Original paper

Comparison of conservative treatment versus transcatheter arterial embolisation for the treatment of spontaneously ruptured hepatocellular carcinoma

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Abstract

Purpose: To elucidate the prognostic factors in the spontaneous rupture of hepatocellular carcinoma (HCC) and to determine whether transcatheter arterial embolisation (TAE) is associated with better prognosis compared to conservative treatment.

Material and methods: A retrospective multicentre study was conducted involving 71 patients with spontaneous rupture of HCC. A conservative treatment group (Cons T group) included 20 patients, while a transcatheter arterial embolisation group (TAE group) included 51 patients.

Results: The median survival time (MST) in the Cons T group was only 16 days and the survival rate was 39% at one month, whereas the MST in the TAE group was 28 days and the one month survival rate was 63%. However, there is no statistically significant difference in the overall survival between Cons T and TAE groups (p = 0.213). Multivariable analysis identified only the presence of distant metastasis as an independent prognostic factor (p = 0.023). A subanalysis including patients without distant metastasis showed that the presence of portal vein tumour thrombosis was a significant prognostic factor (p = 0.015).

Conclusions: Distant metastasis appears to be a prognostic factor in spontaneous rupture of HCC. In cases without distant metastasis, portal vein tumour thrombosis could influence the prognosis. Our data failed to prove any benefit of TAE as the primary management.

Key words: hepatocellular carcinoma, rupture, prognosis, transcatheter arterial embolization (TAE).

Introduction

The spontaneous rupture of hepatocellular carcinoma (HCC) is a rare but life-threatening presentation of this disease and cause of death in 6.4% of such cases in Japan [1]. The affected patients frequently have poor liver function due to liver cirrhosis and advanced tumour stage, and previous reports showed that the one-month mortality rate ranged from 28% to 71% with a median survival period of 4 to 32 weeks [2-8]. The spontaneous rupture of HCC has been treated with several different methods such as conservative treatment (Cons T) and transcatheter arterial embolisation (TAE).
embolisation (TAE). However, due to its relative rarity and difficulty in conducting prospective comparisons, there is little consensus on the appropriate management and prognostic factors. Therefore, we introduced a multi-centre retrospective study to elucidate the prognostic factors in the spontaneous rupture of HCC and to determine whether TAE is associated with better prognosis than Cons T.

### Material and methods

#### Study population and clinical data

This multicentre retrospective study was approved by the Institutional Review Board of each participating institution, and the need for informed consent acquisition was waived.

We retrospectively analysed pooled data obtained from the clinical and radiological records of 71 consecutive patients (56 males and 15 females; age range 32-86 years, mean 65.1 years) with spontaneous rupture of HCC, who were treated between October 1989 and December 2011 in three different sites in two countries: hospital A (15 patients), B (43 patients), and C (13 patients). Cause of liver damage (hepatitis type), Child-Pugh classification (A, B, or C), presence/absence of hepatic encephalopathy, ascites, shock vital (systolic blood pressure < 80 mmHg), portal vein tumour thrombosis, distant metastasis, and past history of HCC treatment, tumour size (maximum diameter on axial CT image), tumour morphology (massive or diffuse), serum α-fetoprotein (AFP), blood chemistry data (serum albumin, total bilirubin, aspartate aminotransferase [AST], alanine transaminase [ALT], blood urea nitrogen [BUN], and creatinine), haemoglobin, prothrombin time, primary management (TAE or conservative), and secondary management (TAE or surgery or none) were recorded.

#### Treatment methods

Attending physician assessed patients’ states and conducted the treatment method (TAE or Cons T) and obtained consent from the patient or patient’s family. TAE was approached from femoral artery with the Seldinger technique. Angiographic catheter was inserted in the hepatic artery and contrast agent was injected, so that branches of bleeding hepatic artery were identified. As an embolic technique, a haemostatic agent and/or pain relief drug was intravenously infused.

#### Statistical analyses

The χ² test for independence or the Fisher exact test was used for comparison of the two groups. To determine factors influencing overall survival, a univariate analysis was performed using the Kaplan-Meier method and a log-rank test. The survival period was defined as the length of time from the onset of the spontaneous rupture of HCC until death. Subsequently, to identify independent prognostic factors, multivariable analysis was performed using the Cox proportional hazard model from which hazard ratios with their confidence intervals and p values were reported. P < 0.05 was considered statically significant for all analyses. All statistical analyses were performed using StatView; SAS software.

### Results

The patients’ characteristics are shown in Table 1. Cause of liver damage was alcoholic in seven patients (10%), hepatitis B in 28 patients (39%), hepatitis C in 18 patients (25%), and non-B non-C in six patients (8%). Eight patients (11%) were in Child-Pugh A class, 34 (48%) in B class, and 22 (31%) in C class. Five patients (7%) had hepatic encephalopathy. Fifty-nine patients (83%) had ascites. Ten patients (16%) had shock vital at the time of admission. Mean tumour size of HCCs was 7.5 cm. Forty-two patients (59%) had past history of HCC treatment. Mean follow-up period was 106.8 days (range 0-2972 days).

Conservative treatment (Cons T group) was employed as the primary management in 20 patients (28%), while transcatheter arterial embolisation (TAE group) was performed in the remaining 51 patients (72%). Hepatic encephalopathy was more frequent in the Cons T group than in the TAE group (p = 0.001). In addition, serum total bilirubin was significantly higher (p = 0.012) and prothrombin time was significantly shorter (p = 0.003) in the Cons T group than in the TAE group. No significant difference was found in the other variables between the two groups.

The median survival time (MST) was 22 days, and one-month mortality rate was 56% in all patients. MST in the Cons T group was 16 days and the survival rate was poor: 75 % at seven days, 60 % at 14 days, 39 % at one month, and 22% at three months. On the other hand, MST in TAE group was 28 days and the survival rate was 83% at seven days, 73% at 14 days, 63% at one month, 27% at three months, 18% at 12 months, and 18% at 24 months. However, there was no statistically significant difference in the survival rate between the Cons T and TAE groups (p = 0.213) (Table 2, Figure 1). Factors associated with significantly lower overall survival included being female (p = 0.006), higher Child-Pugh grade (p = 0.012), presence of hepatic encephalopathy (p < 0.001), presence of portal vein tumour thrombosis (p < 0.001), presence of distant metastasis (p = 0.005), presence of past history of HCC (p = 0.049), lower serum albumin (p = 0.018), higher total bilirubin (p < 0.001), and longer prothrombin time (p = 0.017) (Table 2).

A multivariable analysis admitted factors that were shown to be significant in the univariate analysis. Hepatic encephalopathy, serum total bilirubin, albumin, and
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Table 1. Patient characteristics of the analysed cohort and comparisons between conservative treatment group (Cons T) and transcatheter arterial embolisation (TAE) groups

| Variables                              | Total (n = 71) | Cons T group (n = 20) | TAE group (n = 51) | p value |
|----------------------------------------|---------------|-----------------------|--------------------|---------|
| Patients, n (%)                        | 71            | 20 (28)               | 51 (72)            | 0.378 NS|
| Age (y)                                | 65.1 (13.3)   | 68.2 (10.7)           | 63.8 (14.1)        | 0.378 NS|
| Sex, n (%)                             |               |                       |                    | 0.621 NS|
| Male                                   | 56 (79)       | 15 (75)               | 41 (80)            |        |
| Female                                 | 15 (21)       | 5 (25)                | 10 (20)            |        |
| Cause of liver damage, n (%)           |               |                       |                    | 0.767 NS|
| Alcohol                                | 7 (10)        | 1 (5)                 | 6 (12)             |        |
| Hepatitis B                            | 28 (39)       | 7 (35)                | 21 (41)            |        |
| Hepatitis C                            | 18 (25)       | 4 (20)                | 14 (27)            |        |
| Non-B, non-C                           | 6 (8)         | 1 (5)                 | 5 (10)             |        |
| Child-Pugh classification, n (%)       |               |                       |                    | 0.786 NS|
| A                                      | 8 (11)        | 2 (10)                | 6 (12)             |        |
| B                                      | 34 (48)       | 8 (40)                | 26 (51)            |        |
| C                                      | 22 (31)       | 7 (35)                | 15 (29)            |        |
| Hepatic encephalopathy, n (%)          |               |                       |                    | 0.002 NS|
| Present                                | 5 (7)         | 4 (20)                | 1 (2)              |        |
| Ascites, n (%)                         |               |                       |                    | 0.209 NS|
| Present                                | 59 (83)       | 15 (75)               | 44 (86)            |        |
| Shock vital, n (%)                     |               |                       |                    | 0.719 NS|
| Present                                | 16 (22)       | 4 (20)                | 12 (23)            |        |
| Tumour size (cm)                       | 7.5 (3.9)     | 7.2 (0.8)             | 7.6 (4.1)          | 0.842 NS|
| Tumour morphology, n (%)               |               |                       |                    | 0.778 NS|
| Massive                                | 34 (47)       | 6 (30)                | 28 (54)            |        |
| Diffuse                                | 14 (19)       | 5 (25)                | 9 (17)             |        |
| Portal vein tumour thrombosis, n (%)   |               |                       |                    | 0.326 NS|
| Present                                | 19 (27)       | 7 (35)                | 12 (24)            |        |
| History of HCC treatment, n (%)        |               |                       |                    | 0.089 NS|
| Present                                | 42 (59)       | 15 (75)               | 27 (53)            |        |
| Secondary management, n (%)            |               |                       |                    | 0.083 NS|
| TAE                                    | 6 (8)         | 0 (0)                 | 6 (12)             |        |
| Surgery                                | 1 (1)         | 1 (5)                 | 0 (0)              |        |
| None                                   | 62 (87)       | 19 (95)               | 43 (84)            |        |
| Serum albumin (g/l)                    | 2.85 (0.64)   | 2.81 (0.55)           | 2.87 (0.68)        | 0.720 NS|
| Serum total bilirubin (µmol/l)         | 3.47 (5.08)   | 5.89 (8.62)           | 2.51 (2.39)        | 0.012 NS|
| Serum AFP (ng/ml)                      | 47821 (113213)| 7721 (14084)          | 58132 (125013)     | 0.238 NS|
| AST (U/l)                              | 197.8 (262.5) | 205.0 (218.9)         | 195.0 (278.9)      | 0.889 NS|
| ALT (U/l)                              | 114.7 (240.7) | 96.6 (118.5)          | 121.4 (273.4)      | 0.705 NS|
| Haemoglobin (g/dl)                     | 8.99 (2.49)   | 9.16 (2.53)           | 8.92 (2.50)        | 0.726 NS|
| Prothrombin time (s)                   | 32.8 (24.6)   | 18.7 (15.1)           | 37.8 (25.0)        | 0.003 NS|
| BUN (mg/dl)                            | 24.2 (15.7)   | 26.8 (20.4)           | 23.3 (13.7)        | 0.411 NS|
| CRE (mg/dl)                            | 1.43 (1.47)   | 1.23 (0.79)           | 1.50 (1.65)        | 0.524 NS|

Cons T – conservative treatment, TAE – transcatheter arterial embolization, NS – not significant, AFP – α-fetoprotein, AST – aspartate aminotransferase, ALT – alanine aminotransferase
Continuous variables are indicated in the mean (SD)
Table 2. Univariate analysis searching for factors influencing overall survival

| Variables                        | Number | Median survival (day) | p value (log-rank) |
|----------------------------------|--------|-----------------------|--------------------|
| Age                              |        |                       | 0.316 NS           |
| ≤ 58                             | 24     | 17                    |                    |
| > 58 and < 73                    | 22     | 25                    |                    |
| ≥ 73                             | 25     | 20                    |                    |
| Sex                              |        |                       | 0.006              |
| Male                             | 56     | 25                    |                    |
| Female                           | 15     | 10                    |                    |
| Institution                      |        |                       | 0.855 NS           |
| A                                | 15     | 20                    |                    |
| B                                | 43     | 17                    |                    |
| C                                | 13     | 28                    |                    |
| Primary management               |        |                       | 0.213 NS           |
| TAE                              | 51     | 28                    |                    |
| Cons T                           | 20     | 16                    |                    |
| Child-Pugh classification        |        |                       | 0.012              |
| A                                | 8      | 30                    |                    |
| B                                | 34     | 22                    |                    |
| C                                | 22     | 11                    |                    |
| Hepatic encephalopathy           |        |                       | < 0.001            |
| Absent                           | 64     | 25                    |                    |
| Present                          | 5      | 1                     |                    |
| Ascites                          |        |                       | 0.988 NS           |
| Absent                           | 11     | 17                    |                    |
| Present                          | 59     | 22                    |                    |
| Shock vital                      |        |                       | 0.105 NS           |
| Absent                           | 54     | 28                    |                    |
| Present                          | 16     | 10                    |                    |
| Tumour size (cm)                 |        |                       | 0.832 NS           |
| ≤ 4.3                            | 17     | 29                    |                    |
| > 4.3 and < 7.8                  | 18     | 25                    |                    |
| ≥ 7.8                            | 19     | 11                    |                    |
| Tumour morphology                |        |                       | 0.748 NS           |
| Massive                          | 34     | 22                    |                    |
| Diffuse                          | 14     | 16                    |                    |
| Portal vein tumour thrombosis    |        |                       | < 0.001            |
| Absent                           | 52     | 29                    |                    |
| Present                          | 19     | 10                    |                    |
| Distant metastasis               |        |                       | 0.005              |
| Absent                           | 55     | 25                    |                    |
| Present                          | 16     | 14                    |                    |
| History of HCC treatment         |        |                       | 0.049              |
| Absent                           | 29     | 18                    |                    |
| Present                          | 42     | 28                    |                    |
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Table 2. Cont.

| Variables                        | Number | Median survival (day) | p value (log-rank) |
|----------------------------------|--------|-----------------------|--------------------|
| Serum albumin (g/l)              |        |                       | 0.018              |
| ≤ 2.5                            | 23     | 11                    |                    |
| > 2.5 and < 3.2                   | 21     | 38                    |                    |
| ≥ 3.2                            | 20     | 20                    |                    |
| Serum total bilirubin (µmol/l)   |        |                       | < 0.001            |
| ≤ 1.2                            | 23     | 34                    |                    |
| > 1.2 and < 2.5                   | 23     | 20                    |                    |
| ≥ 2.5                            | 24     | 10                    |                    |
| Serum AFP (ng/ml)                |        |                       | 0.173 NS           |
| ≤ 420                            | 14     | 30                    |                    |
| > 420 and < 15 700               | 15     | 15                    |                    |
| ≥ 15 700                         | 15     | 18                    |                    |
| AST (U/l)                        |        |                       | 0.079 NS           |
| ≤ 63                             | 23     | 28                    |                    |
| > 63 and < 144                   | 23     | 18                    |                    |
| ≥ 144                            | 24     | 13                    |                    |
| ALT (U/l)                        |        |                       | 0.228 NS           |
| ≤ 32                             | 24     | 30                    |                    |
| > 32 and < 62                    | 24     | 17                    |                    |
| ≥ 62                             | 22     | 14                    |                    |
| Haemoglobin (g/dl)               |        |                       | 0.125 NS           |
| ≤ 7.7                            | 23     | 16                    |                    |
| > 7.7 and < 10.0                 | 22     | 22                    |                    |
| ≥ 10.0                           | 25     | 30                    |                    |
| Prothrombin time (s)             |        |                       | 0.017              |
| ≤ 14                             | 23     | 34                    |                    |
| > 14 and < 40                    | 23     | 10                    |                    |
| ≥ 40                             | 23     | 22                    |                    |
| BUN (mg/dl)                      |        |                       | 0.732 NS           |
| ≤ 16.1                           | 24     | 25                    |                    |
| > 16.1 and < 23.3                | 24     | 20                    |                    |
| ≥ 23.3                           | 22     | 25                    |                    |
| CRE (mg/dl)                      |        |                       | 0.974 NS           |
| ≤ 0.8                            | 24     | 25                    |                    |
| > 0.8 and < 1.3                  | 21     | 17                    |                    |
| ≥ 1.3                            | 25     | 18                    |                    |

CI – confidence interval, TAE – transcatheter arterial embolization, Cons T – conservative treatment, NS – not significant, HCC – hepatocellular carcinoma, CI – confident interval, AFP – α-fetoprotein, AST – aspartate aminotransferase, ALT – alanine aminotransferase

prothrombin time were excluded from the analysis because they are included in the Child–Pugh classification. The multivariable analysis identified only the presence of distant metastasis as an independent factor determining lower overall survival (p = 0.023) (Table 3, Figure 2).

We performed an additional subanalysis including 55 patients without distant metastasis. A multivariable analysis showed that the presence of portal vein tumour thrombosis was the only significant independent prognostic factor (p = 0.015) (Table 4, Figure 3).
In the past, patients with spontaneously ruptured HCC were treated by various surgical procedures including peri-hepatic packing, suture plication of bleeding tumour, injection of absolute alcohol, hepatic artery ligation, and liver resection [2-13]. However, because those patients tend to have advanced disease and poor liver function from cirrhosis, invasive surgical interventions may not be tolerated. Thus, less invasive treatments such as TAE or conservative management are chosen in the majority of cases. TAE is considered to be highly effective in controlling haemorrhage due to ruptured HCC, and we expected that it would improve prognosis of the affected patients compared to conservative treatment. In fact, our results showed a better prognosis in the TAE group (MST = 28 days) than in the Cons T group (MST = 16 days), but no significant difference in overall survival was revealed between the two groups ($p = 0.213$).

**Table 3. Multivariable analysis searching for factors influencing overall survival**

| Variables                  | Hazard ratio | 95% CI       | $p$ value |
|----------------------------|--------------|--------------|-----------|
| Sex (female)               | 1.967        | 0.889-4.355  | 0.095 NS  |
| Child-Pugh classification  |              |              |           |
| C                          | 2.208        | 0.574-8.491  | 0.249 NS  |
| B                          | 1.282        | 0.361-4.548  | 0.700 NS  |
| Portal vein tumor thrombosis (present) | 2.080 | 0.962-4.497 | 0.063 NS  |
| Distant metastasis (present) | 2.313       | 1.123-4.767  | 0.023     |
| History of HCC treatment (present) | 1.524       | 0.731-3.174  | 0.261 NS  |

CI – confidence interval, NS – not significant, HCC – hepatocellular carcinoma

**Table 4. Multivariable analysis including patients without distant metastasis**

| Variables                  | Hazard ratio | 95% CI       | $p$ value |
|----------------------------|--------------|--------------|-----------|
| Sex (female)               | 2.249        | 0.894-5.657  | 0.085 NS  |
| Child-Pugh classification  |              |              |           |
| C                          | 1.849        | 0.368-9.283  | 0.455 NS  |
| B                          | 1.379        | 0.303-6.260  | 0.678 NS  |
| Portal vein tumor thrombosis (present) | 2.896       | 1.222-6.864  | 0.015     |
| Distant metastasis (present) | 1.482       | 0.616-3.564  | 0.380 NS  |

CI – confidence interval, NS – not significant, HCC – hepatocellular carcinoma

**Discussion**

In the past, patients with spontaneously ruptured HCC were treated by various surgical procedures including peri-hepatic packing, suture plication of bleeding tumour, injection of absolute alcohol, hepatic artery ligation, and liver resection [2-13]. However, because those patients tend to have advanced disease and poor liver function from cirrhosis, invasive surgical interventions may not be tolerated. Thus, less invasive treatments such as TAE or conservative management are chosen in the majority of cases. TAE is considered to be highly effective in controlling haemorrhage due to ruptured HCC, and we expected that it would improve prognosis of the affected patients compared to conservative treatment. In fact, our results showed a better prognosis in the TAE group (MST = 28 days) than in the Cons T group (MST = 16 days), but no significant difference in overall survival was revealed between the two groups ($p = 0.213$). An earlier retrospective study reported by Kirikoshi et al. showed a significantly better prognosis in patients treated with TAE (MST = 224.8 days) than in those treated with conservative therapy (MST = 13.1 days)
was found in 12-39% of patients with HCC [1,20-22] and factor of ruptured HCC. Portal vein tumour thrombus factor (TAE in 38 patients with ruptured HCC. Although patients portal vein tumour thrombosis was 10 days while that of lower overall survival (Table 2). MST of 19 patients with vein tumour thrombosis was significantly associated with items as possible prognostic factors. The presence of portal conservative treatment may be preferred in such cases.

Despite a multitude of previous studies, no general consensus has been achieved on prognostic factors in patients with spontaneous rupture of HCC. In our multivariable analysis, the presence of distant metastasis was the only significant factor that was associated with lower overall survival (Table 3, Figure 2). Sixteen patients had distant metastasis (lung in 11 cases, lymph node in two cases, peritoneum in one case, adrenal gland in one case, and bone in one case), and their MST was 10 days (22 days in the absence group). Aoki et al. [6] analysed patients with spontaneous rupture of HCC and reported that stage IV group was associated with worse prognosis than the stage I-III group. Ueno et al. [14] reported that extrahepatic metastasis showed prognostic significance in multivariate analysis of unresectable HCC patients treated with transcatheter arterial chemoembolisation therapy. Distant metastasis of HCC has been regarded as a terminal event, and intrahepatic lesions were not actively treated in such cases [15]. However, some previous reports showed that the metastatic lesion of HCC was a minor cause of death and the main cause of death was advanced intrahepatic lesions. In those reports, it was said that if a patient’s liver status is good, treatment for liver and metastatic lesion may improve survival [16-19]. In general, ruptured HCC patient’s liver status was mostly not good. In cases where distant metastasis is present, one should be careful about introducing TAE for treatment of ruptured HCC. Conservative treatment may be preferred in such cases.

Our univariate analysis revealed several additional items as possible prognostic factors. The presence of portal vein tumour thrombosis was significantly associated with lower overall survival (Table 2). MST of 19 patients with portal vein tumour thrombosis was 10 days while that of the absence group was 29 days. Okazaki et al. performed TAE in 38 patients with ruptured HCC. Although patients without portal vein tumour thrombus showed longer MST (133 days) than those with it (90 days), no significant difference in prognosis was demonstrated [13]. Nevertheless, our subanalysis including patients without distant metastasis (n = 55) identified it as an independent prognostic factor (p = 0.015) (Table 4, Figure 3). Thus, we consider that portal vein tumour thrombus could be a prognostic factor of ruptured HCC. Portal vein tumour thrombus was found in 12-39% of patients with HCC [1,20-22] and 18-57% of patient with ruptured HCC [6,12,13]. Yama

The presence of hepatic encephalopathy, which is one of the criteria of Child-Pugh classification, was associated with lower overall survival in our univariate analysis (Table 2). Five patients had hepatic encephalopathy, and their MST was one day, whereas MST of 64 patients without it was 25 days. Kim et al. [7] studied 62 patients with ruptured HCC and found that early deaths were independently associated with the presence of hepatic encephalopathy.

Serum levels of albumin and total bilirubin are also included in the criteria of Child-Pugh classification. In the univariate analysis, lower albumin and higher bilirubin levels were found to be significantly associated with worse prognosis in ruptured HCC (Table 2). Okazaki et al. [13] reported that MST of the lower serum bilirubin value group (≤ 3.0 µmol/l) was 165 days and that of the higher value group (> 3.0 mg/dl) was 13 days, and that there was significant difference in the survival rate between lower and higher value groups. In our study, MST of the lower serum bilirubin value group (≤ 3.0 µmol/l) was 25 days and that of the higher serum bilirubin value group (≥ 3.0 µmol/l) was 14 days.

There were some limitations in our study. Selection bias may exist due to the retrospective nature of this study. The Cons T group was relatively small.

Conclusions

The presence/absence of distant metastasis appears to be a prognostic factor in spontaneous rupture of HCC. In cases of absent metastasis, portal vein tumour thrombosis could influence the prognosis. Although TAE was associated with longer survival than conservative treatment, our data failed to provide evidence of a significant impact of TAE as the primary management of ruptured HCC. TAE should be conducted with caution, especially in patients with advanced disease.

Conflict of interest

The authors declare that they have no conflict of interest.
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