Impact of Repeated Hepatectomy on Liver Regeneration in Hepatocellular Carcinoma: A Propensity Score-based Analysis

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Abstract. *Background:* Repeated hepatectomy is one of the most curative treatments for recurrent hepatocellular carcinoma (HCC). However, it is not clear whether the remnant liver has the same regenerative ability in repeated hepatectomy. This study assessed the regenerative ability of remnant liver after primary and secondary hepatectomy. *Patients and Methods:* This study retrospectively assessed 118 patients who underwent curative anatomical liver resection for HCC. The liver regeneration rate (LRR) was calculated by SYNAPSE-VINCENT based on dynamic computed tomography before and 1 month after liver resection. To reduce any bias, the patients were matched at a 2:1 ratio by propensity score matching (PSM) method. *Results:* Before PSM, the laparoscopic radiofrequency-assisted liver resection (LRR) was higher in secondary hepatectomy than in primary ($p=0.027$). After PSM, there was no significant difference in LRR between the two groups ($p=0.088$). Among 10 patients who underwent both primary and secondary hepatectomy, there was no significant difference in LRR at both hepatectomies ($p=0.80$). *Conclusion:* Hepatic regenerative ability after secondary hepatectomy may not be inferior to that after primary hepatectomy.

Hepatocellular carcinoma (HCC) is one of the most common types of cancer in the worldwide and a major cause of death in many countries (1). Although advances in multimodal treatment options have improved the survival rates of patients with HCC, liver resection remains the most effective treatment

(2, 3). HCC often occurs in livers harboring chronic hepatitis or cirrhosis due to hepatitis B and C (4). Approximately 70% of patients with HCC experience intrahepatic recurrence after hepatectomy (5, 6). Although liver function often decreases over that time, the patient has a good prognosis if the recurrent HCC can be treated identically to the primary tumor (7). With modern advances in surgical procedures and devices, repeated liver resection has become widely accepted as one of the most curative treatments ensuring long-term survival and is non-inferior to primary resection if the liver function is good and withstands surgery (8, 9).

The liver is uniquely characterized by its ability for self-regeneration after an injury (10). Therefore, liver resection is expected to be followed by successful liver regeneration. After a large liver resection, sufficient liver regeneration is necessary for preventing postoperative liver failure. Repeated liver resection is based on the same assumptions, but whether the remnant liver has the same regenerative ability as the primary liver is poorly understood. Some previous investigations have concluded that remnant liver has limited regenerative ability (11, 12). Thus, the safety of repeated liver resection is unknown. The present study compared the regenerative ability of remnant liver after primary and repeated liver resection.

Patients and Methods

Patients. The study enrolled 123 patients diagnosed with HCC who had been consecutively treated by anatomical liver resection under laparotomy between January 2009 and June 2014. Surgery was planned by preoperative simulation at the Department of Gastroenterological Surgery, Kumamoto University. After excluding five patients who had undergone portal vein embolization before liver resection, 118 patients were eligible for the study (Figure 1). Among these patients, 103 underwent primary anatomical liver resection. Fifteen patients underwent secondary anatomical liver resection after primary non-anatomical liver resection. Ten patients underwent both primary and secondary anatomical liver resection. Before surgery, each patient provided written informed consent to participate in the

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study. The study complied with ethical guidelines and was approved by the Institutional Ethics Board (IRB approved number 1040). Preoperative blood was collected within 4 days before liver resection, and postoperative blood was collected on day 28 following surgery. In order to detect any intrahepatic recurrence or distant metastases, ultrasonography and dynamic computed tomography (CT) were performed every 3-4 months in outpatient clinics.

Resection strategy and assessment of liver regeneration. The tumor-bearing portal vein was delineated by dynamic CT (slice thickness 2.5 mm). Anatomical resection was systematically preferred if it preserved the patient's liver function. The estimated resection volumes of all patients scheduled for anatomical liver resection were calculated based on the volume of territories of the tumor-bearing portal vein using SYNAPSE-VINCENT® (Fujifilm Medical Co., Tokyo, Japan). The remnant liver volume after liver resection (RLV) (cm³) was estimated from the future remnant liver volume based on dynamic CT preoperatively; $RLV = \text{preoperative total liver volume (cm}^3\text{)} - \text{estimated resection volume (cm}^3\text{)}$. All patients were examined by dynamic CT 1 month after liver resection, and also calculated liver volume 1 month after liver resection (LV 1 month) (cm³).

The following parameters were calculated by the following formulae:

Liver regeneration rate (LRR) (%) = $100 \times (LV \text{ 1 month} / RLV)$
 Simulated residual liver (%) = $100 \times (RLV / \text{total liver volume})$
 Residual liver 1 month after (%) = $100 \times (LV \text{ 1 month} / \text{total liver volume})$

The study comprised two parts: A: examination of background characteristics; B: comparison between secondary and primary hepatectomy in the same patients (Figure 1).

Statistical analysis. All *p*-values were two-sided. Values are expressed as the median (range). Qualitative and quantitative variables were compared using chi-squared and Mann-Whitney *U*-tests, respectively. To reduce any bias between the primary and secondary hepatectomy groups, the backgrounds of the patients in the two groups were matched by the propensity score matching (PSM) method implemented in R software version 3.1.1 (<http://www.r-project.org>). The patients undergoing primary and secondary hepatectomy were matched in a 2:1 ratio. Nine variables were entered into the propensity model (age, sex, extent of hepatectomy, cholinesterase, operation time, blood loss, fibrosis, total liver volume, and estimated resected volume). The caliper was set to 0.10. All statistical analyses were performed in JMP Version 11 (SAS Institute, Cary, NC, USA), with *p*<0.05 defined as statistically significant.

Results

Study A. Background characteristics: We first compared the patient background and perioperative factors between patients who underwent primary (n=103) and secondary (n=25) hepatectomy in Study A (Figure 1). In the secondary hepatectomy group, the median period between primary and secondary surgery was 29 months. Table I shows the comparison of the patient clinicopathological characteristics

in Study A. Several background factors, including preoperative liver function, RLV, and estimated resection volume per total liver volume, were almost identical in both groups. Factors with marginally significant difference between the two groups were sex (*p*=0.088), fibrosis (*p*=0.069), extent of hepatectomy (*p*=0.021) and blood loss (*p*=0.074). Owing to these marginal differences, the patient backgrounds were matched by PSM. After PSM, we successfully matched 40 patients in the primary and 20 patients in the secondary hepatectomy group, with no significant differences in the main characteristics of the two groups (Table I).

Liver regeneration after liver resection in the secondary and primary hepatectomy groups: To compare the LRRs between the two groups, we recorded the changes in the percentage of liver volume at different time points and calculated the LRRs. The results before PSM are presented in Figure 2A. There was no difference in simulated RLV rate between two groups ($72.0 \pm 14.1\%$ vs. $70.4 \pm 12.5\%$, *p*=0.57). However, LRR was significantly higher in the secondary group than in the primary hepatectomy group ($24.8 \pm 25.1\%$ vs. $15.6 \pm 19.9\%$, *p*=0.027). After PSM, there were no significant differences in RLV 1 month after hepatectomy [secondary (n=20): $72.8 \pm 15.2\%$ vs. primary (n=40): $72.8 \pm 10.6\%$, *p*=0.99] and LRR [secondary (n=20): $20.5 \pm 19.8\%$ vs. primary (n=40): $11.6 \pm 18.0\%$, *p*=0.088] (Figure 2B). Postoperative albumin levels, total bilirubin levels, platelet counts, prothrombin activities, and cholinesterase levels on postoperative day 28 were identical in both groups before and after PSM.

Study B. Comparison between secondary and primary hepatectomy in the same patients: We further assessed liver regeneration after primary or secondary hepatectomy in same patients. Ten patients who had undergone anatomical liver resection at both primary and secondary were enrolled into Study B (Figure 1). The median period between primary and secondary hepatectomy was 33.5 months. Table II shows the clinicopathological characteristics of the patients at the times of primary and secondary hepatectomy. Although the extent of liver resection was larger at secondary hepatectomy, the simulated RLVs and estimated resection liver volume rates were identical at both times. Other background factors were also identical.

Figure 3 shows the liver volume and the LRRs of the patients after their primary and secondary hepatectomies before, simulated residual after, and 1 month after hepatectomy. The LRRs were unchanged after second hepatectomy and after primary hepatectomy ($19.7 \pm 19.1\%$ and $17.8 \pm 13.6\%$, respectively, *p*=0.80). Among the postoperative liver functions at day 28, only the prothrombin activity was significantly lower after the secondary hepatectomy than after the primary hepatectomy.

Table I. Characteristics of patients undergoing primary and secondary hepatectomy (Hx) before and after propensity score matched (PSM) analysis in Study A.

linicopathological factor	Before PSM			After PSM		
	Primary Hx (n=103)	Secondary Hx (n=25)	p-Value	Primary Hx (n=40)	Secondary Hx (n=20)	p-Value
Gender, n						
Male/female	79/24	23/2	0.088	36/4	18/2	>0.99
Age, years						
Median (range)	69 (35-83)	69 (36-79)	0.40	70.5 (35-83)	70 (54-79)	0.60
HBs-Ag, n (%)						
Positive	34 (33%)	13 (52%)	0.14	12 (30%)	9 (45%)	0.39
HCV-Ab, n (%)						
Positive	41 (40%)	9 (36%)	0.73	14 (35%)	8 (40%)	0.92
Diabetes mellitus, n (%)						
Yes	22 (21%)	2 (8%)	0.12	9 (23%)	2 (10%)	0.41
Albumin, g/dl						
Median (range)	4.2 (2.8-5.1)	4.1 (2.8-4.7)	0.39	4.2 (3.0-5.1)	4.1 (2.8-4.7)	0.16
PT, %						
Median (range)	100 (65-150)	98 (78-126)	0.37	102 (65-117)	99 (78-113)	0.19
ChE, U/l						
Median (range)	255 (118-522)	280 (119-351)	0.62	268 (132-364)	277 (119-337)	0.50
ICGR15, %						
Median (range)	10.7 (2.0-29.6)	12.9 (5.9-33.0)	0.24	10.7 (3.3-26.9)	15.4 (8.7-33)	0.24
Child-Pugh classification, n						
5/6/7	90/12/1	22/3/0	0.89	37/2/1	18/2/0	0.52
Stage of fibrosis, n						
F0-2/F3-4	66/37	11/14	0.069	23/17	9/11	0.52
Extent of hepatectomy, n						
1 Segment	3	5	0.021	2	4	0.069
2 Segments	49	10		25	7	
≥3 Segments	51	10		13	9	
Total liver volume, cm ³						
Median (range)	1195 (610-2103)	1116 (780-2436)	0.93	1193 (610-1716)	1203 (780-2436)	0.87
RLV, cm ³						
Median (range)	804 (384-1671)	787 (431-1611)	0.63	824 (502-1426)	810 (431-1611)	0.74
Estimated resection volume/ total liver volume, %						
Median (range)	30.7 (1.5-70.9)	25.5 (5.7-55.6)	0.64	26.8 (9.4-54.1)	24.3 (5.4-55.1)	0.54
Operative time, min						
Median (range)	415.5 (152-753)	404 (268-636)	0.79	421 (152-720)	400 (268-636)	0.78
Blood loss, g						
Median (range)	427.5 (23-3985)	530 (39-10623)	0.073	448 (43-1580)	483 (39-1055)	0.84
Complication, n (%)						
(Clavien-Dindo ≥3)	18 (17%)	8 (32%)	0.083	7 (18%)	6 (30%)	0.28

Discussion

Repeated liver resection is one of the most effective treatments for patients with intrahepatic recurrence (8, 9). However, repeated liver resection was reported to increase the morbidity and mortality of surgery because each liver resection results in postoperative adhesions, which increase intraoperative blood loss and operative time (13). In addition, it is not clear whether the remnant liver has the same regenerative ability as primary liver. This is a factor which should be known in order to prevent liver failure after

repeated liver resection. In this study, we assessed the regenerative ability between patients undergoing primary and secondary hepatectomy who underwent more than segmentectomy. Unexpectedly, although the regenerative ability was significantly higher in the group which underwent secondary than in those which underwent primary hepatectomy, this superiority diminished after PSM in Study A. Moreover, the regenerative abilities after primary and secondary hepatectomy were similar in a subgroup analysis of same 10 patients who had undergone both primary and secondary hepatectomy on Study B. Many factors affect liver

Figure 1. Study design. Hx, Hepatectomy.

Figure 2. Study A: Percentage of liver volume before, simulated residual after, and liver volume at 1 month after hepatectomy (Hx) in the primary and secondary hepatectomy groups before (A) and after (B) propensity-score matching (PSM) method. The table below the figure shows the percentage increase in liver volume between the day and 1 month after hepatectomy. Data are shown as mean±SD.

regeneration after hepatectomy, such as the degree of liver parenchymal loss, liver fibrosis, and the molecular mechanism of regeneration (14-20). However, the degree of liver parenchymal loss and fibrosis did not significantly differ between the two groups. Moreover, there was no

difference in liver regeneration in same 10 patients on Study B. The superior liver regenerative ability after secondary hepatectomy is difficult to explain from the variables investigated in this study. The status of molecular factors affecting liver regeneration, such as tumor necrosis factor-

Table II. Characteristics of patients undergoing both primary and secondary hepatectomy (Hx) in Study B (n=10).

Clinicopathological factor		Primary Hx	Secondary Hx	p-Value
Gender, n	Male/female	10/0		
Age, years	Median (range)	69 (37-77)	72 (41-79)	0.63
HBs-Ag, n (%)	Positive	6 (60%)		
HCV-Ab, n (%)	Positive	3 (30%)		
Diabetes mellitus, n (%)	Yes	0 (0%)		
Albumin, g/dl	Median (range)	4.3 (4.1-4.6)	4.3 (3.7-4.5)	0.44
PT, %	Median (range)	96 (84-111)	95 (82-115)	0.86
ChE, U/l	Median (range)	180 (136-408)	283 (158-339)	0.095
ICGR15, %	Median (range)	11.0 (3.2-16.2)	15.0 (7.9-20.3)	0.16
Child-Pugh classification, n	5/6/7	10/0/0	10/0/0	>0.99
Stage of fibrosis, n	F0-2/3/4	5/5	5/5	>0.99
Extent of hepatectomy, n	1 Segment	2	0	0.014
	2 Segments	8	6	
	≥3 Segments	0	4	
Total liver volume, cm ³	Median (range)	1099.5 (857-1502)	961.5 (780-1661)	0.66
RLV, cm ³	Median (range)	939 (682-1233)	788.5 (431-1394)	0.22
Estimated resection volume/total liver volume, %	Median (range)	18.7 (7.6-24.1)	22.7 (9.8-55.6)	0.13
Operative time, min	Median (range)	362 (274-442)	405 (268-636)	0.13
Blood loss, g	Median (range)	267 (30-560)	515 (39-756)	0.070
Complication, n (%)	Clavien-Dindo ≥3	0 (0%)	2 (20%)	0.084

Figure 3. Study B: Percentage of liver volume before, simulated residual after, and liver volume at 1 month after hepatectomy (Hx) in the group which underwent primary and secondary hepatectomy. The table below the figure shows the percentage increase in liver volume between the day and 1 month after hepatectomy. Data are shown as mean±SD.

alpha, interleukin-6 and the nuclear bile salt receptor, farnesoid X receptor, might differ between patients undergoing primary and secondary liver resection. Further studies are required to explain this.

Modern imaging diagnosis methods such as magnetic resonance imaging and contrast-enhanced ultrasonography enable the early and accurate identification of intrahepatic recurrence. Surgical techniques and perioperative management have also advanced, increasing the safety of repeated liver resection (21). Furthermore, anatomical liver resection better improves the prognosis of patients with HCC than non-anatomical liver resection (22, 23). Thus, it is very important for repeated liver resection to be anatomical, and the number of such patients is expected to increase. To remove regions of the tumor-bearing portal vein safely and accurately, even when planning a secondary liver resection, preoperative simulation and volumetry are required. The non-inferiority of liver regenerative ability after secondary liver resection suggests that when planning a repeat liver resection, the volumetric methods applied at primary liver resection can also be applied at secondary liver resection.

There were certain limitations to this study. Firstly, this study analyzed a relatively small number of patients in a single-institute retrospective study, which may introduce unexpected bias. Secondly, we evaluated liver regeneration only 1 month after hepatectomy by CT volumetry and from blood biochemical findings. To more accurately evaluate the functional liver regeneration, a functional evaluation tool could be applied (24, 25).

In conclusion, the regenerative ability of liver at secondary resection was not inferior to that at primary liver resection. Therefore, the remnant liver might be expected to generate equally well after primary liver resection and repeated resection.

Conflicts of Interest

The Authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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