European Journal of Radiology 84 (2015) 366–371

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Prognosis and therapy for ruptured hepatocellular carcinoma: Problems with staging and treatment strategy

Atsushi Hiraoka[a,*], Tomoe Kawamura[a], Toshihiko Aibiki[a], Tomonari Okudaira[a], Akiko Toshimori[a], Hiroka Yamago[a], Hiromasa Nakahara[a], Yoshifumi Suga[a], Nobuaki Azemoto[a], Hideki Miyata[a], Yasunao Miyamoto[a], Tomoyuki Ninomiya[a], Tadashi Murakami[b], Yoshihiro Ishimaru[b], Hideki Kawasaki[c], Masashi Hirooka[d], Masanori Abe[d], Bunzo Matsuura[d], Yoichi Hiasa[d], Kojiro Michitaka[a]

[a] Gastroenterology Center, Ehime Prefectural Central Hospital, Kasuga-cho 83, Matsuyama, Ehime 790-0024, Japan
[b] Department of Radiology, Ehime Prefectural Central Hospital
[c] Department of Surgery, Ehime Prefectural Central Hospital
[d] Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Ehime, Japan

ARTICLE INFO

Article history:
Received 3 July 2014
Received in revised form
10 November 2014
Accepted 28 November 2014

Keywords:
Hepatocellular carcinoma
Rupture
Prognosis
Transcatheter arterial embolization
Surgical resection

ABSTRACT

Background: There are no clear criteria established for treating a ruptured hepatocellular carcinoma (HCC). To elucidate the clinical features of affected patients, we examined prognosis and therapy choices.
Materials/methods: We enrolled 67 patients treated for a ruptured HCC (HCV 44, HBV 5, HBV + HCV 1, alcohol 2, others 15; naïve HCC 34, recurrent 33) from 2000 to 2013, and investigated their clinical background and prognosis.
Results: Median survival time (MST) for all cases was 4 months. For patients who survived for more than 1 year after rupture, the percentages of Child-Pugh C and positive for portal vein tumor thrombosis (PVTT)/extrahepatic metastasis were less than for those who died within 1 year. Child-Pugh classification (A:B:C = 14:15:5 vs. 4:9:20, $P < 0.001$) was better, while the percentage of patients with multiple tumors was lower [19/34 (55.9%) vs. 29/33 (87.9%), respectively; $P < 0.001$] in the naïve group. The 1- and 3-year survival rates were better in the naïve as compared to the recurrent group (60.6% and 33.3% vs. 12.6% and 0%, respectively; $P < 0.01$). MST according to modified TNM stage (UICC 7th) calculated after exclusion of T4 factor of rupture, stage I was better than others (22.7 vs. (II) 2.2, (III) 1.2, and (IV) 0.7 months) ($P = 0.010$).
Conclusion: In patients with a ruptured HCC, especially those with a single tumor, and without decompensated liver cirrhosis and PVTT/extrahepatic metastasis, better prognosis can be expected with curative treatment. The present naïve group included more of such cases than the recurrent group, indicating the effectiveness of curative therapy.

1. Introduction

Some patients are diagnosed with hepatocellular carcinoma (HCC) following rupture as the initial symptom. In addition, repeated recurrence and progression are often observed, with rupture occurring in some of those cases.

A patient with a ruptured HCC is generally considered to have a poor prognosis and treated as T4 in the 7th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) [1]. In the AJCC/UICC TNM system, T4 is defined as "tumors with direct invasion of adjacent organs other than the gallbladder, or perforation of visceral peritoneum", thus rupture of an HCC is classified as T4. Patient prognosis following rupture of an HCC is generally poor and the mortality rate of acute phase cases has been reported to range from 25% to 75% [2]. However, some affected patients show a good clinical course. In this context, it may be problematic that all ruptured HCC cases are classified as T4. Furthermore, among the various guidelines for treatment of an HCC, there is no clear consensus regarding how to treat a patient following rupture.

* Corresponding author. Tel.: +81 89 947 1111; fax: +81 89 943 4136.
E-mail address: hirage@m.ehime-u.ac.jp (A. Hiraoka).

http://dx.doi.org/10.1016/j.ejrad.2014.11.038
0720-048X/

We retrospectively evaluated the clinical features of HCC rupture cases, as well as therapy and prognosis to clarify the best treatment for affected patients.

2. Materials/methods

From January 2000 to December 2013, total 1460 patients with HCC (naïve HCC 1252, recurrence with past history of treatment 208) (total 4182 admissions) of Ehime Prefectural Central hospital were enrolled. Of those, 67 patients treated for a ruptured HCC (71 ruptures) were enrolled (HCV 44, HBV 5, HBV + HCV 1, alcohol 2, others 15). There were 34 patients without a past history of HCC (naïve group) and 33 recurrent patients (recurrence group). We investigated their clinical backgrounds and prognoses of patients who died within 3 months and of those who died within 1 year after rupture, retrospectively. In addition, we examined factors in patients with a good prognosis and clinical course after rupture. We modified TNM stage (UICC 7th) and used it for evaluation of the prognosis by tumor status after excluded T4 factor of rupture (modified TNM stage).

The diagnosis of HCC was based on past pathological findings, or evidence of tumor formation in the liver (with arterial hypervascularization) shown by dynamic computed tomography (CT) imaging [3] and/or angiography.

Transcatheter arterial embolization (TAE) was performed in cases considered to be tolerant of that treatment and without severely poor hepatic reserve function (total bilirubin over 3 mg/dL) after improvement from hypovolemic shock status. Radiologists and hepatologists performed all of the TAE procedures. A microcatheter was inserted into the artery feeding the ruptured tumor after a conventional hepatic angiography examination. A gelatin sponge (Gelform®, Upjohn, Kalamazoo, MI, USA; or Gelpart®, Nippon Kayaku Co., Ltd., Tokyo, Japan) was used for embolization. The goal of embolization was disappearance of staining of the ruptured tumor. After stabilization of systemic circulation and/or stopping of bleeding in cases with active bleeding upon admittance, surgical resection was planned from 2 weeks to 1 month after the rupture event, especially in cases with good hepatic reserve function and whose tumor(s) were considered to be resectable.

The present study permitted by ethics committee of Ehime Prefectural Central hospital. The authors have no financial conflicts of interest to disclose concerning this study.

2.1. Statistical analysis

Data are expressed as the mean ± standard deviation (SD). Statistical analyses were performed using Student's *t* test for unpaired data, Fischer's exact test, a Mann-Whitney U test, and a log-rank test, as appropriate. All statistical analyses were performed using SPSS 21 J (SPSS Japan Inc., Tokyo, Japan), with a p value less than 0.05 considered to show statistical significance.

3. Results

Of a total 4182 admissions, 71 were ruptured HCCs (1.7%). A rupture occurred in 2.7% of naïve cases (34/1252) and 4.6% of all patients (67/1460). Median survival time (MST) for all cases was 4 months. Twenty-one of the 67 (31.3%) patients with rupture died within 1 month after the event (naïve group 5, recurrence group 16) and 30 (44.8%) died within 3 months. The 1-, 3-, and 6-month, and 1- and 2-year survival rates were 64.1%, 52.0%, 44.7%, 36.7%, and 22.9%, respectively (Fig. 1).

We analyzed the clinical features and therapeutic choices of patients who survived for more than 3 months after rupture ($n = 30$) and those who died within 3 months ($n = 30$) after exclusion of patients who were alive and whose observation period was under 3 months ($n = 7$). Total-bilirubin and Child-Pugh class were better, and the frequencies of single tumor and naive status was greater in those who survived more than 3 months after rupture as compared to those who died within 3 months (Table 1).

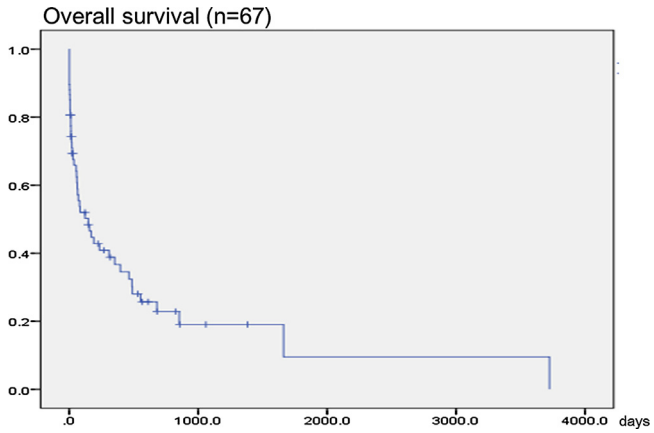

Fig. 1. Survival rates of patients with ruptured HCC ($n = 67$).
The 1-, 3-, and 6-month, and 1- and 2-year survival rates were 64.1%, 52.0%, 44.7%, 36.7%, and 22.9%, respectively.

We analyzed the clinical features and therapeutic choices of those who survived over 1 year after rupture ($n = 17$) and compared them to those who died within 1 year ($n = 38$) after exclusion of patients who were alive and whose observation period was under 1 year ($n = 12$). Among those who were alive over 1 year after rupture, total-bilirubin and albumin levels, and Child-Pugh class were better, while the frequencies of single tumor, negative for portal vein tumor thrombosis (PVTT) and/or extrahepatic metastasis, and naïve status were greater than those of patients who died within 1 year (Table 2).

When TNM stage (UICC 7th) was calculated after exclusion of the T4 factor of rupture (modified TNM), MST for modified TNM stage I was better than that for the other stages (20.7 vs. (II) 2.2, (III) 1.2, and (IV) 0.7 months, respectively; $P = 0.009$) (Fig. 2).

Clinical data for the naïve and recurrence groups are shown in Table 3. The levels of albumin (2.59 ± 0.69 vs. 3.33 ± 0.50 g/dL, $P = 0.021$) and fucosylated alpha-fetoprotein (31.7 ± 27.1 vs. 31.1 ± 33.5, $P = 0.041$), and Child-Pugh classification (A:B:C = 4:9:20 vs. 14:15:5, $P < 0.001$) were worse, while the percentage of patients with multiple tumors was greater [29/33 (87.9%) vs. 19/34 (55.9%), $P < 0.001$] in the recurrence group than the naïve group. There were no significant differences between the groups in regard to other

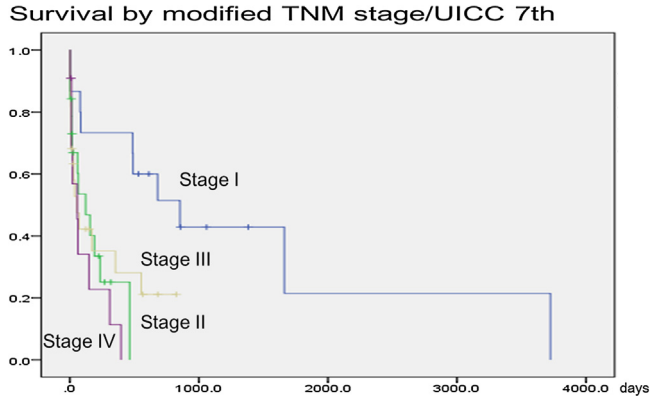

Fig. 2. Survival rates according to modified TNM stage (UICC 7th) calculated after exclusion of T4 factor. The median survival times for modified stage I, II, III, and IV were 20.7, 2.2, 1.2, and 0.7 months, respectively ($P = 0.010$).