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Prognostic Factors for Post-recurrent Survival in Hepatocellular Carcinoma After Curative Resection

RYO SAITO, HIDETAKE AMEMIYA, NAOHIRO HOSOMURA, HIROMICHI KAWAIDA, SUGURU MARUYAMA, HIROKI SHIMIZU, SHINJI FURUYA, HIDENORI AKAIKE, YOSHIHIKO KAWAGUCHI, MAKOTO SUDO, SHINGO INOUE, HIROSHI KONO and DAISUKE ICHIKAWA

First Department of Surgery, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan

Abstract. *Background/Aim: Treatment algorithms for primary and recurrent hepatocellular carcinoma (HCC) are described in the current Japanese Clinical Practice Guidelines; however, primary and recurrent tumors exhibit several differences in oncological characteristics such as clinicopathological features and prognostic factors. This study aimed to investigate the prognostic factors for recurrent HCC including time of recurrence after primary hepatectomy, to elucidate appropriate treatment strategies in these patients. Patients and Methods: One hundred and nine patients who had undergone radical resection of primary HCC at our Hospital and had experienced intrahepatic recurrence were included in this study. Patients were categorized into the early-recurrence (ER, <1 year postoperatively) or the late-recurrence (LR, ≥1 year postoperatively) groups. Clinicopathological features were compared between the two groups for prognostic analyses. Results: Comparison of clinicopathological features between the ER and LR groups revealed that, at the time of recurrence, the ER group had a significantly higher frequency of multiple recurrences compared to the LR group. In univariate prognostic analysis, the time of recurrence (ER or LR) and the number of recurrent tumors (≥3) were significant prognostic factors after recurrence. Multivariate analysis revealed that three or more recurrent tumors and ER were independent prognostic factors for poor survival after recurrence. Conclusion: HCC is likely to recur, and the characteristics of recurrent HCC are distinct from those of primary HCC. To improve post-recurrence poor prognosis, new and more feasible algorithms, such as aggressive surgical treatment for cases with less than three recurrent tumors, which were revealed in the current study, are needed.*

Correspondence to: Daisuke Ichikawa, MD, First Department of Surgery, Faculty of Medicine, University of Yamanashi, 1110 Shimokato, Chuo, Yamanashi, 4093898, Japan. Tel/Fax: +81 552737390, e-mail: dichikawa@yamanashi.ac.jp

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Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide (1), and hepatitis B virus and hepatitis C virus are the two most common causes of lethal disease (2). Except for patients with chronic viral hepatitis, almost all patients with HCC are considered to have a history of chronic inflammation such as alcoholic hepatitis (3) and non-alcoholic fatty liver disease (4). In the current Japanese Clinical Practice Guidelines (5), treatment algorithms are proposed to determine the most suitable treatment strategy according to tumor-associated factors, such as tumor size, number of tumors, and vascular invasion, as well as patient factors, such as hepatic functional reserve, comorbidities, and general condition of the patient (6, 7). Among the several therapeutic approaches, surgical resection is considered the most appropriate treatment for clinically resectable tumors.

However, new lesions frequently develop even after primary curative surgery (8), sometimes as metachronous HCC, that are difficult to differentiate from recurrence of primary tumor (9). Because treatment for metachronous HCC is identical to that for intrahepatic metastatic recurrence of primary tumors, both are considered together as recurrent HCC in clinical practice (10). In the Japanese Clinical Practice Guidelines, the algorithms used for primary HCC determine the treatment strategies for recurrent HCC as well. However, time of recurrence after primary surgery is another factor that can affect long-term outcomes and should also be considered in the determination of optimal treatment approaches for recurrent HCC. Several studies have identified the time of recurrence as a potential prognostic factor, revealing that patients with early recurrence showed a worse post-recurrence survival than those with late recurrence regardless of the cut-off values for the time of recurrence (11-14).

In this study, we examined correlations between the time of recurrence after primary surgery and clinicopathological

factors in patients with HCC and investigated the prognostic impact of the time of recurrence. Furthermore, we assessed prognostic factors for recurrent HCC to elucidate appropriate treatment strategies.

Patients and Methods

Patients. At the University of Yamanashi Hospital, 180 patients underwent radical resection of primary HCC from 2007 to 2014. After exclusion of patients with other hepatic tumors, such as intrahepatic cholangiocarcinoma and metastatic hepatic tumors, and those underwent non-curative surgery for HCC, a total of 119 patients experienced postoperative recurrence after the primary resection. After excluding ten patients with only extrahepatic recurrence, 109 patients with recurrent HCC and postoperative hepatic recurrence were enrolled in this retrospective study. All patients underwent open or laparoscopic hepatectomy according to the principle employed since 2012 which started that partial hepatectomy and lateral hepatectomy were indications for laparoscopic approach. The treatment strategy for recurrence was determined based on the comprehensive evaluation of patient factors such as age, activity of daily living, and reserved hepatic function as well as tumor factors such as number of tumors and tumor size and localization. In general, among the several treatment options, such as radiofrequency ablation and transcatheter arterial chemoembolization, surgical resection was selected for patients with a maximum of three tumors and those with a tumor diameter smaller than 3 cm (15).

Follow-up. All patients enrolled in the study were followed at the study hospital or an affiliated hospitals every 1-3 months by evaluation of tumor markers, such as α-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) (16, 17), and every 3-6 months by dynamic computed tomography or enhanced magnetic resonance imaging in addition to screening with abdominal ultrasonography. The date of tumor recurrence diagnosis by imaging studies was defined as the time of recurrence. In cases with an undisturbed area of the equilibrium phase in enhanced computed tomography, recurrence was defined as the date when a recurrent mass was strongly suspected with hypervascularity or clarification during follow-up.

Correlation between time of recurrence and prognosis. Recurrence was defined as postoperative development of intrahepatic HCC, including true recurrences of the primary tumor and metachronous HCC (18). Patients were divided into two groups according to the time of the recurrence after primary surgery: recurrence in less than one year after surgery [early recurrence (ER), n=34] and recurrence after one year after surgery [late recurrence (LR), n=75]. Clinicopathological features were compared between the two groups. Prognostic analyses were performed to investigate the prognostic significance of the time of recurrence.

Statistical analyses. All continuous data were presented as mean±standard error of the mean or median values. Statistical analyses were conducted using the chi-square test, Fisher's exact probability test, and Student's *t*-test. We assumed several patient's and tumor's valuables, including timing of recurrent and number of recurrent nodules, as possible prognostic factors, and performed prognostic analyses for these factors. Five-year survival rates were calculated using Kaplan-Meier method and statistically analyzed

Table I. *Comparison of clinicopathological features between ER and LR groups*.

Factors	ER (n=34) (%)	LR (n=75) (%)	*p*-Value
Patients factors			
Age			
<70	15 (44.1)	42 (56.0)	0.303
≥70	19 (55.9)	33 (44.0)	
Gender			
Female	8 (23.5)	13 (17.3)	0.445
Male	26 (76.5)	62 (82.7)	
AFP (ng/ml)			
<10	9 (26.5)	39 (52.0)	0.021
≥10	25 (73.5)	36 (48.0)	
PIVKA-II (mAU/ml)			
<40	18 (52.9)	43 (58.1)	0.678
≥40	16 (47.1)	31 (41.9)	
Ethiology Group			
HBV	5 (14.7)	9 (12.0)	0.799
HCV	18 (52.9)	45 (60.0)	
NBNC	10 (29.4)	20 (26.7)	
Others	1 (2.9)	1 (1.3)	
Child-Pugh			
A	31 (91.2)	71 (94.7)	0.675
B	3 (8.8)	4 (5.3)	
ICG R15 (%)			
<15	15 (44.1)	40 (53.3)	0.413
≥15	19 (55.9)	35 (46.7)	
Intra- and post-operative factors			
Blood loss (ml)			
<600	19 (57.6)	37 (50.0)	0.533
≥600	14 (42.4)	37 (50.0)	
Operative time (min)			
<420	23 (67.6)	40 (53.3)	0.21
≥420	11 (32.4)	35 (46.7)	
Hepatectomy section			
≤Sub-segmentectomy	20 (58.8)	64 (85.3)	0.006
≥Segmentectomy	14 (41.2)	11 (14.7)	
Postoperative complication			
CD0-1	18 (52.9)	50 (66.7)	0.203
CD2-3	16 (47.1)	25 (33.3)	
Pathological factors			
Size (mm)			
≤30	19 (55.9)	40 (53.3)	0.838
>30	15 (44.1)	35 (46.7)	
Tumor number			
1	19 (55.9)	51 (68.0)	0.282
≥2	15 (44.1)	24 (32.0)	
T factor			
1-2	18 (52.9)	51 (68.0)	0.14
3-4	16 (47.1)	24 (32.0)	
LN metastasis			
Absent	34 (100.0)	75 (100.0)	NA
Present	0(0.0)	0(0.0)	
Stage			
1-2	18 (52.9)	51 (68.0)	0.14
3-4	16 (47.1)	24 (32.0)	
Vascular invasion			
Absent	24 (70.6)	59 (78.7)	0.467
Present	10 (29.4)	16 (21.3)	

Significant differences are indicated as $p<0.05$. ER; Early recurrence, LR; late recurrence, AFP; α-fetoprotein, PIVKA-II; protein induced by vitamin K absence or antagonist-II, HBV; hepatitis type B virus, HCV; hepatitis type C virus, NBNC; non-B non-C hepatitis, CD; Clavien-Dindo classification, LN; lymph node, NA; not available.

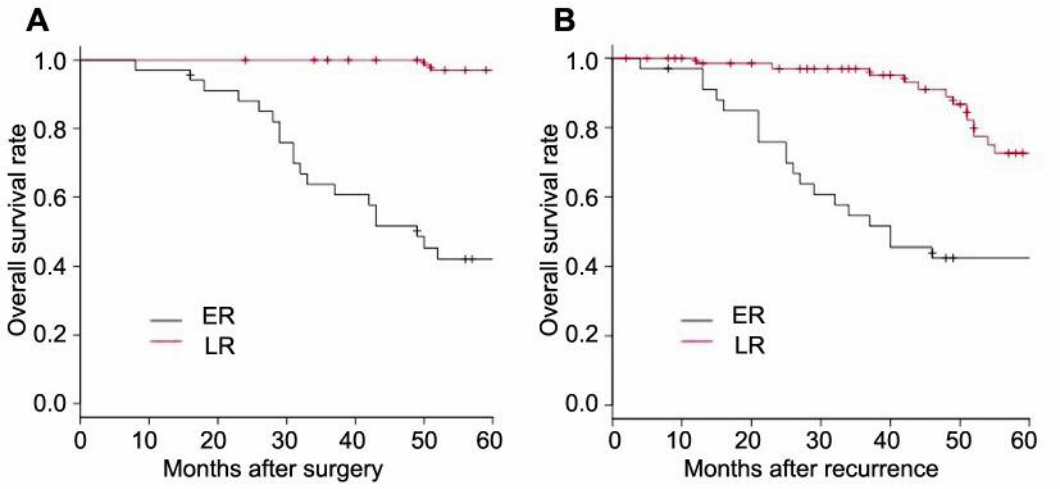

Figure 1. *Overall survival curves after primary surgery (A) and after recurrence according to the time of recurrence diagnosis (B) in the early- and late-recurrence groups. There were significant differences between two groups in both indices (p<0.001).*

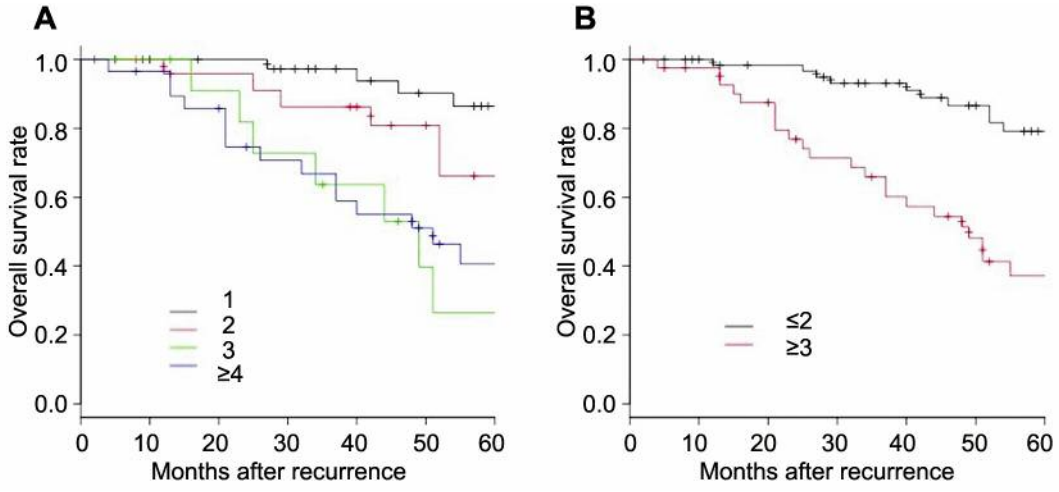

Figure 2. *Post-recurrence overall survival curves according to recurrent tumor numbers (A) and comparison between two groups (≤2 and ≥3) (B). There were no significant differences between recurrent tumor number 2 and 3 groups in A (p=0.032) and between two groups in B (p<0.001) individually.*

using the log-rank test. Multivariate analysis of prognostic factors, including timing of tumor recurrence and number of recurrent nodules, and related to survival was performed using the Cox proportional hazards model. The cut-off value for recurrent tumor size in the prognostic analysis was derived from significant continuous variables using receiver operating characteristic curves, and the cut-off value of recurrent tumor number was determined from exploratory analysis. The significance of differences was accepted at a *p*-value of <0.05. All statistical analyses were conducted with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (19).

Table II. *Survival analyses of each recurrent tumor numbers.*

Recurrent tumor number	n	5-YSRAR (%)	Median OSAR (months)	p-Value
1	41	0.865	NR	0.271 (1 *vs*. 2)
2	26	0.662	NR	0.032 (2 *vs*. 3)
3	13	0.265	49	0.987 (3 *vs*. ≥4)
≥4	29	0.406	51	

Significant differences are indicated as $p<0.05$. 5-YSRAR; 5-year survival rate after recurrence, OSAR; overall survival time after recurrence, NR; not reached.

Table III. *Prognostic analyses after recurrence.*

Prognostic Factors	Factor	Univariate	Multivariate		
		p-Value	HR	95%CI	*p*-Value
Pre-operative factors					
Age	≥70	0.210			
Gender	Female	0.483			
AFP (ng/ml)	≥10	0.056			
PIVKA-II (mAU/ml)	<40	0.324			
Child-Pugh	B	0.183			
ICG R15 (%)	≥15	0.437			
Intra- and post-operative factors					
Blood loss (ml)	<600	0.847			
Duration of surgery (min)	<420	0.581			
Postoperative complication	0-1	0.780			
Hepatectomy section	≥Segmentectomy	0.728			
Pathological factors					
Size (mm)	>30	0.170			
Tumor number	≥2	0.698			
T factor	3-4	0.267			
Stage	3-4	0.267			
Vascular invasion	Present	0.392			
Factors at recurrence					
Age	≥70	0.325			
AFP (ng/ml)	≥10	0.004	1.846	0.963-3.537	0.065
PIVKA-II (mAU/ml)	≥40	0.038	1.142	0.563-2.318	0.713
Size (mm)	≥11	0.416			
Tumor number	≥3	<0.001	3.095	1.476-6.491	0.003
ER/LR	ER	<0.001	2.074	1.063-4.047	0.032

Significant differences are indicated as $p<0.05$. HR; Hazard ratio, CI; confidence interval, AFP; α-fetoprotein, PIVKA-II; protein induced by vitamin K absence or antagonist-II, ER; early recurrence, LR; late recurrence, TACE; transcatheter arterial chemoembolization.

Results

Comparison of clinicopathological features between ER and LR groups. Table I shows the comparison of clinicopathological findings between the two groups. The mean serum AFP level was higher and wide resection was more frequent in the ER group than the LR group. However, there were no significant differences in other clinicopathological factors between the two groups. Conversely, comparison of the clinical findings at the time of recurrence revealed that the ER group had a significantly higher frequency of multiple recurrences compared to the LR group, although there was no significant difference in the serum AFP levels between the two groups.

The analysis of treatment approaches used for the recurrent cases revealed that the patients in the ER group tended to undergo non-surgical treatment approaches, such as radiofrequency ablation and transcatheter arterial chemoembolization, more frequently than those in the LR group. Survival analysis demonstrated that OSAR as well as overall survival were significantly higher in the LR group than the ER group (Figure 1).

Prognostic factors after recurrence. Prior to prognostic analyses, the exploratory prognostic analysis was performed to assess the number of recurrent tumors (Table II). There was a significant difference in the OSAR between the patients with two and three recurrent tumors, whereas the OSARs were not significantly different between the patients with one or two recurrent tumors or between the patients with three and four or more recurrent tumors (Figure 2). Therefore, the optimal cut-off recurrent tumor number was set at three for further analysis.

Table III summarizes the prognostic analyses after recurrence. In addition to the time of recurrence (ER or LR), several factors including serum AFP and PIVKA-II levels and the number of recurrent tumors were prognostic factors as well in univariate analyses. However, none of the preoperative or perioperative clinicopathological factors for primary surgery were significant prognostic factors. Furthermore, the multivariate analysis revealed that three or more recurrent tumors and ER were independent prognostic factors for poor survival after recurrence.

Discussion

In general, HCC is considered to arise from chronic inflammation in the liver due to several factors, such as hepatitis virus infection and alcohol and nonalcoholic fatty liver disease, and patients remain at a high risk for carcinogenesis in the liver even after curative surgery (20). In fact, postoperative new lesions, metachronous HCC, and intrahepatic metastasis from primary HCC frequently develop in the remnant liver, and intensive follow-up programs are recommended to detect recurrence at an early stage and improve postoperative prognosis (21). In the current study, 119 of the 180 patients (66%) had recurrent HCC even after curative hepatectomy, and almost all recurrent HCC lesions were less than 3 cm in diameter at the time of diagnosis (data not shown). Conversely, recurrences were detected more frequently as multiple lesions and were higher in number compared to the primary HCC lesions, which is a potential critical factor that should be considered in treatment strategies.

Same algorithms are used for both primary and recurrent HCC, and several patients and tumor factors are included in the determination of the appropriate treatment strategies. In the current study, we focused on the time of recurrence after primary surgery as a potential prognostic factor for recurrent HCC, which is not considered as a factor in the algorithms. The results clearly demonstrated that patients with ER during the first postoperative year had significantly worse survival than those with LR after the first postoperative year. One plausible explanation for the correlation between the time of recurrence and prognosis is a difference in tumor biology between the early and the late recurring tumors. Another potential reason is that the ER in the majority of ER cases might be a consequence of the so-called intrahepatic metastasis from clinically latent multiple intrahepatic metastases, which might have already been present at the time of primary surgery, with or without multicentric carcinogenesis. In other words, these cases might be in the so-called "latent Stage IV" at the time of primary surgery, subsequently resulting in early recurrence and poor prognosis.

Further prognostic analyses demonstrated that the number of recurrent tumors was correlated with survival after recurrence, as well as the time of recurrence. Multivariate analysis found that the number of recurrent tumors (three or more) and ER (less than one year) were independent and significant poor prognostic factors. These results suggest that these factors should be considered in determining feasible strategies for recurrent HCC and that late recurring cases with less than three recurrent tumors might be candidates for aggressive surgical treatment. Conversely, primary tumor stage, patient age, and tumor markers at the time of recurrence were not independent prognostic factors for recurrent HCC in the current study cohort.

The current study has several limitations. First, the patient cohort was small and did not allow for definitive conclusions on treatment strategies for recurrent HCC. Second, the treatment strategies for recurrent cases were somewhat modified based on the wishes of the patient and the preference of the surgeon in this retrospective study, although the majority of the treatment strategies were determined based on the algorisms in the guidelines. Therefore, large-scale prospective studies are warranted to construct new treatment algorithms for recurrent HCC.

Conclusion

HCC is likely to recur, and the characteristics of recurrent HCC are distinct from those of primary HCC. To improve post-recurrence poor prognosis, new and more feasible algorithms are needed, such as aggressive surgical treatment for cases with less than three recurrent tumors based on the findings of the current study.

Conflicts of Interest

The Authors declare no conflict of interests.

Authors' Contributions

Ryo Saito performed the majority of experiments and wrote the manuscript. Daisuke Ichikawa designed the research and helped to draft the manuscript. All Authors reviewed the manuscript.

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