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Reduction of Intrahepatic Tumour by Hepatic Arterial Infusion Chemotherapy Prolongs Survival in Hepatocellular Carcinoma

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Abstract. *Background/Aim: This study aimed to identify the survival benefit of intrahepatic tumour control by hepatic arterial infusion chemotherapy (HAIC) in hepatocellular carcinoma (HCC) patients with portal vein tumour thrombus (PVTT) or extrahepatic metastasis. Patients and Methods: Between 2010 and 2017, a total of 187 consecutive patients with advanced HCC were treated with HAIC. The survival outcomes and response rates to HAIC were analysed. Results: The intrahepatic objective response (OR) rate of all enrolled patients was 18.7%. The survival outcome of patients with OR was significantly better from those without OR, irrespective of initial distant metastasis. Achievement of intrahepatic OR by HAIC and favourable liver function at the time of best response evaluation were two independent factors associated with better OS. Conclusion: HAIC-induced intrahepatic tumour reduction significantly prolonged patient survival, irrespective of PVTT or initial distant metastasis.*

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and the second most common cause of cancer-related mortality (1). For advanced HCC patients with portal vein tumour thrombus (PVTT) or extrahepatic metastasis, sorafenib and lenvatinib are the first-line standard treatments to significantly improve survival outcomes, although their efficacy is modest and considerable adverse effects have been reported (2-4). Moreover, recent immune checkpoint inhibitors showed objective responses to only selected patients (5).

Hepatic arterial infusion chemotherapy (HAIC) is one of the alternative treatment options available for the patients with advanced HCC. HAIC achieves higher concentrations of the chemotherapeutic agents in the tumour with less systemic toxicity, by direct delivery of the drug, through an implantable port, into the liver (6). Several previous studies have demonstrated that treatment of HCC by HAIC results in better objective response (OR) and patient survival than by sorafenib (7-12). However, until recently, there has been no consensus to suggest HAIC as one of the standard treatment modalities of advanced HCC.

Mortality due to extrahepatic metastasis has been reported to be only 7.6% in advanced HCC; the leading cause of death was progression of intrahepatic disease (13). Several groups have reported that targeted control of intrahepatic tumours with transarterial chemoembolization (TACE) significantly prolongs survival in multinodular HCC patients without PVTT, even in patients with extrahepatic metastases (13-16). Nonetheless, the role of aggressive intrahepatic tumour control has not been clearly elucidated in more advanced HCC with PVTT. This study aimed to determine the survival benefit of intrahepatic tumour reduction by HAIC in advanced HCC patients with PVTT or extrahepatic metastases.

Materials and Methods

Study population. This study was approved by the Institutional Review Board of our Institute (KC18RESI0520). It is a retrospective study from a prospectively collected database. All

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Key Words: Hepatic arterial infusion, intrahepatic tumor, survival, hepatocellular carcinoma, chemotherapy, treatment response.

Table I. *Baseline characteristics of patients.*

Variables	Total (n=187)	
	No.	%
Mean age (year)	55.9±10.0	
Age		
<60	123	65.8
≥60	64	34.2
Gender		
Male	152	81.3
Female	35	18.7
Etiology		
HBV	155	82.9
HCV	12	6.5
Alcohol	10	5.3
HBV + HCV	1	0.5
Others	9	4.8
Tumor maximal diameter		
<10 cm	80	42.8
≥10 cm	107	57.2
Tumor number		
Single	66	35.3
Multiple	121	64.7
Portal vein tumor thrombus		
No	33	17.6
Yes	154	82.4
Vp stage		
Vp 1 or 2	25	16.2
Vp 3	73	47.4
Vp 4	56	36.4
Serum AFP		
<400 ng/ml	77	41.2
≥400 ng/ml	110	58.8
Child-Pugh class		
A	94	50.3
B	93	49.7
C	0	0
BCLC stage		
A	0	0
B	24	12.8
C	163	87.2
Extrahepatic metastasis		
Yes	47	25.1
No	140	74.9
Extrahepatic metastasis		
Lung	19	10.2
Lymph node	24	12.8
Adrenal gland	3	1.6
Bone	6	3.2
Brain	1	0.5
Other sites	2	1.1
Mean HAIC session number	4.6±3.3	
Median HAIC session number	4.0	
Previous treatment		
TACE	77	41.2
RFA	12	6.4
TARE	4	2.1
Liver resection	8	4.3
Sorafenib	6	3.2
RT	10	5.3

HAIC: Hepatic arterial infusion chemotherapy; HBV: hepatitis B virus; HCV: hepatitis C virus; AFP: alpha fetoprotein; BCLC: Barcelona Clinical Liver Cancer; TACE: transarterial chemoembolization; RFA: radiofrequency ablation; TARE: transarterial radioembolization; RT: radiation therapy.

Table II. *Intrahepatic response at the best response evaluation.*

Intrahepatic tumor response	Extrahepatic metastasis at the initial diagnosis		Total patients
	Yes	No	
Complete response (%)	1 (2.1)	3 (2.1)	4 (2.1)
Partial response (%)	6 (12.8)	25 (17.9)	31 (16.6)
Stable disease (%)	29 (61.7)	80 (57.1)	109 (58.3)
Progressive disease (%)	11 (23.4)	32 (22.9)	23 (23.0)
Total (%)	47 (100)	140 (100)	187 (100)

HAIC: Hepatic arterial infusion chemotherapy.

medical records of the patients diagnosed with HCC between January 2010 and December 2017 were reviewed. In our institution, HAIC tends to be the preferred method over sorafenib for the treatment of advanced HCC when it is accompanied by PVTT or the tumour type is infiltrative, even in patients with impaired liver function. During this period, unresectable HCC patients treated by HAIC were enrolled using the following inclusion criteria; age 20-80 years, Child-Pugh class A or B, Eastern Cooperative Oncology Group (ECOG) performance status below 2, no evidence of bone marrow suppression (white blood cell ≥ 3,000/μl, hemoglobin ≥8 g/dl, and platelet ≥7.5×10^4/μl), and preserved renal function (serum creatinine level below 2.0 mg/dl). Patients treated with sorafenib before HAIC were excluded. Finally, a total of 187 consecutive patients with advanced HCC treated with HAIC were enrolled. All patients enrolled in this study were followed up until May 2018, and the patients' survival was confirmed by the National Health Insurance Service.

Diagnosis of HCC. The latest guideline from American Association for the Study of Liver Diseases (AASLD) and Asian Pacific Association for the Study of the Liver (APASL) were used for the diagnosis of HCC (1, 17). The classification of PVTT was based on the Vp stages (18); Vp 1 was defined as tumour invasion distal to the second branch of the portal vein; Vp 2 and Vp 3 were defined as invasions in the second and first branch of the portal vein, respectively; Vp 4 was defined as presence of a tumour thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe (18).

Hepatic arterial infusion chemotherapy and response evaluation. The detailed HAIC protocol was reported in previous studies (19, 20). At least two interventional radiologists with over 5 years of experience performed all the procedures. Chemotherapeutic agents in protocol were 5-fluorouracil (5-FU) (500 mg/m^2) for 3 days and cisplatin (60 mg/m^2) on the second day. All patients were administrated 5-hydroxytryptamine 3 antagonist as the prophylactic anti-emetic drug after treatments. In order to prevent the chemotherapy-induced nephrotoxicity, intravenous hydration was routinely performed before and after the treatments. A recent randomized study demonstrated that adding adriamycin to conventional HAIC (composed of 5-FU plus cisplatin) did not result in a survival benefit (21). Therefore, in this study, patients treated with the regimen of HAIC composed of 5-FU, adriamycin, and cisplatin were also included.

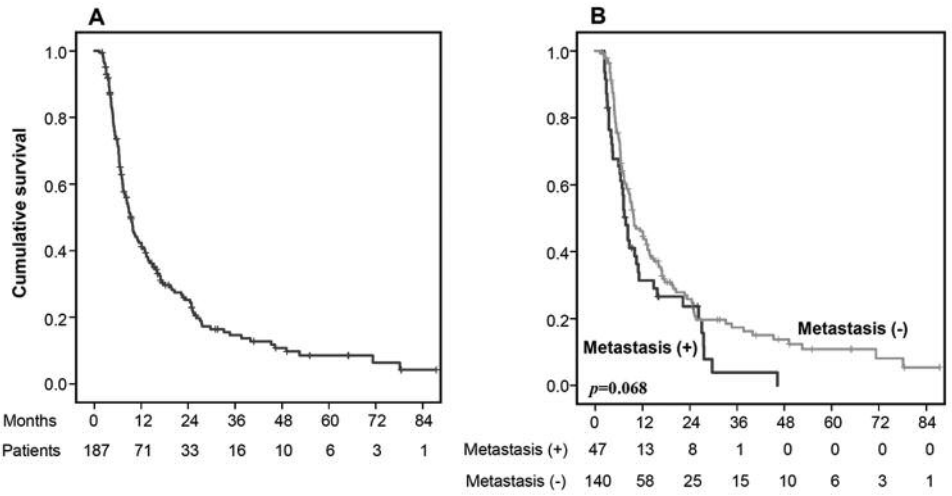

Figure 1. *Kaplan–Meier survival curves for overall survival. (A) Overall survival in all patients. (B) Overall survival according to the presence of initial extrahepatic metastasis.*

HAIC was repeated at 4-6 week intervals when the patients did not present disease progression or a serious complication by the treatments. Liver function was estimated using the Child-Pugh classification at each cycle. In all patients who underwent HAIC, treatment response was evaluated using follow up multiphasic CT or MRI after two or three cycles of treatments. Treatment response evaluation was based on the modified Response Evaluation Criteria in Solid Tumours (mRECIST) (22). In mRECIST, infiltrative-type HCC is considered as a non-target lesion. In these cases, RECIST was applied instead. PVTT, which is also considered as a non-target lesion in mRECIST, was excluded when tumour response was evaluated. The best intrahepatic response was defined as the most favourable result of dynamic imaging studies during HAIC.

Statistical analyses. Continuous variables in the baseline characteristics were described as the means with the range of standard deviation. Categorical variables were compared using the chi-square test and Fisher's exact test. Patients' survival was calculated from the date HAIC started until the date of death. The overall survival (OS) was estimated by Kaplan–Meier method and compared using the log-rank test. Multivariate analysis with a Cox proportional hazard model was performed to find factors affecting patients' OS. *p*-Value below 0.05 was used to define statistical significance. The Statistical Package for the Social Sciences (SPSS, version 24.0, Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Baseline characteristics. Table I summarizes the baseline clinical characteristics of the enrolled patients. The mean age was 55.9 years, and 81.3% of the patients were male. The major cause of the underlying liver disease was hepatitis B virus infection (82.9%). Most patients had PVTT at baseline (82.4%). Among the patients with PVTT, 25 (16.2%) had Vp 1 or 2, 73 (47.4%) had Vp 3, and 56 (36.4%) had Vp 4 PVTT. Among the enrolled patients, 47 (25.1%) patients had extrahepatic metastasis when HAIC was started. Median HAIC session number was 4.0. Overall, 85 patients had a previous local treatment history before the start of HAIC and the most frequent previous treatment modality was TACE.

Intrahepatic response at the best response evaluation. The best intrahepatic treatment response was assessed according to mRECIST after 2 or 3 cycles of HAIC (Table II). The intrahepatic OR rate was 18.7% in all patients. When the patients were subdivided into two groups according to the presence of initial extrahepatic metastasis, 3 (2.1%) patients showed intrahepatic complete response (CR), 25 (17.9%) showed intrahepatic partial response (PR), and 32 (22.9%) showed intrahepatic progressive disease (PD), in the patients without extrahepatic metastasis. In the group with extrahepatic metastasis, 1 (2.1%) patient showed intrahepatic CR, 6 (12.8%) showed intrahepatic PR and 11 (23.4%) showed intrahepatic PD.

Overall survival of the enrolled patients. Next, we analysed the OS (Figure 1) using the Kaplan–Meier method. Figure 1A shows the OS of the total enrolled patients; the median survival period was 9.4 months. The cumulative OS rates at 6, 12, 24, and 36 months were 71.9%, 42.4%, 25.2%, and 14.6%, respectively. The median survival period was 7.7 months in the patients with extrahepatic metastasis and 9.8 months in the patients without extrahepatic metastasis (Figure 1B).

Overall survival according to the best intrahepatic response. To evaluate the importance of the reduction of intrahepatic tumour burden by HAIC, the OS was analysed according to the best intrahepatic response. The patients were subdivided

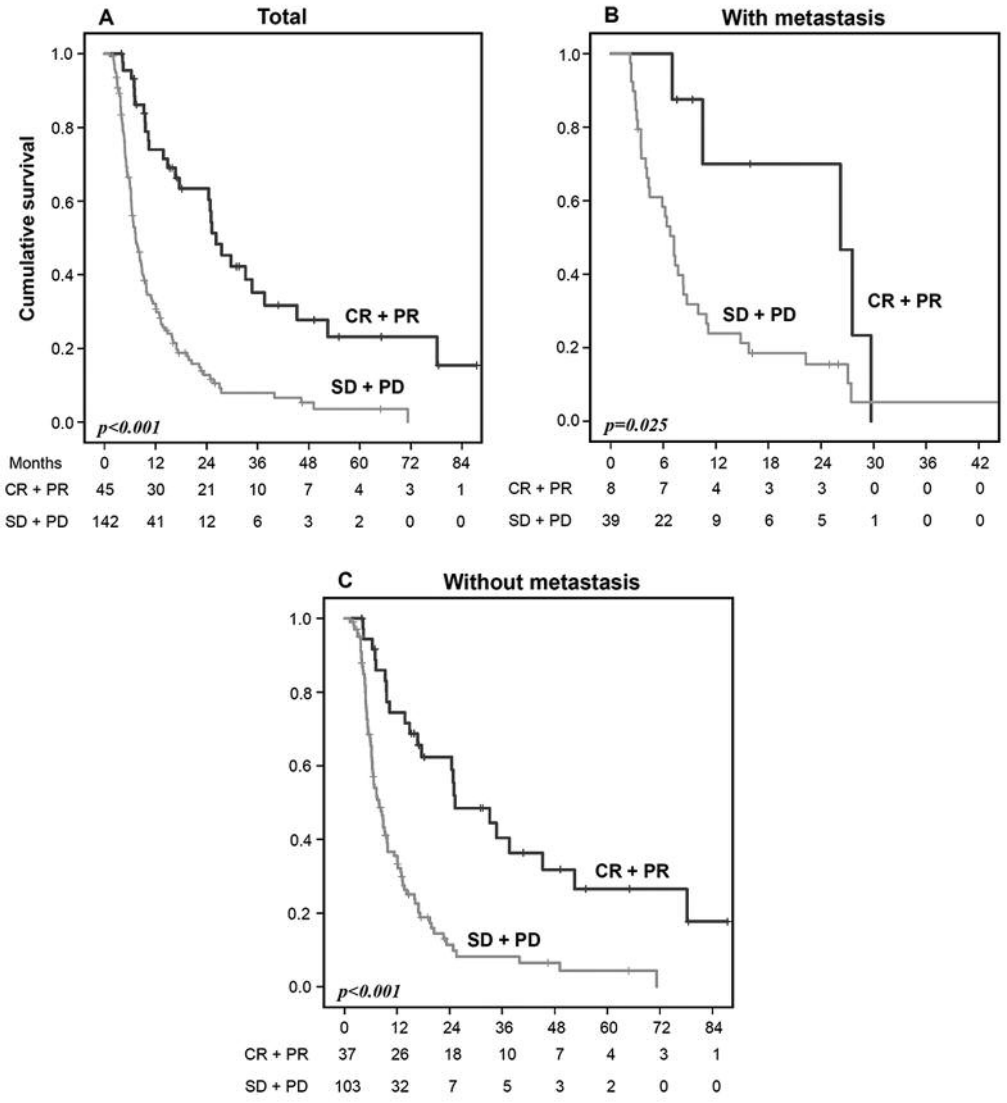

Figure 2. *Kaplan–Meier survival curves for overall survival according to best intrahepatic response to hepatic arterial infusion chemotherapy. (A) All patients. (B) Patients with extrahepatic metastases. (C) Patients without extrahepatic metastases. CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; HAIC: hepatic arterial infusion chemotherapy.*

into two groups by the response to HAIC: CR + PR *vs*. SD + PD (Figure 2). Analyses were performed in the following three groups: all patients, patients with extrahepatic metastasis, and patients without extrahepatic metastasis (Figure 2). In the group with all patients, the patients with intrahepatic CR and PR after HAIC showed significantly better survival outcomes than patients with intrahepatic SD and PD (Figure 2A, $p<0.001$). Similar to these results, the patients with extrahepatic metastasis were found to have a significant survival benefit when intrahepatic CR or PR was obtained by HAIC (Figure 2B, $p=0.025$). The patients without extrahepatic metastasis also had significantly better survival outcomes with intrahepatic CR or PR (Figure 2C, $p<0.001$).

Next, the subgroup analyses were performed with patients having PVTT according to the best intrahepatic response. Similarly to the parent group, patients having PVTT with intrahepatic PR and CR showed better survival outcomes than those with intrahepatic SD and PD by HAIC irrespective of the initial status of distant metastasis. In addition, patients with PVTT were subdivided into two groups by the level of PVTT (Figure 3). For patients with Vp 3 or 4 PVTT, there was also a significant improvement in OS when CR or PR was obtained by HAIC (Figure 3B, $p<0.001$).

Prognostic factors for favourable survival. Univariate analysis was performed to find the factors affecting OS and intrahepatic

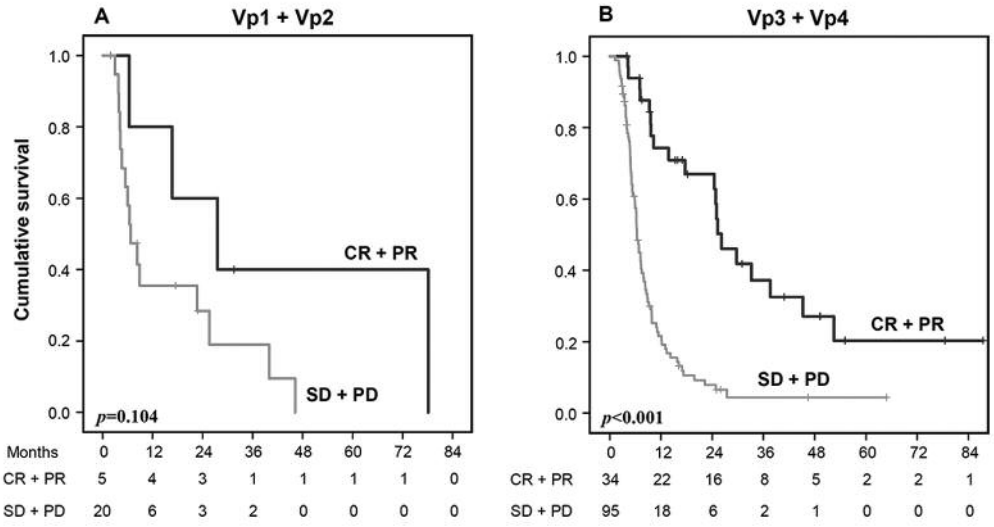

Figure 3. *Kaplan–Meier survival curves for overall survival in patients with portal vein tumour thrombus according to best intrahepatic response. (A) Patients with Vp1 or Vp2 portal vein tumour thrombus. (B) Patients with Vp3 or Vp4 portal vein tumour thrombus. PVTT: Portal vein tumour thrombus; CR: complete response; PR: partial response; S: stable disease; PD: progressive disease.*

PFS (Table III). Tumour maximal diameter <10 cm (p=0.011), AFP response (>20% decrease after the first HAIC, p=0.008) and obtaining favourable intrahepatic OR (p<0.001) were found to be the factors associated with better OS.

Subsequently multivariate analyses with Cox proportional hazard model was performed to investigate independent prognostic factors affecting OS (Table III). The analyses were conducted in two models with different number of parameters. In model 1, the significant factors influencing the favourable survival outcomes were as follows: Child-Pugh class A at the best treatment response evaluation (hazard ratio (HR) =0.586, 95% confidence interval (CI)=0.409-0.840, p=0.004) and obtaining favourable intrahepatic OR (HR=0.330, 95%CI=0.213-0.512, p<0.001). In model 2, the same variables as in model 1 were associated with favourable survival outcomes.

Discussion

The prognosis of advanced HCC with PVTT or extrahepatic metastasis is extremely poor. The therapeutic goal is usually to prolong patient survival with maintaining the hepatic reserve. Sorafenib, a multikinase inhibitor, has since long been standard treatment for advanced HCC in the BCLC staging system (23). However, the Sorafenib HCC Assessment Randomised Protocol (SHARP) trial demonstrated that sorafenib only modestly increased survival in patients with BCLC stage C disease from 7.9 months to 10.7 months (4, 24). For the patients in the Asian-Pacific area, the survival benefit was even less than that observed globally, probably because these patients presented with more aggressive disease and involvement of portal vein, as well as predominant aetiology of chronic hepatitis B (4, 25). Therefore, a major cause of mortality in patients with advanced HCC in Asian-Pacific area is largely due to progression of intrahepatic tumour and resultant hepatic dysfunction. At this point, our study has critical implications. We confirmed that HAIC results in a significant survival benefit in advanced HCC, because it results in significant intrahepatic tumour reduction even in patients with Vp3 or Vp4 PVTT. To the best of our knowledge, thus far no study has focused on the impact of intrahepatic tumour control by HAIC in advanced HCC even with PVTT or extrahepatic metastasis.

Previously, Terashima *et al*. demonstrated that targeting intrahepatic tumours may confer survival benefit for patients with advanced HCC even after sorafenib treatment is discontinued (26). In line with this study, our study further emphasizes that HAIC takes a critical role in the control of intrahepatic tumours of patients with BCLC-C diseases. The presence of intrahepatic tumours was one of the critical prognostic factors of OS for patients with advanced HCC, even for those with extrahepatic spread treated by sorafenib (26). Therefore, targeted control of intrahepatic tumours will clearly influence the prognosis of these patients. As mentioned in the introduction section, extrahepatic tumours account for only 7.6% of cause of death in advanced HCC (26).

One of the factors that significantly affected OS in the multivariate analysis was the maintenance of favourable liver function (Child Pugh class A) after 1st round of HAIC (Table III). A recent study reported that maintaining better the hepatic reserve after HAIC had a prognostic effect on patient survival outcomes in advanced HCC (27). In our study,

Table III. *Univariate and multivariate analysis for overall survival.*

Variables	Univariate analysis for OS		Multivariate analysis for OS			
			Model 1		Model 2	
	Median OS (months)	*p*-Value	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)
Gender						
Male	9.2	0.282				
Female	10.9					
Age						
<60	8.8	0.189	0.683	1.079 (0.748-1.557)		
≥60	12.1					
Etiology						
HBV	9.6	0.592				
HCV	8.6					
Alcohol	4.4					
HBV + HCV	9.6					
Others	3.9					
Tumor maximal diameter						
<10 cm	13.7	0.011	0.081	0.735 (0.528-1.036)	0.091	0.710 (0.478-1.056)
≥10 cm	7.7					
Tumor number						
Single	9.2	0.732				
Multiple	9.4					
Portal vein tumor thrombus						
No	14.8	0.16				
Yes	8.3					
Serum AFP						
<400 ng/ml	13.3	0.08	0.079	0.740 (0.528-1.036)	0.117	0.721 (0.479-1.085)
≥400 ng/ml	7.4					
AFP response†						
No	8.3	0.008				
Yes	13					
Initial Child-Pugh class						
A	9.6	0.374				
B or C	8.3					
Follow-up Child-Pugh class‡						
A	16	0.001	0.004	0.586 (0.409-0.840)	0.035	0.622 (0.401-0.967)
B or C	7.3					
Initial BCLC stage						
B	16	0.058				
C	8.6					
Previous treatment history						
No	7.2	0.141				
Yes	11.4		0.387	1.116 (0.829-1.623)		
Extrahepatic metastasis						
No	7.7	0.068				
Yes	9.8		0.204	1.276 (0.876-1.859)		
Best intrahepatic OR rate						
CR and PR	26.2	<0.001	<0.001	0.330 (0.213-0.512)	<0.001	0.314 (0.181-0.545)
SD and PD	7.3					

OS: Overall survival; HR: hazard ratio; CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus; AFP: alpha fetoprotein; HAIC: hepatic arterial infusion chemotherapy; BCLC: Barcelona Clinical Liver Cancer; OR: objective response; CR: complete response; PR: partial response; SD: stable disease; PD: progression disease. †AFP response was defined with a >20% decrease after the first HAIC. ‡Follow-up Child-Pugh class was evaluated after the first HAIC.

although about 50% of the enrolled patients were in Child-Pugh class B initially, the univariate and multivariate analyses confirmed that maintaining Child-Pugh class A after 1st round of HAIC, not initial liver function, was significantly associated with improved patients' OS (Table III). These results are consistent with the previous report, and suggest that patient liver function should always be re-evaluated when 1st round of HAIC is completed.

The present study has several important limitations. First, this study was performed in a single institution which could cause a selection bias. Second, the number of patients with extrahepatic metastasis was relatively small. However, to the best of our knowledge, this study included the largest number of advanced HCC patients with extrahepatic metastasis treated by HAIC. Third, since the treatment modality was limited to HAIC, the efficacy of intrahepatic tumour control by other treatments available for advanced HCC remains unclear. We tried to perform similar analyses with patients who underwent sorafenib treatment at the same period. However, there were only 3 patients with intrahepatic PR + CR among more than 250 patients after sorafenib treatment, which made the statistical analyses impossible.

In conclusion, intrahepatic tumour reduction by HAIC was found to prolong advanced HCC patients' survival, irrespective of PVTT and the initial status of extrahepatic metastasis. It is critical that the intrahepatic tumour burden be reduced aggressively, even when patients have extrahepatic metastasis or PVTT.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Pil Soo Sung, Keungmo Yang, and Si Hyun Bae contributed to conception, design, acquisition, analysis, and interpretation of data. Jung Suk Oh and Ho Jong Chun contributed to acquisition and interpretation of data. Hee Chul Nam, Jeong Won Jang, Jong Young Choi and Seung Kew Yoon contributed to conception and design. Pil Soo Sung wrote the manuscript.

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