平成２０年度～２２年度

厚生労働科学研究費補助金
がん臨床研究事業
緩和ケアにおけるIVRの確立についての研究

総合研究報告書

研究代表者　荒井　保明

平成２３（２０１１）年　５月

別紙２

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I. 総合研究報告

別紙３

厚生労働科学研究費補助金（がん臨床研究事業）
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緩和ケアにおけるIVRの確立についての研究

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研究要旨
緩和 IVR のうち第Ⅱ相試験までのデータが得られている難治性腹水に対するシャント術、有痛性骨転移に対する経皮的セメント注入術、消化管通過障害に対する経皮経食道胃管挿入術、切除不能悪性大腸狭窄に対するステント治療、大静脈症候群に対するステント治療の５つの IVR について、当該 IVR が緩和ケアにおける標準的治療となり得るかを検証する目的で、既存治療を対照に緩和 IVR の優越性を評価するためのランダム化比較試験のプロトコールを作成し、試験を行った。未だ、試験の終了、結果の提示には至っていないが、本試験は緩和ケアにおける緩和 IVR の位置づけを明確にしようとする世界で初めてのものであり、その結果は緩和ケアに大きな影響を及ぼすと予測される。

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A. 研究目的

Interventional radiology(以下 IVR)は画像誘導下に経皮的手技により治療を行うものであり、迅速性、低侵襲性から、がん治療、特に QOL を考慮した緩和ケアにおける有効性が期待されている。しかし、これまで客観的データに乏しく、標準的治療として導入するためのエビデンスは不十分であった。本研究の目的は、これまでに日本腫瘍 IVR 研究グループ JIVROSG(Japan Interventional Radiology in Oncology Study Group)で行われた臨床試験で緩和ケアにおける標準的治療となる可能性が示された IVR について、既存の治療法とのランダム化比較試験を行い、緩和ケアにおける当該 IVR の位置づけを明らかにすることにある。

B. 研究方法

IVR は外科治療に比べ一般に低侵襲とはいえ侵襲的治療であり、IVR を介入させるランダム化比較試験を緩和段階の症例を対象に行うためには、倫理的に許容され、かつ実行可能な試験デザインの作成が最も難しい課題である。また、緩和段階の症例が呈す症状は極めて多彩であるため、これらの症状に対する標準的自体が必ずしも確立しておらず、臨床現場では医療者と患者との合意により、十分なエビデンス不在のまま、種々の治療が行われているのが現状である。このような状況を勘案し、本研究では１年次にランダム化比較試験の基本デザインの検討を行い、２年次にこの基本デザインに基づき各試験のプロトコールを確定するとともに、試験遂行に関わる環境を整備した上で試験を開始、３年次は各試験を継続して行った。

（倫理面への配慮）
本研究では、ヘルシンキ宣言、臨床試験倫理指針を遵守して臨床試験計画書を作成し、被験者本人に対する文書を用いた説明と文書による同意の取得を必須とするとともに、参加施設の施設倫理審査委員会の承認を受けて試験を行った。試験中に発生した有害事象については、速やかに研究代表者に報告されるとともに、効果安全性評価委員会の評価を受けることとした。被験者の個人情報については、試験の信頼性を担保するため登録時にはこれを要求するが、登録後は与えられた症例登録番号のみで運用し、さらに登録時に用いられた個人情報は、不正なアクセスに対し厳重に保護され、かつ、すべての閲覧が記録されるシステムとされているコンピュータ内に保管することにより、個人情報保護対策を万全とした。

C. 結果

１．基本試験デザインの作成

緩和領域で既存の治療法を対照に IVR を介入治療としてランダム化比較試験を行おうという大胆な試みであるため、１年次は基本となる試験デザインについての検討を行い、以下の結果を得た。

①症例選択規準

緩和段階症例の病態が多彩であることを考慮し、通常の臨床試験で用いられる頻度の高い P.S.(Performance Status)と主要臓器機能保持を採用せず、緩和領域における予後予測指標として用いられる P.P.I.(Palliative Prognostic Index)＜6 を採用する

こととした。
②対象治療
緩和における標準的治療を確定することが困難であり、また、倫理的にも治療内容を限定することは許容されないと判断されたため、対照治療は当該 IVR を除くすべての治療とした。
③評価項目
当該 IVR 治療の有効性評価が可能であり、かつ全身的な QOL への影響、有害事象を総合して最終的な当該 IVR 治療の評価が可能となるよう、主要評価項目を症状特異的 QOL 尺度、副次的評価項目を包括的 QOL 尺度(EQ-5D、SF-8)、有害事象の種類と頻度・程度、生存期間とした。
④評価・比較方法
割付後の患者希望によるクロスオーバーを含む他治療への変更を許容することが倫理的に必須であり、かつ両群の比較可能性を維持するため、主要評価項目ならびに副次的評価項目として測定された QOL について、個々の症例におけるプロトコール治療継続期間中の QOL 曲線を作成し、その曲線下面積(AUC: Area Under the Curve)を比較することとした。なお、解析対象は FAS(full analysis set)として、登録時のベースライン値を共変量とした共分散分析を行い、試験治療群の対照群に対する優越性を検証することとした。
⑤必要症例数の設定
緩和ケアにおける標準的治療が乏しい状況を考慮して、「可能性のある治療法を誤って棄却する可能性」を減じるため、仮説検定での有意水準を両側 10%、信頼係数 90%として必要症例数を設定した。
⑥QOL 測定法
被験者の治療者に対する心理的要因の影響を排除するため、個々の被験者の QOL 測定結果を治療に関わる医療者が知り得ないシステムとし、これを被験者に予め知らせるとともに、測定用紙の回収も治療に関わる医療者以外の者とすることとした。
⑦試験組織
試験組織は JIVROSG とし、データセンター（データ送付先）は JIVROSG 事務局としたが、オンライン登録によるランダム化割付けを確実に行い、かつデータマネージメントの質を担保する観点から、データマネージメントについてはこれを専門とする企業に外部委託することとした。

2.各試験の概要

上記の基本試験デザインをもとに、２年次には以下の５つの緩和 IVR についてランダム比較試験のプロトコールを完成し、試験を開始した。試験の概要は以下の如くである。
①難治性腹水に対するシャント治療の有効性を評価するランダム化比較試験（JIVROSG-0803）
主要評価項目：腹水貯留に伴う症状(NRS)の改善、副次的評価項目：包括的 QOL (EQ-5D、SF-8)の改善、有害事象の内容と頻度、生存期間、予定症例数 40 例、参加施設 14 施設
②有痛性悪性骨腫瘍の疼痛緩和に対する経皮的骨形成術の有効性を評価するランダム化比較試験（JIVROSG-0804）
主要評価項目：背部疼痛症状の改善(NRS,RDQ)、副次的評価項目：包括的 QOL(EQ-5D、SF-8)の改善、背部痛 QOL の改善、有害事象の内容と頻度、生存期間、予定症例数 40 例、参加施設 27 施設
③がんによる消化管通過障害に対する経皮経食道胃管挿入の有効性を評価するランダム化比較試験（JIVROSG-0805）
主要評価項目：症状スコアの改善、副次的評価項目：包括的 QOL (EQ-5D、SF-8) の改善、有害事象の内容と頻度、生存期間、予定症例数 40 例、参加施設 10 施設
④切除不能悪性大腸狭窄に対するステント治療の有効性を評価するランダム化比較試験（JIVROSG-0806）
主要評価項目：症状スコアの改善、副次的評価項目：包括的 QOL (EQ-5D、SF-8) の改善、有害事象の内容と頻度、生存期間、予定症例数 32 例、参加施設 10 施設
⑤悪性大静脈症候群に対する金属ステント治療の有効性を評価するランダム化比較試験（JIVROSG-0807 ）
主要評価項目：症状スコアの改善、副次的評価項目：包括的 QOL (EQ-5D、SF-8) の改善、有害事象の内容と頻度、生存期間、予定症例数 32 例、参加施設 17 施設

3.試験の遂行

２年次から３年次にかけては当該臨床試験を継続して行った。各試験の進捗状況は以下の如くである。
①JIVROSG-0803：8 例登録。症例登録継続中。
②JIVROSG-0804：1 例登録。症例登録継続中。
③JIVROSG-0805：13 例登録。症例登録継続中。
④JIVROSG-0806：1 例登録。症例登録継続中。
⑤JIVROSG-0807：10 例登録。症例登録継続中。

D. 考察

緩和 IVR は欧米でも行われているが、前向き臨床試験による評価は皆無である。このため、少ないとはいえ、侵襲的治療である IVR をどのように緩和の段階で活用すべきかという臨床的疑問に対する回答は、現時点で全く得られていない。一方、我が国の現状に目を向ければ、緩和 IVR に対する理解、認識は甚だ不十分であり、またこれを実施できる IVR 医も少ない。このような、現状を打破するためには、緩和ケアにおける IVR の位置づけを明確にすることが必須であり、仮に IVR が緩和ケアにおける標準的治療であることにエビデンスが示されれば、現状を大きく変える原動力となることが期待される。本研究は、このような背景の

もとに、JIVROSG ですでに第Ⅱ相試験までの評価が行われた行われた５つの緩和 IVR について既存治療とのランダム化比較試験により、当該 IVR が標準的治療となり得るかを評価しようとしたものである。緩和 IVR の臨床試験自体が欧米も含めほぼ皆無である状況に鑑みれば、この研究は極めて先進的であり、かつチャレンジングなものと言える。症例登録は遅延しているが、JIVROSG-0804 については、使用する骨セメント製剤の薬事承認、保険収載などへの過渡期にぶつかったという社会的背景や JIVROSG が高度先進医療として行っていた JIVROSG-0703 試験と競合する部分があったことが要因と考えられ、今後症例登録速度が加速することが見込まれる。また、JIVROSG-0806 試験は、もともと困難が予想された試験であり、症例登録期間を延長しても、継続する予定である。他の３試験については、やや遅れてはいるものの、十分に完了が見込まれる状況にある。本試験が完了した暁には、現在混沌としている緩和ケアにおける IVR の位置づけがエビデンスに基づいて示されることとなり、緩和治療の発展に大きく寄与することが期待される。

E. 結論

第Ⅱ相試験までのデータが得られている難治性腹水に対するシャント術、有痛性骨転移に対する経皮的セメント注入術、消化管通過障害に対する経皮経食道胃管挿入術、切除不能悪性大腸狭窄に対するステント治療、大静脈症候群に対するステント治療の５つの IVR について、当該 IVR が緩和ケアにおける標準的治療となり得るかを検証する目的で、既存治療とのランダム化比較試験のプロトコールを作成し、これを行った。試験は未だ進行中であるが、本試験は緩和 IVR を当該緩和治療における標準的治療に位置づけようとする世界で初めてのチャレンジングな臨床試験であり、本試験の結果は緩和ケアの進歩に大きな影響を与えることが期待される。

F. 健康危険情報

なし。

G. 研究発表

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H. 知的財産権の出願・登録状況
1.特許取得
なし
2.実用新案登録
なし
3.その他
なし

II. 研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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III. 研究成果の刊行物・別刷

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

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

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

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

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

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

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

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

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

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

Subjects and Methods

Study Design

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

Patients

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

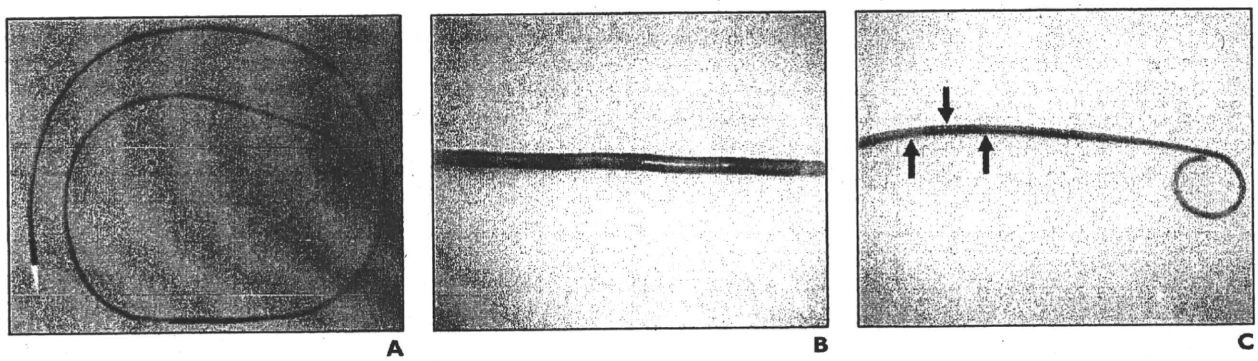

Fig. 1—Transjugular transhepatic peritoneovenous shunt (PVS) catheter.
A, Image shows tapered (5–10-French) transjugular transhepatic PVS catheter.
B, Image shows one-way valve designed to be positioned in right atrium.
C, Image shows pigtail-shaped catheter tip in abdominal portion. Side holes (*arrows*)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

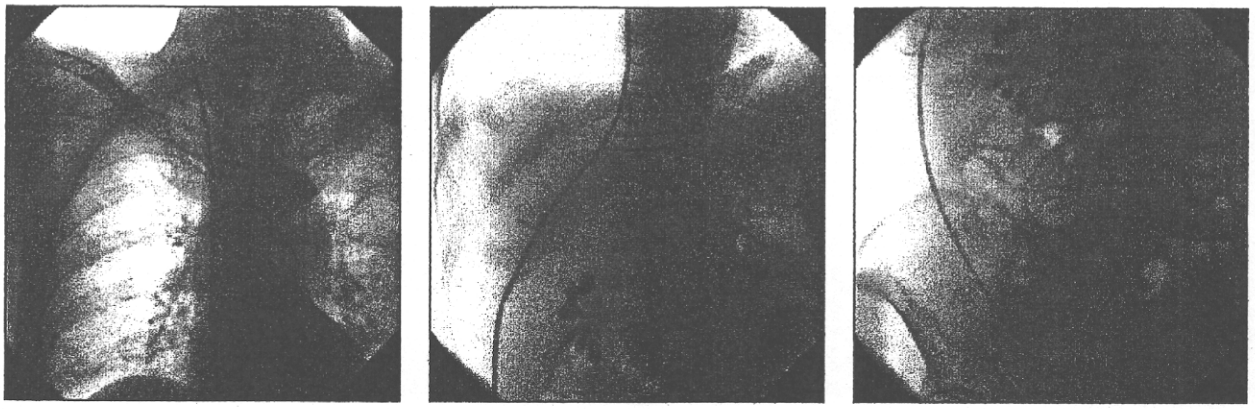

Fig. 2—Radiographs of positioning of transjugular transhepatic peritoneovenous shunt (PVS) catheter.
A, Radiograph shows chest after implantation of transjugular transhepatic PVS catheter.
B, Radiograph shows abdomen after implantation of transjugular transhepatic PVS catheter.
C, Radiograph shows pelvis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

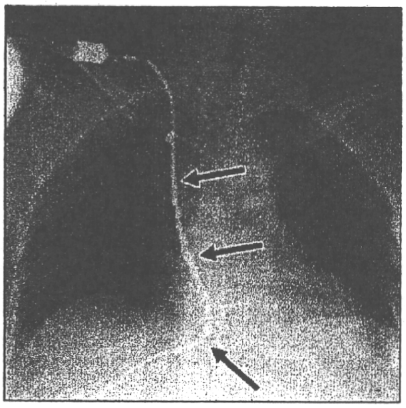

Fig. 3—Fibrin sheath formation around transjugular transhepatic peritoneovenous shunt (PVS) catheter. Angiogram shows tip of transjugular transhepatic PVS catheter at right internal jugular vein. Contrast material stagnated within and around catheter (*arrows*), which is compatible with fibrin sheath,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

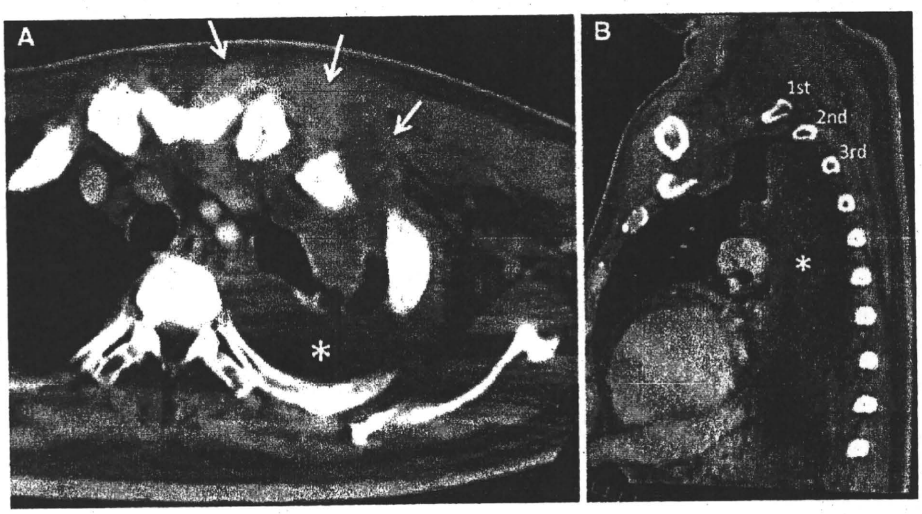

Fig. 1 Axial CT and sagittal reconstruction showing the loculated pleural fluid extending to pulmonary apex in posterior part of thoracic cavity. *Arrows* septic arthritis of left sternoclavicular joint complicated with pyoderma of anterior chest wall. *Asterisk* loculated pleural fluid