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CASE REPORT

Rupture of Hepatocellular Carcinoma: a Tale of 20 Cases from a Tertiary Care Center in Northern India

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Introduction

Approximately 700,000 people die of hepatocellular carcinoma (HCC) each year worldwide, making it the third leading cause of cancer-related deaths [1]. HCC develops in the background of cirrhotic liver in 85–95% of cases [2]. Spontaneous rupture is a potentially life-threatening complication and is the third most common cause of death due to HCC after tumor progression and liver failure [3]. In Asia, approximately 10% of patients with HCC die of rupture each year [4]. There is a distinct geographical variation in the reported incidence of ruptured HCC. In the West, HCC rupture is relatively uncommon, with an incidence of less than 3% [5]. However in Asia, the incidence is relatively higher, ranging between 3 and 26% [6]. The literature on rupture HCC is scarce from India and there is no data on the exact incidence of HCC rupture from India [7, 8].

With earlier detection of HCC, the incidence of rupture is decreasing; however, the mortality due to ruptured HCC in the acute phase is high and has been reported to be between 25 and 75% [9, 10]. There is still a debate concerning the best treatment approach in cases of HCC rupture. The primary goal is correction of hypovolemic shock and stabilization of the patient followed by definitive therapy [3, 10]. Transarterial embolization (TAE) effectively induces hemostasis in the acute stage with a success rate of 53–100% [10–12]. Hepatic resection is associated with improved survival and offers a hope for cure in selected patients [10].

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Patients and Methods

This is a prospective observational study analyzing the clinical and radiological data of 20 patients presenting with ruptured HCC to our institute (a tertiary care center in Northern India) between July 2014 and June 2017. HCC was diagnosed as per the American Association for the study of Liver Diseases (AASLD) practice guidelines for surveillance and diagnosis of HCC and staged according to the Barcelona Clinic Liver Cancer (BCLC- Staging) system [13, 14]. Cirrhosis was diagnosed by presence of any one of the following: (a) presence of ascites with high serum-ascites albumin gradient (SAAG), (b) presence of esophageal varices of grade ≥ 2, and (c) irregular outline of liver and portal vein dimension > 13 mm on ultrasonography. The severity of liver disease was assessed according to both Child Pugh and Model for End stage Liver Disease (MELD) scores. Rupture of HCC was diagnosed by triple-phase computed tomography (TPCT), with at least two of the following findings: (a) peripherally located tumor with a contour bulge, (b) discontinuity of the hepatic surface, and (c) subcapsular hematoma or hemoperitoneum or by demonstration of active extravasation of contrast on CT and/or angiography [15]. The "enucleation sign" (Fig. 1), another important CT finding in rupture of HCC, is defined as separation of tumor content with intraperitoneal rupture into the perihepatic space which is seen as low-attenuating lesion from peripheral enhancing rim on arterial phase imaging [16]. The demographic, clinical, and radiological data of all patients were recorded in the case record form after obtaining informed consent. Ethical clearance was obtained from the Institute Ethics Committee of the Post Graduate Institute of Medical Education and Research Chandigarh (PGIMER), India.

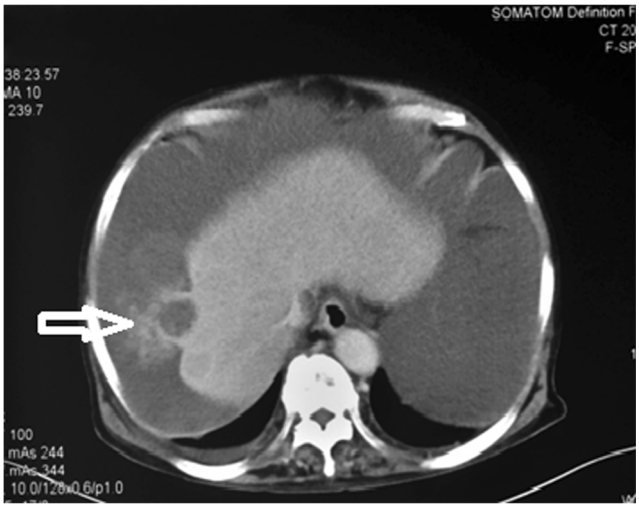

Fig. 1 The "enucleation sign" in a case of rupture of HCC in segment VII (white open arrow) with separation of tumor content into the perihepatic space seen as hypodense center with peripheral rim enhancement on arterial phase of Triple phase computed tomography (TPCT)

Results

Demographic Profile and Clinical Presentation

A total of 20 patients presented with rupture of HCC. Nineteen patients (95%) were males and the mean (SD) age was 57.5 ± 10.99 years (Table 1). The associated co-morbidities were hypertension in 8 patients (40%) and type 2 diabetes mellitus in 2 patients (10%). The underlying etiology of cirrhosis was chronic hepatitis C in 8 patients, (40%) chronic hepatitis B in 4 (20%), alcohol in 4 (20%), and non-alcoholic steato-hepatitis (NASH) in 2 patients (10%). One patient each had primary biliary cholangitis (PBC) and cryptogenic cirrhosis. Cirrhosis was documented in all patients and ruptured HCC was the first clinical presentation of cirrhosis in 6 patients (30%). At the time of presentation, 4 patients had child A (20%), 10 had child B (50%), and 6 had child C (30%) cirrhosis with a mean MELD score of 16.2 ± 8.57 (Table 1). HCC presented in BCLC stage A in 1 patient (5%), BCLC B in 10 (50%), BCLC C in 6 (30%), and BCLC D in 3 patients (15%). The most common symptom at presentation was pain in right hypochondrium or epigastrium in 17 patients (85%) followed by distension of abdomen in 16 patients (80%). Hemoperitoneum was documented on diagnostic paracentesis in 15 patients (75%). Hypovolemic shock was present in 8 patients (40%) at diagnosis.

Tumor Characteristics

TPCT of abdomen revealed the ruptured HCC to be subcapsular in 15 patients (75%), hemoperitoneum was documented in 15 patients (75%), capsular breach (Fig. 2) was seen in 14 patients (70%), active extravasation of contrast in 8 patients (40%), and "enucleation sign" in 5 patients (25%) (Table 1). Conventional hepatic artery angiography was conducted in 14 patients (70%)

Table 1 Demographic, clinical, and radiological profiles of patients with ruptured hepatocellular carcinoma ($n = 20$)

Patients profile	Frequency (%)
Age (mean ± SD) years	57.5 ± 10.99
Gender (male)	19 (95%)
Co-morbidity (hypertension)	8 (40%)
Cirrhosis	20 (100%)
Cirrhosis due to chronic viral hepatitis	12 (60%)
Rupture as first presentation of cirrhosis	6 (30%)
Decompensated cirrhosis	15 (75%)
CTP score	
A	4 (20%)
B	10 (50%)
C	6 (30%)
MELD score (mean ± SD)	16.2 ± 8.57
BCLC stage	
A	1 (5%)
B	10 (50%)
C	6 (30%)
D	3 (15%)
Multifocal HCC	11 (55)
Lobar distribution of HCC	
Right lobe	15 (75)
Left lobe	2 (10)
Bilobar	3 (15)
Size of HCC	
< 5 cm	4 (20)
5–10 cm	14 (70)
> 10 cm	2 (10)
Signs on TPCT suggesting rupture of HCC	
(i) Subcapsular location of HCC	15 (75)
(ii) Exophytic HCC	14 (70)
(iii) Hemoperitoneum	15 (75)
(iv) Breech of liver capsule	14 (70)
(v) Active contrast extravasation	8 (40)
(vi) "enucleation sign"	5 (25)
Signs on angiography suggesting rupture of HCC ($n = 14$)*	
(i) Abnormal tumor blush	12 (86)
(ii) Active extravasation of contrast	5 (36)
Serum AFP levels	
< 20 ng/ml	7 (35)
20–200 ng/ml	5 (25)
201–400 ng/ml	2 (10)
> 400 ng/ml	6 (30)
Macrovascular invasion (present)	3 (15)
Extrahepatic spread (present)	4 (20)
Management	
Transarterial embolization	14 (70)
Conservative	5 (25)
Hepatic resection	1 (5)

CTP Child-Turcotte-Pugh, *MELD* Model for End-Stage Liver Disease, *BCLC* Barcelona Clinic Liver Cancer, *HCC* hepatocellular carcinoma, *TPCT* triple-phase computed tomography, AFP Alpha fetoprotein

Data have been presented as number (percentage) or mean (± SD) wherever applicable.

*Selective hepatic artery angiography as part of transarterial embolization (TAE) was done in 14 patients with ruptured HCC

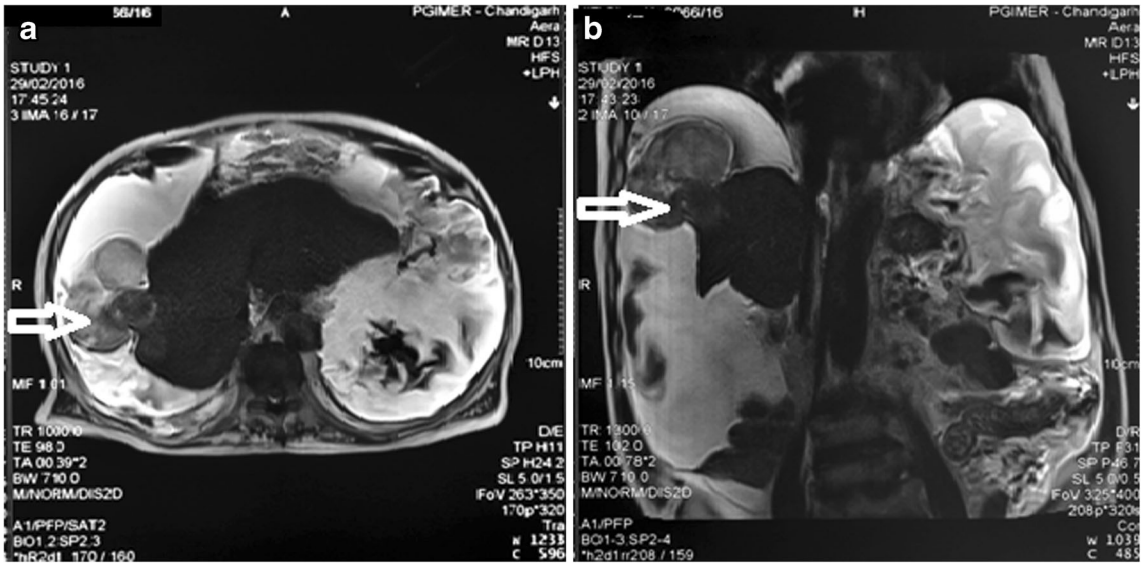

Fig. 2 Rupture of HCC with capsular breech (white open arrows) on axial (**a**) and sagittal (**b**) sections of triple phase computed tomography (TPCT)

as part of achieving hemostasis by TAE. The most common sign on angiography was tumor blush (Fig. 3), seen in 12 patients (86%); however, active extravasation of contrast was documented in only 5 patients (36%). HCC was multifocal in 11 patients (55%); the tumor had an exophytic (protrusion beyond the liver capsule) component in 14 patients (70%). The size of the HCC was ≥ 5 cm in 16 patients (80%), and < 5 cm in 4 patients (20%). The rupture was intraperitoneal in 15 patients (75%), but was contained within the sub-hepatic space in 5 patients (25%). Macrovascular invasion in the form of portal vein thrombosis was seen in 3 patients (15%). Extrahepatic spread was seen in 4 patients (20%), of which 3 involved the lungs and 1 involved the omentum (Table 1).

Management and Treatment Outcomes

In only 3 patients (15%), there was a previous history of HCC being treated with radio-frequency ablation (RFA) followed by transarterial chemoembolization (TACE) in 2 patients and transarterial radioembolization (TARE) in 1 patient. Exposure to sorafenib in the preceding 3 months prior to rupture was present in only 2 patients (10%). In the present study, hemostasis was achieved by transarterial bland embolization (TAE) in 14 patients (70%) which included 2 patients with exploratory laparotomies and perihepatic packing attempted for hemostasis at the referring hospital. TAE was not amenable in 3 patients (15%) due to technical difficulties during the procedure in 2 patients and severe coagulopathy and multi-organ dysfunction in one. Five patients (25%), including 2, where TAE was technically not feasible, received only conservative treatment. TAE was successful in achieving hemostasis in all patients in the acute phase; however, in 4 patients (29%), it was complicated by liver failure and resulted in mortality during the same hospital stay. Hepatic resection was successfully performed in 1 patient (5%). The 30-day mortality in our patients receiving conservative management, TAE, and

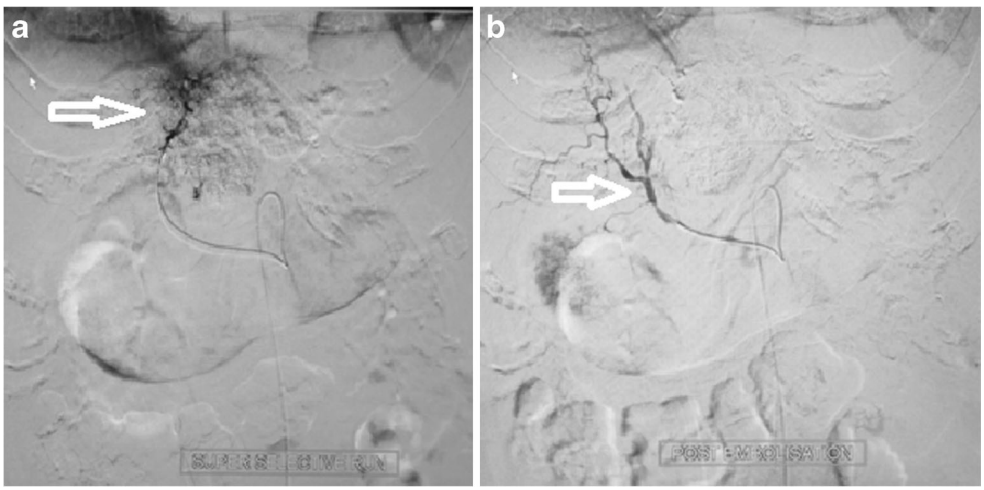

Fig. 3 Selective hepatic artery angiography of ruptured HCC before (**a**) and after (**b**) transarterial embolization (TAE), the abnormal tumor blush (white open arrow) disappeared after a successful TAE

hepatic resection were 100%, 29%, and 0% respectively. The mean (SD) duration of hospital stay was 7.9 ± 5.05 days and the mortality at 3 month was 65%.

Discussion

This is one of the largest series of ruptured HCC cases reported from India. Ruptured HCC was the first clinical presentation of cirrhosis in 30% of patients in our study. The rate of spontaneous rupture without a prior diagnosis has been reported to be between 41 and 75% in the previous study [17]. The most common symptom was pain abdomen present in 85% followed by distension of abdomen in 80% and hypovolemic shock in 40% of cases at diagnosis in our study. The triad of abdominal pain, distension, and shock has been reported to be the commonest presenting symptoms consistent with intraperitoneal hemorrhage [18]. Sudden onset of abdominal pain was the most common symptom at presentation seen in 67% followed by shock in 51% and abdominal distension in 33% according to a previous study by Zhu et al. [6]. Hemoperitoneum was documented on diagnostic paracentesis in 75% of patients in our study, it was considered as a reliable test to confirm the diagnosis in up to 86% of clinically suspected ruptured HCC according to previous study by Miyamoto et al. [4].

Presence of hypertension, liver cirrhosis, HCC size > 5 cm, and protrusion from liver surface (exophytic tumors), portal vein thrombosis, and extrahepatic spread have been found to be the independent predictors of rupture of HCC by Zhu et al. [6]. Co-morbidity like hypertension in 40%, liver cirrhosis in all patients, HCC measuring > 5 cm in 80%, and exophytic lesions in 70% of our patients support the previous report [6]. In 4 of our patients, the lesions were < 5 cm and yet presented with rupture; this was supported by previous study by Tanaka et al. [9]. The explanation for rupture of small HCC incite the vascular hypothesis, which states that the vessels in the ruptured HCC tend to be more friable due to expression of collagenase and subsequent degradation of type IV collagen, which has been demonstrated on biopsy specimen of HCC patients in previous studies by Zhu et al. [19, 20]. Almost half of our patients had advanced HCC at presentation, and BCLC C and BCLC D comprise 45% of all cases in our series. The BCLC staging system for HCC which is the most commonly used staging system to guide therapy and for assessing prognosis does not include ruptured HCC as a separate entity (14). However, the current (Seventh) AJCC/UICC (American Joint Committee on Cancer/Union for International Cancer Control) TNM staging system classifies ruptured HCC as T4 even if the tumor is small, solitary, and without vascular invasion [21].

Different signs of ruptured HCC on TPCT scanning observed in our study have been reported similarly in a previous study where hemoperitoneum was seen in 100%, discontinuity of the hepatic surface in 84%, and enucleation sign and active extravasation of contrast in 36% each [22]. Previous studies have reported the poor sensitivity (13–36%) of angiography in demonstrating active extravasation of contrast in ruptured HCC which was seen in only 36% in our study as well [15]. A contained rupture of HCC was the diagnosis in 25% of our cases which were effectively picked up by TPCT scan. Previous study has reported the sensitivity of CT scan to be 100% in diagnosing early contained rupture [23]. The triad of a large peripherally located HCC with a small intraperitoneal or localized collection and apparent capsular retraction underneath the collection has 100% sensitivity in the diagnosis of an early intraperitoneal rupture [23]. The "enucleation sign" which is seen in 25% of our cases on TPCT has been reported to be highly specific for rupture HCC if associated with surrounding hematoma and/or active contrast extravasation [16]. Previous study has reported the positive rate of a correct diagnosis of ruptured HCC to be 86% by paracentesis, 66% by ultrasonography, 100% by CT scan, and only 20% by angiography [24].

TAE was performed in 70% of our patients successfully achieving hemostasis in all patients; however, in 29%, it was complicated by liver failure. TAE has been shown to be effective in achieving hemostasis in 53–100% of cases in the acute stage [10–12]. TAE has also been shown to be comparable to surgical resection in achieving hemostasis according to previous reports [18]. The 30-day mortality in our patients receiving conservative management, TAE and surgical resection were 100%, 29%, and 0% respectively. The results of conservative treatment are generally poor with a reported hospital mortality of 85–100% and median survival as low as 13 days [25]. The reported overall 30- day mortality after rupture of HCC ranges between 32 and 75% [9, 10]. Liver failure developing in 12–42% of cases during the acute phase has been reported to be the most common cause of mortality after HCC ruptures [10].

Conclusion

Rupture of HCC is a potentially life-threatening complication which can be the first manifestation of cirrhosis, hence needs a high index of suspicion for diagnosis and treatment. Diagnostic paracentesis documenting hemoperitoneum is an important clinical clue. TPCT scan can diagnose HCC rupture with a sensitivity up to 100%. TAE is the least invasive method to achieve hemostasis with a high success rate in the acute settings. Liver failure is an important cause of mortality after rupture of HCC. Hepatic resection, the only potentially curative treatment is possible only in a small subset of patients with ruptured HCC.

Compliance with Ethical Standards

Informed consent was obtained from all patients. Ethical clearance was obtained from the Institute Ethics Committee of the Post Graduate

Institute of Medical Education and Research Chandigarh (PGIMER), India.

Conflicts of Interest The authors declare no conflict of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2014;136:E359–86. https://doi.org/10.1002/ijc.29210.
2. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology. 2004;127(5 Suppl 1):S35–50. https://doi.org/10.1053/j.gastro.2004.09.014.
3. Bassi N, Caratozzolo E, Bonariol L, et al. Management of ruptured hepatocellular carcinoma: implications of therapy. World J Gastroenterol. 2010;16:1221–5. https://doi.org/10.3748/wjg.v16.i10.1221.
4. Miyamoto M, Sudo T, Kuyama T. Spontaneous rupture of hepatocellular carcinoma: a review of 172 Japanese cases. Am J Gastroenterol. 1991;86:67–71.
5. Clarkston W, Inciardi M, Kirkpatrick S, Mc Ewen G, Ediger S, Schubert T. Acute hemoperitoneum from rupture of a hepatocellular carcinoma. J Clin Gastroenterol. 1988;10(2):221–5. https://doi.org/10.1097/00004836-198804000-00025.
6. Zhu Q, Li J, Yan JJ, Huang L, Wu MC, Yan YQ. Predictors and clinical outcomes for spontaneous rupture of hepatocellular carcinoma. World J Gastroenterol. 2012;18(48):7302–7. https://doi.org/10.3748/wjg.v18.i48.7302.
7. Islam M, Deka P, Kapur R, Ansari MM. Non-bleeding spontaneous rupture of hepatocellular carcinoma. Niger J Surg. 2013;19(2):82–4. https://doi.org/10.4103/1117-6806.119241.
8. Rathod K, Sheth R, Shah P, Rege S. Active contrast extravasation in spontaneous rupture of hepatocellular carcinoma: a rare CT finding. J Postgrad Med. 2000;46(1):35–6. http://www.jpgmonline.com/text.asp?2000/46/1/35/319.
9. Tanaka A, Takeda R, Mukaihara S, et al. Treatment of ruptured hepatocellular carcinoma. Int J Clin Oncol. 2001;6:291–5. https://doi.org/10.1007/s10147-001-8030-z.
10. Lai EC, Lau WY. Spontaneous rupture of hepatocellular carcinoma: a systematic review. Arch Surg. 2006;141(2):191–8. https://doi.org/10.1001/archsurg.141.2.191.
11. Yoshida H, Mamada Y, Taniai N, Uchida E. Spontaneous ruptured hepatocellular carcinoma. Hepatol Res. 2016;46:13–21. https://doi.org/10.1111/hepr.12498.
12. Kung CT, Liu BM, Ng SH, Lee TY, Cheng YF, Chen MC, et al. Transcatheter arterial embolization in the emergency department for hemodynamic instability due to ruptured hepatocellular carcinoma: analysis of 167 cases. Am J Roentgenol. 2008;191(6):W231–9. https://doi.org/10.2214/AJR.07.3983.
13. Bruix J, Sherman M. American Association for the Study of Liver Diseases: management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020–2. https://doi.org/10.1002/hep.24199.
14. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19:329–38. https://doi.org/10.1055/s-2007-1007122.
15. Kim HC, Yang DM, Jin W, Park SJ. The various manifestations of ruptured hepatocellular carcinoma: CT imaging findings. Abdom Imaging. 2008;33(6):633–42. https://doi.org/10.1007/s00261-007-9353-7.
16. Singhal M, Sinha U, Kalra N, Duseja A, Khandelwal N. Enucleation sign: a computed tomographic appearance of ruptured hepatocellular carcinoma. J Clin Exp Hepatol. 2016;6(4):335–6. https://doi.org/10.1016/j.jceh.2016.05.004.
17. Liu CL, Fan ST, Lo CM, et al. Management of spontaneous rupture of hepatocellular carcinoma. Single centre experience. J Clin Oncol. 2001;19:3725–32.
18. Felicia L, Tan S, Tan Y-M, et al. Factors affecting early mortality in spontaneous rupture of hepatocellular carcinoma. ANZ J Surg. 2006;76:448–52. https://doi.org/10.1111/j.1445-2197.2006.03750.x.
19. Zhu L, Geng X, Fan S. Relationship between vascular elasticity and spontaneous rupture of hepatocellular carcinoma. Chin-Ger J Clin Oncol. 2003;2(1):18–22.
20. Zhu LX, Liu Y, Fan ST. Ultra structural study of the vascular endothelium of patients with spontaneous rupture of hepatocellular carcinoma. Asian J Surg. 2002;25:157–62.
21. Collaborative Staging Task Force of the American Committee on Cancer. Collaborative Staging Manual and Coding Instructions, version 1.0. Published jointly by the American Joint Committee on Cancer (Chicago, IL) and the U.S. Department of Health and Human Services (Bethesda, Maryland). Bethesda: NIH Publication, 2004; No. 04–5496.
22. Yun SJ, Nam DH. Hepatic angiographic findings of ruptured hepatocellular carcinoma: "sentinel signs" versus extravasation. J Korean Soc Radiol. 2014;70(5):335–42. https://doi.org/10.3348/jksr.2014.70.5.335.
23. Tsitouridis I, Michaelides M, Christopoulou A, et al. Early stage of intraperitoneal rupture of hepatocellular carcinoma: CT and MRI evaluation. Ann Gastroenterol. 2007;20(4):282–5.
24. Zhu LX, Wang GS, Fan ST. Spontaneous rupture of hepatocellular carcinoma. Br J Surg. 1996;83(5):602–7. https://doi.org/10.1002/bjs.1800830507.
25. Hirai K, Kawazoe Y, Yamashita K, et al. Transcatheter arterial embolization for spontaneous rupture of hepatocellular carcinoma. Am J Gastroenterol. 1986;81:275–9.