Impact of Spontaneous Tumor Rupture on Prognosis of Patients With T4 Hepatocellular Carcinoma

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Background and objectives: Compare the outcomes of three groups of patients with T4 hepatocellular carcinoma (HCC): tumor rupture with shock (RS group), tumor rupture without shock (R group), and no tumor rupture (NR group).
Materials and Methods: We retrospectively reviewed 221 patients with T4 HCC from 2010 to 2012. The clinical background and prognosis were analyzed.
Results: Overall in-hospital mortality rate was 18.1%; overall median survival time was 4 months. The NR group were more likely to have multiple and infiltrative tumors ($P < 0.001$). Relative to the NR group, the R + RS group had better survival rates at 6 months (49.2% vs. 32.2%), 1 year (35.3% vs. 21.0%), 3 years (22.5% vs. 11.0%), and 5 years (17.7% vs. 5.5%) ($P = 0.010$). Patients in the RS group had a higher in-hospital mortality rate, but significantly better long-term survival than the NR and R group ($P < 0.001$). Multivariate analysis indicated that Child-Pugh class B or C, presence of portal venous thrombosis, and absence of shock were significantly associated with poor survival.
Conclusion: Patients with tumor rupture and shock had worse in-hospital survival. However, patients without decompensated liver cirrhosis and portal venous thrombosis, and eligible for curative treatment had favorable long-term outcome.
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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common liver cancer and the second leading cause of cancer-related deaths in men worldwide [1,2]. Spontaneous tumor rupture is a life-threatening complication of HCC. Several studies reported poor prognosis of patients with ruptured HCC, with median survival period of 7–21 weeks and a 1-month mortality rate of 34–71% [3–5]. Studies of hepatectomy patients showed those with ruptured HCC had worse prognosis than those with non-ruptured HCC [6,7]. In addition, spontaneous tumor rupture is related to the presence of peritoneal metastatic implants, which is also associated with poor outcome [8].

The seventh edition of AJCC/UICC (American Joint Committee on Cancer/Union for International Cancer Control) TNM staging system assigns all ruptured HCC tumors to T4 [9,10]. However, based on clinical experience, a subgroup of patients who experience tumor rupture during earlier stages and with good hepatic functional reserve may be suitable for curative liver resection and therefore have favorable outcomes. Furthermore, recent studies reported that although tumor rupture had a negative prognostic impact on patient survival, other tumor-related parameters were equally important [3,11]. Thus, it may be inappropriate to assign all HCC patients with tumor ruptures to T4.

In the present study, we retrospectively analyzed the clinical characteristics, treatments, and outcomes of patients with T4 HCC to determine the prognostic impact of spontaneous tumor rupture.

MATERIALS AND METHODS

Patients

From January 2010 to December 2012, 2219 consecutive patients with HCC were registered in the Cancer Registry of Chang Gung Memorial Hospital at Linkou, a tertiary referral hospital in northern Taiwan. A total of 221 of these patients with T4 HCC were enrolled. Spontaneous tumor rupture occurred in 117 patients (5.3% of all HCC patients). Thirty-five (15.8%) patients had regional lymph node metastases and 60 (27.1%) had distant metastases. This retrospective study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB 98-1882B).

Based on retrospective analysis, the 221 patients were classified as having rupture with shock (RS group, n = 35), rupture without shock (R group, n = 82), or no rupture (NR group, n = 104). Demographic parameters, clinical parameters, tumor-related parameters (size, morphology, laterality, multifocality, presence of portal/hepatic venous invasion, presence of bile duct invasion, local invasion

except gallbladder, presence of spontaneous rupture, mean density of ascites, presence of peritoneal seeding), treatment modalities, and outcomes were recorded.

Diagnosis and Management

Spontaneous tumor rupture was diagnosed when a patient presented with abrupt-onset abdominal pain, fullness, or hemodynamic instability and with typical findings on dynamic computed tomography (CT), including HCC with a protruding contour, focal discontinuity of the liver surface, and perihepatic or intraperitoneal hematoma [12]. For patients in the RS group, initial treatment involved stabilization of hemodynamic status by fluid resuscitation and blood transfusion. Transarterial embolization (TAE) was performed in patients with unstable hemodynamic status or with imaging results that suggested active bleeding. In stable patients, the definitive treatment plan was developed by a committee consisting of hepatologists, hepatobiliary surgeons, interventional radiologists, and radiation oncologists. The performance status, tumor factors, liver functional reserve, and socioeconomic status were recorded. The treatment options were hepatectomy, transarterial chemoembolization (TACE), TACE followed by staged surgery, chemotherapy, radiotherapy and targeted therapy, and best supportive care.

Follow Up and Surveillance for HCC

The follow-up protocol included outpatient visits to the clinic and serum liver biochemistry with imaging examinations (dynamic CT or abdominal ultrasonography) at 1 month after discharge and every 3 months thereafter. Tumor progression, remission, or recurrence was determined by dynamic CT images, chest films, and bone scanning. The overall mean follow-up time was 15.2 months [95% confidence interval (CI): 12.1–18.2 months].

Survival Analysis

The date of each patient's last visit or death was recorded for survival analysis. Categorical data were analyzed with a χ^2 test or Fisher's exact test. Continuous variables were analyzed with a Mann–Whitney U test. Survival rates in each group were determined by the Kaplan–Meier method, and differences between groups were analyzed with log-rank tests. Cox-regression analysis was used to identify prognostic factors associated with overall survival. Variables that were significant in the univariate analysis were subjected to multivariate analysis. All statistical analyses were performed using SPSS version 21 (SPSS, Inc., Chicago, IL). P-values less than 0.05 were considered statistically significant.

RESULTS

Patient Demographics

We retrospectively analyzed the records of 221 patients with T4 HCC, with staging according to the seventh edition of the AJCC (Table I). The median age was 62 years old and there were 179 males and 42 females. One hundred and thirty-four (60.6%) patients had hepatitis B, 63 (28.5%) had hepatitis C, and 14 (6.3%) had both hepatitis B and C. Child-Pugh classification indicated that 106 (47.9%) patients were in class A, 71 (32.1%) in class B, and 44 (19.9%) in class C. The median tumor size was 9.9 cm (range: 0.5–22 cm), 134 (60.6%) patients had multiple tumors, and 74 (33.5%) patients had infiltrative tumors. Barcelona Clinic Liver Cancer (BCLC) staging at diagnosis indicated that 4 patients were in stage A, 25 in stage B, 146 in stage C, and 46 in stage D. The median alpha-fetoprotein level at diagnosis was 811 ng/ml (range: 1.6–2.5×10^6 ng/ml).

Management of Patients With T4 HCC

Figure 1 shows the disposition of the 117 patients with ruptured HCC (R and RS group). Thirty-five (29.9%) of these patients with ruptures presented with acute shock (RS group) and 82 (70.1%) presented without shock (R group). Patients in the RS group were given resuscitation with fluid therapy and blood transfusion for initial stabilization; then, 1 patient underwent emergency laparotomy, 31 patients underwent TAE or TACE for hemostasis, and 3 patients were managed conservatively due to advanced disease and poor liver function reserve, of which 2 patients died. After stabilization, a definitive treatment plan was formulated that considered the liver function and tumor stage of each of the 115 patients. Fifteen patients underwent hepatectomy, 10 patients had a staged hepatectomy, 69 patients had serial TACE, 14 patients had palliative chemotherapy, radiotherapy or targeted therapy, and 7 patients underwent best supportive care.

The other 104 patients had locally invasive tumors, but no rupture (NR group). Nine of these patients had a hepatectomy, 4 patients had a staged hepatectomy, 20 patients had serial TACE, 49 patients had palliative chemotherapy, radiotherapy or targeted therapy, and 22 patients underwent best supportive care.

Nodal and Distant Metastases

Thirty-five (15.8%) patients had regional lymph node metastases and 60 (27.1%) had distant metastases. The distant metastases were in the lung (n = 37, 61.7%), bone (n = 12, 20%), heart (n = 6, 10%), distant lymph nodes (n = 8, 13.3%), and the peritoneal cavity (peritoneal carcinomatosis) (n = 16, 26.7%). Twenty-three (38.3%) patients had metastases in more than one location. Patients without ruptures (NR group) had a higher frequency of distant metastases than those with ruptures (R + RS group) (39.4% vs. 16.2%, $P < 0.001$). Among patients with ruptures, more patients without shock (R group) presented with distant metastases than those with shock (RS group) (18.3% vs. 11.4%, $P = 0.264$).

Survival Analysis

Survival analysis indicated that the overall hospital mortality rate was 18.1% (45.7% in RS, 13.4% in R, 12.5% in NR). The overall median survival time was 4.0 months (95%CI: 2.6–5.4 months), 6 months in R + RS group, and 2.8 months in NR group. Patients with ruptures (R + RS) had better survival rates than those without ruptures (NR) at 6 months (49.2% vs. 32.2%), 1 year (35.3% vs. 21.0%), 3 years (22.5% vs. 11.0%), and 5 years (17.7% vs. 5.5%) (Fig. 2, $P = 0.010$).

Figure 3 shows the overall survival rates of the 3 groups. When hospital mortalities were included, the RS group had worse 6-month (40.0% vs. 53.1%) and 1-year (34.3% vs. 35.6%) survival rates compared with the R group. However, the RS group had a better survival rate than the R group and the NR group at 3 years (28.3% vs. 19.9% vs. 11.0%) and 5 years (25.1% vs. 14.6% vs. 5.5%) (Fig. 3a, $P = 0.037$). When we excluded hospital mortalities, the RS group had a significantly better survival rate than the other 2 groups (Fig. 3b, $P < 0.001$).

Comparison of Demographic and Clinical Parameters

Table I compares the characteristics of the 3 groups. Patients in the RS group had a significantly higher hospital mortality rate (45.7%, $P < 0.001$), higher rate of blood transfusion (91.4%, $P < 0.001$), and lower hemoglobin level ($P = 0.001$). The RS group also had a higher white blood cell count ($P < 0.001$), INR level ($P = 0.035$), and ascites density ($P < 0.001$) than the other

TABLE I. Demographic and Clinical Characteristics of Patients With Stage T4 Hepatocellular Carcinoma Who Had Spontaneous Tumor Rupture With Shock (RS Group), Rupture Without Shock (R Group), and no Rupture (NR Group)

	Rupture w/shock (RS group)	Rupture w/o shock (R group)	No rupture (NR group)	P-value
Patients (n)	35	82	104	
Hospital mortality (n,%)	16 (45.7)	11 (13.4)	13 (12.5)	<0.001
Age[a] (years)	63.6 ± 13.4	61.3 ± 13.4	60.0 ± 12.7	0.387
Sex (n, %)				0.148
Male	29 (82.9)	61 (74.4)	89 (85.6)	
Female	6 (17.1)	21 (25.6)	15 (14.4)	
Blood transfusion (n,%)	32 (91.4)	18 (22.0)	2 (1.9)	<0.001
BCLC stage (n, %)				0.022
A	1 (2.9)	2 (2.4)	1 (1.0)	
B	6 (17.1)	14 (17.1)	5 (4.8)	
C	17 (48.6)	51 (62.2)	78 (75)	
D	11 (31.4)	15 (18.3)	20 (19.2)	
Child-Pugh classification (n,%)				0.079
A	14 (40)	50 (61)	42 (40.4)	
B	9 (25.7)	22 (26.8)	40 (38.4)	
C	12 (34.3)	10 (12.2)	22 (21.2)	
HBsAg (n,%)	16 (45.7)	50 (61)	68 (65.4)	0.292
HCVAb (n,%)	11 (31.4)	21 (25.6)	31 (29.8)	0.625
Hemoglobin[a] (g/dl)	10.4 ± 2.6	11.5 ± 2.7	12.4 ± 3.0	0.001
WBC[a] (10^3/ul)	13.1 ± 6.4	10.0 ± 4.3	8.8 ± 4.5	<0.001
INR[a]	1.4 ± 0.4	1.2 ± 0.2	1.3 ± 0.3	0.035
Total bilirubin[a] (mg/dl)	1.7 ± 1.7	1.6 ± 2.0	2.4 ± 4.0	0.218
AST[a] (U/L)	117.9 ± 152.1	135.5 ± 146.4	192.6 ± 459.9	0.441
ALT[a] (U/L)	82.1 ± 118.9	75.8 ± 89.1	98.5 ± 239.0	0.680
Albumin[a] (g/dl)	3.0 ± 0.9	3.4 ± 0.7	3.4 ± 0.8	0.435
Creatinine[a] (mg/dl)	1.4 ± 0.9	1.2 ± 1.0	1.1 ± 0.9	0.590
ALK[a] (U/L)	104.7 ± 76.6	132.2 ± 102.1	168.5 ± 99.9	0.266
AFP > 200 ng/ml (n,%)	13 (37.1%)	46 (56.1%)	63 (60.1%)	0.126
Number of lesions (n,%)				0.004
Single	12 (36.4)	43 (52.4)	30 (28.8)	
Multiple	21 (63.6)	39 (47.6)	74 (71.2)	
Tumor morphology (n,%)				<0.001
Discrete	27 (81.8)	66 (80.5)	52 (50)	
Infiltrative	6 (18.2)	16 (19.5)	52 (50)	
Tumor size[a] (cm)	8.7 ± 3.2	9.6 ± 4.4	10.6 ± 4.5	0.069
Hepatic vein thrombosis (n,%)	8 (22.9)	14 (17.1)	69 (66.3)	<0.001
Portal vein thrombosis (n,%)	7 (20)	24 (29.3)	69 (66.3)	<0.001
Bile duct invasion (n,%)	1 (3)	3 (3.7)	17 (16.3)	0.005
Ascites density[a] (HU)	33.7 ± 20.9	32.4 ± 23.8	8.0 ± 11.5	<0.001

BCLC stage, Barcelona-Clinic Liver Cancer Classification; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C antibody; WBC, white blood cell count; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALK, alkaline phosphatase; AFP, alpha-fetoprotein; HU, Hounsfield unit.
[a]Values are shown as mean ± standard deviation.

groups. Patients in the NR group had more advanced BCLC stage ($P = 0.022$), and were more likely to have multiple tumors ($P = 0.004$), infiltrative tumors ($P < 0.001$), and hepatic or portal venous vein invasion ($P < 0.001$), respectively.

Survival Outcome and Treatment Modality

The cumulative survival rates at 6 months, 1 year, and 3 years were 76.9%, 69.2%, and 61.5% in the staged surgery group; 69.6%, 60.9%, 43.0% in the surgery alone group; 66.2%, 43.4%, 25.7% in the TACE group; 29.1%, 14.1%, and 2.0% in the palliative chemotherapy, radiotherapy or targeted therapy group; 16.7%, 11.0%, 0% in the supportive care group (Fig. 4). Overall survival rates were significantly better in the staged surgery, surgery alone, TACE groups than in the supportive care group ($P < 0.001$ for all comparisons) (Table II).

Multivariate Analysis of Post-Treatment Survival

Multivariate Cox regression analysis (Table III) indicated that advanced Child-Pugh class [odds ratio (OR): 1.89, $P = 0.001$], portal vein thrombosis (OR: 1.77, $P = 0.015$), and absence of shock (OR: 2.13, $P = 0.035$) were significantly and independently associated with poor long-term outcome.

DISCUSSION

Our study of patients with T4 HCC showed that the overall survival rate of patients with ruptured tumors was significantly better than that of those without ruptures. Patients who presented with hemorrhage and shock had greater in-hospital mortality (45.7%), but they also had better long-term survival. To the best of our knowledge, this is the first study to investigate the survival outcomes of three different groups of patients with T4 HCC.

Spontaneous tumor rupture is a life-threatening complication of HCC. The incidence of HCC rupture is higher in Asia than in Western countries, ranging from 2.3% to 26% in Asia compared with less than 3% in the West [4,5]. The incidence of HCC rupture in our study was 5.3%, lower than in a 1995 study in Taiwan (26%) [13]. Other studies reported that ruptured HCC is associated with high in-hospital mortality, above 25% [4,5]. In the current study, 23% of the patients with tumor ruptures died during their hospital stays. In addition, there was a high in-hospital mortality rate (45.7%) for patients with tumor rupture and shock (RS group). Previous studies showed that increased mortality among patients with HCC is related to cirrhosis, high Child-Pugh score, poor liver function (low serum albumin, high serum bilirubin, AST or ALT levels), and severity of bleeding (shock and low hemoglobin level) [4,5,14,15].
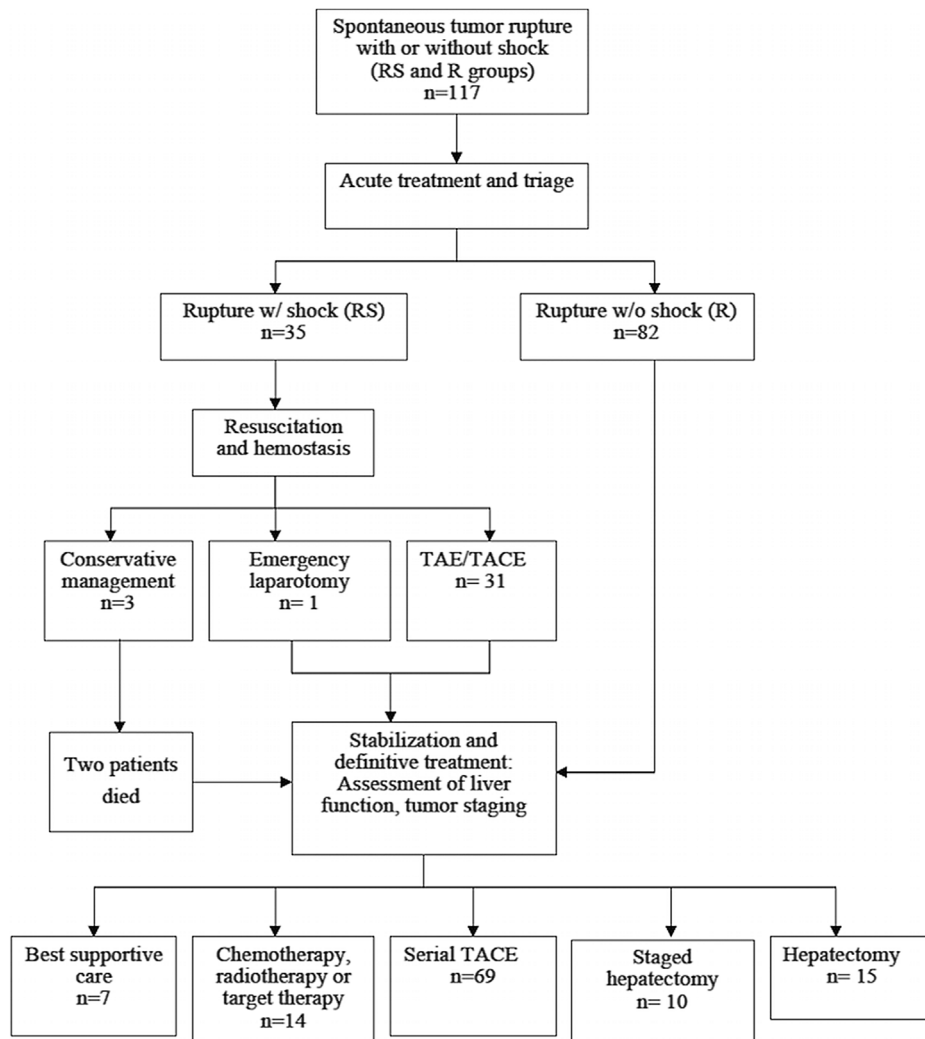
Fig. 1.   Flowchart of patients with T4 hepatocellular carcinoma who had tumor ruptures with shock (RS group) or ruptures without shock (R group).

Treatment of ruptured HCC involves multidisciplinary care, and hemostasis is a primary concern. Transarterial embolization is an effective method for achieving prompt hemostasis and has a success rate of 53–100% [4,5,15,16]. After initial stabilization, the liver functional reserve and tumor stage should be investigated to determine the best treatment. Serial transarterial chemoembolization can be performed in inoperable patients, and curative treatment, such as staged hepatectomy, should be considered for patients with adequate liver functional reserve. Some recent studies reported that combination therapy with sorafanib after surgery, TAE, or TACE was safe and effective [17,18].

Previous studies showed poor overall survival in patients with ruptured HCC relative to those without ruptures [5,6,19]. A recent nationwide study from Japan reported that the 1-, 3-, and 5-years survival rates for patients with ruptured HCC were 41.4%, 21.1%, and 13.3%, respectively [3]. Our study differed from these other studies in that all of our patients had T4 HCC. Our results indicated that patients with ruptured HCC (R + RS group) had better 1-, 3-, and 5-years overall survival than those with locally invasive tumors but without ruptures (NR group). The greater mortality of the NR group may be explained by the more advanced BCLC stage, higher rate of infiltration, presence of multiple tumors, and tumor vascular invasion in this group. In addition,

fewer patients in the NR group underwent surgery relative to the R + RS group (12.5% vs. 21.4%, $P = 0.081$).

Our study identified several factors associated with poor prognosis for long-term survival, including Child-Pugh class B/C, presence of portal venous thrombosis, and absence of shock. Patients with higher Child-Pugh class have more severe liver cirrhosis and poorer liver function, leading to intolerance to aggressive angiographic interventions and surgical resection [16,20]. The presence of main portal venous thrombosis is traditionally considered a contraindication for TAE or TACE due to the potential risk of hepatic insufficiency resulting from ischemia. Although some studies reported successful TACE in patients with main portal venous thrombosis but with preserved liver function and good collateral circulation, patients with ruptured HCC generally have poorer hepatic functional reserve, therefore portal venous thrombosis may be related to their poor outcome [5,21]. The presence of shock, a marker for the severity of a hemorrhage from a tumor rupture, is related to short-term mortality [4,5,15,22,23]. Our study, however, showed that the R group had a worse outcome than the RS group. This may be because the R group had a higher percentage of patients presenting with distant metastases (18.3% vs. 11.4%, $P = 0.264$). Another explanation may be that patients with shock (or another critical condition) often seek medical
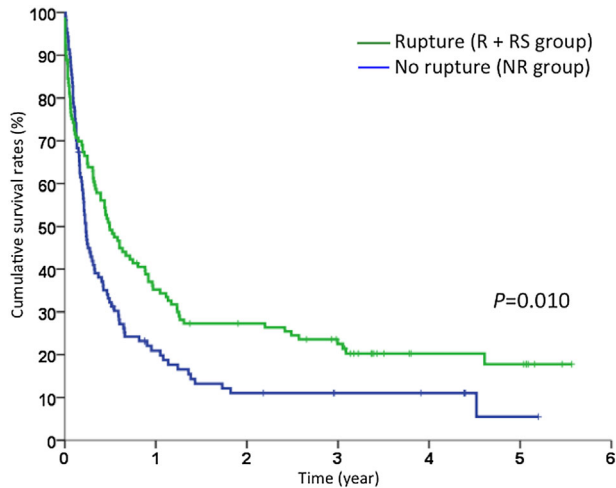
Fig. 2. Cumulative survival rates of T4 hepatocellular carcinoma patients with tumor rupture (R + RS group, green line) and without rupture (NR group, blue line). A log-rank test indicated better overall survival in patients with tumor rupture ($P = 0.010$).

Fig. 4. Cumulative survival rates of T4 hepatocellular carcinoma patients who received different treatments.

care before those without shock; patients without shock may present with insidious symptoms such as moderate epigastric dullness. In addition, tumor size was smaller in the RS group (8.7 ± 3.2 cm) than in the R group (9.6 ± 4.4 cm) and the NR group (10.4 ± 4.5 cm) ($P = 0.069$). In other words, despite the higher in-hospital mortality of the RS group, this group had a better long-term survival. This result supports the use of a more aggressive treatment approach for patients with T4 HCC who present with tumor rupture and shock.

Several lines of evidence indicate that spontaneous tumor rupture is a risk factor for implanted peritoneal metastasis. In 1989, Sonoda et al. reported three cases of implanted peritoneal metastases following tumor rupture [8]. A recent autopsy study found peritoneal seeding in 9.4% of patients, and a strong association with ruptured HCC, direct diaphragmatic invasion, and lymph node metastasis [24]. In the present study, peritoneal carcinomatosis following tumor rupture occurred in 16 (13.6%) patients. In one patient, the implanted tumors were resected along with the primary HCC, and this patient had a favorable outcome. Therefore, in carefully selected patients, a curative treatment strategy may still be effective in the presence of peritoneal seeding.
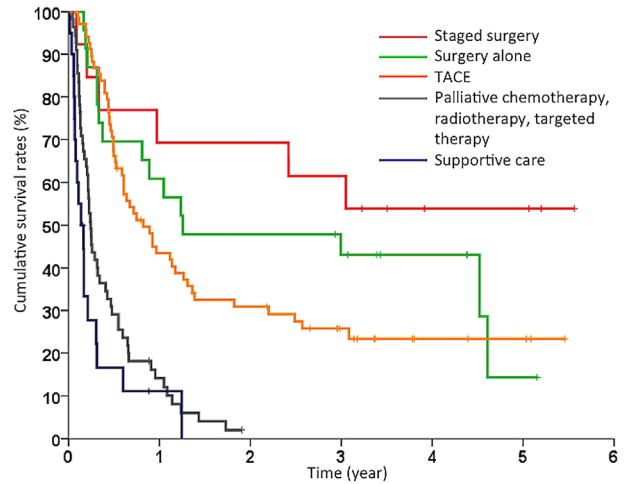
The staging system for HCC is different from other malignancies because it not only takes into account the tumor factors but also on the liver function impairment and general physical status of the patients. Various staging systems adopted in HCC include the AJCC TNM staging system, European systems like BCLC staging system and Asian systems like Okuda staging system [25]. Among these, the AJCC TNM staging system is the only one to address the issue of spontaneous tumor rupture. The seventh edition of the AJCC TNM staging system defines T4 HCC as direct invasion to adjacent organs, other than gallbladder, or perforation of the visceral peritoneum [9,10,26]. Therefore ruptured HCC is classified as T4, even if the tumor is small, solitary, and with no vascular or bile duct invasion [5]. In clinical practice, however, there is significant heterogeneity among T4 lesions. Patients with ruptured HCC and those with locally invasive tumors but without ruptures have very different clinical outcomes and tumor behaviors. The current study of patients with T4 HCC shows better long-term survival in patients with ruptured HCC (R + RS group) than in those without ruptures (NR group). This may be expected, because
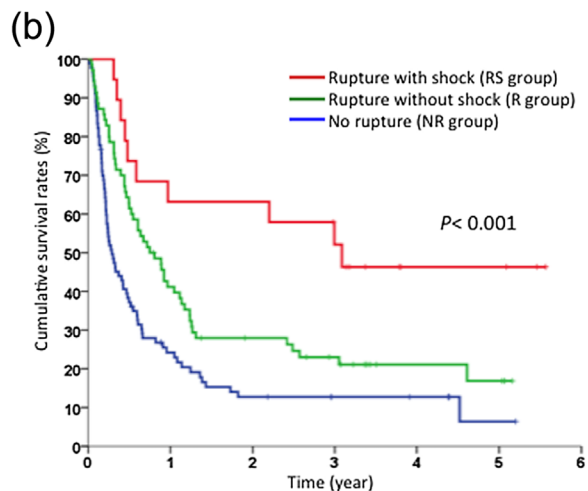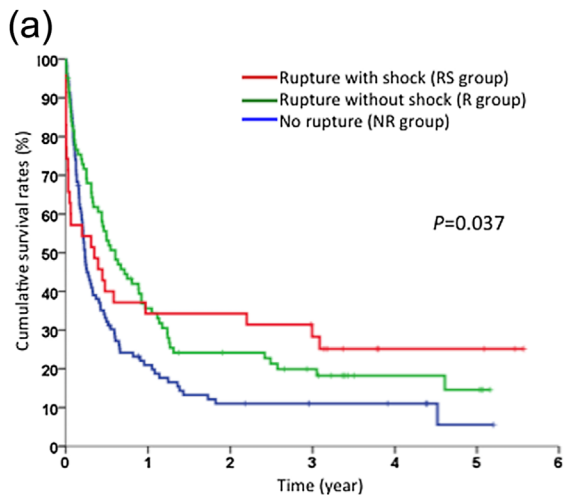

Fig. 3. Cumulative survival rates of T4 hepatocellular carcinoma patients with tumor rupture and shock (RS group), rupture without shock (R group), and no rupture (NR group) including hospital mortalities (**a**) and excluding hospital mortalities (**b**).

TABLE II. Paired Comparison of Survival Rates Among Different Treatment Groups

Reference	*P*-value
Staged surgery	
Supportive care	<0.001
Palliative C/T, R/T, and targeted therapy	<0.001
TACE	0.050
Surgery alone	0.239
Surgery alone	
Supportive care	<0.001
Palliative C/T, R/T, and targeted therapy	<0.001
TACE	0.281
TACE	
Supportive care	<0.001
Palliative C/T, R/T, and targeted therapy	<0.001

C/T, chemotherapy; R/T, radiotherapy; TACE, transarterial chemoembolization.

patients without ruptures tend to have a higher BCLC stage, multiple tumors, and infiltrative tumors. Studies involving hepatectomy patients suggested that the seventh AJCC TNM staging system failed to stratify patients with T3b and T4 tumors and stage III patients into stage IIIA–IIIC [26,27]. In a nationwide study from Japan, Aoki et al. compared the outcomes of patients with and without ruptured HCC and concluded that assigning all cases with ruptured HCC to T4 may lead to overestimation of disease severity. These researchers suggested it would be more appropriate to give additional stages to the baseline TNM staging in cases of ruptured HCC [3]. Another study also supports the proposal that T4 classification should not include all types of ruptured HCC [11].

There are several limitations in this study. The main limitation is its retrospective design, which implies baseline discrepancies in patient selection (different hepatic functional reserve, tumor size, etc.). It is virtually infeasible to prospectively randomize patients with ruptured HCC given varied clinical and tumor status as well as critical clinical conditions. In addition, this study was performed in a single center with relatively small number of patients and shorter follow-up time.

In conclusion, patients with spontaneous rupture of HCC, especially those with shock, had higher in-hospital mortality than other patients with T4 HCC. Nonetheless, after aggressive resuscitation and therapy, patients with ruptures could have favorable long-term outcome, particularly those without decompensated liver cirrhosis and portal venous thrombosis and were eligible for curative treatment. The factors

TABLE III. Multivariate Cox Regression Analysis of Factors Associated With Survival in Patients With T4 Hepatocellular Carcinoma

Parameter	OR	95%CI	*P*-value
AFP			
>200 vs. ≤200 ng/ml	1.37	0.92–2.02	0.118
Child-Pugh classification			
A/B/C	1.89	1.29–2.77	0.001
Hepatic vein thrombosis			
Yes vs. no	1.01	0.63–1.61	0.972
Portal vein thrombosis			
Yes vs. no	1.77	1.12–2.80	0.015
Bile duct invasion			
Yes vs. no	1.43	0.75–2.73	0.281
Tumor morphology			
Infiltrative vs. discrete	1.02	0.63–1.66	0.942
Number of lesions			
Multiple vs. single	1.32	0.84–2.09	0.231
Shock			
No vs. yes	2.13	1.05–4.29	0.035
Tumor rupture			
Yes vs. no	0.91	0.60–1.38	0.659

AFP, alpha-fetoprotein.

associated with poor long-term survival include Child-Pugh class B/C, presence of portal venous thrombosis, and absence of shock. Our results suggest it may be inaccurate to classify all HCC patients with tumor ruptures as stage T4.

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