J Gastrointest Surg (2016) 20:2021–2034
DOI 10.1007/s11605-016-3280-2

ORIGINAL ARTICLE

Surgical Outcomes for the Ruptured Hepatocellular Carcinoma: Multicenter Analysis with a Case-Controlled Study

Shogo Tanaka[1] · **Masaki Kaibori**[2] · **Masaki Ueno**[3] · **Hiroshi Wada**[4] · **Fumitoshi Hirokawa**[5] · **Takuya Nakai**[6] · **Hiroya Iida**[2] · **Hidetoshi Eguchi**[4] · **Michihiro Hayashi**[5] · **Shoji Kubo**[1]

Received: 20 July 2016 / Accepted: 13 September 2016 / Published online: 7 October 2016

Abstract

Background While spontaneously ruptured hepatocellular carcinoma (HCC) has a poor prognosis, the true impact of a rupture on survival after hepatic resection is unclear.

Methods Fifty-eight patients with ruptured HCC and 1922 with non-ruptured HCC underwent hepatic resection between 2000 and 2013. To correct the difference in the clinicopathological factors between the two groups, propensity score matching (PSM) was used at a 1:1 ratio, resulting in a comparison of 42 patients/group. We investigated outcomes in all patients with ruptured HCC and compared outcomes between the two matched groups.

Results Of the 58 patients with ruptured HCC, 7 patients (13 %) died postoperatively. Overall survival (OS) rate at 5 years after hepatic resection was 37 %. Emergency hepatic resection was an independent risk factor for in-hospital death and Child-Pugh class B for unfavorable OS in multivariate analysis. Clinicopathological variables were well-balanced between the two groups after PSM. No significant differences were noted in incidence of in-hospital death (ruptured HCC 12 % vs non-ruptured HCC 2 %, $p = 0.202$) or OS rate (5/10-year; 42 %/38 % vs 67 %/30 %, $p = 0.115$).

Conclusion Emergency hepatic resection should be avoided for ruptured HCC in Child-Pugh class B patients. Rupture itself was not a risk for unfavorable surgical outcomes.

Keywords Child-Pugh class B · Extrahepatic recurrence · Milan criteria

✉ Shogo Tanaka
m8827074@msic.med.osaka-cu.ac.jp

1 Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abenoku, Osaka 545-8585, Japan

2 Department of Surgery, Hirakata Hospital, Kansai Medical University, Hirakata, Osaka, Japan

3 Second Department of Surgery, Wakayama Medical University, Wakayama, Japan

4 Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan

5 Department of General and Gastroenterological Surgery, Osaka Medical College, Takatsuki, Osaka, Japan

6 Department of Surgery, Faculty of Medicine, Kinki University, Osaka-Sayama, Osaka, Japan

Introduction

One life-threatening complication of hepatocellular carcinoma (HCC) is the spontaneous rupture of the tumor, leading to intra-peritoneal hemorrhaging and shock. The incidence of a spontaneous HCC rupture has been reported as 3–26 %[1–5] and is associated with a high rate of in-hospital death (32–75 %).[3,4,6–8] Furthermore, spontaneous HCC rupture is known to occur at the advanced tumor stage in patients with a poor liver function, leading to a poorer prognosis than that of patients with a non-ruptured HCC, even after R0 hepatic resection.[9–11] Thus, the current TNM staging system for HCC, defined by the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC),[12] classifies all ruptured HCCs as T4.

However, the prognostic influence is still controversial. Some articles reported that the rupture itself is not a prognostic factor.[13,14] Discrepancies in patient backgrounds and the liver function might partially influence the prognosis. Thus, an analysis after matching the patients' backgrounds and liver function as well as tumor-related factors will be essential to clarify the impact of the ruptured HCC on postoperative survival.

The high incidence of postoperative recurrence is another issue. The details of postoperative recurrence in patients with ruptured HCC are unclear. Patients who have suffered from spontaneous HCC rupture have a higher incidence of peritoneal dissemination after a hepatic resection than those with a non-ruptured HCC.[15] However, there are some reports that a ruptured HCC did not increase the risk for dissemination after a hepatic resection.[16,17] Furthermore, the recurrence patterns, such as intra- and extrahepatic recurrence, also vary.[13,14]. Thus, because of the low incidence of spontaneous HCC rupture, the heterogeneity of patients, and the choice of treatment at presentation (emergency or staged),[10,14,16,18] the true impact of tumor rupture on survival or recurrence after a hepatic resection has not been clarified.

In the present study, clinical data were collected from six university hospitals. We investigated the clinical findings and surgical outcomes of all patients who had spontaneous HCC ruptures and compared them with the findings of non-ruptured HCC patients to clarify the characteristics of patients with spontaneous rupture of HCC. In addition, after selection by matching at a ratio of 1:1 according to propensity scores, we compared the surgical outcomes and analyzed the true impact of the rupture on survival after hepatic resection.

Materials and Methods

Patients

From January 2000 to December 2013, a total of 58 consecutive patients with spontaneously ruptured HCC underwent R0 hepatic resection at six university hospitals (Department of Hepato-Biliary-Pancreatic Surgery, Osaka City Graduate School of Medicine, Osaka, Japan; Department of Surgery, Hirakata Hospital, Kansai Medical University, Hirakata, Osaka, Japan; Second Department of Surgery, Wakayama Medical University, Wakayama, Japan; Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan; Department of General and Gastroenterological Surgery, Osaka Medical College, Takatsuki, Osaka, Japan; and Department of Surgery, Faculty of Medicine, Kinki University, Osaka-Sayama, Osaka, Japan) (ruptured group). Patients found to have lymph node metastasis, distant organ metastasis, or peritoneal dissemination using preoperative diagnostic imaging or during surgery were excluded from the study. During the same period, 1922 patients underwent curative hepatic resection for a non-ruptured HCC (non-ruptured group). The 58 patients with ruptured HCC were matched at a ratio of 1:1 according to a propensity score[19–21] based on their age, sex, underlying hepatic diseases, liver function test findings, tumor-related factors, histological variables, and type of hepatic resection to adjust for differences between the two groups.

This study was approved by the institutional review board from each participating institution and conducted in accordance with the mandates of the Declaration of Helsinki. Informed consent was obtained from all patients for their data to be used for research purposes.

Parameters

The clinical data of all patients were retrospectively collected, including the patients' baseline characteristics (age, sex [number of males/females]) and number and proportion of patients with positivity for hepatitis B surface antigen (HBV) and for anti-hepatitis C virus antibody (HCV), non-B non-C hepatitis (NBC), alcohol abuse, pathologically proven liver cirrhosis (hepatitis activity index score, fibrosis score 4[22,23]), liver function test findings (serum concentration of total bilirubin, albumin, prothrombin time, aspartate aminotransferase, and alanine aminotransferase, platelet count, and distribution of patients with Child-Pugh class [A/B/C]), tumor-related factors (serum level of alpha fetoprotein [AFP], tumor size, number of patients with a tumor or tumors [solitary or multiple], number and proportion of patients with major vessel invasion [tumor invasion to main or first branch of portal vein and/or to major hepatic vein or inferior vena cava], and distribution of patients with clinical stage without rupture factor according to AJCC/UICC classification), histological variables (number and proportion of patients according to tumor differentiation [well, moderately, poorly, undifferentiated, and unknown], histological number of patients with a tumor or tumors [solitary or multiple], and number and proportion of patients with portal vein invasion and hepatic vein invasion), and number and proportion of the patients according to types of hepatic resection (partial, segmentectomy, sectionectomy, and hemihepatectomy or more). Additionally, in the ruptured group, the symptoms at rupture (number and proportion of patients who complained of abdominal pain and who developed hypovolemic shock), number and proportion of patients with initial treatment for the rupture (transcatheter arterial embolization [TAE], conservative treatment because of spontaneous hemostasis, and emergency hepatic resection), timing of hepatic resection (number and proportion of staged hepatic resection), and duration from the rupture to surgery were investigated. The overall survival (OS) time was defined as the interval from the hepatic resection to the date of death or the last follow-up examination. The recurrence time was defined as the duration between the day of hepatic resection and the day when recurrence was diagnosed by image assessment. The date of follow-up was censored on July 31, 2015. The details regarding recurrence were as follows: presence or absence of dissemination during the follow-up period, intrahepatic or extrahepatic initial recurrence, and initial recurrence met or beyond the Milan criteria.[24]

Types of Hepatic Resection

The hepatic anatomy and type of hepatic resection were classified according to The Brisbane 2000 Terminology of Liver Anatomy and Resections.[25] R0 hepatic resection was defined as the complete macroscopic removal of the tumor.

Follow-Up Methods

All patients were followed up at least every 3 months after discharge. The follow-up evaluations included a physical examination, liver function tests, chest radiographs to check for pulmonary metastases, and ultrasonography, computed tomography, or magnetic resonance imaging to check for recurrence in the remnant liver or other abdominal organs. Chest computed tomography was performed if the chest radiographs showed any abnormalities. Bone metastasis was diagnosed from magnetic resonance imaging and/or bone scintigraphy. Positron emission tomography was performed if necessary. Patients who developed recurrence were treated by appropriate treatments (repeat hepatic resection, ablation therapy, transcatheter arterial chemoemblizaton, sorafenib, or best supportive care; selection of these treatments depended on the recurrent tumor situation.).

Propensity Score Matching (PSM)

To avoid confounding differences in the treatment outcome due to "rupture" with those stemming from baseline differences between the two groups, we performed our analyses not only with the complete patient cohort but also a propensity score-matched subset. Logistic regression was used to calculate propensity scores for patients in the ruptured and non-ruptured groups. The following variables were entered into the propensity model: age, sex, underlying hepatic diseases (presence or absence of HBV and HCV, NBC, alcohol abuse, and liver cirrhosis), liver function tests (serum concentration of total bilirubin, albumin, prothrombin time, AST, and ALT, platelet counts, and Child-Pugh class), tumor-related factors (serum concentration of AFP, tumor size, tumor number, presence or absence of macrovacular invasion, and AJCC/UICC Stage without rupture factor), histological variables (differentiation, tumor number, and presence or absence of portal vein invasion and hepatic vein invasion), and type of hepatic resection. PSM was performed using a 1:1 ratio without replacement and a caliper width of 0.1. Receiver operating characteristic (ROC) curves were used to assess the accuracy of PSM, as a predictor of "rupture" indicated by a propensity score. The resulting subset of score-matched patients in the ruptured and non-ruptured groups was used in subsequent analyses.

Statistical Analysis

Continuous variables are expressed as the median (range). Baseline characteristics between the patients with spontaneous ruptured HCC and the other patients were analyzed using the Mann–Whitney *U* test. Differences in categorical variables were analyzed using the chi-squared test or Fisher's exact test. We used the Kaplan-Meier method to calculate the OS and DFS rates, and differences between the two groups were evaluated using the log-rank test. Cox's proportional hazard model with stepwise variable selection was used to estimate the risk factors for unfavorable survival and recurrence after hepatic resection in patients with ruptured HCC. In this study, continuous values were converted into categorical data using their median values, and all of the variables of patients' backgrounds, liver function test findings, tumor-related factors, pathological variables, and types of hepatic resection were investigated univariately. Variables with a p value <0.10 by a univariate analysis were entered into a multivariate analysis. Logistic regression was used univariately and multivariately to estimate the relative risk of in-hospital death in the ruptured group. The variables in this group with a p value <0.10 by a univariate analysis were also entered into a multivariate analysis. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS® v.22.0 software program (IBM Corp., Armonk, NY, USA).

Results

Clinicopathological Features and Surgical Outcomes of All Patients with a Ruptured HCC

In the 58 patients in the ruptured group, the median age was 65 years, and 50 (86 %) were male (Table 1). The most common initial symptom was abdominal pain (44 patients, 75 %). Ten patients (17 %) developed hypovolemic shock upon admission or soon after admission. All patients were diagnosed as having suffered a spontaneous rupture by a physical examination, diagnostic imaging, and laboratory tests. Emergency TAE was performed in 41 (71 %) of the 58 patients, and hemostasis was achieved in 40 of them (98 %). This led to staged hepatic resection; however, one patient required emergency hepatic resection for intractable bleeding soon after TAE. Emergency hepatic resection without a TAE was performed in four patients, and the remaining 13 patients achieved

Table 1 Clinical characteristics in patients with ruptured and non-ruptured hepatocellular carcinoma who underwent hepatic resection

	Before propensity matching					After propensity matching				
	Ruptured		Non-ruptured		p value	Ruptured		Non-ruptured		p value
	Group		Group			Group		Group		
Variables	($n = 58$)		($n = 1922$)			($n = 42$)		($n = 42$)		
Backgrounds										
Median age (range), years	65	(36–80)	68	(19–89)	0.024	65	(48–79)	65	(47–79)	0.723
Sex (male/female), *n*	50/8		1460/462		0.084	36/6		37/5		1.000
Underlying hepatic diseases					<0.001					0.627
HBV, *n* (%)	24	(44)	352	(18)		19	(45)	15	(36)	
HCV, *n* (%)	18	(29)	1016	(53)		14	(33)	15	(36)	
HBV+HCV, *n* (%)	0	(0)	49	(3)		0	(0)	0	(0)	
NBC, *n* (%)	16	(27)	505	(26)		9	(21)	12	(29)	
Alcohol abuse, *n* (%)	10	(16)	332	(17)	1.000	7	(17)	6	(14)	0.763
Liver cirrhosis, *n* (%)	18	(30)	739	(38)	0.275	13	(31)	14	(33)	0.815
Rupture										
Abdominal pain, *n* (%)	44	(75)				31	(74)			
Shock, *n* (%)	10	(17)				8	(19)			
TAE, *n* (%)	41	(71)				29	(69)			
Conservative treatments, *n* (%)	13	(22)				11	(26)			
Timing of hepatic resection										
Emergency hepatic resection, *n* (%)	5	(9)				2	(5)			
Staged hepatic resection, *n* (%)	53	(91)				40	(95)			
Duration from rupture to surgery, median (range), days	40	(0–129)				43	(0–129)			
Laboratory data										
Total bilirubin, median (range), mg/dL	0.8	(0.3-3.0)	0.7	(0.1-6.0)	0.116	0.8	(0.4-2.5)	0.8	(0.3-6.0)	0.770
Albumin, median (range), g/dL	3.7	(2.0-4.5)	3.9	(1.5-5.2)	0.005	3.8	(2.5-4.5)	3.7	(2.9-4.3)	0.057
Prothrombin time, median (range), %	85	(52–112)	88	(14–143)	0.041	86	(53–112)	82	(59–109)	0.576
Child-Pugh class (A/B/C), *n*	51/7/0		1813/49/2		0.041	40/2/0		41/1/0		0.557
Platelet median (range), $\times 10^6/\mu L$	19.2	(6.4–47.9)	14.7	(0.8–62.3)	<0.001	17.5	(7.9–31.7)	15.9	(3.5–48.2)	0.444
AST, median (range), IU/L	40	(16–135)	41	(7–222)	0.869	36	(16–135)	42	(15–164)	0.376
ALT, median (range), IU/L	33	(7–130)	38	(5–454)	0.335	31	(10–112)	40	(9–270)	0.212
Tumor-related factors										
AFP, median (range), ng/mL	154	(2–261,351)	16.3	(1–1,260,000)	0.001	78.8	(2.0–70,828)	49.5	(2.8–175,000)	0.816
Tumor size, median (range), cm	6.3	(2.2–25.0)	3.5	(0.3–25.0)	<0.001	5.4	(2.2–18.0)	4.4	(2.0–18.0)	0.165

Table 1 (continued)

Variables	Before propensity matching				p value	After propensity matching				p value
	Ruptured Group		Non-ruptured Group			Ruptured Group		Non-ruptured Group		
	(n = 58)		(n = 1922)			(n = 42)		(n = 42)		
Tumor number (solitary/multiple), n	46/12		1485/437		0.874	35/7		35/7		1.000
Major vessel invasion[a], n (%)	4	(11)	76	(4)	0.305	2	(5)	3	(7)	1.000
AJCC/UICC stage (without rupture factor)					0.099					0.256
I, n (%)	42	(72)	1357	(71)		31	(74)	34	(81)	
II, n (%)	6	(10)	373	(19)		6	(14)	1	(2)	
IIIA, n (%)	6	(10)	116	(6)		3	(7)	4	(10)	
IIIB, n (%)	4	(7)	76	(4)		2	(5)	3	(7)	
Histological variables										
Differentiation					0.001					0.299
Well, n (%)	0	(0)	237	(12)		0	(0)	2	(5)	
Moderate, n (%)	35	(59)	1188	(62)		23	(55)	26	(62)	
Poor, n (%)	21	(38)	382	(20)		17	(40)	11	(26)	
Undifferentiated, n (%)	0	(0)	9	(0.5)		0	(0)	0	(0)	
Unknown, n (%)	2	(3)	106	(6)		2	(5)	3	(7)	
Tumor number (solitary/multiple), n	45/13		1540/382		0.618	34/8		35/7		0.776
Portal vein invasion, n (%)	26	(49)	656	(34)	0.094	14	(33)	8	(19)	0.136
Hepatic vein invasion, n (%)	8	(17)	168	(9)	0.235	5	(12)	2	(5)	0.236
Types of hepatic resection										
Partial, n (%)	20	(34)	1017	(53)	0.019	16	(38)	22	(52)	0.118
Segmentectomy, n (%)	10	(17)	262	(14)		8	(19)	3	(7)	
Sectionectomy, n (%)	9	(16)	278	(14)		9	(21)	4	(10)	
Hemihepatectomy or more, n (%)	19	(33)	365	(19)		9	(21)	13	(31)	
In-hospital death, n (%)	7	(13)	39	(2)	<0.001	5	(12)	1	(2)	0.202

AFP alpha fetoprotein, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *AJCC/UICC* American Joint Committee on Cancer/Union for International Cancer Control, *HBV* positivity for hepatitis B surface antigen, *HCC* hepatocellular carcinoma, *HCV* positivity for hepatitis C virus antibody, *NBC* non-B non-C hepatitis, *TAE* transcatheter arterial embolization

[a] Tumor invasion to main or first branch of portal vein and/or to major hepatic vein or inferior vena cava

spontaneous hemostasis. These patients were managed conservatively, including a transfusion to stabilize their general condition. Thereafter, they underwent staged hepatic resection.

The duration from diagnosis of the rupture to surgery was 40 days (range 0–129 days). In-hospital death occurred in seven patients (12 %), with details as follows: 3 of the 5 patients (60 %) who underwent emergency hepatic resection, 4 of the 40 patients (10 %) who underwent staged hepatic resection ($p = 0.021$ vs. emergency hepatic resection), and 0 of the 13 patients (0 %) who were hemodynamically stabilized by conservative treatments followed by hepatic resection ($p = 0.012$ vs. emergency hepatic resection). The causes of in-hospital death in the ruptured group were liver failure ($n = 5$), respiratory failure ($n = 1$), and disseminated intravascular coagulation ($n = 1$).

A multivariate logistic regression analysis indicated that emergency hepatic resection ($p = 0.026$, odds ratio 12.4, 95 % confidence interval [CI] 1.3–113.2) was an independent risk factor for in-hospital death (Table 2). The OS rate at 5 and 10 years after hepatic resection was 37 and 34 %, respectively. The multivariate analysis also indicated that Child-Pugh B was an independent risk factor for an unfavorable OS ($p = 0.035$, hazard ratio 2.80, 95 % CI 1.1–7.3, Table 3). No patients with Child-Pugh class B were alive beyond 37 months after hepatic resection.

Comparisons of the Clinicopathological Features and Surgical Outcome for Patients with a Ruptured HCC and a Non-ruptured HCC (All Populations)

Comparisons between the ruptured group and the non-ruptured group (all populations) are shown in Table 1. Ruptured HCC patients tended to be younger (mean age 65 vs. 68 years old) and have a higher prevalence of HBV infection than the non-ruptured patients. In the liver function tests, the mean serum concentration of albumin and prothrombin time was lower in the ruptured group than in the non-ruptured group. Regarding tumor-related factors, the mean serum level of AFP was higher and tumor size larger in the ruptured group than in the non-ruptured group. According to the AJCC/UICC classification without rupture factor, the proportion of patients with stage III was higher in the ruptured group than in the non-ruptured group. In histological variables, the proportion of patients with poorly differentiated HCC was higher in the ruptured group than in the non-ruptured group. According to the types of hepatic resection, the proportion of patients who underwent a hemihepatectomy or more was higher in the ruptured group than in the non-ruptured group.

The incidence of in-hospital death was higher in the ruptured group than in the non-ruptured group (13 vs. 2 %, $p < 0.001$). The mean and median follow-up periods were 39 and 22 months (range 0–159 months) in the ruptured group, and 49 and 41 months (range 0–174 months) in the non-ruptured group, respectively. There was no significant difference in the DFS rates between the two groups ($p = 0.131$, Fig. 1). However, the OS rates at 3, 5, and 10 years after hepatic resection in the ruptured group were 48, 37, and 34 %, respectively, which were significantly worse than those of the non-ruptured group (78, 65, and 42 %, respectively; $p < 0.001$, Fig. 2). If patients with in-hospital death were excluded, the OS rates at 3, 5, and 10 years after hepatic resection were 55, 42, and 38 % in the ruptured group, and 79, 66, and 43 % in the non-ruptured group, respectively ($p = 0.006$). During the follow-up period, the proportion of patients with postoperative recurrence was similar, with 34 patients (67 %) in the ruptured group vs. 1157 patients (61 %) in the non-ruptured group ($p = 0.471$, Table 4). However, peritoneal dissemination was detected in four (8 %) patients in the ruptured group during the follow-up period ($p = 0.001$), and as the initial recurrence in two of these patients. The incidence of extrahepatic recurrence was higher in the ruptured group than in the non-ruptured group (24 vs. 10 %, $p = 0.022$). Furthermore, the proportion of patients with postoperative recurrence beyond the Milan criteria was significantly higher in the ruptured group than in the non-ruptured group (79 vs. 55 %, $p = 0.005$).

PSM

The logistic regression model of propensity score (within a caliper width of 0.1) in the two groups and the above covariates were appropriately based on the assessment of goodness-of-fit statistics, as proposed by Lemeshow and Hosmer ($p = 0.979$).[26] The ROC area under the curve of the propensity score for rupture was 0.853 (95 % CI = 0.813–0.893). After PSM, 42 patients from each group were selected for further subset analyses.

Comparisons of the Clinicopathological Features and Surgical Outcomes of Patients with a Ruptured HCC and a Non-ruptured HCC (After PSM)

The clinicopathological variables were similar between the two matched groups (Table 1). The incidence of in-hospital death was five patients (12 %) in the ruptured group and one (2 %) in the non-ruptured group ($p = 0.202$). The mean and median follow-up periods were 44 and 25 months (range 1–157 months) in the ruptured group, and 54 and 49 months (range 1.7–142 months) in the non-ruptured group, respectively. There was no significant difference in the DFS rate ($p = 0.624$, Fig. 3) or OS rate ($p = 0.115$, Fig. 4) between the groups. In the rupture group, the OS rate rapidly decreased

Table 2 Risk factors for unfavorable overall survival in patients with ruptured hepatocellular carcinoma after hepatic resection

		Overall survival rate (%)		Univariate	Multivariate		
Variables	*n*	5 years	10 years	*p* value	*p* value	Hazard ratio	(95 % CI)
Backgrounds							
Age							
≥65 years	31	43.0	38.3	0.482			
<65 years	27	29.5	29.5				
Sex				0.546			
Male	50	38.0	34.2				
Female	8	29.2	29.2				
Underlying hepatic diseases				0.368			
HBV	24	46.7	46.7				
HCV	18	26.8	26.8				
NBC	16	34.8	23.2				
Alcohol abuse				0.142			
Presence	10	72.0					
Absence	48	33.3	30.3				
Liver cirrhosis				0.529			
Presence	18	23.0	23.0				
Absence	40	43.3	39.0				
Treatment for rupture							
TAE				0.951			
Performed	41	35.3	35.3				
Not performed	17	42.4					
Timing of hepatic resection				0.134			
Emergency	5	20.0					
Two-staged	53	38.9	35.3				
Liver function tests							
Total bilirubin				0.62			
≥0.7 mg/dL	37	32.0	32.0				
<0.7 mg/dL	21	46.8	39				
Albumin				0.147			
≤3.7 g/dL	30	30.9	24.7				
>3.7 g/dL	28	43.7	43.7				
Prothrombin time				0.623			
≤86 %	31	28.0	28.0				
>86 %	27	45.5	39				
Child-Pugh class				0.004	0.035	2.802	(1.077–7.294)
A	51	43.3	39.7				
B	7	0	0				
Platelet				0.407			
$\leq 16.2 \times 10^4/\mu L$	19	45.2	45.2				
$>16.2 \times 10^4/\mu L$	39	32.9	28.2				
AST				0.529			
≥41 IU/L	26	30.3	30.3				
<41 IU/L	32	42.6	36.5				
ALT				0.491			
≥38 IU/L	33	36.3	36.3				
<38 IU/L	25	37.6	31.3				

Table 2 (continued)

		Overall survival rate (%)		Univariate	Multivariate		
Variables	*n*	5 years	10 years	*p* value	*p* value	Hazard ratio	(95 % CI)
Tumor-related factors							
AFP				0.071	0.513	1	(1.00–1.00)
≥154 ng/mL	28	25.6	25.6				
<154 ng/mL	30	47.0	41.2				
Tumor size				0.051	0.335	1.489	(0.663–3.341)
≥6.7 cm	27	21.0	21.0				
<6.7 cm	31	48.0	44.0				
Tumor number				0.578			
Solitary	46	40.0	35.6				
Multiple	12	27.8	27.8				
Major vessel invasion[a]				0.254			
Presence	4	25.0					
Absence	54	37.9	34.5				
Histological variables							
Differentiation				0.144			
Moderately	35	47.8	42.5				
Poorly	21	27.8	22.2				
Unknown	2	–	–				
Portal vein invasion				0.14			
Presence	26	24.6	–				
Absence	32	48.4	42.3				
Hepatic vein invasion				0.182			
Presence	8	18.8	–				
Absence	50	39.9	36.6				
Histological number				0.536			
Solitary	45	43.6	39.2				
Multiple	13	18.8	–				
Type of hepatic resection				0.126			
Partial	20	52.6	46.1				
Segmentectomy	10	42.0					
Sectionectomy	9	23.3					
Hemihepatectomy or more	19	17.2					

AFP alpha fetoprotein, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *HBV* positivity for hepatitis B surface antigen, *HCC* hepatocellular carcinoma, *HCV* positivity for hepatitis C virus antibody, *NBC* non-B non-C hepatitis, *TAE* transcatheter arterial embolization

[a] Tumor invasion to main or first branch of portal vein and/or to major hepatic vein or inferior vena cava

within 3 years after hepatic resection. In contrast, in the non-ruptured group, the OS rate gradually decreased during the follow-up period (median survival time: 40 months in the ruptured group vs. 74 months in the non-ruptured group). Moreover, if patients with in-hospital death were excluded, the OS rates at 3, 5, and 10 years after hepatic resection were 58, 48, and 43 % in the ruptured group, and 85, 68, and 31 % in the non-ruptured group, respectively ($p = 0.321$). Furthermore, there was no significant difference in the proportion of patients with postoperative recurrence (65 vs. 73 %, $p = 0.427$), extrahepatic recurrence (13 vs. 3 %, $p = 0.201$), and recurrence beyond the Milan criteria (71 vs. 60 %, $p = 0.407$, Table 4).

Discussion

Hemostasis is the prime purpose of the initial treatment of a spontaneously ruptured HCC. Some have recommended that emergency hepatic resection be performed when the patient's condition permits[5,27,28]; however, the mortality rate has been reported to be high and widely varied (range 5.8–

Table 3 Univariate and multivariate logistic analysis for mortality after hepatic resection for ruptured hepatocellular carcinoma

	Univariate			Multivariate		
Variables	*p* value	Odds ratio	(95 % CI)	*p* value	Odds ratio	(95 % CI)
Backgrounds						
Age						
≥65 years	0.835	1.19	(0.24–5.80)			
<65 years		1				
Sex						
Male	0.999	–				
Female		1				
Underlying hepatic diseases						
HBV (versus NBC)	0.166	0.19	(0.018–2.00)			
HCV (versus NBC)	0.874	0.88	(0.15–5.06)			
NBC	–	1				
Alcohol abuse						
Presence	0.826	0.78	(0.08–7.28)			
Absence		1				
Liver cirrhosis						
Presence	0.475	1.80	(0.36–9.04)			
Absence		1				
Treatment for rupture						
TAE						
Performed	0.963	1.04	(0.18–5.98)			
Not performed		1				
Timing of hepatic resection						
Emergency hepatic resection	0.006	18.38	(2.34–144.04)	0.026	12.36	(1.35–113.20)
Staged hepatic resection		1			1	
Liver function tests						
Total bilirubin						
≥0.7 mg/dL	0.656	1.48	(0.26–8.42)			
<0.7 mg/dL		1				
Albumin						
≤3.7 g/dL	0.279	2.60	(0.46–14.66)			
>3.7 g/dL		1				
Prothrombin time						
≤86 %	0.835	1.19	(0.249–5.84)			
>86 %						
Child-Pugh class						
A	0.175	3.68	(0.56–24.12)			
B		1				
Platelet						
≤16.2 × 104/μL	0.547	1.64	(0.33–8.20)			
>16.2 × 104/μL		1				
AST						
≥41 IU/L	0.489	1.76	(0.36–8.67)			
<41 IU/L		1				
ALT						
≥38 IU/L	0.415	0.49	(0.09–2.75)			
<38 IU/L		1				

Table 3 (continued)

	Univariate			Multivariate		
Variables	*p* value	Odds ratio	(95 % CI)	*p* value	Odds ratio	(95 % CI)
Tumor-related factors						
AFP						
≥154 ng/mL	0.207	3.04	(0.54–17.17)			
<154 ng/mL		1				
Tumor size						
≥6.7 cm	0.552	1.62	(0.33–8.00)			
<6.7 cm		1				
Tumor number						
Solitary	0.139	3.5	(0.67–18.43)			
Multiple						
Major vessel invasion[a]						
Presence	0.039	9.80	(1.12–85.42)	0.323	3.79	(0.27–53.52)
Absence		1			1	
Histological variables						
Differentiation (versus moderately)						
Moderately		1				
Poorly	0.507	1.78	(0.32–9.74)			
Unknown	0.124	10.67	(0.52–217.23)			
Histological number						
Solitary	0.678	1.46	(0.25–8.54)			
Multiple		1				
Portal vein invasion						
Presence	0.15	3.57	(0.63–20.19)			
Absence		1				
Hepatic vein invasion						
Presence	0.244	3.00	(0.47–19.04)			
Absence		1				
Types of hepatic resection (versus segmentectomy)						
Partial	0.998	0				
Segmentectomy		1				
Sectionectomy	0.6	0.50	(0.04–6.68)			
Hemihepatectomy or more	0.947	1.07	(0.16–7.15)			

AFP alpha fetoprotein, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *HBV* positivity for hepatitis B surface antigen, *HCC* hepatocellular carcinoma, *HCV* positivity for hepatitis C virus antibody, *NBC* non-B non-C hepatitis, *TAE* transcatheter arterial embolization

[a] Tumor invasion to main or first branch of portal vein and/or to major hepatic vein or inferior vena cava

71.4 %).[5,29,30] In addition, Yang et al.[10] recently reported that the incidence of in-hospital death in patients who underwent emergency hepatic resection (2 of 28 patients [7 %]) was higher than that in patients who underwent a staged hepatic resection (2 of 115 patients [1.5 %]), although not significantly different. However, TAE can effectively induce hemostasis in hemodynamically unstable patients, with the most recent reports citing a hemostasis success rate of more than 90 %.[16,31] In addition, in the present study, only one patient failed to achieve hemostasis with TAE (success rate of 98 %), and emergency hepatic resection for patients with a ruptured HCC was an independent risk factor for in-hospital death. Even if the patient is hemodynamically stable, non-surgical treatments, such as TAE and transfusion, allow for the improvement of a patient's general condition and planning for staged hepatic resection.

It is well known that ruptured HCC is associated with larger-sized tumors with higher incidence with vascular invasion than non-ruptured HCC,[9,14,18] leading to the performance of large-volume liver resection, such as hemihepatectomy or more extended resection[9]; this agreed with the present findings among all populations. Furthermore, in the present study,

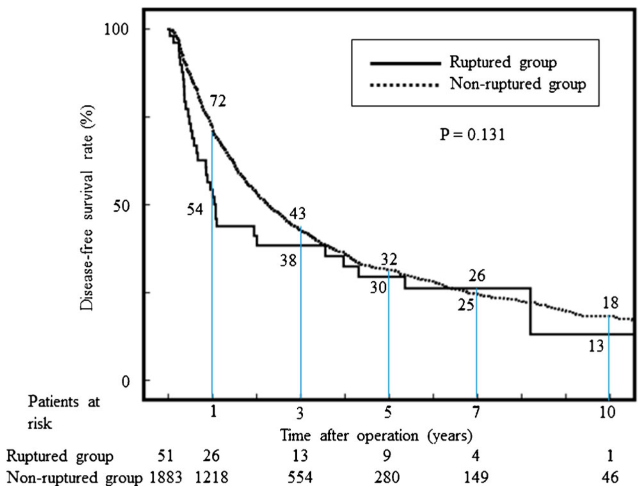

Fig. 1 The disease-free survival rate after hepatic resection for patients with a ruptured hepatocellular carcinoma (ruptured group) and those with a non-ruptured hepatocellular carcinoma (non-ruptured group) among all populations (before propensity score matching)

the presence of major vessel invasion was a possible risk factor for in-hospital death. Such a situation would increase the difficulty and risk of hepatic resection, which may contribute in part to the high incidence of in-hospital death.

In some cases of a ruptured HCC, an elaborate approach should be considered, as ruptured HCCs are generally large bulging tumors walled off by a hematoma and/or adhesion; non-meticulous mobilization of the tumor could lead to re-rupture or hemorrhaging. Given this evidence, TAE and/or conservative treatment (even if spontaneous hemostasis is achieved) might be an effective and minimally invasive modality as an initial treatment procedure for a spontaneously ruptured HCC, and clinicians should be careful when selecting emergency hepatic resection. Some cases of ruptured HCC with a poor liver function or liver cirrhosis have been

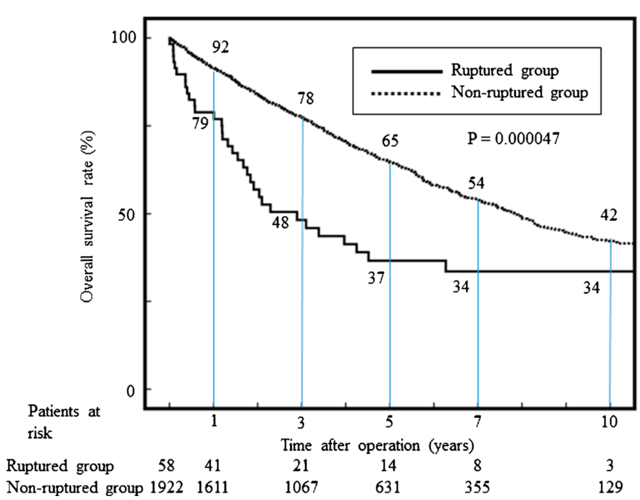

Fig. 2 The overall survival rate after hepatic resection for patients with a ruptured hepatocellular carcinoma (ruptured group) and those with a non-ruptured hepatocellular carcinoma (non-ruptured group) among all populations (before propensity score matching)

associated with an increased 30-day mortality as well as unfavorable OS.[11,32] The findings from our study also suggest that surgical treatment for ruptured HCC patients with a poor liver function (Child-Pugh class B) should not be performed out of consideration of the poor prognosis.

A Japanese nationwide survey of patients with HCC found that spontaneous HCC rupture occurred in a heterogeneous population of patients where the risk factors for rupture differed according to the underlying hepatic diseases, such as positivity for the hepatitis B and hepatitis C virus antigens, and non-B non-C hepatitis.[18] In addition, a comparison of the OS according to each TNM stage of the AJCC/UICC and LCSGJ classifications (without the rupture factor) indicated that the TNM stage of spontaneously ruptured HCCs corresponded to an additional 0.5–2.0 TNM stage without the rupture factor. However, these results included patients who underwent all treatments, including hepatic resection, ablation therapy, TAE, and best supportive care. On closer inspection, we found that the prognosis of patients who underwent curative treatments (hepatic resection or ablation therapy) was much better than that of patients who underwent other treatments. Chan et al.[9] also reported that the OS of patients with ruptured HCC ($n = 84$) and non-ruptured HCC ($n = 1254$) and stage I and II ruptured HCC according to the AJCC/UICC classification (without a rupture factor) corresponded with those values in stage II and III non-ruptured HCC, respectively.

In contrast, Uchiyama et al.[13] reported that the OS of patients with a ruptured HCC ($n = 27$) divided by TNM stage according to LCSGJ and AJCC/UICC classifications (without a rupture factor) was better than those with a non-ruptured HCC ($n = 1004$). This evidence seems to suggest that not all ruptured HCC should be defined as T4. However, in these previous studies, the number of patients, background, and tumor-related factors were very different between the ruptured HCC and non-ruptured HCC patients. Thus, our case-matched study decreased the bias between the ruptured and non-ruptured groups and allowed us to investigate the true impact of rupture on survival.

In the present study, the OS rate at 5 years was 37 % (42 % after PSM), which corresponded with the values in recent reports (approximately 30 %, range 10–55 %,).[9–11,13,14,16,18,31] Some reports have indicated that a ruptured HCC is a risk factor for an unfavorable OS,[9,10] which agreed with our results among all populations even if patients with in-hospital death were excluded. However, after PSM, there was no significantly difference in OS rate between the two groups ($p = 0.115$). Moreover, if patients with in-hospital death were excluded, OS rates at 5 and 10 years was 48 and 43 % in the ruptured group, and 68

Table 4 Postoperative recurrence after hepatic resection for ruptured and non-ruptured hepatocellular carcinoma

	Before propensity matching					After propensity matching				
	Ruptured		Non-ruptured			Ruptured		Non-ruptured		
	($n = 51$)		($n = 1883$)		p value	($n = 37$)		($n = 41$)		p value
Recurrence, n (%)	34	(67)	1157	(61)	0.471	24	(65)	30	(73)	0.427
Dissemination, n (%)	4	(8)	7	(0.4)	<0.001	1	(3)	0	(0)	1.00
	($n = 34$)		($n = 1157$)			($n = 24$)		($n = 30$)		
Initial recurrence sites[a]					0.022					0.201
Intrahepatic, n (%)	26	(76)	1038	(90)		21	(88)	29	(97)	
Extrahepatic, n (%)	8	(24)	119	(10)		3	(13)	1	(3)	
Situation of initial recurrence[a]					0.005					0.407
Met Milan criteria, n (%)	7	(21)	523	(45)		7	(29)	12	(40)	
Beyond Milan criteria, n (%)	27	(79)	634	(55)		17	(71)	18	(60)	

[a] Among the patients with postoperative recurrence

and 31 % in the non-ruptured group, respectively ($p = 0.321$). The ruptures were more frequently observed in patients with a high AFP concentration, large tumor, and poorly differentiated HCC before PSM, which have been established as risk factors for an unfavorable OS after hepatic resection for patients with HCC,[33–39] indicating a ruptured HCC tends to be associated with an advanced grade of malignancy. Indeed, a large tumor is known to increase the risk for extrahepatic recurrence.[37,40,41] In addition, in our study, the proportion of patients with extrahepatic recurrence and with recurrence beyond the Milan criteria was higher in the ruptured group than in the non-ruptured group among all populations, which reflects the postoperative recurrence pattern of a large tumor.[37,40] However, after adjusting for the incidence of these known prognostic factors by PSM, there was no significant difference in the pattern of recurrence between the groups.

Given this evidence, the rupture itself does not appear to be a prognostic factor for unfavorable OS. Rather, advanced tumor-related factors such as large tumor, high AFP concentration, and poorly differentiated HCC seem to be more closely associated with a poor prognosis. Two previous studies using PSM also found no marked difference in the DFS and OS between patients with a ruptured HCC and non-ruptured HCC[14,16]; however, the number of matched patients was very small ($n = 18$,[16] and 14[14]). Our results ($n = 42$) emphasize these prior findings. A high incidence of peritoneal dissemination may also be a characteristic of a ruptured HCC,[15,42] which agreed with our results before PSM. However, there was no significant difference in the incidence of peritoneal

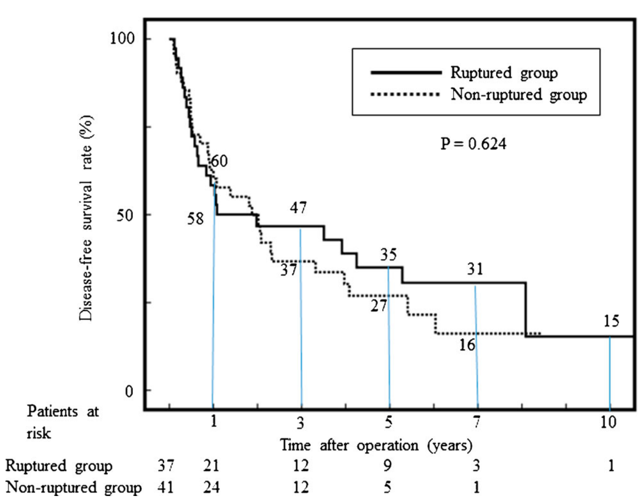

Fig. 3 The disease-free survival rate after hepatic resection for patients with a ruptured hepatocellular carcinoma (ruptured group) and those with a non-ruptured hepatocellular carcinoma (non-ruptured group) after propensity score matching

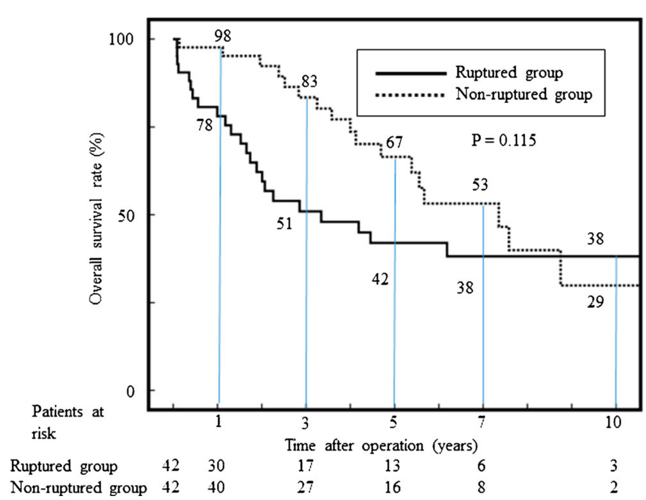

Fig. 4 The overall survival rate after hepatic resection for patients with a ruptured hepatocellular carcinoma (ruptured group) and those with a non-ruptured hepatocellular carcinoma (non-ruptured group) after propensity score matching

dissemination between the groups after PSM. Yang et al.[10] suggested that early resection may reduce the rate of occurrence of peritoneal dissemination; however, the influence of postoperative peritoneal dissemination on survival could not be investigated in the current study because the number of patients was small ($n = 4$).

Several limitations associated with the present study warrant mention. This study was retrospective in nature, and the number of patients with ruptured HCC was not very large, despite this being a multicenter study. In addition, the initial treatment for the rupture differed among ruptured patients. Further studies are needed to evaluate the detailed surgical outcome of patients with ruptured HCC.

Conclusions

This multicenter analysis with a case-controlled study by PSM showed that a rupture itself was not a risk factor for postoperative recurrence and unfavorable survival. However, clinicians should be careful when selecting emergency hepatic resection and must keep in mind that the prognosis of patients classified as Child-Pugh class B is poor.

Contribution of Authors Design of work: S Tanaka, S Kubo

Acquisition, analysis, and interpretation of data: S Tanaka, M Ueno, H Wada, F Hirokawa, T Nakai, H Iida, H Eguchi

Drafting and revising: S Tanaka, M Kaibori, M Ueno, M Hayashi, S Kubo

Final approval: S Tanaka, M Ueno, S Kubo

Agreement to be accountable for all aspects of the work: S Tanaka, M Kaibori, M Ueno, H Wada, F Hirokawa, T Nakai, H Iida, H Eguchi, M Hayashi, S Kubo

Compliance with Ethical Standards

Funding No financial supports

References

1. Chen MF, Hwang TL, Jeng LB, Jan YY, Wang CS: Clinical experience with hepatic resection for ruptured hepatocellular carcinoma. Hepatogastroenterology 1995;42:166–168.
2. Bassi N, Caratozzolo E, Bonariol L, Ruffolo C, Bridda A, Padoan L, Antoniutti M, Massani M: Management of ruptured hepatocellular carcinoma: Implications for therapy. World J Gastroenterol 2010;16:1221–1225.
3. Chen CY, Lin XZ, Shin JS, Lin CY, Leow TC, Chang TT: Spontaneous rupture of hepatocellular carcinoma. A review of 141 taiwanese cases and comparison with nonrupture cases. J Clin Gastroenterol 1995;21:238–242.
4. Liu CL, Fan ST, Lo CM, Tso WK, Poon RT, Lam CM, Wong J: Management of spontaneous rupture of hepatocellular carcinoma: Single-center experience. J Clin Oncol 2001;19:3725–3732.
5. Vergara V, Muratore A, Bouzari H, Polastri R, Ferrero A, Galatola G, Capussotti L: Spontaneous rupture of hepatocelluar carcinoma: Surgical resection and long-term survival. Eur J Surg Oncol 2000;26:770–772.
6. Chen WK, Chang YT, Chung YT, Yang HR: Outcomes of emergency treatment in ruptured hepatocellular carcinoma in the ed. Am J Emerg Med 2005;23:730–736.
7. Lai EC, Lau WY: Spontaneous rupture of hepatocellular carcinoma: A systematic review. Arch Surg 2006;141:191–198.
8. Tan FL, Tan YM, Chung AY, Cheow PC, Chow PK, Ooi LL: Factors affecting early mortality in spontaneous rupture of hepatocellular carcinoma. ANZ J Surg 2006;76:448–452.
9. Chan AC, Dai JW, Chok KS, Cheung TT, Lo CM: Prognostic influence of spontaneous tumor rupture on hepatocellular carcinoma after interval hepatectomy. Surgery 2016;159:409–417.
10. Yang T, Sun YF, Zhang J, Lau WY, Lai EC, Lu JH, Shen F, Wu MC: Partial hepatectomy for ruptured hepatocellular carcinoma. Br J Surg 2013;100:1071–1079.
11. Li J, Huang L, Liu CF, Cao J, Yan JJ, Xu F, Wu MC, Yan YQ: Risk factors and surgical outcomes for spontaneous rupture of bclc stages a and b hepatocellular carcinoma: A case–control study. World J Gastroenterol 2014;20:9121–9127.
12. American Joint Committee on Cancer (AJCC). Cancer Staging Manual, 7th edition. New York: Springer, 2009.
13. Uchiyama H, Minagawa R, Itoh S, Kajiyama K, Harimoto N, Ikegami T, Yoshizumi T, Shirabe K, Takenaka K, Maehara Y: Favorable outcomes of hepatectomy for ruptured hepatocellular carcinoma: Retrospective analysis of primary r0-hepatectomized patients. Anticancer Res 2016;36:379–385.
14. Sada H, Ohira M, Kobayashi T, Tashiro H, Chayama K, Ohdan H: An analysis of surgical treatment for the spontaneous rupture of hepatocellular carcinoma. Dig Surg 2016;33:43–50.
15. Sonoda T, Kanematsu T, Takenaka K, Sugimachi K: Ruptured hepatocellular carcinoma evokes risk of implanted metastases. J Surg Oncol 1989;41:183–186.
16. Lee HS, Choi GH, Kang DR, Han KH, Ahn SH, Kim do Y, Park JY, Kim SU, Choi JS: Impact of spontaneous hepatocellular carcinoma rupture on recurrence pattern and long-term surgical outcomes after partial hepatectomy. World J Surg 2014;38:2070–2078.
17. Mizuno S, Yamagiwa K, Ogawa T, Tabata M, Yokoi H, Isaji S, Uemoto S: Are the results of surgical treatment of hepatocellular carcinoma poor if the tumor has spontaneously ruptured? Scand J Gastroenterol 2004;39:567–570.
18. Aoki T, Kokudo N, Matsuyama Y, Izumi N, Ichida T, Kudo M, Ku Y, Sakamoto M, Nakashima O, Matsui O, Makuuchi M: Prognostic impact of spontaneous tumor rupture in patients with hepatocellular carcinoma: An analysis of 1160 cases from a nationwide survey. Ann Surg 2014;259:532–542.
19. Drake C, Fisher L: Prognostic models and the propensity score. Int J Epidemiol 1995;24:183–187.
20. Robins JM, Mark SD, Newey WK: Estimating exposure effects by modelling the expectation of exposure conditional on confounders. Biometrics 1992;48:479–495.
21. Rosenbaum PR, Rubin DB: The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41–55.
22. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ: Classification of chronic hepatitis: Diagnosis, grading and staging. Hepatology 1994;19:1513–1520.
23. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, Kiernan TW, Wollman J: Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981;1:431–435.
24. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L: Liver

transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699.
25. Belghiti J, Clavien PA, Gadzijev E, Garden JO, Lau WY, Makuuchi M, Strong RW: The Brisbane 2000 terminology of liver anatomy and resection. HPB 2000;2:333–339.
26. Lemeshow S, Hosmer DW, Jr.: A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol 1982;115:92–106.
27. Cherqui D, Panis Y, Rotman N, Fagniez PL: Emergency liver resection for spontaneous rupture of hepatocellular carcinoma complicating cirrhosis. Br J Surg 1993;80:747–749.
28. Leung KL, Lau WY, Lai PB, Yiu RY, Meng WC, Leow CK: Spontaneous rupture of hepatocellular carcinoma: Conservative management and selective intervention. Arch Surg 1999;134:1103–1107.
29. Hai L, Yong-Hong P, Yong F, Ren-Feng L: One-stage liver resection for spontaneous rupture of hepatocellular carcinoma. World J Surg 2005;29:1316–1318.
30. Lai EC, Wu KM, Choi TK, Fan ST, Wong J: Spontaneous ruptured hepatocellular carcinoma. An appraisal of surgical treatment. Ann Surg 1989;210:24–28.
31. Zhang DZ, Zhang K, Wang XP, Cai H: Patients with spontaneously ruptured hepatocellular carcinoma benefit from staged surgical resection after successful transarterial embolization. Asian Pac J Cancer Prev 2015;16:315–319.
32. Hsueh KC, Fan HL, Chen TW, Chan DC, Yu JC, Tsou SS, Chang TM, Hsieh CB: Management of spontaneously ruptured hepatocellular carcinoma and hemoperitoneum manifested as acute abdomen in the emergency room. World J Surg 2012;36:2670–2676.
33. Kaibori M, Kubo S, Nagano H, Hayashi M, Haji S, Nakai T, Ishizaki M, Matsui K, Uenishi T, Takemura S, Wada H, Marubashi S, Komeda K, Hirokawa F, Nakata Y, Uchiyama K, Kwon AH: Clinicopathological features of recurrence in patients after 10-year disease-free survival following curative hepatic resection of hepatocellular carcinoma. World J Surg 2013;37:820–828.
34. Tanaka S, Kubota D, Lee SH, Oba K, Matsuyama M: Effectiveness of laparoscopic approach for acute appendicitis. Osaka City Med J 2007;53:1–8.
35. Hanazaki K, Kajikawa S, Koide N, Adachi W, Amano J: Prognostic factors after hepatic resection for hepatocellular carcinoma with hepatitis c viral infection: Univariate and multivariate analysis. Am J Gastroenterol 2001;96:1243–1250.
36. Matsumoto T, Kubota K, Aoki T, Iso Y, Kato M, Shimoda M: Clinical impact of anatomical liver resection for hepatocellular carcinoma with pathologically proven portal vein invasion. World J Surg 2016;40:402–411.
37. Tanaka S, Iimuro Y, Hirano T, Hai S, Suzumura K, Fujimoto J: Outcomes of hepatic resection for large hepatocellular carcinoma: Special reference to postoperative recurrence. Am Surg 2015;81:64–73.
38. Cucchetti A, Qiao GL, Cescon M, Li J, Xia Y, Ercolani G, Shen F, Pinna AD: Anatomic versus nonanatomic resection in cirrhotic patients with early hepatocellular carcinoma. Surgery 2014;155:512–521.
39. Yip VS, Gomez D, Tan CY, Staettner S, Terlizzo M, Fenwick S, Malik HZ, Ghaneh P, Poston G: Tumour size and differentiation predict survival after liver resection for hepatocellular carcinoma arising from non-cirrhotic and non-fibrotic liver: A case-controlled study. Int J Surg 2013;11:1078–1082.
40. Mok KT, Wang BW, Lo GH, Liang HL, Liu SI, Chou NH, Tsai CC, Chen IS, Yeh MH, Chen YC: Multimodality management of hepatocellular carcinoma larger than 10 cm. J Am Coll Surg 2003;197:730–738.
41. Ishii T, Hatano E, Yasuchika K, Taura K, Seo S, Uemoto S: High risk of lung metastasis after resection of hepatocellular carcinoma more than 7 cm in diameter. Surg Today 2014;44:1900–1905.
42. Shuto T, Hirohashi K, Kubo S, Tanaka H, Hamba H, Kubota D, Kinoshita H: Delayed hepatic resection for ruptured hepatocellular carcinoma. Surgery 1998;124:33–37.