

# Clinical features of extrahepatic recurrence after curative hepatectomy for hepatocellular carcinoma: simple parameters predicting extrahepatic recurrence

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## Research Article

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# Abstract

## Background

Extrahepatic recurrence (EHR) after curative hepatectomy for hepatocellular carcinoma (HCC) is associated with a poor prognosis. We investigated the features of EHR and identified its predictive factors.

## Methods

This retrospective study included 398 treatment-naive patients who underwent curative hepatectomy for HCC at two tertiary hospitals. Multivariate analysis via Cox-regression was performed to identify the variables associated with EHR.

## Results

EHR was diagnosed in 94 patients (23.6%) over a median follow-up period of 5.92 years, most commonly in the lungs (42.6%). The 5-/10-year cumulative rates of HCC recurrence and EHR were 63.0%/75.6% and 18.1%/35.0%, respectively. The median time to EHR was 2.06 years. Intrahepatic HCC recurrence was not observed in 38.3% of patients on EHR diagnosis. On multivariate analysis, bile duct invasion, tumor necrosis, sum of tumor size > 7 cm, macrovascular invasion, first recurrence free survival < 1 year, and serum alpha fetoprotein > 400 IU/mL during recurrence were predictive of EHR. Four risk levels and their respective EHR were defined: very low risk, 2-/5-year, 0.7%/14.2%; low risk, 2-/5-year, 6.4%/31.0%; intermediate risk, 2-/5-year, 21.9%/73.1%; and high risk, 2-/3-year, 70.8%/100.0%.

## Conclusion

Our predictive model clarifies the clinical course of EHR and could improve the follow-up strategy to improve outcomes.

## Introduction

Despite recent advances in the diagnosis and treatment of hepatocellular carcinoma (HCC), HCC continues to be associated with poor prognosis, ranking third among cancer-related mortality worldwide [1, 2]. Curative hepatectomy remains the treatment of choice for HCC, especially in settings where liver transplantation is not feasible [3]. However, the long-term prognosis after curative hepatectomy remains unsatisfactory, with the 5-year rate of HCC recurrence ranging between 60% and 70% [4, 5]. Therefore, identifying risk factors of HCC recurrence and standardizing the perioperative management protocol could be important to improve long-term prognosis after curative hepatectomy for HCC.

According to current practice, curative hepatectomy is indicated over other local therapies, such as radiofrequency ablation (RFA), for patients with advanced HCC, having larger size tumors and/or presence of microvascular tumor invasion. The more advanced disease status of patients who undergo curative hepatectomy could explain the comparatively higher risk of HCC recurrence after curative hepatectomy than RFA. Current treatment guidelines recommend surveillance after treatment, with either curative hepatectomy or RFA, including abdominal computed tomography (CT) and measurement of serum alpha fetoprotein (AFP) levels [6, 7]. This recommendation, however, does not consider differences in the risk of recurrence between patients treated using curative hepatectomy and those treated with RFA [8]. Moreover, although intrahepatic recurrence (IHR) is the most common type of recurrence, extra-hepatic recurrence (EHR) is possible, with the most common sites of EHR being the lungs, lymph nodes, and bones, which are difficult to evaluate using conventional abdominal CT imaging[9–11]. Considering the aggressive nature of metastatic hepatic tumors and the limited treatment options for recurrent HCC, the prognosis for patients with EHR is generally worse than that for those with IHR. Despite the dismal prognosis of EHR, few studies showed improved outcomes with metastasectomy in selected patients [12, 13]. Thus, early identification would be important to improve oncological outcomes and survival. However, at present, there is insufficient data on the clinical course and pathological progression after curative hepatectomy for HCC to identify predictive factors of EHR. Accordingly, our aim in this study was to determine the risk factors of EHR among patients who had undergone curative hepatectomy as the initial treatment for HCC and to use these risk factors to construct a simple parametric model to predict EHR.

## Results

### Baseline Characteristics of Enrolled Patients

Among 398 patients, EHR was identified in 94 (23.6%). The 10-year cumulative rate of HCC recurrence was 75.6%, with a rate of 35.0% for EHR (Fig. 1). Compared to those without EHR, those with EHR were younger and had a higher serum alkaline phosphatase level, a lower serum albumin level, absence of fatty change in the liver, and a more advanced HCC stage (Table 1). Serum AFP level at the time of first recurrence of HCC after curative hepatectomy was higher and the time interval to the first recurrence was also significantly shorter in the EHR group.

Table 1  
Baseline characteristics of enrolled patients

	Patients without extrahepatic recurrence (n = 304)	Patients with extrahepatic recurrence (n = 94)	p-value
Age (years)	59.11 ± 10.02	56.01 ± 10.45	<b>0.010</b>
Male (n, %)	259 (85.2)	85 (90.4)	0.196
Aetiology of liver cirrhosis, n (%)	176 (63.1) / 21 (7.5)	56 (65.9) / 6 (7.1)	0.897
HBV / HCV	24 (8.6) / 17 (6.1)	10 (11.8) / 4 (4.7)	
Alcohol / Combined	1 (0.4) / 40(14.4)	0 (0.0) / 9 (10.6)	
NASH / Unknown			
ALP (U/L)	86.88 ± 28.21	99.25 ± 49.72	<b>0.023</b>
Albumin (mg/dL)	4.35 ± 0.48	4.13 ± 0.45	<b>&lt; 0.001</b>
ALBI grade ≥ 2, n (%)	47 (15.5)	23 (24.7)	0.041
ICG R15	10.33 ± 7.62	10.99 ± 8.08	0.496
Serum AFP (IU/mL)	1 238.91 ± 5 186.36	2 009.83 ± 7 844.33	0.277
PIVKA-II (mAU/mL)	1 254.27 ± 2 969.15	788.25 ± 1 491.46	0.610
Tumor size	4.18 ± 2.41	5.16 ± 3.69	<b>&lt; 0.001</b>
Tumor numbers	1.26 ± 0.83	1.32 ± 0.79	0.525
BCLC stage, n (%)	34 (11.2) / 234 (77.2) / 35 (11.6)	6 (6.4) / 68 (72.3) / 20 (21.3)	<b>0.045</b>
0 / A / ≥B			
Pathological mUICC stage, n (%)	43 (14.5) / 183 (61.6) / 71 (23.9)	7 (8.0) / 49 (56.3) / 31 (35.6)	<b>0.012</b>
I / II / ≥III			
Radiological mUICC stage, n (%)	48 (15.8) / 205 (67.7) / 50 (16.5)	10 (10.6) / 59 (62.8) / 212 (26.6)	<b>0.001</b>
I / II / ≥III			
Beyond Milan criteria, n (%)	75 (24.8)	45 (47.9)	<b>&lt; 0.001</b>

Values are presented as mean ± SD. SD, standard deviation; HBV, hepatitis B virus; HCV, hepatitis C virus; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; BCLC, Barcelona Clinic Liver Cancer; mUICC, modified Union for International Cancer Control

	Patients without extrahepatic recurrence (n = 304)	Patients with extrahepatic recurrence (n = 94)	p-value
Metastatic lymph nodes, n (%)	0 (0.0)	2 (2.1)	0.011
Macrovascular invasion, n (%)	6 (2.0)	8 (8.5)	0.003
mUICC T stage at 1st recurrence, n (%)	0 (0.0) / 81 (45.8)	6 (6.5) / 19 (20.7)	< 0.001
0 / 1	67 (37.9) / 25 (14.1)	32 (34.8) / 22 (23.9)	
2 / 3	4 (2.3)	13 (14.1)	
4			
Serum AFP at 1st recurrence	209.12 ± 1 098.83	1 225.05 ± 5 775.70	0.045
Hospital stay, days (median, range)	13 (5–69)	13 (4–60)	0.015
Time to first recurrence, months (median, range)	42.54 (0.16-157.91)	10.14 (0.23-100.34)	< 0.001
Follow-up duration, months (median, range)	75.21 (2-177)	38.93 (3-150)	0.857
Values are presented as mean ± SD. SD, standard deviation; HBV, hepatitis B virus; HCV, hepatitis C virus; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; BCLC, Barcelona Clinic Liver Cancer; mUICC, modified Union for International Cancer Control			

## Clinical Features of Patients with EHR

The most common site of the first HCC recurrence in the EHR group was intrahepatic (66.0%), with the most common initial site of EHR being the lungs (42.6%), followed by the lymph nodes (19.1%), peritoneum (18.1%), and bone (14.9%) (Supplementary Table S1). In half of the cases, EHR was confined to the abdominal cavity, identified by abdominal imaging, while in the other 48.9% of cases, EHRs were identified within the thoracic cavity, including the lungs and the bony structures of the thoracic spine. The median time to EHR was 2.06 years. At the time of EHR diagnosis, 36 patients (38.3%) had no IHR. At the time of first HCC recurrence, EHR was identified in 32 patients (34.0%).

## Comparison of Surgical Findings Between Patients With and Without EHR

Microvascular and serosal invasion were more prevalent among patients with EHR than in those without (16.9 *versus* 29.8% and 2.1 *versus* 6.5%, respectively) (Table 2). Moreover, the presence of satellite nodules and tumor necrosis in resected specimens was more prominent in patients with EHR than in those without (13.0 *versus* 31.2% and 46.9 *versus* 68.8%, respectively).

Table 2  
Comparison of surgical findings in patient groups with and without extrahepatic recurrence

	<b>Patients without extrahepatic recurrence (n = 304)</b>	<b>Patients with extrahepatic recurrence (n = 94)</b>	<b>p- value</b>
Margin involvement, n (%)	9 (3.0)	6 (6.5%)	0.134
Microvascular invasion, n (%)	51 (16.9)	28 (29.8)	<b>0.006</b>
Serosal invasion, n (%)	6 (2.1)	6 (6.5)	<b>0.034</b>
Bile duct invasion, n (%)	1 (0.3)	2 (2.25)	0.085
Capsule formation, n (%)	211 (73.3)	64 (68.8)	0.405
Multicentricity, n (%)	34 (11.7)	9 (9.7)	0.593
Satellite nodule, n (%)	38 (13.0)	29 (31.2)	<b>&lt; 0.001</b>
Underlying liver cirrhosis, n (%)	201 (66.1)	61 (64.9)	0.827
Intrahepatic metastasis, n (%)	3 (1.0)	2 (2.1)	0.830
Necrosis, n (%)	136 (46.9)	64 (68.8)	<b>&lt; 0.001</b>
Haemorrhage, n (%)	139 (47.9)	53 (57.0)	0.121
Fatty change, n (%)	109 (38.0)	29 (31.9)	0.291
Cell type, n (%)	53 (17.5)	22 (23.4)	0.213
Clear type	271 (89.4)	89 (94.6)	
Hepatic type	240 (79.2)	70 (74.5)	
Classic type			
Major Edmondson Steiner grade, n (%)	14 (4.8) / 152 (52.2)	4 (4.3) / 39 (41.9)	0.336
1 / 2	116 (39.9) / 9 (3.1)	46 (49.5) / 4 (4.3)	
3 / 4			
Worst Edmondson Steiner grade, n (%)	2 (0.7) / 46 (15.8)	2 (2.2) / 14 (15.1)	0.665
1 / 2	178 (61.2) / 65 (22.3)	55 (59.1) / 22 (23.7)	
3 / 4			



# Comparison of Characteristics Between Patients with Early and Non-early EHR

Both the radiologic and pathologic mUICC stages were more advanced in the early EHR than in the non-early EHR group (Supplementary Table S2). The early EHR group also had a markedly shorter RFS and shorter time interval to EHR development (Fig. 2). Moreover, the proportion of tumors with an mUICC stage  $\geq$  III at the time of first recurrence was larger in the early EHR than in the non-early EHR group. Of note, in 54.8% of patients in the early EHR group, EHR was the first presenting recurrence after curative hepatectomy.

## Analysis of Factors Associated with EHR

In the multivariate analysis, the following factors were retained as independent predictors of EHR: bile duct invasion identified on pathological assessment of resected specimens [odds ratio (OR): 8.639,  $p = 0.003$ ]; macrovascular invasion on imaging studies (OR: 3.097,  $p = 0.007$ ); first recurrence free survival  $< 1$  year (OR: 3.050,  $p < 0.001$ ); serum AFP  $> 400$  IU/mL at the time of the first recurrence (OR: 2.409,  $p = 0.001$ ); sum of tumor size  $> 7$  cm (OR: 1.986,  $p = 0.013$ ); and tumor necrosis on pathological assessment of resected specimens (OR: 1.940,  $p < 0.011$ ) (Table 3). Regarding factors associated with early EHR, serum alkaline phosphatase (ALP)  $> 120$  U/L, a pathological mUICC stage III or IVa, surgical margin involvement, absence of fatty change in the liver, and macrovascular invasion were found to be closely associated on multivariate analysis (Table 4).

Table 3  
Univariate and multivariate analyses of factors associated with extrahepatic metastasis

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> - value	HR (95% CI)	<i>p</i> - value
Serum albumin < 3.7 mg/dL	2.930 (1.698–5.057)	< 0.001		
Serum alkaline phosphatase > 130 U/L	2.800 (1.222–6.416)	0.015		
ALBI grade ≥ 2	1.889 (1.175–3.036)	0.009		
Pathologic mUICC stage (III, IVa)	2.398 (1.586–3.626)	< 0.001		
Multiple tumors <sup>1</sup>	1.980 (1.183–3.313)	0.009		
Major Edmondson Steiner grade ≥ 3	1.529 (1.016–2.299)	0.042		
Surgical margin involvement	2.749 (1.200–6.298)	0.017		
Venous / Lymphatic involvement	2.043 (1.312–3.180)	0.002		
Serosa invasion	3.167 (1.380–7.271)	0.007		
Bile duct invasion	5.720 (1.401–23.350)	0.015	<b>8.639 (2.046–36.485)</b>	<b>0.003</b>
Satellite nodule	2.632 (1.694–4.090)	< 0.001		
Tumor necrosis	2.333 (1.504–3.620)	< 0.001	<b>1.940 (1.166–3.230)</b>	<b>0.011</b>
Sum of tumor size > 7 cm	3.792 (2.394–6.004)	< 0.001	<b>1.986 (1.152–3.422)</b>	<b>0.013</b>
Beyond Milan criteria	2.832 (1.881–4.263)	< 0.001		

HR, hazards ratio; CI, confidence interval; mUICC, modified Union for International Cancer Control; CT, computed tomography; MRI, magnetic resonance imaging; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein

1, number of tumors examined at pathologic findings.

	Univariate analysis		Multivariate analysis	
Macrovascular invasion	4.005 (1.934–8.295)	< 0.001	3.097 (1.359–7.056)	0.007
BCLC stage C	2.271 (1.382–3.731)	0.001		
1st recurrence free survival < 1 year	5.748 (3.787–8.722)	< 0.001	3.050 (1.887–4.929)	< 0.001
Serum AFP > 400 IU/mL at 1st recurrence	3.127 (1.935–5.057)	< 0.001	2.409 (1.421–4.084)	0.001
HR, hazards ratio; CI, confidence interval; mUICC, modified Union for International Cancer Control; CT, computed tomography; MRI, magnetic resonance imaging; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein				
1, number of tumors examined at pathologic findings.				

Table 4  
Univariate and multivariate analyses of factors associated with early extrahepatic recurrence

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> - value	HR (95% CI)	<i>p</i> - value
Serum ALP > 120 U/L	2.790 (1.279–6.084)	0.010	2.362 (1.018–5.478)	0.045
Pathologic mUICC stage (III, IVa)	3.418 (1.634–7.151)	0.001	2.610 (1.154–5.901)	0.021
Worst Edmonson Steiner grade ≥ 4	2.221 (1.063–4.643)	0.034		
Surgical margin involvement	2.991 (1.043–8.576)	0.041	4.035 (1.280–12.725)	0.017
Venous / Lymphatic involvement	1.890 (0.925–3.860)	0.081		
Absence of fatty change	3.582 (1.249–10.276)	0.018	3.246 (1.114–9.461)	0.031
Sum of tumor size > 7 cm	2.142 (1.055–4.347)	0.035		
Macrovascular invasion	3.818 (1.559–9.351)	0.003	3.207 (1.169–8.799)	0.024
HR, hazards ratio; CI, confidence interval; ALP, alkaline phosphatase; mUICC, modified Union for International Cancer Control; AFP, alpha-fetoprotein				

## Prediction of EHR

Based on our multivariate analyses, the following six variables were used to build a parametric model to predict EHR. The risk of EHR was then stratified into four levels based on the number of predictive factors present, as follows: very low risk, no risk factors; low risk, 1 risk factor; intermediate, 2–3 risk factors; and high,  $\geq 4$  risk factors. The cumulative rate of EHR was then calculated using the Kaplan-Meier survival curve analysis for each risk level (Fig. 3). The 1-, 2-, 5-, and 10- year cumulative rates of EHR were significantly related to the numbers of risk factors present: very low risk – 0.7%, 0.7%, 4.8%, and 14.2%, respectively; low risk – 2%, 6.4%, 11.2%, and 31.0%, respectively; intermediate risk – 21.9%, 34.2%, 50.5%, and 73.1%, respectively; and high risk – 70.8% (1 year) and 100% after 3 years. The median time to development of EHR was 161.9 months for the very-low risk level, 127.1 months for the intermediate risk level, and 12.0 months for the high-risk level.

## Discussion

Based on the results of a large series of patients who underwent curative hepatectomy for HCC, we proposed a simple parametric model predicting the risk of EHR development. This model is straightforward and easy-to-use, consists of six easy-to-obtain variables that constitute not only the essentials of pre- and post-operative clinical parameters, but also the postoperative pathologic findings. Due to the lack of consensus on follow-up strategies for the detection of EHR after resection, our prediction models may aid in monitoring patients for individual risk and in appropriately assigning patients for participation in clinical trials for postoperative adjuvant therapy (e.g., patients would be categorized as intermediate or high risk, if they present with a predicted 5-year EHR rate as 50.5% or 100%, respectively).

Recent studies reported improved prognosis for recurrent HCC based on the pattern of IHR [5, 18]. However, these studies did not clarify the clinical features and pathological course of EHR, with the absence of models to predict EHR after curative treatment for HCC, limiting the early detection of EHR. In our study, we identified the risk factors of EHR after curative hepatectomy for HCC and used these factors to stratify the risk for EHR into four levels. Our findings highlight the necessity for a predictive score based on risk stratification to inform optimal surveillance for prompt detection of EHR to improve patient outcomes.

Current results of HCC recurrence and EHR development rates suggest some distinction from our previous study of HCC patients who underwent RFA [19]. In that study, the median time to first HCC recurrence and EHR after RFA was 1.75 years and 2.68 years, respectively, with 1-, 3-, 5-, 8-, and 10-year rates of EHR development of 1.0%, 2.9%, 8.1%, 15.7%, and 33.7%, respectively. These rates were comparably lower than those we now report after curative hepatectomy.

With regard to the pattern of HCC recurrence, the most common initial site of recurrence was within the intra-hepatic area, which was consistent with a previous report [20]. Another study identified IHR as being the most common initial site of recurrence, with EHR developing after several treatments for IHR [21]. Uchino et al. reported that 82.2% of HCC patients with EHR presented with IHR, a finding comparable to

those of our previous study [19]. Therefore, multiple IHRs can be an indication of EHR risk in patients with HCC [22].

In our study cohort, the lungs were the most common site of EHR (42.6%). Thoracic metastases, which included the lungs and the vertebrae of the thoracic spine, were thus, relatively common as previously reported [23]. Thoracic metastases reflect a systemic involvement with poor prognosis as they are largely not curable. Of further concern is the fact that thoracic metastases may not be detected using conventional surveillance methods that rely on abdominal imaging. Therefore, the use of chest CT images should be included in the surveillance strategy for patients at risk for EHR after curative hepatectomy for HCC for the early detection of thoracic metastases. In addition, the rate of EHR at the time of the initial recurrence of HCC after hepatectomy was 34%, with 38.3% of these patients having no sign of IHR at the time of EHR diagnosis. Therefore, even if intra-hepatic HCC lesions are stable, close surveillance for possible development of EHR may be necessary.

Regarding the risk factors for EHR, bile duct invasion, necrotic HCC, large tumor size (sum > 7 cm), macrovascular invasion, first RFS < 12 months, and AFP level > 400 IU/mL at the time of first recurrence were associated with EHR after curative hepatectomy. Vascular invasion is a well-known prognostic indicator of HCC. Natsuizaka et al. showed that vascular invasion was more frequently observed in patients with EHR at the first diagnosis of HCC [1]. Senthilnathan et al. also reported a two-fold increase in EHR in the presence of portal vein invasion than without portal vein invasion (24% *versus* 12%) [24]. Yang et al. reported that EHR was more common among patients with vascular invasion, intrahepatic metastasis, and more advanced HCC stages [11]. However, whether bile duct invasion of HCC has a significant impact on its prognosis remains an issue of controversy. Two previous studies did not show any significant difference in the prognosis of patients with bile duct invasion after curative surgery than those without [25, 26]. However, Ikenaga et al. reported that the median survival of HCC patients with bile duct invasion after surgery was significantly shorter than that of patients without bile duct invasion (11.4 *versus* 56.1 months,  $p = 0.002$ ) [27]. Moreover, Shao et al. reported that HCC patients with bile duct invasion developed early recurrence (< 1 year) after resection more frequently (recurrence rate, 70.3%) than those without bile duct invasion [28]. Our findings were consistent with those of these latter studies, with bile duct invasion being significantly associated with EHR after curative hepatectomy.

A recent study revealed that the presence of tumor necrosis is associated with an advanced tumor stage, HCC recurrence, and patient survival after curative hepatectomy for HCC [29]. In agreement with these findings, we also identified necrotic HCC to be associated with a high rate of EHR. HCC tumors > 6 cm in size were also predictive of EHR after curative resection for HCC [30], with the predictive cut-off in our study being close at > 7 cm. Similarly, our finding of a significant association between first recurrence free survival of < 12 months and EHR was consistent with the report by Kim et al. that reported EHR to develop more frequently among patients with early HCC recurrence [31]. They suggested that aggressive tumor pathology was, therefore, a risk factor of early HCC recurrence.

Recent studies have shown high AFP level to be an independent risk factor of HCC invasiveness [32–36]. However, only one previous study has reported an association between AFP level and EHR after curative HCC treatment [37]. In relation to the same, our previous study on RFA in EHR for HCC demonstrated an association between AFP levels and HCC recurrence when the AFP level was > 400 IU/mL. Similarly, this study also identified a serum AFP level > 400 IU/mL at the time of first recurrence to be predictive of high risk (OR: 2.409, 95% CI: 1.421–4.084). We stratified the risk for EHR into four levels based on the number of predictive factors present for EHR. We demonstrate that the cumulative rates of EHR and the median time to EHR correlated with these four risk levels. Therefore, our novel parametric model, albeit simple, could assist clinicians in identifying patients at high risk for EHR before surgery.

We identified involvement of the margin of resection as a significant risk factor of early EHR (OR: 4.035, 95% CI: 1.28-12.725), which is consistent with a previous study [38]. The frequency of diffuse steatosis in early HCCs peaks at a diameter of about 1.5 cm, decreasing as a function of increasing tumor size and grade [39]. Thus, diffuse fatty change is uncommon in HCCs > 3 cm and with progressing HCC disease status, and is also not usually observed in patients with poorly differentiated HCC [39, 40]. Therefore, the absence of fatty change in the liver with HCC is associated with the tumor aggressiveness. In our study, the proportion of patients with the absence of fatty change in the liver was higher for the early EHR than for the non-early EHR group.

We finally note that 54.8% in the early EHR group exhibited EHR at the time of first recurrence. This underlines the importance of identifying patients who are at high risk for early EHR, which may inform on the best strategy for surveillance after surgery for the rapid identification of EHR development.

The limitations of our study should be noted in the interpretation of results. First, the diagnosis of EHR was mostly based on medical imaging and, thus, the possibility of other primary cancers from an origin other than the liver could not be completely ruled out. However, in circumstances when the origin of the tumor was not certain, pathologic confirmation was performed at the discretion of the treating physician. Secondly, this was a retrospective study based on medical records from patients enrolled from two tertiary hospitals. Therefore, the effect of bias on results cannot be denied. Third, there was no uniform post-treatment or surveillance schedule, and the surveillance modality used for each patient was at the discretion of the treating physician. Moreover, patients underwent different treatment modalities for local HCC recurrence depending on the tumor and patient status. There may be diverse conditions in terms of tumor stage, liver reserve function, and patients' physical performance status. However, we tried to overcome these limitations by using a considerable number of patients with a long-term follow-up duration in multiple tertiary centers. There is a need to conduct a well-organized prospective study to validate more effective methods of EHR prediction and management.

In conclusion, we present a simple parametric model to predict EHR after curative hepatectomy for HCC. This tailored approach may be useful for the early detection of EHR and permit a more refined estimation of risk on an individual basis.

## Methods

### Patients

Between January 2004 and December 2013, 493 consecutive patients who underwent surgical resection for HCC at two tertiary hospitals were evaluated for study enrolment. The inclusion criteria were age  $\geq 18$  years and a diagnosis of HCC. Patients with hepatic tumors other than HCC were excluded. After screening, 398 patients were enrolled (Supplementary Fig. S1). Baseline clinical and tumor characteristics, resection method, pathological findings, status of recurrence, and recurrence free survival (RFS) were assessed retrospectively.

### Statement of Ethics

The design of our cohort study was approved by the Institutional Review Board of Chonnam National University Hospital (IRB No. CNUH-2019-203). Owing to the retrospective design of our study and the use of de-identified data, the requirement for informed consent was waived. The study was performed in compliance with the Helsinki Declaration of 1975.

### Data Collection

The following information was extracted from patients' medical records for analysis: age, sex, underlying diseases (including hepatitis infection status and alcohol use), blood chemistry [including the Child-Pugh score and model for end stage liver disease (MELD) score], serum AFP level, pathological findings (tumor size, histological grade, micro-vascular invasion, and presence of satellite lesions), and abdominal imaging for tumor staging at the time of HCC diagnosis. Data on blood chemistry, serum tumor markers, and abdominal imaging obtained at each follow-up visit were also obtained for analysis. Measured data at the time of first recurrence were also evaluated.

### Baseline HCC Staging and Follow-up

HCC was diagnosed according to the guidelines of the Korean Liver Cancer Study Group and the National Cancer Center [14]. HCC staging at the time of diagnosis was determined using the modified Union for International Cancer Control (mUICC) staging system [15] and the Barcelona Clinic Liver Cancer (BCLC) classification system [16]. Abdominal CT or magnetic resonance (MR) imaging (MRI) and assessment of serological tumor markers were routinely performed at 1 month after surgical resection and at each 3-6-month follow-up visit.

Tumor size was measured by radiologic modalities, with CT or MRI. The histological differentiation of HCC was graded according to the criteria of Edmondson and Steiner [17]. The presence of macrovascular invasion was detected on CT imaging or MRI, while microvascular invasion was defined as invasion of vascular structures on microscopic analysis of resected tumor specimens. Bile duct invasion and tumor necrosis were confirmed from pathological findings of resected tumor specimens.

### Diagnosis of EHR

Most cases of EHR were diagnosed during routine follow-up studies, with few cases diagnosed during evaluation of new onset symptoms or based on significant elevation in AFP or serial AFP without definite intra-hepatic lesions. The diagnosis of EHR was confirmed by contrast-enhanced CT imaging or MRI, as well as by pathological examination in some patients. In addition, bone scintigraphy, positron emission tomography (PET)-CT, and brain MR or CT imaging were also performed at the discretion of the treating physician. Chest radiographs were obtained routinely at the time of admission, as well as when pulmonary symptoms were present. Early EHR was defined as EHR developing within the first year after initial curative hepatectomy.

## Statistical Analysis

The data were expressed as mean  $\pm$  standard deviation or median and range, as appropriate for the data type and distribution. Univariate analyses were performed using chi-squared test or student's *t*-test, as appropriate. Variables with a *p*-value  $\leq 0.05$  on univariate analyses were included in a multivariate logistic regression analysis to identify factors predictive of EHR. The multivariable Cox regression model was built using stepwise backward selection of variables, with variables having a *p*-value  $\leq 0.05$  retained as predictive factors. Risk levels of EHR were defined based on the number of risk factors present, with Kaplan-Meier survival curves constructed for each risk level. The median RFS rates at 1 and 2 years were calculated for each risk level.

All statistical analyses were performed using SPSS software (version 25.0, IBM Corp., Armonk, NY, USA).

## Declarations

Acknowledgments: Data available on request

Author contributions:

J.H.Y and C.H.J wrote the manuscript. S.K.C. and C.H.J designed the concept of the study. W.J.L, S.M.K, K.T.K, H.J.K, Y.S.K, and H.Y.K. analyzed data. J.H.Y interpreted the data and S.K.C, S.B.C, C.H.J supervised the project.

Competing interests: The author(s) declare no competing interests.

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## Tables

**Table 1. Baseline characteristics of enrolled patients**

	Patients without extrahepatic recurrence (n=304)	Patients with extrahepatic recurrence (n=94)	p-value
Age (years)	59.11 ± 10.02	56.01 ± 10.45	<b>0.010</b>
Male (n, %)	259 (85.2)	85 (90.4)	0.196
Aetiology of liver cirrhosis, n (%)	176 (63.1) / 21 (7.5)	56 (65.9) / 6 (7.1)	0.897
HBV / HCV	24 (8.6) / 17 (6.1)	10 (11.8) / 4 (4.7)	
Alcohol / Combined NASH / Unknown	1 (0.4) / 40(14.4)	0 (0.0) / 9 (10.6)	
ALP (U/L)	86.88 ± 28.21	99.25 ± 49.72	<b>0.023</b>
Albumin (mg/dL)	4.35 ± 0.48	4.13 ± 0.45	<b>&lt;0.001</b>
ALBI grade ≥ 2, n (%)	47 (15.5)	23 (24.7)	0.041
ICG R15	10.33 ± 7.62	10.99 ± 8.08	0.496
Serum AFP (IU/mL)	1 238.91 ± 5 186.36	2 009.83 ± 7 844.33	0.277
PIVKA-II (mAU/mL)	1 254.27 ± 2 969.15	788.25 ± 1 491.46	0.610
Tumor size	4.18 ± 2.41	5.16 ± 3.69	<b>&lt;</b> <b>0.001</b>
Tumor numbers	1.26 ± 0.83	1.32 ± 0.79	0.525
BCLC stage, n (%)			<b>0.045</b>
0 / A / ≥B	34 (11.2) / 234 (77.2) / 35 (11.6)	6 (6.4) / 68 (72.3) / 20 (21.3)	
Pathological mUICC stage, n (%)	43 (14.5) / 183 (61.6) / 71 (23.9)	7 (8.0) / 49 (56.3) / 31 (35.6)	<b>0.012</b>
I / II / ≥III			
Radiological mUICC stage, n (%)	48 (15.8) / 205 (67.7) / 50 (16.5)	10 (10.6) / 59 (62.8) / 212 (26.6)	<b>0.001</b>
I / II / ≥III			
Beyond Milan criteria, n (%)	75 (24.8)	45 (47.9)	<b>&lt;</b> <b>0.001</b>
Metastatic lymph nodes, n (%)	0 (0.0)	2 (2.1)	<b>0.011</b>
Macrovascular invasion, n (%)	6 (2.0)	8 (8.5)	<b>0.003</b>
mUICC T stage at 1 <sup>st</sup> recurrence, n (%)	0 (0.0) / 81 (45.8)	6 (6.5) / 19 (20.7)	<b>&lt;0.001</b>
0 / 1	67 (37.9) / 25 (14.1)	32 (34.8) / 22 (23.9)	
2 / 3	4 (2.3)	13 (14.1)	
4			
Serum AFP at 1 <sup>st</sup>	209.12 ± 1 098.83	1 225.05 ± 5 775.70	<b>0.045</b>

recurrence			
Hospital stay, days (median, range)	13 (5-69)	13 (4-60)	<b>0.015</b>
Time to first recurrence, months (median, range)	42.54 (0.16-157.91)	10.14 (0.23-100.34)	<b>&lt;0.001</b>
Follow-up duration, months (median, range)	75.21 (2-177)	38.93 (3-150)	<b>0.857</b>

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Values are presented as mean  $\pm$  SD. SD, standard deviation; HBV, hepatitis B virus; HCV, hepatitis C virus; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; BCLC, Barcelona Clinic Liver Cancer; mUICC, modified Union for International Cancer Control

**Table 2. Comparison of surgical findings in patient groups with and without extrahepatic recurrence**

	Patients without extrahepatic recurrence (n=304)	Patients with extrahepatic recurrence (n=94)	p-value
Margin involvement, n (%)	9 (3.0)	6 (6.5%)	0.134
Microvascular invasion, n (%)	51 (16.9)	28 (29.8)	<b>0.006</b>
Serosal invasion, n (%)	6 (2.1)	6 (6.5)	<b>0.034</b>
Bile duct invasion, n (%)	1 (0.3)	2 (2.25)	0.085
Capsule formation, n (%)	211 (73.3)	64 (68.8)	0.405
Multicentricity, n (%)	34 (11.7)	9 (9.7)	0.593
Satellite nodule, n (%)	38 (13.0)	29 (31.2)	<b>&lt;0.001</b>
Underlying liver cirrhosis, n (%)	201 (66.1)	61 (64.9)	0.827
Intrahepatic metastasis, n (%)	3 (1.0)	2 (2.1)	0.830
Necrosis, n (%)	136 (46.9)	64 (68.8)	<b>&lt;0.001</b>
Haemorrhage, n (%)	139 (47.9)	53 (57.0)	0.121
Fatty change, n (%)	109 (38.0)	29 (31.9)	0.291
Cell type, n (%)			0.213
Clear type	53 (17.5)	22 (23.4)	
Hepatic type	271 (89.4)	89 (94.6)	
Classic type	240 (79.2)	70 (74.5)	
Major Edmondson Steiner grade, n (%)			0.336
1 / 2	14 (4.8) / 152 (52.2)	4 (4.3) / 39 (41.9)	
3 / 4	116 (39.9) / 9 (3.1)	46 (49.5) / 4 (4.3)	
Worst Edmondson Steiner grade, n (%)			0.665
1 / 2	2 (0.7) / 46 (15.8)	2 (2.2) / 14 (15.1)	
3 / 4	178 (61.2) / 65 (22.3)	55 (59.1) / 22 (23.7)	

**Table 3. Univariate and multivariate analyses of factors associated with extrahepatic metastasis**

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Serum albumin < 3.7 mg/dL	2.930 (1.698-5.057)	<0.001		
Serum alkaline phosphatase >130 U/L	2.800 (1.222-6.416)	0.015		
ALBI grade ≥ 2	1.889 (1.175-3.036)	0.009		
Pathologic mUICC stage (III, IVa)	2.398 (1.586-3.626)	<0.001		
Multiple tumors <sup>1</sup>	1.980 (1.183-3.313)	0.009		
Major Edmondson Steiner grade ≥3	1.529 (1.016-2.299)	0.042		
Surgical margin involvement	2.749 (1.200-6.298)	0.017		
Venous / Lymphatic involvement	2.043 (1.312-3.180)	0.002		
Serosa invasion	3.167 (1.380-7.271)	0.007		
Bile duct invasion	5.720 (1.401-23.350)	0.015	<b>8.639 (2.046-36.485)</b>	<b>0.003</b>
Satellite nodule	2.632 (1.694-4.090)	<0.001		
Tumor necrosis	2.333 (1.504-3.620)	<0.001	<b>1.940 (1.166-3.230)</b>	<b>0.011</b>
Sum of tumor size > 7 cm	3.792 (2.394-6.004)	<0.001	<b>1.986 (1.152-3.422)</b>	<b>0.013</b>
Beyond Milan criteria	2.832 (1.881-4.263)	<0.001		
Macrovascular invasion	4.005 (1.934-8.295)	<0.001	<b>3.097 (1.359-7.056)</b>	<b>0.007</b>
BCLC stage C	2.271 (1.382-3.731)	0.001		
1 <sup>st</sup> recurrence free survival < 1 year	5.748 (3.787-8.722)	<0.001	<b>3.050 (1.887-4.929)</b>	<b>&lt;0.001</b>
Serum AFP > 400 IU/mL at 1 <sup>st</sup> recurrence	3.127 (1.935-5.057)	<0.001	<b>2.409 (1.421-4.084)</b>	<b>0.001</b>

HR, hazards ratio; CI, confidence interval; mUICC, modified Union for International Cancer Control; CT, computed tomography; MRI, magnetic resonance imaging; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein  
1, number of tumors examined at pathologic findings.

**Table 4. Univariate and multivariate analyses of factors associated with early extrahepatic recurrence**

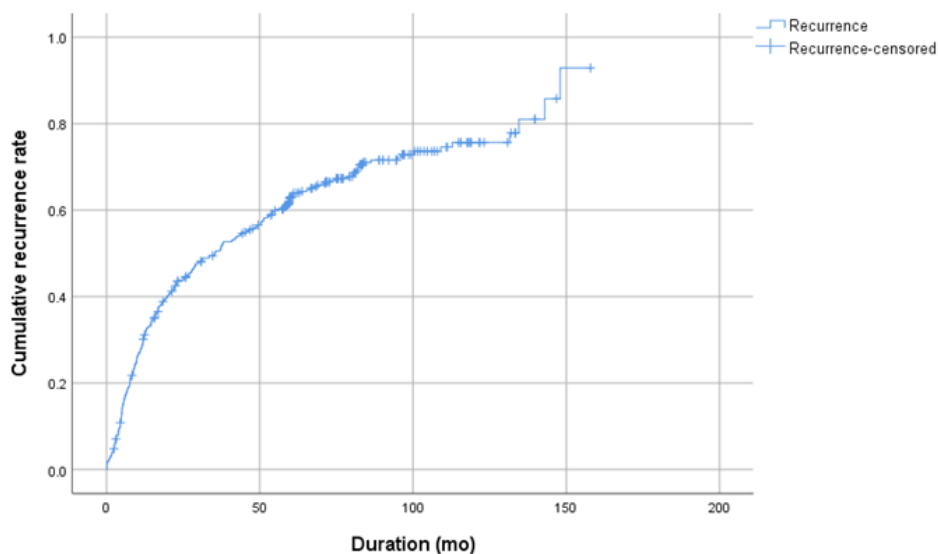
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> - value	HR (95% CI)	<i>p</i> - value
Serum ALP > 120 U/L	2.790 (1.279-6.084)	0.010	<b>2.362 (1.018-5.478)</b>	<b>0.045</b>
Pathologic mUICC stage (III, IVa)	3.418 (1.634-7.151)	0.001	<b>2.610 (1.154-5.901)</b>	<b>0.021</b>
Worst Edmonson Steiner grade ≥4	2.221 (1.063-4.643)	0.034		
Surgical margin involvement	2.991 (1.043-8.576)	0.041	<b>4.035 (1.280-12.725)</b>	<b>0.017</b>
Venous / Lymphatic involvement	1.890 (0.925-3.860)	0.081		
Absence of fatty change	3.582 (1.249-10.276)	0.018	<b>3.246 (1.114-9.461)</b>	<b>0.031</b>
Sum of tumor size > 7 cm	2.142 (1.055-4.347)	0.035		
Macrovascular invasion	3.818 (1.559-9.351)	0.003	<b>3.207 (1.169-8.799)</b>	<b>0.024</b>

HR, hazards ratio; CI, confidence interval; ALP, alkaline phosphatase; mUICC, modified Union for International Cancer Control; AFP, alpha-fetoprotein

## Figures

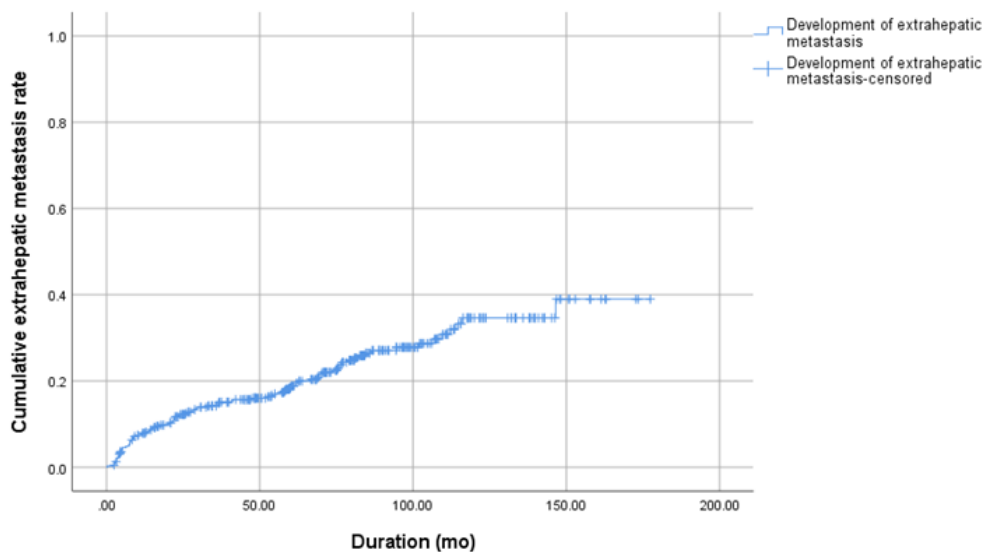


A.



Patients at risk	Total	1yr	3yr	5yr	7yr	10yr	12yr
Recurrence	0/398	120	197	241	261	267	270

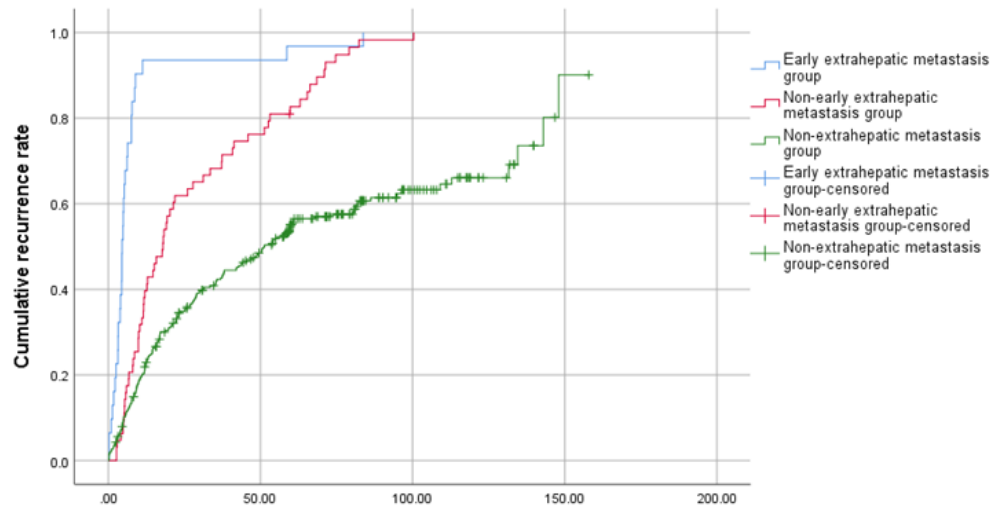
B.



Patients at risk	Total	1yr	3yr	5yr	7yr	10yr	12yr
EHM	0/398	15	46	55	73	92	93

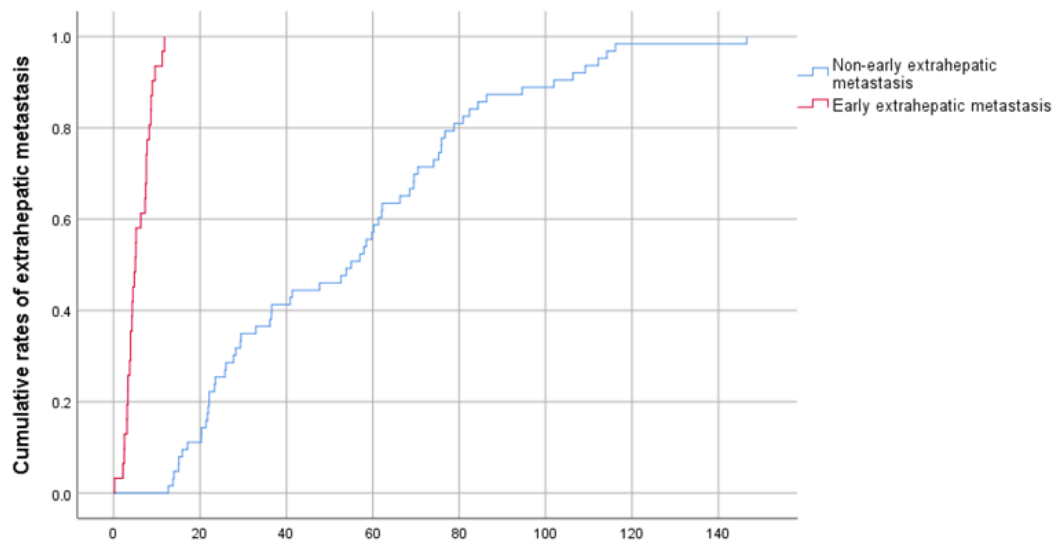
**Figure 1**

Recurrence curves of hepatocellular carcinoma (HCC) after surgical resection (A): Cumulative rates of HCC recurrence; the 1-, 3-, 5-, 7-, and 10-year cumulative rates of recurrence were 30.4%, 50.5%, 63.0%, 71.0%, and 75.6%, respectively; (B): Cumulative rates of extrahepatic recurrence (EHR); the 1-, 3-, 5-, 7-, and 10-year cumulative rates of EHR were 7.9%, 14.2%, 18.1%, 25.5%, and 35.0%, respectively.



A.

Patients at risk	Total	Follow-up duration (months)					
		1yr	3yr	5yr	7yr	10yr	12yr
Early EHM	0/31	29	31	31	31	31	31
Non-early EHM	0/63	25	43	52	61	62	62
Non-EHM	0/304	66	125	159	169	174	177



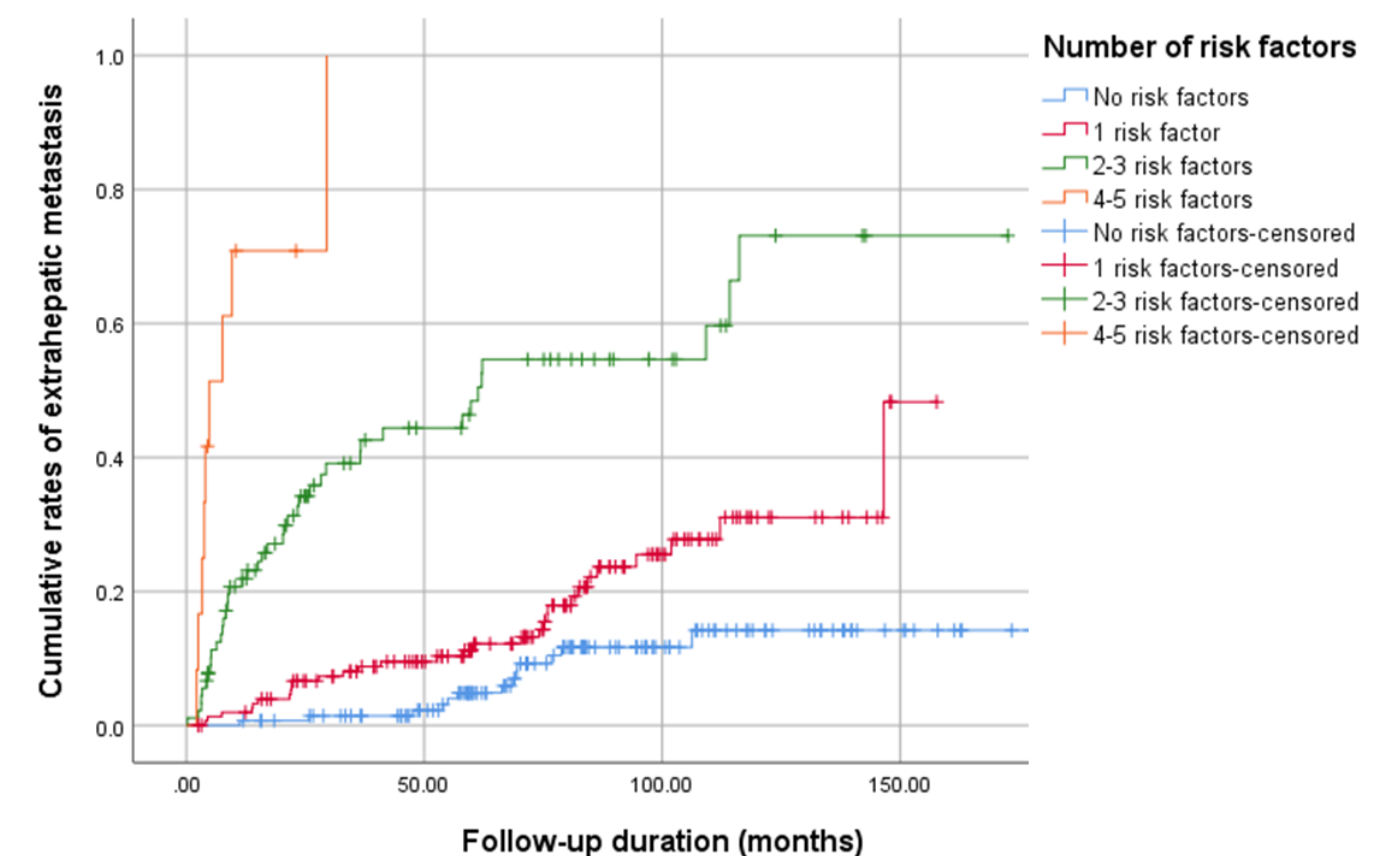
B.

Patients at risk	Total	Follow-up duration (months)					
		1yr	3yr	5yr	7yr	10yr	12yr
Early EHM	0/31	31	31	31	31	31	31
Non-early EHM	0/63	0	23	36	53	62	63

**Figure 2**

Comparison of (A) the recurrence rate of hepatocellular carcinoma (HCC) between the early extrahepatic recurrence (EHR), non-early EHR, and non-EHR group, and (B) the cumulative rate of EHR between the early EHR and non-early EHR group. The 6-month cumulative recurrence rates among early EHR, non-early EHR, and non-EHR groups were 77.7%, 39.7%, and 21.9%, respectively. The 2-, 3-, 5-, 7-, and 10-year

cumulative rates of EHR in the non-early EHR group were 25.4%, 34.5%, 57.1%, 84.1%, and 98.4%, respectively.



No. of risk factors	Tot al	1yr	3yr	5yr	7yr	10yr	12yr
0	141	1	2	6	12	13	13
1	155	3	12	16	24	29	29
2-3	90	19	31	36	39	42	42
4-5	12	8	12	12	12	12	12

**Figure 3**

Cumulative rate of extrahepatic recurrence after curative hepatectomy, stratified by the number of risk factors present.

## Supplementary Files

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