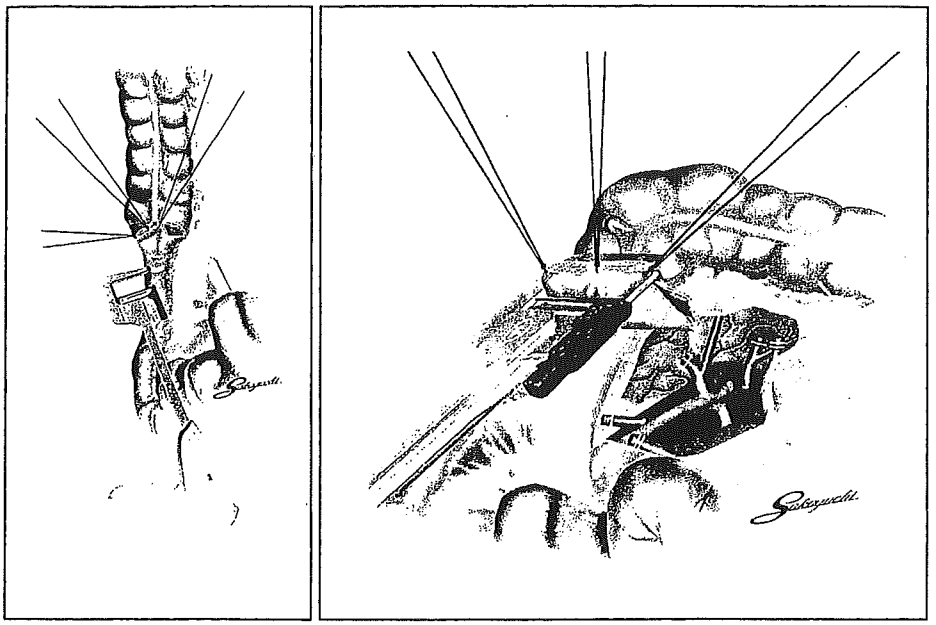

図2　手術手技②

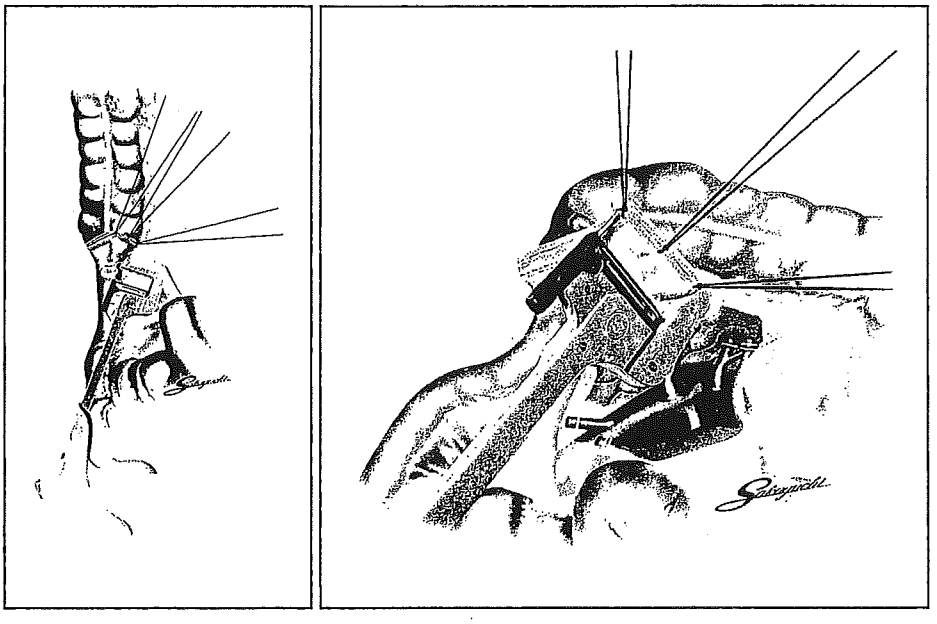

図3　手術手技③

合計3針掛けこれを吊り上げ，前壁をかみ込まないようにT型linear staplerで縫合する．この内翻縫合断端は唯一腸管内に出血する可能性がある部分であるため，十分に止血を確認する必要がある．止血がみられる場合には同部に内側より1針全層縫合する．前壁はその中央に1針，先に縫合した後壁端のさらに少し後壁寄りに縫合線を十分確認しながら漿膜側に結節ができるように1針，さらにその中央に1針掛ける．これらを水平に吊り上げ外翻するようにT型linear staplerで縫合する（図2）．前壁の残った3分の1も同様に外翻縫合する（図3）．外翻部分の出血も確認し，必要であれば縫合止血する．漿膜-漿膜縫合は内腔を狭める可能性があるため，原則として追加していない．しかし，断端からの出血のある場合やそれぞれの縫合線の重なり合う場所で肉眼的にステイプラーが交差していないと思われる場合，あるいは縫合線の重なり合う場所に緊張がかかるような

表1　大腸切除術後の三角吻合症例の内訳

術式別症例数	開腹下大腸切除術	197
	腹腔鏡下大腸切除術	147
吻合部位別症例数	回腸-結腸吻合	141
	S状結腸-結腸または直腸吻合	203
疾患別症例数	腫瘍性病変	338
	憩室症	4
合計		344

表2　三角吻合症例の合併症

縫合不全	2/341例
吻合部出血	0/341例
吻合部狭窄	0/341例

場合には，その部位に漿膜-漿膜縫合を追加する．最後にストーマ孔が母指1指分以上あることと，sealing testで空気漏れのないことを十分に確認して終了する．空気漏れの確認には，どちらかの腸管に腸鉗子を掛け，もう1つの腸管側から内腔にある空気を送っていき縫合部に圧をかける．外側より生理食塩水をかけて空気漏れの有無を確認する．

3．全周外翻吻合

すべて外翻縫合を行うには前壁外翻縫合から開始する．前記したのと同様に，全層支持糸を端より少し前壁寄りにそれぞれ1針ずつ，その中央に1針，合計3針掛けこれを吊り上げ，後壁をかみ込まないようにT型linear staplerで縫合する．180度回転させると，最初の前壁縫合が回転しているので外翻の後壁縫合が完成した状態となり，残りの前壁3分の2も前記と同様に外翻縫合する．後壁内翻の三角吻合と同じく，最後にストーマ孔が母指1指分以上あることと，sealing testで空気漏れのないことを十分に確認して終了する．

■■■

結　果

1999年以後の大腸切除後の端々三角吻合は344例である．腹腔鏡下大腸切除術197例，開腹大腸切除147例に行われ，疾患別にみると，大腸の腫瘍性病変が338例，憩室性疾患が6例であった．部位別にみると右側結腸切除後の回腸結腸吻合141例，大腸大腸吻合203例であった（**表1**）．術後の合併症では，再建腸管の血流不全で術後再手術を行った例が3例存在したが，いずれも再手術前に縫合不全はなかった．残りの341例中縫合不全は2例に生じたのみで，吻合部出血や吻合部狭窄はみられなかった（**表2**）．上記患者のうち253例において術後経過観察中に大腸内視鏡検査が施行されたが，吻合部に狭窄などの異常所見を認めたものはなかった．

■■■

考　察

消化管手術後の腸管吻合の1つである端々三角吻合は，器械吻合法として存在するものの，わが国ではあまり知られておらず文献的にもその報告は少ない[1]．しかし，われわれは端々吻合が可能で合併症が少ないこと，手技が簡便で短時間に行えること，経済的にも負担が多くないことから，1999年から消化管吻合の第1選択法として行っており，2004年にその手技を報告した[2]．

上記のように，日本での消化管吻合における三角吻合の報告は少なく，わずかに食道切除術時[3]と胃切除術時[4]の文献が散見されるのみである．それらの中でも指摘されているように，三角吻合の利点はまず吻合部狭窄が少ないことである．食道切除後の食道胃管吻合部の狭窄は従来より頻度の高いものであり，それがわが国で同吻合法が食道切除術に行われている理由かもしれない．そのほかにも縫合線からの出血が確実に確認できることから術後吻合部出血の可能性が低いことや，あるいは今回示したように縫合不全の率が低いことなど，利点は多いと考える．また，近年普及しつつある腹腔鏡下大腸切除術における再建では，小切開創から腸管を体外に引き出して吻合を行うのが一般的であるが，ときとして引き出す腸管の余

裕が少なく，functional end to end が難しい場合がある．そのような場合には，縫い代分だけあれば引き出す腸管がそれほど長くなくても三角吻合は十分可能である[5]．

最後に，器械吻合で問題とされる経済的な点であるが，三角吻合の場合，タイコヘルスケア社のTA®30 を使用すると，本体 1 つと替えのカートリッジが 2 つの合計価格が 70,000 円であり，functional end to end で器械吻合すると仮定した場合の 106,000 円と比較すると低価格で収まるという利点もある．また，これら吻合用の器械は，大腸切除再建術においては 1 症例 4 個まで保険の請求が可能であるため，病院負担という点からみてもデメリットはない．

文　献

1) Venkatesh KS, Morrison N, Larson DM, et al：Triangulating stapling technique：an alternative approach to colorectal anastomosis. Dis Colon Rectum **36**：73-76, 1993
2) 福長洋介，東野正幸，西口幸雄，他：大腸切除術後再建における端端三角吻合．手術 **58**：247-250, 2004
3) 古川良幸，平井勝也，山本　尚，他：三角吻合による頸部食道胃管吻合の有用性と基礎的検討．日外会誌 **102**（臨増）：409, 2001
4) 永田松夫，本田一郎，山本　宏，他：三角法による頸部における食道胃端端吻合術．手術 **55**：2077-2081, 2001
5) Fukunaga Y, Higashi M, Tanimura S, et al：A novel laparoscopic technique for stapled colon and rectal anastomosis. Tech Coloproctol **7**：192-197, 2003

（FUKUNAGA Yosuke, et al 大阪市立総合医療センター消化器外科：〒 534-0021 大阪市都島区都島本通 2-13-22）

CPT-11＋TS-1併用化学療法により腹膜播種が消失しCRとなった1例

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田中 純一　近藤 礎　岸本 朋乃　中山 貴寛　今村 博司
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〔*Jpn J Cancer Chemother* 32(11): 1768-1770, *October*, 2005〕

A Case of Peritoneal Dissemination Disappeared by CPT-11＋TS-1 Combination Chemotherapy: Hiroyoshi Takemoto, Mutsumi Fukunaga, Ryota Ooshiro, Makoto Fujishima, Kazuyoshi Yamamoto, Junichi Tanaka, Motoi Kondo, Tomono Kishimoto, Takahiro Nakayama, Hiroshi Imamura, Seizo Masutani, Masayuki Tatsuta, Takatoshi Kawasaki and Hiroshi Furukawa (*Dept. of Surgery, Sakai Municipal Hospital*)

Summary

A patient is a 35-year-old man. By a diagnosis of descending colon cancer, descending colon ablative operation and D1 lymph node dissection were performed on April 22, 2004. It was P3H0N1SE, Stage IV in perioperative findings. Abdominal CT showed peritoneal dissemination of 1.7 cm at the right under the abdominal wall wound and 1.2 cm in the rectovesical pouch on May 18, 2004. CPT-11＋TS-1 combination chemotherapy was started on June 22nd.

In the five weeks of the combination chemotherapy, continuous infusion of CPT-11 (150 mg/body day 1 and 15) was twice administered, and oral administration of TS-1 (120 mg/body/day) was given for 3 weeks (day 1-21). Peritoneal dissemination disappeared after the two-course end, and we judged it as CR. Furthermore, we were certain that we obtained CR after the three-course end. The adverse event was only neutropenia of grade 1. The fourth course was not administered, but recurrence has not been observed. Abdominal CT showed no recurrence on March 3, 2005 since the combination chemotherapy ended 6 months ago. Key words: Colon cancer, CPT-11, TS-1

要旨　症例は35歳，男性。2004年4月22日下行結腸癌の診断にて下行結腸切除術，D1郭清施行。術中所見ではP3H0N1SE，Stage IVであった。5月18日腹部CTではダグラス窩に1.2 cmおよび腹壁創直下に1.7 cmの腹膜播種を認めた。6月22日よりCPT-11＋TS-1併用化学療法を開始した。投与方法は5週（35日）の間にCPT-11を2回点滴（150 mg/body day 1 and 15）し，TS-1を3週（day 1～21）内服（120 mg/body/day）した。2コース終了後には腹膜播種消失し，CR inとなった。さらに3コース終了後のCTでCR確定となった。この間の有害事象はgrade 1の好中球減少のみであった。4コース目の投与は行わなかったが，その後も再発することなく経過し，化学療法終了後から約6か月経過した2005年3月3日撮影の腹部CTでも再発は認めず，現在もCRのまま経過している。

はじめに

今回，われわれはCPT-11＋TS-1併用化学療法により腹膜播種が消失し，CRとなった1例を経験したので報告する。

I. 症　例

患者: 35歳，男性。

既往歴: 2～3年前にC型肝炎でインターフェロン療法施行されていた。

現病歴: 2003年ごろより，便の血液付着に気付くも放置していた。2004年になり，腹痛を訴え近医受診。大腸内視鏡検査施行し，下行結腸癌を指摘。同年4月5日当院紹介受診となった。

II. 手術所見

2004年4月22日下行結腸切除術，D1郭清施行。術中所見ではP3H0N1SE，Stage IV，大網の腫瘤を摘出したところ，腹膜播種との診断であった。摘出標本の病理組織診断ではmod ss ly1 v2 nlであった。

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Ⅲ. 経　過

術後は順調に経過し，2004年5月1日退院となった。5月18日施行の腹部CTではダグラス窩に1.2 cmおよび腹壁創直下に1.7 cmの腹膜播種を認めた。これに対し，6月22日よりCPT-11＋TS-1による化学療法を開始した。投与方法は5週（35日）の間にCPT-11を2回点滴（150 mg/body×2）し，TS-1を3週（21日）内服（120 mg/body/day）した。1コース終了時のCTではダグラス窩の腫瘤は0.5 cm，腹壁創直下の腹膜播種は0.9 cmと著明に縮小しPR inとなり，2コース終了後には腹膜播種消失し，CR inとなった。さらに3コース終了後のCTでCR確定となった（図1，2）。この間の有害事象はgrade 1の好中球減少のみであった。

その後，4コース目施行予定であったが施行直前の血液検査で飲酒によると思われる肝機能障害を認め，投与を延期したが，その後もなかなか回復しなかった。結局患者希望もあり4コース目の投与は行わなかった。しかし，その後も再発することなく経過し，化学療法終了後から約6か月経過した2005年3月3日撮影の腹部CTでも再発は認めず，現在もCRのまま経過している。

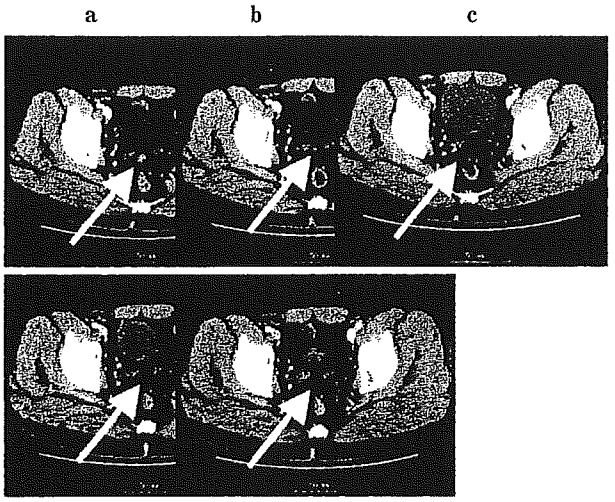

図1　腹膜播種（ダグラス窩）
a: 化学療法前
b: 1コース終了後 PR in
c: 2コース終了後 CR in
d: 3コース終了後 CR確定
e: 化学療法終了後6か月

Ⅳ. 考　察

国内の大腸癌化学療法においては，これまで5-FU/LVあるいはCPT-11単剤での治療が主流であった。一方欧米では，5-FU/LV＋CPT-11併用療法により，それまで標準療法とされてきた5-FU/LV療法に比べ約2～3か月の延命効果が認められている[1,2]。しかしながら，5-FU/LV持続投与との併用では安全性は高いものの，その煩雑性から，より安全で簡便な治療法が求められている。一方，TS-1は大腸癌を対象とした第Ⅱ相試験[3]の結果，優れた効果と安全性が確認されており，その薬物動態は持続投与法に近似していることからもCPT-11との併用療法が，5-FU/*l*-LV＋CPT-11療法に代わり得る治療法として期待されている。

CPT-11＋TS-1併用化学療法は，進行・再発胃癌に対して数々の第I/II相臨床試験が実施されている。さらに，TS-1の適応追加後もいくつかの有用な報告例があり，すでに第Ⅱ相臨床試験の報告[4]もある。本症例にて施行したのは，大阪消化管癌化学療法研究会（OGSG）で行われたレジメンである。藤谷らの報告[5]では，奏効率50.0%，CR症例も1例あり，grade 3以上の有害事象は少なく，生存期間中央値は423日と極めて良好な成績がでている。

本症例においてもCPT-11＋TS-1併用化学療法を3コース施行し，腹膜播種が消失後も6か月間CRを継続している。またgrade 3以上の有害事象もなく，外来での投与が十分に可能であった。

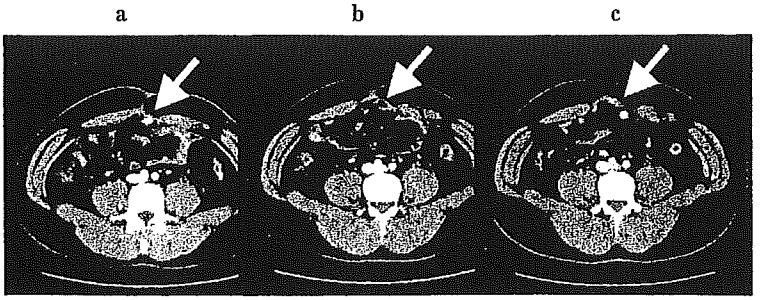

図2　腹膜播種（腹壁創直下）
a: 化学療法前，b: 1コース終了後，c: 化学療法終了後6か月

結　語

CPT-11＋TS-1併用化学療法により腹膜播種が消失し，CRとなった1例を経験した。有害事象も重篤なものはなく，外来でも施行可能な化学療法である。

本論文の要旨は第27回日本癌局所療法研究会において発表された。

文　献

1) Douillard Y, Cunningham D, Roth AD, *et al*: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomized trial. *Lancet* **355**: 1041, 2000.
2) Saltz LB, Cox JV, Blanke C, *et al*: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* **343** (13): 905, 2000.
3) Ohtsu A, Baba H, Sakata Y, *et al*: Phase II study of S-1, a novel oral fluoropyrimidine derivative, in patients with metastatic colorectal carcinoma. S-1 Cooperative Colorectal Carcinoma Study Group. *Br J Cancer* **83**(2): 141-145, 2000.
4) 小松嘉人，結城敏志，浅香正博・他: 大腸癌化学療法の実際　進行再発大腸癌に対する治療戦略-新規抗癌剤併用療法 CPT-11＋TS-1 の第Ⅱ相臨床試験（第一報）を中心に．日癌治療会誌　**39**(2): 283, 2004.
5) 藤谷和正，滝内比呂也，楢原啓之・他: 切除不能進行・再発胃癌に対する CPT-11＋TS-1 併用 I/II 相試験．癌の臨床　**49**(7): 605, 2003.

特集 大腸がん患者の治療方針

3．大腸がん手術—切除の実際

4）結腸の手術

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View Points !

▶がんの進行度に応じて，局所切除，部分切除，区域切除，半切除，（亜）全切除を選択する。

▶流域動脈と腫瘍の局在に応じて合理的なリンパ節郭清範囲を決定することが重要である。

▶Stage 0～Ⅳまで，全てのStageで手術適応があり，全Stageを合わせた5年生存率は70%を超えている。

▶StageⅡ，Ⅲにおける開腹手術と腹腔鏡手術のrandomized controlled studyが進行中である。

総 論

- 結腸は虫垂・盲腸からS状結腸までと範囲が広く，術式はがんの局在や進行度に応じて選択しなければならない。
- 腸管の長さは個体差が大きく，切除腸管の長さではなく，切除される流域動脈により術式や郭清範囲が決まる。
- 上腸間膜動脈からの血流が盲腸，上行結腸，横行結腸を支配し，主幹動脈は，回結腸動脈，右結腸動脈，中結腸動脈である。
- 下腸間膜動脈からの血流が下行結腸，S状結腸を支配し，主幹動脈は，左結腸動脈と数本のS状結腸動脈である。
- 結腸がんでは，腫瘍から10cm以上離れた壁在リンパ節および傍腸管リンパ節転移はまれで，5 cm以内に限局していることが多い。
- 結腸がんではリンパ節転移の大部分が2本の流域動脈に挟まれた領域に限局している。
- 結腸のリンパ管の走行は動脈に沿うことを原則としており，図1の模式図にあてはめて腫瘍の占拠部位別にリンパ節の郭清範囲を決定することは合理的である[1)]。
- 大腸癌治療ガイドラインによるStage 0～Ⅲの治療方針では，2 cm以上のStage 0，SM軽度浸潤癌を除くStageⅠ，StageⅡ及びStageⅢが腸管切除＋リンパ節郭清の適応となっている[2)]。
- 大腸がん手術におけるリンパ節郭清度は術前画像診断あるいは術中所見による壁深達度およびリンパ節転移度から決定する。
- 大腸癌治療ガイドラインによるStage 0～Ⅲの手術治療方針では，N（－）の場合，M癌でD_0またはD_1郭清，SM癌でD_2郭清，MP癌でD_2またはD_3郭清が推奨され，壁深達度がSS，SE，Siまたは壁深達度にかかわらずN(＋）の場合はD_3郭清の適応とされている（図2）[2)]。
- StageⅣで転移巣の切除が不可能な場合でも，臨床症状（出血，狭窄など）や予後を

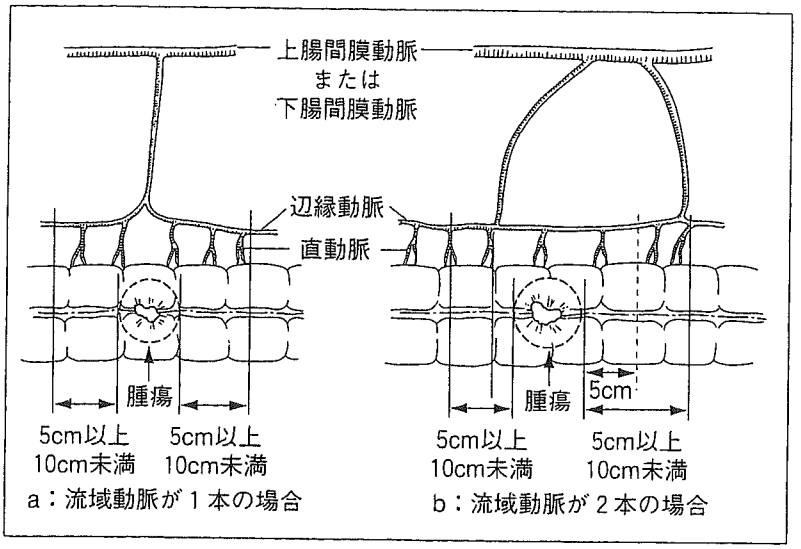

図1　流域リンパ節の郭清法（文献1）より引用）

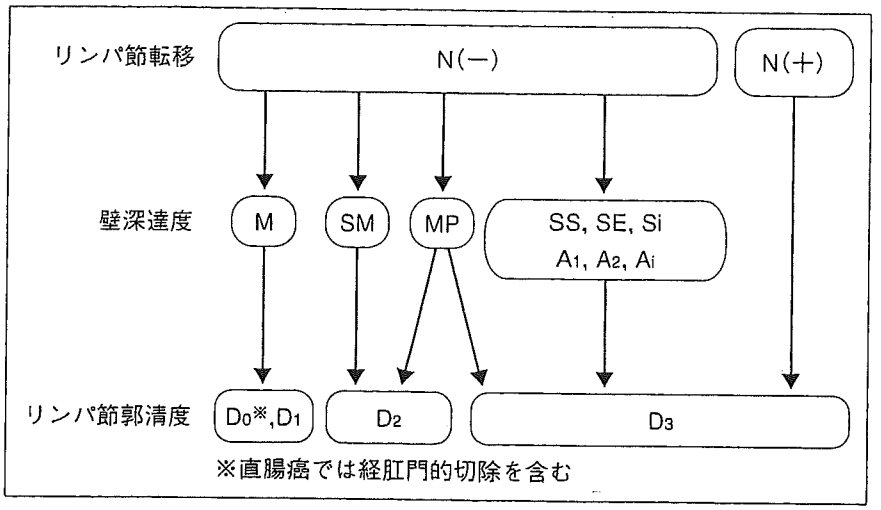

図2　Stage 0～StageⅢ大腸がんの手術治療方針（文献2）より引用）

考慮して原発巣切除が行われる。

- 吻合は手縫いによる端々吻合が多く行われていたが，最近では自動縫合器を用いた機能的端々吻合（functional end to end anastiomosis）の頻度が高くなっている。
- 結腸がん切除後の5年生存率は，Stage 0：94.8%，StageⅠ：90.6%，StageⅡ：83.6%，StageⅢa：76.1%，StageⅢb：62.1%，StageⅣ：14.3%，全Stage：71.4%であり，結腸がんは根治切除が施行できれば比較的予後が良好ながんである（表1）。
- 家族性大腸腺腫症（FAP），遺伝性大腸がん（HNPCC），多発大腸がん，潰瘍性大腸炎合併大腸がん（colitic cancer）などの特殊ながんは，大腸（亜）全摘術の適応となる[3]。

各　論（図3）

1．回盲部切除術

- 盲腸がん，虫垂がんおよび中間リンパ節領域の血管が回腸結腸動脈になる回盲弁近くの上行結腸がんが適応となる。

2．右半結腸切除術

- 回結腸動脈＋右結腸動脈を切除した場合は右結腸切除術，回結腸動脈＋右結腸動脈＋

表1　部位別累積5年生存率（下段：症例数）

	Stage 0	Stage Ⅰ	Stage Ⅱ	Stage Ⅲa	Stage Ⅲb	Stage Ⅳ	全 Stage
盲腸 (C)	90.2% 110	86.7% 149	81.4% 252	69.3% 209	59.5% 137	9.8% 225	63.7% 1082
上行結腸 (A)	96.3% 209	90.9% 257	83.7% 698	73.9% 398	57.3% 254	14.2% 409	68.3% 2225
横行結腸 (T)	94.5% 176	89.1% 199	82.6% 447	70.1% 270	60.1% 143	9.6% 261	67.8% 1496
下行結腸 (D)	94.7% 129	90.3% 151	82.8% 267	70.9% 152	57.8% 67	18.5% 115	73.4% 881
S 状結腸 (S)	95.2% 559	91.4% 1149	84.5% 1373	81.4% 879	67.4% 394	16.6% 781	75.0% 5153
結腸 (C～S)	94.8% 1183	90.6% 1905	83.6% 3037	76.1% 1908	62.1% 995	14.3% 1791	71.4% 10819

大腸がん研究会・大腸がん全国登録1991～1994年度症例

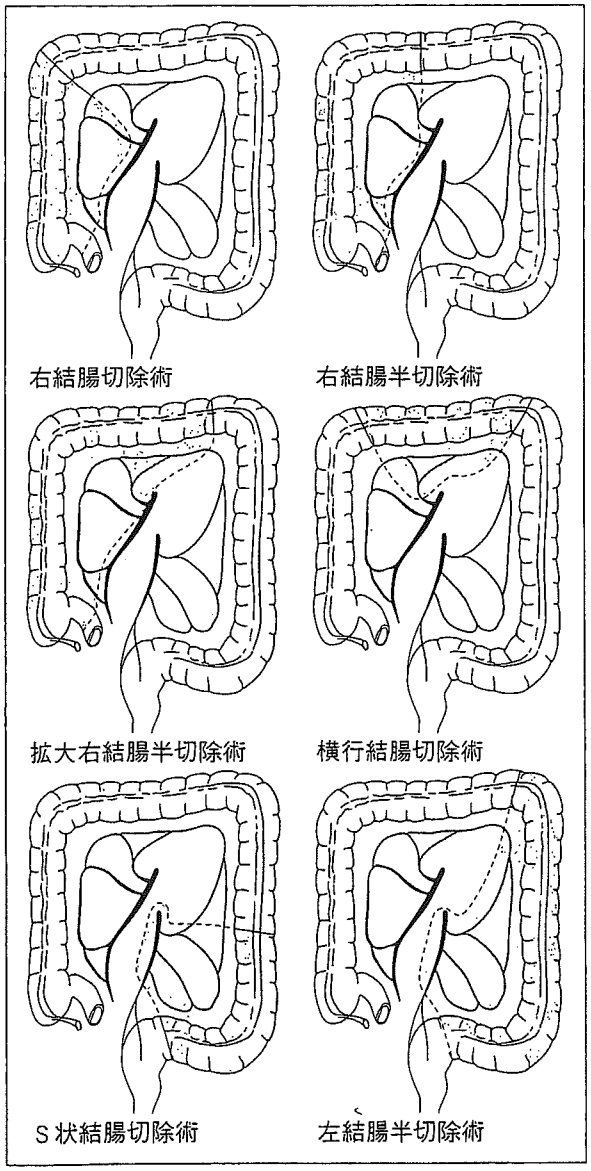

図3　結腸切除の基本（文献4）より引用）

中結腸動脈右枝を切除した場合は右半結腸切除術，回結腸動脈＋右結腸動脈＋中結腸動脈右枝および左枝を切除した場合は拡大右半結腸切除術とよぶ。

- 胃結腸静脈幹から回結腸静脈根部までの surgical trunk の露出が郭清に重要である。

3．横行結腸切除術

- 中結腸動脈の切除を行うが，肝彎曲部寄りのがんでは右半結腸切除術を，脾彎曲部寄りのがんでは左半結腸切除術を施行することが多い。
- 図1にあてはめてリンパ節郭清範囲を決めることで回盲弁温存が可能である。

4．左半結腸切除術

- 横行結腸左側および下行結腸のがんが対象となる。
- 中結腸動脈左枝および左結腸動脈切除を基本とするが，腫瘍の局在や進行度と主幹動脈の位置関係で手術の variation が多い。
- 脾臓損傷に注意を要する。

5．S状結腸切除術

- S状結腸がんが適応となる。
- 腸管の長さに固体差が大きく，下腸間膜動脈を根部で切除すればD_3郭清を行える[5]が，リンパ節転移陰性例では進行度に応じた郭清と腸管切除を行う。

腹腔鏡手術

- 早期結腸がんに対する腹腔鏡手術の適応はコンセンサスが得られている。
- 欧米での報告では，進行結腸がんにおける開腹手術と腹腔鏡手術の長期予後に差を認めていない[6]。
- 腹腔鏡手術では開腹手術以上に手技に施設間格差のあることを認識する必要がある。
- 日本では結腸がんのStageⅡ，Ⅲに対する開腹手術と腹腔鏡手術のrandomized controlled study（日本臨床腫瘍研究グループJCOG0404）が進行中であり，進行結腸がんの腹腔鏡手術は臨床研究の域にある。

文　献

1）高橋慶一ほか：大腸癌の外科的治療(1)標準的治療（結腸）．コンセンサス癌治療　1(2)：66－69（2002）
2）大腸癌研究会編：大腸癌治療ガイドライン（医師用）2005年版．金原出版，東京（2005）p. 6－23
3）柳　秀憲ほか：大腸癌に対する括約筋温存大腸全摘術．手術　57(6)：673－687（2003）
4）高橋　孝：結腸切除術／右半・横行・左半結腸切除術．消化器外科，手術のための局所解剖アトラス　6(7)：920－935（1983）
5）大腸癌研究会編：大腸癌取扱規約改訂第6版．金原出版，東京（1998）
6）The Clinical Outcomes of Surgical Therapy Study Group：A comparison of laparoscopically assisted and open colectomy for colon cancer．N Engl J Med　350：2050－2059（2004）

Original Paper

Value of Serum Carbohydrate Antigen 19-9 for Predicting Extrahepatic Metastasis in Patients with Liver Metastasis from Colorectal Carcinoma

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KEY WORDS:
CA19-9; CEA; Colorectal carcinoma; Liver metastasis; Extrahepatic metastasis

ABBREVIATIONS:
Carcinoembryonic Antigen (CEA); Carbohydrate Antigen 19-9 (CA19-9); Microwave Coagulation Therapy (MCT); Radiofrequency Ablation (RFA)

ABSTRACT

Background/Aims: Serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are frequently elevated in patients with colorectal carcinoma. However, the predictive utility of these two markers has not been fully investigated in patients with liver metastasis.

Methodology: We retrospectively analyzed data obtained from 90 hepatectomy or non-hepatectomy patients with liver metastases from colorectal carcinoma. We examined correlation between serum levels of CEA and CA19-9 and other clinicopathologic factors and performed univariate and multivariate analyses to determine the impact of these tumor markers on extrahepatic metastasis after admission to our hospital.

Results: CEA elevation correlated to advanced age (≥60 years), and CA19-9 elevation correlated with the site (colon) of primary tumor. Univariate analysis showed that treatment without hepatectomy, ≥4 hepatic tumors, and CA19-9 elevation had been an adverse effect on extrahepatic disease-free survival time after admission. Multivariate analysis showed that CA19-9 elevation (risk ratio, 1.84) and treatment without hepatectomy (risk ratio, 1.62) had a significant effect on extrahepatic disease-free time.

Conclusions: In patients with colorectal liver metastasis, elevation of serum CA19-9 is a risk factor for extrahepatic metastasis, and CEA appears to be useless for predicting extrahepatic metastasis in these patients.

INTRODUCTION

Survival of patients with liver metastasis from colorectal carcinoma has improved because the indications for hepatic resection have been extended (1-4) and chemotherapy methods have been refined (5-7). The results of surgical treatment, however, are still unsatisfactory. About 70% of patients with liver metastasis who undergo hepatic resection develop intra- and/or extrahepatic metastasis after surgery (2,4,8-10). Factors influencing recurrence or death from disease after hepatic resection for liver metastasis have been investigated (2,4,8-11), and the presence of extrahepatic metastasis is considered one of the most adverse factors against patient survival after hepatic resection (2,10). It is important for hepatobiliary surgeons to be able to identify risk factors for extrahepatic metastasis in patients with liver metastasis.

Serum levels of tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are reported to be useful for detecting advanced tumor or predicting postoperative recurrence in patients with colorectal carcinoma (12). Some authors have reported preoperative serum CEA level to be useful for predicting recurrent disease or death from disease in patients with liver metastasis of colorectal carcinoma (2,4). Others, however, have reported that serum CEA is not an independent factor predicting outcome after hepatic resection (9,10,13). Therefore, the prognostic value of CEA in patients suffering from liver colorectal metastasis is still controversial. Moreover, the prognostic value of serum CA19-9 has not been fully investigated in such patients (14).

We investigated risk factors for extrahepatic metastasis to clarify the prognostic value of preoperative serum CEA and CA19-9 levels in patients with resectable and non-resectable liver metastasis from colorectal carcinoma.

METHODOLOGY

Between September 1982 and September 2001, 155 patients with liver metastasis from colorectal carcinoma were admitted to the Department of Surgery I, Oita Medical University. Of these, 90 patients had serum CEA and CA19-9 levels measured at the time of admission, and those 90 were enrolled in this study.

Of the 90 patients, 55 underwent hepatic resection and/or thermal ablation therapy, including microwave coagulation therapy (MCT) and radiofrequency abla-

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tion (RFA). The remaining 35 underwent only chemotherapy including transarterial and/or systemic infusion therapy. The criteria for hepatic resection at our institution are less than 4 hepatic tumors, no extrahepatic metastasis, and no contraindications for surgery. Some exceptional cases were included in this study: one patient with a solitary lung metastasis underwent hepatic and pulmonary resections during the same hospitalization; 1 patient with local recurrence of rectal carcinoma and 1 with multiple lung metastases of colon carcinoma underwent palliative limited hepatic resection and/or RFA; 13 patients with ≥4 hepatic tumors underwent hepatic resection and/or thermal ablation therapy (MCT and/or RFA).

Relations between tumor markers and other clinicopathologic factors were investigated **(Table 1)**. Serum levels of CEA and CA19-9 were determined by chemiluminescence enzyme immunoassay; cut-off values were 5ng/mL and 36.4 U/mL, respectively. We obtained the results of histologic study of the primary colorectal carcinoma, including nodal metastasis, tumor grade (well differentiated or other type), and lymphatic or venous permeation. Complete histologic descriptions of the primary tumor were available for 79 of the 90 patients. Nine patients did not undergo resection of the primary tumor because of the presence of synchronous extrahepatic metastasis or locoregional advanced tumor. Two patients underwent resection of the primary colorectal carcinoma at another hospital and complete histologic data were not available to us; only nodal status was provided in 1 case, and only venous permeation, tumor grade, and nodal status was provided in the other. The interval between colorectal surgery and detection of hepatic metastasis was defined as hepatic disease-free survival time. When colorectal surgery was not performed, the hepatic disease-free survival time was defined as the interval between the detection of colorectal carcinoma and that of hepatic metastasis. Correlation between CEA or CA19-9 and other clinicopathologic factors was evaluated by chi-square or Fisher's exact probability test.

In investigating risk factors for extrahepatic metastasis, we considered a total of 13 clinicopathologic factors including serum levels of CEA and CA19-9, all of which are shown in **Table 2**. Patient outcomes were determined by referring to the files for the status of each patient in November 2002. The mean and median follow-up periods were 19.3 and 16.0 months, respectively from the date of admission to our institute. We investigated patient outcome (survival or death), follow-up time, cause of death, site of extrahepatic metastasis, and extrahepatic disease-free survival time. Survival rates were calculated by the Kaplan-Meier method. Each clinicopathologic factor was evaluated by univariate log-rank test, and significant variables were then examined by multivariate analysis with the Cox proportional hazards model. *P* values of less than 0.05 were considered statistically significant.

RESULTS

Clinicopathologic Characteristics

Clinicopathologic characteristics of the 90 patients are summarized in **Table 1**. The patient group comprised 50 men and 40 women whose mean age at the time of admission was 64.3 years (range, 33 to 84 years). Of the 90 patients, 43 had colorectal carcinoma and liver metastases synchronously and the remaining 47 had liver metastases metachronously at the time of admission. Mean and median intervals between colorectal surgery and admission at our institute due to liver metastasis were 8.2 months and 3.0 months, respectively. Thirty-seven patients had a solitary liver metastasis, and the remaining 53 had multiple metastases (median number of hepatic tumor, 2.0) with a mean tumor size of 37.9mm (median 30.0mm, range 10 to 120mm). Tumor cell invasion into lymph and blood vessels and lymph node metastasis at the primary site were documented in 58 of 79 (73.4%) patients, 42 of 79 (53.2%), and 49 of 80 (61.3%), respectively. Mean serum CEA and CA19-9 levels at the time of admission were 265.5ng/mL (median,

TABLE 1 Correlation between Tumor Markers and Other Clinicopathologic Factors

Clinical variable	No. of Patient	CEA <5 (ng/mL)	CEA ≥5 (ng/mL)	CEA *P* value	CA19-9 <36.4 (U/mL)	CA19-9 ≥36.4 (U/mL)	CA19-9 *P* value
Sex				0.80			0.14
Male	50	15	35		29	21	
Female	40	13	27		17	23	
Age (years)				0.04			0.89
<60	28	13	15		14	14	
≥60	62	15	47		32	30	
Primary Site				0.42			<0.01
Colon	60	17	43		23	37	
Rectum	30	11	19		23	7	
Nodal metastasis				0.18			0.21
Absent	31	7	24		19	12	
Present	49	18	31		23	26	
Tumor grade				0.96			0.62
Well	25	8	17		14	11	
Non-well	54	17	37		27	27	
Lymphatic permeation				0.13			0.08
Absent	21	9	12		14	7	
Present	58	16	42		26	32	
Venous permeation				0.19			0.57
Absent	37	9	28		20	17	
Present	42	16	26		20	22	
Interval (months)				0.54			0.71
<12	67	22	45		35	32	
≥12	23	6	17		11	12	
Number of Metastases				0.11			0.41
<4	59	15	44		32	27	
≥4	31	13	18		14	17	
Tumor size (cm)				0.06			0.11
<5	68	25	43		38	30	
≥5	22	3	19		8	14	
Hepatectomy				0.60			0.96
Not done	35	12	23		18	17	
Done	55	16	39		28	27	

CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

TABLE 2 Univariate Analysis for Extrahepatic Disease-free Survival after Admission

Clinical variable	No. of patient	Extrahepatic disease-free survival rate 1 year	3 year	*P* value
Sex				0.10
Male	49	44.8	26.3	
Female	40	58.5	37.5	
Age (years)				0.36
<60	27	50.9	0	
≥60	62	51.3	36.4	
Primary Site				0.86
Colon	59	51.3	28.6	
Rectum	30	50.7	38.0	
Nodal metastasis				0.16
Absent	31	60.5	48.9	
Present	48	50.5	21.0	
Tumor grade				0.11
Well	24	70.0	50.7	
Non-well	54	48.0	25.2	
Lymphatic permeation				0.26
Absent	21	70.8	37.6	
Present	57	48.6	34.9	
Venous permeation				0.12
Absent	37	63.9	39.5	
Present	41	46.8	30.1	
Interval (months)				0.28
<12	66	46.3	26.0	
≥12	23	64.9	40.8	
Number of Metastases				0.02
<4	59	56.9	41.8	
≥4	30	38.3	-	
Tumor size (cm)				0.93
<5	68	51.5	30.1	
≥5	21	50.1	35.8	
Hepatectomy				<0.01
Performed	54	65.3	43.5	
Not performed	35	28.5	-	
CEA (ng/mL)				0.87
<5	27	54.6	35.8	
≥5	62	49.4	29.2	
CA19-9 (U/mL)				0.04
<36.4	45	61.4	41.4	
≥36.4	44	39.7	20.9	

14ng/mL, range 0 to 13,850) and 1,200 U/mL (median, 29 U/mL, range 0 to 55,000), respectively. Serum CEA and CA19-9 levels were elevated in 62 (68.9%) and 44 (48.9%) of the 90 patients, respectively.

Correlation between Serum Levels of Tumor Markers and Clinicopathologic Factors

Correlation between the tumor markers and other clinicopathologic factors are shown in **Table 1**. Among the 11 other clinicopathologic factors, serum CEA elevation was associated with age ≥60 years ($p=0.04$), and serum CA19-9 elevation was correlated with the site of primary tumor ($p<0.01$). Serum CEA levels tended to correlate with the number ($p=0.11$) and size ($p=0.06$) of hepatic tumors. Serum CA19-9 levels tended to correlate with lymphatic permeation ($p=0.08$) and size of the hepatic tumor ($p=0.11$). In the present study, serum levels of both CEA ($p=0.60$) and CA19-9 ($p=0.96$) at the time of admission did not correlate with the type of therapy performed at our institute (hepatectomy and/or ablation *vs.* chemotherapy only).

Patient Outcome

By November 2002, 54 of the 90 patients had died of colorectal carcinoma; one of postoperative complication; and 4 of unrelated diseases (suicide, necrotizing myositis, acute myocardial infarction, or primary gastric carcinoma); 18 were alive without disease, and 13 were alive with disease. In total, 89 patients were included in further survival analyses; 1 patient was excluded because of perioperative death. Cancer-related survival curves of patients according to type of therapy are shown in **Figure 1**. The 5-year survival rate was 43.1% in the 54 patients who underwent hepatic resection and/or thermal ablation, and 0% in the 35 patients who underwent only chemotherapy. The extrahepatic disease-free survival rate of the 89 patients was 51.1% at 1 year and 31.8% at 3 years. The total number of sites showing extrahepatic metastasis was 69 in 50 patients. Metastatic sites were the lung (34.8%), the peritoneum (27.5%), lymph nodes (17.4%), local (10.1%), bone (4.3%), adrenal gland

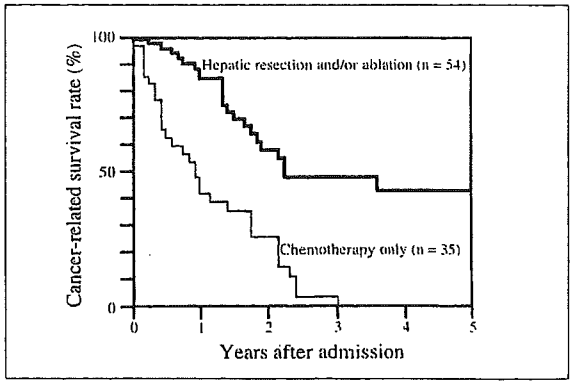

FIGURE 1 Cancer-related survival according to kind of therapy. Survival rates at 1 year, 3 years, and 5 years after admission are 84.9%, 48.5%, and 43.1% in patients who underwent hepatectomy and 58.0%, 0%, and 0% in those who underwent chemotherapy. Curves drawn by the Kaplan-Meier method.

TABLE 3 Sites of Extrahepatic Metastasis in Patients with Liver Metastasis from Colorectal Carcinoma

Site of extrahepatic metastasis	No. of patients (%)
Lung	24 (34.8)
Peritoneum	19 (27.5)
Lymph node	12 (17.4)
Local	7 (10.1)
Bone	3 (4.3)
Adrenal	2 (2.9)
Spleen	1 (1.4)
Brain	1 (1.4)
Total	69 (100)

(2.9%), spleen (1.4%), and brain (1.4%) **(Table 3)**. One-year and 3-year extrahepatic disease-free survival rates and the results of univariate analysis by log-rank test are shown in **Table 2**. Among the 13 clinicopathologic factors investigated, ≥4 hepatic metastases, non-hepatectomy, and serum CA19-9 elevation (>36.4 U/mL) correlated with a short period before the occurrence of extrahepatic metastasis. Extrahepatic disease-free survival curves according to CEA and CA19-9 levels are shown in **Figure 2**. Although serum CA19-9 levels did not correlate with types of therapy, the extrahepatic disease-free survival rate in patients with serum CA19-9 elevation was significantly worse than it was in patients without such elevation **(Figure 2B)**. Extrahepatic disease-free survival rates did not differ according to serum CEA levels **(Figure 2A)**.

Multivariate analysis of the three significant factors derived from univariate analysis (≥4 hepatic metastases, non-hepatectomy performed, and serum CA19-9 elevation), serum CA19-9 elevation (risk ratio, 1.84; 95% confidence interval; [CI], 1.04 to 3.29) and non-hepatectomy (risk ratio, 1.62; 95%CI, 1.20 to 2.21) proved to be significant risk factors for extrahepatic metastasis in patients with liver metastasis from colorectal carcinoma **(Table 4)**.

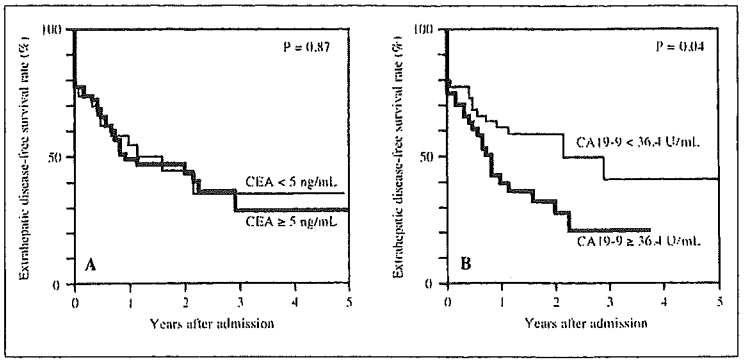

FIGURE 2 Extrahepatic disease-free survival according to serum levels of CEA or CA19-9 in patients with liver metastases from colorectal carcinoma. Curves drawn by the Kaplan-Meier method and tested by the log-rank test.

DISCUSSION

The number of patients undergoing hepatic resection for liver metastasis from colorectal carcinoma has increased, and the results of surgical treatment at 5 years after resection have improved. The 5-year survival and disease-free survival rates have been reported to be 26% to 47% (2,4,8-11,13,15), and 15% to 28% (2,4,8-11), respectively. Risk for the recurrence or cancer-related death after hepatic resection has been investigated, and most authors agree on the following risk factors: hepatic disease-free interval (2,9,11), number (4,9,10,13) or size (9,10) of metastatic lesions, preoperative serum level of CEA (4,15), nodal metastasis in the hepatic hilum (2), and modes of spread around the hepatic tumor (11,16). Some authors reported the following patient selection criteria for liver resection of colorectal metastasis: 1) medical fitness for major laparotomy, 2) no preoperative imaging sign of disseminated disease, and 3) complete resection of hepatic metastasis with acceptable postoperative hepatic function (2,10,13). Existence of extrahepatic metastasis is not an exclusion criterion; however, the percentage of patients with extrahepatic metastasis is low, reported to be 1.8% to 11.3% (2,10,13,15). This suggests that radically resectable extrahepatic metastasis should be treated as such (1); however, most patients with extrahepatic metastasis are contraindicated for liver resection. Moreover, extrahepatic metastasis is one of the worst prognostic factors for outcome after hepatic resection (2,10). Therefore, identification of risk factors for extrahepatic metastasis is important in patients with liver metastasis of colorectal carcinoma.

CA19-9 is identified by the mouse monoclonal antibody 1116 NS 19-9 raised against a human colonic carcinoma cell line (17). CA19-9 is a type of sialylated lacto-N-fucopentose II expressed on the cell surface of many colorectal cancer cells (18). CA19-9 has been shown to serve as a ligand for endothelial leukocyte adhesion molecule-1, and it may actually play a role in the adhesion of cancer cells to endothelial cells, resulting in hematogenous metastasis (19). Some clinical studies showed increased preoperative serum CA19-9 level in patients with colorectal carcinoma to be as a predictor of postoperative liver metastasis (20,21). Only a few investigators mentioned the utility of serum CA19-9 in patients with colorectal liver metastasis. Shirabe *et al.* (14) showed that preoperative serum level of CA19-9 did not affect patient survival after hepatic resection. Wang *et al.* (22) showed the serum level of CA19-9 to be an independent prognostic factor in patients with metastatic colorectal cancer. In the present study, although the type of therapy (hepatic resection and/or thermal ablation vs. chemotherapy alone) was not related to serum levels of CEA or CA19-9, elevation of serum CA19-9 was significantly related to extrahepatic metastasis in patients with colorectal liver metastasis. This suggests that serum CA19-9 is an independent risk factor for extrahepatic metastasis in patients with colorectal liver metastasis.

CEA is also known as the most sensitive tumor

TABLE 4 Multivariate Analysis for Extrahepatic Metastasis after Admission

Clinical variable	Regression coefficient	Risk ratio	95% confidence interval	*P* value
CA19-9 (U/mL)	0.6081			0.035
<36.4		1		
≥36.4		1.837	1.043-3.291	
Hepatectomy	0.4845			0.002
Performed		1		
Not performed		1.623	1.195-2.211	
Number of Metastases	0.3051			0.329
<4		1		
≥4		1.357	0.732-2.494	

marker for many carcinomas, including colorectal malignancy (23). Preoperative serum CEA elevation is reported to be 61.3% to 85.6% in patients with colorectal liver metastases (8-10,14). Serum CEA is reported to be a predictor of postoperative outcome or early recurrent disease in patients with colorectal carcinoma (12,24). Some authors have shown the utility of CEA as a prognostic factor in patients with colorectal metastasis who undergo hepatic resection (2,4). Other authors have shown that preoperative serum CEA level is not related to patient survival after hepatic resection (10,13,14). Similar to results from previous reports, serum CEA was elevated in 68.9% of our patients with liver metastasis. However, serum CEA elevation was not adversely related to occurrence of extrahepatic metastasis in our patients. Our results suggest that to determine risk of extrahepatic metastases serum CA19-9 should be considered, not serum CEA.

In the present study, local control of hepatic tumor (hepatic resection and/or thermal ablation) in patients with colorectal liver metastasis favorably affected the time to occurrence of extrahepatic metastasis. This can be explained as follows. First, synchronous extrahepatic metastasis was frequently seen in patients who had not undergone hepatectomy. Second, liver metastasis could produce extrahepatic hematogenous deposits. Several investigators (11,14,16) showed liver metastasis from colorectal carcinoma invading the portal vein, hepatic vein, bile duct, and perineural or periportal lymphatic system, and suggested that this mode of spread would cause secondary extrahepatic metastasis (e.g. lung or hepatic hilar lymph node metastasis). Nakajima *et al.* (25) showed that location of the liver adjacent to the hepatic vein was a significant predictor of recurrence in the lung. They indicated that lung metastasis after hepatic resection would be associated with cancer cell spread through the hepatic vein. Previous reported findings and our present results suggest that leaving the metastatic liver tumor might promote extrahepatic metastasis in patients with liver metastasis.

In conclusion, serum CA19-9 elevation is a risk factor for extrahepatic metastasis, and CEA appears to be useless for predicting extrahepatic metastasis in patients with resected or non-resected colorectal liver metastasis. In patients with colorectal liver metastasis and serum CA19-9 elevation, extrahepatic metastasis should be considered, and systemic chemotherapy, rather than transhepatic arterial infusion therapy should be performed.

REFERENCES

1 **Ambiru S, Miyazaki M, Ito H, Nakagawa K, Shimizu H, Kato A, Nakamura S, Omoto H, Nakajima N:** Resection of hepatic and pulmonary metastases in patients with colorectal carcinoma. Cancer 1998; 82:274-278.

2 **Minagawa M, Makuuchi M, Torzilli G, Takayama T, Kawasaki S, Kosuge T, Yamamoto J, Imamura H:** Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 2000; 231:487-499.

3 **Bolton JS, Fuhrman GM:** Survival after resection of multiple bilobar hepatic metastases from colorectal carcinoma. Ann Surg 2000; 231:743-751.

4 **Choti MA, Sitzmann JV, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, Lillemoe KD, Yeo CJ, Cameron JL:** Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002; 235:756-766.

5 **Wagman LD, Kemeny MM, Leong L, Terz JJ, Hill LR, Beatty JD, Kokal WA, Riihimaki DU:** A prospective, randomized evaluation of the treatment if colorectal cancer metastatic to the liver. J Clin Oncol 1990; 8:1885-1893.

6 **Kokudo N, Seki M, Ohta H, Azekura K, Ueno M, Sato T, Moroguchi A, Matsubara T, Takahashi T, Nakajima T, Aiba K:** Effects of systemic and regional chemotherapy after hepatic resection for colorectal metastases. Ann Surg Oncol 1998; 5:706-712.

7 **Lorenz M, Müller HH, Schramm H, Gassel HJ, Rau HG, Ridwelski K, Hauss J, Stieger R, Jauch KW, Bechstein W, Encke A:** Randomized trial of surgery versus surgery followed by adjuvant hepatic arterial infusion with 5-fluorouracil and folinic acid for liver metastases of colorectal cancer. Ann Surg 1998; 228:756-762.

8 **Registry of Hepatic Metastases:** Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of indications for resection. Surgery 1988; 103:278-288.

9 **Nordlinger B, Guiguet M, Vallant JC, Balladur P, Boudjema K, Bachellier P, Jaeck D:** Surgical resection of colorectal carcinoma metastases to the liver: a prognostic scoring system to improve case selection, based on 1568 patients. Cancer 1996; 77:1254-1262.

10 **Fong Y, Cohen AM, Fortner JG, Enker WE, Turbull AD, Coit DG, Marrero AM, Prasad M, Blumgart LH, Brennan MF:** Liver resection for colorectal metastases. J Clin Oncol 1997; 15:938-946.

11 **Sasaki A, Aramaki M, Kawano K, Yasuda K, Inomata M, Kitano S:** Prognostic significance of intrahepatic lymphatic invasion in patients with hepatic resection due to metastases from colorectal carcinoma. Cancer 2002; 95:105-111.

12 **American Society of Clinical Oncology:** Clinical practice guidelines for the use of tumor markers in breast and colorectal cancer. J Clin Oncol 1996; 14:2843-2877.

13 **Ambiru S, Miyazaki M, Isono T, Ito H, Nakagawa K, Shimizu H, Kusashiro K, Furuya S, Nakajima N:** Hepatic resection of colorectal metastases: analysis of prognostic factors. Dis Colon Rectum 1999; 42:632-639.

14 **Shirabe K, Takenaka K, Gion T, Fujiwara Y, Shimada M, Yanaga K, Maeda T, Kajiyama K, Sugimachi K:** Analysis of prognostic risk factors in hepatic resection for metastatic colorectal carcinoma with special reference to the surgical margin. Br J Surg 1997; 84:1077-1080.

15 **Nagashima I, Oka T, Hamada C, Naruse K, Osada T, Muto T:** Histopathologic prognostic factors influencing long-term prognosis after surgical resection for hepatic metastases from colorectal cancer. Am J Gastroenterol 1999; 94:739-743.

16 **Yamamoto J, Shimada K, Kosuge T, Yamasaki S, Sakamoto M, Fukuda H:** Factors influencing survival of patients undergoing hepatectomy for colorectal metastases. Br J Surg 1999; 86:332-337.

17 **Koprowski H, Steplewski Z, Mitchell K, Herlyn M, Herlyn D, Fuhrer P:** Colorectal carcinoma antigens detected by hybridoma antibodies. Somatic Cell Genetics 1979; 5:957-972.

18 **Magnani JL, Nilsson B, Brockhaus M, Zopf D, Steplewski Z, Koprowski H, Ginsburg V:** A monoclonal antibody-defined antigen associated with gastrointestinal cancer is a ganglioside containing sialylated lacto-N-fucopentose II. J Biol Chem 1982; 257:14365-14369.

19 **Berg EL, Magnani J, Warnock RA, Robinson MK,**

Butcher EC: Comparison of L-selectin and E-selectin ligand specificities: the L-selectin can bind the E-selectin ligands sialyl Le(x) and sialyl Le(a). Biochem Biophys Res Commun 1992; 184:1048-1055.

20 **Ueda T, Shimada E, Urakawa T:** The clinicopathologic features of serum CA 19-9-positive colorectal cancer. Jap J Surg 1994; 24:518-522.

21 **Kouri M, Pyrhonen S, Kuusela P:** Elevated CA 19-9 as the most significant prognostic factor in advanced colorectal carcinoma. J Surg Oncol 1992; 49:78-85.

22 **Wang WS, Lin JK, Chiou TJ, Liu JH, Fan FS, Yen CC, Lin TC, Jiang JK, Yang SH, Wang HS, Chen PM:** CA 19-9 as the most significant prognostic factor of metastatic colorectal cancer. Hepatogastroenterology 2002; 49:160-164.

23 **Gold P, Freedman So:** Specific carcinoembryonic antigen of the human digestive system. J Exp Med 1965; 122:467-481.

24 **Wanebo HJ, Rao B, Pinsky CM, Hoffman RG, Stearns M, Schwartz MK, Oettgen HF:** Preoperative carcinoembryonic antigen level as a prognostic indicator in colorectal cancer. N Engl J Med 1978; 299:448-451.

25 **Nakajima Y, Nagao M, Ko S, Kanehiro H, Hisanaga M, Aomatsu Y, Ikeda N, Shibaji T, Ogawa S, Nakano H:** Clinical predictors of recurrence site after hepatectomy for metastatic colorectal cancer. Hepatogastroenterology 2001; 48:1680-1684.

Original Paper

Risk Factors for Early Extrahepatic Metastasis in Patients with Liver Metastasis from Colorectal Carcinoma

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KEY WORDS:
Colorectal cancer; Liver metastasis; Extrahepatic metastasis; Hepatic resection

ABBREVIATIONS:
Radiofrequency Ablation Therapy (RFA); Carcinoembryonic Antigen (CEA)

ABSTRACT

Background/Aims: Hepatic resection is one of the most effective therapies for colorectal liver metastasis. However, extrahepatic metastasis is frequently encountered within a short time postoperatively. We attempted to clarify the risk factors for extrahepatic metastasis in patients with colorectal liver metastasis.

Methodology: We retrospectively analyzed data obtained from 116 consecutive patients with colorectal liver metastasis. To determine predictors of extrahepatic metastasis within 1 year of admission for treatment of colorectal liver, we examined 12 clinicopathologic factors by univariate and multivariate logistic regression analyses.

Results: Eighty-five underwent hepatectomy and/or thermal ablation (hepatectomy group) and 31 underwent only chemotherapy (non-hepatectomy group). Thirty-one in the hepatectomy group and 19 in the non-hepatectomy group developed extrahepatic metastasis at 1 year after admission. Univariate analysis showed that treatment without hepatectomy and lymphatic vessel permeation at the primary site were significant predictive factors for extrahepatic metastasis within 1 year. Multivariate analysis showed lymphatic permeation of the primary tumor, and treatment without hepatectomy to be significantly related to the occurrence of extrahepatic metastasis within 1 year.

Conclusions: The two factors that we identified put patients with colorectal liver metastasis at high risk for extrahepatic metastasis. Systemic chemotherapy may be needed to prevent extrahepatic disease in such patients.

INTRODUCTION

Hepatic resection is one of the most effective therapies for liver metastasis from colorectal carcinoma (1,2). Methods of patient selection for hepatic resection in cases of colorectal liver metastasis have been considered, and thus there have been many investigations into risk factors predicting poor prognosis or recurrent disease after hepatectomy (3-9). Extrahepatic metastasis has been identified as one of the most adverse factors affecting outcome of patients with liver metastases from colorectal carcinoma (4,8). Unfortunately, extrahepatic metastasis is frequently encountered within several months after hepatic resection for liver metastases from colorectal carcinoma (10-13). Being able to predict early extrahepatic metastasis is very important in determining treatment options, particularly surgery, for patients admitted for liver metastasis from colorectal carcinoma. However, the indications for surgical resection in cases of liver metastasis from colorectal carcinoma vary from institution to institution (3,4,6,8), and selection bias may have influenced reported studies of outcomes after hepatic resection. Thus, we investigated risk factors for extrahepatic metastasis in patients with resectable and non-resectable liver metastasis from colorectal carcinoma.

METHODOLOGY

Between January 1984 and December 2000, 134 patients with liver metastasis from colorectal carcinoma were admitted to the Department of Surgery I, Oita University Faculty of Medicine. Of these 134 patients, 18 were excluded from the present study. Two died in the hospital after hepatectomy, 2 died of unrelated diseases within 1 year after hepatectomy, 2 were of lost to follow-up, and in 12 colectomy was not performed because of the advanced stage of the disease. One hundred and sixteen, for whom outcome at 1 year after admission was clear, were enrolled in the present study.

We perform hepatectomy for liver metastases from colorectal carcinoma according to the following criteria: fewer than 4 hepatic tumors, no extrahepatic metastasis, adequate residual liver function after resection, and absence of contraindications to surgery. Some exceptional cases were included in this study: 1 patient with solitary lung metastasis underwent hepatic and pulmonary resections under the same

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anesthesia; 1 patient with local recurrence of rectal carcinoma and 1 with multiple lung metastases of colon carcinoma underwent palliative limited hepatic resection and radiofrequency ablation therapy (RFA); 18 patients with more than 4 hepatic tumors underwent hepatic resection and/or thermal ablation therapy, including microwave coagulation or RFA.

Of the 116 patients with liver metastasis from colorectal carcinoma, 85 underwent hepatic resection and/or thermal ablation therapy (hepatectomy only, n=74: hepatectomy with thermal ablation therapy, n=5; and thermal ablation therapy only, n=6) (hepatectomy group), and 31 patients underwent systemic or transhepatic arterial infusion chemotherapy (non-hepatectomy group). Most patients in the hepatectomy group received no adjuvant chemotherapy by transhepatic arterial infusion therapy. At the time of admission, extrahepatic metastasis was found in 3 hepatectomy group patients and in 11 non-hepatectomy group patients (**Figure 1**).

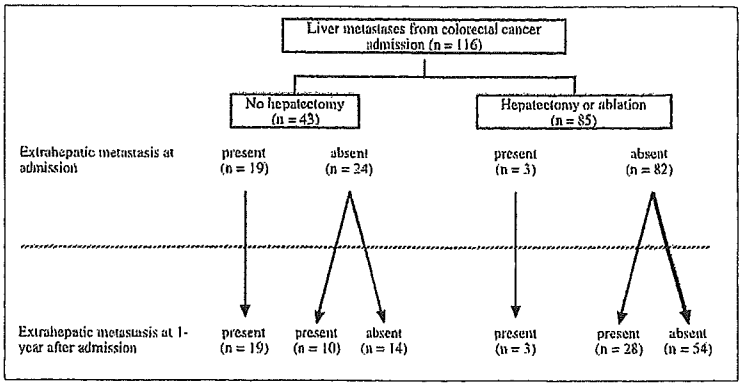

FIGURE 1 Outcome of patients with liver metastasis form colorectal carcinoma. Note that at 1 year after admission, 19 of 31 non-hepatectomy patients and 31 of 85 hepatectomy patients showed extrahepatic metastasis.

We analyzed a total of 12 clinicopathologic factors, all of which are shown in **Table 1**. Patient outcomes were determined by referring to clinical records as of December 31, 2001. All patients in the hepatectomy group were regularly followed up at our outpatient clinic and prospectively monitored for recurrence by monthly assessment of serum tumor markers and by ultrasound or contrast computed tomography study every 4 months. The mean and median follow-up periods after admission to our institute were 29.8 and 21.5 months, respectively. We investigated patient outcome (survival or death), follow-up time, cause of death, sites of extrahepatic metastasis, and extrahepatic disease-free survival time. We also investigated overall survival rates after admission by univariate analysis according to presence or absence of extrahepatic metastasis. Survival rates were calculated by the Kaplan-Meier method and analyzed by log-rank test. The presence or absence of extrahepatic metastasis 1 year after admission was taken as the endpoint of analysis. Clinicopathologic factors were evaluated by logistic regression analysis, and significant variables were then subjected to multivariate analysis. *P* values of less than 0.05 were considered significant.

RESULTS

Clinicopathologic Characteristics

Clinicopathologic characteristics of the 116 patients are summarized in **Table 1**. The patient group comprised 68 men and 48 women whose mean age at the time of admission was 62.1 years (median, 64; range, 33 to 84 years). Fifty-three had synchronous colorectal carcinoma and liver metastasis, and 63 had metachronous occurrences. Mean and median intervals between colorectal surgery and detection of liver metastasis were 9.1 months and 4.0 months, respectively. Fifty-one patients had a solitary liver metastasis and 65 had more than one with a mean tumor size of 41.1mm (median, 30.0mm; range, 5 to 150mm). We were unable to obtain complete histologic findings of the primary colorectal carcinoma in 6 of the 116 cases: they underwent colorectal resection at another institute prior to liver metastasis, but the complete histological record could not be obtained. Invasion of the primary tumor into the lymphatics or blood vessels was documented for 110 patients in 89 (80.9%) and 60 (54.5%) patients, respectively. The serum carcinoembryonic antigen (CEA) level at the time of admission was documented for 112 patients; mean CEA level was 153.5ng/mL (median, 19.8ng/mL; range, 0.9 to 4,490ng/mL).

Patient Outcomes

At 1 year after admission, 31 patients had died of the disease. A total of 50 patients had extrahepatic metastasis by 1 year after admission. This first extrahepatic metastasis occurred most in the lung (48.0%), followed by the lymph nodes (18.0%), peritoneum (14.0%), local (12.0%), bone (4.0%), skin (2.0%), and pleura (2.0%). The overall 1-, 3-, and 5-year survival rates were 87.0%, 43.9%, and 29.0%, respectively in the hepatectomy group and 35.5%, 0%, and 0%, respectively in the non-hepatectomy group. We classified the 116 patients into 4 groups according to the type of treatment and the presence or absence of extrahepatic metastasis 1 year after admission: hepatectomy and no extrahepatic metastasis (group A, n=54), hepatectomy and extrahepatic metastasis (group B, n=31), non-hepatectomy and no extrahepatic metastasis (group C, n=12), and non-hepatectomy and extrahepatic metastasis (group D, n=19). Survival curves for the groups are shown in **Figure 2**. Patients in group A showed the best outcome ($p<0.01$). Patients in group D showed the worst outcome ($p<0.01$). Patients in group B showed a poor outcome, similar to that of patients in group C. Of the 85 patients in the hepatectomy group, 50 showed extrahepatic metastasis during follow-up duration, and the mean and median intervals between hepatectomy and/or thermal ablation and subsequent extrahepatic metastasis were 12.2 months and 10.0 months, respectively.

Risk Factors for Extrahepatic Metastasis in Patients with Liver Metastasis from Colorectal Carcinoma

The results of univariate analysis by logistic regression modeling in relation to extrahepatic metastasis within 1 year after patient admission are shown in **Table 1**. Lymphatic permeation of primary tumor cells ($p=0.02$) and treatment without hepatectomy ($p=0.02$) were found to be significant risk factors for extrahepatic metastasis within 1 year. Vascular permeation of primary tumor cells tended to correlate with extrahepatic metastasis, but the relation did not reach statistical significance ($p=0.06$). Multivariate analysis by logistic regression modeling showed that lymphatic permeation of the primary tumor ($p<0.05$), and treatment without hepatectomy ($p=0.03$) were significantly related to extrahepatic metastasis within 1 year after admission of patients **(Table 2)**.

TABLE 1 Univariate Analysis for Extrahepatic Metastasis within 1 Year (Logistic Regression Model)

Clinical variable	No. of patients	Regression coefficient	Odds ratio	95% confidence interval	*P* value
Sex		-0.197			0.31
Male	68		1.00		
Female	48		0.68	0.314-1.430	
Age (years)		-0.019			0.92
<60	40		0.96	0.441-2.084	
≥60	76		1.00		
Primary Site		0.148			0.45
Colon	72		1.34	0.629-2.916	
Rectum	44		1.00		
Dukes' Stage		-0.159			0.42
A+B	42		0.73	0.331-1.572	
C	72		1.00		
Unknown	2				
Tumor grade		0.192			0.33
Well	46		1.00		
Non-well	67		1.47	0.686-3.201	
Unknown	3				
Lymphatic permeation of colorectal cancer		1.334			0.02
Present	89		3.80	1.285-14.00	
Absent	21		1.00		
Unknown	6				
Vascular permeation in colorectal cancer		0.754			0.06
Present	60		2.12	0.983-4.710	
Absent	50		1.00		
Unknown	6				
Interval (months)		-0.460			0.28
<12	82		1.00		
≥12	34		0.632	0.270-1.426	
Number of Metastases		0.470			0.27
<4	85		1.00		
≥4	31		1.60	0.699-3.691	
Tumor size (cm)		0.426			0.30
<5	81		1.00		
≥5	34		1.53	0.682-3.451	
Unknown	1				
CEA (ng/mL)		0.552			0.18
<10	39		1.00		
≥10	73		1.74	0.789-3.931	
Unknown	4				
Hepatectomy		0.507			0.02
Performed	85		1.00		
Not performed	31		2.76	1.196-6.578	

CEA: carcinoembryonic antigen.

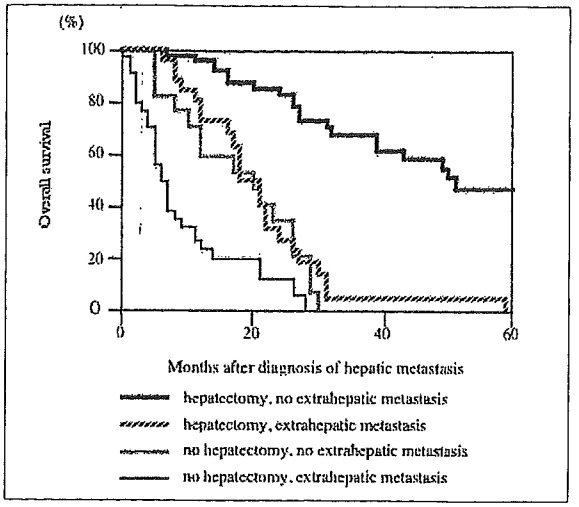

FIGURE 2 Survival curves of patients with liver metastasis from colorectal carcinoma according to presence of hepatectomy and extrahepatic metastasis 1 year after admission. Note that survival curves of hepatectomy patients with extrahepatic metastases are not significantly better than those of non-hepatectomy patients without extrahepatic metastasis.

DISCUSSION

Hepatic resection is at present the most effective therapy for liver metastasis from colorectal carcinoma. The 5-year disease-free survival rate after hepatic resection is reported at 15 to 26 percent (2,7,8). More than 70 percent of patients experience disease recurrence after hepatic resection. To improve patient survival after hepatic resection, prognostic factors have been investigated (3-9). Factors indicating a worse prognosis most often found in previous studies are a short interval between hepatic and colorectal surgeries (4,6-8), large number or size of hepatic tumor (4,6-8), unclear surgical margin (3-5,7), presence of nodal metastasis of the hepatic hilum (8), and presence of extrahepatic metastasis (3-5).

The most frequent sites of metastatic deposits from colorectal carcinoma are the liver, lung, bone, and peritoneum in that orders (11,12). Extrahepatic recurrence is considered one of the most adverse factors influencing patient survival after hepatic resection for liver metastasis from colorectal carcinoma (3-5). Therefore, knowing the clinicopathologic factors that predict extrahepatic metastasis in patients with liver metastases from colorectal carcinoma is very important. However, only a few studies of extrahepatic recurrence in such patients have been reported (9,14,15). In our previous investigation of patients who underwent hepatic resection, a short period between colorectal and hepatic surgeries (<12

months), large hepatic tumor (>5cm), and intrahepatic lymphatic invasion were associated with extrahepatic recurrence after hepatectomy (9). Nakajima *et al.* (14) showed tumor located adjacent to the hepatic vein to be a risk factor for pulmonary recurrence after hepatic resection. Yamada *et al.* (15) showed nodal metastasis of primary colorectal cancer to be a risk factor for extrahepatic recurrence after hepatectomy. All studies were conducted in patients who underwent hepatic resection. Our study group comprised both hepatectomy and non-hepatectomy, and lymphatic permeation in the primary colorectal region and treatment without hepatic resection were significant risk factors for early occurrence of extrahepatic metastasis. The results of our current and previous (9) studies suggest that cancer cells infiltrating into the lymphatic system have a direct effect on extrahepatic metastasis in patients with liver metastasis from colorectal carcinoma.

Indications for hepatic resection to treat liver metastasis from colorectal carcinoma have remained controversial even though factors predicting survival after hepatic resection have been fully investigated (3-9). Absolute contraindications to resection of colorectal liver metastasis have not been established, but most authors agree that patients should not be offered resection if they have uncontrolled primary disease or such widespread hepatic involvement that residual liver function after resection would be inadequate (16). Recent studies showed that resection of multiple bilobar hepatic metastases or both liver and pulmonary metastases can result in long-term survival in selected patients (17,18). Only a few reports specify indications for hepatic resection (3,4,6,8), and indication for surgical treatment of colorectal liver metastasis differs by institution. When prognostic factors for survival are investigated only in patients who have undergone hepatic resection, selection bias is of concern. Thus, in the present study, we used both resectable and non-resectable disease to investigate the risk factors for extrahepatic metastasis after admission.

TABLE 2 Results of Multivariate Analysis by Logistic Regression Model

Clinical variable	Regression coefficient	Risk ratio	95% confidence interval	*P* value
Lymphatic permeation of colorectal cancer	1.209		1.082-12.79	0.04
Present		3.35		
Absent		1		
Hepatectomy	0.508		1.138-6.975	0.03
Performed		1		
Not performed		2.76		
Vascular permeation in colorectal cancer	0.568		0.776-4.071	0.18
Present		1.76		
Absent		1		

In previous studies, the date of examination was taken as a clinical endpoint, and statistical analysis was performed by log-rank test or proportional hazards model (3-9,14,15). In the present study, 50 of the 85 patients who underwent hepatic resection developed extrahepatic metastasis, and more than half of the 50 developed the extrahepatic metastasis within 10 months after hepatic resection. We showed previously that microscopic hepatic vein invasion did not affect extrahepatic disease-free survival of patients after hepatic resection (9). Together, our findings suggest that early extrahepatic metastasis in patients with liver metastasis originates from the primary colorectal carcinoma rather than from the hepatic tumor. To exclude the influence of extrahepatic metastasis originating from liver metastasis (late extrahepatic metastasis), we defined the endpoint as 1 year after admission and analyzed the data by logistic regression.

In conclusion, the two factors that we identified put patients with liver metastasis from colorectal carcinoma at high risk for extrahepatic metastasis. Systemic chemotherapy may be needed to prevent extrahepatic disease in such patients.

REFERENCES

1 **Cady B, McDermott WV:** Major hepatic resection for metachronous metastases from colon cancer. Ann Surg 1985; 201:204-209.

2 **Registry of Hepatic Metastases:** Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of indications for resection. Surgery 1988; 103:278-288.

3 **Ekberg H, Tranberg KG, Andersson R, Lundstedt C, Hagerstrand I, Ranstam J, Bengmark S:** Determinants of survival in liver resection for colorectal secondaries. Br J Surg 1986; 73:727-731.

4 **Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, Marrero AM, Prasad M, Blumgart LH, Brennan MF:** Liver resection for colorectal metastases. J Clin Oncol 1997; 15:938-946.

5 **Nagashima I, Oka T, Hamada C, Naruse K, Osada T, Muto T:** Histopathological prognostic factors influencing long-term prognosis after surgical resection for hepatic metastases from colorectal cancer. Am J Gastroenterol 1999; 94:739-743.

6 **Hohenberger P, Schlag PM, Gerneth T, Herfarth C:** Pre- and postoperative carcinoembryonic antigen determinations in hepatic resection for colorectal metastases: predictive value and implications for adjuvant treatment based on multivariate analysis. Ann Surg 1994; 219:135-143.

7 **Nordlinger B, Guiguet M, Vaillant J-C, Balladur P, Boudjema K, Bachellier P, Jaeck D:** Surgical resection of colorectal carcinoma metastases to the liver: a prognostic scoring system to improve case selection, based on 1568 patients. Cancer 1996; 77:1254-1262.

8 **Minagawa M, Makuuchi M, Torzilli G, Takayama T, Kawasaki S, Kosuge T, Yamamoto J, Imamura H:** Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 2000; 231:487-499.

9 **Sasaki A, Aramaki M, Kawano K, Yasuda K, Inomata M, Kitano S:** Prognostic significance of intrahepatic lymphatic invasion in patients with hepatic resection due to metastases from colorectal carcinoma. Cancer 2002; 95:105-111.

10 **Hughes KS, Simon R, Songhorabodi S, Adson MA, Ilstrup DM, Fortner JG, Maclean BJ, Foster JH, Daly JM, Fitzherbert D:** Resection of the liver for colorectal car-