

Long-term results of elective hepatectomy for the treatment of ruptured hepatocellular carcinoma

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Abstract

Background/Purpose. According to the *General rules for the clinical and pathological study of primary liver cancer*, compiled by the Liver Cancer Study Group of Japan, ruptured hepatocellular carcinoma (HCC) is classified as stage 4, even if the tumor is small and solitary. We examined the long-term results of elective hepatectomy for the treatment of ruptured HCC.

Methods. A first hepatectomy was performed without operative death in 193 patients with HCC. Ten patients had ruptured HCC (ruptured group) and 183 patients had nonruptured HCC (nonruptured group). The extension of HCC was macroscopically classified as stage 1 in 23 patients, stage 2 in 71, stage 3 in 53, and stage 4 in 46.

Results. Cumulative survival rates in the ruptured group at 1, 5, and 10 years were 90.0%, 67.5%, and 20.3%, respectively. The cumulative survival rate was lower in patients with stage 4 disease in the nonruptured group than that in patients in the ruptured group ($P < 0.05$). Cumulative survival rates did not differ significantly between patients in the ruptured group and those with stage 2 or stage 3 disease.

Conclusions. Survival rates after elective hepatectomy in patients with ruptured HCC are good, even if the disease is classified as stage 4.

Key words Hepatocellular carcinoma · Rupture · Hepatectomy

Introduction

Spontaneous rupture of hepatocellular carcinoma (HCC) is potentially life-threatening.¹ Accurate diagnosis and proper management by procedures such as transarterial embolization (TAE) or operation are urgent needs. However, the operative mortality rates for emer-

gency hepatectomy (28.5%–54.5%)^{2–4} remain high. We have previously reported that TAE followed by elective hepatectomy is an effective treatment for ruptured HCC.⁴

Staging of HCC is usually done according to the tumor-node-metastasis (TNM) classification system of the International Union Against Cancer (UICC),⁵ which is based on tumor extension and is used worldwide. The *General rules for the clinical and pathological study of primary liver cancer*, compiled by The Liver Cancer Study Group of Japan (LCSGJ), base their classifications on TNM staging.⁶ Both the TNM staging system of the UICC and the LCSGJ rules classify HCC with perforation of visceral peritoneum as T4, the most advanced stage, even if the tumor is small and solitary. Rupture of HCC can lead to peritoneal dissemination and recurrence. Even if only palliative, surgical treatment of peritoneal dissemination of HCC may improve survival and lead to a better quality of life in selected patients.⁷ In this study, we examined the long-term results of elective hepatectomy for the treatment of ruptured HCC.

Patients, materials, and methods

Between 1986 and 2002, we studied 193 patients with HCC who underwent a first hepatectomy without operative death at the Department of Surgery, Nippon Medical School Hospital, Tokyo. The subjects were 153 men and 40 women. HCC was associated with liver cirrhosis in 112 patients, chronic hepatitis in 77, and a normal liver in 4. The Child-Pugh class⁸ was A in 90 patients and B in 103. The ages of the patients ranged from 25 to 80 years (mean 62.4 years).

Ten patients had ruptured HCC (ruptured group) and 183 patients had nonruptured HCC (nonruptured group). Extension of HCC was macroscopically classified according to the LCSGJ rules⁶ as stage 1 in 23

Offprint requests to: H. Yoshida

Received: October 26, 2007 / April 11, 2007

patients, stage 2 in 71, stage 3 in 53, and stage 4 in 46. Ruptured HCC was classified as stage 4 in accordance with the rules. All patients with stage 1 and stage 2 disease underwent curative operations, defined as no evidence of residual cancer in the remnant liver on macroscopic examination or diagnostic imaging after hepatic resection. Noncurative operations with residual HCC were performed in 4 patients with stage 3 disease and in 7 with stage 4 disease (5 with nonruptured HCC and 2 with ruptured HCC).

A clinical diagnosis of ruptured HCC was suspected when patients presented with epigastric or right upper-quadrant abdominal pain, abdominal distension, or shock. The diagnosis was then confirmed by abdominal paracentesis, ultrasonography, or computed tomography. For emergency treatment of ruptured HCC, TAE was attempted by selectively placing a catheter in the proper hepatic artery or a branch thereof. Embolization was done with gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, MI, USA), and iodized oil (Lipiodol Ultrafluid; Andre Guerbet, Aulnay-sous-Bois, France). All 10 patients in the ruptured group received emergency TAE, resulting in hemostasis. Liver function is poor immediately after intraabdominal hemorrhage. Therefore, after stabilization of hemodynamic status and recovery from the initial insult of the ruptured tumor, patients underwent a full clinical evaluation to decide whether operation was indicated.

Analysis

The statistical significance of differences between groups in demographic characteristics, clinical findings, survival rates, and recurrence rates was assessed by the Mann-Whitney *U*-test, the Wilcoxon rank-sum test, or the χ^2 test, as appropriate. A *P* value of <0.05 was considered to indicate statistical significance.

Results

Sex, age, findings in the noncancerous portion of the liver, and follow-up period did not differ significantly between the ruptured and the nonruptured groups. Liver damage (according to Child-Pugh class) was significantly more severe in the ruptured group than in the nonruptured group (*P* < 0.05). Curative operation was performed in a significantly higher proportion of patients in the nonruptured group than in the ruptured group (*P* < 0.05; Table 1).

Cumulative survival rates are shown in Fig. 1. At 1, 3, 5, 8, and 10 years, cumulative survival rates were, respectively, 90.0%, 67.5%, 67.5%, 40.5%, and 20.3% in the ruptured group and 82.9%, 65.9%, 53.0%, 32.5%, and 27.1% in the nonruptured group (Fig. 1a). In the nonruptured group, the cumulative survival rate in patients with stage 1 disease was higher than that in patients with stage 2 (*P* < 0.005), stage 3 (*P* < 0.005), or stage 4 (*P* < 0.0001) disease, and the rate in the nonruptured group was also higher than that in the ruptured group (*P* < 0.05). The cumulative survival rate in patients with stage 4 disease in the nonruptured group was lower than that in patients with stage 2 (*P* < 0.001) or stage 3 disease (*P* < 0.005) in the nonruptured group, and the rate was also lower than that in patients in the ruptured group (*P* < 0.05). There were no significant differences in cumulative survival rates among patients in the ruptured group, patients with stage 2 disease, and patients with stage 3 disease (Fig. 1b).

Cumulative disease-free survival rates in the patients who underwent curative operation are shown in Fig. 2. Cumulative disease-free survival rates at 1, 3, 5, 8, and 10 years were, respectively, 75.0%, 50.0%, 37.5%, 37.5%, and 37.5% in the ruptured group, as compared with 74.8%, 42.7%, 27.6%, 25.9%, and 9.7% in the nonruptured group (Fig. 2a). The cumulative disease-free survival rate of the patients with stage 4 disease in the nonruptured group was lower than the rates in the patients with stage 1 (*P* < 0.05), stage 2 (*P* < 0.005), or stage 3 disease (*P* < 0.05) (Fig. 2b). In the ruptured

Table 1. Characteristics of patients

	Ruptured group	Nonruptured group	<i>P</i>
n	10	183	
Sex (M/F)	8/2	145/38	NS
Age (years)	61.3 ± 7.3 ^a	62.4 ± 9.2 ^a	NS
Degree of liver damage (Child-Pugh grade A/B)	1/9	89/94	<i>P</i> < 0.05
Findings in the noncancerous portion (cirrhosis/chronic hepatitis/normal liver)	4/6/0	108/71/4	NS
Staging (Stage 1/2/3/4)	0/0/0/10	23/71/53/36	
Curative operation (+/-)	8/2	174/9	<i>P</i> < 0.05
Follow-up period (months)	57.1 ± 39.9 ^a	43.5 ± 31.0 ^a	NS

^aMean ± SD

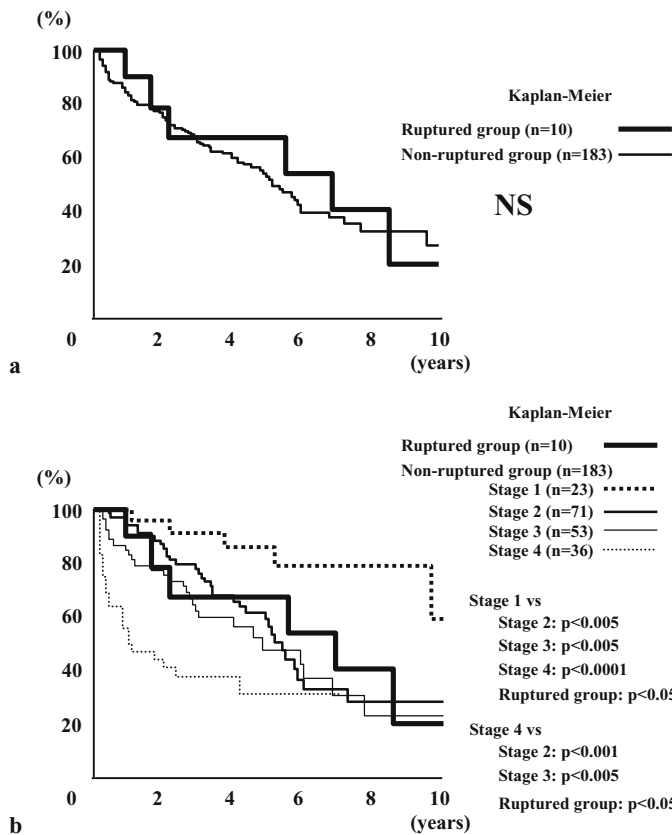


Fig. 1. Cumulative survival rates. NS, not significant

group, two patients died from intrahepatic recurrence of HCC, 11 and 83 months, respectively, after the operation. Two patients died from disseminated recurrence of HCC, 26 and 67 months, respectively, after the operation. One patient with intrahepatic recurrence of HCC died of brain hemorrhage 20 months after the operation. One patient without recurrence of HCC died of liver failure 103 months after the operation.

Discussion

The cumulative survival rate of patients in the ruptured group was higher than that of patients with stage 4 disease in the nonruptured group and was similar to that in patients with stage 2 or stage 3 disease. The cumulative disease-free survival rate of patients in the ruptured group was similar to that of patients with stage 1, stage 2, or stage 3 disease in the nonruptured group. Despite the relatively good outcome we observed in the ruptured group, the TNM classification of the UICC⁵ and the LCSGJ rules⁶ classify ruptured HCC as T4, even if the tumor is small and solitary.

Spontaneous rupture is relatively common in patients with HCC. The mechanism of spontaneous rupture of

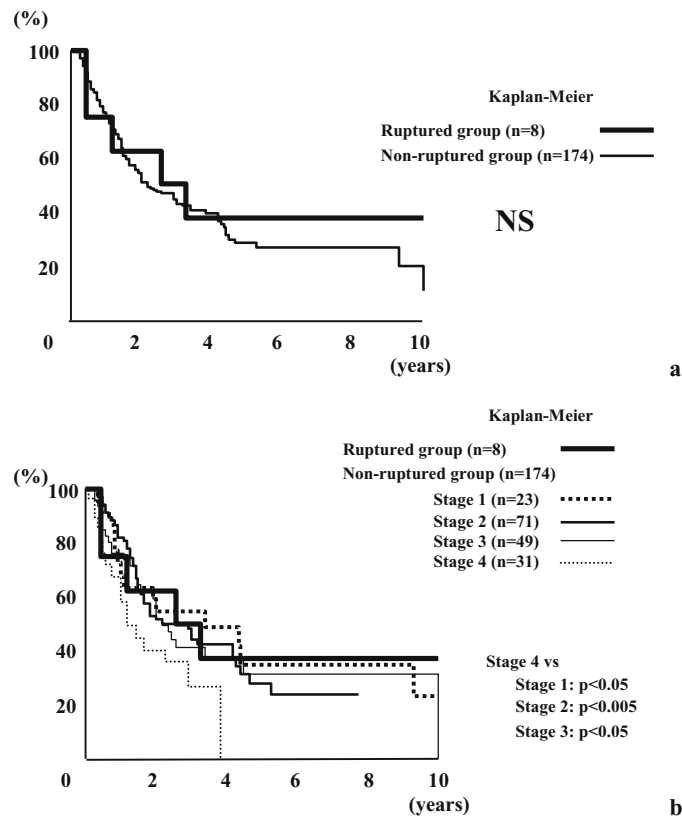


Fig. 2. Cumulative disease-free survival rates of patients who underwent curative operation

HCC in the peritoneum remains unclear, but rupture has been attributed to central necrosis in a rapidly growing HCC, hemorrhage and venous congestion inside a tumor, coagulopathy due to underlying cirrhosis, and minor trauma causing a sudden increase in pressure within the tumor.⁹⁻¹³

When confronted with this life-threatening condition, hemostasis is of prime concern. Several studies have proposed that selective hepatic artery ligation² or emergency hepatectomy¹⁴ are the treatments of choice in patients with limited tumor² and preserved liver function (Child-Pugh grade A or B), with TAE as the next-best choice.¹⁴ However, TAE is effective in controlling 70%–100% of bleeding HCCs, with an in-hospital mortality rate of 0–29.4%,^{3,4,14-17} whereas hepatic artery ligation achieves a similar rate of hemostasis (68.1%–100%), but with a higher in-hospital mortality rate (67%–76.6%).^{2,3} TAE is thus a less invasive treatment for ruptured HCC than hepatic artery ligation. Operative mortality rates for emergency hepatectomy (28.5%–54.5%)²⁻⁴ are higher than those for elective hepatectomy (0%).^{4,13,18} In the present study, all 10 patients with ruptured HCC (ruptured group) were treated by TAE, followed by elective operation.

The combination of acute hemorrhage and cancer in patients with rupture of HCC requires a two-step therapeutic approach. The initial goals of treatment are to achieve hemostasis and stabilize cardiorespiratory reserve; hepatic reserve should then be evaluated.^{19–27} Next, a two-stage hepatectomy should be performed.^{9,18} Zhu et al.⁹ reported that most episodes of ruptured HCC could be effectively managed by TAE, followed by hepatectomy in patients with resectable lesions. Their recommendations are supported by the results of Shimada et al.,²⁸ who found that the median survival of patients with ruptured HCC was marginally shorter after TAE alone than after TAE followed by hepatic resection (158 vs 375 days; *P*, not significant).

Rupture of HCC can lead to peritoneal dissemination and recurrence, so the TNM classification of the UICC⁵ and the LCSGJ rules⁶ might classify ruptured HCC as T4. Recurrence of HCC can rarely be caused by peritoneal dissemination in patients with ruptured HCC. In the present study, peritoneal dissemination occurred in two of the ten patients in the ruptured group. Although surgical treatment of peritoneal dissemination of HCC is not curative, surgery may improve survival and provide a good quality of life in selected patients.⁷

If ruptured HCC were not to be classified as T4 in the LCSGJ rules,⁶ the ten patients with ruptured HCC in this study would be classified according to these rules as stage 2 in four patients, stage 3 in three, and stage 4 in three. Noncurative operations with residual HCC were performed in only two of our patients with ruptured HCC.

Staging of HCC is usually based on the TNM classification system, which evaluates tumor extension. However, remnant liver function is also an important determinant of outcome in patients with HCC. The Cancer of the Liver Italian Program (CLIP) score is the most widely used staging system that integrates tumor stage with liver disease stage.²⁹ Recently, Kudo et al.³⁰ proposed a simple scoring system for HCC, designated the Japan Integrated Staging (JIS) system. This system combines tumor stage (TNM of the LCSGJ) and the Child-Pugh classification.⁸ The stratification ability of the JIS scoring system is much better than that of the CLIP scoring system. The JIS scoring system is also better than the CLIP scoring system for identifying patients with the best prognoses.³⁰ If the classification of HCC with peritoneal perforation is changed, use of the JIS scoring system might enhance the ability to predict outcome.

Conclusion

We conclude that survival rates after elective hepatectomy in patients with ruptured HCC are good, even if

ruptured HCC is classified as T4 according to the UICC and LCSGJ systems. TAE followed by elective hepatectomy is considered an effective strategy for patients with ruptured HCC.

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