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医療機器開発推進研究事業
高度医療技術の効率化及び標準化の開発に関する研究

総括研究報告書

研究代表者　嘉山　孝正

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I. 総括研究報告

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高度医療技術の効率化及び標準化の開発に関する研究

研究代表者　嘉山孝正　国立がん研究センター中央病院　理事長

研究要旨

従前の研究にて開発を進めていた放射線治療計画用 MRI シミュレイターが、本研究とは別途の企業開発により実用化されたため、外科的治療に匹敵する非侵襲的局所治療を行うための高度医療技術の開発、評価に研究内容を変更した。研究の大枠を「局所療法を正確に誘導する画像技術」と「確実な治療効果を挙げ得る局所療法」に大別し、具体的なテーマとして、前者については、「CT、MRI の volume data と患者の体表位置情報から任意穿刺方向の画像を表示する技術」、「磁性体不可の MRI 下で穿刺を誘導する画像技術」、「Adaptive Radiation Therapy のために種々の画像情報を統合する技術」、「ホウ素中性子捕捉療法(BNCT)のための PET-CT 画像による画像支援技術」を、後者については「経皮的凍結療法」、「Electric Poration(ナノナイフ)」、「収束超音波」、「ホウ素中性子捕捉療法(BNCT)」を採り上げ、本年度は、既存の磁気誘導技術を用いた小型穿刺用プローブをプロトタイプの作成、アーチファクトのない MRI 用穿刺針作成の着手、光学式ナビゲーションシステムの開発、放射線治療装置付属のコーンビーム CT 装置で線量分布を表示可能とする CT 値−電子密度変換テーブルの作成、レーザーを用いた体表面位置決め支援システムの開発を行うともに、新しい局所治療法である経皮的凍結療法、収束超音波治療、Electric poration 治療（ナノナイフ）に関する臨床試験の研究計画書を作成した。

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A. 研究目的

ゲノム解明や分子レベルからの創薬によりがんに対する薬物療法は飛躍的に進歩した。しかし、未だ大部分の癌腫において治癒を齎すレベルには達しておらず、治癒を齎す治療法の主軸は依然として侵襲的な外科治療に委ねられているのが現状である。よって、外科治療に匹敵あるいは凌駕する非侵襲的治療法の開発は、がん患者の QOL 向上のみならず、合併症低減や治療期間短縮等に伴う医療費抑制など、超高齢(倫理面への配慮)化社会となりつつある本邦のがん医療全般に好ましい影響を与える点で、極めて重要な課題である。このような非侵襲的治療を可能とするためには、1）局所治療法を正確に病巣に誘導する画像誘導技術、2）病巣において確実な治療効果をあげうる局所治療法、の開発が必須であり、本研究はこのための高度医療技術を開発するとともに、臨床試験により評価し、標準化することを目的とする。

B. 研究方法

画像誘導技術については、経皮的穿刺治療における誘導技術として、1）CT や MRI で得た volume データと患者体表の位置情報より体表面からの任意方向の画像を表示する技術、2）磁性体を持ち込むことのできない MRI 装置内での穿刺を誘導する技術を、放射線治療における誘導技術として、3）種々治療画像の統合による Adaptive Radiation Therapy の技術、4）ホウ素中性子捕捉療法(BNCT)のための PET-CT 画像による画像支援技術、を採り上げ、その開発を行った。また、新しい局所治療技術については、1）経皮的凍結療法、2）収束超音波療法、3）electric poration、4）BNCT を採り上げ、機器導入等、環境が整った経皮的凍結療法、収束超音波療法、electric poration について、その安全性と有効性を評価するための第 I/II 相臨床試験計画を立案した。

これまでの研究については機器開発であり直接的

に患者に関わる部分がなかったが、臨床研究計画書作成にあたっては、ヘルシンキ宣言、臨床試験倫理指針を遵守し、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うこととした。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ている。また、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. 研究結果

I. 画像誘導技術

1）CT や MRI で得た volume データと患者体表の位置情報より体表面からの任意方向の画像を表示する技術

磁気誘導を用いた同様の技術は、すでに穿刺用超音波誘導画像の補助的手段としての機器が臨床応用されているが、その利点を最大限に生かすためには、「標的部位の動きの有無」（呼吸などにより移動する部位か、あるいは、頭蓋内、後腹膜、骨盤腔のように移動の限られた部位か）、ならびに、仮想穿刺ラインを確認するための「確認画像」の2つの点からこの技術応用を再検討すべきと判断された。動きのないない部位における従来の磁気誘導の誤差は臨床的に許容可能な範囲であり、この場合には従来の超音波装置との連動がかえって装置の大型化を招く原因となっており、この点から、磁気誘導単独による装置の小型化、特に穿刺用プローブの小型化を行うこととした。一方、胸部や腹部など動きある部位の穿刺では、例え呼吸同期を行った場合にも必ず一定の誤差が生じること、臨床的には 21G 程度の細い穿刺針の非的中は問題となはならず、その非的中針自体が次の穿刺のガイドに用いられること、反面、その針が特に MR ガイド下ではアーチファクトによりガイドとなり得ないことより、MRI 画像においてガイドとなり得るアーチファクトの少ない穿刺針を開発することとし、これに着手した。

2）磁性体を持ち込むことのできない MRI 装置内での穿刺を誘導する技術

非磁性体のみが許容される MRI 下の誘導画像技術について議論がなされたが、最終的には、MRI 画像が影響を受けない距離からの光学的な誘導以外には現時点で解決可能な技術がないと結論された。これに基づき、レーザービームを用いた装置のプロトタイプを開発した。磁気誘導に比べての最大の利点は誤差が数 mm 以下と少ない点、穿刺部周囲に器具を必要としないため、穿刺手技の障害とならない点が確認されたが、反面、術者の手や穿刺針自体をもビームを遮断する原因となるため、穿刺手技の改良も合わせ、装置の実用化を進める必要のあることが判明した。

3）種々治療画像の統合による Adaptive Radiation Therapy の技術

Coned BeamCT、2方向透視、体表レーザースキャンデータの統合により、CT 撮影なしに Adaptive Radiation Therapy を可能とする技術として、放射線治療装置に付属のコーンビーム CT 装置(CBCT)を用いて線量分布まで表示可能とする、CT 値－電子密度変換テーブルを完成した（従来は、CBCT から CT 値を求めること不可能であったため、別途、治療計画用 CT 撮影を行わなければ線量分布を算出、表示することができなかった）。この過程で、呼吸が CBCT からの電子密度情報に大きく影響することが判明した。あわせて、治療計画用 CT 時と治療時の患者の体形変化を検知可能にするための、レーザービームを用いた体表面位置決め支援システムの開発を行い、プロトタイプを作成した。

4）ホウ素中性子捕捉療法(BNCT)のための PET-CT 画像による画像支援技術

本年度は BNCT 装置の設置には至っていないため、基礎的検討として、熱外中性子の核反応による壁材等の放射化に関する情報収集と放射化の計算を行い、最適なホウ素含有壁材を決定した。また、ターゲットのリチウムの放射化によって発生する大量の放射性ベリリウムの廃棄貯蔵について基礎的検討を行った。

II.局所治療技術

以下に概要を示す各局所治療技術についての臨床試験計画書を作成した。

①腹部・骨盤内実質臓器に対する経皮的凍結治療の第 I/II 相試験（JIVROSG-1101）

目的：切除適応のない腹部・骨盤内実質臓器の悪性腫瘍（すでに保険収載されている小腎がんを除く）に対する経皮的凍結治療の安全性、有効性の評価。

試験方法：日本腫瘍 IVR 研究グループ(JIVROSG)による多施設共同研究として施行。高度医療評価制度での施行を予定。第 I 相試験部分には JIVROSG 3x3 法（Ann Oncol. 20:1943-7, 2009）を使用。主要評価項目を安全性の評価、副次的評価項目を腫瘍壊死効果、腫瘍縮小効果、有害事象の内容と頻度として、目標症例数 23 例、症例登録期間 3 年、全試験期間 5 年を予定。

②有痛性骨軟部・骨盤内腫瘍に対する経皮的凍結治療の第 I/II 相試験（JIVROSG-1102）

目的：既存の治療が不適あるいは不応で、薬物の増量以外に疼痛を軽減する手段のない骨軟部・骨

盤内腫瘍に対する経皮的凍結治療の安全性、有効性の評価。
試験方法：JIVROSG による多施設共同研究として施行。高度医療評価制度での施行を予定。第 I 相試験部分には JIVROSG 3x3 法を使用。主要評価項目を安全性の評価、副次的評価項目を疼痛改善の程度と期間、有害事象の内容と頻度として、目標症例数 23 例、症例登録期間 3 年、全試験期間 3 年 6 ヶ月を予定。
③有痛性後腹膜・骨盤内腫瘍に対する収束超音波治療の第 I/II 相試験（JIVROSG-1103）
目的：既存の治療が不適あるいは不応で、薬物の増量以外に疼痛を軽減する手段のない有痛性後腹膜腫瘍に対する収束超音波治療の安全性、有効性の評価。
試験方法：JIVROSG による多施設共同研究として施行。高度医療評価制度での施行を予定。第 I 相試験部分には JIVROSG 3x3 法を使用。主要評価項目を安全性の評価、副次的評価項目を疼痛改善の程度と期間、有害事象の内容と頻度として、目標症例数 23 例、症例登録期間 3 年、全試験期間 3 年 6 ヶ月を予定。
④腹部実質臓器に対する Electric Poration 治療の第 I/II 相試験（JIVROSG-1104）
目的：切除適応のない腹部実質臓器の悪性腫瘍に対する Electric Poration 治療の安全性、有効性の評価。
試験方法：JIVROSG による多施設共同研究として施行。高度医療評価制度での施行を予定。第 I 相試験部分には JIVROSG 3x3 法を使用。主要評価項目を安全性の評価、副次的評価項目を腫瘍壊死効果、腫瘍縮小効果、有害事象の内容と頻度として、目標症例数 23 例、症例登録期間 3 年、全試験期間 5 年を予定。
⑤骨軟部腫瘍に対する Electric Poration 治療の第 I/II 相試験（JIVROSG-1105）
目的：切除適応のない骨軟部腫瘍に対する Electric Poration 治療の安全性、有効性の評価。
試験方法：JIVROSG による多施設共同研究として施行。高度医療評価制度での施行を予定。第 I 相試験部分には JIVROSG 3x3 法を使用。主要評価項目を安全性の評価、副次的評価項目を腫瘍壊死効果、腫瘍縮小効果、有害事象の内容と頻度として、目標症例数 23 例、症例登録期間 3 年、全試験期間 5 年を予定。

D. 考察

超高齢化社会となりつつある本邦のがん医療においては、治療の非侵襲性が重要な課題であり、薬物療法に大きな期待がもたれている。ゲノム解明や分子レベルからの創薬により薬物療法は飛躍的に進歩しているが、未だ大部分の癌腫において治癒を齎すレベルには達しておらず、また、薬物療法に要する費用は医療全般を圧迫する大きな要因となっている。このため、治癒を齎す治療法の主軸は依然として外科治療であるが、高齢患者に対しては、その侵襲性が問題である。よって、外科治療に匹敵あるいはこれを凌駕する非侵襲的治療法の開発は、本邦のがん医療における危急の課題と言える。本研究は、これを可能とするための高度医療技術を開発するとともに、臨床試験により評価し、標準化することを目的に行われた。

画像誘導技術では、1）CT や MRI で得た volume データと患者体表の位置情報からの任意方向の画像を表示する技術については、既存の技術を生かしながらも従来の補助的手段としての発想から脱却し、標的部位の動きの有無により、より臨床に即した技術への展開を図り、本年度の研究により明確なゴールが提示された。特に、穿刺された非的中針を新たなガイドとする考え方は、従来の工学的側面のみに依存した考え方に臨床的側面からの発想を導入した斬新なものと言える。動きのない部位に用いる小型穿刺用プローブの開発は比較的容易であり実現性が高いが、一方、MRI でアーチファクトの少ない穿刺針の開発は容易でなく、次年度に持ち越された。2）MRI 装置内での穿刺を誘導する技術としてのレーザービームを用いた装置については、ビームを遮断しない穿刺手技の改良を要すものの、すでにプロトタイプで実用可能性が見込まれ、誤差の少ない穿刺誘導用画像として比較的早期での実用化が見込まれる。3）Adaptive Radiation Therapy のための画像技術の統合は、それぞれの技術が一定度の完成域に到達しなければ実現困難なものであるが、放射線治療装置付属の CBCT を用いて線量分布表示可能とする CT 値－電子密度変換テーブルの完成は、極めて大きな前進であり、レーザービームを用いた体表面位置決め支援システムの開発と合わせ、実用化に大きく迫ったと考えらえる。

局所治療技術では、新たな局所治療技術である経皮的凍結治療、収束超音波治療、Electric Poration 治療に関する 5 本の臨床試験計画が作成されたがこれらの治療法は欧米では一部で行われているものの、本邦では小腎がんに対する経皮的凍結治療を除き、いずれも薬事法未承認の治療であり、これを高度医療評価制度による多施設共同研究として行うことの意義は、治療法としての評価のみならず、将来の本邦への導入において大きな意味をもつものと考えられる。くわえて、これらの治療法についての前向き臨床試験による評価は世界的に見てもほとんどなく、科学的意義も極めて大きいと考えられる。なお、BMCT については、病院設置型での導入は世界初であるため、本年度は装置設置に向けての基礎データの収集に終止したが、これも将来 BMCT が世界に普及する上での重要な基礎データになるものと思われる。

E. 結論

外科的治療に匹敵する非侵襲的局所治療を行うための高度医療技術の開発、評価を目的に、「局所療法を正確に誘導する画像技術」と「確実な治療効果を挙げ得る局所療法」のふたつの大きなテーマとして研究を行った。BNCT については機器設置前であるため基礎的検討に留まったが、その他の画像技術については、問題が明確化され、その一部で実用化に繋がる可能性の高い結果を得るに至った。また、新しい3つの局所治療技術について、5つの臨床試験計画書を作成し、科学的評価を行うための準備を完了した。

F. 健康危険情報

なし。

G. 研究発表

1.論文発表

（主任研究者）嘉山孝正

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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

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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

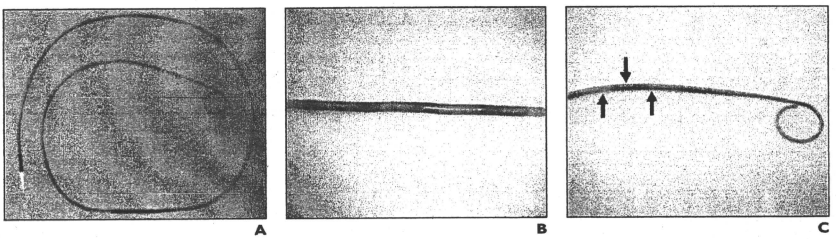

Fig. 1—Transjugular transhepatic peritoneovenous shunt (PVS) catheter.
A, Image shows tapered (5–10-French) transjugular transhepatic PVS catheter.
B, Image shows one-way valve designed to be positioned in right atrium.
C, Image shows pigtail-shaped catheter tip in abdominal portion. Side holes (*arrows*)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

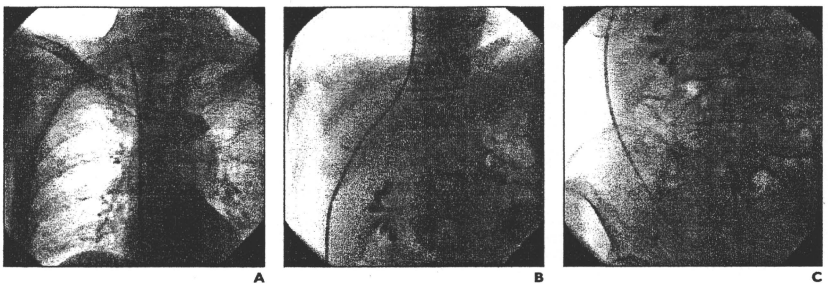

Fig. 2—Radiographs of positioning of transjugular transhepatic peritoneovenous shunt (PVS) catheter.
A, Radiograph shows chest after implantation of transjugular transhepatic PVS catheter.
B, Radiograph shows abdomen after implantation of transjugular transhepatic PVS catheter.
C, Radiograph shows pelvis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

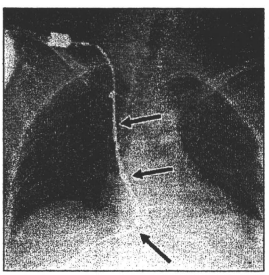

Fig. 3—Fibrin sheath formation around transjugular transhepatic peritoneovenous shunt (PVS) catheter. Angiogram shows tip of transjugular transhepatic PVS catheter at right internal jugular vein. Contrast material stagnated within and around catheter (*arrows*), which is compatible with fibrin sheath,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

Acknowledgments

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