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医療技術実用化総合研究事業

「消化器外科手術における合成吸収糸使用の手術部位感染抑制効果に関する多施設共同並行群間無作為化比較試験」

平成22年度　総括研究報告書

研究代表者　前原　喜彦

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Ⅰ　総括研究報告

厚生労働省科学研究費補助金（医療技術実用化総合研究事業）
総括研究報告書

消化器外科手術における合成吸収糸使用の手術部位感染抑制効果に関する多施設共同並行群間無作為化比較試験

研究代表者　前原喜彦　　九州大学大学院医学研究院
消化器・総合外科　教授

研究要旨　　皮下・腹壁縫合糸については、欧米において絹糸と合成吸収糸の無作為化臨床試験とメタアナリシスで、合成吸収糸の有効性が確立しているが、腹腔内で合成吸収糸を使用することで手術部位感染(Surgical Site Infection：SSI)が減少するというエビデンスは確立していない。本臨床試験の目的は、以下の点である。推奨されている周術期の患者管理を行い、消化器手術の腹腔内での絹糸使用群と合成吸収糸使用群のSSI発生率を比較し、合成吸収糸使用の有効性を検討する。これまでに、上部消化管、下部消化管、肝、膵の臓器別に吸収糸群、非吸収糸群の目標症例数を設定し、2年間の症例登録期間を経てSSI発生率を比較する。effect size（2 群間の治療効果の差）を推定し、将来の大規模臨床第Ⅲ相試験を実施するためにランダム化臨床第Ⅱ相試験を行う。主要評価項目を手術部位感染(SSI)の総発生率とし、副次評価項目は部位別(表層、深部、臓器体腔)感染発生率、SSI発生後治癒確認までの日数、術後在院日数とする。胃切除術270例、大腸切除術270例、肝切除術320例、膵頭十二指腸切除術290例　合計1150例を設定し、2年間の症例登録期間を経てSSI発生率を比較する無作為化臨床第Ⅱ相試験を行う。試験プロトコールの作成の中で、症例の選択基準、除外基準、SSI防止に関する予防策の統一など、試験結果の精度に関する議論を十分に重ねてきた。生物統計家により登録症例数設計を行い、胃切除術270例、大腸切除術270例、肝切除術320例、膵頭十二指腸切除術290例　合計1150例を計画した。インターネットを利用した登録システムであるEDCシステムを準備し、平成21年2月16日より症例登録を開始した。平成23年3月31日現在、胃：271例、大腸271例、肝臓：337例、膵臓：295例、合計1174例が登録された。主要評価項目であるSSI発生割合は、合成吸収糸群/絹糸群で、胃：14.2%/8.3% (p=0.1314)、大腸：17.6%/13.5% (p=0.4031)、肝：12.9%/9.8% (p=0.3774)、膵臓：41.4%/32.4% (p=0.1145)とすべての臓器において有意差は無いが、合成吸収糸群のSSI発生割合が高かった。「胃」「大腸」「肝臓」「膵」の4臓器において示された結果は、従来の考え方である「合成吸収糸を用いることが絹糸を用いるよりSSIの発生を軽減できる」との仮説と正反対の結果であった。「今回用いられた合成吸収糸Vicrylでは絹糸よりもSSIの発生を軽減できる」とは言えない。絹糸に比較して、コストのかかる合成吸収糸VicrylのSSI発生に係る優位性を保証する根拠は否定され、このことは、無制限な医療費の増大を抑制する結果につながると考えられた。

研究分担者氏名及び所属施設
研究者氏名

前原　喜彦	九州大学	消化器・総合外科 教授	國土　典宏	東京大学	肝胆膵・移植外科 教授
土岐祐一郎	大阪大学	消化器外科 教授	小林　道也	高知大学	医療管理学 教授
掛地　吉弘	九州大学	消化器・総合外科 准教授	澤　芳樹	大阪大学	心臓血管・呼吸器外科 教授
鴻江　俊治	九州大学	外科分子治療学講座 教授	高山　忠利	日本大学	消化器外科 教授
武冨　紹信	九州大学	消化器・総合外科 助教	夏越　祥次	鹿児島大学	消化器外科 教授

馬場　秀夫　熊本大学　消化器外科
教授
黒木　保　長崎大学　移植・消化器外科学
講師
吉田　和弘　岐阜大学　腫瘍外科
教授
赤澤　宏平　新潟大学　医療情報部
教授
竹内　正弘　北里大学　臨床統計部門
教授
山中　竹春　九州がんセンター　臨床研究部
室長
山本　雅一　東京女子医科大学　消化器外科
教授
上坂　克彦　静岡県立静岡がんセンター
肝胆膵外科　部長
上本　伸二　京都大学　肝胆膵・移植外科
教授
山上　裕機　和歌山県立医科大学
外科学第2講座　教授
島田　光生　徳島大学　消化器・移植外科学
教授
寺島　雅典　静岡県立静岡がんセンター
胃外科　部長
江見　泰徳　九州大学　消化器・総合外科
特任准教授
小菅　智男　国立がんセンター中央病院
肝胆膵外科　副院長

A. 研究目的

欧米先進諸国では、消化器手術において手術用絹糸は使用されなくなっている。これは、合成吸収糸が発売された当初、多くの動物実験と臨床試験において絹糸と合成吸収糸の比較試験が行われ、皮下、腹壁縫合における合成吸収糸の有効性が証明された結果である。米国CDC(Center for disease control and prevention)の手術部位感染(SSI)防止ガイドライン中に多くの参照文献として掲載されており、ガイドラインの本文には、絹糸の存在下では感染の危険性が増加すると記載されている。手術創に絹糸が存在すると、細菌が付着しやすく感染を助長する(Elek et al.,Br J Exp Pathol 1957)。一方わが国では、依然として手術用絹糸が広く使用されている。皮下・腹壁縫合については、欧米において絹糸と合成吸収糸の無作為化臨床試験とメタアナリシスで、合成吸収糸の有効性が確立している(Weilland et al,Am J Surg 1998;Riet,et al,Br J Surg 2001)が、腹腔内で合成吸収糸を使用することで手術部位感染(SSI)が減少するというエビデンスは確立していない。本臨床試験の目的は、以下の２点である。

1) CDCにより推奨されている周術期の患者管理を行い、消化器手術の腹腔内での絹糸使用群と全合成吸収糸使用群のSSI発生率を比較し、合成吸収糸使用の有効性を検討する。

2) 腹腔内感染発症例において、絹糸使用群と合成吸収糸使用群の治癒期間について比較検討する。

これまでに、九州大学第二外科にて腹腔内での結紮・縫合糸に関する調査を盛り込むSSIサーベイランス(総数903例)がプロスペクティブに施行され、特に大腸手術(386例)において吸収糸群のSSIが絹糸群に比べて有意に低率であったと報告し(吸収糸群13.9%、絹糸群22.4% P=0.03)、吸収糸の有用性を示唆している(Watanabe et al,Surgery Today, 2008)。しかしながら、腹腔内の絹糸使用と合成吸収糸使用における手術部位感染についての臨床比較試験は行われておらず、本臨床試験でエビデンスの創出を図る。絹糸がSSI発生の点で劣っていることを示唆する報告は散見されるが、腹腔内での吸収糸・非吸収糸の使用とSSIに関するmega-RCTは存在せず、どの種類の消化器手術で吸収糸使用がどれくらい有用なのか、本臨床試験で明らかにする意義は大きい。

外科術後感染症で最も多い感染症が手術部位感染(SSI)であり、その発生は患者満足度を低下させるだけでなく入院期間の延長を伴い、医療経済上も大きなマイナスインパクトを与える。本研究は開腹消化器手術における吸収糸の使用が手術部位の感染症発症を抑えるという効果の臨床的エビデンス創出に関する研究である。本研究で手術部位感染症が予防できれば術後の合併症を減らすことが可能となり、消化器手術を受ける国民の医療が安全に行え、在院日数が短縮し、通常の包括医療で済む患者の割合が増す。本臨床試験の結果は、科学的な根拠に基づいた質の高い医療の国民への提供と医療経済の効率化に貢献できると考える。

B. 研究方法

上部消化管、下部消化管、肝、膵の臓器別に吸収糸群、非吸収糸群について目標症例数を設定し、２年間の症例登録期間を経てSSI発生率を比較する。effect size(2群間の治療効果の差)を推定し、将来の大規模臨床第Ⅲ相試験を実施するために臨床第Ⅱ相試験を行う。

「消化管外科手術における合成吸収糸使用の手術部位感染抑制効果に関する多施設共同並行群間無作為化比較試験」

「肝切除および膵頭十二指腸切除における合成吸収糸使用の手術部位感染抑制効果に関する多施設共同並行群間無作為化比較試験」

上記二つの臨床第Ⅱ相試験を行う。

(1) 研究計画および方法

1) 多施設共同並行群間無作為化比較試験

2) 試験材料：滅菌済み手術用絹糸、合成吸収性縫合糸(Polyglactin910,Polydioxanone)

3) 対象疾患：本研究の対象疾患は、以下の通りとする。

胃部分切除術：胃全摘術
合成吸収糸群135例、絹糸群135例
結腸・直腸切除術：
合成吸収糸群135例、絹糸群135例
肝切除手術：
合成吸収糸群160例、絹糸群160例
膵頭十二指腸切除手術：
合成吸収糸群145例、絹糸群145例
割り付け因子
消化管：施設、術式、腹腔鏡補助
肝膵：施設、　　(肝) 肝硬変の有無
　　(膵) 糖尿病の有無

4) 周術期管理法を下記の項目について規定する。術前の患者準備、抗菌薬の予防投与を統一する。手術手技：筋膜には合成吸収糸を使用し、閉鎖式(吸引)ドレーンを用いる。
術後の管理法：手術部位感染が疑われた場合には必ず細菌培養検査を提出する。

5) 評価項目

主要評価項目：手術部位感染(SSI)の総発生率
副次評価項目：部位別(表層、深部、臓器体腔)感染発生率、SSI発生後治癒確認までの期間術後在院日数

6) 手術部位感染(SSI)の評価基準：CDCによる手術部位感染の定義に準拠

①表層切開部創感染
②深部切開部創感染
③臓器体腔創感染

7) 登録の手順

施設登録及び症例登録は、Webシステムを用い、データセンターにおける中央登録制とする。

8) 症例登録期間：平成21年2月16日～

追跡終了日：最終症例登録の1ヶ月後
全研究期間：2年1ヶ月

(2) 研究体制

研究代表者および研究分担者の施設で対象患者の登録をEDCシステムを用いて登録・データセンターに行う。無作為化割付された術式を行い、決められた術後管理を行い手術部位感染率を比較する。割り付け結果の施行確認を手術室で第三者施行。通常直接介助の看護師を想定する。SSIの判定は、割り付け結果を知らないSSI判定能力のある主治医・術者以外の医療者が行う。（他の外科医、ICTリンクナース、ICTメンバー）

(倫理面への配慮) 本試験に関与するすべての者は「世界医師会ヘルシンキ宣言」、および「臨床研究に関する倫理指針」に従う。

説明文書・同意書(様式)および同意撤回書は試験責任医師が作成する。また、作成した説明文書・同意書(様式)は試験開始前に所属する医療機関の倫理審査委員会に提出し、その承認を得る。試験に携わる関係者は被験者の個人情報保護に最大限の努力をはらう。

データセンターが医療機関へ照会する際の被験者の特定は、試験責任医師および試験分担医師が管理する被験者識別コードまたはデータセンターが発行した登録番号を用いて行う。原資料の直接閲覧を行ったモニタリング担当者、監査担当者、規制当局の担当者などは、そこで得られた情報を外部へ漏洩しない。

主任研究者等が試験で得られた情報を公表する際には、被験者が特定できないよう十分に配慮する。

＜プロトコル＞

平成20年度の当該研究課題「消化器外科手術における合成吸収糸使用の手術部位感染抑制効果に関する多施設共同並行群間無作為化比較試験」の採択に際して、当研究のプロトコルの細部に関して推敲を重ねてきた。平成20年9月9日に東京で開催された班会議において、研究代表者、研究分担者により具体的なプロトコル内容について審議を行い、最終的には平成20年11月6日にプロトコルが完成した。各研究分担者へ発送し、現在、各研究分担者施設の倫理審査委員会の承認を得た。また審議の過程で、消化管領域の参加施設が１１施設、肝・胆・膵領域の参加施設が１７施設へと拡大し、より迅速な症例の集積が可能となった。

＜症例登録およびデータマネジメント＞

上記プロトコルの検討・確定とともに、臨床試験遂行にあたり症例登録・データマネジメントを外部機関に委託することを決定した。データマネジメント部分を研究担当者から切り離し、データの質および信頼性を確保する目的である（品質保

証・管理)。イーピーエス株式会社と契約を進め、Ｗｅｂシステム（ＥＤＣシステム）による症例登録、データ収集管理構築を鋭意進めている。また、臨床試験のプロトコルは大学病院医療情報ネットワーク（UMIN）「臨床試験登録システム」に登録を行った。

C. 研究結果

上記進捗状況を踏まえて平成21年2月16日から症例登録、試験治療を開始した。平成21年8月研究協力施設を募集し、17施設の参加を得て、順調に登録が進んだ。胃は平成21年11月までに271例、大腸は平成22年5月までに271例、肝臓は平成21年10月までに337例、膵臓は平成22年6月までに295例、合計1174例が登録された。現在、試験観察期間も全症例で終了している。症例報告データを集計し、データマネジメント作業の上、データ固定した。主要評価項目であるSSI発生割合は、合成吸収糸群/絹糸群で、胃：14.2%/8.3% (p=0.1314)、大腸：17.6%/13.5% (p=0.4031)、肝：12.9%/9.8% (p=0.3774)、膵臓：41.4%/32.4% (p=0.1145)とすべての臓器において有意差は無いが、合成吸収糸群のSSI発生割合が高かった。

D. 考察

本試験は、腹部手術におけるSSIの発生に関して、腹腔内結紮糸として合成吸収糸を用いることが絹糸を用いるよりSSIの発生を軽減できるとの仮説を検証すべき今後の臨床第３相試験を前提として、無作為化第２相試験として実施された。しかしながら、予想した結果とは反対に、SSI発生割合は合成吸収糸群が絹糸群より有意差はないものの高い値を示した。したがって、本試験の結果は第３相試験を実施することを推奨しない。

E. 結果

「胃」「大腸」「肝臓」「膵」の4臓器において示された結果は、従来の考え方である「合成吸収糸を用いることが絹糸を用いるよりSSIの発生を軽減できる」との仮説と正反対の結果であった。「今回用いられた合成吸収糸Vicrylでは絹糸よりもSSIの発生を軽減できる」とは言えない。絹糸に比較して、コストのかかる合成吸収糸VicrylのSSI発生に係る優位性を保証する根拠は否定され、このことは、無制限な医療費の増大を抑制する結果につながると考えられた。

F. 健康危険情報

特記すべきことなし。

G. 研究発表

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特集/大腸癌肝転移に対する治療４．集学的治療 b)術前化学療法併用肝切除
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Ⅱ　研究成果の刊行に関する一覧

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
	該当なし						

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
Kochi M	Irinotecan plus S-1 for liver metastases of gastric cancer.	Hepatogastro enterology.	56	1755-1759	2009
Watanabe Y	Use of a bridging autologous hepatic vein graft for extended right-liver transplantation.	Transplant International	22	1193-1194	2009
Nakayama H	Reconstruction by lateral pancreaticogastrostomy after pancreatoduodenectomy.	The Nihon University Journal of Medicine	51	53-58	2009
Kawai M	How do we predict the clinically relevant pancreatic fistula after pancreaticoduodenectomy?--an analysis in 244 consecutive patients.	World J Surg.	33(12)	2670-2678	2009
Tani M	A pancreaticoduodenectomy is acceptable for periampullary tumors in the elderly, even in patients over 80 years of age.	J Hepatobiliary Pancreat Surg.	16(5)	675-680	2009
Tani M	A prospective randomized controlled trial of internal versus external drainage with pancreaticojejunostomy for pancreaticoduodenectomy.	Am J Surg.	199(6)	759-764	2010
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Yamazaki S	The technical advance and impact of caudate lobe venous reconstruction in left liver: additional safety for living-related donor liver transplantation.	Transplant International.	23	345-349	2010
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Hashimoto D	Can the physiologic ability and surgical stress (E-PASS) scoring system predict operative morbidity after distal pancreatectomy?	Surgery Today	40(7)	632-637	2010
Uchiyama K	Risk factors for postoperative infectious complications after hepatectomy:	J Hepatobiliary Pancreat Sci.	18(1)	67–73	2011
辛島龍一他	特集/大腸癌転移に関する治療　4.集学的治療　b)術前化学療法併用肝切除	外科	72(2)	148-152	2010

Ⅲ 研究成果の刊行物・別刷

Irinotecan Plus S–1 for Liver Metastases of Gastric Cancer

Mitsugu Kochi, Masashi Fujii, Noriaki Kanamori, Teruo Kaiga, Riki Okubo, Ken Hagiwara, Tomoya Funada, Hidenori Tamegai and Tadatoshi Takayama
Department of Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan
Corresponding Author: Dr Mitsugu Kochi, Department of Digestive Surgery, Nihon University School of Medicine, 30-1 Ohyaguchi Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan.
Tel: +81339728111, (Ext. 2472), Fax: +81339578299, E-mail: gann@med.nihon-u.ac.jp

ABSTRACT

Background/Aims: This retrospective study evaluated the efficacy of and compliance with combined irinotecan hydrochloride (CPT-11) and S-1 chemotherapy in patients with liver metastases of gastric cancer.
Methodology: A total of 28 gastric cancer patients with liver metastases received first-line chemotherapy. The response rate, overall survival, and toxicity were evaluated. Fourteen patients were treated with CPT-11+S-1 and they were compared with 14 patients who received *cis*-diamminedichloroplatinum (CDDP)+S-1.
Results: The CPT+S-1 group showed a higher response rate than the CDDP+S-1 group (57.1% [95%CI31.2-83.1%] vs. 42.9% [95%CI16.9-68.8%]; $p<0.44$). The median survival time of the CPT-11+S-1 group was significantly longer than the CDDP+S-1 group (16.1months [95%CI10.5-21.2] vs. 7.3months [95%CI2.2-14.7]; hazard ratio for death, 0.35 [95%CI 0.14-0.83]; $p<0.02$). By multivariate analysis for the treatment with CPT-11+S-1 was identified as an independent prognostic factor. The most common adverse effect of CPT-11+S-1 therapy was leukopenia (57.1%), which was Grade 3 in 3 patients (21.4%). However, all patients recovered rapidly and there were no significant differences of toxicity between the two regimens.
Conclusions: CPT-11+S-1 therapy will achieve significantly longer survival than CDDP+S-1 without severe toxicity in gastric cancer patients with liver metastases.

KEY WORDS: Cancer; Gastric; Metastasis; Liver; Chemotherapy; Prognosis; CPT–11 and S–1

ABBREVIATIONS: Topoisomerase I (Topo I); Median Survival Time (MST); Complete Response (CR); Partial Response (PR); Stable Disease (SD); Progressive Disease (PD)

INTRODUCTION

The prognosis of gastric cancer patients with liver metastases is poor, partly because multiple metastases are common. Palliative surgery cannot be expected to improve the survival of these patients (1-3). Their median survival time (MST) is reported to be 8.8 months (4), and a standard chemotherapy regimen has not yet been established.

Recently, several chemotherapy regimens that employ S-1, CDDP, and CPT-11 have achieved good response and survival outcomes in Japanese patients with gastric cancer, including those with unresectable tumors. S-1 is an oral anticancer drug that contains tegafur, a prodrug of 5-fluorouracil (5-FU), and the modulators 5-chloro-2,4-dihydroxypyridine (gimeracil) and potassium oxonate at a molar ratio of 1:0.4:1. The response rate to S-1 was 53.6% in an early phase II study and 44.6% in a late phase II study performed in patients with advanced gastric cancer, including previously treated patients (5-6). CPT-11 is an anticancer drug that inhibits the activity of topoisomerase I (Topo I) (7). It has achieved a response rate of 18.4% in eligible patients with advanced or recurrent gastric caner (8). Combined therapy with CPT-11 and S-1 has also been shown to be safe and effective, with response rates of 50% or better and an MST of 311-444 days. In particular, the combination of CPT-11 plus S-1 is reported to achieve a high response rate (58%) for liver metastases from gastric cancer when a certain regimen is employed (9-12).

This study was designed to assess the efficacy of treatment with CPT-11 plus S-1 for gastric cancer patients who had liver metastases by comparison with a control group who received CDDP plus S-1.

METHODOLOGY

Patients

Between January 2004 and December 2007, 14 gastric cancer patients with liver metastases were treated with CPT-11 plus S-1 as first-line chemotherapy. The response rate and overall survival of this group were compared with those of a historical control group, which was composed of 14 gastric cancer patients with liver metastases who received CDDP plus S-1 as first-line chemotherapy. The histological diagnosis was established by endoscopic biopsy in all patients. Staging was done by a complete physical examination, complete blood count and biochemical profile, gastrointestinal contrast study, total body computed tomography (CT) scanning, and abdominal ultrasound. Eligibility criteria were as follows: (1) measurable or assessable liver metastases; (2) age <80 years, (3) no prior chemotherapy, (4) no peritoneal metastasis, (5) performance status <3 (Eastern Cooperative Oncology Group scale), (6) ad-

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TABLE 1 Treatment Schedule

CPT-11+S-1	Weekly		
	1	2	3
TS-1 80mg/m^2 (po)	IIIIIII	IIIIIII	
CPT-11 90mg/m^2 (i.v. 2hr)	I	I	

CDDP+S-1	Weekly				
	1	2	3	4	5
TS-1 80mg/m^2 (po)	IIIIIII	IIIIIII		IIIIIII	
CDDP 70mg/m^2 (i.v. 2hr)	I				

TABLE 2 Baseline Characteristics

Clinical features	n (%) S-1+CPT-11 n=14	CDDP+S-1 n=14	*p* value
Gender			0.54
Male	12 (85.8)	13 (7.1)	
Female	2 (14.2)	1 (92.9)	
Age (Year)			
Median [Range]	66 [34-78]	67 [45-78]	
Gastrectomy			0.22
no	8 (57.1)	11 (78.6)	
yes	6 (42.9)	3 (21.4)	
Location			0.69
Upper	5 (35.7)	6 (42.9)	
Middle+Lower	9 (64.3)	8 (57.1)	
Liver metastasis			0.69
single metastasis	5 (35.7)	4 (28.6)	
multiple liver metastasis	9 (64.3)	10 (71.4)	
Lymph node metastasis			0.28
negative	3 (21.4)	1 (7.1)	
positive	11 (78.6)	13 (92.9)	
Histrogical type			0.62
Intestinal	12 (85.8)	11 (78.6)	
Diffuse	2 (14.2)	3 (21.4)	
CEA			0.22
negative	6 (42.9)	3 (21.4)	
positive	8 (57.1)	11 (78.6)	
CA19-9			0.13
negative	9 (64.3)	5 (35.7)	
positive	5 (35.7)	9 (64.3)	

equate hematologic, hepatic, renal and cardiac function (i.e., white blood cell count between 4,000 and 12,000/mm^3, absolute neutrophil count >2,000/mm^3, platelet count >100,000/mm^3, hemoglobin >9.5g/dl, transaminases within twice the upper limit of normal, serum bilirubin <1.5mg/dl, blood urea nitrogen <25mg/dl, and serum creatinine <1.5mg/dl), and (7) provision of written informed consent.

Treatment schedule

The CPT-11 plus S-1 regimen involved administration of CPT-11 (90mg/m^2) as a 2-h intravenous infusion on days 1 and 8, and administration of S-1 (80mg/m^2) once daily on days 1 to 14. This cycle was repeated every 3 weeks (**Table 1**). The regimen for the CDDP plus S-1 group was administration of S-1 (80 mg/m^2) once daily on days 1 to 14 and days 21 to 28, and administration of CDDP (70mg/m^2) as a 2-h intravenous infusion on day 8. This cycle was repeated every 5 weeks.

Evaluation

The response of measurable disease to treatment was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria (13). Tumor dimensions of liver metastasis were assessed by CT scanning. Adverse events that occurred during treatment were assessed according to the Common Toxicity Criteria of the National Cancer Institute (NCI-CTC) (National Cancer Institute 1999).

Statistical analysis

Overall survival curves were generated by the Kaplan-Meier method, and differences between the two groups were compared by the log-rank test. Prognostic factors were investigated by multivariate analysis with the Cox proportional hazards model. Statistical significance was accepted at a $p<0.05$.

RESULTS

Patients characteristics

The baseline characteristics of the patients in the CPT-11 plus S-1 group and the CDDP plus S-1 group are summarized in **Table 2**. There were no statistically significant differences between the two groups with regard to baseline characteristics.

Treatment and dose intensity

The mean number (mean ± SD) of CPT-11 plus S-1 treatment cycles was 11.5 ± 7.17 (range: 2-25), while the mean number of CDDP plus S-1 treatment cycles was 3.43 ± 2.21 (range: 1-7). After the failure of CPT-11 plus S-1 therapy, second-line chemotherapy was administered to 6 patients (docetaxel and/or CDDP).

Tumor response of liver metastasis

Among the 14 patients enrolled in the CPT-11 plus S-1 group, 2 patients achieved a complete response (CR), 6 achieved a partial response (PR), 4 showed no change (SD), and 2 had progressive disease (PD). The response rate was 57.1% (95% confidence interval (95%CI): 31.2-83.1%) (**Table 3**). In the CDDP plus S-1 group (n=14), 1 patient achieved CR, 5 achieved PR, 1 showed NC, and 8 had PD. The response rate was 42.9% (95%CI: 16.9-68.8%). There was a higher response rate with the CPT-11 plus S-1 regimen, but the difference was not significant (p<0.44).

Overall survival

The MST of the CPT-11 plus S-1 group was 16.1 months (95%CI: 10.5-21.2), while that of the CDDP plus S-1 group was 7.3 months (95%CI: 2.2-14.7) (**Figure 1**). Patients in the CPT-11 plus S-1 group showed significantly longer survival than those in the control group (hazard ratio for death, 0.35 (95%CI 0.14-0.83); p<0.02).

According to the results of multivariate analysis, treatment with CPT-11 plus S-1 was identified as an independent prognostic factor (**Table 4**).

Toxicity

All patients in the CPT plus S-1 received the complete regimen of chemotherapy as scheduled. As shown in **Table 5**, the most common adverse effects of CPT-11 plus S-1 were gastrointestinal toxicity (71.4%). Eight patients (57.1%) developed leukopenia of Grade 2 or more, and three patients (21.4%) had Grade 3 leukopenia. However, these patients recovered promptly after receiving granulocyte-colony stimulating factor (G-CSF). There were no significant differences of toxicity between the two regimens.

DISCUSSION

In this study, treatment with CPT plus S-1 achieved higher response rate and significantly better survival than CDDP plus S-1 without severe toxicity in gastric cancer patients who had liver metastases. Surgery may also provide better local control and prolong survival by tumor debulking in patients with advanced gastric cancer (14-15), but it is less effective in patients with very advanced disease and palliative surgery is unlikely to prolong the survival of such patients (16). In particular, the prognosis of gastric cancer patients with multiple liver metastases is still very poor (1-4).

Recently, several chemotherapy regimens have been developed based on the concept of biochemi-

TABLE 3 Tumor Response of Liver Metastasis

	n (%)				
CR	**PR**	**SD**	**PD**	**RR**	
CPT-11+S-1	2 (14.3)	6 (42.9)	4 (28.6)	2 (14.3)	8 (57.1)
CDDP+S-1	1 (7.1)	5 (35.7)	1 (7.1)	7 (50.0)	6 (42.9)

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; RR=response rate; CI=Confidence interval

TABLE 4 Multivariate Analysis

Clinical features	**Risk ratio**	**95%CI**	***p* value**
CA19-9			0.0003
negative	1		
positive	29.1	4.6-182.9	
Histrogical type			0.01
diffuse type	1		
intestinal type	12.5	1.8-85.6	
CPT-11+S-1			0.01
yes	1		
no	9.6	1.7-85.6	
CEA			0.01
negative	1		
positive	8.9	1.6-48.3	
Gastrectomy			0.19
no	1		
yes	4.2	0.5-36.9	
Lymph node metastasis			0.41
negative	1		
positive	4.2	0.1-140.9	
Gender			0.39
Female	1		
Male	6.7	0.1-495.2	
Age			0.67
>68	1		
≤68	1.4	0.3-6.4	
Location			0.71
Middle+Lower	1		
Upper	1.2	0.3-3.9	
Liver metastasis			0.97
single metastasis	1		
multiple liver metastasis	1.02	0.3-3.9	

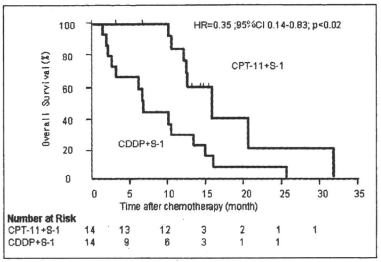

FIGURE 1 Survival of patients in the CPT-11+S-1 group and control group. Patients in the CPT-11+S-1 group had a significantly better survival than those with control group ($p<0.02$)

cal modulation, and have achieved a good clinical response in patients with gastric cancer. S-1 is a fluoropyrimidine that inhibits dihydropyrimidine dehydrogenase (DPD), and it has achieved the highest response rate among many oral anticancer agents in patients with unresectable advanced gastric cancer. Several phase I/II studies of combined therapy with CDDP plus S-1 that indicated a better efficacy have been performed in Japan and the USA (17-18). In these studies, the combination achieved a response rate of 74% and a median survival time of 383 days (18). The improved survival was suggested to be the result of a stronger effect on lymph node metastases (6, 17). Neoadjuvant chemotherapy with CDDP plus S-1 has also been examined in patients with metastatic disease involving more than 5 lymph nodes (19). It was reported that AFP-producing gastric cancer is characterized by frequent liver metastasis and can be treated successfully by preoperative combination chemotherapy (21-22). However, other studies have shown that a significant survival benefit is not achieved by chemotherapy in patients with liver metastases of gastric cancer (6, 17, 18). CPT-11 is an anticancer drug that inhibits topoisomerase I (Topo I) (7). Combined therapy with CPT-11 plus S-1 was developed in Japan and a higher response rate was reported (9-12). In phase I/II studies, this combination achieved a response rate of 62% and a median survival time of 444 days (11). Such results indicated that the efficacy of CPT-11 plus S-1 therapy was comparable to that of CDDP plus S-1. Especially in patients with renal dysfunction, CPT-11 plus S-1 could be recommended over CDDP plus S-1 therapy.

From 2002, we began using CDDP plus S-1 as first-line therapy for liver metastases of gastric cancer. However, the response rate was only 42.9%, which was lower than reported previously and the survival benefit achieved was not satisfactory. On the other hand, we noted a good response and better survival when CPT-11 plus S-1 was used as first-line treatment in patients with renal dysfunction. Therefore, we have applied this regimen as first-line treatment for liver metastases of gastric cancer since 2004. This study showed that the CPT-11 plus S-1 regimen caused fewer adverse events (21.4%) and achieved a better response rate (57.1%) in patients with liver metastases of gastric cancer, while also improving survival. In fact, the cumulative survival rate of the CPT-11 plus S-1 group was significantly better than that of the CDDP plus S-1 group (hazard ratio for death, 0.35 (95%CI 0.14-0.83); $p<0.02$). Prolongation of survival by this regimen may be explained by the chemosensitivity of liver metastases from gastric cancer to CPT-11. Treatment with CPT-11 plus S-1 was identified as an independent prognostic factor by multivariate analysis, suggesting that treating liver metastases may improve the prognosis of gastric cancer patients. To our knowledge, this is the first report in which survival was compared between CPT-11 plus S-1 and CDDP plus S-1 regimens.

The present study conclude that CPT-11 plus S-1 therapy is effective against advanced gastric cancer and improves the prognosis. Curative surgery may also become possible after CPT-11 plus S-1 therapy, resulting in long-term disease-free survival. Moreover, this regimen could be improved further by adding other new anticancer drugs such as docetaxel, oxaliplatin, or molecular-targeting agents.

TABLE 5 Adverse Events of Chemotherapy

n(%)	CPT-11+TS-1		CDDP+TS-1	
	All grades	Grade3	All grades	Grade3
Leukopenia	8 (57.1)	3 (21.4)	8 (57.1)	1 (7.1)
Noutropenia	8 (57.1)	3 (21.4)	4 (28.6)	1 (7.1)
Thrombocytopenia	0 (0)	0 (0)	4 (28.6)	3 (21.4)
Nausea/Vomit	10 (71.4)	1 (7.1)	9 (64.8)	0 (0)
Diarrhea	4 (28.6)	1 (7.1)	4 (28.6)	0 (0)
Hand-foot skin reaction	4 (28.6)	0 (0)	4 (28.6)	0 (0)
Alopecia	6 (42.9)	0 (0)	2 (14.3)	0 (0)
Liver dysfunction	1 (7.1)	0 (0)	1 (7.1)	0 (0)

Transplant International

LETTER TO THE EDITOR

Use of a bridging autologous hepatic vein graft for extended right-liver transplantation

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Living-donor liver transplantation (LDLT) using a right-liver graft is a routine procedure in adults. The use of an allogenic cryopreserved vein for hepatic vein reconstruction facilitates full vascularization and minimizes graft congestion [1]. However, there is a constant risk of graft shortage in such procedures. In this study, we have reported the use of an autologous hepatic vein extracted from the resected liver of the recipient for overcoming graft shortage during hepatic vein reconstruction.

A 53-year-old man with hepatitis B cirrhosis underwent LDLT; the donor was his 31-year-old son. The graft weighed 740 g, and it included a right hepatic vein (RHV), middle hepatic vein (MHV), middle RHV (mRHV), and inferior RHV (iRHV). We decided to use a cryopreserved iliac vein (length, 65 mm; diameter, 22 mm) as a homograft for reconstructing the hepatic veins. The double inferior vena cava (IVC) method was used to obtain a sufficient length of the cryopreserved vein for anastomosis to the RHV and iRHV [1]. The other short hepatic veins, including the MHV, were to be anastomosed directly to the homograft.

Hepatic vein reconstruction using the homograft was performed on the back table (Fig. 1). The superior end of the homograft was sealed with continuous sutures. End-to-end anastomoses were performed between the inferior forked ends of the homograft and the iRHV and mRHV and between the RHV and the homograft. However, the venous graft was insufficient for direct anastomosis of the MHV to the homograft. Therefore, we used the RHV from the diseased liver as an autologous bridging vein graft.

The recipient's IVC was semi-clamped, and a 5-cm-long longitudinal incision was made. The homograft was incised similarly and anastomosed to the IVC in a side-to-side manner. Computed tomography after transplantation revealed clear enhancement of the hepatic veins, the homograft and the autologous graft. There was no stenosis of the anastomosis (Fig. 2). The patient is doing well 40 months after transplantation.

Living-donor liver transplantation (LDLT) with an extended right-liver graft requires hepatic vein reconstruction with multiple anastomoses, and various procedures

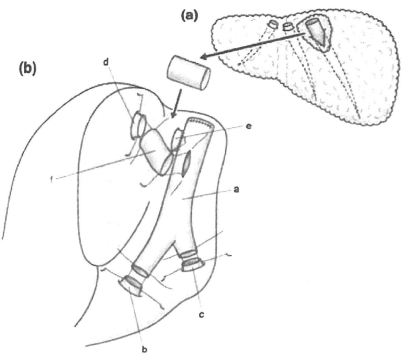

Figure 1 Hepatic venous reconstruction. (a) The RHV was extracted from the resected liver. (b) The anastomosis of the RHV, MHV, iRHV and mRHV to the homograft and the autologous hepatic vein graft was performed on the back table.

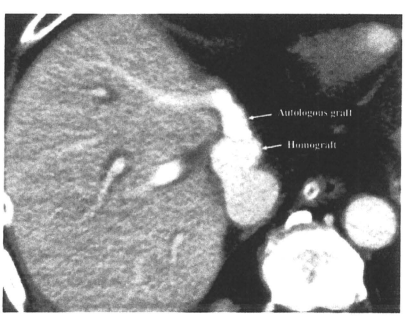

Figure 2 A computed tomographic scan obtained 1 week after transplantation. The autologous graft and homograft are clearly enhanced, suggesting good drainage and patency.

have been described for venous reconstruction [2–4]. Graft congestion can be minimized by reconstructing the short hepatic veins, such as the mRHV and iRHV, along with the MHV and RHV [3]. In our case, the distance between the MHV and homograft was longer than what we had anticipated; therefore, we faced a shortage of the cryopreserved venous graft. In this situation, we considered two options for venous reconstruction: one was a separate, direct anastomosis of the MHV, and the other was the extraction of an autologous venous graft from a hepatic vein of the resected liver or from the recipient's saphenous vein. Procurement of a venous graft from the resected liver is a less invasive and more convenient procedure. However, extraction of an autologous graft from the saphenous vein is recommended if the resected liver is carcinomatous. We have successfully used a similar bridging autologous graft for portal vein reconstruction [5].

Thus, a bridging autologous hepatic vein graft extracted from the resected liver is a convenient alternative graft for hepatic venous reconstruction in LDLT.

Yoshifumi Watanabe,[1] Tadatoshi Takayama,[1]
Shintaro Yamazaki,[1] Osamu Aramaki,[1]
Masamichi Moriguchi,[1]
Tokio Higaki,[1] Kazuto Inoue[1]
and Masatoshi Makuuchi[2]
1 Department of Digestive Surgery,
Nihon University School of Medicine
2 Japanese Red Cross Medical Center, Tokyo, Japan

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RECONSTRUCTION BY LATERAL PANCREATICOGASTROSTOMY AFTER PANCREATODUODENECTOMY

Hisashi NAKAYAMA, M.D., Tadatoshi TAKAYAMA, M.D. and
Takao OKUBO, M.D.

Department of Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan
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RECONSTRUCTION BY LATERAL PANCREATICOGASTROSTOMY AFTER PANCREATODUODENECTOMY

Hisashi NAKAYAMA, M.D., Tadatoshi TAKAYAMA, M.D. and
Takao OKUBO, M.D.

Department of Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan
(Received February 16, 2009: Accepted March 23, 2009)

Radical resection by pancreatoduodenectomy and decompression of the sclerotic pancreatic duct is a requisite treatment for patients with cancer of the head of the pancreas complicated by chronic pancreatitis. This report describes a novel technique involving side-to-side pancreaticogastrostomy following pancreatoduodenectomy to effect decompression of the pancreatic duct in such patients. The procedure involves the initial opening of the pancreatic duct by means of a longitudinal incision, followed by incision of the posterior gastric wall and side-to-side anastomosis of the pancreas with it. The technique offers a safe method of reconstruction after radical resection of pancreatic cancer and, as a surgical therapy for chronic pancreatitis, can effectively improve patient quality of life.

Introduction

For patients with chronic pancreatitis accompanied by intrapancreatic ductal stone, protein plaque, and chronic pain, the most common drainage procedure involving lateral pancreaticojejunostomy is known to be effective.[1,2] Furthermore, cancer of the head of the pancreas may occasionally develop in patients with chronic pancreatitis,[3] and pancreatoduodenectomy (the Whipple procedure) is indicated. This report describes a novel technique that employs lateral pancreaticogastrostomy to bring about an effective decompression of the pancreatic duct after pancreatoduodenectomy in patients with cancer of the head of the pancreas complicated by chronic pancreatitis.

Surgical Technique

Our procedure is indicated for patients with cancer of the head of the pancreas, together with a dilated main pancreatic duct due to chronic pancreatitis, and/or intraductal calculi. Radical resection of the cancer by pancreatoduodenectomy and

Reprint requests to: Hisashi Nakayama, M.D., Department of Digestive Surgery, Nihon University School of Medicine, 30-1 Oyaguchi kami-cho, Itabashi-ku, Tokyo 173-8610, Japan. Tel.: +81-3-3972-8111, Fax.: +81-3-3957-8299. E-mail: hnakayam@med.nihon-u.ac.jp.