Clinical Characteristics and Treatment Outcomes of Hepatocellular Carcinoma with Inferior Vena Cava/Heart Invasion

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Abstract. *Background: The prognosis and treatment outcomes of hepatocellular carcinoma (HCC) with inferior vena cava (IVC)/heart invasion have not been established. This study aimed to investigate the clinical characteristics and treatment outcomes of patients with HCC extending to IVC/heart and ascertained whether active treatment beyond best supportive care (BSC) can prolong overall survival. Patients and Methods: We retrospectively reviewed 50 patients with HCC extending to IVC/heart who were admitted from November 1987 to November 2010. They were stratified into a control group with BSC alone (n=18) and a treated group with active treatment more than BSC (n=32). Results: The mean age was 56.5 years and male gender predominated (n=39, 78.0%). Treatment modalities in the treated group included systemic chemotherapy using 5-fluorouracil with/without cisplatin (n=10, 31.3%), transarterial chemoembolization (n=8, 25.0%), intra-arterial chemotherapy (n=3, 9.4%), concurrent chemoradiation therapy (n=3, 9.4%), radiation (n=2, 6.2%), surgery (n=1, 3.1%), and of the combination above (n=5, 15.6%). Active treatment more than BSC was the only independent predictor of overall survival and the overall survival of the treated group was significantly better than that of the control group (median 4.0 vs. 2.0 months, p=0.003). Conclusion: The prognosis of HCC with IVC/heart invasion is poor. However, if patients are cautiously selected, active treatment beyond BSC might provide a survival benefit in patients with HCC extending to IVC/heart.*

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and constitutes over 5% of all cancer (1-3). Because South Korea is a highly endemic area of chronic hepatitis B virus infection, HCC is the third leading cause of cancer-related deaths (3-5). The prognosis of HCC is generally poor, with a median survival of several months because the diagnosis often occurs at an advanced tumor stage or with impaired underlying liver function (5, 6). When HCC extends to the inferior vena cava (IVC) or the heart, the prognosis becomes grave, with a reduced median survival of only 2 to 3 months (7). Indeed, patients with HCC extending to the IVC may develop secondary Budd-Chiari syndrome, pulmonary infarction, and lung metastasis (7, 8), whereas HCC extension to the heart can induce sudden pulmonary embolism, intractable heart failure, and ball-valve thrombosis syndrome, which carry the threat of sudden death (7-9).

At present, no established effective treatment strategy for HCC that extends to IVC/heart has yet been reported. Some investigators have insisted that several treatment modalities, including palliative surgery, chemotherapy (systemic or intra-arterial), transarterial chemoembolization (TACE), radiation therapy, or their combination, might help to prolong the overall survival in these patients (7, 10-12). However, to date, only a few reports with very small sample sizes have investigated the treatment outcome and prognosis of HCC extending to the IVC/heart because of its low prevalence (12, 13). Thus, the clinical role of active treatment beyond best supportive care (BSC) *vs*. only BSC for these patients is unclear.

Abbreviations: HCC, hepatocellular carcinoma; IVC, inferior vena cava; TACE, transarterial chemoembolization; BSC, best supportive care; CT, computed tomography; MRI, magnetic resonance imaging; TNM, tumor-Node- Metastasis; LCSGJ, Liver Cancer Study Group of Japan.

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We investigated the clinical characteristics and treatment outcomes of patients with HCC that extended to IVC/heart and ascertained whether active treatment beyond BSC is superior to BSC alone in terms of prolonging the overall survival.

Patients and Methods

Patients. From November 1987 to November 2010, 11,140 consecutive patients were newly diagnosed with HCC at Severance Hospital (Yonsei University, College of Medicine, Seoul, Korea). Out of these patients, 52 had IVC/heart invasion at the time of HCC diagnosis (incidence rate, 0.5%). However, two patients with evidence of severe renal and respiratory failure that might have affected overall survival were excluded. Thus, a total of 50 patients were recruited for the analysis, and their medical records were reviewed. The medical records included demographic characteristics, laboratory results, tumor characteristics, tumor stages, imaging study results, and treatment modalities.

To investigate whether active treatment beyond BSC is superior to BSC alone in terms of affecting the overall survival of the patients, we stratified the 50 patients into two groups: a control group with BSC alone (n=18) and a treated group with active treatment beyond BSC (n=32). Although ten (55.6%) patients with Child-Pugh A or B liver function in the control group were recommended to undergo active treatment as opposed to BSC, they refused after being advised of the possible side-effects of any invasive treatment.

All patients were followed-up until December 2010. This study was approved by the Institutional Review Board of Severance Hospital of Yonsei University Health System, Seoul, Korea (IRB number 4-2010-0321).

Diagnosis of HCC and IVC/heart invasion. The diagnosis of HCC was performed by histology for five patients and by clinical criteria for 45 patients based on the guidelines proposed by the Korea Liver Cancer Study Group and the National Cancer Center (14). According to these criteria, a patient is considered clinically positive for HCC if they have one or more risk factors (hepatitis B virus infection, hepatitis C virus infection, or cirrhosis) and one of the following: a serum α-fetoprotein level of >400 ng/ml and a positive finding with at least one of three typical imaging studies [spiral computed tomography (CT), contrast-enhanced dynamic magnetic resonance imaging (MRI), or hepatic angiography] or a serum α-fetoprotein level of <400 ng/ml and positive findings on at least two out of the three imaging studies. A positive finding for typical HCC with dynamic CT or MRI was indicative of arterial enhancement followed by venous washout in the delayed portal/venous phase. The stage of HCC was determined in accordance with Tumor-Node-Metastasis (TNM) stage of the Liver Cancer Study Group of Japan (LCSGJ) (15).

IVC and heart invasion, defined as direct invasion from the liver to the heart or intra-cardiac tumor thrombosis, were diagnosed using CT, MRI, positron-emission tomography, or echocardiography.

Treatment modalities for HCC in the treated group. As systemic chemotherapy, patients received 5-fluorouracil (1000 mg/m^2 for 24 h on days 1 to 3) with/without cisplatin (80 mg/m^2 for 4 h on day 2) every 4 weeks (16). TACE was carried out using a solution of 20 to 50 mg doxorubicin hydrochloride in 5 to 20 ml of a mixed solution of lipiodol and contrast agent. Embolization was subsequently performed using gelatin sponge particles (17). During intra-arterial chemotherapy, patients received 5-fluorouracil at 500 mg/m^2 for 5 h on days 1 to 3, and cisplatin at 60 mg/m^2 for 2 h on day 2 through the hepatic artery every 4 weeks (18). Concurrent chemoradiation therapy was carried out over 5 weeks, and during the first and fifth weeks of radiation therapy (in 25 fractions of 1.8 Gy, total of 45 Gy), concurrent continuous-infusion hepatic arterial 5-fluorouracil (at a dose of 500 mg/d) was delivered through a hepatic arterial catheter (19). Surgery, such as thrombectomy, was performed for the purpose of palliation.

Statistical analysis. Independent Student's *t*-tests and chi-square tests were used to compare the baseline characteristics of the patients. We identified independent prognostic factors of overall survival using Cox's proportional hazard regression model. Survival times of the patients were estimated from the date of HCC diagnosis to death. Cumulative survival rates between the control group and the treated group were analyzed using the Kaplan-Meier method, and the differences between curves were assessed by the log-rank test. All data were analyzed using PASW Statistics 18 (PASW, Chicago, IL, USA). A value of $p<0.05$ was considered statistically significant.

Results

Baseline characteristics. The baseline characteristics of the study population are summarized in Table I. The mean age of the patients was 56.5 years, and males predominated (n=39, 78.0%). The most common etiology of underlying liver disease was hepatitis B virus infection (n=41, 82.0%).

Patients in the treated group were significantly older (59.9±8.1 *vs*. 50.4±15.5 years), had a higher proportion of preserved liver function of Child-Pugh class A (56.3% *vs*. 22.2%), higher albumin levels (3.4±0.5 *vs*. 3.1±0.5 g/dl), and lower bilirubin levels (1.2±0.7 *vs*. 3.1±2.4 mg/dl) compared with the control group (all $p<0.05$). The TNM stages of LCSGJ were not significantly different between the two groups ($p=0.335$).

Intrahepatic tumor status. Most patients (n=47, 94.0%) had HCC tumors larger than 2 cm, and portal vein thrombosis was noted in 24 (48.0%) patients. There was no significant difference between the two groups in terms of intrahepatic HCC status, with the exception of the higher proportion of single tumors in the control group than in the treated group (66.7% *vs*. 31.3%, $p=0.049$).

IVC, heart invasion and extrahepatic tumor status. There was no statistical difference in the extent of IVC and heart invasion ($p=0.323$). Out of 25 patients with heart invasion, 3 (12.0%) had direct cardiac invasion from the liver, and the other 22 (88.0%) had intracardiac tumor thrombosis. In the control group, nine (50.0%) patients had IVC invasion only, and the others had both IVC and heart invasion, whereas IVC invasion

Table I. *Baseline characteristics of patients in this study.*

Variable	Total (n=50)	Control group (n=18, 36.0%)	Treated group (n=32, 64.0%)	*p*-Value
Age (years)	56.5±12.1	50.4±15.5	59.9±8.1	0.025
Male	39 (78.0)	15 (83.3)	24 (75.0)	0.724
Etiology, HBV/HCV/other[a]	41 (82.0)/4 (8.0)/5 (10.0)	14 (77.8)/2 (11.1)/2 (11.1)	27 (84.3)/2 (6.3)/3 (9.4)	0.916
Major symptom at diagnosis				0.331
Abdominal pain	10 (20.0)	4 (22.2)	6 (18.8)	
Abdominal distension	11 (22.0)	6 (33.4)	5 (15.6)	
General weakness	5 (10.0)	2 (11.1)	3 (9.4)	
Asymptomatic	8 (16.0)	2 (11.1)	6 (18.8)	
Other[b]	16 (32.0)	4 (22.2)	12 (37.4)	
Child-Pugh class, A/B/C	22 (44.0)/19 (38.0)/9 (18.0)	4 (22.2)/6 (33.3)/8 (44.4)	18 (56.3)/13 (40.6)/1 (3.1)	0.001
Laboratory findings				
Albumin (g/dl)	3.3±0.6	3.1±0.5	3.4±0.5	0.035
Alanine aminotransferase (IU/l)	77.4±142.3	127.1±228.1	49.4±34.8	0.169
Prothrombin time (s)	13.9±2.1	14.4±2.8	13.6±1.5	0.287
Total bilirubin (mg/dl)	1.9±1.8	3.1±2.4	1.2±0.7	0.001
Alpha-fetoprotein (ng/ml)	851.0 (0.7-50000.0)	1265.9 (0.7-30300.0)	783.5 (2.0-50000.0)	0.549
Tumor factors				
Tumor number, single/multiple	22 (44.0)/28 (56.0)	12 (66.7)/6 (33.3)	10 (31.3)/22 (68.7)	0.049
Tumor size, <2 cm/≥2 cm	3 (6.0)/47 (94.0)	2 (11.1)/16 (88.9)	1 (3.1)/31 (96.9)	0.130
Extent of cardiovascular invasion, IVC/heart/both	25 (50.0)/2 (4.0)/23 (46.0)	9 (50.0)/0 (0.0)/9 (50.0)	16 (50.0)/2 (6.3)/14 (43.7)	0.323
Portal vein thrombosis	24 (48.0)	9 (50.0)	15 (46.9)	0.832
Extrahepatic metastasis	13 (26.0)	4 (22.2)	9 (28.1)	0.746
TNM stage of LCSGJ, I/II/III/IV	1 (2.0)/5 (10.0)/18 (36.0)/26 (52.0)	1 (5.6)/2 (11.1)/8 (44.4)/7 (38.9)	0 (0.0)/3 (9.4)/10 (31.2)/19 (59.4)	0.335

Variables are expressed as n (%) or median (range). [a]Including alcohol or mixed or unknown etiologies. [b]Including dyspnea, chest discomfort, and palpable mass. HBV, Hepatitis B virus; HCV, hepatitis C virus; IVC, inferior vena cava; TNM, Tumor-Node-Metastasis; LCSGJ, Liver Cancer Study Group of Japan.

was identified in 16 (50.0%), heart invasion in 2 (6.3%), and both in 14 (43.7%) patients in the treated group.

Extrahepatic metastasis other than of the IVC and the heart was noted in 13 (26.0%) patients, and the lung was the only site of metastasis. The incidence of lung metastasis was similar between the control and treated groups (22.2% *vs*. 28.1%; p=0.746).

Treatment modalities in the treated group. In the treated group, systemic chemotherapy using 5-fluorouracil with/without cisplatin, TACE, intra-arterial chemotherapy, concurrent chemoradiation therapy, radiation only, surgery, and their combination were carried out according to their own indications (Table II).

Table II. *Treatment modalities of treated group (n=32).*

Treatment modality	n (%)	Child-Pugh class (n)		
		A	B	C
Systemic chemotherapy	10 (31.3)	8	1	1
Transarterial chemoembolization	8 (25.0)	3	5	0
Intra-arterial chemotherapy	3 (9.4)	0	3	0
Chemoradiation	3 (9.4)	3	0	0
Radiation	2 (6.2)	2	0	0
Operation	1 (3.1)	0	1	0
Combined modality	5 (15.6)	2	3	0

Causes of mortality. By the end of follow-up, 48 patients had died (all 18 patients in the control group and 30 patients in the treated group). One remained alive, and another was lost to follow-up. The causes of mortality in the control and treated groups are indicated in Table III, and they were not significantly different between the two groups (p=0.057).

Independent predictors of overall survival and treatment outcomes. In the multivariate analysis to identify independent predictors of overall survival (Table IV), only active treatment beyond BSC affected the overall survival of patients with invasion of IVC/heart (p=0.047; hazard ratio=0.509; 95% confidence interval=0.262-0.992). The median survival of all

Table III. *Causes of mortality [n, (%)].*

	Total (n=48)	Control group (n=18)	Treated group (n=30)
Hepatic failure	21 (43.8)	8 (44.4)	13 (43.3)
Disease progression	14 (29.2)	5 (27.8)	9 (30.0)
Upper gastrointestinal bleeding	3 (6.3)	0 (0.0)	3 (10.0)
Cardiac problems	2 (4.1)	2 (11.1)	0 (0.0)
Unknown	8 (16.6)	3 (16.7)	5 (16.7)

patients was 4.0 (range, 1.0-83.0) months. The Kaplan-Meier survival curves showed that the overall survival of the treated group was significantly better than that of the control group [median, 4.0 (range, 1.0-83.0) *vs*. 2.0 (range, 1.0-11.0) months; log-rank test, p=0.003] (Figure 1).

Considering that Child-Pugh class was of borderline significance (p=0.077), we selected only patients with Child-Pugh class A for further analysis. Although the median survival of the treated group (n=18) was better than that of the control group (n=4) (7.0 *vs*. 3.0 months), it did not reach statistical significance (p=0.406). Active treatment beyond BSC was only of borderline significance for patients with liver function of Child-Pugh class A (p=0.090).

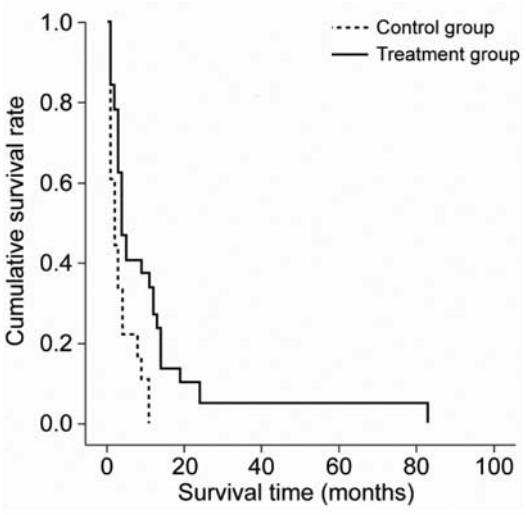

Figure 1. *Survival curves of the control (n=18) and treated groups (n=32). The overall survival of the treated group was significantly better than that of the control group (median 2.0 vs. 4.0 months; log-rank test, p=0.003).*

Discussion

Since cases of HCC extending to the IVC/heart are very rare at only a 1% to 4% prevalence (9, 20), it is difficult to conduct randomized controlled trials for specific treatment. Therefore, the effective treatment modalities for such cases are not yet established, and the prognosis remains unclear (12, 13). Until recently, case reports of HCC extending to the IVC/heart were rarely reported (20, 21), but few large-scale clinical studies of patients with HCC extending to IVC/heart were published (7). Although our study was not a randomized controlled trial targeting a relatively large number of patients, we stratified patients who refused any invasive treatment beyond BSC into a control group and analyzed whether active treatment beyond BSC was superior to BSC alone in terms of prolonging the overall survival of patients with HCC extending to the IVC/heart.

In our study, eight (16.0%) patients had no symptoms, whereas five (10.0%) complained of dyspnea or chest discomfort, which might have been related to IVC/heart invasion. Considering that this study was retrospective, some patients may have died without further evaluation for IVC/heart invasion because symptoms related to IVC/heart invasion are often nonspecific. Thus, the proportion of asymptomatic patients who had HCC with IVC/heart invasion might be much higher in clinical practice. Indeed, asymptomatic cases have been reported in several previous studies (21, 22). Because the prognosis becomes poorer and the risk of sudden death always exists in patients with HCC extending to the IVC/heart, the possibility of such invasion in patients with advanced HCC should be kept in mind. After prompt diagnosis, active treatment beyond BSC for such cases might prevent sudden death and prolong survival according to our results.

Although the difference was small, the median survival of the treated group was significantly better than that of the control group (4.0 *vs*. 2.0 months). To date, various treatment modalities such as palliative surgery, chemotherapy (systemic or intra-arterial), TACE, and radiation have been applied to patients with HCC extending to the IVC/heart. Despite a small sample size of five patients, Lin *et al*. (22) suggested that aggressive surgical treatment could prolong the survival of patients. Interestingly, two out of five patients who received postoperative TACE in the specific study survived longer than those treated with surgical resection alone. Chern *et al*. (7) suggested that TACE is an effective treatment in patients with advanced HCC invading IVC and heart, and the median survival of TACE-responders in this study was significantly longer than that of TACE-nonresponders (13.5 *vs*. 3.3 months). According to Zeng *et al*. (11), the median survival of untreated patients was 1 month, and treated patients survived much longer (TACE, 4.0 *vs*. resection, 5.0 *vs*. combination with and without external beam radiation therapy, 8.0 months). Thus, they proposed that a combination with radiation therapy is an alternative treatment approach for such cases. However, the study population of Zeng *et al*. included patients with only portal

Table IV. *Univariate and multivariate analyses to identify independent factors for overall survival.*

Variable	Univariate	Multivariate		
	p-Value	Hazard ratio	95% Confidence interval	*p*-Value
Male	0.556			
Age	0.151			
Presence of symptoms at admission				
Yes *vs*. no	0.744			
Alanine aminotransferase (IU/l)	0.133			
Alpha-fetoprotein (ng/ml)	0.357			
Child-Pugh class				
B/C *vs*. A	0.017	1.793	0.938-3.425	0.077
C *vs*. A/B	0.148			
TNM stage of LCSGJ				
II-IV *vs*. I	0.153			
III-IV *vs*. I-II	0.808			
IV *vs*. I-III	0.175			
Active treatment for HCC than BSC				
Yes *vs*. no	0.009	0.509	0.262-0.992	0.047

TNM, Tumour-Node-Metastasis; LCSGJ, Liver Cancer Study Group of Japan; HCC, hepatocellular carcinoma; BSC, best supportive care. Reference value: Child-Pugh class A and no active treatment for HCC than BSC.

vein thrombosis, which might prolong survival (median, 4-8 months) more than in the treated group in our study (4 months). Finally, Fukuda *et al*. (10) reported that five patients survived longer than 5 years after an aggressive surgical approach combined with chemotherapy (intra-arterial chemotherapy or chemolipiodolization).

The only independent predictor of overall survival in the present study was active treatment beyond BSC. However, because Child-Pugh class was of borderline significance in the multivariate analysis, we only selected patients with Child-Pugh class A to exclude the potential effect of liver function. Although the difference did not reach statistical significance, the overall survival of the treated group was longer than the one of the control group, and active treatment beyond BSC for HCC was of borderline statistical significance (p=0.090), which might indicate that the role of active treatment beyond BSC might be revealed if the sample size were larger or patients receiving active treatment beyond BSC were carefully selected.

Of the 50 patients, one in the treated group was still alive, with a survival time of 20.0 months, at the end of follow-up in our study. This patient underwent concurrent chemoradiation therapy followed by nine cycles of systemic chemotherapy. The longest survival (83.0 months) in the treated group was observed a patient treated with ten cycles of systemic chemotherapy followed by six cycles of TACE. However, during 15.0 months of follow-up loss, HCC progressed with hematogenous lung metastasis and the patient died of disease progression. In contrast, two patients have survived for 11.0 months in the control group.

This study has several limitations. Firstly, we were unable to histologically confirm whether an intracardiac mass was HCC invasion or a benign cardiac tumor such as a myxoma. However, the incidence of cardiac tumors is reported to be as low as 0.02%, which might not greatly influence the result; furthermore, the intracardiac masses were radiologically consistent with HCC. Secondly, although it was concluded that active treatment beyond BSC improved overall survival, it was difficult to investigate the efficacy of each treatment modality because of the small sample size. Thirdly, patients in the treated group had better liver function than did those in the control group, although liver function was insignificant in the multivariate analysis. Because this study was retrospective, randomization was not possible. Although all patients in the control group refused to receive active treatment beyond BSC, the decision of treatment might have been biased, which may have stratified patients with relatively good liver function into the treated group and prolonged the overall survival in the treated group.

In conclusion, the prognosis of HCC extending to the IVC/heart is very poor, with a median survival of less than 4 months, and active treatment beyond BSC was identified as the only independent predictor of overall survival. Thus, if patients are carefully selected, active treatment beyond BSC might be superior to BSC alone in terms of a survival benefit in patients with HCC extending to the IVC/heart.

Declaration of Interest

The Authors declare that there is no conflict of interest.

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