

Ruptured HCC and Variables in Management-Case Series and Literature Review

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Abstract

Rupture in Hepatocellular carcinoma is a rare occurrence and can present as a surgical emergency. Most of these patients are cirrhotic with large tumours in superficial locations. They can be managed by either TAE or surgery which may be one stage or two stage (after a period of optimization). The survival in these patients is poor and various variables like tumour size, tumour pathology, liver cirrhosis and hemodynamic stability. We wish to describe a series of 7 patients and review literature for variables in management of this subset of HCC patients.

Keywords: HCC; Rupture; Single stage resection; Two stage resection

Introduction

The study includes retrospective cases of rupture of HCC operated in our department from since 2012. Variables including size, location, cirrhosis grade, tumour grade, focality, performance status, surgical treatment, post-operative variables including morbidity and mortality are analysed. We wish to present our data on ruptured HCC. seven patients (4M:3F) presented with rupture of HCC. (Table 1) Most common mode of presentation was sudden onset abdominal pain (100%), followed by giddiness (71.4%). Hemodynamic instability was present in 28.5% (n=2). On evaluation, it was found that all were cirrhotic and that 85.71% (n=6) were HbsAg+ and one was of unknown cause for cirrhosis. The lesions were single in 85.71% (n=6) and multiple in 1 patient. The lesions were present in right lobe (n=3), left lobe (n=3) and bilobar (n=1). The mean diameter of the lesions was 6.9 cm (range-3-12 cm). The grade of differentiation was well differentiated in all amenable for surgical resection. Two patients were diagnosed intraoperative and five with preoperative imaging. The surgeries (n=5) included emergency surgery in 2 patients with no preoperative diagnosis of RHA ligation and non-anatomical resection of segment 3/4 in one patient. The other five patients were treated by the two stage therapeutic approach where a trial of non-operative management is given to optimize the patient followed by definite surgery. The duration of the trial was a mean of 5.6 days for the patients followed by left hepatectomy in 2 patients and right hepatectomy in one patient. Two patients were managed conservatively one which was followed by TACE and the other by BSC only. On follow up of these patients, 3 patients (42.8%) died during follow up period of 30 months and there was one recurrence after non anatomical resection at 9 months which was managed by RFA. The grade of cell differentiation was classified according to the Edmondson and Steiner system [1].

Incidence

The incidence of Hepatocellular carcinoma (HCC) is gradually increasing and it is the fifth most common cancer in the world [2]. Spontaneous rupture is the third leading cause of HCC-related death, after tumor progression and liver failure. It is seen in 3%-15% of all cases of HCC, with a lower incidence in Western than Eastern literature [3]. Though the incidence of ruptured HCC has reduced in the recent past, owing to better early diagnosis, it is still remains a significant health problem in the east [4,5].

Ruptured HCC is common in males between 44 and 68 years reflecting the general incidence of HCC [3,6] and is more common involving the left lobe due to the lesser anatomical span of the left lobe and the greater propensity to protrude and thereby chance of injury

when compared to the relative safety under the ribcage on the right [7].

Etiology

A number of factors [8,9] have been proposed like erosion of vessels, rapid tumour growth with necrosis, increased vascular pressure due to thrombosis of veins by tumor thrombi or emboli [10] which may cause shunting of blood [11,12], hyperdynamic circulation [13], direct capsular invasion or pressure necrosis, vascular dysfunction in tumour tissue [14], extensive tumour infiltration of liver with concomitant poor nutrition [11,15] and even hypertension [16]. Even minor trauma, portal hypertension and TACE are known precipitating factors for rupture. [17,18]. The most plausible explanation seems to be direct capsular invasion or pressure necrosis of the capsule resulting in rupture [17].

Clinical Features

In most cases of spontaneous rupture of HCC, these patients usually present to the emergency department with abdominal pain and hypotension [7,9].

Preoperative diagnosis of HCC rupture is difficult with an accurate pre-operative diagnosis of ruptured HCC was obtained in only 25% of cases, despite shock present in 33% to 90% of the patients [5]. 20% to 33% of the diagnoses are still made only during an emergency exploratory laparotomy [5,6].

It is often difficult for deciding on an appropriate treatment strategy, especially if patient is hemodynamically unstable. Symptoms are related to the position of the tumor with deeper tumors being asymptomatic or producing pain while those on the free surfaces give rise to hemoperitoneum [19]. Previously large tumors were only thought to rupture now, smaller tumors, particularly those with an aggressive behavior, are also at risk [19]

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Table I: Data on ruptured HCC.

	Age	sex	cirrhosis	Etiology cirrhosis	HCC size (segment)	Grading	Hemodynamic instability	Treatment	Prognosis
1	32	F	+	-	3*3 cm seg 3	G1	+	Emergency non Anatomical resection segment 3/4	Local Recurrence at 9 months- RFA-on follow up
2	56	M	+	HBSAg+	6*6 cm, seg 2,3	G1	-	Conservative management (3 days) followed by LH (left hepatectomy)	Follow up-1 year
3	37	F	+	HBSAg+	7*8 cm, seg 5,6	G1	-	Conservative management (2 days) followed by RH (right Hepatectomy)	Follow up -2 years
4	50	M	+	HBSAg+	10*8,seg 7	G1	+	Emergency RHA ligation/biopsy/BSC	Post op Liver failure. Death on POD 8.
5	52	M	+	HBSAg+	RL-10*9 cm, seg 7,8 LL-5*4 cm, seg 2,3	-	-	Conservative management (2 weeks) followed by TACE.	Death 2 months
6	51	F	+	Hbsag+	12*12 cm seg 6	-	-	Conservative followed by BSC	Death POD 12
7	73	M	+	HBSAg+	4*4 cm seg 3,4	G1	-	Conservative management (12 days) followed by LH	Follow up -6 months

Kanematsu et al. [20] reported that protrusion of the tumor is a relevant prognostic factor in rupture. Abnormal clotting and thrombocytopenia seen in cirrhosis may also worsen the bleeding due to rupture. Ruptured HCC may cause noncritical blood-tinged ascites in approximately 33% of patients [21].

Investigations

Hepatic enzymes may be elevated [15]. Although red cell Tc-99m scintigraphy [22] and CT can help to identify the source of intra-abdominal bleeding [23], they are usually diagnosed during operation [24] or at autopsy [10,11,15].

Ruptured HCC has been detected using CECT, gray-scale and Doppler ultrasonography [25]. The following CT findings are useful for diagnosing a ruptured HCC: hemoperitoneum, HCC with surrounding perihepatic hematoma, active extravasation of contrast materials, tumor protrusion from the hepatic surface, focal discontinuity of the hepatic surface and an enucleation sign [26].

In one study, spontaneous hemoperitoneum could be diagnosed in only 13% of patients on the basis of abdominal CT and ultrasound studies [27]. Conventional angiography also demonstrates extravasations of contrast from the tumour only in 13%-35% of cases [28]. Abdominal paracentesis is reliable to confirm the diagnosis of rupture [8,29].

Treatment

There are two main treatment modalities in vogue in the treatment of ruptured HCC.

Trans-cutaneous arterial catheter embolization (TAE)

TAE in ruptured HCC serves two roles. In patients with advanced liver disease (child C) or multifocal HCC, TAE is clearly the most appropriate approach [19]. In patients with Child C status the postprocedure mortality after TAE is high implying functional reserve of liver is paramount regardless of treatment type.

TAE may also be used as a bridge to secure hemostasis in the acute phase after rupture followed by definite resection [9]. In the acute phase, transarterial embolization for hemostasis has a high success rate (53%100%). It has a lower 30-day mortality rate than open surgical methods (0%-37% vs 28%-75%) [9].

In a study [30], multivariate analysis showed that a maximum tumor size not exceeding 7 cm was the only independent factor

determining long-term survival after initial successful TAE. However, the demerits of TAE which include rebleeding, liver abscess, liver failure (most common cause of death in TAE patients) and implanted peritoneal metastases must be borne in mind when planning TAE [31].

Resection

Liver resection has been advocated for both haemostasis and to provide a definitive treatment [5,9]. Resection may be an option either immediately in the acute phase at presentation (single stage approach) or after a delayed phase of conservative management (delayed or two stage therapeutic approach).

One stage or immediate surgical resection

In the 1960s to 1980s, various procedures to secure hemostasis included perihepatic packing, suture plication of bleeding tumors, hepatic artery ligation, and liver resection. These achieved a high rate of hemostasis but were associated with a high in-hospital mortality rate [33-35].

Today, one stage hepatectomy with limited resection is done in centres with acceptable outcomes also [33,34] but should ideally be reserved for patients with a small and easily accessible tumor and a noncirrhotic liver [6,10].

A study by Batutla [36] showed the inhospital mortality and survival after immediate single stage resection as follows (Table II).

It is to be noted Liver failure occurs in 12% to 42% of patients during the acute phase [9]. However, prolonged survival can be achieved in selected patients undergoing one-stage hepatectomy, although the survival results were inferior to those of the patients without ruptured HCC [16].

Two stage approach or staged approach or Delayed resection

The rationale for a delayed approach [9] to resection is that bleeding and shock are strong negative prognostic factors in an already decompensated liver. Therefore in this approach, the first step of treatment is achieving hemostasis in the acute phase after rupture. The patient is treated by conservative approach [9] and hemostatic procedure like TAE or other surgical hemostatic procedure may be carried out to secure haemostasis [36-39].

Conservative treatment

For ruptured HCC [9] includes correction of coagulopathy, close monitoring, and urgent medical imaging to confirm the diagnosis after initial resuscitation.

Table II: A study by Batutla showed the in-hospital mortality and survival after immediate single stage resection.

Studies	Year	Patients	Emergency resections (%)	Cirrhotic (%)	Hospital mortality (%)	Survival (months)
Ong and Taw [29]	1972	42	13 (31%)	7/13 (53%)	5 (38%)	6
Nagasue et al. [36]	1979	11	4 (36%)	4/4 (100%)	2 (50%)	-
Chearanai et al. [8]	1983	63	1 (2)	nr	-	4
Lai et al. [37]	1989	60	7 (12)	3/7 (43)	5 (72)	2
Dewar et al. [38]	1991	37	11 (30)	10/11 (91)	6 (55)	4 (1-7)
Leung et al. [42]	1999	40	11 (28)	6/11 (54)	6 (50)	nr
Tanaka et al. [3]	2001	12	5 (42)	5/5 (100)	2 (40)	14.7
Yeh et al. [33]	2002	60	10 (16)	nr	nr	nr
Battutla et al. [35]	2006	21	5 (24)	1/5 (20)	0	25 (17-82)

Although associated with complications like rebleeding and a mortality rate of around 30%, TAE is the best method to achieve hemostasis without surgery [9,40]. Other open surgical hemostatic techniques include perihepatic packing, suture plication of bleeding tumors, injection of absolute alcohol, hepatic artery ligation (HAL) which are second-line treatment when TAE fails or is not available [9]. These hemostatic may have high rate of hemostasis (70-82%) but are unfortunately associated with a high in-hospital mortality rate (44-62%) [9].

Patients in the TAE alone group had a better prognosis than those in the conservative treatment and surgical hemostasis groups [41]. In this study, on comparing the outcomes of five treatment methods for ruptured HCC: conservative treatment, surgical hemostasis, transarterial embolization (TAE), and one- and two-stage resections, there was no significant difference in the median survival time between the conservative treatment and surgical hemostasis groups and also no significant difference was observed between the one-stage and two-stage resection groups.

After the acute phase of rupture, the optimal time (delay) to carry out staged liver resection is unknown and may vary from 10 to 126 days [9].

After delay, resection may be done with peritoneal washing by saline solution to reduce the chance of spreading peritoneal cancer which may be a complication of TAE [33,42]. Laparoscopy and laparoscopic ultrasonography [43,44] may be done before definite resection which decreases unnecessary exploratory laparotomy (by 63% and 30% respectively) and enables these subsets to be presented to down staging (ablative therapy, TACE, internal radiation or chemotherapy) and then be subjected again to salvage surgery.

On short term analysis, staged liver resection has a higher resection rate (21%-56% vs 13%-31%) and a lower in hospital mortality rate (0%-9% vs 17%-100%) and a better survival rate (1-year survival, 54.2%-100%; 3-year survival, 21.2%-48%; 5-year survival, 15%-21.2%) than single stage resection [9].

The long-term outcomes of staged liver resection are uncertain if it's the same for hepatocellular carcinoma with and without rupture when patients with the same tumor stage and liver functional state are compared [9].

Other Treatment Modalities

Radio frequency ablation (RFA)

RFA can be used for hemostasis [45,46] during laparotomy and as a curative option in ruptured HCC. It has greatly reduced the hospital mortality rate when used for hemostasis when compared with conventional hepatic artery ligation.

Conservative treatment or supportive care

Conservative treatment for ruptured HCC includes close monitoring without active intervention. It is most commonly used for

inoperable patients in a moribund state and is associated with poor results [8,47].

Intratumoral injection

Sunderland and colleagues reported another alternative method of treating patients with ruptured HCC with alcohol with some success [48].

Injection of new chemicals such as isoamyl 2-cyanoacrylate (CA) [47] and OK-432 [48] has also been tried in ruptured HCC with mixed results [49,50].

Prognosis

Short term

In a review, the average 30-day mortality rates among patients who received conservative treatment, emergency hepatic resection and TAE were 71%, 50% and 48%, respectively [7]. Staged hepatic resection has a much lower in-hospital mortality rate (0-9%) and higher survival rates than one stage resection [9].

Other factors have been linked to short-term mortality, such as the presence of cirrhosis [35,51], the presence of hepatic encephalopathy [30], a high Child-Pugh score [30,35,51,52], a high serum bilirubin level [51,52], a high serum aspartate aminotransferase level [51], a high serum alkaline phosphatase level, [51], a prolonged prothrombin time [51], an increased indocyanine green retention rate at 15 min [50], a low serum albumin level (all of which are associated with poor liver function) [52,53], a high serum α -fetoprotein level [51], the severity of hemorrhage from the rupture (shock and hemoglobin level on admission) [2,30,35,51,52], a high creatinine level, a higher incidence of acute respiratory failure, worsened neurological status, Portal vein thrombosis [52], a large maximum tumor size [30] and unsuccessful TAE (best supportive care only) [30,53]. Mortality rates after immediate resection in acute rupture phase are as high as 25-100% [9] and serum bilirubin level, shock on admission, and pre-rupture disease state are important prognostic factors predicting survival in the acute phase [9].

Long-term

Long-term survival overall survival is poorer [6,54] in patients with ruptured HCC than in those with non-ruptured HCC. [49] where the following variables like maximum tumor diameter (odds ratio [OR], ≥ 16.34 [>5 vs ≤ 2 cm]; 4.66 [$2-5$ vs ≤ 2 cm]; 3.50 [>5 vs $2-5$ cm]), Child-Pugh grade (OR, 2.57), 99 plasma des- γ -carboxyprothrombin value (OR, 1.66), platelet count (OR, 0.71), age (OR, 0.71 [≥ 60 vs <60 years]) and Egge's gross classification (OR, 1.42 [massive vs nodular]) were independently related to spontaneous tumor rupture on multivariate logistic regression analysis [54] where the model selected contained 25,404 cases. However, Yeh et al. [33] reported that patients with ruptured HCC had a similar overall survival but a poorer disease free survival than those with non-ruptured HCC.

The TNM classification of the AJCC/UICC [55] and the LCSIJ rules [56] classify ruptured HCC as T4, even if the tumor is small and

solitary. Mizuno [57] compared survival rates between patients with ruptured HCC and patients with non-ruptured HCC who had similar background factors, such as disease stage (stage IVA) according to the LCSGJ rules and liver function and found no significant difference in overall survival or disease-free survival between them [52]. Patients' stratified by TNM staging showed that tumor rupture had an additional impact corresponding to the addition of 0.5 to 2 to the baseline tumor staging which affects survival significantly when compared to those without rupture.

Conclusion

Spontaneous ruptured HCC is a life threatening surgical emergency whose management depends on the tumour load and underlying liver disease. It is to be noted that the outcomes of selected subgroups of ruptured HCC may be on par to non-ruptured cases. Curative resection is possible in a Child A-B patient. The timing of surgical resection may be delayed if feasible. TAE can be palliative procedure in compromised liver multifocal-bilobar HCC or a bridge by providing haemostatic control for a delayed resection.

Conflict of Interest

Authors deny any conflict of interest.

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