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Risk Factors for Deterioration of Remnant Liver Function After Hepatic Resection for Hepatocellular Carcinoma

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Abstract. *Background/Aim: After primary resection of hepatocellular carcinoma (HCC), the impact of patient's characteristics at the initial hepatectomy, on long-term remnant liver function has not been reported. The aim of this study was to identify factors associated with the deterioration of remnant liver function among patients who developed recurrent HCC. Patients and Methods: A total of 51 patients with intrahepatic recurrence after initial hepatic resection for HCC were included. We retrospectively investigated the relation between patient characteristics and the degree of deterioration of remnant liver function upon recurrence. Results: In univariate analysis, significant predictors of deterioration of remnant liver function consisted of preoperative gastro-esophageal varices (p=0.0101), preoperative transcatheter arterial chemoembolization (p=0.0230) and hepatectomy beyond Makuuchi's criteria (p=0.0101). In multivariate analysis, the only significant independent predictor of deterioration of remnant liver function was hepatectomy beyond Makuuchi's criteria (p=0.0498). Conclusion: Hepatectomy beyond Makuuchi's criteria at the initial hepatectomy may predict deterioration of remnant liver function upon recurrence of HCC.*

Hepatocellular carcinoma (HCC) is the fifth most common cancer and one of the leading causes of cancer-related deaths worldwide (1, 2). The treatment strategy for HCC includes surgical treatment, local therapy, transcatheter arterial chemoembolization (TACE) and systemic chemotherapy. Hepatic resection has been established as a curative treatment of HCC with improved outcome due to advances in diagnostic modalities, surgical techniques and perioperative care (3, 4). However, the long-term prognosis after curative resection remains unsatisfactory because of a high tumor recurrence rate. The cumulative 5-year recurrence rate is above 70% (5, 6) and recurrence is confined to the liver in 80% to 95% of cases (7, 8).

Repeated hepatectomy for recurrent HCC has been reported to be a highly effective treatment in selected patients. The 5-year survival rate after repeated hepatectomy has been reported to be between 22% and 83% with a median rate of 52% (8, 9). Repeated hepatectomy is reserved for patients with good liver function and, therefore it is important to maintain post-hepatectomy liver function. The recovery of post-hepatectomy liver function could be affected by patient's baseline liver function and extent of hepatic resection.

To our knowledge, the impact of patient's characteristics at the initial hepatectomy on long-term remnant liver function has never been reported. The aim of this study was to identify factors associated with the deterioration of remnant liver function among patients who developed recurrent HCC.

Patients and Methods

The study included 70 patients who underwent detailed examination of the remnant liver function for intrahepatic recurrence after initial hepatic resection for HCC in the Department of Surgery, Jikei University Hospital, Tokyo, Japan between December 2009 and June 2018. Of these, 19 patients were excluded from the analysis due to other malignancies (n=1) and lack of data (n=18). Finally, 51 patients were included in the final analysis.

Intrahepatic recurrence of HCC was defined as newly detected hypervascular hepatic tumor by ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) or angiography. For intrahepatic recurrence of HCC, repeated hepatic resection, local therapy (radiofrequency ablation or percutaneous ethanol injection therapy), liver transplantation, TACE or systemic chemotherapy was given based on hepatic functional reserve judged mainly by indocyanine green retention rate at 15 min (ICGR15), and the number and location of the recurrent tumors.

Generally, the extent of hepatic resection was determined based on ICGR15. Selection of patients for hepatectomy and the extent of

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hepatic resection were based on the Makuuchi's criteria (10). Anatomical resection was defined as lobectomy, segmentectomy or subsegmentectomy.

Bile leakage was defined as bile discharge from the abdominal drainage tube or fluid collection by CT which was confirmed as bile by aspiration or drainage. Liver failure was defined as an increasing prothrombin time-international normalized ratio (PT-INR) and increasing serum bilirubin concentration on or after postoperative day 5 (11). The clinical stage was based on the sixth edition of Tumor-Nodes-Metastasis (TNM) system (12). Deterioration of remnant liver function was defined as an increased Child-Pugh score upon examination at the time of recurrence detection in comparison with that at the initial hepatectomy.

The patients' characteristics were classified into two groups for log-rank test and Cox proportional hazard regression model. The patients' age was classified as ≤70 and >70 years. Interval between initial hepatectomy and recurrence was classified as ≤2 and >2 year. Platelet (Plt) count was classified as ≤100 and >100×10^3/μl. Maximum tumor diameter was classified as ≤20 and >20 mm. Tumor number was classified as ≤3 and more.

Firstly, the clinical variables in relation to deterioration of remnant liver function upon recurrence were evaluated by univariate and multivariate analyses using the following 19 factors: age, gender, hepatitis B viral status, hepatitis C viral status, Plt count, ICGR15, Child-Pugh classification, gastro-esophageal varices, preoperative TACE, hepatectomy beyond Makuuchi's criteria, anatomical hepatectomy, intraoperative blood loss, operative time, the ratio of remnant liver volume to total liver volume (%RLV), postoperative bile leakage, postoperative liver failure, TNM stage, surgical margin and liver cirrhosis at the initial hepatectomy.

Next, the clinical variables in relation to overall survival after recurrence were evaluated by univariate and multivariate analyses using the following 9 factors: age, gender, interval between initial hepatectomy and recurrence, Plt count, Child-Pugh classification, degree of deterioration of remnant liver function, maximum tumor diameter, tumor number and treatment upon recurrence. Presence or absence of deterioration of remnant liver function upon recurrence was determined using the following factors: age, interval between initial hepatectomy and recurrence, plt count, maximum tumor diameter, tumor number and treatment upon recurrence.

This study was approved by the Ethics Committee of The Jikei University School of Medicine [21-121].

Statistical analysis. The data were expressed as an average±SD. Analysis of overall survival after recurrence was performed using the log-rank test. Univariate analysis was performed using the non-paired *t*-test or Chi-square test. Multivariate analyses were performed using logistic-regression analysis and the Cox proportional regression model. All *p*-values were considered statistically significant when the associated probability was less than 0.05.

Results

Patient characteristics at the initial hepatectomy and association between deterioration of remnant liver function upon recurrence and patient characteristics by univariate and multivariate analyses. Characteristics of patients, intraoperative data and postoperative course at the initial hepatectomy are summarized in Table I. Tables II and III list the association between deterioration of remnant liver function upon recurrence and patient characteristics. In univariate analysis, significant predictors of deterioration of remnant liver function upon recurrence consisted of preoperative gastro-esophageal varices (p=0.0101), preoperative TACE (p=0.0230) and hepatectomy beyond Makuuchi's criteria (p=0.0101). In multivariate analysis, the only significant independent predictor of deterioration of remnant liver function upon recurrence was hepatectomy beyond Makuuchi's criteria (p=0.0498).

Table I. *Patient characteristics at the initial hepatectomy.*

Factor	Average or number	Range or %
Age (years)	68	47-87
Gender		
Male	46	90%
Female	5	10%
HBsAg (+)	10	20%
HCVAb (+)	17	33%
Plt count (10^3/μl)	151	51-392
Alb (g/dl)	3.7	2.6-4.6
T-Bil (mg/dl)	0.9	0.3-2.0
PT (%)	82.9	54-100
ICGR15 (%)	15	3-52
Child-Pugh classification		
A	48	94%
B	3	6%
Gastro-esophageal varices (yes)	10	20%
Preoperative TACE (yes)	11	22%
Hepatectomy beyond Makuuchi's criteria (yes)	10	20%
Anatomical hepatectomy (yes)	25	49%
Intraoperative blood loss (ml)	884	0-6,620
Operative time (min)	420	126-693
%RLV (%)	88.7	45-99.7
Postoperative bile leakage (yes)	2	4%
Postoperative liver failure (yes)	1	2%
TNM stage		
I	26	51%
II	21	41%
III	4	8%
Surgical margin (positive)	4	8%
Liver cirrhosis (yes)	23	45%

HBsAg: Hepatitis B surface antigen; HCVAb: hepatitis C antibody; Plt: platelet; Alb: albumin; T-Bil: total bilirubin; PT: prothrombin time; ICGR15: indocyanine green retention rate at 15 min; TACE: transcatheter arterial chemoembolization; %RLV: the ratio of remnant liver volume to total liver volume; TNM: tumor-nodes-metastasis.

Patient characteristics upon recurrence and univariate and multivariate analysis of overall survival after recurrence. Patient characteristics upon recurrence are summarized in Table IV. Table V and VI list the relationship between the clinical variables and overall survival after recurrence. In univariate analysis, Plt count ≤100×10^3/μl (p=0.0125) and

Table II. *Predictive factors at the initial hepatectomy for deterioration of remnant liver function by univariate analysis.*

Factor	Deterioration of remnant liver function		*p*-Value
	No (n=37)	Yes (n=14)	
Age (years)	68.8±7.2	64.6±8.9	0.0887
Gender (Male:Female)	33:4	13:1	0.6942
HBsAg (+:–)	9:28	1:13	0.1678
HCVAb (+:–)	12:25	5:9	0.8244
Plt count (10^3/μl)	146±71	167±69	0.3474
ICGR15 (%)	17±7.5	18.1±13.6	0.7102
Child-Pugh classification (A:B)	34:3	14:0	0.2721
Preoperative gastro-esophageal varices (yes:no)	4:33	6:8	0.0101
Preoperative TACE (yes:no)	5:32	6:8	0.0230
Hepatectomy beyond Makuuchi's criteria (yes:no)	4:33	6:8	0.0101
Anatomical hepatectomy (yes:no)	17:20	8:6	0.4753
Intraoperative blood loss (ml)	855.8±1,141.2	957.9±1,098.6	0.7748
Operative time (min)	419.9±148.3	419.9±162.9	0.9999
%RLV (%)	89±11.9	87.8±11.2	0.7374
Postoperative bile leakage (yes:no)	1:36	1:13	0.4660
Postoperative liver failure (yes:no)	0:37	1:13	0.1006
TNM stage (I:others)	21:16	5:9	0.1798
Surgical margin (positive:negative)	4:33	0:14	0.2000
Liver cirrhosis (yes:no)	16:21	7:7	0.6652

HBsAg: Hepatitis B surface antigen; HCVAb: hepatitis C antibody; Plt: platelet; ICGR15: indocyanine green retention rate at 15 min; TACE: transcatheter arterial chemoembolization; %RLV: the ratio of remnant liver volume to total liver volume; TNM: tumor-nodes-metastasis.

Table III. *Predictive factors at the initial hepatectomy for deterioration of remnant liver function by multivariate analysis.*

Factor	Odds ratio (95%CI)	*p*-Value
Preoperative gastro-esophageal varices (yes)	4.066 (0.776-21.306)	0.0969
Preoperative TACE (yes)	4.208 (0.846-20.919)	0.0790
Hepatectomy beyond Makuuchi's criteria (yes)	5.233 (1.001-27.349)	0.0498

CI: Confidence interval; TACE: transcatheter arterial chemoembolization.

treatment except for repeated hepatectomy (p=0.0316) were associated with significantly poorer overall survival after recurrence. In multivariate analysis, Plt count ≤100×10^3/μl (p=0.0153) and treatment except for repeated hepatectomy (p=0.0350) were the independent factors associated with poor overall survival after recurrence (Figure 1).

Association between patient characteristics upon recurrence and deterioration of remnant liver function. Table VII lists the association between patient characteristics upon recurrence and deterioration of remnant liver function. In patients with deterioration of remnant liver function, repeated hepatectomy was significantly less frequently selected as compared to those without deterioration of remnant liver function (p=0.0367).

Discussion

Preoperative liver function and surgical procedure at the initial hepatectomy could affect long-term remnant liver function of HCC. Nakamura *et al*. have reported that severity of post-hepatectomy liver failure affected long-term recovery of liver function and remnant liver hypertrophy after hepatectomy (13). In the current study, only one patient developed post-hepatectomy liver failure. The present study demonstrated that the significant predictors of deterioration of remnant liver function consisted of preoperative gastro-esophageal varices, preoperative TACE and hepatectomy beyond Makuuchi's criteria. Of note, the %RLV was comparable between patients with and without deterioration of remnant liver

Table IV. *Patient characteristics upon recurrence.*

Factor	Average or number	Range or %
Age (years)	70	48-87
Interval between initial hepatectomy and recurrence (months)	22.9	2.8-79.2
Plt count (10^3/μl)	141	40-298
Alb (g/dl)	3.8	2.1-5.3
T-Bil (mg/dl)	1.2	0.3-14.1
PT (%)	81.9	50-100
Child-Pugh classification		
A	42	82%
B	7	14%
C	2	4%
Deterioration of remnant liver function (yes)	14	27%
Maximum tumor diameter (mm)	14.4	5.2-34.4
Number of tumors		
1	33	65%
2	7	14%
3	5	10%
More	6	12%
Treatment		
Repeated hepatectomy	23	45%
RFA or PEIT	7	14%
TACE or TAI	18	35%
Liver transplantation	1	2%
None	2	4%

Plt: Platelet; Alb: albumin; T-Bil: total bilirubin; PT: prothrombin time; RFA: radiofrequency ablation; PEIT: percutaneous ethanol injection therapy; TACE: transcatheter arterial chemoembolization; TAI: transhepatic arterial infusion.

Table V. *Univariate analysis of overall survival after recurrence for hepatocellular carcinoma.*

Factor	N	Overall survival after recurrence	
		Median (years)	*p*-Value
Age (years)			
≤70	25	1.79	0.4411
>70	26	2.95	
Gender			
Male	46	1.31	0.7860
Female	5	2.49	
Interval between initial hepatectomy and recurrence (year)			
≤2	32	2.32	0.3584
>2	19	2.48	
Plt count (×10^3/μl)			
≤100	11	1.80	0.0125
>100	40	2.49	
Child-Pugh			
A	42	2.53	0.0789
B or C	9	2.14	
Deterioration of remnant liver function			
Yes	14	2.14	0.5162
No	37	2.53	
Maximum tumor diameter (mm)			
≤20	45	2.45	0.7453
>20	6	2.57	
Number of tumors			
≤3	45	2.45	0.4395
More	6	1.99	
Treatment			
Repeated hepatectomy	23	3.03	0.0316
Others	28	1.80	

Plt: Platelet.

function. Gastro-esophageal varices and preoperative TACE have been reported to be risk factors predicting poor prognosis for patients with HCC (14, 15) and liver function has been acknowledged as a prognostic factor for the patients with HCC (16). The current study demonstrated that the presence of gastro-esophageal varices and preoperative TACE were associated with deterioration of post-hepatectomy liver function, which could explain why these two factors were poor prognostic factors of HCC. Makuuchi's criteria are helpful for safe hepatectomy in patients with HCC. Miyagawa S *et al*. have reported that the hospital and operative mortality rates were 2.3% and 0.6% in hepatic resection based on Makuuchi's criteria (17). Our study showed that Makuuchi's criteria were also useful predictors of long-term remnant liver function.

The present study demonstrated that Plt count ≤100×10^3/μl and treatment except for repeated hepatectomy were independent factors associated with poor overall survival after recurrence. Previous studies have reported on prognostic factors of recurrent HCC after hepatic resection; Cheng Z *et al*. have reported that the 5-year survival of patients with early recurrence of HCC (within 2 years) was significantly lower than those with late recurrence (later than 2 years) (18). Chen WT *et al*. have reported that multiple initial tumors, multiple recurrences, extrahepatic recurrence, recurrent tumor size >2 cm, post-hepatectomy period until recurrence <1 year and non-resectional treatment of recurrent tumors were independent prognostic factors for post-recurrence survival rates (19). Since, in the current study, repeated hepatectomy was selected in patients without deterioration of remnant liver function, the maintenance of liver function after initial hepatectomy needs to be kept in mind for the follow-up of post-hepatectomy patients with HCC.

The current study had several limitations. First, our analyses were retrospectively performed in a single institution. Second, the sample size was not large enough because only patients who underwent detailed study of the

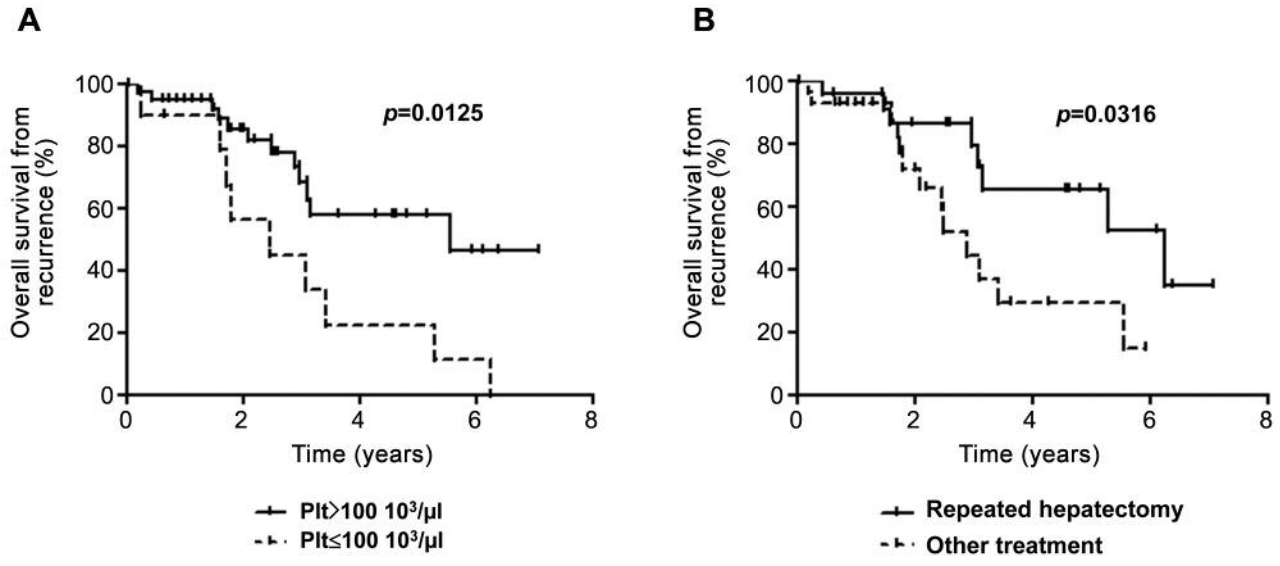

Figure 1. *Kaplan–Meier curves of overall survival after recurrence in relation to platelet counts (A) and treatment modality for recurrence (B).*

Table VI. *Multivariate analysis of overall survival after recurrence for hepatocellular carcinoma.*

Factor	Odds ratio (95%CI)	*p*-Value
Plt (≤100×10^3/μl)	2.943 (1.230-7.043)	0.0153
Treatment (repeated hepatectomy)	0.361 (0.140-0.931)	0.0350

CI: Confidence interval; Plt: platelet.

Table VII. *Patient characteristics upon recurrence in relation to deterioration of remnant liver function.*

Factor	Deterioration of liver function		*p*-Value
	No (n=37)	Yes (n=14)	
Age (years) (≤70:>70)	17:20	8:6	0.4753
Interval between initial hepatectomy and recurrence (year) (≤2:>2)	21:16	11:3	0.1504
Plt count (10^3/μl) (≤100:>100)	7:30	4:10	0.4545
Maximum tumor diameter (mm) (≤20:>20)	33:4	12:2	0.7311
Number of tumors (≤3:more)	31:6	14:0	0.1087
Treatment (repeated hepatectomy:others)	20:17	3:11	0.0367

CI: Confidence interval; Plt: platelet.

remnant liver function for intrahepatic recurrence were analyzed. However, a unique strong point of this study was that this is the first report identifying risk factors for deterioration of remnant liver function after hepatectomy for HCC.

In conclusion, hepatectomy beyond Makuuchi's criteria was the significant independent predictor of deterioration of remnant liver function upon recurrence. Deterioration of remnant liver function limits the possibility of repeated hepatectomy.

Conflicts of Interest

Rui Marukuchi and the other co-authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Rui Marukuchi: Design of the study, drafting of the article and collection of data; Kenei Furukawa: Design of the study, analysis of data and revision of the article; Ryota Iwase: Analysis of data; Jungo Yasuda: Collection of data; Hironori Shiozaki: Collection of data; Shinji Onda: Collection of data; Takeshi Gocho: Collection of data; Hiroaki Shiba: Revision of the article; Katsuhiko Yanaga: Conception of the study and final approval of the article.

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