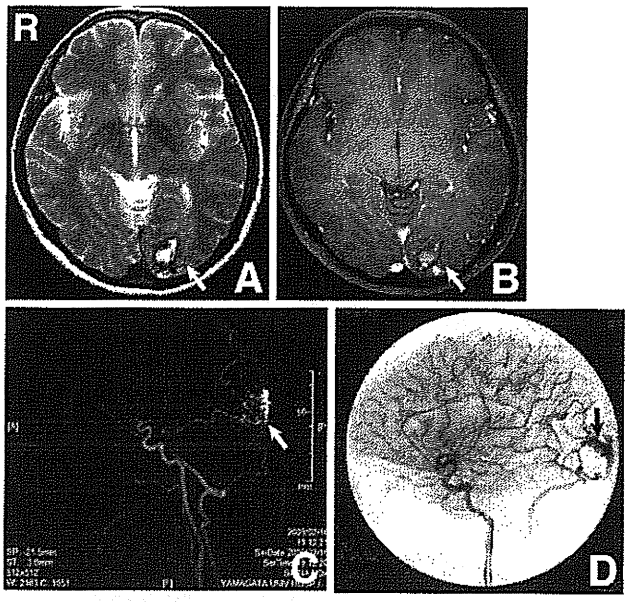

Fig. 1 Preoperative T_2-weighted magnetic resonance (MR) image (A), T_1-weighted MR image after administration of contrast medium (B), and time-resolved imaging of contrast-kinetics image (C) showing left occipital hemorrhage (*arrow*). Selective left common carotid digital subtraction angiogram (D) revealing a Spetzler-Martin grade 2 arteriovenous malformation in the left occipital lobe (*arrow*).

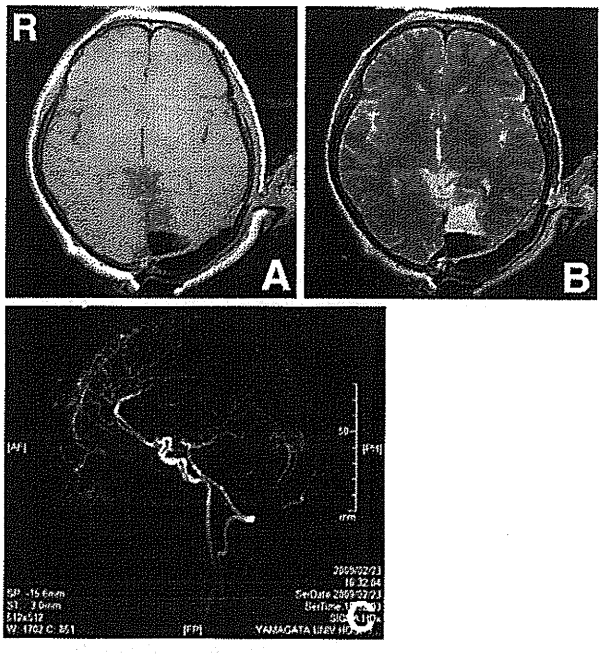

Fig. 2 Intraoperative T_1-weighted (A) and T_2-weighted (B) magnetic resonance images, and time-resolved imaging of contrast-kinetics image (C) showing complete removal of the arteriovenous malformation.

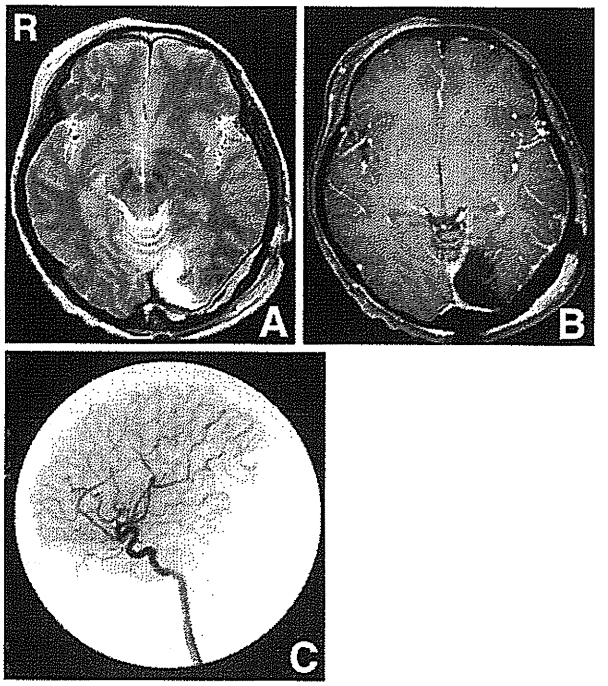

Fig. 3 Postoperative T_2-weighted magnetic resonance (MR) image (A), T_1-weighted MR image after administration of contrast medium (B), and selective left common carotid digital subtraction angiogram (C).

30 time-resolved phases with a frame rate of 2.0 seconds per volume. About 15 ml of gadopentetate dimeglumine (Magnevist; Bayer HealthCare Pharmaceuticals Inc., Wayne, New Jersey, USA) was injected at 3.5 ml/sec with a power injector (Sonic Shot Gx; Nemoto Kyorindo Co., Ltd., Tokyo). iMR imaging and iTRICKS revealed successful removal of the AVM (Fig. 2). No surgical complications were detected.

The postoperative course was uneventful. The patient was discharged without new neurological deficits. Postoperative MR imaging and conventional angiography also revealed complete removal of the AVM (Fig. 3).

Discussion

This report describes the successful use of iMR imaging and iTRICKS at 1.5 T for confirmation of complete resection of the AVM. Partial resection does not confer any improvement over the natural history risk of hemorrhage of AVMs, and may actually increase the risk of hemorrhage.[14] Postoperative or intraoperative angiography is critical to assess residual AVMs and can also facilitate surgery. The true incidence of residual lesions after resection of intracranial AVMs is not well documented. In one report, a residual nidus was not detected during AVM surgery using intraoperative angiography, but following occlusion of the patient's femoral artery after surgery. ICG videoangiography was used to detect and totally remove the AVM.[16] The spatial and temporal resolution of conventional angiography (typically $0.2 \times 0.2\,mm^2$ and 1

frame per 0.3–0.5 sec) is superior to that of 1.5 T TRICKS (0.94 × 1.5 mm^2, 1 frame per 2.0 sec), but false negatives were found in 18% of patients in a series of intraoperative angiography with AVM surgery.[13] Ultrasonography and ICG videoangiography are useful and easy tools for AVM surgery as there is no need to move the microscope from the surgical field or interrupt the operation.[2,6,16,17] However, ultrasonography has poor spatial resolution. ICG videoangiography can detect only superficial architecture, and may fail to detect residual nidus intraoperatively.[6,16] The spatial and temporal resolution of TOF MR angiography images is also not adequate for AVM surgery.[15]

iMR imaging at 1.5 T can be advantageous over the conventional assessments of residual nidus and unanticipated brain events during AVM surgery and can potentially improve the cure rate. The combined use of iMR imaging with iTRICKS is important for verification of the surgical results. iMR imaging can be used to visualize any residual nidus precisely using suitable, commercially available protocols. TRICKS, a new technique, can be used for time-resolved three-dimensional MR digital subtraction angiography because it can achieve the temporal and spatial resolution needed for evaluation of AVMs.[8] TRICKS at 3 T has various advantages compared to conventional angiography for preoperative assessment of AVMs.[9] TRICKS achieved 96% sensitivity and 100% specificity both in nidus detection and in early venous filling detection. The Spetzler-Martin grades showed excellent correlation with catheter angiography findings. Compared to lower field strengths, iMR imaging at 1.5 T has several advantages, as the higher intrinsic signal/noise ratio allows the acquisition of images with higher spatial and temporal resolution, and the TRICKS protocol is feasible at this field strength.

This case report demonstrates the efficacy of iMR imaging and iTRICKS at 1.5 T during AVM neurosurgery. iMR imaging with iTRICKS is an excellent technique for intraoperative quality control and documentation of neurosurgical outcomes.

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Address reprint requests to: Kaori Sakurada, MD, Department of Neurosurgery, Yamagata University Faculty of Medicine, 2-2-2 Iidanishi, Yamagata 990-9585, Japan.
e-mail: kasakura@med.id.yamagata-u.ac.jp

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

Yasuaki Arai[1]
Yoshitaka Inaba[2]
Miyuki Sone[3]
Hiroya Saitoh[4]
Yoshito Takeuchi[1,5]
Yasukazu Shioyama[6,7]
Yasuo Nakajima[8]

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[1]Department of Diagnostic Radiology, National Cancer Center, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Address correspondence to Y. Arai (arai-y3111@mvh.biglobe.ne.jp).

[2]Department of Diagnostic and Interventional Radiology, Aichi Cancer Center Hospital, Nagoya, Japan.

[3]Department of Radiology, Iwate Medical University, Morioka, Japan.

[4]Department of Radiology, Asahikawa-Kosei General Hospital, Asahikawa, Japan.

[5]Department of Radiology, Kyoto First Red Cross Hospital, Kyoto, Japan.

[6]Department of Diagnostic Radiology, Ibaragi Prefectural Central Hospital, Kasama, Japan.

[7]Department of Radiology, Dokkyo Medical University, Shimotsuka, Japan.

[8]Department of Radiology, St. Marianna University, School of Medicine, Kawasaki, Japan.

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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 hepatic 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/mm^3/dL or higher, platelet count of 50,000/mm^3/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, PaO_2 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 H_2O 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

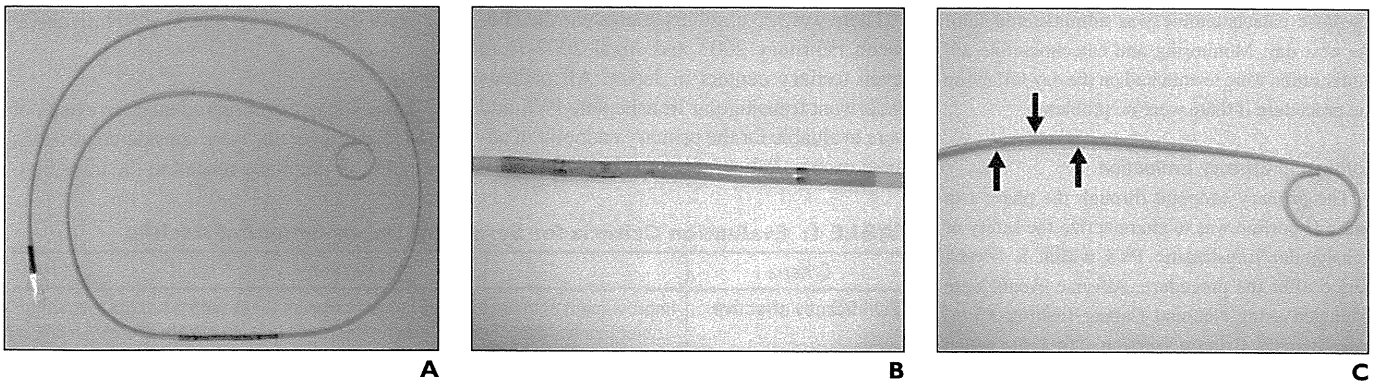

Fig. 1—Transjugular transhepatic peritoneovenous shunt (PVS) catheter.
A, Image shows tapered (5–10-French) transjugular transhepatic PVS catheter.
B, Image shows one-way valve designed to be positioned in right atrium.
C, Image shows pigtail-shaped catheter tip in abdominal portion. Side holes (*arrows*) to collect ascites are seen along 8.2-French section.

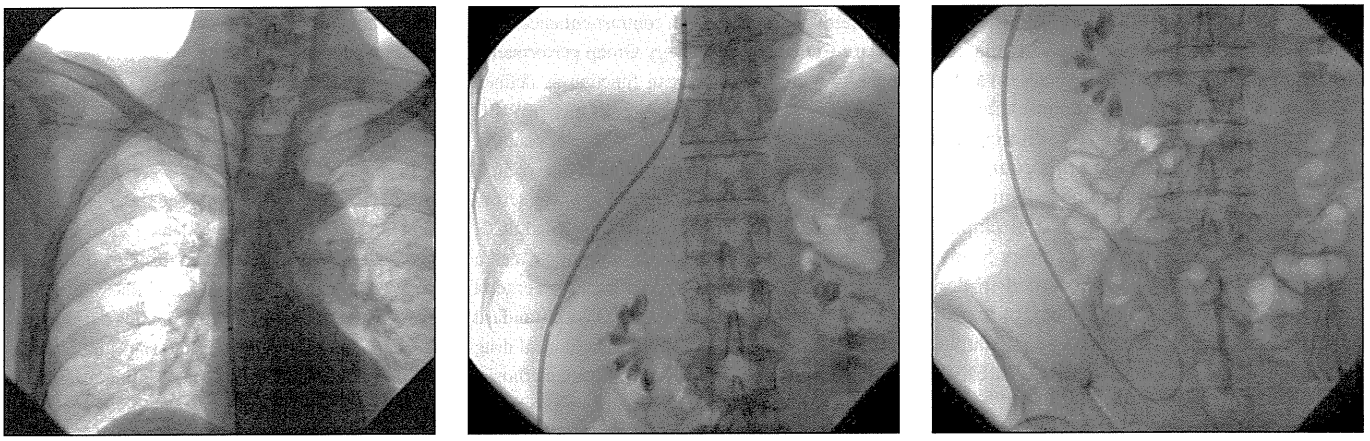

Fig. 2—Radiographs of positioning of transjugular transhepatic peritoneovenous shunt (PVS) catheter.
A, Radiograph shows chest after implantation of transjugular transhepatic PVS catheter.
B, Radiograph shows abdomen after implantation of transjugular transhepatic PVS catheter.
C, Radiograph shows pelvis 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 procedure 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 summarized 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 (± SD) pressure gradient between the abdominal cavity and central vein was 17 ± 6 cm H_2O. 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 ≤ 95% from pretreatment weight, decrease in abdominal girth to ≤ 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 dysfunction 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 previous 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)

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)

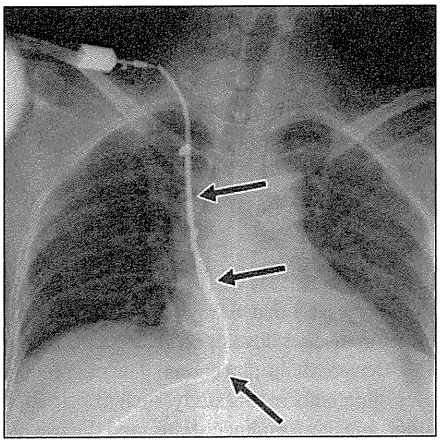

Fig. 3—Fibrin sheath formation around transjugular transhepatic peritoneovenous shunt (PVS) catheter. Angiogram shows tip of transjugular transhepatic PVS catheter at right internal jugular vein. Contrast material stagnated within and around catheter (*arrows*), which is compatible with fibrin sheath, 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 observed. 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. Nevertheless, 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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Phase II Clinical Study on Stent Therapy for Unresectable Malignant Colorectal Obstruction (JIVROSG-0206)

Yoshitaka Inaba, MD, Yasuaki Arai, MD,† Hidekazu Yamaura, MD,* Yozo Sato, MD,* Mina Kato, MD,* Hiroya Saito, MD,‡ Takeshi Aramaki, MD,§ Mikio Sato, MD,‖ Takashi Kumada, MD,¶ and Yoshito Takeuchi, MD†; Japan Interventional Radiology in Oncology Study Group (JIVROSG)*

Purpose: A phase II study of stent therapy for unresectable malignant colorectal obstruction was conducted to ascertain the clinical efficacy, safety, and procedural feasibility.

Methods: Inclusion criteria comprised unresectable obstruction of the rectum or sigmoid colon; no other apparent stenosis; performance status by Eastern Cooperative Oncology Group ≤ 3; and maintained major organ function. The treatment protocol was to place an uncovered metal stent through the anus in an obstructive portion under x-ray fluoroscopic guidance. The patients were followed for 4 weeks after therapy, and the degree of improvement in subjective symptoms lasting ≥ 2 weeks was assessed as effective when the patient was decompressed with stent, or ineffective when not decompressed. Rate of clinical efficacy was defined as the proportion of effective cases.

Results: The participants of the study comprised 33 patients (13 men and 20 women; mean age, 60 y). Rate of procedure completion was 97.0% (32/33). Treatment was effective in 27 patients, ineffective in 4, and unassessable in 1, yielding a clinical efficacy rate of 81.8% (27/33). Death owing to underlying disease (n=3), stent removal owing to anal pain (n=1), and occlusion at another location (n=1) were noted. No recurrences were seen among clinically effective cases. Adverse reactions included grades 2 to 3 diarrhea (n=12), pain (n=5), bleeding (n=1), and dysuria (n=1), but no grade 4 adverse reactions or treatment-related deaths were identified.

Conclusions: Stent therapy for unresectable malignant colorectal obstruction is effective, safe, and feasible.

Key Words: malignant colorectal obstruction, metal stent, palliation, supportive care, phase II study

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In patients with acute colorectal obstruction owing to unresectable malignancy, colostomy or a transanal ileus tube has been used to decompress the obstructed bowel as a palliative treatment.[1–3] However, considering their general status, poor prognosis, and quality of life, a less-invasive treatment is desirable as an alternative mode of palliation.

From the *Aichi Cancer Center Hospital, Nagoya; †National Cancer Center Hospital, Tokyo; ‡Asahikawa-Kosei General Hospital, Asahikawa; §Shizuoka Cancer Center Hospital, Nagaizumi; ‖Ryugasaki Saiseikai Hospital, Ryugasaki; and ¶Ogaki Municipal Hospital, Ogaki, Japan.

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Reprints: Yoshitaka Inaba, MD, Department of Diagnostic and Interventional Radiology, Aichi Cancer Center Hospital, 1-1, Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan. E-mail: 105824@aichi-cc.jp.

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Since self-expanding metal stents were first reported to relieve acute colorectal obstruction in 1991,[4] colorectal stenting has found increasing acceptance for use in palliation, because the technique is less invasive than colostomy and does not lower the quality of life compared with the placement of an ileus tube over a long period.[5–9] This approach has been used not only for palliation, but also as a bridge to surgery for potentially resectable colorectal tumors with obstruction.[10,11]

Few prospective clinical trials have been conducted to ascertain the safety and efficacy of colorectal stenting. On the basis of this background, this multicenter phase II study of stent therapy for patients with unresectable colorectal obstruction was conducted by Japan Interventional Radiology in Oncology Study Group (JIVROSG).

MATERIALS AND METHODS

Study Design and Patient Eligibility

We designed a multicenter phase II clinical study to evaluate the clinical efficacy of stent therapy for unresectable malignant colorectal obstruction. Clinical efficacy was evaluated as the primary end point and the incidence and severity of adverse events and procedural feasibility were evaluated as secondary end points.

This study was carried out for patients with malignant obstruction in whom stent was used as a definitive therapy and not as a bridge to future surgical intervention. As inclusion criteria, unresectable malignant colorectal obstruction had to satisfy the following conditions: the presence of stricture or obstruction of the rectum or sigmoid colon from unresectable malignant tumor with symptoms of acute large bowel obstruction; range of colorectal stricture or obstruction extending between the area 5 cm from the anal verge and the level of the iliac crest as seen from contrast enema and including cases in which the rectum or sigmoid colon was resected earlier; no apparent stenosis in the gastrointestinal tract on the oral side from the target colorectal obstruction from a clinical perspective; maintenance of principal organ function (no apparent heart failure, platelet count $\geq 50{,}000/mm^2$, total serum bilirubin level ≤ 3.0 mg/dL, and serum creatinine ≤ 2.0 mg/dL); performance status according to the Eastern Cooperative Oncology Group classification of ≤ 3; expectation of patient survival >4 weeks; and written informed consent obtained from patients before participation.

Patients in whom a colostomy was desirable, in whom a high possibility of resection of the rectum or sigmoid colon obstruction or a need for preoperative decompression for final surgery was observed, or in whom bleeding from the rectum or sigmoid colon obstruction required hemostatic procedures, were excluded.

The study was approved by the ethics committee of the Japanese Society of Interventional Radiology and the institutional review boards of the participating hospitals.

Treatment Protocol and Evaluation Method

In this study, stent therapy for unresectable malignant colorectal obstruction was defined as the placement of an uncovered metal stent in the obstructed portion of the rectum or sigmoid colon caused by an unresectable malignant tumor, using a transanal technique under x-ray fluoroscopic guidance (Fig. 1).

Contrast enema was performed using a water-soluble contrast medium, and the length of the stricture or obstructed portion of the rectum or sigmoid colon was measured. A guide wire was inserted through the anus far enough to pass through the obstructed portion under x-ray fluoroscopic guidance. A stent introducer was placed over the guide wire and inserted to place the stent in the target location. Concurrent use of an endoscope was allowed, and no regulations were enforced regarding whether balloon dilation was performed before or after stent placement.

As colorectal stents are not approved in Japan, the stents used were the uncovered Ultraflex stent system (Boston Scientific, Natick, MA) for the esophagus (Fig. 2). Assuming some migration, selection of lengths ≥ 3 cm longer than the stricture was recommended. The length of this stent delivery catheter is restricted to 100 cm and the target area was limited to the rectum apart from a close region of the anus to preserve the anal function and the sigmoid colon.

A 4-week evaluation and observation period was established after the stent therapy, during which subjective and objective symptoms were checked, blood tests were conducted, and abdominal radiographs were taken the day after treatment and each week thereafter. Level of improvements in subjective symptoms on the day after treatment and on each

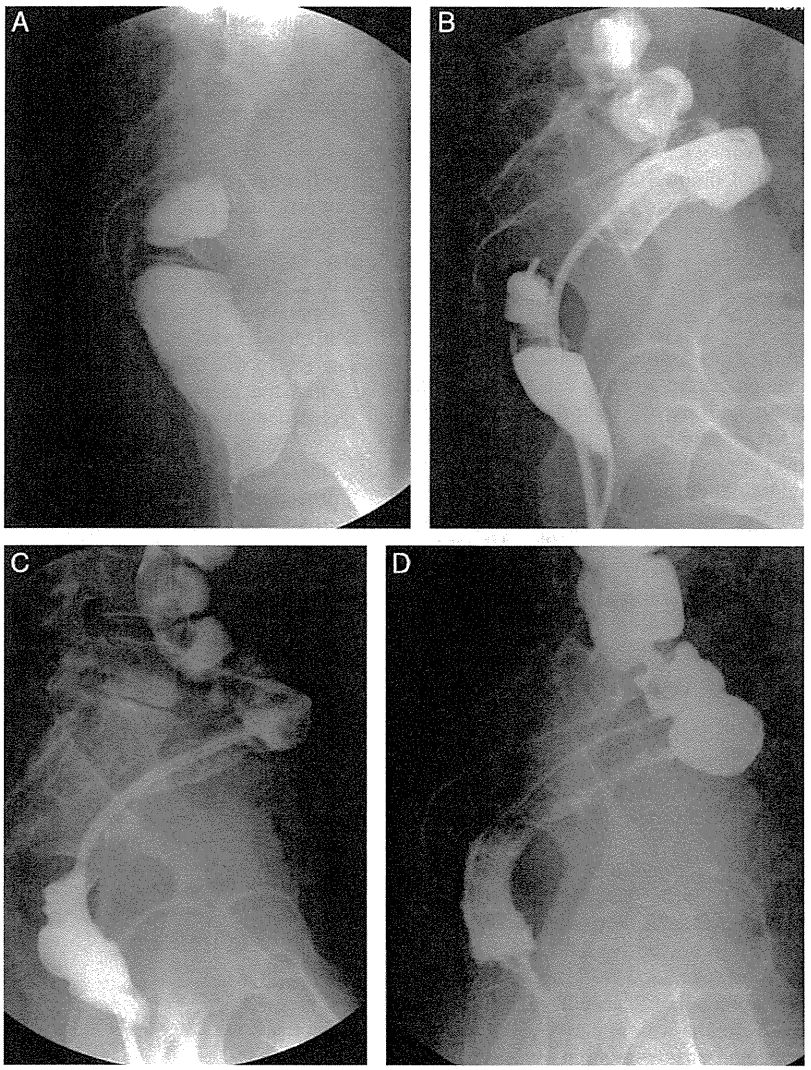

FIGURE 1. A 47-year-old woman who underwent rectal stenting for Schnitzler metastasis using an uncovered Ultraflex stent (length, 15 cm; diameter, 18 mm). A, Contrast enema using a water-soluble contrast medium showed that the rectum was completely obstructed. B, A catheter was passed through the obstructed portion and contrast medium was injected. C, A guide wire was inserted through the anus far enough to pass through the obstructed portion. A stent delivery catheter was placed over the guide wire under x-ray fluoroscopy. D, The stent was appropriately placed on the obstructed portion.

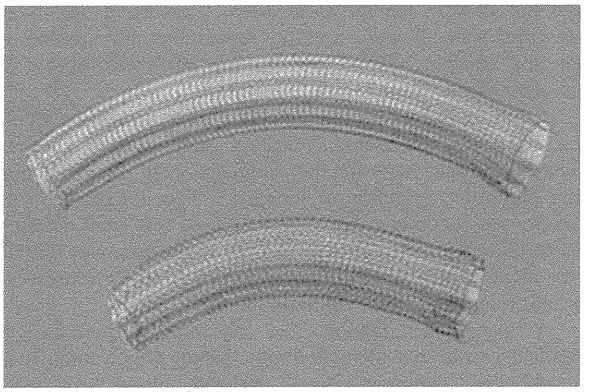

FIGURE 2. Uncovered Ultraflex esophageal stent.

subsequent week was evaluated. Treatment was considered to be "effective" in cases of improvement in defecation, gas elimination status, and abdominal symptoms for ≥ 2 weeks or "ineffective" when no improvement in symptoms was seen, whether the patient was decompressed with the stent or not decompressed. The rate of clinical efficacy was taken to be the proportion of effective cases compared with the total number of registered cases. Adverse reactions were assessed using National Cancer Institute-Common Toxicity Criteria (version 2.0). Procedural feasibility was assessed based on the rate of treatment protocol completion. The follow-up investigation was conducted after 4 weeks.

Statistics

When conducting a 1-sample binomial test for the number of cases in which severe adverse reactions or a need to assess the efficacy rate exist, the predicted value of complications for adverse reactions is 10%, and $\geq 30\%$ of cases with severe adverse reactions are inadmissible, 30 cases would be required under conditions of $\alpha = 0.05$, $\beta = 0.20$. For the efficacy rate, when the expected efficacy rate is taken to be 80% and the threshold efficacy rate to be 50%, 19 cases are required under conditions of $\alpha = 0.05$, $\beta = 0.20$. Accordingly, 30 cases were considered necessary in this study, and predicting a deviation from the protocol in 10% of these cases, the scheduled number of registered cases was 33.

RESULTS

The participants of the study comprised 33 patients who were enrolled between February 2003 and September 2007, all of whom satisfied the inclusion criteria. A patient summary is shown in Table 1.

The rate of procedure completion was 97.0% (32/33), indicating the feasibility of the procedure. In 1 patient in whom the procedure failed, the obstructed portion was rigid and the stent delivery catheter could not be passed through. Table 2 shows the details of the procedure. No complications were seen accompanying the procedure. The clinical efficacy rate was 81.8% (27/33). Treatment was effective in 27 patients, ineffective in 4 patients, and unassessable in 1 patient because the effects could not be assessed for >2 weeks. The procedure failed in 1 patient. In the 27 patients in whom the procedure was clinically effective, no reobstruction was seen during the observation period. Confirmed events during the observation period were death from underlying disease in 3 patients (effective, n=2; unassessable, n=1), stent removal because of severe anal pain in 1 patient (ineffective, n=1), and gastrointestinal tract stenosis on the oral side in 1 patient (ineffective, n=1). Confirmed grades 2 to 3 adverse reactions were diarrhea in 12 patients (36.4%), pain in 5 patients (15.2%), bleeding in 1 patient (3.0%), and dysuria in 1 patient (3.0%). No grade 4 adverse reactions or treatment-related deaths were encountered. In the 27 patients who could be followed for 4 weeks after the stent placement, no stent movement beyond the obstructed portion was seen on abdominal radiography.

According to the follow-up investigation until November 2007, the median of a total follow-up period after the procedure was 78 days (3-1303 d). Finally, 4 patients were alive, 27 were dead, and 2 were censored because of transfer to another hospital. Cumulative median survival time after stent therapy was 91 days (95% confidence interval, 60-122 d) in all the 33 patients. In the 25 long-term effective cases over 4 weeks, reobstruction was seen in 4 cases on median 115 days after stent placement. In the reobstruction cases, stent replacement was performed in 2 cases and no reintervention was done in 2 others because of poor patient's condition.

TABLE 1. Characteristics of the 33 Patients

Age (y)	
Median (range)	60 (34-84)
Sex	
Male	13
Female	20
ECOG performance status	
0	0
1	17
2	7
3	9
Earlier therapy	
None	23
Resection	10
Radiotherapy	5
Intrinsic stricture	
Primary rectosigmoid cancer	11
Recurrent rectosigmoid cancer	7
Extrinsic stricture	
Peritoneal cancer dissemination	13
Recurrent uterine cancer	2
Sricture length (cm)	
Mean (range)	7.8 (3-20)

ECOG indicates Eastern Cooperative Oncology Group.

TABLE 2. Stenting Procedures

Predecompression using transanal ileus tube	11
Procedure with endoscopy	13
Predilation using balloon	4
Stenting	
Success	32
Failure	1
No. stents	
1	28
2	4
Length of stent (cm)	
7	3
10	15
15	18

DISCUSSION

Since the report by Song et al[12] in 1991, stent therapy for gastrointestinal obstruction has been widely used, mainly for esophageal stenosis. In Japan, stent therapy was approved for malignant esophageal obstruction in 1996, and has been used as palliation for esophageal obstruction caused by malignant tumors and esophagobronchial fistula. Other than the esophagus, stents are used for gastric, duodenal, and colorectal obstruction,[13] and in other countries duodenal and colorectal stents are commercially available.[14]

Many reports have described the effectiveness of stents for colorectal obstruction, from palliation for unresectable obstruction to being a bridge to surgery for potentially resectable obstruction. In Japan, similar reports are occasionally seen, but the medical procedure of stent placement other than in the esophagus was not recognized, and colorectal stents that can be used in other countries have not yet been approved and thus cannot be used. Therefore, although some reports have suggested the use of such techniques, no prospective clinical trials have verified the safety and effectiveness of colorectal stents. This multicenter phase II clinical trial was aimed at confirming the clinical efficacy of stent therapy for unresectable malignant colorectal obstruction, using an esophageal stent that was one of the few gastrointestinal stents that could be obtained in Japan. At the time this study was started, the gastrointestinal stents that could be used were the Ultraflex stent (Ultraflex esophageal stent system; Boston Scientific, Natick, MA) and Z-stent (Cook-Z stents; William Cook Europe, Bjaeverskov, Denmark). The Ultraflex stent was available in both uncovered and covered types, but the Z-stent was available in covered types only. This study was restricted to uncovered stents only out of concern for migration,[15] and so was limited to the use of uncovered Ultraflex stents. In addition, as users were prohibited from modifying stent placement kits, the possible range of stent placement was limited by the length of the delivery system that was provided.[16] As a result, we used the stents for obstruction in the region from the rectum to the sigmoid colon.

In this study, the success rate for stent placement in the target area was 97%, indicating high procedural feasibility. Improvements of clinical symptoms were seen in 82% of enrolled patients, thus clinical efficacy was also good. However, even when stent placement was successful, 15.6% (5/32) of patients did not show improvement of clinical symptoms. This was similar to past reports.[8,17–19] Reasons for those unimproved patients were the existence of a separate stenosis on the oral side from the area of stent placement, decreased gastrointestinal function from widespread peritonitis carcinomatosis, and stent removal because of intense pain caused by stimulation of the stent edge on the lower rectum. As these causes cannot be accurately determined before stent placement, we recognize the difficulty of selecting only those patients who will show improvements in clinical symptoms. No complications were seen during stent placement, and adverse reactions such as diarrhea, pain, and bleeding after placement of the stent were similar to those in past reports.[8,17–19] Unacceptable stent migration completely beyond the obstructed portion was not seen within 4 weeks. No grade 4 adverse reactions, digestive tract perforations, or treatment-related deaths were encountered, and safety was judged to be within the acceptable range.

Limitations of this study include a lack of objectivity, as improvements in subjective symptoms were taken as the indicator of efficacy, and insufficient evidence for taking a period of 2 weeks for improvements in symptoms as indicative of effective treatment. Moreover, the stent used was an esophageal stent, and the length, diameter, flexibility, and expansive force may not be optimal for the treatment of colorectal obstruction.

In conclusion, these results indicated that this treatment method offers sufficient procedural feasibility and leads to a high level of improvement in symptoms, indicating that this treatment method should prove effective in alleviating symptoms in patients with terminal cancer with this kind of condition. In future, evaluations through clinical trials will be needed to assess whether this treatment could become a standard palliative treatment for patients showing symptoms of colorectal obstruction.

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CLINICAL INVESTIGATION

Radiological Insertion of Denver Peritoneovenous Shunts for Malignant Refractory Ascites: A Retrospective Multicenter Study (JIVROSG-0809)

Shunsuke Sugawara · Miyuki Sone · Yasuaki Arai · Noriaki Sakamoto · Takeshi Aramaki · Yozo Sato · Yoshitaka Inaba · Yoshito Takeuchi · Teruko Ueno · Kiyoshi Matsueda · Michihisa Moriguchi · Takahiro Tsushima

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Abstract
Purpose Peritoneal venous shunts (PVSs) are widely used for palliating symptoms of refractory malignant ascites and are recognized as one of the practical methods. However, reliable clinical data are insufficient because most previous reports have been small studies from single centers. We conducted a retrospective, multicenter study to evaluate the safety and efficacy of radiologically placed PVSs in patients with malignant refractory ascites.
Methods A total of 133 patients with malignant ascites refractory to medical therapies were evaluated for patient characteristics, technical success, efficacy, survival times, adverse events, and changes in laboratory data.
Results PVSs were successfully placed in all patients and were effective (i.e., improvement of ascites symptoms lasting 7 days or more) in 110 (82.7%). The median duration of symptom palliation was 26 days and median survival time was 41 days. The most frequent adverse event was PVS dysfunction, which occurred in 60 (45.1%) patients, among whom function was recovered with an additional minimally invasive procedure in 9. Abnormalities in coagulation (subclinical disseminated intravascular coagulation) occurred in 37 (27.8%) patients, although only 7 (5.3%) developed clinical disseminated intravascular coagulation. Other major adverse events were gastrointestinal bleeding (9.8%), sepsis (3.8%), and acute heart failure (3.0%). PVS was least effective in patients with elevated serum creatinine, bloody ascites, or gynecologic tumor.
Conclusions Radiological PVS is a technically feasible and effective method for palliating the symptoms from refractory malignant ascites, but preoperative evaluation and monitoring the postprocedural complications are mandatory to preclude severe adverse events after PVS.

Keywords Denver shunt · Interventional radiology · Malignant ascites · Palliative therapy · Peritoneovenous shunt

S. Sugawara (✉) · M. Sone
Department of Radiology, Iwate Medical University School of Medicine, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan
e-mail: suga_shun@hotmail.com

Y. Arai · N. Sakamoto · Y. Takeuchi
Division of Diagnostic Radiology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

T. Aramaki · M. Moriguchi · T. Tsushima
Division of Diagnostic Radiology, Shizuoka Cancer Center, 1007, Shimo-nagakubo, Nagaizumi-cho, Suntoh-gun, Shizuoka 411-8777, Japan

Y. Sato · Y. Inaba
Department of Interventional and Diagnostic Radiology, Aichi Cancer Center Hospital, 1-1, Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan

T. Ueno · K. Matsueda
Department of Diagnostic Imaging, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31, Ariake, Kohtoh-ku, Tokyo 135-8550, Japan

Present Address:
S. Sugawara
Department of Radiology, Ebara Hospital, 4-5-10, Higashi-yukigaya, Ohta-ku, Tokyo 145-0065, Japan

Introduction

Malignant ascites in patients with advanced cancer often is resistant to medical treatment. Symptoms from ascites result in a progressive deterioration in quality of life (QOL). Whereas diuretics and paracentesis have been

traditionally used to relieve symptoms, their use among physicians is inconsistent [1, 2]. In particular, although paracentesis can provide immediate relief, the effects are temporary and may be complicated by hypotension, secondary peritonitis, and the loss of protein and electrolytes contained in ascites fluid, among others [1, 2].

One means of palliating the various symptoms of refractory ascites is peritoneovenous shunts (PVSs) [3–15]. A variety of shunts have been designed [16–18]. One widely used technique for nonsurgical peritoneovenous shunting is radiological insertion of the Denver shunt. To date, however, most reports of PVSs for malignant refractory ascites have been derived from small studies at single centers only, and the lack of large, prospective, safety and efficacy studies has hampered evidence-based decision making on the use of PVSs and limited their routine use in malignant refractory ascites [5, 6, 9–11, 14, 15, 19, 20].

We evaluated the safety and efficacy of radiologically inserted PVSs in patients with refractory malignant ascites at five Japanese institutions. This study was conducted by Japan Interventional Radiology in Oncology Study Group (JIVROSG) as JIVROSG-0809.

Materials and Methods

Patients

Inclusion criteria were cytologically confirmed or clinically diagnosed malignant ascites, malignant ascites refractory to medical therapy, and ascites-induced deterioration in quality of life (QOL). Patients with ascites due to liver cirrhosis were excluded. The study protocol was approved by the institutional review board of all participating institutions before data collection.

From May 2001 to July 2008, 133 of 139 patients who underwent percutaneous insertion of PVSs met the selection criteria at five Japanese institutions and were enrolled (see Appendix Table 5).

Procedure for PVS Placement

All PVSs were inserted by interventional radiologists in the angiography suite by using a previously reported technique [20–23]. Percutaneous placement was performed under local anesthesia with image guidance by ultrasonography or fluoroscopy. PVSs were inserted on the right side except in patients with a central venous port in the right subclavian vein. Intravenous analgesic and sedative use was conducted in accordance with the local practice of the participating hospital, as was prophylactic use of antibiotics, catecholamines, or gabexate mesylate.

The PVS system consisted of a 16-F peritoneal catheter with side holes, a 12-F venous catheter, and a chamber with a one-way valve, which connected the two catheters. Preprocedural paracentesis was performed when ascites was prominent. Initially, a 3-cm to 5-cm long skin incision was made over the lower rib cage and a pocket for the chamber was created with forceps. The chamber was placed on the lower rib cage to allow it to be manually compressed to prevent occlusion of the system. Through a subcutaneous tunnel, the venous catheter was pulled out via a small incision on the upper chest wall and inserted into the subclavian vein using a Seldinger technique with a 12-F peel-away introducer under image guidance. The peritoneal catheter was inserted into the abdominal cavity with a 16-F peel-away introducer using a similar technique. After checking the position of the entire system by fluoroscopy, the incisions were closed with silk, nylon, or absorbable thread. The procedure time, defined as the time from local anesthesia to the completion of suturing, was recorded.

Study Outcomes

The primary outcome of interest was the clinical efficacy of the PVS, which was evaluated from subjective symptoms and classified into two groups: (1) effective, defined as duration of improvement of symptoms of ascites of 7 days or more; and (2) ineffective, duration of improvement of less than 7 days. In patients with multiple symptoms from ascites, the PVS was judged effective when at least one symptom was improved for 7 days or more without the other symptoms becoming worse.

Secondary outcomes included patient characteristics, toxicity profile, changes in laboratory data, overall survival time (OS), and duration of palliation. Adverse events (AEs) were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3. Grade 2 to 5 hematologic and nonhematologic AEs observed by the attending physicians were collected from the case report forms. Laboratory data before and after PVS placement were collected for blood counts, prothrombin times (PT), fibrinogen, fibrin degradation products (FDPs), and blood chemistry. Shunt dysfunction was defined as PVS system-related AE, and it was evaluated in another category. OS was defined as the time from the first PVS placement to death as a result of any cause. The palliation period was defined as the total duration of symptom palliation.

Statistical Analysis

Demographic and baseline variables, including survival time, were summarized by descriptive statistics. Survival time, duration of symptom palliation (<4 W or not) were compared using the χ^2 test and Mann–Whitney U test.

Pre- and postoperative body weight and abdominal girth were compared by using the Mann–Whitney *U* test. Factors associated with efficacy and toxicity (preoperative laboratory data, characteristics of ascites, and primary disease) were identified on the χ^2 test and Mann–Whitney *U* test. Statistical significance was set at 0.05. SPSS software, version 17 (SPSS, Chicago, IL) was used for all analyses.

Results

Patient Demographics

Characteristics of the total of 133 consecutive patients are listed in Table 1. Gastrointestinal (GI) cancer (43.6%) was the most common primary tumor. Performance status was 3 or 4 in 36.9% of patients. The most frequent symptoms from ascites were abdominal distention (98.5% of patients) and anorexia (65.4%). Cytological examination of ascites was performed in 54.8% of patients and malignant cytology was reported in 36.8%. Preoperative abdominal girth was 87.4 ± 10.1 cm ($n = 71$) and preoperative body weight was 55.6 ± 11 kg ($n = 107$).

Table 1 Baseline characteristics of patients

Characteristic	No. of patients ($N = 133$)	%
Age (yr)		
Mean	58.3	
Median	58	
Range	27–82	
Sex		
Male	71	53.4
Female	62	46.6
Site of primary tumor		
Colorectal cancer	33	24.8
Gastric cancer	25	18.8
Pancreatic cancer	21	15.8
Liver/bile duct cancer	16	12
Breast cancer	10	7.5
Ovarian cancer	9	6.8
Others	19	14.3
Performance status (ECOG[a])		
0	0	0
1	19	14.3
2	52	39.1
3	44	33.1
4	5	3.8
Unknown	13	9.8
Symptom		
Abdominal distention	131	98.5
Anorexia	87	65.4
Nausea/vomiting	10	7.5
Dyspnea	7	5.3
Lower extremity edema	7	5.3
Abdominal pain	6	4.5
Malaise	4	3.0
Back pain	3	2.3
Gait difficulty	1	0.8
Characteristics of ascites		
Property		
Clear	71	53.4
Bloody	21	15.8
Chylous	9	6.8
Bilious	1	0.8
Not evaluated	31	23.3
Viscosity		
Serous	90	67.7
Mucinous	9	6.8
Not evaluated	34	25.6
Cytology		
Malignant	49	36.8
Nonmalignant	24	18
Not performed	59	44.4
Unknown	1	0.8

[a] Eastern Cooperative Oncology Group

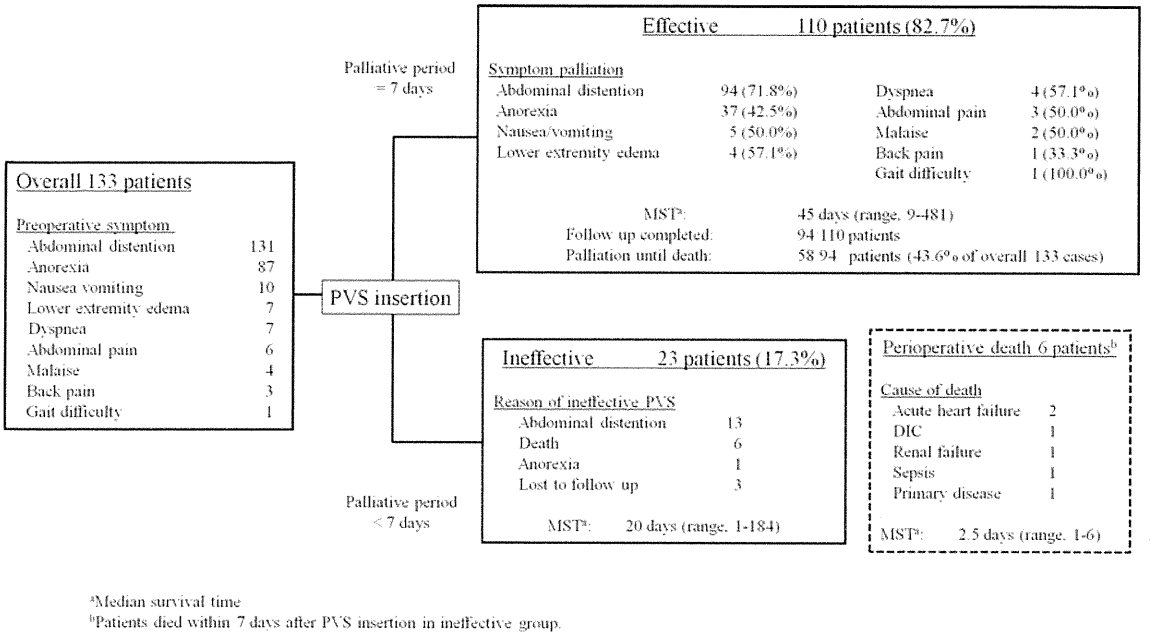
PVS Placement

PVS was successfully placed in all patients (100%) without any procedure-related AE. One patient developed grade one pneumothorax, which did not require additional intervention. The median procedure time was 60 *(range, 11–160) min, and the median length of hospital stay after PVS placement was 17 (range, 1–130) days.

Efficacy

PVS placement satisfied the efficacy criteria in 110 (82.7%) patients (Fig. 1). Palliation of symptoms until death, which was one criterion of efficacy, was achieved in 58 patients (43.6%). With regard to individual symptoms, PVS was effective for abdominal distention in 94 of 131 patients (71.8%), anorexia in 37 of 87 (42.5%), and nausea/vomiting in 5 of 10 (50%).

Median follow-up period was 41 (range, 1–481) days and was continued until death in 115 (86.5%) patients. Median time to symptom palliation was 2 (range, 1–9)



[a]Median survival time
[b]Patients died within 7 days after PVS insertion in ineffective group.

Fig. 1 Efficacy and safety of PVS insertion

days, median duration of palliation was 26 (range, 1–330) days, median duration of hospitalization was 17 (range, 1–130) days, and median survival time was 41 (range, 1–481) days.

At 7 days after PVS placement, mean abdominal girth and body weight decreased significantly (decrease ratio: −6.2% and −3.2%; $P < 0.001$), and no significant change was seen in performance status ($P = 0.342$).

Adverse Events

The profile of nonhematologic AEs, except for primary tumor progression, is listed in Table 2. Sixty patients (45.1%) demonstrated 85 AEs over grade 2, of whom 44 patients developed AEs of grade 3 or higher. Six patients died within 7 days after PVS placement (Fig. 1). Preoperative serum creatinine level was 3.9 mg/dl in the patient who died of renal failure. After 7 days, fatal AEs (grade 5) except for primary tumor progression occurred in 11 patients, due to DIC in 3, GI bleeding in 3, and DIC with GI bleeding, GI bleeding with liver dysfunction, myocardial infarction, bowel perforation, pneumonitis in one patient each.

GI bleeding was found in 13 patients (9.8%): upper GI bleeding in 7 patients; lower GI bleeding in 2; upper and lower GI bleeding in 2; biliary tree bleeding in 1; and unknown origin in 1. Among these patients, observation or conservative therapy was selected in seven patients. Additionally, transfusion in four patients, endoscopic variceal ligation for esophageal varices in one, and embolization therapy using interventional radiological technique in one were performed. Clinical DIC was found in seven patients (5.3%), and five patients died of DIC. Grade 5 DIC and GI bleeding occurred in the same two patients. Abnormalities in coagulation without clinical symptoms (subclinical DIC) after PVS insertion were seen in 37 (27.8%) patients, but they did not progress to clinical DIC. Other severe nonhematologic AEs that appeared in more than one patient included sepsis (3.8%), bowel obstruction (3.8%), acute heart failure/pulmonary edema (3%), venous thrombosis (2.3%), pleural effusion (2.3%), respiratory failure (2.3%), fever (1.5%), and liver dysfunction/failure (1.5%).

Regarding grade 2 or higher AEs involving hematologic and other laboratory data, a total of 98 patients (73.7%) demonstrated 189 AEs (Table 3). Anemia was the most frequent AE, developing in 71 (53.4%) patients. This occurred within 7 days in 88.7% of these patients, and the change in grade was 2 or less in 97.2%.

Patency and Function of the PVS

PVS dysfunction (recurrence of symptoms) was observed in 60 (45.1%) patients (Fig. 2). PVS imaging findings by chamber shuntography, Doppler ultrasound, or radionuclide scanning revealed occlusion in 11 patients and patency in 19 (Fig. 2). Of these 60 patients, paracentesis was required in 22. Ten patients underwent a secondary intervention involving the PVS, nine of whom achieved symptom palliation.

Factors Associated with Safety and Efficacy

Subgroup analyses were performed for preexisting abnormalities in laboratory data, primary tumor site, and ascites

Table 2 Adverse events

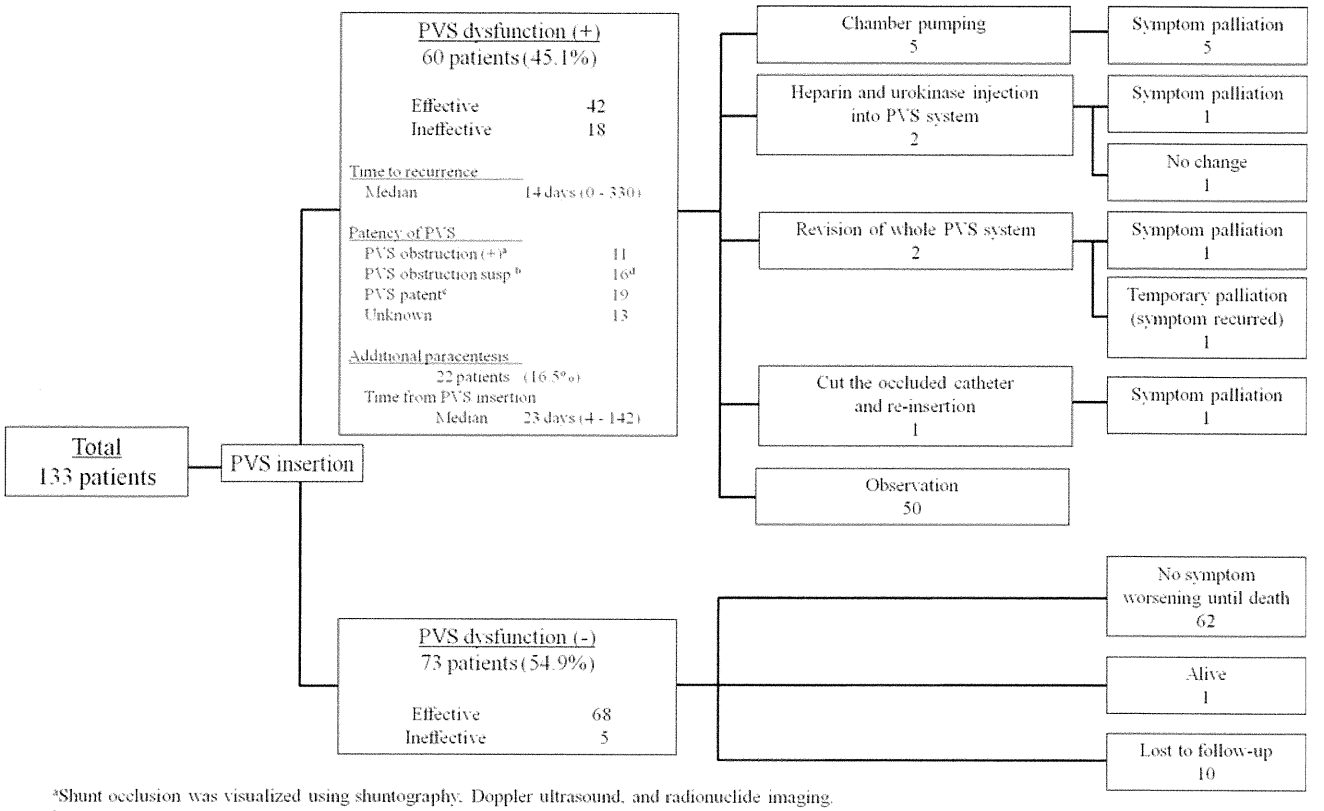
Adverse event	Overall	%	Days to onset (range)	Grade ≥3	%
Any	60 pts	45.1		44	33.1
GI bleeding	13	9.8	10 (2–28)	11	8.3
Fever	11	8.3	1.9 (0–6)	2	1.5
Venous thrombosis	8	6	4 (2–17)	3	2.3
Pulmonary embolism	1	0.8	15	1	0.8
Clinical DIC	7	5.3	2 (1–7)	7	5.3
Pleural effusion	6	4.5	7 (3–11)	3	2.3
Respiratory failure	3	2.3	2 (0–3)	3	2.3
Pneumonitis	1	0.8	42	1	0.8
Sepsis	5	3.8	5 (2–51)	5	3.8
Bowel obstruction	5	3.8	24 (3–123)	5	3.8
Bowel perforation[a]	1	0.8	36	1	0.8
Nausea	1	0.8	6	1	0.8
Acute heart failure/pulmonary edema	4	3	0.5 (0–2)	4	3
Myocardial infarction	1	0.8	41	1	0.8
Cerebrovascular ischemia	1	0.8	40	1	0.8
Liver dysfunction/failure	2	1.5	10.5 (1–20)	2	1.5
Abdominal pain	1	0.8	20	1	0.8
Renal failure	1	0.8	1	1	0.8
Hyperglycemia	1	0.8	10	1	0.8
Diarrhea	3	2.3	1	–	–
Wound dehiscence	2	1.5	Unknown	–	–
Wound infection	2	1.5	17 (17)	–	–
Fatigue	1	0.8	1	–	–
Edema	1	0.8	3	–	–
Pneumothorax	1	0.8	0	–	–
Hypotension	1	0.8	1	–	–
Rigors/chills	1	0.8	1	–	–

[a] Bowel perforation was thought to be unrelated to PVS insertion

Table 3 Laboratory data adverse events

	No.	%	Change in grade[a] after PVS				Days from PVS placement		
			+1	+2	+3	+4	1	2–7	8–14
Any	98 patients	73.7							
Leukopenia	6	4.5	0	4	1	1	1	4	1
Anemia	71	53.4	43	26	2	–	48	15	8
Thrombocytopenia	12	9	1	7	2	2	3	6	3
Hypoalbuminemia	26	19.5	26	–	–	–	10	6	10
Fibrinogen, decreased	8	6	–	3	4	1	2	4	2
Bilirubin, increased	17	12.8	10	7	–	–	9	2	6
ALT, increased	11	8.3	7	4	–	–	1	4	6
AST, increased	16	12	10	5	1	–	6	5	5
Creatinine, increased	4	3	4	–	–	–	1	1	2
Hypernatremia	1	0.8	–	–	1	–	–	–	1
Hyponatremia	6	4.5	–	5	1	–	–	2	4
Hyperkalemia	4	3	1	3	–	1	–	–	4
Hypokalemia	7	5.3	–	3	4	–	5	2	–

[a] Grade was defined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3



[a]Shunt occlusion was visualized using shuntography, Doppler ultrasound, and radionuclide imaging.
[b]Shunt occlusion was suspected for the cause of symptom recurrence clinically, although shunt occlusion was not visualized.
[c]Shunt patency was confirmed by imaging.
[d]For the cause of shunt dysfunction, one case of fibrin sheath formation in superior vena cava or subclavian vein and 1 case of tumor growth with encasement of peritoneal catheter was suspected.

Fig. 2 Patency and PVS function

characteristics, with additional analysis for the duration of symptom palliation and survival time. Of these, grade 2 or higher elevated serum creatinine ($P = 0.014$) and bloody ascites ($P = 0.045$) at baseline were significantly associated with a shorter duration of palliation (4 weeks or less; Table 4). Patients with gynecologic tumors had a shorter duration of symptom palliation than other patients ($P = 0.047$), but these included more patients with bloody ascites ($P = 0.018$). Patients with gastric cancer had statistically significantly short survival times (4 weeks or less; $P = 0.046$), whereas those with a grade 2 or greater decrease in serum albumin demonstrated a tendency to shorter duration of symptom palliation, albeit that this was not statistically significant ($P = 0.053$; Table 4).

Discussion

In this study, we investigated experience in a number of institutions with radiologically inserted Denver PVS in 133 patients with malignant ascites. PVSs were effective in 110 (82.7%) patients with malignant refractory ascites, and the median duration of symptom palliation was 41 days. Technical success was achieved in all patients without any major procedure-related AEs. These findings are consistent with previous reports of radiological insertion of PVSs (62–87.5%), confirming the feasibility and safety of radiological insertion of a PVS in patients with refractory malignant ascites [3, 21–23].

Our findings also confirmed previous results that the onset of symptom improvements was rapid [22]. Consistent with this, however, PVS insertion may result in rapid changes in circulatory dynamics as well as the rapid introduction of various agents present in ascites into the circulation. Although causality has not been clarified and a range of contributing factors may be present, the high rates of major AEs seen in the present and previous studies [2, 4, 6, 9–11, 15, 19–24] remain important considerations, and emphasize the importance of pre-procedural evaluation of general patient status, including cardiac and renal functions, and meticulous postprocedural management for 48 h to detect DIC or other AEs [1, 4].

The clinical effectiveness rate of PVS placement in our patients with malignant ascites of 82.7% is comparable to those of previous reports [1, 2, 4, 8, 12, 19, 23, 25]. In our study, PVS placement was particularly effective for

Table 4 χ^2 test analysis of preoperative variables and duration of symptom palliation/survival time

Variable	*N*	Grade[a]	*N* (%)	Duration of symptom palliation		*P* value	Duration of survival time		*P* value
				≥4 weeks (*n* = 64)	<4 weeks (*n* = 69)		≥4 weeks (*n* = 89)	<4 weeks (*n* = 44)	
Primary tumor	133								
Colorectal cancer			33 (24.8)	21 (32.8)	12 (17.4)	0.063	27 (30.3)	6 (13.6)	0.059
Gastric cancer			25 (18.8)	8 (12.5)	17 (24.6)	0.117	12 (13.5)	13 (29.5)	0.046[b]
Pancreatic cancer			21 (15.8)	13 (20.3)	8 (11.6)	0.254	17 (19.1)	4 (9.1)	0.216
Liver/bile duct cancer			16 (12)	8 (12.5)	8 (11.6)	1	12 (13.5)	4 (9.1)	0.653
Breast cancer			10 (7.5)	6 (9.4)	4 (5.8)	0.651	7 (7.9)	3 (6.8)	1
Ovarian cancer			9 (6.8)	3 (4.7)	6 (8.7)	0.566	5 (5.6)	4 (9.1)	0.701
Gynecologic cancer			12 (9)	4 (6.3)	8 (11.6)	0.44	7 (7.9)	5 (11.4)	0.733
Ascites	133								
Clear			71 (53.4)	32 (50.0)	39 (56.5)	0.562	48 (53.9)	23 (52.3)	1
Bloody			20 (15)	5 (7.8)	15 (21.7)	0.045[c]	8 (9)	12 (27.3)	0.012[b]
Chylous			9 (6.8)	7 (10.3)	2 (2.9)	0.134	7 (7.9)	2 (4.5)	0.726
Serous			90 (67.7)	39 (60.9)	51 (73.9)	0.158	56 (62.9)	34 (77.3)	0.142
Mucinous			9 (6.8)	4 (6.3)	5 (7.2)	1	6 (6.7)	3 (6.8)	1
Abnormal LD	*N*			(*n* = 63)	(*n* = 69)		(*n* = 88)	(*n* = 44)	
Leukocytosis	132	>2	3 (2.3)	2 (3.2)	1 (1.4)	0.936	3 (3.4)	0 (0)	0.536
				(*n* = 63)	(*n* = 69)		(*n* = 88)	(*n* = 44)	
Anemia	132	>2	72 (54.5)	34 (54)	38 (55.1)	1	48 (54.5)	24 (54.5)	1
		>3	17 (12.9)	10 (15.9)	7 (10.1)	0.471	11 (12.5)	6 (13.6)	1
				(*n* = 63)	(*n* = 67)		(*n* = 88)	(*n* = 42)	
Creatinine, increased	130	>1	55 (42.3)	24 (38.1)	31 (46.3)	0.444	36 (40.9)	19 (45.2)	0.781
		>2	17 (13.1)	3 (4.8)	14 (20.9)	0.014[b]	9 (10.2)	8 (19.0)	0.264
				(*n* = 62)	(*n* = 64)		(*n* = 86)	(*n* = 40)	
Hyponatremia	126	>1	79 (62.7)	35 (56.5)	44 (68.8)	0.214	53 (61.6)	26 (65)	0.868
		>3	24 (19)	11 (17.7)	13 (20.3)	0.888	17 (19.8)	7 (17.5)	0.954
				(*n* = 61)	(*n* = 66)		(*n* = 86)	(*n* = 41)	
Hypoalbuminemia	127	>2	98 (77.2)	42 (68.9)	56 (84.8)	0.053	63 (73.3)	35 (85.4)	0.196
		>3	7 (5.5)	3 (4.9)	4 (6.1)	1	5 (5.8)	2 (4.9)	1

[a] Grade was defined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3

[b] $P < 0.05$ with χ^2 test

LD laboratory data

abdominal distention, although anorexia was not sufficiently palliated. Various pathophysiologic mechanisms other than ascites may play a role in anorexia, including effects intrinsic to the tumor itself, gastrointestinal obstruction, and AEs from the PVS.

Body weight and abdominal girth were significantly reduced 7 days after PVS insertion, which objectively demonstrates the efficacy of PVSs. A previous report recommended measuring body weight and abdominal girth to evaluate PVS efficacy [9]; however, measurement of abdominal girth is not particularly reproducible because the measurement may depend on the observer or position of the patient, which is sometimes difficult to do in patients at end of life. The efficacy of PVS should be evaluated based on subjective changes in symptoms, taking into consideration that PVS insertion is a palliative intervention.

Patients with gastrointestinal malignancies have shorter life expectancy than those with gynecological malignancies [1, 8–10, 15, 26]. Consistent with this, survival time in patients with gastric cancer in this study was significantly shorter than that for other patients, which was probably due to the disease itself. Considering that symptom palliation may improve QOL, the poor prognosis of the primary disease should not be overly emphasized in evaluating indications for PVS placement. Our study did not demonstrate improvements in performance status (Fig. 1), which also has been reported previously [11].

Shunt dysfunction, a frequent AE in previous studies, was observed in 45.1% of our patients [2, 6, 9, 13, 15, 19, 23, 25]. Causes of shunt dysfunction include mechanical obstruction, such as a kink in the catheter, venous thrombosis in the subclavian or central vein, and a fibrin sheath around the catheter [2, 4, 5, 8, 15, 20, 23, 24]. These causes are sometimes revealed by imaging using ultrasonography, shuntography, or contrast-enhanced computed tomography [20, 23], and function often can be recovered by additional minimally invasive intervention. Imaging procedures to determine the cause of shunt dysfunction should be undertaken.

In our study, abnormalities in coagulation without clinical symptoms (subclinical DIC) after PVS insertion were seen in 37 (27.8%) patients, and only 7 patients (5.3%) developed clinical DIC. These results are comparable to previous studies [1–4, 7, 10–12, 15, 19]. The reported incidence of clinical DIC varies, ranging from 0–33%, and the relevant coagulopathy has not been identified [1, 3, 9–12, 21, 22, 24]. The detection of clinical DIC after PVS placement using laboratory data only appears to be difficult.

Decreases in serum creatinine and BUN levels were seen in the postoperative period. Possible reasons include increases in circulatory blood volume and renal blood flow, which result in increased urine volume [14]. The progression of anemia after PVS insertion may be due to the inflow of ascites into the circulatory system, with resulting transient dilution of blood cells [4, 7, 11, 14]. Severe AEs, such as DIC and GI bleeding, which may occur after PVS insertion [5, 19, 21, 22], should be considered in these patients.

In the subgroup analysis, we found that renal dysfunction was associated with a short duration of symptom palliation. Furthermore, acute renal failure was a cause of early postprocedural death. Bieligk et al. [9] reported that preoperative renal function is predictive of prognosis after PVS insertion. These findings highlight the importance of assessing renal function before PVS placement. In particular, careful consideration should be given to determining the placement in patients with insufficient urine volume, who may be unable to tolerate the rapid increase in plasma volume immediately after PVS insertion [7–9, 15].

A low preoperative serum albumin level was associated with a short duration of symptom palliation. A possible explanation is that the low colloid osmotic pressure of this condition may lead to extravascular transudation of water and impaired production of a sufficient urine volume in response to increased circulatory blood volume after PVS, resulting in unsatisfactory reduction in ascites volume.

Other prognostic factors associated with a short duration of symptom palliation included bloody ascites, gynecologic primary tumor, and a high white blood cell (WBC) count before PVS placement. Bloody ascites is known to be an unfavorable factor and probably results from thrombosis in the PVS system [1, 15]. Gynecological malignancies tend to have a short palliation period, and most of the patients with gynecological malignancies in this study had bloody ascites.

Several limitations of the study warrant mention. First, given its retrospective case series design, evaluation of AEs, duration of symptom palliation, and survival time may have been biased. Furthermore, because it was a multicenter study, the methods used to evaluate these variables were likely not uniform. Unlike previous studies, our study consisted of a large number of patients from multiple institutions; particularly given the difficulty of prospective evaluation of palliative treatment for terminal patients, the present study may provide helpful information for clinical decision making in PVS placement for patients with refractory malignant ascites. Second, the appropriateness of the timing of our evaluation of PVS efficacy, at 7 days after the procedure, is uncertain. Additionally, if ascites was removed with PVS insertion, it can palliate symptoms separately from an effect of the PVS. The various studies on PVS for malignant ascites conducted to date did not establish a definite postprocedural period for evaluation but were rather limited to survival time and shunt dysfunction rate or shunt patency time [3, 5, 6, 9–12, 14, 15, 19–24]. Although no consensus on how to evaluate PVS efficacy has been established, our procedure of determining efficacy 7 days after PVS insertion is reasonable, given that survival time in patients with malignant ascites is limited. In addition, patients with advanced malignancies may deteriorate rapidly, due to the primary disease and other pathophysiologies (e.g., bowel obstruction, renal dysfunction) further confounding evaluation. This difficulty highlights the current lack of knowledge on assessing outcomes in end-of-life decision making and underscores the need for further study on this area.

In conclusion, the present study suggests that radiological PVS insertion is technically feasible and yields an adequate rate of symptom palliation in patients with symptomatic refractory ascites. Although shunt dysfunction is a frequent AE, recovery of function may be obtained with appropriate additional interventions. Because changes in laboratory data, including subclinical DIC, and cardiac dysfunction or other nonhematologic AEs may occur after PVS insertion, preoperative evaluation of cardiac and renal function and postoperative management of systemic conditions are essential to preclude severe AEs after PVS.

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

See Table 5.