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Original Article

Survival outcomes of hepatic resection compared with transarterial chemoembolization or sorafenib for hepatocellular carcinoma with portal vein tumor thrombosis

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Background/Aims: Treating hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) remains controversial. We compared the outcomes of hepatic resection (HR), transarterial chemoembolization (TACE), and sorafenib therapy as treatments for HCC with PVTT.

Methods: Patients diagnosed as HCC with PVTT between January 2000 and December 2011 who received treatment with sorafenib, HR, or TACE were included. Patients with main PVTT, superior mesenteric vein tumor thrombosis, or Child-Turcotte-Pugh (CTP) class C were excluded. The records of 172 patients were analyzed retrospectively. HR, TACE, and sorafenib treatment were performed is 40, 80, and 52 patients respectively. PVTT was classified as either involving the segmental branch (type I) or extending to involve the right or left portal vein (type II).

Results: The median survival time was significantly longer in the HR group (19.9 months) than in the TACE and sorafenib groups (6.6 and 6.2 months, respectively; both $P<0.001$), and did not differ significantly between the latter two groups (P=0.698). Among patients with CTP class A, type I PVTT or unilobar-involved HCC, the median survival time was longer in the HR group than in the TACE and sorafenib groups ($P=0.006$). In univariate analyses, the initial treatment method, tumor size, PVTT type, involved lobe, CTP class, and presence of cirrhosis or ascites were correlated with overall survival. The significant prognostic factors for overall survival in Cox proportional-hazards regression analysis were initial treatment method (HR vs. TACE: hazard ratio=1.750, $P=0.036$; HR vs. sorafenib: hazard ratio=2.262, $P=0.006$), involved lobe (hazard ratio=1.705, $P=0.008$), PVTT type (hazard ratio=1.617, $P=0.013$), and CTP class (hazard ratio=1.712, $P=0.012$).

Conclusions: Compared with TACE or sorafenib, HR may prolong the survival of patients with HCC in cases of CTP class A, type I PVTT or unilobar-involved HCC. **(Clin Mol Hepatol 2016;22:160-167)**

Keywords: Hepatocellular carcinoma; Portal vein tumor thrombosis; Transarterial chemoembolization; Hepatic resection; Sorafenib

Abbreviations:

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CT, computed tomography; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hepatic resection; MELD, model for end-stage liver disease; PIVKA-II, protein induced by vitamin K absence or antagonist-II; PT, prothrombin time; PVTT, portal vein tumor thrombosis; RFA, radiofrequency ablation; TACE, transarterial chemoembolization

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INTRODUCTION

Hepatocellular carcinoma (HCC) has one of the highest incidence rates of all malignancies worldwide. Incidence rates of HCC in Asian and African countries are generally higher than those in Western countries because the prevalence of chronic hepatitis B infection is generally higher in Asia and Africa.[1] For early detection of HCC, liver imaging and assessments of alpha-fetoprotein (AFP) levels have been recommended for patients with underlying viral liver disease.[2] Nevertheless, many patients are diagnosed as a cancer at the advanced stage.[1,2] Portal vein tumor thrombosis (PVTT) is a poor prognostic factor detected in 20–60% of HCC cases. The median survival time among patients with HCC with PVTT has been reported as 2.7–4.0 months without intervention.[3-6] In clinical practice, however, the treatment of patients with HCC with PVTT is complicated and controversial.[7,8] As per the Barcelona Clinic Liver Cancer (BCLC) guidelines, HCC with PVTT is classified as stage C (advanced stage) and sorafenib is recommended for treatment.[7] However, various treatments have been applied to improve the prognosis of patients with HCC with PVTT in a real clinical field. According to the National Survey for Primary Liver Cancer in Japan, the survival of patients with HCC with PVTT can be improved by some therapeutic modalities, including surgery, radiation therapy, transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), and combined treatments.[9] However, the available data on patients with HCC with PVTT have generally been insufficient for comparisons of the survival outcomes associated with different treatment modalities. Although the recommended treatment, sorafenib, was associated with superior outcomes when compared with best supportive care,[10] no studies have compared sorafenib with other treatments, such as TACE, radiation or surgery.

The aim of this study was to retrospectively compare the survival outcomes of patients with HCC with PVTT after treatment with hepatic resection (HR), TACE or sorafenib. In addition, we sought to identify factors that influenced survival outcomes.

MATERIALS AND METHODS

Study Design

Patients who received HR, TACE, or sorafenib as an initial treatment for HCC with PVTT at any of the three tertiary university hospitals between January 2000 and December 2011 were selected for this retrospective study. PVTT was classified according to 4 types, as described by Shi et al.[11] Type I PVTT is defined as tumor thrombi involving the segmental branches of the portal vein or above. Type II PVTT is defined as tumor thrombi extending to involve the right/left portal vein. Type III PVTT is defined as thrombi involving the main portal vein. Type IV PVTT is defined as thrombi involving the superior mesenteric vein. Cases involving type III or type IV PVTT were excluded because HR and TACE are rarely applied in these cases. Accordingly, the current study only included cases of HCC with type I or type II PVTT.

Patients

The European Association for the Study of the Liver guideline was used for diagnosis of HCC. All HR cases were confirmed by histological review. Patients were enrolled according to the following inclusion criteria: 1) a case of HCC with no previous treatment, 2) presence of PVTT on imaging studies, and 3) the size of the main HCC lesion was less than 10 cm. Patients who satisfied any of the following criteria were excluded: 1) presence of extrahepatic spreading, 2) the Child-Turcotte-Pugh (CTP) class C, or 3) the case involved type III or type IV PVTT. The technique of arterial embolization was administered as the standard TACE procedure. After tumor stain, Doxorubicin was infused maximally 50 mg. Hepatic angiography to confirm occlusion of the tumor feeding artery and to look for another residual vascular tumor blush as well. The following parameters were analyzed as potential predators of survival, age, gender, liver cirrhosis status, liver function status, CTP class, Model For End-Stage Liver Disease (MELD) score, platelet count, prothrombin time (PT), total bilirubin level, alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level, albumin level, and etiology of liver disease.

Follow-up

In the HR group, the first follow-up was 3 weeks after HR. In the TACE group, the first follow-up was performed 3 weeks after treatment. The patients were monitored for tumor recurrence or progression on the basis of AFP levels as well as contrast computed tomography (CT) or magnetic resonance imaging findings. Thereafter, contrast CT scans were performed once every 3 months for surveillance until disease progression in the HR and TACE groups. In the sorafenib group, contrast CT was performed once every 6 weeks for the same purpose. On each of the follow-up days, each patient underwent blood tests, including blood cell

counts and liver function tests. In the TACE group, additional TACE sessions were performed every 4 weeks until the tumor was completely ablated or the tumor had progressed. For patients who developed cancer recurrence after HR, adequate local treatments were applied, such as TACE, radiofrequency ablation (RFA), or reoperation. Patients who showed no response or progression after sorafenib treatment received best supportive care or another local treatment.

Statistical Analyses

SPSS 19 statistical software (SPSS Inc., Chicago, IL, USA) was used for data analysis. Overall survival was calculated using the life-table method. For univariate analyses, the ANOVA test was used for continuous data and the chi square test and two tailed Fisher exact test for categorical data. Survival curves were estimated using the Kaplan-Meier method and the differences between groups were evaluated by log-rank test. Prognostic relevance was evaluated by Cox's proportion hazard regression

Table 1. Patient characteristics at baseline

	HR (n=40)	TACE (n=80)	Sorafenib (n=52)	*P*-value
Age, y (mean±SD)	55.0±12.9	58.3±10.5	57.3±12.4	0.348
Sex (M/F)	30/10	67/13	44/8	0.420
Cirrhosis, no. (%)	27 (67.5)	73 (91.3)	51 (98.1)	<0.001
Etiology				0.116
HBV	31	54	39	
HCV	4	8	2	
Alcohol	3	11	11	
Unkown	2	7	0	
CTP class, no. (%)				0.059
A	35 (87.5)	58 (72.5)	45 (86.5)	
B	5 (12.5)	22 (27.5)	7 (13.5)	
Ascites, no. (%)	2 (5.0)	27 (33.8)	9 (17.3)	0.001
Tumor size, cm, no. (%)				<0.001
≦5	20 (50.0)	10 (12.5)	8 (15.4)	
>5	20 (50.0)	70 (87.5)	44 (84.6)	
PVTT site, no. (%)				0.002
Segmental	26 (65.0)	31 (38.8)	16 (30.8)	
Lobar	14 (35.0)	49 (61.3))	36 (69.2)	
Lobe, no. (%)				<0.001
Unilobe	39 (97.5)	44 (55.0)	39 (75.0)	
Bilobe	1 (2.5)	36 (45.0)	13 (25.0)	
AFP (ng/mL, mean±SD)	10,728±25,073	27,302±71,902	16,663±35,668	0.266
PIVKA-II (mAU/mL, mean±SD)	4,236±13,166	13,348±34,992	7,411±24,758	0.038
PT (sec, mean±SD)	12.1±1.7	12.8±1.8	12.5±1.3	0.072
Total bilirubin (T) (mg/dL, mean±SD)	0.9±0.9	1.3±1.3	1.2±0.7	0.162
AST (IU/L, mean±SD)	77.0±81.0	95.2±83.2	112.1±106.4	0.184
ALT (IU/L, mean±SD)	48.9±60.1	57.8±53.0	42.2±28.5	0.192
Albumin (g/dL, mean±SD)	4.0±0.6	3.6±0.5	3.5±0.6	<0.001
MELD score (mean±SD)	8.3±3.0	9.2±2.7	8.9±2.1	0.198

HR, hepatic resection; TACE, transarterial chemoembolization; HBV, hepatitis B virus; HCV, hepatitis C virus; CTP, Child-Turcotte-Pugh; PVTT, portal vein tumor thrombosis; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; PT, prothrombin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MELD, model for end-stage liver disease.

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analysis. Values of $P<0.05$ were considered significant.

Ethics statement

The study protocol was approved by the Institutional Review Board of Keimyung University Dongsan Hospital.

RESULTS

Patient characteristics at baseline

A total of 172 patients with HCC with PVTT were included in our analysis; 40 patients underwent HR, 80 patients underwent TACE, and 52 patients received sorafenib therapy as the initial treatment. The clinical characteristics of the three groups of patients are summarized in Table 1. The median ages in the HR, TACE, and sorafenib groups were 55.0, 58.3, and 57.3 years, respectively. There were no significant differences at baseline in terms of age, sex, or CTP class between the groups. Cirrhosis (as clearly proved by imaging) was present in 68% (28/40 patients) of the HR group, 91% (73/80 patients) of the TACE group, and 98% (51/52 patients) of the sorafenib group, constituting a significant difference ($P<0.001$). There are also significant differences in terms of the tumor size, PVTT site, and lobe between the groups ($P<0.001$, $P=0.002$, $P<0.001$). However, no significant differences in terms of hepatic function scores, including the CTP class and MELD scores, were observed between the groups. In addition, no significant difference in platelet count, PT, bilirubin level, etiology of liver disease, and other hepatic function markers was observed between the three groups.

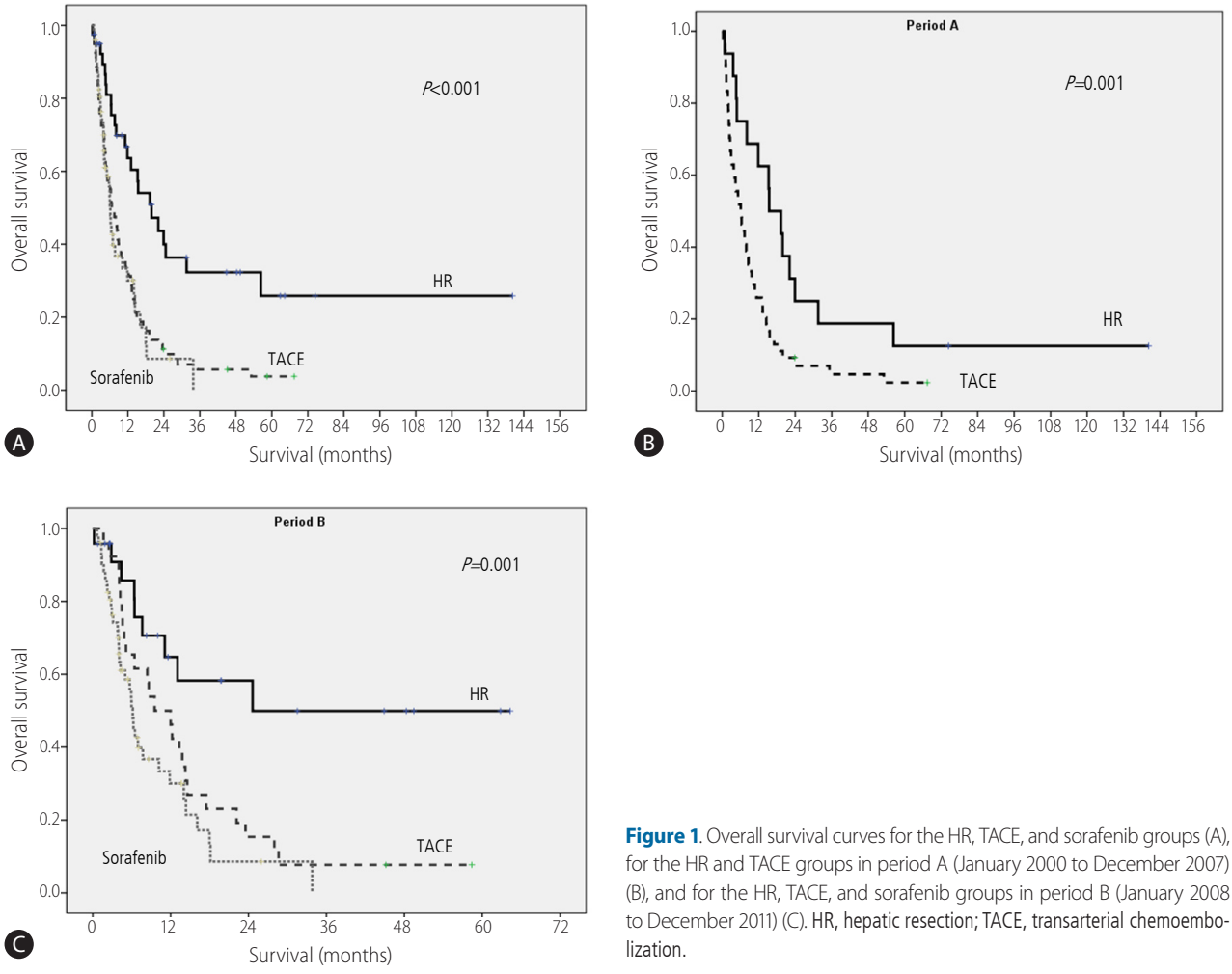

Figure 1. Overall survival curves for the HR, TACE, and sorafenib groups (A), for the HR and TACE groups in period A (January 2000 to December 2007) (B), and for the HR, TACE, and sorafenib groups in period B (January 2008 to December 2011) (C). HR, hepatic resection; TACE, transarterial chemoembolization.

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Survival analyses

The median survival times in the HR, TACE, and sorafenib groups were 19.9, 6.6, and 6.2 months, respectively (P<0.001, Fig. 1A). The HR group had significantly longer median survival period than the TACE and sorafenib groups (P<0.001 and P<0.001). However, there was no significant difference between the median survival times of the TACE and sorafenib groups (P=0.698).

In consideration of the approval date for sorafenib in South Korea, we performed an additional analysis that was stratified into two periods: January 2000 to December 2007 (period A) and January 2008 to December 2011 (period B). In period A, the median survival times in the HR and TACE groups were 15.4 months and 6.1 months, respectively (P=0.007; Fig. 1B). In period B, the median survival times in the HR, TACE, and sorafenib groups were 24.6 months, 9.5 months, and 6.2 months, respectively (P=0.001; Fig. 1C). As the result of total period, the median survival time of the HR group was significantly longer than that of the TACE and sorafenib groups in period B (P=0.001 and P=0.001). The median survival times of the TACE group also did not differ significantly from those of the sorafenib group (P=0.148).

Subgroup analyses

In a subgroup analysis limited to patients with CTP class A during period B, overall survival was significantly longer in the HR group (24.6 months) than in the TACE group or sorafenib group (12.0 months and 6.5 months, P=0.030 and P=0.001). However, the median survival times did not differ significantly between the TACE and sorafenib groups (P=0.203). For patients with CTP class B during period B, there was no difference in the median survival times between three groups (P=0.123). For patients with type I PVTT during period B, the median survival times were significantly different between the HR, TACE, and sorafenib groups (P=0.003; Fig. 2A). A significant difference in median survival times was observed only between the HR and sorafenib groups with type I PVTT (P=0.002). However, median survival times between the HR and TACE groups and between the TACE and sorafenib groups were not significantly different (P=0.069 and P=0.087). For type II PVTT during period B, however, there were no significant differences in median survival times between three groups (P=0.499; Fig. 2B). In a subgroup analysis of patients with tumors <5cm in size in period B, no significant difference in overall survival was observed between three groups (P=0.307). However, among patients with tumors >5 cm in size in period B, overall survival times were significantly longer in the HR group (24.6 months) than in the TACE and sorafenib groups (9.5 months and 5.9 months, P=0.038 and P=0.007). Among patients without ascites, the HR group had significantly better overall survival than the TACE or sorafenib groups (P=0.001). In a subgroup analysis limited to patients with CTP class A, type I PVTT and HCC in unilobe, the HR group had significantly longer overall survival (23.9 months) than the sorafenib group (11.9 months, P=0.006). However, median survival times of the HR group did not differ from those of the TACE group (14.5 months, P=0.082). Treatment-specific 1-, 2-, and 3-year survival rates during period B are shown in Table 2.

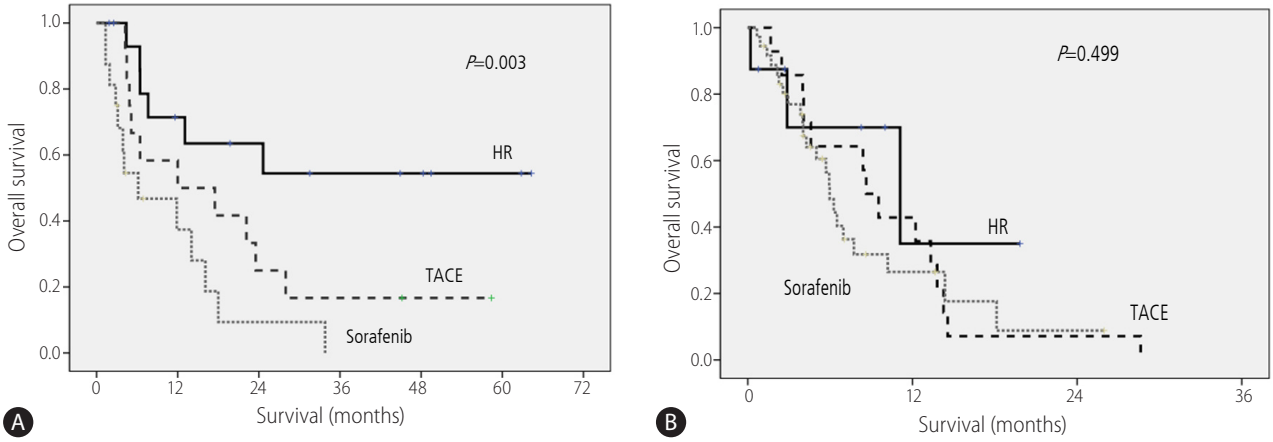

Figure 2. Overall survival curves for patients with type I PVTT who received HR, TACE, or sorafenib in period B (January 2008 to December 2011) (A) and for patients with type II PVTT in period B (B). HR, hepatic resection; TACE, transarterial chemoembolization; PVTT, portal vein tumor thrombosis.

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Table 2. Comparison of overall survival rates according to treatment method in period B

Treatment by tumor type		Patients no.	Survival rate (%)			
			1 year	2 year	3 year	*P*-value
All HCC	HR	24	64.7	58.3	49.9	<0.001
	TACE	26	46.2	15.4	7.7	
	Sorafenib	52	30.0	8.6	0	
CTP class						
A	HR	21	65.7	58.4	48.6	0.004
	TACE	20	50.0	15.0	10.0	
	Sorafenib	45	33.5	9.6	0	
B	HR	3	66.7	66.7	66.7	0.124
	TACE	6	33.3	16.7	0	
	Sorafenib	7	0	0	0	
PVTT site						
Type I PVTT	HR	16	71.4	54.4	54.4	0.003
	TACE	12	50.0	25.0	16.7	
	Sorafenib	16	37.4	9.4	0	
Type II PVTT	HR	8	35.0	0	0	0.499
	TACE	14	35.7	7.1	0	
	Sorafenib	36	26.5	8.8	0	
Size						
≤5 cm	HR	14	65.0	52.0	52.0	0.307
	TACE	3	66.7	0	0	
	Sorafenib	8	57.1	14.3	0	
>5 cm	HR	10	64.8	64.8	48.6	0.005
	TACE	23	43.5	17.4	8.7	
	Sorafenib	44	23.2	7.7	0	
Lobe						
Unilobe	HR	25	67.5	60.8	52.1	0.001
	TACE	15	60.0	20.0	6.7	
	Sorafenib	39	31.8	10.6	0	
Bilobe	HR	1	0	0	0	<0.001
	TACE	10	27.3	9.1	9.1	
	Sorafenib	13	20.8	0	0	

HCC, hepatocellular carcinoma; HR, hepatic resection; TACE, transarterial chemoembolization; CTP, Child-Turcotte-Pugh; PVTT, portal vein tumor thrombosis.

Univariate and multivariate analyses of overall survival for all patients

Between overall survival and 20 variables with known values for all patients were evaluated by univariate analysis. In the univariate analyses, initial treatment method, tumor size, PVTT type, lobe, CTP class, and presence of cirrhosis or ascites were correlated with overall survival. In multivariate Cox proportional hazards regression analysis, initial treatment method (HR vs. TACE hazard ratio=1.750; 95% confidence interval [CI], 1.037-2.953; *P*=0.036, HR vs. sorafenib hazard ratio=2.262; 95% CI, 1.270-4.027; *P*=0.006), lobe (hazard ratio=1.705; 95% CI, 1.147-2.535; *P*=0.008), PVTT type (hazard ratio=1.617; 95% CI, 1.108-2.359; *P*=0.013), and CTP class (hazard ratio=1.712; 95% CI, 1.125-2.607; *P*=0.012) were significant prognostic factors for overall survival (Table 3).

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Table 3. Multivariate analysis of the overall survival for all patients

Variables	Hazard ratio	95% CI	*P*-value
Treatment			
HR vs. TACE	1.750	1.037-2.953	0.036
HR vs. Sorafenib	2.262	1.270-4.027	0.006
Lobe	1.705	1.147-2.535	0.008
PVTT site	1.617	1.108-2.359	0.013
CTP class	1.712	1.125-2.607	0.012

CI, confidence interval; HR, hepatic resection; TACE, transarterial chemoembolization; PVTT, portal vein tumor thrombosis; CTP, Child-Turcotte-Pugh.

DISCUSSION

According to the BCLC staging system, chemotherapy with a molecular-targeted agent is the only treatment option for patients with advanced HCC. In 2008, a large randomized, controlled study showed that patients with advanced HCC who received sorafenib treatment had a median survival benefit of approximately 3 months, as compared with the placebo group.[10] Other studies have shown that TACE is more effective than best supportive care, even though the outcomes of TACE remain poor.[12-15] However, the treatment of locally advanced HCC remains controversial. In Asian countries, various treatment methods have been attempted. The Asian Pacific Association for the Study of the Liver and the Japan Society of Hepatology recommended TACE, HAIC, ablation, or surgical treatment for locally advanced HCC.[16,17] Peng et al.,[18] who conducted a retrospective study of patients with HCC with PVTT comparing HR and TACE, concluded that HR provided a survival benefit for patients with resectable HCC with PVTT. Shi et al. also suggested that HR was associated with better clinical results than TACE for the treatment of HCC with PVTT.[11]

In our study, sorafenib (the standard of care for patients with HCC with PVTT) was compared with HR and TACE. As previously reported, HR was associated with a longer median survival time and greater overall survival rates than sorafenib or TACE. The outcomes of HR were most notably superior to the outcomes of TACE or sorafenib for advanced HCC patients with good hepatic function, CTP class A and type I PVTT. Despite significant differences between the three groups in terms of albumin levels at baseline, the levels were within the normal range. At baseline, significant differences were also observed for other variables, including ascites status and liver cirrhosis status. However, there were no significant differences in MELD scores and CTP classes. We performed subgroup analyses of patients without ascites and patients belonging to CTP class A. In both of these subgroups, HR was associated with significantly better survival than TACE or sorafenib. Accordingly, we believe that the differences in baseline laboratory characteristics and liver cirrhosis did not influence our assessment of effectiveness. In addition, the presence of cirrhosis has not been included as a meaningful factor in any guideline's treatment algorithm for patients with HCC. Because sorafenib was approved in South Korea partway through the study period, we divided our enrollment period into two periods: A and B. We found that HR was associated with superior survival in both period A and period B. However, in the HR group, the median survival time was 15.4 months in period A and 24.6 months in period B, and in the TACE group, the median survival time was and 6.1 months in period A and 9.5 months in period B. These results may be explained by advancements in TACE, operative techniques, and bedside care. Recently, there have been further developments in the treatment methods and techniques for HCC. Therefore, it is debatable whether sorafenib alone is the best choice for patients with advanced-stage HCC, according to the BCLC.[7] There are some limitations to the current study. First, it is a retrospective design. Second, there may be selection bias because patients with relatively good hepatic function and easy-to-resection HCC might be included in the HR group. Third, the sample size was small and limited to South Korea. Because of differences in underlying liver diseases, our results may not be applicable to patients with HCC with PVTT in other countries. Fourth, portal hypertension and the indocyanine green clearance level were not assessed in all of the enrolled patients, although these factors are strongly associated with prognosis. Fifth, TACE, RFA, HAIC, operations, molecular-targeted agents, and other treatment modalities were applied for recurrent or remnant tumor after initial treatment.

Despite these limitations, this retrospective study indicated that HR, as a first treatment option, may provide better long term survival than TACE or sorafenib for resectable HCC patients with type I PVTT and good hepatic function. Therefore, we suggest that treatment strategies for HCC with PVTT should not be limited to sorafenib. To prolong the survival of patients with advanced BCLC

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stage HCC, the selection of treatment method should be considered according to CTP class, the extent of PVTT, and location of lesion.

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Conflicts of Interest

The authors have no conflicts to disclose.

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