Original

Clinical Outcomes and Prognostic Factors Associated with Survival after Balloon-occluded Retrograde Transvenous Obliteration of Gastric Varices

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Abstract : We evaluated clinical outcomes and prognostic factors associated with survival after balloon-occluded retrograde transvenous obliteration (B-RTO) of gastric varices in patients with portal hypertension. Of 50 patients with gastric varices who underwent B-RTO, 46 (94.0%) patients in whom B-RTO was technically successful were reviewed retrospectively. Gastric and esophageal varices after B-RTO were evaluated by contrast-enhanced computer tomography and endoscopy, respectively. Liver function parameters and Child-Pugh scores were estimated before and at 1 year after B-RTO. The cumulative survival rate was calculated, and univariate and multivariate analyses were used to assess the prognostic factors. No major complications occurred in any of the patients following B-RTO and no recurrence or bleeding of gastric varices was noted. Of the 42 patients who were followed up for the progression of esophageal varices, 13 (31.0%) had worsened varices and of these, 6 (14.3%) showed bleeding. Prothrombin activity had significantly improved at 1 year after B-RTO, although there were no changes in other liver function parameters. The overall cumulative survival rates at 1, 3, and 5 years after B-RTO were 91.6%, 70.9%, and 53.6%, respectively. Multivariate analysis identified the occurrence of advanced hepatocellular carcinoma (HCC) during the observation period as a prognostic factor for survival (hazard ratio = 4.1497, 95% CI = 1.32314 – 13.0319, $P = 0.0148$). B-RTO of gastric varices is an effective treatment ensuring lower recurrence and bleeding rates; however, these patients require careful observation for progression of esophageal varices. The management of HCC is crucial for achieving long-term survival after B-RTO.

Key words : balloon-occluded retrograde transvenous obliteration (B-RTO), gastric varices, esophageal varices, prognostic factor

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Introduction

Portal hypertension causes gastroesophageal varices, which present a certain bleeding risk. The prevalence of gastric fundal varices (“gastric varices”) in patients with portal hypertension is approximately 30%, which is lower than that of esophageal varices¹⁻³⁾. Although gastric varices also have lower reported bleeding rates [10–36%⁴⁻⁶⁾] than esophageal varices, the clinical outcomes of bleeding from gastric varices are comparatively worse and more serious than those associated with esophageal varices. Gastric variceal rupture is associated with a 25–55% mortality rate^{3, 4, 7, 8)} due to rapid and abundant blood flow in the major collateral veins.

Various endoscopic, surgical, and interventional techniques have been applied to treat gastric varices. In 1984, Olson *et al*⁹⁾ first described a retrograde approach using a balloon catheter inserted into the draining vein of a gastroduodenal shunt via the femoral vein, with ethanol as the sclerotic agent and metal coils used to induce gastric variceal thrombosis. In 1991, Kanagawa *et al*¹⁰⁾ introduced a balloon-occluded retrograde transvenous obliteration (B-RTO) technique in Japan; this procedure is now widely performed because of its satisfactory therapeutic efficacy and low recurrence rates. Satisfactory prognosis has been reported after B-RTO, with cumulative survival rates at 1, 3, and 5 years of over 90%, 71–97%, and 54–82%, respectively¹¹⁻¹⁶⁾.

The effectiveness of the treatment may be due to extreme changes in hepatic hemodynamics after B-RTO. According to portal phase splenic arteriography and computed tomography (CT) arterial portography via the splenic artery under conditions similar to those induced with the B-RTO procedure, the enhancement of the intrahepatic portal vein and liver parenchyma was depicted more clearly with occlusion of the major portosystemic shunts because of increased hepatopetal portal flow¹⁷⁾. B-RTO with the occlusion of a major portosystemic shunt thus may increase the hepatic blood flow and possibly improve liver function. However, elevation of portal pressure may be expected after obliteration of a major portosystemic shunt, thus leading to ascites, aggravation of esophageal varices, and the appearance of ectopic varices, which are potential concerns for B-RTO. Consequently, B-RTO for patients with poor liver function reserve should be considered carefully; here, endoscopy appears to be extremely important for identifying worsening esophageal varices.

The development of hepatocellular carcinoma (HCC) and the Child-Pugh classification were reported as prognostic factors associated with survival after B-RTO^{11, 15, 18)}. However, few studies have examined these prognostic factors in detail. This study evaluated clinical outcomes after B-RTO of gastric varices and investigated the prognostic factors associated with survival.

Methods

We retrospectively reviewed the medical records of all portal hypertension patients who

Table 1. Clinical characteristics of the 46 patients

Age, years		63.7 ± 11.3
Gender	Male : Female	28 : 18
Cause of liver disease	HBV : HCV : AL : others	1 : 25 : 12 : 8
Child-Pugh classification	A : B : C	28 : 17 : 1
Form of esophageal varices	No : F0-1 : F2-3	17 : 21 : 8
Form of gastric varices	F1 : F2 : F3	6 : 26 : 14
Sarin's classification of gastric varices	GOV2 : IGV1	29 : 17
Concomitant or past history of HCC (%)		8 (17.4%)

underwent B-RTO of gastric varices at Showa University Hospital from January 2000 to October 2010.

Patients

We initially reviewed 50 patients with gastric varices who underwent B-RTO at our hospital. In 46 (94.0%) of these patients, B-RTO was technically successful, with complete thrombosis of the varices being achieved, as proved by contrast-enhanced CT. These patients were followed up and their cases were retrospectively reviewed. Table 1 summarizes the patient characteristics.

The varices were related to hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, habitual alcohol consumption, and other conditions. According to the Child-Pugh classification system, 28 patients were categorized into class A, 17 into class B, and 1 was classified under class C. None had mild to severe ascites or symptomatic hepatic coma. The gastric varices in the fundus were subdivided into two types according to Sarin's classification^{3, 7)}: large gastric varices with esophageal varices (GOV2) and isolated gastric varices (IGV1). GOV2 and IGV1 were found in 29 (63.0%) and 17 (37.0%) patients, respectively. Twenty of the total patients (43.5%) had a history of bleeding from the gastric varices, although because the bleeding had already stopped during the endoscopic observation, B-RTO was scheduled without any endoscopic therapy. In the 26 remaining patients, B-RTO was performed as a prophylactic treatment. Twenty-nine (63.0%) patients had esophageal varices before B-RTO; of these, 28 had no previous episodes of bleeding, and thus endoscopic treatment for the esophageal varices was not performed before B-RTO. The endoscopic findings of the varices were evaluated according to the general rules proposed by the Japanese Research Society for Portal Hypertension¹⁹⁾. Eight (17.4%) patients had concomitant or past history of HCC without portal vein tumor thrombus, but the tumor was well controlled when B-RTO was performed.

B-RTO procedure

The presence of a portosystemic shunt, such as a gastorenal shunt, was confirmed in all patients by multidetector-row CT or magnetic resonance imaging before B-RTO, which

was performed according to the method reported by Kanagawa *et al*¹⁰⁾. In brief, a balloon catheter with a diameter of 8–20 mm (Terumo-Clinical Supply, Tokyo, Japan or Selecon MP catheter, Clinical Supply, Gifu, Japan) was inserted into the outlet of a gastorenal shunt via the right femoral or right jugular vein. Balloon-occluded venography (B-RTV) was performed with an inflated balloon to confirm the demonstration of both gastric varices and collateral veins. A microcatheter (Renegade, Boston Scientific Japan, Tokyo, Japan) was advanced close to the variceal cavity through the balloon catheter. If the gastric varices did not appear because the collateral veins were dilated, then the collateral veins were embolized by using 50% glucose metal coils. When the gastric varices were visualized and retention of the contrast medium in these varices was identified, 5% EOI was injected into the varices through the catheter under balloon occlusion of the balloon catheter. The 5% EOI consisted of 10% ethenolamine olate (Oldamin, Takeda Pharmaceutical, Tokyo, Japan) diluted with the same volume of iopamidol (Iopamiron 300, Schering, Osaka, Japan). To prevent renal damage due to EOI-induced hemolysis, 4000 units of human haptoglobin (Yoshitomi, Osaka, Japan) was intravenously administered before the injection of 5% EOI. In general, the balloon catheter was positioned, 5% EOI was injected into the gastric variceal complex, and then the catheter was left in place overnight in all but 6 patients for whom the catheter was withdrawn after 30–60 min. On the next day, the balloon was deflated and the catheter was withdrawn after confirming thrombosis of the gastric varices by B-RTV.

Follow-up examination

To evaluate the therapeutic efficacy of B-RTO of gastric varices, we performed contrast-enhanced CT 5–7 days after the procedure. Thereafter, contrast-enhanced CT was performed every 6–12 months to examine for the recurrence of gastric varices. Endoscopy was also performed to evaluate esophageal and gastric varices 4–8 weeks after B-RTO. Risky varices were defined as those of moderate or large size (F2 or F3) and/or those with one of several marks (red wall marking, cherry red spot, or hematocystic spot). If the endoscopic findings revealed risky varices and/or bleeding episodes of esophageal varices after B-RTO, endoscopic treatment such as endoscopic variceal ligation (EVL) and/or endoscopic injection sclerotherapy (EIS) was performed immediately. After the first observation without findings of worsening or treatment of esophageal varices, endoscopy was performed every 6–12 months. Routine physical and laboratory examinations were conducted every 2–3 months. Depending on the patient's condition, the attending physician determined the follow-up interval.

Statistical analysis

The results were expressed as the mean and standard deviation (SD), median and range (minimum-maximum), or percentage. The time courses of the liver function tests after

B-RTO were analyzed by using a paired t-test. The cumulative survival curve was calculated according to the Kaplan-Meier method for all the patients in whom B-RTO was successfully performed and complete thrombosis of gastric varices was achieved. The distributions of survival were analyzed in relation to prognostic factors such as age, gender, cause of liver disease, Child-Pugh classification, concomitant esophageal varices, form of gastric varices, location of gastric varices, and concomitant advanced HCC during the observation periods. Advanced HCC was defined as HCC with portal vein tumor thrombus and/or metastases to other organs. Univariate analyses (log-rank tests) were used to determine the differences in these distributions. The factors that appeared to have a significant impact on survival were entered in a Cox proportional hazards model to test significant effects, simultaneously adjusting for multiple factors. A *P*-value of less than 0.05 was considered statistically significant in all the tests. Statistical software (Ekuseru-Toukei 2008, Social Survey Research Information Co., Ltd., Tokyo, Japan) was used for all the analyses.

Results

Outcomes of B-RTO

B-RTO was technically successful in 46 (94.0%) of 50 patients; the 4 remaining patients had several draining routes and collateral veins without gastroduodenal shunts, which could not be occluded despite the use of 50% glucose and metal coils, resulting in insufficient accumulation of 5% EOI. Of these 4 patients, 3 underwent gastric devascularization and splenectomy (Hassab's operation), while 1 underwent percutaneous transhepatic obliteration. In the remaining 46 patients, B-RTO was performed twice in 1 patient only. The balloon catheter was placed overnight in 40 patients and for 30–60 min in 6 patients. No major complications were encountered with B-RTO.

Recurrence of gastric varices

Among the 46 patients, only 1 patient was lost to follow-up immediately after the first evaluation. The 45 remaining patients were followed up for the recurrence of gastric varices over the median observation period of 10 months (mean: 20.3 ± 22.5 months; range: 1–88 months). No recurrence or bleeding from the gastric varices was noted during the observation period in any of the patients.

Progression of esophageal varices

Of the 46 patients, 42 were followed up for the progression of esophageal varices (Table 2). These varices worsened in 13 (31.0%) patients; moreover, 6 (14.3%) of them bled during the median observation period of 11.5 months (mean: 19.1 ± 19.6 months; range: 1–71 months). The patients with worsened or bleeding esophageal varices underwent EVL or EIS. Of the 15 patients without esophageal varices before B-RTO, 6 showed disease progression, wherein 2 required emergency or elective treatment, 2 received prophylactic

Table 2. Worsening of esophageal varices after B-RTO

No. of patients	Follow-up patients	Worsening of esophageal varices after B-RTO		No treatment	Endoscopic treatment	
					Emergent/Elective	Prophylactic
No varices (17)	15	Yes	6	2	2	2
		No	9	9	0	0
F0-1 varices (21)	20	Yes	6	2	3	1
		No	14	14	0	0
F2-3 varices (8)	7	Yes	1	0	1	0
		No	6	4	0	2

Table 3. Changes in laboratory data and Child-Pugh scores

	Patients, no	Before B-RTO	1 year after B-RTO	p-value
Prothrombin time	26	75.3 ± 12.3	83.2 ± 11.7	0.0037
Albumin	29	3.3 ± 0.6	3.5 ± 0.6	0.1475
Total bilirubin	29	1.3 ± 0.8	1.3 ± 0.7	0.9594
Child-Pugh score	29	6.2 ± 1.1	6.1 ± 1.4	0.6018

treatment, and 2 received no treatment. Of the 20 patients with F0-1 esophageal varices before B-RTO, 14 showed no changes; however, 6 showed disease progression, wherein 3 required emergency or elective treatment, 1 received prophylactic treatment, and 2 were observed without endoscopic treatment. Among the 7 patients with F2-3 esophageal varices before B-RTO, 6 showed no changes, but 2 received prophylactic treatment immediately after B-RTO. Of the 4 remaining patients, 3 were not treated endoscopically, since 1 underwent liver transplantation 12 months after B-RTO, 1 died from advanced HCC, and 1 was transferred to another hospital. One patient attended our hospital for further treatment. One patient with F2 esophageal varices suffered a bleeding episode and required emergency treatment.

Changes in laboratory data and Child-Pugh scores

On average, the prothrombin activity significantly improved from 75.3±12.3% before B-RTO to 83.2 ± 11.7% at 1 year after B-RTO ($n = 26$; Table 3). However, the serum albumin level, total bilirubin level, and Child-Pugh scores did not change significantly after B-RTO.

Survival rate and clinical background

The median survival period was 13.5 months (mean: 24.8±23.5 months; range: 1–92 months). The overall cumulative survival rates at 1, 3, and 5 years after B-RTO were 91.6%, 70.9%, and 53.6%, respectively (Fig. 1). In all, 13 (28.3%) patients died of the

Fig. 1. Cumulative survival rate after B-RTO

The overall cumulative survival rates at 1, 3, and 5 years were 91.6%, 70.9%, and 53.6%, respectively.

Table 4. Univariate analysis of prognostic factors affecting survival rate

	Variable	p-value
Age	Over 70 years	0.0288
Gender	Male	0.9501
Cause of liver disease	HBV + HCV	0.2577
Child-Pugh classification	B + C	0.9794
Concomitant esophageal varices		0.3880
Form of gastric varices	F3	0.8721
Location of gastric varices	GOV2	0.9849
Advanced HCC		0.0064

following causes : advanced HCC, 9 patients ; liver failure, 2 patients ; and other malignancies, 2 patients. Of these, 3 patients died due to bleeding from esophageal varices and advanced HCC with portal vein tumor thrombus that occurred in the observation period after B-RTO.

Prognostic factors affecting the overall survival

The univariate analysis identified age (> 70 years) and occurrence of advanced HCC as significant prognostic factors related to survival (Table 4). The multivariate analysis showed that the survival rate was significantly lower in the patients with advanced HCC than in those without HCC (hazard ratio = 4.1497, 95% CI = 1.3214 – 13.0319 ; Table 5). The survival rates at 1, 3, and 5 years after B-RTO were 95.2%, 82.7%, and 65.2%, respectively, in the patients without advanced HCC and 76.2%, 50.8%, and 33.9%, respectively, in those with advanced HCC (Fig. 2).

The median survival period was 18.0 months (range : 1–92 months) in the patients without advanced HCC ($n = 36$) and 12.5 months (range : 3–66 months) in those with advanced HCC ($n = 10$).

Table 5. Multivariate analysis of prognostic factors affecting survival rate

	HR	95% Confidence intervals	p-value
Age : over 70 years	2.7916	0.8158 9.5529	0.1019
Advanced HCC	4.1497	1.3214 13.0319	0.0148

Fig. 2. Cumulative survival rates of the patients with and without advanced HCC during the observation period after B-RTO

The patients who developed advanced HCC had poorer cumulative survival rates than those who did not (95.2%, 82.7%, and 65.2% vs. 76.2%, 50.8%, and 33.9% at 1, 3, and 5 years after B-RTO, respectively; $P = 0.0054$).

Discussion

Since its introduction by Kanagawa *et al*⁽¹⁰⁾, B-RTO has become widely accepted as a minimally invasive, highly effective treatment for gastric varices. In the present study, all the 46 patients who underwent technically successful B-RTO remained free of gastric variceal recurrence during the observation period; their cumulative survival rates after B-RTO were 91.6% in the first year, 70.9% in the third year, and 53.6% in the fifth year. Further, the median survival periods were 5.5 months longer in the patients without advanced HCC than in those with advanced HCC. These results, which are similar to those reported previously⁽¹¹⁻¹⁶⁾, suggest that successful B-RTO has a stable long-term therapeutic effect.

Reported success rates of B-RTO of gastric varices are approximately 90%^(11, 12, 14, 15); however, not all patients can be treated with this procedure. B-RTO may be associated with several technical difficulties leading to unfavorable results because of the complicated venous anatomy. The draining route from gastric varices is variable among patients, and unexpected collateral veins often develop. In general, B-RTO can be performed when there is a single gastorenal shunt with minute collateral veins. "stepwise injection"⁽²⁰⁾ and/or a "downgrading method"⁽²¹⁾ have been attempted in cases with one gastorenal shunt and developing collateral veins. In cases of gastric varices without a gastorenal shunt, standard B-RTO is

impossible to perform. However, gastric varices without gastrosplenic shunts are relatively infrequent; such a condition was detected by B-RTO and arteriography in only 4 (3%) of 130 patients in a previous study²²⁾. In the present study, 4 (6.0%) of 50 patients did not have a detectable gastrosplenic shunt; therefore, B-RTO was not technically successful in these cases because the varices had several outflow routes that could not be occluded by any means. There are few reports of successful B-RTO through the main outflow routes with the exception of gastrosplenic shunts. For example, if the dilated left inferior phrenic vein is the only draining vein from the gastric varices, complete B-RTO is possible by inserting a balloon catheter into this vein through the inferior vena cava²³⁾.

Obliterating a major portosystemic shunt via B-RTO causes hemodynamic changes. Some reports indicated that B-RTO increases the portal blood flow to liver parenchyma¹⁷⁾, thus contributing to improved liver function and reducing circulating ammonia levels^{18, 24-26)}. In our study, no changes were observed in the serum albumin level, total bilirubin level, or Child-Pugh scores; however, prothrombin activity was significantly improved at 1 year after B-RTO. Our findings thus indicated that B-RTO is valuable not only for reducing mortality due to bleeding of gastric varices, but also for improving liver function. However, an increase in portal pressure cannot be avoided, and therefore, B-RTO does carry certain risks for the development of ascites^{14, 27)}, aggravation of esophageal varices²⁸⁾, and appearance of ectopic varices²⁹⁾. Some patients suffer worsening of esophageal varices after B-RTO at a frequency of 14.3–54.4%¹³⁾, with 13 of our 42 (31.0%) patients with esophageal varices showing worsening during the median observation period of 11.5 months. In a previous study¹³⁾, patients without esophageal varices before B-RTO did not develop these varices, while those with F1 varices before B-RTO were not considered to need immediate treatment because the varices did not progress rapidly. However, patients with F2 varices are at a higher risk of worsening and require endoscopic treatment of their esophageal varices without delay after B-RTO. The present study found no association between the worsening of esophageal varices and the form of the varices before B-RTO. In fact, 2 (13.3%) of the 15 patients without esophageal varices and 3 (15.0%) of the 20 patients with F0-1 esophageal varices underwent emergency or elective endoscopic treatment after hemorrhage, but no changes were observed in 6 of 8 patients with F2 esophageal varices. Patients with F2-3 varices, no varices, and F0-1 varices therefore require careful observation to prevent the rupture of esophageal varices after B-RTO. Incidentally, endoscopic treatment for our patients with F0-1 esophageal varices was not performed before B-RTO. We consider that esophageal varices that progress to F2-3 after B-RTO can be managed more easily than those before B-RTO, because of the development or worsening of esophageal varices after B-RTO indicating aggravation of portal hypertension.

Some reports have described the presence or absence of concomitant HCC and Child-Pugh classification as prognostic factors related to survival^{11, 15, 18)}. Our strategy of treatment for gastric varices excluded patients with Child-Pugh class C and concomitant advanced

HCC, because the benefit of B-RTO remains unclear in Child-Pugh class C patients³⁰⁾. We considered that the occurrence of advanced HCC is significantly associated with survival after B-RTO because of poor prognoses in the observation period. The development of HCC in chronic liver disease was the most common cause of death in our patients. Satisfactory survival would depend upon careful management for preventing the advancement of HCC.

In conclusion, B-RTO of gastric varices is an effective treatment ensuring low recurrence and bleeding rates; however, these patients require careful observation for the progression of esophageal varices. The present study also identified the occurrence of advanced HCC as a prognostic factor for survival in patients with gastric varices after B-RTO. We believe that B-RTO will become the standard treatment for gastric varices with gastroduodenal shunts, although treating worsened esophageal varices may be necessary after B-RTO.

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