

Diagnosis and Management of Ruptured Hepatoma: Single Center Experience Over 10 Years

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SUMMARY

Introduction: Spontaneous rupture is a dramatic presentation of HCC and it carries high mortality rate. To study the outcomes of ruptured HCC patients managed at a tertiary referral centre in Malaysia.

Methods: A retrospective review of all ruptured HCC patients managed as inpatient at the Department of Hepatobiliary Surgery, Hospital Selayang between January 2001 and December 2010. Data was retrieved from the hospital electronic medical records, Powerchart (Cerner Corporation Inc., USA) and supplemented with registry from Interventional Radiology record of chemoembolization and registry from hepatobiliary operative surgery records.

Results: There were 22 patients admitted with confirmed diagnosis of ruptured HCC over 10 years period. The common clinical findings on presentation were abdominal pain and presence of shock (36.4%). The mortality rate was 81.8% with only four patients noted to be alive during the follow up. One year overall survival for ER and DR are 40.0% and 72.7% respectively and the median survival in patients treated with DR was 433.3 days whereas it was 212.5 days in ER group.

Conclusions: This study supports the clinical practice of TAE should be the first line treatment followed by staged surgery in suitable candidates with ruptured HCC.

INTRODUCTION

Hepatocellular carcinoma (HCC) has been a significant health problem especially in the developing countries and the incidence is rising in developed countries. About ¾ of HCC are attributed to chronic Hepatitis B virus (HBV) and Hepatitis C Virus (HCV) infections. According to the data from Globocan 2008¹, HCC has been identified as 5th most common cancer in men and seventh in the women. The survey also reported estimated 748,300 new liver cancer cases occurred in the world during 2008; in which 85% of these cases were from developing countries. It was noted liver cancer rates are highest in west and Central Africa and in East and Southeast Asia. HCC is 2nd leading cause of carcinoma death in men and sixth leading cause among women. About 695,500 people worldwide died from liver cancer in 2008. In Malaysia, HCC was noted among the 10th most common cancer among males in Peninsular Malaysia by National Cancer Registry report in 2004².

Spontaneous rupture of HCC is a dramatic presentation of the disease. The presentation in ruptured HCC may vary from asymptomatic to hypovolemic shock which makes the diagnosis difficult. The condition carries high mortality rate. Its incidence is as high as 15% in Asia compared to the unusual occurrence in western countries with an incidence of <3%, with a reported mortality rate of 50%³⁻¹¹. Ruptured HCC is a life threatening condition. The manifestation also can be considered as one the uncommon complication of HCC. Its incidence is as high as 15% in Asia and the mortality rate has been reported in the range of 32% to 100%. There are few options of treatment available for the patients presenting with ruptured HCC: emergency hepatic resection, packing, ligation of hepatic artery and transcatheter arterial embolization (TAE).

It was noted that due to delayed presentation of this condition and associated decompensated liver function, the mortality is high among patients undergoing emergency surgery. In our centre, the patients were subjected to multidisciplinary approach including TAE, facilitating selection of the suitable patients for delayed resection though some of them had to undergo emergency liver resection. The aim of this study was to analyze the disease free survival and overall survival of patients presented as ruptured HCC to a tertiary Hepato-Pancreato-Biliary (HPB) referral centre in Malaysia.

MATERIALS AND METHODS

A retrospective review was carried out on all patients who were admitted with final diagnosis of ruptured HCC in the Department of HPB Surgery, Selayang Hospital, Malaysia from January 2001 till December 2010. Data was collected on the patients' demographics, clinical presentation, investigative modalities during the first presentation (blood, tumor marker), Child's score, type of treatment given, operative data, histopathological results and the outcome. The outcomes that were studied include disease free survival and patient's overall survival. The required data was retrieved from the hospital electronic medical records, Powerchart(Cerner Corporation Inc., USA) and supplemented with registry from Interventional Radiology record of chemoembolization and registry from hepatobiliary operative surgery records.

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Statistical analyses

This is a case series and descriptive study and therefore there was no statistical inference was done. Descriptive analysis and Kaplan-Meier plot were derived using SPSS version 19.0 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.).

RESULTS

Twenty two patients who were admitted to the HPB department at the Hospital Selayang from January 2001 to December 2010 with a diagnosis of ruptured HCC were included in this study. The initial diagnosis was made clinically and radiologically. The patients were grouped according the treatments they received. The emergency resection (ER) group was defined as patients who underwent emergency liver resection (n=15). The TAE group was defined as patients who had only TAE as treatment (n=2). The delayed resection (DR) group was defined as patients who underwent hemostasis by TAE followed by delayed resection (n=5).

Profile

Out of the 22 patients, 19 (86.4%) were male and 3 (13.6%) were female. Their ages ranged from 23 to 82 years. The ethnic distribution showed the majority of the patients were Chinese, comprising 15 patients (68.2%), followed by Malays 27.3% and there was one patient from other races (aborigine). There were no Indian patients presented with ruptured HCC during this 10 year duration of the study. The patients were referred from all over Malaysia, from government hospitals as well as private hospitals. Some patients were referred immediately after the initial presentation with the diagnosis of ruptured HCC after stabilization whereas there were cases which were diagnosed as ruptured HCC after radiological investigation when they came for consultation.

Symptoms

The study investigated the percentage of symptoms presence. The symptoms recorded are shock, jaundice, epigastric pain, right hypochondriac (RHC) pain, abdominal pain, encephalopathy, previous history of HCC treatment and history of diabetes mellitus (DM). The result is presented in Table I. The common clinical findings on examination were tachycardia (12 patients with the percentage of 54.6%), abdominal tenderness (45.5%) and hypotension (40.9%). Overall, nine out of 22 patients (40.9%) presented with signs of shock. Only two of the patients (9.1%) had ascites. None of the patients were documented to have fever.

Laboratory results

The commonest liver enzyme noted to be deranged in ruptured HCC patients was AST (11 patients with percentage of (50%). The ALP was noted to be deranged in five patients (22.7%) whereas ALT was deranged in nine patients (40.9%). The GGT was deranged in seven patients (31.8%). The total hyperbilirubinemia was present in eight of 22 patients (36.4%). Thirteen patients (40.9%) were noted to have hypoalbuminemia. Though 17 patients (77.2%) presented with anemia but five patients who presented with ruptured HCC had normal Hb levels. TWBC was elevated in seven patients whereas four patients had thrombocytopenia.

Prothombin time was prolonged in six patients (27.3%). Renal impairment was not noted in majority of the patients presenting with ruptured HCC. The AFP was noted to be elevated in 13 patients (59%). The two parameters which were significantly deranged in majority of the patients were serum albumin and hemoglobin level.

Hepatitis status and history of alcoholism

Nineteen out of 22 patients (86.4%) who had ruptured HCC had hepatitis B infection whereas only one patient had Hepatitis C infection. There were no patients with both hepatitis B and C infections documented. There were two patients (9.1%) who had no hepatitis B or C infections in this group of patients. There was history of alcoholism in 27.3% of the patients.

Classification of child's score

Analysis of Child's score in these patients showed 16 patients (72.3%) were scored as Child's A whereas only two patients were in Child's C classification as shown in the Table II.

Embolization and type of surgery done

There were seven patients (31.8%) who underwent TAE as initial treatment. It was successful in five patients (71.4%). Both of the unsuccessful TAE patients were in poor Child's score (Child's C and poor Child's B) and were not fit for surgery. Twenty patients underwent surgery in this group of patients where 15 patients were subjected to emergency surgery [these patients will be grouped as emergency resection group (ER) without TAE. One of the patients in this group underwent laparotomy and noted to have advanced disease with very cirrhotic liver intraoperatively, so no liver resection was done. Five patients who had successful TAE underwent delayed surgery where these patients were grouped as delayed resection group (DR) (See Figure 1).

Characteristics and Histopathological Features

The commonest site of ruptured tumor in HCC was left lateral segments (35%). The number of tumors were analysed based on radiological findings on initial presentation and intraoperative findings. About 45.5% (10 patients out of 22 patients) of patient had single tumor on diagnosis. Nine of the patients were noted to have multiple tumors on diagnosis. Out of 22 cases, 55% of the cases at least one tumor > 5cm and there were 7 cases the tumor size was more than 10cm. Even small size HCC (<5cm) has a risk of rupture as noted in this study in 45% of the cases. All the cases noted to have spontaneous rupture of tumor and there was no other aetiology noted. On diagnosis of ruptured HCC, 7 patients (31.8%) were documented to have extrahepatic disease. Seven patients (36.8%) were noted to have microvascular invasions and 16 patients (84.2%) of the patients had R0 resection done (clear margins). Nine out of 19 patients had positive satellite nodules on the histopathological examination.

Outcome

The hospital stay of the patients ranged from 2 to 60 days with mean of 14.5 days of duration of admission.

Eleven patients out of 20 patients were noted to have recurrence during their follow up after receiving surgical treatment. Out of the 22 patients analyzed, mortality rate

Table I: Presence of symptoms

Presence of symptoms	Frequency	Percentage
Shock	8	36.4%
Jaundice	1	4.5%
Epigastric pain(EPI pain)	8	36.4%
RHC Pain	10	45.5%
Abd Pain	5	22.7%
Encephalopathy (Encep)	0	0%
HCC treatment (HCC treat)	4	18.2%
Diabetes mellitus	4	18.2%

Table II: Child's criteria

Child's criteria	Frequency	Percentage
A (5-6)	16	72.3%
B (7-9)	4	18.2%
C (10-15)	2	9.1%

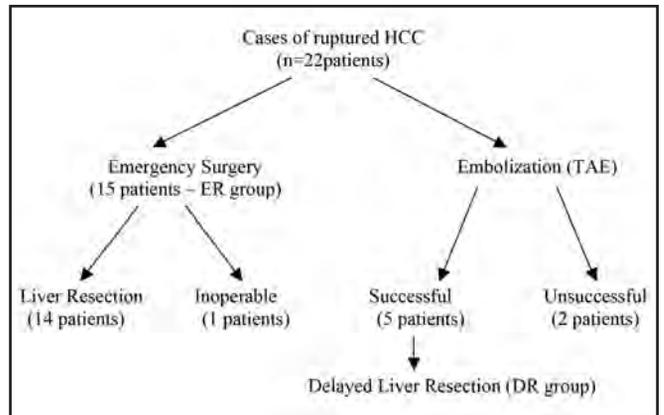


Fig. 1 :An overview of the clinical course of the patients presenting with ruptured HCC.

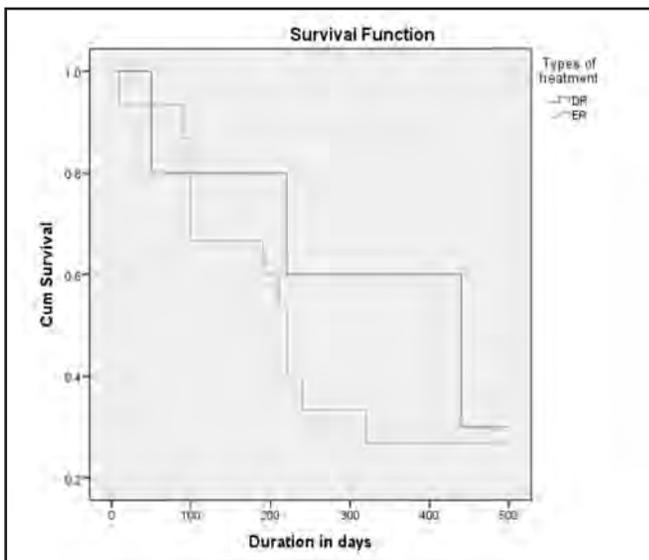


Fig. 2 : Survival function of mortality in days between DR and ER (Overall survival).

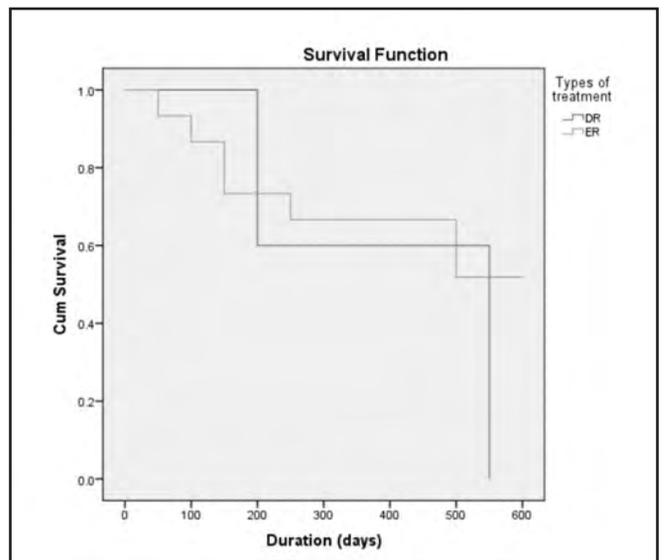


Fig. 3 : Survival function of recurrence in days between ER and DR (Disease free survival).

was 81.8%. Only 4 patients (18.2%) noted be alive during the follow up. The median survival of patients treated with DR was 433.3 days and ER was 212.5 days. In other words, one year survival for ER and DR are 40.0% and 72.7% respectively. The median survival of patients treated with DR was 525.0 days however no median survival for ER. In other words, one year survival for DR and ER are 60.0% and 66.7% respectively (See Figure 2 and Figure 3).

DISCUSSION

In Malaysia, according to the 2nd National Cancer Registry report (NCR)², HCC was identified as 10th commonest cancer among males in Peninsular Malaysia. In the NCR report, it was noted that the incidence in male was 378 per 100,000 population and 152 per 100,000 population in female in Peninsular Malaysia in 2003. The male to female ratio was 3.9:1.6. Among male patients, the ethnic composition of the patients in the HCC was made up of 35.6% of Malays, 59.4% of Chinese and 5% Indians. In this study, ruptured HCC was

noted to be common among male patients (86.4%), as HCC itself has male preponderance¹¹. As the Chinese patients has the highest incidence of HCC among ethnics in Malaysia, the distribution of ruptured HCC also showed similar pattern among the ethnics.

However, this may not be true incidence of all patients in Malaysia with ruptured HCC as there are also other hepatobiliary centers and private hospitals that may have treated these patients. Furthermore, there may have been ruptured HCC patients who was never admitted to Hospital Selayang but seen as outpatient for consultation, missed from the registry if the final diagnosis was not documented as ruptured HCC. Ruptured HCC was noted to be rare presentation among Indian population in this country though the documented incidence among Indian males was only 5% according to the NCR report². It must be taken into consideration that in this series, only patients with ruptured HCC were included. This could lead to bias in the study demographic characteristic.

Relevant history of tachycardia and hypotension indicating shock on presentation or presence of shock during presentation were the significant features in clinical presentation of ruptured HCC patients as has been noted by some groups in literature^{6-7,10}. The fact that ruptured HCC in this series occurred in two patients whom were non alcoholics with no HBV/HCV infection indicates the etiology of HCC may not be important in determining the risk for HCC rupture. This indicates the 30 day mortality for this study is 13.6% (including 2 patients died due unsuccessful TAE) but among the 20 patients that underwent surgery, the 30 day mortality was 4.5%. This is low compared to the figures documented in many other studies for ruptured HCC which ranged from 25% to 75%¹²⁻²². The 30 day mortality rate for ruptured HCC is influenced by old age, low hemoglobin level, serum bilirubin level, high serum AST level, shock on hospital admission, patients comorbid, prolonged prothrombin and presence of hepatic encephalopathy and unsuccessful embolization^{13-14,20-21,23-25}.

In this study, 55% of patients underwent surgery had small sized tumor which is <5cm in contrast to the reports from the literature which stated ruptured HCCs tend to be large(>5cm)²⁶. The spontaneous rupture of hepatocellular carcinoma carries high morbidity and mortality. Overall, the initial treatment goals are hemodynamic stabilization, hemostasis, and preservation of functioning liver tissue. The treatment options available are conservative management, emergency hepatic resection, packing, ligation of hepatic artery and transcatheter arterial embolization (TAE) and delayed surgery^{13,26-27,21,28-31}. It was noted that due to delayed presentation of this condition and associated decompensated liver function, the mortality is high among patients undergoing emergency surgery³².

There is strong evidence in the literature to support the benefit of delayed surgery after successful TAE^{13-14,26-27,31-34}. Delayed surgery noted to give better results than an aggressive approach. It also gives time to build up patient once hemodynamic stability is achieved by TAE for liver resection once patient is stable and ready. This study showed lower in hospital mortality in delayed surgical group as has been noted in the literature^{13,26,28}. The median overall survival of patients treated with DR (433.3 days) was longer than ER (212.5 days). The overall mortality rate in this study was 60%. Only four patients were noted to be alive at end of the study. The one year survival rate for ER and DR are 40% and 72.7% respectively. This is similar to what has been observed few other studies^{26,35-37}, supporting TAE as first line treatment followed by surgery in ruptured HCC. In the published studies, the 1-year survival ranged from 54% - 77%, and the 3-year survival rates ranged from 35% - 48% for patients with DR. In this study, 55% of the patients noted to have recurrence during their follow up. The 1-year disease free survival for ER and DR are 60% and 66.7% respectively.

This is a case series study where stronger evidence from more sample needs to be evaluated although it might takes few decades to get these data. Meanwhile, the disease incidence and prevalence in Malaysia might have been under reported in this study since the finding was reported only in single and tertiary center. However, with ten years of data, some important pattern had been seen and earlier outcome were been investigated.

CONCLUSIONS

Ruptured HCC is a life threatening hepatobiliary emergency. Findings of shock symptoms and signs with coagulopathy clinically and biochemically may support high index of suspicion of the diagnosis. The 30 days mortality in the surgical group was low (4.5%). This study supports the clinical practice of TAE should be the first line treatment followed by staged surgery in suitable candidates with ruptured HCC.

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Figures legend

Figure 1 and Figure 2

DR = Delayed Liver Resection

ER = Emergency surgery

REFERENCES

1. American Cancer Society. Global Cancer Facts & Figures 2nd Edition. Atlanta: American Cancer Society; 2011
2. GCC Lim, Y Halimah (Eds). Second Report of the National Cancer Registry. Cancer Incidence in Malaysia 2003. National Cancer Registry. Kuala Lumpur 2004
3. Hung MC, Wu HS, Lee YT, Hsu CH, Chou DA, Huang MH. Intraoperative metastasis of hepatocellular carcinoma after spontaneous rupture: a case report. *World J Gastroenterol* 2008; 14: 3927-31.
4. 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
5. Battula N, Madanur M, Priest O, Srinivasan P, O'Grady J, Heneghan MA, et al. Spontaneous Rupture of hepatocellular carcinoma: a Western experience. *Am J Surg* 2009;197: 164-7.
6. Dewar GA, Griffin SM, Ku KW, Lau WY, Li AK. Management of bleeding liver tumours in Hong Kong. *Br J Surg* 1991; 78: 463-6.
7. Miyamoto M, Sudo T, Kuyama T. Spontaneous rupture of hepatocellular carcinoma: a review of 172 Japanese cases. *Am J Gastroenterol* 1991; 86: 67-71.
8. Nagasue N, Inokuchi K. Spontaneous and Traumatic Rupture of Hepatoma. *Br J Surg* 1979; 66: 248-50.
9. Chen MF, Hwang TL, Jeng LB, Jan YY, Wang CS. Surgical treatment for spontaneous rupture of hepatocellular carcinoma. *Surg Gynecol Obstet* 1988; 167: 99-102.
10. Ong GB, Chu EP, Yu FY, Lee TC. Spontaneous Rupture Of Hepatocellular Carcinoma. *Br J Surg* 1965; 52: 123-9.
11. Lin CC, Chen CH, Tsang YM, Jan IS, Sheu JC. Diffuse intraperitoneal metastasis after spontaneous rupture of hepatocellular carcinoma. *J Formos Med Assoc* 2006; 105: 577-82.
12. Xu HS, Yan JB. Conservative management of spontaneous ruptured hepatocellular carcinoma. *Am Surg* 1994; 60: 629-33.
13. Li WH, Cheuk EC, Kowk PC, Cheung MT. Survival after transarterial embolization for spontaneous ruptured hepatocellular carcinoma. *J Hepatobiliary Pancreat Surg* 2009; 16: 508-12.
14. Kirikoshi H, Saito S, Yoneda M, Fujita K, Mawatari H, Uchiyama T. Outcomes and factors influencing survival in cirrhotic cases with spontaneous rupture of hepatocellular carcinoma: a multicenter study. *BMC Gastroenterol* 2009; 9: 29.
15. Ong GB, Taw JL. Spontaneous rupture of hepatocellular carcinoma. *BMJ* 1972; 4: 146-9.
16. Nouchi T, Nishimura M, Maeda M, Funatsu T, Hasumura Y, Takeuchi J. Transcatheter arterial embolization of ruptured hepatocellular carcinoma associated with liver cirrhosis. *Dig Dis Sci* 1984; 29: 1137-41.
17. Cherqui D, Panis Y, Rotman N, Fagniez PL. Emergency liver resection for spontaneous rupture of hepatocellular carcinoma complicating cirrhosis. *Br J Surg* 1993; 80: 747-9.
18. Chen CY, Lin XZ, Shin JS, Lin CY, Leow TC, Chen CY. Spontaneous rupture of hepatocellular carcinoma: a review of 141 Taiwanese cases and comparison with nonruptured cases. *J Clin Gastroenterol* 1995; 21: 238-42.
19. Leung KL, Lau WY, Lai PBS, Yiu RYC, Meng WCS, Leow CK. Spontaneous rupture of hepatocellular carcinoma: Conservative management and selective intervention. *Arch Surg* 1999; 134: 1103-7.

20. Liu CL, Fan ST, Lo CM, Tso WK, Poon RT, Lam CM. Management of spontaneous rupture of hepatocellular carcinoma: single center experience. *J Clin Oncol* 2001; 19: 3725-32.
21. Bassi N, Caratozzolo E, Bonariol L, Ruffolo C, Bridda A, Padoan L. Management of ruptured hepatocellular carcinoma: Implications for therapy. *World J Gastroenterol* 2010; 16: 1221-5.
22. Kung CT, Liu BM, Ng SH, Lee TY, Cheng YF, Chen MC. Transcatheter arterial embolization in the emergency department for hemodynamic instability due to ruptured hepatocellular carcinoma: analysis of 167 cases. *AJR Am J Roentgenol* 2008; 191: W231-239.
23. Okazaki M, Higashihara H, Koganemaru F, Nakamura T, Kitsuki H, Hoashi T. Intraoperative hemorrhage from hepatocellular carcinoma: emergency chemoembolization or embolization. *Radiology* 1991; 180: 647-51.
24. Corr P, Chan M, Lau WY, Metreweli C. The role of hepatic arterial embolization in the management of ruptured hepatocellular carcinoma. *Clin Radiol* 1993; 48: 163-5.
25. 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: 338-341.
26. Buczkowski AK, Kim PT, Ho SG, Schaeffer DF, Lee SI, Owen DA. Multidisciplinary management of ruptured hepatocellular carcinoma. *J Gastrointest Surg* 2006; 10: 379-86.
27. Maoz D, Sharon E, Chen Y, Grief F. Spontaneous hepatic rupture: 13-year experience of a single center. *Eur J Gastroenterol Hepatol* 2010; 22: 997-1000.
28. Lai EC, Lau WY. Spontaneous rupture of hepatocellular carcinoma: a systematic review. *Arch Surg* 2006; 141: 191-8.
29. Choi BG, Park SH, Byun JY, Jung SE, Choi KH, Han JY. The findings of ruptured hepatocellular carcinoma on helical CT. *Br J Radiol* 2001; 74: 142-6.
30. Yang JD, Roberts LR. Hepatocellular Carcinoma: A Global View. *Nat Rev Gastroenterol Hepatol* 2010; 7: 448-58.
31. Leung KL, Lau WY, Lai PBS, Yiu RY, Meng WC, Leow CK. Spontaneous rupture of hepatocellular carcinoma: Conservative management and selective intervention. *Arch Surg* 1999; 134: 1103-7.
32. Tarantino L, Sordelli I, Calise F, Ripa C, Perrotta M, Sperlongano P. Prognosis of patients with spontaneous rupture of hepatocellular carcinoma in cirrhosis. *Updates Surg* 2011; 63: 25-30.
33. Tanaka A, Takeda R, Mukaiharu S, Hayakawa K, Shibata T, Itoh K. Treatment of ruptured hepatocellular carcinoma. *International Journal of Clinical Oncology*. 2001;6(6): 291-5.
34. Marini P, Vilgrain V, Belghiti J. Management of spontaneous rupture of liver tumors. *Digestive Surgery* 2002; 19: 109-13.
35. Shimada R, Imamura H, Makuuchi M, Soeda J, Kobayashi A, Noike T. Staged hepatectomy after emergency transcatheter arterial embolization for ruptured hepatocellular carcinoma. *Surgery* 1998; 124: 526-35.
36. Shuto T, Hirohashi K, Kubo S, Tanaka H, Hamba H, Kubota D. Delayed hepatic resection for ruptured hepatocellular carcinoma. *Surgery* 1998; 124: 33-7.
37. Yeh CN, Lee WC, Jeng LB, Chen MF, Yu MC. Spontaneous tumor rupture and prognosis in patients with hepatocellular carcinoma. *Br J Surg* 2002; 89: 1125-9.