inotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol 2007 ; 25 : 1670-1676.

11) Cassidy J, Clarke S, Diaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 2008 ; 26 : 2006-2012.

12) Grothey A, Hedrick EE, Mass RD, et al. Response-independent survival benefit in metastatic colorectal cancer: a comparative analysis of N9741 and AVF2107. J Clin Oncol 2008 ; 26 : 183-189.

13) Doi T, Boku N, Kato K, et al. Phase I/II study of capecitabine plus oxaliplatin (XELOX) plus bevacizumab as first-line therapy in Japanese patients with metastatic colorectal cancer. Jpn J Clin Oncol 2010 ; 40 : 913-920.

14) Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2009 ; 27 : 663-671.

15) Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009 ; 360 : 1408-1417.

16) Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010 ; 28 : 4697-4705.

17) Bokemeyer C, Bondarenko I, Hartmann JT, et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Ann Oncol 2011 Jan 12, published on line.

18) Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg 2006 ; 243 : 1-7.

19) Kesmodel SB, Ellis LM, Lin E, et al. Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery for colorectal cancer liver metastases. J Clin Oncol 2008 ; 26 : 5254-5260.

20) Vauthey JN, Mentha G, Terris B. et al. Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. Histopathology. 2010 ; 56 : 430-439.

21) Adam R, Wicherts DA, de Haas RJ, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? J Clin Oncol 2009 ; 27 : 1829-1835.

Summary

A novel strategy for liver metastases from colorectal cancer

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Control of the liver metastases is essential to improve the prognosis of patients with colorectal cancer. The EORTC40983 trial showed that perioperative chemotherapy with FOLFOX4 for resectable liver metastases from colorectal cancer could improve the prognosis compared with surgery alone. Since this trial was published, perioperative chemotherapy for resectable liver metastases has been recommended in the clinical practice guidelines of the National Comprehensive Cancer Network (NCCN). In the Japanese guideline, it is explained that perioperative chemotherapy should be performed in a clinical trial designed adequately because the safety in the Japanese population has not been confirmed.

Chemotherapy with molecular targeting agents is widely accepted for unresectable liver metastases from colorectal cancer. Several trials have reported that chemotherapy with a molecular targeting agent can downsize tumor for curative resection, and the conversion rate from unresectable to resectable after chemotherapy is 10～15%.

Thus it is expected that surgery combined with the latest chemotherapy can increase resectability and improve the prognosis of patients with liver metastases.

セミナー

がん診療における漢方の役割

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はじめに

がん診療における漢方薬の役割については，最近の臨床試験の実施などから得られたエビデンスそして分子レベルでの薬理機構の解明により，科学的根拠に基づいた医療貢献の可能性が明らかになりつつある。一方，多種類の漢方薬全般においてしっかりとした知見が得られるには，相当の時間を要する状況にもある。したがって，今日，提示されている約20がん種のがん診療ガイドラインにおいて，漢方薬の使用に関しての推奨度AあるいはBとして示されているのは必ずしも十分とは言い難いのが現状である（表1）。一方で，がん医療上の漢方薬の有用性を示唆する報告は急増しており，国内外のがん診療の専門家，指導者の間でのコンセンサスが形成された内容は少なくない[1]。またその薬理作用に関する解明の成果が，高名なジャーナルにpublishされるなど[2,3]，今後の臨床展開に期待が寄せられ，がん診療の支持療法あるいは緩和医療において大きな役割を果たすことになるものと考えられる。厚生労働省の「がん診療ガイドラインの作成（新規・更新）と公開の維持およびその在り方に関する研究」や「臓器別の学術団体によるガイドラインの新規作成・更新への努力」などにより，多くのガイドラインが存在している。薬剤師にあってはこれらの知見を掌握するとともに，がん医療現場へ正確で有益な漢方薬の最新情報提供を果たしうると，他の医療従事者，特に医師，看護師を介して，そして誰よりも患者へ光明を投じる機会が多くなりうると考えられる。チーム医療が推進される中で，がん薬物療法チーム，栄養サポートチーム，緩和医療チーム，在宅医療チームなどにおいて，薬剤師の役割に大きな期待が寄せられている。本稿ではがん医療における漢方薬の位置づけの概要を掌握していただき，チーム医療の一貫として貢献していただきたく，がん医療における漢方薬の有用性が示唆されている内容の一部を紹介をさせていただく。

表1　漢方薬記載のあるがん関連症状・徴候関連ガイドライン

推奨度	診療ガイドライン
A	心身症，男性下部尿路症状
B	肝がん，呼吸器感染症，前立腺肥大症
C	抗がん剤適正使用，NASH-NAFLD，ペインクリニック，がん疼痛治療

がん医療における漢方薬の役割と意義

1．がん診療におけるチーム医療と漢方薬の関わり

がん診療におけるチーム医療については，米国MDアンダーソン病院のそれがよく紹介されている。しかし，米国の医療施設全体に同様のチーム医療が行き渡っているかというと，必ずしもそうとは言えないのが実情のようである。本邦でもチーム医療の有用性に関するコンセプトの認識を深め，その普及が図られた。近年では保険診療支払において緩和医療，栄養サポートそしてがん薬物療法においてはその行為に加算が認められるに到っている。その結果として，一人一人の患者を中心とした集学的医療（図1）に配慮が成され，客観性ある医療管理と高レベルの知識・技術の提供が可能となっている。北島による，「日本型チーム医療のひとつの理想像」

Key words　がん／漢方／ガイドライン／有害事象／エビデンス

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として提言した内容は注目すべき点がある[4]。すなわち，臨床病期や医療提供段階別のチーム医療が望ましく，その形の例として，①診断を中心としたチーム，②治療を中心としたチーム，③リハビリテーション・精神的支援を中心としたチーム，④在宅医療・緩和医療を中心としたチーム，を提案した。これらのチーム間において医療提供専門スタッフによる柔軟な連携構築が成されることにより，患者への貢献度は膨らむことが推察されよう。このような本邦のチーム医療の推進の中で，先ず図2において，実際には既に高頻度に用いられているであろう代表的な漢方薬を，チーム医療別に概略的に紹介し入門としたい。

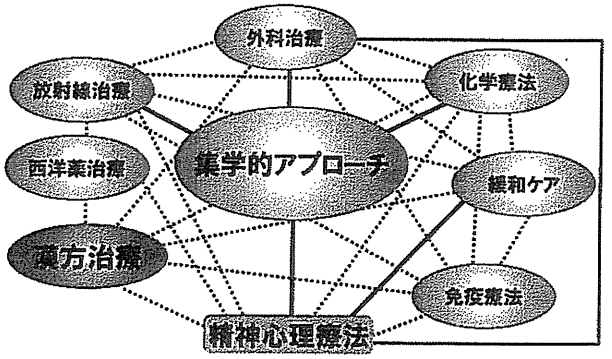

図1　集学的がん治療の在り方

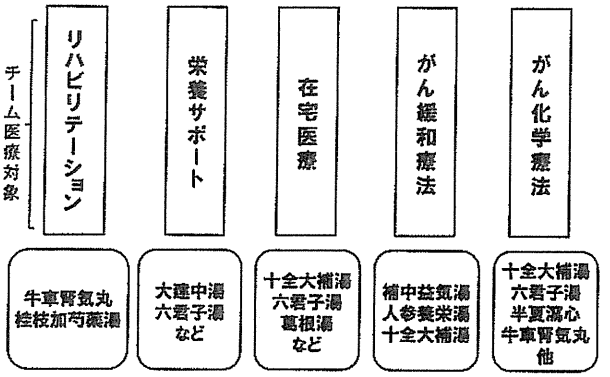

図2　チーム医療 ―薬剤師の役割―

2．がん患者の代表的症状と漢方薬の役割

がん患者の症状については，がん種や病期，あるいは転移巣の有無や転移部位によって異なる。表2にその代表的な症状と治療に用いられている代表的な漢方薬を列記した。併せて臨床医学的に認知されている薬理作用についても紹介した[5]。尚，ここに紹介した漢方薬以外にも有用性の示唆されている漢方薬は多く存在するが，使用頻度が少ないためここではその紹介を割愛させていただく。

今後，漢方薬については臨床症状別に解説されるなどの解り易い処方ガイドラインが公表されることが望ましい。さらには個別化医療における究極ともいえる個人の病態に対する有用性を判定しうる簡易な漢方適用決定(診断)法の開発，そして西洋薬を同じ土台に載せての有用性の比較あるいは選択基準について情報公開が成されていくことが望ましい。現状では，患者の症状緩和のために，特徴を生かした活用を図り，QOL向上と生命の尊厳に結びつく医療の実践に適用させたいものである[6]。

3．抗がん剤治療における漢方薬の役割

抗がん剤の継続投与完遂例では，生命予後延長効果が得られるとのエビデンスは衆知のことである。一方，抗がん剤投与に伴う有害事象の発生頻度は高く，時に有害事象が重症化することもあり，患者のQOLの維持・改善そして生命をおびやかす病態発生からの回避への努力は，医療者の絶対的任務あるいは責務といえる。発生頻度の高い有害事象を表3

表2　がん患者の症状対応に用いる漢方薬

症状	漢方薬	他の薬理作用
全身倦怠感	十全大補湯	免疫力強化・QOLを改善・副作用軽減全般
	補中益気湯	食欲不振改善・術後の体力改善
嘔気・嘔吐	六君子湯	がん術後の消化器症状（消化管運動調節）特に食道・胃移行部及び胃運動について改善
	茯苓飲	胃酸の逆流防止 E-G 結合部の接器部運動障害改善
便秘・イレウス	大建中湯	がん術後の消化器症状改善（消化管運動調節），オピオイドによる便秘改善
再発・転移症状	十全大補湯	全身倦怠感改善（QOL 向上），化学療法・放射線治療の有害事象軽減
食欲不振	六君子湯	(上記の“六君子湯の項”を参照)
骨髄抑制	十全大補湯	(上記の“十全大補湯の項”を参照)
腎毒性軽減	十全大補湯	同上
末梢神経障害	牛車腎気丸	化学療法時の神経障害性疼痛軽減（パクリタキセルなど）
下痢	半夏瀉心湯	化学療法（イリノテカン）中の下痢を改善
吃逆	呉茱萸湯	化学療法中の吃逆を改善
口内炎	立効散	(特になし)
消化管出血	田七人参	(特になし)

表3　抗がん剤の有害事象と漢方

有害事象	主たる薬剤	漢方薬
食欲不振・上腹部膨満感		六君子湯
下痢	イリノテカン	半夏瀉心湯
末梢神経障害	オキサリプラチン タキサン系	牛車腎気丸 芍薬甘草湯
全身倦怠感		補中益気湯，十全大補湯，人参養栄湯
筋肉痛		芍薬甘草湯
貧血（骨髄抑制）		十全大補湯
便秘	オピオイド	大建中湯

持木彫人ほか．外科治療．2010，103（6），p.591．より

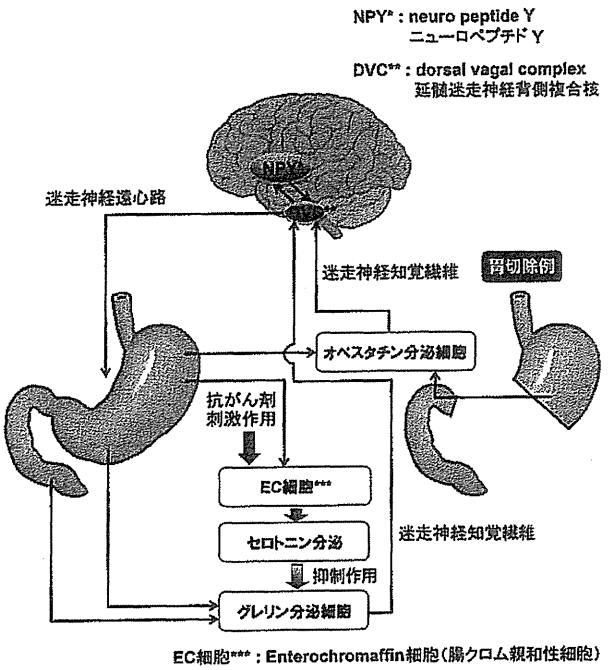

図3　視床下部・下垂体系，内分泌系，免疫系の相関

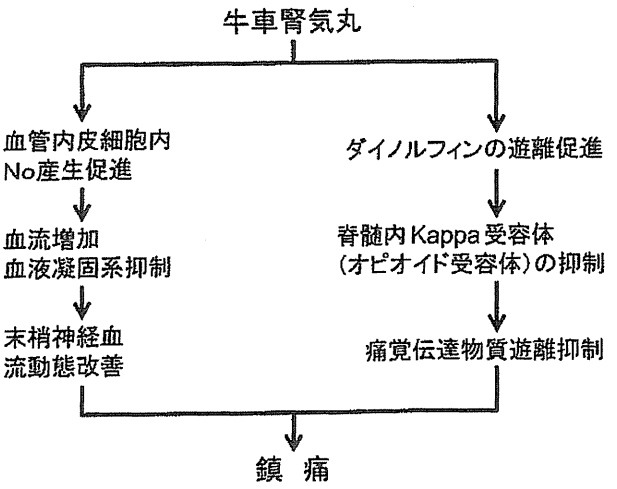

図4　牛車腎気丸の鎮痛作用順序

に紹介する。DNA合成阻害に直接関与する抗がん剤において，共通にみられる有害事象は，消化器症状（食思不振，悪心，嘔吐など）や骨髄抑制（好中球減少，血小板減少，貧血，倦怠感など）が代表的である。発症抑制に有用な漢方薬としては，前者については六君子湯が，後者については補中益気湯，十全大補湯，が紹介されよう。六君子湯については，詳細な臨床研究によりその有用性の根拠が本邦より科学的に証明されており[3]，その関連説明として解り易く図3に示した。半夏瀉心湯の口内炎発生防止作用も良く知られている[7]。一方，イリノテカンによる下痢，オキサリプラチンやタキサン系薬剤による末梢神経障害，のような特異的な有害事象に対しては，牛車腎気丸，芍薬甘草湯の有用性が知られ，前者の薬理機序については図4に示す知見が得られており，動物を用いた研究で明らかにされた[8]。

4．漢方薬と西洋薬の併用における注意点

漢方薬の医療上の長い歴史を振り返ると，単剤服用時の有害事象あるいは二次的有用事象については，既に経験的に明らかである。しかし，西洋薬との併用における注意点については，必ずしも強調されているとは言えない。表4にその代表的な併用に伴う生体反応を紹介した。がん患者において，処方頻度の高い組み合わせとなりうるかという視点からみると，特段，協調すべき組み合わせはないと言えるが，担がん患者の平均年齢を考えると，併存疾患からありうる組み合わせということも常に念頭に置いておかなくてはならない。

表4　漢方薬との併用による生じうる生体反応

漢方薬	他剤	報告内容
安中散	ニューキノロン系抗菌薬	抗菌剤吸収阻害
甘草含有漢方薬	クリチルリチン製剤	偽アルドステロン症発症
柴朴湯	テオフィリン	テオフィリン血中濃度増加
四逆散	ニカルジピン	薬物代謝酵素阻害
小柴胡湯	インターフェロン製剤	間質性肺炎の惹起・増悪
小青竜湯	アストフィリン	花粉症患者の咳症状の持続化
大建中湯	アカルボース	腸閉塞様症状を惹起

5．著者の経験

がん患者に漢方薬を適用する機会の多くは，がん治療における補完的療法，支持療法としてである。その場合の個々の漢方薬の有効率（奏効率）が如何ほどかというような事実を西洋薬と比較をした厳密な研究発表は極めて少ないことが課題として指摘さ

表5　著者の処方内容に関する経験頻度

症状分類	具体的症状	処方高頻度	処方低頻度
全身倦怠感		十全大補湯，人参養栄湯，大建中湯， 補中益気湯	四物湯，八味地黄丸，人参湯，六君子湯， 小柴胡湯，大柴胡湯，真武湯
胃・腸運動改善	消化機能低下 腹水・がん性腹膜炎， 下痢，便秘 過敏性大腸症候群 嘔気・嘔吐 口渇感 口内炎	六君子湯，大建中湯， 柴苓湯（小柴胡湯＋五苓散） 瀉心湯類，半夏瀉心湯，桂枝加芍薬湯 大柴胡湯，大黄 桂枝加芍薬湯 半夏瀉心湯，大柴胡湯 白虎加人参湯，滋陰降火湯 小柴胡湯	桂枝湯，小建中湯 真武湯 潤腸湯，麻子仁丸 半夏瀉心湯，四君子湯 麦門冬湯，牛車腎気丸 茵陳五苓散
呼吸器症状	去痰 咳嗽 虚弱者	小竜湯 人参湯，小建中湯	清肺湯 小青竜湯，柴朴湯，清肺湯
慢性腎障害	軽度機能低下 頻尿・膀胱炎	小柴胡湯，補中益気湯 八味地黄丸（男），人参湯	柴胡桂枝湯
皮膚症状	のぼせ・熱感 下肢だるさ・冷え	黄連解毒湯 八味地黄丸，牛車腎気丸	
筋痙攣	こむら返り	芍薬甘草湯	
末梢循環不全	下半身冷え 手足 更年期障害	牛車腎気丸，八味地黄丸 人参養栄湯 桂枝茯苓丸	 加味逍遥散，当帰芍薬散

れている。著者は，随症（証）による治療方針を立案することが望ましいと考えている。しかし，知識と処方経験により，表5に示したような使用頻度にて通常の処方動向としている。東洋医学的な指摘としては，体型，全身状態，表情などについての「問診」，「望診」，そして「脈診」，「舌診断」，「腹診」そして四肢の症状・徴候を重視すべきとされている。もちろんひとつの“症”に対し有用とされる漢方薬は複数存在し，適切な選択と変更への努力姿勢を忘れてはならない。

漢方薬が経口剤で，担がん症例あるいは外科治療例に適用することなどから，消化管の状況，特に腸内細菌や消化液成分・分泌量の差などは，漢方薬の有用性を左右する。無効時などにおいて，漢方薬の処方変更を常に考えておくこと，前項で触れたように，浮腫，皮膚症状（掻痒感，発疹など），消化管症状（食欲不振，下痢，便秘），肝機能障害の発生などに注意を要する。表5に示した薬剤の使用頻度として高い低いの背景は別にして，全身状態の程度，随症の程度で有害事象の発症程度も異なるようである。ここには一般に広く有用とされていて，処方頻度の高い薬剤を具体例として提示したと理解していただきたい。

全身倦怠感については，十全大補湯，人参養栄湯が多く用いられ，衰弱度が進行している場合には四物湯，人参湯，八味地黄丸などを用いる。

消化器症状については，消化管運動回復に六君子湯を頻用し，“虚証例”には小建中湯を用いている。消化器がん，婦人科がん，泌尿器科がんの腹膜播種・転移に由来する腹水のコントロールには柴苓湯，小柴胡湯が有用とされている。

更年期障害，卵巣機能不全には，加味逍遥散，桂枝茯苓丸，当帰芍薬散を用いる。

6．エビデンスの確立を目指して

がん医療における漢方薬への期待は，米国での臨床研究にもみられる。例えば，Mayo Clinicでは大建中湯を用いた消化管運動改善の有用性を検討しており，FDAの認可を得てさらなる臨床薬理試験を行っている[2]。本邦でもDKT（Daikenchuto）フォーラムという大規模研究組織を形成してエビデンス確立のために広くその臨床応用の有用性および薬理学的機序の解析が進められている。この他，六君子湯についても先に紹介したような消化管ホルモンを中心とした分子レベルでの作用機序の解明により，欧米からの信頼度の高い薬剤として注目されつつある。

おわりに

担がん症例でQOLの向上を目指した補助療法，支持療法を必要とする場合に，症状・徴候別の薬剤使用を原則としていると，多剤投与になりがちである。その回避とともに，有益な処方を目指すために，質の高い情報の収集と提供が望まれる。漢方薬については，多目的応用が可能と考えられるだけに，薬剤師がそのことを示唆できるならば，患者に益をもたらしうる。科学的エビデンスとして確立しつつある漢方薬は少なからず存在するが，多くは不十分な状況にある。したがって，がん診療ガイドラインに明記されていない内容も少なくない。ゆえに，ガイドライン以外の新しい知見に対する正しい理解と普及に務めていただきたい。

文　献

1）Kono T, Kanematsu T, Kitajima M：Exodus of Kampo, traditional Japanese medicine, from the complementary and alternative medicines：is it time yet? Surgery, 146(5)：837-840, 2009

2）Manabe N, Camilleri M, Rao A, et al：Effect of daikenchuto (TU-100) on gastrointestinal and colonic transit in humans. Am J Physiol Gastrointest Liver Physiol, 298(6)：G970-G975, 2010

3）Takeda H, Sadakane C, Hattori T, et al：Rikkunshito, an herbal medicine, suppresses cisplatin-induced anorexia in rats via 5-HT2 receptor antagonism. Gastroenterology, 134(7)：2004-2013, 2008

4）北島政樹：チーム医療のコンセプトは，ただひたすら患者さんのために．漢方医学，35：206-209, 2011

5）安達　勇：漢方薬の取り入れ方のコツ．緩和医療．JOHNS, 26：627-631, 2010

6）伊東俊雅：漢方薬のがん治療・緩和ケア領域での応用．ファルマシア，47：397-402, 2011

7）Kono T, Satomi M, Chisato N, et al：Topical application of Hangeshashinto (TJ-14) in the treatment of chemotherapy-induced oral mucositis, World J Oncol, 1(6)：232-235, 2010

8）Nishioka M, Shimada M, Kurita N, et al：The Kampo medicine, Goshajinkigan, prevents neuropathy in patients treated by FOLFOX regimen. Int J Clin Oncol：Published online：22 January, 2011

UFT/LV 内服療法にて長期 CR が得られている大腸癌術後多発肺転移の 1 例

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〔*Jpn J Cancer Chemother* 38(12): 2520-2522, *November*, 2011〕

A Case of Lung Metastases after Surgery for Colon Cancer Demonstrating Complete Response for More Than Six Years after Treatment with UFT/LV: Yoshiyuki Sakamoto[*1], Akihiko Murata[*1], Motoi Koyama[*1], Hajime Morohashi[*1], Shinji Tsutsumi[*1], Shinnosuke Yonaiyama[*1], Takayuki Morita[*2] and Kenichi Hakamada[*1] ([*1]*Dept. of Surgery, Hirosaki University School of Medicine*, [*2]*Dept. of Surgery, Aomori Prefectural Central Hospital*)

Summary

A 54-year-old femal with cecal cancer underwent Rt. hemicolectomy in December 2000. The lesion was mod, ss, p1 (+), n1, stage IV. The level of CEA increased around August 2002. Abdominal CT revealed a recurrent tumor in the RLQ in July 2003, peritoneal dissemination was suspected. In December 2003, we performed a partial resection of the ileum and transverse colon including initial anastomosis. Lung metastases were found by chest CT in right S4, S5, S9 and S3, S8 in February 2004. Because of experience of severe side effect of intravenous chemotherapy, UFT/LV was administered from February 2004. Chest CT revealed the disappearance of tumor in September 2004, and no signs of recurrence were observed for 65 months. Key words: Multiple lung metastases, UFT/LV, Colorectal cancer

要旨 症例は 54 歳，女性。2000 年 12 月，盲腸癌に対し右半結腸切除術を施行。C，2 型，2.5×3.5 cm，SE，N1，P1，H0，M (−)，Stage IV，Cur B。mod，ss，ly2，v2，n1，p1 であった。2002 年 8 月ごろより徐々に CEA の上昇を認めた。2003 年 7 月，腹部 CT 検査にて右下腹部に腫瘍性病変が認められ，腹膜播種が疑われた。12 月，多発腹膜結節に巻き込まれた回腸・横行結腸・S 状結腸部分切除術を施行。2004 年 2 月の術後 follow up CT にて両肺野に多発する小結節像を認め，肺転移と判断された。化学療法による強い副作用の経験から本人と相談の結果，UFT/LV の内服療法を開始した。9 月の胸部 CT にて腫瘍の縮小を認めた。その後，肺野の結節像はさらに縮小し，2011 年 2 月の胸部 CT では CR の状態を維持している。

はじめに

大腸癌治療ガイドライン 2010 年版では，切除不能進行再発大腸癌に対する化学療法として FOLFOX 療法，FOLFIRI 療法，5-FU/LV 療法に各種分子標的薬を加えたレジメンおよび経口抗癌剤である UFT/LV 療法を推奨している[1]。今回われわれは，高度な有害事象のため経静脈的な化学療法が施行できず，UFT/LV 内服療法にて長期 CR が得られている大腸癌術後多発肺転移の 1 例を経験したので報告する。

I. 症 例

患者: 54 歳，女性。

主訴: 右下腹部痛。

既往歴: 12 歳時，虫垂切除。35 歳時，卵巣茎捻転にて手術。

現病歴: 2000 年 11 月，右下腹部痛を訴え，前医を受診。精査にて盲腸癌の診断を得た。12 月，手術目的に当科紹介となり，右半結腸切除術を施行した。

入院時検査成績: CEA 3.2 ng/dL と正常範囲内であった。

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手術所見: 腫瘍は盲腸に存在し，その周辺に腹膜播種と思われる結節も認めたため，それも一塊として切除した。C，2型，2.5×3.5 cm，SE，N1，P1，H0，M（−），Stage IV，Cur B。

病理組織学的所見: mod，ss，ly2，v2，n1，p1，stage IV（大腸癌取扱い規約第6版）。

術後経過: stage IV，Cur Bであったため，術後補助化学療法として5-FU 750 mg iv/w，UFT 200 mg 2×1/dayを投与した（PMC療法）が，嘔気・嘔吐など高度な有害事象のため2コースで投与中止となった。2002年8月ごろより徐々にCEAの上昇を認めた。2003年7月，腹部CT検査を施行（図1a）。右下腹部に腫瘤が認められたため，腹膜播種が疑われた。10月の腹部CT（図1b）にて右下腹部腫瘍の増大およびCEA 32.0 ng/mLと上昇を認めたため12月，前回吻合部を含めた再発腫瘤を切除（回腸・横行結腸部分切除），およびS状結腸間膜にも腫瘤を認めたため，S状結腸部分切除術を施行した（図2a,b）。術後，CPT-11 80 mg civ/2w，5′-DFUR 400 mg 2×1/dayの投与を行ったが，今回も有害事象のため，わずか3コースで投与中止となった。その後外来followとしていたが，2004年2月の胸部CTにて両側肺に多発する結節像（右肺S4，S5，S9，左肺S3，S8に結節性病変）が認められ，肺転移と判断された（図3a）。過去の化学療法による有害事象の経験から，本人と相談の

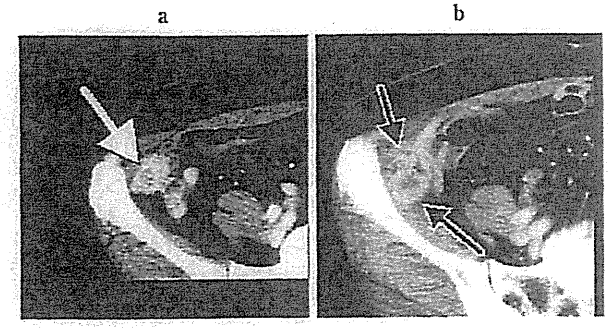

図1 腹部CT像
a: 2003年7月31日。
b: 2003年10月24日。CT像にて腫瘍の増大および周囲への毛羽立ちを認める。

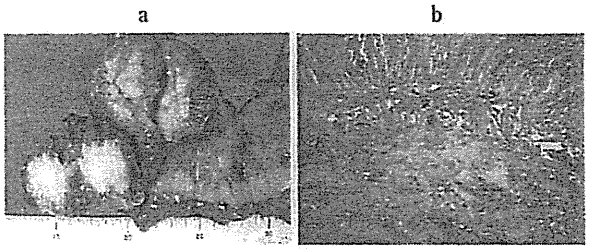

図2 再発手術時の摘出標本（a）および病理組織像（b）

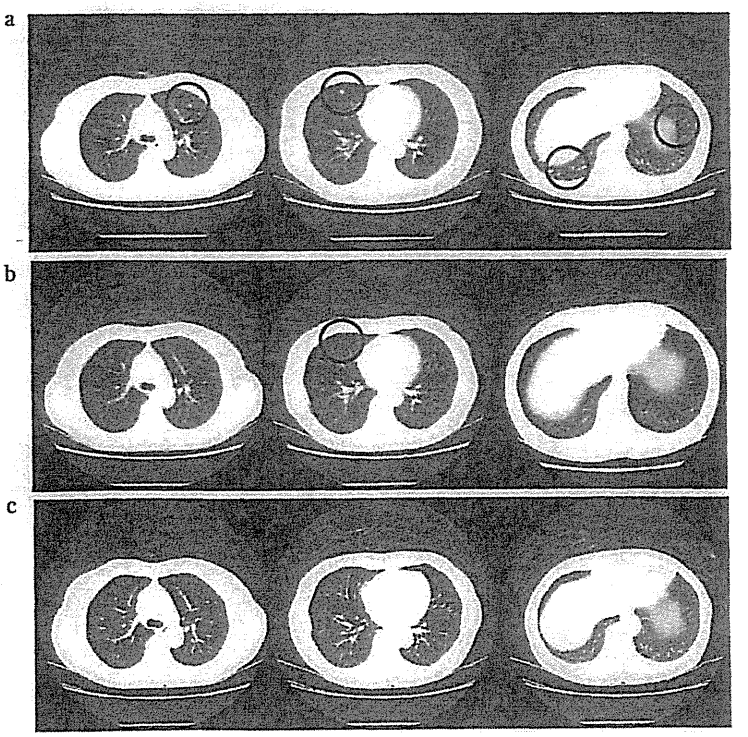

図3 胸部CT像
a: 2004年2月（UFT/LV内服前）。
b: 2004年9月（UFT/LV内服後）。
c: 2011年2月（CRを維持）。

上UFT/LVの内服療法を低用量（UFT 200 mg/LV 50 mg 2×1/day）で開始することとなった。内服開始7か月後の胸部CTでは，腫瘍サイズの縮小が認められた(図3b)。2011年2月の胸部CTでは，画像上CRを維持している（図3c)。

Ⅱ. 考　察

現在，本邦において切除不能進行再発大腸癌に対しては，大腸癌治療ガイドラインによりFOLFOX療法，FOLFIRI療法などに各種分子標的薬を加えた全身化学療法が推奨されている[1]。実際これらのレジメンを使用することにより，Tournigandらの報告[2]では，生存期間の中央値がFOLFOX6→FOLFIRIで20.6か月，FOLFIRI→FOLFOX6で21.5か月と，いずれも20か月を超えている。一方，UFT/LV内服療法は転移性結腸直腸癌の初回治療において，5-FU/LVの静注療法との比較で同等な生存期間が得られ，有害事象の発現頻度はむしろ低い[3]と報告されており，抗腫瘍効果についても同等以上の効果が期待される。有害事象も下痢などの消化器症状がみられることがあるものの，静注療法に比べると軽微であり，再発大腸癌へ行った症例でCR例も散見される[4,5]。自験例では術後補助療法として，初回手術後は5-FU，再発手術後はCPT-11の経静脈的投与を行ったが，いずれもgrade 2～3の有害事象が認められ，継続は困難であった。本人への十分なインフォームド・コンセントの下，UFT 200 mg/day，LV 50 mg/dayを4週間投与1週間休薬の投与法でUFT/LV内服療法を行った。約7か月間の治療期間で腫瘍縮小が認められ，現在では画像上CRを維持している。約7年近くの内服治療を行っているが，以後どの程度治療を継続したほうがよいかは，今後の研究が待たれるところである。また現在のところ，CEAの上昇や腹膜播種などの所見も認められず，FOLFOXやFOLFIRIなどの強力な化学療法を行わなくても，UFT/LV内服療法にて十分な抗腫瘍効果が得られている症例であると思われた。

文　献

1) 大腸癌研究会/編: 大腸癌治療ガイドライン．医師用2010年版，金原出版，東京，2010, pp25-29.
2) Tournigand C, André T, Achille E, *et al*: FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 22(2): 229-237, 2004.
3) Douillard JY, Hoff PM, Skillings JR, *et al*: Multicenter phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 20(17): 3605-3616, 2002.
4) 岡村幹郎，上泉　洋，川村典生・他: UFT/Leucovorin内服療法が著効した大腸癌術後肺転移の1例．癌と化学療法 35(7): 1205-1207, 2008.
5) 亀山仁史，瀧井康公，野村達也・他: UFT/LV療法でCRが得られた再発大腸癌の3例．癌と化学療法 35(11): 1951-1954, 2008.

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Effects of S-1 as a second-line chemotherapy for patients with relapsed pancreatic cancer

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Abstract. Adjuvant chemotherapy with gemcitabine is the standard treatment in Japan for patients who have undergone resection of pancreatic cancer. However, few reports have described suitable regimens for patients who present cancer relapse following adjuvant chemotherapy. In the present study, we retrospectively evaluated the efficacy and safety of S-1, an oral fluoropyrimidine derivative, as a second-line chemotherapy for patients who had suffered relapse of pancreatic cancer following adjuvant chemotherapy with gemcitabine. A total of 51 patients with pancreatic cancer suffered relapse after curative resection and subsequent adjuvant chemotherapy with gemcitabine at our institution. A group of 26 of these patients were administered S-1 orally twice daily after meals at a dose of 80 mg/m^2 for body surface areas for 14 consecutive days, followed by a 7-day rest (S-1 group). The remaining 25 patients received no additional anticancer drugs other than continuation of gemcitabine (GEM/BSC group). During a median follow-up period of 35 months, a significant difference was observed in overall survival (OAS) between the S-1 group and the control group (median OAS, 20.9 vs. 13.7 months; p=0.0157, log-rank test). Furthermore, there was a significant inter-group difference in survival after relapse (SAR) (median SAR, 11.4 vs. 6.20 months; p=0.0025, log-rank test). No increase in grade 3/4 hematological and non-hematological toxicity was observed in the S-1 group. In conclusion, second-line chemotherapy using a combination of S-1 and adjuvant chemotherapy with gemcitabine may be an efficient and beneficial strategy for patients with relapsed pancreatic cancer.

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Key words: second-line chemotherapy, S-1, gemcitabine, pancreatic cancer

Introduction

Pancreatic cancer is one of the most aggressive types of malignancy, with the majority of patients exhibiting surgically unresectable disease at the time of diagnosis (1). Surgical resection is the only potentially curative therapy, but even in resectable cases the overall 5-year survival rate is only 15-20% (2-3). Accordingly, surgical resection, as well as other forms of adjuvant therapy are required for improving the prognosis of such patients.

Since Neoptolemos *et al* reported the significant effect of postoperative chemotherapy on survival time after curative resection for pancreatic cancer (4), a number of studies have focused on adjuvant postoperative chemotherapy for improving the outcome of patients with pancreatic cancer (5-6). Gemcitabine (GEM), a deoxycytidine analogue of arabinosylcytosine, is one of the most promising chemotherapeutic agents to have emerged in recent years. Oettle *et al* reported that adjuvant chemotherapy with GEM was capable of prolonging not only disease-free survival, but also overall survival following curative resection for pancreatic cancer (7). That report, known as the CONKO-001 study, resulted in the adoption of GEM as a standard form of adjuvant chemotherapy following resection of pancreatic cancer. However, few reports have described suitable regimens for patients who suffer relapse after adjuvant chemotherapy.

Thus, we retrospectively evaluated the efficacy and safety of S-1, an oral fluoropyrimidine derivative (8), as a second-line chemotherapy for patients who had suffered relapse after adjuvant chemotherapy with GEM.

Patients and methods

Patients. Between 2001 and 2009, 51 patients with pancreatic cancer treated at our institution suffered relapse after curative resection and subsequent adjuvant chemotherapy with GEM. A group of 26 of these patients received S-1 orally twice daily after meals at a dose of 80 mg/m^2 for body surface areas for 14 consecutive days, followed by a 7-day rest (S-1 group). After the disease was judged to be progressive, 10 patients underwent a third-line chemotherapy. In total, 3 patients were administered paclitaxel at

Table I. Patient characteristics.

	S-1	GEM/BSC	p-value
Patients	26	25	
Gender (male/female)	14/12	14/11	0.903
Age (years)	63.8 (50-78)	68.4 (48-81)	0.091
Pathological stage[a] (I/II/III/IV)	6/18/0/2	4/20/0/1	0.416
T factor (T1,2/T3,4)	3/23	4/21	0.406
N factor (N0/N1)	9/17	14/11	0.125
Operative procedure (head/distal resection)	20/6	18/7	0.938
Resection status (R0/R1)	23/3	22/3	0.959
Recurrence pattern (liver met.[b]/local rec.[c]/dissemination[d])	6/16/4	8/13/4	0.188
Median of disease-free survival (months)	6.40	5.86	0.602

GEM/BSC, gemcitabine group. [a]UICC sixth edition; [b]liver metastasis; [c]local recurrence; [d]peritoneal dissemination.

80 mg/m^2; 4 patients returned to chemotherapy with GEM (at 1000 or 800 mg/m^2); 2 patients were administered GEM and S-1 concurrently; and 2 patients underwent the two-drug chemotherapy with CDDP and CPT-11. The remaining 25 patients were not administered any other anticancer drugs other than continuation of GEM (GEM/BSC group). If GEM was continued after disease recurrence, it was administered at 1000 mg/m^2 bi-weekly for as long as possible. Among the latter 25 patients, 5 (20%) continued to receive GEM, and 20 (80%) were not administered any other anticancer drugs. The differences between the S-1 and GEM groups were analyzed with regard to patient demographics, clinical characteristics, overall survival (OAS), and survival after recurrence (SAR).

Statistical analysis. Demographic and clinical characteristics were expressed as means, medians and ranges (continuous outcomes). Groups were compared using the Wilcoxon rank-sum test for continuous outcomes and the Fisher's exact test for categorical outcomes. Survival distributions were estimated using the Kaplan-Meier method, and groups were compared using the log-rank test. Differences were considered to be significant at $p<0.05$. The data were analyzed using the Stat View software program (Abacus Concepts, Inc., Berkeley, California, USA).

Results

Patient characteristics. Patient characteristics in the S-1 and GEM/BSC groups are shown in Table I. This retrospective study included 51 patients (26 in the S-1 group and 25 in the GEM/BSC group). The following parameters were compared between the groups: gender, age, final stage, T factor, N factor, operative procedure employed, R0/R1 resection rate, and pattern of recurrence. However, the two groups were statistically similar. Disease-free survival periods for the two groups were estimated by the Kaplan-Meier method. The median disease-free survival period was 6.4 months in the S-1 group and 5.9 months in the GEM/BSC group; the difference was not significant (p=0.6019).

Survival. Survival periods after recurrence in the two groups were compared using the Kaplan-Meier method (Fig. 1). The median survival period after recurrence was 11.4 months in the S-1 group and 6.2 months in the GEM/BSC group, with survival in the former being significantly longer than that in the latter (p=0.025). The estimated OAS in the S-1 and GEM/BSC groups at 3 years was 24.7 and 7.6%, respectively, again being significantly longer in the former than in the latter (p=0.0157) (Fig. 2). The median period until progression and the 6-month progression-free survival rate were 5.4 months and 38.5%, respectively (Fig. 3).

Toxicity. The toxicity profiles are shown in Table II. Severe adverse events (grade 3/4) included leukopenia (3.8%), neutropenia (7.7%), anorexia (3.8%), and fatigue (3.8%). No treatment-related death occurred.

Efficacy of S-1 in terms of recurrence pattern. Among the 51 patients studied, 16 suffered relapse with liver or lung metastasis, 10 developed peritoneal dissemination, and 25 had local recurrence. The efficacy of S-1 in terms of the various patterns of recurrence was evaluated (Table III). The median OAS of the patients who developed lung or liver metastasis and peritoneal dissemination was 10.5 and 13.5 months in the S-1 group and 11.6 and 8.7 months in the GEM/BSC group, respectively. A log-rank test using the Kaplan-Meier method revealed significant difference between the two groups. However, the median OAS of the patients who developed local recurrence was 26.9 months in the S-1 group and 17.8 months in the GEM/BSC group (p=0.0469). This result indicates that S-1 was capable of prolonging the OAS in patients who developed local recurrence.

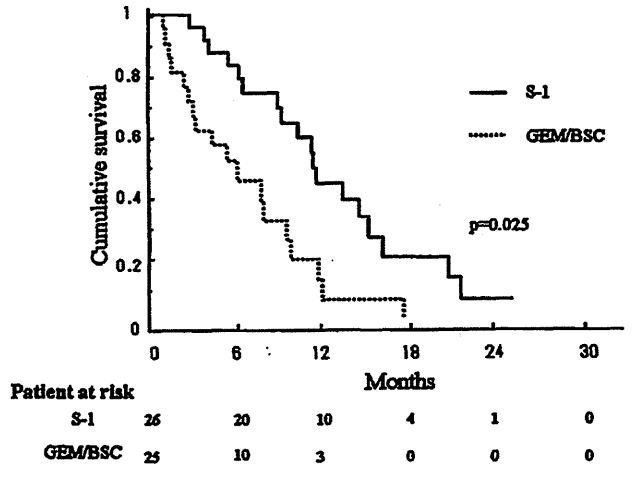

Figure 1. Kaplan-Meier curves for survival periods after recurrence in the S-1 group (solid line) and the GEM/BSC group (dotted line).

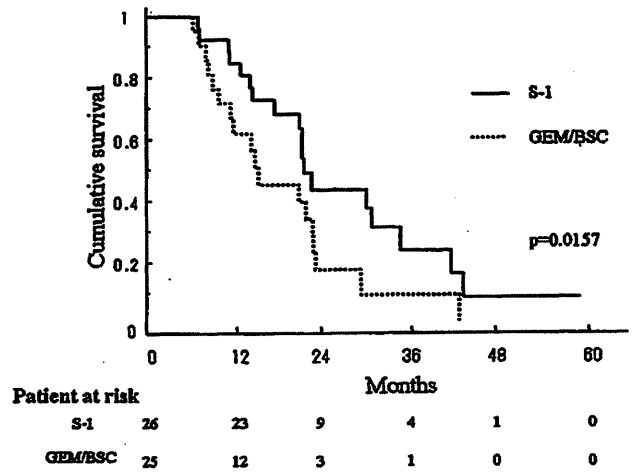

Figure 2. Kaplan-Meier curves for overall survival periods in the S-1 group (solid line) and the GEM/BSC group (dotted line).

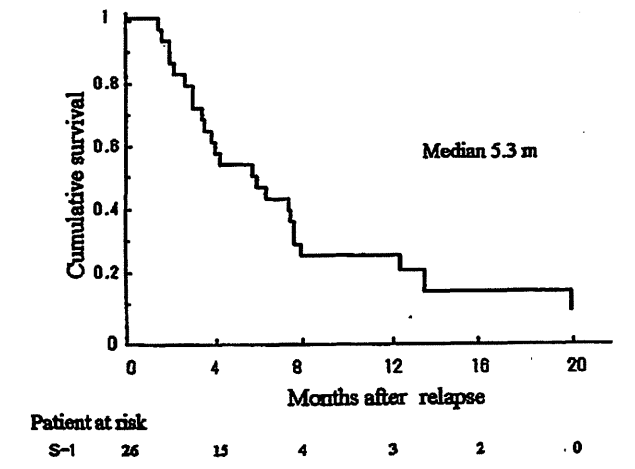

Figure 3. Kaplan-Meier curves for progression-free survival period in the S-1 group. m, months.

Table II. Drug-related adverse effects.

	S1 group (n=26)	
	G1/2 (%)	G3/4 (%)
Hematological toxicity		
Leukopenia	4 (15.4)	1 (3.8)
Neutropenia	3 (11.5)	1 (3.8)
Anemia	1 (0.4)	0 (0.0)
Thrombopenia	0 (0.0)	0 (0.0)
Non-hematological toxicity		
Appetite loss	2 (7.7)	2 (7.7)
Diarrhea	0 (0.0)	0 (0.0)
Nausea	1 (3.8)	0 (0.0)
Vomiting	3 (11.5)	0 (0.0)
Fatigue	3 (11.5)	1 (3.8)

Table III. Efficacy of S-1 in terms of recurrence pattern.

	S-1 MST (months)	GEM/BSC MST (months)	p-value (log-rank)
Liver metastasis	10.5	11.6	0.796
Peritoneal dissemination	13.5	8.7	0.152
Local recurrence	26.9	17.8	0.046

MST, median survival time.

Discussion

In this retrospective study, we investigated the efficacy and feasibility of S-1 as second-line chemotherapy after adjuvant chemotherapy with GEM for patients with pancreatic cancer. Our results show that the administration of S-1 as a second-line chemotherapy was capable of prolonging not only the survival period after relapse (median 11.4 vs. 6.2 months), but also the overall survival period (median 20.9 vs. 13.7 months). Second-line chemotherapy with S-1 combined with adjuvant chemotherapy using GEM may therefore be an efficient and beneficial strategy for pancreatic cancer patients.

Neoptolemos *et al* previously demonstrated that adjuvant chemotherapy was potentially beneficial for patients with pancreatic cancer, whereas adjuvant chemoradiotherapy had a deleterious effect on survival (6). Tani *et al* have reported that adjuvant chemotherapy was an independent factor affecting long-term survival in patients with locally advanced pancreatic cancer who had undergone surgery (10). Oettle *et al* have shown that adjuvant chemotherapy with GEM for pancreatic cancer patients was significantly effective for prolonging disease-free survival (7), and their subsequent study revealed that it was also capable of prolonging OAS (9). In their study, Ueno *et al* have shown that GEM prolonged disease-free survival in patients who had undergone macroscopically curative resection of pancreatic cancer (8). Since these reports

were published, adjuvant chemotherapy with GEM has been the standard treatment in Japan for patients following resection of pancreatic cancer. However, few reports have described the optimal regimens for patients who suffer relapse after adjuvant chemotherapy. In the present study, we retrospectively evaluated the efficacy and safety of S-1, an oral fluoropyrimidine derivative, as second-line chemotherapy for patients suffering disease relapse after adjuvant chemotherapy with GEM.

S-1 is an oral anticancer drug consisting of tegafur, a prodrug of 5-FU, and two biochemical modulators, 5-chloro-2,4-dihydroxypyridine and potassium oxonate (11). S-1 has been shown clinically to exert potent antitumor activity against various solid tumors (12-15). Okusaka *et al* have reported that S-1 is a promising agent for advanced pancreatic cancer, with a response rate of 37.5% and an MST of 9.2 months (16) In our present study, the MST after recurrence was prolonged for up to 11.4 months by S-1 administration. The median progression-free survival time after administration of S-1 was estimated to be 5.4 months. Results show that second-line chemotherapy with S-1 was capable of maintaining progression-free survival for approximately 6 months, but also extended survival for an additional 6 months. This may have been due to the fact that the toxicity of S-1 was sufficiently mild to allow the introduction of third-line chemotherapy.

In general, S-1 should be administered orally for 28 conse-cutive days, followed by a 14-day rest. However, the incidence of adverse reactions tended to be high (83.2%), and 20.3% of all adverse reactions were reported to be of grade 3 or more severe (12,16). Therefore, certain previous reports have proposed that S-1 should be administered for 2 weeks, followed by a 1-week rest, rather than for 4 weeks followed by a 2-week rest. Tsukuda *et al* have reported that, in patients with advanced head and neck cancer, a 2-week administration of S-1 followed by a 1-week rest was safer and more tolerable than 4-week administration followed by a 2-week rest (18). With regard to the administration of S-1 for advanced or recurrent gastric cancer, Kimura *et al* have reported that the rate of adverse reactions was 77% in the 2-week regimen, compared with 93% for the 4-week regimen. They also reported that the total 6-month compliance for S-1 was much more favorable for the 2-week regimen than for the 4-week regimen. These authors concluded that the 2-week regimen may mitigate adverse reactions and prolong the medication period (19). In the present study, S-1 was administered orally for 14 consecutive days, followed by a 7-day rest (2-week regimen). Neither hematological nor non-hematological adverse events were frequent. Severe adverse effects (grade 3/4) were almost not evident, and the medication time was therefore prolonged. This may have contributed to prolonging not only progression-free but also overall survival.

S-1 administration was not capable of prolonging the OAS of patients who had suffered relapse in the form of either peritoneal dissemination or liver or lung metastasis, and was effective only for local recurrence. S-1 administration allowed patients who had suffered local recurrence to survive longer than those who continued with GEM, or received best supportive care. In a phase II study report, Okusaka *et al* stated that S-1 administration was effective against metastatic pancreatic cancer. In their study, although 90% of patients had liver metastasis, a relatively long MST (9.3 months) was observed (16). In the present study, as only a small number of patients developed relapse in the form of liver metastasis, the effectiveness of S-1 may not have reached a significant level.

In conclusion, following not only major surgical treatment, but also cancer relapse, patients experience a relatively severe condition. S-1, an oral anticancer drug, is capable of maintaining a reasonable quality of life under such conditions (20). Since this study revealed a promising anticancer effect of S-1 and a significantly long survival time, S-1 is a potentially beneficial drug for second-line chemotherapy following adjuvant chemotherapy with GEM in patients with pancreatic cancer.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T and Thun MJ: Cancer statistics. CA Cancer J Clin 58: 71-96, 2008.
2. Bradley EL: Long-term survival after pancreatoduodenectomy for ductal adenocarcinoma: the emperor has no clothes? Pancreas 37: 349-351, 2008.
3. Yeo CJ, Cameron JL, Lillemoe KD, *et al*: Pancreaticoduodenectomy for cancer of the head of pancreas: 201 patients. Ann Surg 221: 721-733, 1995.
4. Neoptolemos JP, Dunn AA, Stocken DD, *et al*: Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomized controlled trial. Lancet 358: 1576-1585, 2001.
5. Ueno H, Kosuge T, Matsuyama Y, Yamamoto J, Nakao A, Egawa S, Doi R, Monden M, Hotori T, Tanaka M, Shimada M and Kanemitsu K: A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer. Japanese Study Group of Adjuvant Therapy for pancreatic cancer. Br J Cancer 101: 908-915, 2009.
6. Neoptolemos P, Stocken DD, Friess H, *et al*: A randomized trial of chemoradiation therapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 350: 1200-1210, 2004.
7. Oettle H, Post S, Neuhaus P, *et al*: Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 297: 267-277, 2007.
8. Ueno H, Okusaka T, Ikeda M, Takezako Y and Morizane C: Phase II study of S-1 in patients with advanced biliary tract cancer. Br J Cancer 91: 1769-1774, 2004.
9. Neuhaus P, Riess H, Post S, *et al*: CONKO-001: Final results of the randomized, prospective, multicenter phase III trial of adjuvant chemotherapy with gemcitabine versus observation in patients with resected pancreatic cancer (PC). J Clin Oncol 26: 214, 2008 (suppl; abstr LBA4504).
10. Tani M, Kawai M, Terasawa H, Ina S, *et al*: Prognostic factor for long-term survival in patients with locally invasive pancreatic cancer. J Hepatobiliary Pancreat Surg 14: 545-550, 2007.
11. Shirasaka T, Shimamoto Y, Ohshimo H, *et al*: Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 7: 548-557, 1996.
12. Sakata Y, Ohtsu A, Horikkoshi N, Sugimachi K, Mitachi Y and Taguchi T: Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1M tegafur-0.4M gimestat-1M otastat potassium) in advanced gastric cancer patients. Eur J Cancer 34: 1715-1720, 1998.
13. Saeki T, Takashima S, Sano M, *et al*: A phase II study of S-1 Cooperative Study breast cancer – a Japanese trial by the S-1 Cooperative Study Group, Breast Cancer Working Group. Breast Cancer 11: 194-202, 2004.
14. Fukushima M, Satake H, Uchida J, *et al*: Preclinical antitumor efficacy of S-1: A new oral formulation of 5-fluorouracil on human tumor xenografts. Int J Oncol 13: 693-698, 1998.
15. Ueno H, Okusaka T, Ikeda M, Takezako Y and Morizane C: An early phase II study of S-1 in patients with metastatic pancreatic cancer. Oncology 68: 171-178, 2005.

16. Okusaka T, Funakoshi A, Furuse J, Boku N, Yamao K, Ohkawa S and Saito H: A late phase II study of S-1 for metastatic pancreatic cancer. Cancer Chemother Pharmacol 61: 615-621, 2008.
17. Sugimachi K, Maehara Y, Horikoshi N, *et al*: An early phase II study of oral S-1, a newly developed 5-fluorouracil derivatives for advanced and recurrent gastrointestinal cancers. Oncology 57: 202-210, 1999.
18. Tsukuda M, Kida A, Kono N, Yoshihara T, Hasegawa Y, Sugita M and Chemotherapy Study Group of Head and Neck Cancer: Randomized scheduling feasibility study of S-1 for adjuvant chemotherapy in advanced head and neck cancer. Br J Cancer 93: 884-889, 2005.
19. Kimura Y, Kikkawa N, Iijima S, *et al*: A new regimen for S-1 therapy aiming at adverse reaction mitigation and prolonged medication by introducing a 1-week drug-free interval after each 2-week dosing session: efficacy and feasibility in clinical practice. Gastric Cancer 6: 34-39, 2003.
20. O'Neill VJ and Twelves CJ: Oral cancer treatment: developments in chemotherapy and beyond. Br J Cancer 87: 933-937, 2002.

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Results of Hepatic Arterial Infusion Chemotherapy in Patients with Unresectable Liver Metastases

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Keywords
Unresectable liver metastases · Colorectal cancer · Hepatic arterial infusion chemotherapy, HAIC

Summary
Background: Colorectal cancer most commonly metastasizes to the liver. However, in patients with liver metastases precluding radical resection, we still have no other choice but to depend almost completely on anticancer chemotherapy. We report the results of hepatic arterial infusion chemotherapy (HAIC) in patients with multiple unresectable metastases throughout the liver and likely to develop liver failure in the near future. **Patients and Methods:** A total of 284 advanced colorectal cancer patients were treated. Of these patients, 40 and 24 had synchronous and metachronous liver metastases, respectively. Of these liver metastasis patients, 27 had unresectable metastases. 14 of the patients with unresectable liver metastases (likely to develop liver failure in the near future) but without extrahepatic lesions underwent HAIC. The chemotherapy regimen consisted of 5-fluorouracil 600 mg/m^2 and leucovorin 250 mg/m^2. **Results:** HAIC resulted in a complete response, partial response, stable disease, and progressive disease in 2, 7, 3, and 2 patients, respectively. The 1- and 2-year survival rates were 79 and 50%, respectively. **Conclusion:** Colorectal cancer patients with unresectable liver metastases without extrahepatic lesions and likely to develop liver failure in the near future showed relatively good results with no serious side effects. We suggest that HAIC is an effective treatment in selected patients.

Schlüsselwörter
Nicht resektable Lebermetastasen · Kolorektales Karzinom · Hepatisch intraarterielle Chemotherapie, HIC

Zusammenfassung
Hintergrund: Kolorektale Karzinome metastasieren am häufigsten in die Leber. Bei Patienten mit Lebermetastasen, die eine Radikalresektion ausschließen, ist jedoch die Chemotherapie nach wie vor die einzige Therapieoption. Wir berichten hiermit von den Ergebnissen, die mit der hepatisch intraarteriellen Chemotherapie (HIC) bei Patienten mit multiplen, nicht resektablen Metastasen in der gesamten Leber und bevorstehendem Leberversagen erzielt wurden. **Patienten und Methoden:** Insgesamt wurden 284 Patienten mit fortgeschrittenem kolorektalem Karzinom behandelt. Bei 40 Patienten bestanden synchrone und bei 24 Patienten metachrone Lebermetastasen, die in 27 Fällen nicht resektabel waren. 14 Patienten mit nicht rektablen Lebermetastasen (und bevorstehendem Leberversagen), aber ohne extrahepatische Läsionen erhielten HIC. Das chemotherapeutische Regime bestand aus 5-Fluorouracil 600 mg/m^2 und Leucovorin 250 mg/m^2. **Ergebnisse:** HIC führte zu komplettem Ansprechen, partiellem Ansprechen, Krankheitsstabilisierung bzw. Krankheitsfortschreiten bei 2, 7, 3 bzw. 2 Patienten. Das 1- bzw. 2-Jahres-Überleben waren 79 bzw. 50%. **Schlussfolgerung:** Patienten mit einem kolorektalen Karzinom und nicht resektablen Lebermetastasen, bei denen keine extrahepatischen Läsionen bestehen und baldiges Leberversagen zu erwarten ist, zeigten ein relativ gutes Ansprechen ohne ernsthafte Nebenwirkungen. Wir sind der Ansicht, dass HIC eine effektive Behandlung bei selektierten Patienten ist.

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Introduction

The most commonly involved organ for metastasis and recurrence in colorectal cancer is the liver, which affects the prognosis [1–4]. Surgical removal has the best outcome of all treatments for resectable liver metastases, and chemotherapy is the first-choice therapy for unresectable cases [5–10]. The main administration routes of chemotherapy are systemic administration and hepatic arterial infusion chemotherapy (HAIC). The advantages of HAIC are: i) the concentration of the drug that reaches the tumor is higher; ii) a reduced drug concentration in systemic organs due to drug metabolism in the liver decreases adverse drug reactions, and the maximum dosage can be increased [11–13]. Therefore, it is suggested that the efficacy of HAIC is higher in patients with only liver metastases. We administered HAIC to patients with unresectable liver metastases and no extrahepatic lesions, in whom hepatic failure was likely to occur due to extensive metastases.

Patients and Methods

A total of 284 advanced colorectal cancer patients were treated at the University of Fukui Hospital (Japan) between 2001 and 2005. Of these, 40 and 24 had synchronous and metachronous liver metastases, respectively. Of these liver metastasis patients, 27 had unresectable metastases (synchronous in 20 and metachronous in 7). 14 of the patients with unresectable liver metastases (constituting a prognostic factor) but without extrahepatic lesions underwent HAIC. In these patients, liver metastases had spread to both hepatic lobes and occupied at least 40% of the liver, as evaluated by computed tomography (CT) scan, and liver failure was likely to occur in the near future. All patients were evaluated for performance status (PS) according to the Eastern Cooperative Oncology Group scale. All patients had a PS of 0. This study was retrospectively analyzed.

A hepatic arterial infusion catheter with a side port was inserted through the right femoral artery using the Seldinger technique, and the catheter tip was placed in the gastroduodenal artery to allow drug flow from the side port into the hepatic artery. The gastroduodenal artery was coiled to prevent drug inflow, and the drug was allowed to flow into the hepatic artery under angiography guidance (fig. 1). A 5-french catheter (Sophysa Sa, Orsay, Cedex, France) was inserted intraluminally from the right femoral artery with a subcutaneously implanted reservoir. 14 patients were treated by HAIC via a subcutaneously implanted injection port. There were no complications that were considered to have been caused by surgical procedures. The chemotherapy regimen consisted of 5-fluorouracil (5-FU) 600 mg/m^2 and leucovorin (LV) 250 mg/m^2. A once-weekly infusion for 6 weeks was defined as 1 course. The patients underwent 4 courses of chemotherapy at the end of which response to treatment was evaluated by CT scan. After that, tumor status was assessed every 1–2 courses. All CT scans were reviewed by 2 radiologists. Response rates and adverse events were evaluated according to the RECIST criteria [14, 15] and Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, respectively. Complete response (CR) was defined as the disappearance of all disease. Partial response (PR) was defined as at least a 30% reduction in the sum of the longest diameters of all measured lesions by at least 4 weeks. Progressive disease (PD) was defined as an increase in lesions by 20% or greater, or the appearance of new lesions. Responses not falling into any of these categories were classified as stable disease (SD). When extrahepatic metastases were detected, and their presence was a prognostic factor, patients were converted from HAIC to systemic chemotherapy.

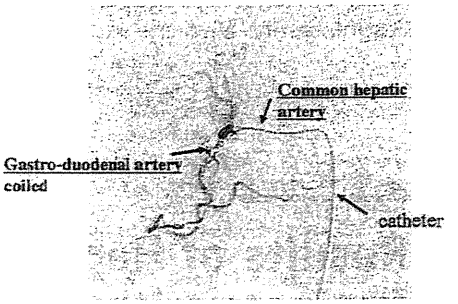

Fig. 1. A hepatic arterial infusion catheter with a side port was inserted in the gastroduodenal artery through the right femoral artery using the Seldinger technique, and the catheter tip was placed in the gastroduodenal artery.

Table 1. Intermittent hepatic arterial infusion of 5-fluorouracil and leucovorin

n	Response	Extrahepatic metastasis	Follow-up, months	Clinical outcome
1	CR	lymph node	52	death
2	PR	lung	16	death
3	CR		69	survival
4	SD	peritoneum	14	death
5	SD	peritoneum	26	death
6	PR	lung, bone	34	survival
7	PR		27	death
8	PR	lung	48	survival
9	PR		38	death
10	PR		17	death
11	PD	lung, lymph node	6	death
12	PR		14	death
13	SD	lung, lymph node	12	death
14	PD		10	death

CR = Complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Table 2. Tumor response

Patients, n	Response				Disease control rate, %
	CR	PR	SD	PD	
14	2	7	3	2	86

CR = Complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Results

HAIC resulted in CR, PR, SD, and PD in 2, 7, 3, and 2 patients, respectively (tables 1 and 2). Figure 2 shows the CT appearances of the 2 patients who achieved a CR. The first patient was a 55-year-old man with sigmoid colon cancer and multiple hepatic metastases, 5 cm in diameter, in both lobes of the liver (T3, N2, M1 (liver), stage IV). First, we locally controlled the sigmoid colon cancer by sigmoid colectomy, and the patient subsequently underwent HAIC for unresectable liver metastases (fig. 2a). After completion of 4 courses of

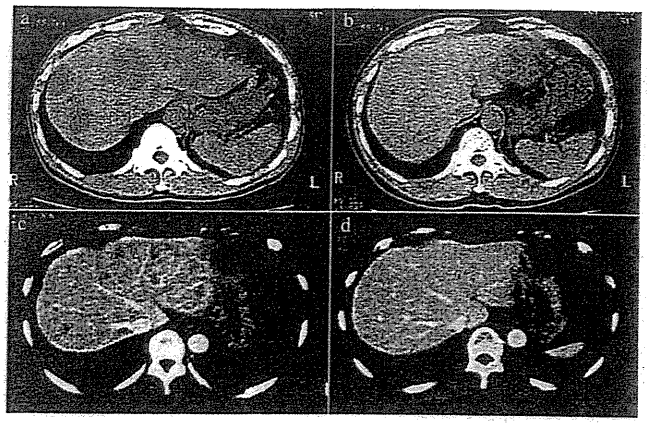

Fig. 2. Abdominal computed tomography of 2 patients. **a,b** Case 1: multiple liver metastases **a** before treatment, and **b** after treatment when no metastases could be detected; **c,d** Case 2: multiple liver metastases **c** before treatment, and **d** after treatment when no metastases could be detected.

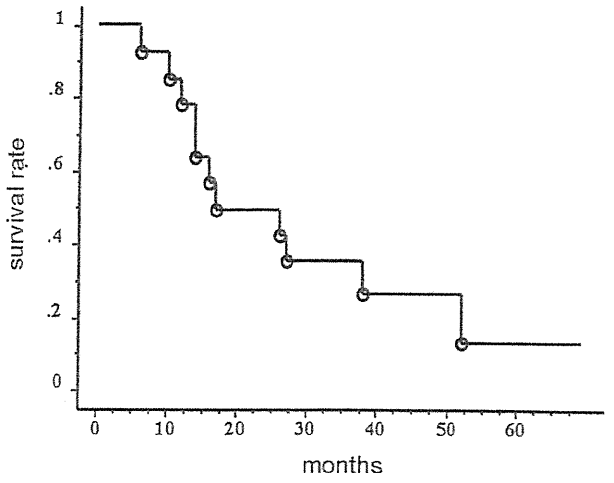

Fig. 3. Overall survival rate for 14 patients.

treatment, no metastases could be detected by CT (fig. 2b). Subsequently, the patient received pyrimidine fluoride anticancer drugs, and has shown no signs of exacerbation for 69 months. No adverse events were observed. The second patient (figs. 2c and d) was a 57-year-old woman with rectal cancer and multiple hepatic metastases, 2.5 cm in diameter, in both lobes of the liver (T3, N1, M1 (liver), stage IV). We locally controlled the rectal colon cancer by low anterior resection before administering HAIC for unresectable liver metastases. After completion of 4 courses of treatment, no metastases could be detected by CT (fig. 2d). No adverse events were observed. Subsequently, the patient received pyrimidine fluoride anticancer drugs, showed recrudescence of liver metastases and lymph node and splenic recurrence after 2 years, and underwent systemic chemotherapy (FOLFIRI: irinotecan/5-FU/LV, followed by FOLFOX: oxaliplatin/5-FU/LV). However, the patient's condition gradually deteriorated, leading to death from cancer 4 years and 6 months after surgery.

Table 3. Toxicity (CTCAE v3.0)

Toxicity	Grade 1–2, n (%)	Grade 3–4, n (%)
Diarrhea	2 (14)	0 (0)
Appetite loss	7 (50)	0 (0)
Pigmentation	6 (43)	0 (0)
Neutropenia	4 (29)	0 (0)

As shown in figure 3, the overall 1- and 2-year survival rates were 79 and 50%, respectively, and the mean survival time (MST) was 21.5 months. Side effects were observed in the form of grade 1–2 diarrhea, appetite loss, pigmentation, and neutropenia, but these were not serious. Quality of life (QoL) remained satisfactory, allowing administration of the scheduled 4 courses of chemotherapy (table 3). Extrahepatic metastases were detected after the start of HAIC and became a prognostic factor in 8 of the 14 patients, who were then converted from HAIC to systemic chemotherapy (table 1).

The 13 patients who developed extrahepatic metastases (lung, peritoneum, bone) but not liver failure, were started on systemic chemotherapy such as FOLFIRI or FOLFOX. The final MST was 18.5 months. No significant difference was noted between the survival time with HAIC and systemic chemotherapy.

Discussion

Liver metastasis is considered to be the decisive prognostic factor for colon cancer. It is thought that liver metastases are already present in approximately 10% of colon cancer patients at the time of the first surgery, and that multiple metastases are present in the liver as a whole in approximately 4% of patients [1–4].

There are currently various opinions regarding the indications for HAIC as a chemotherapeutic approach. Two such opinions are that this therapy is indicated: i) in the case of imminent liver failure due to extensive liver metastases; and ii) when there is metastatic liver cancer for which systemic chemotherapy would be ineffective. It has been reported that in the treatment of unresectable liver metastases HAIC improves the response rate compared to systemic chemotherapy, that hepatic artery infusion therapy maintains QoL, and that both response rate and survival rate are better with HAIC than with systemic chemotherapy [12]. Conversely, it has also been reported that, although HAIC improves the response rate compared to systemic chemotherapy, it does not show any beneficial effects on survival [16]. Outcomes with HAIC have thus been inconsistent.

The present study was carried out in order to investigate HAIC by focusing on 14 patients with unresectable liver

metastases that had spread to both hepatic lobes and occupied at least 40% of the whole liver, and for whom liver failure was considered to be the decisive prognostic factor. All adverse reactions, regardless of the symptoms, were rated as grade 1, with no serious adverse reactions of grade 3 or higher. QoL was maintained well. Both incidence and grade of adverse reactions were low when compared with the FOLFIRI and FOLFOX systemic chemotherapy regimens (table 3) [17, 18].

Among the present patients, the 1-year survival rate was 79%, the 2-year survival rate was 50%, and the MST was 21.5 months (fig. 3). These results were about the same as the 1-year and 2-year survival rates with the FOLFIRI and FOLFOX systemic chemotherapy regimens, and some of the patients survived for a relatively long period of time [17, 18]. Kemeny et al. [12] reported that there are many cases in which extrahepatic lesions appear although HAIC is able to control metastatic foci in the liver itself. We also observed development of extrahepatic lesions in 8 (57%) of the 14 patients, and it can be surmised that there is a limit to how much the survival rate can be increased with HAIC alone. The following scenario can be thought to explain the development of extrahepatic lesions in the case of HAIC. Pharmacologically, HAIC achieves a higher drug concentration in liver lesions when compared with delivery by systemic chemotherapy, resulting in good efficacy in relation to tumors. However, approximately 60% of the anticancer drug administered by HAIC is metabolized in the liver, which reduces the drug concentration delivered to the body as a whole and allows development of extrahepatic lesions. When efficacy was assessed after switching the treatment to systemic chemotherapy in the 8 patients who developed extrahepatic lesions, all were rated as having PD, indicating that treatment efficacy was poor. However, the anticancer drug concentrations that reached the extrahepatic lesions themselves were higher in the case of systemic chemotherapy when compared with HAIC. Accordingly, it is possible that the suppression of tumor progression was fairly good.

Kemeny et al. [19] reported a response rate of 88% and an MST of 22 months or more when patients with resectable liver metastases from colon cancer were treated with a combination of HAIC and systemic chemotherapy. The findings indicate that for patients with recurrence in other organs, which is a risk associated with HAIC alone, addition of systemic chemotherapy to the treatment regimen enables more effective suppression of cancer progression and prolongs survival.

Recently, molecularly targeted drugs such as bevacizumab, cetuximab and panitumumab have been developed, and they have been successful in further extending patient survival [20–22]. The mean survival time has been steadily extended since then, recently reaching approximately 30 months [20, 21]. However, to date, there are no reported large-scale trials showing clear improvements in outcome for HAIC of molecularly targeted drugs. This issue warrants more detailed study in the future.

Based on the study findings presented above, when consideration is given to efficacy against hepatic metastases (in patients likely to develop liver failure in the near future), adverse reactions, and QoL, HAIC is useful; however, when considering the risk of recurrence in organs other than the liver, systemic chemotherapy is necessary. Further study is required in order to effectively implement both of these treatment modalities and to determine whether it is possible to increase treatment efficacy and prolong survival, even in patients with unresectable liver metastases but without extrahepatic lesions.

Disclosure Statement

There were no conflicts of interest to declare.

References

1 Obrand DI, Gordon PH: Incidence and patterns of recurrence following curative resection for colorectal carcinoma. Dis Colon Rectum 1997;40:15–24.
2 Kotake K, Honjo S, Koyama Y: Multi-institutional registry of large bowel cancer in Japan, cases treated in 1996. Japan, Japanese Society for Cancer of the Colon and Rectum Press, 2000.
3 Kotake K, Honjo S, Koyama Y: Multi-institutional registry of large bowel cancer in Japan, cases treated in 1997. Japan: Japanese Society for Cancer of the Colon and Rectum Press, 2001.
4 Kotake K, Honjo S, Koyama Y: Multi-institutional registry of large bowel cancer in Japan, cases treated in 1998. Japan: Japanese Society for Cancer of the Colon and Rectum Press, 2003.
5 Adam R, Pascal G, Castaing D, Azoulay D, Delvart V, Paule B, Levi F, Bismuth H: Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? Ann Surg 2004;240:1052–1061.
6 Curley SA, Izzo F, Abdalla E, Vauthey JN: Surgical treatment of colorectal cancer metastasis. Cancer and Metast Rev 2004;23:165–182.
7 Ruers T, Bleichrodt RP: Treatment of liver metastases, an update on the possibilities and results. Eur J Cancer 2002;38:1023–1033.
8 Kobayashi H, Mochizuki H, Sugihara K, Morita T, Kotake K, Teramoto T, Kameoka S, Saito Y, Takahashi K, Hase K, Oya M, Maeda K, Hirai T, Kameyama M, Shirouzu K, Muto T: Characteristics of recurrence and surveillance tools after curative resection for colorectal cancer: a multicenter study. Surgery 2007;141:67–75.
9 Murata S, Moriya Y, Akasu T, Fujita S, Sugihara K: Resection of both hepatic and pulmonary metastases in patients with colorectal carcinoma. Cancer 1998;83:1086–1093.
10 Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, Giacchetti S, Paule B, Kunstlinger F, Ghémard O, Levi F, Bismuth H: Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240:644–657.
11 Collins JM: Pharmacokinetic rationale for intra-arterial therapy; in Howell SB (ed): Intra-Arterial and Intracavitary Cancer Chemotherapy. Boston, MA, Martinus Nijhoff Publishers, 1984.
12 Kemeny NE, Niedzwiecki D, Hollis DR, Lenz HJ, Warren RS, Naughton MJ, Weeks JC, Sigurdson ER, Herndon JE 2nd, Zhang C, Mayer RJ: Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). J Clin Oncol 2006;24:1395–1403.

13 Kerr DJ, McArdle CS, Ledermann J, Taylor I, Sherlock DJ, Schlag PM, Buckels J, Mayer D, Cain D, Stephens RJ; Medical Research Council's Colorectal Cancer study group, European Organisation for Research and Treatment of Cancer Colorectal Cancer study group: Intrahepatic arterial versus intravenous fluorouracil and folinic acid for colorectal cancer liver metastases: a multicentre randomised trial. Lancet 2003;361:368–373.
14 Fleming ID, Cooper JS, Henson DE: American Joint Committee on Cancer. AJCC Cancer Staging Manual, ed 5. Philadelphia, PA, Lippincott-Raven Publishers, 1997.
15 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–216.
16 Mocellin S, Pilati P, Lise M, Nitti D: Meta-analysis of hepatic arterial infusion for unresectable liver metastases from colorectal cancer: the end of an era? J Clin Oncol 2007;25:5649–5654.
17 Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR: A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004;22:23–30.
18 Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A: FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229–237.
19 Kemeny N, Jarnagin W, Paty P, Gönen M, Schwartz L, Morse M, Leonard G, D'Angelica M, DeMatteo R, Blumgart L, Fong Y: Phase I trial of systemic oxaliplatin combination chemotherapy with hepatic arterial infusion in patients with unresectable liver metastases from colorectal cancer. J Clin Oncol 2005;23:4888–4896.
20 Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F, Cassidy J: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013–2019.
21 Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P: Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360:1408–1417.
22 Siena S, Cassidy J, Tabernero J, Burkes RL, Barugel ME, Humblet Y, Cunningham D, Xu F, Gansert JL, Douillard J: Randomized phase III study of panitumumab (p mab) with FOLFOX4 compared to FOLFOX4 alone as first-line treatment (tx) for metastatic colorectal cancer (mCRC): PRIME trial. Gastrointestinal Cancers Symposium 2010;abstr 283.

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^{18}F-fluorodeoxyglucose Positron Tomography is Useful in Evaluating the Efficacy of Multidisciplinary Treatments for So-called Borderline Unresectable Pancreatic Head Cancers

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Abstract : Currently, computed tomography (CT) is widely used to evaluate the efficacy of treatments on tumor regression in unresectable pancreatic head carcinomas. Recently, ^{18}F-fluorodeoxyglucose positron emission tomography (PET) examination has been used for the initial diagnosis of pancreatic tumors, for diagnosis of distant metastasis, and for recurrences of pancreatic carcinomas. PET has also been used for the qualitative diagnosis of existing tumors. The current study was designed to observe if PET examination can be used to gauge the efficacy of multidisciplinary treatments, and to estimate the prognosis for unresectable pancreatic head carcinomas in similar clinical stages and during therapy. This was a prospective cohort study and included 18 cases. All cases were unresectable pancreatic head cancers diagnosed as TNM classification stage 3, and had undergone identical multidisciplinary treatment regimens. The level of tumor markers, tumor-size reduction, and maximum standardized uptake values (SUV_{max}) were correlated with prognosis. Pearson's correlation and Kaplan-Meyer survival rate curves were used for statistical analysis. Tumor-size reduction in CTs and the transition of tumor markers were not related to patient prognosis. Cases in which post-treatment SUV_{max} values were reduced to < 3.0 were correlated with a more favorable prognosis and demonstrated extended survival rates. PET examination can be used to estimate the prognosis of unresectable pancreatic head carcinomas which have undergone multidisciplinary treatments.

Key Words : FDG-PET, unresectable pancreatic cancer, SUV_{max}, multidisciplinary treatments, hyperthermia

Introduction

Excision rates for invasive pancreatic ductal carcinomas remain low, and the disease continues to be treated primarily with chemoradiotherapy. Consequently, the methods used to evaluate therapeutic

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