

Impact of Treatment for Gastroesophageal Varices on Survival in Patients with Hepatocellular Carcinoma

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New treatment modalities have been introduced to manage gastroesophageal varices, but their impact on prognosis of patients with the varices and hepatocellular carcinoma is not conclusive. The aim of the present study was to evaluate the influences of the variceal treatment on survival of such patients. Seventy-five patients, who were given a diagnosis of hepatocellular carcinoma and died between 1997 and 2004, were retrospectively reviewed in the endoscopic findings and treatments of gastroesophageal varices and causes of death. Additionally, the survival curves were compared between the groups with and without gastroesophageal varices or between the groups with and without the variceal treatments. Sixty (80.0%) of 75 patients had gastroesophageal varices, and 16 (26.7%) among them received the variceal treatments for variceal bleeding or the risk. Nine patients were endoscopically proven esophageal variceal bleeding, and 5 of them had received primary prophylaxis. Fifty-two (69.3%) and 2 (2.7%) of 75 patients died of the progression of hepatocellular carcinoma and the variceal bleeding, respectively. No significant difference was observed in the distribution of causes of death between patients with and without gastroesophageal varices ($p=0.7695$), while in patients with varices, the distribution of causes of death significantly differed between those with and without therapy ($p=0.0020$). Survival curves, however, did not differ significantly either between the groups with and without gastroesophageal varices ($p=0.5502$) or between the groups with and without variceal treatments ($p=0.4446$). Our study suggests that the overall survival rates in patients with hepatocellular carcinoma may be not affected by gastroesophageal varices if the varices are treated depending on the conditions. This may be originated from the improved management of varices in addition to the limited life-span because of tumor progression.

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Introduction

Acute gastroesophageal variceal bleeding is one of the major causes of death in patients with liver cirrhosis and portal hypertension, and many treatment modalities have been shown to arrest bleeding and prevent rebleeding.^{1,2} Additionally, recent study showed that there has been a significant reduction in bleeding related mortality in such patients over the past 40 years.³ On the other hand, the prognosis of patients with liver cirrhosis may largely differ depending on the presence of hepatocellular carcinoma (HCC), although it has been demonstrated that cirrhotic patients developing a HCC during the last 5 years of surveillance survived longer than previously.⁴ Therefore, it is important to analyse whether gastroesophageal varices and its treatments affect the prognosis also in patients with HCC. In this

regard, we showed previously that gastroesophageal variceal bleeding was the cause of death in 7% of 177 patients with HCC, but the presence of varices was not a significant prognostic factor.⁵ However, a relationship between the improved variceal treatments and survival rates in patients with HCC is still controversial. Thus, we evaluated the overall impact of the gastroesophageal variceal treatment on the prognosis in such patients.

Patients and Methods

Patients

From January 1997 to December 2004, a total of 82 patients with HCC were followed up until death in Second Department of

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Internal Medicine, Nagasaki University School of Medicine, Japan. Excluding 7 patients without endoscopic examination for any reason, such as tumor in oral cavity, poor general condition and refuse of patient, the medical records of the remaining 75 patients (50 men and 25 women; mean age, 66.7 years; range, 18-87 years) were collected and analyzed in this study. Flow chart of patients is summarized in Figure 1.

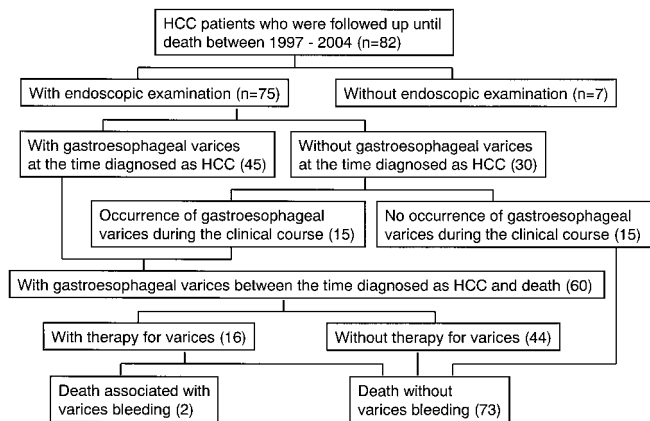


Figure 1. Flow chart of patients.

Diagnosis and treatment of HCC

A diagnosis of HCC was given by ultrasonography, computed tomography, or abdominal angiography, and was confirmed histologically when necessary. All patients received any treatment for HCC, including transcatheter arterial embolization, transcatheter arterial infusion, percutaneous ethanol injection therapy, surgical operation, systemic chemotherapy, and supportive care (some patients were treated with multiple modalities). These patients were followed up for the condition of HCC, and the treatments for HCC were repeated when necessary.

Endoscopic diagnosis, treatment, and follow-up of gastroesophageal varices

Gastroesophageal varices were examined by endoscopic specialists, and were assessed for the form, the fundamental color, and the red color sign according to the criteria proposed by the Japanese Research Society for Portal Hypertension.⁶ Any treatment for varices was indicated as a rule for a varix of F3 form or a varix of F2 form accompanied by red color sign in addition to variceal bleeding. In esophageal varices, endoscopic variceal ligation (EVL) and endoscopic injection sclerotherapy (EIS) were performed using a device for elastic band ligation (Varioligator, TOP Co. Ltd., Tokyo, Japan) and 5% ethanolamine oleate, respectively. In gastric varices, the fundal varices with risk of rupture were treated by balloon-occluded retrograde transvenous obliteration (B-RTO) because the gastro-renal shunt was present. One patient received transjugular intrahepatic portosystemic shunt (TIPSS) for gastroesophageal varices. In spite

of the presence or treatment of gastroesophageal varices, the patients were followed up by endoscopy every 3-12 months until death unless contraindicated by their physical conditions, and treatment for the varices was repeated when necessary.

Statistical analysis

Clinical characteristics of HCC patients were compared between those with and without gastroesophageal varices or between the groups with and without treatments; categorical variables were compared by Fisher's exact test for contingency table, while continuous variables were compared by Student's *t*-test. Survival curves were estimated using the Kaplan-Meier method and were compared between the groups by log-rank test. The Wilcoxon rank-sum test was also used for comparing the distributions of the survival time between the groups. FREQ in the SAS[®] system⁷ and StatView 5.0⁸ were used for the calculations.

Results

Baseline characteristics

The baseline characteristics of HCC patients are summarized in Table 1. No baseline factors showed a significant difference between those with and without gastroesophageal varices; alcoholic history was marginally significant ($p=0.0757$). Similarly, in patients with gastroesophageal varices, no factors showed a significant difference between those with and without variceal treatment except for Child-Pugh classification ($p=0.0217$). No patients received β -adrenergic blockers during the observation period.

Endoscopic finding, treatment, and follow-up of gastroesophageal varices

As shown in Figure 1, 45 of 75 patients with endoscopic examination had gastroesophageal varices at the time diagnosed as HCC, and 15 of the remaining 30 patients developed gastroesophageal varices during the clinical course. Among 60 patients (80.0%) with gastroesophageal varices, 46 had esophageal varices without gastric varices, and 5 had gastric varices without esophageal varices, and 9 had both varices. In 55 patients with esophageal varices, the number of patients with variceal forms of F1, F2 and F3 were 37, 12 and 6, respectively, and 45 had red color sign while 10 did not (Table 1). Sixteen (26.7%) of 60 patients with gastroesophageal varices underwent treatments for gastroesophageal varices, including EVL, EIS, B-RTO, and TIPSS (some patients were treated with multiple modalities). Of course, esophageal variceal form and positivity of red color sign were significantly different between the groups without and with variceal treatments; the number of patients with variceal forms of F1, F2 and F3 were 34, 6, 1 and 3, 6, 5 in the groups without and with variceal treatments, respectively ($p<0.0001$), and the number of patients without and with red color sign were 39 and 2, and 6 and 8 in the groups without and with

Table 1. Clinical characteristics of HCC patients

Factor	Without varices (n=15)	With varices (n=60)	P-value ^a	With varices		P-value ^b
				Without therapy (n=44)	With therapy (n=16)	
Age (years)	67.1±8.0 ^c	66.6±8.3	0.8349	67.7±7.4	63.8±10.2	0.1147
Gender (M/F)	11/4	39/21	0.7606	27/17	12/4	0.3767
Alcohol (-/+)	2/13	23/37	0.0757	16/28	7/9	0.7650
Etiology (HCV/HBV/Others)	11/2/2	42/11/7	1.0000	33/6/5	9/5/2	0.3127
Child-Pugh (A/B/C)	11/1/3	37/14/9	0.3414	24/14/6	13/0/3	0.0217
HCC stage (I/II/III/IVA/IVB)	1/4/5/4/1	6/19/19/11/5	0.9780	5/12/13/10/4	1/7/6/1/1	0.5424
Liver damage ^d (A/B/C)	9/3/3	21/28/11	0.1397	15/21/8	6/7/3	1.0000
PV invasion (-/+)	10/5	47/13	0.3349	33/11	14/2	0.4814
Therapy for HCC ^e (PEIT/TAE, TAI/Op/Others)	4/14/1/1	18/50/9/6		13/38/7/5	5/12/2/1	
EV (-/+)	15/0	5/55	<0.0001	3/41	2/14	0.6023
Form (F1/F2/F3)	NA	37/12/6		34/6/1	3/6/5	<0.0001
RC-sign (-/+)	NA	45/10		39/2	6/8	<0.0001
GV (-/+)	15/0	46/14	0.0588	37/7	9/7	0.0379

^aComparison between patients without varices and those with varices.

^bComparison between patients without therapy and those with therapy.

^cMean±standard deviation.

^dClassification was based on reference 9.

^eEach group included patients who received two or more therapies for HCC, and therefore no comparison was made between the groups. HCC=Hepatocellular carcinoma; M=Male; F=Female; HCV=Hepatitis C virus; HBV=Hepatitis B virus; PV=Portal vein; PEIT=Percutaneous ethanol injection therapy; TAE=Transcatheter arterial embolization; TAI=Transcatheter arterial infusion; Op=Operation; EV=Esophageal varices; RC=Red color; GV=Gastric varices.

Table 2. Classification of 16 patients with variceal treatment by therapeutic method and prophylaxis

Prophylaxis	Therapeutic method for gastroesophageal varices			
	EVL (n=9)	EVL+EIS (n=2)	B-TRO (n=4)	EIS+B-RTO+TIPSS (n=1)
Primary	4	1	4	
Secondary	2	1		1
Primary+Secondary	3			

EVL=Endoscopic variceal ligation; EIS=Endoscopic injection sclerotherapy; B-RTO=Balloon-occluded retrograde transvenous obliteration; TIPSS=Transjugular intrahepatic portosystemic shunt.

variceal treatments, respectively ($p<0.0001$) (Table 1). Nine of 16 patients with variceal treatments had primary prophylaxis (EVL: 4; EVL+EIS: 1; B-RTO: 4) and 3 patients had primary and secondary prophylaxis by EVL, and the remaining 4 patients, in whom the conditions of varices were uncertain before variceal bleeding, had therapy for variceal bleeding with secondary prophylaxis (EVL: 2; EVL+EIS: 1; EIS+B-RTO+TIPSS: 1) (Table 2). Five of the 12

patients with primary prophylaxis (4 for esophageal varices and 1 for gastric varices) suffered esophageal variceal bleeding during follow-up, and 2 patients of them could not have intensive therapy for variceal bleeding because of poor general condition. On the other hand, any of the 15 patients without gastroesophageal varices or 44 patients without variceal treatments never suffered variceal bleeding.

Causes of death

Outcome of patients is summarized in Tables 3. We observed 2 cases (2.7%) of death associated with variceal bleeding; one patient, who did not have gastric varices, had been prophylactically treated with EVL+EIS for esophageal varices, but died of esophageal varices bleeding. Another had gastroesophageal varices and died of the rupture of esophageal varices that showed no bleeding risk 12 months before, while the gastric varices were well controlled with B-RTO. Another 52 patients (69.3%) died of HCC, 8 patients (10.7%) of hepatic failure and 13 patients (17.3%) of liver-unrelated causes. No significant difference was observed in the distribution of causes of death between patients with and without gastroesophageal varices ($p=0.7695$), while in patients with varices, the distribution of causes of death significantly differed between those with and without therapy ($p=0.0020$) (Table 3).

Influences of gastroesophageal varices and their treatments on survival

No significant difference was observed in the survival time between the patients without gastroesophageal varices and those with gastroesophageal varices ($p=0.3369$); the 25th, 50th and 75th sample percentiles of survival times in patients without gastroesophageal varices were 124, 365 and 969 days, respectively, while those in patients with gastroesophageal varices were 319, 562 and 1088 days, respectively (Table 3). Kaplan-Meier survival curves of the both groups were similar ($p=0.5502$) (Figure 2). In patients with gastroesophageal varices, no significant difference was observed in the survival time between the patients without variceal treatments and those with variceal treatments ($p=0.3365$); the 25th, 50th and 75th sample percentiles of survival times in patients without variceal treatments were 269, 542 and 893 days, respectively, while those in patients with variceal treatments were 381, 569 and 1531 days, respectively (Table 3). There was no significant difference in the Kaplan-Meier survival curves between the two groups ($p=0.4446$) (Figure 3).

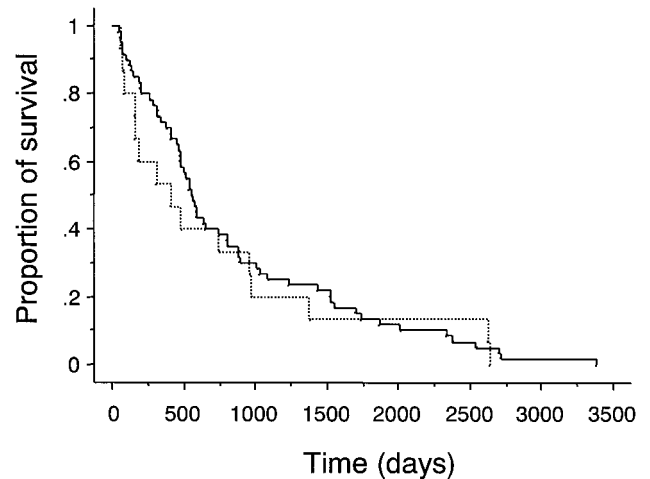


Figure 2. Kaplan-Meier survival curves in the two groups of patients with HCC. The solid line indicates the group with gastroesophageal varices, and the dotted line the group without gastroesophageal varices. The difference between the two groups was not significant ($p=0.5502$).

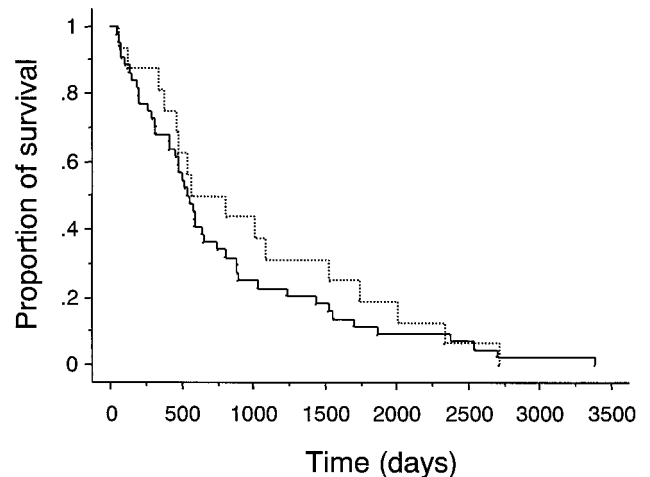


Figure 3. Kaplan-Meier survival curves in the two groups of patients with HCC and gastroesophageal varices. The solid line indicates the group without treatment for gastroesophageal varices, and the dotted line the group with treatment for gastroesophageal varices. The difference between the two groups was not significant ($p=0.4446$).

Table 3. Classification of 75 HCC patients by cause of death

Cause of death	Without varices (n=15)	With varices (n=60)	With Varices	
			Without therapy (n=44)	With therapy (n=16)
HCC	10	42	35	7
Hepatic failure	1	7	2	5
Variceal bleeding	0	2	0	2
Others	4	9	7	2
Survival time (days) ^a	(124, 365, 969)	(319, 562, 1088)	(269, 542, 893)	(381, 569, 1531)

HCC=Hepatocellular carcinoma.

^aEach triplet gives the 25th, 50th and 75th sample percentiles of survival time distribution.

Discussion

Acute esophageal variceal bleeding is a serious complication of portal hypertension.^{1,2} The majority of patients with HCC have gastroesophageal varices, because they frequently have liver cirrhosis as background liver disease. Thus, previous reports have indicated that variceal bleeding was the cause of death in 7 to 10% of patients with HCC.^{4,5,10} Therapies for gastroesophageal varices, including EIS, EVL, TIPSS, or B-RTO, have been suggested to be effective for the prognosis among patients with liver cirrhosis,^{3,11,12} although the role of EVL and EIS in primary prophylaxis is not established.² Several randomized controlled studies have shown that EVL is highly effective compared with EIS in controlling esophageal variceal bleeding in such patients.¹³ However, recurrent bleeding is much more frequent in patients with HCC, especially with portal vein thrombosis, than in those without HCC.¹⁴ Akanuma et al.¹⁰ reported that the large size of coexisting HCC tumor was an independent risk factor for esophageal variceal bleeding. Large HCC tumors may be prone to aggravate portal hypertension by increasing portal blood flow because portal vein is often the main drainage vessel of HCC lesions. On the other hand, HCC is a common cause of mortality in patients with liver cirrhosis in spite of significant improvement in management of HCC.⁴ Thus, it is not conclusive how the advance of treatments for gastroesophageal varices affects the limited prognosis of HCC patients. Previous reports showed that prophylactic EIS might improve survival in patients with HCC,^{15,16} but EIS had no beneficial effects on survival in patients with poor disease status.¹⁶ Additionally, Chen et al.¹⁴ reported that after emergent EVL for acute esophageal variceal bleeding, maintained EVL might lower the rate of recurrent bleeding compared with demanded EVL in patients with Child-Pugh A and B, but survival was similar in both EVL groups. On the other hand, the effects of TIPSS and B-RTO on the prognosis of HCC patients remain obscure. Thus, we studied whether the gastroesophageal varices and their various treatments affect the overall survival in the patients with HCC.

Nine patients were endoscopically proven esophageal variceal bleeding. Five of them had received primary prophylaxis, and the remaining 4 patients, in whom the conditions of varices were uncertain before variceal bleeding, had therapy for variceal bleeding with secondary prophylaxis, while none of 44 patients without any variceal treatments suffered esophageal variceal bleeding until death. Thus, the patients with prophylactic treatment suffered from esophageal variceal bleeding with higher incidence rate compared to the untreated patients. However, it is not feasible to evaluate the effect of prophylactic treatment for gastroesophageal varices in this study because the treatment was performed according to the predefined criteria, causing inherent biases between both groups. Consistent with previous reports in patients with liver cirrhosis,¹⁷ B-RTO was effective to control gastric fundal varices also in patients with HCC. Two of 12 patients with primary prophylaxis (one for esophageal varices and the other for gastric varices) could not have intensive therapy for esophageal variceal bleeding because of the terminal nature of their condition, resulting in death. Caution should be

employed in the aggravation of esophageal varices after the treatment for gastric varices. This is not a randomized controlled trial, and therefore, it is difficult to evaluate the true influences of the varices and their treatments on the prognosis of HCC patients. However, an important point of the current study was that the overall survival was not different by the presence or the severity of gastroesophageal varices in patients with HCC when any treatments were given depending on the variceal conditions. This looks to be associated with the improved management of gastroesophageal varices and the limited life-span from HCC. Additionally, this result may substantiate no need for aggressive treatment for varices in patients with HCC and gastroesophageal varices showing no bleeding risk.

In conclusion, survival time in patients with HCC did not differ significantly either between the groups with and without gastroesophageal varices or between those with and without variceal treatments, indicating that the presence of varices may not affect the overall prognosis, if the treatment for varices could be performed whenever necessary. A prospective study to evaluate the true efficacy of various treatments for gastroesophageal varices in patients with HCC will be needed.

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