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Third Liver Resection for Re-recurrent Hepatocellular Carcinoma: Assessment of the Prognostic Factors of Long-term Survival

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Abstract

Background/Aim: Second hepatic resection is a well-established and effective treatment for recurrent hepatocellular carcinoma (HCC). Despite this, the recurrence rate of HCC remains high. The efficacy of third liver resection for re-recurrent HCC is uncertain, and prognostic factors affecting survival after third hepatectomy have not been comprehensively evaluated. This study aimed to investigate the short- and long-term outcomes of third liver resection for re-recurrent HCC and identify prognostic factors affecting survival.

Patients and Methods: In total, 27 patients who underwent three liver resections for primary, recurrent, and re-recurrent HCC were retrospectively reviewed. The prognostic factors of long-term survival were evaluated using clinical data including those of previous liver resections.

Results: No cases of perioperative mortality after third liver resection for re-recurrent HCC were found. The median overall survival and disease-free survival were 38.3 and 5.8 months, respectively. The 5-year overall survival and disease-free survival rates were 56.8% and 10.9%, respectively. Clinical parameters such as tumor marker level, primary tumor size, and surgical interval of the third liver resection and of the first and second surgeries were significantly associated with long-term survival.

Conclusion: The survival rate of third liver resection for re-recurrent HCC in our study was similar to that reported for second and third hepatectomies in previous studies. Clinical information on previous surgeries could be a useful determinant of third liver resection for re-recurrent HCC.

Keywords: Recurrent hepatocellular carcinoma, third liver resection, repeat hepatectomy, prognostic factors.

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Introduction

Hepatocellular carcinoma (HCC) is an aggressive tumor with a high rate of recurrence even after curative resection (1-4). Despite the expanded use of new systemic therapies including immune checkpoint inhibitors (5), recent studies still support curative treatments (surgery or local ablative therapy) as a useful intervention to achieve improved prognosis for recurrent HCC (6, 7). Although no valid prospective studies have compared liver resection and ablative therapy, repeat resection is preferred whenever feasible, as it offers better prognosis and local disease control (8, 9). Repeat hepatectomy is not only a safe treatment option for intrahepatic relapse but is also associated with a prolonged postoperative survival comparable to that of first liver resection (4, 10-20). The Japanese guidelines recommend treatment for recurrent HCC after the initial therapy. Several studies have shown that clinical information such as time to recurrence, liver status, and tumor characteristics including tumor number and vascular invasion, are prognostic factors of survival after second liver resection (11, 21, 22).

However, there are only a few reports on further hepatectomy for re-recurrent HCC, most of which have a limited number of patients. Thus, the feasibilities, limitations, and survival benefits of third or more resections have not been validated (10, 23, 24). To the best of our knowledge, only one study has investigated the prognostic factors of survival after third liver resection (24).

At our institution, relatively aggressive repeat liver resections have been conducted on patients with recurrent and re-recurrent HCC. The current study aimed to assess the demographic and tumor characteristics and the surgical and long-term outcomes of patients who underwent first to third liver resections. Furthermore, the prognostic factors of overall survival (OS) and disease-free survival (DFS) were evaluated using data on not only third liver resection but also previous surgeries.

Patients and Methods

Patients and data collection. From April 2009 to May 2020, 38 patients underwent third liver resection for recurrent HCC after second liver resection at the Japanese Red Cross Medical Center. Eleven patients who had the first and/or second hepatectomy at other institutions were excluded. A total of 27 patients who had all three liver resections conducted at our institution were analyzed. The medical records and clinical data collected from a prospective database were retrospectively reviewed. Data such as tumor marker levels, intervals between each surgery, and tumor characteristics during the first, second, and third liver resections were evaluated. None of the participants had missing data for each variable of interest. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration, following STROBE guidelines (25). The institutional review board approved this study (no.1480). Informed consent was obtained in the form of opt-out on the website of our institution, and the requirement for individual informed consent was waived as we removed any patient identifiers from the dataset prior to analysis.

Preoperative examination and surgical indications for repeat hepatectomy. All patients underwent standard blood tests, contrast-enhanced computed tomography scan of the chest and abdomen, and ethoxybenzyl magnetic resonance imaging before surgery. Prior to liver resection, to evaluate liver functional reserve, the indocyanine green test was performed. Moreover, the functional remnant liver volume was calculated using a three-dimensional simulation software. The corrected indocyanine green retention rate at 15 minutes (ICG-r15) was calculated as the ICG-r15 from the disappearance curve. The indication criteria for repeat hepatectomy at our institution were similar to those of first liver resection, as described in previous studies (26, 4). Liver resection was indicated for patients who fulfilled the Makuuchi's criteria (27, 28), which are used to determine the maximum tolerable operative procedure based on the

ICG-r15. Additionally, patients with tumors that could be resected (with a standard number of ≤5 tumors) based on preoperative imaging tests were considered eligible. The surgical indications were not affected by the location of recurrent tumors or previous surgical procedures.

Surgical procedures. When adequate surgical margin was anticipated, partial resections or anatomical segmentectomy were performed rather than major hepatectomy. Preoperative portal vein embolization was not required in all cases. Laparotomy was performed *via* a J incision, and intraoperative ultrasonography was conducted to identify the extent of the tumor and to determine the line of resection. Hepatectomy was performed under intermittent Pringle maneuver using the Kelly clamp crushing technique (28).

Definition and grading of postoperative complications. All postoperative complications were recorded and classified according to the Clavien-Dindo classification (CDC). Postoperative bile leakage was defined as fluid with an elevated bilirubin level (at least three times higher than the serum bilirubin level) in the abdominal drain or intraabdominal fluid on or after postoperative day 3 or the need for radiological intervention due to biliary collections or relaparotomy caused by biliary peritonitis according to the International Study Group of Liver Surgery criteria (ISGLS). Postoperative hepatectomy liver failure was diagnosed based on increased international normalized ratio and concomitant hyperbilirubinemia on or after postoperative day 5 according to the ISGLS.

Postoperative follow-up. Patients were postoperatively reviewed in clinic two weeks after discharge, followed by follow-up outpatient visits every three months, where laboratory tests including tumor markers were conducted. All patients would consent to undergo a postoperative CT every six months.

Statistical analysis. The Kaplan-Meier method was used to estimate survival probabilities, which were compared using the log-rank test. OS and DFS were defined as survival from the date of the third hepatectomy to the last follow-up contact. Univariate analyses were conducted to calculate preoperatively and postoperatively known predictors (which include factors associated with the first and second hepatectomy) that affect survival. The cut-off values for each prognostic factor were determined based on the median value of each factor, with the exception of ICG-r15 and α-fetoprotein (AFP) levels. The cut-off points for these two predictors were adopted from previous reports on repeat liver resection (11, 24). A p-value of <0.05 was considered statistically significant. Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface of R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. Multivariate analysis was omitted due to small sample size.

Results

Demographic characteristics of the patients. Table I shows the demographic characteristics of the patients. There were 19 male patients and eight female patients, with a median age of 68 years. The etiologies of HCC were as follows: hepatitis B virus, n=10; hepatitis C virus, n=8; alcoholic liver disease, n=3; and nonalcoholic steatohepatitis, n=2. One patient received preoperative treatment (transcatheter arterial embolization). The median intervals between each liver resection were as follows: from the first to second, 12.2 months; from the first to third, 23.5 months; and from the second to third, 8.2 months. All patients had Child-Pugh class A disease. The median ICG-r15 was 15.9%. The AFP and protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels were more likely to increase before the second liver resection.

Surgical outcomes and tumor characteristics. Table II shows the surgical outcomes and tumor characteristics. The median surgical time was 637 min, and the median

Table I. *Demographic characteristics of the patients.*

Demographic characteristics		
Age, years	Median (range)	68 (26-80)
Sex	Male/female	19/8
Preoperative treatment	TACE/RFA/none	1/0/26
Portal vein embolism	Presence/absence	1/26
Hepatitis B virus	Positive/negative	10/17
Hepatitis C virus	Positive/negative	8/19
Alcohol	Positive/negative	3/24
Nonalcoholic steatohepatitis	Positive/negative	2/25
Months from the first to second hepatectomy	Median (range)	12.2 (1.7-84.3)
Months from the first to third hepatectomy	Median (range)	23.5 (4.4-114.7)
Months from the second to third hepatectomy	Median (range)	8.2 (1.7-38.0)
Preoperative laboratory data		
Platelet level ($\times 10^4/\mu l$)	Median (range)	15.4 (5.1-31.9)
Total bilirubin level (mg/dl)	Median (range)	0.6 (0.3-1.4)
Albumin level (g/dl)	Median (range)	4.1 (2.8-3.9)
Prothrombin time % (%)	Median (range)	90 (56-112)
ICG-r15 (%)	Median (range)	15.9 (5.9-27.7)
Child-Pugh classification	A/B/C	27/0/0
HbA1c (%)	Median (range)	5.8 (5.1-7.6)
AFP level (ng/ml)		
1st	Median (range)	8 (2-323)
2nd	Median (range)	24 (2-2,233)
3rd	Median (range)	7 (2-14,480)
PIVKA-II (mAU/ml)		
1st	Median (range)	26 (14-4,330)
2nd	Median (range)	79 (11-20,700)
3rd	Median (range)	29 (11-2,003)

TACE: Transcatheter arterial chemoembolization; RFA: radiofrequency ablation; ICG-r15: indocyanine green retention rate at 15 minutes; AFP: α-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II.

Table II. *Surgical outcomes and tumor characteristics.*

Surgical outcomes		
Surgical time, min	Median (range)	637 (296-939)
Volume of blood loss, ml	Median (range)	660 (110-2,055)
Extent of hepatectomy	Anatomical/ nonanatomical	8/19
Curability	A1/A2/B/C	6/13/4/4
Blood transfusion (RBC)	Presence/absence	3/24
Blood transfusion (FFP)	Presence/absence	26/1
Tumor characteristics		
Pathological stage		
1st	I/II/III/IVA/IVB	2/14/6/4/1
2nd	I/II/III/IVA/IVB	10/14/3/0/0
3rd	I/II/III/IVA/IVB	7/15/3/2/0
Main tumor size, cm	Median (range)	1.2 (0.7-4)
Number of tumors	1/2/3/4/5/6	14/8/2/2/0/1
Vascular involvement	Positive/negative	4/23
Intrahepatic metastasis	Positive/negative	0/27
Surgical margin	Positive/negative	3/24

RBC: Red blood cells; FFP: fresh frozen plasma.

Table III. *Postoperative outcomes.*

Complications		
Bile leakage	Absence/CDC grades 1/2/≥3	13/14/0/0
Liver failure	Absence/CDC grade 1/2/≥3	25/1/1/0
Postoperative course		
Length of hospital stay, days	Median (range)	16 (10-38)
90-day mortality	Presence/absence	0/27
Prognosis		
Overall survival, months	Median (range)	38.3 (0.6-158.8)
Disease-free survival, months	Median (range)	5.8 (0.6-70.3)

CDC: Clavien-Dindo classification.

blood loss volume was 660 ml. Eight patients underwent anatomical hepatectomy, and 19 had partial hepatectomy. The median tumor size was 1.2 cm. In total, 13 patients had ≥2 tumors. Four and three patients presented with vascular involvement and positive surgical margin, respectively. Pathological staging in each liver resection was evaluated, and results showed a relatively advanced cancer progression during the first liver resection.

Postoperative complications and short- and long-term outcomes. The overall morbidity rate was 59.3%. Approximately 51.8% (n=14) of the patients had bile leakage, all of which were grade A according to ISGLS severity grading. Furthermore, 7.4% (n=2) developed liver failure. Grade A and B liver failure occurred in one patient each.

None of the patients had other common complications such as intraabdominal abscess, pleural effusion, intractable ascites, and wound infection. The 90-day mortality rate after the third liver resection was 0%. The median OS and DFS were 38.3 and 5.8 months, respectively, with a median follow-up period of 38.8

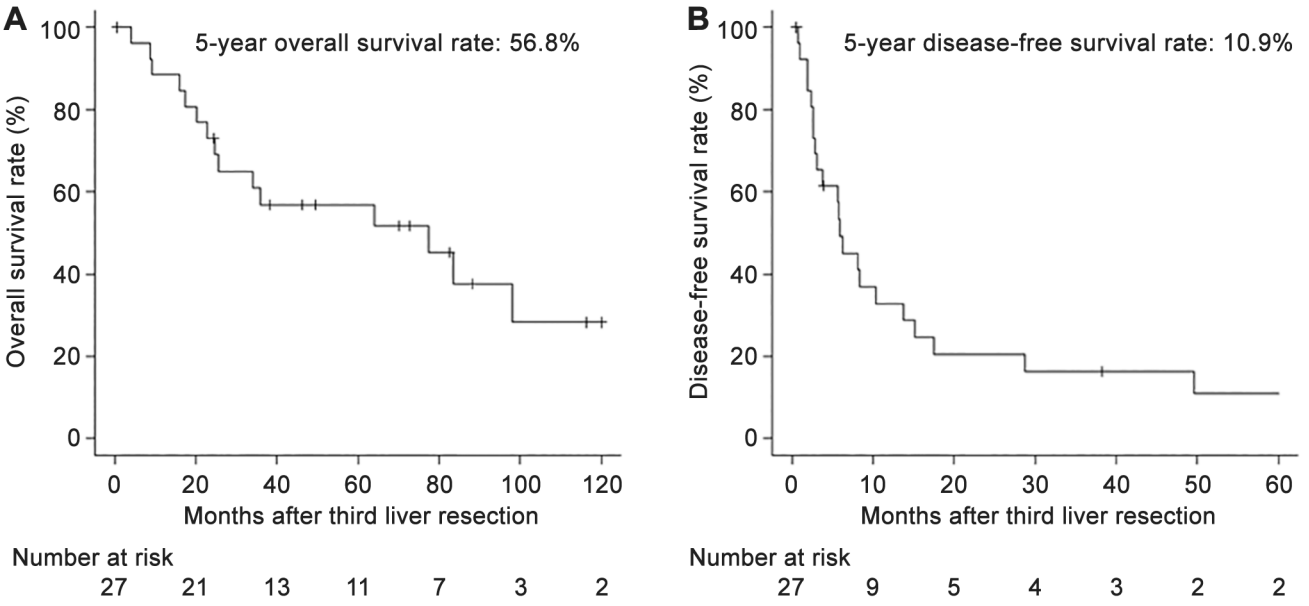

Figure 1. *Survival curves of patients who underwent third hepatectomy for re-recurrent hepatocellular carcinoma (HCC). The overall survival curves (A) and disease-free survival curves (B) of patients with third hepatectomy for re-recurrent HCC. The 5-year survival rate and disease-free survival rate after the third hepatic resection were 56.8% and 10.9%, respectively.*

months (Table III). Figure 1 shows the survival curves obtained using the Kaplan-Meier test. The 5-year OS rate and DFS rate after the third hepatic resection were 56.8% and 10.9%, respectively (Figure 1A and B).

Prognostic factors of OS and DFS after the third hepatectomy. An ICG-r15 of ≥10%, AFP level of ≥100 ng/ml before the second and third hepatectomy, ≥3 disease stage based on the third hepatic resection, primary tumor size of ≥5 cm based on the first surgery and ≥2 cm based on the second and third surgery, and positive vascular involvement during the third surgery were found to be associated with poor OS. An ICG-r15 of ≥10%, interval of <1 year from the first to second hepatectomy, interval of <2 years from the first to third hepatectomy, interval of <8 months from the second to third hepatectomy, AFP level of ≥100 ng/ml before the second hepatic resection, PIVKA-II level of >30 mAU/ml, nonanatomical hepatectomy, primary tumor size of ≥5 cm based on the first surgery, and positive vascular involvement during the third surgery were associated with poor DFS (Table IV).

Postoperative treatments after the third liver resection. Of the 27 patients, three underwent fourth and fifth resections, and one patient underwent sixth surgery. Additionally, one patient received a living-donor liver transplant following the fourth liver resection. A total of 11 and four patients received transcatheter arterial chemoembolization and radiofrequency ablation, respectively. Three patients were treated with sorafenib tosylate and six patients received radiation therapy for bone metastasis.

Discussion

This study investigated the treatment outcome of third hepatic resection for re-recurrent HCC. Results revealed that the survival outcomes of third liver resection were comparable with those of second and third liver resection, as reported in previous studies (10, 11, 20, 23,

Table IV. *Prognostic factors based on the univariate analysis.*

			(n=27)	5-year overall survival	*p*-Value	3-year disease-free survival	*p*-Value
Preoperative factors							
Age, years (<68/≥68)			13/14	51.3%/61.5%	0.99	15.4%/17.1%	0.67
Sex (male/female)			19/8	59.8%/50.0%	0.99	30.0%/11.1%	0.23
Hepatitis virus (positive/negative)			18/9	52.9%/64.8%	0.96	17.6%/13.3%	0.96
ICG-r15 (<10%/≥10%)			7/20	16.7%/69.3%	<0.01	NA/21.5%	0.02
Preoperative treatment (presence/absence)			1/26	NA/55.1%	0.94	NA/17.1%	0.60
Interval from the first to second hepatectomy (<12/≥12 months)			11/16	30.0%/74.5%	0.14	NA/27.3%	0.03
Interval from the first to third hepatectomy (<24/≥24 months)			14/13	35.7%/83.3%	0.21	NA/37.0%	<0.01
Interval from the second to third hepatectomy (<8/≥8 months)			8/19	30.8%/84.6%	0.09	NA/30.8%	0.04
AFP level	(<100/≥100 ng/ml)	1st	21/6	58.9%/50.0%	0.83	16.3%/16.7%	0.76
		2nd	25/2	61.8%/NA	0.03	17.8%/NA	<0.01
		3rd	22/5	65.8%/20.0%	0.04	20.5%/NA	0.25
PIVKA-II level	(<25/≥25 mAU/ml)	1st	7/20	44.4%/60.0%	0.60	33.3%/10.8	0.46
	(<80/≥80 mAU/ml)	2nd	20/7	62.3%/42.9%	0.85	23.2%/NA	0.33
	(<30/≥30 mAU/ml)	3rd	20/7	62.0%/42.9%	0.61	34.6%/NA	0.04
Surgical factors							
Extent of hepatectomy (anatomical/nonanatomical)			8/19	60%/55.6%	0.82	NA/24.2%	0.03
Surgical time (<11/≥11 h)			14/13	69.2%/43.3%	0.14	231.1%/8.8%	0.49
Volume of blood loss (<700/≥700 ml)			15/12	64.3%/47.6%	0.48	21.4%/9.5%	0.85
Tumor factors							
Stage	(≤2/≥3)	1st	16/11	60.0%/54.5%	0.63	14.8%/18.2%	0.41
		2nd	24/3	59.8%/33.3%	0.11	18.7%/NA	0.60
		3rd	22/5	65.8%/20.0%	0.01	20.4%/NA	0.05
Main tumor size, cm	(<5/≥5 cm)	1st	16/11	80.0%/21.8%	<0.01	26.7%/NA	<0.01
	(<2/≥2 cm)	2nd	21/6	63.7%/33.3%	<0.01	21.5%/NA	0.15
	(<2/≥2 cm)	3rd	17/10	74.5%/30.0%	<0.01	25.0%/NA	0.17
Number of tumors	(≤1/≥2)	1st	21/6	53.8%/66.7%	0.96	11.0%/33.3%	0.28
		2nd	15/12	55.0%/58.3%	0.59	16.3%/16.7%	0.54
		3rd	14/13	50.0%/64.8%	0.3	8.0%/25.0%	0.15
Vascular involvement	(Positive/negative)	1st	19/8	66.7%/37.5%	0.56	18.2%/12.5%	0.42
		2nd	24/3	60.3%/33.3%	0.27	18.7%/NA	0.34
		3rd	23/4	67.6%/NA	<0.01	19.4%/NA	<0.01

ICG-r15: Indocyanine green retention rate at 15 minutes; NA: not applicable; RFA: radiofrequency ablation; PIVKA-II: protein induced by vitamin K absence or antagonist-II.

24). The prognostic factors of OS and DFS were calculated using data on not only third liver resection but also first and second surgery. Clinical information including main tumor size and tumor maker levels could be prognostic factors of third liver resection for re-recurrent HCC.

Three previous studies have evaluated the long-term outcomes of third or more liver resection, as shown in Table V (10, 23, 24). The OS and DFS rates in this study were compared with those of previous reports. Only one of these studies has investigated the prognostic factors of patients who underwent third or more liver resection. Results showed that a tumor size of ≥5 cm and a disease-free interval of <1 year were significant predictors of poor OS and DFS, respectively, based on a multivariate analysis (24). These results are in accordance with our findings.

Unlike the postoperative outcomes in previous systematic reviews on second liver resection for recurrent HCC, the OS rates in this study did not significantly decrease

Table V. *Previous studies on the long-term outcomes of third or more hepatectomy for re-recurrent hepatocellular carcinoma.*

Year	Author (Ref)	Number of patients	Follow-up period	5-year overall survival rate	5-year disease-free survival rate
2009	CC. Wu (10)	35	30 months (median)	59.4%	33.8%
2013	Y. Yamashita (23)	46	52 months (mean)	43%	19%
2015	Y. Mise (24)	110	38.4 months (median)	68.9%	12.6%

(11, 20). However, the median DFS decreased. These reports have shown that time to recurrence, need for blood transfusion, microvascular permeation, tumor number and size, underlying liver functional status and reserve, and macrovascular invasion were the prognostic factors associated with survival based on multivariate analyses conducted at >1 time point (11). Unlike other studies, our study found that all predictors except tumor number and requirement of blood transfusion were predictors.

The abovementioned comparison with previous reports indicates that the OS of patients who undergo third liver resection for re-recurrent HCC is similar to that of patients who undergo second liver resection. Moreover, some prognostic factors were similar between second and third liver resection. In addition, our research revealed that disease staging at re-recurrence and clinical information on previous surgery such as main tumor size and tumor marker level could be prognostic factors and, therefore, might be a determinant of third hepatectomy for re-recurrent HCC.

With the growing adoption of minimally invasive surgery, some reports have indicated the efficacy and safety of laparoscopic repeat liver resection in selected patients with recurrent HCC (29-31). When combined with our findings, these results suggest that a third liver resection using a minimally invasive approach could be developed as a feasible treatment option for re-recurrent HCC.

Study limitations. The number of patients was low, and only patients who underwent three hepatectomy procedures at our institution were included. These could have caused decreased statistical power. Furthermore, as mentioned in previous studies, retrospective findings might have been affected by selection bias as surgical treatments were offered to patients with favorable tumor characteristics and liver function (24).

Conclusion

The long-term outcomes of 27 patients who underwent third hepatic resections for re-recurrent HCC in this study were similar to those of patients in previous reports. In addition to the prognostic factors of survival in patients who undergo second hepatectomy, clinical information on previous surgeries including tumor size and tumor marker level can be a valuable predictor of survival after third hepatectomy against re-recurrent HCC.

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None.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Mayuko Kori: conceptualization, methodology, formal analysis, investigation, resources, data curation, writing – original draft, writing – review and editing, and visualization. Kei Shimada: methodology, investigation, and writing – review and editing. Takuya Hashimoto: conceptualization, methodology, validation, writing – review and editing, and supervision.

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