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ORIGINAL ARTICLE

Outcomes and Prognostic Factors of Spontaneously Ruptured Hepatocellular Carcinoma

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Abstract

Background Spontaneous tumor rupture is a rare and life-threatening complication of hepatocellular carcinoma (HCC). The best treatment strategy remains unclear.

Methods The clinical data of 137 patients with spontaneously ruptured HCC from 2010 to 2015 were reviewed retrospectively. We investigated the outcome and prognostic factors of various treatment strategies.

Results Of the 137 patients, 53, 45, 3, and 36 patients underwent transcatheter arterial chemoembolization (TACE) alone, liver resection (LR) (LR alone or TACE + LR), surgical hemostasis, and conservative therapy. The patients undergoing LR had longest overall survival (OS). In the TACE alone group, independent factors affecting 30-day mortality were MELD score ≥ 12, AFP ≥ 1000 ng/ml, and largest tumor size ≥ 10 cm. AFP ≥ 1000 ng/ml, largest tumor size ≥ 10 cm, and no tumor capsule were significantly associated with poorer OS. In the LR group, largest tumor size ≥ 10 cm and no tumor capsule were the only independent prognostic factors for poorer OS and recurrence-free survival (RFS). Hypovolemic shock was an independent prognostic factor for poorer OS. The differences in OS between the TACE + LR group and LR alone group were not significant ($P = 0.955$). However, the RFS is significantly better in the LR alone group than those in the TACE + LR group ($P = 0.031$).

Conclusion For resectable tumor, LR is the treatment of choice for patients with spontaneous ruptured HCC and preserved liver function. The delay in LR due to preoperative TACE may account for its worse RFS compared with LR alone. In patients with an unresectable tumor, TACE therapy alone improved survival over conservative therapy.

Keywords Hepatocellular carcinoma · Rupture · Prognosis · Liver resection · Transarterial embolization

Abbreviations

HCC	Hepatocellular carcinoma
TACE	Transcatheter arterial chemoembolization
RFA	Radiofrequency ablation
CT	Computed tomography
CTP	Child–Turcotte–Pugh
MELD	Model for End-stage Liver Disease
BCLC	Barcelona Clinic Liver Cancer
AJCC	American Joint Committee on Cancer
ECOG	Eastern Cooperative Oncology Group
ICG15	Indocyanine green retention rate at 15 min
IVC	Inferior vena cava
OS	Overall survival
RFS	Recurrence-free survival
LR	Liver resection
PT	Prothrombin time
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
TB	Total bilirubin
AFP	Alpha-fetoprotein
HBV	Hepatitis B virus
HCV	Hepatitis C virus
PVTT	Portal vein tumor thrombosis

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common tumor worldwide and the second most common cause of cancer-related death.[1] The latest data indicate that the incidence and mortality of HCC are decreasing in China because of the control of hepatitis B and C virus infections.[2] Spontaneous rupture of the tumor with intraperitoneal hemorrhage is a rare and life-threatening complication of HCC. Ruptured HCC occurs in 2.3 to 26% patients with HCC in Asia and less than 3% in the West.[3]

Ruptured HCC usually occurs in patients with chronic liver hepatitis and cirrhosis. Owing to the hypovolemic shock and liver function failure, the reported in-hospital mortality is extremely high, ranging from 25 to 75%.[4] Previous studies reported that prognosis of ruptured HCC is poor, a median survival of 1.2–4 months if untreated.[5] As a result, the current TNM staging systems for HCC assign the ruptured HCC as T4.[6] Various treatments have been used to secure hemostasis and treat the tumor, including emergent or staged liver resection, perihepatic packing, suture plication, hepatic artery ligation, transarterial chemoembolization (TACE), and radiofrequency ablation (RFA).[3, 4] Patient's liver function and tumor characteristics directly affect the choice of treatment. However, there is still no consensus on selecting the most appropriate treatment strategy to reduce the in-hospital mortality and improve the long-term survival.

Therefore, we conducted the retrospective study to review the experience of management in 137 patients with spontaneous ruptured HCC during a 5-year period at a single center. We aimed to compare the long-term results and determine the prognostic factors associated with the outcome in patients undergoing conservative therapy, TACE, and liver resection.

Methods

Patients

From January 2010 to December 2015, a total of 137 consecutive patients with spontaneously ruptured HCC were admitted in the Hepatic Surgery Center of Tongji Hospital, Wuhan, China. Diagnosis of spontaneous rupture of HCCs was based on the typical findings shown by dynamic computed tomography (CT) or MRI. Abdominal paracentesis was routinely performed for confirmation. The patients' demographics, hemodynamic status, medical history, tumor characteristics, laboratory data, treatment modality, operative details, histological variables, and survival and recurrence data were recorded and analyzed retrospectively. Shock at the time of admission was defined as a systolic blood pressure < 90 mmHg and a pulse rate > 100 beats/min. Child–Turcotte–Pugh (CTP) and Model for End-stage Liver Disease (MELD) scores were assessed, and HCC staging was performed using the Barcelona Clinic Liver Cancer (BCLC) staging system and the eighth edition of AJCC (American Joint Committee on Cancer) classification, excluding tumor rupture from the staging. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tongji Hospital.

Treatment

All patients with ruptured HCC immediately received intravenous fluids, and/or blood transfusion, if necessary. In hemodynamically unstable patients or patients with continuous intra-abdominal hemorrhage, TACE or conservative therapy was the first intervention. If TACE or conservative therapy failed, emergency hepatectomy were performed for patients with resectable tumor and preserved liver function within 3 days of admission. In other patients, surgical hemostasis including perihepatic gauze packing and microwave ablation were used to stop bleeding. After the patient's hemodynamic status was stabilized, we conduct a full preoperative assessment to develop the definitive treatment plan. The evaluation included the tumor status, cardiopulmonary function, Eastern Cooperative Oncology Group (ECOG) score, serological status, Child–Pugh score, imaging scans, indocyanine green retention rate at 15 min (ICG15), and liver volume measurement. Then, in selected patients, staged hepatectomy was performed after hemostasis by TACE or spontaneous cessation of bleeding by conservative therapy. TACE was the first-choice therapy for patients for whom surgery was not available. Figure 1 shows the various managements of patients with ruptured HCC.

Operative Treatment

The liver resection contraindications included poor liver function (Child C), multifocal HCC, poorly controlled hepatic encephalopathy, severe coagulopathy, main portal vein or hepatic vein system invasion, distant metastasis, heart or lung function that was unable to tolerate surgical treatment, and poor performance status.

All operations were conducted by experienced hepatobiliary surgeons. The Pringle maneuver might be applied with cycles of clamp/unclamp times of 10/5 min during the procedure. If massive bleeding from the main hepatic veins occurred, the infrahepatic inferior vena cava (IVC) was occluded during liver transection. Hepatic parenchymal transection was conducted with a combination of Kelly forceps and ERBE VIO (Tubingen, Germany) bipolar forceps. Small-diameter vessels were electrocoagulated and

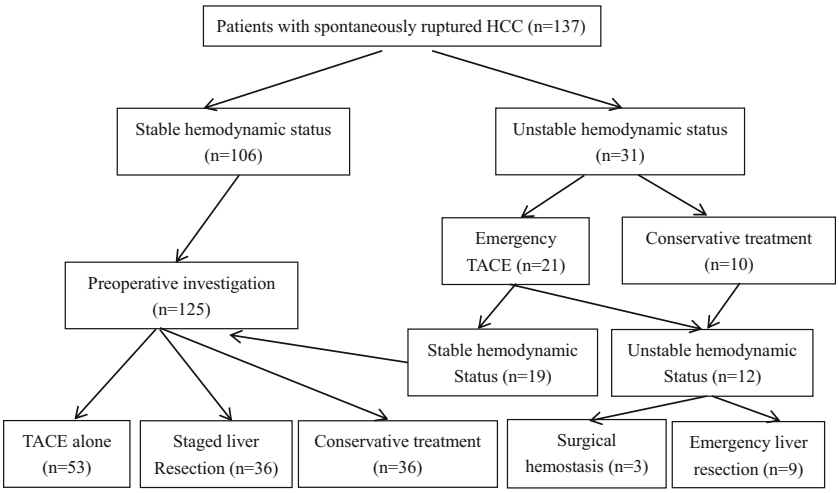

Fig. 1 Treatment algorithm for spontaneous rupture of HCC

the larger vessels ligated. A distinct resection margin of more than 1 cm was requested if it was possible. Major hepatectomy was defined as resection of three or more Couinaud liver segments, and minor hepatectomy as resection of fewer than three segments. Peritoneal lavage with large quantity of distilled water was performed to avoid tumor cells seeding.

TACE

Relative contraindications to TACE included main portal vein thrombosis, arteriovenous shunting and Child–Pugh C cirrhosis, severe coagulopathy, and hepatic encephalopathy. Common hepatic angiography was performed to visualize the tumor blood supply and localize the bleeding site, and then a microcatheter was selectively inserted into the artery feeding the ruptured tumor. Embolization was performed with a variety of embolic agents. The interventional radiologist chose the type and amount of embolic agent at the time of the procedure. After embolization, angiography was used to confirm the successful blockade of tumor feeding arteries. Success of embolization was defined as cessation of angiographic extravasation, stabilization of hemoglobin without further need for transfusion, and hemodynamic stability within 48 h after the procedure.

Conservative Therapy

Patients contraindicated for surgery or TACE/TAE or who declined aggressive managements received only vigorous and careful conservative treatments, including active resuscitation with intravascular fluid, replacement of blood or albumin, correction of coagulopathy, antimicrobial therapy, analgesics, diuretics, etc.

Follow-Up

All patients were followed up with liver function test, AFP measurement, liver ultrasonography, enhanced CT or MRI, and chest X-ray at 1 month after discharge, at 2-month intervals for 1 year and every 3 months thereafter. The overall survival (OS) time was defined as the interval from the date of rupture to the date of death or the last follow-up examination. Recurrence-free survival (RFS) was defined as the time between the curative resection of HCC and confirmation of recurrence. Patients with recurrence or local tumor progression were scheduled for further treatment. The choice of treatment was determined by tumor characteristics, patient preference, and results of the discussion by our multidisciplinary team. The treatments include repeat liver resection, local ablation therapy, TACE, external radiation therapy, sorafenib, or best supportive care.

Statistical Analysis

Descriptive statistics were reported as mean and standard deviation values for normally distributed variables or as median and interquartile range for non-normally distributed variables. Categorical variables were expressed as number (percentages) and compared using the χ^2 or Fisher's exact tests. Student's t test was applied to normally distributed continuous variables. The Mann–Whitney U test was used for non-normally distributed variables. The median values regarding age and MELD score were set as the cut-off values to determine high or low levels in the univariate analysis. The cumulative survival rate was analyzed using Kaplan–Meier method, and the differences were compared using the log-rank test. Predictors of 30-day survival and overall survival were evaluated using the logistic regression model and the Cox proportional hazards model, respectively. $P < 0.05$ was considered significant. Statistical analyses were performed using SPSS 24.0 software for Windows.

Table 1 The clinical data of 137 patients with spontaneous ruptured HCC

Variables	Total ($n = 137$)	Conservative ($n = 36$)	TACE alone ($n = 53$)	Liver resection ($n = 45$)	P value
Age	47.8 ± 13.4	52.4 ± 17.7	47.4 ± 12	44 ± 9.6	0.147[1], **0.016[2]**, 0.093[3]
Gender, male/female	124 (90.5%)/13 (9.5%)	33 (91.7%)/3 (8.3%)	49 (92.5%)/4 (7.5%)	39 (86.7%)/6 (13.3%)	1.000[1], 0.722[2], 0.543[3]
Hospital stay	11 (6–19)	5 (2–9)	9 (6–16)	16 (12–23)	< 0.001[1], < 0.001[2], 0.001[3]
Symptoms					0.492[1], 0.552[2], 0.219[3]
Sudden onset of right-upper quadrant abdominal pain	76 (55.5%)	18 (50%)	32 (60.4%)	25 (55.6%)	
Abdominal distension	44 (32.1%)	13 (36.1%)	13 (24.5%)	17 (37.8%)	
Shock on admission	17 (12.4%)	5 (13.9%)	8 (15.1%)	3 (6.7%)	
Treatment before rupture	20 (14.6%)	11 (30.6%)	7 (13.2%)	2 (4.4%)	**0.046[1]**, **0.001[2]**, 0.212[3]
Child–Pugh class, A/B + C	46 (33.6%)/91 (66.4%)	7 (19.4%)/29 (80.6%)	15 (28.3%)/38 (71.7%)	23 (51.1%)/22 (48.9%)	0.342[1], **0.003[2]**, **0.021[3]**
MELD	10 (8–14)	12 (9–18)	12 (9–15)	8 (6–10)	0.285[1], **< 0.001[2]**, **< 0.001[3]**
Hemoglobin (g/l)	96 ± 24.9	94.6 ± 28.9	93.4 ± 12	100.8 ± 25.6	0.664[1], 0.339[2], 0.063[3]
Platelet (× 10^9/l)	136 (90.5–212)	126 (78.8–250)	133 (85–212.5)	157 (102.5–207.5)	0.789[1], 0.665[2], 0.535[3]
Total bilirubin (mg/dl)	1.1 (0.64–1.75)	1.44 (0.77–3.26)	1.3 (0.76–2.1)	0.8 (0.58–1.39)	0.316[1], **0.001[2]**, **0.004[3]**
Albumin (g/l)	31 (27.2–35.2)	29.2 (24–34.7)	31 (28–35.1)	34 (28.5–37.2)	0.08[1], **0.013[2]**, 0.126[3]
ALT (IU/l)	41 (24–73.5)	47.5 (28.3–81.5)	54 (31.5–79)	28 (20–43.5)	0.741[1],**0.011[2]**, **0.002[3]**
AST (IU/l)	66 (31–141)	98.5 (44–172)	75 (43.5–197.5)	31 (22–71)	0.887[1], **< 0.001[2]**, **< 0.001[3]**
Creatinine (mg/dl)	0.88 (0.7–1.11)	0.87 (0.61–1.38)	0.92 (0.73–1.26)	0.81 (0.68–0.94)	0.528[1], 0.291[2], **0.019[3]**
Prothrombin time (s)	15 (14–17.5)	16.0 (14.7–19.8)	15.3 (14.5–17.7)	14.2 (13–15.5)	0.324[1], **0.001[2]**, **0.001[3]**
AFP (ng/ml)	1029 (67.4–11,512)	473 (21.1–46,265)	1185 (105.4–13,030)	1035 (17.5–8516)	0.751[1], 0.747[2], 0.51[3]
Etiology, n (%) HBV/HCV/others	130 (94.9%)/5 (3.6%)/2 (1.5%)	34 (94.4%)/2 (5.6%)/0	51 (96.2%)/3 (5.7%)/0	42 (93.3%)/1 (2.2%)/2 (4.5%)	1.000[1], 0.43[2], 0.851[3]
Liver cirrhosis, n (%)	118 (86.1%)	33 (91.7%)	49 (92.5%)	34 (75.6%)	1.000[1], 0.057[2], **0.021[3]**
Portal hypertension, n(%)	45 (32.8%)	14 (38.9%)	22 (41.5%)	9 (20.0%)	0.805[1],0.061[2], **0.023[3]**
Tumor number, 1/≥2	75 (54.7%)/62 (45.3%)	14 (38.9%)/22 (61.1%)	22 (41.5%)/31 (58.5%)	37 (82.2%)/8 (17.8%)	0.805[1], **< 0.001[2]**, **< 0.001[3]**
Largest tumor size (cm)	9 (6.8–12)	9.6 (6.9–12)	10 (8–12)	7 (5.1–10)	0.314[1], **0.049[2]**, **0.001[3]**
Tumor location, Left/right/bilateral	20 (14.6%)/67 (48.9%)/50 (36.5%)	4 (11.1%)/14 (38.9%)/18 (50%)	7 (13.2%)/21 (39.6%)/25 (47.2%)	9 (20%)/31 (68.9%)/5 (11.1%)	0.944[1], 0.001[2], **0.001[3]**
Tumor capsule, n (%)	34 (24.8%)	5 (13.9%)	14 (26.4%)	15 (33.3%)	0.157[1],0.044[2], 0.455[3]
Portal vein invasion, n (%)	35 (25.5%)	13 (36.1%)	17 (32.1%)	4 (8.9%)	0.693[1], **0.003[2]**, **0.005[3]**
Hepatic vein invasion, n (%)	6 (4.4%)	4 (11.1%)	1 (1.9%)	1 (2.2%)	0.166[1], 0.235[2], 0.988[3]
Bile duct invasion, n (%)	3 (2.2%)	0	3 (5.7%)	0	0.393[1], –,[2] 0.302[3]
Extrahepatic metastasis, n (%)	5 (3.6%)	3 (8.3%)	2 (3.8%)	0	0.654[1], 0.167[2], 0.498[3]
TNM, I + II/III + IV	64 (46.7%)/73 (53.3%)	12 (33.3%)/24 (66.7%)	16 (30.2%)/37 (69.8%)	35 (77.8%)/10 (22.2%)	0.754[1], **< 0.001[2]**, **< 0.001[3]**
BCLC, A + B/C + D	84 (61.3%)/53 (38.7%)	13 (36.1%)/23 (63.9%)	30 (56.6%)/29 (43.4%)	39 (86.6%)/6 (13.4%)	0.058[1], **< 0.001[2]**, **0.001[3]**
Mortality in 30 days	43 (31.4%)	28 (77.8%)	13 (24.5%)	2 (4.4%)	< 0.001[1], < 0.001[2], 0.006[3]
Median survival time, (days)	118 (20–470)	18 (8–33)	136 (34–324)	702 (221–1473)	< 0.001[1], < 0.001[2], < 0.001[3]

MELD Model for End-stage Liver Disease, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *AFP* alpha-fetoprotein, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *BCLC* Barcelona Clinic Liver Cancer

1: Compared between conservative therapy and TACE alone

2: Compared between conservative therapy and liver resection

3: Compared between TACE alone and liver resection

Results

Clinical Characteristics of Patients

A total of 137 consecutive patients with ruptured HCC were managed according to the flow chart (Fig. 1) at the hepatic surgery center, Tongji Hospital, during the study period. Their baseline characteristics are summarized in Table 1. Mean age was 47.8 years and 124 (90.5%) were male. The most common presentation was abdominal pain, which was present in 76(55.5%) patients. Seventeen (12.4%) patients presented with shock. The most common etiology of HCC was hepatitis B infection in 130 (94.9%) patients. One hundred eighteen patients (86.1%) had a history of liver cirrhosis. Twenty patients (14.6%) had previously been treated for their HCC. Forty-six patients were classified as Child–Pugh class A, 72 as class B, and 19 as class C. Seventy-five (54.7%) patients had a single HCC and 62 (45.3%) patients had multiple HCC. Median largest tumor size was 9 cm (IQR, 6.8–12). Moreover, 48.9% of the tumors were in the right hemiliver, 14.6% of the tumors were in the left hemiliver, and 36.5% had bilateral involvement. Median alpha-fetoprotein concentration was 1029 ng/ml (IQR, 67.4–11,512). Our 30-day mortality rate was 31.4%. One hundred twenty-five patients died during the follow-up. The median of overall survival was 118 days (IQR, 20–470 days). The 30-day, 3-month, 6-month, 1-year, and 3-year overall survival rate is 69.4%, 58.2%, 38.8%, 29.9%, and 13.9%, respectively.

Comparison of Clinical Parameters and Overall Survival by Treatment Modality

The demographics of the following three groups are outlined in Table 1: liver resection (LR) ($n = 45$), TACE alone ($n = 53$), and conservative management ($n = 36$). As only three patients underwent surgical hemostasis, this sample was too small for statistically meaningful results, and they were not included in the analysis.

The TACE alone group and conservative management group were similar with regard to the age, sex distribution, liver function, presence of cirrhosis and portal hypertension, tumor characteristic, and tumor stage. Comparing the LR group with TACE alone group, Child–Pugh classification, MELD score, and the levels of hepatorenal function (TB, ALT, AST, Cr, PT) were better, and the percentage of patients with liver cirrhosis, portal hypertension, multiple and bilateral tumors, large tumor size, and portal vein invasion was lower in the LR group than the TACE alone group. The TACE alone group had a more advanced TNM and BCLC stage as compared to the LR group.

Figure 2 shows the overall survival curves stratified according to treatment modality. The patients who received liver resection had a significantly (LR vs. TACE, $P < 0.001$; LR vs. conservative treatment, $P < 0.001$) longest overall survival time compared with those who did not receive liver resection. Conservative treatment without any aggressive management had poorest results in our patients, with median survival of only 18 days. The survival curve for TACE alone group lay between the curves for LR group and conservative treatment group, and was significantly different from these two curves (TACE vs. LR, $P < 0.001$; TACE vs. conservative treatment, $P < 0.001$).

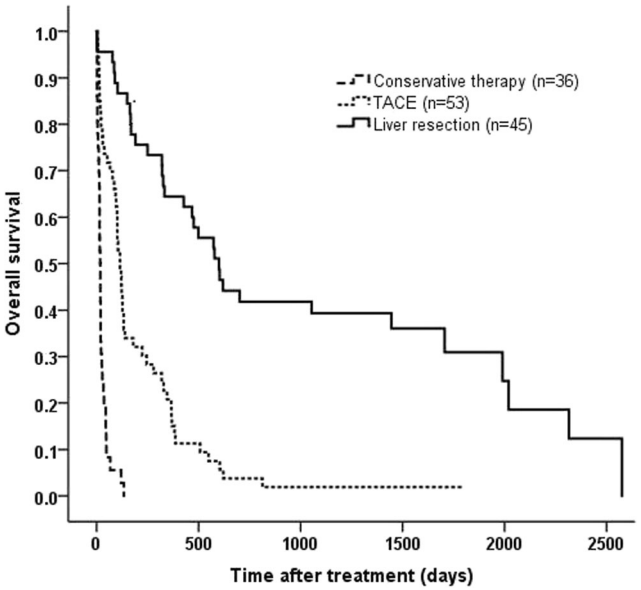

Fig. 2 Overall survival curves stratified according to the main treatment modality. The median survival time of patients undergoing conservative therapy, TACE, and liver resection were 18, 136, and 702 days, respectively ($P < 0.001$)

Outcomes of Patients Treated by TACE Alone

Fifty-three patients underwent TACE alone. Out of 53 patients, 47 (88.7%) patients had a successful embolization. Thirteen patients (24.5%) died within 30 days after TACE. The causes of death were hypovolemic shock in five patients, hepatic failure in four, respiratory failure in three, and hepatorenal syndrome in one. The median survival time was 136 days (IQR, 34–324 days). The 30-day, 3-month, 6-month, 1-year, and 3-year overall survival rate was 75.5%, 66.0%, 34.0%, 20.8%, and 1.9%, respectively. Fifty-two patients died during the follow-up.

Predictors of 30-day survival were analyzed (Table 2). Univariate analysis showed that Child C status, higher MELD score, decreased albumin level, alpha-fetoprotein (AFP) ≥ 1000 ng/ml, largest tumor size ≥ 10 cm, and BCLC C and D were all associated with a poorer 30-day survival. Multivariate logistic regression analysis showed that only MELD score ≥ 12, AFP ≥ 1000 ng/ml, and largest tumor size ≥ 10 cm were independent factors differentiating the two groups (Table 3).

Table 2 Univariate analysis of variables associated with 30-day survival for 53 patients with spontaneous rupture of hepatocellular carcinoma undergoing TACE alone

Variables	Mortality group ($n = 13$)	Survival group ($n = 40$)	P value
Age (years), < 50	8 (61.5%)	20 (50%)	0.469
Gender, male	13 (100%)	36 (75%)	0.561
Shock on admission	4 (30.8%)	4 (10%)	0.17
Child–Pugh class, A + B	9 (69.2%)	38 (95%)	0.041
MELD, ≥ 12	10 (76.9%)	16 (40.0%)	0.021
Hemoglobin (g/l)	89.2 ± 22.5	94.7 ± 21.3	0.43
Platelet ($\times 10^9$/l)	176 (97–254.5)	121 (82.5–202)	0.269
Total bilirubin (mg/dl)	1.64 (0.94–3.45)	1.14 (0.66–1.97)	0.094
Albumin (g/l)	28 (22.8–32)	31.5 (28.7–35.2)	0.031
ALT (IU/l)	59 (32.5–85)	51 (31.3–80.5)	0.612
AST (IU/l)	103 (54.4–314.5)	74.5 (42.3–150.8)	0.420
Creatinine (mg/dl)	0.92 (0.68–1.78)	0.91 (0.75–1.2)	0.528
Prothrombin time (s)	16 (15–21.3)	15 (14.3–17.5)	0.121
AFP (ng/ml), ≥ 1000	11 (84.6%)	17 (42.5%)	0.008
Liver cirrhosis	12 (92.3%)	37 (92.5%)	1.000
Portal hypertension	4 (30.8%)	18 (45%)	0.366
Tumor number, ≥ 2	10 (76.9%)	21 (52.5%)	0.121
Largest tumor size (cm), ≥ 10	11 (84.6%)	21 (52.5%)	0.04
Tumor location, bilateral	9 (69.2%)	16 (40%)	0.067
Portal vein invasion	6 (46.2%)	11 (27.5%)	0.363
No tumor capsule	12 (92.3%)	27 (61.5%)	0.161
TNM, III + IV	11 (84.6%)	26 (65%)	0.322
BCLC, C + D	9 (69.2%)	14 (35%)	0.031
Treatment before rupture	3 (23.1%)	4 (10%)	0.46

MELD Model for End-stage Liver Disease, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *AFP* alpha-fetoprotein, *BCLC* Barcelona Clinic Liver Cancer

Next, we examined factors that might affect the OS outcome (Table 4). The 12 risk factors for poorer OS were age ≥ 50, hypovolemic shock, higher MELD score, higher total bilirubin lever, AFP ≥ 1000 ng/ml, tumor number ≥ 2, largest tumor size ≥ 10 cm, bilateral tumor, portal vein invasion, no tumor capsule, and TNM stage ≥ III. On multivariate analysis, three independent factors for poorer OS were identified. They were AFP ≥ 1000 ng/ml, largest tumor size ≥ 10 cm, and no tumor capsule.

Table 3 Multivariate analysis of the independent risk factors of 30-day mortality for 53 patients with spontaneous rupture of hepatocellular carcinoma undergoing TACE alone

Variables	OR	95% CI	P value
MELD (< 12/≥ 12)	8.956	1.578–50.825	0.013
AFP (ng/ml) (< 1000/≥ 1000)	7.931	1.259–49.977	0.027
Largest tumor size (cm) (< 10/≥ 10)	8.382	1.221–57.528	0.031
Child–Pugh class (A + B/C) [a]	–	–	–
Albumin (g/l)[a]	–	–	–
BCLC (A + B/C + D)[a]	–	–	–

Hosmer and Lemeshow statistic, $P = 0.941$

MELD Model for End-stage Liver Disease, *AFP* alpha-fetoprotein, *BCLC* Barcelona Clinic Liver Cancer

[a] Predictors rejected from the model

Outcomes of Patients Treated by Surgical Resection Procedure

Forty-five patients underwent liver resection. The 6-month, 1-year, and 3-year OS rate and RFS rate is 77.8%, 64.4%, 44.2%, and 73.9%, 49.3%, 24.6%, respectively. The median survival time was 702 days (IQR, 221–1473 days). The median RFS was 270 days (IQR, 86–759 days). Two patients (4.4%) died within 30 days after LR. Thirty-three patients died and 38 patients had recurrence during the follow-up. Liver recurrence developed in 32 patients, liver and lung recurrence in 3 patients, and peritoneal dissemination in 3 patients.

On univariate analysis, hypovolemic shock, Child–Pugh class C, higher total bilirubin level, AFP ≥ 500 ng/ml, largest tumor size ≥ 10 cm, no tumor capsule, BCLC C and D, major LR, blood loss ≥ 1000 ml, and poor differentiation were found to be significantly associated with poorer OS. Hypovolemic shock, largest tumor size ≥ 10 cm, no tumor capsule, TNM

Table 4 Univariate and multivariate analysis of variables associated with OS for 53 patients with spontaneous rupture of hepatocellular carcinoma undergoing TACE alone

Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (< 50/≥ 50)	2.231	1.219–4.083	0.009			
Gender (male/female)	0.78	0.276–2.2	0.638			
Hypovolemic shock (yes/no)	2.360	1.079–5.164	0.032			
Child–Pugh class (A + B/C)	0.726	0.298–1.768	0.48			
MELD	1.064	1.001–1.131	0.045			
Hemoglobin (g/l)	1.004	0.99–1.017	0.608			
Platelet ($\times 10^9$/l) (< 100/≥ 100)	0.817	0.462–1.445	0.488			
Total bilirubin (mg/dl)	1.13	1.05–1.217	0.001			
Albumin (g/l)	1.061	0.968–1.065	0.513			
ALT (IU/l)	1.001	0.998–1.003	0.552			
AST (IU/l)	1.000	1.000–1.001	0.316			
Creatinine (mg/dl)	0.919	0.46–1.837	0.811			
Prothrombin time (s)	1.004	0.94–1.071	0.914			
AFP (ng/ml) (<1000/≥1000)	0.314	0.174–0.567	< 0.001	0.469	0.243–0.904	0.024
Liver cirrhosis (yes/no)	0.426	0.148–1.222	0.112			
Portal hypertension (yes/no)	0.82	0.466–1.442	0.49			
Tumor number (1/≥2)	0.372	0.203–0.684	0.001			
Largest tumor size (cm) (< 10/≥ 10)	0.376	0.209–0.678	0.001	0.342	0.168–0.694	0.003
Tumor location (unilateral/bilateral)	0.528	0.3–0.93	0.027			
Portal vein invasion (yes/no)	1.881	0.019–3.472	0.043			
Tumor capsule (yes/no)	0.168	0.077–0.356	< 0.001	0.205	0.084–0.5	< 0.001
TNM (I + II/III + IV)	0.415	0.22–0.785	0.007			
BCLC (A + B/C + D)	0.673	0.388–1.169	0.16			
Treatment before rupture (yes/no)	0.603	0.268–1.358	0.222			

MELD Model for End-stage Liver Disease, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *AFP* alpha-fetoprotein, *BCLC* Barcelona Clinic Liver Cancer

Table 5 Univariate and multivariate analysis of variables associated with OS for 45 patients with spontaneous rupture of hepatocellular carcinoma undergoing liver resection

Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	0.985	0.954–1.027	0.58			
Gender (male/female)	0.733	0.279–1.925	0.528			
Hypovolemic shock (yes/no)	7.931	2.215–28.4	0.001	6.147	1.502–25.168	0.012
Child–Pugh class (A + B/C)	0.133	0.037–0.475	0.002			
MELD (< 12/≥ 12)	0.447	0.182–1.101	0.08			
Hemoglobin (g/l)	0.995	0.981–1.01	0.53			
Platelet ($\times 10^9$/l) (< 100/≥ 100)	1.032	0.391–2.719	0.95			
Total bilirubin (mg/dl)	1.875	1.028–3.421	0.041			
Albumin (g/l)	0.986	0.939–1.035	0.566			
ALT (IU/l)	1.003	0.999–1.006	0.105			
AST (IU/l)	1.002	1.000–1.003	0.051			
Creatinine (mg/dl)	1.391	0.33–5.859	0.653			
Prothrombin time (s)	1.051	0.969–1.139	0.231			
AFP (ng/ml) (< 500/≥ 500)	0.328	0.137–0.783	0.012			
Liver cirrhosis (yes/no)	0.827	0.381–1.795	0.631			
Portal hypertension (yes/no)	1.889	0.794–4.497	0.151			
Tumor number (1/≥ 2)	0.612	0.246–1.522	0.291			
Largest tumor size (cm) (< 10/≥ 10)	0.144	0.06–0.344	< 0.001	0.249	0.098–0.63	0.003
Within Milan (yes/no)	0.905	0.403–2.03	0.808			
Tumor location (bilateral/unilateral)	1.303	0.392–4.336	0.666			
Tumor capsule (yes/no)	0.058	0.013–0.258	< 0.001	0.076	0.015–0.389	0.002
TNM (I/II + III)	0.481	0.213–1.083	0.077			
BCLC (A + B/C + D)	0.159	0.056–0.452	0.001			
Type of LR (major/minor)	3.09	1.038–9.203	0.043			
Bleeding stop before LR (yes/no)	1.485	0.57–3.876	0.418			
Intra-abdominal hemorrhage, (< 1000 ml/≥ 1000 ml)	0.763	0.38–1.534	0.448			
Blood loss (< 1000 ml/≥ 1000 ml)	0.405	0.188–0.873	0.021			
Blood transfusion (yes/no)	1.419	0.654–3.076	0.376			
Differentiation, (high + moderate/poor)	0.363	0.169–0.717	0.009			
Staged LR vs. emergency LR	1.486	0.57–3.876	0.418			

MELD Model for End-stage Liver Disease, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *AFP* alpha-fetoprotein, *BCLC* Barcelona Clinic Liver Cancer, *LR* liver resection

II + III, BCLC C and D, major LR, and poor differentiation were associated with poorer RFS. In multivariate analysis, hypovolemic shock, largest tumor size ≥ 10 cm and no tumor capsule were the only independent prognostic factors for poorer OS. Largest tumor size ≥ 10 cm and no tumor capsule were the only independent prognostic factors for poorer RFS. Staged LR or emergency LR was not associated with OS or RFS (Tables 5 and 6).

A further analysis of patients who underwent LR revealed that 32 patients had LR only and 13 patients underwent TACE before LR. Preoperative and operative details in the two groups are shown in Tables 7 and 8. The median time between diagnosis and LR was significantly longer in the TACE + LR group than in LR alone group. There was no statistically significant difference between the two groups (LR alone vs. TACE + LR) in terms of baseline characteristics, surgery time, estimated blood loss, blood transfusion, blood occlusion, and postoperative complication rates. As illustrated in Fig. 3, there was no significant difference in OS rate between the two groups ($P = 0.955$). The cumulative RFS was significantly better in the LR alone group than in the TACE + LR group ($P = 0.031$).

Discussion

Spontaneous rupture of HCC is an infrequent but life-threatening complication of HCC that accounts for 6–10% mortality in patients with HCC.[7, 8] The mechanism of spontaneous rupture has not been fully elucidated. Various

Table 6 Univariate and multivariate analysis of variables associated with RFS for 45 patients with spontaneous rupture of hepatocellular carcinoma undergoing liver resection

Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	0.995	0.965–1.026	0.745			
Gender (male/female)	0.739	0.305–1.786	0.502			
Hypovolemic shock (yes/no)	20.495	1.858–226.0	0.014			
Child–Pugh class (A + B/C)	0.188	0.022–1.631	0.129			
MELD (< 12/≥ 12)	0.972	0.341–2.775	0.958			
Hemoglobin (g/l)	0.992	0.978–1.006	0.248			
Platelet ($\times 10^9$/l) (< 100/≥ 100)	1.252	0.514–3.049	0.621			
Total bilirubin (mg/dl)	1.569	0.844–2.916	0.155			
Albumin (g/l)	0.978	0.929–1.029	0.383			
ALT (IU/l)	1.003	0.999–1.007	0.114			
AST (IU/l)	1.001	0.999–1.004	0.163			
Creatinine (mg/dl)	1.081	0.277–4.219	0.911			
Prothrombin time (s)	1.079	0.972–1.198	0.155			
AFP (ng/ml) (< 500/≥ 500)	0.57	0.29–1.12	0.103			
Liver cirrhosis (yes/no)	0.962	0.462–2.001	0.917			
Portal hypertension (yes/no)	1.929	0.769–4.839	0.162			
Tumor number (1/≥ 2)	0.563	0.243–1.302	0.179			
Largest tumor size (cm), (< 10/≥ 10)	0.119	0.045–0.315	< 0.001	0.223	0.083–0.597	0.003
Within Milan (yes/no)	0.663	0.3–1.466	0.31			
Tumor location (bilateral/unilateral)	0.808	0.281–2.319	0.692			
Tumor capsule (yes/no)	0.131	0.051–0.339	< 0.001	0.167	0.06–0.46	0.001
TNM (I/II + III)	0.445	0.209–0.946	0.035			
BCLC (A + B/C + D)	0.267	0.085–0.839	0.024			
Type of LR (major/minor)	3.647	1.195–11.13	0.023			
Bleeding stop before LR (yes/no)	1.446	0.598–3.493	0.413			
Intra-abdominal hemorrhage, (< 1000 ml/≥ 1000 ml)	0.944	0.487–1.832	0.865			
Blood loss (< 1000 ml/≥ 1000 ml)	0.558	0.264–1.181	0.127			
Blood transfusion (yes/no)	1.894	0.876–4.093	0.105			
Differentiation (high + moderate/poor)	0.364	0.17–0.777	0.029			
Staged LR vs. emergency LR	1.446	0.598–3.493	0.413			

MELD Model for End-stage Liver Disease, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *AFP* alpha-fetoprotein, *BCLC* Barcelona Clinic Liver Cancer, *LR* liver resection

Table 7 Comparison of preoperative data of ruptured HCC patients between liver resection alone and TACE + liver resection

Variables	LR alone ($n = 32$)	LR + TACE ($n = 13$)	P value
Age	43.4 ± 9.8	45.5 ± 9.3	0.531
Gender (male/female)	28 (87.5%)/4 (12.5%)	11 (84.6%)/2 (15.4%)	0.796
Hospital stay	15.5 (12–19)	20 (9–31)	0.347
Hypovolemic shock (yes/no)	2 (6.3%)/30 (93.7%)	1 (7.7%)/12 (92.3%)	1.000
Child–Pugh class (A + B/C)	30 (93.8%)/2 (6.2%)	12 (92.3%)/1 (7.7%)	1.000
Hemoglobin (g/l)	102 (89.8–119.3)	99.1 (84.5–111.5)	0.414
Platelet ($\times 10^9$/l)	161.5 (108.3–211)	132 (91.9–198)	0.324
Total bilirubin (mg/dl)	0.65 (0.58–1.3)	0.82 (0.54–1.48)	0.467
Albumin (g/l)	34.8 (29.2–37.3)	33 (25.3–38)	0.507
ALT (IU/l)	26 (20.3–37)	43 (18.5–107)	0.067
AST (IU/l)	30.5 (22.5–53)	66 (20–94)	0.224
Creatinine (mg/dl)	0.85 (0.71–0.92)	0.77 (0.64–1.07)	0.709
Prothrombin time (s)	13.9 (12.9–15.1)	15 (13.5–16.4)	0.093
AFP (ng/ml) (< 500/≥ 500)	11 (34.4%)/21 (65.6%)	5 (38.5%)/8 (61.5%)	1.000
Liver cirrhosis (yes/no)	23 (71.9%)/9 (28.1%)	11 (84.6%)/2 (15.4%)	0.604
Portal hypertension (yes/no)	5 (15.6%)/27 (84.4%)	4 (30.8%)/9 (69.2%)	0.459
Tumor number (1/≥ 2)	27 (84.4%)/5 (15.6%)	10 (76.9%)/3 (23.1%)	0.871
Largest tumor size (cm) (< 10/≥ 10)	23 (71.9%)/9 (28.1%)	8 (61.5%)/5 (38.5%)	0.746
Tumor location (unilateral/bilateral)	29 (90.6%)/3 (9.4%)	11 (84.6%)/2 (15.4%)	0.954
Tumor capsule (yes/no)	13 (40.6%)/19 (59.4%)	2 (15.4%)/11 (84.6%)	0.201
Portal vein invasion (yes/no)	1 (3.1%)/31 (96.9%)	3 (23.1%)/10 (76.9%)	0.12
TNM (I + II/III + IV)	25 (78.1%)/7 (21.9%)	9 (69.2%)/4 (30.8%)	0.805
BCLC (A + B/C + D)	29 (90.7%)/3 (9.3%)	10 (76.9%)/3 (23.1%)	0.458

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *AFP* alpha-fetoprotein, *BCLC* Barcelona Clinic Liver Cancer, *LR* liver resection

hypotheses have been formulated to explain the precise mechanism, including increased intratumor pressure with the invasion and occlusion of hepatic veins by tumor cells, rapid growth of tumor and necrosis, coagulopathy, trauma, portal

Table 8 Comparison of perioperative data of ruptured HCC patients between liver resection alone and TACE + liver resection

Variables	Total ($n = 45$)	LR alone ($n = 32$)	TACE + LR ($n = 13$)	P value
Time between diagnosis and LR	5 (2–17)	4 (2–6)	18 (14–55)	< 0.001
Type of LR (major/minor)	4 (8.9%)/41 (91.1%)	2 (6.3%)/30 (93.7%)	2 (15.4%)/11 (84.6%)	0.691
Bleeding stop before LR (yes/no)	36 (80%)/9 (20%)	25 (78.1%)/7 (21.9%)	11 (84.6%)/2 (15.4%)	0.934
Intra-abdominal hemorrhage	800 (150–1000)	1000 (425–100)	200 (100–1000)	0.097
Blood loss (ml)	400 (300–1450)	450 (300–1500)	400 (350–800)	0.597
Blood transfusion (yes/no)	32 (71.1%)/13 (28.9%)	25 (78.1%)/7 (21.9%)	7 (53.8%)/6 (46.2%)	0.206
Blood occlusion (yes/no)	30 (66.7%)/15 (33.3%)	23 (71.9%)/9 (28.1%)	7 (53.8%)/6 (46.2%)	0.416
Duration of blood occlusion (min)	14 (10–18)	12 (10–17)	15 (11–20)	0.471
Operation time (min)	224 (187–258)	222 (180–259)	230 (216–272)	0.353
Differentiation (high + moderate/poor)	30 (66.7%)/15 (33.3%)	24 (75%)/8 (25%)	6 (46.2%)/7 (53.8%)	0.131
Complication	21 (46.7%)	12 (37.5%)	9 (69.2%)	0.053
Wound infection	1	0	1	
Bile leak	2	2	0	
Pleural effusion	15	8	7	
Pneumonia	2	1	1	
Abdominal infection	1	1	0	
In-hospital mortality (30 days)	2 (4.4%)	2 (6.3%)	0 (0%)	1.000

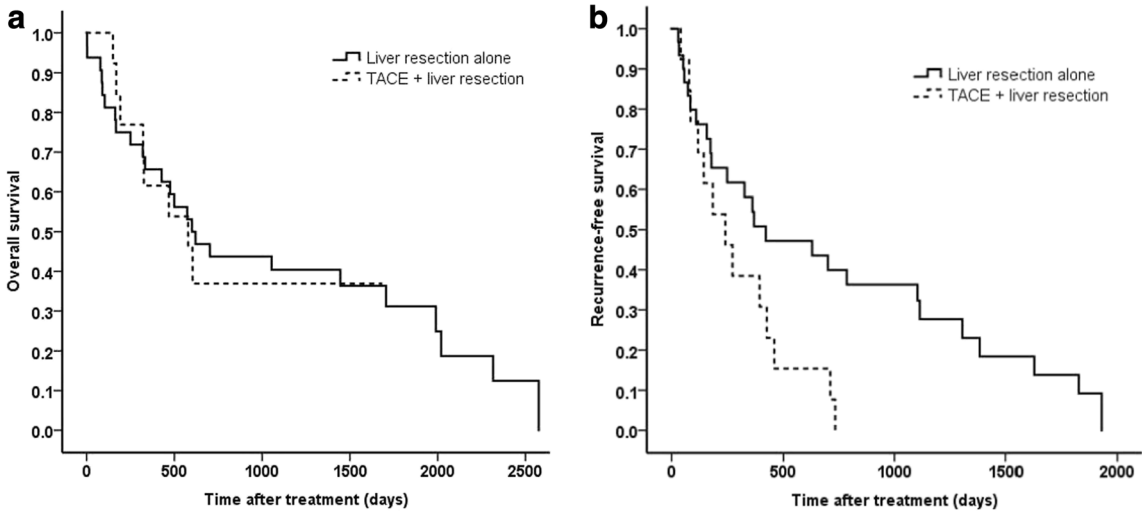

Fig. 3 **a** Overall survival and **b** recurrence-free survival of patients with ruptured HCC undergoing liver resection alone compared with TACE + liver resection (**a** $P = 0.955$; **b** $P = 0.031$)

hypertension, subcapsular location, and large tumor dimensions.[3, 4] Zhu et al.[9] postulated that vascular dysfunction due to increased collagenase expression and increased collagen IV degradation, rendering blood vessels stiff and friable, was correlated to spontaneous rupture.

The management of spontaneous rupture of HCC remains a big challenge for physicians because patients often present with hemodynamic instability, coagulopathy, and liver dysfunction. In the acute phase, hemostasis is the primary objective and tumor treatment is secondary. From the 1960s to the 1980s, open surgical method is the main treatment to stop bleeding.[4] Various surgical procedures were reported to be effective in hemostasis, such as perihepatic packing,[10] suture plication of bleeding tumors,[7] absolute alcohol injection,[11] hepatic artery ligation (HAL),[12] and liver resection.[13] Open surgical procedures achieve a high rate of hemostasis but are associated with a high in-hospital mortality rate.[14]

Since the 1980s, TAE/TACE has been increasingly used as an effective, less invasive treatment for achieving immediate hemostasis.[3] The rate of successful embolization by TACE in our patients with ruptured HCC is 88.7%, comparable to previously reported rates (83–100%).[14, 15] Despite the high success rate of hemostasis, 13 patients (24.5%) died within 30 days after TACE. Higher 30-day mortality rates in such patients (30–55.6%) have been reported in other recent studies.[16–18] Previous studies found indicators reflecting the severity of bleeding, the degree of deterioration of liver function, and tumor burden were associated with 30-day mortality rates in patients with ruptured HCC treated by TAE/TACE.[17–19] In an 8-year retrospective cohort study of 167 cases, Kung et al.[20] found that portal venous thrombosis and serum creatinine level were significant predictors of short-term survival. Li et al.[18] found that a low albumin level was the only independent risk factor for early mortality. In the present study, we found that MELD score ≥ 12, AFP ≥ 1000 ng/ml, and largest tumor size ≥ 10 cm were independent factors for poor short-term survival, consistent with a previous study. It is controversial that whether the portal vein tumor thrombosis (PVTT) affects the short-term survival of patients with ruptured HCC.[21] TACE is generally contraindicated in patients with complete occlusion due to main PVTT. In our study, among 17 patients with portal vein invasion, only 2 patients have main PVTT. Moreover, whenever possible, super-selective TACE was used to minimize the risk of the ischemic necrosis of normal parenchyma and subsequent liver failure. These may be the main reason why we did not find a correction between PVTT and short-term mortality after TACE.

Few studies examined the independent risk factor affecting long-term survival in patients with ruptured HCC treated by TAE/TACE. In a multicenter study, Kirikoshi et al.[22] reported a maximum tumor size not exceeding 7 cm was the only independent factor determining long-term survival. Other recent studies revealed that not only tumor-related factors (tumor burden, location, PVTT, and α-fetoprotein level) but also host-related factors (the degree of liver damage) are significant predictors of long-term survival in those patients.[17, 23] In addition to the above factors, we revealed that the absence of a tumor capsule was associated with significantly worse survival. Tumor capsule were considered to be important risk factors for patients with HCC after TACE.[24] Compared with non-encapsulated tumors, capsulated tumors showed a much lower incidence of direct liver invasion, tumor microsatellites, microvascular invasion, and tumor recurrence.[25, 26]

TAE/TACE can offer hemostasis in ruptured HCC; however, the therapeutic effect is apparently inferior to hepatectomy.[27–29] In the current study, the overall survival rate of patients who underwent liver resection was significantly higher than those of other treatments. The 6-month, 1-year, and 3-year OS rate and RFS rate is 77.8%, 64.4%, 44.2%, and 73.9%, 49.3%, 24.6%, respectively, which are consistent with

those reported in other studies.[29–31] Independent prognostic factors affecting OS and RFS included hypovolemic shock, largest tumor size ≥ 10 cm, and no tumor capsule. Shock has been observed in many other series to be an important, independent factor affecting overall and 30-day mortality.[32–34] It is important to improve liver function and resuscitate the patients from shock before operation. Large tumor size and no tumor capsule suggest advanced disease with significant tumor load and strong tumor invasiveness.

Some surgeons recommend emergency hepatectomy in the acute phase whenever conditions permit.[14, 35, 36] Emergency hepatectomy combines the benefit of hemostasis and a definitive treatment in a single operation. Ong and Taw suggest that a delay in liver resection after initial hemostasis might compromise the resection rate.[10] However, emergency liver resection carries an in-hospital mortality of 16.5 to 100% and the poor long-term survival.[4] In view of the major drawbacks associated with emergency hepatectomy, a two-stage hepatectomy is recommended as the procedure of choice for the treatment of ruptured HCC.[7, 14, 29, 37] Initial hemostasis with conservative therapy or TACE followed by liver resection afforded patients time to recover from the insult in the acute phase. When compared with one-stage emergency liver resection, staged liver resection has a much lower in-hospital mortality rate (0–9%) and a better survival rate (1-year survival rate, 54.2–100%; 3-year survival rate, 21.2–55.2%; 5-year survival rate, 15–41.4%).[4, 34] In the present study, emergency or staged LR was not a significant prognostic factor for OS and RFS. Possible reasons may be the accurate selection of emergency surgical patients based on strict evaluation of liver function reserve. For those patients with unstable hemodynamic status after conservative or TACE treatment who were not suitable for hepatectomy, less invasive methods were used, including perihepatic packing in one case and RFA in two cases. Cheung et al. found that the use of RFA for hemostasis during laparotomy greatly reduced the hospital mortality rate when compared with conventional hepatic artery ligation.[38]

There is no study, to our knowledge, on the optimal time to carry out staged liver resection. Some studies believed that TAE or TACE should always be performed as a preliminary step before surgery.[27, 29, 39] However, the possible dissemination of cancer cells at the time of rupture of a HCC has been a matter of concern.[7] Moreover, the bleeding usually stopped spontaneously with initial conservative therapy in the majority of patients.[31] In this study, we investigated the prognostic effect of the preoperative TACE on OS and RFS in patients treated by liver resection. The median time between diagnosis and LR was significantly longer in the TACE + LR group than in LR alone group. Although there was no difference in OS between LR alone group and TACE + LR group, RFS was significantly better in LR alone group. Intrahepatic spread or distant metastasis of tumor cells due to delayed LR was probably the main reason for the poorer RFS in TACE + LR group. Early resection of ruptured HCC and removal of hematoma and intra-abdominal hemorrhage may reduce the chance of postoperative recurrence and improve long-term prognosis.

There are many reports of peritoneal recurrence after spontaneous HCC rupture.[40, 41] However, it remains debatable whether spontaneous rupture of HCC increases peritoneal recurrence rates. Mizuno et al.[42] demonstrated that the recurrence pattern after hepatectomy is similar between ruptured HCC and non-ruptured HCC. Hiraoka et al.[43] found the dissemination of HCC cells after rupture in only 7.7% of 67 patients. Our long-term follow-up showed that only 3 of the 38 (7.9%) recurrent HCC cases exhibited peritoneal dissemination. Most patients experienced intrahepatic recurrence. Uchiyama et al.[44] believed that HCC fragments or cells released into the peritoneal cavity may not survive unless there are appropriate blood vessels nourishing these cells. Moreover, for patients undergoing LR, distilled water peritoneal lavage intraoperatively can quickly eradicate liberated HCC cells and improve long-term outcomes.[45] These may be the reason why peritoneal recurrence of ruptured HCC is relatively rare.

There are several limitations in this study. First, the study is inherently limited by its retrospective study design. There is a possibility of selection bias. Second, most of patients in this study had HBV-related HCC, which is different from HCC cases in Japan and Western countries. Third, the absolute number of patients who underwent liver resection was not very large. This relatively small sample size has made it difficult to achieve significance in statistical analysis of the data. Therefore, a large-scale multicenter study may be warranted to further confirm our results.

In summary, spontaneous rupture was a serious complication of HCC with a 30-day mortality of 31.4% and a median survival of 118 days. The severity of bleeding, the degree of deterioration of liver function, and tumor-related characteristics should be considered during treatment decision-making. TAE/TACE might be an effective and minimally invasive modality as an initial hemostasis procedure. Patients with ruptured HCC could have favorable long-term survival after curative liver resection. For patients with stable vital signs, preserved liver function, and resectable tumor, immediate liver resection should be considered after hemostasis and optimization of a patient's general condition. The delay in liver resection due to preoperative TACE may account for its worse RFS compared with liver resection alone. In patients with an unresectable tumor, TACE therapy improved survival over conservative therapy.

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