

# Risk Factors for Patients with Stage IVB Hepatocellular Carcinoma and Extension into the Heart: Prognostic and Therapeutic Implications

Chung Hwan Jun,<sup>1\*</sup> Da Woon Sim,<sup>1\*</sup> Sang Ho Kim,<sup>2</sup> Hyoung Ju Hong,<sup>1</sup> Min Woo Chung,<sup>1</sup>  
Sung Bum Cho,<sup>1</sup> Chang Hwan Park,<sup>1</sup> Young Eun Joo,<sup>1</sup> Hyun Soo Kim,<sup>1</sup>  
Sung Kyu Choi,<sup>1</sup> and Jong Sun Rew<sup>1</sup>

<sup>1</sup>Division of Gastroenterology, Department of Internal Medicine, Chonnam National University Medical School, Gwangju;

<sup>2</sup>Department of Internal Medicine, Mokpo Jung-Ang Hospital, Mokpo, Korea.

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Corresponding author: Dr. Sung Kyu Choi,  
Division of Gastroenterology,  
Department of Internal Medicine,  
Chonnam National University Medical School,  
42 Jebong-ro, Dong-gu,  
Gwangju 501-757, Korea.  
Tel: 82-62-220-6296, Fax: 82-62-225-8578  
E-mail: [estevanj@naver.com](mailto:estevanj@naver.com)

\*Chung Hwan Jun and Da Woon Sim  
contributed equally to this work.

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**Purpose:** To evaluate the risk factors of hepatocellular carcinoma (HCC) extension into the right atrium (RA) and determine poor prognostic factors for HCC extension to the heart. **Materials and Methods:** A total of 665 patients who were newly diagnosed with HCC were analyzed retrospectively from January 2004 to July 2012. The patients were divided into two groups: 33 patients with HCC extending into the RA and 632 HCC patients during the same period. The patients with HCC extending into the RA were subdivided into shorter survival group (<2 months) and longer survival group (≥2 months). **Results:** The prevalence of HCC extending to the RA was 4.96%. In multivariate analysis, a modified Union Internationale Contre le Cancer (UICC) stage higher than IVA, hepatic vein invasion, concomitant inferior vena cava and portal vein invasion, and multinodular tumor type were risk factors for HCC extending to the RA. In multivariate analysis, Cancer of the Liver Italian Program (CLIP) score >3 ( $p=0.016$ , OR: 13.89) and active treatment ( $p=0.024$ , OR: 0.054) were associated with prognostic factors in patients HCC extending into the RA. Active treatment such as radiation ( $n=1$ ), transcatheter arterial chemoembolization (TACE) ( $n=11$ ), Sorafenib ( $n=1$ ), and combined modalities ( $n=2$ ) were performed. **Conclusion:** Modified UICC stage higher than IVA, vascular invasion and multinodular tumor type are independent risk factors for HCC extending to the RA. Active treatment may prolong survival in patients HCC extending into the RA.

**Key Words:** Active cancer treatment, hepatocellular carcinoma, metastasis, right atrium, prognosis

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the seventh most common carcinoma worldwide and the third most common cause of cancer-related mortality.<sup>1</sup> HCC is a highly malignant tumor with a propensity for invading intrahepatic vascular struc-

tures, the portal vein (PV), and the hepatic vein (HV). Infrequently, the tumor thrombi within the HV may extend into the inferior vena cava (IVC) and the right atrium (RA). The prevalence of intra-atrial tumor growth in autopsied cases of HCC ranges from 1 to 4.8%.<sup>2-4</sup> With advances in imaging, intra-atrial tumor growth has been increasingly recognized in HCC patients.<sup>5-7</sup> When HCC extends into the IVC or the heart, the prognosis is poor, with a median survival period of only 2-3 months.<sup>8</sup> The prognosis of HCC patients with extrahepatic metastasis is unsatisfactory and often not well known. The median survival period is 4.9 months (range, 1-37 months).<sup>9</sup>

HCC extension into the heart can induce sudden pulmonary embolism, intractable heart failure, secondary Budd-Chiari syndrome, and ball-valve thrombosis syndrome, and all of these complications can cause sudden death.<sup>6,10</sup>

Aggressive surgical treatment and nonsurgical local treatment modalities<sup>11-15</sup> are efficacious, although such procedures are usually prohibited in most patients with advanced HCC because of underlying cirrhosis and the advanced stage of the primary tumor. No established risk factors, prognostic factors or effective treatment strategies for HCC cases that extend into the heart have been reported to date. Chun, et al.<sup>16,17</sup> reported that active treatment, such as radiation, systemic chemotherapy, and transcatheter arterial chemoembolization (TACE) beyond supportive care, may provide a survival benefit in patients with HCC that extends into the IVC/heart, but this study was limited by a small sample size.

Therefore, the current study aimed to evaluate the risk factors and predictive factors for poor prognosis of patients with HCC extending into the RA.

## MATERIALS AND METHODS

### Patients

From January 2004 to December 2012, a total of 1042 patients with newly diagnosed HCC were admitted to the Division of Gastroenterology at Chonnam National University Hospital in Gwangju, Korea. Overall, 377 patients were excluded because laboratory data available at the end of the follow-up period were incomplete. Information for 665 patients with newly diagnosed HCC were evaluated retrospectively. Among these patients, 33 patients had RA invasion during HCC followed up. In total, 632 patients who were diagnosed during the same period served as the comparison group. To describe the risk factors of HCC extension into

the RA and determine predictive factors for poor prognosis in patients with HCC extending into RA, the data collected from the medical records included demographics, laboratory results, tumor characteristics, tumor stage, imaging studies, treatment modalities, and overall survival.

### Diagnosis of HCC with RA invasion

The diagnosis of HCC was based on the following guidelines proposed by the Korea Liver Cancer Study Group and the National Cancer Center<sup>18</sup>: 1) nodules >2 cm in diameter with a typical pattern of HCC in one imaging study or alpha-fetoprotein (AFP) levels >200 ng/mL and 2) nodules between 1 and 2 cm in diameter with a coincidental typical vascular pattern in two imaging studies. If these criteria were not met, biopsies were performed. Clinical staging was based on the modified Union Internationale Contre le Cancer (UICC) tumor-node-metastasis classification and Cancer of the Liver Italian Program (CLIP) scores.<sup>18,19</sup> RA invasion was defined as direct invasion from the liver into the RA or intra-cardiac tumor thrombosis and diagnosed using CT, MRI, positron emission tomography, or echocardiography during follow-up of HCC and new symptom development, such as aggravated dyspnea, ascites, and chest discomfort. HCC with RA invasion was commonly diagnosed using CT. On imaging, the RA embolus was commonly observed as having a regular, slightly irregular round, orbicular-ovate, or lobulated type. In the arterial phase, the embolus demonstrated slight enhancement, whereas in the portal phase and the delayed phase, the contrast media were partially discharged.<sup>20</sup>

### HCC treatment

Surgical resection, percutaneous ethanol injection therapy, radiofrequency ablation (RFA), TACE, Sorafenib, and radiation were performed based on the guidelines of the Korea Liver Cancer Study Group and the National Cancer Center.<sup>18,21</sup>

### Treatment modalities for HCC that extended into the RA

Medical chart review showed that 18 patients received supportive care and 15 patients received active treatment according to the individual situation such as economic state, Eastern Cooperative Oncology Group score, and patient's will to treat. To evaluate whether active treatment was superior to supportive care alone in terms of the overall survival of patients, we stratified 33 patients into the following two groups: a supportive care group (n=18) and an active

treatment group (n=15). All of the patients were followed through December 2012.

### Definition for poor prognosis group

According to Chern, et al.,<sup>8</sup> when HCC extends into the IVC or the heart, median survival period is only 2-3 months. Therefore, we defined poor prognosis group as survival time shorter than 2 months.

### Ethics statement

Written informed consent was obtained from all of the patients regarding the nature and the purpose of the treatment, and this study was approved by the IRB of our institution.

### Statistical analysis

Continuous variables were expressed as mean±standard deviation. A Student's t-test and Pearson's chi-squared test or Mann-Whitney test were used to compare the baseline characteristics of the patients. Factors that were significant in the univariate analysis were entered into a stepwise multivariate analysis to determine which risk factors retained statistical significance and which factors were dependent on other factors. The survival times were estimated from the

date of HCC diagnosis until death. Null hypotheses of no differences were rejected if the *p* values were less than 0.05 or, equivalently, if the 95% CI of the odds ratio estimates excluded 1. We performed statistical analysis using SPSS 20.0 (SPSS Inc., IBM Company, Chicago, IL, USA).

## RESULTS

### Patient characteristics

The median duration of follow-up was 857 days (2-3906 days). The mean age of the patients was 59.7 years (range 32-87 years), and there were 561 men (84.4%) and 104 women (15.6%) included in the study. Overall, 373 patients (56.1%) were positive for hepatitis B surface antigen, 105 patients (15.8%) were positive for antibodies against hepatitis C virus (anti-HCV Ab), 121 patients (18.2%) were chronic alcohol drinkers, 36 patients (5.4%) had a combined etiology, and 30 patients (4.5%) had an unknown etiology. Regarding treatment method, 433 patients (65.1%) underwent TACE, 83 (12.5%) RFA, 76 (11.4%) surgery, 2 (0.3%) radiation therapy (RT), 16 (24.1%) Sorafenib, 6 (0.9%) hepatic arterial infusion chemotherapy, and 49 (7.3%) supportive care.

**Table 1. Clinical Characteristics of Each Group of Patients**

Variables	HCC with RA invasion (n=33)	HCC during the same period (n=632)	<i>p</i> value
Sex (M/F)	29/4	532/100	0.637
Age	60.88±11.11	59.68±10.72	0.534
Cause of HCC (HBV vs. non HBV) (%)	21 (63.6)	384 (60.8)	0.855
(HBV/HCV/alcohol/mixed/others)	15/3/6/6/3	358/102/115/30/27	
Modified UICC stage >IVA (%)	33 (100)	32 (5.1)	<0.001
(I/II/III/IVA/IVB)	0/0/0/0/33	92/237/151/120/32	
CLIP score >3 (%)	16 (48.5)	41 (6.5)	<0.001
(0/1/2/3/4/5/6)	0/1/6/10/12/3/1	212/213/99/67/29/11/1	
Portal vein invasion (yes, %)	21 (63.6)	158 (25)	<0.001
HV invasion (yes, %)	27 (81.8)	126 (19.9)	<0.001
IVC invasion (yes, %)	33 (100)	34 (5.4)	<0.001
Multinodular tumor type (yes, %)	25 (75.7)	396 (62.6)	<0.001
Tumor size (cm)	9.09±4.86	4.79±3.78	<0.001
AST, U/L	90.39±80.30	66.62±52.94	0.105
ALT, U/L	50.7±41.52	48.16±45.21	0.753
LDH, U/L	577.64±240.50	473.72±313.78	0.087
CRP, mg/dL	3.5±3.79	1.29±2.40	0.003
AFP, IU/mL	9885±16973	4189±24167	0.183
Child-Pugh score	6.76±1.22	5.93±1.24	<0.001
Follow-up duration, median (range)	123 (2-467) days	634 (5-3906) days	0.001

UICC, Union Internationale Contre le Cancer; CLIP, Cancer of the Liver Italian Program; IVC, Inferior vena cava; AFP,  $\alpha$ -fetoprotein; CRP, C-reactive protein; HCC, hepatocellular carcinoma; RA, right atrium; HCV, hepatitis C virus; HV, hepatic vein; HBV, hepatitis B virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.

There were significant differences between the characteristics of the two groups (HCC with RA invasion vs. newly diagnosed HCC during the same period), including the modified UICC stage, the CLIP score, the Child-Pugh score, the serum C-reactive protein (CRP) levels, PV invasion, HV invasion, IVC invasion, tumor size, tumor type, and the duration of follow-up. The clinical characteristics of the two groups are shown in Table 1.

A total of 13 patients (39.3%) had aggravated abdominal distension and/or dyspnea, 11 patients (33.3%) had non-specific symptoms (fatigue or poor oral intake), 8 patients (24.2%) had aggravated right upper quadrant pain, and 1 patient (3%) had chest discomfort on diagnosis of HCC with RA invasion. Suspicious right heart failure signs, such as aggravated ascites/dyspnea (39.3%), were the dominant symptoms.

#### Risk factors for advanced HCC with RA invasion in uni-and multivariate analysis

Of a total of 665 patients with newly diagnosed HCC in our institution, 33 patients (4.96%) had RA invasion during HCC follow-up. In the univariate analysis, a modified UICC stage greater than IVA, a CLIP score >4, serum CRP levels >0.8 mg/dL, PV invasion, HV invasion, concomitant IVC and PV invasion, a tumor size  $\geq 5$  cm, a multinodular tumor type, and lymph node involvement were risk factors for HCC with RA invasion.

In the multivariate analysis, a modified UICC stage great-

er than IVA, HV invasion, concomitant IVC and PV invasion, and a multinodular tumor type were identified as independent risk factors (Table 2).

#### Predictive factors for poor prognosis in patients with HCC extending into the RA

According to survival time, 9 patients survived less than 2 months, 24 patients survived longer than 2 months. The patients with HCC extending into the RA were subdivided into shorter survival group (<2 months) and longer survival group ( $\geq 2$  months). There were no significant differences between the characteristics of the two groups (shorter survival group vs. longer survival group) including gender, age, cause of HCC, antiviral treatment, the modified UICC stage, the Child-Pugh score, the serum CRP, AFP levels, HV invasion, IVC invasion, tumor size, tumor type, lymph node, distant metastasis except PV thrombosis ( $p=0.054$ ), CLIP score >3 ( $p=0.057$ ), and active treatment ( $p=0.07$ ).

In multivariate analysis, CLIP score >3 ( $p=0.016$ , OR: 13.89) and active treatment ( $p=0.024$ , OR: 0.054) were associated with prognostic factors in patients HCC extending into the RA (Table 3). Regarding to treatment course of patients with longer survival >6 months, TACE (n=3), RT (n=1), TACE+RT (n=1), and Sorafenib (n=1) were performed.

#### Active treatment vs. supportive care in patients with HCC that extended into the RA

The median duration of follow-up in patients with HCC that

**Table 2.** Uni- and Multivariate Analysis of the Independent Variables Related to RA Metastasis

Univariate analysis			
Variables	OR	95% CI	p value
UICC stage greater than IVA	33.87	15.28-75.06	<0.001
CLIP score >4	15.12	6.97-32.75	<0.001
CRP >0.8 mg/dL	6.3	2.74-14.2	<0.001
Portal vein invasion	3.57	2.3-10.0	<0.001
Hepatic vein invasion	14.49	5.88-35.71	<0.001
Concomitant IVC and portal vein invasion	18.51	8.62-42.0	<0.001
Tumor size $\geq 5$ cm	14.18	4.26-47.15	<0.001
Multinodular tumor type	5.29	2.25-12.47	<0.001
Lymph node involvement	4.31	1.51-12.34	0.006
Multivariate analysis			
Variables	OR	95% CI	p value
UICC stage greater than IVA	9.68	3.67-25.48	<0.001
HV invasion	4.98	1.54-16.09	0.007
Concomitant IVC and portal vein invasion	4.14	1.34-4.14	0.013
Multinodular tumor type	5.99	1.90-18.85	0.002

UICC, Union Internationale Contre le Cancer; CLIP, Cancer of the Liver Italian Program; IVC, inferior vena cava; AFP,  $\alpha$ -fetoprotein; CRP, C-reactive protein; HV, hepatic vein; RA, right atrium; OR, odd ratio; CI, confidence interval.

extended into the RA was 123 days (range 2-467 days) (Fig. 1). Survival curve of patients with HCC and RA invasion between active treatment and supportive care are shown in

Fig. 2.

The mean age of these patients was 60.88 years (range 37-86 years), and there were 28 men (84.8%) and 5 women

**Table 3. Uni- and Multivariate Analysis of the Variables Related to Poor Prognosis**

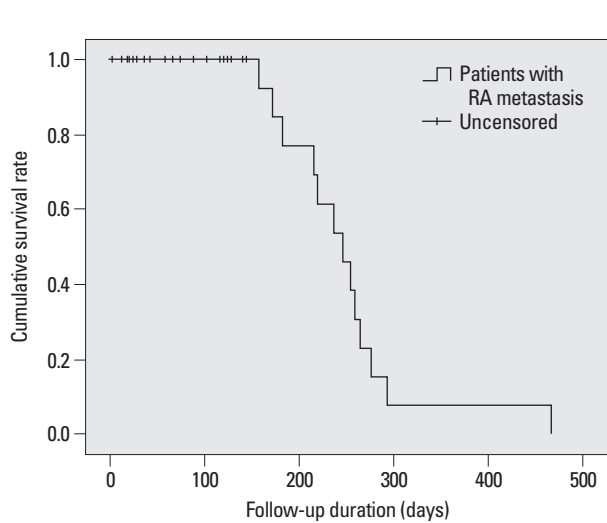
Univariate analysis			
Variables	OR	95% CI	p value
CLIP score >3	8.5	1.40-51.48	0.02
Modified UICC stage >IVA	1.2	0.239-6.025	0.825
Uninodular tumor type	0.188	0.031-1.122	0.067
Distant metastasis except RA	3.33	0.664-16.736	0.144
Lymph node metastasis	1.6	0.154-16.605	0.694
Active treatment	0.089	0.01-0.832	0.034
Child-Pugh score >7	0.857	0.188-7.222	0.868
Multivariate analysis			
Variables	OR	95% CI	p value
Active treatment	0.054	0.004-0.676	0.024
CLIP >3	13.89	1.635-118.07	0.016

CLIP, Cancer of the Liver Italian Program; UICC, Union Internationale Contre le Cancer; RA, right atrium; OR, odd ratio; CI, confidence interval.

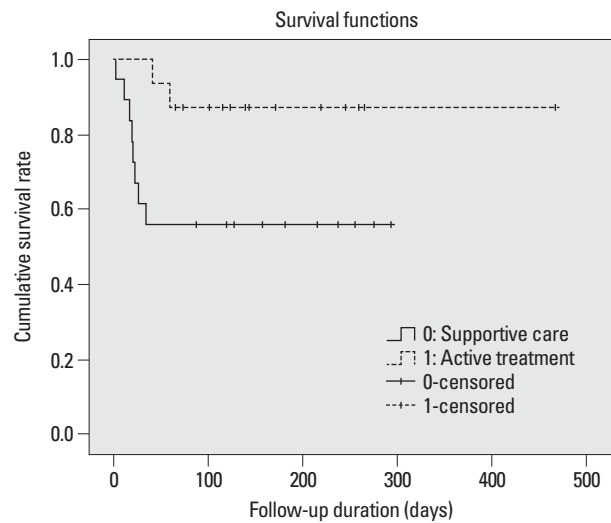
**Table 4. A Comparison of the Active Treatment Group and the Supportive Care Group According to Patients with HCC That Extended into the RA**

Variables	Active treatment (n=15)	Supportive care (n=18)	p value
Sex (M/F)	13/2	15/3	1.0
Age	62.2±11.18	59.95±10.97	0.56
CLIP score >3 (%)	6 (40)	8 (44.4)	1
(1/2/3/4/5/6)	1/4/4/5/0/1	0/2/6/7/3/0	
Portal vein thrombosis (yes, %)	8 (53.3)	13 (72.2)	0.3
Tumor type (multinodular) (%)	12 (85.7)	13 (72.2)	0.426
(Uninodular/multinodular/massive/diffuse)	0/10/3/2	0/8/8/2	
Tumor size (cm)	8.08±4.02	9.99±5.46	0.275
Child-Pugh score	6.94±1.43	6.53±0.91	0.345

CLIP, Cancer of the Liver Italian Program; HCC, hepatocellular carcinoma; RA, right atrium.



**Fig. 1.** The survival curve of patients with HCC extending into the RA. HCC, hepatocellular carcinoma; RA, right atrium.



**Fig. 2.** The survival curves of patients in the supportive care and active treatment groups with HCC and RA invasion (log rank test,  $p=0.037$ ).

(15.2%). The mean CLIP score was 3.39 (range 1-6), and the mean Child-Pugh score was 6.46 (range 5-11). There were no significant differences between the two groups (active treatment vs. supportive care) according to age, CLIP scores, Child-Pugh scores, PV invasion, tumor size, tumor type (Table 4). The treatment modalities in the active treatment group, including radiation, TACE, Sorafenib, and combined modalities, were performed according to the indications or situation for each patient (Table 5). After active treatment, most of patients who had right heart failure sign and chest discomfort had more improvement of symptom.

The causes of mortality in the best supportive care group included hepatic failure (n=6/18, 33.3%), tumor progression (n=5/18, 27.7%), upper gastrointestinal bleeding (n=2/18, 11.1%), ruptured HCC (n=2/18, 11.1%), sepsis due to pneumonia (n=1/18, 5.5%), and unknown causes (n=2/18, 11.1%).

In the active treatment group, the causes of mortality included hepatic failure (n=3/14, 21.4%), tumor progression (n=1/14, 7.1%), upper gastrointestinal bleeding (n=4/14, 28.5%), ruptured HCC (n=3/14, 21.4%), and cardiac problems (n=3/14, 21.4%). One patient is still alive until last follow-up.

## DISCUSSION

The clinical course of HCC with a tumor thrombus in the PV, IVC, or RA is dismal. The median survival times of patients with an IVC tumor thrombus have been reported to be as short as 2-3 months without effective treatment.<sup>22</sup> Because cases of HCC extending into the IVC/heart are rare and occur at a prevalence of 1-4%,<sup>10,23</sup> effective treatment strategies and prognosis for these patients remain unclear.<sup>24,25</sup> A few large-scale clinical studies of patients with HCC extending into the IVC/heart have been published,<sup>8,16</sup> and no research has been done regarding the risk factors and the outcomes for HCC extending into the RA.

In our retrospective study, risk factors/predictive factors for prognosis and treatment outcomes were assessed with

univariate and multivariate analysis.

The current study showed that HCC that extends into the RA is a rare disease (4.96%).

A modified UICC stage greater than IVA, HV invasion, concomitant PV and IVC invasion, and multinodular HCC are risk factors for advanced HCC with RA invasion. A CLIP score  $\leq 3$ , active treatment may prolong survival in patients with HCC extending into RA. To the best of our knowledge, this study is the first to characterize the risk factors and predictive factors for poor prognosis of HCC extending into the RA.

In an autopsy study of 439 HCC cases, Kojiro, et al.<sup>3</sup> found intra-atrial tumor growth in 18 cases. In addition, a continuous tumor thrombus that involved the RA, the IVC, and the HV was observed in 15 cases, and the tumors were observed to cross the tricuspid valve and enter the ventricle in five cases. Consistent with the findings of another studies,<sup>3,20</sup> our study found a prevalence of HCC with RA invasion of 4.96%, and HV and IVC invasion were observed in most cases. IVC invasion was observed in 100% of the HCC cases with RA invasion. In our study, a modified UICC stage greater than IVA, HV invasion, concomitant IVC and PV invasion, and a multinodular tumor type were independent risk factors for HCC that extended into the RA. Therefore, tumor seeding through the venous system may be the most important route for HCC with RA invasion. As for symptoms, 13 patients (39.3%) had aggravated abdominal distension and/or dyspnea, 11 patients (33.3%) had non-specific symptoms (fatigue or poor oral intake), 8 patients (24.2%) had aggravated right upper quadrant pain, and 1 patient (3%) had chest pain. Because right heart failure signs (39.3%) were the dominant symptoms in patients with HCC that extended into the heart, we suggest that heart involvement should be suspected when HCC patients with high risk factors develop right heart failure signs, such as dyspnea, aggravated ascites, and/or lower leg edema.

In agreement with Chern's study, our study found that the median survival time for HCC patients with RA invasion was 123 days (approximately 4.1 months).

In regard with predictive factors for poor prognosis, nei-

**Table 5. Treatment Modalities in the Treated Group**

Variables	n (%)	F/U duration (days)	Child-Pugh score (mean)
Radiation	1 (6.6)	171	7
Sorafenib	1 (6.6)	245	6
TACE	11 (73.3)	136	6.8
Combined modality	2 (13.2)	155	6.5

TACE, transcatheter arterial chemoembolization; F/U, followed up.

ther liver function nor tumor stage are associated with survival. No active treatment and CLIP score >3 are significantly associated with short-term mortality.

As for treatment modalities, the results of earlier studies on surgical resection for the treatment of HCC with a metastatic IVC and RA tumor thrombus are disappointing results, with a mean survival time of approximately 8 months.<sup>26</sup> Recent studies have found that TACE is the most widely used and effective treatment in patients with advanced HCC with IVC/RA invasion, and this treatment has been shown to provide a survival benefit to selected patients.<sup>8,13,20</sup> Oral thalidomide and external beam radiation therapy have also been effective in advanced HCC with IVC/RA tumor thrombi; however, these treatment modalities were evaluated in small scale studies.<sup>14,27</sup> Chun, et al.<sup>16</sup> reported that active treatment, such as radiation, systemic chemotherapy, and TACE beyond supportive care, provided a survival benefit in patients with HCC that extended into the IVC/heart. In consistent with other studies, our study demonstrated that the active treatment such as RT, TACE, and Sorafenib prolong survival of patients with HCC extending into RA. However, it was difficult to evaluate the efficacy of each treatment modality because of the small sample size. To date, no effective therapies have been advanced for the treatment of HCC with IVC and RA tumor thrombi. Therefore, further studies are required to develop treatment strategies for HCC with IVC and RA invasion.

This study had several limitations. First, this was a retrospective, single-center analysis. Second, we did not confirm whether the intra-cardiac masses indicated HCC invasion or a benign cardiac tumor, such as myxoma. However, the incidence of cardiac tumors is low (0.02%), therefore, this might not have greatly influenced the results. Furthermore, the intra-cardiac masses were consistent with HCC according to the radiological findings. Third, we had a small sample size for comparing the poor prognosis factors among the patients with HCC extending to RA invasion.

In conclusion, HCC that extends into the RA is a rare disease (4.96%), and the median survival time of the patients in our study was 123 days.

A modified UICC stage greater than IVA, HV invasion, concomitant PV and IVC invasion, and multinodular HCC are risk factors for advanced HCC with RA invasion. Active treatment beyond supportive care may prolong survival.

However, larger prospective studies are needed to confirm these findings.

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