

tially useful method for management of vascular complications associated with nephrostomy.

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CASE REPORT

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Ultrasound-guided thrombin injection for the treatment of an iatrogenic hepatic artery pseudoaneurysm: a case report

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Abstract

Introduction: Percutaneous transhepatic portal embolization is often performed to expand the indications for hepatic resection. Various etiologies of hepatic artery pseudoaneurysm have been reported, but regardless of the etiology, hepatic artery pseudoaneurysm is usually managed with an endovascular approach or open surgery, depending on the location and clinical symptomatology. However, it is difficult to manage hepatic artery pseudoaneurysm after percutaneous transhepatic portal embolization, since embolization of the hepatic artery may cause hepatic infarction.

Case presentation: A 58-year-old Japanese man with hilar bile duct cancer underwent percutaneous transhepatic portal embolization to expand the indication for hepatic resection. Two days after percutaneous transhepatic portal embolization, our patient suddenly complained of abdominal pain. Contrast-enhanced computed tomography confirmed a pseudoaneurysm arising from a segmental branch of his right hepatic artery. Since embolization of the hepatic arterial branches may cause hepatic infarction, ultrasound-guided thrombin injection therapy was successfully performed for the pseudoaneurysm.

Conclusion: We performed a thrombin injection instead of arterial embolization to avoid hepatic infarction. The rationale of this choice may be insufficient. However, ultrasound-guided percutaneous thrombin injection therapy may be considered as an alternative to percutaneous transarterial embolization or surgical intervention for an iatrogenic hepatic artery pseudoaneurysm.

Introduction

Percutaneous transhepatic portal embolization (PTPE) is often performed to expand the indications for hepatic resection. Various etiologies of hepatic artery pseudoaneurysm (HAP) have been reported, but regardless of the etiology, HAP is usually managed with an endovascular approach or open surgery, depending on the location and clinical symptomatology. However, it is difficult to manage HAP after PTPE, since embolization of the hepatic artery may cause hepatic infarction. We herein describe a case of PTPE complicated by a HAP, in which the HAP was successfully managed with an ultrasound (US)-guided thrombin injection technique.

Case presentation

A 58-year-old Japanese man with hilar bile ductal carcinoma underwent preoperative PTPE to expand the indication for right hepatic resection. We punctured the anterior branch of his right portal vein with a 21-gauge needle under US-guidance. A 5-Fr sheath was advanced into the portal branch and a 5-Fr balloon catheter was inserted into the anterior and posterior branches of his right portal vein. After inflating the balloon, absolute alcohol was injected. A portography confirmed the complete occlusion of these portal branches. Finally, two 5 mm × 5 cm 0.035-inch coils were deployed to perform tract embolization after PTPE. During these procedures our patient was asymptomatic.

Two days later, our patient suddenly complained of an acute abdominal pain, but his vital signs remained stable. A contrast-enhanced computed tomography (CT) confirmed the presence of a pseudoaneurysm arising from a

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segmental branch of his right hepatic artery: the pseudoaneurysm measured 20 × 15 mm in size with a narrow neck surrounded by hematoma (Figure 1a). Percutaneous transarterial embolization (TAE) of the pseudoaneurysm was considered to be inappropriate, since TAE may cause hepatic infarction because of an already occluded portal vein. Under US and digital subtraction angiography (DSA) guidance (Figure 1b), the pseudoaneurysm was punctured with a 21-gauge needle and 1500 U of human-derived thrombin was injected into the pseudoaneurysm (Figure 2). Total occlusion of the pseudoaneurysm was confirmed by DSA and follow-up CT (Figure 3), and an occlusion of the segmental branch of his right hepatic artery was avoided. Our patient was followed-up for four weeks after the procedure using US, and there was no evidence of recurrent pseudoaneurysm or hepatic infarction. The left lobe of his liver became hypertrophic.

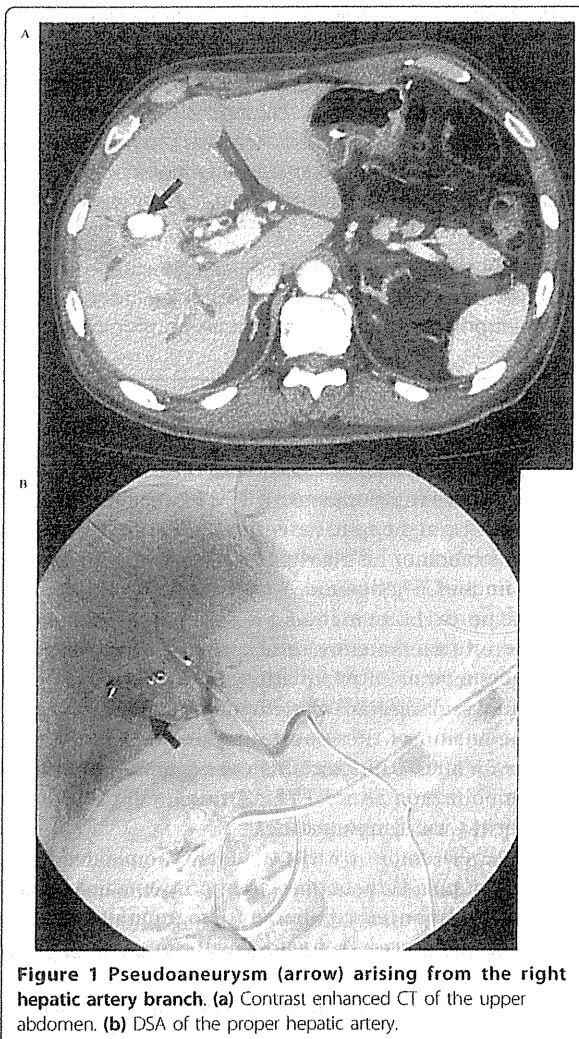


Figure 1 Pseudoaneurysm (arrow) arising from the right hepatic artery branch. (a) Contrast enhanced CT of the upper abdomen. (b) DSA of the proper hepatic artery.

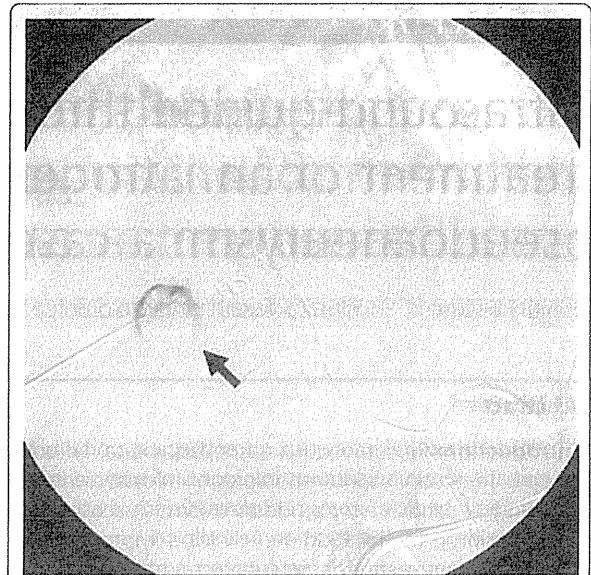


Figure 2 US-guided thrombin injection therapy for an iatrogenic hepatic artery pseudoaneurysm with 21G needle (arrow).

He underwent a right hepatectomy 30 days after the procedure, and his postoperative course was uneventful.

Discussion

Post-traumatic HAP is uncommon, and accounts for approximately 1% of hepatic trauma cases [1,2]. Other causes include chronic pancreatitis, orthotopic liver transplantation, arteriosclerosis, cystic medial necrosis, polyarteritis nodosa, necrotizing vasculitis, acute pancreatitis and hepatocellular carcinoma [2]. Most HAPs occur extrahepatically, predominantly in the right hepatic artery [2]. Intrahepatic HAPs account for only about 20% of all HAPs and are often a complication of percutaneous procedures such as transhepatic cholangiography, transhepatic catheter placement or liver biopsy [3]. The incidence of intrahepatic HAP occurring after trauma is relatively uncommon.

There is only one report of PTPE complicated by HAP, and it occurred in one of 47 procedures (2.1%) [4]. However, to the best of our knowledge, there have been no reports in the English literature describing treatment of HAP complicated by PTPE. In the present case, we suspected that the HAP may have been caused by unexpected damage of the hepatic arterial branch when we accessed his right portal vein. Rupture of a HAP is associated with a high mortality rate, thus it mandates an early detection and prompt intervention [1,2]. Although clinical diagnosis can be made by noninvasive methods such as CT and Doppler US, selective catheter arteriography remains the most sensitive modality for detecting a



Figure 3 Confirmation of the total occlusion of the pseudoaneurysm on (a) DSA and (b) follow-up CT.

HAP. In a study by Tobben *et al.* [5], catheter arteriography detected all HAPs in ten patients, compared with only 67% by CT and 33% by Doppler US. Selective arteriography may also show active bleeding and anatomic variations such as an anomalous or replaced hepatic artery [6], and can be used in simultaneous diagnosis and treatment. The recent extended utilization of high-resolution vascular imaging modalities may have a greater contribution.

Selective arterial embolization is currently considered to be the most appropriate technique in the treatment of visceral pseudoaneurysms, with a success rate of more than 80% and a low complication rate [7]. Various agents for embolization have been used successfully, such as ethanol, gel foam particles, microcoils, n-butyl-2-cyanoacrylate glue, polyvinyl alcohol particles and thrombin [8,9] as well as metallic stents and detachable silicone balloons [10].

Percutaneous thrombin injections for the treatment of visceral [11], renal [12] and extremity pseudoaneurysms

have been employed since 1986 and were first described by Cope and Zeit [13], and can be performed under Doppler US-guidance. This method has yielded excellent results for femoral pseudoaneurysms, and can be carried out without the need of anesthesia equipment or an operating theater. We selected the percutaneous thrombin injection technique under US and DSA-guidance to avoid hepatic artery occlusion which may result in hepatic infarction.

As well as the possibility of a recurrent pseudoaneurysm after a percutaneous thrombin injection, complications such as thromboembolism and allergic reactions have limited its use [13]. The use of bovine-derived thrombin may pose a potential risk of an allergic response and hemorrhage in patients with a known allergy to bovine-derived products or previous exposure to topical thrombin [13]. Another consequence of bovine thrombin exposure is the potential development of antibodies to human clotting proteins and thrombin, in particular factor V, resulting in coagulopathy and excessive bleeding [14]. Such complications are not seen with newer human-derived thrombin.

Conclusion

A HAP is one of the possible complications following PTPE. Generally, such a complication will be managed by an endovascular approach. Although minor hepatic infarction can occur after hepatic arterial embolization, liver damage induced by hepatic arterial embolization in such cases may usually be within an acceptable range. We performed thrombin injection instead of arterial embolization to avoid hepatic infarction. The rationale for this choice may be insufficient. However, US-guided percutaneous thrombin injection therapy may be considered as an alternative to TAE or surgical intervention for an iatrogenic HAP.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Authors' contributions

HT reviewed relevant literature and drafted the manuscript. All authors provided clinical expertise and participated in drafting the manuscript. And all authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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RESEARCH

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Feasibility of externalized peritoneovenous shunt (EPVS) for malignant ascites

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Abstract

Purpose: To evaluate a new modified peritoneovenous shunt therapy, the externalized peritoneovenous shunt (EPVS) system placement, used to treat patients with malignant ascites.

Methods: We retrospectively reviewed 10 patients, who were not suited for conventional peritoneovenous shunts (PVS), with malignant ascites, which was refractory to medical therapies. Patient characteristics, technical success, efficacy, duration of EPVS placement, adverse events, and outcome were evaluated. Clinical efficacy of the EPVS was evaluated by the change in subjective symptoms.

Results: The primary reasons for applying EPVS were severe anasarca in 4 patients, potential PVS dysfunction in 3 patients, poor performance status in 2 patients, and a history of PVS occlusion in 1 patient. EPVS was successfully placed in all patients, and it provided clinical efficacy in 8 patients (80%). Early death occurred within 7 days after EPVS placement in 2 patients because of renal failure. The median duration of EPVS placement was 10.4 days (range, 2-28 days). In 6 patients (60%), the EPVS was exchanged to conventional PVS sequentially, since the initial EPVS placement resulted in an improvement of the subjective symptoms of the patients, without serious complications.

Conclusion: EPVS placement may be an option for patients with malignant ascites who may not be appropriate for conventional PVS placement.

Keywords: Denver shunt, peritoneovenous shunt (PVS), externalized peritoneovenous shunt (EPVS), malignant ascites, palliative therapy

Background

A peritoneovenous shunt (PVS), which is also known as a Denver shunt, may be effective for palliating symptoms in patients with malignant ascites, which contribute to a deterioration of the patient's quality of life (QOL) and which are refractory to conservative nonsurgical therapies. Various shunts have been designed to use as peritoneovenous shunting [1,2], and radiological insertion of the Denver shunt may be the most widely used technique for nonsurgical PVS implantation in our country. However, the mortality rate of PVS implantation has been reported to be rather high, and indications are limited [3-6]. Possible contraindications for PVS

implantation include ascites that is infected, hemorrhagic, chylous, or with loculated malignant effusion, advanced cardiac or renal failure, elevated serum bilirubin levels (6 mg/dL), portal hypertension, massive pleural effusion, coagulation disorders, and poor performance status (PS).

In addition, since a long subcutaneous tunnel should be constructed in the implantation of a PVS, a PVS once implanted in the subcutaneous tissue cannot be readily modified, even when the system may get infected or occluded [7], particularly in patients with severe anasarca. Furthermore, postoperative incisional separation of wound is considered to be main inappropriate reason for PVS in patients with sever anasarca.

We applied an externalized peritoneovenous shunt (EPVS) in 10 patients in whom conventional PVS was considered to be inappropriate due to various reasons

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and evaluated the feasibility of this new alternative method. And EPVS was inserted to estimate the patients whether they can tolerate subsequent PVS placement.

Patients and methods

We retrospectively reviewed 10 patients with refractory malignant ascites who underwent EPVS placement between January 2005 and December 2010. There were 32 cases of conventional PVS during the same period. Inclusion criteria of EPVS were as follows: (1) malignant ascites was confirmed cytologically or clinically, (2) ascites was refractory to conservative nonsurgical therapies, (3) there was no evidence of infection of the ascites, (4) QOL was deteriorated because of the ascites, and (5) conventional PVS was considered to inappropriate because of severe anasarca, potential PVS dysfunction, history of PVS occlusion or poor PS.

Potential PVS dysfunction was defined as possible shunt dysfunction due to particular characteristics of ascites such as bloody or chylous. Poor PS was defined as a life expectancy that was considered to be less than a month. These patients did not have liver dysfunction, portal hypertension, massive pleural effusion, or coagulation disorders. Refractory ascites was diagnosed when the ascites failed to respond to conservative therapy (fluid restriction to 1000 mL/day, 100 mg/day of spironolactone, or 40 mg/day of furosemide for 4 weeks), or when the patients had intolerance to these conservative therapies because of azotemia [8-10].

We employed a PVS kit (Denver-PAK; Denver Biomaterials, Inc., Golden, CO, USA) in all patients. Procedures were carried out under local anesthesia by interventional radiologists. The abdominal catheter was inserted into the Douglas cavity through the 16-F sheath. Then the venous catheter was inserted into the right or the left subclavian vein and was placed at the lower portion of the superior vena cava through the 12-F sheath. Ultrasound and X-ray fluoroscopy was used for the guidance of the catheters insertion (Figure 1).

Technical success was defined as the creation of the shunt and catheter insertions into both the abdominal cavity and superior vena cava. Immediately after the procedures, 500 mg of hydrocortisone sodium succinate and 20 mg of furosemide were administered intravenously to reduce acute biochemical reactions related to the shunting and strain on hemodynamics. For the patients with normal renal function ($n = 8$), 2 g/day of cefazolin (CEZ) was given intravenously for 3 days. In all patients ($n = 10$), 3 $\mu\text{g}/\text{kg}/\text{min}$ of catecholamines was administered in order to maintain more than 1000 ml/day of urine volume for 3 days. In the patients who had less than 10×10^3 cells/ mm^3 of blood platelets ($n = 2$), 100 mg/day of gabexate was administered for 7 days. Central venous pressure was continuously monitored in

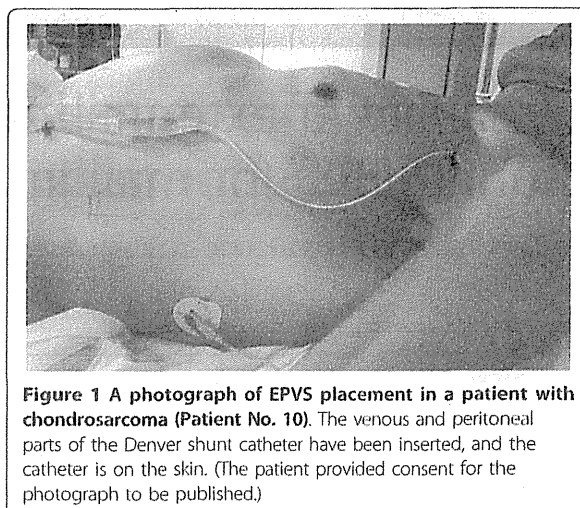


Figure 1 A photograph of EPVS placement in a patient with chondrosarcoma (Patient No. 10). The venous and peritoneal parts of the Denver shunt catheter have been inserted, and the catheter is on the skin. (The patient provided consent for the photograph to be published.)

order to minimize fluid overload, and chest X-ray pictures were checked in order to detect pulmonary edema.

Patient characteristics, technical success, efficacy, the duration of EPVS placement, adverse events, and outcome were retrospectively evaluated. Technical success was defined as the creation of the shunt with catheter insertions into both the abdominal cavity and the superior vena cava. We also evaluated hematological parameters, abdominal girth, and diuresis before and after EPVS placement. Improvement of anasarca was evaluated as a decrease of abdominal girth.

We asked patients about subjective symptoms before and after the EPVS procedures. Clinical efficacy of the EPVS was evaluated by the change in subjective symptoms. Each EPVS procedure was classified into 2 groups: effective, in which the duration of the improvement of at least one of 3 subjective symptoms from the ascites (abdominal distention, anorexia, and nausea/vomiting) was 7 days or more; ineffective, in which there was no subjective improvement, or the duration of symptom improvement was less than 7 days. If EPVS was exchanged to PVS within 7 days, EPVS was judged effective when at least one of 3 subjective symptoms from the ascites was improved before EPVS was exchanged to PVS.

PS was evaluated by the Eastern Cooperative Oncology Group Performance Status (ECOGPS) [11]. Adverse events (AEs) were categorized according to the clinical practice guidelines of the Society of Interventional Radiology. Major AEs were defined as those necessitating an increased level of care, major therapy, or prolonged hospitalization, and those resulting in permanent sequelae or death. Minor AEs were defined as those necessitating nominal therapy or observation only [12].

When conventional PVS therapy was followed by EPVS implantation, a subcutaneous tunnel was created

first, and the center part of the device was placed. The abdominal catheter was exchanged by injecting saline solution into the abdominal cavity in order to prevent damage to the adjacent organs. The venous side catheter was also exchanged using a guidewire.

Informed consent was obtained from each patient before EPVS implantation was performed, and the institutional review board of our institution approved this technique. This study was conducted in accordance with the amended Helsinki Declaration.

Results

Characteristics of the 10 patients (3 men and 7 women; mean (SD) age, 52 (13) years; range, 22-69) are listed in Table 1. The reasons for the use of EPVS placement instead of a conventional PVS were poor PS in 4 patients, severe anasarca in 4 patients, potential PVS dysfunction in 4 patients, and a history of PVS occlusion in 2 patients (with overlap). The patency period of initial PVS in the patients (No. 4 and No. 8) who had a history of PVS occlusion was 192 and 69 days. Subsequent PVS placement might be possible because the function of initial PVS did not have any problems for a long period. However, EPVS placement was performed because characteristics of ascites were bloody and chylous.

Technical success was obtained in all patients without any major AEs that were associated with the procedure. EPVS placement provided clinical efficacy in 8 (80%) patients, and the procedure was effective for abdominal distention in 8 patients, anorexia in 5 patients, and nausea/vomiting in 4 patients (with overlap). The largest abdominal girth was resolved in all patients. However, given the low sample size, we were unable to perform a statistical analysis to test for a correlation between hematological parameters, abdominal girth, and diuresis, before or after EPVS placement (Table 2).

The median duration of EPVS placement was 10.4 days (range, 2-28 days). The EPVS was exchanged to conventional PVS sequentially in 6 patients (60%), since the initial EPVS placements resulted in improvement of subjective symptoms without major AEs, and the patients' life expectancies were suspected to be more than a month. In these 6 patients, the EPVS system was removed and exchanged to conventional PVS on the same day. There were no cases of EPVS and PVS dysfunction on the follow-up period. Patency period of EPVS and PVS were 10.4 days (range 2-28 days) and 106 days (9-196 days).

The median survival duration was 74.0 days (range, 2-200 days). The survival durations of the patients with

Table 1 Patient characteristics for 10 patients who received EPVS

No.	age	sex	primary disease	nature of ascites	PS	indication for EPVS	EPVS duration, days	survival duration, days	outcome	AEs
1	22	F	synovial sarcoma	serous	3	poor PS	6	6	not effective	renal failure**
2	64	M	mesothelioma	serous	1	potential PVS dysfunction	3	133	effective*	none
3	46	M	lymphoma	serous	4	anasarca, poor PS	14	23	effective*	pulmonary edema**, diarrhea
4	62	F	ovary cancer	bloody	1	history of PVS occlusion	4	200	effective*	none
5	49	F	colon cancer	bloody	1	anasarca, potential PVS dysfunction	4	77	effective*	none
6	57	F	mesothelioma	serous	1	potential PVS dysfunction	16	133	effective*	none
7	56	F	breast cancer	chylous	1	potential PVS dysfunction	3	114	effective*	none
8	48	F	lung cancer	chylous	1	anasarca, history of PVS occlusion	28	28	effective	diarrhea, anemia
9	50	F	cholangiocarcinoma	chylous	4	anasarca, poor PS	24	24	effective	diarrhea
10	69	M	chondrosarcoma	serous	4	poor PS	2	2	not effective	renal failure**
median	52.3						10.4	74.0		

The EPVS system was removed and exchanged to conventional PVS on the same day.

PS: Eastern Cooperative Oncology Group Performance Status.

EPVS: externalized peritoneovenous shunt.

PVS: peritoneovenous shunt, AEs: adverse events.

*: EPVS was exchanged to conventional PVS.

**: major adverse event.

Table 2 Hematological parameters, abdominal girth, and diuresis, before and after EPVS placement

	Preoperative Period	3-POD	7-POD	14-POD
Cr, mg/dL	1.1 (0.6)	1.2 (0.7)	1.1 (0.8)	1.1 (0.9)
BUN, mg/dL	21.2 (10.6)	22.6 (13.7)	23.5 (13.7)	27.8 (15.8)
Albumin, g/dL	2.3 (0.3)	2.4 (0.4)	2.6 (0.5)	2.5 (0.6)
PT, %	70.1 (13.8)	60.8 (12.5)	68.6 (13.10)	67.6 (10.4)
Platelets, 10 ³ cells/mm ³	35.8 (9.1)	26.7 (10.6)	25.3 (8.7)	29.3 (6.8)
Largest abdominal girth, cm	87.5 (9.6)	84.1 (10.6)	81.7 (5.1)	80.2 (4.8)
Diuresis, 24 h, mL	978 (466)	1723 (560)	1612 (416)	1334 (506)

Data are presented as mean (SD).

POD: postoperative day.

PT: prothrombin time.

poor PS (PS 3 or 4; n = 4) were less than 1 month (range, 2-24 days).

Three patients (30%) had major AEs. Acute death occurred within 7 days after EPVS placement in 2 patients (No. 1 and No.10) because of renal failure which had been occurred by hypovolemia since preoperative days. Before EPVS placement, these patients had renal dysfunction and low serum albumin levels. As one patient (No. 3) experienced pulmonary edema just after the EPVS placement, we clumped the catheter to avoid hyperperfusion on the 3rd postoperative day until the pulmonary edema was resolved on the 5th postoperative day.

Minor AEs were observed at 30% (diarrhea in three patients and anemia in one patient) and were resolved conservatively.

Discussion

Our results suggest that EPVS placement for refractory ascites is effective and can be adopted even for patients who were not suitable for a conventional PVS implantation because of anasarca, poor PS, potential PVS dysfunction, or history of PVS occlusion. However, EPVS placement resulted in a 20% procedure-related early death. We suggest that careful assessment of the procedure-related risks and close monitoring after EPVS implantation are essential.

Malignant ascites in patients with advanced cancer is often resistant to treatment. Troublesome symptoms from ascites result in progressive deterioration of the patients' QOL. Diuretics and paracentesis have been traditionally employed to relieve the symptoms associated with ascites. However, their use has been inconsistent among physicians. It is sometimes difficult for patients or caregivers to bring patients to the place where paracentesis is performed. Repeated paracentesis requires frequent trips to

the hospital with risks of hypovolemia, hypotension, and hypoproteinemia from ascites removal [6].

Although paracentesis can provide immediate relief, the effects may be temporary, and complications, such as bleeding, hypotension, secondary peritonitis, and loss of protein and electrolytes, may occur [13,14]. Since the first report by LeVeen et al. [1], the Denver PVS has been considered as one of the most common procedures used to treat intractable malignant ascites, in which other conservative medical therapies may not be effective [1-7].

Although PVS is simple and an about 70% clinical effectiveness is expected, AEs, such as pulmonary edema, pulmonary arterial embolism, and disseminated intravascular coagulation (DIC), following PVS implantation may frequently occur. In addition, shunt replacement (removal) is often warranted due to shunt infection or occlusion of the system [3-7]. Efficacy of PVS would not be superior to that of paracentesis in short period, therefore PVS implantation has been considered to be a contraindication in patients with malignant ascites due to gastrointestinal malignant tumors, and a shunt should only be used when the life expectancy of the patients expected to derive a benefit from it is more than 2 or 3 months ([3-5,15]).

Bieligk et al. [7] reported that preoperative impaired renal function was a predictive factor of poor prognosis after PVS insertion. Thus, careful consideration should be taken in deciding on placement in patients with insufficient urine volume, who may be unable to tolerate the rapid increase in plasma volume immediately after PVS insertion [5,7]. In fact, in our study, early death occurred within 7 days after EPVS placement in 2 patients because of progressive renal failure. Before EPVS placement, these patients had renal dysfunction and low serum albumin levels. After EPVS placement, ascites volume was decreased in these patients, although they had impaired production of sufficient urine volume. A possible explanation is that the low colloid osmotic pressure of these conditions may lead to extravascular transudation of water, resulting in renal failure due to hypovolemia [5,7,16,17].

Our EPVS procedure has some advantages over conventional (PVS) implantation. Not only EPVS is placement technically simpler, but EPVS may be less invasive for patients. A subcutaneous long tunnel is not need for EPVS. We can easily maintain the system, and the flow control is easily performed at any time. This is a very important advantage of EPVS placement, since PVS insertion may result in rapid changes in circulatory dynamics, as well as rapid introduction of various agents present in ascites into the circulation. For example, when severe complications, such as pulmonary edema or dyspnea, occur, we can readily occlude the shunt

system by clamping the catheter. Conversely, pumping the chamber is easily performed. Thus, we can educate the patients and their family members on how to control the flow. It is easy to explain the mechanism of the PVS to patients and their families. Besides device maintenance, replacement and removal of the EPVS system are also far easier than conventional PVS [6,18]. We suspect that an EPVS placement can also be a preparatory step for standard conventional PVS implantation. In our series, in six patients, EPVS has been successfully exchanged to a conventional PVS system.

The development of a PVS that can be turned on or off would be a useful development, even though this would not really get around the anasarca problem. If a flow control valve could be incorporated into the circuit (like a ventriculoperitoneal shunt for hydrocephalus), this might solve some of the problems that can occur with PVS implantation.

There are a number of possible limitations with EPVS implantation. First, there are no consistent preoperative indicators associated with poor patient survival after EPVS placement, and it is difficult to know which patients will achieve a high rate of palliation with a low morbidity and mortality rate [3-6]. In cases of anasarca, it may be adequate to exchange EPVS so that abdominal distension will resolve. However, in other cases, it is difficult to seize a favorable occasion to convert from EPVS to conventional PVS. In our small cohort, a conversion to PVS depends upon the condition of the patients, and we could not but have tentative period or factors to decide when EPVS is exchanged to PVS. An improvement in nutritional status can improve the chance of a successful conversion to PVS. However, it is not easy to improve nutritional status in a patient at the end of life. We suspect the success of the conversion can occur if the major AEs are avoided after EPVS placement because EPVS placement is a temporary system that is used temporarily in place of conventional PVS. Previous studies have emphasized meticulous post-procedural management for 48 hours in order to detect major AEs [4,19]. Therefore, we suspect that increased attention should be given for more than 48 hours after the procedure. Second, EPVS placement may have a higher risk for system infection and migration, although we did not have any such cases in our series. However, the duration of the EPVS placements in this study is considerably short to define infection risks for any tunneled catheter, such as that used for pleural effusion, dialysis, central lines, etc. [6,18]. Third, there is an economical issue: when patients were able to get the favorable clinical course associated with EPVS placement, they had to pay for another Denver shunt kit in order to convert the EPVS system to PVS.

Additional limitations of the study include the following: the study was retrospectively performed, there were

a small number of patients, and the follow-up period was very short. No consensus on how to evaluate the efficacy of PVS or EPVS has been established [20,21]. Our subjective procedure for determining the efficacy 7 days after EPVS insertion is controversial. Additionally, if ascites was removed with the PVS implantation procedure itself, it can palliate symptoms separately from an effect of the EPVS. We evaluated the improvement of anasarca as a decrease of abdominal girth, and there was no weight data in all patients. No consensus on how to evaluate anasarca in patients with malignant ascites. Abdominal girth may not an appropriate index of anasarca because abdominal girth may also represent decrease of ascites after PVS insertion.

A previous study recommended measuring body weight in order to evaluate PVS efficacy, but it may be occasionally difficult to measure body weight in patients at the end of life. In addition, patients with advanced malignancies may deteriorate rapidly due to the primary disease and other pathophysiologies that further confound evaluation. We attempted to minimize fluid overload. However, flow control is a regular and needed issue for percutaneous shunts, and it is difficult to assess circulatory dynamics [10]. In future studies, we need to assemble a larger cohort that we will follow over a longer term in order to evaluate efficacy and complications.

Conclusion

In conclusion, EPVS placement may be an option method for patients with malignant ascites, who may not be appropriate for conventional PVS implantations. Our preliminary experience encourages further studies into the efficacy of EPVS placement.

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Authors' contributions

HT reviewed relevant literature and drafted the manuscript. All authors provided clinical expertise and participated in drafting the manuscript. And all authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Phase I/II Study of Transjugular Transhepatic Peritoneovenous Venous Shunt, a New Procedure to Manage Refractory Ascites in Cancer Patients: Japan Interventional Radiology in Oncology Study Group 0201

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OBJECTIVE. This multicenter phase I/II study evaluated the safety and the efficacy of transjugular transhepatic peritoneovenous shunt (PVS), a new palliative treatment for malignant refractory ascites.

SUBJECTS AND METHODS. Patients with refractory malignant ascites and patent hepatic veins and vena cava were included in this study. Eligible patients underwent the placement of transjugular transhepatic PVS catheter via the jugular vein into the abdominal cavity through the hepatic vein. In phase I, a step-by-step analysis of the safety was performed. The safety and the efficacy were determined through phases I and II.

RESULTS. Thirty-three patients were entered in this study, nine in phase I and 24 in phase II. Transjugular transhepatic PVS was technically successful in all patients. No severe adverse events were observed during the placement procedure. After the placement, 22 adverse events (grade 2 or higher) occurred. Frequent adverse events were hypoalbuminemia (24%) and decrease in hemoglobin (18%), which resolved within 1 week without additional treatment. The clinical efficacy rate at 1 week after the procedure was 67%. Occlusion of the catheter due to fibrin sheath was observed in seven patients, and the revision of the system was performed.

CONCLUSION. Transjugular transhepatic PVS is a safe and feasible procedure for managing refractory ascites in patients with cancer. Sufficient efficacy was observed in our initial experience, but a larger clinical trial is warranted.

Malignant ascites is defined as abnormal accumulation of intraperitoneal fluid as a consequence of advanced cancer [1–3]. It is often refractory to medical therapies and is associated with a decline in patients' quality of life [1–3]. Management of malignant ascites is still a major unsolved problem in the palliative care of patients with cancer.

The causes of refractory (i.e., resistant to various medical treatments) ascites include dissemination of malignant tumor, portal hypertension, and obstruction of the inferior vena cava or portal vein. In patients with portal hypertension or mechanical venous obstruction, a transjugular intrahepatic portosystemic shunt (TIPS) or stent placement in the obstructed vein may be the treatment of choice for reducing production of ascites [4–6]. However, patients for whom these procedures are not appropriate or for whom these definitive treatments fail require palliative treatment, such as paracentesis or peritoneovenous shunt (PVS) [1, 7–9].

The Denver shunt has been widely used for PVS, and favorable clinical outcomes have been reported [1, 7, 10–12]. An implantable shunt tube with a one-way valve allows ascites to drain into the systemic circulation. The shunt tube can be implanted either surgically or percutaneously. Recent studies have shown the feasibility of the percutaneous implantation, which is less invasive than surgical implantation [7, 11–13]; however, extensive subcutaneous tunneling is very invasive compared with other interventional radiology procedures. In addition, removing or exchanging the system in cases of infectious or occlusive complications is not easy. Consequently, the development of less invasive and exchangeable PVS is desirable.

Arai et al. [14] have described a novel PVS, transjugular transhepatic PVS, in 10 patients with malignant ascites. This is a PVS through the hepatic vein with minor penetration of hepatic parenchyma using a TIPS needle. With this technique, transjugular access to the abdominal cavity is possible, and

the long subcutaneous tunneling required for the Denver shunt is not necessary. Transjugular transhepatic PVS may be less invasive and more advantageous if catheter exchange is needed; however, a prospective clinical trial is mandatory for evaluating this completely new interventional technique. Thus, we conducted a phase I/II clinical trial (Japan Interventional Radiology in Oncology Study Group [JIVROSG] 0201) that aimed to determine the safety and the efficacy of transjugular transhepatic PVS, a new palliative treatment for malignant refractory ascites.

Subjects and Methods

Study Design

This study is a prospective multiinstitutional single-arm noncomparative phase I/II study for evaluating the safety and efficacy of transjugular transhepatic PVS for the treatment of malignant refractory ascites. The study design of the phase I portion consisted of the JIVROSG 3 × 3 method, which has been described in detail elsewhere [15]. In brief, this is a step-by-step safety evaluation in the first nine patients: a cohort of three patients is treated with transjugular transhepatic PVS, and if no severe adverse events occur during the observation period of 4 weeks, the next cohort of three patients is treated followed by the next observation period, and finally the third cohort of three patients is treated. The phase II portion was designed to enroll an additional 24 patients. To determine study outcomes, all enrolled patients were included in the intention-to-treat analysis.

Patients

Patients with refractory malignant ascites interfering with their daily life were eligible for participation in this study. Additional inclusion criteria were as follows: clear and serous ascites; patent he-

patic veins and vena cava on contrast-enhanced CT; Eastern Cooperative Oncology Group performance status of 0–3; adequate organ function as defined by a hemoglobin level of 8.0 g/dL or higher, WBC count of 3000/mm³/dL or higher, platelet count of 50,000/mm³/dL or higher, prothrombin time of 50% or more, bilirubin level of 2.0 mg/dL or lower, serum creatinine level of 2.0 mg/dL or lower, normal ECG, PaO₂ level 70 mm Hg or higher at room air; and a life expectancy of at least 4 weeks. Exclusion criteria were as follows: manageable ascites with standard anticancer treatments; planned intraperitoneal drug administration; ascites caused by liver cirrhosis, mesothelioma, pseudomyxoma, or mucin-producing tumors; hemorrhagic or chylous ascites; active infectious disease; varices or ulcers in upper gastrointestinal tract; a history of hepatectomy; implanted cardiac pacemaker; or pregnant or nursing.

The study protocol was approved by the institutional review board at each institution before patient enrollment. Written informed consent was obtained from all patients. This study is registered under Clinical Trials Registry number C000000040 (www.umin.ac.jp/ctr/index.htm).

Technique of Transjugular Transhepatic PVS

Transjugular transhepatic PVS procedures were performed using a dedicated transjugular transhepatic PVS catheter and a TIPS system (Rösch-Uchida Transjugular Liver Access Kit, Cook Medical). The transjugular transhepatic PVS catheter is a urethane catheter with a hydrophilic coating, 8.2-French in diameter and 120 cm in length, accommodating a 0.035- or 0.038-inch guidewire at the tapered tip (Fig. 1). It has a tapered 5-French pigtail-shaped tip, five side holes along the 8.2-French section 14–40 cm from the tip, and a one-way valve located 70–80 cm from the tip. We designed a tapered pigtail catheter to soften its tip so as to avoid injury to the abdominal organs. The diameter of the

section containing the valve is 10-French. The pressure-activated one-way valve opens when the internal pressure is greater than 2 cm H₂O pressure, thus allowing fluid to flow one way from the abdominal cavity to the vein.

Prophylactic IV antibiotics were administered just before the procedure. Each patient underwent conscious sedation with analgesics, and sedatives were administered according to individual needs. The patient was placed in the supine position on an angiography table. After administration of local anesthesia, the internal jugular vein was punctured under ultrasound guidance and an 11-French hemostatic sheath was placed into the inferior vena cava. A 5-French selective angiographic catheter was inserted through the sheath into a peripheral branch of the hepatic vein, and digital subtraction angiography was performed to confirm the shape of the hepatic vein and the position of the catheter tip. The 11-French sheath was advanced deeper into the hepatic vein by the over-the-wire technique. The choice of hepatic venous branch depended on its shape to fit the curve of the Rösch-Uchida needle of TIPS system. An inner catheter of the TIPS system was inserted into the tip of the sheath, and a Rösch-Uchida needle with a 5-French catheter was passed through the liver parenchyma to access the abdominal cavity. A stiff 0.035-inch Amplatz guidewire (Cook Medical) was inserted into the abdominal cavity through the catheter connecting to the abdominal cavity. The 11-French hemostatic sheath without a curved guiding cannula was advanced to the abdominal cavity, and the backward flow of ascites from the sheath was confirmed.

Subsequently, a transjugular transhepatic PVS catheter was inserted into the abdominal cavity through the 11-French hemostatic sheath, and then the sheath and guidewire were removed. The position of the transjugular transhepatic PVS catheter

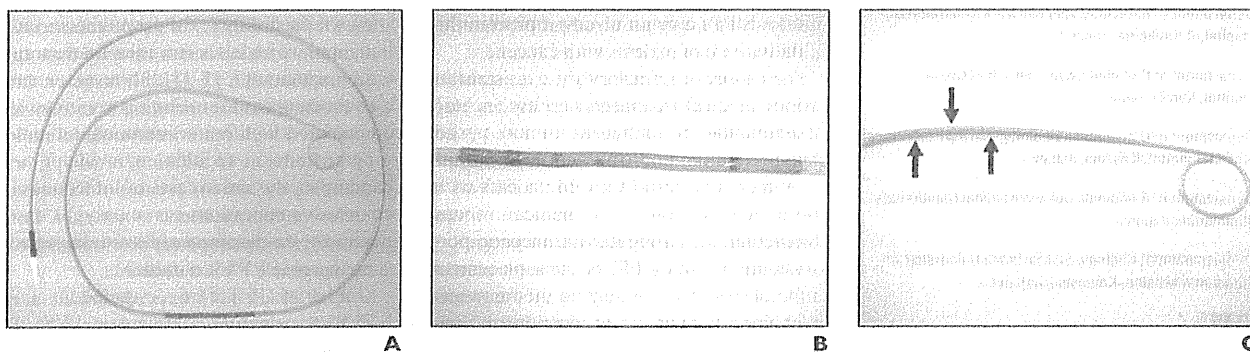


Fig. 1—Transjugular transhepatic peritoneovenous shunt (PVS) catheter.

A, Image shows tapered (5–10-French) transjugular transhepatic PVS catheter.

B, Image shows one-way valve designed to be positioned in right atrium.

C, Image shows pigtail-shaped catheter tip in abdominal portion. Side holes (arrows) to collect ascites are seen along 8.2-French section.

Transjugular Transhepatic Peritoneovenous Shunt

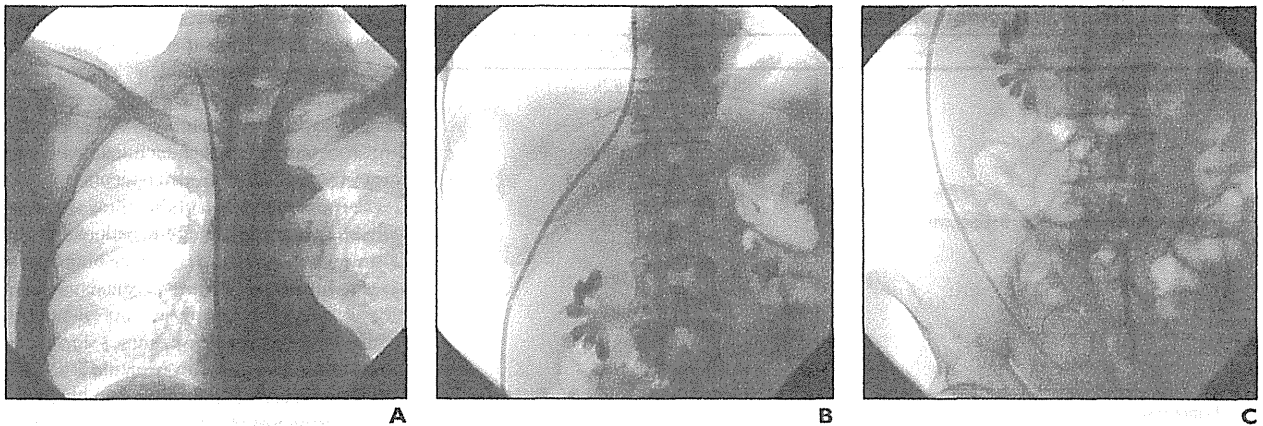


Fig. 2—Radiographs of positioning of transjugular transhepatic peritoneovenous shunt (PVS) catheter. **A**, Radiograph shows chest after implantation of transjugular transhepatic PVS catheter. **B**, Radiograph shows abdomen after implantation of transjugular transhepatic PVS catheter. **C**, Radiograph shows pelvis after implantation of transjugular transhepatic PVS catheter.

was adjusted so that the tip and side holes were in ascites, and the one-way valve was in the superior vena cava. After the backward flow of ascites from the transjugular transhepatic PVS catheter was confirmed and the position of the transjugular transhepatic PVS catheter was verified by fluoroscopy, the catheter was sutured to the skin of the neck. The external section of the catheter was cut at 2–3 cm from the insertion site and capped with a small silicone cap. We did not totally implant the proximal tip of the catheter subcutaneously because we assumed that adverse events resulting from implanted proximal tip, such as bleeding or infection, might be considerable and confound the safety assessment of the “transhepatic” PVS, which is unique for the transjugular transhepatic PVS. The position of the catheter was recorded by radiography (Fig. 2). Abdominal and central venous pressure were measured and recorded during the procedure.

After the procedure was completed, vital signs of the patient were monitored, and continuous IV low-dose catecholamine was administered until the next day. Monitoring and catecholamine administration were terminated on the day following the procedure if there were no problems.

Safety and Efficacy Evaluation

The primary endpoint through the phase I to phase II portion was to characterize the safety of transjugular transhepatic PVS within a 4-week period after the procedure. Adverse events were evaluated using National Cancer Institute Common Toxicity Criteria (version 2.0) [16], which were the standard criteria for evaluating cancer treatments at the time of initiation of this study.

Secondary endpoints were the rate of technical success of the procedure and clinical efficacy. Clinical efficacy was evaluated at 1 week after the proce-

dures and was followed up until death or the time of termination of the study. Because established standard criteria for symptom evaluation for ascites did not exist, we defined the efficacy criteria (Table 1).

Statistical Methods

This study was designed to detect the incidence of adverse events, which was the primary endpoint. The required number of patients was calculated to be 33, which included a dropout rate of 10%, and was based on the following variables: α , 0.05; power, 0.8; unacceptable rate of adverse events, 30%; estimated lowest rate of adverse events, 10%; and predicted rate of adverse events, 10%. Statistical analyses for patient demographics and adverse events were descriptive. The statistical significance level was set at 0.05 using a two-sided test. All statistical analyses were performed with PASW software (version 18, SPSS).

Results

Patient Characteristics and Follow-Up Period

There were 33 eligible patients enrolled between February 2003 and April 2007 from seven tertiary centers in Japan. All patients underwent transjugular transhepatic PVS and were evaluable for the primary endpoint of adverse events. Patient characteristics are sum-

marized in Table 2. The median follow-up period was 34 days (range, 8–144 days). Eight patients died within 30 days after undergoing the transjugular transhepatic PVS procedure. In all subjects, the cause of deaths was judged to be disease progression, and the judgments were approved by the safety and efficacy evaluation committee, which is independent from this clinical trial group.

Results of Procedures

The transjugular transhepatic PVS catheter was successfully implanted in all patients. The access site was the right internal jugular vein in 28 patients (85%) and the left internal jugular vein in five patients (15%). Peritoneal access was established through the right hepatic vein in 32 patients (97%) and the middle hepatic vein in one patient (3%). The mean (\pm SD) pressure gradient between the abdominal cavity and central vein was 17 ± 6 cm H₂O. The duration of the procedure was 53 ± 30 minutes.

Safety

Table 3 lists the observed adverse events of grade 2 or higher that were considered possibly, probably, or definitely related to the transjugu-

TABLE 1: Evaluation Criteria for Symptom Improvement of Ascites

Criteria	Definition
Significantly effective	Improvement of the subjective symptom for > 1 week with ≥ 1 of the following objective findings of improvement: decrease in body weight to $\leq 95\%$ from pretreatment weight, decrease in abdominal girth to $\leq 90\%$, and decrease in dose of diuretics
Moderately effective	Improvement of the subjective symptom for > 1 week without objective findings of improvement
Not effective	Not significantly effective and not moderately effective

TABLE 2: Patient Demographics

Characteristic	Value (n = 33 Patients)
Age (y), median (range)	53.2 (33–77)
Sex	
Male	11 (33)
Female	22 (67)
Performance status (Eastern Cooperative Oncology Group score)	
0	1 (3)
1	11 (33)
2	6 (18)
3	15 (45)
Primary site	
Stomach	13 (39)
Pancreas	4 (12)
Lung	3 (9)
Colon	2 (6)
Breast	2 (6)
Other	9 (27)
Use of diuretics	
Yes	26 (79)
No	7 (21)

Note—Except for age, all data are no. (%) of patients.

lar transhepatic PVS procedure. Overall, the transjugular transhepatic PVS procedure was well tolerated, with no severe adverse events encountered during the implantation. The most frequent adverse events were hypoalbuminemia (24%) and decrease in hemoglobin (18%), both of which occurred within 1–2 days after the procedure and resolved within 1 week. No grade 4 adverse events were encountered. No bleeding event related to the penetration of hepatic parenchyma was observed, and disseminated intravascular coagulation syndrome did not occur in any of the patients.

Clinical Efficacy

The efficacy of transjugular transhepatic PVS is summarized in Table 4. The clinical efficacy rate (significantly effective or moderately effective) 1 week after the procedure was 67%. In seven patients for whom the procedure was initially effective (significantly or moderately effective), an increase in ascites volume and progression of subjective symptoms was again observed 19–51 days (median, 25 days) after the transjugular transhepatic PVS procedure. The cause of the reincrease in ascites was catheter dysfunction in all seven patients. Catheter dys-

function was caused by fibrin sheath formation around the one-way valve in all patients, which was confirmed by angiography via the transjugular transhepatic PVS catheter (Fig. 3). Subsequently, additional treatments, such as catheter exchange or stripping of the fibrin sheath using a catheter and a guidewire, were undertaken. These procedures corrected the malfunctioning catheter in all patients; however, in five patients, reocclusion occurred within 10 days.

Discussion

This phase I/II study was performed as the initial step in the evaluation of transjugular transhepatic PVS. The JIVROSG 3 × 3 method, which was developed and validated in pre-

vious studies [15] by our group, was used for the phase I portion of this study. Because the concept of “dose escalation” in a phase I drug study is not applicable, the same transjugular transhepatic PVS intervention was performed throughout the study, and clinical efficacy was evaluated in all enrolled patients.

The inclusion criteria of this study were established according to the indications for the Denver shunt. In addition, patency of the vena cava, no history of cardiac pacemaker, no history of hepatic lobectomy, and no dilated intestine were included to secure a safe access route for transjugular transhepatic PVS. The exclusion criteria (i.e., cirrhosis and high risk for gastrointestinal bleeding) were added because of previous reports of severe adverse events resulting from PVS placement in cirrhotic patients [7, 11, 17, 18]. Won and coworkers [7] reported that 63% of 55 patients with refractory ascites developed variceal bleeding after Denver shunt placement. The characteristics of patients in this study, such as primary tumor, age, performance status, and the use of diuretics, may be consistent with typical patients with malignant refractory ascites.

For most of our study patients, the access site and the hepatic vein penetration site were the right internal jugular vein and the right hepatic vein, respectively, most likely because of the familiarity with right internal jugular access and the selection of the right hepatic vein resulting from experience with TIPS placement or other interventional procedures. In a few patients, however, the left internal jugular vein and middle or left hepatic vein were used, and the feasibility of these access sites was shown. Technical success was achieved in all patients from seven participating institutions, and the procedure time was approximately 1 hour. Thus, this technique is presumed to be feasible and can be generalized.

Concerning the safety of transjugular transhepatic PVS, it is significant that eight patients died within 30 days after transjugular transhepatic PVS placement, because patients considered to have 4 or more weeks

TABLE 3: Summary of Adverse Events Occurring in 33 Patients

Adverse Events	Grade 2	Grade 3	Grade 4	Total (%)
Decrease in hemoglobin	3	3	0	6 (18)
Hypoalbuminemia	8	0	0	8 (24)
Skin irritation at the access site	3	0	0	3 (9)
Pleural effusion	3	0	0	3 (9)
Congestive heart failure	0	1	0	1 (3)
Fever	1	0	0	1 (3)

Transjugular Transhepatic Peritoneovenous Shunt

TABLE 4: Clinical Efficacy of Transjugular Transhepatic Peritoneovenous Shunt for Malignant Refractory Ascites

Efficacy Parameter	No. (%) (n = 33 Patients)
Significantly effective	11 (33)
Moderately effective	11 (33)
Not effective	11 (33)

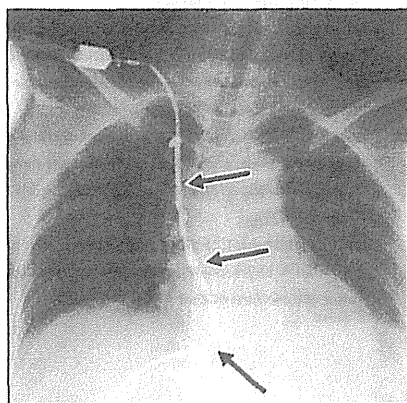


Fig. 3—Fibrin sheath formation around transjugular transhepatic peritoneovenous shunt (PVS) catheter. Angiogram shows tip of transjugular transhepatic PVS catheter at right internal jugular vein. Contrast material stagnated within and around catheter (arrows), which is compatible with fibrin sheath, is seen.

of life expectancy were enrolled. However, previous reports on PVS have also described early patient deaths independent from the procedure [1–3, 19, 20]. Thus, this phenomenon can be understood as a general tendency in patients with malignant refractory ascites who are candidates for PVS. Decreases in serum albumin and hemoglobin have been reported in previous studies of PVS and were explained as the results of transient dilution caused by the inflow of ascites into the blood circulation [3]. Transient pleural effusion and congestive heart failure have also been reported as adverse events after PVS and could be also explained by the increased blood volume caused by the inflow of ascites. Thus, these adverse events in our study are not thought to be specific to transjugular transhepatic PVS but to be the general results of PVS. Skin inflammation around the transjugular transhepatic PVS catheter insertion site was an adverse event unique to this procedure, although it was not a severe adverse event. Bleeding events related to the penetration of hepatic parenchyma, which was considered as an adverse event specific to transjugular transhepatic PVS, were not ob-

served. Therefore, on the basis of these safety results, the transjugular transhepatic PVS procedure is thought to be sufficiently safe to apply future clinical usage and evaluation.

Concerning efficacy, 67% of patients achieved symptomatic improvement (significantly effective or moderately effective). The efficacy of PVS in previous studies is controversial because the evaluation criteria, including objective findings, varied and the comparability was uncertain [1, 3]. Given that the goal of this treatment is to palliate subjective symptoms, precise and consistent evaluation of the efficacy of transjugular transhepatic PVS in comparison with previous reports of PVS is impossible. However, in most of the previous reports, efficacy rates based on the improvement of symptoms were approximately 70%. Therefore, the efficacy of transjugular transhepatic PVS with regard to symptom improvement is equivalent to that in previous reports of other types of PVS.

The reason for fibrin sheath formation in seven of the 22 patients in whom the procedure was judged as significantly effective or moderately effective may be that the intravascular catheter used in transjugular transhepatic PVS is longer than the intravascular catheters used in other types of PVS or that the transjugular transhepatic PVS catheter has a one-way valve in the central vein. If these explanations are correct, they are intrinsic drawbacks of transjugular transhepatic PVS and cannot be avoided. However, no increase in ascites was seen in the other 15 patients. There have also been quite a few reports of fibrin sheath formation in previous PVS procedures [21]. The device of transjugular transhepatic PVS is developing and can be improved. Thus, the efficacy of transjugular transhepatic PVS should not be denied on the basis of this rate of fibrin sheath formation. In cases of fibrin sheath formation, exchanging the transjugular transhepatic PVS catheter is much easier compared with exchanging catheters of other implanted shunt systems, such as Denver shunts. This attribute seems to be a great advantage of transjugular transhepatic PVS. Neverthe-

less, improvement of the device may be the key for better clinical outcome in transjugular transhepatic PVS, particularly in the surface of the catheter where the fibrin sheath is formed. Antithrombogenic coating on the catheter would be one of the solutions. Other possibilities for refining the transjugular transhepatic PVS system include improvement of the function of the one-way valve and enlargement of the inner diameter of the catheter.

The following study limitations should be noted. The first is that the sample size was limited to 33 patients. Thus, there is a possibility that uncommon adverse events of transjugular transhepatic PVS were not detected. The second limitation is that this study was a single-arm and noncomparative study. Although the reported clinical efficacy of Denver PVS is 77.95% according to a systematic review by Becker et al. [1], which is higher than our results of 67%, we cannot determine the superiority in efficacy without direct comparison by randomized controlled trial.

With this clinical trial, we conclude that the newly developed transjugular transhepatic PVS is feasible and a safe procedure for managing refractory ascites in patients with cancer, and transjugular transhepatic PVS has sufficient efficacy to be evaluated by a larger clinical trial in the future. In addition, improvement of the transjugular transhepatic PVS catheter is needed to reduce fibrin sheath formation and to obtain better clinical outcomes.

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Case Report

Hepatic Arterial Infusion Chemotherapy Prior to Standard Systemic Chemotherapy in Patients with Highly Advanced Unresectable Liver Metastases from Colorectal Cancer: A Report of Three Patients

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We administered hepatic arterial infusion chemotherapy (HAIC) prior to FOLFOX to three patients with unresectable liver metastases from colorectal cancer. The patients' disease state was found to be highly advanced based on both computed tomography findings and liver function tests. The treatment strategy included an initial administration of HAIC to control liver metastases and improve liver function in order to facilitate the subsequent safe administration of FOLFOX without drug loss. As the HAIC regimen, 1,000 mg/m² of 5-FU was administered weekly by continuous 5-h infusion after performing laboratory investigations through an implanted port-catheter system. After 3 HAIC cycles administered over 3 consecutive weeks, the mean alkaline phosphatase levels decreased from 969.3 IU/l to 422 IU/l due to shrinkage of the liver metastases. Thereafter, FOLFOX without drug loss could be safely initiated for all patients. Two patients succumbed 488 and 333 days after HAIC was initiated; the third patient is still alive and has been followed-up for 1215 days. The combined use of HAIC and standard systemic chemotherapy could be a feasible and efficacious treatment in highly advanced cases of liver dysfunction.

Key words: colorectal cancer, hepatic arterial infusion chemotherapy, liver metastasis, port-catheter system

Systemic chemotherapy is usually the preferred treatment for unresectable liver metastases from colorectal cancer [1]. With recent advances in new drugs and the standardization of chemotherapy regimens for colorectal cancer, patient survival has been prolonged. Currently, FOLFOX (5-fluorouracil

(5-FU)/leucovorin with oxaliplatin) and FOLFIRI (5-FU/leucovorin with irinotecan) are used as standard chemotherapy regimens [1, 2], and the median survival with these regimens is reported to be 20.6-21.5 months [2]. The addition of bevacizumab to these regimens further prolongs the survival [3]. However, in patients with highly advanced unresectable liver metastases, it is vital but very difficult to select the initial treatment regimen because it is often impossible to perform further treatment if the initial treatment

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fails. Fakih MG has reported that three patients with metastatic colon cancer and severe liver dysfunction were treated by FOLFOX [4]. After the initial improvement in disease status, disease progression was noted in 2 patients at 4 and 7 months from the inception of therapy, while treatment was ongoing in the third patient at 5 months.

Repeated hepatic arterial infusion chemotherapy (HAIC) through an implanted port-catheter system is an effective therapy for unresectable liver metastases from colorectal cancer [5-7]. Compared to systemic chemotherapy, HAIC increases the possibility of tumor response and might improve liver function by shrinking liver metastases [7-10]; however, a comparison was not made between HAIC with FOLFOX and HAIC with FOLFIRI in those reports. The administration of high doses of 5-FU, which is used as an HAIC regimen in Japan, is particularly associated with a good tumor response and patient-survival rates, and has fewer and less severe adverse events [5, 11].

We administered HAIC prior to FOLFOX to 3 patients with highly advanced unresectable liver metastases from colorectal cancer; further treatment in the event of failure of the initial treatment was considered impossible in these patients. The treatment strategy involved an initial administration of HAIC to control liver metastases and improve liver function in order to facilitate the subsequent safe administration of FOLFOX without drug loss. This strategy was formulated on the basis of the high tumor-response rate and the fewer and less severe adverse effects associated with HAIC.

Case Report

This report was approved by our institutional review board, and written informed consent was

obtained from each patient.

Between November 2006 and April 2007, 69 patients were admitted to undergo initial therapy for colorectal cancer at our institution. Of those patients, three consecutive patients (2 men and 1 woman; mean age, 56.0 years) had highly advanced synchronous liver metastases. In all three patients, liver metastases were judged to be unresectable due to liver dysfunction and multiple metastases in both the right and left lobes of the liver. The primary cancer sites were the descending colon (n=1), sigmoid colon (n=1), and rectum (n=1). The patient characteristics are shown in Table 1.

Our treatment strategy was as follows. First, surgical resection of primary colorectal cancer was performed. Next, we repeatedly administered HAIC through an implanted port-catheter system as the initial treatment for liver metastases, considering our patients' advanced state of disease, as indicated by both the computed tomography (CT) findings (Aquilion 64; Toshiba, Tokyo, Japan) and the results of liver function tests. As the HAIC regimen, 1,000 mg/m² of 5-FU was administered weekly by continuous 5-h infusion after performing laboratory investigations [5]. The levels of alkaline phosphatase (ALP) were more than 2.5 times the upper limit of normal (ULN; 875 IU/l) due to the liver metastases; thus, this value was used as an index for HAIC continuation. HAIC was administered weekly to control the liver metastases until the ALP levels were within 1.5 times the ULN (525 IU/l). Thereafter, FOLFOX without drug loss was started.

The patients underwent curative surgical resection of primary colorectal cancer and lymph node metastases. Metastases in N1 lymph nodes were observed in 2 patients; 1 patient showed N2 lymph node metastases. Extrahepatic metastases in the lung, bone, brain,

Table 1 Patients Characteristics

Case	Age (y.o)/Sex	Primary Site	Liver Function before starting HAIC/after HAIC					Tumor Marker before starting HAIC/after HAIC		Liver Metastases Volume (%) ⁵ before starting HAIC/after 3 times HAIC	Follow-up Period(d)	Alive/Dead
			ALP (IU/l)	LDH (IU/l)	AST (IU/l)	ALT (IU/l)	T-BIL (mg/dl)	CEA	CA19-9			
1	58/F	D-colon	971/349	710/303	37/23	27/8	0.4/0.5	3,258.9/389.3	11,184/1,302	42.8/33.9	333	Dead
2	55/M	S-colon	927/401	1,045/312	59/27	54/27	0.4/0.4	65.4/42.1	70/56	53.6/45.2	1,215	Alive
3	55/M	rectum	1,010/516	714/303	32/22	26/22	0.7/0.6	92.8/23.6	13/1.4	31.9/22.3	488	Dead

D-colon, descending colon; S-colon, sigmoid colon; HAIC, hepatic arterial infusion chemotherapy; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-BIL, total bilirubin. ⁵Liver metastases volume (%) was estimated using the following formula: liver metastases volume (ml)/[normal liver parenchymal volume (ml) + liver metastases volume (ml)] × 100.

and peritoneum were not observed in the patients.

Radiological placement of the port-catheter system was performed at 14, 20, and 21 days after surgery (Fig. 1). All placement procedures were performed in an angiography suite under local anesthesia. Prior to catheter placement, the patients underwent angiography and arterial embolization to allow arterial mapping and prevent extrahepatic influx of 5-FU; these procedures were performed using a 4-French angiographic catheter (Clinical Supply, Gifu, Japan) that was inserted from the left femoral artery. The extrahepatic arteries that branched from the hepatic artery such as the right gastric artery and the posterior superior pancreaticoduodenal artery were embolized with microcoils (Trufill; Cordis, Miami Lakes, FL, USA) through a 2.1-French microcatheter (Sniper 2; Clinical Supply) inserted coaxially. Next, a 4-French angiographic catheter was inserted from the right femoral artery and advanced to the common hepatic artery via the celiac artery. An indwelling catheter (W spiral catheter; PIOLAX, Yokohama, Japan) with a side hole was then inserted using the catheter-exchange method. The catheter tip was inserted into the gastropiploic artery such that the side hole was placed in the common hepatic artery. The gastropiploic artery around the tip of the indwelling catheter was embolized using microcoils

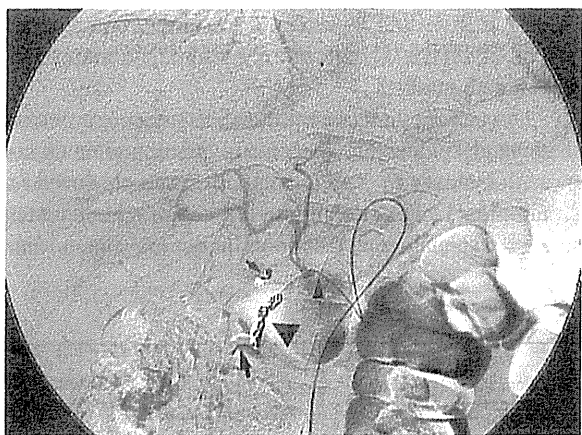


Fig. 1 Arteriogram via port shows that all hepatic arteries are well-visualized. The catheter tip is inserted into the gastropiploic artery (arrow). The side hole is placed into the common hepatic artery (small arrowhead). To prevent an extrahepatic influx of anticancer agents, the gastroduodenal artery (arrowhead) and right gastric artery (small arrow) are embolized with microcoils.

through a microcatheter inserted coaxially via the angiographic catheter inserted from the left femoral artery. Finally, the proximal end of the indwelling catheter was connected to a port implanted in the subcutaneous pocket created in the right thigh. No complications such as hematoma, infections, and hepatic artery injuries and occlusions occurred during or after the procedure.

On the following day, digital subtraction angiography and CT were performed during injection of a contrast medium through the implanted port-catheter system to confirm that the catheter was not dislodged and to ensure that the entire liver was perfused adequately [12]. Thereafter, HAIC was administered through the port-catheter system. After the administration of 5-FU, this system was flushed and filled with 2ml heparin solution (1,000IU/ml). The results of the liver function tests of the patients before starting HAIC were as follows: mean ALP, 969.3IU/l; mean lactate dehydrogenase (LDH), 823IU/l; mean aspartate aminotransferase (AST), 42.7IU/l; mean alanine aminotransferase (ALT), 35.7IU/l; and mean total bilirubin (T-BIL), 0.5mg/dl (Table 1). In all patients, the percentage of liver involvement with metastases exceeded 30% (mean, 42.8%), as determined using contrast-enhanced CT and a workstation (Ziostation; Ziosoft, Tokyo, Japan).

After starting HAIC, no adverse events were observed in any of the patients. The ALP levels and other liver function parameters decreased to <1.5 times the ULN after 3 HAIC cycles administered over 3 consecutive weeks (Table 1). The results of the liver function tests performed after HAIC administration were as follows: mean ALP, 422IU/l; mean LDH, 306IU/l; mean AST, 24IU/l; mean ALT 19IU/l; and mean T-BIL, 0.5mg/dl. Though three patients had stable disease, according to RECIST criteria [13], on contrast-enhanced CT, the percentage of liver involvement with metastases decreased (mean, 33.8%) (Fig. 2). Thereafter, FOLFOX without drug loss could be safely initiated for all patients, and the chemotherapy regimen was changed to FOLFIRI after FOLFOX had failed.

FOLFOX and FOLFIRI were administered a total of 12 times in case 1 and 11 times in case 3, respectively. The systemic chemotherapy failed to produce a positive response in these patients and could not be continued. Their performance status worsened be-