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ORIGINAL RESEARCH

Hepatic Arterial Infusion Chemotherapy Combined Lenvatinib and PD-1 Inhibitor Showed Improved Survival for Infiltrative Hepatocellular Carcinoma: A Multicenter Cohort Study

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Purpose: Lenvatinib and programmed cell death protein-1 (PD-1) inhibitor on infiltrative hepatocellular carcinoma (HCC) have obtained demonstrated efficacy and still need improvement. Hepatic arterial infusion chemotherapy (HAIC) has shown promising results for advanced HCC. This study aimed to compare the efficacy of HAIC combined Lenvatinib and PD-1 inhibitor versus Lenvatinib combined PD-1 inhibitor for infiltrative HCC.

Patients and Methods: A total of 232 patients were enrolled. There were 114 patients received Lenvatinib combined PD-1 inhibitor (Len+PD-1 group) and 118 patients received HAIC combined Lenvatinib and PD-1 inhibitor (HAIC+Len+PD-1 group). Overall survival (OS), progression-free survival (PFS) and safety of patients were compared between the two groups by propensity score–matching (PSM).

Results: The 6-, 12-, and 24-month OS rates were 93.8%, 65.1% and 13.4% in Len+PD-1 group, and 100%, 77.3% and 32.1% in HAIC+Len+PD-1 group, respectively. The 3-, 6-, and 12-month PFS rates were 86.4%, 45.7% and 14.1% in Len+PD-1 group, and 95.1%, 59.3% and 25.9% in HAIC+Len+PD-1 group, respectively. The HAIC+Len+PD-1 group had obviously better survival than the Len+PD-1 group both in OS (P=0.002) and PFS (P=0.004). Subgroup analysis revealed that OS in patients with metastasis was improved with HAIC+Len+PD-1 treatment. Patients with alpha-fetoprotein (AFP) response after treatment showed better survival than the non-response. In addition, HAIC+Len+PD-1 group showed manageable adverse events (AEs).

Conclusion: Patient with infiltrative HCC, HAIC+Len+PD-1 treatment had longer OS and PFS than Len+PD-1 treatment. Early AFP response was an effective indicator of better survival and tumor response to therapy.

Plain language summary: Infiltrative hepatocellular carcinoma (HCC) is an odd group that is not well adjudicated in the current staging systems, and treatment options for patients with infiltrative HCC are challenging with scant and insufficient clinical evidence. In this multi-center study, we innovatively analyzed the outcome of hepatic arterial infusion chemotherapy (HAIC) combined lenvatinib and PD-1 inhibitor (HAIC+Len+PD-1) was associated longer progression-free survival and overall survival than Lenvatinib plus PD-1 inhibitor combination (Len+PD-1) for patient with infiltrative HCC. In addition, further intragroup analysis revealed that OS of patients with and without metastasis in Len+PD-1 group was significant difference. However, no difference was observed in OS for patients with and without metastasis in HAIC+Len+PD-1 group. Patients with alpha-fetoprotein (AFP) response after treatment showed better survival than the non-response. Our research provides evidence that HAIC combined Lenvatinib and PD-

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1 inhibitor results in clinically significant improvements in infiltrative HCC. It could be recommended as a first choice for infiltrative HCC therapy.

Keywords: infiltrative hepatocellular carcinoma, hepatic arterial infusion chemotherapy, lenvatinib, PD-1 inhibitor, alpha-fetoprotein response

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and still ranks the third leading cause of cancer-related death.[1] HCC can be divided as nodular and infiltrative types, and the majority comprise the single or multiple nodular type with tumor capsule.[2] The infiltrative type accounts for 7%–13% of HCC.[3] Most researches on the characteristics of HCC focus on the nodular type, while there are few reports on infiltrative HCC.[4] In fact, infiltrative HCC is not infrequently encountered, particularly in areas endemic for hepatitis B virus (HBV), such as in China.[5,6] It has peculiar morphological and clinical characteristics that differs from the nodular HCC.[7] Infiltrative HCC has a diffuse, permeative appearance, a bad-demarcated boundary on imaging. Thus, it often leads to very poor prognosis due to difficulty in early detection and frequent portal vein invasion, high tumor burden.[2] Despite its clinical importance, the prognosis of infiltrative HCC is relatively infrequently documented.

Currently, treatment options for patients with infiltrative HCC are challenging with scant and insufficient clinical evidence, and it is often included in advanced HCC.[8] The systemic therapy has become the standard of care for infiltrative HCC, and the outcomes usually vary.[9] Lenvatinib is a commonly used targeted drug in the treatment of advanced HCC and demonstrated to be effective and generally manageable tolerability.[10] However, the therapeutic response of monotherapy was still unsatisfactory.[11] Programmed cell death protein-1 (PD-1) inhibitor, as promising immunotherapy, the durable objective responses show the potential effectiveness in advanced HCC.[12] Various studies have shown exciting antitumor activity and manageable safety of PD-1 inhibitor for HCC treatment.[13] Lenvatinib combination with the pembrolizumab, has generated encouraging results in clinical trials.[14] Combination therapy may provide synergistic effects and improved the prognosis than Lenvatinib alone for advanced HCC.[15]

Hepatic arterial infusion chemotherapy (HAIC) with oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOX) has been proved to improve the survival of patients with advanced HCC.[16] In recent years, HAIC has attracted much attention due to the high tumor response and favorable survival.[17,18] Recent studies have proven that Sorafenib combined HAIC yielded significantly better survival compared to sorafenib or HAIC alone.[19,20] Studies have proven that HAIC combined system therapy has a promising synergic efficacy in advanced HCC.[21,22] However, the combination therapy of HAIC combined Lenvatinib and PD-1 inhibitor have not been focused on the infiltrative HCC with HBV positive. Thus, we conducted this analysis to compare the effectiveness of HAIC, Lenvatinib and PD-1 inhibitor versus Lenvatinib and PD-1 inhibitor on the prognosis of patients with infiltrative HCC.

Material and Methods

Patients and Study Design

Patients diagnosed with infiltrative HCC from January 2019 to December 2021 were retrospectively reviewed at the Chinese PLA General Hospital, The First Affiliated Hospital of Jinzhou Medical University, Hunan Provincial People's Hospital, Sun Yat-sen University Cancer Center. This study was centrally approved by the ethics committee of the four centers and was conducted according to the guidelines of the Declaration of Helsinki.[23] The Ethics Committee Board of the Chinese PLA General Hospital approved this retrospective study and waived the requirement due to this retrospective study.

HCC was diagnosed by imaging studies (contrast-enhanced computed tomography [CT] and/or magnetic resonance imaging [MRI]), in accordance with the American Association for the Study of Liver Disease (AASLD) guidelines.[24] Contrast-enhanced CT or MRI was conducted within 2 weeks for each patient before starting treatment, and images were reviewed and evaluated independently by two experienced radiologists. Infiltrative HCC was characterized as follows:

nonencapsulated arterial phase hyperenhancement; tumor washout in the period of portal phase, and noncircular, ill-defined margin[25] (Figure 1).

Patients meeting the following criteria were included: (1) primary infiltrative HCC according to imaging (MRI or CT) characteristic; (2) Child-Pugh class A or B, and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; (3) no history of other malignancies; (4) in HAIC combined Lenvatinib and PD-1 inhibitor group (HAIC+Len+PD-1), patients received HAIC as initial treatment, and Lenvatinib and PD-1 inhibitor were given within one week after first HAIC; (5) in Lenvatinib and PD-1 inhibitor group (Len+PD-1), patients received Lenvatinib and PD-1 inhibitor synchronously as initial treatment.

Patients were excluded from the analysis for any of the following reasons: (1) advanced HCC with tumor capsule; (2) under 18 years or over 80 years; (3) transarterial chemoembolization (TACE) as initial treatment; (4) patients received Sorafenib or other targeted system therapy with/without PD-1 inhibitor; (5) incomplete tumor image data; (6) lost to follow-up after treatment within 3 months. The flow chart of patient selection is presented in Figure S1.

Treatment and Assessment of Response

The HAIC procedure was performed by an experienced radiologist. The microcatheter was inserted into the proper hepatic artery according to the tumor location and affected hepatic segments. After the patient returned to the ward, the FOLFOX-based regimen was intra-arterially administered through the microcatheter. The FOLFOX regimen was as follows: 85 or 135 mg/m^2 oxaliplatin from hours 0 to 2 on day 1, 400 mg/m^2 leucovorin from hours 2 to 4 on day 1, and 400 mg/m^2 fluorouracil bolus at hour 5 on day 1, and 2400 mg/m^2 fluorouracil over 46 h on days 1 and 2. HAIC was repeated every 3–4 weeks. Patients received 2–6 cycles of HAIC. We divided patients into two levels according to HAIC cycles.

The prescription dosage of Lenvatinib was 12 mg (body weight ≥60 kg) or 8 mg (body weight <60 kg) orally once a day. According to the guidelines for the administration of Lenvatinib, the drug dose was reduced, or the treatment was interrupted in patients who developed grade ≥3 severe adverse events (AEs) or any unacceptable grade 2 drug-related AEs, other treatments were recommended after tumor progression. For PD-1 inhibitor (sintilimab, toripalimab, and camrelizumab), the dose was applied according to the drug instruction. In HAIC+Len+PD-1 group, the discontinuation of HAIC depended on tumor response and patients' condition and choice. After HAIC was discontinued, patients still accept Lenvatinib plus PD-1 inhibitor as maintenance therapy.

Tumor imaging response was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v 1.1).[26] In brief, the complete response (CR) was defined as the no enhancement of the tumor. Partial response

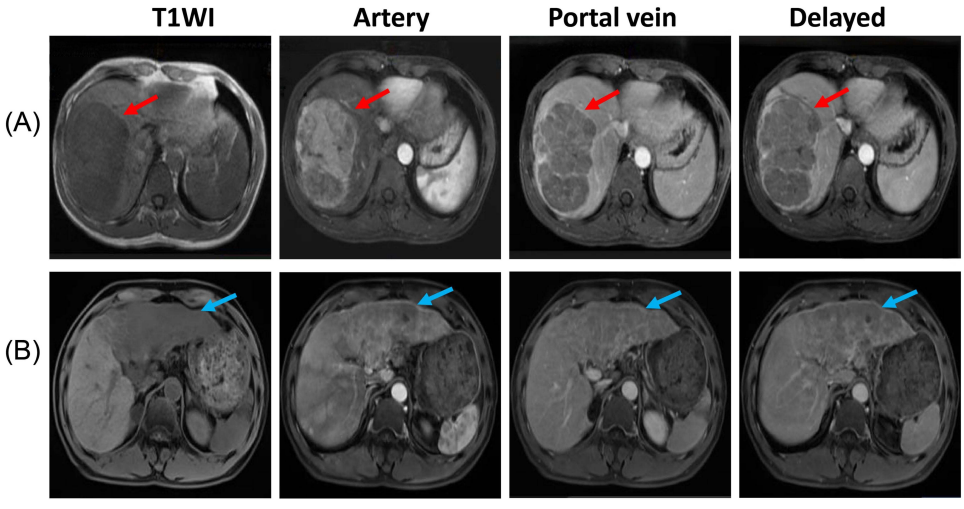

Figure 1 The imaging features between nodular and infiltrative hepatocellular carcinoma (HCC). (**A**) the nodular HCC presented with circular nodule and clear boundary, (**B**) infiltrative HCC has the diffuse and permeative appearance, lacking a well-demarcated boundary. (Red arrows represented nodular HCC, and the blue arrows represented infiltrative HCC).

(PR) was defined as ≥30% shrinking in diameter of the targeted tumors. Progressive disease (PD) was defined as at least 20% increase in the sum of diameter of the targeted tumors, or the appearance of new lesion. Stable disease (SD) neither met the CR nor PR and PD. Objective response rate (ORR) was the sum of CR and PR, and the disease control rate (DCR) was the sum of CR, PR and SD. Tumor assessments were done every 6–8 weeks (irrespective of dose interruptions) until radiological progression. Patients who without disease progression continued the evaluation every 6–8 weeks.

Follow-Up and Definitions

Patients were evaluated at least once every 3–4 weeks after HAIC treatment. Each follow-up visit consisted of image examination (contrast-enhanced CT/MRI), and laboratory tests including AFP, albumin, bilirubin, aspartate transaminase (AST), alanine transaminase (ALT) and prothrombin time (PT). The median follow-up period in the entire cohort was 15.6 (range: 5.5–45.9) months and the follow-up period for this study was terminated on March 31, 2023.

The primary endpoint for the study was overall survival (OS). OS was defined as the time from the date of accepting the initial treatment to the date when patients died or last follow-up. The secondary endpoints included progression-free survival (PFS) and safety. PFS was defined as the time from the date of accepting the initial treatment to tumor progression or last follow-up. Tumor stage was assessed by systemic imaging (contrast-enhanced CT or MRI or positron emission tomography/computer tomography [PET/CT]). We used the Albumin-Bilirubin (ALBI) grade to evaluate liver function.[27] Portal vein tumor thrombus (PVTT) type according to Cheng's criteria.[28] For patient with alpha-fetoprotein (AFP) positive (a baseline AFP level of >20 ng/mL), an AFP response was defined as a decrease in AFP of more than 20% to the baseline value after six weeks of first HAIC or Lenvatinib and PD-1 inhibitor administration.

Statistical Analysis

Propensity score-matching (PSM) analysis was used to reduce the effect of selection bias and potential confounding between the two groups. Propensity scores were estimated using a multivariate logistic regression model, by inserting the following variables: tumor size, tumor number, AFP level, PVTT, hepatic vein tumor thrombus (HVTT), ALBI grade, metastasis, antivirus (patients received the antivirus drug entecavir or tenofovir). Patients were matched 1:1 using the nearest neighbor method with a caliber of 0.05 (Figure S2), and the matching process has been described in previous study.[29]

To evaluate difference between the two groups, the Pearson $\chi 2$ test and Fisher's exact test were used to compare categorical variables. The survival curves of OS and PFS were constructed according to the Kaplan–Meier method with the Log rank test. All statistical tests were 2 sides, and $P < 0.05$ was considered significant. The statistical analyses were performed using the Statistical Package for the Social Science (SPSS) software (version 22.0, SPSS Inc., Chicago, IL, USA) for Windows and R software for Windows (Version 4.3.1; http://www.r-project.org).

Results

Baseline Characteristics

There were 1055 patients with advanced HCC who received Lenvatinib and PD-1 inhibitor with/without HAIC. A total of 305 patients were infiltrative HCC, and 232 patients were included for analysis according to the criteria. Among them, 114 patients received Lenvatinib combined with PD-1 inhibitor (Len+PD-1 group), and 118 patients received HAIC combined with Lenvatinib and PD-1 inhibitor (HAIC+Len+PD-1 group). PSM generated 81 pairs of patients (Table 1). All patients were HBV positive, and more than half of the patients were with virus replication. Compared to the Len+PD-1 group, the HAIC+Len-PD-1 group showed more proportion of patients with tumor size ≤10 cm, satellites, AFP >400 ng/mL, PVTT, ALBI grade 1 in the entire cohort. After PSM, there were no significant difference between the two groups. The patient's characteristics in the entire cohort and PSM cohort are summarized in Table 1.

Table 1 Baseline Characteristics of Patients with Infiltrative HCC in Different Treatment Groups

Characteristics	Entire Cohort			Propensity Score-Matched Cohort		
	Len+PD-1 Group (n=114)	HAIC+Len+PD-1 Group (n=118)	*P* value	Len+PD-1 Group (n=81)	HAIC+Len+PD-1 Group (n=81)	*P* value
Age			0.768			0.359
≤ 60	97 (85.1)	102 (86.4)		72 (88.9)	68 (84.0)	
>60	17 (14.9)	16 (13.6)		9 (11.1)	13 (16.0)	
Sex)			0.230			0.828
Male	93 (81.6)	103 (90.4)		68 (84.0)	69 (85.2)	
Female	21 (18.4)	15 (9.6)		13 (16.0)	12 (14.8)	
ALT, U/L			0.159			0.199
≤ 40	39 (34.2)	51 (43.2)		28 (34.6)	36 (44.4)	
>40	75 (65.8)	67 (56.8)		53 (65.4)	45 (55.6)	
AST, U/L			0.129			0.181
≤ 40	18 (15.8)	28 (23.7)		14 (17.3)	21 (25.9)	
>40	96 (84.2)	90 (76.3)		67 (82.7)	60 (74.1)	
Tumor size, cm			0.005			0.501
≤ 10	26 (22.8)	47 (39.8)		24 (29.6)	28 (34.6)	
>10	88 (77.2)	71 (60.2)		57 (70.4)	53 (65.4)	
Satellites			0.023			0.711
No	26 (22.8)	43 (36.4)		18 (22.2)	20 (24.7)	
Yes	88 (77.2)	75 (63.6)		63 (77.8)	61 (75.3)	
AFP, ng/mL			0.017			1.000
≤ 400	49 (43.0)	33 (28.0)		27 (33.3)	27 (33.3)	
>400	65 (57.0)	85 (72.0)		54 (66.7)	54 (66.7)	
PVTT type			0.033			0.156
No	23 (20.2)	13 (11.0)		14 (17.3)	12 (14.8)	
I-II	37 (32.4)	56 (47.5)		33 (40.7)	42 (51.9)	
III–IV	54 (47.4)	49 (41.5)		34 (42.0)	27 (33.3)	
HVTT			0.171			1.000
No	92 (80.7)	103 (87.3)		67 (82.7)	67 (82.7)	
Yes	22 (19.3)	15 (12.7)		14 (17.3)	14 (17.3)	
ALBI grade			0.048			0.368
Grade 1	20 (17.5)	37 (31.4)		16 (19.8)	23 (28.4)	
Grade 2	87 (76.3)	76 (64.4)		63 (77.8)	55 (67.9)	
Grade 3	7 (6.2)	5 (4.2)		2 (2.4)	3 (3.7)	
Metastasis			0.611			0.753
No	59 (51.8)	65 (55.1)		43 (53.1)	41 (50.6)	
Yes	55 (48.2)	53 (44.9)		38 (46.9)	40 (49.4)	
BCLC stage			0.326			0.464
B	13 (11.4)	9 (7.6)		11 (13.6)	8 (9.9)	
C	101 (88.6)	109 (92.4)		70 (86.4)	73 (90.1)	
HBV DNA			0.666			0.147
>1000 IU/mL	66 (57.9)	65 (55.1)		54 (66.7)	45 (55.6)	
≤1000 IU/mL	48 (42.1)	53 (44.9)		27 (33.3)	36 (44.4)	
Anti-virus			0.056			0.864
No	39 (34.2)	27 (22.9)		24 (29.6)	25 (30.9)	
Yes	75 (65.8)	91 (77.1)		57 (70.4)	56 (69.1)	
Cirrhosis			0.248			0.317
No	52 (45.6)	45 (38.1)		30 (37.0)	24 (29.6)	
Yes	62 (54.4)	73 (61.9)		51 (63.0)	57 (70.4)	

(*Continued*)

Table 1 (Continued).

Characteristics	Entire Cohort			Propensity Score-Matched Cohort		
	Len+PD-1 Group (n=114)	HAIC+Len+PD-1 Group (n=118)	*P* value	Len+PD-1 Group (n=81)	HAIC+Len+PD-1 Group (n=81)	*P* value
Portal hypertension			0.499			0.864
No	81 (71.1)	79 (66.9)		57 (70.4)	56 (69.1)	
Yes	33 (28.9)	39 (33.1)		24 (29.6)	25 (30.9)	

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer staging system; HAIC, Hepatic arterial infusion chemotherapy; HBV DNA, hepatitis B virus deoxyribonucleic acid; HVTT, hepatic vein tumor thrombus; Len, Lenvatinib; PD-1, programmed cell death protein-1; PVTT, portal vein tumor thrombus.

Overall Survival Analysis Between Len+PD-1 and HAIC+Len+PD-1 Groups

Patients in the entire cohort, the median OS were 13.2±0.7 months (95% confidence interval [CI], 11.8–14.5) and 17.8 ±1.7 months (95% CI, 14.5–21.1) in the Len+PD-1 group and HAIC+Len+PD-1 group, respectively. The 6-, 12-, and 24-month OS rates were 92.9%, 60.4% and 12.0% in Len+PD-1 group, and 99.2%, 71.7% and 36.1% in HAIC+Len+PD-1 group, respectively. After PSM, the median OS were 13.9±1.0 months (95% CI, 12.0–15.8) and 17.8±2.1 months (95% CI, 13.7–21.9) in the Len+PD-1 group and HAIC+Len+PD-1 group, respectively. The 6-, 12-, and 24-month OS rates were 93.8%, 65.1% and 13.4% in Len+PD-1 group, and 100%, 77.3% and 32.1% in HAIC+Len+PD-1 group. The HAIC +Len+PD-1 group had obviously better OS than the Len+PD-1 group both in the entire cohort (hazard ratio [HR], 0.58; 95% CI, 0.39–0.73; *P* <0.001) (Figure 2A) and in the PSM cohort (HR, 0.56; 95% CI, 0.39–0.81; *P* =0.003) (Figure 2B).

Univariable analysis of OS and PFS after PSM was presented in Supplementary Table 1. Multivariable analysis after PSM revealed that Len+PD-1 therapy (HR, 1.70; 95% CI, 1.16–2.49; *P*=0.006), PVTT type III–IV (HR, 3.79; 95% CI, 1.94–7.40; *P* <0.001), metastasis (HR, 1.64; 95% CI, 1.11–2.22; *P*=0.012), BCLC C stage (HR, 3.71; 95% CI, 1.28–10.79; *P*=0.016) were risk factors related with poorer OS (Table 2).

Progression-Free Survival Analysis Between Len+PD-1 and HAIC+Len+PD-1 Groups

Patients in the entire cohort, the median PFS was 5.3±0.4 months (95% CI, 4.5–6.1) in Len+PD-1 group, and 6.8±0.7 months (95% CI, 5.5–8.0) in HAIC+Len+PD-1 group, respectively. The 3-, 6-, and 12-month PFS rates were 84.2%, 41.2% and 11.8% in Len+PD-1 group, and 90.7%, 58.5% and 20.3% in HAIC+Len+PD-1 group. After PSM, the median PFS was 5.6±0.5 months (95% CI, 4.5–6.6) in Len+PD-1 group, and 7.6±0.8 months (95% CI, 6.0–9.2) in HAIC+Len +PD-1 group. The 3-, 6-, and 12-month PFS rates were 86.4%, 45.7% and 14.1% in Len+PD-1 group, and 95.1%, 59.3% and 25.9% in HAIC+Len+PD-1 group, respectively. The HAIC+Len+PD-1 group had significantly better PFS than Len +PD-1 group both in the entire cohort (HR, 0.65; 95% CI, 0.49–0.85; *P* =0.002) (Figure 2C) and in the PSM cohort (HR, 0.61; 95% CI, 0.44–0.86; *P* =0.003) (Figure 2D).

The multivariable Cox regression analysis was performed in PSM cohort. The results revealed that Len+PD-1 therapy (HR, 1.81; 95% CI, 1.27–2.57; *P*=0.001), ALT>40 U/L (HR, 1.78; 95% CI, 1.24–2.56; *P*=0.002), satellites (HR, 1.93; 95% CI, 1.25–2.96; *P*=0.003), PVTT type III–IV (HR, 2.41; 95% CI, 1.40–4.12; *P*=0.002), metastasis (HR, 1.47; 95% CI, 1.04–2.08; *P*=0.028) were risk factors related with poorer PFS (Table 2).

Efficacy Evaluation

Tumor response was evaluated according to RECIST v 1.1, and the results in PSM cohort were presented in Table 3. In the 3-month evaluation, there were four patients in the HAIC+Len+PD-1 group who achieved CR. ORR was 25.9%, 50.6% and the DCR was 70.3%, 82.7% in Len+PD-1 group, HAIC+Len+PD-1 group, respectively. The proportion of CR, PR, SD, PD in two groups was an obvious difference (*P*=0.005) (Table 3). In the 6-month evaluation, ORR was

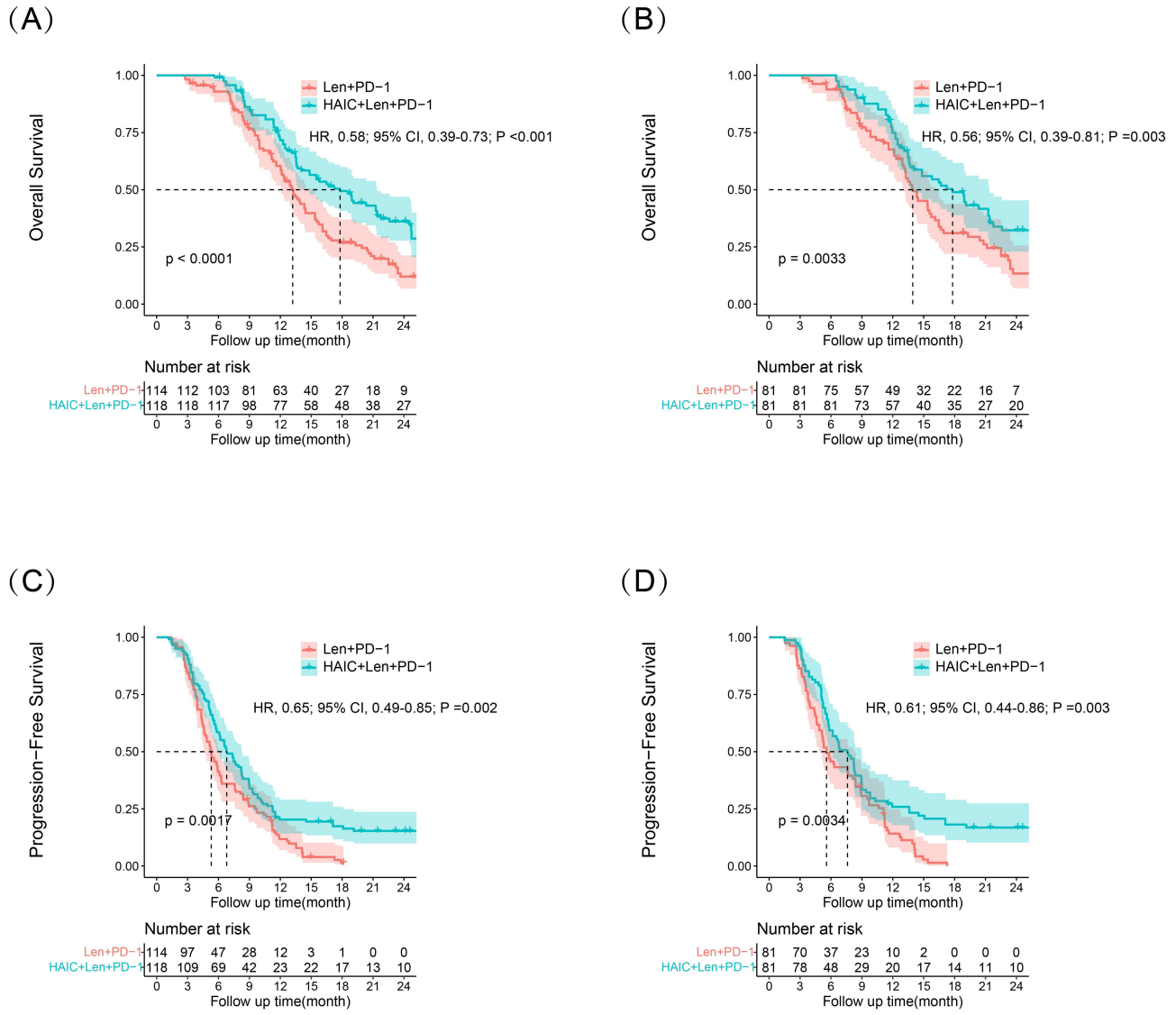

Figure 2 Kaplan–Meier curves of OS in the entire cohort (**A**) and in the PSM (**B**), and PFS in the entire cohort (**C**) and in the PSM cohort (**D**) of patients with infiltrative HCC who were treated Len+PD-1 of HAIC+Len+PD-1 treatment.

20.9%, 44.5% and the DCR was 43.2%, 51.9% in Len+PD-1 group, HAIC+Len+PD-1 group, respectively. Similarly, the proportion of CR, PR, SD, PD in two groups was an obvious difference (*P*=0.001) (Table 3).

Subgroup Analysis of Metastasis on Prognosis

Patients were stratified into two groups by absence or presence of extrahepatic metastasis. There were 78 patients with metastasis and 84 patients without metastasis in PSM cohort. The medium OS of patients with and without metastasis were 12.1±0.7 months and 16.5±1.0 months in Len+PD-1 group, and 16.5±1.8 months and 21.7±4.5 months in HAIC +Len+PD-1 group. Significant difference was observed in OS between the two groups with metastasis (HR, 0.56; 95% CI, 0.33–0.93; *P*=0.021) (Figure 3A) and without metastasis (HR, 0.54; 95% CI, 0.31–0.94; *P*=0.025) (Figure 3B). Patients in Len+PD-1 group showed poorer survival than HAIC+Len+PD-1 group both in patients with and without metastasis. In intragroup analysis, significant difference was observed in OS of patients with and without metastasis in Len+PD-1 group (HR, 0.58; 95% CI, 0.35–0.97; *P*=0.034) (Figure 3C). However, no difference was observed in OS for patients with and without metastasis in HAIC+Len+PD-1 group (HR, 0.79; 95% CI, 0.46–1.35; *P*=0.391) (Figure 3D).

Table 2 Multivariate Analysis of Prognostic Factors for OS and PFS After PSM

Variables	Overall Survival		Progression-Free Survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treatment type				
Len+PD-1 vs HAIC+Len+PD-1	1.70 (1.16–2.49)	0.006	1.81 (1.27–2.57)	0.001
ALT, U/L				
>40 vs ≤40	-	-	1.78 (1.24–2.56)	0.002
Satellites				
Yes vs No	-	-	1.93 (1.25–2.96)	0.003
PVTT type				
No	Reference	0.421	Reference	0.518
I–II	1.27 (0.71–2.27)	<0.001	1.18 (0.72–1.92)	0.002
III–IV	3.79 (1.94–7.40)		2.41 (1.40–4.12)	
Metastasis				
Yes vs No	1.64 (1.11–2.22)	0.014	-	-
BCLC stage				
C vs B	3.71 (1.28–10.79)	0.016	-	-

Abbreviations: ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer staging system; CI, confidence interval; HAIC, Hepatic arterial infusion chemotherapy; HR, hazard ratio; Len, Lenvatinib; PD-1, programmed cell death protein-1; PVTT, portal vein tumor thrombus.

Table 3 Efficacy Outcomes in Two Groups According to RECIST v1.1 in PSM Cohort

Variables	Evaluation	Len+PD-1 Group (n=81)	HAIC+Len+PD-1 Group (n=81)	*P* value
3-Month Evaluation	CR	0 (0)	4 (4.9)	0.005
	PR	21 (25.9)	37 (45.7)	
	SD	36 (44.4)	26 (32.1)	
	PD	24 (29.7)	14 (17.3)	
6-Month Evaluation	CR	0 (0)	5 (6.2)	0.001
	PR	17 (20.9)	31 (38.3)	
	SD	18 (22.2)	6 (7.4)	
	PD	46 (56.8)	39 (48.1)	

Abbreviations: CR, complete response; Len, Lenvatinib; PD-1, programmed cell death protein-1; PD, progressive disease; PR, partial response; SD, stable disease.

Subgroup Analysis on Patients with AFP Response

A total of 142 (87.7%, [142/162]) patients with AFP positive were analyzed in PSM cohort. There were 57 patients with non-response and 85 patients with AFP response. The median OS were 12.6±0.5 months (95% CI, 11.6–13.7) and 21.3±0.7 months (95% CI, 19.9–22.7) in the AFP non-response group and AFP response group, respectively. The median PFS were 4.5±0.4 months (95% CI, 3.6–5.3) and 9.8±1.0 (95% CI, 7.8–11.8) months in the AFP non-response group and AFP response group, respectively. Compared with the AFP non-response group, the AFP response group had significantly better OS (HR, 0.30; 95% CI, 0.21–0.44; $P<0.001$) (Figure 4A) and PFS (HR, 0.14; 95% CI, 0.10–0.22; $P<0.001$) (Figure 4B).

There were 40 patients in Len+PD-1 group and 53 patients in HAIC+Len+PD-1 group achieved AFP response. The patients of AFP response were obviously higher in HAIC+Len+PD-1 group ($P=0.039$). We further analyzed the prognosis of different treatment (Len+PD-1 vs HAIC+Len+PD-1) in AFP response or non-response groups. No difference was observed in OS (Figure S3A and B) and PFS (Figure S3C and D) of different treatment in AFP response or non-response patients.

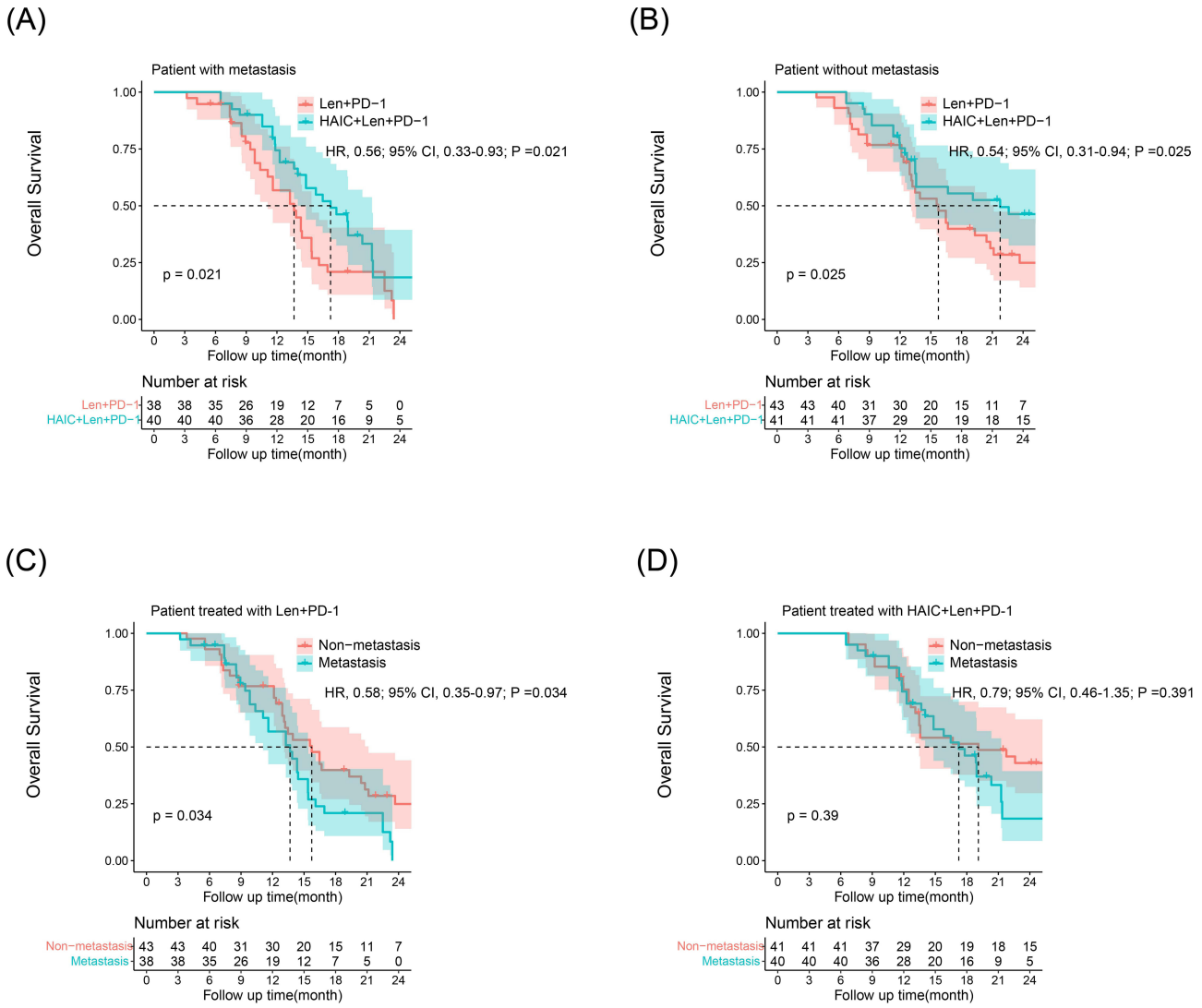

Figure 3 Kaplan–Meier curves of OS in patients with or without metastasis in PSM cohort. The OS rate of patient with metastasis (**A**) and without metastasis (**B**) between two groups; The OS rate of patients with and without metastasis in Len+PD-1 group (**C**) and HAIC+Len+PD-1 group (**D**), respectively.

Treatment-Related Adverse Events

Treatment-related deaths did not occur in this study and treatment-related AEs occurred in most patients. The main AEs were recorded in Supplementary Table 2. All of 232 patients received at least 3 months of Lenvatinib plus PD-1 inhibitor and 2–6 cycles of HAIC in HAIC+Len+PD-1 group. The median duration of Lenvatinib was 6.8 (range, 3.0–18.0) months in Len+PD-1 group and 9.5 (range, 4.5–24.0) months in HAIC+Len+PD-1 group. Median duration of PD-1 inhibitor was 15.0 (range, 6.0–24.0) months. For grade 1–2 of AEs, patients were alleviated after accepting symptomatic treatment or dose reduction. For grade 3–4 of AEs, patients were temporary stopped Lenvatinib or PD-1 inhibitor administration until the AEs alleviated or disappeared, and PD-1 inhibitor infusion and low dose of Lenvatinib continued if possible after recovery.

Discussion

Infiltrative HCC was defined as an irregular-shaped, hypo-vascular permeative masses usually accompanied with tumor thrombosis.[2] It may have diagnostic challenge because it is often difficult to distinguish from background changes in cirrhosis at imaging.[6] In China, most patients with infiltrative HCC often presented with obvious cirrhosis or HBV infection.[30] Infiltrative HCC with diffused tumor behavior is more aggressive than nodular type with capsule.[31] Most

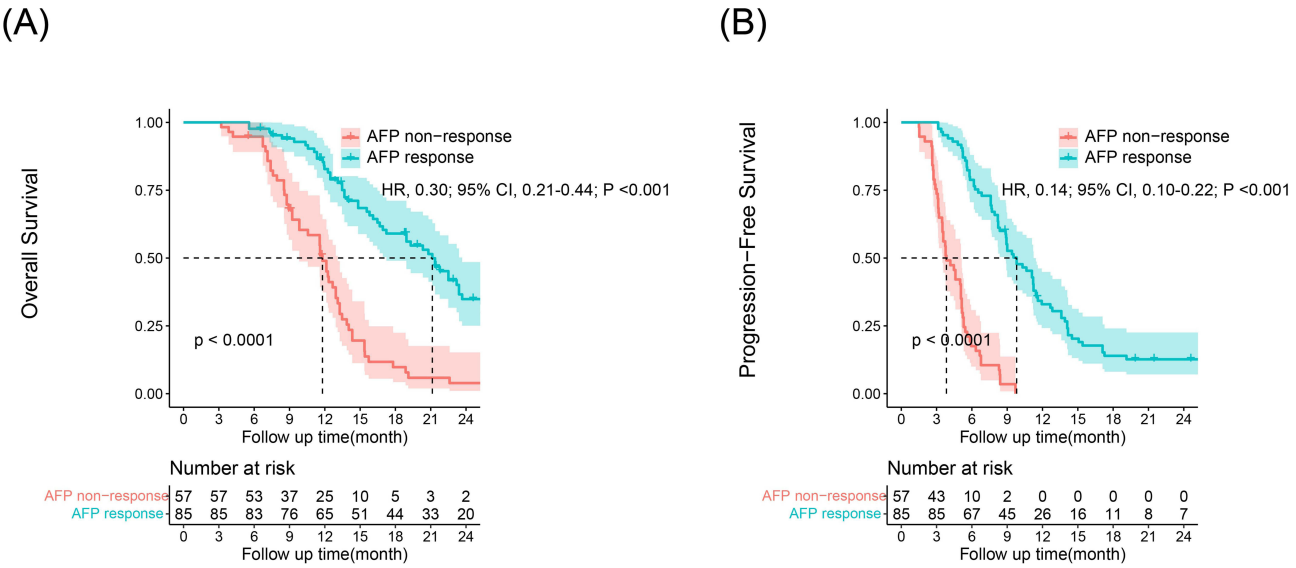

Figure 4 Kaplan–Meier survival curves for OS (**A**) and PFS (**B**) of patients with different alpha-fetoprotein (AFP) response after treatment.

infiltrative HCC diagnosed at an advanced stage, occupying an entire hepatic lobe or the entire liver, and associated with PVTT or metastasis.[32] Treatment for this subtype of advanced HCC was usually system therapy as such as Lenvatinib plus PD-1 inhibitors or atezolizumab plus bevacizumab.[33,34] However, the prognosis of infiltrative HCC was not well studied and there still need further evidence to address its clinical importance. In this study, we analyzed 232 infiltrative HCC patients who were treated with Len+PD-1 (n=114) or HAIC+Len+PD-1 (n=118). We found that, compared with Len+PD-1 treatment, HAIC+Len+PD-1 treatment had significantly better OS and PFS both in the entire and PSM cohorts. Subgroup analysis revealed that combination of HAIC and Lenvatinib and PD-1 inhibitor was both superior to Lenvatinib and PD-1 inhibitor patients with or without metastasis, and AFP response was a useful indicator of prognosis.

The Food and Drug Administration (FDA) has approved atezolizumab plus bevacizumab as first choice for advanced HCC.[35] However, due to the practicality of China, Lenvatinib plus PD-1 inhibitor is much cheaper than atezolizumab plus bevacizumab.[36] Thus, Lenvatinib plus PD-1 inhibitor were usually recommended for infiltrative HCC.[21,22] Additionally, the locoregional approaches like transcatheter arterial of chemotherapy (TACE) or HAIC have been widely employed as an effective therapy for advanced HCC.[16,37] For patients with infiltrative HCC, local therapy may provide benefits to improve the tumor control rate and prolong the survival.[38] In clinical practice, doctors preferred to choose HAIC rather than TACE with the following reasons. Firstly, TACE has the high risk of causing hepatic failure due to the poor hepatic reserve of patients with infiltrative HCC, while HAIC without the procedure of embolism has the low probability of hepatic failure.[39,40] Secondly, infiltrative HCC with a diffuse permeative appearance has multi blood supply such as hepatic artery, portal vein, or duodenal artery, thus, the outcome of TACE was limited.[8,41] Thirdly, study has reported that HAIC is more effective and tolerable than TACE in infiltrative HCC.[4] Finally, HAIC could improve the local tumor control and stimulate massive tumor antigen expression which create an amicable environment for the PD-1 inhibitor.[17]

Given the limited number of literatures about infiltrative HCC, the available data are too small. In the present study, we included the largest cases as far as we know reported and compared the prognosis of Len+PD-1 with HAIC+Len+PD-1 on infiltrative HCC with multicenter data. We also spare no effort to control the homogeneity of HCC patients, including patients with PVTT or metastasis enrolled for analysis. Our results showed that the 6-, 12-, and 24-month OS rates were 93.8%, 65.1% and 13.4% in Len+PD-1 group, and 100%, 77.3% and 32.1% in HAIC+Len+PD-1 group, respectively, which revealed that HAIC combination of Lenvatinib with PD-1 inhibitor had obviously improved the survival of patients with infiltrative HCC. An C et al reported that 1-, 2-year OS rates were 38.2%, 8.4% for HAIC alone of infiltrative HCC[4]. Han K reported the 6-, 12-, and 24-month OS rates were 48%, 25%, and 12% for TACE of infiltrative HCC.[42] The OS of patients in HAIC+Len+PD-1 group and Len+PD-1 group in our study were better than the studies above. What's more, the base-line of patients in our study was poorer than studies of An C and Han K. Finn *RS*

et al conducted the clinical trial of Lenvatinib and pembrolizumab on advanced HCC, and the median PFS and OS were 8.6 months and 22.0 months, respectively.[14] The median PFS and OS in Lenvatinib+PD-1 group in our study were 5.6 months and 13.9 months in PSM cohort.[14] Both the PFS and OS in our study were lower than Finn *RS* et al due to the more aggressive of tumor characteristics of infiltrative HCC.

Although infiltrative HCC is not uncommon, it remains not fully illustrated in the literatures, especially the system therapy on this subtype. In the present study, we not only compared the efficacy of different treatment regimens, but also conducted detailed subgroup analyses of different treatment modalities. Interestingly, we found that patients in Len+PD-1 group showed poorer survival than HAIC+Len+PD-1 group both in with and without metastasis. However, survival is not influenced by metastasis in HAIC+Len+PD-1 group. The underlying reasons for these results might be complicated, but it may be explained by the following aspects. First, HAIC as an effective local therapy could control availably tumors in liver, Lenvatinib and PD-1 as system maintenance therapy could competently inhibit the tumor from progression. Thus, locoregional and systemic combinations could comprehensively control tumor more effectively than system therapy.[43] Second, HAIC could induce immunogenic cell death which creates a friendly environment for the immune system by augmenting tumor-specific T-cell stimulation and recruiting.[44] PD-1 inhibitor could enhance the killing effect of CD8+T cells and relieve immunosuppression within the tumor, which improved inhibition of metastasis.[45] Third, Lenvatinib could attenuate CD4+ regulatory T cells and myeloid-derived suppressor cells and boost the differentiation of dendritic cells in tumors 9. Therefore, combination of Lenvatinib and PD-1 inhibitor after HAIC creates an effective antitumor immune response for CD8+T cells. These reasons may explain the result that survival is not influenced by metastasis for patients in HAIC+Len+PD-1 group.

AFP level is considered as an indicator of tumor stage and tumor burden, and a high AFP level is often associated with more invasive tumor characteristics, such as vascular invasion, intrahepatic spread, and metastasis.[46,47] In our study, AFP >20 ng/mL was set as positive because this cutoff level was usually used as the abnormal threshold.[48] Moreover, changes in AFP have been considered as association with tumor responses after various treatments, and several studies have addressed the value of the AFP response in predicting prognosis.[49,50] However, there was no study as far as we know using AFP forecasting tumor response in the infiltrative HCC. Our study revealed that an AFP decrease of more than 20% within 6 weeks after first treatment indicated better survival in infiltrative HCC patients. Compared with the AFP non-response group, the AFP response group had significantly better OS and PFS. It was suggested that AFP response might be appropriate as an early predictor of prognosis in infiltrative HCC patients. Further studies are needed to illustrate our result.

This study has several limitations. First, as a retrospective study, the selection bias existed in determining patients adding HAIC therapy. Because it was not only the choice of doctors but also the patient's tolerance and affordability, but we tried to minimize such limitation by PSM. Second, although we have carefully selected patients with several clinical characteristics, the influence of measured and unmeasured confounders on the outcome of patients is inevitable. For example, heterogeneous HAIC regime and patient's response to Lenvatinib or PD-1 inhibitor, and their combinations might make some sense to the outcome in some extent unknown. Third, three kinds of PD-1 inhibitors were used in our study, the three PD-1 inhibitors were approved by the National Medical Products Administration and available in Chinese hospitals, and these PD-1 inhibitors have demonstrated efficacy in HCC in clinical trials. Fourth, although we have included data from multiple centers, the number of patients included in the analysis is limited, there may be some influence on the results due to insufficient sample size, future prospective and large-scale multicenter study, which is needed to verify our findings, which could serve as a guideline to treat the infiltrative HCC.

Conclusion

In summary, our study indicated that HAIC combined Lenvatinib and PD-1 inhibitor were associated with longer OS and PFS than Lenvatinib plus PD-1 inhibitor for patient with infiltrative HCC. In addition, we found that AFP response was an early indicator of better survival and tumor response to therapy in infiltrative HCC.

Data Sharing Statement

Data available from the Qunfang Zhou upon reasonable request and with permission of four hospitals authority in China.

Ethics Statement

The Ethics Committee Board of the Chinese PLA General Hospital approved this retrospective study and waived the requirement for patient consent for this retrospective review. We solemnly promised that this study strictly abided by relevant laws and regulations and did not disclose patient personal information and related information to any other personnel and organizations to ensure the security and confidentiality of patient information.

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Disclosure

The authors declare no conflicts of interest.

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