RESEARCH ARTICLE

Patients with Spontaneously Ruptured Hepatocellular Carcinoma Benefit from Staged Surgical Resection after Successful Transarterial Embolization

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Abstract

Background: Surgical resection of spontaneously ruptured hepatocellular carcinoma (HCC) after successful transarterial embolization (TAE) remains controversial. The aim of this study was to investigate its efficacy in a series of cases. Materials and Methods: We retrospectively examined ruptured HCC cases from Jan 2000 to Dec 2008; all of these 126 cases received TAE as the initial therapy. Subsequently, 74 cases received staged surgical resection, and the remaining 52 cases underwent repeated TACE. The baseline demographic data, tumor characteristics, and long term survival were recorded and compared. Results: The demographic and baseline characteristics were comparable between the hepatic resection and TACE groups; furthermore, no significant difference in the tumor characteristics was detected between the two groups. The differences in in-hospital, 30-day and 90-day mortality between the two groups were not significant (P>0.05). However, the 1-, 3-, and 5-year overall survival rates were 85.1%, 63.5%, and 37.8%, respectively, in the hepatic resection group, which were significantly higher than those in the TACE group (69.2%, 46.2%, and 17.3%, respectively, P=0.004). Univariate and multivariate analyses indicated that these patients benefitted from hepatic resection compared with TACE with respect to long-term outcomes. Conclusions: Staged hepatic resection after TAE is an effective treatment that results in superior long-term survival to repeated TACE.

Keywords: Hepatocellular carcinoma - liver resection - transarterial embolization - ruptured

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Introduction

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer worldwide and is the second leading cause of cancer-related death; most of the HCC disease burden is found in Asia and Africa due to hepatitis B (HBV) or C (HCV) infection (Jemal et al., 2011). The overall prognosis of HCC remains disappointing. Due to the hypervascularity of this disease, HCC can exhibit rapid progression, direct invasion of the surrounding tissues or spontaneous tumor rupture (Jin et al., 2013). Spontaneous rupture is an uncommon and life-threatening presentation with an incidence of <3% in Western countries, 10% in Japan, 12.4% in Thailand and 14.5% in Hong Kong (Liang et al., 2013), and its mortality rate is high, ranging from 32% to 66.7% (Zhu et al., 2012). Several treatment modalities, including transarterial embolization (TAE), TACE, and emergency or staged liver resection, have been described. Open surgery was the primary method used to treat HCC rupture from the 1960s to the 1980s(Jin et al., 2013). However, due to the large tumor volume and impaired liver function inherent in HCC rupture, TAE has recently been reported provide a survival benefit (Kirikoshi et al., 2009; Jin et al., 2013). At our center, TAE was applied to all ruptured HCC cases exhibiting compensated liver function (Child A or B) and no thrombosis of the main portal vein. However, to the best of our knowledge, whether the optimal treatment approach for ruptured HCC after successful TAE is staged hepatic resection or repeated TACE remains under debate. Some groups have argued that TACE should be the first treatment for these patients due to their advanced stage, poor overall prognosis, large tumor volume, impaired liver function, and implantation metastasis (Li et al., 2009; Toshikuni et al., 2011; Shin et al., 2011). However, other studies have reported a survival benefit from staged hepatectomy in these cases (Battula et al., 2009; Miyoshi et al., 2011). In this study, we compared the long-term outcomes of ruptured HCC cases that underwent hepatic resection or TACE after successful TAE as the initial therapy for hemostasis.

Materials and Methods

Between Jan 2000 and Dec 2008, 126 patients diagnosed with ruptured HCC at our hospital who

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underwent successful TAE for hemostasis were retrospectively reviewed. Ruptured HCC was suspected when the patients presented with sudden-onset abdominal pain, distention, and shock. Ruptured HCC was confirmed based on contrast-enhanced abdominal computed tomography (CT): active extravasation of the contrast material, HCC surrounded by a perihepatic hematoma displaying high attenuation, protrusion of the contour, and focal discontinuity of the hepatic surface. Abdominal paracentesis was routinely performed for confirmation. TAE was the first intervention at our center. The tumor location, active bleeding site, and portal vein were assessed during TAE using 5 mL of iodized-oil contrast medium followed by feeding artery embolization using gelatin sponge particles. If TAE failed, emergency laparotomy was performed in combination with compensation for liver function. After successful TAE and hemodynamic stabilization, the cardiopulmonary function, ECOG score, serological status, Child-Pugh score, and imaging scans were evaluated for the preparation of hepatic resection. However, only a subset of patients underwent hepatic resection due to patient consent, age, liver function, ECOG score, tumor location, the tumor characteristics, and the comprehensive evaluation results. TACE was the first–choice therapy for patients for whom surgery was not available. Surgical hepatic resection and TACE procedures have been suggested in a previous study (Lei et al., 2013). At our center, surgery is performed by the chief physician or the deputy chief physician, each of whom has more than ten years of surgical experience.

The inclusion criteria were the following: spontaneously ruptured HCCs; acceptance of TAE as the initial therapy; ECOG score of 0-1; Child-Pugh grade A or B liver function; received staged liver resection or repeated TACE at our center; and completed regular postoperative follow-up visits or inspections. The exclusion criteria were the following: distant metastasis; heart or lung function that was unable to tolerate surgical treatment; surgery not possible due to other diseases; Child-Pugh grade C liver function; other liver cancer; performance of other treatment modalities; and acceptance of hepatic resection as the initial therapy for hemostasis. Ultimately, 126 cases were included in the pooled analysis in our study. We categorized these cases into two groups according to the staged therapy: the hepatic resection group (n=74) and the TACE group (n=52). The baseline demographic characteristics, tumor characteristics, and long-term survival were compared between the two groups, and univariate analysis was performed. Multivariate analysis was used to detect the risk factors of overall survival after successful TAE for ruptured HCC.

During the follow–up visits, the patients presented to our clinical department on a regular basis. Within three months after the surgery, the patients presented for relevant monthly follow-up examinations, including abdominal ultra-sonography, AFP, liver function, and standard blood examination. On the third month after the surgery, we conducted routine enhanced CT scanning of the abdomen to further assess tumor recurrence. When the color ultra-sonography indicated suspicious recurrence, we advised the patients to undergo enhanced CT or MRI inspection in combination with measurement of the AFP level. In the case of recurrence in the hepatic resection cases, we recommended the appropriate treatment plan (e.g., re-resection, radiofrequency-mediated ablation, or HIFU) according to the patient's characteristics, the characteristics of the tumor, and other relevant factors. For the TACE cases displaying clear arterial hypervascularization, repeated TACE was recommended.

Statistical analysis

The baseline demographic and tumor characteristics of the patients are expressed as the medians and frequencies. The categorical variables were compared using the chi-squared and 2-tailed Fisher's exact tests. The continuous variables were compared using the Mann-Whitney U-test. The long term outcomes of resection and TACE were compared via univariate analysis. Multivariate analysis was performed using Cox regression hazard analysis to calculate the hazard ratios and the P-values of independent variables for overall survival. Survival curves were estimated using the Kaplan-Meier method and were compared using the log-rank test. Overall survival was calculated from the initial TAE. A 2-tailed $p<0.05$ was considered to be significant. All statistical analyses were performed using the SPSS 17.0 statistical package (SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics

Based on the inclusion and exclusion criteria, 126 cases were included in the present study, and TAE for hemostasis was successful in all cases. Seventy-four cases underwent staged hepatic resection, and 52 cases underwent TACE for adjuvant therapy. Table 1 presents the demographic characteristics before TAE for the two groups. Most of the tumors were secondary to HBV infection (114 cases, 90.5%), although a few cases were secondary to HCV (4 cases, 3.2%) or alcohol liver cirrhosis (3 cases, 2.4%). The liver function was compensated in all cases, and no cases exhibited Child-Pugh grade C liver function. The most common reason for hospital admission was abdominal pain or distension (113 cases, 89.7%). Additionally, 28 cases in the hepatic resection group and 20 cases in the TACE group presented to our emergency department with hypovolemic shock. Sixty-three cases (50%) required a blood transfusion to stabilize the circulation. These patients exhibited decreased levels of Hb and PLT but elevated PT levels and heart rate. However, none of these characteristics significantly differed between the two groups (All P>0.05).

After TAE, the vital signs (heart rate and blood pressure) and the Hb levels (4-5 hour/time) were monitored to evaluate the effectiveness of TAE and to detect possible persistent hemorrhage. After 5-7 days of continuous monitoring, hemostatic and liver-protecting therapies were implemented. Blood transfusion resulted in the recovery of the Hb, PLT and PT levels. With respect to the preoperative tumor characteristics, the mean tumor number was 2.1, which was slightly but not significantly lower in the TACE group than in the hepatic resection group (p=0.253), and

the overall tumor diameter was comparable between the two groups (p=0.957). Alternatively, the mean AFP level was lower in the hepatic resection group than in the TACE group; however, this difference was not significant. When we categorized the cases into four subgroups according to the AFP level, the two treatment groups did not exhibit any significant differences.

For the 74 patients who underwent staged hepatic resection, 2 patients died in the hospital secondary to postoperative complications: one case died due to liver function failure, and the other case died due to lung infection. However, no in-hospital deaths were observed in the TACE group (2.7% *vs* 0%, p=0.234). The 30-day mortality rate included three cases (and a death due to a car accident) in the hepatic resection group and 2 cases in the TACE group (both died due to liver function failure) that died secondary to postoperative complications (4.1% *vs* 3.8%, p=0.953). The 90-day mortality rate included 5 patients in the hepatic resection group and 4 patients in the TACE group, all of whom died due to tumor recurrence (6.8% *vs* 7.7%, p=0.842).

After a 5-year follow-up, the hepatic resection group exhibited a significantly higher overall survival rate than the TACE group: the 1-, 3-, and 5-year overall survival rate was 85.1%, 63.5%, and 37.8% in the hepatic resection group and 69.2%, 46.2%, and 17.3% in the TACE group,

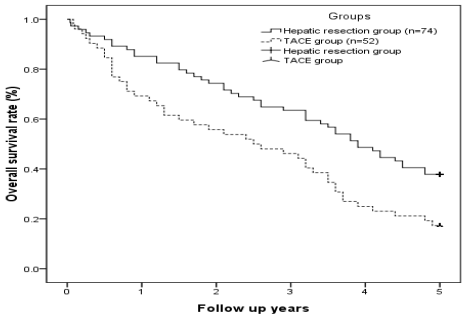

Figure 1. Long-term Outcome Comparison between the Staged Hepatic Resection Group and the TACE group: the Overall 1-, 3- and 5-year Survival Rates were 85.1%, 63.5%, and 37.8% in the Hepatic Resection Group and 69.2%, 46.2%, and 17.3% in the TACE Group, Respectively (P=0.004)

Table 1. Demographic Characteristics of the 126 Cases before TAE

	Hepatic resection group 74	TACE group 52	P value
Age	49.2±12.6	50.3±13.6	0.652
Gender (male/female)	52/22	35/17	0.724
BMI (kg/m^2)	23.5±2.4	23.4±2.2	0.893
Etiology (HBV/HCV/alcohol/negative)	67/2/2/3	47/1/1/3	0.953
Liver cirrhosis (yes/no)	68/6	47/5	0.646
Child-Pugh score (A/B/C)	40/34/0	30/22/0	0.687
MELD score	5.4±2.0	5.2±1.6	0.590
Presentation at admission			0.875
Abdominal pain	42	30	
Abdominal distension	26	15	
Other	6	7	
Hypovolemic shock (yes/no)	28/46	20/32	0.944
Hemoglobin (g/L)	91.5±28.1	87.8±23.8	0.444
Platelet (*10^9/L)	123.5±81.4	124.6±79.5	0.941
Prothrombin time (s)	12.8±1.6	12.5±1.5	0.355
Heart rate(beats/min)	108.6±16.1	106.4±14.0	0.418
Diabetes (yes/no)	6/58	3/49	0.617
Hypertension (yes/no)	7/57	4/48	0.730
Blood transfusion (yes/no)	39/35	24/28	0.900

Table 2. Baseline and Tumor Characteristics before Hepatic Resection or TACE

	Hepatic resection group 74	TACE group 52	P value
Child-Pugh score (A/B)	62/12	45/7	0.672
Hemoglobin (g/L)	103.2±17.4	97.9±16.6	0.087
Platelet (*10^9/L)	151.2±88.5	145.0±75.2	0.684
Prothrombin time (s)	11.8±1.5	11.8±1.3	0.951
Tumor number	2.1±1.3	2.4±1.8	0.253
Tumor diameter	7.5±2.1	7.5±2.4	0.957
AFP level (ng/ml)	1812.2±6714.8	2647.2±10827.8	0.595
AFP level			0.689
0-400 ng/ml	42	30	
400-800 ng/ml	3	8	
800-1200 ng/ml	10	2	
≥1200 ng/ml	19	12	

respectively (Figure 1, p=0.004). The patients in the hepatic resection group who died within the 5–year follow-up period exhibited a median overall survival duration of 29.0 months, whereas those in the TACE group exhibited a median overall survival duration of 24.3 months (p=0.207). The most common cause of death in the hepatic resection group was tumor recurrence (39 cases, 84.8%) followed by liver failure (4 cases, 8.7%).

Of the data shown in the tables, the following variables significantly influenced overall survival based on univariate analysis: the AFP level (≥400 ng/ml *vs* <400 ng/ml; p=0.031), the tumor diameter (≥8 cm *vs* <8 cm, p=0.042), and the treatment protocol (TACE *vs* hepatic resection, p=0.005). Based on the multivariate Cox analysis, the TACE treatment protocol (hazard ratio 2.32, confidence interval 1.43-3.36, p=0.002) was identified as a significant risk factor for overall survival.

Discussion

HCC is a common cause of death, especially in cases of spontaneous rupture. To date, the mechanism underlying spontaneous rupture is unclear. Some investigators have correlated spontaneous rupture with vascular dysfunction in the tumor tissue and have identified portal hypertension and/or minor mechanical injury as risk factors(Zhu et al., 2004). Rupture occurs in certain small tumors and at a higher frequency in large tumors (Battula et al., 2009). In our present study, 16 tumors displaying a diameter of less than 5 cm ruptured, and these patients represented 12.7% of all patients experiencing rupture. Various alternative hypotheses have been formulated to explain the precise mechanism that leads to HCC rupture: subcapsular location, dimensions, portal hypertension, tumor necrosis, and locally increased venous pressure due to the reduction of outflow caused by neoplastic invasion (Castells et al., 2001). Noconsensus opinion has been established regarding the optimal treatment for ruptured HCC, but the primary objective of initial management is hemostasis via either TAE or surgery. The initial treatment should focus exclusively on hemostasis. TAE is minimally invasive and has been shown to be effective for initial hemostasis in cases exhibiting hepatic insufficiency, liver cirrhosis and hemoperitoneum because liver function affects outcomes. Emergency hepatectomy is recommended in non-cirrhotic cases exhibiting preserved liver function. However, in China, most HCC cases are caused by HBV infection; in our study, 90.5% of the HCC cases were caused by HBV infection.TAE has been reported to be effective for achieving immediate hemostasis for ruptured HCC. Alternatively, primary resection for ruptured HCC is typically conducted in an emergency setting without precise information about tumor progression. Therefore, at our center, all ruptured HCC cases were recommended to undergo TAE as the first hemostasis treatment. Previous studies have suggested that multidisciplinary management, including TAE and postponed surgery, in selected patients may improve short term mortality. Although a few investigators have aimed to investigate the survival benefit of surgery *vs* TAE as the initial hemostasis therapy (Jin et al., 2013), to our knowledge, this is the first study to investigate the survival benefit of staged hepatic resection *vs* staged TACE for cases in which successful TAE served as the initial hemostasis therapy.

With respect to the survival benefits between the hepatic resection and TACE groups, the current study revealed significantly higher 1-, 3-, and 5-year overall survival in the hepatic resection group. Although TACE is less invasive than open surgical resection, hepatic resection may remove the tumor targets, which may be the primary reason for the survival benefit observed after hepatic resection. However, hepatic resection patients may accept other adjuvant therapies, such as TACE, which may also contribute to the survival benefit in the hepatic resection cases. In two case series of staged resection after TAE for ruptured HCC from Japan, no in-hospital mortality was observed, and the 1- and 3-year survival rates of 71-77% were 48%-54%, respectively (Shimada et al., 1998; Shuto et al., 1998; Gao et al., 2012), which are lower than our outcomes. In our series, the 1-, 3- and 5-year overall survival rates were 85.1%, 63.5%, and 37.8%, respectively. The primary reasons for these improvements in our study include the following: the implementation of new surgical techniques, such as the Pringle maneuver or hemi-hepatic vascular inflow occlusion (Huang et al., 2014); new equipment, such as Cusa Bipolar coagulation forceps; new concepts, such as lobe or segment resection for HCC (Bruix et al., 2014); and new postoperative therapies, such as Sorafenib (Bruix et al., 2014; Gores et al., 2014).

The potential for the dissemination of cancer cells has been a matter of concern(Shuto et al., 1998). Although it appears likely that spontaneous tumor rupture results in the dissemination of tumor cells, there have been few reports of ruptured HCC resulting in fatal peritoneal dissemination(Shuto et al., 1998). Our long-term follow-up showed that only 6 of the 51 (11.8%) recurrent HCC cases exhibited peritoneal dissemination; for 41 other patients (80.4%), recurrence was observed in the residual liver. This rate of peritoneal dissemination is comparable to that of hepatic resection for non-ruptured HCC(Jianyong et al., 2014). Based on the results of the univariate and multivariate analyses, we suggest that for the treatment of ruptured HCC after successful TAE, hepatic resection may represent the optimal treatment to improve the overall prognosis. Therefore, we believe that hepatic resectionshould be recommended to such patients; however, liver function, the ECOG score, the remnant liver volume, and other factors should also be considered.

Our study contains several limitations. First and importantly, this study is inherently limited by its retrospective study design; all of the data were retrospectively collected and analyzed at a single center. However, our study included all eligible patients at our center. Second, most of the HCC cases were caused by HBV infection, which differs from HCC cases in Japan or Western countries, where HCV infection or alcohol use is the more common cause. Thus, further studies including these patient groups should be performed. Our future work will focus on a multi-center random comparative study using a large sample.

In conclusion, due to the survival benefit of staged

hepatic resection compared with TACE, the present study suggests that staged hepatic resection should be performed when possible.

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