Original Article

DOI: 10.5582/bst.2020.03329

Selection of patients with esophageal varices for liver resection of hepatocellular carcinoma

Yutaka Midorikawa[1,*], Tadatoshi Takayama[1], Tokio Higaki[1], Osamu Aramaki[1], Nao Yoshida[1], Kenichi Teramoto[1], Shingo Tsuji[2]

[1] Department of Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan;
[2] Genome Science Division, Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo, Japan.

SUMMARY The presence of esophageal varices (EV) is a phenotype of portal hypertension, and the indications of liver resection for hepatocellular carcinoma (HCC) in patients with concomitant EV are conflicting. This retrospective study aimed to elucidate if there is justification for liver resection in patients with EV. The surgical outcomes were compared between the patients who underwent resection for HCC with EV (EV group) and those without EV (non-EV group) after propensity-score matching. More bleeding was prevalent ($P < 0.001$) and refractory ascites was more frequently observed ($P = 0.031$) in the EV group ($n = 277$) compared with the non-EV group ($n = 277$); however, the numbers of patients with morbidities ($P = 0.740$) and re-operation ($P = 0.235$) were not significantly different between the two groups. After a median follow-up period of 3.0 years, the median overall and recurrence-free survival periods of patients with EV were 4.8 years (95% confidence interval [CI], 4.1-5.9) and 1.7 years (1.5-2.0), respectively, and were significantly shorter than those of patients without EV (7.6 years [95% CI, 6.3.9.7], $P < 0.001$, and 2.2 years [1.9-2.5], $P = 0.016$). On multivariate analysis, the independent factors for overall survival in the EV group were indocyanine green clearance rate at 15 minutes, des-gamma carboxyprothrombin, and the presence of multiple tumors. Considering that liver resection for patients with EV can be safely performed, it should not be contraindicated. However, surgical outcomes of these patients were unsatisfactory, suggesting that candidates for resection for HCC should be carefully selected.

Keywords liver resection, esophageal varices, hepatocellular carcinoma

1. Introduction

The presence of esophageal varices (EV) is a phenotype of portal hypertension (*1*). The Barcelona Clinic Liver Cancer (BCLC) staging system proposed that liver resection is recommended only for Child-Pugh class A and B patients with a single hepatocellular carcinoma (HCC); additionally, those with portal hypertension are not candidates for operation due to the high frequency of postoperative mortality and worse patient survival (*2*). In contrast, as long as EVs are properly managed, based on the endoscopic findings before surgery, the presence of EV is not included in the exclusion criteria for resection in the treatment algorithms, according to the Clinical Practice Guidelines for Hepatocellular Carcinoma in Japan (*3*).

The indications for liver resection in patients with HCC and EV are conflicting. Consistent with the BCLC staging system, previous reports demonstrated that patients with portal hypertension were not candidates for liver resection due to concomitant cirrhosis and thrombocytopenia, especially in Western countries (*4,5*). On the other hand, recent studies have reported that the presence of EV (*6-8*) or portal hypertension (*9-12*) is not an absolute contraindication for liver resection because the surgical outcomes of patients with HCC who underwent appropriate management for EV were acceptable. Thus, the outcomes of surgical resection for HCC in patients with portal hypertension are not completely understood.

To elucidate if there is justification for liver resection for HCC in patients with EV, we compared the surgical outcomes of patients with HCC who had EV to those of patients who did not have EV, and estimated the safety of operation and prognosis in these patients.

2. Patients and Methods

2.1. Patients

The study group was comprised of patients who

underwent liver resection for HCC at Nihon University Itabashi Hospital between 2000 and 2018. Among these patients, those who underwent initial and curative resection were included in this study. All patients were closely observed during each outpatient office visit after the operation. Each participant provided written, informed consent, and this study was approved by the institutional review board of Nihon University (RK-200908-8). The study design was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

2.2. Esophageal varices

Upper gastrointestinal endoscopy was performed as previously described (*13*). Briefly, endoscopy was performed by two operators with expertise in the assessment of patients before surgery. Subsequently, patients with gastric or esophageal varices were defined as the EV group, while those without varices were part of the non-EV group. Surgical outcomes between the two groups were compared after propensity-score matching to adjust for patient background information, including age, sex, hepatitis viral infection, alcohol abuse, diabetes mellitus, tumor status, and tumor markers. Propensity scores were matched using a caliper width of 0.2 and one-to-one pair matching was carried out.

EVs were staged as none (no veins above the esophageal mucosal surface; F0), small (minimally elevated veins above the esophageal mucosal surface; F1), medium (tortuous veins occupying less than one-third of the esophageal lumen; F2), or large (those occupying more than one-third of the esophageal lumen; F3), according to the General Rules for Recording Endoscopic Findings of Esophagogastric Varices based on Beppu's classification (*14*). Interventional treatments, such as endoscopic variceal ligation, are required for severe EVs (F2/F3 EVs or F1 EVs with red-color signs) before surgery (*13*).

2.3. Surgical procedure

All patients underwent liver resection *via* an open approach. The indications for liver resection were determined based on the Clinical Practice Guidelines for Hepatocellular Carcinoma in Japan (*3*), and the surgical procedure was determined by assessing the liver functional reserve, including the total serum bilirubin level and indocyanine green clearance rate at 15 minutes (ICGR15) (*15*). The liver was transected under ultrasonographic guidance using the clamp-crushing method with the inflow-blood-occlusion technique (*16*). Curative resection was defined as the complete removal of recognizable HCC with macroscopically tumor-free surgical margins. Anatomical resection was defined as liver resection over subsegmentectomy, and major resection included segmentectomy, hemihepatectomy, and trisegmentectomy.

2.4. Follow-up after surgery

All patients were followed for postoperative recurrence, as described previously (*17*). Briefly, tumor marker levels, such as alpha-fetoprotein (AFP) and des-gamma carboxyprothrombin (DCP) were measured, and imaging modalities, including computed tomography and ultrasonography, were performed every three months in all patients. Recurrence was diagnosed by dynamic computed tomography and/or gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging. The date of recurrence was defined as the date of examination when HCC recurrence was noted. In patients with recurrent HCC, the recurrence-free period was defined as the time between the date of surgery and the date of recurrence. Recurrent HCC was managed aggressively by performing repeated liver resection, transcatheter arterial chemoembolization, radiofrequency ablation, and chemotherapy according to the status of the HCC and liver function at the time of recurrence.

2.5. Complications

Complications specific to liver resection were defined as described previously (*18*). Morbidities were defined as complications with Clavien-Dindo classification grade ≥ 3b (*19*). In-hospital death was defined as the state of death within 90 days after liver resection.

2.6. Statistical analyses

Data collected from each group were statistically analyzed using Fisher's exact test and Wilcoxon rank-sum test, as appropriate. Survival rates were calculated using the Kaplan-Meier method and subsequently compared using the log-rank test. Prognostic factors for overall survival were identified using the Cox proportional hazards regression model. A P-value < 0.10 was set as the cutoff value for elimination. The following 17 variables, which were considered potential confounders, were examined: age (≥ *vs*. < 70 years), sex, positive for hepatitis B virus and C virus infection, alcohol abuse, diabetes mellitus, Child-Pugh classification (5 *vs*. 6 or 7), platelet count (≥ *vs*. $10 \times 10^4/\mu L$), ICGR15 (≥ *vs*. < 15%), serum AFP level (≥ *vs*. < 100 ng/mL), serum DCP level (≥ *vs*. < 100 ng/mL), and pathological findings of the main tumor [maximal tumor size [≥ *vs*. < 3.0 cm], multiple tumors (solitary *vs*. tumor number ≥ 2], tumor thrombus, tumor differentiation grade [poorly *vs*. well or moderately], surgical margin, and liver cirrhosis). All statistical analyses were performed using JMP version 12.0.1 (SAS Institute, Cary, NC, USA) and R version 3.4.0 (The R Foundation for Statistical Computing,

Vienna, Austria). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patients

A total of 1,302 patients underwent initial and curative resection for HCC; they were divided into patients with gastric or esophageal varices (EV group, $n = 277$) and those without varices (non-EV group, $n = 1,025$) by upper gastrointestinal endoscopy before surgery (Figure 1). Before propensity-score matching, the liver function was worse, and hepatitis C virus infection ($P < 0.001$) and liver cirrhosis were more frequent ($P < 0.001$) in the EV group (Tables 1 and 2). In contrast, tumor status was more advanced, and AFP levels were lower ($P = 0.041$), while the DCP level was higher ($P = 0.004$) in the non-EV group. In the EV group, 56 patients (20.2%) were diagnosed with severe EV and underwent endoscopic variceal ligation.

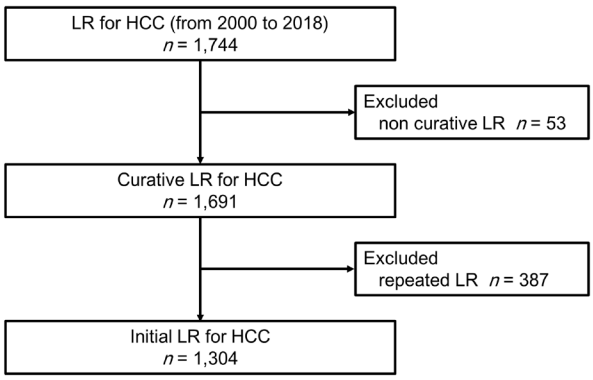

Figure 1. Flow diagram of patient recruitment and follow-up. LR, liver resection; HCC, hepatocellular carcinoma

3.2. Operative procedure

After one-to-one propensity matching, patients in the non-EV group underwent anatomic resection ($P = 0.002$) and major liver resection ($P = 0.003$) more frequently compared with those in the EV group (Table 3). The amount of bleeding was higher ($P < 0.001$) and the overall complication rate was more frequent ($P = 0.005$) in the EV group; however, the morbidity rate (Clavien-Dindo classification grade ≥ 3b) was not different between the two groups ($P = 0.740$). Regarding complications specific to liver resection for HCC, there

Table 1. Patient background

Items	Before propensity-score matching			After propensity-score matching		
	EV (+) ($n = 277$)	EV (−) ($n = 1,025$)	*P*	EV (+) ($n = 277$)	EV (−) ($n = 277$)	*P*
Age, years	68 (36-85)	69 (32-86)	0.093	68 (36-85)	68 (35-85)	0.774
Sex, male	201 (72.5)	792 (77.2)	0.111	201 (72.5)	202 (27.0)	1
Hepatitis B	42 (15.1)	169 (16.4)	0.646	42 (15.1)	52 (18.7)	0.308
Hepatitis C	173 (62.4)	569 (45.7)	< 0.001	173 (62.4)	161 (58.1)	0.339
Alcoholic	76 (27.4)	273 (26.6)	0.818	76 (27.4)	79 (28.5)	0.849
Diabetes mellitus	79 (28.5)	342 (33.3)	0.129	79 (28.5)	73 (26.3)	0.634
Child-Pugh, ≥ 6	96 (34.6)	196 (19.1)	< 0.001	96 (34.6)	54 (19.4)	< 0.001
Platelet, × 10^4/μL	10.4 (3.8-66.0)	15.8 (2.4-68.6)	< 0.001	10.4 (3.8-66.0)	14.7 (2.4-51.0)	< 0.001
ICGR15, %	17.8 (2.0-65.5)	11.6 (1.3-56.4)	< 0.001	17.8 (2.0-65.5)	12.1 (1.9-56.4)	< 0.001
Alpha-fetoprotein, ng/mL	19 (1-39,596)	12 (1-541,432)	0.041	19 (1-39,596)	18 (1-11,927)	0.751
DCP, mAU/mL	50 (1-75,000)	70 (1-75,000)	0.004	50 (1-75,000)	46 (6-21,851)	0.869

Data are presented as median (range) or *n* (%). ICGR15, indocyanine green clearance rate at 15 minutes; DCP, des-gamma-carboxy prothrombin.

Table 2. Pathology

Items	Before propensity-score matching			After propensity-score matching		
	EV (+) ($n = 277$)	EV (−) ($n = 1,025$)	*P*	EV (+) ($n = 277$)	EV (−) ($n = 277$)	*P*
Tumor size, cm	2.8 (0.7-13.0)	3.4 (0.5-21.0)	< 0.001	2.8 (0.7-13.0)	2.9 (0.5-16.0)	0.948
Multiple	72 (25.9)	254 (24.7)	0.696	72 (25.9)	76 (27.4)	0.773
Vascular invasion	64 (23.1)	319 (31.1)	0.009	64 (23.1)	64 (23.1)	1
Differentiation grade, por	25 (9.0)	114 (11.1)	0.380	25 (9.0)	27 (9.7)	0.884
Tumor exposure, positive	20 (7.2)	91 (8.8)	0.466	20 (7.2)	17 (6.1)	0.734
Cirrhosis	188 (67.8)	260 (25.3)	< 0.001	188 (67.8)	90 (32.4)	< 0.001

Data are presented as median (range) or *n* (%).

were two patients (0.3%) with liver failure only in the EV group (P = 0.499), and refractory ascites was more frequent in the EV group (17 patients [6.1%]) than in the non-EV group (six patients [2.1%]) (P = 0.031).

In this series, 17 (6.1%) patients in the EV group and 10 (3.6%) patients in the non-EV group underwent re-operation (P = 0.235) for severe postoperative complications, including intraperitoneal hemorrhage in 11 patients (1.9%), intra-peritoneal abscess in five patients (0.9%), bile leakage in four patients (0.7%), portal vein thrombus in two patients (0.3%), wound infection in two patients (0.3%), gastrointestinal perforation in two patients (0.3%), and ileus in one patient (0.2%). Two patients (0.3%) died after the operation; one died from rapture of the varices, while another died from liver failure in the EV group (P = 0.499).

Table 3. Operative data

Items	EV (+) (n = 277)	EV (−) (n = 277)	P
Operative time, min	312 (113-632)	300 (97-705)	0.337
Clamp time, min	66 (0-485)	66 (0-516)	0.606
Bleeding, mL	316 (5-3,887)	235 (10-3,500)	< 0.001
Transfusion	17 (6.1)	15 (5.4)	0.855
Anatomic resection	66 (23.8)	99 (35.7)	0.002
Major resection	13 (4.6)	33 (11.9)	0.003
Complications			
Overall†	131 (47.2)	98 (35.3)	0.005
Liver failure	2 (0.7)	0	0.499
Ascites	17 (6.1)	6 (2.1)	0.031
Morbidities	21 (5.7)	18 (4.3)	0.740
Re-operation	17 (6.1)	10 (3.6)	0.235
Intra-peritoneal hemorrhage	6 (2.1)	5 (1.8)	1
Intra-peritoneal abscess	4 (1.4)	1 (0.3)	0.372
Bile leakage	2 (0.7)	2 (0.7)	1
Portal venous thrombus	2 (0.7)	0	0.499
Others	3 (1.0)	2 (0.7)	1
Operative death	2 (0.7)	0	0.499
Hospital stay, days	14 (8-190)	13 (5-81)	0.112

Data are presented as median (range) or n (%). †, Only complications specific to liver resection were enumerated.

3.3. Survival

After a median follow-up of 3.0 years (range, 0.2-16.3), a total of 345 patients (62.2%) had recurrence: 325 patients (94.2%) experienced recurrence in the remnant liver, 11 patients (3.1%) experienced recurrence in the distant sites including the lung, lymph nodes, peritoneum, and bone, and 9 patients (2.6%) had both intra- and extrahepatic recurrence (Table 4). Resection for recurrent HCC was performed more frequently in the non-EV group (P = 0.087).

The median overall and recurrence-free survival periods in the EV group (n = 277) were 4.8 years (95% confidence interval [CI], 4.1-5.9) and 1.7 years (1.5-2.0), respectively, and were significantly shorter compared with those in the non-EV group (n = 277) (7.6 years [95% CI, 6.3-9.7], P < 0.001, and 2.2 years [1.9-2.5], P = 0.016) (Figure 2). The 5-year overall survival rates were 48.9% and 66.5%, and the 5-year recurrence-free survival rates were 19.6% and 27.4% in the EV and non-EV groups, respectively. On multivariate analysis, the independent factors for overall survival

Table 4. Treatment for recurrence

Items	EV (+) (n = 189)	EV (−) (n = 156)	P
Recurrent sites			1
Intrahepatic	178 (94.1)	147 (94.2)	
Distant sites	6 (3.1)	5 (3.2)	
Both	5 (2.6)	4 (2.5)	
Treatments			0.093
Second resection	56 (29.6)	60 (38.4)	
TACE/TAI	118 (62.4)	83 (53.2)	
RFA	2 (1.0)	4 (2.5)	
Chemotherapy	5 (2.6)	8 (5.1)	
Radiation therapy	2 (1.0)	0	
None	5 (2.6)	1 (0.6)	

Data are presented as n (%). TACE, transcatheter arterial chemoembolization; TAI, transcatheter arterial infusion; RFA, radiofrequency ablation.

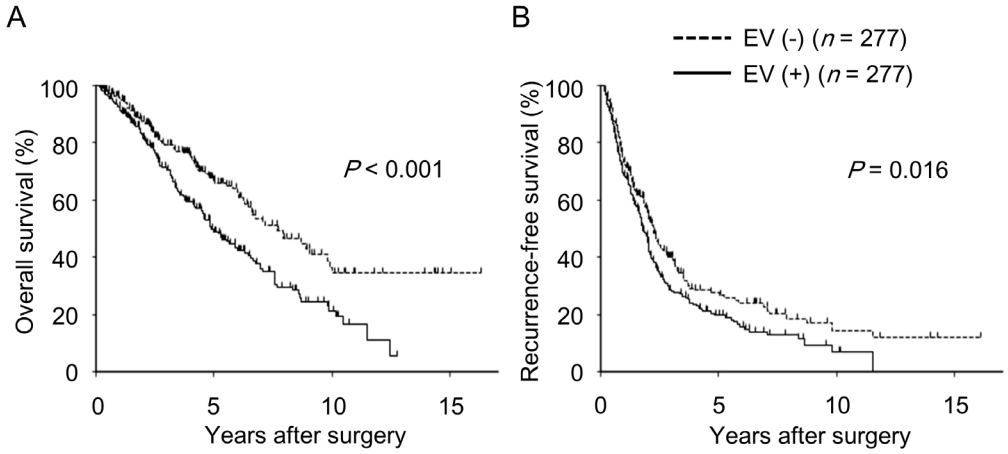

Figure 2. Overall survival and recurrence-free survival of patients with HCC. There were significant differences between patients with EV and those without EV in overall survival **(A)** and recurrence-free survival **(B)**. EV, esophageal varices; HCC, hepatocellular carcinoma

in the EV group were ICGR15 (P = 0.019), DCP (P = 0.002), and multiple tumors (P = 0.016) (Table 5). The median overall survival times were significantly shorter in patients with ICGR15 ≥ 15% (4.6 years [range, 4.1-5.7 years] versus 7.5 years [6.5-9.8 years], P < 0.001), those with DCP ≥ 100 mAU/mL (4.5 years [range, 3.5-6.0 years] versus 6.9 years [6.0-7.6 years], P < 0.001), and those with multiple tumors (4.3 years [range, 3.4-5.7 years] versus 6.7 years [6.0-7.8 years], P < 0.001) in the EV group (Figure 3).

4. Discussion

Our study demonstrated that liver resection for patients with gastric or esophageal varices can be safely performed. However, survival in the EV group was

Table 5. Prognostic factors for survival of patients with EV

Items	Univariate			Multivariate		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Age	1.19	0.85-1.67	0.296			
Sex	0.89	0.62-1.29	0.541			
Hepatitis B	1.04	0.63-1.64	0.847			
Hepatitis C	0.90	0.63-1.30	0.586			
Alcohol	0.90	0.60-1.30	0.594			
Diabetes mellitus	0.82	0.54-1.23	0.363			
Child-Pugh	1.33	0.95-1.86	0.090	1.08	0.76-1.54	*0.545*
Platelet	1.02	0.73-1.43	0.864			
ICGR15	1.57	1.10-2.27	0.011	1.54	1.07-2.26	*0.019*
Alpha-fetoprotein	1.15	0.78-1.66	0.467			
DCP	2.03	1.43-2.85	< 0.001	1.75	1.21-2.52	*0.002*
Tumor size	1.57	1.12-2.20	0.008	1.40	0.98-1.99	*0.059*
Multiple tumor	1.67	1.16-2.37	0.006	1.60	1.09-2.33	*0.016*
Tumor thrombus	1.28	0.86-1.86	0.213			
Differentiation grade	1.02	0.53-1.76	0.947			
Surgical margin	0.94	0.44-1.74	0.858			
Cirrhosis	1.38	0.96-2.04	0.079	1.22	0.82-1.84	*0.327*

EV, esophageal varices; ICGR15, indocyanine green clearance rate at 15 minutes; DCP, des-gamma-carboxy prothrombin.

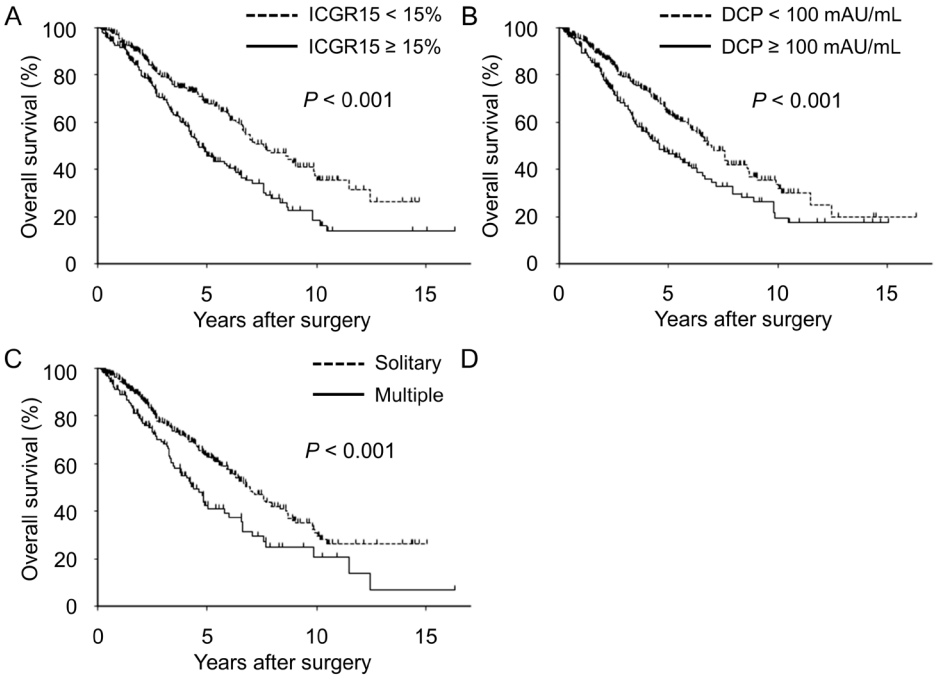

Figure 3. Overall survivals of patients with HCC in the EV group. (A) The median overall survival of patients with ICGR15 ≥ 15% (n =170) was significantly shorter than those with ICGR15 < 15% (n =107) (P < 0.001). **(B)** The median overall survival of patients with DCP ≥ 100 mAU/mL (n =97) was significantly shorter than those with DCP < 100 mAU/mL (n = 180) (P < 0.001). **(C)** The median overall survival of patients with multiple tumor (n =72) was significantly shorter than those with solitary tumor (n =205) (P < 0.001). HCC, hepatocellular carcinoma; EV, esophageal varices; ICGR15, indocyanine green clearance rate at 15 minutes; DCP, des-gamma-carboxy prothrombin.

significantly worse than that in the non-EV group; therefore, indications for liver resection for such patients should be carefully determined.

Liver cirrhosis was more frequent and liver function was poorer in the EV group than in the non-EV group in this study. Consistent with a previous report (*20*), the amount of bleeding was larger in the EV group, despite the fact that major resection was less frequent. Considering that the augmentation of blood loss increases postoperative complications in resection for HCC (*21*), overall complication rate was more frequent in the EV group in this study. In particular, the presence of refractory ascites was more frequent in the EV group (*22,23*). However, the frequency of severe complications, such as liver failure, did not differ between the two groups. Re-operation was often performed for intra-peritoneal hemorrhage, intra-peritoneal abscess, and bile leakage, but its frequency also was not significantly different between the two groups. Because perioperative prophylactic management of gastric or esophageal varices is effective for preventing rupture after surgery (*11,13*), we supposed that liver resection for HCC in patients with varices could be safely performed and should not be contraindicated (*6,8,24*).

Due to poor liver function, anatomical resection and major resection were less frequent in the EV group (*15*); this could negatively affect the survival of patients undergoing non-anatomical resection (*25*). Furthermore, liver function, which is one of the most influential predictors of survival for patients with HCC, was worse (*26,27*). Therefore, consistent with a previous study (*6*), both overall and recurrence-free survival were significantly shorter in the EV group. Nevertheless, it has been shown that patients with HCC with EVs are no longer a contraindication to liver resection because the presence of EV is not always a negative predictor for survival of patients (*6,8,24*). Resection could even provide a survival benefit for patients with portal hypertension and a history of Child-Pugh class A cirrhosis (*10*). Actually, unlike in the BCLC treatment strategy, portal hypertension is not a contraindication for liver resection in the Clinical Practice Guidelines for Hepatocellular Carcinoma in Japan (*3*).

Multivariate analysis showed that ICGR15, DCP, and multiple tumors were independent factors for overall survival (*28,29*). Certainly, liver resection for HCC patients with EV can be safely performed and it may provide survival benefits for such patients. However, the prognosis of patients with unfavorable liver function and advanced HCC is extremely poor. Therefore, indications for liver resection for patients with such factors and EV should be carefully determined.

This study has several limitations. First, the most appropriate control group in this study included patients undergoing other treatments such as transcatheter arterial chemoembolization (*30*) or radiofrequency ablation (*31*). Survival benefits of liver resection could have been revealed for the first time by comparing the survival rates of patients undergoing surgery with those of patients undergoing other treatments. However, this study was based on the patient records of the surgical department; therefore, we have no data for patients with EV who underwent other treatments. Second, this retrospective study was likely affected by selection bias, especially in the EV group. Generally, the liver function of patients with HCC was worse, and patients with poorer general conditions, which did not appear as abnormal laboratory data, might have been excluded.

In conclusion, the survival of patients with gastric or esophageal varices was significantly shorter than that of patients without varices. However, liver resection of such patients could be safely performed and should not be contraindicated. On the other hand, the prognosis of patients with EV who had unfavorable liver function and/or advanced tumor was unsatisfactory; therefore, candidates for surgery for such patients should be carefully selected based on their liver function and tumor status.

Acknowledgements

This work was mainly supported by Japan Agency for Medical Research and Development, Grant/Award Number: JP20hk0102049 and The 106th Annual Congress of The Japan Surgical Society (JSS) Memorial Surgical Research Fund.

References

1. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology. 2017; 65: 310-335.
2. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018; 391:1301-1314.
3. Kokudo N, Takemura N, Hasegawa K, *et al*. Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. Hepatol Res. 2019; 49:1109-1113.
4. Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, Visa J, Bru C, Rodés J. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology. 1996; 111: 1018-1022.
5. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999; 19: 329-338.
6. Harada N, Shirabe K, Maeda T, Kayashima H, Ishida T, Maehara Y. Surgical Resection for Hepatocellular Carcinoma with Concomitant Esophageal Varices. World J Surg. 2015; 39: 2510-2518.
7. Kawano Y, Sasaki A, Kai S, Endo Y, Iwaki K, Uchida H, Shibata K, Ohta M, Kitano S. Short- and long-term outcomes after hepatic resection for hepatocellular carcinoma with concomitant esophageal varices in

patients with cirrhosis. Ann Surg Oncol. 2008; 15: 1670-1676.
8. Liu HT, Cheng SB, Wu CC, Yeh HZ, Chang CS, Wang J. Impact of severe oesophagogastric varices on liver resection for hepatocellular carcinoma in cirrhotic patients. World J Surg. 2015; 39: 461-468.
9. Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, Ramacciato G, Grazi GL, Pinna AD. Is portal hypertension a contraindication to hepatic resection? Ann Surg. 2009; 250: 922-928.
10. Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, Imamura H, Sugawara Y, Kokudo N, Makuuchi M. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology. 2008; 134: 1908-1916.
11. Takemura N, Aoki T, Hasegawa K, Kaneko J, Arita J, Akamatsu N, Makuuchi M, Kokudo N. Hepatectomy for hepatocellular carcinoma after perioperative management of portal hypertension. Br J Surg. 2019; 106: 1066-1074.
12. Ohkubo T, Midorikawa Y, Nakayama H, Moriguchi M, Aramaki O, Yamazaki S, Higaki T, Takayama T. Liver resection of hepatocellular carcinoma in patients with portal hypertension and multiple tumors. Hepatol Res. 2018; 48: 433-441.
13. Yamazaki S, Takayama T, Nakamura M, Higaki T, Matsuoka S, Mizuno S, Moriyama M. Prophylactic impact of endoscopic treatment for esophageal varices in liver resection: a prospective study. J Gastroenterol. 2014; 49: 917-922.
14. Beppu K, Inokuchi K, Koyanagi N, Nakayama S, Sakata H, Kitano S, Kobayashi M. Prediction of variceal hemorrhage by esophageal endoscopy. Gastrointest Endosc. 1981; 27: 213-218.
15. Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S, Kawasaki S. Surgery for small liver cancers. Semin Surg Oncol. 1993; 9: 298-304.
16. Takayama T, Makuuchi M, Kubota K, Harihara Y, Hui AM, Sano K, Ijichi M, Hasegawa K. Randomized comparison of ultrasonic *vs* clamp transection of the liver. Arch Surg. 2001; 136: 922-928.
17. Midorikawa Y, Takayama T, Shimada K, Nakayama H, Higaki T, Moriguchi M, Nara S, Tsuji S, Tanaka M. Marginal survival benefit in the treatment of early hepatocellular carcinoma. J Hepatol. 2013; 58: 306-311.
18. Midorikawa Y, Kubota K, Takayama T, Toyoda H, Ijichi M, Torzilli G, Mori M, Makuuchi M. A comparative study of postoperative complications after hepatectomy in patients with and without chronic liver disease. Surgery. 1999; 126: 484-491.
19. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240: 205-213.
20. Abe H, Midorikawa Y, Mitsuka Y, Aramaki O, Higaki T, Matsumoto N, Moriyama M, Haradome H, Abe O, Sugitani M, Tsuji S, Takayama T. Predicting postoperative outcomes of liver resection by magnetic resonance elastography. Surgery. 2017; 162: 248-255.
21. Aramaki O, Takayama T, Higaki T, Nakayama H, Okubo T, Midorikawa Y, Moriguchi M. Preoperative diagnosis with versus without MRI in resection for hepatocellular carcinoma. Surgery. 2015; 158: 1512-1520.
22. Belli A, Cioffi L, Russo G, Belli G. Liver resection for hepatocellular carcinoma in patients with portal hypertension: the role of laparoscopy. Hepatobiliary Surg Nutr. 2015; 4: 417-421.
23. Itoh S, Uchiyama H, Ikeda Y, Morita K, Harada N, Sugimachi K, Kawanaka H, Korenaga D, Yoshizumi T, Takenaka K, Maehara Y. Post-hepatectomy Refractory Ascites in Cirrhotic Patients with Hepatocellular Carcinoma: Risk Factor Analysis to Overcome this Problematic Complication. Anticancer Res. 2017; 37: 1381-1385.
24. Chang CY, Hsieh WY, Chau GY, Chen PH, Su CW, Hou MC, Lei HJ, Huo TI, Huang YH, Lin HC, Wu JC. Esophageal varices are not predictive of patient prognosis after surgical resection of hepatocellular carcinoma. Eur J Gastroenterol Hepatol. 2018; 30: 1368-1377.
25. Hasegawa K, Kokudo N, Imamura H, Matsuyama Y, Aoki T, Minagawa M, Sano K, Sugawara Y, Takayama T, Makuuchi M. Prognostic impact of anatomic resection for hepatocellular carcinoma. Ann Surg. 2005; 242: 252-259.
26. Ho SY, Liu PH, Hsu CY, Chiou YY, Su CW, Lee YH, Huang YH, Lee FY, Hou MC, Huo TI. Prognostic Performance of Ten Liver Function Models in Patients with Hepatocellular Carcinoma Undergoing Radiofrequency Ablation. Sci Rep. 2018; 8: 843.
27. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, O'Beirne J, Fox R, Skowronska A, Palmer D, Yeo W, Mo F, Lai P, Iñarrairaegui M, Chan SL, *et al.* Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 2015; 33: 550-558.
28. Torzilli G, Donadon M, Belghiti J, Kokudo N, Takayama T, Ferrero A, Nuzzo G, Vauthey JN, Choti MA, De Santibanes E, Makuuchi M. Predicting Individual Survival After Hepatectomy for Hepatocellular Carcinoma: a Novel Nomogram from the "HCC East & West Study Group". J Gastrointest Surg. 2016; 20: 1154-1162.
29. Yagi R, Midorikawa Y, Moriguchi M, Nakayama H, Aramaki O, Yamazaki S, Higaki T, Takayama T. Liver resection for recurrent hepatocellular carcinoma to improve survivability: a proposal of indication criteria. Surgery. 2018; 163: 1250-1256.
30. Cucchetti A, Djulbegovic B, Tsalatsanis A, Vitale A, Hozo I, Piscaglia F, Cescon M, Ercolani , Tuci F, Cillo U, Pinna AD. When to perform hepatic resection for intermediate-stage hepatocellular carcinoma. Hepatology. 2015; 61: 905-914.
31. Zhang K, Jiang L, Jia Z, Zhang Y, He R, Ding Z, Mu Y. Radiofrequency ablation plus devascularization is the preferred treatment of hepatocellular carcinoma with esophageal varices. Dig Dis Sci. 2015; 60: 1490-1501.

Received August 2, 2020; Revised September 12, 2020; Accepted September 27, 2020.

**Address correspondence to:*
Yutaka Midorikawa, Department of Digestive Surgery, Nihon University School of Medicine, 30-1, Oyaguchikami-machi, Itabashi-ku, Tokyo 173-8610, Japan.
E-mail: mido-tky@umin.ac.jp

Released online in J-STAGE as advance publication October 15, 2020.