80% by 5 years[4,6-8]. Intrahepatic recurrences of HCC may result from intrahepatic metastasis originating from the primary HCC or from ongoing multicentric carcinogenesis related to chronic HCV infection. In addition, sustained underlying HCV-related hepatic damage may compromise hepatic functional reserve, worsening clinical outcome. Thus, prevention of HCC recurrence and preservation of liver function are both highly important priorities in improving prognosis of patients with HCV-related HCC.

Interferon (IFN) therapy for patients with HCV infection is effective as evident by reduction of serum alanine transaminase (ALT) activity and eradication of HCV. Accordingly, IFN is valuable in minimizing hepatic necrosis, inflammation, and fibrosis, as well as reducing the likelihood of hepatocarcinogenesis[9-16]. The primary goal of treatment of patients with HCV infection is elimination of the virus. Several studies have reported recently that IFN therapy provided after curative treatment for HCV-related HCC prevents HCC recurrences and improves survival[17-23]. Such improvement of prognosis is more predominant when IFN therapy results in elimination of HCV RNA[24]. However, most patients with HCV-related HCC also have liver cirrhosis. Many centers do not advocate IFN therapy of patients with compensated cirrhosis, mainly because of the disappointing sustained virological response (SVR) rates in such patients[25]. Several studies indicated that the response of cirrhotic patients to antiviral therapy is low[26-28]. The reasons for the low SVR rate in such patients include inability to administer IFN at recommended doses due to adverse effects and dose-limiting cytopenia. On the other hand, several investigators suggested that the use of low-dose IFN therapy for viral elimination was as effective in the treatment of cirrhotic patients with HCV as it is in non-cirrhotic patients[29,30]. Furthermore, they indicated that the same therapy could improve the underlying liver histology. There is evidence to suggest that low-dose IFN therapy might be beneficial in HCV-related cirrhosis, not only because it prevents the progression of liver disease, but also because it reduces the risk of hepatocarcinogenesis[31,32]. In this regard, low-dose IFN therapy seems to be tolerable without significant life-threatening adverse effects than the standard dose of IFN.

However, it is not known whether low-dose IFN after curative treatment of primary HCC could slow disease progression or reduce the rate of clinical decompensation in cirrhotic patients, in addition to prevention of HCC recurrence. Several studies used the standard dose of IFN after HCC treatment[17,23,33], and studies using low-dose IFN therapy for HCV-related cirrhosis after HCC treatment also reported that such regimen may reduce late recurrence of HCC[34].

In this prospective case controlled trial, we assessed the efficacy of low-dose intermittent IFN therapy on HCV-related liver cirrhosis after curative treatment of primary HCC in terms of overall survival, HCC recurrence, and liver function.

MATERIALS AND METHODS

Patients

A total of 176 consecutive patients received their initial treatment for HCV-related primary HCC at Hiroshima University Hospital between August 2001 and December 2006. Of these, 67 patients with HCC underwent first medical or surgical therapeutic intervention with curative intent (defined as complete tumor eradication with no visible residual tumor in computed tomographic images, or resection of all evident tumor tissue). Medical treatments included percutaneous radiofrequency (RF) ablation and ethanol injection, while surgical procedures included hepatic resection and RF ablation under laparotomy. Among these 67 patients, 52 patients with liver cirrhosis (LC), which was diagnosed clinically and pathologically, were considered for this prospective study. Figure 1 shows our study flow. Among these 52 patients with HCV-related LC, we assessed 42 patients who met the following inclusion criteria: (1) the presence of up to three tumors with none exceeding 30 mm in diameter or a solitary tumor less than 50 mm in diameter; (2) tumor-node-metastasis (TNM) stage of Ⅰ, Ⅱ or Ⅲ; (3) detectable serum HCV RNA; (4) all seronegativity for hepatitis B marker including hepatitis B surface antigen, hepatitis B anti-core antibody and hepatitis B surface antibody ; (5) compensated cirrhosis with a Child-Pugh class A or B; (6) platelet count $\geq$ 40000/μL; and (7) absence of local recurrence during the follow-up period and of any ectopic intrahepatic recurrence within 12 wk after treatment for primary HCC. We used the TNM classification system

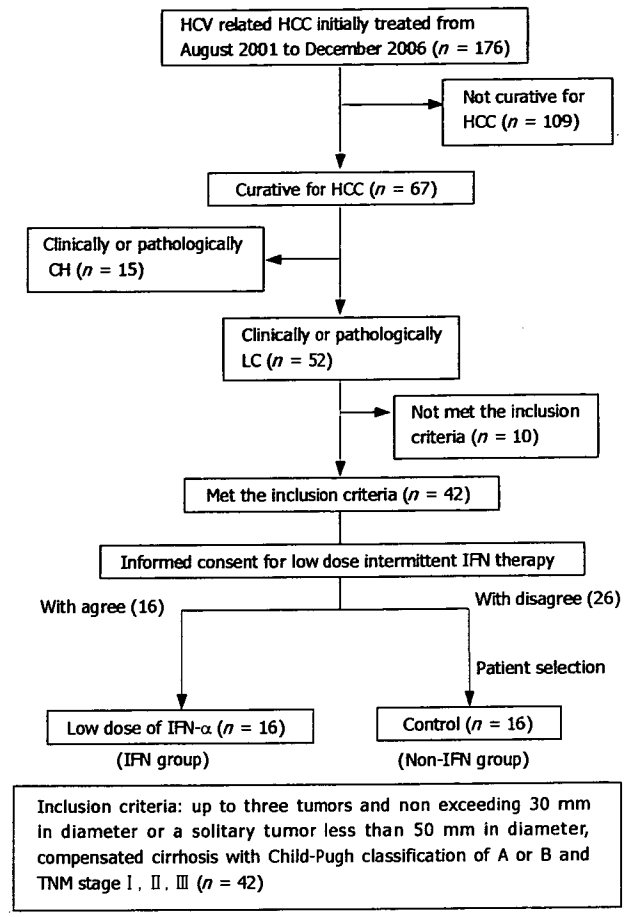

Figure 1 Schematic flow chart of enrolled patients.

Table 1 Characteristics of participating patients

	Interferon group	Non-interferon group	*P* value
No. of patients	16	16	
Age in years (range)	68.5[1] (53-73)	67.5[1] (58-75)	NS
Gender (Male/Female)	10/6	11/5	NS
Albumin (g/dL)	3.7[1] (3.0-4.8)	3.7[1] (3.0-4.5)	NS
Platelet count ($\times 10^4$/L)	8.0[1] (4.5-14.2)	8.4[1] (4.6-14.3)	NS
ICG R-15 (%)	17.3[1] (6.1-40.8)	18.2[1] (5-45)	NS
Alanine aminotransferase (IU/L)	59[1] (35-99)	58[1] (21-143)	NS
Alpha fetoprotein (ng/mL)	54[1] (5.3-293.6)	38[1] (5.0-1217)	NS
Child-Pugh score (A/B)	13/3	13/3	NS
Main tumor size (mm)	15[1] (10-50)	18[1] (10-40)	NS
No. of HCC tumors (single/multiple)	9/7	10/6	NS
Stage (Ⅰ/Ⅱ/Ⅲ)	8/3/5	7/5/4	NS
Treatment (medical/surgical)	8/8	9/7	NS
HCV genotype (1/2)	12/4	14/2	NS
Viral loads (low/high)	6/10	5/11	NS

ICG-R15: Indocyanine green retention at 15 min; Low viral loads: HCV RNA < 100 KIU/mL, high viral loads: HCV RNA ≥ 100 KIU/mL. [1]median.

of the Liver Cancer Study Group of Japan as a staging system for HCC[35]. The underlying liver condition leading to LC was identified by histopathological examination of resected tissue samples. When this was not available, laboratory tests were performed including serum albumin, platelet, prothrombin time and indocyanine green retention at 15 min (ICG-R15), and radiological examination such as ultrasonography and computed tomography.

Of the 42 patients with LC who met the above eligibility criteria, 16 patients received low-dose IFN therapy after signing a written informed consent (IFN group). Of the remaining 26 patients who rejected IFN therapy, we selected 16 patients as the control (non-IFN group). These 16 patients, who met the eligibility criteria mentioned above, were matched by age, gender, tumor size, number of tumors, TNM stage of HCC, serum albumin level, platelet counts, ICG-R15 and Child-Pugh class with patients of the IFN group. Thus, a total of 32 patients (16 in the IFN group and 16 in the non-IFN group) were enrolled in this study. All agreed to participate in the research protocol, which was approved by the hospital research ethics board. Table 1 shows the baseline characteristics of patients of the two groups. The data indicates no significant differences between the groups for age, gender, liver function, tumor characteristics, and therapeutic methods used against primary HCC.

IFN therapy

In the IFN group, patients received 3 MIU of natural IFN-alpha (human lymphoblastoid IFN; Sumiferon, Dainippon Sumitomo Pharmaceuticals, Osaka, Japan) intramuscularly three times weekly for at least 48 wk as long as possible. IFN therapy commenced within 12 wk after initial treatment for HCC. Patients received post-treatment IFN therapy up to the detection of HCC recurrence, and then patients who could have curative treatment for recurrent HCC restarted IFN therapy when possible. However, patients who had advanced liver dysfunction or untreatable progressive HCC did not receive IFN therapy. In the control group, none of the patients received IFN therapy after curative treatment of HCC; instead, they were on ursodeoxycholic acid (UDCA) and stronger neo minophagen C (SNMC).

Follow-up

After curative treatment for primary HCC, all patients underwent liver function tests, serum tumor marker assays such as alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist (PIVKA)-Ⅱ, every month, abdominal ultrasonography every 3 mo, and dynamic computed tomography (CT) every 6 mo. If recurrences of HCC were suspected, additional examinations including CT during arteriography or tumor biopsy were performed. Recurrence of HCC was defined as any new nodules appearing as hyperattenuation by CT during hepatic arteriography or as hypoattenuation in CT performed during arterioportography. Hypovascular HCC was confirmed histopathologically by fine-needle aspiration biopsy. Patients with recurrent HCC were treated medically or surgically, with curative intent if possible. Patients without curative treatment of recurrent HCC then received transcatheter chemoembolization. After repeated transcatheter chemoembolization, patients were finally unable to receive any treatment for recurrent HCC.

End points

We analyzed the outcome of this prospective study in December 2006. We compared the rate of HCC recurrence and the survival rate between IFN group and control group. We assessed whether low-dose of IFN therapy was effective in inhibiting recurrence of HCC, preserving liver function and prolonging survival. In addition, we also assessed the cumulative rate of deviation from objective of any treatment against recurrent HCC due to progression of HCC and/or underlying liver dysfunction.

Statistical analysis

The Chi-square and Fisher exact tests were used for categorical variables, while Student's *t*-test and the Mann-Whitney *U* test were used for continuous and ordinal variables, as appropriate. The Kaplan-Meier method used to assess cumulative survival and recurrence rates calculated from the date of diagnosis to the date of

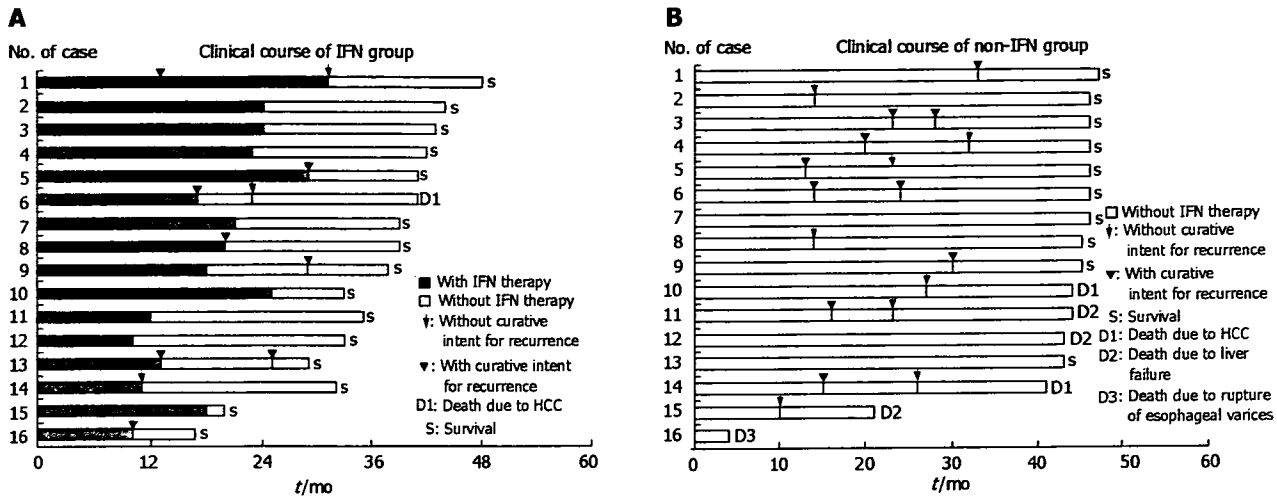

Figure 2 **A**: Clinical course of the interferon group. Patients who had a curative treatment for primary HCC received 3 MIU of natural interferon-alpha three times weekly for at least 48 wk as long as possible except Cases 12, 14 and 16. Recurrent HCCs were treated with or without curative treatment; **B**: Clinical course of the non-interferon group. Patients who had a curative treatment of primary HCC did not receive IFN therapy. Recurrent HCCs were also treated with or without curative treatment.

disease recurrence or death. Surviving patients and patients who died of causes unrelated to the liver were defined as censored cases, while patients who died of causes related to the liver were defined as noncensored cases. The log-rank test was used to compare survival and recurrence curves. *P* values below 0.05 were considered to indicate statistical significance. The JMP version 5.1 statistical software package (SAS Institute, Cary, NC) was used for analysis of data.

RESULTS

Clinical course of IFN group

Figure 2A shows the clinical course of 16 patients of the IFN group from the initial treatment of primary HCC to the date of data analysis. The duration of low-dose IFN therapy ranged from a minimum of 10 mo to a maximum of 25 mo (median 16 mo). Although 8 patients did not have HCC recurrence, HCC recurred in 8 patients after initial treatment of HCC during a median follow-up period of 37 mo. Of the recurred patients, 7 developed HCC recurrence during IFN therapy (Cases 1, 5, 6, 8, 13, 14 and 16) except 1 patient (Case 9) who had HCC recurrence after discontinuation of IFN therapy. Of the 8 patients with HCC recurrence, 4 were treated with surgical resection therapy (Cases 5, 9, 13 and 16), 3 patients with percutaneous RF ablation therapy (Cases 1, 6 and 8) and 1 patient transcatheter chemoembolization (Case 14). Of these patients, a patient with transcatheter chemoembolization (Case 14) could not have curative treatment and repeated transcatheter chemoembolization. He was excluded from the study concerning the next recurrence. Of the 7 patients with curative treatment for HCC recurrence, 2 restarted IFN therapy, one continued IFN therapy until next recurrence (Case 1), which was not curative, and the other continued until intolerant generalized fatigue (Case 8). The remaining 5 patients (Cases 5, 6, 13, 14 and 16) were followed without IFN therapy because of rejection of IFN therapy. Although one of these 5 patients was not curative for first recurrence (Case 14), he was tolerant to repeated transcatheter chemoembolization and was still alive at the date of data analysis. Two patients without curative treatment at the second recurrence (Cases 1 and 6) were also relatively tolerant to the repeated medical treatment such as transcatheter chemoembolization. Of these patients, one died of progression of HCC in spite of repeated transcatheter chemoembolization and hepatic arterial infusion (Case 6), another was alive at the date of data analysis (Case 1). Of 3 patients without curative treatment of HCC, two survivors' status of HCC were not progressive (stage II and stage III) and underlying liver function could be tolerant to the treatment such as transcatheter chemoembolization because of relatively preserved function (Cases 1 and 14).

The 16 patients who received IFN therapy included 2 patients with virological response (Cases 2 and 3) and 14 patients who did not get SVR [3 transient responders (Cases 8, 9 and 11), and 11 non-responders (Cases 1, 4, 5, 6, 7, 10, 12, 13, 14, 15 and 16)]. Among the 14 patients who did not show SVR, 8 were biochemical responders with normalized ALT (Cases 1, 4, 5, 7, 9, 10, 13 and 16), including 4 transient responders and 4 non-responders. Two sustained virological responders who received IFN therapy for 96 wk have viral characteristics of genotype 1 and low viral load. Among the patients who did not show SVR, 7 discontinued IFN treatment because of recurrence of HCC, while 2 patients restarted IFN therapy after the curative treatment of recurrent HCC. None of the patients who received IFN therapy developed life-threatening side effects.

Clinical course of non-IFN group

Among the non-IFN group, the first recurrence of HCC occurred in 13 patients during a median follow-up period of 45 mo (Figure 2B). HCC recurred in 6 of the 7 non-IFN patients who had a sustained normalized ALT. Of the 13 patients with recurrent HCC among the non-IFN group, 4 were treated with hepatic resection (Cases 1, 4, 9 and 11),

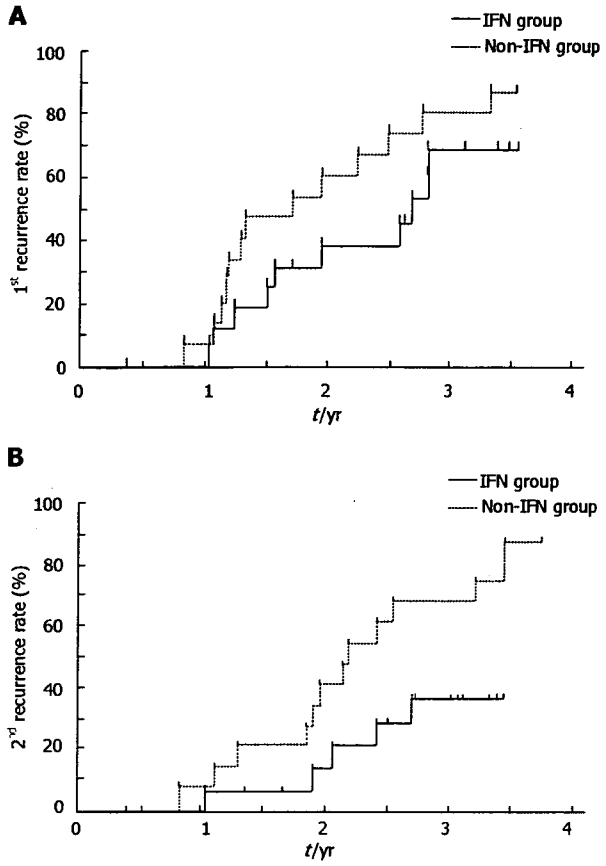

Figure 3 **A**: Cumulative rate of first recurrence. Rates of first recurrence for the IFN and non-IFN groups. The rate of first recurrence of HCC in the IFN group was not significantly different from that of the non-IFN group (P= 0.157); **B**: Cumulative rate of second recurrence. Rates of second recurrence for the IFN and non-IFN group. The rate of second recurrence of HCC in the IFN group was not significantly different from that of the non-IFN group (P= 0.056).

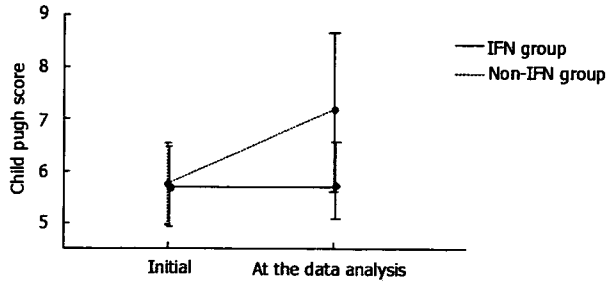

Figure 4 Effect of IFN therapy after curative treatment of HCC on Child-Pugh scores. IFN-treated patients were less likely to show deterioration of hepatic function. The average scores of Child-Pugh of the IFN group were significantly better preserved than the non-IFN group (P= 0.0008).

6 with local ablation including percutaneous RF ablation or ethanol injection (Cases 3, 5, 6, 7, 10 and 14) and 3 with transcatheter chemoembolization (Cases 2, 8 and 15). Of the 13 recurrent patients, 5 patients (2 received ethanol injection and 3 transcatheter chemoembolization) could not be treated curatively and was excluded from the study concerning the next recurrence. These 5 patients were treated repeatedly with transarterial chemoembolization after first recurrence. Among the remaining 8 patients who were treated curatively for first recurrence, 7 developed a second recurrence (Cases 3, 4, 5, 6, 9, 11 and 14). Among these 7 patients with second recurrence, 2 were treated curatively for HCC [1 with RF ablation (Case 3) and 1 with hepatic resection (Case 6)], while the remaining 5 patients were not (4 patients due to uncontrolled multiple HCC and one patient due to underlying liver dysfunction). The latter group of 5 patients received transarterial chemoembolization repeatedly after second recurrence.

Comparison of the first and second recurrence rates of HCC

We compared the overall cumulative rates for first and second recurrence between IFN and non-IFN groups (Figure 3). The 1-, 2- and 3- year rates of first recurrence of HCC in the IFN and non-IFN group were not different (0% *vs* 6.7%, 38.1% *vs* 60% and 68.6% *vs* 80%, respectively, Figure 3A, P = 0.156). The 1-, 2- and 3-year rates of second recurrence in the IFN and non-IFN groups were 0% *vs* 6.7%, 13.5% *vs* 33.3% and 35.9% *vs* 67%, respectively (Figure 3B, P = 0.056).

Liver function

Patients of the IFN group were less likely to develop worsening of hepatic dysfunction compared with the non-IFN group. We compared the average score determined for Child-Pugh classification at initial treatment of HCC with that at the time of data analysis (Figure 4). Although the difference in the Child-Pugh classification score between the two groups at initial treatment of HCC was not significant, the score was significantly worse at the time of data analysis in the non-IFN group than IFN group (P = 0.0008).

Deviation from objects of any treatments for recurrent HCC

At the date of data analysis, patients who developed recurrent HCC were treated repeatedly, as possible, for the purpose of curative treatment including surgical resection and ablative therapy such as RF ablation and ethanol injection. Patients who were difficult to treat with curative intent received transcatheter chemoembolization or hepatic arterial infusion. Although patients with recurrent HCC received repeated treatments, some patients finally could not be treated because of excessive progression of HCC or liver dysfunction. Figure 5 shows that the cumulative rate of deviation from objects of any treatment for recurrent HCC between the IFN group and non-IFN group. In the IFN group, one patient could not receive treatment due to progressively advanced HCC in later period. On the other hand, 8 patients in the non-IFN group could not receive treatment because of underlying liver dysfunction (n = 2) and progressively advanced HCC (n = 6). The 1-, 2- and 3- year rates of deviation from objects of any treatment for recurrent HCC in the IFN and non-IFN group were 0% *vs* 6.7%, 0% *vs* 20% and 0% *vs* 27%, respectively (P = 0.048). Thus, the IFN group tended to be treatable for recurrent HCC compared with the non-IFN group.

Survival of patients

At the date of data analysis, 1 patient among the IFN

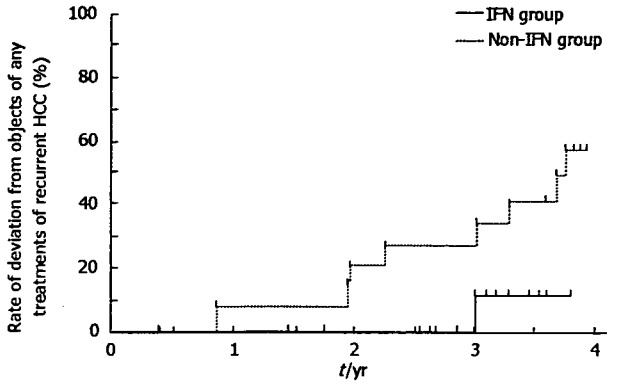

Figure 5 Cumulative rate of deviation from objects of any treatment of recurrent HCC. Recurrent HCC tended to be treatable later in the IFN group than non-IFN group (P= 0.048).

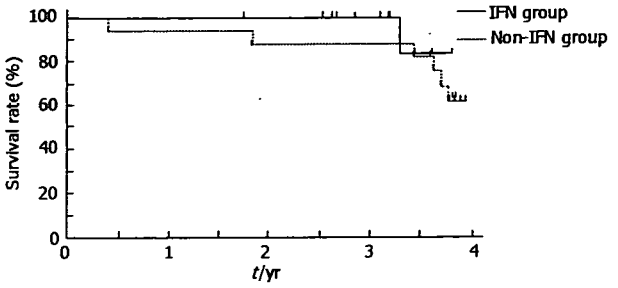

Figure 6 Cumulative survival rate. Comparison of the cumulative survival rates of the IFN and non-IFN groups. The cumulative survival rate was not significantly different between the two groups (P= 0.45).

group and 6 patients among the non-IFN group had died of liver disease. Of the 8 recurrence patients among the IFN group, 1 died of advanced multiple HCC and none died of liver failure. On the other hand, of the 13 recurrence patients among the non-IFN group, 2 died of advanced HCC and 2 died of liver failure in spite of the relatively early stage of HCC. Among the 3 patients without recurrent HCC of the non-IFN group, 1 died of liver dysfunction and 1 died of ruptured esophageal varices.

With regard to the cumulative survival rates of the IFN and non-IFN groups (Figure 6), the respective rates of survival were 100% *vs* 93.7% at 1 year, 100% *vs* 87.5% at 2 years, 100% *vs* 87.5% at 3 years and 83.3% *vs* 61.4% at 4 years. Thus, the cumulative survival rate was not significantly different between the two groups for first 4 years after curative treatment of HCC (P = 0.45). The median survival time following the first treatment of HCC was 37 mo (range, 17 to 45) for the IFN group and 45 mo (range, 4 to 47) for the non-IFN group.

DISCUSSION

HCC recurrence is still a risk even if HCV-related HCC is treated with curative intent. Most of such patients with HCC have underlying liver cirrhosis, and deterioration of underlying hepatic function may be a hindrance to treatment of recurrent HCC and be associated with prognosis. The present prospective case controlled study of cirrhotic patients shows that low-dose intermittent IFN therapy after curative treatment of HCC could preserve liver function and increase the chance of treatment for recurrent tumor.

Previous studies indicated that IFN therapy after curative treatment of HCC was effective in inhibiting or delaying the development of recurrent HCC[17-23,34,36]. Although several recent studies have reported the efficacy of chemoprevention with IFN therapy after treatment of HCV-related HCC, the basis of the benefit was not clear. Shiratori *et al*[23,33] and Ikeda *et al*[17] reported that IFN therapy in cirrhotic patients reduced recurrence of HCC and improved prognosis. Although they used standard IFN dosage per time, there are no other reports on the effect of low-dose IFN therapy after curative treatment of primary HCC in cirrhotic patients. Sakaguchi *et al*[21] reported that low-dose, long-term, intermittent IFN therapy in patients who had curative HCV-related HCC suppressed recurrence of HCC and improved survival, though it was not clear whether their patients had underlying liver cirrhosis or not. On the other hand, Mazzaferro *et al*[34] indicated that low-dose intermittent IFN therapy seemed to reduce late recurrence in patients with HCV-related cirrhosis after resection of HCC. Considered together, these results suggest that low-dose IFN therapy is potentially useful for cirrhotic patients when used as long as possible. However, our results of low-dose intermittent IFN therapy showed no significant difference in recurrence between those who received IFN therapy and those who did not. Unfortunately, since the difference in treatment outcome between the above three studies might be due to the use of different IFN regimens (e.g. dosage and frequency), and background characteristics of cirrhotic patients (e.g., performance status), the results varied and no standard IFN regimen to pursue after curative treatment of HCV-related HCC could be advocated.

The design of the present study was not randomized controlled type, and differed in details of the IFN protocol and characters of patients from the other studies. Although there was no significant difference in the recurrence rate between the IFN and non-IFN groups, the recurrence rate in the later period of observation including second recurrence appeared to be lower in patients with IFN therapy. Furthermore, the recurrent HCC in patients on IFN therapy did not seem to be aggressive compared with that in patients without IFN therapy, probably because they could be treated with curative intent during the observation period. Thus, low-dose intermittent IFN therapy seemed to have delayed or reduced the chance of development of recurrent HCC in the later period of observation, although IFN did not completely inhibit HCC recurrence in our cirrhotic patients.

Most cirrhotic patients cannot receive a standard full-dose IFN regimen due to underlying liver dysfunction and unfavorable complication such as cytopenia. Hence, it could be difficult to achieve SVR in most cirrhotic patients on low-dose intermittent IFN therapy. Valla *et al*[37] performed a randomized, controlled trial of IFN-alpha 2b but the results showed a lack of any benefits in terms of sustained biochemical response, liver function test

results, histology, occurrence of decompensation or HCC, or prolongation of survival. On the other hand, Everson and coworkers[29,30] suggested that the use of low-dose IFN therapy for viral elimination was as effective in the treatment of cirrhotic patients with HCV as it is in non-cirrhotic patients. Several recent studies have reported that IFN therapy following HCC treatment improved liver function of patients with HCV-related HCC, although it is not clear which specific IFN action is important for these benefits. We also demonstrated that preservation of liver function was significantly better in the IFN group than in the non-IFN group even when HCV was not completely eradicated. Thus, hepatic functional preservation increases the chance of treatment for recurrent. Therefore, the cumulative rate of deviation from objects of any treatment for recurrent HCC might be lower in patients with IFN therapy than in patients without IFN therapy as we showed that low-dose IFN resulted in less advanced recurrence and hepatic functional preservation. Although the survival rates were not significantly different between the two groups in our observation period, we need a longer observation to determine differences in survival rates. Although we also assessed the correlation between the observed beneficial effects of the low-dose intermittent IFN therapy and HCV genotype, we could not reach the clear conclusion due to small sample size. In the future, the study with large sample size may be needed to conclude.

In our study, only about 12.5% (2/16) of patients who received IFN therapy had sustained viral elimination. And there were no significant difference in population of patients with normalized ALT between the IFN and non-IFN group (n = 10, n = 7, respectively). In spite of these results, patients treated with low-dose intermittent IFN therapy have a hepatic functional preservation greater than IFN untreated patients who received continuous medication with UDCA or SNMC after curative treatment of HCC. Although the mechanism of this reason is not well known, we suggested that the anti-inflammatory activity by low-dose intermittent IFN therapy may be stronger than medication with UDCA or SNMC and induce regression or retardation of underlying hepatic fibrosis, and finally, inhibits the progression of hepatic dysfunction.

Adverse effects such as reduction in blood counts by low-dose of IFN-alpha were not observed in our study, although neutropenia and/or thrombocytopenia were identified before IFN therapy. Furthermore, none of the patients required dose reduction in our study. Although 4 patients discontinued IFN therapy because of generalized fatigue, 2 of these patients restarted IFN therapy after that. Therefore, low-dose intermittent IFN-alpha therapy can be used relatively safely for cirrhotic patients with thrombocytopenia. However, patients who can not receive even low-doses of IFN also exist due to severe cytopenia or advanced liver cirrhosis. Medication with UDCA or SNMC or phlebotomy may be useful in decreasing ALT level for those patients.

Most cirrhotic patients who had received curative treatment for primary HCC have a limited hepatic reserve or thrombocytopenia. Therefore, low-dose intermittent IFN therapy might be effective for better prognosis. However, further studies of larger samples followed-up for longer periods should be conducted to establish a definite conclusion about the effect of low-dose IFN therapy for the prevention of progressive liver disease and effect of treatment for recurrent HCC.

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The long-term outcome of patients with bleeding gastric varices after balloon-occluded retrograde transvenous obliteration

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Background. The purpose of our study was to evaluate the long-term outcome and complications of balloon-occluded retrograde transvenous obliteration (B-RTO) in patients with hemorrhage from gastric fundal varices. ***Methods.*** Thirty-four consecutive patients with bleeding from gastric varices who were treated with B-RTO were enrolled in this study between December 1994 and September 2005 (urgent cases, n = 12; elective cases, n = 22). The long-term outcome, complications, and various liver functions were evaluated. ***Results.*** Complete obliteration was achieved in 31 of 34 (91%) patients with an acute bleeding episode. In one of the remaining patients, there was a technical failure, and the other two had only partial obliteration. The two patients with partial obliteration did not obtain hemostasis. Thus, the rate of hemostasis was 94% (31/33). Gastric varices disappeared in all patients with complete obliteration during the treatment. The rate of gastric variceal eradication was 91%. Variceal rebleeding from esophageal varices occurred in three patients. The rate of rebleeding was 10% (3/31). Rebleeding from gastric varices was not observed after complete obliteration. None of the patients showed worsening of their Child-Pugh score. Although the 5-year cumulative worsening rate of esophageal varices was 52%, neither portal hypertensive gastropathy nor ectopic varices were observed. The patients with worsening esophageal varices were successfully treated with an endoscopic procedure. The 5-year survival rate was 68%. ***Conclusions.*** B-RTO is useful for treatment of bleeding gastric varices, achieving high eradication of gastric varices, a low rebleeding rate, and a fairly good prognosis with improved hepatic function.

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Introduction

Gastric fundal varices with hemorrhage are associated with a higher mortality rate than esophageal variceal bleeding,[1–3] and optimal management of gastric varices therefore requires a multidisciplinary approach. Generally, various treatment modalities such as pharmacotherapy, balloon tamponade, endoscopic procedures, interventional radiologic treatment, and surgery have been widely performed. In uncontrolled hemorrhage or rebleeding from gastric varices, a transjugular intrahepatic portosystemic shunt (TIPS) is an important tool.[4–13] However, even patients with gastric varices with portal pressure gradients of <12 mmHg can hemorrhage, and TIPS is not always effective in such patients with low initial portal pressure gradients.[6,8] Balloon-occluded retrograde transvenous obliteration (B-RTO) is an interventional radiologic technique that was developed in Japan.[14–16] This procedure involves occlusion of blood flow by inflation of a balloon catheter into an outflow shunt, such as a gastrorenal shunt, and injection of 5% ethanolamine oleate into gastric varices in a retrograde manner. B-RTO has been safely performed for gastric varices with almost complete eradication.

In patients with gastric varices, low portal pressure gradients are associated with the presence and size of a spontaneous gastrorenal shunt, which is present in up to 85% of such patients.[3,17,18] If a large spontaneous shunt is present and the portal pressure gradient (as measured by hepatic vein wedge pressure gradient) is <12 mmHg, B-RTO should be considered.[19] However, the majority of reports in the literature pertain to prophylactic treatment, and the long-term outcome after

B-RTO has not yet been fully demonstrated.[14,16,20–24] In the present study, we describe the long-term outcome of patients with bleeding from gastric varices after B-RTO. In addition, we review the literature on the usefulness of B-RTO in the treatment of gastric varices with hemorrhage.[15,25–36]

Patients and methods

Patients

Between December 1994 and September 2005, 133 patients diagnosed with cirrhosis of the liver underwent an urgent endoscopy for a history of hematemesis or melena. In 87 patients, the primary indication was esophageal variceal hemorrhage, in 38 patients, gastric variceal hemorrhage, and in eight patients, acute non-variceal upper gastrointestinal bleeding, such as erosion or ulcer. Among 38 patients with gastric variceal bleeding, 18 had bleeding signs, such as spurting bleeding and adhesion clots. We treated four patients endoscopically for gastroesophageal varices. Among the remaining 14 patients with isolated gastric variceal bleeding, we treated eight by endoscopic hemostasis, such as endoscopic variceal ligation or clipping, or endoscopic procedures such as injection sclerotherapy using 5% ethanolamine oleate or tissue adhesives, and six by balloon tamponade. The other 20 patients had already stopped bleeding at endoscopy. Thus, 14 bleeding patients were treated with B-RTO after the above-mentioned hemostasis, and 20 patients with isolated gastric varices were treated with B-RTO. In this study, these 34 consecutive patients with bleeding from gastric fundal varices were enrolled at Hiroshima University Hospital between December 1994 and September 2005 (Fig. 1). Patient characteristics are shown in Table 1.

An urgent case of bleeding gastric varices is defined as bleeding within 24 h of the initial hemostasis, and an elective case of bleeding gastric varices is defined as bleeding after 24 h of initial hemostasis.[37] Twelve patients had urgent cases, and 22 had elective cases. The patients comprised 26 men and eight women with a mean age of 60 years. Among the 33 patients with liver cirrhosis, the causes were viral liver cirrhosis (n = 17: hepatitis B surface antigen-positive, n = 2; anti-hepatitis C virus antibody-positive, n = 15), alcoholic liver cirrhosis (n = 10), primary biliary cirrhosis (n = 1), autoimmune hepatitis (n = 1), and unknown (n = 4: negative for viral markers). Child-Pugh classifications were grade A (n = 12), grade B (n = 18), and grade C (n = 3). The one remaining patient was diagnosed with an extrahepatic presinusoidal obstruction (EHO). Endoscopic findings for gastric varices were evaluated according to the general rules for recording endoscopic findings of esophagogastric varices.[37,38] Briefly, gastric varices were classified according to their relationship to the cardiac orifice: Lg-c if they were adjacent to the cardiac orifice, Lg-f if they were distant from the cardiac orifice, and Lg-cf if they extended from the cardiac orifice to the fornix. Among 27 patients, the location of the gastric varices was Lg-f, and it was Lg-cf in seven patients. The gastric varices were classified by morphology into F1, tortuous; F2, nodular; or F3, tumorous. The morphol-

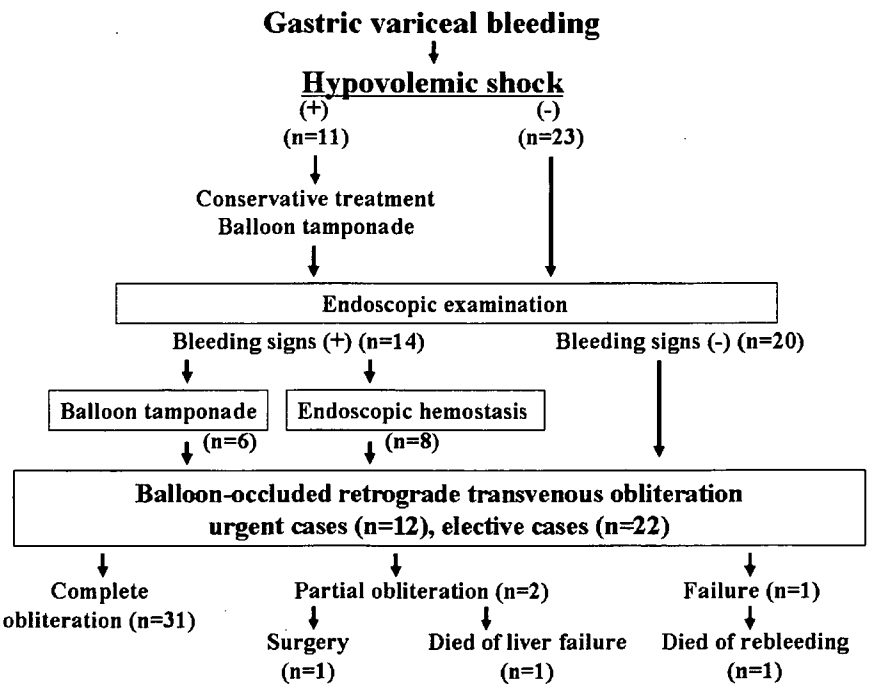

Fig. 1. Schematic flow diagram showing clinical courses and results of patients with bleeding from gastric fundal varices

Table 1. Characteristics of patients

	Urgent cases	Elective cases	*P* value
Number	12	22	
Age (years)[a]	56 (26–80)	60 (24–82)	0.239
Sex (male/female)	9/3	17/5	0.637
Etiology (viral/alcohol/other)	7/3/2	10/7/5	0.781
Child's grade (A/B/C)	4[b]/5/3	9/13/0	0.071
Location of GV[c] (Lg-f/Lg-c/Lg-cf)	10/0/2	17/0/5	0.521
Form of GV[c] (F1/F2/F3)	0/8/4	0/10/12	0.205
Hirota[21] grade[d] (1/2/3/4/5)	3/3/2/4/0	1/4/8/8/1	0.480

B-RTO, balloon-occluded retrograde transvenous obliteration; GV, gastric varices; Lg-f, gastric varices separated from the cardiac orifice; Lg-c, gastric varices adjacent to the cardiac orifice; Lg-cf, gastric varices continuing from the cardiac orifice to the gastric fundus; F1, straight small-caliber varices; F2, moderately enlarged, beady varices; F3, markedly enlarged, nodular, or tumor-shaped varices

[a] Data are mean values (range)

[b] The patient with extrahepatic presinusoidal obstruction was included as Child's grade A

[c] Endoscopic findings for gastric varices were evaluated according to the general rules for recording endoscopic findings of esophagogastric varices[37,38]

[d] Criteria for difficulty of retrograde transvenous obliteration according to retrograde venography under balloon occlusion[21]

ogy was F1 in no patients, F2 in 18 patients, and F3 in 16 patients. When patients showed signs of bleeding on endoscopic examination (Fig. 2a), temporary hemostasis was achieved with balloon tamponade or endoscopic procedures such as injection sclerotherapy using 5% ethanolamine oleate or tissue adhesives, or endoscopic variceal ligation or clipping (Fig. 2b). Portosystemic collaterals such as a gastrorenal shunt were evaluated by contrast-enhanced computed tomography (CT) (Fig. 2c). The study was approved by the institutional review boards of the participating clinical sites before study initiation, and the study was conducted according to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients at the time of enrollment.

Balloon-occluded retrograde transvenous obliteration

After we confirmed that gastric variceal bleeding was controlled, we performed angiography and B-RTO. Selective angiography of the celiac and superior mesenteric arteries was performed before B-RTO to evaluate portosystemic collaterals. All patients were in stable condition at the time of treatment. In patients with a gastrorenal shunt, a 6-French balloon catheter (Selecon MP Catheter; Clinical Supply, Gifu, Japan) was inserted into the inferior vena cava through the right femoral vein. In those without a gastrorenal shunt, other catheterizable main draining veins such as a gastrocaval shunt were examined using a 5.5-French balloon catheter (Artec Balloon Catheter, B-RTO type II SML; Create Medic, Tokyo, Japan). The catheter was advanced into any outflow vessels such as a gastrorenal shunt or gastrocaval shunt. If necessary, both shunts were occluded using two balloon catheters. During balloon occlusion of outflow vessels, retrograde venography was performed to determine the hemodynamics of the gastric varices and collateral veins. On the basis of the adrenal venogram obtained during balloon occlusion, the degree of progression of the gastric varices and collateral veins was graded in accordance with Hirota et al.[21] Then, B-RTO was performed by injecting 5% ethanolamine oleate (Oldamin; Grelan Pharmaceutical, Tokyo, Japan) through the outflow vessels during balloon occlusion. Especially in the case of Hirota's grade 3 or 4 varices,[21] additional specialized techniques to treat minor collaterals were utilized.[15,18,21,23,28,30,39,40] If occlusion of minor collateral vessels was necessary, a 50% glucose solution, ethanol, and embolic coils were used. With or without these interventions, a 2.8-French microcatheter (Rapid transit; Johnson and Johnson, New Brunswick, NJ, USA) was introduced through a balloon catheter to the gastric varices, and 2.5–5 ml of 5% ethanolamine oleate was injected intermittently into the gastric varices under fluoroscopy (Fig. 2d). When varices and inflow vessels such as a short gastric vein or a posterior gastric vein could be visualized in their entirety, injection was suspended. Human haptoglobin was administered to prevent renal dysfunction related to hemolysis occurring as a systemic effect of 5% ethanolamine oleate before B-RTO. To avoid incomplete therapeutic efficacy and pulmonary infarction due to an unstable thrombus, we left the catheter in the vein with the balloon inflated for about 20 h and removed it after retrograde venography. If obliteration of gastric varices was insufficient on retrograde venography, additional B-RTO was subsequently performed until opacification of inflow vessels. All patients underwent gastrointesti-

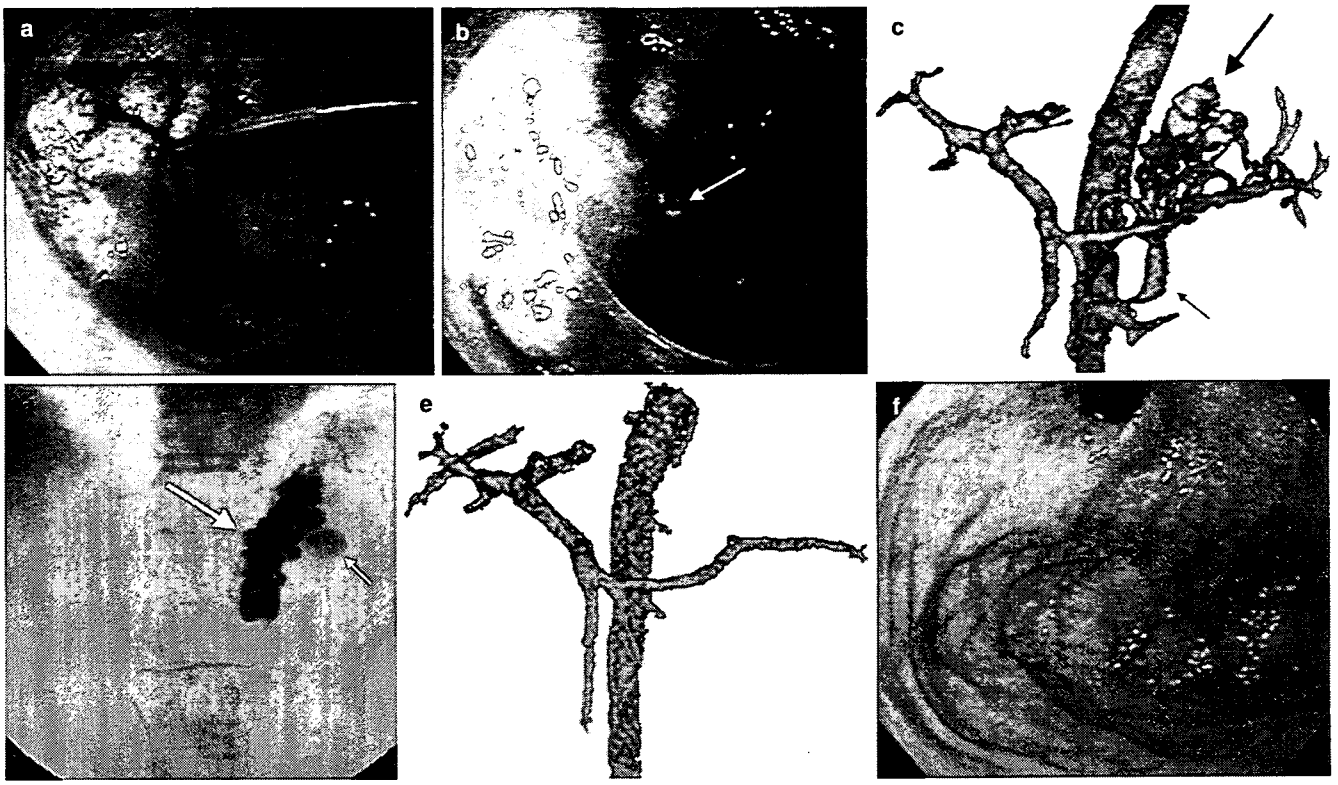

Fig. 2a–f. A 78-year-old man with alcoholic liver cirrhosis. **a** Endoscopic examination reveals huge gastric fundal varices with spurting bleeding. **b** After cyanoacrylate glue was injected intravariceally, gastric variceal bleeding stopped and the glue spilled from the rupture site (*arrow*). **c** Three-dimensional computed tomography (CT) portogram a few hours after endoscopic treatment reveals gastric varices (*large arrow*) and a gastrorenal shunt (*small arrow*). **d** Venogram shows retrograde obliteration. Gastric fundic varices (*large arrow*) were completely obliterated by 5% ethanolamine oleate injected in retrograde manner during balloon occlusion. Subsequently, the posterior gastric vein (*small arrow*) was opacified in retrograde manner. **e** Three-dimensional CT portogram obtained 1 week after balloon-occluded retrograde transvenous obliteration (B-RTO) reveals disappearance of the gastric varices and gastrorenal shunt. **f** Endoscopic examination obtained 1 year after B-RTO reveals complete eradication of the gastric varices

nal endoscopy and contrast-enhanced CT approximately 1 week after B-RTO (Fig. 2e). When the contrast-enhanced CT scan showed gastric varices with low attenuation, including of the afferent veins or the draining veins of the gastric varices, we considered obliteration to be complete. On the other hand, when contrast-enhanced CT showed gastric varices with partial enhancement, we considered the obliteration to be partial. Two radiologists interpreted the angiograms and retrograde venograms during balloon occlusion.

Follow-up and statistical analysis

The hepatic functional reserve was estimated based on the Child-Pugh score. Follow-up diagnostic imaging, such as gastrointestinal endoscopy or contrast-enhanced CT, and examination of hepatic function were performed consecutively at 1, 3, 6, and 12 months, and then every 6 months or 1 year after B-RTO. Any patients who died of causes unrelated to the liver, such as from gastric cancer or leukemia, were withdrawn from the study on the day of death. The cumulative survival rate and cumulative worsened rate of esophageal varices were analyzed using the Kaplan-Meier method and compared with a log rank test. Changes in serum laboratory values were assessed by repeated measures analysis of variance. A value of $P < 0.05$ was considered significant.

Results

Efficacy and complications

A representative clinical course of B-RTO is shown in Fig. 2. Overall complete obliteration was achieved in 31 of 34 (91%) patients with an acute bleeding episode. In urgent cases, complete obliteration was achieved in 10 of 12 (83%) patients, and in elective cases, complete

obliteration was achieved in 21 of 22 (95%) patients. In one of the remaining patients, there was a technical failure because of difficulty with catheter insertion into a gastrocaval shunt, and the other two had only partial obliteration. The patient with failure of B-RTO obtained spontaneous hemostasis but died of gastric variceal rebleeding 1 year later. The two patients with partial obliteration of B-RTO did not obtain hemostasis. One underwent Hassab's devascularization 9 days after B-RTO and survived, and the other died of liver failure (Fig. 1). Thus, the rate of hemostasis was 94% (31/33). Among 31 patients with complete obliteration, the follow-up gastrointestinal endoscopy showed disappearance of gastric varices in 30 patients (Fig. 2f); the other patient died of pneumonia 1 month after B-RTO.

In the patients with complete obliteration, the average dose of 5% ethanolamine oleate was 23.3 ml. Regarding complications, epigastralgia or low back pain was observed in 26 of 34 patients. Pyrexia (>38°C) was observed in nine of 34 patients. However, no patient experienced rebleeding from gastric varices or was treated for shock during angiography or B-RTO. None of the patients developed acute renal failure, hepatic encephalopathy, or hepatic failure.

Cumulative survival

Table 2 lists the outcomes of 34 patients treated with B-RTO. The median follow-up period for all 34 patients was 33 months (range, 1–107 months). Ten patients (29%) died, and the median period to death was 30 months (range, 1–87 months). The causes of death were hepatocellular carcinoma (n = 3), liver failure (n = 6), and bleeding from gastric varices (n = 1). Among 31 patients with complete obliteration of B-RTO, no patients died of hemorrhage from gastric varices or esophageal varices. The overall cumulative survival rate was 90%, 75%, 68%, and 55% at 1, 3, 5, and 7 years after B-RTO, respectively. At 5 years after B-RTO, the cumulative survival rate of urgent cases and elective cases was 74% and 65%, respectively (Fig. 3).

Aggravation of portal hypertension and hepatic function

We examined the aggravation of portal hypertension and hepatic function among patients with complete obliteration of B-RTO. Newly appeared gastric varices were not observed, while ten patients showed worsening of esophageal varices: appearance of red spots on the esophageal mucosa and F2 or F3 morphology of

Table 2. Outcome after balloon-occluded retrograde transvenous obliteration

	Urgent cases	Elective cases	*P* value
Number	12	22	
Complete success	10	21	0.279
Worsening of EV	6	6	0.185
Result (living/died)	9/3	15/7	0.510
Cause of death (HCC/hepatic failure/variceal bleeding)	1/2/0	2/4/1	0.708
Follow-up period (months)[a]	38 (4–97)	32 (1–107)	0.631

EV, esophageal varices; HCC, hepatocellular carcinoma
[a] Data are mean values (range)

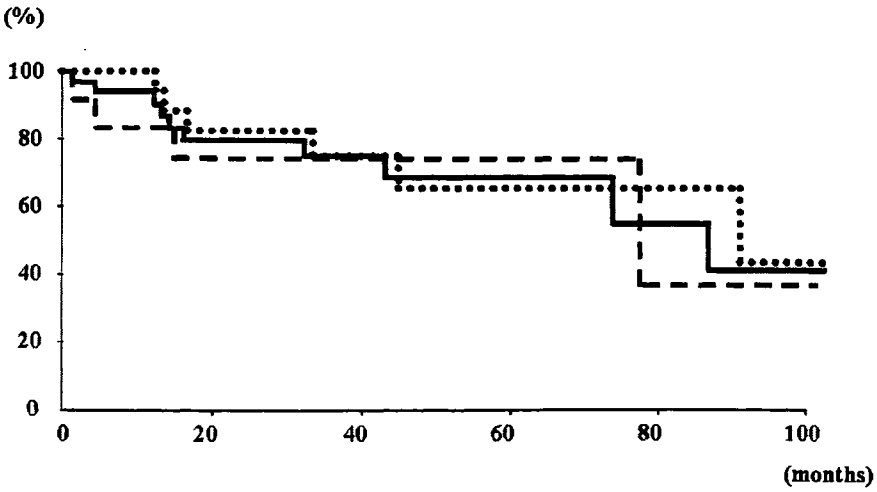

Fig. 3. Cumulative survival after B-RTO. The *solid line* shows overall cases, the *broken line* shows urgent cases, and the *dotted line* shows elective cases

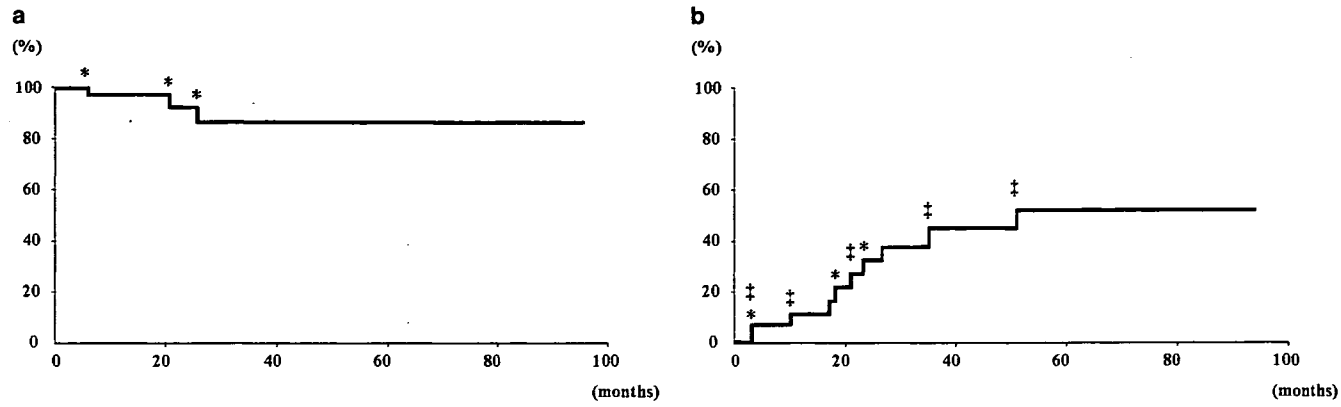

Fig. 4. **a** Kaplan-Meier analyses of cumulative variceal rebleeding. The *asterisk* shows bleeding from esophageal varices ($n = 3$). **b** Overall cumulative worsening rate of esophageal varices after B-RTO: 10 of 31 patients (32%) showed worsening of esophageal varices. The *asterisks* show the times at which patients with bleeding from esophageal varices were treated with endoscopic procedures. The *double daggers* show the times at which patients at risk of hemorrhage from esophageal varices were treated with endoscopic procedures. The remaining patients with worsening esophageal varices without hemorrhage received strict follow-up examinations

esophageal varices. Among these ten patients, three had bleeding esophageal varices and five were in danger of hemorrhage from esophageal varices. They underwent endoscopic procedure (endoscopic injection sclerotherapy, $n = 6$, and endoscopic variceal ligation, $n = 2$). The remaining two patients without hemorrhage were given strict follow-up examinations. No patients died of hemorrhage from esophageal varices. Variceal bleeding occurred in three patients from esophageal varices. The rate of rebleeding was 10% (3/31). Rebleeding from gastric varices was not observed after treatment that achieved complete obliteration. The rate of freedom from rebleeding was 97%, 86%, 86%, and 86% at 1, 3, 5, and 7 years after B-RTO, respectively (Fig. 4a). The overall cumulative worsening rate of esophageal varices was 15%, 39%, 52%, and 52% at 1, 3, 5, and 7 years after B-RTO, respectively (Fig. 4b). Portal hypertensive gastropathy is the term used to describe the endoscopic appearance of gastric mucosa with a characteristic mosaic-like pattern with or without red spots. According to McCormack's classification,[41] almost all patients had mild grade portal hypertensive gastropathy and no patient showed a deterioration of grade or bled from portal hypertensive gastropathy. Ectopic varices were not observed at any time during the study period after B-RTO.

There was no significant difference in Child-Pugh score between before and after B-RTO. Among the various parameters of the Child-Pugh score, the serum albumin level was significantly improved (3.33 ± 0.65 vs. 3.55 ± 0.52 g/dl; $P = 0.04$, before and 4 weeks after B-RTO, respectively). The albumin level improved significantly from 1 to 6 months after B-RTO. However, the albumin level did not continue to improve more than 1 year after B-RTO.

Discussion

At first variceal bleeding, pharmacotherapy should ideally be used to achieve hemostasis and protect against rebleeding.[42] In good responders, drug therapy improves the results in patients with esophageal varices bleeding, although only 30%–40% of patients reduce their portal pressure by >20% from baseline or to levels ≤12 mmHg. However, especially with respect to hemorrhage from gastric fundal varices, the outcome after pharmacotherapy is often unsatisfactory at present. In cases of upper gastrointestinal bleeding, an endoscopic examination is necessary to find the bleeding point and to classify the varices. If active bleeding is observed, then hemostatic procedures are required. Some endoscopic treatments may achieve hemostasis in over 90% of cases; however eradication of gastric varices and rebleeding rates are unsatisfactory.[43–46] It is difficult to treat huge gastric fundal varices by endoscopic injection sclerotherapy without balloon occlusion of gastrorenal shunts.[47,48] B-RTO can obliterate gastric varices from draining veins under balloon occlusion, and also obliterate afferent veins in a retrograde manner, even in patients with huge gastric varices. In Japan, B-RTO has been performed in about 3000 patients.[49] In most cases, the available literature reports prophylactic eradication of high-risk gastric varices. For acute bleeding, B-RTO can be performed after any hemostatic procedure, which is the main limitation of B-RTO. Results of B-RTO in patients with hemorrhage are summarized in Table 3. The success rate was high (95%), which is similar to the prophylactic situation. A low rate of rebleeding was observed after B-RTO. Considering these issues, it is desirable to perform B-RTO after endoscopic hemostatic procedures in patients with bleeding gastric fundal

Table 3. Summary of balloon-occluded retrograde transvenous obliteration results in patients with gastric variceal bleeding

Reference number	Authors	Number of patients	Hemostasis		Eradication of varices
			Endoscopic therapy	Other procedure	
15	Chikamori et al. 1996	6	2	4	6
25	Saeki et al. 1996	2	2	0	2
26	Sonomura et al. 1998	4	0	4	4
27	Kin et al. 1998	6	0	6	6
28	Chikamori et al. 2000	6	5	1	6
29	Fukuda et al. 2001	9	Not described	Not described	9
31	Miyamoto et al. 2003	4	4	0	4
32	Kim et al. 2003	13	Not described	Not described	12
33	Choi et al. 2003	8	Not described	Not described	8
34	Ninoi et al. 2005	35	Not described	Not described	33
35	Sugimori et al. 2005	6	Not described	Not described	6
36	Arai et al. 2005	11	4	0	11
	Our series	34	8	6	31
Total number of patients		144			138

varices. At that time, endoscopic variceal ligation or clipping can be performed. However, patients should be referred to an institution in which B-RTO or injection sclerotherapy using tissue adhesives can be performed immediately after such transient endoscopic hemostatic procedures.

Another problematic long-term sequel of B-RTO is the development or worsening of esophageal varices, which occurs in about 50% of patients.[23,29,31,34] In the present study, a similar rate of worsening esophageal varices was observed. Those patients were all successfully treated endoscopically. Generally, esophageal varices are managed more easily than gastric varices. Esophageal varices that developed after B-RTO were also easier to treat. Elevation of the portal pressure gradient may be expected owing to obliteration of major shunts, such as gastrorenal shunts. Indeed, development or worsening of esophageal varices after B-RTO indicates aggravation of portal hypertension. However, ectopic varices or severe portal hypertensive gastropathy were not observed after B-RTO in the present study.

Although the long-term outcome after B-RTO has not yet been fully demonstrated, some reports have shown improvement of the Child-Pugh score after B-RTO.[24,29] In the present study, liver function, especially the serum albumin value, increased significantly from 1 to 6 months after B-RTO. Moreover, some studies demonstrated that portosystemic encephalopathy improved more after B-RTO than after TIPS.[21,50] An increase in portal blood flow from obliteration of large portosystemic shunts might contribute to improvement in liver function. This was confirmed by Doppler ultrasound before and after B-RTO, and in a hemodynamic study after balloon occlusion of a gastrorenal shunt.[31,51,52] Liver function improved in patients with Child-Pugh class B or C disease as well as in those with class A disease. However, radiological or surgical occlusion of a portosystemic shunt is sometimes accompanied by liver failure when the portal pressure gradient increases 60% or more from baseline after the procedure.[53] Partial splenic arterial embolization can reduce the portal pressure and lead to a good outcome in such cases treated by radiological occlusion of a portal systemic shunt.[54,55] At present, it appears that B-RTO is applicable in Child-Pugh class A or B patients, while the benefit remains unclear in Child-Pugh class C patients. With respect to long-term prognosis, the cumulative survival rate was 68% at 5 years after B-RTO in the present study. Our results are consistent with those of other reports, including with regard to B-RTO for prophylaxis.[23,29,34,56] Considering the factors affecting prognosis, the presence or absence of concomitant hepatocellular carcinoma and the Child-Pugh classification were important factors affecting survival after B-RTO.[29,34] Among the complications of chronic liver disease, B-RTO can reduce deaths due to gastric varices, which are one of the most difficult variceal sites to treat.

The technique of B-RTO is complicated and is not yet standardized in Japan. For successful treatment, additional specialized techniques to treat minor collaterals are required.[15,18,21,23,28,30,39,40] Such techniques result in a decreased use of 5% ethanolamine oleate and may avoid sclerosant-related complications such as hemoglobinemia. In cases with Hirota's grade 3 or 4 in particular,[21] techniques such as stepwise injection of 5% ethanolamine oleate, use of high concentrated glucose or ethanol, coil embolization of minor collaterals, or double-balloon catheterization are needed. By using

these strategies and techniques based on the hemodynamic feature,[15,18,21,23,28,30,39,40] radiologists worldwide could treat patients with gastric varices with gastrorenal shunts by B-RTO. Indeed, usefulness of B-RTO has recently been reported from outside of Japan,[32,33] including in the review, guideline, and educational sections of the journals *Gastroenterology*, *Gut*, and *Radiographics*, respectively.[3,6,18,40]

B-RTO is not feasible in patients without gastrorenal shunts. Ninoi et al.[24] demonstrated that antegrade transhepatic obliteration using metallic coils and 5% ethanolamine oleate eradicated gastric varices in patients difficult to treat with B-RTO. While percutaneous transhepatic obliteration only in afferent vessels resulted in transient hemostasis,[57] antegrade obliteration, including of gastric varices, is reported to be effective as well as B-RTO.[24] Similar efficacy was also demonstrated in patients with ectopic varices.[58] When hemostasis is performed by TIPS in patients with refractory bleeding, embolization together with TIPS should be performed, as recommended by American Association for the Study of Liver Diseases practice guidelines.[12] At the same time, direct obliteration via the TIPS route would be desirable.[10,12,13,58] Especially, the use of long-acting occlusion agents such as liquids in addition to metallic coils could obliterate at the peripheral level of the collateral vessels feeding the varices, and lead to a low incidence of rebleeding.[13,58] These results support the findings that embolization of both esophageal varices and their feeders is essential to lower the recurrence rate after sclerotherapy.[59] It is desirable to obliterate both varices and the peripheral collateral vessels using 5% ethanolamine oleate, the distribution of which can be monitored, although agent-related complications are sometimes reported. No rebleeding from gastric varices after B-RTO might indicate successful embolization of both gastric varices and afferent veins. Thus, it is important in the treatment of gastric varices with hemorrhage to obliterate varices directly in addition to reducing portal pressure. In bleeding gastric varices, direct obliteration using 5% ethanolamine oleate in a retrograde or antegrade manner is desirable with or without TIPS, and whether the portal pressure gradient is more or less than 12 mmHg. When direct obliteration is performed without TIPS, possible ectopic varices or portal hypertensive gastropathy should be considered, although the such aggravation of portal hypertension was not observed in the present study.

In conclusion, B-RTO treatment of bleeding gastric varices achieved high eradication of gastric varices, a low rebleeding rate, and a fairly good prognosis with improved hepatic function.

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RAPID COMMUNICATION

Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma

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Abstract

AIM: To assess the clinical features and prognosis of 151 patients with extrahepatic metastases from primary hepatocellular carcinoma (HCC), and describe the treatment strategy for such patients.

METHODS: After the diagnosis of HCC, all 995 consecutive HCC patients were followed up at regular intervals and 151 (15.2%) patients were found to have extrahepatic metastases at the initial diagnosis of primary HCC or developed such tumors during the follow-up period. We assessed their clinical features, prognosis, and treatment strategies.

RESULTS: The most frequent site of extrahepatic metastases was the lungs (47%), followed by lymph nodes (45%), bones (37%), and adrenal glands (12%). The cumulative survival rates after the initial diagnosis of extrahepatic metastases at 6, 12, 24, and 36 mo were 44.1%, 21.7%, 14.2%, 7.1%, respectively. The median survival time was 4.9 mo (range, 0-37 mo). Fourteen patients (11%) died of extrahepatic HCC, others died of primary HCC or liver failure.

CONCLUSION: The prognosis of HCC patients with extrahepatic metastases is poor. With regard to the cause of death, many patients would die of intrahepatic HCC and few of extrahepatic metastases. Although most of HCC patients with extrahepatic metastases should undergo treatment for the primary HCC mainly, treatment of extrahepatic metastases in selected HCC patients who have good hepatic reserve, intrahepatic tumor stage (T0-T2), and are free of portal venous invasion may improve survival.

Key words: Hepatocellular carcinoma; Extrahepatic metastases; Prognosis; Causes of death

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a highly malignant tumor with frequent intrahepatic metastasis. The prognosis of HCC patients has improved because of progress in therapeutic procedures, such as surgical resection, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and transcatheter arterial chemoembolization (TACE)[1-3]. Moreover, progress in diagnostic modalities, such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and digital subtraction angiography (AG) has led to a better detection of patients with early and small HCC or asymptomatic extrahepatic metastases.

The above improvements in survival and diagnostic modalities have resulted in increased detection of extrahepatic metastases from primary HCC and further increases are anticipated in the future. Several groups have investigated extrahepatic metastases from HCC, but many of such cases were in autopsy cases, in a small number of cases or case reports[4-15]. At present, the prognosis of patients with extrahepatic metastases from primary HCC is poor[16,17]. In this regard, there is only little information about the causes of death of such patients[18], and there is no consensus on the treatment strategy for extrahepatic metastases from HCC. For example, what treatment strategy should be used to treat intrahepatic HCC or extrahepatic metastases? Among patients with extrahepatic metastases from primary HCC, which patients should be treated? To our knowledge, there are no reports that

deal directly with these questions. In this relatively large study, we retrospectively assessed the clinical features and prognosis of 151 patients with extrahepatic metastases from primary HCCs, and described the treatment strategy for such patients.

MATERIALS AND METHODS

Patients

From June 1990 to December 2005, 995 consecutive patients with HCC were admitted to our hospital. Among these patients, 880 were initially diagnosed with HCC in our hospital while the others were treated previously for HCC in other hospitals. Extrahepatic metastases from primary HCC were detected in 151 (15.2%) of 995 patients. None of the patients was treated for extrahepatic metastases. All the 151 HCC patients with extrahepatic metastases (117 men and 34 women, median age: 64 years, range: 21-82 years) were enrolled in the present study.

Table 1 summarizes the clinical profile of the 151 patients at the initial diagnosis of extrahepatic metastases. These 151 patients were divided into groups A and B. Group A was consisted of 68 patients presented with extrahepatic metastases together with primary HCC at the initial diagnosis of HCC, group B was composed of 83 patients who received treatment for intrahepatic HCC, and developed extrahepatic metastases during the follow-up period. Among them, 37 (25%) patients were treated previously for primary HCC in other hospitals, 90 patients were of performance status (PS) of 0, 43 patients of 1, 9 patients of 2, 6 patients of 3, and 3 patients of 4[19]. The etiology of the background liver disease was hepatitis B virus (HBV) in 33 patients, hepatitis C virus (HCV) in 89 patients, HBV and HCV in 5 patients, and non-B non-C in 24 patients. The hepatic reserve was Child-Pugh grade A in 88 patients, grade B in 48 patients, and grade C in 15 patients. We evaluated the primary tumor stage according to the Liver Cancer Study Group of Japan criteria[20], based on the following three conditions (T factor): solitary, < 2 cm in diameter, and no vessel invasion. T1 was defined as fulfilling the three conditions, T2 as fulfilling two of the three conditions, T3 as fulfilling one of the three conditions, T4 as fulfilling none of the three conditions. The primary HCC tumor stage at the first diagnosis of extrahepatic metastases was T0 (no intrahepatic HCC) in 11 (7%) patients, T1 in 4 (3%) patients, T2 in 13 (9%) patients, T3 in 43 (28%) patients, and T4 in 80 (53%) patients. Twenty seven of 28 patients with intrahepatic tumor stage T0-T2 were treated previously for intrahepatic HCC. The median size of the main intrahepatic primary tumor was 48 mm (range, 0-160 mm). Intrahepatic tumor morphology was nodular type in 83 (55%) patients, non-nodular type in 57 (38%) patients, and no intrahepatic HCC in 11 (7%) patients. Table 1 lists the sites of extrahepatic metastases at enrollment. Among the 151 patients with extrahepatic metastases, the sites of metastases were the lungs in 63 patients, lymph nodes in 60 patients, bones in 51 patients, adrenal glands in 16 patients and other locations (e.g., peritoneum, pancreas and nasal passages). In some patients, two or more distant metastatic tumors were found in one or more organs.

Table 1 Clinical profile of 151 HCC patients with extrahepatic metastases at the initial diagnosis of extrahepatic metastases

Age (yr)	64 (21-82)
Sex (male/female)	117/34
Etiology (HBV/HCV/HBV + HCV/others)	33/89/5/24
PS (0/1/2/3/4)	90/43/9/6/3
Intrahepatic tumor stage (T0/1/2/3/4)	11/4/13/43/80
Intrahepatic main tumor size (mm)	48 (0-160)
Intrahepatic tumor volume (< 50% / ≥ 50%)	103/48
Intrahepatic tumor morphology (nodular type/non nodular type/no intrahepatic HCC)	83/57/11
Grade of portal vein invasion (Vp 0/1/2/3/4)	74/0/26/28/23
Child-Pugh grade (A/B/C)	88/48/15
AFP (ng/mL)	741.8 (< 5-861600)
DCP (mAU/mL)	1300 (< 10-391400)
Site of extrahepatic metastases, *n* (%)	
Lung	63 (42)
Lymph nodes	60 (40)
Bone	51 (34)
Adrenal	16 (11)
Peritoneum	1 (0.7)
Pancreas	1 (0.7)
Nasal passages	1 (0.7)

Data are expressed as medians and ranges unless indicated otherwise. HBV: hepatitis B virus; HCV: hepatitis C virus; PS: Eastern Cooperative Oncology Group performance status; T0: no intrahepatic HCC; Portal invasion assessed Vp1: tumor thrombus in a third or more of the peripheral branches; Vp2: in the second branch; Vp3: in the first branch; Vp4: in the trunk; AFP: alpha-fetoprotein; DCP: Des-γ-carboxy prothrombin.

Hepatocellular carcinoma

A definitive diagnosis of HCC was based on the finding of typical hypervascular radiological features or histopathological examination of needle biopsy specimen. HCC was also assessed by US, CT, and/or AG. Furthermore, CT was obtained during arterial portography and computerized tomographic hepatic arteriography. Further assessment of HCC was conducted by measuring α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP).

Extrahepatic metastases were diagnosed by CT, MRI, bone scintigraphy, X-ray, and/or positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG), or diagnosed by histopathological examination of surgically resected specimen or biopsy. When we suspected extrahepatic metastases with HCC, we always ruled out other malignancies (such as gastric cancer, colon cancer and lung cancer) by several imaging modalities, serological tumor markers and/or pathological examination.

Follow- up

All the 151 HCC patients with extrahepatic metastases were followed up during the observation period and no one was lost to follow-up. The median follow-up period was 4.9 mo (range, 1-37 mo). After the diagnosis of HCC, all patients were screened at regular intervals for the development of intra/extra hepatic metastases by clinical examination, AFP, DCP, and/or various imaging modalities. Serological tumor markers were measured once every month. US, CT or MRI was performed once every three to six months.

Statistical analysis and ethical considerations

Differences between groups were examined for statistical significance using the Mann-Whitney test (*U*-test) and χ^2 test where appropriate. Cumulative survival rate was assessed by the Kaplan-Meier life-table method and the differences were evaluated by the log rank test. The following 15 potential predictors were assessed in this study: PS (0 *vs* 1-4), age (≤ 65 *vs* > 65 years), sex (M *vs* F), Child-Pugh stage (A *vs* B, C), intrahepatic tumor stage (T0-T2 *vs* T3, T4), main intrahepatic tumor size (≤ 50 *vs* > 50 mm), intrahepatic tumor volume (≤ 50% *vs* > 50%), intrahepatic tumor morphology (nodular type *vs* non nodular type), portal venous invasion (Vp 0-2 *vs* > Vp 3, 4), AFP (≤ 400 ng/mL *vs* > 400 ng/mL), DCP (≤ 1000 mAU/mL *vs* > 1000 mAU/mL), site of extrahepatic metastases (lung *vs* others, bone *vs* others, only lymph node *vs* others), and treatment for extrahepatic metastases (performed *vs* not performed). All factors that were at least marginally associated with the survival after diagnosis of extrahepatic metastases ($P < 0.05$) were entered into a multivariate analysis. The hazard ratio and 95% confidence interval (95% CI) were calculated to assess the relative risk confidence. All analyses described above were performed using the SPSS program (version 11.0, SPSS Inc., Chicago, IL).

The study protocol was approved by the Human Ethics Review Committee of Graduate School of Biomedical Sciences, Hiroshima University and a signed consent form was obtained from each patient.

RESULTS

Site of extrahepatic metastases

Table 2 lists the sites of extrahepatic metastases identified throughout the follow-up period. The most frequent site of metastases that were identified throughout the follow-up period was the lung (n = 71 patients, 47%), followed by lymph nodes (n = 68 patients, 45%), bone (n = 56 patients, 37%), and adrenal glands (n = 18 patients, 12%). Brain metastases were identified in 2 (1%) patients. One (0.7%) patient each had metastases in the peritoneum, pancreas, nasal passages, muscle, skin, diaphragm, and colon. Autopsy was performed in 14 cases with metastases. Despite the detection of extrahepatic metastases in these 14 patients before autopsy, additional extrahepatic metastases were detected on postmortem examination (lymph nodes, diaphragm, and colon). At the first diagnosis of extrahepatic metastases, 109 (72%) patients had single-organ metastases, while the others had multiple organ metastases.

Among the 71 patients with lung metastases, 23 patients had bilateral lung metastases, 14 had additional extrapulmonary site of metastatic disease. The size of pulmonary nodules ranged from 9 to 30 mm at initial diagnosis of extrahepatic HCC. Few patients had symptoms (cough, dyspnea, and pleural effusion) related to lung metastases, and 8 patients who had severe symptoms died subsequently of respiratory failure. The median survival period of these 8 patients was 4.3 mo (range, 2.5-14.4 mo).

Table 2 Sites of extrahepatic HCC detected throughout the entire follow-up period

Site	Patients (n = 151), n (%)
Lung	71 (47)
Lymph nodes	68 (45)
Bone	56 (37)
Adrenal	18 (12)
Brain	2 (1)
Peritoneum	1 (0.7)
Pancreas	1 (0.7)
Nasal	1 (0.7)
Muscle	1 (0.7)
Skin	1 (0.7)
Diaphragm	1 (0.7)
Colon	1 (0.7)

Among the 68 patients with lymph node metastases, metastases were identified in 64 regional lymph nodes. The most common site was in the paraaortic nodes (31/64), followed by portohepatic nodes (21/64), periceliac nodes (6/64) and peripancreatic nodes (6/64). The majority of patients with regional lymph nodes metastases were asymptomatic, but few regional lymph nodes (portohepatic nodes) caused obstructive jaundice. Distant nodal metastases were found at 17 sites. The most common site was the mediastinum nodes (10/17), followed by subclavicular nodes (3/17), iliac nodes (2/17), cardiophrenic node (1/17), and retrocrural node (1/17). All distant lymph node metastases were not associated with clinical symptoms in this study.

Fifteen of 56 patients with bone metastases had multiple bone metastases at the initial diagnosis of bone metastases. The total number of bone metastatic sites was 88. The most frequent site was the vertebra (63/88; cervical vertebrae = 9, thoracic vertebrae = 38, and lumbar vertebrae = 16), followed by the ribs (8/88). Bone metastases were diagnosed by CT, MRI, bone scintigraphy, and/or PET with FDG.

Of the 18 patients with adrenal gland metastases, 13 had right adrenal gland metastases, 4 had left adrenal gland metastases and only one patient had bilateral metastases. These metastases were not associated with symptoms.

Treatments of extrahepatic metastases

All patients with Child-Pugh grade other than C or PS other than 2-4 were treated for intrahepatic HCC, and many of them were continuously treated after the diagnosis of extrahepatic metastases. On the other hand, HCC patients with Child-Pugh grade C or PS of 2-4 received supportive care. Forty-nine (32%) of 151 patients were treated for extrahepatic metastases by surgical resection, TACE, systemic chemotherapy, and/or radiotherapy. The 49 patients had extrahepatic metastases that were considered to worsen prognosis.

Surgical resection was performed in three (2%) patients (with regional lymph node, adrenal gland and lung metastases). The survival periods after surgical resection of extrahepatic metastases were 7 mo (in patients with lymph node metastases), 23 mo (in patients adrenal gland metastases), and 37 mo (in patients with lung metastases).