



# Impact of spontaneous rupture on the survival outcomes after liver resection for hepatocellular carcinoma: A propensity matched analysis comparing ruptured versus non-ruptured tumors



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## ABSTRACT

**Introduction:** Spontaneous rupture of HCC (srHCC) is a life-threatening sequela of HCC characterized by a high mortality. Liver resection (LR) is the ideal therapeutic strategy as it not only arrests hemorrhage but also remove the offending tumour. We sought to determine the impact of spontaneous rupture on the survival outcomes of patients after LR by performing a propensity score matched (PSM) analysis comparing patients who underwent LR for srHCC versus non-ruptured (nrHCC).

**Methods:** From 2000 to 2015, a total of 67 patients who underwent LR for srHCC which met the study criteria were included. 1:2 PSM was performed comparing 49 of 67 patients with srHCC with 98 nrHCC selected from a cohort of 724 patients who underwent LR during the study period.

**Results:** Median survival following LR for srHCC was 21.9 months, while 5-year overall survival (OS) and disease-free survival (DFS) was 43.1% and 19.4% respectively. After 1:2 PSM analysis, there was no significant difference between LR for srHCC (n = 49) versus nrHCC (n=98) in terms of OS [21.9 (interquartile range (IQR), 11.8–44.0 vs 27.4 (IQR, 6.9–57.8) months, HR 1.02, CI 0.63–1.66, p = 0.94], DFS [11.8 (IQR, 5.6–25.6) vs 13.77 (IQR, 4.5–34.9) HR 0.74, CI 0.54–1.02, p = 0.06] and length of stay [8 (IQR, 7–11) vs 7 (IQR, 6–10) HR 0.93, CI 0.068–1.29], p = 0.68].

**Conclusion:** LR for clinically stable patients with srHCC provides survival and recurrence outcomes that are comparable to patients with nrHCC.

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## Introduction

Hepatocellular Carcinoma (HCC) is the most common primary liver malignancy in the world with approximately 500,000 cases diagnosed annually [1]. Spontaneous tumour rupture (srHCC) occurs in up to 20% of these cases and can result in massive intraperitoneal hemorrhage, with reported mortality rates of over 25% [2–12]. In the event that life-threatening hemorrhage is successfully controlled, tumour rupture frequently impacts patient survival negatively by causing intraperitoneal tumour seeding and

peritoneal metastases.

The initial management of srHCC is early resuscitation of the patient and adequate tumoral hemostasis [11]. Various treatment options have been proposed for the management of srHCC. The decision to employ transarterial embolization (TAE), surgical resection (upfront or staged) or conservative management depends on multiple factors, primarily centred upon the hemodynamic stability of the patient [11], availability of facilities and expertise as well as the overall oncologic and survival benefit of the undertaken treatment modality. In the ideal clinical scenario, liver resection (LR) is the optimal treatment modality for srHCC as it not only achieves hemostasis, but also potentially curative resection. LR can be performed as an emergency or staged procedure following initial hemostasis (e.g. TAE) and when carefully applied to selected patients,

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long-term survival can be achieved [12–16]. One of the contentious points in srHCC is the true impact of tumour rupture on the survival outcomes of patients. Several of the earlier cases series reporting poor outcome of surgical intervention for srHCC are confounded by the inherent heterogeneity of the patient populations, with a significant percentage of the sample population having extensive multifocal disease or poor liver function [5,10]. Since then, several studies have shown that tumour rupture per se does not always negatively impact survival. Furthermore, assignment of T4 disease to all srHCC may be overstating the severity of the disease [17]. Thus, where feasible, patients with srHCC should potentially not be denied a potentially curative surgical resection [15,18–21].

Given the controversies surrounding the true impact of tumour rupture on HCC, we sought to critically appraise the role of LR in the management of srHCC using a propensity matched analysis. The primary objective of this study is to determine the impact of spontaneous rupture on the survival outcomes of patients after LR. The secondary objective was to identify prognostic factors following LR for srHCC.

## Methods

From 2000 to 2015, a total of 88 patients were identified to have undergone LR for srHCC. Following exclusion of patients who had previous interventions for HCC and missing data (Table 2), a total of 67 patients were included in the final analysis. Clinicopathologic data were retrospectively collected and analysed after a propensity matched analysis. The control group used for comparison was selected from 724 consecutive patients who underwent LR for primary non-ruptured HCC (nrHCC) during the study period.

Spontaneous rupture was defined as an event occurring in the absence of abdominal trauma or iatrogenic injury to the hepatoma. The diagnosis of srHCC was confirmed either via contrast enhanced Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of the abdomen showing features of active contrast extravasation from the liver tumour or intraoperative findings of tumour rupture and hemoperitoneum. All resected specimens were histologically confirmed to be ruptured HCC.

Routine hematologic and biochemical investigations were performed prior to surgery which included a complete blood count, renal panel, liver function test, coagulation profiles as well as a screen for hepatitis serology (Hepatitis B and/or C). Assessment of liver function was determined via calculation of the Child-Pugh score.

### Data collection

Patient clinico-demographic, hematologic as well as biochemical variables were collected from a prospectively maintained electronic clinical database (Sunrise Clinical Manager, version 5.8, Eclipsys Corporation, Atlanta, Georgia). Tumour specific characteristics such as size, grade, margins, presence of cirrhosis, number of nodules, presence of satellite lesions, major vascular (defined as either portal or hepatic vein invasion) and microvascular invasion were determined based on histopathologic examination and information was extracted from the aforementioned clinical database. Tumour grading was based on a system as described by Edmondson and Steiner on a scale of 1–4, a high-grade tumour is defined as one that is either grade 3 or 4.

All patient's pre-operative health status was determined via the American Society of Anaesthesiologist (ASA) physical status classification system. Operative variables including duration of surgery, total blood loss, volume of blood transfusion, ASA status as well as type of liver resection were extracted from an institution electronic operative database (Operating theatre management (OTM), IBM, Armonk, New York). Hemodynamic instability at presentation as

defined as either a systolic blood pressure of <90 mmHg or heart rate of >100. Major liver resection was defined as resection of  $\geq 3$  Couinaud liver segments while a minor resection is one that involves resection of fewer than 3 segments. Rupture type was defined as either sealed or free intraperitoneal rupture; the former refers to srHCC that is walled off in the abdominal cavity by adjacent structures (E.g. Omentum, Surface of Diaphragm etc) while the latter refers to free intra-peritoneal rupture. End-points of this study were overall-survival and disease-free survival. The former was defined as time from which partial hepatectomy for srHCC was performed until death from any cause or till conclusion of the observation period whereas the latter was determined from time of partial hepatectomy until recurrent disease was detected or until conclusion of the observation period.

### Follow up

All patients were followed up at intervals of 3–6 months after surgery with either contrast CT imaging of the abdomen, MRI of the liver or if indicated, an ultrasound of the liver. The diagnosis of recurrence was based on typical findings of HCC on CT or MRI.

### Statistical analysis

Continuous patient demographic and clinical characteristic variables were summarized as median (interquartile range) and compared between ruptured and non-ruptured study groups using the Wilcoxon rank-sum test. Categorical variables were summarized as frequency (percentage) and compared between groups using Fisher's exact test.

Association between patient demographic and clinical variables and study outcome variables overall survival and disease-free survival were initially investigated using univariate Cox regression, with variables significant at  $p < 0.2$  entered as candidate variables into a selection list of a multivariable Cox regression analysis. Survival curves were calculated using the Kaplan-Meier method.

Comparisons of overall survival (OS) and disease-free survival (DFS) between the ruptured and non-ruptured study groups incorporated propensity score matching among patients to assure comparability among the groups relative to measured potential confounders owing to differences between baseline patient characteristics, biochemical and histopathologic indices that might have influenced prognosis on srHCC patients. The following variables were included in the propensity model: age, gender, hepatitis status, cirrhosis, tumour grade, ALT, AST, ASA status, child status, tumour size, number of nodules, type of resection (major vs minor resection), microvascular invasion, major vascular involvement, serum creatinine, platelet count, transfusion amount and AJCC TNM stage (negating rupture factor). Propensity score matching (PSM) among patients was performed using a 1:2 ratio of srHCC to non-ruptured HCC (nrHCC) patients, with matching patients selected without replacement using a caliper width of 0.1. Fifty of 67 srHCC were matched with 100 of 724 nrHCC. The marginal Cox regression approach [40] was employed to identify risk factors associated with overall survival and disease-free survival while taking into the correlation among patients within matching clusters. All reported  $p$ -values are two tailed and statistical significance was set at  $p < 0.05$ . All statistical analyses were done using SAS software version 9.4 (SAS institute, Cary, NC, US).

## Results

### Clinicopathologic characteristics

Clinicopathologic and demographic features of pre and post-

**Table 1**  
Patient and disease demographics of patients with rHCC and nrHCC (after matching).

Clinical variables	srHCC (n = 67)	srHCC (n = 49)	nrHCC (n = 98)	p-value <sup>a</sup>
Male Gender	57 (85.1)	42 (85.7)	86 (87.8)	DNC/0.7959
Age (yr)	65 (59–74)	64 (56–72)	66.3 (58.0–73.0)	0.6594/0.7828
ASA status				0.9139/0.6765
ASA 1	1 (1.5)	1 (2)	5 (5.1)	
ASA 2	42 (62.7)	33 (67.3)	64 (65.3)	
ASA 3	23 (34.3)	14 (28.6)	27 (27.6)	
ASA 4	1 (1.5)	1 (2.0)	2 (2.0)	
Cirrhosis	21 (31.3)	19 (38.8)	32 (32.7)	0.4913/0.4687
Child Pugh Classification				0.6532/0.6787
A	46 (68.7)	37 (75.5)	77 (78.6)	
B	21 (31.3)	12 (24.5)	21 (21.4)	
Hepatitis status	29 (43.2)	29 (59.2)	66 (67.3)	0.3395/0.3632
Tumour size (mm)	95 (60–140)	85 (55–110)	76.5 (40–120)	0.9805/0.6341
Number of nodules	1(1–1)	1 (1–1)	1 (1–1)	0.9736/0.7345
High grade (Grade 3 or 4)	36 (53.7)	28 (57.1)	46 (46.9)	0.2332/0.2946
Major resection	33 (49.3)	21 (42.9)	46 (46.9)	0.6411/0.7261
Microvascular invasion	43 (64.2)	27 (55.1)	47 (48.0)	0.3562/0.4850
Major vascular invasion	12 (17.9)	7 (14.2)	11 (11.2)	0.5777/0.6016
Platelet (x 10 <sup>9</sup> )	244 (174–329)	225 (174–296)	224 (165–296)	0.8876/0.7677
Serum AST (U/L)	54(32.5–79.5)	50 (30–68)	49.5 (30–81)	0.4387/1.0000
Serum ALT (U/L)	29 (21.5–53)	30 (21–57)	38 (27–56)	0.6537/0.1559
Bilirubin (μmol/L)	17 (12–21)	16 (12–21)	16 (12–20)	0.4878/0.4752
TNM	2(1–2)	2 (1–2)	2 (1–2)	0.8005/0.7900
Prothrombin time (Sec)	11.3 (10.6–12.5)	11.40 (10.7–12.1)	10.9 (10.4–11.5)	0.0044/0.0039
Albumin (g/L)	34 (28.8–38.3)	34 (30–39)	36 (32–40)	0.0764/0.2096

Note: Categorical variables are summarized as n (%), and continuous variables as median (IQR).  
Abbr.: DNC = Did not converge to a solution.

<sup>a</sup> Adjusted/unadjusted p-values for correlation due to 2:1 propensity score matching of controls for each case. Adjusted p-values are from generalized mixed model analysis on logarithms of continuous variables (normalizing transformation required except for age) with matched clusters as random effects and ruptured/non-ruptured groups as a fixed effect. Categorical variables were modelled using binomial or multinomial outcome distributions and logit or generalized logit links. Unadjusted p-values are from Wilcoxon rank-sum tests on continuous and count variables and Fisher's exact test on categorical variables.

**Table 2**

Characteristics of patients excluded from the final analysis.

Transarterial chemoembolization (TACE)	4
Transarterial embolization (TAE)	4
Radiofrequency ablation (RFA)	1
Chemotherapy	1
Rupture from tumour recurrence	2
Missing data	9

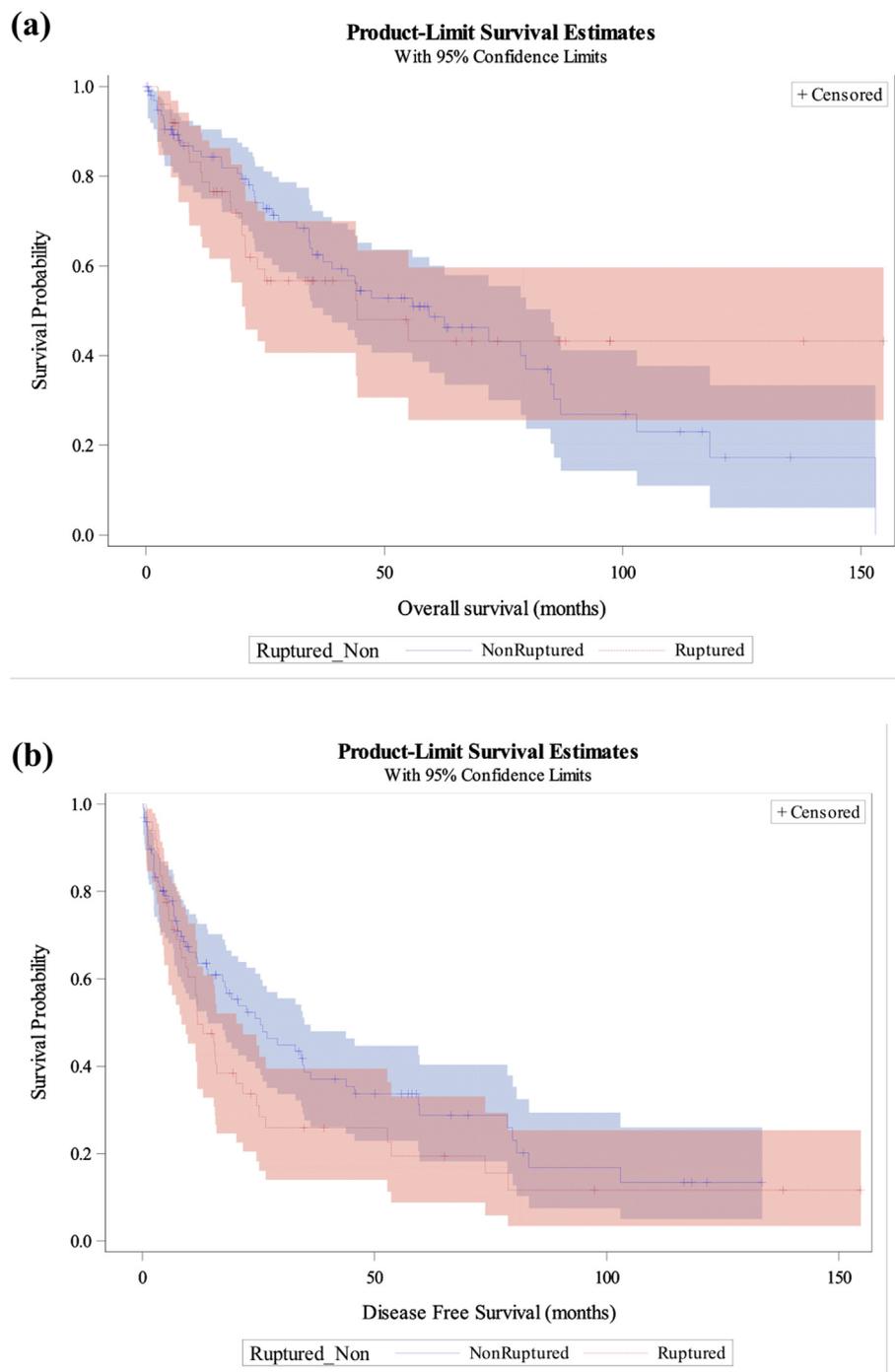
propensity matched cohorts are summarized in [Table 1](#). A total of 67 consecutive patients undergoing single stage LR for srHCC at the Singapore General Hospital were identified. Among them, a total of 57 (85.1%) were male. The median age of presentation was 65 years (range, 59–74 years). Hepatitis B and C positivity were identified in 29 (43.2%) and 7 (10.4%) patients respectively. Cirrhosis was noted in 21 (31.3%) of patients while 46 (68.7%) patients had Child's A liver

function. Majority of patients had a pre-operative ASA status of 2 (n = 42, 62.7%). Only 7 patients (10.4%) were noted to have hemodynamic instability from srHCC at presentation. For the hemodynamically unstable patients, the median time interval to surgery was 1 day (Range 1–3 days).

Major hepatic resection was performed in 33 (49.3%) patients. Major vascular and microvascular invasion were present in 12 (17.9%) and 43 (64.2%) patients. Median tumour size was 95 mm (range, 60–140 mm) and 33 (49.3%) had a tumour size >10 cm. Sealed rupture was noted in 30 (46.3%) patients. Among the resected HCC specimens, 36 (53.7%) were found to have high grade features.

#### Survival analysis

[Fig. 1a](#) and [b](#) demonstrates the Kaplan Meier survival curves for OS and DFS comparing the srHCC and PSM nrHCC. The 1, 3 and 5-



**Fig. 1.** Kaplan meier estimates of (a) Overall Survival (OS) and (b) Disease Free Survival (DFS) following partial hepatectomy for srHCC.

year OS was 78.7%, 56.7% and 43.1% for the ruptured group respectively (median, 21.9 months) and 84.3%, 62.4% and 48.6% for the non-ruptured group (median, 27.4 months) (log-rank p-value, 0.44). The 1, 3 and 5-year DFS for the srHCC was 49.6%, 25.8% and 19.4% respectively (median, 11.8 months) and 63.5%, 38.6% and 28.9% respectively (median, 13.8 months) for the non-ruptured group (log-rank p-value, 0.12). Median length of stay for srHCC and nrHCC was 8 and 7 days respectively (log-rank p-value, 0.68).

#### Propensity-score matched analysis

Table 3 summarises the outcome measures of patients undergoing LR for both srHCC and nrHCC prior to and after propensity matched analysis. Before propensity scoring both OS (HR 2.27, CI 1.43–3.60,  $p < 0.01$ ) and DFS (HR 2.00, CI 1.25–3.20,  $p < 0.01$ ) were significantly shorter in the nrHCC group. In contrast, the length of stay (LOS) was longer in the srHCC group compared to the nrHCC group, although this was not statistically significant (HR 0.77, 0.56–1.06,  $p = 0.11$ ). Following propensity matched analysis,

**Table 3**  
Outcomes following propensity matched analysis for ruptured and non-ruptured HCC following partial hepatectomy.

Outcomes before propensity matched analysis for ruptured and non-ruptured HCC following partial hepatectomy				
	srHCC (n = 67)	nrHCC (n = 724)	HR, 95% CI	p-value
Overall survival (median, IQR), m	1023.4 (5.8–35.2)	40.2 (15.9–71.8)	2.27 (1.43–3.60)	<0.01
Disease free survival (median, IQR), m	8.4 (3.7–20.2)	20.7 (7.2–49.7)	2.00 (1.25–3.20)	<0.01
Length of stay (median, IQR), m	8 (6–11)	6 (5–9)	0.77 (0.56–1.06)	0.11
Outcomes following propensity matched analysis for ruptured and non-ruptured HCC following partial hepatectomy				
	srHCC (n = 49)	nrHCC (n = 98)	HR, 95% CI	p-value
Overall survival (median, IQR), m	21.9 (11.77–44.03)	27.4 (6.9–57.8)	1.02 (0.64–1.66)	0.94
Disease free survival (median, IQR), m	11.8 (5.6–25.6)	13.77 (4.5–34.9)	0.74 (0.54–1.02)	0.06
Length of stay (median, IQR), d	8 (7–11)	7 (6–10)	0.93 (0.68–1.29)	0.68

there was no statistically significant difference in OS (HR 1.02, CI 0.64–1.66,  $p = 0.94$ ), DFS (HR 0.74, CI 0.54–1.02,  $p = 0.06$ ) and LOS (HR 0.93, CI 0.68–1.29),  $p = 0.68$ ).

#### Predictors of overall survival and disease-free survival in srHCC

Tables 4 and 5 summarises the clinicopathologic variables that affect OS or DFS. On univariate analysis it was identified that a positive tumour margin post-LR, absolute tumour size, tumour size >10 cm and alpha-feto protein (AFP) levels were independent predictors of both OS and DFS. Additional variables on univariate analysis associated with poorer OS are patient's child status and creatinine levels whereas variables associated with poorer DFS were microvascular invasion and bilirubin levels (All variables  $p < 0.05$ ).

In the multivariable Cox-regression analysis, only a positive tumour margin post-LR was associated with both a poorer OS (HR 10.439, CI 2.136–51.012,  $p = 0.0038$ ) and DFS (HR 5.776, CI 1.577–21.147,  $p = 0.0081$ ). In terms of DFS, elevated bilirubin was additionally found to be a negative predictor (HR 1.061, CI 1.019–1.105,  $p = 0.0043$ ) whereas absolute tumour size (HR 1.459, CI 1.202–1.771,  $p = 0.0001$ ), creatinine (HR 1.012, CI 1.001–1.023,  $p = 0.0322$ ), need for blood transfusion (HR 5.445, CI 1.842–16.095,

$p = 0.0022$ ), platelet count (HR 0.991, CI 0.985–0.997,  $p = 0.0032$ ), Child's status (HR 10.545, CI 2.368–46.956,  $p = 0.0020$ ) and AFP (HR 1.000, CI 1.000–1.000,  $p = 0.0010$ ) were found to negative predictors of OS on multivariable analysis.

#### Discussion

Traditionally, srHCC has been considered a terminal event with an extremely poor prognosis [10]. Despite advances in the management of HCC in general, tumour rupture remains a formidable clinical challenge to surgeons. The optimal management plan is contingent on the hemodynamic status of the patient, extent of tumour burden as well as the patient's underlying liver function. Transarterial embolization (TAE) has been described as effective minimally invasive procedure to control hemorrhage, particularly in a hemodynamically unstable patient [22] while allowing a proper workup of a patient's tumour burden and optimization of the patient's general status [23,24]. Traditionally viewed as a destination therapy for the once perceived terminal event of HCC, currently TAE is increasingly considered as a bridge to subsequent potentially curative surgery in selected patients.

An early study published at our institution [11] revealed that surgery was associated with better 30-day survival when compared

**Table 4**  
Univariate analysis of factors associated with overall survival and disease-free survival in patients with srHCC.

Variable	Overall survival HR (95% CI)	P-value	Disease-free survival HR (95% CI)	P-value
Age (years)	0.993 (0.960–1.027)	0.6727	0.989 (0.962–1.017)	0.4395
Hepatitis B positivity	1.309 (0.660–2.595)	0.4404	1.001 (0.562–1.783)	0.9981
Hepatitis C positivity	1.076 (0.372–3.115)	0.8921	1.238 (0.508–3.020)	0.6386
Child Pugh status	2.516 (1.229–5.151)	<b>0.0116</b>	1.758 (0.918–3.367)	0.0888
Cirrhosis	1.239 (0.619–2.480)	0.5450	1.224 (0.665–2.254)	0.5164
Tumour size (cm)	1.096 (1.020–1.179)	<b>0.0126</b>	1.095 (1.025–1.169)	<b>0.0067</b>
Tumour >10 cm	2.334 (1.147–4.749)	<b>0.0193</b>	2.340 (1.274–4.298)	<b>0.0061</b>
High grade	0.881 (0.449–1.730)	0.7136	0.909 (0.511–1.617)	0.7453
Multinodularity	1.678 (0.800–3.520)	0.1712	1.435 (0.740–2.782)	0.2856
Satellite lesions	2.024 (0.979–4.188)	0.0572	1.649 (0.863–3.152)	0.1302
Microvascular invasion	1.893 (0.909–3.938)	0.0880	1.994 (1.066–3.728)	<b>0.0307</b>
Major vascular invasion	1.925 (0.832–4.452)	0.1257	1.618 (0.748–3.501)	0.2216
Rupture type (sealed vs free)	1.203 (0.601–2.407)	0.6011	1.308 (0.728–2.348)	0.3694
Type of resection (major vs minor)	1.492 (0.756–2.944)	0.2485	0.979 (0.551–1.741)	0.9434
Margin involvement	5.686 (2.176–14.861)	<b>0.0004</b>	3.455 (1.289–9.260)	<b>0.0137</b>
Shock	1.515 (0.573–4.010)	0.4026	1.658 (0.681–3.987)	0.2677
Blood loss (mls)	1.000 (1.000–1.000)	0.6824	1.000 (1.000–1.000)	0.8358
Need for transfusion	1.748 (0.857–3.563)	0.1245	1.619 (0.879–2.984)	0.1222
Albumin (g/dl), Continuous	0.969 (0.924–1.017)	0.2005	0.985 (0.947–1.024)	0.4508
Bilirubin (umol/L), Continuous	1.031 (0.993–1.071)	0.1108	1.050 (1.020–1.082)	<b>0.0011</b>
Creatinine (umol/L), Continuous	1.006 (1.001–1.011)	<b>0.0106</b>	0.989 (0.978–1.001)	0.0633
Prothrombin time (seconds), Continuous	1.201 (0.956–1.509)	0.1149	1.185 (0.982–1.431)	0.0773
Platelet count ( $\times 10^9$ ), Continuous	1.002 (0.999–1.006)	0.1471	1.002 (0.999–1.005)	0.1161
AFP (ug/L), Continuous	1.000 (1.000–1.000)	<b>0.0036</b>	1.000 (1.000–1.000)	<b>0.0375</b>
AST (U/L), Continuous	1.001 (0.998–1.004)	0.4429	1.001 (0.999–1.003)	0.3559
ALT (U/L), Continuous	0.999 (0.993–1.005)	0.7705	1.000 (0.995–1.005)	0.9342

**Table 5**  
Multivariable analysis of variables associated with overall survival and disease-free survival in patients with srHCC.

Variables	Overall Survival			Disease Free Survival		
	Hazard Ratio	95% CI	P-Value	Hazard ratio	95% CI	P-Value
Tumour size (cm)	1.459	1.202–1.771	<b>0.0001</b>	1.081	0.998–1.171	0.0556
Margin involvement	10.439	2.136–51.012	<b>0.0038</b>	5.776	1.577–21.147	<b>0.0081</b>
Creatinine	1.012	1.001–1.023	<b>0.0322</b>	0.983	0.965–1.003	0.0890
Tumour size >10 cm	3.610	0.979–13.333	0.0537			
Need for transfusion	5.445	1.842–16.095	<b>0.0022</b>			
Platelet count (x 10 <sup>9</sup> )	0.991	0.985–0.997	<b>0.0032</b>			
Child status	10.545	2.368–46.956	<b>0.0020</b>			
AFP (ug/L)	1.000	1.000–1.000	<b>0.0010</b>			
Prothrombin time (seconds)				1.192	0.925–1.536	0.1745
Bilirubin (umol/L)				1.061	1.019–1.105	<b>0.0043</b>

with medical therapy or TAE. Since then, supporting literature has similarly challenged traditional dogma and advocated surgical resection after analysis of their results showed outcomes far exceeding that of conservative treatment [25,26] or locoregional embolization therapeutic procedures [26]. On the other hand, some consider surgery to be too aggressive for too little benefit in patients with srHCC, based only on limited studies confounded by heterogeneity and selection bias [5,10]. Studies comparing outcomes between patients with srHCC and nrHCC have also been inconsistent; with several studies reflecting poorer outcomes [17,27–29] following srHCC while others fail to find such an association [16,19,30]. In light of this, we performed a PSM analysis to evaluate the true impact of tumour rupture on HCC survival outcomes. As shown by our data, there were no differences in terms of OS, DFS, LOS and 90-day mortality between patients with srHCC, with similarly matched nrHCC suggesting that patients who undergo hepatectomy for srHCC may benefit from outcomes not dissimilar from nrHCC. These findings echoed three earlier studies that similarly performed propensity scoring to account for potential confounders, all of which similarly reported no difference in overall survival or disease-free survival between patients with srHCC versus those with nrHCC [18,20,22]. The 3 and 5-year OS in our study was 52% and 40% respectively, and this was not observed in earlier studies reporting only conservative or locoregional therapies [25,26].

HCC is a highly vascular tumour and srHCC often represents a state of advanced tumour burden and poor liver function [27]. As with the principles in surgical management of HCC, an adequate functional reserve is necessary before curative resection can be offered [31–33] with an aim to achieve an adequate negative resection margin. In this present study, the presence of a positive surgical margin was an independent negative predictor of both poorer overall survival (OS) and disease-free survival (DFS) and is similarly supported by findings of previous studies [34–37]. Multivariable analysis has also identified elevated bilirubin levels to be an independent predictor of poorer DFS whereas absolute tumour size, serum creatinine, need for blood transfusion, child's status and AFP were found to be independent predictors of poorer OS.

The association between tumour size and risk of spontaneous rupture has been described by several authors [27,29,38] but the impact of tumour size on survival and recurrence in srHCC is less clear. In our study, the median tumour size for patients with srHCC was 95 mm and falls into the category of what most would consider “large” HCC [39]. Tumour size has been long viewed as an important predictor of survival [40], although this may be attributed to other associated confounding factors such as multifocality, higher tumour grade and vascular invasion [39–41] rather than absolute tumour size per se. In addition, larger tumour sizes may also be

correlated with increasing serum concentrations of AFP [42–45] which have also been shown in this study and others to negatively impact survival [46,47]. Although this present study similarly suggests a negative association between increasing tumour size and survival in patients with srHCC undergoing hepatectomy, its true relevance in the context of srHCC to overall survival remains uncertain.

The operative mortality in cirrhotic patients undergoing liver resection for HCC is known to be higher [35,47,48] and is reaffirmed by this present study; patients with higher Child's Pugh status were associated with a poorer overall survival post liver resection and these findings were consistent with studies published elsewhere [20,49,50]. Other prognostic factors such as an elevated bilirubin and creatinine levels have also likewise been shown previously to negatively influence survival in srHCC [51,52]. It has been suggested that patients with srHCC and Child's B liver function avoid surgery in view of its risk for poorer outcomes [20]. Nonetheless, our series seem to reflect a subgroup of patients with Child's B liver function that seem to benefit from operative intervention: such patients tended to have lower tier Child's B scores (median score = 7) and the majority underwent minor hepatectomy. These findings appear to corroborate with several other studies [13,53,54] and highlight the importance of careful patient selection amongst those with impaired liver function.

All patients in our series had undergone a single-stage hepatectomy. Generally, single-stage hepatectomy for srHCC draws concerns given the indeterminate nature of liver functional reserve; coupled with the patient's hemodynamic instability and systemic coagulopathy, an inadvertent vicious cycle is created which worsens liver function and subsequently precludes patients for surgical resection [5,55]. It is therefore imperative to identify, ideally in a pre-operative context, patients who would benefit most from upfront surgical resection in srHCC in order to avoid futile surgery. In a recent study published by our institution [56], an AFP >200 ng/ml was identified to be a pre-operative predictor of early mortality while a tumour size of >10 cm and free tumour rupture (defined as tumour rupture that is not walled off by adjacent structures) was found to be a predictor of early tumour recurrence. The risk of tumour recurrence was much higher in patients with both pre-operative predictors. The findings of this propensity matched analysis, coupled with the available pre-operative predictors, provides improvement in the selection of patients with srHCC who potentially benefit from curative resection.

In the present surgical series, only 7 patients (10.4%) with srHCC was unstable at presentation but these 7 patients responded to conservative resuscitative measures and recovered well enough to undergo surgery. In general, patients who persistently unstable after rupture of HCC will benefit from emergent TAE for initial stabilisation [22,57]. In an attempt to improve patient homogeneity

our study did not evaluate the group of hemodynamically unstable patients who had initial TAE for hemostasis. As such, the impact of patient hemodynamic stability in relation to survival and/or recurrence may not have been accurately reflected. Nonetheless, it is in our experience that patients with srHCC and hemodynamic instability prioritize resuscitative efforts with a focus on early hemostasis using TAE; the overall benefit of emergency one-stage hepatectomy for such patients remains to be conclusively elucidated.

This paper has several limitations; firstly, the study is retrospective and hence subject to potential confounders and biases. We attempted to minimize this effect by performing a propensity matched analysis of known confounding factors. Ideally, a randomized controlled trial (RCT) would be preferred to minimize biases that would otherwise be encountered in observational studies. However, performing an RCT in this setting would be impractical, given that srHCC is a relatively uncommon event; furthermore, the setting of srHCC means that patients are often managed emergently and the process of identification, recruitment and randomization may result in clinically unacceptable treatment delays. Secondly, given that this is a single centre study coupled by the uncommon occurrence of srHCC, our sample size is small which may give rise to type 2 errors. Thirdly, because srHCC is a rare event and some of these may even be clinically silent depending on the extent of rupture and hemorrhage, a complete spectrum of srHCC is difficult to fully elucidate. However, as this study is confirmed by detailed pathological examination of all surgically resected specimens, we believe it represents an accurate picture of the true survival of srHCC. Finally, it is important to emphasize that the patient in this surgical series consisted of a well-selected subset of patients with srHCC which had a well-preserved liver function and did not require preoperative treatment prior to LR and hence these results would likely not be applicable to all patients presenting with srHCC.

In conclusion, our study demonstrates that LR should be offered for the clinically stable patient with srHCC, the survival benefit of surgery approaches that of nrHCC. Identification of negative predictors of poor outcomes can give invaluable information in the consideration for surgery.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejso.2019.03.044>.

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