 0.05$ on univariable testing were entered into multivariable models. All tests were two-sided, with $P < 0.05$ considered statistically significant. The number of events relative to variables included in multivariable Cox models was considered to minimize overfitting.

Results

Patient Characteristics

Between January 2019 and January 2024, we included 66 treatment-naïve patients with uHCC who received HAIC+L+P. (Figure 1). Baseline characteristics are summarized in Table 1. The cohort had a median age of 57.0 years, and men accounted for 93.9% (62/66). Liver function was generally preserved, with 90.9% classified as Child–Pugh A. Hepatitis B virus infection was prevalent, with 84.8% (56/66) of patients testing positive for hepatitis B surface antigen (HBsAg).

Regarding tumor burden, most patients presented with advanced disease. A total of 81.8% (54/66) of patients were classified as BCLC stage C, and 83.3% (55/66) had multiple intrahepatic lesions. The median maximum tumor diameter was 9.6 cm (IQR, 8.2–13.0), and tumors larger than 5 cm were observed in 90.9% (60/66) of patients. Vascular invasion was present in 68.2% (45/66) of cases, while extrahepatic metastasis, including lymph node and distant metastases, was observed in 45.5% (30/66) of patients.

Survival Analysis

Patients received a median of 4 HAIC cycles (IQR, 3–5) and a median of 5 pembrolizumab cycles (IQR, 3–9). Following treatment, 6 patients (9.1%) underwent curative-intent surgical resection.

At a median follow-up of 19.9 months (IQR, 11.4–27.5), median PFS was 9.63 months (95% CI, 6.59–12.68), with 3- and 6-month PFS rates of 73.7% and 42.3%, respectively (Figure 2). Median OS was 27.50 months (95% CI, 18.17–36.83) (Figure 3), and OS rates at 6, 12, and 18 months were 93.8%, 79.1%, and 62.2%, respectively (Figure 3).

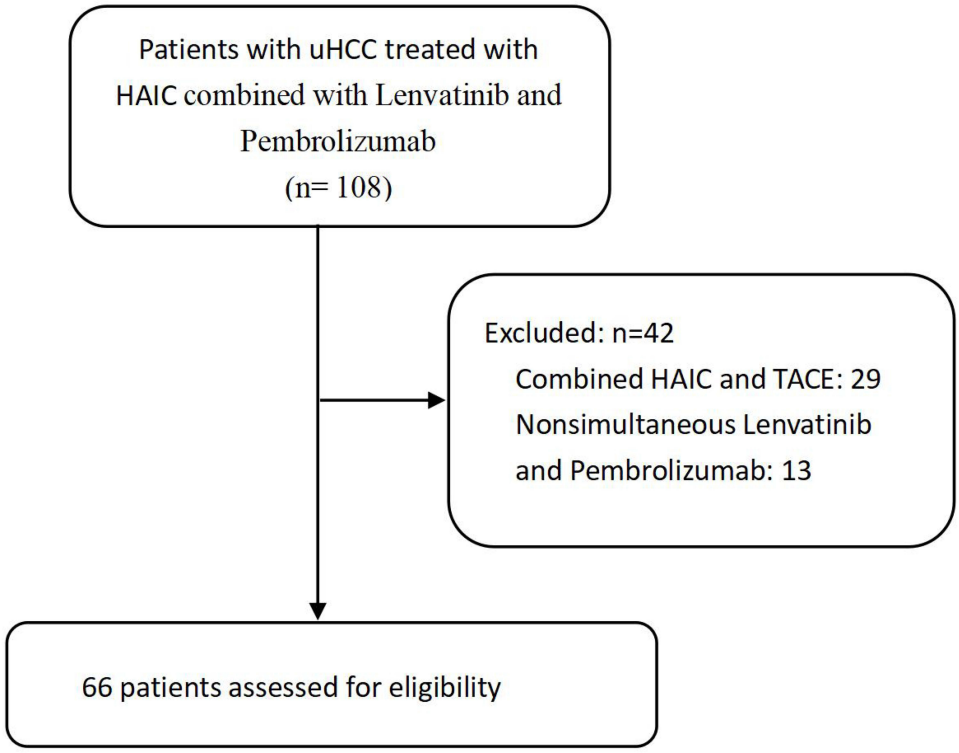

Figure 1 The flowchart of the study.

Tumor Response

Most patients experienced a substantial decrease in target-lesion burden relative to baseline (Figure 4). Using RECIST 1.1, the ORR was 47.0% (31/66) and the DCR was 90.9% (60/66). With mRECIST-based evaluation, the ORR rose to 66.7% (44/66), whereas the DCR remained unchanged at 90.9% (60/66).

Table 1 Baseline Characteristics

Characteristics	Levels	HAIC+L+P (n=66)
Age,years	Median(IQR)	57.0 (48.0 to 62.0)
Gender	Male	62 (93.9%)
	Female	4 (6.1%)
ECOG PS Score	0	42 (63.6%)
	1	24 (36.4%)
HBsAg	Positive	56 (84.8%)
	Negative	10 (15.2%)
Liver cirrhosis	Yes	36 (54.5%)
	No	30 (45.5%)
AFP, ng/mL	>400	36 (54.5%)
	≤400	30 (45.5%)
Tumor number	Single	11 (16.7%)
	Multiple	55 (83.3%)
Tumor size,cm	Median(IQR)	9.6 (8.2 to 13.0)
Tumor size,cm	>5cm	60 (90.9%)
	≤5cm	6 (9.1%)
Extrahepatic metastasis	Positive	30 (45.5%)
	Negative	36 (54.5%)

(*Continued*)

 https://doi.org/10.2147/JHC.S600557

Table 1 (Continued).

Characteristics	Levels	HAIC+L+P (n=66)
Vascular invasion	Positive	45 (68.2%)
	Negative	21 (31.8%)
Child Pugh grades	A	60 (90.9%)
	B	6 (9.1%)
BCLC stage	B	12 (18.2%)
	C	54 (81.8%)
PLT, 10E9/L	Median(IQR)	193.5 (142.8 to 279)
ALT, U/L	Median(IQR)	39.9 (29.6 to 63.9)
AST, U/L	Median(IQR)	59.6 (41.6 to 104.6)
Albumin, g/L	Median(IQR)	40.7 (37.4 to 43.7)
Total bilirubin, umol/L	Median(IQR)	16.5 (12.0 to 22.2)

Abbreviations: IQR, interquartile range; ECOG PS score, Eastern Cooperative Oncology Group performance status score; AFP, α-Fetoprotein; BCLC, Barcelona Clinic Liver Cancer; PLT, Platelet Count; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase.

Under mRECIST criteria, 1 patient (1.5%) achieved CR, whereas no CR were observed according to RECIST 1.1. PR were observed in 31 patients (47.0%) based on RECIST 1.1 and in 43 patients (65.2%) based on mRECIST. SD was observed in 29 patients (43.9%) according to RECIST 1.1 and in 16 patients (24.2%) according to mRECIST. PD occurred in 6 patients (9.1%) under both evaluation criteria, with disease progression primarily driven by the development of distant metastases (5/6) (Table 2).

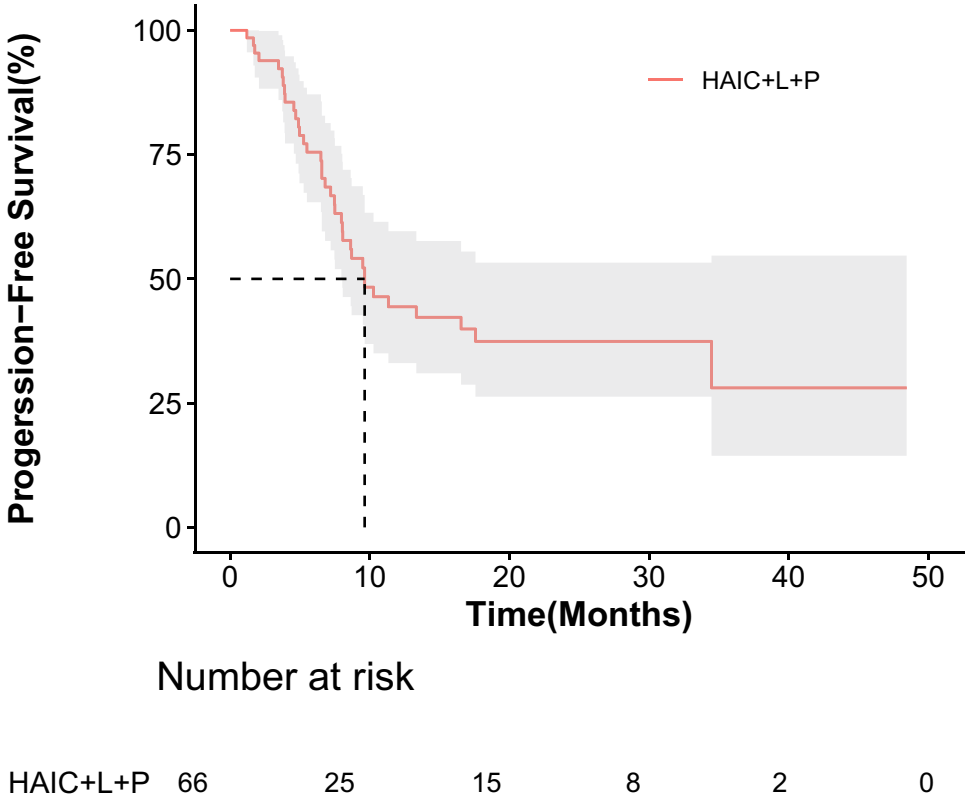

Figure 2 Kaplan–Meier curves for progression-free survival.

https://doi.org/10.2147/JHC.S600557

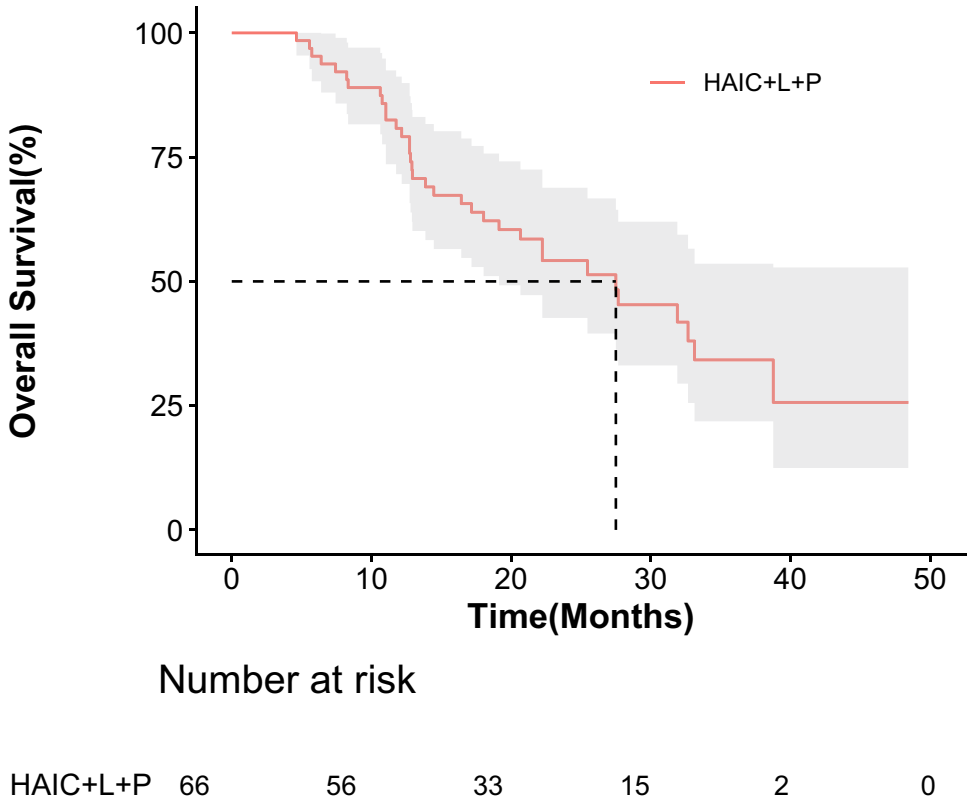

Figure 3 Kaplan–Meier curves for overall survival.

Prognostic Factor Analysis

Cox proportional hazards models were used to explore variables associated with PFS and OS. On univariable analysis, patients with AFP ≤400 ng/mL had better OS, whereas a serum ALB level ≤40 g/L was linked to inferior outcomes for both OS and PFS.

These relationships persisted after multivariable adjustment. AFP ≤400 ng/mL remained an independent favorable factor for OS (hazard ratio [HR], 0.42; 95% CI, 0.21–0.85; P = 0.007). Conversely, ALB ≤40 g/L independently predicted poorer OS (HR, 2.91; 95% CI, 1.44–5.88; P = 0.001) and shorter PFS (HR, 2.15; 95% CI, 1.10–4.21; P = 0.025) (Table 3).

Safety

All adverse events (AEs) were manageable. The most frequent treatment-related AE was abdominal pain, and the most common laboratory abnormality was a decrease in albumin. Grade ≥3 adverse events occurred in 25.8% of patients, with no treatment-related deaths observed (Table 4). The treatment-related adverse events were managed with standard supportive care, dose modification, temporary treatment interruption, or permanent discontinuation when clinically indicated.

Discussion

In this single-arm retrospective cohort, we assessed HAIC+L+P as initial therapy for uHCC patients. The combination demonstrated encouraging antitumor activity, with a mPFS of 9.63 months and a mOS of 27.50 months. Given the relatively short median follow-up duration of 19.9 months, overall survival data should be interpreted with caution as they may not yet be fully mature.The ORR ranged from 47.0% by RECIST 1.1 to 66.7% by mRECIST, and the DCR reached 90.9%. Notably, 9.1% of patients underwent surgical resection during treatment, which may reflect the potential for selected patients to achieve sufficient disease control to allow consideration of curative-intent local therapies.

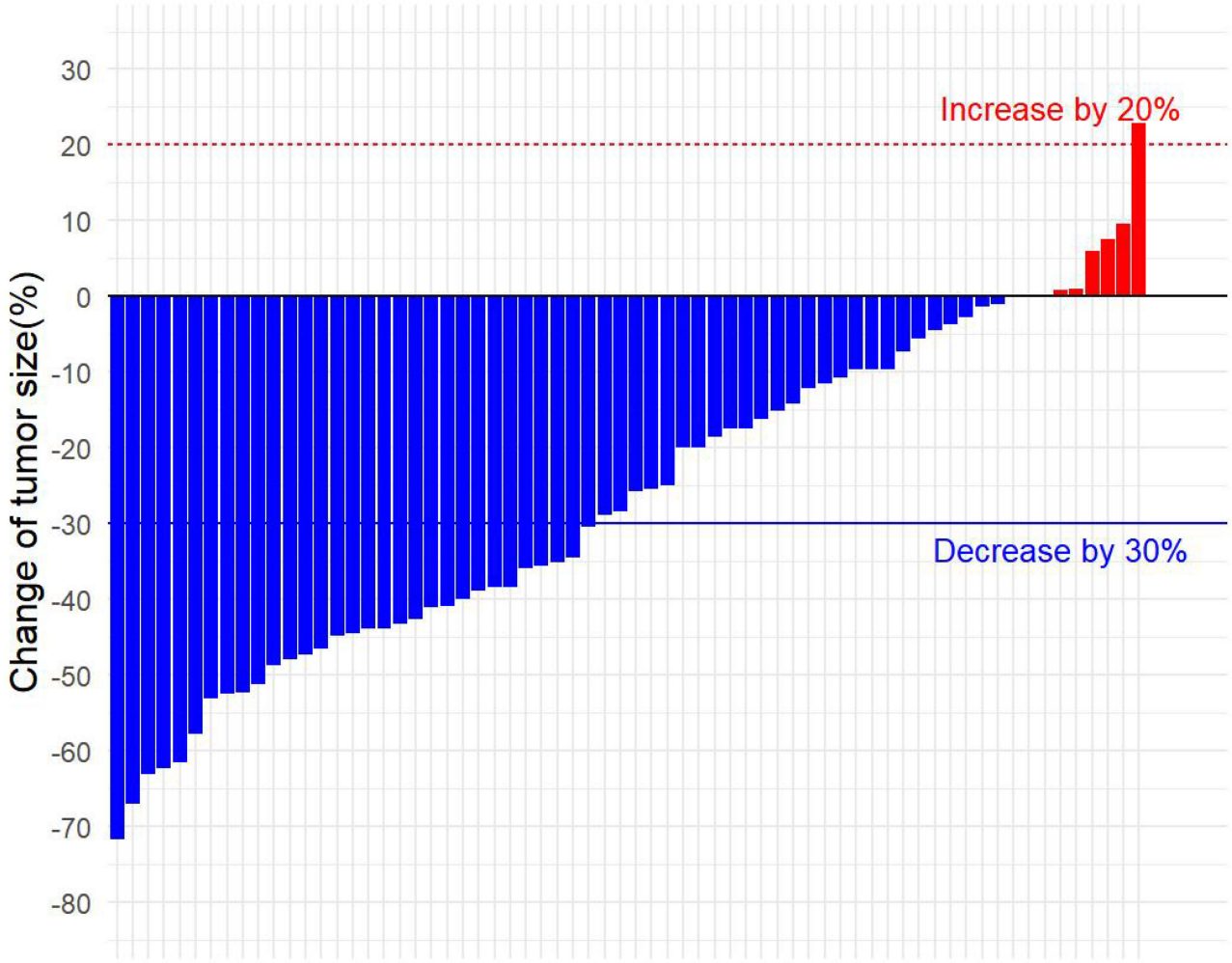

Figure 4 Change of tumor size after treatment.

The efficacy of HAIC+L+P is biologically plausible given the complementary mechanisms of its components. HAIC enables high intrahepatic exposure to cytotoxic agents with limited systemic distribution, which may be particularly relevant in patients whose prognosis is driven by uncontrolled intrahepatic disease. Lenvatinib provides antiangiogenic and antiproliferative effects, and PD-1 blockade with pembrolizumab may restore antitumor immunity. The higher ORR assessed by mRECIST than by RECIST 1.1 is consistent with locoregional approaches that induce tumor necrosis without immediate size reduction.[25]

A clinically informative comparator is LEAP-012, which evaluated TACE plus lenvatinib plus pembrolizumab in unresectable, non-metastatic HCC amenable to embolization. LEAP-012 reported a longer median PFS (14.6 months) than observed in our cohort (9.63 months). LEAP-012 also achieved a higher ORR by mRECIST (71%) than our study (66.7%), while the ORR by RECIST 1.1 was identical (47% in both studies). These differences should be interpreted in light of patient selection: LEAP-012 included only non-metastatic patients and a substantial proportion of BCLC B disease, with tumors <10 cm, whereas our cohort comprised predominantly BCLC C patients (81.8%), with frequent vascular invasion (68.2%) and extrahepatic metastasis (45.5%), and a median tumor size close to 10 cm. Thus, cross-study comparisons are inherently limited, and the numerically lower PFS and mRECIST ORR in our study likely reflect a less favorable baseline profile and broader clinical heterogeneity rather than reduced activity of the systemic backbone. Notably, despite these adverse features, HAIC+L+P maintained high disease control and clinically meaningful responses, suggesting that substituting HAIC for TACE may be a potential feasible strategy for patients beyond the conventional embolization-eligible population. This hypothesis requires confirmation in prospective comparative studies.

https://doi.org/10.2147/JHC.S600557

Table 2 Tumor Response

Therapeutic Response Assessment	Evaluation of Patients (n=66) RECIST 1.1	Evaluation of Patients (n=66) mRECIST
Complete response (CR, %)	0 (0)	1 (1.5)
Partial response (PR, %)	31 (47.0)	43 (65.2)
Stable disease (SD, %)	29 (43.9)	16 (24.2)
Progression disease (PD, %)	6 (9.1)	6 (9.1)
Overall response rate (ORR, %)	31 (47.0)	44 (66.7)
Disease control rate (DCR, %)	60 (90.9)	60 (90.9)

Abbreviations: RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

Table 3 Univariate and Multivariate Analyses of Prognostic Factors on OS and PFS

Variables	Overall Survival				Progression-Free Survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age, years (>60/≤60)	1.40 (0.70–2.77)	0.338			1.25 (0.65–2.44)	0.505		
Gender (male/female)	1.18 (0.28–4.97)	0.824			0.71 (0.21–2.36)	0.579		
HBsAg (positive/negative)	1.20 (0.46–3.10)	0.709			1.05 (0.44–2.54)	0.908		
ECOG score (1/0)	1.96 (0.98–3.93)	0.059			1.61 (0.83–3.14)	0.161		
Liver cirrhosis (yes/no)	1.51 (0.77–2.99)	0.234			1.22 (0.62–2.37)	0.566		
AFP, ng/mL (≤400/>400)	0.42 (0.21–0.85)	0.017	0.37 (0.18–0.76)	0.007	0.71 (0.37–1.37)	0.303		
Tumor number (multiple/single)	2.07 (0.72–5.94)	0.175			1.97 (0.69–5.60)	0.206		
Tumor size, cm (>5/≤5)	4.79 (0.65–35.34)	0.125			1.27(0.39–4.14)	0.697		
Extrahepatic metastasis (Yes/No)	1.93 (0.92–4.06)	0.081			1.40(0.64–3.09)	0.403		
Lymph node metastases (No/Yes)	0.57 (0.25–1.26)	0.165			0.92 (0.45–1.90)	0.830		
BCLC stage (B/C)	1.46 (0.65–3.29)	0.363			1.19 (0.56–2.54)	0.652		
PLT, 10E9/L (≤100/>100)	0.93 (0.36–2.42)	0.887			1.07 (0.41–2.77)	0.887		
ALT, U/L (≤40/>40)	0.79 (0.40–1.55)	0.491			0.94 (0.49–1.82)	0.864		
AST, U/L (≤40/>40)	1.32 (0.54–3.19)	0.541			0.60 (0.29–1.25)	0.175		
ALB, g/L (≤40/>40)	2.91 (1.44–5.88)	0.003	3.24 (1.59–6.63)	0.001	2.15 (1.10–4.21)	0.025	2.15 (1.10–4.21)	0.025

Abbreviations: ECOG, Eastern Cooperative Oncology Group; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; PLT, Platelet Count; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALB, Albumin.

Table 4 Treatment-Related Adverse Events

Adverse Event	Grade 1–2	Grade 3–4
	No.(%)	No.(%)
Rash	6 (9.1)	0
Vomiting	12 (18.2)	0
Diarrhoea	5 (7.6)	0
Abdominal pain	14 (21.2)	0
Elevated blood pressure	4 (6.1)	0
Hyperbilirubinemia	20 (30.3)	7 (10.6)
Hypoalbuminemia	41 (62.1)	0
Thrombocytopenia	21 (31.8)	6 (9.1)
Leukopenia	14 (21.2)	4 (6.1)

Our findings also provide context relative to systemic therapy alone. In LEAP-002, pembrolizumab plus lenvatinib yielded a median OS of 21.2 months and a median PFS of 8.2 months, with 78% of patients classified as BCLC C.[24] Although direct comparisons are not appropriate, the survival outcomes observed in our cohort support the hypothesis that adding an intrahepatic intensification component (HAIC) may be clinically relevant in advanced disease with substantial liver tumor burden.

Consistent with prior reports of HAIC-based triple therapy, our outcomes were broadly aligned with published real-world experiences.[23,24,26,27] In studies combining HAIC with TKIs and immune checkpoint inhibitors, meaningful response and survival benefits have been reported, including cohorts treated with HAIC plus bevacizumab-based immunotherapy and cohorts treated with HAIC plus lenvatinib and PD-1 inhibitors. In our study, OS and PFS appeared favorable, while ORR and DCR were comparable across studies, supporting the activity of this regimen in uHCC.

The safety profile of HAIC+L+P was manageable. No toxicity-related deaths occurred, and grade ≥3 AEs were observed in 25.8% of patients, consistent with the known toxicity spectra of HAIC, lenvatinib, and PD-1 blockade. Supportive care and standard dose adjustments allowed most patients to continue treatment.

Several limitations should be noted. First, the retrospective, single-center, single-arm design and the absence of a control group limit causal interpretation and may introduce potential selection bias, therefore, the results should be interpreted as hypothesis-generating rather than confirmatory. Second, the cohort size was modest, and subsequent treatments after disease progression were heterogeneous and not standardized, which may have influenced OS. Third, tumor response assessments were performed in routine clinical practice without centralized blinded radiological review. Finally, baseline heterogeneity, including BCLC stage B/C disease, vascular invasion, and extrahepatic metastasis, may affect interpretation. Accordingly, given the retrospective design, small sample size, and heterogeneous patient population, the findings should be interpreted with caution. Further subgroup analyses stratified by disease stage and tumor burden may provide additional insights and should be explored in future studies. What's more, these results should be confirmed in prospective, multicenter studies incorporating prespecified stratification and standardized post-treatment sequencing.

In summary, HAIC combined with lenvatinib and pembrolizumab was associated with encouraging antitumor activity and a manageable safety profile in this real-world cohort. These findings support further prospective evaluation of this regimen.

Data Sharing Statement

All data that support the findings of this study are provided within the article. Requests for additional information should be addressed to the corresponding author.

Ethics Approval

The study was performed according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center (Approval number: B2023-673-01).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors declare no conflicts or competing interests related to this study.

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