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TECHNICAL NOTE

A New Method of an Axial Puncture Approach for Draining Loculated Pleural Effusions

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Abstract
Purpose The authors devised a new method of an axial puncture approach through the pulmonary apex (PA) for percutaneous catheter drainage (PCD) of loculated fluid collections extending to the PA. The purpose of this report is to introduce the new procedure.
Methods Percutaneous catheter drainage by the axial puncture approach was performed in two patients with limited supine position and loculated pleural fluid collection in the posteromedial part of thoracic cavity.
Results The procedures succeeded in two patients without difficulties while keeping them in a supine position, even if the loculated fluids exist in the posterior side of thoracic cavity.
Conclusions Percutaneous catheter drainage by the axial puncture approach is particularly effective in patients with limited supine positions and loculated pleural fluid collection in the posteromedial part of thoracic cavity.

Keywords Percutaneous catheter drainage · Loculated pleural fluid · Axial puncture · Pulmonary apex

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Introduction

The patients with pleural fluid collections and empyema usually have been treated by needle thoracentesis and chest tube drainage. However, technical difficulties and failures may occur as a result of improper placement of the needle and tube, particularly when there are loculated and multiple inaccessible pleural fluid collections. Percutaneous catheter drainage (PCD) of pleural fluid collections using computed tomography (CT), ultrasonographic (US), and fluoroscopic guidance has widely been accepted in such a difficult case [1–3]. The success rate of PCD is 80–90% [2–4]. A patient may be placed in the optimal position (supine, prone, oblique, erect) to allow needle placement into the fluid. However, PCD of a loculated fluid collection in the posteromedial part of thoracic cavity is technically difficult, because a puncture approach through the back of the patient with a contralateral decubitus or prone position is usually needed. The procedure provides relatively a lot of burden from the standpoint of patient's care during the procedure and the following observation. Particularly in patients with limited supine positions, the puncture approach through the back is not indicated. We devised a new method of axial puncture approach through pulmonary apex (PA) under fluoroscopic guidance for the pleural fluid extending to PA. The procedure can be achieved by

keeping a patient in the supine position and already has been successful in two patients without difficulties. We will introduce the technique and its advantages of this new procedure.

Materials and Methods

The first patient (50s man) with diabetes mellitus had been suffering from septic arthritis of left shoulder joint and sternoclavicular joint complicated with pyoderma of anterior chest wall spreading to the level of the ipsilateral axillary line with positive β streptococcus at blood culture examination. He had dyspnea and chest pain due to large amount of pleural fluid extending to PA in left hemithorax (Fig. 1A, B). The conventional intercostal approach for PCD was not indicated because of the pyoderma. It also was difficult due to his shoulder pain to place the patient in the optimal position to insert the needle into the fluid. Therefore, PCD by the axial puncture approach through left PA was performed.

The second patient (40s man) was admitted into the hospital with a diagnosis of multiple loculated empyema in right hemithorax. He was treated by chest drainage with a 22-Fr tube of which the entry was made in the midaxillary line at the fifth intercostal level just after admitting. Because the patient's symptoms included chest pain, dyspnea, and high fever >39° were worsening the next morning, an artificial ventilation was started. Computed tomography examination revealed that the tube failed to drain the loculated fluid collection on the posteromedial side extending to PA. It was difficult to place the patient in the optimal position to insert an additional drainage into the residual loculated fluid. Therefore, the axial approach was selected.

Procedure of the Axial Puncture Approach

Indication of this procedure includes patients with loculated pleural fluid collection in the posteromedial part of thoracic cavity who are limited to supine positions or have difficulty of puncture approach through the back. It is essential to the indication that the pleural fluids are extending to PA.

In two patients, PCD by the axial puncture approach was performed under fluoroscopic guidance on anteroposterior view. Fast of all, they were placed in the supine position on the examination table. The longitudinal puncture line was decided to overlap the part of the first rib running downward under fluoroscopy. The initial target was the superior aspect of the posterior third rib. The entry site on the skin was decided to be located just above the posterior third rib. The entry site can be decided on the monitor of CT taken before the procedure. Keep placing a cursor of CT monitor on the target point of the posterior third rib, the slice level on the CT monitor was adjusted to the level of the skin. As a result, the entry site pointed by the cursor was located around the skin covering trapezius muscle, and the depth of the entry site was almost equivalent to around the tip of spinous process of the seventh cervical spine which could be palpable. Actually, a patient was placed in supine position. The entry was decided by both the location of the first rib under fluoroscopic monitor and the palpation of the tip of the spinous process of seventh cervical spine, which should be confirmed on the prior CT examination beforehand in each case. After local anesthesia and dermal cut on the entry region, a 20-cm length, 18-gauge coaxial needle was axially and horizontally punctured and advanced overlapping the first rib on A-P view under fluoroscopy to reach the superior aspect of the third rib (Fig. 2A, B).

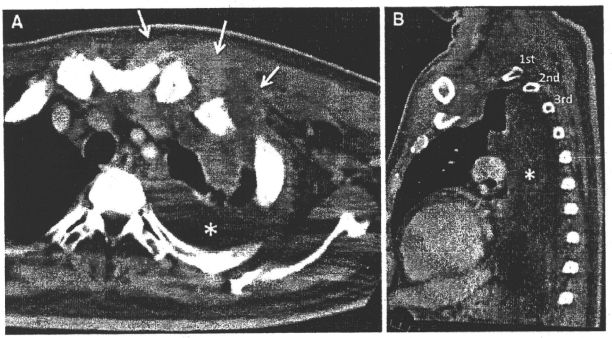

Fig. 1 Axial CT and sagittal reconstruction showing the loculated pleural fluid extending to pulmonary apex in posterior part of thoracic cavity. *Arrows* septic arthritis of left sternoclavicular joint complicated with pyoderma of anterior chest wall. *Asterisk* loculated pleural fluid

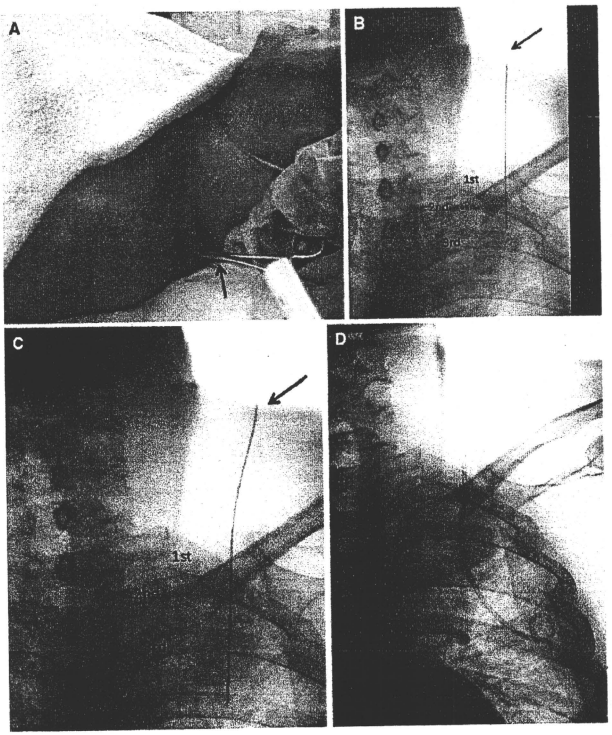

Fig. 2 The procedure of axial puncture approach. **A** The puncture site pointed by surgical forceps. **B** The puncture needle reached superior aspect of the third rib. **C** The insertion of the needle into the pleural effusion. **D** An 8-Fr Uracil pig-tail drainage catheter was placed into the most dependent (inferior) part of the fluid

Then, after the tip of the needle was removed just a little, it was inclined ventrally and inserted to pass the intercostal space of the second and third rib (Fig. 2C). Herein, the lateral or oblique view under fluoroscopy was not helpful to decide the puncture direction, because of X-rays permeable attenuation due to their shoulders.

The insertion of the needle into the pleural effusion is confirmed by an aspiration of the collected fluid. A j-tip 0.035-inch stainless guide wire is passed through the needle into the most dependent (inferior) part of the fluid. An 8-Fr Uracil pig-tail drainage catheter (Cook, USA) is placed by using an 8-Fr dilator by Seldinger technique (Fig. 2D).

Results

The axial puncture approach was successful in those two patients without technical difficulties. They had no significant symptoms during the procedure, even with only local anesthesia. There was no serious complication during the procedures and the draining periods. The spending time during the procedure was within 20 min in both patients. The fluid drained was respectively transudate and parapneumonic effusion (Fig. 3A, B). The first patient was relieved from chest pain and dyspnea after starting PCD. Removal of the catheter was respectively 4 weeks and

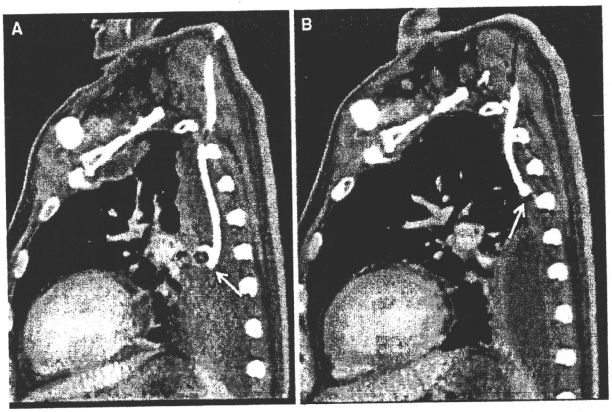

Fig. 3 Sagittal reconstructed CT after the procedure. **A** The sagittal CT image taken on the next day after the procedure. **B** The CT taken after 2 weeks

2 days when each of the loculated fluids was almost disappeared. The second patient had the residual fluid collection in the posterior lower part of the thoracic cavity, which was drained by an additionally inserted 32-Fr chest tube, followed by surgical debridement. They left the hospital after 35 and 26 days, respectively.

Discussion

The axial approach through PA is a new approach method for PCD of pleural fluid collection. This procedure has the following advantages: (1) able to achieve the procedure by keeping a patient in supine position; and (2) able to achieve the procedure only under fluoroscopic guidance. Because the conventional intercostal approach method is unfeasible to PCD of loculated pleural fluid collections in the posteromedial part of thoracic cavity, the approach method to puncture the back of the patient placed in contralateral decubitus position often is selected. However, the approach from the back provides relatively a lot of burden to medical staff from the standpoint of patient care during the procedure and the observation period. In addition, in a case that is limited to the supine position, PCD is not indicated. Therefore, the axial approach is at least feasible for the patients with the limited supine position as well as with no indication of puncture approach through the back. Actually, PCD by the axial approach was very useful in the two patients, because the procedures and observations in patient's supine position were less stressful.

It is the technical key that the initial target is the superior aspect of the posterior third rib. As seen on Fig. 1B of the sagittal CT image, the thoracic cage apparently curves backward at the range from the level of the first rib to the forth. The transverse distance between the second and the third rib is longer than that between the third and the fourth rib. It is easier to pass the needle between the second and third rib into the pleural fluid. The procedure aiming at the superior aspect of second rib would have higher risk of pulmonary injury, because the needle would be advanced more ventrally and closely to the border between the fluid and lung tissue. Those are the reasons why the initial puncture target is the superior aspect of the third rib. However, this anatomical characteristic does not apply to patients with scoliosis or skeletal deformity of thoracic cage. The axial puncture approach is not indicated for them; another puncture approach except for between the second and the third rib may be able to be introduced. Further investigation is needed in the future.

It has been reported that major complications from chest tube drainage of pleural fluid collection consist of chest wall hematoma, infection, hemothorax, laceration and infarction of the lung, and subdiaphragmatic placement with injury to the spleen, liver, and stomach [5, 6]. The puncture needle by the axial approach craniocaudally passes between the posterior second rib and the scapula. Considering the anatomy around the needle tract, hemothorax, chest wall hematoma, and pulmonary laceration may occur. The arteries supplying around the needle tract consist of branches of subclavian, axillary, and intercostal

arteries. The risk of injury to the intercostal arteries is considered to be lower than that of conventional intercostal approach, because each of them runs under the rib. However, it has been reported that existence of collateral intercostal arteries running on the ribs causes vascular complications [7]. So, there is always the need to pay attention to vascular injury at PCD by the axial approach. To avoid pulmonary laceration, it is necessary to confirm the fluid collection extending to PA on CT, and not to insert the needle tip deeply into the fluid. There is almost no risk of injury to the subdiaphragmatic organs or brachial nerve plexus. Brachial plexus runs through the interscalene triangle bounded by anterior and middle scalene muscles. In other words, the puncture site just above trapezius muscle is located in the dorsal side of the scalene muscles. As a result, there is no risk of injury to the brachial plexus.

Percutaneous catheter drainage by the axial approach to drain the fluid collection extending to PA is technically simple and safe, and useful from a standpoint of patient care because of no needs to alternate the patient's position. In addition, this approach may be applicable to lung biopsy or radiofrequency ablation for lesions existing around PA by using CT in near future. Further investigation with an accumulation of the number of patients is necessary to verify the safety and efficacy of this procedure.

Conflict of interest None.

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CLINICAL INVESTIGATION

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

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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

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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

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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

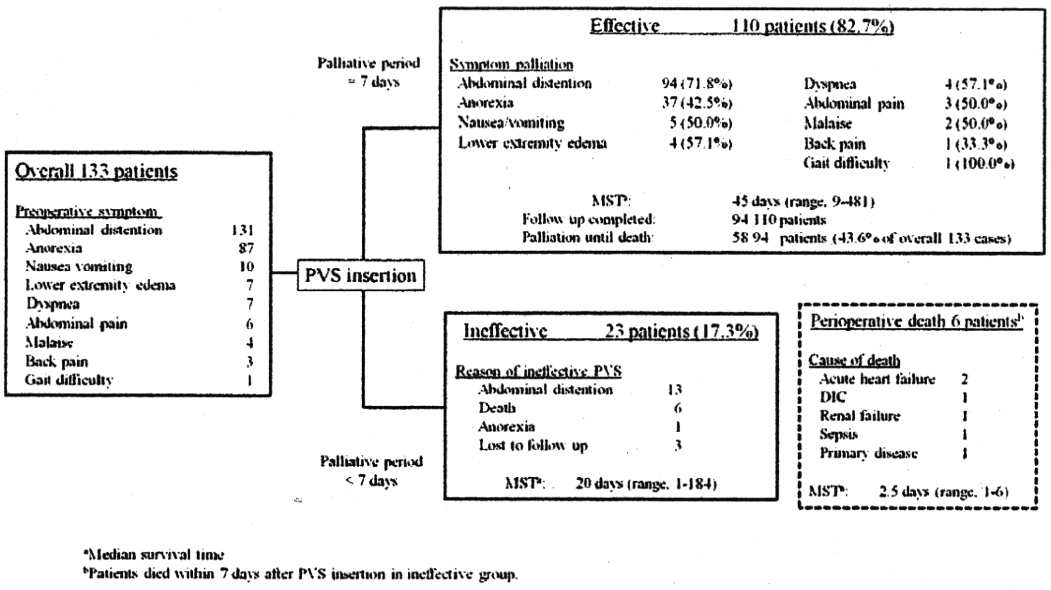
PVS Placement

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)



*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

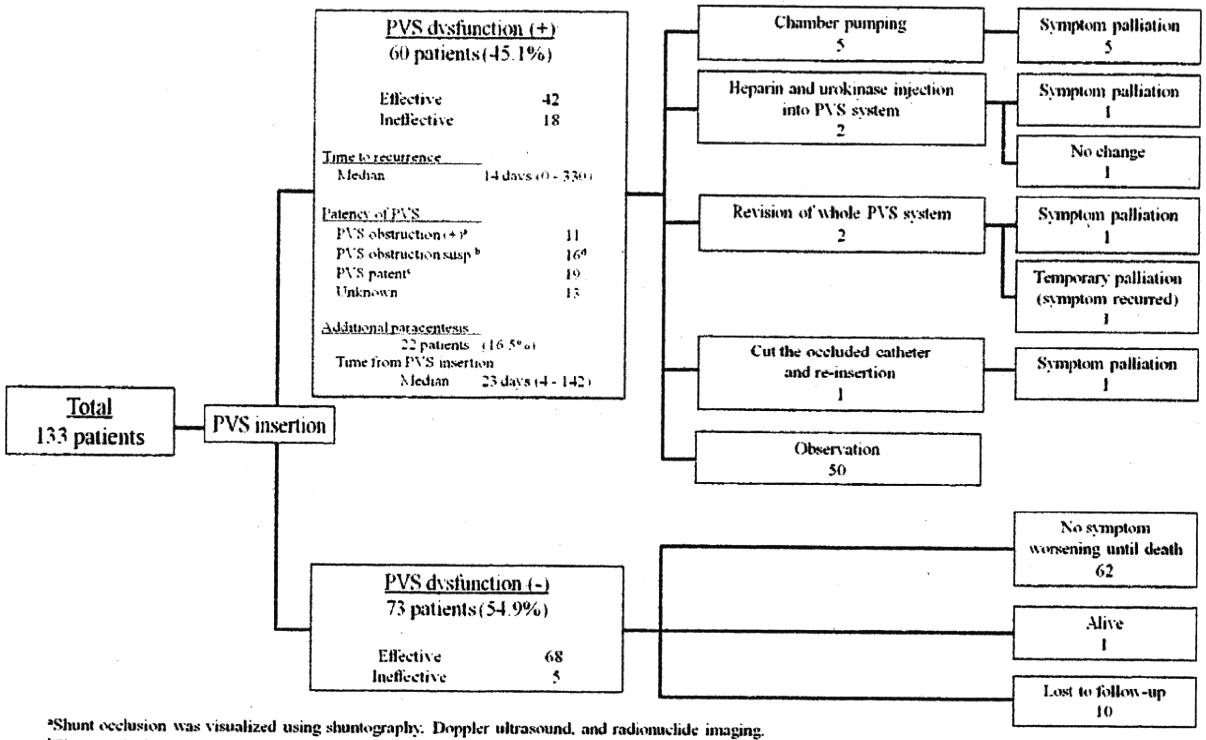
Adverse event	Overall	%	Days to onset (range)	Grade ≥3	%
Any	60 pts	45.1		44	33.1
GI bleeding	13	9.8	10 (2–28)	11	8.3
Fever	11	8.3	1.9 (0–6)	2	1.5
Venous thrombosis	8	6	4 (2–17)	3	2.3
Pulmonary embolism	1	0.8	15	1	0.8
Clinical DIC	7	5.3	2 (1–7)	7	5.3
Pleural effusion	6	4.5	7 (3–11)	3	2.3
Respiratory 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.

Table 5 Five Japanese institutions enrolled in this study

Institution	No. of enrolled patients ($N = 133$)	%
Aichi Cancer Center Hospital and Research Institute	29	21.8
Iwate Medical University Hospital	23	17.3
The Cancer Institute Hospital of Japanese Foundation for Cancer Research	20	15
National Cancer Center	26	19.5
Shizuoka Cancer Center	35	26.3

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Original Study

Hepatic Arterial Infusion of 5-Fluorouracil for Patients With Liver Metastases From Colorectal Cancer Refractory to Standard Systemic Chemotherapy: A Multicenter, Retrospective Analysis

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Abstract

Introduction: This retrospective study evaluated the safety and efficacy of hepatic arterial infusion chemotherapy (HAIC) with 5-fluorouracil (5-FU) for patients with liver metastases from colorectal cancer refractory to standard systemic chemotherapy. **Patients and Methods:** Fifty-five patients who had shown disease progression during the prior standard systemic chemotherapy with oxaliplatin, irinotecan, and 5-FU were enrolled. The treatment was weekly HAIC with 5-FU 1000 mg/m^2/5 hours through an indwelling catheter-port system. **Results:** No major adverse reaction was observed other than grade 3 leukocytopenia (3.6%) and hyperbilirubinemia (1.8%). The overall response rate and disease control rate were 18.2% and 70.9%, respectively. The median progression-free survival and median overall survival (OS) were 2.8 months, and 6.7 months, respectively. The initial sites of disease progression were liver in 14, other than liver in 27, and both in 6. Multivariate analysis identified Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1 and number of extrahepatic metastatic sites (NMS) ≤ 1 as favorable prognostic factors for OS (hazard ratio [HR], 8.277; 95% CI, 3.60-19.0; P = .000 for ECOG PS; and HR, 2.456; 95% CI, 1.30-4.61; P = .005 for NMS). **Conclusion:** HAIC with 5-FU may be a safe and effective treatment for patients with colorectal liver metastases refractory to standard systemic chemotherapy.

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Keywords: 5-FU, Alkaline phosphatase, Prognostic factor, Third-line chemotherapy

Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide and remains a major cause of cancer-related deaths. For advanced CRC, irinotecan and oxaliplatin are widely used in both first-line and second-line treatments, in combination with 5-fluorouracil (5-FU) and leucovorin (LV). This approach has yielded improvements in response rates and survival.[1,2] The treatment options for disease refractory to these standard treatments are limited, although cetuximab benefits some patients during third-line chemotherapy.[3,4] In clinical practice, novel approaches need to be developed and established to improve prognoses further.

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About half of CRC patients develop liver metastases during the course of their disease. Moreover, more than half of the patients who die of CRC manifest liver metastases at autopsy, and the majority of these patients die of liver failure.[5] Several randomized studies showed that hepatic arterial infusion chemotherapy (HAIC) during first-line therapy is associated with a higher tumor response rate, but not significantly prolonged survival.[6-8] On the other hand, positive data are also available for the effects of HAIC on survival. Kemeny et al reported on the advantages of HAIC in a well-designed randomized study.[9] Unfortunately, they did not use irinotecan and oxaliplatin, key drugs in standard systemic chemotherapy, as the initial treatment in their systemic group. Thus, it remains to be proven that hepatic arterial therapy results in longer survival compared with recent standard systemic chemotherapy. However, because the direct infusion of antitumor agents into tumors at a higher concentration than with systemic chemotherapy using HAIC can enhance antitumor effects and reduce toxicity,

HAIC may be effective for patients with liver metastases from CRC refractory to standard systemic chemotherapy. Therefore, we conducted a multicenter, retrospective study to evaluate the efficacy and tolerability of HAIC with 5-FU and to analyze prognostic factors in these patients.

Patients and Methods

Patient Selection

Four participating centers in Japan provided the data of 55 patients with liver metastases from CRC treated with HAIC and 5-FU between April 2005 and March 2008. All selected patients fulfilled the criteria of (1) histologically confirmed colorectal adenocarcinoma, (2) predominant disease with liver metastases, (3) previous exposure to and failure of the 3 drugs oxaliplatin, irinotecan, and 5-FU, (4) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 3, (5) adequate bone marrow and renal/hepatic function, and (6) the performance of HAIC with single-agent 5-FU. This study received the approval of the Institutional Review Board at the center that required it.

Treatment

Under local anesthesia, an indwelling catheter with a sidehole was inserted from the left subclavian artery or right femoral artery. The catheter tip was inserted into the gastroduodenal artery and fixed to the vascular wall by metallic coils and a mixture of n-butyl cyanoacrylate (NBCA) and iodized oil, and the sidehole was placed within the common hepatic artery. The proximal end of the catheter was connected to an implanted port and embedded subcutaneously. When an aberrant hepatic artery was found, hepatic arterial blood flow was redistributed, using coils to convert multiple hepatic arteries to a single arterial blood supply. If necessary, extrahepatic arterial branches arising from the hepatic artery and parasitic arteries with hepatopetal blood flow were also occluded, using coils and a mixture of NBCA and iodized oil. The appropriate drug distribution through the indwelling catheter was confirmed according to computed tomography (CT) via the injection of contrast material through the implanted port before the initiation of therapy.[10-12]

As treatment, 5-FU (1000 mg/m^2) was administered via continuous 5-hour infusion once a week, using a continuous-infusion device.[13] Treatment was repeated weekly until the appearance of unacceptable toxicity, the progression of hepatic lesions, or a marked enlargement of extrahepatic lesions.

Evaluation

During treatment, a blood cell count and liver function tests were performed every week. Intravenous contrast-enhanced CT and CT arteriography via the implanted port were performed every 1-2 months. Toxicities were graded according to the Common Toxicity Criteria for Adverse Events, version 3.0, and the responses limited to a liver metastasis were evaluated regardless of the disease outside the liver. A sum of the longest diameters for all target legions of liver metastasis was compared with that before treatment. Hepatic response was classified as a partial when a 30% or more reduction in the sum without new lesions in the liver was obtained, and as progressive when a 20% or greater enlargement or new lesions in the liver was evident. Otherwise, hepatic disease was classified as stable. Hepatic progression-free survival (H-PFS) was defined as the date from the initiation of HAIC to the date of hepatic progression or death from any cause.

Overall survival (OS) was calculated from the date of initiating HAIC to death, and was censored on the date of the last follow-up of a surviving patient. Overall progression-free survival (PFS) was defined as the time from initiating HAIC to the documented progression of disease at any site or to date of death from any cause, according to the Response Evaluation Criteria for Solid Tumors.

Statistical Analysis

Statistical analyses were conducted using Dr. SPSS II, version 11.0.1J (SPSS, Inc.; Chicago, IL). The OS, PFS, and H-PFS were estimated using the Kaplan-Meier method, and 95% confidence intervals (CIs) were provided for proportions. Univariate and multivariate Cox regression analyses were performed to assess factors prognostic of OS, including age, ECOG PS, number of extrahepatic metastatic sites, location of primary site, history of primary resection, synchronicity or metachronicity of a liver metastasis, number of previous regimens, and data from clinical laboratory tests (eg, alkaline phosphatase [ALP], carcinoembryonic antigen [CEA], and white blood cell count [WBC]). Multivariate analysis was undertaken for variables demonstrating $P < .10$ after univariate analysis, and $P < .05$ was considered statistically significant. The relationships between H-PFS and OS were analyzed using simple linear regression. Multiple correlation coefficients (r) were calculated to draw regression lines.

Results

Patient Characteristics

The baseline characteristics of the 55 patients in this study are summarized in Table 1. The median age was 62 years (range, 30-78 years). Thirteen patients (23.6%) demonstrated an ECOG PS of 2 or 3. Thirty-six patients (65.5%) had synchronous hepatic metastases, and 45 (81.8%) had extrahepatic disease. The median baseline ALP, CEA, and WBC values were 781 IU/L (range, 228-3916 IU/L), 808 ng/mL (range, 9-36,787 ng/mL), and 7020/mm^2 (range, 2090-21,100/mm^2), respectively. Twenty-four patients (43.6%) had previously received 3 or more regimens. All patients had received oxaliplatin, irinotecan, and 5-FU, and these agents had proven ineffective. All patients had received FOLFOX (5-FU plus LV with oxaliplatin), 44 patients had received FOLFIRI (5-FU plus LV with irinotecan), and 5 patients had received irinotecan alone, 5 patients had received a 5-FU bolus plus LV with irinotecan, and 1 patient had received a combination of irinotecan and S-1.

Treatment Course

A catheter-port system was implanted successfully in all patients. The routes of catheter insertion included the left subclavian artery in 41 patients and the right femoral artery in 14 patients. The median number of hepatic arterial infusion courses was 12 (range, 1-58 courses), and the median duration of treatment was 3.3 months (range, 0.3-17.2 months). During the treatment period, abnormalities of drug distribution to the liver were observed via follow-up CT arteriography in seven patients (12.7%). The development of a collateral blood supply to the liver (inferior phrenic artery in 5 patients, gastroduodenal artery in 2 patients, adrenal artery in 1 patient, and

Table 1 Patient Characteristics

Characteristic	Patients (N = 55)
Sex (Male/Female)	32/23
Age, Years (≤ 60/> 60)	23/32
PS (ECOG) (0/1/2/3)	24/18/9/4
Extrahepatic Metastatic Site (0/1/≥ 2)	10/24/21
Primary Site (Colon/Rectum)	34/21
Primary Resection (No/Yes)	12/43
Liver Metastases (Metachronous/Synchronous)	19/36
Number of Previous Regimens (2/≥ 3)	31/24
Previous Therapy Using FOLFOX	55
Previous Therapy Using Regimen Containing Irinotecan (FOLFIRI/Others)	55 (11/44)
Baseline ALP, IU/L (≤ 300/> 300)	6/49
Baseline CEA, ng/mL (≤ 50/> 50)	7/48
Baseline WBC, /mm^2 (≤ 10,000/> 10,000)	42/13

Abbreviations: ALP = alkaline phosphatase; CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = 5-fluorouracil/leucovorin/irinotecan; FOLFOX = 5-fluorouracil/leucovorin/oxaliplatin; PS = performance status; WBC = white blood cell

Table 2 Adverse Events

Adverse Event	Grades 1 and 2 (%)	Grade 3 (%)
Leukocytopenia	0	2 (3.6)
Thrombocytopenia	1 (1.8)	0
Nausea	1 (1.8)	0
Stomatitis	1 (1.8)	0
Hyperbilirubinemia	0	1 (1.8)

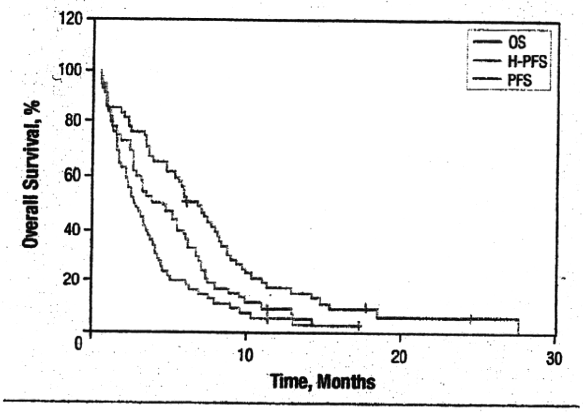
Table 3 Response and Survival

Response Measure	Patients (N = 55; %)
CR	0
PR	10 (18.2)
SD	29 (52.7)
Disease Control (Complete Response + Partial Response + Stable Disease)	39 (70.9)
PD	10 (18.2)
Not Evaluable	6 (10.9)
Survival, Months (95% CI)	
PFS	2.8 (2.0-3.6)
H-PFS	4.6 (2.8-6.3)
OS	6.7 (4.8-8.5)

Abbreviations: CR = complete response; H-PFS = hepatic progression-free survival; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease

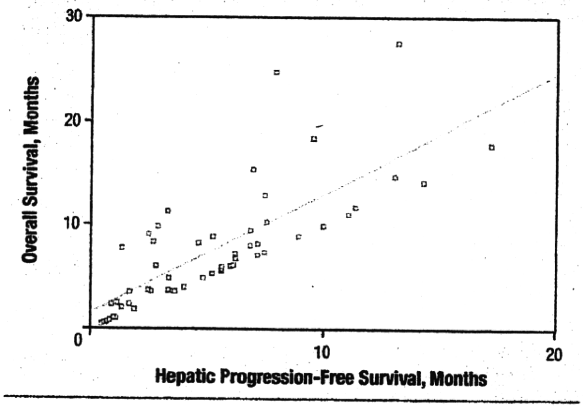
replaced left hepatic artery in 1 patient) was detected, and these collateral vessels were embolized using interventional radiology techniques in all of these patients, and HAIC was then continued. In 4

Figure 1 Kaplan-Meier Curve for Overall Survival, Hepatic Progression-Free Survival, and Progression-Free Survival



Abbreviations: H-PFS = hepatic progression-free survival; OS = overall survival; PFS = progression-free survival

Figure 2 Linear Regression Line ($y = 1.19x + 1.54$) and Corresponding Correlation ($r^2 = 0.54$) for Relationship Between Hepatic Progression-Free Survival and Overall Survival



patients (7.3%), HAIC was terminated because of hepatic arterial occlusion 1.2-8.5 months after initiating treatment. Two of these patients underwent HAIC with mitomycin C from a collateral artery, and 1 underwent systemic chemotherapy (FOLFOX plus bevacizumab) as subsequent therapy. The remaining 2 patients underwent no subsequent anticancer therapy.

Toxicity

Toxicities related to HAIC are listed in Table 2. No life-threatening toxicity was evident. Hematologic toxicities were generally mild, with grade 3 leukocytopenia in 2 patients (3.6%) and grade 2 thrombocytopenia in 1 patient (1.8%). Nonhematologic toxicities were also mild, with grade 3 hyperbilirubinemia in 1 patient (1.8%) and grade 1 nausea and stomatitis in 1 patient each (1.8%).

Efficacy

The hepatic tumor response is listed in Table 3. Six of 55 patients (10.9%) could not be evaluated because they died within 1 month

Table 4 Prognostic Factors

Variable	Overall Survival					
	Univariate			Multivariate		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age (≤ 60 Years/> 60 Years)	0.749	0.41-1.35	.339	–	–	–
PS (0 or 1/≥ 2)	7.943	3.48-18.1	.000	8.277	3.60-19.0	.000
Number of Extrahepatic Metastatic Sites (0 or 1/≥ 2)	2.592	1.39-4.82	.003	2.456	1.30-4.61	.005
Primary Site (Rectum or Colon)	0.627	0.34-1.13	.126	–	–	–
Primary Resection (No or Yes)	1.129	0.56-2.27	.734	–	–	–
Hepatic Metastasis, Synchronous (No or Yes)	0.657	0.36-1.18	.165	–	–	–
Number of Previous Regimens (2/≥ 3)	0.88	0.49-1.55	.661	–	–	–
ALP, IU/L (≤ 300/> 300)	1.232	0.52-2.91	.635	–	–	–
CEA, ng/mL (≤ 50/> 50)	2.278	0.88-5.83	.086	1.857	0.71-4.86	.207
WBC, /mm^2 (10,000/> 10,000)	1.291	0.65-2.54	.46	–	–	–

Abbreviations: ALP = alkaline phosphatase; CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group; PS = performance status; WBC = white blood cell

after initiating HAIC and had undergone no follow-up CT. No patients manifested the disappearance of a liver metastasis, and 10 patients demonstrated a hepatic partial response, resulting in a hepatic response rate of 18.2%. In addition, 29 patients had stable disease, resulting in a hepatic disease control rate of 70.9%. Ten (18.2%) exhibited hepatic progressive disease.

After a median follow-up of 6.1 months (range, 0.5-27.5 months), 53 patients had experienced progressive disease or died, and the remaining 2 patients continued their HAIC without progression for 11.3 and 17.2 months. The median overall PFS and H-PFS were 2.8 months (95% CI, 2.0-3.6 months) and 4.6 months (95% CI, 2.8-6.3 months), respectively (Figure 1). The initial sites of disease progression in these 47 patients included the liver in 14, sites other than the liver in 27, and both in 6. The median OS was 6.7 months (95% CI, 5.0-8.3 months; Figure 1).

Correlation Between Hepatic Progression-Free Survival and Overall Survival

Among the 47 patients who died or whose disease progressed, the relationship between OS and H-PFS, as assessed by a simple linear regression analysis, yielded a multiple correlation coefficient (r^2) of 0.54. The formula for the resulting regression line was $y = 1.19x + 1.54$ (Figure 2).

Prognostic Factors

A univariate analysis of OS showed that ECOG PS, number of extrahepatic metastatic sites, and serum CEA level significantly affected patients' prognoses. The results of Cox regression analyses of various prognostic factors are given in Table 4. A multivariate analysis revealed that ECOG PS and the number of extrahepatic metastatic sites were independent prognostic factors (hazard ratio [HR], 8.277; 95% CI, 3.60-19.0; and $P = .000$ for ECOG PS; and HR, 2.456; 95% CI, 1.30-4.61; and $P = .005$ for number of extrahepatic metastatic sites).

Discussion

Systemic chemotherapy for advanced CRC has improved considerably in recent years. The combination of infusional 5-FU and LV with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) is considered standard therapy during first-line treatment, with a crossover to irinotecan-containing or oxaliplatin-containing second-line regimens.[1,2,14] The use of all 3 active drugs reportedly contributes to prolonged survival.[2] In addition, the systemic administration of new targeted agents such as bevacizumab and cetuximab has brought further increases in antitumor activity.[15-17]

Despite these recent advances, the clinical courses of patients after the failure of 5-FU, oxaliplatin, and irinotecan are not satisfactory.[18,19] Before the approval of cetuximab in Japan, a dihydropyrimidine dehydrogenase–inhibitory oral fluoropyrimidine, known as S-1 was a treatment option for patients with CRC refractory to these 3 key drugs. However, S-1 produced no objective response and a median OS of only 4.8 months.[20] In clinical trials, monotherapy with cetuximab yielded a survival benefit with a response rate of 10.8% and a median OS of 6.9 months over best supportive care with a median OS of 4.6 months, and cetuximab combined with irinotecan produced a favorable response of 20% and a median OS of around 10 months.[4,5,21,22] To the best of this author's knowledge, no reports have described HAIC with 5-FU for advanced CRC refractory to the above 3 cytotoxic agents. This study demonstrated that the hepatic response rate for HAIC with 5-FU was 18.2%, and the median OS was 6.7 months. These results seem compatible with those of cetuximab alone, which is a standard therapy after 5-FU, oxaliplatin, and irinotecan have failed. Furthermore, HAIC could be placed in a fourth-line regimen after the failure of cetuximab for patients with predominantly liver metastases.

Some studies reported that the level of ALP is a useful prognostic factor in patients with metastatic CRC.[23,24] The present results suggest that the prognosis of patients with hepatic dysfunction because of liver metastases may be poor. In this study, 89.1% of the patients had high levels of ALP (≥ 300 U/L). All manifested uncontrolled liver metastases that had been considered the prognosis-limiting factor. In addition, 23.6% of the patients had an ECOG PS ≥ 2, and 43.6% had previously received 3 or more regimens of

systemic chemotherapy. Despite these poor patient baseline characteristics, HAIC demonstrated a survival value compatible with that of cetuximab alone.

To determine the indications for HAIC, especially in patients with extrahepatic disease, is very difficult. Kemeny et al reported that if extrahepatic metastases were absent, some patients with extensive hepatic metastases previously treated by systemic chemotherapy became resectable with combined therapy using HAIC and systemic chemotherapy.[25] However, combined systemic chemotherapy with 5-FU, oxaliplatin, and irinotecan is usually used as first-line treatment, and thus many patients with both extensive hepatic metastases and extrahepatic metastases have already been treated with these drugs. The methods of treating such patients thus remain an unresolved issue. In the present study, although 81.8% of the patients also had metastases at extrahepatic sites, HAIC was administered because the hepatic lesion was considered to be the prognosis-limiting factor. The correlation between H-PFS and OS in this study suggests that the control of liver metastases, even in patients with extrahepatic disease, may be important in prolonging OS. On the other hand, a multivariate analysis indicated that patients with ≥ 2 extrahepatic metastatic sites had a significantly poorer prognosis, with a median OS of only 4.8 months. These results suggest that the indications for HAIC should be limited by the extent of extrahepatic metastases.

Recently, some clinical studies of HAIC combined with systemic chemotherapy were conducted, and demonstrated remarkable efficacy.[26,27] Gallagher et al reported that HAIC plus systemic irinotecan showed promising results in patients with colorectal liver metastases previously treated with systemic oxaliplatin, resulting in a response rate of 44% and MST of 20 months.[28] In the present study, patients had been refractory to both oxaliplatin and irinotecan and were therefore treated with HAIC alone. In terms of further investigation, HAIC combined with molecular targeted agents could be undertaken.

In third-line and subsequent treatments, clinicians should be especially vigilant regarding adverse effects, because these patients often manifest complications, with various symptoms attributable to their disease and the toxicities of previous therapy. Reportedly, 10%–42% of patients develop grade 3-4 toxicities during third-line systemic chemotherapy.[4,5,18-22] In contrast, in this study, grade 3 toxicities were evident in only 5.5% of patients. Therefore, HAIC may be feasible in heavily pretreated patients, if indicated.

Conclusion

In conclusion, our multicenter, retrospective study demonstrated that HAIC with 5-FU may benefit patients with liver metastases from CRC refractory to standard systemic chemotherapy. Patients with a good PS and limited extrahepatic metastases seem to be optimal candidates for this therapy. This study was clearly limited by its small number of patients and retrospective design. The role of HAIC in patients previously treated using standard, systemic chemotherapy should thus be evaluated in a prospective clinical trial. However, no reports, to the best of this author's knowledge, have described HAIC in this situation, and thus the present results offer background data for future trials. A large-scale, prospective study is required to clarify the clinical benefits of HAIC in this setting.

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Disclosures

The authors have no relevant relationships to disclose.

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