

# Extrahepatic recurrence of hepatocellular carcinoma after curative hepatic resection

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**Backgrounds/Aims:** This study was designed to compare the recurrence patterns after curative hepatectomy, to compare the prognosis according to the initial site of metastasis, and to investigate the independent predictive factors associated with extrahepatic recurrence in hepatocellular carcinoma (HCC) patients after curative hepatectomy.

**Methods:** From January 2000 to July 2009, 307 patients underwent curative hepatectomies for HCC at our institution; 152 patients showed recurrences. Patients were divided into 2 groups according to their initial recurrence site: the intrahepatic recurrence (IHR) group and extrahepatic recurrence (EHR) group. The IHR group was comprised of 111 patients and the EHR group was comprised of 41 patients. The study investigated the preoperative, intraoperative, and postoperative factors related to the recurrence pattern retrospectively and compared the prognoses of the patients.

**Results:** A five-year survival rate after an initial recurrence was lower in the EHR group (21.5%) than the IHR group (36.3%) ( $p < 0.001$ ). The preoperative alpha-fetoprotein (AFP) level was an independent risk factor for extrahepatic recurrence ( $p = 0.014$ ). **Conclusions:** Patients with a preoperative AFP level greater than 200 ng/ml have a higher incidence of extrahepatic metastases after a curative resection of HCC. Increased level of preoperative AFP is an indication for a short-term follow up hepatectomy. (Korean J Hepatobiliary Pancreat Surg 2012;16:93-97)

**Key Words:** Hepatocellular carcinoma; Hepatectomy; Recurrence

## INTRODUCTION

The five-year survival rate for hepatocellular carcinoma patients following hepatectomy is approximately 50%.<sup>1-3</sup> One of the main causes of such poor prognosis is tumor recurrence.<sup>1,4</sup> The 5-year tumor recurrence rate is up to 80%.<sup>1,4</sup> HCC recurrence after curative hepatectomy often occurs in the liver (64-86.5%), and extrahepatic recurrences are relatively infrequent.<sup>5-7</sup> Extrahepatic recurrences have a worse prognosis, mostly likely from their presentation at multiple sites with aggressive features. Many patients with extrahepatic recurrences are poor candidates for surgical resections. Chemotherapy might be considered the only treatment for systemically advanced HCC, but it is ineffective and requires further investigation.<sup>5,8,9</sup> The objective of our study is to evaluate the patterns and clinicopathologic features of the extrahepatic recurrence of HCC after curative resection, based on data from HCC

patients at the Korea Cancer Center Hospital.

## METHODS

From January 2000 to July 2009, 307 patients underwent curative hepatic resection for HCC at the Korea Cancer Center Hospital, Seoul, Korea. The medical records of all the patients were retrospectively reviewed. Patients with distant metastases or other malignant neoplasms at initial diagnosis were excluded.

Among the 307 patients, 240 (78%) were men and 67 (22%) were women. The mean age was 54.2 years, ranging from 26 to 77 years. The mean follow-up period was 40.9 months, ranging from 2 to 120 months. After curative resection, all the patients were followed every 3 months for 2 years as outpatients until the recurrence or metastasis was found. The complete blood cell count (CBC); liver function tests (LFTs) (including aspartate

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aminotransferase (AST), alanine aminotransferase (ALT), and prothrombin time (PT)); tumor markers, including alpha-fetoprotein (AFP) and protein induced vitamin K absence or antagonist II (PIVKA-II); and abdominal computed tomography (CT) scans were obtained. Patients with elevated tumor marker levels and no evidence of metastasis in an abdominal CT or those who showed suspicious lesions in the lower lungs in an abdominal CT scan underwent a chest CT scan. The follow-up interval was lengthened in the patients who did not show recurrence for first 2 years period, being every 4 to 6 months thereafter. Patients with viral hepatitis or liver cirrhosis had a life-long follow up every 6 months.

During the follow up period, HCC recurrences occurred in 152 patients. One hundred and eleven patients had intrahepatic recurrences (IHR) at the time when the first recurrence was observed, and these patients were defined as the IHR group (n=111). Forty-one patients had extrahepatic recurrences (EHR), with or without additional intrahepatic recurrence, and they were defined as the EHR group (n=41). The clinicopathological characteristics and the clinical outcomes between the IHR group and the EHR group were compared.

The Statistical Package for Social Sciences (SPSS) for Windows Korean version 14.0 was used to perform statistical analyses. The survival rates were calculated using the Kaplan-Meier method. The comparison of categorical variables was performed with chi-square and logistic regression. A *p*-value < .05 was considered statistically significant.

## RESULTS

The five- and 10-year overall survival rates among the

**Table 1.** Sites of extrahepatic recurrence

Site	n
Lung	24
Lymph node	5
Bone	4
Brain	3
Peritoneum	3
Adrenal gland	2
Inferior vena cava	1
Diaphragm	1
Pancreas	1

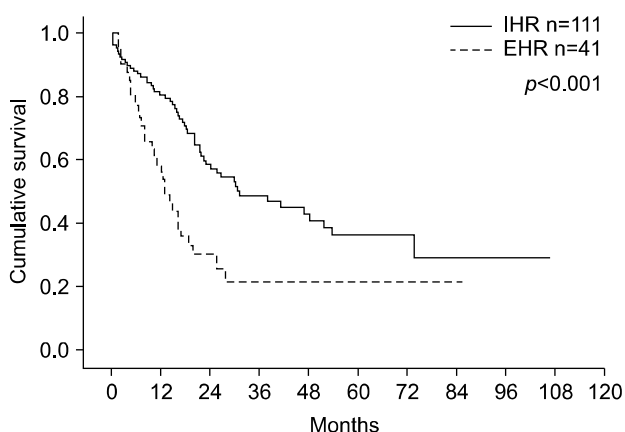
total 307 patients were 65.1% and 55.4%. The five- and 10-year disease-free survival rates were 46.6% and 40.5%.

Among 41 patients with extrahepatic recurrence, 25 had only extrahepatic recurrence and 16 had both intra- and extrahepatic recurrence. The lung was the most frequent site of initial extrahepatic recurrence, in 24 patients, followed by the lymph node and bone (Table 1). The five-year survival rates in the IHR and EHR groups after recurrence were 36.3% and 21.5%, respectively (*p* ≤ 0.001) (Fig. 1).

The clinicopathological and patient characteristics of the IHR group was compared with the EHR group. Factors related to extrahepatic recurrence by univariate analysis were female gender, preoperative ICG R15 < 10%, preoperative AFP level > 200 ng/ml, major anatomical resection, and tumor size > 5 cm. The number of patients with liver cirrhosis was larger in the IHR group. The rate of recurrence at less than 6 months after resection was high in the EHR group (Table 2).

The factors that related to the EHR after univariate analyses were subjected to multivariate analysis. The time to initial recurrence, which also showed significant relation to extrahepatic recurrence, was excluded from evaluation by multivariate analysis. A preoperative AFP > 200 ng/ml was the only independent factor related to extrahepatic recurrence after multivariate analysis (Table 3).

Depending on the site, the character of the recurrence and the patients medial condition, various treatment mo-



**Fig. 1.** Comparison of survival rates between intrahepatic recurrence (IHR) and extrahepatic recurrence (EHR) groups after curative resection of hepatocellular carcinoma. The IHR group shows a better cumulative survival curve than the EHR group. The five-year survival rate of IHR and the EHR groups were 36.3% and 21.5%, respectively.

**Table 2.** A comparison of the clinical characteristics of recurrent hepatocellular carcinoma patients between the intrahepatic recurrence (IHR) and extrahepatic recurrence (HER) groups

Factors	IHR (n=111)	EHR (n=41)	p-value
Sex (male : female)	96 : 15	27 : 14	0.004
Age ( $\leq 60$ years : $> 60$ years)	77 : 34	29 : 12	0.871
Viral hepatitis etiology (NBNC : HBV : HCV : HBV+HCV)	21 : 80 : 7 : 1	6 : 33 : 0 : 2	0.137
Child class (A : B)	106 : 5	40 : 1	0.562
ICG R15 ( $\leq 10\%$ : $> 10\%$ )	55 : 55	29 : 9	0.005
AFP ( $\leq 200$ : $> 200$ )	81 : 30	19 : 22	0.002
Resection type (non-anatomical : anatomical)	47 : 63	4 : 36	$< 0.001$
Resection range (minor resection : major resection)	70 : 41	11 : 29	$< 0.001$
Intraoperative RBC transfusion (no : yes)	76 : 35	30 : 11	0.575
Postoperative complication (no : yes)	57 : 54	25 : 16	0.291
Tumor size ( $\leq 5$ cm : $> 5$ cm)	73 : 38	15 : 26	0.001
Tumor number (single : multiple)	87 : 17	34 : 6	0.843
Edmonson-Steiner histologic grade (1+2 : 3+4)	66 : 34	23 : 14	0.676
Cirrhosis (no : yes)	55 : 56	29 : 12	0.020
Vascular invasion (no : yes)	101 : 10	35 : 6	0.316
Time to initial recurrence ( $\leq 6$ months : $> 6$ months)	34 : 77	20 : 21	0.031

NBNC, non-B non-C infection; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; ICG R-15, indocyanine green retention rate at 15 min; AFP, alpha-fetoprotein; RBC, red blood cells

**Table 3.** Multivariate analysis predicting the extrahepatic recurrence after a hepatectomy

Factor	Odds ratio	p-value	95% CI
Alpha-fetoprotein ( $\leq 200$ vs. $> 200$ )	3.16	0.014	1.26-7.90

CI, confidence interval

dalities were employed for the patients who had an extrahepatic recurrence. Table 4 shows the different management strategies applied for these patients. Although most patients with extrahepatic recurrence, regardless of recurrence site, died within 2 years of the recurrence, we did notice that there were long-term survivors among the patients who had lung metastases with surgical resection. However, because of the small number of patients and the diverse treatment strategies applied, a statistical analysis was not possible.

## DISCUSSION

Due to the increased sensitivity of diagnostic modalities and effective screening strategies, the rate of early detection of HCC has risen, and this has resulted in improved survival rates for HCC patients. Numerous treatment options, including surgical resection, are available to manage HCC. Patients with systemically advanced HCC or with impaired liver function continue to present management challenges, especially with advanced HCC, for

which there is no definitive effective systemic treatment, with the exception of chemotherapy, such as sorafenib, which still requires more evidence regarding its efficacy.<sup>10,11</sup>

The purpose of this study was to identify factors related to EHR, which are known as having a worse prognosis as compared to IHR after curative resection of HCC. Many studies have shown that elevated preoperative AFP levels relate to a poor prognosis. Farinati's large multicenter survey of 1,158 patients with HCC reported that patients with AFP  $> 400$  ng/ml had a poor prognosis.<sup>12</sup> Tangkijvanich et al.<sup>13</sup> also demonstrated that HCC patients with AFP levels  $> 400$  ng/ml showed poor prognoses. In our study, AFP levels  $> 200$  ng/ml was significantly related to extrahepatic recurrence. This suggests that elevated preoperative AFP is a risk factor for extrahepatic recurrence and thus a poorer prognosis. A recent study by Yang et al. identified the presence of circulating hepatocellular cancer stem cells in the peripheral blood of HCC patients.<sup>14</sup> Further study showed that the recurrence rate of HCC after hepatectomy related to the preoperative levels of circulating cancer stem cells. The circulating

**Table 4.** Management of extrahepatic recurrence

Patient No.	Initial recur site	Initial Mx	Follow-up
1	Pancreas	TACE	Dead 19 mos after recur
2	Lung	ChemoTx	Dead 20 mos after recurrence
3	Liver+lung	Conservative Mx	Dead 13 mos after recurrence
4	Brain	ChemoTx	Dead 17 mos after recurrence
5	Lung	Conservative Mx	Dead 7 mos after recurrence
6	Peritoneum	Conservative Mx	Dead 2 mos after recurrence
7	Bone	Conservative Mx	Dead 2 mos after recurrence
8	Liver+lung	ChemoTx	Dead 8 mos after recurrence
9	Lung	OP	Alive for 84 mos
10	Lung	OP	Alive for 48 mos
11	Liver+brain	TACE+RT	Dead 8 mos after recurrence
12	Lung	Conservative Mx	Dead 10 mos after recurrence
13	Peritoneum	ChemoTx	Dead 2 mos after recurrence
14	IVC	TACE	Dead 13 mos after recurrence
15	Lung+lymph node	Conservative Mx	Dead 28 mos after recurrence
16	Liver+lung	Conservative Mx	Dead 6 mos after recurrence
17	Lung	Conservative Mx	Dead 5 mos after recurrence
18	Liver+lymph node	ChemoTx+RT	Dead 13 mos after recurrence
19	Liver+lung+bone	ChemoTx+RT	Dead 5 mos after recurrence
20	Liver+lung	TACE	Dead 15 mos after recurrence
21	Liver+lung	TACE	Dead 14 mos after recurrence
22	Lymph node	ChemoTx	Dead 16 mos after recurrence
23	Liver+lung	OP	Dead 7 mos after recurrence
24	Peritoneum	ChemoTx	Alive for 63 mos
25	Lung	ChemoTx	Dead 30 mos after recurrence
26	Lung+brain	Conservative Mx	Dead 16 mos after recurrence
27	Lung	ChemoTx	Dead 2 mos after recurrence
28	Lung	OP	Alive for 45 mos
29	Liver+adrenal gland	ChemoTx	Dead 4 mos after recurrence
30	Liver+lung	ChemoTx	Dead 7 mos after recurrence
31	Liver+lung	TACE+ChemoTx	Dead 4 mos after recurrence
32	Bone	Conservative Mx	Dead 12 mos after recurrence
33	Liver+lymph node	TACE	Dead 10 mos after recurrence
34	Adrenal gland	OP	Alive for 18 mos
35	Lung	OP	Alive for 29 mos
36	Liver+lung	ChemoTx	Alive for 26 mos
37	Liver+lung	TACE+ChemoTx	Alive for 24 mos
38	Diaphragm	OP+RT	Alive for 23 mos
39	Liver+lymph node	OP+TACE	Alive for 20 mos
40	Lung	OP	Alive for 18 mos
41	Liver+bone	TACE	Alive for 14 mos

Mx, management; TACE, transarterial chemoembolization; ChemoTx, chemotherapy; OP, Operation; IVC, inferior vena cava; RT, radiation therapy

stem cell levels were found to be a strong predictor of extrahepatic recurrence after hepatectomy.<sup>15</sup> We expect future research to reveal the influence of cancer stem cell levels and preoperative AFP levels on extrahepatic recurrence.

The prognosis of recurrent HCC relates strongly to whether the patient is a candidate for local treatment of the lesion. According to a study by Shimada et al., the survival rate was higher in patients with recurrent HCC

who underwent loco-regional treatments (such as hepatectomy, lipiodolization, and percutaneous ethanol injection) than in patients with systemic recurrence who were not eligible for local treatment.<sup>16</sup> Lo et al.<sup>17</sup> reported that even the isolated extrahepatic recurrence of HCC can have an improved survival rate with surgical resection of both primary and metastatic lesions, compared to systemic disease. Our study also had long term survivors among those who had aggressive local treatment for extrahepatic

recurrence. In our institution, we try to apply aggressive surgical treatment to all eligible candidates.

In summary, extrahepatic recurrence occurred in 27.0% of all recurrent patients after curative hepatectomy. Early recurrence (within 6 months) was more frequent in the EHR group. Prognosis was poorer in the EHR group. Among all the other preoperative factors evaluated, AFP was the only predictive factor for extrahepatic recurrence. The most common site of extrahepatic recurrence was the lung.

In conclusion, we suggest careful follow-up of patients at high-risk for extrahepatic recurrence, especially in the early postoperative period, and aggressive management for extrahepatic recurrence. Development of differentiated follow-up strategies can be beneficial for patients with higher risk of extrahepatic recurrence. Further study and long-term follow up are needed to elucidate the effect of these measures on prognosis.

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