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ORIGINAL RESEARCH

Survival Benefit of Synchronous Lenvatinib Combined PD-1 Inhibitors for Advanced Hepatocellular Carcinoma Beyond Oligometastasis

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Purpose: Strategies therapy for hepatocellular carcinoma (HCC) beyond oligometastasis are limited. The optimal sequence of systemic treatment for advanced HCC is not yet clear. Our study aims to evaluate the effectiveness of simultaneous lenvatinib combined PD-1 inhibitor on advanced HCC beyond oligometastasis.

Patients and Methods: A total of 232 patients were enrolled in our retrospective study. Patients divided into three groups. (a) Lenvatinib plus simultaneous PD-1 inhibitor (Simultaneous group, n=58); (b) patients received PD-1 inhibitor before the tumor progression with continued lenvatinib administration (Before PD group, n=77); (c) patients received PD-1 inhibitor after the tumor progression (After PD group, n=97). To analyze overall survival (OS) and progression-free survival (PFS) among the three groups.

Results: The estimated 6-, 12-, 18- and 24-mon OS for Simultaneous group patients were 100%, 93.1%, 63.4%, 48.3%, whereas the OS rates were 100%, 78%, 36.3%, 23.6% in Before PD group, and 99%, 61.2%, 22.1%, 7.5% in After PD group. The OS rates were obviously improved with the use of simultaneous PD-1 inhibitor among the three groups (P <0.001). The estimated 3-, 6-, 9- and 12-month PFS rates for patients were 89.6%, 44.8%, 24.6%, 6% in After PD group, 90.9%, 59.7%, 27.3%, 12.4% in Before PD group and 98.3%, 81%, 51.7%, 39.7% in Simultaneous group, respectively. PFS rate was significantly different among the three groups (P <0.001).

Conclusion: Synchronous administration of lenvatinib and PD-1 inhibitors improved survival rate significantly. The synchronous combination could represent a promising strategy in HCC beyond oligometastasis.

Keywords: lenvatinib, PD-1 inhibitor, hepatocellular carcinoma beyond oligometastasis, simultaneous, prognosis

Introduction

Hepatocellular carcinoma (HCC), typically occurs in chronic liver disease and cirrhosis patients, is an invasive tumor.[1] HCC treatments include resection, liver transplantation, local therapy and systemic therapy. Resection was recommended in early-stage HCC which is restricted in liver.[2] However, when patients experience or subsequently develop with distant metastasis, they would be classified into advanced stage.[3] As recommended by updated Barcelona Clinical Liver cancer (BCLC) treatment algorithms, systemic therapy is the mainstay treatment for advanced HCC.[4] Evidence showed that extrahepatic metastases and recurrence have been the main tumor-caused death.[5] The compliance rate between HCC and metastasis is relatively high.[6] Metastases are usually associated with relatively high tumor burden and vascular invasion. Recent studies have shown that those patient populations have a poor outcomes with locoregional therapies, thus may be more suitable for initial systemic treatment. Furthermore, the LAUNCH trial suggests that for patients with high tumor

burden and/or macrovascular invasion, the combination of transarterial chemoembolization (TACE) and lenvatinib may have better outcomes compared to lenvatinib monotherapy.[7]

Lungs are the most common sites of metastases, followed by lymph nodes, bones and adrenal gland.[8] Patients with five or fewer metastases were defined as oligometastasis, which may be suitable for local treatment.[9] The survival of HCC patients is often determined based on the degree of liver dysfunction. If they have good physical state and liver function, they may still not be considered as advanced, even with large tumor volume, vascular invasion and distant metastases.[10] The prognosis of patients with multi-metastases has improved with the emerging therapies.[11] Convincing studies have shown that after killing the foci within oligometastasis, local therapy could achieve long-term disease-free survival.[12] Compared to patients with oligometastasis, the prognosis was significantly worse in patients beyond oligometastasis.[13] At the present age of molecularly targeted systemic therapy, increasingly tolerable and effective choice is being made to control advanced HCC beyond oligometastasis.[14]

Although lenvatinib is a first-line treatment in advanced HCC, new combinations are still needed to overcome the limitations of single therapy.[15] In terms of immune checkpoint inhibitors, including immune checkpoint related inhibitors targeting programmed cell death receptor 1 (PD-1) and its ligand 1 (PD-L1), cytotoxic T lymphocyte associated antigen (CTLA-4), has revealed promising results.[16] Currently, the combined use of PD-1 inhibitor and lenvatinib is a hot topic in clinical application, showed stronger anti-tumor effects in clinical trials.[17,18] Lenvatinib could inhibit immunosuppressive effects and neovascularization of tumor microenvironments, by enhancing the antitumor immune response, would strengthen the clinical benefit of PD-1 antibodies.[18] In fact, the time patients received the PD-1 inhibitor and lenvatinib can be synchronous or different in the real world.[19] However, there was no study reporting synchronous or non-synchronous differences between lenvatinib and PD-1 inhibitor in advanced HCC. Thus, in this multi-center study, we aim to compare the effectiveness of synchronous and non-synchronous of PD-1 inhibitor and lenvatinib on the advanced HCC beyond oligometastasis.

Materials and Methods
Patients and Study Design
Patients who met the inclusion criteria would be enrolled: (1) Histologically or clinically confirmed HCC; (2) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; and Child-Pugh class A or B;(3) Barcelona Clinic Liver Cancer (BCLC) stage C beyond oligometastasis (more than five metastases); (4) prothrombin activity > 40%, international normalized ratio (INR) < 1.26; (5) serum creatinine concentration not exceeding 1.5 times the upper normal limit. Patients were not eligible for the following reasons: (a) advanced HCC with five or fewer metastasis; (b) under 18 or over 75 years old;(c) incomplete clinical data; (d) portal vein tumor thrombus (PVTT) were involving the superior mesenteric vein; (e) there was tumor thrombus in the atrium or vena cava.

This study was conducted in patients with advanced HCC beyond oligometastasis at Hunan Provincial People's Hospital from January 2018 to December 2019. The study complied with the guidelines of the Declaration of Helsinki[20] and approved by the ethics committee of Hunan Provincial People's Hospital. Due to being a retrospective study, informed consent was waived. The data was maintained with confidentiality.

Treatment and Response Assessment
All individuals underwent magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT) within 2 weeks prior to the lenvatinib application. Patients were divided into three groups. (a) Lenvatinib plus PD-1 inhibitor simultaneous (Simultaneous group); patients who received PD-1 inhibitor and lenvatinib at the same time, or patients received PD-1 inhibitor within 2 weeks of lenvatinib. (b) Patients received PD-1 inhibitor before the tumor progression (Before PD group); Patients received the PD-1 inhibitor more than 3 months after lenvatinib with continued administration at the condition that the tumor did not occur progression. (c) Patients received PD-1 inhibitor after the tumor progression (After PD group); patients received PD-1 inhibitor after tumor progression after lenvatinib stopped.

Information regarding of initiation, completion of treatment, and adverse events (AEs) during therapy was methodically recorded. The prescribed dosage of lenvatinib was 8 milligrams (for patients with a body weight <60 kg) or 12

milligrams (for patients with a body weight ≥60 kg) orally per day. The PD-1 inhibitor dose was applied based on the drug instruction (including nivolumab, pembrolizumab, tislelizumab, sintilimab, toripalimab, camrelizumab).

Outcomes and Definitions

Overall survival (OS) was the main objective, and progression-free survival (PFS) was the secondary endpoint. OS was defined as the duration from receiving lenvatinib to death or the last follow-up. PFS was defined as the duration from receiving lenvatinib to tumor progression or the last follow-up. Albumin-Bilirubin (ALBI) grade were used to evaluate liver function.[21] According to systemic imaging (either contrast-enhanced CT of the chest or bone scan, MRI or contrast-enhanced CT of abdomen or brain or positron emission tomography/computer tomography (PET/CT), tumor stage was assessed. According to Cheng's criteria,[22] PVTT included four categories: type I, tumor thrombus involving the portal vein segmental branches or higher; type II, tumor thrombus involving either the right or left portal vein; type III, tumor thrombus affecting the main portal vein; type IV, the superior mesenteric vein was involved by tumor thrombus. Patients receiving TACE, ablation or surgery before lenvatinib were registered, and drug-related complications were also recorded.

Follow-Up

This study was followed up until April 30, 2021. Patients should undergo evaluation at least once every 6 weeks after therapy. Each follow-up included experimental tests and abdominal imaging examination (contrast-enhanced CT and/or MRI). Experimental tests of prothrombin time (PT), alanine transaminase (ALT), aspartate transaminase (AST), alfa-fetoprotein (AFP), albumin and bilirubin should be conducted every 6 weeks after treatment to evaluate liver function and treatment response. A maximum of two lesions per organ and five lesions in total were chosen as target tumors. Based on the Response Evaluation Criteria in Solid Tumors 1.1 (RECST 1.1), tumor imaging response was evaluated.[23] In brief, the outcome was divided into four types, including complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD). The CR was described as the disappearance of tumor arterial enhancement. PR was described as a targeted tumor diameter reduction of ≥ 30%. PD was described as new lesion appeared, or a minimum growth of 20% in the overall diameter of the targeted tumors. SD was neither CR nor PR and PD compliant. The sum of CR and PR were counted as objective response rate (ORR). The combination of CR, PR and SD were counted as the disease control rate (DCR).

Statistical Analysis

For comparison of difference among three groups, the Pearson $\chi 2$ test was investigated to compare categorical variables and ANOVA was used to analyze continuous variables. According to the Kaplan-Meier method with the Log rank test, the survival curves overall survival (OS) and progression-free survival (PFS) were constructed. Determined the survival rates at 6, 12, 18, and 24 months using the z-test life table. The results were analyzed using the R software for Windows (Version 3.6.4 http://www.r-project.org) and Statistical Package for the Social Science (SPSS) software (version 22.0, SPSS Inc., Chicago, IL, USA) for Windows. All statistical tests were bilateral, and $P < 0.05$ was considered significant.

Results

Baseline Characteristics

A total of 232 patients enrolled in the study (Supplementary Figure 1). Ninety-seven patients received PD-1 inhibitor after the tumor progression with stopping lenvatinib administration (After PD group); 77 patients received PD-1 inhibitor before the tumor progression with continued lenvatinib administration (Before PD group); 58 patients received lenvatinib plus PD-1 inhibitor simultaneous (Simultaneous group). The median follow-up time was 22.9 months. All patients in the primary analysis set were followed up for 6 months. A comparison of the baseline clinical and laboratory parameters was shown in Table 1. In this cohort, most patients were primary HCC, and a high proportion of patients were received TACE or sorafenib. About half of patients had different PVTT involvement, and most patients in three groups have more 3

Table 1 Clinical Characteristics of Patients with Advanced Hepatocellular Carcinoma (HCC) Beyond Oligometastasis by Type of Different Treatments: (1) Patients Received PD-1 Inhibitor After the Tumor Progression (After PD Group); (2) Patients Received PD-1 Inhibitor Before the Tumor Progression (Before PD Group); (3) Patients Received Lenvatinib Plus Simultaneous PD-1 Inhibitor (Simultaneous Group)

Variables	After PD group (n=97)	Before PD group (n=77)	Simultaneous group (n=58)	*P value*
Sex				
Male	82 (84.5)	70 (90.9)	50 (86.2)	0.449
Female	15 (15.5)	7 (9.1)	8 (13.8)	
Age, *years*				
< 60	65 (67.0)	63 (81.8)	48 (82.8)	0.028
≥ 60	32 (33.0)	14 (18.2)	10 (17.2)	
HCC type				
Primary	84 (86.6)	65 (84.4)	47 (81.0)	0.651
Recurrent	13 (13.4)	12 (15.6)	11 (19.0)	
Before treatment				
Ablation/radiotherapy	39 (40.2)	38 (49.4)	20 (34.5)	0.204
TACE	79 (81.4)	58 (75.3)	41 (70.7)	0.021
Before sorafenib administration				
Yes	76 (78.4)	66 (85.7)	48 (82.8)	0.447
No	21 (21.6)	11 (14.3)	10 (17.2)	
PVTT type				
No	47 (48.5)	35 (45.5)	33 (56.9)	0.563
I	5 (5.2)	4 (5.2)	6 (10.3)	
II	20 (20.6)	15 (19.5)	8 (13.8)	
III	25 (25.7)	23 (29.8)	11 (19.0)	
Tumor number in liver				
≤3	19 (19.6)	18 (23.4)	15 (25.9)	0.643
> 3	78 (80.4)	59 (76.6)	43 (74.1)	
Tumor size, cm				
≤5	17 (17.5)	12 (15.6)	5 (8.6)	0.590
>5, <10	51 (52.6)	41 (53.2)	31 (53.4)	
≥10	29 (29.9)	24 (31.2)	22 (38.0)	
Metastasis location				
Lung	33 (34.0)	32 (41.6)	26 (44.8)	0.133
Other organs	24 (24.7)	24 (31.2)	19 (32.8)	
Lung + other organs	40 (41.3)	21 (27.2)	13 (22.4)	
ALBI grade				
I	40 (41.2)	29 (37.7)	25 (43.1)	0.900
II	51 (52.6)	45 (58.4)	30 (51.7)	
III	6 (6.2)	3 (3.9)	3 (5.2)	
AFP level, *ng/mL*				
<20	20 (20.6)	17 (22.1)	12 (20.7)	0.787
≥ 20, < 400	34 (35.1)	23 (29.9)	15 (25.9)	
≥ 400	43 (44.3)	37 (48.0)	31 (53.4)	
ALT, *U/L*				
≤ 40	51 (52.6)	30 (39.0)	28 (48.3)	0.197
> 40	46 (47.4)	47 (61.0)	30 (51.7)	
AST, *U/L*				
≤ 40	35 (36.1)	22 (28.6)	18 (31.0)	0.558
> 40	62 (63.9)	55 (71.4)	40 (69.0)	

(Continued)

Table 1 (Continued).

| Variables	After PD group (n=97)	Before PD group (n=77)	Simultaneous group (n=58)	*P value*
HBsAg positive	46 (47.4)	40 (51.9)	28 (48.3)	0.829
Portal hypertension	29 (29.9)	20 (26.0)	10 (17.2)	0.214
Cirrhosis	54 (55.7)	32 (41.6)	21(36.2)	0.039
CRE, μmol/L	73.1±29.4	72.8±30.7	70.1±28.1	0.815
Neutrophile, *x 10⁹/L*	4.2±2.0	4.7±2.9	4.5±2.7	0.393
Platelet count, *x 10⁹/L*	195.6±109.3	219.4±114.2	203.2±105.1	0.363
Hemoglobin, *g/L*	133.4±26.2	131.1±22.1	134.1±23.0	0.681

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; CRE, creatinine; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; TACE, transarterial chemoembolization;

tumors and a large HCC (>5 cm). Most patients had lung or lung-related metastasis. As showed in Table 1, except the age ($P =0.028$), there were no significant difference in baseline characteristics among the 3 groups.

Overall Survival (OS) Analysis

During the follow-up period, 168 (72.4%) patients died, 72 (93.5%) patients occurring in the Before PD group, 58 (59.8%) patients in the After PD group, 32 (55.2%) patients in the Simultaneous group ($P =0.031$). The medium OS were 13.37±0.63 (95% CI: 12.51–14.96) months, 16.10±1.73 (95% CI: 12.70–19.50) months and 20.57±3.03 (95% CI: 14.64–26.50) months in After PD group, Before PD group and Simultaneous group, respectively. The estimated 6-, 12-, 18- and 24-month OS rates for patients in the Simultaneous group were 100.0%, 93.1%, 63.4%, 48.3%, whereas the OS rates were 100.0%, 78%, 36.3%, 23.6% in Before PD group, and 99.0%, 61.2%, 22.1%, 7.5% in After PD group (Supplementary Table 1). There was a statistically significant difference between Simultaneous group and Before PD ($P <0.001$) or After PD group ($P <0.001$) (Figure 1A). In addition, the difference was also statistically significant between the Before PD and After PD group ($P =0.043$).

Supplementary Table 2 presented the univariate analysis of OS. Multivariate analysis exhibited that type of PVTT I (HR=3.63; 95% CI: 1.73–7.59; $P =0.001$), type of PVTT II (HR=1.93; 95% CI: 1.26–2.96; $P =0.003$), type of PVTT III

(A)

(B)
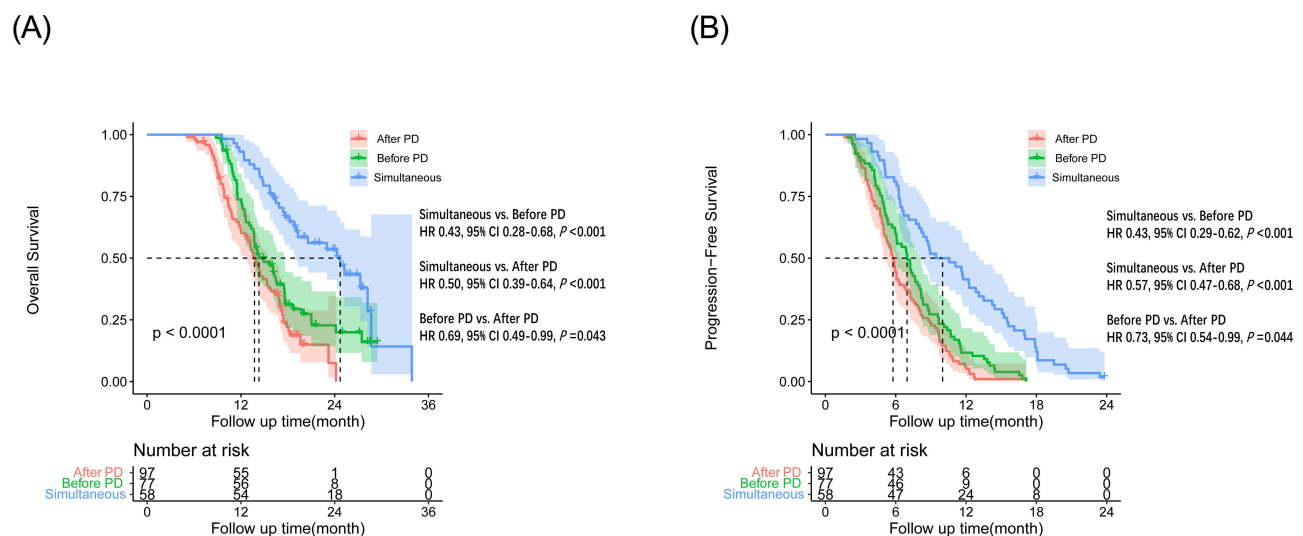
Figure 1 Kaplan–Meier curves for overall survival (OS) in 232 patients with HCC beyond oligometastasis by different treatments (Patients received PD-1 inhibitor after the tumor progression (After PD group); patients received PD-1 inhibitor before the tumor progression (Before PD group); patients received lenvatinib plus simultaneous PD-1 inhibitor (Simultaneous group)). (**A**) The OS ($P <0.001$) and PFS (**B**) ($P <0.001$) curves of After PD group, Before PD group, Simultaneous group, respectively.

(HR=1.78; 95% CI: 1.15–2.77; P =0.010), metastasis of other organs (HR=2.09; 95% CI: 1.39–3.14; P <0.001), metastasis of lung plus other organs (HR=1.56; 95% CI: 1.02–2.37; P =0.041), Before PD (HR=2.37; 95% CI: 1.5–3.74; P <0.001), After PD (HR=3.97; 95% CI: 2.49–6.35; P <0.001) were associated with poorer OS (Table 2).

Progression-Free Survival (PFS) Analysis

The medium PFS were 6.56±3.23 (95% CI: 5.92–7.19) months, 7.54±0.42 (95% CI: 6.71–8.37) months and 10.86±0.69 (95% CI: 9.50–12.22) months in After PD group, Before PD group, Simultaneous group, respectively. The estimated 3-, 6-, 9- and 12-month PFS rates for patients in After PD group were 89.6%, 44.8%, 24.6%, 6.0%, respectively, whereas the PFS rates were 90.9%, 59.7%, 27.3%, 12.4% in Before PD group and 98.3%, 81.0%, 51.7%, 39.7% in Simultaneous group, respectively. (Supplementary Table 1). The difference was statistically significant among Simultaneous group and Before PD or After PD group (P <0.001) (Figure 1B). In addition, there was also a significance between the Before PD and After PD group (P =0.044).

Supplementary Table 2 presented the univariate analysis of PFS. Multivariate analysis exhibited that other organs metastasis (HR=1.48; 95% CI: 1.04–2.11; P =0.032), lung plus other organs metastasis (HR=1.45; 95% CI: 1.04–2.02; P =0.027), AFP >400 ng/mL (HR=1.52; 95% CI: 1.07–2.16; P =0.021), After PD treatment (HR=3.43; 95% CI: 2.32–5.07; P <0.001), Before PD treatment (HR=2.41; 95% CI: 1.64–3.54; P <0.001) were associated with poorer PFS. (Table 2).

Efficacy Evaluation

Efficacy data was evaluated based on RECIST 1.1 evaluation. The following results were presented in Table 3. Here, we assessed the 3-month, 6-month tumor response in each group. In the 3-month evaluation, there was one patient achieved complete response in the Simultaneous group. ORR was 18.6%, 19.5%, 37.9%, and the DCR was 69.1%, 74.0%, 82.8% respectively in After PD group, Before PD group, Simultaneous group. The proportion of CR, PR, SD, PD in three groups was obvious difference (P =0.001) (Table 3). In the 6-month evaluation, there were two patients achieved CR in the Simultaneous group, and one patient in the Before PD group. ORR was 15.5%, 18.2%, 44.8% and the DCR was 41.2%, 46.8%, 67.2% in After PD group, Before PD group, Simultaneous group. The proportion of CR, PR, SD, PD in three groups was obvious difference (P <0.001) (Table 3).

Table 2 Multivariate Analyses of Prognostic Factors on Overall Survival (OS) and Progression-Free Survival (PFS) in 232 Patients with HCC Beyond Oligometastasis

Variables	Comparison	OS		PFS	
		HR (95% CI)	P value	HR (95% CI)	P value
Type of PVTT	0	Reference		Reference	
	I	3.63 (1.73–7.59)	0.001	1.56 (0.91–2.79)	0.102
	II	1.93 (1.26–2.96)	0.003	1.14 (0.79–1.65)	0.494
	III	1.78 (1.15–2.77)	0.010	1.23 (0.84–1.81)	0.289
Metastasis location	Lung	Reference			
	Lung+ other organs	1.56 (1.02–2.37)	0.041	1.45 (1.04–2.02)	0.027
	Other organs	2.09 (1.39–3.14)	<0.001	1.48 (1.04–2.11)	0.032
Types of treatment	Simultaneous	Reference		Reference	
	Before PD	2.37 (1.5–3.74)	<0.001	2.41 (1.64–3.54)	<0.001
	After PD	3.97 (2.49–6.35)	<0.001	3.43 (2.32–5.07)	<0.001
AFP level, ng/mL	<20			Reference	
	≥20, <400			1.45 (0.99–2.14)	0.058
	≥400			1.52 (1.07–2.16)	0.021

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; HR, hazard ratio; OS, overall survival; PVTT, portal vein tumor thrombus; PD, progressive disease; PFS, progression-free survival;

Table 3 Efficacy Outcomes in 232 Patients with HCC Beyond Oligometastasis by Different Treatments: After PD Group; Before PD Group; Simultaneous Group

Variables	Evaluation	After PD (n=97)	Before PD (n=77)	Simultaneous (n=58)	*P value*
3-month evaluation	CR	0 (0.0)	0 (0.0)	1 (1.7)	0.001
	PR	18 (18.6)	15 (19.5)	21 (36.2)	
	SD	49 (50.5)	42 (54.5)	26 (44.8)	
	PD	30 (30.9)	20 (26.0)	10 (17.3)	
6-month evaluation	CR	0 (0.0)	1 (1.3)	2 (3.4)	<0.001
	PR	15 (15.5)	13 (16.9)	24 (41.4)	
	SD	25 (25.8)	22 (28.6)	13 (22.4)	
	PD	57 (58.7)	41 (53.2)	19 (32.8)	

Abbreviations: CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease;

Subgroup Analysis

In order to further clarify the impact of different type of metastasis on the prognosis, patients were subdivided into other organs, lung metastasis, lung plus other organs. The OS rates were significantly increased with the use of simultaneous PD-1 inhibitor in three groups of patients (Table 4) (Figure 2A). The medium OS of patients with lung metastases were 16.93±1.12 months, 17.60±1.00 months, 27.27±1.48 months in After PD group, Before PD group, Simultaneous group respectively, and there was obviously significant (P <0.001) among the three groups (Figure 2B). The medium OS for other organs were 13.20±1.95 months, 14.10±0.98 months, 20.57±4.43 months in After PD group, Before PD group, Simultaneous group. There was significant difference for patients with lung and other organs metastases among the three groups (P =0.002) (Table 4) (Figure 2C). However, for patients with lung and other organs, there was limited improvements of OS, no difference was observed among the three groups (P =0.496) (Figure 2D).

The PFS rates were significantly improved with the use of simultaneous PD-1 inhibitor among the three groups (Table 4) (Figure 3A). The medium PFS of lung metastasis were 7.33±1.30 months, 7.23±0.83 months, 12.23±0.96 months in After PD group, Before PD group, Simultaneous group respectively, and the difference is significant (P <0.001) (Table 4) (Figure 3B). Similar results were observed in the other organs metastasis and lung and other organs (Table 4) (Figure 3C and D).

Table 4 Medium Overall Survival (OS) and Progression-Free Survival (PFS) Rates of Different Metastases Location in in Patients with HCC Beyond Oligometastasis by Different Treatments (Simultaneous Group, After PD Group, Before PD Group)

Variables		After PD (95% CI)	Before PD (95% CI)	Simultaneous (95% CI)	*P value*
Lung	Medium OS	16.93±1.12 (14.77–19.1)	17.60±1.00 (15.65–19.55)	27.27±1.48 (24.36–30.18)	<0.001
	Medium PFS	7.33±1.30 (4.78–9.88)	7.23±0.83 (5.62–8.85)	12.23±0.96 (10.36–14.11)	<0.001
Other organs	Medium OS	13.20±1.95 (9.39–17.02)	14.10±0.98 (12.19–16.01)	20.57±4.43 (11.88–29.25)	0.002
	Medium PFS	5.03±0.84 (3.39–6.67)	5.97±0.96 (4.09–7.85)	8.77±0.77 (7.25–10.28)	0.002
Lung +other organs	Medium OS	11.97±1.02 (9.98–13.96)	12.6±0.89 (10.86–14.34)	14.4±0.70 (13.03–15.77)	0.496
	Medium PFS	5.60±0.63 (4.36–6.84)	6.87±0.87 (5.17–8.56)	6.27±0.92 (4.47–8.07)	0.029

Abbreviations: CI, confidence interval; OS, overall survival; PD, progressive disease; PFS, progression-free survival;
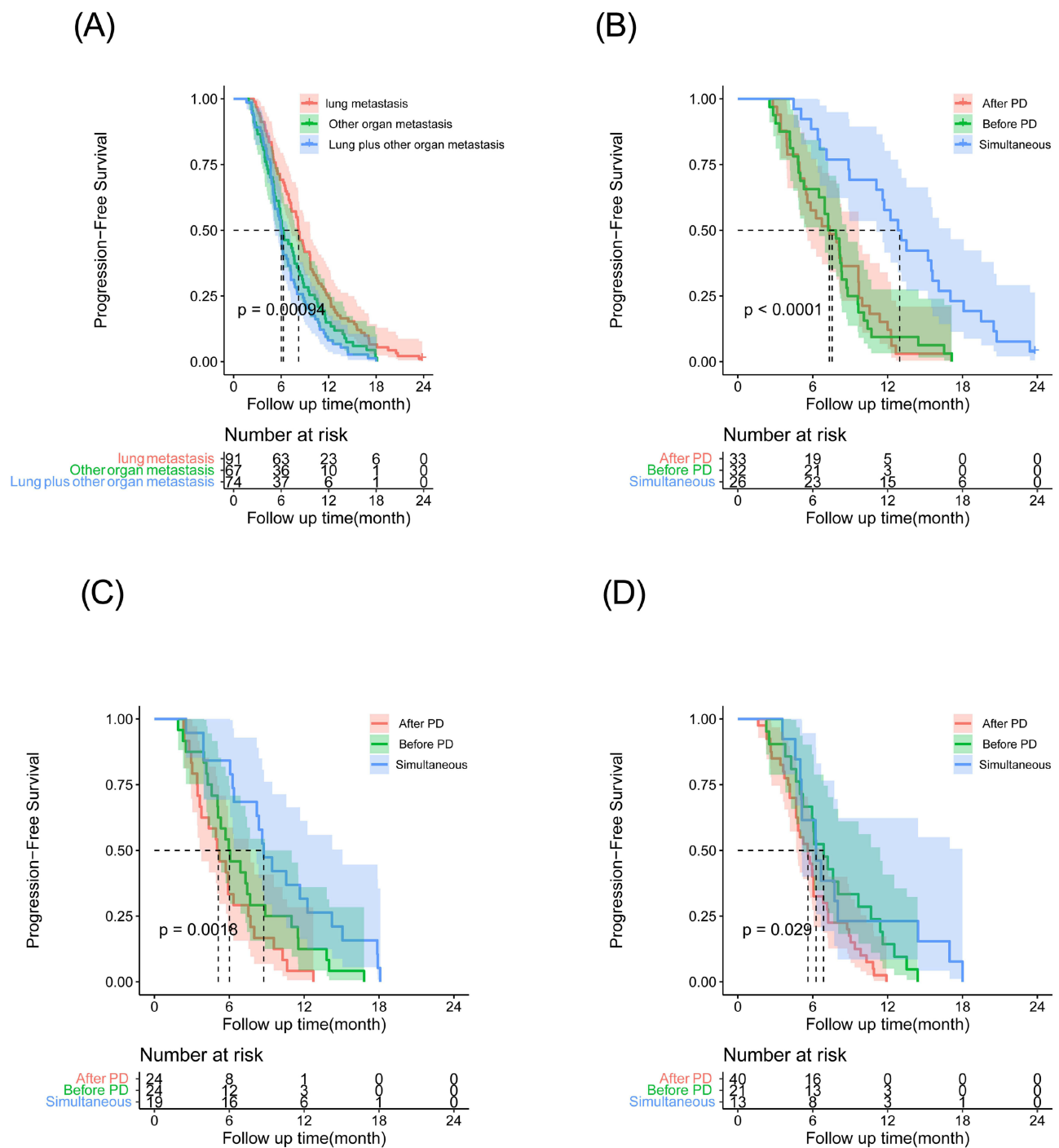
(A)

(B)

(C)

(D)
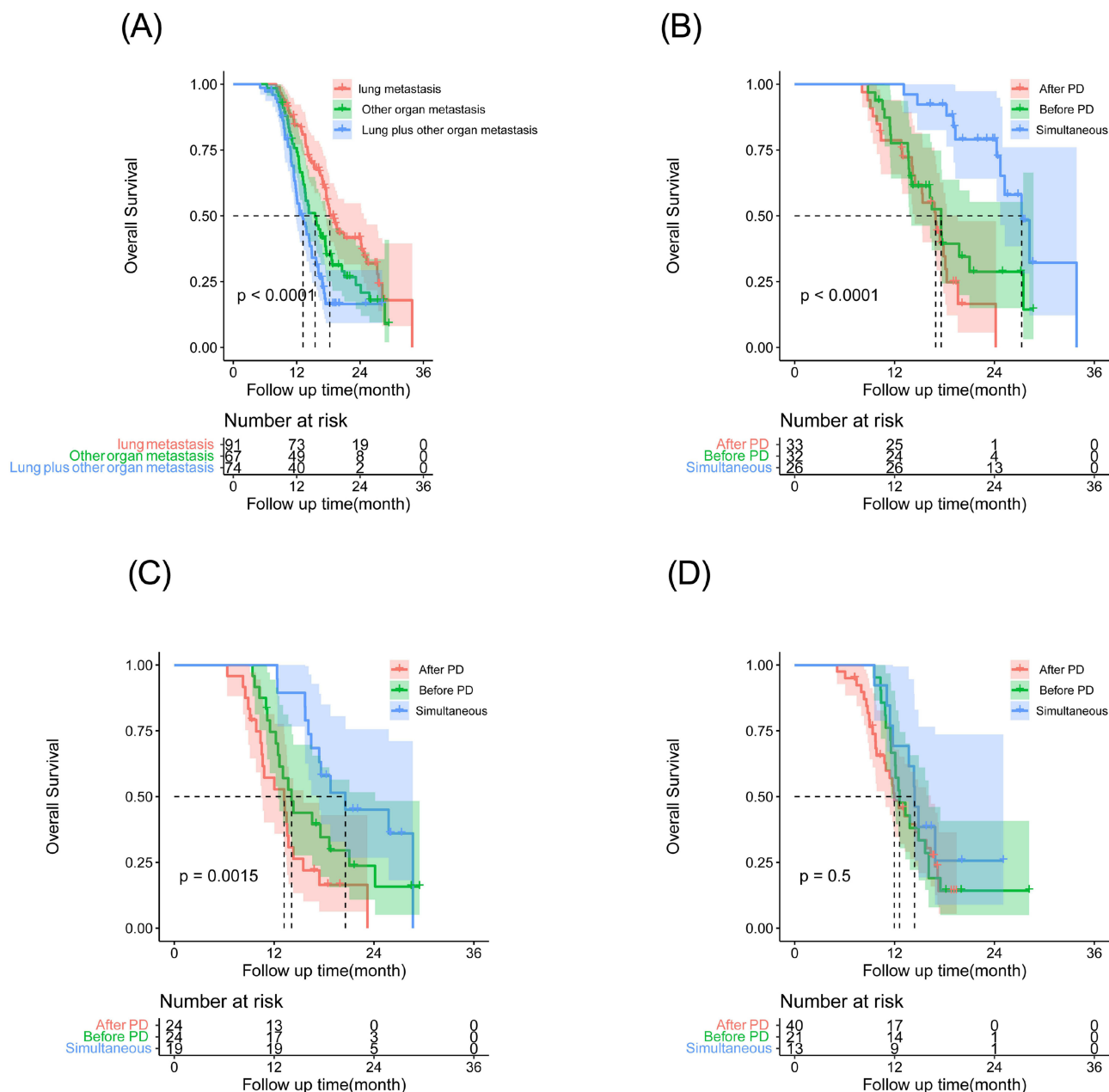
Figure 2 Kaplan–Meier curves for overall survival (OS) in patients with HCC beyond oligometastasis by different treatments: After PD group; Before PD group; Simultaneous group. (**A**) The OS rates of lung, other organ, lung and other metastasis in the whole cohort (P <0.001). (**B**) The lung metastasis OS rates of the group of After PD group, Before PD group, Simultaneous group, respectively (*P* <0.001); (**C**) The other organ metastasis OS rates of the group of After PD group, Before PD group, Simultaneous group, respectively (*P* =0.002); (**D**) The lung metastasis and other metastasis OS rates of the group of After PD group, Before PD group, Simultaneous group, respectively (*P* = 0.496).

Safety

Most patients experienced treatment-related adverse events, with the main adverse events recorded in Supplementary Table 3. Hypertension and decreased appetite were the most common of all adverse events. There were 99 (42.6%, [99/232]) patients with hypertension, 82 (82.8%, [82/99]) patients with grade 1–2 and 17 (17.2%, [17/99]) patients with grade 3–4 hypertension. A total of 98 (42.2%, [98/232]) patients with decreased appetite, and all patients had grade 1–2 decreased appetite. No treatment-related deaths occurred in the three groups. Patients with grade 1–2 adverse events can improve their condition after accepting symptomatic treatment or dose reduction. Patients with grade 3–4 adverse events temporarily stop the lenvatinib and PD-1 inhibitor treatment until the adverse effects were relieved or disappeared.

Figure 3 Kaplan–Meier curves for progression-free survival (PFS) in patients with HCC beyond oligometastasis by different treatments: After PD group; Before PD group; Simultaneous group. (**A**) The PFS rate of lung, other organ, lung and other metastasis in the whole cohort (*P* <0.001); (**B**) The PFS rate of lung metastasis in After PD group, Before PD group, Simultaneous group, respectively (*P* <0.001); (**C**) The PFS rates of other organ metastasis the in After PD group, Before PD group, Simultaneous group, respectively (*P* =0.002); (**D**) The PFS rates of lung metastasis and other metastasis in After PD group, Before PD group, Simultaneous group, respectively (*P* = 0.029).

Discussion

Treatment options for advanced HCC have rapidly evolved currently. The currently approved first-line targeted drugs for treatment include sorafenib, lenvatinib, cabozantinib, ramolizumab, apatinib, and donafinib.[24] The current effectiveness of monotherapy immune checkpoint inhibitor treatment is limited, with a maximum of no more than 30% or even lower. In addition, there is still room for improvement in targeted therapy for HCC. Clinical evidences reporting on the

combination of lenvatinib plus pembrolizumab in advanced HCC were satisfactory and promising.[17] This kind of tyrosine kinase inhibitors and immune checkpoint inhibitors represented a new era for advanced HCC therapy. Antiangiogenic drugs can block tumor angiogenesis, thereby cutting off its nutritional supply and causing tumor cell death. In this study, we compared the synchronous and non-synchronous application of PD-1 inhibitor in advanced HCC patients beyond oligometastasis, and we found that synchronous combination of lenvatinib with PD-1 inhibitors lead to survival improvements significantly.

In a carefully designed prospective trials, lenvatinib and PD-1 inhibitor were administered simultaneously.[17] The optimal sequence of systemic treatment for advanced HCC is not yet clear. There is no literature reporting of lenvatinib and PD-1 inhibitor administration in real world study. Due to the rapid development and changes in new therapies (especially systemic therapies) and indications for various treatments, and only few studies exploring the sequence of effective treatment options or combining modern systemic therapies with liver targeted therapies, it is difficult to develop a procedural approach for the treatment of HCC. In fact, not all patients accepted both medications at the same time, and it involved the patients' choice, financial affordability and doctor's recommendation.

Here, we compared the prognosis of different combination of lenvatinib and PD-1 inhibitors in practical applications comprehensively. We classified patients into three groups: (a) lenvatinib plus simultaneous PD-1 inhibitor (Simultaneous group); (b) Patients received PD-1 inhibitor before the tumor progression (Before PD group); (c) Patients received PD-1 inhibitor after the tumor progression (After PD group). Our study revealed that lenvatinib with synchronous administration of PD-1 inhibitor were superior to treatment with the non-synchronous therapy (including the After PD and Before PD group) in patients with advanced HCC beyond oligometastasis. The OS and PFS were significantly longer than patients with non-synchronous therapy. The medium OS of Simultaneous group were 20.57 months, which was 4.47 months longer than Before PD group (16.10 months), 7.20 months longer than After PD group (13.37 months). The medium PFS of Simultaneous group were 10.86 months, which was 3.32 months longer than Before PD group (7.54 months), 4.3 months longer than After PD group (6.56 months).

The results of LEAP-002 are consistent with the efficacy and safety of early studies, and there is no significant statistical difference between lenvatinib plus pembrolizumab and the placebo group.[25] Another Retrospective multicenter study revealed that the combination of lenvatinib and carlizumab showed better efficacy than lenvatinib alone, the medium PFS were 10.3 and 7.5 months.[26] In the recent clinic trial of lenvatinib plus pembrolizumab administrated simultaneously on unresectable HCC, the medium OS and PFS were 22.0 and 9.3 months respectively.[17] Our result in Simultaneous group was a little shorter than that reported, the reason may that in our study, the patients were all with multi-metastases. However, the 3 months evaluation of response (ORR and DCR) in Simultaneous group were not obvious lower than reported (37.9% vs 41.0%), (82.8% vs 86.0%).[17] Although in our investigation, more advanced stage of HCC was reported, most individuals accepted the radiotherapy, TACE or ablation before enrolled for analysis, and the primary tumor and metastases were controlled to a certain extent. Besides, TACE, ablation or radiotherapy caused the tumor necrosis, which stimulated the immune response of the system. Scientific research suggested that the immuno-modulatory effect of lenvatinib complemented PD-1 inhibitor activity through reversed the immunosuppressive effects of VEGF in the tumor microenvironment, thus increasing tumors sensitivity to combination therapy.[27]

The REFLECT study of lenvatinib in the treatment of unresectable HCC showed medium OS and PFS were 13.6 and 8.9 months respectively.[28] In our research, the After PD group OS and PFS were 13.37 and 6.56 months. The OS was similar with REFLECT study, and the PFS was shorter than it. In our study, the patients enrolled were more advanced, and a shorter PFS is acceptable After lenvatinib progression, patients benefited more after adding the PD-1 inhibitor than REFLECT. There was almost 10 months post-PFS survival. In KEYNOTE-224 trial, patients with advanced HCC were progression of sorafenib or intolerant to it, then these patients received pembrolizumab, the OS was 12.9 months.[29] Similarly, in CheckMate 040 trial, the OS was 15 months.[30] It was not surprising that the OS of these results were better than the After PD group due to the more advanced stage of patients in our study. The outcome in our After PD group provided preliminary exciting result that PD-1 inhibitor demonstrated considerable antitumor effects after lenvatinib failure.

In our study, patients with PVTT, other organs metastasis, lung plus other organs metastasis were associated with lower survival rates in the multivariate analysis. An increasing number of studies have reported the efficacy and safety of

lenvatinib in patients with HCC complicated with PVTT.[31–35] Many studies had revealed that PVTT as a crucial factor associated with poorer OS,[36] and in advanced HCC, extrahepatic metastases had also been shown to be a poor prognostic factor. Lung is the most common extrahepatic metastatic site in advanced HCC patients, accounting almost 20–40% of HCC metastases (followed by lymph nodes, bones, and adrenal glands).[37,38] Nevertheless, there are few literatures reports on the prognosis of different kind of extrahepatic metastases. We divided metastases into lung, other organs, lung plus other organ. And analysis was conducted on the prognosis of different therapy (Synchronous, Before PD, After PD) for different types of metastatic tumors. The result showed that patients with lung metastases or patients with other organs metastases, both OS and PFS were the best with the use of simultaneous PD-1 inhibitor among the three group. However, for patients with lung and other organs, there was no difference among the three groups. This observation revealed that for patients with lung and other organs, there was limited improvement of OS among the different treatments.

Several limitations that need to be clarified. Firstly, this was a retrospective study, which inevitably has selection bias even we conduct multi-center research. Secondly, it is impossible to completely exclude interference from the doctor and patient self-choice in terms of patient enrollment and medication, since it was a real-world study about the application of lenvatinib and PD-1 inhibitor. Further prospective randomized could be designed to prove our results. Thirdly, although it was a multi-centers study, the insufficient sample size may have some impact on the results. Last but not least, we did not compare the differences between targeted therapy combined immunotherapy and local treatment. The combination of targeted drugs and immune checkpoint inhibitors, or the combination of two immune checkpoint inhibitor drugs, combined with comprehensive treatment, including tumor ablation therapy, interventional therapy, radiotherapy. These are all treatment plans that we need to constantly explore in the future to find more effective and accurate treatment methods to combat HCC.

Conclusion

In conclusion, our research showed that synchronous combination of lenvatinib with PD-1 inhibitors can significantly improve advanced HCC beyond oligometastasis. The simultaneous combination of lenvatinib and PD-1 inhibitors for the treatment of HCC with multi-metastases may be a promising strategy, as these agents induce the optimal tumor response in a complementary manner.

Abbreviations

HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer staging system; TACE, transcatheter arterial chemoembolization; PD-1, programmed death receptor-1 (PD-1); AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ALT, alanine transaminase; AST, aspartate aminotransferase; OS: overall survival; PFS, progression-free survival.

Data Sharing Statement

It is available by contacting the corresponding author.

Ethics Approval and Informed Consent

The Ethics Committee Board of Hunan Provincial People's Hospital approved this retrospective study and waived the requirement for patient consent for this retrospective review. We solemnly promise that this study will strictly abide by relevant laws and regulations, and will 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 in this work.

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