Journal of Gastrointestinal Surgery (2021) 25:941–953
https://doi.org/10.1007/s11605-020-04555-0

ORIGINAL ARTICLE

Surgical Outcomes of Spontaneously Ruptured Hepatocellular Carcinoma

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Received: 27 July 2019 / Accepted: 18 February 2020 / Published online: 3 April 2020
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Abstract

Background Surgical and oncological outcomes in ruptured hepatocellular carcinoma (HCC) are not well known. The objective of this study was to review and compare survival outcomes and recurrence rates between ruptured and unruptured HCC.

Methods Data of patients with ruptured HCC who underwent curative surgical resection between January 2000 and December 2016 were retrospectively reviewed. To compare survival outcomes between ruptured and unruptured HCC, 1:2 individual matching was conducted.

Results The 1-, 3-, and 5-year overall survival (OS) rates were 88.8%, 67.0%, and 51.9%, respectively. The 1-, 3-, and 5-year disease-free survival (DFS) rates were 51.7%, 32.8%, and 25.0%, respectively. OS and DFS rates were significantly lower in the ruptured HCC group than the matched unruptured HCC group. HCC recurred in 63 patients (70.8%), 33 (52.4%) of whom presented with both intrahepatic and extrahepatic recurrences. Mean recurrence interval was 12.6 ± 13.8 months. The 1-, 3-, and 5-year survival rates after recurrence were 61.6%, 40.2%, and 33.6%, respectively. Mean survival time after recurrence was 26.4 ± 29.5 months. Incidence of peritoneal seeding (PS) was 18.0%, and eight of them demonstrated solitary lesion. Mean recurrence interval was 5.9 ± 8.2 months. The 1-, 3-, and 5-year OS rates after recurrence were significantly lower in patients with PS (49.7%, 18.7%, and 9.3%, respectively) than in patients without PS.

Conclusions Hepatectomy in ruptured HCC did show worse survival outcome compared with unruptured HCC and bear a high risk of PS. However, surgical resection combined with transcatheter arterial chemoembolization could help in achieving acceptable oncological outcomes.

Keywords Carcinoma · Hepatocellular · Rupture · Spontaneous · Hepatectomy

Abbreviations

HCC	Hepatocellular carcinoma
AJCC/UICC	American Joint Committee on Cancer/Union for International Cancer Control
LCSGJ	Liver Cancer Study Group of Japan
HBV	Hepatitis B virus
PS	Peritoneal seeding
AFP	Alpha fetoprotein
PET	Positron emission tomography
CT	Computed tomography
MRI	Magnetic resonance imaging
TACE	Transcatheter arterial chemoembolization
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
OS	Overall survival
DFS	Disease-free survival

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Introduction

Spontaneous rupture of hepatocellular carcinoma (HCC) occurs occasionally. Recently, the reported incidence rate of spontaneous rupture of HCC varied from 2.3 to 5.9%[1–4], which has decreased compared with its previously reported incidence of up to 15%, owing to advances in the surveillance system for high-risk group and diagnostic imaging modality[5–7]. Rapid tumor growth leading to intra-tumoral necrosis and tumor hypervascularity with friable feeder artery associated with degeneration of elastin and type IV collagen was the suggested causes of tumor rupture in HCC, although the exact pathogenesis of rupture remains unclear.

HCC rupture management requires a stepwise, multidisciplinary approach that considers hemostasis for bleeding from the ruptured tumor and HCC treatment. A recent review suggested that transarterial embolization followed by elective hepatectomy is effective in patients with ruptured HCC[8].

With the development of surgical techniques (hepatic resection, angiographic intervention, and critical care medicine), various treatment modalities for ruptured HCC have been introduced. However, mortality rates in ruptured HCC are still high[9] and oncological outcomes are still insufficient. Moreover, whether tumor rupture is a poor prognostic factor after hepatectomy for ruptured HCC remains controversial. Several studies showed that ruptured HCC had inferior outcomes compared with unruptured HCC[1,10–14]. In selected cases, HCC has low recurrence rate and showed oncological outcome comparable to that of unruptured HCC[15–20].

Although the TNM staging system of the 8th edition of American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) classifies tumor rupture as T4, the general rules of the 6th edition of the Liver Cancer Study Group of Japan (LCSGJ) do not consider tumor rupture for T staging[21–23], indicating that the actual HCC rupture effect on oncological outcomes still needs to be elucidated. Several studies reported the actual outcomes of ruptured HCC. However, most previous studies are limited by small study population, short duration of follow-up period, and non-comparative design.

This study aimed to retrospectively review and compare survival outcomes and recurrence rates in patients with ruptured HCC who underwent surgical resection at a single center in hepatitis B virus (HBV)-endemic area to elucidate the actual oncological outcome and analyze the recurrence pattern of ruptured HCC with a focus on peritoneal seeding (PS).

Materials and Methods

Study Population

Clinical data of adult patients (≥ 18 years) who underwent hepatectomy for spontaneously ruptured HCC from January 2000 to December 2016 at Asan Medical Center, Seoul, South Korea, were retrospectively reviewed.

Between January 2000 and December 2016, 7602 patients with HCC underwent liver resection. Among them, 115 had ruptured HCC at the time of diagnosis, of which 26 cases of non-curative resection were excluded. Finally, 89 patients were retrospectively reviewed (Fig. 1).

We performed 1:2 individual matching between the ruptured HCC group and unruptured HCC group and included 85 patient pairs. Matching variables were the number and maximal size of tumors, preoperative alpha fetoprotein (AFP) value, hypermetabolic activity on preoperative positron emission tomography (PET), and presence of macro- and microvascular invasion on pathology.

Diagnosis

Diagnosis of ruptured HCC was made based on computed tomography (CT) or magnetic resonance imaging (MRI) findings and was confirmed through laparotomy and gross findings (hemoperitoneum or hematoma around the tumor accompanied by disruption of tumor integrity). CT is a valuable imaging modality in ruptured HCC diagnosis as it can detect tumor and free intraperitoneal fluid containing high attenuation or blood clot close to tumor[24–26]. In patients with unruptured HCC, chest CT, PET, and bone scan were performed to identify extrahepatic metastasis and assess the disease extent in patients with ruptured HCC with stable vital signs. The assessment of hepatic functional reservoir was focused on the indirect signs of portal hypertension, including thrombocytopenia (< 100,000/uL), prolonged prothrombin time, varix on endoscopy, ascites, splenomegaly, or surface nodularity on imaging studies. Total bilirubin, albumin, and indocyanine green retention tests were taken together. Liver lobar or segmental volume was measured to estimate the remnant liver volume after hepatectomy using CT volumetry software Picture Archiving and Communication System (PetaVision for Clinics, South Korea).

Staging System

The staging system followed the TNM classification (8th Edition) developed by AJCC/UICC and LCSGJ (6th Edition, in Japanese): "General Rules for the Clinical and Pathological Study of Primary Liver Cancer"[21, 23].

Treatment Algorithm

Transcatheter arterial chemoembolization (TACE) was considered first to control bleeding from tumor when a patient presented with overt symptoms and signs of significant bleeding (altered hemodynamic profiles, intolerable pain, and abrupt change in serum hemoglobin). After the patient's status

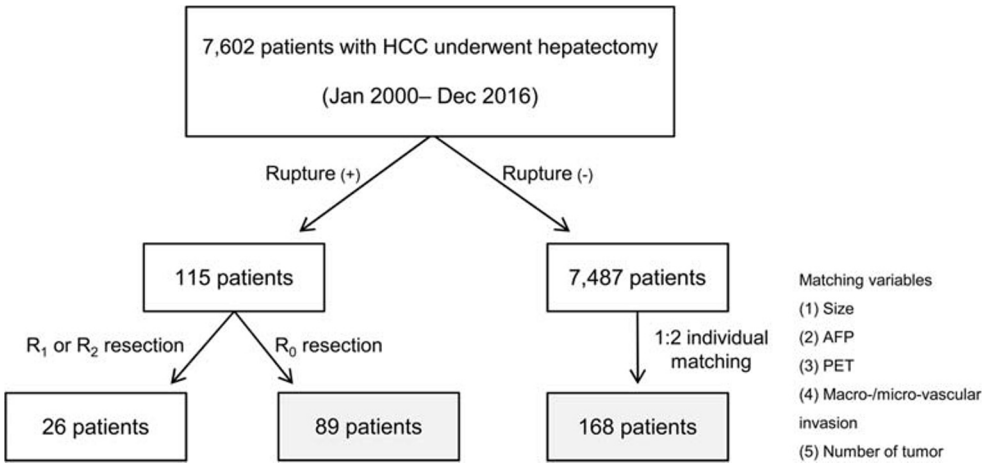

Fig. 1 Flow diagram of patient selection

had stabilized, hepatic functional reservoir and extrahepatic metastasis were evaluated, followed by hepatectomy. In principle, the timing of the hepatectomy for ruptured HCC was as early as possible after the evaluation for HCC and functional reservoir of the liver were completed. The assessment on HCC extent was performed through CT scan with 3 weeks interval after TACE and the timing for the hepatectomy was determined accordingly.

Criteria to determine the eligibility for hepatectomy were basically same as in case with unruptured HCC; without any evidence of indirect signs portal hypertension including thrombocytopenia (< 100,000/uL), prolonged prothrombin time, varix on endoscopy, ascites, splenomegaly, or surface nodularity on imaging studies, normal ranged liver function test including total bilirubin and indocyanine green test, and acceptable general condition without any contraindication in general anesthesia for major operation.

One-stage surgical resection of ruptured HCC was considered the primary treatment when the extent of the hematoma or hemoperitoneum was minimal, and the patient had stable condition for full evaluation of tumor extent and liver function.

TACE Protocol

Cisplatin (2 mg/kg body weight) was used in patients who underwent TACE. A microcatheter with a diameter of < 2.4 Fr was used, and cisplatin was infused for 15 minutes into the segmental, lobar, or proper hepatic artery, depending on the location and volume of the tumor. Before the 15-min cisplatin infusion, a certain amount of cisplatin was set aside and mixed at a 1:1 ratio in an emulsion of iodized oil (lipiodol; Guerbet, Roissy, France), which was infused (dose, 3–20 mL according to the tumor size) into the segmental feeding artery, followed by embolization with Gelfoam slurry (Upjohn, Kalamazoo, MI, USA) until stasis of arterial flow was confirmed.

Surgical Technique

Likewise in unruptured HCC, the fundamental principle in hepatectomy for ruptured HCC also follows the anatomical resection. The extent of resection was determined through the remnant liver volume and liver functional reservoir. Anatomical hepatectomy was the primary choice, and the extent of hepatectomy was individualized according to the estimated future remnant liver volume on CT volumetry and hepatic functional reserve. Various standard techniques for liver resection were implemented depending on the conditions of the operative field (Pringle maneuver and hanging maneuver). The Glissonean or individual approach and parenchymal transection with Cavitron ultrasonic surgical aspirator, energy device, or crush–clamp were chosen on a case-by-case basis and surgeon's preference.

Response to Treatment (mRECIST)

The Modified Response Evaluation Criteria in Solid Tumors (mRECIST) was incorporated in assessing response to the TACE prior to hepatic resection[27, 28]. The mRECIST criteria only focus on HCC and only consider the viable portion (i.e., the area enhanced after injection during the arterial phase).

Statistical Analysis

All statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) and SAS (SAS version 9.3, Cary, NC). Descriptive statistics for numerical variables are recorded as mean ± standard deviation, and categorical variables are presented as relative frequencies (percentages). We used chi-squared or Fisher's exact test for comparing categorical data and Student's *t* test or Mann–Whitney test for numerical data. A logistic regression model was used for univariate and multivariate analyses. To compare the outcomes of unruptured HCC, the 85 patients in the ruptured HCC group

were individually matched 1:2 to an unruptured HCC group using the greedy method, by the size and number of tumors, preoperative AFP value, hypermetabolic activity on preoperative PET, and presence of macro- and microvascular invasion on pathology. The adequacy of the individual matching was described with standardized difference. Patient survival was analyzed using the Kaplan–Meier method and compared by log-rank test. $p < 0.05$ was considered to indicate significant difference.

Ethical Considerations

The study was approved by the Institutional Review Board of Asan Medical Center, University of Ulsan, Seoul, South Korea (approval number 2017-0477), which waived the requirement for informed consent due to the retrospective nature of the analyses.

Results

Demographics and Clinicopathological Features

Demographic characteristics and clinicopathological features of patients are described in Table 1. The most common primary liver disease and symptom were HBV and pain, respectively. For all 10 asymptomatic patients, ruptured HCC was incidentally identified during diagnostic evaluation for liver tumor.

Treatment

In 38 patients with stable condition, surgical resection was conducted as a primary treatment. TACE was initially performed in the other 51 patients to control bleeding or stabilize the patient's condition to progress to the staged hepatic resection. In this group, the mean interval between the TACE and hepatectomy was 89 ± 137 days. Among patients who underwent TACE prior to hepatectomy, response to TACE was evaluated through mRECIST. Complete response was achieved in 19.6% of patients ($n = 10$), partial response was demonstrated in 56.9% ($n = 29$), stable disease was presented in 17.6% ($n = 9$), and progressive disease occurred in 5.9% ($n = 3$).

Right hepatectomy was performed in 23.6% ($n = 21$) of patients, followed by left hepatectomy in 14.6% ($n = 13$), monosegmentectomy in 12.4% ($n = 11$), right anterior sectionectomy in 11.2% ($n = 10$), right posterior sectionectomy in 10.1% ($n = 9$), left lateral sectionectomy in 9.0% ($n = 8$), partial hepatectomy in 7.9% ($n = 7$), and others (including right or left trisectionectomy, central bisectionectomy, segment 5 and 6 bisegmentectomy) in 11.2% ($n = 10$). The perioperative mean amount of red blood cell transfusion was 2.1 ± 2.8 units (range 0–16 units). A total of 42 patients (47.2%) did not require transfusion. The mean length of hospital stay was 23.1 ± 10.0 days (range 9–47 days). Neither in-hospital mortality nor post-hepatectomy liver failure occurred.

Survival Outcomes

The 1-, 2-, and 5-year overall survival (OS) rates of the patients were 88.8%, 67.0%, and 51.9%, respectively. The mean survival time was 43.6 ± 34.3 months (Fig. 2a). In the univariate and multivariate analyses for OS in the ruptured HCC group, the gross feature of the tumor (infiltrative type) and variant HCC (sarcomatoid type) were independent significant risk factors (Table 2). HCC recurred in 63 of the 89 patients with ruptured HCC. The actual recurrence rate of ruptured HCC was 70.8%. The 1-, 3-, and 5-year disease-free survival (DFS) rates were 51.7%, 32.8%, and 25.0%, respectively (Fig. 2b). The mean DFS time was 24.5 ± 27.8 months. On the multivariate analysis, AFP > 1000 ng/mL and microvascular invasion were associated with recurrence (Table 2).

Comparison of Survival Outcomes between Ruptured and Unruptured HCC

Prior to the 1:2 individual matching, a significant difference was found between the ruptured and unruptured HCC group in terms of tumor size, hypermetabolism on PET, and macrovascular and microvascular invasion (Table 3). To compare survival outcomes of patients with ruptured HCC with 1:2 matched patients with unruptured HCC, 85 patients with ruptured HCC and 168 matched patients of unruptured HCC were finally included in each group. After 1:2 matching, matching variables showed a standardized difference < 0.1, verifying the adequacy of the matching result (Table 3).

OS and DFS rates of the ruptured HCC group were significantly lower than those of the matched unruptured HCC group ($p = 0.041$ and $p = 0.011$, respectively) (Fig. 3a, b). In the ruptured HCC group, the 1-, 3-, and 5-year OS rates were 87.1%, 65.4%, and 48.4%, respectively. In addition, the 1-, 3-, and 5-year OS rates in the matched unruptured HCC group were 84.5%, 72.9%, and 68.7%, respectively. The 1-, 3-, and 5-year DFS rates in the ruptured HCC group were 48.2%, 31.7%, and 25.2%, respectively. In the matched unruptured HCC group, the 1-, 3-, and 5-year DFS rates were 65.8%, 46.3%, and 42.6%, respectively. In the matched set, the rupture per se was an independent significant risk factor for patient death and recurrence of HCC (Table 4).

Table 1 Demographics and clinical characteristics and clinicopathological features of patients

		$n = 89$
Age, mean		54.7 ± 12.3 (32–90)
Sex (M/F)		76 (85.4%)/13
CTP score		5.8 ± 0.8
CTP class		A 75 (84.3%)
		B 14 (15.7%)
MELD score		8.9 ± 2.6
Primary liver disease		HBV 67 (75.3%)
		ALC 9 (10.1%)
		NBNC, non-ALC 13 (14.6%)
Symptoms		Shock 3 (3.4%)
		Pain 72 (80.9%)
		Bleeding 4 (4.5%)
		No symptoms 10 (11.2%)
Preoperative laboratory result		
AFP (ng/mL)		11,622 ± 49,737 (Median 23.7)
Leukocyte ($\times 10^3$/uL)		9.6 ± 5.6
Hemoglobin (g/dL)		12.4 ± 2.3
Platelet ($\times 10^3$/uL)		228.6 ± 134.1
AST (IU/L)		65.1 ± 61.2
ALT (IU/L)		60.7 ± 114.2
Total bilirubin (mg/dL)		1.0 ± 0.5
Albumin (g/dL)		3.5 ± 0.5
Creatinine (mg/dL)		1.03 ± 1.32
PT (INR)		1.11 ± 0.10
PT (%)		85.5 ± 13.6
Pathology		
Number of tumor	1	82 (92.1%)
	2	4 (4.5%)
	3	2 (2.2%)
	5	1 (1.1%)
Maximum tumor size (cm)		7.9 ± 3.6
Satellite nodule (+)		9 (10.1%)
Histology	Nodular	68 (76.4%)
	Infiltrative	2 (2.2%)
	Other	5 (5.6%)
	Totally necrosis	14 (15.7%)
Edmondson grade	I	1 (1.1%)
	II	13 (14.6%)
	III	40 (44.9%)
	IV	21 (23.6%)
Steiner grade	I	1 (1.1%)
	II	29 (32.6%)
	III	37 (41.6%)
	IV	8 (9.0%)
Macrovascular invasion		7 (7.9%)
Microvascular invasion		30 (33.7%)
Glisson capsule invasion		29 (32.6%)
Cirrhosis		31 (34.8%)

Table 1 (continued)

		n = 89
BCLC	A	18 (20.2%)
	B	62 (69.7%)
	C	9 (10.1%)
AJCC stage[a]	IIIB	89 (100%)
LCSGJ stage[b]	II	50 (56.2%)
	III	36 (40.4%)
	IVA	3 (3.4%)
PET	Not done (performed)	31 (34.8%)
	Hypermetabolic	50 (56.2%)
	Isometabolic	8 (9.0%)

AFP, alpha-fetoprotein; *AJCC*, American Joint Committee on Cancer; *ALC*, alcoholic liver cirrhosis; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *BCLC*, Barcelona Clinic Liver Cancer; *CTP*, Child–Turcotte–Pugh; *HBV*, hepatitis B virus; *INR*, international normalized ratio; *LCSGJ*, Liver Cancer Study Group of Japan; *MELD*, model for end-stage liver disease; *NBNC*, non-HBV non-hepatitis C virus; *PET*, positron emission tomography; *PT*, prothrombin time

[a] AJCC Stage 8th Edition

[b] LCSGJ 6th Edition

Recurrence Pattern and Survival Outcomes after Recurrence in Ruptured HCC

Of the 63 patients with recurrence in ruptured HCC group, 52.4% (*n* = 33) showed both intrahepatic and extrahepatic recurrences, followed by intrahepatic recurrences only in 19 patients (30.2%) and extrahepatic metastases only in 11 patients (17.5%). The mean interval time to recurrence was 15.1 ± 12.7 months for intrahepatic recurrence only, 4.4 ± 2.4 months for extrahepatic recurrence only, and 13.5 ± 15.8 months for both intrahepatic and extrahepatic metastases.

The lung was the most common single extrahepatic recurrence site (43.2%, *n* = 19), followed by PS (13.6%) and bone (6.8%). Multiple extrahepatic metastases occurred in 15 patients (34.1%), with the lung (*n* = 15) and PS (*n* = 10) as the most common sites of recurrence. In regard to risk factors for extrahepatic metastasis, age > 50 years, infiltrative HCC, and presence of microvascular invasion were associated with

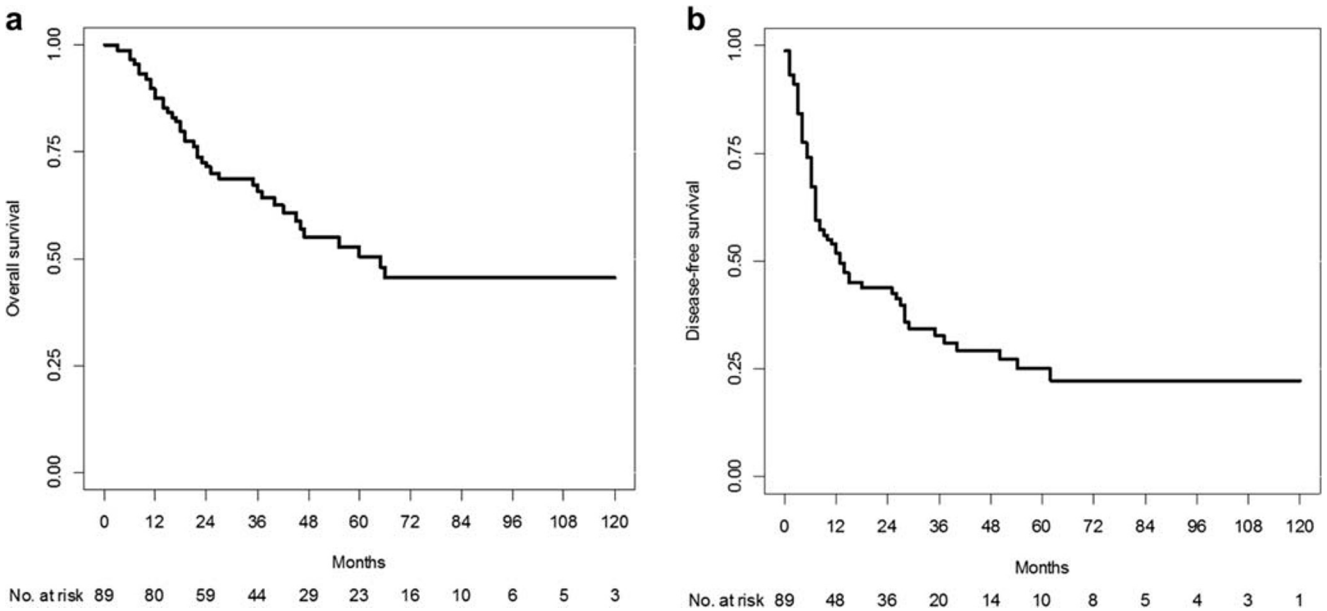

Fig. 2 **a** Overall survival. The 1-, 3-, and 5-year overall patient survival rates were 88.8%, 67.0%, and 51.9%, respectively. The mean overall survival time was 43.6 ± 34.3 months. **b** Disease-free survival. The 1-, 3-, and 5-year disease-free survival rates were 51.7%, 32.8%, and 25.0%, respectively. The mean disease-free survival time was 24.5 ± 27.8 months

Table 2 Univariate and multivariate analyses for patient survival (patient death = 39) and disease-free survival (recurrence = 63)

		Patient survival				Disease-free survival			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (years)	≥60	0.534 (0.26–1.10)	0.088			0.704 (0.41–1.20)	0.196		
Sex	Female	1.906 (0.90–4.02)	0.090			1.218 (0.62–2.41)	0.570		
CTP class	B	1.143 (0.50–2.60)	0.749			0.595 (0.28–1.25)	0.171		
MELD score	≥10	0.638 (0.28–1.45)	0.281			0.659 (0.36–1.20)	0.171		
Primary disease	HBV	2.250 (0.80–6.36)	0.126			1.799 (0.85–3.81)	0.125		
	ALC	0.304 (0.03–2.73)	0.287			0.874 (0.29–2.67)	0.813		
AFP (ng/mL)	≥1000	1.882 (0.95–3.74)	0.072			2.424 (1.40–4.19)	0.002	2.954 (1.60–5.46)	0.0006
BCLC	A	1	0.795			1	0.763		
	B	1.304 (0.50–3.41)	0.588			0.880 (0.46–1.68)	0.697		
	C	1.551 (0.42–5.79)	0.514			1.182 (0.44–3.17)	0.740		
LCSGJ stage	II	1	0.068			1	0.007		
	III	1.702 (0.89–3.27)	0.110			1.661 (1.00–2.77)	0.052		
	IVA	4.491 (1.03–19.65)	0.046			5.571 (1.68–18.48)	0.005		
Number of tumor	>1	1.481 (0.53–4.18)	0.457			1.307 (0.62–2.75)	0.479		
Maximal tumor size (cm)	≥10	1.457 (0.74–2.89)	0.281			1.190 (0.67–2.10)	0.549		
Totally necrotic	Yes	0.401 (0.14–1.14)	0.086			0.515 (0.24–1.08)	0.080		
Gross feature	Nodular	1	0.005	1	0.004	1	0.048		
	Infiltrative	10.16 (2.27–45.54)	0.002	11.32 (2.50–51.29)	0.002	4.917 (1.16–20.85)	0.031		
	Other	1.659 (0.58–4.75)	0.346	1.532 (0.53–4.42)	0.430	1.082 (0.39–3.01)	0.880		
	Totally necrotic	0.439 (0.15–1.26)	0.125	0.453 (0.16–1.30)	0.141	0.530 (0.25–1.12)	0.098		
Histology	HCC	1	0.010	1		1	0.101		
	Variant	6.374 (1.47–27.70)	0.013	6.785 (1.53–30.19)	0.012	2.397 (0.58–9.94)	0.228		
	Totally necrotic	0.417 (0.15–1.18)	0.100			0.525 (0.25–1.11)	0.091		
Edmondson grade	3	1.281 (0.54–3.02)	0.571			1.390 (0.70–2.77)	0.348		
	4	0.708 (0.25–2.02)	0.518			0.832 (0.37–1.89)	0.661		
Steiner grade	3	0.791 (0.39–1.60)	0.515			0.738 (0.42–1.30)	0.294		
	4	0.697 (0.23–2.12)	0.525			0.892 (0.38–2.10)	0.794		
Satellite nodule	Present	1.130 (0.44–2.90)	0.798			1.223 (0.58–2.57)	0.596		
Macrovascular invasion	Yes	1.955 (0.68–5.64)	0.215			2.506 (1.06–5.92)	0.036		
Microvascular invasion	Yes	1.868 (0.96–3.65)	0.067			2.237 (1.31–3.83)	0.003	2.135 (1.17–3.90)	0.014
Glisson invasion	Yes	1.309 (0.67–2.56)	0.432			0.999 (0.58–1.72)	0.998		
Milan criteria	Beyond	0.788 (0.33–1.90)	0.596			1.180 (0.56–2.50)	0.665		

AFP, alpha-fetoprotein; *ALC*, alcoholic liver cirrhosis; *BCLC*, Barcelona Clinic Liver Cancer; *CTP*, Child–Turcotte–Pugh; *HBV*, hepatitis B virus; *HCC*, hepatocellular carcinoma; *LCSGJ*, Liver Cancer Study Group of Japan; *MELD*, model for end-stage liver disease

Table 3 Baseline characteristics of patients with unruptured and ruptured HCC before and after individual matching

	Total set				Matched set		
	Unruptured $n = 3605$	Ruptured $n = 89$	p value	Standardized difference	Unruptured $n = 168$	Ruptured $n = 85$	Standardized difference
Age, mean	56.2 ± 10.0	54.7 ± 12.3	0.259	0.136	57.2 ± 11.0	54.4 ± 12.4	0.236
Sex (M/F)	2887 (80.1%)/718	76 (85.4%)/13	0.214	0.141	134 (79.8%)/34	72 (84.7%)/13	0.130
Maximal tumor size (cm)	4.7 ± 3.7	7.9 ± 3.6	< 0.001	0.898	7.8 ± 4.3	7.9 ± 3.6	0.034
PET							
Not done (performed)	857 (23.8%)	31 (34.8%)	< 0.001	0.698	59 (35.1%)	30 (35.3%)	0.005
Isometabolic	1320 (36.6%)	8 (9.0%)			16 (9.5%)	8 (9.4%)	
Hypermetabolic	1428 (39.6%)	50 (56.2%)			93 (55.4%)	47 (55.3%)	
Macrovascular invasion	238 (6.6%)	7 (7.9%)	< 0.001	0.479	13 (7.7%)	7 (8.2%)	0.024
Microvascular invasion	676 (18.8%)	30 (33.7%)	< 0.001	0.663	58 (34.5%)	29 (34.1%)	0.014
AFP (ng/mL)	8207 ± 71,585	11,622 ± 49,737	0.655	0.055	14,908 ± 62,974	12,151 ± 50,846	0.048
Number of tumor							
Solitary	3383 (94.2%)	82 (92.1%)	0.424	0.080	156 (92.9%)	79 (92.9%)	0.003
Multiple	210 (5.8%)	7 (7.9%)			12 (7.1%)	6 (7.1%)	

AFP, alpha-fetoprotein; *ALC*, alcoholic liver cirrhosis; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *CTP*, Child–Turcotte–Pugh; *HBV*, hepatitis B virus; *INR*, international normalized ratio; *MELD*, model for end-stage liver disease; *NBNC*, non-HBV non-hepatitis C virus; *PT*, prothrombin time

extrahepatic metastasis in the univariate analysis. LCSGJ stage IVA and HCC other than nodular or infiltrative were associated with extrahepatic metastasis on the multivariate analysis.

The 1-, 3-, and 5-year survival rates after recurrence were 61.6%, 40.2%, and 33.6%, respectively. The mean survival time after recurrence was 26.4 ± 29.5 months (Fig. 4a). Variant HCC, recurrence sites including extrahepatic

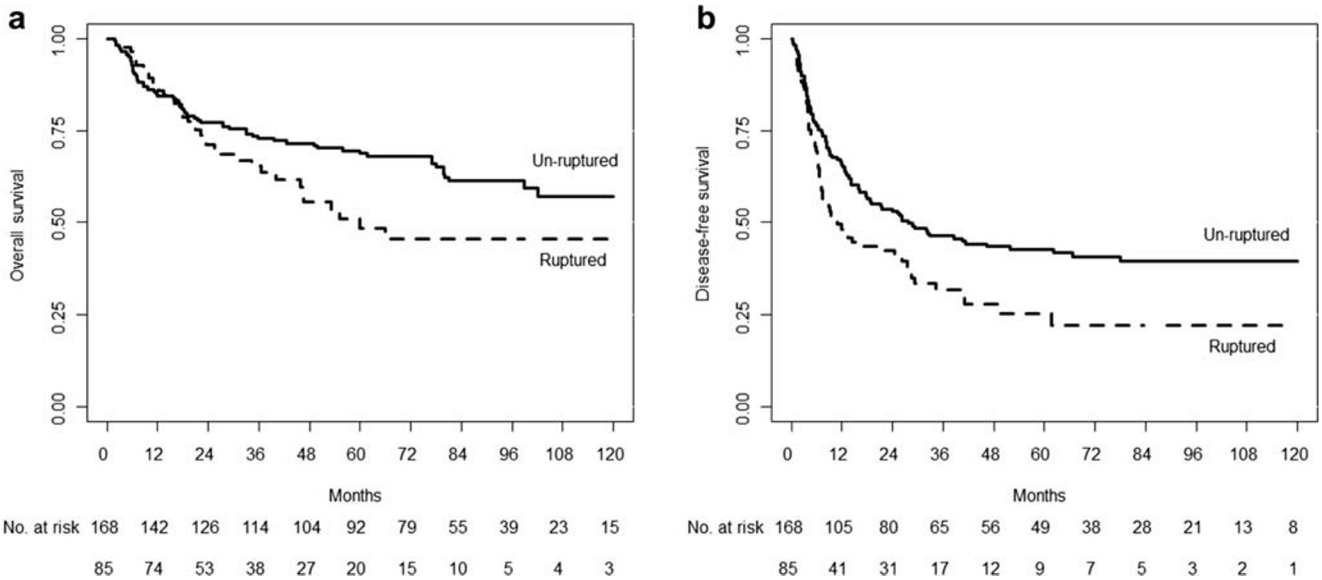

Fig. 3 **a** Overall survival of patients with ruptured HCC and matched unruptured HCC ($p = 0.041$). The 1-, 3-, and 5-year patient survival rates in the ruptured HCC group were 87.1%, 65.4%, and 48.4%, respectively. The 1-, 3-, and 5-year patient survival rates in the unruptured HCC group were 84.5%, 72.9%, and 68.7%, respectively. **b** Disease-free survival of patients with ruptured HCC and matched unruptured HCC ($p = 0.011$). The 1-, 3-, and 5-year disease-free survival rates in the ruptured HCC group were 48.2%, 31.7%, and 25.2%, respectively. The 1-, 3-, and 5-year disease-free survival rates in the unruptured HCC group were 65.8%, 46.3%, and 42.6%, respectively

Table 4 Outcomes in matched set

	Unruptured	Ruptured	Unadjusted		Adjusted*	
			OR (95% CI)	*p* value	OR (95% CI)	*p* value
1:2 (85 pairs)	168	85				
Death	61	37	1.492 (1.02–2.19)	0.041	1.488 (1.01–2.14)	0.046
Recurrence	94	60	1.535 (1.10–2.14)	0.011	1.559 (1.09–2.23)	0.015
Death after recurrence	51	35	1.450 (0.97–2.17)	0.072	1.324 (0.84–2.09)	0.228

In matched set, the risks of each outcome were compared using Cox regression model with robust standard errors and adjusted through adding adjusted variables to analysis

*Adjusted variables: age, CTP class, MELD score, gross feature, Steiner grade

recurrence, and presence of PS were associated with poor survival after recurrence in the multivariate analysis. Survival after recurrence in patients with only intrahepatic recurrence was significantly higher than in patients with extrahepatic recurrence ($p < 0.001$) (Fig. 4b).

PS occurred in 16 patients (18.0%) after surgical resection of ruptured HCC. Of 16 patients with PS, 9 (56.3%) demonstrated simultaneous intrahepatic recurrences and 7 (43.7%) presented with extrahepatic metastases only. Concurrent lung metastases were found in 10 patients (62.5%). In patients with PS, the mean interval between the hepatectomy and recurrence was 5.9 ± 8.2 months, which is significantly shorter than in those without PS (14.6 ± 14.7 months, $p = 0.005$). On the multivariate analysis, risk factors associated with PS were AFP > 1000 ng/mL and tumor size > 5 cm. The survival after recurrence was significantly lower in patients with PS than in patients without PS ($p = 0.026$) (Fig. 4c).

Except in only one patient with PS who manifested a disseminated pattern, peritoneal metastases were solitary lesion ($n = 8$) or multiple but countable lesions ($n = 7$). Eight patients who were eligible for excision underwent surgical resection for PS nodules. Patients who underwent surgical resection for PS mass demonstrated better survival outcome than those who did not undergo excision ($p = 0.027$) (Fig. 4d).

Discussion

Management of ruptured HCC comprises a two-step approach, i.e., TACE followed by surgical resection, to acquire hemostasis and stabilization of the patient first and then complete treatment with oncological surgery thereafter[1,7,8,29]. The Korean Liver Cancer Association (KLCA)-National Cancer Center recommended in their practice guidelines that hepatectomy should be considered as the primary treatment for patients with ruptured HCC with stable hemodynamic state, even though several studies reported poorer long-term survival in these patients compared with those with unruptured HCC[30]. In the management of ruptured HCC, acute phase management dealing with bleeding issue and long-term oncological outcome should be both considered in the decision for treatment modalities.

Through advances in diagnostic imaging modalities and surveillance system for high-risk group (chronic viral hepatitis or liver cirrhosis), earlier diagnosis of HCC with stable hemodynamics in patients with ruptured HCC is now attainable. In these patients, we can consider primary hepatectomy without any previous treatment for hemostasis. In this study, patients who underwent primary hepatic resection first or staged hepatectomy after TACE showed similar OS ($p = 0.503$) (data not shown). This result implies that elective primary hepatectomy for ruptured HCC after full evaluation of the patient with stable hemodynamic is a feasible treatment option.

Several studies reported high in-hospital mortality in patients with ruptured HCC, widely ranging from 23.1 to 77.8% according to (emergency) treatment modalities[31]. Recent reports have presented continued decreasing trend of 30-day or in-hospital mortality in patients with ruptured HCC[17]. Moreover, in patients who were eligible for hepatectomy, a 30-day mortality rate was 7.3%, which is better than the overall mortality rate of 35.6% in patients receiving conservative management, TACE, and surgical hemostasis[32]. Studies on short-term outcome of patients with ruptured HCC revealed that poor liver reserve, advanced liver disease, severe hemorrhage, and shock on admission were associated with hospital mortality[17,31,33]. In this study, no in-hospital mortality or post-hepatectomy liver failure occurred. With the development of diagnostic modality and widespread use of CT as surveillance method, earlier diagnosis of HCC is now possible, and this can explain the indolent or stable condition of patients in the present study. Altogether, these results suggest that tailored management of acute phase depending on the degree of emergency, followed by complete evaluation of the tumor extent and liver functional reserve, improves short-term survival outcome.

Similar to short-term outcome, a wide spectrum of reported long-term survival outcome for ruptured HCC is

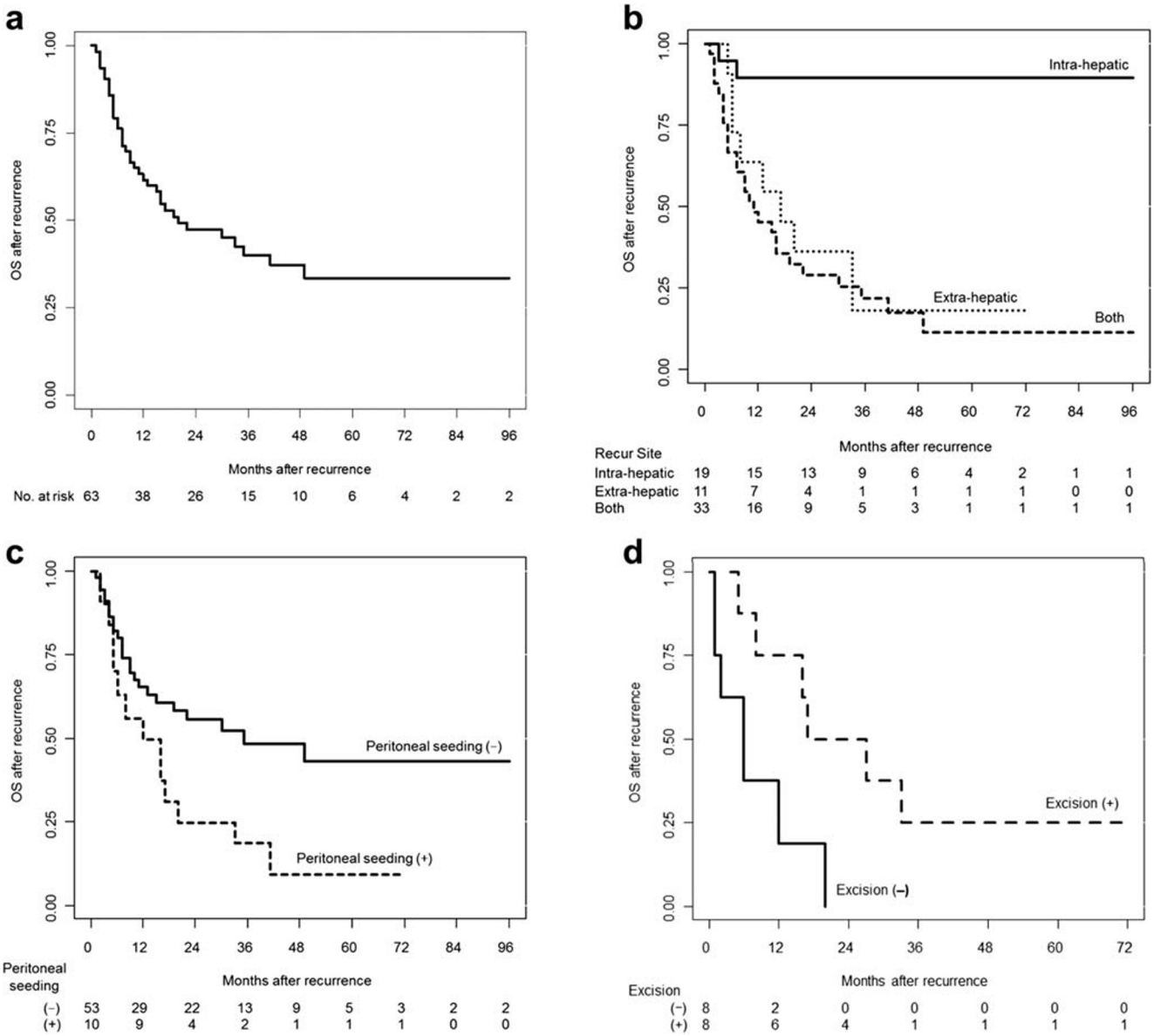

Fig. 4 **a** Overall survival after recurrence. The 1-, 3-, and 5-year survival rates after recurrence were 61.6%, 40.2%, and 33.6%, respectively. The mean survival time after recurrence was 26.4 ± 29.5 months. **b** Overall survival after recurrence according to the pattern of recurrence ($p < 0.001$ between intrahepatic and extrahepatic and both). The 1-, 3-, and 5-year survival rates after recurrence in patients with only intrahepatic recurrence were 89.5%, 89.5%, and 89.5%, respectively. The mean survival time after recurrence was 40.5 ± 34.7 months. The 1-, 3-, and 5-year survival rates after recurrence in patients with only extrahepatic recurrence were 63.6%, 18.2%, and 18.2%, respectively. The mean survival time after recurrence was 21.3 ± 19.4 months. The 1-, 3-, and 5-year survival rates after recurrence in patients with both intrahepatic and extrahepatic recurrences were 45.5%, 21.9%, and 11.7%, respectively. The mean survival time after recurrence was 20.1 ± 26.9 months. **c** Overall survival after recurrence according to the presence of PS ($p = 0.026$). The 1-, 3-, and 5-year survival rates after recurrence in patients without PS were 65.3%, 48.4%, and 43.0%, respectively. The mean survival time after recurrence was 48.0 ± 35.8 months. The 1-, 3-, and 5-year survival rates after recurrence in patients with PS were 49.7%, 18.7%, and 9.3%, respectively. The mean survival time after recurrence was 19.1 ± 18.3 months. **d** Overall survival after recurrence in patients with PS according to the surgical excision ($p = 0.027$). The mean survival time after recurrence in patients who received surgical excision for seeding mass was 28.4 ± 21.9 months, and those who did not was 9.9 ± 6.5 months

found. Even for the prognosis after surgical resection for ruptured HCC, survival outcomes varied from 37.7 to 90.0% for 1-year OS rate and from 14.7 to 67.5% for 5-year OS rate[1,11,34]. In the present study, OS rates were also within these previously reported ranges. This might be attributed to variations in operative techniques, heterogeneity in patient characteristics, and tumor characteristics included in studies.

Several studies compared the oncological outcomes between patients with ruptured and unruptured HCC.

Moreover, whether tumor rupture itself affects the OS and recurrence is controversial. In our study, patients with ruptured HCC showed inferior survival outcome compared with matched patients with unruptured HCC. As in the present study, several studies reported inferior outcomes of ruptured HCC than unruptured HCC[1,10–14]. Conversely, a number of studies verified that HCC rupture had low recurrence rate and showed comparable oncological outcome to that of unruptured HCC[15–20]. Based on recently reported comparable survival outcome in patients with ruptured HCC, the general rules of the 6th edition of LCSGJ no longer take tumor rupture into consideration for T staging, where the rupture was classified as T4 in the 5th edition[21, 22]. Aoki et al. suggested through a nationwide survey of the survival for patients with ruptured HCC that tumor rupture itself had an additional negative effect on patient survival which was correspondent to the addition of 0.5 to 2.0 TNM stage (both LCSGJ classification and AJCC/UICC staging system)[1]. Chan et al. also indicated the effect of tumor rupture as increasing T stage by 1 for otherwise T1–T2 tumors[13]. Adverse effect on the prognosis for patients with ruptured HCC was limited to early-stage tumor and was not substantially strong so as to outweigh other tumor-related parameters. Nonetheless, aggressive surgical resection for ruptured HCC is still valid to prolong survival outcome just as in treatment strategy for unruptured HCC.

Liu et al. demonstrated that extrahepatic recurrence after hepatic resection in the ruptured HCC group (45.5%) was significantly more common than in the unruptured group (25.8%), and although not significant, intraperitoneal extrahepatic recurrence rate in the ruptured group (20%) tended to be higher than that in the unruptured HCC group (14%)[14]. Chan et al. suggested that patients with ruptured HCC were more likely to develop tumor recurrence after hepatectomy, and the pattern of recurrence was more likely to be extrahepatic or concomitant intrahepatic and extrahepatic metastasis[13].

PS from HCC is uncommon. Recently reported PS rate of HCC after hepatectomy was 3.0%–5.6%[13,35,36]. However, when it comes to ruptured HCC, the reported PS rate was greater, ranging from 11.1 to 20%[19,34]. In accordance with previous reports, the present study showed a PS rate of 18%. Previous studies suggested that tumor cell seeding in the peritoneum derived from HCC rupture resulted in increased incidence of PS in patients with ruptured HCC[37–39]. The mechanism of PS in ruptured HCC is hypothesized as a direct implantation, which is different from adenocarcinoma in intra-abdominal organs demonstrating hematogenous or lymphatic dissemination to peritoneum. In the present study, considering the pattern and timing of recurrence in PS, "implantation" of tumor cells through rupture rather than "hematogenous spread" of tumor is suggested as a mechanism for PS.

In patients with recurrence after hepatectomy for ruptured HCC, we could expect to prolong survival through multidisciplinary treatments, including surgical excision of recurrent disease while controlling intrahepatic recurrence through TACE. In the present study, patients with PS showed earlier recurrence and worse survival outcome than patients without PS. However, as shown in our study result, patients with PS who were suitable for surgical excision for seeding mass manifested prolonged survival after recurrence. Kwak et al. suggested that HCC rupture itself was an independent risk factor for PS, but not an independent risk factor for OS[4]. On constant vigilance against the increased risk of PS, the result of this study suggests that follow-up surveillance CT or MRI should include the whole abdomen (pelvis) after resection of ruptured HCC, which could enable earlier detection of PS nodules.

Limited effective treatment options are available for HCC with disseminated PS. Hyperthermic intraperitoneal chemotherapy combined with cytoreductive surgery for HCC patient with PS was reported feasible to prolong survival in well-selected cases[40,41]. The effectiveness of sorafenib is not well-documented in HCC with PS. Among eight patients with PS who were not amenable to surgical resection in this study, two patients were treated with sorafenib, and both of them showed progressive disease. Various systemic agents of multi-kinase (lenvatinib, regorafenib, and cabozantinib) and immune checkpoint inhibitors (nivolumab and pembrolizumab) were recently granted approval for advanced HCC with promising outcomes[42]. This evolving landscape of systemic therapy for HCC could benefit recurrence in patients with ruptured HCC with PS.

Conclusion

In conclusion, surgical resection for ruptured HCC showed worse outcome than unruptured HCC. Spontaneous rupture of HCC itself had a negative effect on patient survival and disease recurrence. In patients with ruptured HCC, the risk of PS also increased. However, hepatectomy as a mainstay of assertive management combined with TACE in these patients could prolong survival outcome. Even after recurrence, aggressive treatment still stands for improved survival outcome after recurrence.

Author Contributions Our manuscript has 13 authors, all of whom contributed significantly to this study. Jae Hyun Kwon, Gi-Won Song, and Sung-Gyu Lee made substantial contributions to study conception and design. Shin Hwang, Ki-Hun Kim, Chul-Soo Ahn, Deok-Bog Moon, Tae-Yong Ha, Dong-Hwan Jung, Gil-Chun Park, Young-In Yoon, Ju Hyun Shim, and Kyong Won Kim participated in data acquisition and analysis. Jae Hyun Kwon and Gi-Won Song participated in the drafting of the article and critical revisions to ensure appropriate communication of important intellectual content.

Funding Information The present work was supported by a fund from the National Research Foundation of Korea (NRF-2015K1A4A3046807).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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