Article published online: 2021-07-22

Outcome of conventional transarterial chemoembolization (cTACE) in the management of spontaneously ruptured hepatocellular carcinoma

Yashwant Patidar, Rohit Khisti, Ankusha Yadav, Amar Mukund, Shiv K Sarin[1]

Departments of Interventional Radiology and [1]Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

Correspondence: Dr. Yashwant Patidar, Department of Interventional Radiology, Institute of Liver and Biliary Sciences, D-1 Vasant Kunj, New Delhi - 110 070, India. E-mail: dryashwantpatidar@gmail.com

Abstract

Background and Objectives: Hepatocellular carcinoma (HCC) is a highly vascular tumor and mortality after spontaneous rupture of HCC remains considerably high. There are no definitive guidelines for the management of ruptured HCC and no fixed protocol has been proposed in the literature. We evaluated the outcome of conventional transarterial chemoembolization (cTACE) in the management of spontaneously ruptured HCC and factors affecting the outcome of cTACE. **Materials and Methods:** This is a single center retrospective study analyzing the outcome of patients presenting with spontaneous rupture of HCC who received cTACE from January 2014 to June 2017. These patients were followed up periodically for clinical and imaging findings to ascertain the technical effectiveness along with survival. **Results:** Sixteen patients were identified who received cTACE for ruptured HCC. Majority of the patients (81.3%) had abdominal pain, while 25% had hypovolemic shock at initial presentation. Complete response and partial response were seen in 35.7% and 57.1% of patients, respectively. One patient (7.1%) showed progressive disease in form of peritoneal spread along the liver surface. The overall cumulative survival rates at 30 days, 180 days, and at 1 year were 87.5%, 72.2%, and 54.1%, respectively. **Conclusion:** cTACE is safe in patients with spontaneous HCC rupture and it leads to immediate hemostasis along with overall survival advantage. Achieving quick hemostasis may be a key to better outcome.

Key words: Conventional transarterial chemoembolization; hepatocellular carcinoma; ruptured hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is a highly vascular tumor that almost always occurs in the setting of liver cirrhosis. It is the fifth most common cancer in the world and is gradually increasing.[1] In western countries, though the incidence of HCC is on a rise, but incidence of ruptured HCC remains low, with an incidence of <3%. In Asian countries, the incidence is relatively high with reported rates of 2.3–26%.[2] However, with better surveillance and earlier detection of HCC, the incidence of ruptured HCC is gradually decreasing.

The outcomes of ruptured HCC are usually poor. Mortality after spontaneous rupture of HCC remains considerably

Access this article online	
Quick Response Code:	Website: www.ijri.org
	DOI: 10.4103/ijri.IJRI_252_18

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Cite this article as: Patidar Y, Khisti R, Yadav A, Mukund A, Sarin SK. Outcome of conventional transarterial chemoembolization (cTACE) in the management of spontaneously ruptured hepatocellular carcinoma. Indian J Radiol Imaging 2019;29:177-81.

high. There are no definitive guidelines for the management of ruptured HCC and no fixed protocol has been proposed. In patients with unresectable tumors, conventional transarterial chemoembolization (cTACE) is a reasonable approach as it obtains immediate hemostasis and provides survival as well by causing tumor necrosis.

The objectives of this study were to study outcome of patients with spontaneously ruptured HCC managed by cTACE and to evaluate the factors affecting the outcome of cTACE.

Materials and Methods

Patient population

In this single center retrospective study, data of all patients receiving TACE from January 2014 to June 2017 were evaluated. Sixteen patients were identified in which cTACE was performed for spontaneously ruptured HCC. Diagnosis in these patients was based on clinical features like sudden abdominal pain, hypovolemic shock, abdominal distension and multiphasic dynamic contrast-enhanced (CE) abdominal computed tomography (CT), or magnetic resonance imaging (MRI) with characteristic findings of a ruptured HCC [Figure 1]. Typical finding included presence of hepatic tumor with features of HCC associated with either of the following: peritumoral or paratumoral active contrast extravasation, discontinuity of tumor capsule with high attenuating perihepatic or intraperitoneal fluid accumulation.

Methods

Clinical characteristics and data collection

Clinical, laboratory, and radiological data along with outcomes were collected from electronic medical records for all patients included in this study. Clinical data included age, sex, time of rupture, presenting symptoms, presence of shock (systolic blood pressure <90 mmHg), and etiology of cirrhosis, and presence of ascites, jaundice, and hepatic encephalopathy (grade 2 or more). The diagnosis of liver cirrhosis was made on the basis of a history of ascites, hepatic encephalopathy, jaundice, or variceal bleeding (hepatic decompensation) and the presence of clinical signs or endoscopic evidence of portal hypertension as well as radiological examinations consistent with liver cirrhosis.

Laboratory data including serum levels of alanine/aspartate aminotransferase (SGOT/SGPT), total bilirubin, albumin, INR, alpha-fetoprotein, hemoglobin, creatinine, Child–Pugh score, and MELD score on presentation were collected. Tumor characteristics included number of tumors, lobar distribution of lesions, and diameter of the largest tumor.

Exclusion criteria for this study were: Patients with Child–Pugh Class C, total bilirubin level >5 mg/dl, main portal vein thrombosis, uncontrolled systemic infection, refusal to TACE, TACE using drug eluting bead TACE (DEB TACE).

Procedure

Patients with a ruptured HCC received cTACE within a span of 2–6 h of diagnosis. The protocol for managing these patients include: initial fluid resuscitation, hemodynamic stabilization, and symptom management along with performance of CECT/CE-MRI within 24 h of presentation to emergency department. After clinical, imaging and laboratory evaluation of patients, super selective cTACE procedure was performed. cTACE was done using a mixture of epirubicin and iodized oil (lipiodol) injected under fluoroscopic control. After injecting the drug-lipiodol mixture, embolization of the target artery was performed using gelfoam/polyvinyl alcohol particles (PVA) until stasis of contrast was demonstrated [Figure 2]. In case of multiple tumors, TACE was done only for the ruptured lesion. In patients surviving after 1 month, other lesions were subsequently managed according to their Barcelona Clinic Liver Cancer (BCLC) stage.

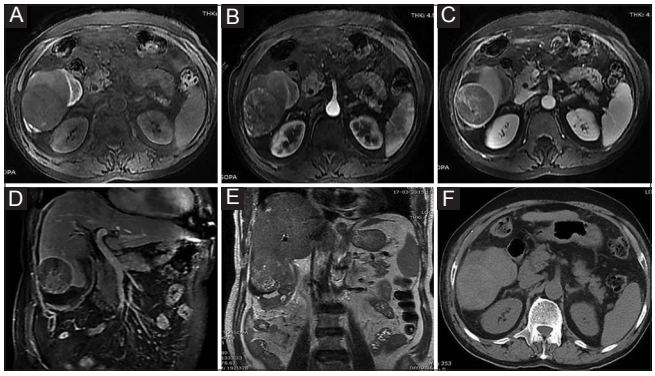

Figure 1 (A-F): Magnetic resonance imaging upper abdomen in unenhanced fat saturated T1W (A), axial contrast-enhanced fat saturated images in the arterial (B), and portal venous phase (C) showing a large partially exophytic well-encapsulated lesion in segment-VI of liver displaying arterial phase enhancement and washout in portal venous phase suggestive of hepatocellular carcinoma with associate T1 hyperintense perilesional fluid suggest rupture. Coronal post-contrast delayed venous phase T1W image (D) and T2W coronal image (E) shows discontinuity along the inferior capsular margin of lesion with subcapsular collection further confirm the finding. Axial non-contrast computed tomography scan image (F) at same level also shows lesion with perilesional hyperdense fluid collection

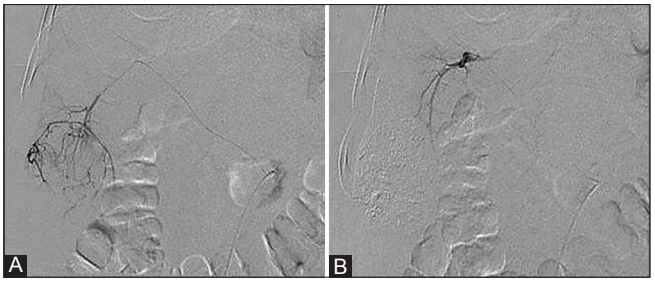

Figure 2 (A and B): Pre-TACE angiographic image after super selective cannulation of posterior branch of right hepatic artery showing tumor blush (A) and Post- TACE angiographic image showing uniform deposition with lipiodol mixed with drug in the tumor and stasis in the tumor feeding vessel (B)

Survival time from the diagnosis and TACE for spontaneously ruptured HCC were collected from hospital records.

Follow up

Tumor response to TACE was assessed by multiphasic CECT/MRI according to modified RECIST (response evaluation criteria for solid tumors) criteria [Figures 3 and 4] for all patients with >30 days survival. On the basis of tumor response at 1 month further treatment and follow-up was planned. A repeat TACE was offered to patients showing partial response with preserved liver functions and no contraindications.

Statistical analysis

Results are expressed as mean or percentages. All statistical analyses were performed by using a statistical software program (SPSS20; SPSS, IMB Corp. Limited, Armonk). Kaplan–Meier method was used to estimate the overall survival rate.

Results

A total of 16 patients with ruptured HCC who underwent primary cTACE were included in this study (mean age – 59 years, M: F = 3:1). The clinical data of these patients are summarized in Table 1. Successful cTACE was performed within a mean time of 3.2 h of diagnosis (range 2–6 h) with imaging evidence of hemostasis and complete coverage of tumor by lipiodol seen in all patients.

Most common etiology for liver cirrhosis in the study was chronic viral hepatitis (68.75%) while other being non-alcoholic steatohepatitis (18.75%) and ethanol-related chronic liver disease (12.5%). At presentation, 81.3% of patients had abdominal pain while 25% had hypovolemic shock. The identified lesions showed evidence of tumor rupture and all of them were at subcapsular location or exophytic. Fourteen (85.71%) patients had a solitary HCC while two had two or more tumors. Twelve (75%) patients had tumor in the right lobe, while four had tumor in the left lobe. Mean Child–Pugh score was 6.25 and mean MELD score was 8.75 in our study population. The mean tumor size was 6.65 cm. The median survival time was 280 days (range, 10–376 days). The overall cumulative survival rates at

Table 1: Clinical characteristics of patients with a spontaneously ruptured hepatocellular carcinoma

Variable	Baseline
Age (mean±SD)	59.00±16.605
Sex	
M (*n*, %)	12 (75%)
F (*n*, %)	4 (25%)
Etiology of cirrhosis	
Chronic viral hepatitis (*n*, %)	11 (68.75%)
NASH (*n*, %)	3 (18.75%)
Ethanol (*n*, %)	2 (12.5%)
Abdominal pain (*n*, %)	13 (81.3%)
Hypovolemic shock (*n*, %)	4 (25%)
Jaundice/ascites/encephalopathy	0 (0%)
Child score	6.25±0.856
MELD score	8.75±1.983
Hb (g/dl)	10.275±2.9261
Serum bilirubin (mg/dl)	1.050±0.6387
SGOT (IU/L)	36.50±8.656
SGPT (IU/L)	33.25±12.741
Serum albumin (g/dl)	3.125±0.5285
INR	1.245±0.2047
AFP (ng/ml)	26947.18±27184.92
Serum creatinine (mg/dl)	0.858±0.3056
Mean maximum tumor size (cm)	6.650±1.2765
Number of HCC	
Solitary	14 (85.71%)
Multiple	2 (14.28%)
Lobar distribution	
Right lobe	81.3%
Left lobe	18.8%
30-day survival	87.5%
Median survival (days)	280.470
Tumor response at 1 month (*n*=14)	
Complete response	5 (35.71%)
Partial response	8 (57.14%)
Progressive disease	1 (7.1%)

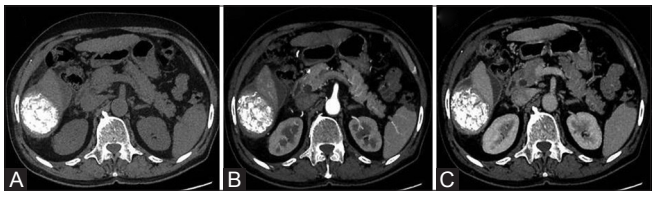

Figure 3 (A-C): Follow up at 1 month. Axial computed tomography scan images in unenhanced (A), arterial (B), and portal venous phase (C) showing uniform lipiodol deposition in the tumor without any arterially enhancing component suggestive of complete response. There is resolving subcapsular hematoma seen along the inferior margin of the liver

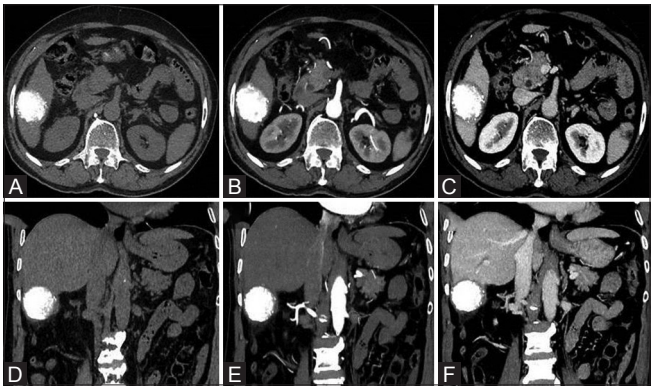

Figure 4 (A-F): Follow up at 12 months. Axial and coronal computed tomography in unenhanced (A and D), arterial (B and E), and portal venous phase (C and F) showing uniform lipiodol deposition in the tumor without any arterially enhancing component suggestive of complete response. Also noted is resolution of peritumoral fluid

30 days, 180 days, and at 1 year were 87.5%, 72.2%, and 54.1%, respectively.

At 1 month, 14 patients survived and underwent repeat imaging (multiphasic CECT/MRI). Complete response was seen in five patients (35.71%), while eight patients (57.14%) showed partial response. One patient (7.1%) showed a new lesion with presence of peritoneal spread along the liver surface adjacent to the site of rupture, suggesting progressive disease. Of eight patients showing partial response, six received repeat TACE (second session) after 1–2 months after primary TACE. Two patients did not receive repeat TACE due to renal impairment in one while elevated serum bilirubin in the other. At follow up four patients continued to show partial response, while two patients showed complete response after second session of TACE.

The overall cumulative survival rates at 30 days, 180 days, and at 1 year were 87.5%, 72.2%, and 54.1%, respectively as depicted by the Kaplan–Meier graph analysis [Figure 5].

Discussion

Spontaneous rupture of HCC is a life-threatening complication and is usually associated with a poor outcome. It can result in sudden death unrelated to progression of HCC or hepatic cirrhosis.

According to the literature, risk factors for tumor rupture are not well known although rapid growth of the tumor with necrosis, rupture by splitting of the overlying non-tumorous liver parenchyma, blood vessel erosion, coagulopathy and occlusion of hepatic veins by tumor thrombi, or invasion with resultant increased intratumoral pressure could be responsible.[3] Zhu *et al.* postulated that spontaneous rupture of HCC may be related to vascular dysfunction resulting from degeneration of elastin and degradation of type IV collagen, rendering the blood vessels stiff and weak and causing them to split easily when the vascular load increases from hypertension or minor trauma.[4,5]

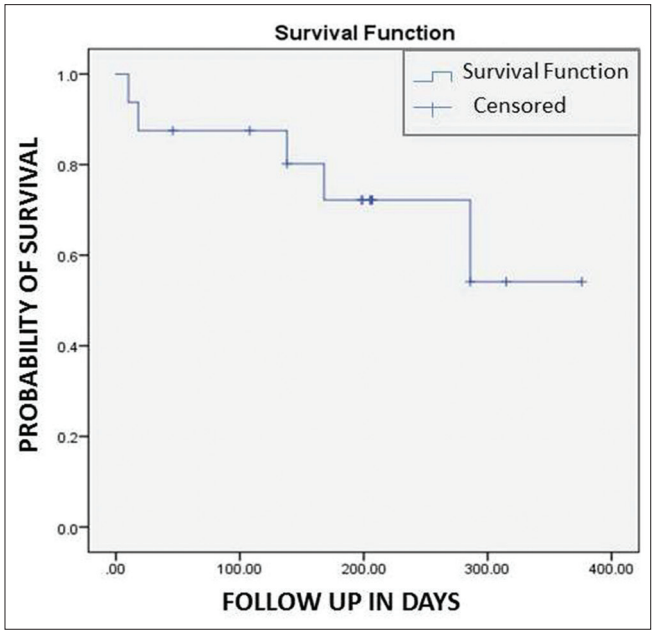

Figure 5: Kaplan–Meier analysis shows overall cumulative survival rate of TACE in spontaneously ruptured hepatocellular carcinoma

Diagnosing ruptured HCC can be difficult with 20–33% of the diagnoses made only during an emergency exploratory laparotomy.[6,7] In our patients diagnosis was based on multiphasic CE abdominal CT or MRI with characteristic findings of a ruptured HCC. A sudden onset of abdominal pain (66–100%) is the most common symptom. Shock is present in 33–90% of patients.[8–11]. In our study, 81.3% of patients had abdominal pain while 25% had hypovolemic shock. In our study none of the patients had jaundice, refractory ascites, or encephalopathy at presentation. Another important observation was subcapsular location of all ruptured HCC along with a right lobe and male predominance. Same has been observed in the systematic review by Moris *et al*.[8]

The primary aim of managing a ruptured HCC is to achieve hemostasis, and successful hemostasis is an important factor determining early mortality. Various management options in these patients include surgical procedures like perihepatic packing, suture plication of bleeding tumors, injection of absolute alcohol, hepatic artery ligation (HAL), and liver resection.[3]

TACE is a minimally invasive and effective treatment modality for management of cases of ruptured HCC in patients having relatively preserved liver function. In this study, TACE was technically successful and achieved hemostasis in all our patients. Previously 100% technical success rate was achieved in few studies.[3,12-14].

The reported 30-day mortality rate of a spontaneously ruptured HCC is between 35–67%.[9,15] In those treated with transarterial embolization, 30-day mortality rate varies from 16.7% (Sato *et al.*, 1985)[16] to 36.4% (Ngan *et al.*, 1998).[17] In our study using cTACE, the 30-day mortality rate was 12.5%, slightly better than previous studies. Lesser amount of blood loss (mean hemoglobin 10.27 g/dl) and presence of hypovolemic shock in only 25% of our patient population increased the chance of survival. This may be attributed to early diagnosis and prompt performance of cTACE leading to quick hemostasis. Also, majority of our patients had relatively preserved liver function (child Class A, mean Child–Pugh score 6.25) without jaundice, refractory ascites, or encephalopathy which probably increased the survival. Early performance of cTACE may be the key factor in determining the outcomes in patients presenting with spontaneous rupture of HCC, as achieving hemostasis

before massive blood loss may prevent global ischemia and multiorgan failure leading to poor outcome as observed in our study.

Kim *et al.* evaluated the efficiency of TACE for a spontaneously ruptured HCC.[18] Technical success rate achieved was 100% while overall cumulative survival rate at 30 and 180 days were 68.6% and 31.4%, respectively. In our study, overall cumulative survival rate at 30 days, 180 days, and at 1 year were 87.5%, 72.2%, and 54.1%, respectively.

Thus, TACE is a minimally invasive management option with excellent technical success rate for hemostasis. TACE shows high 30-day survival in patients with a ruptured HCC. The primary aim of managing a ruptured HCC is to achieve hemostasis, which is an important factor determining early mortality while tumor necrosis provided by administration of chemotherapeutic drug simultaneously in the same session confers survival benefit. Another advantage of cTACE is microembolic effect provided by the lipiodol which is helpful in penetrating deep inside the tumor, this is followed by embolization using gelfoam/PVA which embolizes the small arterial feeders supplying the tumor. This combined approach results in higher rate of hemostasis. Further tendency of lipiodol to stay within the tumor tissue for prolonged period of time might prevent further progression of rupture. Also super selective cannulation for administration of chemotherapeutic drug and embolization helps in preserving the liver function. Hence, cTACE may be advantageous over bland transarterial embolization (TAE), however, a comparative study may be needed to categorically state the same.

There were limitations in this study. This is a single center and a retrospective study, also the numbers of patients with spontaneously ruptured HCC treated with TACE were small. Conservative management or surgical treatment for ruptured HCC was not evaluated and compared. Some of our patients (n = 6) also received second session of TACE which would have added to improved overall survival.

In conclusion, cTACE is safe and effective in managing patients with ruptured HCC. TACE not only achieves immediate hemostasis with high success rate but also provides improved survival due to treatment of underlying HCC in the same session. Further, an early diagnosis with quick hemostasis leads to a better outcome.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907-17.
2. Yoshida H, Mamada Y, Taniai N, Uchida E. Spontaneous ruptured hepatocellular carcinoma. Hepatol Res 2016;46:13-21.
3. Lai EC, Lau WY. Spontaneous rupture of hepatocellular carcinoma- A systematic review. Arch Surg 2006;141:191-8.
4. Zhu LX, Geng XP, Fan ST. Spontaneous rupture of hepatocellular carcinoma and vascular injury. Arch Surg 2001;136:682-7.
5. Zhu LX, Liu Y, Fan ST. Ultrastructural study of the vascular endothelium of patients with spontaneous rupture of hepatocellular carcinoma. Asian J Surg 2002;25:157-62.
6. Vergara V, Muratore A, Bouzari H, Polastri R, Ferrero A, Galatola G, *et al*. Spontaneous rupture of hepatocellular carcinoma: Surgical resection and long-term survival. Eur J Surg Oncol 2000;26:770-2.
7. Liu CL, Fan ST, Lo CM, Tso WK, Poon RT, Lam CM, *et al*. Management of spontaneous rupture of hepatocellular carcinoma: Single-center experience. J Clin Oncol 2001;19:3725-32.
8. Moris D, Chakedis J, Sun SH, Spolverato G, Tsilimigras DI, Ntanasis-Stathopoulos I, *et al*. Management, outcomes, and prognostic factors of ruptured hepatocellular carcinoma: A systematic review. J Surg Oncol 2018;117:341-53.
9. Sahu SK, Chawla YK, Dhiman RK, Singh V, Duseja A, Taneja S, *et al*. Rupture of hepatocellular carcinoma: A review of literature. J Clin Exp Hepatol 2018. doi: 10.1016/j.jceh. 2018.04.002.
10. Miyamoto M, Sudo T, Kuyama T. Spontaneous rupture of hepatocellular carcinoma: A review of 172 Japanese cases. Am J Gastroenterol 1991;86:67-71.
11. Xu HS, Yan JB. Conservative management of spontaneous ruptured hepatocellular carcinoma. Am Surg 1994;60:629-33.
12. Okazaki M, Higashihara H, Koganemaru F, Nakamura T, Kitsuki H, Hoashi T, *et al*. Intraperitoneal hemorrhage from hepatocellular carcinoma: Emergency chemoembolization or embolization. Radiology 1991;180:647-51.
13. Castells L, Moreiras M, Quiroga S, Alvarez-Castells A, Segarra A, Esteban R, *et al*. Hemoperitoneum as a first manifestation of hepatocellular carcinoma in western patients with liver cirrhosis: Effectiveness of emergency treatment with transcatheter arterial embolization. Dig Dis Sci 2001;46:555-62.
14. Leung CS, Tang CN, Fung KH, Li MKW. A retrospective review of transcatheter hepatic arterial embolization for ruptured hepatocellular carcinoma. J R Coll Surg Edinb 2002;47:685-8.
15. Yang H, Chen K, Wei Y, Liu F, Li H, Zhou Z, *et al*. Treatment of spontaneous ruptured hepatocellular carcinoma: A single-center study. Pak J Med Sci 2014;30:472-6.
16. Sato Y, Fujiwara K, Furui S, Ogata I, Oka Y, Hayashi S, *et al*. Benefit of transcatheter arterial embolization for ruptured hepatocellular carcinoma complicating liver cirrhosis. Gastroenterology 1985;89:157-9.
17. Ngan H, Tso WK, Lai CL, Fan ST. The role of hepatic arterial embolization in the treatment of spontaneous rupture of hepatocellular carcinoma. Clin Radiol 1998;53:338-41.
18. Kim JY, Lee JS, Oh DH, Yim YH, Lee HK. Transcatheter arterial chemoembolization confers survival benefit in patients with a spontaneously ruptured hepatocellular carcinoma. Eur J Gastroenterol Hepatol 2012;24:640-5.