

Clinical impact of surgical treatment for the spontaneously ruptured resectable hepatocellular carcinoma

A single institution experience

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Abstract

Spontaneously ruptured hepatocellular carcinoma (srHCC) is a fatal complication of hepatocellular carcinoma (HCC). In addition, emergency treatment is frequently fraught with difficulties. This study aimed to investigate the prognosis and recurrence pattern in patients undergoing hepatectomy for the srHCC. This retrospective study included 11 patients with srHCC treated using either emergency hepatectomy or emergency transarterial embolization (TAE) followed by staged hepatectomy between January 2015 and December 2019. The patients visited the emergency room because of a sudden rupture of HCC without being diagnosed with HCC. We analyzed the prognosis, recurrence rate, and survival in these patients after hepatectomy. Four of the 11 patients in this study were classified as Child–Pugh class A and 7 as Child–Pugh class B. Nine patients visited for sudden onset of abdominal pain, and 2 for sudden onset of shock. The median hemoglobin level at the time of the visit was 11.5 g/dL (interquartile range: 9.8–12.7). Five patients underwent one-stage hepatectomy and 6 underwent emergency TAE hemostasis followed by staged hepatectomy. Median overall survival and recurrence-free survivals were 23 and 15 months, respectively. Recurrence occurred in 7 patients (4 in the one-stage group and 3 in the staged group). Among patients with recurrence, 6 had intrahepatic recurrence and 3 peritoneal metastases. Patients with srHCC who undergo staged hepatectomy can achieve a relatively good prognosis. The most common sites of recurrence after hepatectomy are intrahepatic and peritoneal. Peritoneal metastases are more likely to occur after one-stage hepatectomy.

Abbreviations: AFP = alpha-fetoprotein, AJCC = American Joint Committee on Cancer, ALT = aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, CT = computer tomography, HCC = hepatocellular carcinoma, INR = international normalized ratio, IQR = interquartile range, ISGLS = International Study Group of Liver Surgery, MELD = model for end-stage liver disease, MRI = magnetic resonance imaging, PHLF = post-hepatectomy liver failure, RFS = recurrence-free survival, srHCC = spontaneously ruptured hepatocellular carcinoma, TACE = transcatheter arterial chemoembolization, TAE = transcatheter arterial embolization.

Keywords: emergency, hepatectomy, hepatocellular carcinoma, spontaneously ruptured

1. Introduction

Spontaneously ruptured hepatocellular carcinoma (srHCC) is a serious life-threatening complication of hepatocellular carcinoma (HCC), because of hemodynamic instability and hepatic insufficiency.^[1,2] The suggested causes of tumor rupture in HCC include both rapid tumor growth leading to intratumoral necrosis and tumor hypervascularity with friable feeder artery. The risk factors for HCC rupture have been reported

to include liver cirrhosis, hypertension, tumor size >5 cm, vascular thrombosis, and extrahepatic invasion of the tumor.^[3]

With advances in the surveillance system for patients with risks of developing HCC and diagnostic imaging modality, the reported incidence rate of srHCC varies from 2.3% to 5.9%.^[4,5] However, we still occasionally encounter patients with ruptured HCC in an emergency. In resectable HCC patients who experience spontaneous rupture, emergent hepatectomy has been considered, because of the benefit of hemostasis and a definitive

The data used to support the findings of this study are included in the article.

The study was approved by the Institutional Review Board of Chungbuk National University Hospital (IRB No.: 2021-07-018).

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treatment provided in a single operation. However, recent studies suggested emergency transarterial embolization (TAE) followed by staged hepatectomy.^[5,6]

Hepatectomy has been reported to achieve a better survival rate.^[7] However, patients with ruptured HCC after hepatectomy have a higher incidence of recurrence or peritoneal metastases, because the tumor cells spill over, possibly forming seeds and multiple nodules.^[8,9] Thus, the optimal treatment for srHCC has not been clarified.

We aimed to retrospectively review the prognostic outcomes and recurrence pattern in patients undergoing hepatectomy for spontaneously ruptured resectable HCC.

2. Patients and methods

2.1. Patients

Among HCC patients who underwent diagnosed and hepatectomy at Chungbuk National University Hospital from January 2015 to December 2019, those who underwent emergency or staged hepatectomy for ruptured HCC were retrospectively analyzed. The patients in this study had neither been screened nor treated for HCC before admission. The visit was prompted by a sudden onset of abdominal pain or shock. Patients who previously had HCC-related therapy or those who had HCC rupture revealed by postoperative pathology were excluded from the study. Patients were managed using initial resuscitation in the emergency department. The diagnosis of ruptured HCC was based on symptoms and computed tomography (CT) scans or magnetic resonance imaging (MRI).

The study was approved by the Institutional Review Board of Chungbuk National University Hospital (IRB No.: 2021-07-018), which waived the requirement for informed patient consent due to the retrospective nature of the analyses.

2.2. Perioperative variables

Preoperative variables included patient demographics (age, body mass index [BMI]). Laboratory tests included hemoglobin, platelets, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alpha-fetoprotein (AFP), and international normalized ratio (INR). Intraoperative details included operative time, intraoperative blood transfusion, and surgical approach, while tumor characteristics included

tumor size, necrosis, vascular invasion, Glisson's capsule invasion, Edmondson's grading, and cirrhosis.

The liver function reservoir was assessed using the Child–Pugh classification and the Model for End-Stage Liver Disease (MELD) score. Major complication was defined as post-hepatectomy liver failure (PHLF). PHLF was based on the International Study Group of Liver Surgery (ISGLS).^[10] In the current study, the American Joint Committee on Cancer (AJCC) 8th edition and Barcelona Clinic Liver Cancer (BCLC) Staging were used to classify the tumors.^[11,12] The diagnosis of all patients was confirmed by pathology.

2.3. Surgical treatment

In the present study, hepatectomy was divided into one-stage hepatectomy and staged hepatectomy. When patients presented with unstable hemodynamic conditions such as significantly decreased hemoglobin and tachycardia, but the CT scan showed an enlarged mass with peripheral enhancement, suspicious defects in the abdominal wall, fluid collection in the abdominal cavity, but no clear active bleeding, one-stage hepatectomy was performed.

If the patient had contrast extravasation and active bleeding seen on the CT scan, TAE was performed first as an emergency treatment to control the bleeding. After the condition of the patient became stable and there was no active bleeding, staged hepatectomy was performed.

The types of hepatectomy were divided into minor resections and hemihepatectomy. Minor resections included tumorectomy and hepatic segmentectomy. While anatomic resection is the primary choice for a hepatectomy method, the surgical approach should be selected based on the reserve of liver function and intraoperative findings.

Depending on the intraoperative situation, the pringle maneuver was chosen to be performed, the liver parenchyma separated using CUSA and the peritoneal cavity was washed with saline.

2.4. Follow-up and prognosis

After discharge, all patients were monitored using a regular follow-up. Follow-up was performed every 3 months for the first year after discharge and every 6 months thereafter until November 2021. All patients were monitored regularly for recurrence by AFP levels assessment and CT contrast scans, and additional imaging techniques were performed as necessary.

The types of recurrence in the current study included intrahepatic and extrahepatic. In the event of recurrence during follow-up, a treatment plan was developed based on the type of recurrence and the patient's overall condition, including resection, transcatheter arterial chemoembolization (TACE), chemoradiotherapy, sorafenib, and immune checkpoint inhibitor therapy.

Overall survival was defined as the time interval from the date of hepatectomy to the date of death or the last follow-up examination. Recurrence-free survival (RFS) was the time during which a patient survived without evidence of recurrence after hepatectomy.

3. Statistical analyses

The Mann–Whitney *U* test or Kruskal–Wallis test were used to compare continuous variables according to the normality of the distribution and homogeneity of the variance. The χ^2 test was used for categorical variables. The Kaplan–Meier method was used to calculate the survival curves and log rank test was used to compare differences in survival. The *P* value less than .05 was considered statistically significant. SPSS 23.0 for Windows 10 was used for statistical analyses.

4. Results

4.1. Patient characteristics

During the study period, 86 HCC patients underwent surgery at our hospital from January 2015 to December 2019. Among them, 11 patients had srHCC. Of the 11 patients with ruptured HCC, 5 underwent one-stage hepatectomy and 6 underwent staged hepatectomy. Therefore, the patients were divided into one-stage group (5) and staged group (6). Figure 1 depicts the flow chart of the management of spontaneously ruptured hepatocellular carcinoma at our institution.

In all patients, the median age and BMI were 59 (interquartile range [IQR]: 56–64) and 23.44 (range, 20.99–25.35), respectively. According to the Child–Pugh classification, Child–Pugh A was observed in 4 (36.4%) and B in 7 (63.6%) patients. In the one-stage group, Child–Pugh class A was seen in 3 (60%) and class B in 2 (40%) patients. In the staged group, Child–Pugh class A was seen in 1 (16.7%) and class B in 5 (83.3%) patients. There was no significant difference between the 2 groups (*P* = .137). The median MELD score was 8 (range, 7–10), and 5 (45.5%) patients had cirrhosis. In the one-stage group, the median MELD score was 8 (range, 8–11). In the staged group, the median MELD score was 9 (range, 7–10). There was no significant difference between the 2 groups (*P* = .537). According to AJCC tumor staging, stage IIIA was diagnosed in 6 (54.5%) and IIIB in 5 (45.5%) patients, while according to BCLC staging, 3 (27.3%) patients had stage B and 8 (72.7%) stage C. In the one-stage group, according to AJCC, 3 (60%) patients

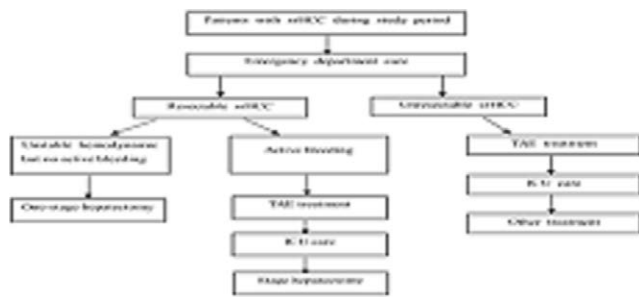


Figure 1. Flowchart of included patients with spontaneously ruptured hepatocellular carcinoma.

were stage IIIA and 2 (40%) patients were stage IIIB, according to BCLC, 2 (40%) were stage B and 3 (60%) were stage C. In the stage group, according to AJCC, 3 (50%) patients were stage IIIA and 3 (50%) were stage IIIB. according to BCLC, 1 (16.7%) were stage B and 5 (83.3%) were stage C. There was no significant difference between the 2 groups ($P = .740$ and $P = .387$, respectively). In the one-stage group, the median tumor size was 5.0 cm (range, 4.5–15.0). In the stage group, the median tumor size was 6.5 cm (6.0–8.0). There was no significant difference between the 2 groups ($P = .247$). Table 1 describes in detail the clinicopathological characteristics of the patients with srHCC.

4.2. Surgical variables and complications

Of the 11 patients, 6 (54.5%) underwent emergency TAE treatment followed by staged hepatectomy. The median time from TAE treatment to hepatectomy was 8 days (range, 8–15).

The median intraoperative blood transfusion volume in the one-stage group was 1200 mL (range, 1000–1400) and in the staged group 800 mL (range, 600–1300). There was no significant difference between the 2 groups ($P = .177$). In the one-stage group, 3 (60%) patients underwent minor resection and 2 (40%) hemihepatectomy; in the staged group, 4 (66.7) patients underwent minor resection, and 2 (33.3%) hemihepatectomy. There was no significant difference in the type of hepatectomy between the 2 groups ($P = .819$).

No in-hospital mortality. PHLF occurred in 6 patients including 4 (80.0%) in the one-stage group and 2 (33.3%) in the staged group. There was no significant difference in major complications between the 2 groups ($P = .122$). Table 1 shows the distribution of perioperative variables and complications in patients in one-stage and staged groups.

4.3. Overall survival and recurrence-free survival

The median overall survival and RFS after hepatectomy were 23 months (range, 17–38) (Fig. 2A) and 15 months (range, 10–31) (Fig. 2B), respectively, in patients with srHCC. In the one-stage group, the median survival was 23 months (range, 23–61), and in the staged group, it was 31 months (range, 14–38).

Table 1

Baseline characteristics of patients with ruptured hepatocellular carcinoma before and after undergoing hepatectomy.

	All (n=11)	One-stage hepatectomy (n=5)	Staged hepatectomy (n=6)	P value
Age	59(56–64)	57(56–66)	62(58–64)	.429
BMI (kg/m ²)	23.44(20.99–25.35)	23.44(20.99–27.43)	21.67(21.15–25.35)	.792
Hemoglobin (g/dL)	11.5(9.8–12.7)	11.5(9.1–13.7)	11.8(10.2–12.7)	1.000
Platelet (×10 ³ /uL)	157(106–169)	159(103–222)	157(148–166)	1.000
AST (IU/L)	31(28–63)	28(28–66)	35(28–63)	.662
ALT (IU/L)	29(23–48)	28(26–62)	37(23–48)	.792
Total bilirubin (mg/dL)	0.75(0.45–0.89)	0.82(0.45–0.89)	0.46(0.38–1.15)	.662
Albumin (g/dL)	3.6(3.1–4.2)	4.1(3.0–4.7)	3.6(3.2–3.8)	.931
INR	1.09(1.05–1.24)	1.07(1.04–1.48)	1.09(1.06–1.21)	.931
AFP (ng/mL)	4.49(3.59–56.77)	33.31(2.27–624.33)	4.49(3.62–21.7)	.662
Child–Pugh Class (A/B)	4(36.4%)/7(63.6%)	3(60%)/2(40%)	1(16.7%)/5(83.3%)	.137
MELD	8(7–10)	8(8–11)	9(7–10)	.537
Operative time (min)	165(155–185)	175(160–280)	165(155–175)	.537
Blood transfusion (mL)	1000(600–1300)	1200(1000–1400)	800(600–1300)	.177
Type of hepatectomy				.819
Minor	7(63.6%)	3(60%)	4(66.7%)	
Major	4(36.4%)	2(40%)	2(33.3%)	
Tumor size (cm)	6.0(5.0–8.0)	5.0(4.5–15.0)	6.5(6.0–8.0)	.247
Cirrhosis	5(45.5%)	2(40%)	2(33.3%)	.740
Necrosis	8(72.7%)	3(60%)	5(83.3%)	.387
Vascular invasion	7(63.6%)	2(40%)	5(83.3%)	.137
Glisson capsule invasion	8(72.7%)	4(80%)	4(66.7%)	.621
Edmondson grade (I/II/III/IV)	3(27.3%)/6(54.5%)/2(18.2%)	1(20%)/3(60%)/1(20%)	2(33%)/3(50%)/1(17%)	.885
BCLC (B/C)	3(27.3%)/8(72.7%)	2(40%)/3(60%)	1(16.7%)/5(83.3%)	.387
AJCC(IIIA/IIIB)	6(54.5%)/5(45.5%)	3(60%)/2(40%)	3(50%)/3(50%)	.740
Major complication	6(54.5%)	4(80.0%)	2(33.3%)	.122
Recurrence	7(63.6%)	4(80%)	3(50.0%)	.303

Variables are expressed as median (interquartile range) or n (%).

AFP = alpha-fetoprotein, AJCC = American Joint Committee on Cancer, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, INR = international normalized ratio, MELD = model for end-stage liver disease.

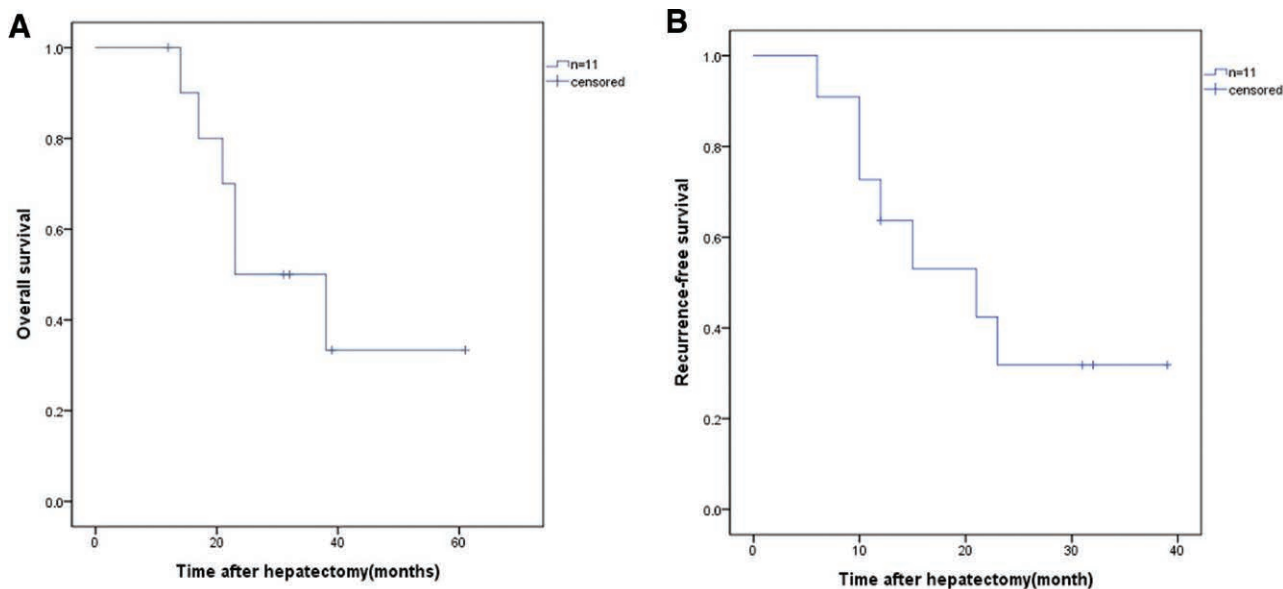


Figure 2. Overall survival and recurrence-free survival in patients with spontaneously ruptured hepatocellular carcinoma. (A) Overall survival in patients with spontaneously ruptured hepatocellular carcinoma. (B) Recurrence-free survival in patients with spontaneously ruptured hepatocellular carcinoma.

There was no significant difference between the 2 groups ($P = .978$) (Fig. 3A). In the one-stage group, the median RFS was 12 months (range, 10–32), and in the staged group, it was 21 months (range, 12–31). There was no significant difference between the 2 groups ($P = .372$) (Fig. 3B).

4.4. Recurrence location after hepatectomy

Of the 11 patients in the present study, 7 (63.6%) experienced recurrence. In the one-stage group, 4 (80%) patients experienced recurrence. In the stage group, 3 (50%) patients experienced recurrence. There was no significant difference in the recurrence rate between the 2 groups ($P = .303$). Of these patients, 4 (80%) underwent one-stage hepatectomy and 3

(50%) staged hepatectomy. Among the patients with recurrence, 4 showed both intrahepatic and extrahepatic recurrence, 2 had intrahepatic recurrence and 1 had extrahepatic recurrence. Of the patients with extrahepatic recurrence, 3 had peritoneal metastases and all underwent one-stage hepatectomy. Of the 3 patients with peritoneal metastases, 2 underwent peritoneal mass resection. Table 2 summarizes the details of RFS, recurrence sites, and treatment modality after recurrence, as well as the treatment period for recurrence patients.

5. Discussion

The current research was conducted in patients who had not received a diagnosis or treatment for HCC and who presented

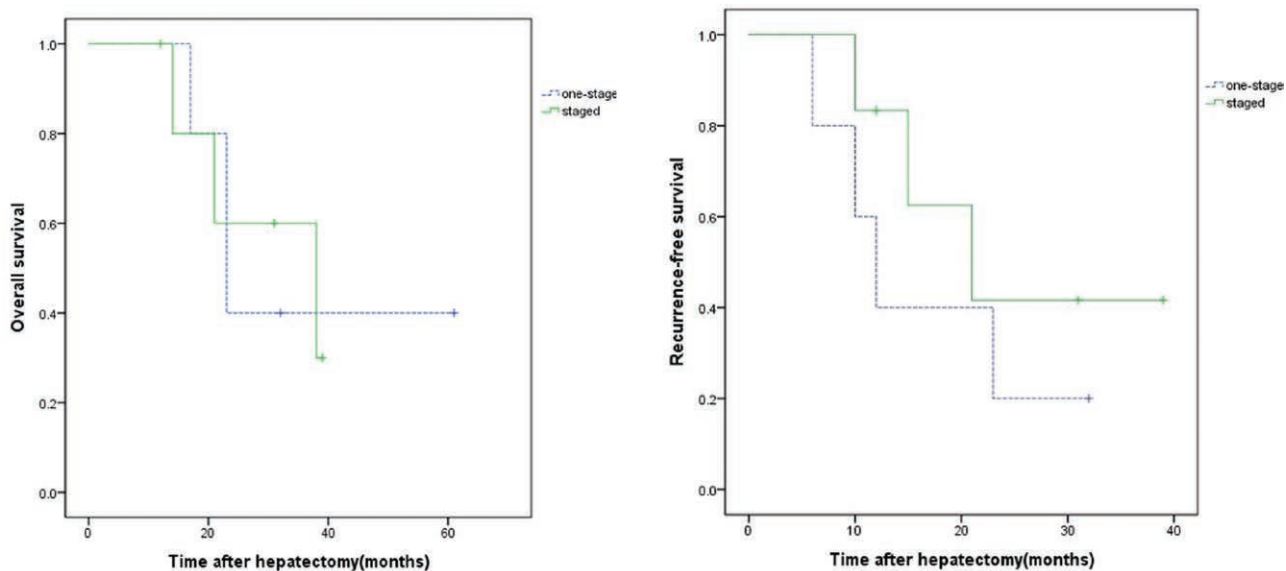


Figure 3. Overall survival and recurrence-free survival in patients with spontaneously ruptured hepatocellular carcinoma who underwent one-stage hepatectomy and staged hepatectomy. (A) Overall survival in patients with spontaneously ruptured hepatocellular carcinoma who underwent one-stage hepatectomy and staged hepatectomy [log rank (Mantel-Cox); $P = .978$]. (B) Recurrence-free survival in patients with spontaneously ruptured hepatocellular carcinoma who underwent one-stage hepatectomy and staged hepatectomy [log rank (Mantel-Cox); $P = .372$].

Table 2**Details of the location of recurrence and the treatment modalities after recurrence.**

	Surgical method	Range of hepatectomy	Recurrence location	Treatment modalities after recurrence	RFS
Case 1	One-stage	Right hepatectomy	Intrahepatic and peritoneal	Chemotherapy	23 mo
Case 2	One-stage	Right hepatectomy	Intrahepatic and peritoneal	Peritoneal tumor resection followed by Chemoradiation	10mo
Case 3	One-stage	Left lateral sectionectomy	Peritoneal	Peritoneal tumor resection	12 mo
Case 4	One-stage	Tumorectomy	Intrahepatic	Chemoradiation	6 mo
Case 5	staged	Left lateral sectionectomy	Intrahepatic and lung	TACE followed by Chemoradiation	21 mo
Case 6	staged	Right hepatectomy	Intrahepatic and colon	TACE followed by Chemotherapy	10 mo
Case 7	staged	Left lateral sectionectomy	Intrahepatic	TACE	15 mo

mo = months, RFS = recurrence-free survival, TACE = transarterial chemoembolization.

to the emergency room with a sudden srHCC. Due to the unpredictability of such rupture, detailed information on HCC and liver function reserves cannot be gathered in advance, as a consequence, emergency treatment is frequently fraught with difficulties.

An uncommon but potentially fatal complication of HCC is a spontaneous rupture, which is characterized by hepatic insufficiency and hemodynamic instability. However, the mechanism of tumor rupture is unclear. Combined with the analysis of previous studies,^[6] the pathogenesis of HCC rupture may be related to the following factors: The expansive growth and intratumoral pressure of HCC may cause compression and congestion of tumor veins. Rapid growth of the tumor leads to the inadequate blood supply to the tumor, resulting in hypoxia and ischemia, causing massive necrosis. Liver dysfunction caused by coagulation disorders, cirrhosis, and hypertension may lead to increased intrahepatic arterial and venous pressure as well as thinning of the vessel wall, thus accelerating HCC bleeding.

When encountering ruptured HCC, even if the ruptured bleeding is temporarily controlled by nonsurgical methods, there is still a possibility of rebleeding.^[5,6] Some clinicians recommend the one-stage hepatectomy because not only it stops bleeding, but also allows radical resection of the tumor.^[13] In the current study, there was no in-hospital mortality. As a result, one-stage hepatectomy is effective in such emergencies. However, because ruptured HCC is usually a bulging tumor formed by hematoma and adhesions, in the absence of hemostasis, tumor mobilization may lead to re-bleeding of the tumor, which may further damage liver function. In the current study, although there was no significant difference between the 2 groups, the intraoperative transfusion volume was higher in the one-stage group than in the staged group. This is because complications such as rebleeding during tumor mobilization can be prevented when initial hemostasis is performed by TAE.^[14] Furthermore, the current study also showed that the incidence of PHLF after one-stage hepatectomy was higher than that of staged hepatectomy (80.0% vs. 33.3%). The rate of major postoperative complications, especially postoperative liver failure, was also found to be higher in the one-stage hepatectomy group than in the staged hepatectomy group in the study by Zhou et al^[14] Some studies reported that the prognosis of staged hepatectomy after TAE hemostasis was similar to that in patients with unruptured HCC who underwent hepatectomy.^[15,16] Therefore, staged hepatectomy after TAE hemostasis may be a better option.

Several studies have reported that tumor rupture should add 0.5 to 2 stages to the baseline TNM stage; however, aggressive surgical resection of ruptured HCC can still be effective in prolonging patient survival.^[4,5] Yang et al also found that patients with HCC who experienced the rupture after hepatectomy had significantly higher survival rates than those who did not undergo hepatectomy.^[17] In the present study, the median survival was 23 months (IQR: 17–38).

Combined with previous studies and analyses, the survival of hepatectomy was significantly better than that of nonsurgical treatment.^[6,18]

Previous studies have concluded that patients with ruptured HCC who underwent staged hepatectomy have better survival and RFS than those who underwent one-stage hepatectomy.^[19] In the current study, there was no significant difference in survival and RFS between the one-stage and staged groups due to the small number of patients. However, patients who underwent staged hepatectomy were able to achieve better survival and RFS than those who underwent one-stage hepatectomy. Regarding the recurrence rate, there were also no significant differences between the 2 groups; however, patients who underwent staged hepatectomy had a lower recurrence rate than those who underwent one-stage hepatectomy (50% vs. 80%).

Regarding the recurrence location, intrahepatic recurrences were observed to be the most common, and intrahepatic multifocal recurrences were more common than intrahepatic unifocal recurrences.^[19] Consistent with this, in the present study, 7 patients had a recurrence, 6 of whom had intrahepatic metastases, with multifocal intrahepatic recurrence that occurred in 5 cases and unifocal intrahepatic recurrence in one case.

Peritoneal metastases were not uncommon in ruptured HCC after hepatectomy.^[9] The rate of peritoneal metastasis after ruptured HCC was 11.1%–20%.^[20] In the present study, 3 patients had peritoneal metastases. It has been suggested that this happens because tumor cell spillover creates seeding in the peritoneum.^[8,9] Some researchers recommend one-stage hepatectomy because early removal of the hematoma and resection of the tumor could decrease the incidence of peritoneal metastases or recurrence.^[8] It has also been indicated that hepatectomy performed within 8 days of rupture, including one-stage hepatectomy, results in significantly fewer patients with peritoneal metastases.^[21] However, some studies concluded that the timing of surgery did not have a significant effect on postoperative recurrence or peritoneal metastases.^[14] However, in the current study, all 3 patients who developed peritoneal metastases underwent one-stage hepatectomy. Due to the small number of patients, the exact cause needs further investigation.

Regarding the time interval between TAE and hepatectomy in this study, the median interval was 8 days (range, 8–15). However, the time between TAE and surgery is also not clearly defined. In the literature, the interval between TAE and surgery ranged from 10 days to 8 weeks.^[22]

Our study has some limitations. First, retrospective design includes possible omissions in the file, leading to a potentially biased study. Second, due to the low incidence of srHCC, limited number of patients was included in this analysis; thus, larger sample sizes are needed in future investigations regarding recurrence, in particular of peritoneal metastases. Third, this study did not analyze patient data in comparison to those who did not undergo hepatectomy.

6. Conclusion

In conclusion, when unpredictable srHCC occurs, either one-stage or staged hepatectomy is an effective treatment that can save lives. Patients who underwent staged hepatectomy after TAE hemostasis had better postoperative outcomes than those who underwent one-stage hepatectomy. The most common recurrence locations are intrahepatic and peritoneal. Peritoneal metastases are more likely to occur after one-stage hepatectomy.

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