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Spontaneous rupture of hepatocellular carcinoma: Optimal timing of partial hepatectomy

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ABSTRACT

Background: Partial hepatectomy has been used to treat patients with resectable hepatocellular carcinoma (HCC) which spontaneously ruptured. It is still controversial as to whether emergency partial hepatectomy (EmPH) should be carried out at the time of rupture, or the patients should initially be managed by operative or non-operative treatment to stop the bleeding, followed by staged early or delayed partial hepatectomy when the patient's condition becomes stable.

Methods: Consecutive 10-year patients with ruptured HCC managed at our center were included in this study. Patients who underwent partial hepatectomy were further subdivided into the EmPH group, the staged early partial hepatectomy (SEPH) group, and the staged delayed partial hepatectomy (SDPH) group. Univariate and multivariate analyses of factors affecting overall survival(OS) were conducted before and after propensity score matching analyses amongst the included patients. OS, postoperative mortality, recurrence free survival (RFS), and peritoneal metastatic rates were compared. The risk factors of peritoneal metastases were determined using the COX regression analysis.

Results: The 130 patients who underwent partial hepatectomy were subdivided into the EmPH group (surgery at the time of rupture, n = 30), the SEPH group (surgery ≤ 8 days of rupture, n = 67), and the SDPH group (surgery > 8 days of rupture, n = 33). The remaining 86 patients underwent non-surgical treatment. Partial hepatectomy was an independent predictor of better OS (HR 2.792, $P < 0.001$). For resectable HCC, the 30-day mortality, OS, and RFS were similar between the EmPH group, and the staged partial hepatectomy (SPH) group which included the patients who underwent SEPH and SDPH. The SEPH group had significantly better OS and RFS. Multivariate COX regression analysis demonstrated that SDPH was strongly associated with postoperative peritoneal dissemination (OR 28.775, $P = 0.003$).

Conclusion: Partial hepatectomy provided significantly better survival than non-surgical treatment for patients who presented with ruptured HCC. Early partial hepatectomy within 8 days of rupture which included EmPH (carefully selected) and SEPH, resulted in significantly less patients with peritoneal dissemination and better long-term survival outcomes (especially RFS) than SDPH.

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent cancer-related mortalities worldwide [1,2]. Spontaneous rupture of HCC, a life-threatening complication, occurs in 3%–15% of patients with HCC [3–5]. The mortality rates of spontaneously ruptured HCC remain high in the acute phase, ranging from 25% to 75% [5–8]. The treatment options for these patients include supportive care,

Abbreviations: HCC, hepatocellular carcinoma; TAE, transcatheter arterial embolization; EmPH, emergency partial hepatectomy; SEPH, staged early partial hepatectomy; SDPH, staged delayed partial hepatectomy; SPH, staged partial hepatectomy; OS, Overall survival; RFS, recurrence-free survival; TACE, transarterial chemoembolization; PSM, propensity score matching; MST, median survival time.

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transcatheter arterial embolization (TAE), emergency liver resection, and staged hepatectomy after the bleeding has stopped with either non-surgical or surgical treatment [3–5]. Partial hepatectomy aiming at long-term survival is often considered as futile in treating ruptured HCC because it is classified as a stage T4 disease according to the AJCC/UICC classification [9], as ruptured HCC is considered to result in peritoneal spread. However, many studies have shown partial hepatectomy can provide better survival outcomes than non-surgical treatments in patients with ruptured but resectable HCC [5,7,10,11]. Emergency partial hepatectomy carried out at the time of HCC rupture has been reported to result in very high operative mortality rates of 7.6%–50% [7,8,10,12]. Staged partial hepatectomy (SPH) carried out after the bleeding has been stopped by non-surgical or surgical means in a hemodynamically stable patient is recommended by many surgeons because of its perioperative safety and acceptable long-term survival outcomes [13–15]. The main problem with SPH is the high rate of postoperative peritoneal dissemination [16]. To our knowledge, only a few studies have been performed to find out the postoperative peritoneal dissemination in patients with ruptured HCC [16,17]. Moreover, there have been no studies which focused on the best timing to carry out staged partial hepatectomy on long-term survival outcomes.

This retrospective study was carried out on patients with ruptured HCC who were managed in our center over a 10 years period. The aims were to determine the best treatment strategies at the time of HCC rupture and to determine the best time for partial hepatectomy in patients with ruptured but resectable HCC.

Patients and methods

Patients

The data on consecutive patients who were diagnosed and managed as HCC from January 2005 to June 2015 at our department were retrospectively reviewed. Patients who were diagnosed as ruptured HCC entered into this study.

The diagnosis of HCC followed the criteria of the EASL Clinical Practice Guideline published in 2018 based either on histopathology in patients who underwent surgery, or on two medical imagings which showed typical radiological features of HCC with or without a raised serum level of alpha fetoprotein [18].

The diagnosis of ruptured HCC was based on clinical symptoms of acute abdominal pain on admission, signs of peritonitis, with or without hemodynamic instability in a patient with a diagnosis of HCC. Diagnostic abdominal paracentesis was performed if necessary when no contraindication was identified.

The primary goal during the acute phase of management was to maintain hemodynamic stability using intravenous fluid resuscitation, with blood transfusion if required. The patients were closely monitored in the intensive care unit. Coagulopathies in patients were corrected with fresh frozen plasma, platelet concentrates and intravenous vitamin K. Transhepatic arterial embolism (TAE) was used if the bleeding continued, except in patients who were moribund. In some patients presenting with a ruptured but resectable HCC who were considered by the surgeons on admission to have a low operative risk for liver resection, emergency partial hepatectomy was carried out with the aim to combine a 'curative' liver resection with hemostasis by resecting the ruptured tumor. For the remaining patients with ruptured HCC after the bleeding was stopped, by either non-surgical or surgical treatment, a detailed investigation was carried out after the patients became hemodynamically stable. The evaluation included the Eastern Cooperative Oncology Group Score, cardiopulmonary assessment, serological tests, Child-Pugh Score, tumor status, indocyanine green retention rate at 15 min, imaging studies and liver volumetry measurements.

Child-Pugh grade C was recognized as an absolute contraindication for surgery. Other contraindications included main portal vein tumor thrombosis, intractable hepatic encephalopathy, severe coagulopathy, poor performance status, distant metastasis, and heart, renal or lung function that was unable to tolerate the operation. Partial hepatectomy was comprised of a single or multiple liver resections aiming to excise all macroscopic tumors. The operations were performed by experienced liver surgeons after careful exploration of the abdominal cavity to exclude extrahepatic metastases. The amount of hemorrhage was carefully recorded. Complications after hepatectomy were classified using the modified Clavien-Dindo classification [18].

The main aim of laparotomy was for hemostasis using packing, alcohol injection, suture-plication, and as the last resort ligation of the feeding artery which supplied the bleeding tumor. Emergency partial hepatectomy (EmPH) was defined as partial hepatectomy carried out at the time of HCC rupture [15] or within 24 h after hospital admission [11]. EmPH was only carried out in patients with a resectable HCC in a hemodynamic stable condition and the surgeon considered the resection to be technically safe, especially the tumor is located in the peripheral segments and the estimated blood loss is limited during liver resection. In addition, when hemostasis was not achieved with non-surgical treatment, emergency laparotomy was performed. Staged partial hepatectomy (SPH) was defined as a 3-staged procedure in which the first stage aimed at hemostasis using conservative treatment, TAE or laparotomy. The second stage aimed at stabilization of the patient and work-up to assess resectability of the tumor. The third stage aimed at 'curative' liver resection for patients with good liver function and resectable HCC. A staged early partial hepatectomy (SEPH) was defined as a SPH from $\leq$8th days of HCC rupture. A staged delayed partial hepatectomy was defined as a SPH carried out >8 days after rupture of HCC. Based on the theory of the maximum sum of sensitivity and specificity, we determined the timing value for predicting survival in receiver operating characteristic curve analysis. The optimum cut-off value of the timing from tumor rupture to surgery was 192.5 h, which is equal to day 8.

During the study period, follow-up data were obtained via outpatient visits, telephone contact by our research nurse, or readmissions. All patients were monitored closely for residual HCC, HCC recurrence and/or metastases. The study was censored on December 1, 2017. The treatments offered for residual HCC, HCC recurrence and/or metastases were made by a multidisciplinary team of specialists, and included reoperation, percutaneous ablative therapy, percutaneous ethanol injection, TACE, external radiotherapy, systemic chemotherapy, or sorafenib (since 2008). Recurrence free survival (RFS) was defined as the interval from the date of definitive liver resectional operation to the date of HCC recurrence or the last date of follow-up if there was no evidence of recurrence. Overall survival (OS) was defined from the date of definitive liver resectional operation, or from the date of ruptured HCC for patients who did not undergo partial hepatectomy, to the date of death or the last date of follow-up. All patients gave informed consents before the treatments. This study was pre-registered on "ClinicalTrials.gov" with an analysis plan (NCT03516890).

Statistical analysis

All analyses were carried out using the SPSS 24.0 (IBM) and R software 3.4.4 for Windows. A two-sided $P < 0.05$ was considered statistically significant. Survival analysis of the OS and RFS rates was performed using the Kaplan-Meier method and compared by the log-rank test. Propensity score matching (PSM) was performed

to adjust for differences in the baseline data as described by Rubin and Rosenbaum [19]. Cox regression was performed in the multivariable analysis for all the patients before and after PSM, and for balancing the differences in the variables between the EmPH group and the SPH group. In addition, the Cox regression analysis on factors relating to postoperative peritoneal metastases was performed.

Results

Demographics and clinicopathologic features of all patients with ruptured HCC

Of the 228 patients who presented with ruptured HCC, 86 underwent non-surgical treatment which included TAE for hemostasis (n = 50) or correction of coagulopathy (n = 36). Among the remaining 142 patients who underwent surgical treatment, 12 patients underwent surgical treatment only to stop bleeding from the ruptured HCC, such as using microwave coagulation therapy, hepatic artery ligation, or suture ligation. Partial hepatectomy was carried out in 216 patients, including 30 patients who underwent EmPH, and 100 patients staged partial hepatectomy (SPH). For SPH, 67 underwent early SPH (the SEPH group) and 33 delayed SPH (the SDPH group) (Fig. S1). The patient demographics and clinicopathologic features are shown in Table S1. Of the 18 patients who underwent emergency TAE for hemostasis, the bleeding could not be controlled in 2. They subsequently underwent emergency laparotomy for hemostasis. The patients who received emergency operation showed a higher 30-day mortality than staged operation (11.8% vs 0.9%, $P = 0.014$). But there are no significances between EmPH and SPH (3.3% vs 0%, $P = 0.231$). Only 1 patient with ruptured HCC after a traffic accident died of myocardial infarction after emergency partial hepatectomy. No patient died within 30 days after SEPH and SDPH (Table S2).

Comparison of clinicopathologic characteristics before and after PSM

As shown in Table S3, there were more patients who had advanced tumors and poorer hepatic function in the non-surgical group.

After PSM, there were 35 matched pairs of patients which included 35 patients who underwent partial hepatectomy and 35 matched patients who underwent non-surgical treatment. Although there was no significant difference in the tumor parameters, there was a significantly higher 30-day mortality rate (11 vs 1 death, $P = 0.002$) in the non-surgical treatment group compared to the patients who underwent partial hepatectomy (Table S4).

Survival analysis before and after PSM

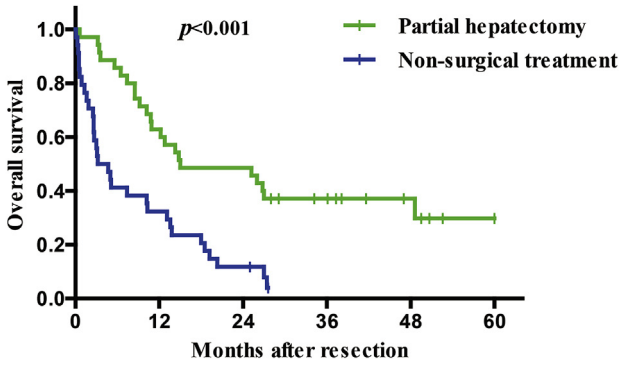
The median survival time (MST) was 13.7 (IQR 7.2–35.4) months in the partial hepatectomy group and 2.5 (IQR 0.5–7.4) months in the non-surgical treatment group ($P < 0.001$) (Fig. S2). Multivariable analyses showed that non-surgical treatment was an independent risk factor of poor OS (HR: 3.141, 95% CI: 2.198–4.488, $P < 0.001$) (Table S5).

In the propensity score-matched cohorts, patients who underwent non-surgical treatment exhibited a significantly shorter survival time than the partial hepatectomy group (HR: 3.029, 95% CI:

Table 1
Univariate and multivariate analysis of the predictive factors associated with overall survival after propensity matching.

	Univariate analysis		Multivariate analysis	
Variables	Hazard ratio*	*P* value	Hazard ratio*	*P* value
Sex				
Male/female	0.911 (0.390–2.127)	0.830		
Age (years)				
>50/≤50	0.796 (0.463–1.368)	0.409		
Treatment				
Non-surgical treatment/hepatectomy	3.029 (1.745–5.258)	**<0.001**	2.792 (1.581–4.930)	**<0.001**
Cirrhosis				
Yes/no	0.855 (0.483–1.515)	0.592		
Portal hypertension				
Yes/no	1.072 (0.553–2.077)	0.836		
Tumor size (cm)				
>5/≤5	2.091 (0.986–4.435)	0.064		
Tumor number				
Multiple/solitary	1.476 (0.853–2.551)	0.164		
Macroscopic vascular invasion				
Yes/no	2.473 (1.275–4.798)	**0.007**	1.643 (0.828–3.264)	0.156
Hemorrhagic shock				
Yes/no	1.169 (0.643–2.125)	0.608		
Distant metastasis				
Yes/no	2.029 (0.799–5.153)	0.137		
AST (U/L)				
>40/≤40	2.792 (1.607–4.851)	**<0.001**	1.981 (1.088–3.607)	**0.025**
AFP (ng/mL)				
>400/≤400	2.517 (1.442–24.392)	**0.001**	1.954 (1.067–3.577)	**0.030**
Platelet ($\times 10^9$/L)				
>100/≤100	1.068 (0.573–21.989)	0.836		
Hemoglobin on admission (g/L)				
>120/≤120	1.095 (0.597–2.010)	0.770		
Sorafenib				
Yes/no	0.738 (0.102–5.355)	0.763		
Child-Pugh				
B–C/A	1.183 (0.694–2.018)	0.537		

* Values in parentheses are 95% confidence intervals.
AST, aspartate aminotransferase; AFP, a-fetoprotein.



No. at risk						
Partial hepatectomy	35	22	17	10	5	1
Non-surgical treatment	35	11	4	0	0	0

Fig. 1. Overall survival between the partial hepatectomy group and the non-surgical group after propensity score matching.

1.745–5.258, $P < 0.001$) (Table 1 and Fig. 1). The corresponding MSTs were 3.2 (IQR 1.3–13.8) months and 15.0 (IQR 8.5–37.3) months. Multivariable analysis showed that non-surgical treatment was an independent risk factor of poor OS (HR: 2.792, 95% CI: 1.581–4.930, $P < 0.001$) (Table 1).

Differences between the EmPH group and the SPH group

No significant differences were found in the Barcelona Clinic Liver Cancer staging between the 2 groups (Table S6). A Cox regression model was carried out to adjust the variables (Table S7). .

Although worse liver function and hemodynamic instabilities were more commonly found in patients who underwent emergency partial hepatectomy (EmPH) than those who underwent staged partial hepatectomy (SPH), no significant differences were observed in the OS and RFS rates between the 2 groups of patients (Fig. S3).

Staged early partial hepatectomy (SEPH) versus staged delayed partial hepatectomy (SDPH)

Among the 100 SPH patients, 67 were classified into the SEPH group (≤8 days) and 33 into an SDPH group (>8 days). Not surprisingly, the latter group consisted of significantly more patients who underwent TAE treatment for hemostasis (7.5% vs 33.3%, $P = 0.001$). There were no significant differences in the demographics and clinicopathologic variables between the 2 groups (Table 2).

The postoperative 1-, 2-, 3-, 4-, and 5-year RFS rates were 38.8%, 25.4%, 23.7%, 21.7%, and 18.6% for the SEPH group vs 24.2%, 6.1%, 0%, 0%, and 0% for the SDPH group, respectively (Fig. 2). The difference in RFS was significant ($P = 0.006$). The postoperative 1-, 2-, 3-, 4-, and 5-year OS rates were 59.7%, 40.3%, 31.2%, 27.0%, and 24.3% for the SEPH group vs 48.5%, 24.3%, 21.2%, 8.0%, and 0% for the SDPH group, respectively. There were no significances in OS between the 2 groups ($P = 0.068$). However, the survival curves between the two groups became more divergent as the time of follow-up increased (Fig. 2). Furthermore, patients who received early hepatectomy with "curative intent" (EmPH + SEPH group) had significantly better OS and DFS than those who underwent SDPH (Fig. S4).

The postoperative peritoneal dissemination rates were 3.3%, 4.5%, and 33.5% in the EmPH group, SEPH group, and SDPH group, respectively. Patients in the SDPH group exhibited a significantly higher rate of peritoneal dissemination ($P < 0.001$; Table S2).

Association between staged delayed partial hepatectomy (SDPH) and peritoneal dissemination

To further identify the risk factors of peritoneal dissemination, univariate and multivariate COX regression analyses were applied. The timing of hepatectomy was a major variable that was significantly associated with the postoperative peritoneal dissemination rate ($P < 0.001$), with a HR in the SDPH group being 28.775 (95% CI, 3.102–266.958, $P = 0.003$) (Table 3). These results demonstrated that a long delay in partial hepatectomy was independently associated with postoperative peritoneal dissemination.

Discussion

HCC rupture is a life-threatening complication accounting for about 6–10% of mortality in patients with HCC [2,3]. Typical symptoms of HCC rupture are sudden onset of epigastric pain accompanied by clinical signs of shock and peritoneal irritation. As bleeding and hemorrhagic shock have the greatest influence on prognosis of these patients [5,7,10], the initial treatment should aim at resuscitation and hemodynamic stabilization by using intravenous fluid infusion, blood transfusion, correction of coagulopathy and other supportive measures. TAE is an effective method to achieve hemostasis [13,20]. Staged partial hepatectomy following emergency TAE has been shown to improve long-term survival than TAE alone [13]. Other palliative treatments to stop bleeding at the time of HCC rupture include hepatic artery ligation, suturing of bleeding tumor, packing and microwave (or radiofrequency) ablation [2,3,6,21]. The leading cause of death for ruptured HCC in the short-term has been reported to be due to bleeding [22]. The rebleeding and in-hospital mortality rates are also high in non-resectional cases [2–4,23]. In our study, the 30-day mortality rate of palliative surgery was 25.0%. In contrast, liver resection resulted in improved survival outcomes in selected patients with hemodynamics stability [5,7,10,11]. In the present study, PSM showed partial hepatectomy to offer better survival outcomes than non-surgical treatments.

Our study was carried out in one of the largest liver surgery centers in China. All surgeons had extensive experience in liver resection for tumors. When patients were diagnosed with ruptured HCC, partial hepatectomy (either emergency or staged), was considered if the tumor was resectable. Emergency liver resection was carried out for patients who were hemodynamically stable. The total rate of hepatic resection in this study for patients with

Table 2
Comparison between the staged early partial hepatectomy group and the staged late partial hepatectomy group.

Variables	Staged early partial hepatectomy (n = 67)	Staged late partial hepatectomy (n = 33)	*P* value‡
Age (years)†	48.6 (10.0)	46.1 (13.3)	0.287¶
Sex ratio (M: F)	61 : 6	28 : 5	0.554
HBs-Ag (+)	60 (89.6)	29 (87.9)	1.000
HCV-Ab (+)	2 (3.0)	2 (6.1)	0.845
Tumor size (cm)*	7.9 (5.0–10.0)	8.0 (6.0–11.0)	0.635§
Tumor number			
1	55 (82.1)	22 (66.7)	0.160§
2–3	5 (7.5)	6 (18.2)	
≥4	7 (10.4)	5 (15.2)	
Macroscopic vascular invasion	11 (16.4)	7 (21.2)	0.557
Cirrhosis	50 (74.6)	25 (75.8)	0.902
Portal hypertension	7 (10.4)	3 (9.1)	1.000
Child-Pugh			
A	60 (89.6)	30 (90.9)	1.000
B	7 (10.4)	3 (9.1)	
Tumor differentiation			
Well or moderate	35 (52.5)	16 (48.5)	0.724
Poor	32 (47.8)	17 (51.5)	
BCLC stage			
A	42 (62.7)	17 (51.5)	0.410§
B	11 (16.4)	9 (27.3)	
C	14 (20.9)	7 (21.2)	
Hemorrhagic shock	3 (4.5)	5 (15.2)	0.145
Hemoglobin (g/L)†	123.2 (22.7)	115.1 (25.5)	0.111¶
Platelet ($\times 10^9$/L)†	187.9 (92.1)	181.1 (83.0)	0.720¶
RBC transfusion during hospitalization	33 (49.3)	18 (54.5)	0.619
AFP≥400 (ng/mL)	41 (61.2)	22 (66.7)	0.594
ALT (U/L)*	29.0 (23.0–41.0)	35.0 (22.5–60.0)	0.461§
AST (U/L)*	36.0 (26.0–67.0)	40.0 (29.0–65.0)	0.895§
Albumin (g/L)†	36.6 (5.0)	35.3 (6.8)	0.292¶
Total bilirubin (umol/L)*	15.8 (10.8–20.4)	13.5 (10.7–16.5)	0.113§
Sorafenib	3 (4.5)	1 (3.0)	1.000
Preoperative TAE	5 (7.5)	11 (33.3)	**0.001**
Hemostasis achieved before operation	61 (91.0)	30 (90.9)	1.000
Estimated intraperitoneal bleeding (ml)*	400 (100–700)	200 (100–550)	0.434§
Intraoperative RBC transfusion	34 (50.7)	14 (42.4)	0.433
Hepatic inflow occlusion	31 (46.3)	15 (45.5)	0.939
Duration of clamping (min)†	11.8 (7.9)	15.9 (6.7)	0.092¶
Local surgical resection margin			
R0	65 (97.0)	32 (97.0)	1.000
R1+R2	2 (3.0)	1 (3.0)	
Type of hepatectomy			
Anatomical	12 (17.9)	7 (21.2)	0.692
Non-anatomical	55 (82.1)	26 (78.8)	
Extent of hepatectomy			
Major	7 (10.4)	6 (18.2)	0.444
Minor	60 (89.6)	27 (81.8)	
Morbidity	39 (58.2)	23 (69.7)	0.266
Clavien-Dindo grades I-II	34 (87.2)	18 (78.3)	0.572
Clavien-Dindo grades III-IV	5 (12.8)	5 (21.7)	

Values in parentheses are percentages unless indicated otherwise; values are *median (i.q.r.) and †mean(s.d.).
‡χ^2 test (with Yates' correction), except §Wilcoxon's rank-sum test, and ¶Student's *t*-test.
HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; BCLC, Barcelona Clinic Liver Cancer; RBC, red blood cell; AFP, a-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TAE, transcatheter arterial embolization.

ruptured HCC was 52.4% (129 of 246), which is very high among the reported studies [2,3,5,24]. Our postoperative 1-, 3-, and 5-year OS and RFS rates for patients with ruptured HCC are comparable to the other reported studies [11,13–15,24–29].

The appropriate timing to perform liver resection remains controversial. Emergency hepatectomy has been advocated to achieve both hemostasis and tumor removal [6,7,12,20]. Although effective in controlling bleeding, one-stage emergency liver resection has been reported to result in high in-hospital mortality rates (range 16.5–100%) [3,27,30]. With improvements in diagnosis, perioperative care, and surgical techniques, the in-hospital mortality from emergency liver resection has decreased in recent years (range 1.1–13.0%) [12,15,24,28,29]. In the present study, there was an overall in-hospital mortality rate of 3.3% (only one patient), which was lower than the reported mortality rates in other studies. This study showed that the hospital mortality and long-term survival rates after EmPH for ruptured HCC can be close to those patients after staged delayed partial hepatectomy, and EmPH can be a safe and feasible treatment option in selected patients. The 30-day mortality rate for all the emergency operations, including liver resection and palliative hemostatic procedures such as microwave coagulation therapy, hepatic artery ligation, or suturing ligation, was significantly higher than the staged operations (11.8% vs 0.9%, $P = 0.014$) (Table S2). This significantly higher 30-day mortality can be explained by the high operative mortality in palliative surgery aiming only to stop bleeding (25.0%, 4 of 12). Patients who received emergency operation may suffer more risk of unresectable HCC which is the main reason for high 30-day mortality than staged operation, so EmPH should be carefully selected. At the time of HCC rupture, most clinicians advocate TAE to stop the bleeding, stabilize

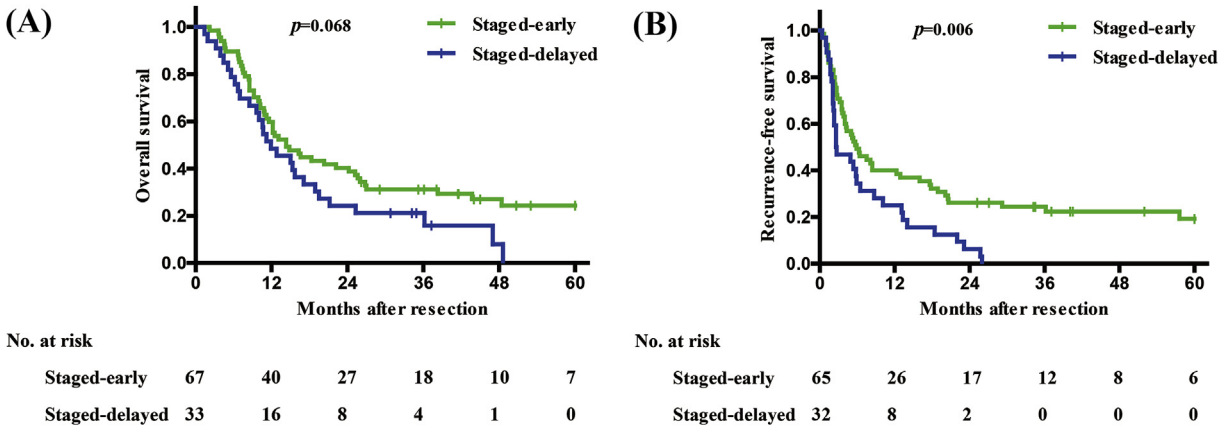


Fig. 2. Overall survival (A) and recurrence-free survival (B) between the staged early partial hepatectomy group and the staged late partial hepatectomy group after resection.

Table 3
Univariate and multivariate COX regression analysis of postoperative peritoneal dissemination

	Univariate analysis		Multivariate analysis	
Variables	Hazard ratio*	*P* value	Hazard ratio*	P value
Age (years)	0.948 (0.904–0.995)	**0.029**	0.941 (0.881–1.005)	0.069
Sex (female)	1.032 (0.232–4.579)	0.967		
Tumor number (multiple)	1.126 (0.316–4.015)	0.855		
Maximum tumor size (>5 cm)	0.898 (0.123–6.579)	0.916		
Tumor differentiation (poorly)	1.685 (0.608–4.671)	0.316		
Macroscopic vascular invasion	5.029 (1.642–15.401)	**0.005**	10.192 (2.616–39.707)	**0.001**
Estimated intraperitoneal bleeding (ml)	0.999 (0.998–1.000)	0.229		
Cirrhosis	0.654 (0.232–1.840)	0.421		
Portal hypertension	0.844 (0.111–6.437)	0.870		
RBC transfusion	1.254 (0.446–3.526)	0.668		
Child-Pugh (B)	0.875 (0.245–3.123)	0.837		
AFP (≥400 ng/mL)	2.764 (0.859–8.896)	0.088		
Hepatic inflow occlusion	1.334 (0.482–3.691)	0.579		
Resection margin (R1+R2)	12.942 (2.641–63.418)	**0.002**	2.262 (0.209–24.443)	0.502
Type of hepatectomy (anatomical)	1.217 (0.342–4.329)	0.761		
Timing of hepatectomy		**<0.001**		**<0.001**
SEPH	1.277 (0.133–12.313)	0.832	3.109 (0.278–34.768)	0.357
SDPH	12.286 (1.567–96.354)	**0.017**	28.775 (3.102–266.958)	**0.003**

*Values in parentheses are 95% confidence intervals.
RBC, red blood cell; AFP, a-fetoprotein; SEPH, staged early partial hepatectomy; SDPH, staged delayed partial hepatectomy.

the patients, followed by interval staged hepatectomy after a period of hemodynamic stabilization. Several studies have shown that staged hepatectomy is better than emergency hepatectomy for ruptured HCC with a lower hospital mortality and better long-term survival [13–15,31]. However, a higher incidence of peritoneal dissemination has been reported by delaying partial hepatectomy in patients with resectable but ruptured HCC [16,17,32,33]. Ong and Taw [6] found a delay in liver resection after initial hemostasis compromised the subsequent resection rate. Furthermore, postoperative peritoneal dissemination has been reported to be higher in staged hepatectomy patients than in emergency cases [24]. This study showed a delay in hepatectomy for more than 8 days (SDPH) to be an independent risk factor of postoperative peritoneal dissemination, and patients who underwent SDPH after more than 8 days of HCC rupture had worse long-term survival outcomes. Thus, when a staged hepatectomy strategy is considered for ruptured HCC and partial hepatectomy should be carried out as soon as possible. If both options (EmPH or SEPH) are reasonable, SEPH will be preferred due to the three aspects as followings. Firstly, the patients suffering EmPH treatment seemed to have a higher 30-day mortality than SEPH (In this study 3.3% vs 0%) according to the published literatures. Secondly, if SEPH could be an option, the HCC rupture patient could be given more accurate preoperative evaluation including contrast-enhanced CT or MRI, ICG test, cardiopulmonary function assessment, and etc., which could make the patient safer and decrease the risk of unresectable HCC after laparotomy. Thirdly, there is no statistical difference in the peritoneal dissemination rate between EmPH and SEPH (3.3% vs 4.5%). The patients with SEPH have less peritoneal dissemination rate and better long-term survival outcomes than those in SDPH group. Thus, whether from aspects of lower peritoneal dissemination or better short-term/long-term survival, SEPH is preferred.

HCC with peritoneal dissemination is considered to be at a late stage. The mechanism of peritoneal dissemination involves spillage of tumor seedings into the peritoneal cavity followed by formation of metastatic deposits [34]. There is no recommended treatment for disseminated peritoneal diseases. A few reports have shown that surgical resection for isolated peritoneal secondaries was the only treatment that prolonged survival [35]. Furthermore, peritoneal dissemination markedly deteriorates patient's quality of life. To prevent the occurrence of peritoneal dissemination at the time of ruptured HCC, attempts to use 5-fluorouracil combined with a large amount of distilled water have been used for peritoneal irrigation. Despite these efforts, postoperative peritoneal dissemination is an

inevitable event in a significant proportion of patients with HCC rupture. In the present study, 15 patients (11.5%) were diagnosed with peritoneal dissemination during follow-up after partial hepatectomy. Specifically, the rate of peritoneal dissemination was 3.3% (n = 1), 4.5% (n = 3), and 33.3% (n = 11) in the emergency, staged early, and staged delayed partial hepatectomy groups, respectively [5,24,25]. Using multiple COX regression analyses, the timing of partial hepatectomy was the major risk factor influencing peritoneal dissemination. The staged interval time for partial hepatectomy have been reported to vary from 10 to 126 days at different centers [3,5,13,14]. In our study, only 33 patients (25.4%) underwent partial hepatectomy more than 8 days from the time of HCC rupture, a time much shorter than those reported by other authors [3,5,14,24]. This probably explains the low incidence rate of postoperative peritoneal dissemination in our study. Peritoneal dissemination has been reported from 1 to 105 months after surgery for HCC rupture [16,17,34]. The survival benefit of decreasing peritoneal dissemination can only be observed in long-term follow-up studies.

There are several limitations in this study. First, this is a retrospective study with its inherent defects. Second, although our center is a high-volume center for HCC, the patient number is still limited. Finally, the main aetiological factor of HCC in this study was hepatitis B infection, which is different from that in Western countries. Whether the results of our study can be applied to patients in the West is still not known.

In summary, emergency partial hepatectomy was safe and feasible in selected patients with ruptured HCC. Staged early partial hepatectomy was better than staged delayed partial hepatectomy in resulting in less peritoneal dissemination, better survival time, improved quality of life, and decrease in hospital stay and cost. The time interval between HCC rupture and staged partial hepatectomy should be less than 8 days.

Abbreviations used for Partial Hepatectomy for ruptured HCC

Emergency Partial Hepatectomy (EmPH) – partial hepatectomy at time of rupture	Early partial hepatectomy (EPH)
Staged early partial hepatectomy (SEPH) – partial hepatectomy from 3 to 8 days of HCC rupture after patient was stabilized	Staged partial hepatectomy (SPH)
Staged delayed partial hepatectomy (SDPH) – partial hepatectomy > 8 days of HCC rupture.	

Clinical trial number

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Authors' contributions

Jing-jing Wu and Peng Zhu contributed equally as co-first authors. Peng Zhu, Bi-xiang Zhang and Xiao-ping Chen contributed to the design of this study. Jing-jing Wu, Zhan-guo Zhang, Bi-xiang Zhang, Zhi-wei Zhang, Zhi-yong Huang, Wan-guang Zhang and Xiao-ping Chen contributed to data collection. Chang Shu contributed to interpretation of data. Wan Yee Lau, Jing-jing Wu, Peng Zhu and Abdoul-aziz Mba'nbo-koumpa contributed to drafting and revision of this manuscript. The final version of this manuscript was approved by all authors.

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Conflict of interest

Jing-jing Wu, Peng Zhu, Zhan-guo Zhang, Bi-xiang Zhang, Chang Shu, Abdoul-aziz Mba'nbo-koumpa, Zhi-wei Zhang, Zhi-yong Huang, Wan-guang Zhang, Wan Yee Lau and Xiao-ping Chen declared that they have no conflicts of interest to disclose.

Compliance with ethical standards and ethical approval

The treatments and research were in accordance with the ethical standards set by the Declaration of Helsinki and approval by Ethics Committee of Tongji Hospital.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.02.033.

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