開腹移行率は、高齢者では29.3%であったが、非高齢者では12.3%であった。

D. 考察

高齢者に対してはより低侵襲の治療でのぞむべきである。今回解析したデータからは、LACであるために術後合併症が増加している傾向はなく、出血量の減少、術後在院日数の短縮という利点が認められた。長期成績についてはさらに多くの症例での検討が必要であるが、少なくとも術後早期のQOLについては満足できると考えられた。開腹移行率が高齢者において高いことは、手術時間を短縮する術者の意図があると予想できるが、詳細は明かでない。

E. 結論

今後増加すると予想される高齢者の大腸癌に対して、低侵襲である腹腔鏡手術が有用となる可能性がある。現在行われているJCOG0404は75歳以下の検討であるが、75歳超のいわゆる後期高齢者でも多施設ランダム化比較試験による検証が求められる。

F. 健康危険情報

なし。

G. 研究発表

1. 論文発表

1) 井出義人、岡田一幸、太田英夫、丸山憲太郎，横内秀起、衣田誠克、保本卓、村田幸平全身状態不良（PS=3）大腸癌多発肝転移に対して肝動注＋CPT-11療法が著効した1症例 癌と化学療法 34(12) 2059－2061

2) 冨丸慶人、保本卓、松永寛紀、井出義人、池田宜子、丸山憲太郎，横内秀起、衣田誠克、村田幸平　大腸癌肺転移に対するラジオ波焼灼療法　癌と化学療法 34(12) 2029－2031

3) 永井健一、村田幸平，瀬下巌，井出義人，丸山憲太郎，衣田誠克　魚骨の胃穿通に対して腹腔鏡下異物除去術を施行した1例 日本内視鏡外科学会雑誌　12(4) 391－395

4) K Ezumi, H Yamamoto, K Murata, M Higashiyama, B Damdinsuren, Y Nakayama, N Kyo, J Okami, CY Ngan, I Takemasa, M Ikeda, M Sekimoto, N Matsuura, M Monden. Aberrant Expression of Connexin 26 Is Associated with Lung Metastasis of Colorectal Cancer. Clin Cancer Res. 14(3) 677-684

5) R.Kawabata, Y.Doki, O.Ishikawa, H.Nakagawa, K.Takachi, I.Miyashiro, Y.Tsukamoto, H.Ohigashi, Y.Sasaki, K.Murata, S.Ishiguro, S.Imaoka. Frequent Brain Metastasis after Chemotherapy and Surgery for Advanced Esophageal Cancers. Hepato-gastroenterology 54 1043-1048

2. 学会発表

1) 村田幸平、井出義人、瀬下巌、富丸慶人、松永寛紀、横山茂樹、米田光里、丸山憲太郎、横内秀起、衣田誠克　マルチフラップゲートを用いた腹腔鏡下大腸癌手術　第107回日本外科学会定期学術集会

2) 富丸慶人、村田幸平、井出義人、瀬下巌、松永寛紀、横山茂和、米田光里、丸山憲太郎、横内秀起、衣田誠克　高齢者の大腸癌に対する腹腔鏡手術の有用性　第107回日本外科学会定期学術集会

3) 井出義人、村田幸平、冨丸慶人、瀬下巌、松永寛紀、池田宣子、丸山憲太郎、横内秀起、衣田誠克　大腸癌イレウスに対する経肛門イレウスチューブ用いた一期的腹腔鏡下手術　第62回日本消化器外科学会定期学術総会

4) 村田幸平、井出義人、瀬下巌、冨丸慶

人、松永寛紀、池田伸子、丸山憲太郎、横内秀起、衣田誠克　進行大腸癌手術を易しくするコツ　第62回日本消化器外科学会定期学術総会

5) 冨丸慶人、村田幸平、松永寛紀、井出義人、池田宣子、瀬下巌、丸山憲太郎、横内秀起、衣田誠克　高齢者における腹腔鏡下大腸癌手術　第49回日本消化器病学会大会

6) 村田幸平、井出義人、松永寛紀、岡田一幸、太田英夫、池田宣子、丸山憲太郎、横内秀起、衣田誠克　手術ビデオの開示について　第20回日本内視鏡外科学会総会

7) 井出義人、松永寛紀、岡田一幸、池田宣子、太田英夫、丸山憲太郎、横内秀起、衣田誠克、村田幸平　下部直腸癌に対し腹腔鏡下にて反転法を試みるも断端陽性にてISRを行った一手術例　第20回日本内視鏡外科学会総会

H. 知的財産権の出願・登録状況（予定を含む。）

なし。

研究成果の刊行に関する一覧表

書籍：

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
伴登　宏行	癒着症例	腹腔鏡下大腸切除研究会	腹腔鏡下大腸切除ハンドブック	へるす出版	東京	2007	88-91

雑誌：

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kitano S, Shiraishi N, Sugihara K, Tanigawa N, the Japanese Laparoscopic Surgery Study Group	A multicenter study on oncologic outcome of laparoscopic gastrectomy for early cancer in Japan	Ann Surg	245(1)	68-72	2007
Sasaki A, Kai S, Endo Y, Iwaki K, Uchida H, Tominaga M, Okunaga R, Shibata K, Ohta M, Kitano S	Prognostic value of preoperative peripheral blood monocyte count in patients with colorectal liver metastasis after liver resection	J Gastrointest Surg	11(5)	596-602	2007
Yasuda K, Inomata M, Shiromizu A, Shiraishi N, Higashi H, Kitano S	Risk factors for occult lymph node metastasis of colorectal cancer invading the submucosa and indications for endoscopic mucosal resection	Dis Colon Rectum	50(9)	1370-1376	2007
猪股雅史，白石憲男，北野正剛	内視鏡外科における基礎研究の進歩	医学のあゆみ	220(8)	612-616	2007
安田一弘，白石憲男，北野正剛	消化器癌に対する腹腔鏡下手術と内視鏡治療の境界	カレントテラピー	25(6)	57-59	2007
猪股雅史，衛藤　剛，白石憲男，北野正剛，小西文雄，杉原建一，渡邉昌彦，森谷冝皓	進行結腸癌に対する腹腔鏡下手術－厚生労働省班研究に基づく本邦の現況－	日本内視鏡外科学会雑誌	13(1)	47-52	2007
Akasu T, Yamaguchi T, Fujimoto Y, Ishiguro S, Yamamoto S, Fujita S, Moriya Y.	Abdominal sacral resection for posterior pelvic recurrence of rectal carcinoma: analyses of prognostic factors and recurrence patterns	Ann Surg Oncol	14	74-83	2007

河村 裕, 小西文雄	早期大腸癌－EMR, 鏡視下手術の対象となるもの	外科治療	96	501-505	
Kinugasa Y, Murakami G, Suzuki D, Sugihara K	Histological identification of fascial structures posteriorolateral to the rectum	Br J Surg	94	620-626	2007
Nakamura T, Kokuba Y, Mitomi H, Onozato W, Hatate K, Satoh T, Ozawa H, Ihara A, Watanabe M	Comparison between the oncologic outcome of laparoscopic surgery and open surgery for T1 and T2 rectosigmoidal and rectal carcinoma : Mached case-control study	Hepato-gastroenterology	54	1094-1097	2007
前田耕太郎, 花井恒一, 佐藤美信, 升森宏次, 小出欽和, 船橋益夫	低位前方切除時の安全な消化管器械吻合	手術	61(9)	1314-1318	2007
Matsuoka H, Masaki T, Sugiyama M, Atomi Y, Ohkura Y, Sakamoto A	Morphological characteristics of lateral pelvic lymph nodes in rectal carcinoma	Langenbecks Arch Surg	392(5)	543-547	2007
Kobayashi A, Sugito M, Ito M, Saito N	Predictors of successful salvage surgery in local pelvic recurrences of rectosigmoid colon and rectal cancers	Surg Today	37	853-859	2007
奥田準二、田中慶太朗、近藤圭策、加藤哲也、茅野 新、田代圭太郎、谷川允彦	大腸癌に対する腹腔鏡下手術の現状と問題点	癌の臨床	53(12)	739-746	2007
工藤進英, 工藤由比, 池原伸直, 小林泰俊, 石田文生, 樫田博史, 遠藤俊吾, 日高英二, 辰川貴志子, 浜谷茂治	側方発育型大腸腫瘍（LST）の治療に消化器外科医はどう関わるべきか	消化器外科	30(5)	629-635	2007
斉田芳久、中村 寧、榎本俊行、炭山嘉伸	腹腔鏡下大腸手術における吻合の工夫	臨床外科	63	223-228	2008
岡島正純、恵木浩之、吉満政義、川原知洋、栗田雄一、金子 真	内視鏡外科手術技術の客観的評価への挑戦：Hiroshima University Endoscopic Surgical Assessment Device	日本消化器外科学会雑誌	40(3)	355	2007
福永正氣, 杉山和義, 永仮邦彦, 菅野雅彦, 坂本修一, 須田 健, 飯田義人, 吉川征一郎,	直腸癌に対する内視鏡手術	外科治療	96	43-52	2007

伊藤泰智，勝野剛太郎，津村秀憲，木所昭夫					
Hasegawa H, Ishii Y, Nishibori H, Endo T, Watanabe M, Kitajima M	Short- and midterm outcomes of laparoscopic surgery compared for 131 patients with rectal and rectosigmoid cancer	Surg Endosc	21(6)	920-924	2007
三上和久，宗像康博，沖田浩一，佐近雅宏，関野　康，村中　太	手術手技　新しい内視鏡下体内結紮法の提案	日鏡外会誌	12	567-571	2007
齊藤修治，山口茂樹，石井正之，絹笠祐介，赤本伸太郎，奥本龍夫，富岡寛行，間　浩之，川崎誠一，小島隆司	腹腔鏡下大腸癌手術の現状と短期成績	癌の臨床	53	729-732	2007
Fukunaga Y, Higashino M, Tanimura S, Kishida S, Fujiwara Y, Ogata, A, Osugi H	Laparoscopic mesorectal excision with preservation of the pelvic autonomic nerves for rectal cancer	Hepato-Gastroenterology	54(73)	85-90	2007
Nozaki I, Kurita A, Nasu J, Kubo Y, Aogi K, Tanada M, Takashima S	Higher incidence of gastric remnant cancer after proximal than distal gastrectomy	Hepatogastroenterology	54	1604-1608	2007
小澤平太，國場幸均，旗手和彦，熊本浩志，佐藤武郎，小野里航，中村隆俊，井原　厚，渡邊昌彦	大腸癌に対する腹腔鏡手術	北里医学	37(1)	25-27	2007
山岸茂，藤井正一，樅山将士，永野靖彦，大田貢由，市川靖史，國崎主税，池　秀之，大木繁男，嶋田　紘	【直腸癌に対する腹腔鏡手術の問題点】 直腸癌に対する腹腔鏡手術における縫合不全の危険因子-縫合器、吻合器とその操作を中心に-	癌の臨床	53	131-136	2007
谷田　司，能浦真吾，大植雅之，関　洋介，後藤邦仁，本告正明，岸健太郎，高地　耕，山田晃正，宮代勲，大東弘明，矢野雅彦，石川　治，今岡真義，村田幸平，亀山雅男	大腸癌腹腔洗浄細胞診の意義と腹膜播種の予防	癌と化学療法	34(12)	1934-1939	2007

12. トラブルシューティング (6) 癒着症例

腹腔鏡下手術は，腹腔内という制限された空間で行う。その空間を作るのを困難にする大きな原因は，腹腔内の癒着である。自験例に基づき，癒着の対処法について述べる。

A. 対　象

筆者自身が執刀した腹腔鏡下大腸切除術358例中，腹部手術既往例の内訳を**表11**に示す。

112例（31％）に125回の腹部手術が行われていた。多いのは虫垂切除の56例，婦人科疾患に対する手術44例であった。さらに胃良性疾患に対する胃切除術と開腹胆嚢摘出術が7例と続く。95％の症例で癒着を剝離し，手術を遂行できた。ちなみに腹腔鏡下手術後は腹腔内癒着が少ないのが実感できる。

表11. 腹部手術既往症例の内訳

腹部手術既往症例	症例数
虫垂切除術	56
婦人科良性疾患	
子宮摘出	31
卵巣摘出	2
卵管結紮術	9
婦人科悪性疾患	
卵巣癌	1
子宮癌	1
胃良性疾患	7
胃悪性疾患	2
開腹胆嚢摘出術	7
腹腔鏡下胆嚢摘出術	2
腹腔鏡下大腸切除術	3
腹腔鏡下子宮摘出術	2
腸閉塞	2
泌尿器科手術	4
	重複を含む

癒着が原因で開腹手術に移行したのは6例であった。5例はS状結腸切除を予定した症例で，うち4例は肥満者であった。胆嚢摘出術2例，子宮摘出術2例の既往があった。癒着に加え，肥満のため小腸が視野から排除できず，開腹手術に移行した。このような症例では後腹膜アプローチが有効かもしれない。

肥満がなかった2例では卵巣癌術後が1例，子宮癌術後が1例であった。この2例は後腹膜の広範なリンパ切郭清が行われていた。卵巣癌術後症例では回盲部切除術を予定したが，右骨盤壁に小腸がべったりと癒着しており，損傷してしまった。子宮癌術後症例では，進行S状結腸癌に対し手術したが，周囲のリンパ節郭清をされた左総腸骨動脈に腫瘍が癒着していた。開腹して，動脈の外膜を削るようにして，切除した。

この2例では本人，家族から前回手術時の正確な情報が得られなかったため，腹腔鏡下手術を予定してしまったが，絶対的な禁忌である。

B. トロッカーの挿入

安全にトロッカーを挿入することが第一歩である。腹腔内の癒着を超音波検査で評価し，マッピングするという報告があり，有用とされている。

われわれは上腹部手術既往症例では下腹部に，下腹部手術既往例では上腹部に，病変の対側の側腹部にopen laparoscopy法で第1トロッカーを挿入している（**図103**）。超音波検査をしていないが，今のところ大きな問題はない。

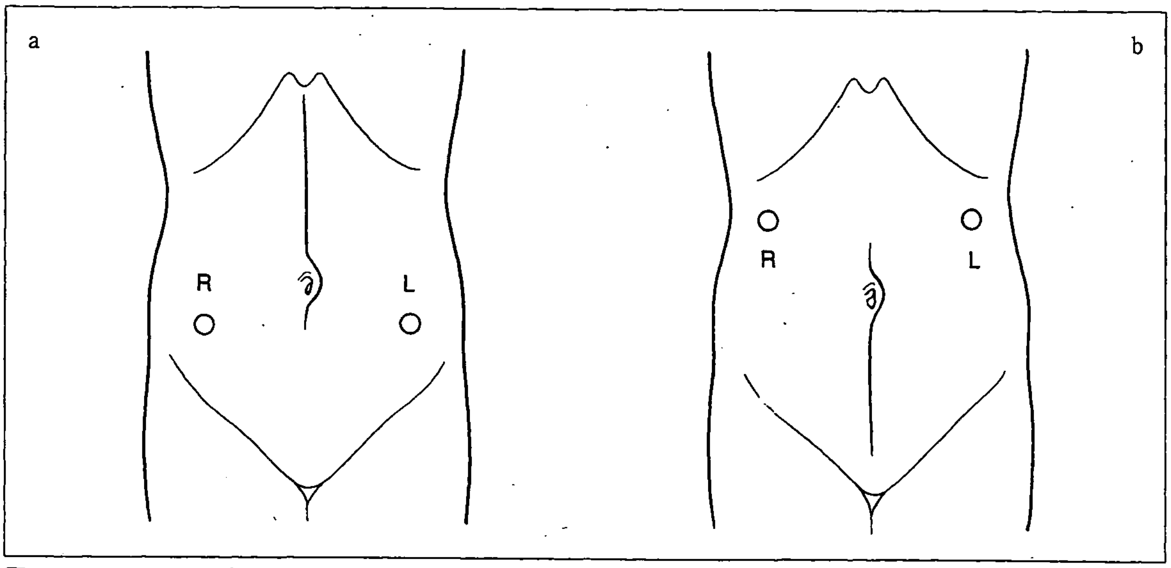

図103. トロッカーの挿入

a：上腹部手術既往例では，下腹部に第１トロッカーをopen laparoscopy法で挿入する。左側結腸切除ではRの部位に，右側結腸切除ではLの部位に留置する

b：下腹部手術既往例では上腹部に第１トロッカーを挿入する。同様に左側結腸切除ではRの部位に，右側結腸切除ではLの部位に留置する

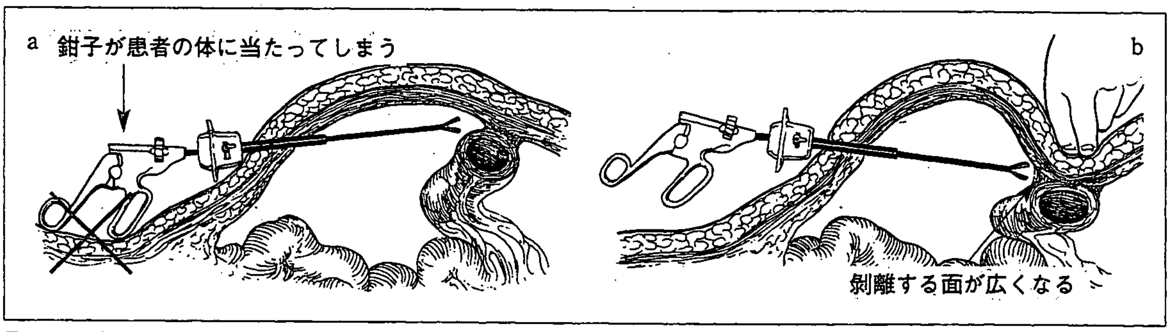

図104. 腹壁との癒着の剝離

a：腹壁を膨らませたままであれば，鉗子が上向きになり，患者の体に当たってしまい，操作できなくなる

b：癒着部位を外から押し下げることにより，鉗子が上を向かなくなり，操作が容易になる。さらに癒着臓器と腹壁の癒着している面が広く展開される

C．剝離の実際

一番重要なのは，深追いしない，無理をしないことである。前述した卵巣癌術後で小腸を損傷した症例では，術後に腸閉塞で再手術し，さらに創感染が起こり，腹壁瘢痕ヘルニアとなってしまった。低侵襲であるべき術式の適応を誤ったばかりに，逆に患者に大きな負担をかけてしまったのである。

ただ，なるべく腹腔鏡下で剝離しておいたほうが，開腹に移行してからの操作が楽である。とくに腹壁との癒着を剝離しておけば，開腹時の臓器損傷の心配がなくなる。その見極めを自問自答しながら，手術をしている。

腹腔内の癒着を 3 つに分けた。実際はこれらが組み合わさっていることが多い。

1）腹壁との癒着

腸管や大網が腹壁と癒着しているものである。ワーキングスペースを作成するために，まず剝離しなければならない癒着である。胃切除術や開腹胆囊摘出術の上腹部の術後では，大網だけでなく小腸が癒着していることが多い。一方，虫垂切除術，子宮摘出術などの下腹部の術後では，大網のみが癒着していることがほとんどである。

正中部の剝離を行うときに腹壁を膨らませたままだと，鉗子が上方向に向かい，鉗子の手元が患者の大腿部，前胸部などに当たって操作ができなくなる。図104のように癒着部位を体外から押すことにより，鉗子の向きが水平から下方向となり，操作が楽になる。さらに腹壁と癒着臓器の角度が広がり，剝離する面が明瞭に展開できるようになる。

腸管を剝離するときは，損傷しないことがもっとも重要である。筆者は熱損傷が怖いので通電を行わず，鋏で鋭的に行っている。腸管と腹壁の境界が明瞭でないときは，あえて壁側腹膜に切り込むようにしている。万が一腸管を損傷した場合は，針糸で仮に縫合しておき，小開腹をしたときに腹壁外に取り出し，直視下で修復している。大網の剝離は出血しないように超音波切開凝固装置で行っている。

2）腸管の癒着

視野を展開するために腸管を移動させるのを妨げるような腸管と腸管，腸管と腸間膜の癒着である。

S状結腸が非常に長い例ではS状結腸間膜同士，S状結腸と大動脈の前面の腹膜，さらにS状結腸と横行結腸の癒着などに遭遇することが多い。このときには十二指腸，下腸間膜動脈根部の確認やS状結腸の展開ができない（図105a）。また，横行結腸間膜と小腸間膜が癒着し，回結腸動静脈の根部や十二指腸が確認できない症例もある（図105b）。

したがって郭清すべき血管の根部，切除すべき腸管が展開できるように根気よく剝離するしかない。不十分な視野展開ではオリエンテーションがつかず，副損傷をきたしやすいので，よい視野を得るためにトロッカーを追加するのを惜しんではならない。

剝離の実際は開腹手術と変わりはない。剝離しやすいところから始め，剝離創がわからないときは，あえて切除側の腸管の漿膜ぎりぎりや，腸間膜に切り込むこともある。

3）結腸と周囲の癒着

もっとも多いのは子宮摘出や卵巣摘出後の骨盤側壁とS状結腸の癒着（図106a）で，時に非常に硬いことがある。胆囊摘出後，胃切除後の横行結腸と肝門部の癒着（図106b）もこれに含めた。

切除すべき結腸が癒着している場合がほとんどなので，剝離層がわからないときには，その結腸の漿膜を少し損傷してもいいような気持ちで剝離をしているが，その外側には尿管や総胆管，十二指腸といった重要臓器があることを念頭に入れ，慎重のうえにも慎重に行う。他部位の操作を終えてしまい，その癒

着部位の上で小開腹をすれば，直視下に剝離を行うことも可能である。

婦人科癌で後腹膜の広範なリンパ節郭清をした症例以外は，慎重に根気よく剝離を行えば，腹腔鏡下手術を遂行することは可能である。しかし，いったん臓器を損傷すれば，患者により大きな侵襲を加えてしまうことを常に念頭に入れ，手術に取り組むべきである。

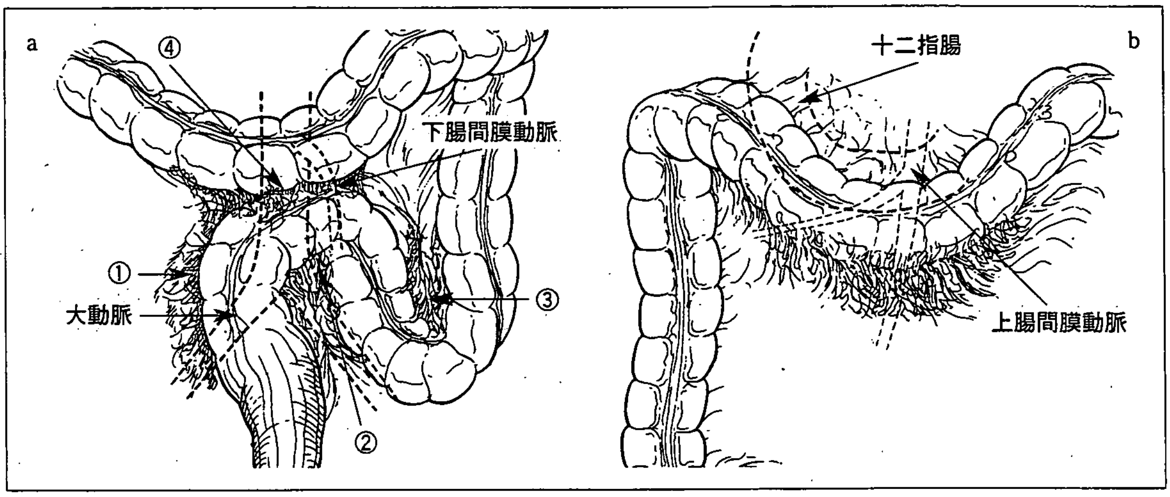

図105. 腸管の癒着の剝離
a：S状結腸が長い症例ではS状結腸の癒着が強いことがある。①S状結腸と大動脈前面の腹膜との癒着，②，③：S状結腸間膜同士の癒着，④S状結腸と横行結腸の癒着
b：横行結腸間膜と小腸間膜が癒着し，回結腸動静脈の根部や十二指腸が確認できないことがある

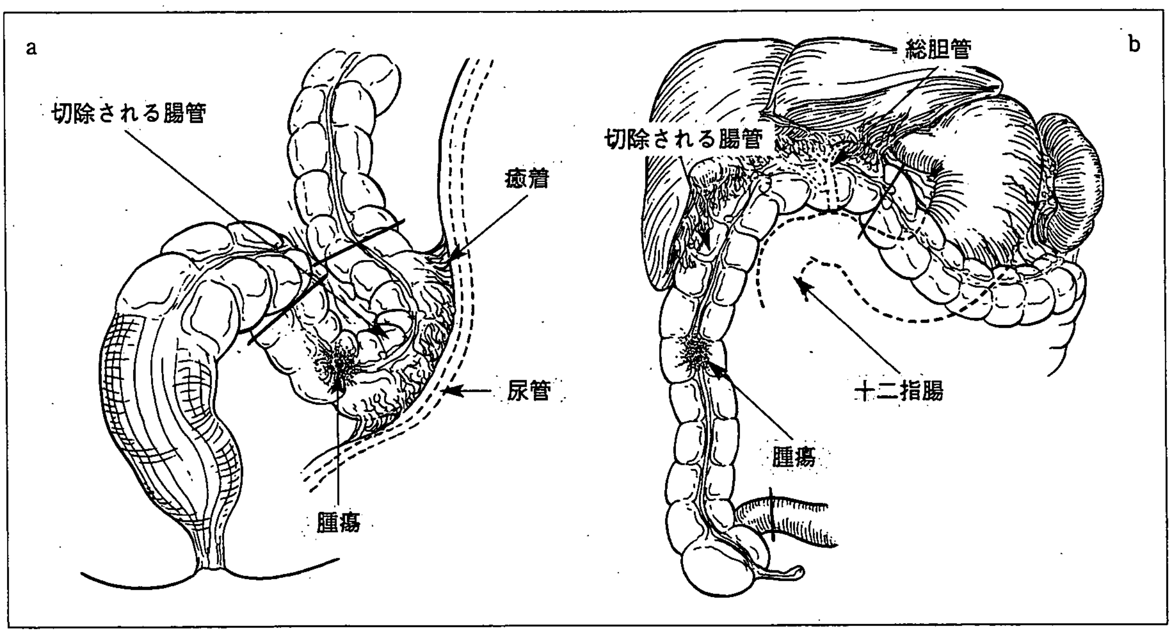

図106. 結腸と周囲の癒着の剝離
a：婦人科の手術後の癒着が一般的である。腫瘍切除のため，剝離した腸管は切除されることが多い
b：胆囊摘出術後，胃切除術後は横行結腸が肝門部に癒着することが多い

A Multicenter Study on Oncologic Outcome of Laparoscopic Gastrectomy for Early Cancer in Japan

Seigo Kitano, MD, PhD, Norio Shiraishi, MD, PhD,* Ichiro Uyama, MD, PhD,† Kenichi Sugihara, MD, PhD,‡ Nobuhiko Tanigawa, MD, PhD,§ and the Japanese Laparoscopic Surgery Study Group*

Background: Laparoscopic surgery for gastric cancer is technically feasible, but it is not widely accepted because it has not been evaluated from the standpoint of oncologic outcome. We conducted a retrospective, multicenter study of a large series of patients in Japan to evaluate the short- and long-term outcomes of laparoscopic gastrectomy for early gastric cancer (EGC).
Methods: The study group comprised 1294 patients who underwent laparoscopic gastrectomy during the period April 1994 through December 2003 in 16 participating surgical units (Japanese Laparoscopic Surgery Study Group). The short- and long-term outcomes of these patients were examined.
Results: Distal gastrectomy was performed in 1185 patients (91.5%), proximal gastrectomy in 54 (4.2%), and total gastrectomy in 55 (4.3%); all were performed laparoscopically. The morbidity and mortality rates associated with these operations were 14.8% and 0%, respectively. Histologically, 1212 patients (93.7%) had stage IA disease, 75 (5.8%) had stage IB disease, and 7 (0.5%) had stage II disease (the UICC staging). Cancer recurred in only 6 (0.6%) of 1294 patients treated curatively (median follow-up, 36 months; range, 13–113 months). The 5-year disease-free survival rate was 99.8% for stage IA disease, 98.7% for stage IB disease, and 85.7% for stage II disease.
Conclusions: Although our findings may be considered preliminary, our data indicate that laparoscopic surgery for EGC yields good short- and long-term oncologic outcomes.

(*Ann Surg* 2007;245: 68–72)

In Japan, the incidence of early gastric cancer has increased to more than 50% of the overall incidence of gastric cancer because of the development of diagnostic instruments and increased use of mass and individual screenings.[1,2] For the management of patients with early gastric cancer (EGC), minimally invasive therapies, such as endoscopic and laparoscopic procedures, have been available since the 1980s.[3,4] Since the first report of laparoscopy-assisted distal gastrectomy (LADG) in 1994, LADG has been widely adopted for EGC and the number of patients undergoing LADG has been increasing in Japan.[5] Laparoscopy-assisted gastrectomy (LAG) is now performed not only as distal gastrectomy but also as proximal gastrectomy and total gastrectomy.[6–8]

Several small retrospective studies analyzing the short-term outcome of LAG showed that patients who underwent LAG had less pain, earlier recovery to active daily life, a shorter hospital stay, and better quality of life than patients who underwent conventional open surgery.[9–11] However, LAG for the treatment of malignancies remains controversial because of the lack of large-scale study data on the short-term and long-term outcomes.

To clarify the short- and long-term outcomes of LAG for EGC, we examined the clinical data obtained by 16 surgical departments that are members of the Japanese Laparoscopic Surgery Study Group.

MATERIALS AND METHODS

The study included 1294 patients with EGC who underwent LAG in one of the 16 participating departments during the period 1994 through 2003. The patients who underwent LAG in each institution for that period were all registered for the present study. All tumors were adenocarcinomas that were shown by preoperative gastric endoscopy and barium meal study to be present only in the mucosal or submucosal layer of the stomach and were not candidates for endoscopic mucosal resection. Patients with cancer in another organ or with previous upper abdominal laparotomy or with cardiac, pulmonary, or hepatic insufficiency were not included. The exclusion criteria in insufficiency of the organs were 1) operative cardiovascular risk greater than New York Heart Association II, 2) operative pulmonary risk greater than Hugh-Jones II, and 3) severe liver disease (Child classes B and C). All participating surgeons were personally responsible for obtaining the written informed consent of their patients. According to the location of the tumor, LADG, laparoscopy-assisted proximal gastrectomy (LAPG), or laparoscopy-assisted total gastrectomy (LATG) was performed.

From the *Department of Surgery I, Oita University Faculty of Medicine, Oita, Japan; †Department of Surgery, Fujita Health University Hospital, Nagoya, Japan; ‡Department of Surgical Oncology, Tokyo Medical and Dental University, Tokyo, Japan; and §Department of Surgery, Osaka Medical College, Osaka, Japan.
Supported in part by a Grant-in-Aid for Cancer Research from the Japanese Ministry of Health, Labor, and Welfare (No. 13-17).
Reprints: Seigo Kitano, MD, Department of Surgery I, Oita University Faculty of Medicine, 1-1 Idaigaoka, Yufu, Oita 879-5593, Japan. E-mail: geka1@med.oita-u.ac.jp.

ISSN: 0003-4932/07/24501-0068
DOI: 10.1097/01.sla.0000225364.03133.f8

As described previously,[5,6,8] LAG consisted of the following procedures: 1) laparoscopic dissection of the lesser and greater omentum, ligation and division of the main vessels to mobilize the stomach under pneumoperitoneum, 2) laparoscopic D1+α, D1+β, or D2 lymph node dissection, based on the Guidelines of the Japan Gastric Cancer Association, and 3) resection of the distal two thirds (LADG), proximal third (LAPG), or total stomach (LATG), depending on the location of the tumor, followed by reconstruction by the Billroth-I, esophagogastrostomy, or Roux-en-Y method through a 5- to 7-cm-long minilaparotomy incision. To establish techniques of LAG as an oncologic surgery, the laparoscopic procedures for lymph node dissection in each institution had been reviewed by video examination in the group conferences.

Data obtained for each patient included the following: age, sex, body mass index, previous laparotomy, surgical procedure, operation time, conversion to open surgery, postoperative complications, postoperative oncologic outcome, histologic type of tumor, depth of tumor invasion, lymph node metastasis, and clinical stage according to the UICC staging and the WHO classification of tumors.[12,13]

All patients were monitored postoperatively by physical examination, and blood tests including a test for serum carcinoembryonic antigen at least every 3 months for the first year, every 6 months for the next 2 years, and every year for 5 years, and thereafter by abdominal ultrasonography, computed tomography, chest radiography, and gastroscopy at least once each year.

Data were compared between the three types of laparoscopic surgeries (LADG, LAPG, and LATG). Differences in categorical variables such as postoperative complications, tumor recurrences, and other clinicopathologic factors were analyzed by χ^2 test, and differences in continuous variables were analyzed by Student t test. Survival rates were calculated by the Kaplan-Meier method. A P value of <0.05 was considered significant.

RESULTS

Laparoscopic procedures consisted of 1185 (91.5%) LADGs, 54 (4.2%) LAPGs, and 55 (4.3%) LATGs, and the total patient group comprised 872 men and 422 women. The clinicopathologic characteristics of the study patients are shown in Table 1. The percentages of female patients and of mildly obese patients were greater in the LADG group than in the other groups. D1+β and D2 lymph node dissection were performed frequently in the LADG group because of the high frequency of signet-ring cells carcinoma. The operation time of LATG was longer than that of LADG or LAPG. There were no other differences between groups in patient characteristics or pathologic characteristics of tumors. According to UICC staging, there were 1212 (93.7%) stage IA tumors, 75 (5.8%) stage IB tumors, and 7 (0.5%) stage II tumors.

Intraoperative and postoperative complications occurred in 25 (1.9%) of the 1294 patients and 167 patients (12.9%), respectively (Table 2). Conversion to open surgery was required in only 14 cases (1.1%) because of intraoperative complications: bleeding in 9 cases, mechanical trouble in 3, and others in 2. Bleeding was the most frequent intraoperative complication, and it resulted mainly from the injury to the branches of the left gastric artery, short gastric vein, or spleen. Intraoperative complications occurred more frequently during LAPG than during other laparoscopic procedures ($P < 0.05$). The most frequent postoperative complications were anastomotic stenosis, anastomotic leakage, and wound infection, and there was no significant difference in the incidence of postoperative complications between laparoscopic procedures. Intraoperative and postoperative complications were not associated with any of the factors studied,

TABLE 1. Clinicopathologic Characteristics of Patients With Early Gastric Cancer

	No. of Patients			
	LADG (n = 1185)	LAPG (n = 54)	LATG (n = 55)	P
Patients				
Age (yr)	62.7 ± 11	63.7 ± 9	62.1 ± 12	NS
Male/female	786/399	41/13	45/10	<0.05*
BMI (<25/25–30/>30)	1002/176/7	40/13/1	52/2/1	<0.05*
Post-EMR (yes/no)	49/1136	2/52	0/55	NS
Previous laparotomy (presence/absence)	120/1065	5/49	6/49	NS
Operation				
Lymph node dissection (D1+α/D1+β/D2)	429/549/207	31/20/3	6/45/4	<0.05*
Operation time (min)	253.1 ± 19	229.4 ± 31	271.4 ± 26	<0.05*
Tumor				
Histologic type (tubular adenocarcinoma/signet-ring cell carcinoma/others)	933/223/29	50/3/1	46/5/4	<0.05*
Tumor depth (mucosa/submucosa)	729/456	25/29	27/28	<0.05*
Lymph node metastasis (N0/N1/N2)	1111/68/6	49/4/1	52/3/0	NS
Tumor staging† (stage IA/IB/II)	1111/68/6	49/4/1	52/3/0	NS

Data are mean ± SD or number. NS, not significant; BMI, body mass index.
*Statistical significance.
†Tumor staging is classified by UICC staging.

TABLE 2. Intraoperative and Postoperative Complications

	No. (%) of Patients			
Complications	**LADG (n = 1185)**	**LAPG (n = 54)**	**LATG (n = 55)**	**P**
Intraoperative	20 (1.7%)	4 (7.4%)	1 (1.8%)	<0.05*
Bleeding	11	1	0	
Perforation	0	1	0	
Organ injury	5	0	0	
Machine trouble	1	2	1	
Others	3	0	0	
Postoperative	151 (12.7%)	10 (18.5%)	6 (10.9%)	NS
Bleeding	13	0	1	
Anastomotic stenosis	35	3	0	
Anastomotic leakage	25	3	0	
Intraabdominal abscess	17	0	0	
Pancreas injury	12	0	2	
Ileus	3	0	0	
Respiratory complication	9	0	0	
Wound infection	16	2	2	
Port-metastasis	0	0	0	
Others	21	2	1	

NS, not significant.
*Statistical significance.

including sex, age, body mass index, history of laparotomy and tumor stage.

There were only 6 cancer recurrences, 1 local recurrence, 1 lymph node recurrence, 2 peritoneal disseminations, 1 liver metastasis, and 1 skin metastasis at the abdominal wall different from the port-site, during the median follow-up period of 36 months (range, 13–113 months). The cancer in all 6 recurrent cases invaded to the deeper submucosal layer. In 3 of 6 cases, lymph node metastasis (N2) was detected histologically, and the tumors were classified as stage II tumors. Recurrence was not associated with any surgical procedure, complications, or conversion to open gastrectomy. The 5-year disease-free survival rate was 99.8% for stage IA disease, 98.7% for stage IB disease, and 85.7% for stage II (Fig. 1). The 5-year disease-free survival rate was 99.4% for patients who underwent LADG, 98.7% for those who underwent LAPG, and 93.7% for those who underwent LATG (Fig. 2).

DISCUSSION

This retrospective multicenter study is the first investigation of short- and long-term outcomes of LAG for EGC in a large series of patients in Japan. Both the mortality rate and the morbidity rate associated with LAG were shown to be as low as those of conventional open gastrectomy,[14] and the 5-year survival rate of patients who underwent LAG for EGC was as good as that of patients who underwent conventional open surgery for EGC.[15,16]

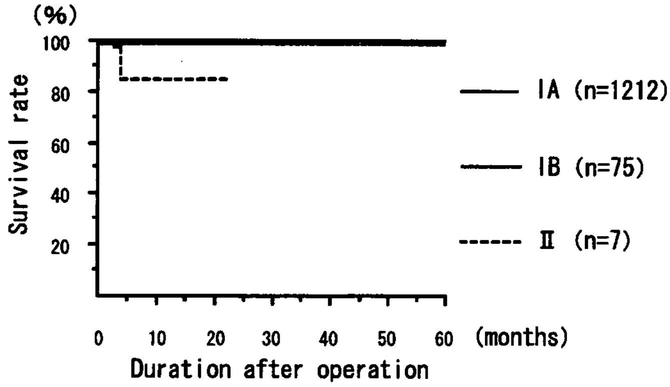

FIGURE 1. The disease-free survival rate in 1294 treated patients with early gastric cancer. The 5-year disease-free survival rate was 99.8% for stage IA, 98.7% for stage IB, and 85.7% for stage II. Tumor staging system is used with classification by the UICC staging.

Since LADG for EGC was first reported in 1994,[5] several laparoscopic procedures for EGC have been developed and have been performed by a limited number of surgeons.[6–8] Over the last decade, the number of LAGs for early cancer has rapidly increased, and the indication for LAG has extended to advanced cancer.[17] Several studies of the short-term outcome of LAG in comparison to open gastrectomy showed the several advantages of LAG, including less invasiveness, less pain, earlier recovery of bowel movement, and shorter hospital stay.[9–11] We have reported additional advantages of LADG, including less impaired respiratory function, better preservation of postoperative T_H1 cell-mediated immune function, and better postoperative quality of life.[18] Some studies, however, indicated technical difficulties and limitations in lymph node dissection performed during LAG.[19] Therefore, we performed a retrospective multicenter study to clarify the technical feasibility and oncologic outcome of LAG for EGC in Japan.

The prognosis of patients with EGC is known to be excellent, with 5-year survival rates of 90% or more.[15,16] Multivariate analysis has shown that lymph node metastasis is the only significant predictive factor for recurrence of

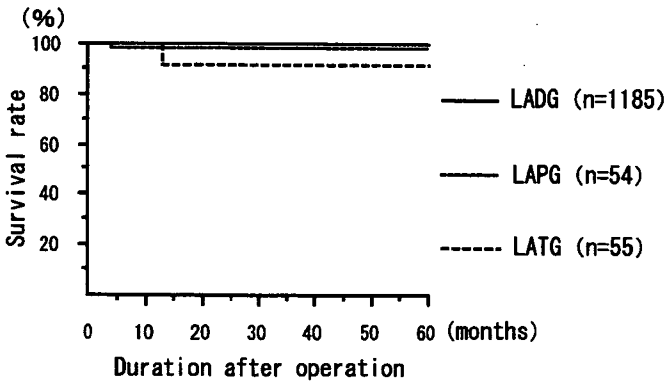

FIGURE 2. The disease-free survival rate according to operation. The 5-year disease-free survival rate was 99.4% for LADG, 98.7% for LAPG, and 93.2% for LATG.

EGC.[20] Several recent studies showed that the extent of lymph node metastasis in patient with EGC was associated with tumor size and depth of invasion.[21] However, the extent of lymph node dissection for EGC remains controversial.[22] In the patients included in the present study, the lymph node dissection was performed laparoscopically according to the Guidelines of the Japanese Gastric Cancer Association. Several studies have evaluated laparoscopic lymph node dissection. Adachi et al, in a retrospective study of 96 patients with EGC, showed that the number of lymph nodes dissected laparoscopically was no different from that of lymph node dissected during open surgery.[9] Yano et al also conducted a retrospective study of patients with EGC and reported that the number of resected lymph nodes in $D1+\alpha$ lymph node dissection did not differ between LAG and open gastrectomy.[23] On the contrary, Miura et al showed less number of dissected lymph nodes along major curvature and the celiac and splenic arteries in LAG than open gastrectomy.[24] In the present retrospective study, which covered a quite long time period, the number of resected lymph nodes could not be evaluated because data of the number of resected lymph nodes in several institutions were incomplete. To establish techniques of LAG as an oncologic surgery, the laparoscopic procedures for lymph node dissection in each institution had been reviewed by video examination in the group conferences.

There are few studies on the long-term outcome of LAG for EGC. Huscher et al[25] recently showed, on the basis of the first prospective randomized trial in small series of 59 patients with EGC or advanced gastric cancer comparing the 5-year results of subtotal gastrectomy against those of with laparoscopic and open approaches, that LAG is a safe oncologic procedure; ie, the oncologic outcome matches that of conventional open surgery.[25] Our preliminary prospective randomized trial with a mean follow-up period of 21.5 months showed no difference in curability between laparoscopic and open procedures for EGC.[26] Weber et al also did not observe a difference in the 18-month survival rate between patients with gastric cancer who underwent LAG and those who underwent open gastrectomy.[27] Although the present multicenter study of a large patient series was an uncontrolled study and the follow-up period was short, the survival rate of patients with EGC who underwent LAG was shown to be good. These data suggest that LAG is feasible for EGC from the standpoint of oncologic outcome.

Several studies have investigated mortality and morbidity associated with LAG. Huscher et al reported LAG-associated mortality and morbidity rates of 3.3% and 26.7%, respectively, in a randomized trial, and these rates were the same as those of open gastrectomy.[25] Adachi et al reported, on the basis of a retrospective study comparing 49 LAGs and 53 open gastrectomies, that there was no difference in the incidence of operative complications.[9] Tanimura et al, in a retrospective study of 160 LAGs, showed that major complications such as anastomotic leakage and pancreatic injury occurred in only 6 cases (3.8%).[8] Shimizu et al reported the mortality and morbidity rates in 85 patients who underwent initial LAG were 0% and 11.8%, respectively.[28] In the present study, the mortality and morbidity rates were 0% and 14.8%, respectively, and the rate of conversion to open surgery was 1.1%. The conversion to open surgery in LAG for EGC was not associated with worse short- and long-term outcome in the present study. As laparoscopic surgeries for gastrointestinal disease have been considered as technically complex procedures with longer operation time, the significance of learning curve has been emphasized to perform them safely.[29,30] Although, in the present study, it seemed to take more 30 to 60 minutes to perform LAG than open gastrectomy, the incidence of operative complications was as low for LAG as it was for open surgery. These findings suggest that LAG with longer operation time is safe for EGC.

CONCLUSION

Our multicenter study of a large patient series showed that LAG is safe for EGC, with an oncologic outcome as good as that of conventional open surgery. Results of this retrospective nonrandomized clinical analysis should be confirmed by large-scale prospective randomized trials.

ACKNOWLEDGMENTS

The following centers and surgeons participated in the multicenter study initiated by the Japanese Laparoscopic Surgery Study Group (JLSSG): Seigo Kitano, Norio Shiraishi, Masafumi Inomata, Kazuhiro Yasuda, Oita University Faculty of Medicine (Oita); Ichiro Uyama, Masahiro Ochiai, Fujita Health University Hospital (Aichi); Kenichi Sugihara, Kazuyuki Kojima, Masayuki Enomoto, Masamichi Yasuno, Tokyo Medical and Dental University (Tokyo); Nobuhiko Tanigawa, Osaka Medical University (Osaka); Hitoshi Katai, National Cancer Center Hospital (Tokyo); Shinei Kudo, Showa University Northern Yokohama Hospital (Yokohama); Shinichi Sakuramoto, Kitasato University, School of Medicine (Kanagawa); Shuji Takiguchi, Morito Monden, Osaka University (Osaka); Shinya Tanimura, Masayuki Higashino, Yosuke Fukunaga, Osaka City General Hospital (Osaka); Yugo Nagai, Izumi Otsu Municipal Hospital (Osaka), Hirokazu Noshiro, Kyusyu University Graduate School of Medicine (Fukuoka), Ken Hayashi, Showa Inan General Hospital, Center on Endoscopic Surgery (Nagano); Hideki Hayashi, Takenori Ochiai, Graduate School of Medicine, Chiba University (Chiba); Tetsu Fukunaga, The Cancer Institute Hospital of Japanese Foundation for Cancer Research (JFCR) (Tokyo); Masaki Fukunaga, Juntendo Urayasu Hospital, Juntendo University School of Medicine (Chiba); Minoru Matsuda, Tomokazu Hoshi, Shinichi Kasai, Surugadai Nihon University Hospital (Tokyo); Tatsuo Yamakawa, Nobuo Murata, Teikyo University, Mizonokuchi Hospital (Kanagawa); Katsuhiko Yanaga, Jikei University School of Medicine (Tokyo).

REFERENCES

1. Matsukuma A, Furusawa M, Tomoda H, et al. A clinicopathological study of asymptomatic gastric cancer. *Br J Cancer*. 1996;74:1647–1650.
2. Adachi Y, Mori M, Maehara Y, et al. Prognostic factors of node-negative gastric carcinoma: univariate and multivariate analyses. *J Am Coll Surg*. 1997;184:373–377.
3. Tada M, Murakami A, Karita M, et al. Endoscopic resection of early gastric cancer. *Endoscopy*. 1993;25:445–450.

4. Kitano S, Shimoda K, Miyahara M, et al. Laparoscopic approaches in the management of patients with early gastric carcinoma. *Surg Laparosc Endosc*. 1995;5:359–362.
5. Kitano S, Iso Y, Moriyama M, et al. Laparoscopy-assisted Billroth I gastrectomy. *Surg Laparosc Endosc*. 1994;4:146–148.
6. Uyama I, Sugioka A, Matsui H, et al. Laparoscopic side-to-side esophagogastrostomy using a linear stapler after proximal gastrectomy. *Gastric Cancer*. 200;4:98–102.
7. Mochiki E, Kamimura H, Haga N, et al. The technique of laparoscopically assisted total gastrectomy with jejunal interposition for early gastric cancer. *Surg Laparosc*. 2002;16:540–544.
8. Tanimura S, Higashino M, Fukunaga Y, et al. Laparoscopic with regional lymph node dissection for upper gastric cancer. *Gastric Cancer*. 2003;6:64–68.
9. Adachi Y, Shiraishi N, Shiromizu A, et al. Laparoscopy-assisted Billroth I gastrectomy compared with conventional open gastrectomy. *Arch Surg*. 2000;135:806–810.
10. Adachi Y, Suematsu T, Shiraishi N, et al. Quality of life after laparoscopy-assisted Billroth I gastrectomy. *Ann Surg*. 1999;229:49–54.
11. Mochiki E, Nakabayashi T, Kamimura H, et al. Gastrointestinal recover and outcome after laparoscopy-assisted versus conventional open distal gastrectomy for early gastric cancer. *World J Surg*. 2002;26:1145–1149.
12. Sobin LH, Wittekind CH. *TNM Classification of Malignant Tumors*, 6th ed. Heidelberg: Springer-Verlag, 2002.
13. Hamilton S, Aaltonen L. *Pathology and Genetics of Tumors of the Digestive System*. New York: WHO Publications, 2000.
14. Sasako M. Risk factors for surgical treatment in the Dutch Gastric Cancer Trial. *Br J Surg*. 1997;84:1567–1571.
15. Maruyama K, Sasako M, Kinoshita T, et al. Surgical treatment for gastric cancer: the Japanese approach. *Semin Oncol*. 1996;23:360–368.
16. Siewert JR, Sendler A. The current management of gastric cancer. *Adv Surg*. 1999;33:69–93.
17. Kitano S, Bandoh T, Kawano K. Endoscopic surgery in Japan. *Minim Invasive Ther Allied Technol*. 2001;10:215–219.
18. Fujii K, Sonoda K, Izumi K, et al. T lymphocyte subsets and Thl/Th2 balance after laparoscopy-assisted distal gastrectomy. *Surg Endosc*. 2003;17:1440–1444.
19. Fujiwara M, Kodera Y, Kasai Y, et al. Laparoscopy-assisted distal gastrectomy with systemic lymph node dissection for early gastric carcinoma: a review of 43 cases. *J Am Coll Surg*. 2003;196:75–81.
20. Isozaki H, Tanaka N, Okajima K. General and specific prognostic factor of early gastric carcinoma treated with curative surgery. *Hepatogastroenterology*. 1999;46:1800–1808.
21. Yasuda K, Shiraishi N, Suematsu T, et al. Rate of detection of lymph node metastasis is correlated with the depth of submucosal invasion in early stage gastric carcinoma. *Cancer*. 1999;85:2119–2123.
22. Hioki K, Nakane Y, Yamamoto M. Surgical strategy for early gastric cancer. *Br J Surg*. 1990;77:1330–1334.
23. Yano H, Monden T, Kinuta M, et al. The usefulness of laparoscopy-assisted distal gastrectomy in comparison with that open distal gastrectomy for early gastric cancer. *Gastric Cancer*. 2001;4:93–97.
24. Miura S, Kodera Y, Fujiwara M, et al. Laparoscopy-assisted distal gastrectomy with lymph node dissection: a critical reappraisal from the viewpoint of lymph node retrieval. *J Am Coll Surg*. 2004;198:933–938.
25. Huscher CGS, Mingoli A, Sgarzini G, et al. Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomized prospective trial. *Ann Surg*. 2005;241:232–237.
26. Kitano S, Shiraishi N, Fujii K, et al. A randomized controlled trial comparing open vs laparoscopy-assisted distal gastrectomy for the treatment of early gastric cancer: an interim report. *Surgery*. 2002;131(suppl):306–311.
27. Weber KJ, Reyes CD, Gagner M, et al. Comparison of laparoscopic and open gastrectomy for malignant disease. *Surg Endosc*. 2003;17:968–971.
28. Shimizu S, Noshiro H, Nagai E, et al. Laparoscopic gastric surgery in a Japanese institute: analysis of the initial 100 procedures. *J Am Coll Surg*. 2003;197:372–378.
29. Rege RV, Joehl RJ. A learning curve for laparoscopic splenectomy at an academic institution. *J Surg Res*. 1999;81:27–32.
30. Schlachta CM, Mamazza J, Seshadri PA, et al. Defining a learning curve for laparoscopic colorectal resections. *Dis Colon Rectum*. 2001;44:217–222.

J Gastrointest Surg (2007) 11:596–602
DOI 10.1007/s11605-007-0140-0

Prognostic Value of Preoperative Peripheral Blood Monocyte Count in Patients with Colorectal Liver Metastasis after Liver Resection

Atsushi Sasaki · Seiichiro Kai · Yuichi Endo · Kentaro Iwaki · Hiroki Uchida · Masayuki Tominaga · Ryoki Okunaga · Kohei Shibata · Masayuki Ohta · Seigo Kitano

Published online: 27 March 2007

Abstract Prognostic values of leukocyte subset counts in peripheral blood of cancer patients have not yet been fully investigated. We retrospectively examined the relation between preoperative absolute counts of peripheral blood leukocyte subsets and clinicopathologic factors and long-term prognosis in 97 patients with liver metastasis from colorectal cancer who underwent hepatic resection. Median preoperative peripheral blood leukocyte subset counts were as follows: neutrophils 3148/mm^3; lymphocytes 1574/mm^3; monocytes 380/mm^3. Univariate analysis indicated significantly worse 5-year cancer-related survival for patients with a peripheral blood monocyte count >300/mm^3 (67.5%) than for patients with a count ≤300/mm^3 (36.8%). Multivariate analysis showed a preoperative peripheral blood monocyte count >300/mm^3 and preoperative CEA level (>10 ng/ml) to be independent predictive factors for cancer-related survival after hepatic resection. The preoperative peripheral monocyte count correlated positively with white blood cell and neutrophil counts, but not with the tumor number, interval between colorectal and hepatic surgery, or preoperative serum CEA level. Our findings indicate that a preoperative absolute peripheral blood monocyte count >300/mm^3 is an independent predictive factor for cancer-related survival of patients with colorectal liver metastasis who have undergone hepatic resection.

Keywords Colorectal cancer · Liver metastasis · Peripheral blood · Monocyte count · Prognosis

Introduction

The incidence of colorectal carcinoma is increasing worldwide. Approximately 30–50% of patients with colorectal cancer suffer recurrence after curative colorectal resection.[1] The organ that most frequently contains metastatic deposits from colorectal cancer is the liver, followed by the lung, bone, and peritoneum. Hepatic resection is considered the most effective therapy for colorectal liver metastasis, and the reported overall survival rate after hepatic resection is 26–51%.[2–5] Several clinicopathologic factors that influence patient survival after hepatic resection have been identified; these include the interval between colorectal and hepatic surgeries,[2,4,5] the number of hepatic metastases,[3,4–6] size of the liver tumor,[4] the preoperative serum carcinoembryonic antigen (CEA) level,[3,5,7] lymphatic invasion in the liver,[8] and nodal metastasis in the hepatic hilum.[2] Most investigators agree that the interval between colorectal and hepatic surgeries, the number of hepatic tumors, and the preoperative serum CEA level are the most important determinants of long-term survival after hepatic resection.

A few studies of peripheral blood cells in cancer patients have indicated that a decreased lymphocyte count or increased monocyte and/or neutrophil count in the peripheral blood is a predictor of a poor prognosis in cancer patients.[9–12] Moreover, the relation between preoperative

A. Sasaki (✉) · S. Kai · Y. Endo · K. Iwaki · H. Uchida · M. Tominaga · R. Okunaga · K. Shibata · M. Ohta · S. Kitano
Department of Surgery I,
Oita University Faculty of Medicine,
1-1 Hasama-mach, Yufu, Oita 879-5593, Japan
e-mail: sasakia@med.oita-u.ac.jp

A. Sasaki
Department of Surgery, National Hospital Organization Miyazaki Hospital,
Miyazaki, Japan

inflammatory status and prognosis after treatment for patients with malignant tumors has been investigated. Some investigators identified preoperative C-reactive protein (CRP) elevation as an independent predictive factor for short-term survival of patients with colorectal cancer.[13–15] It was speculated that progressive tumor destroys surrounding tissue and leads to a nonspecific inflammatory reaction or that CRP is upregulated by proinflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor.[13,14] In addition, several authors have shown that some patients with advanced malignant tumor fall into immunosuppressive status, which might contribute to a poor prognosis in patients who undergo curative resection.[16,17]

Dendritic cells (DCs) identify antigen-presenting cells and mature DCs lead to activation of antigen-specific cytotoxic lymphocytes.[18] DCs can derive from peripheral monocytes. Immunotherapy based on DCs has been performed recently in patients with various types of malignant tumor; however, the results have not been satisfactory.[19–22] Several investigators suggested poor function of peripheral blood DCs obtained from cancer patients, especially those with advanced-stage disease.[23] To the contrary, some investigators have shown that DCs with regulatory function (regulatory DCs) cause immunosuppression by activated and differentiated regulatory T cells in patients with malignant tumor.[24] The DCs may be included in the peripheral blood monocyte subset or may differentiate from peripheral monocytes.

To date, the prognostic value of preoperative leukocyte subset counts in peripheral blood has not been investigated in patients with colorectal liver metastasis. Therefore, the aim of this study was to clarify the prognostic value of preoperative peripheral blood leukocyte subset counts, especially the absolute monocyte count, in patients with colorectal cancer who have undergone hepatic resection.

Materials and Methods

During the period January 1985 through March 2004, 132 patients with colorectal liver metastases underwent hepatic resection at the Department of Surgery I, Oita University Faculty of Medicine. Thirty-five of these patients were excluded from the study: three (2.3%), who died of postoperative complications within 30 days; two who had obvious residual tumor at the time of surgery; 25 whose preoperative peripheral leukocyte subset counts were not obtained; one whose hepatic tumor had fallen into complete necrosis, and four whose clinicopathologic data were not certain. Thus, 97 patients who underwent hepatic resection with a curative intent were included in this study. All patients underwent regular follow-up examinations at our outpatient clinic and were monitored for recurrence by assessment of serum tumor markers every 2 months and by ultrasonography or contrast computed tomography study every 4–6 months. We defined cancer recurrences when metastatic tumors were identified by radiologic examinations, such as computed tomography, ultrasonography, and bone scintigraphy.

Upon admission to our hospital, a complete blood count and blood chemistry profile were routinely obtained for each patient. The absolute count of peripheral blood leukocytes (normal count 2950–8970/mm^3) and of each subset were included. Leukocytes were divided into neutrophil (normal percentage 42.2–74.7%), lymphocyte (normal percentage 17.7–46.5%), monocyte (normal percentage 1.3–8.0%), eosinophil (normal percentage 0–8.4%), and basophil (normal percentage 0–1.1%) subsets, and the absolute counts of neutrophils, lymphocytes, and monocytes were determined. The serum biochemistry data included the carcinoembryonic antigen (CEA) level (normal <5 ng/ml).

We investigated 13 clinicopathologic variables, i.e., sex, age, interval between colorectal and hepatic resection, number of hepatic metastases, diameter of hepatic tumor, preoperative CEA level, site of primary tumor, grade of primary cancer, status of nodal metastasis of primary colorectal cancer, leukocyte (neutrophil, lymphocyte, and monocyte) subset counts, and extent of hepatic resection (Table 1). The extent of hepatic resection was defined according to Couinaud's classification system, with minor hepatic resection defined as resection of fewer than two segments and major hepatic resection as resection of two or more segments.

Patient outcomes were determined on the basis of clinical data obtained from patients' medical records as of June 30, 2006. The mean and median follow-up periods of surviving patients after hepatic resection were 44.2 and 30 months, respectively. The prognostic significance of clinicopathologic factors in relation to cancer-related survival was investigated by univariate and multivariate analyses. Data were censored in the analysis of cancer-related survival if a patient was living or had died of unrelated disease and in the analysis of disease-free survival if a patient was living or had died of unrelated disease without recurrent colorectal carcinoma. Survival rates were calculated by the Kaplan–Meier method, and differences were analyzed by univariate log-rank analysis. In the comparisons of clinicopathologic factors and leukocyte counts, continuous variables were analyzed by Kruskal–Wallis test, and nominal variables were analyzed by Fisher's exact probability test. Variables with a P value of <0.1 in univariate analysis were used in subsequent multivariate analysis based on the Cox proportional hazards model. P value <0.05 was considered significant in all

Table 1 Results of Univariate Analysis of Cancer-Related Survival after Hepatic Resection

Clinical Variable	No. of Patients	5-Year Cancer-related Survival Rate (%)	*P* value
Sex			
Male	60	40.9	0.88
Female	37	51.9	
Age (years)			
≤60	32	46.2	0.70
>60	65	45.1	
Interval (months)			
<12	64	38.3	0.10
≥12	33	56.9	
CEA (ng/ml)			
≤10	41	64.1	<0.01
>10	56	31.7	
Tumor size (mm)			
<50	74	49.8	0.18
≥50	23	34.8	
Tumor grade			
Well-differentiated	54	49.0	0.17
Moderately/poorly	43	38.5	
Primary organ			
Colon	65	43.9	0.39
Rectum	31	49.6	
Colon+rectum	1	0	
Tumor number			
<4	87	48.1	0.07
≥4	10	0	
Primary nodal metastasis			
Absent	41	44.1	0.72
Present	56	48.1	
Lymphocyte count (/mm^3)			
≤1500	43	45.6	0.63
>1500	54	44.3	
Neutrophil count (/mm^3)			
≤3000	44	58.2	
>3000	53	35.5	
Monocyte count (/mm^3)			
≤300	22	67.5	0.04
>300	75	36.8	
Extent of hepatic resection			
Major	38	45.7	0.97
Minor	59	44.4	

Interval means period between colorectal and hepatic surgeries. CEA = carcinoembryonic antigen; moderately/poorly, moderately or poorly differentiated.

analyses. Statistical analysis was performed with JMP software (JMP, SAS Institute Inc, Cary, NC).

Results

Patient Characteristics

The 97 patients who underwent hepatic resection with a curative intent comprised 60 men and 37 women with a mean age of 62.6 years. The mean and median intervals between colorectal and hepatic surgery were 12.2 and 7 months, respectively. The mean number and size of hepatic tumors were 1.8 (range 1–8) and 39.1 mm (range 10–130 mm), respectively. Patients had the following number of metastatic liver tumors: 1 (n=55), 2 (n=18), 3 (n=10), 4 (n=4), 5 (n=3), 6 (n=2), and 8 (n=1). The mean preoperative serum CEA level was 49.9 ng/ml (range 0–915.0 ng/ml; median 13.8 ng/ml). The primary tumor was located in the colon in 65 patients, in the rectum in 31 patients, and in both the colon and rectum in 1 patient. According to Dukes' classification system, 41 of the primary tumors were at stage A or B tumors, and 56 were stage C tumors. Metastatic liver tumors were graded as well differentiated (n=54) and moderately to poorly differentiated (n=43). Thirty-eight patients underwent major hepatic resection, and 59 underwent minor hepatic resection.

Mean and median peripheral blood cell counts were as follow: leukocytes 5748.6/mm^3 and 5510/mm^3, respectively (range 2300–10,410/mm^3); neutrophils 3391.8/mm^3 and 3148/mm^3 (range 1079–6966/mm^3); lymphocytes 1657.4/mm^3 and 1574/mm^3 (range 589–3662/mm^3); and monocytes 419.7/mm^3 and 380/mm^3 (range 136–1183/mm^3). The patients were stratified according to absolute counts of each peripheral blood leukocyte subset as follows: ≤3000/mm^3 (n=44) and >3000/mm^3 (n=53) for neutrophils; ≤1500/mm^3 (n=43) and >1500/mm^3 (n=54) for lymphocytes; and ≤300/mm^3 (n=22) and >300/mm^3 (n=75) for monocytes.

Survival

Of the 97 patients who underwent hepatic resection for colorectal liver metastasis, 47 (48.5%) had died by June 30, 2006. The causes of death were as follows: colorectal cancer (n=43) and unrelated diseases (n=4; liver cirrhosis in one, necrotizing myositis in one, acute myocardial infarction in one, and pneumonia in one). The 5-year cancer-related survival and disease-free survival rates were 44.9 and 31.4%, respectively.

Recurrent disease was found in 14 of the 22 (63.6%) patients with a monocyte count ≤300/mm^3 and in 49 of the 75 (65.3%) patients with a monocyte count >300/mm^3. Five-year cancer-related and disease-free survival rates after hepatic resection were 67.5 and 37.5%, respectively, for patients with a peripheral blood monocyte count ≤300/mm^3 and 36.8 and 29.6%, respectively, for those with a count >300/mm^3. Univariate analysis of the 13 clinicopathologic factors examined in relation to cancer-related survival after hepatic resection revealed that the cancer-related survival rate after hepatic resection was significantly worse for patients with a monocyte count >300/mm^3 than for those with a monocyte count ≤300/mm^3 (P=0.04; Table 1 and Fig. 1) as well as for those with an elevated preoperative serum CEA level (≥10 ng/ml) or large number (≥4) of liver tumors. The disease-free survival rate did not differ between groups stratified according to monocyte counts (P=0.24; Fig. 2). There was no statistical relation between cancer-related survival or disease-free survival and the absolute peripheral blood lymphocyte or neutrophil count. Multivariate analysis of the two significant factors revealed that a peripheral blood monocyte count >300/mm^3; relative risk (RR), 1.55; confidence interval (CI), 1.04–2.54; and preoperative serum CEA elevation (>10 ng/ml) (RR, 2.70; CI, 1.36–5.84) negatively influenced cancer-related survival after hepatic resection (Table 2).

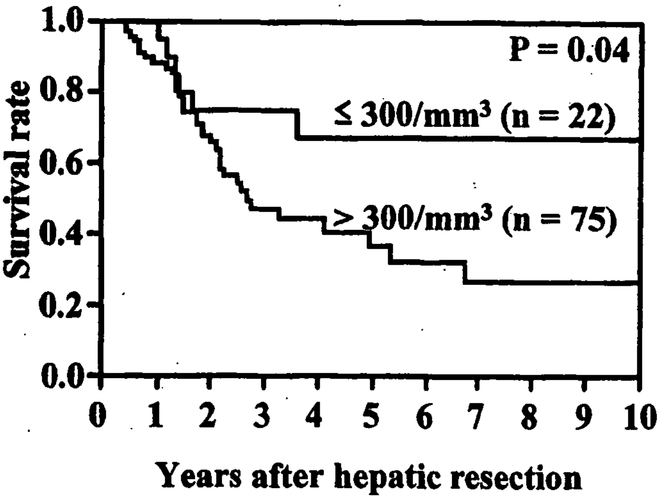

Figure 1 Cancer-related survival curves according to absolute count of preoperative peripheral blood monocyte count. Cancer-related survival rate is significantly better for patients with a count ≤300/mm^3 than for patients with a count >300/mm^3 (P<0.04).

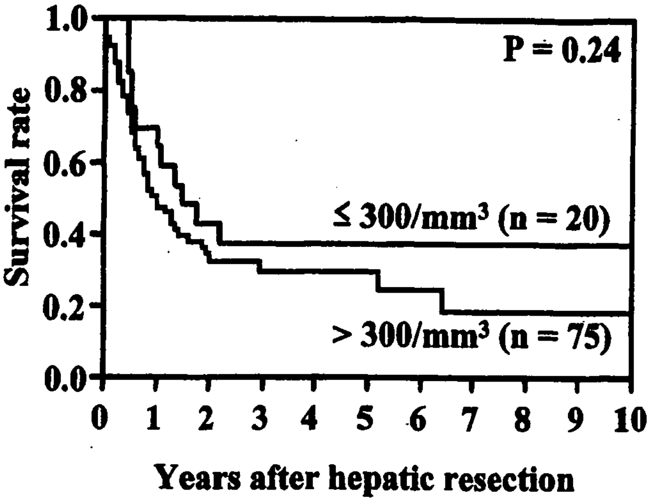

Figure 2 Disease-free survival curves according to absolute preoperative peripheral blood monocyte count. Disease-free survival rates do not differ between patients stratified according to peripheral blood monocyte counts (P=0.24).

Relation Between Peripheral Blood Monocyte Count and Clinicopathologic Factors in Patients with Colorectal Liver Metastasis

We analyzed 13 clinicopathologic factors in relation to peripheral blood monocyte counts, as shown in Table 3. The peripheral blood monocyte count was positively related to the preoperative peripheral blood leukocyte and neutrophil counts. However, other factors, including those reflective of tumor progression (interval between colorectal

Table 2 Results of Multivariate Analyses of Cancer-Related and Disease-free Survival after Hepatic Resection

Clinical Variable	Cancer-related Survival	
	RR (CI)	*P* value
CEA (ng/mL)		
≤10	1.00	< 0.01
>10	2.70 (1.36–5.84)	
Tumor number		
<4	1.00	0.27
≥4	1.71 (0.63–3.88)	
Monocyte count (/mm^3)		
≤300	1.00	0.03
>300	1.55 (1.04–2.54)	

CEA = carcinoembryonic antigen; RR = relative risk; CI = confidence interval

and hepatic surgery, preoperative serum CEA level, and the number and size of hepatic tumors), did not relate to the preoperative peripheral blood monocyte count.

Discussion

Risk factors for a poor outcome after hepatic resection for patients with colorectal liver metastases have been investigated. Several investigators agree that the short period between colorectal and hepatic surgeries, large number of metastatic liver tumors, preoperative serum CEA elevation, and presence of extrahepatic metastasis were strong predictive factors for survival after hepatic resection.[2–6] We previously investigated preoperative risk factors that affect survival of patients with colorectal liver metastasis and showed that the interval between colorectal and hepatic surgeries, number of liver tumors, and preoperative serum CEA level are independent risk factors influencing cancer-

Table 3 Clinicopathologic Factors in Relation to Peripheral Blood Monocyte Count

Variable	No. of Patients	Peripheral Blood Monocytes (/mm3)		*P* value
		<300	≥300	
Sex				
Male	60	11	49	0.20
Female	37	11	26	
Age (years)	97	62.7	62.6	0.73
Interval (months)*				0.08
<12	64	11	53	
≥12	33	11	22	
CEA (ng/ml)	97	41.6	52.3	0.22
Primary organ				
Colon	65	14	51	0.69
Rectum	31	8	23	
Colon+rectum	1	0	1	
Tumor number	97	1.55	1.89	0.09
Tumor size (mm)	97	35.4	40.2	0.77
Tumor grade				
Well-differentiated	54	11	43	0.54
Moderately/Poorly	43	11	32	
Primary nodal metastasis				
Absent	41	9	32	0.88
Present	56	13	43	
WBC count (/mm^3)	97	4704.1	6054.9	<0.01
Neutrophil count (/mm^3)	97	2623.7	3617.1	<0.01
Lymphocyte count (/mm^3)	97	1574.3	1681.8	0.24
Extent of hepatic resection				
Major	38	9	29	0.85
Minor	59	13	46	

CEA, carcinoembryonic antigen; moderately/poorly, moderately or poorly differentiated; WBC, white blood cell. *Interval means period between colorectal and hepatic surgeries. Continuous variable is expressed by mean value.

related survival after hepatic resection.[5] However, only a small number of clinicopathologic factors predictive of long-tem survival after hepatic resection have been reported. In the present study, we clarified that the absolute peripheral blood monocytes count and the serum CEA level are independent preoperative prognostic factors. The absolute peripheral blood monocyte count might be available to patient selection for hepatic resection or indication for postoperative adjuvant chemotherapy in patients with colorectal liver metastasis.

Several investigators have reported a relation between preoperative peripheral blood leukocyte subset counts and prognosis in patients with malignant tumors, such as carcinoma of the stomach,[9] neck and head,[10] and other organs.[11,12] Some investigators have reported that preoperative leukocyte subset counts in peripheral blood can be indicative of tumor progression or of prognosis in cancer patients. Bruckner et al.[9] showed that a pretreatment absolute neutrophil count <6000/mm^3, lymphocyte count >1500/mm^3, and monocyte count 300–900/mm^3 were independent indicators of a good prognosis for patients with metastatic gastric cancer. Elias et al.[10] analyzed mononuclear cell percentages in 55 patients with epidermoid carcinoma of the head and neck and found that high lymphocyte (≥30%) and low monocyte percentages (<10%) correlated with early-stage disease and were associated with a good prognosis. Riesco reported that cancer curability correlated positively with pretreatment peripheral leukocyte count and negatively with the pretreatment neutrophil count in patients with various types of cancer.[11] Recently, we reported that an increased preoperative peripheral blood monocyte count (>300/mm^3) correlated negatively with disease-free survival after hepatic resection in patients with hepatocellular carcinoma (HCC).[12] However, there have been no reports describing the prognostic significance of preoperative leukocyte subset counts in patients with colorectal cancer.

Several investigators have reported cut-off values for the preoperative peripheral blood monocyte count as it pertains to survival analysis. Bruckner et al.[9] reported that a monocyte count of 300–900/mm^3 was an independent indicator of a good outcome in gastric cancer patients with ambulatory status. In our previous investigation in HCC patients, we used a cut-off value of 300/mm^3 for peripheral blood monocytes.[12] Although the normal peripheral blood monocyte count is described by our institution as a percentage of the white blood cell count (1.3–8.0%), we decided upon a cut-off value of 300/mm^3 in the present study, according to the previous reports.

The mechanism explaining the relation between an increase in the number of peripheral blood monocytes and decrease survival remains unclear. Some studies have indicated that preoperative systemic inflammation as determined by the serum CRP level adversely affects survival after curative resection in patients with colorectal cancer.[13–15] Because the serum CRP level was shown to correlate with tumor stage, it was speculated that tumor progression might destroy tissue surrounding the tumor.[14] In our previous study of HCC patients, the absolute peripheral blood monocyte count also correlated with tumor progression.[12] However, in the present study, the peripheral blood monocyte count did not relate to tumor progression, i.e., to the interval between colorectal and hepatic surgery, the size and number of hepatic tumors, or the preoperative serum CEA level. Moreover, the preoperative peripheral blood monocyte count was significantly related to cancer-related survival but not to disease-free survival after hepatic resection. These findings suggest that growth of a recurrent tumor is more rapid in patients with a high monocyte count than in those with a low monocyte count. Thus, proinflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor, produced by the increased number of peripheral blood monocytes, might stimulate cancer cell growth,[13,14] or DCs derived from peripheral blood monocytes might have regulatory function for host immunity against the tumor.

The monocyte subset in peripheral blood includes the DC population. DCs, which are antigen-presenting cells and which activate the anti-tumor immune response of the tumor-bearing host, have been used for immunotherapy for malignant tumor.[20–22] Recently, several investigators showed that regulatory DCs in the peripheral blood might induce proliferation of CD4$^+$CD25$^+$ regulatory T cells, which inhibits the proliferation or activation of CD4$^+$CD25$^-$ or CD8$^+$CD25$^-$ T cells and suppresses host anti-tumor immunity.[24,25] We did not investigate functions of DCs and natural killer cells in peripheral blood. Our results, however, support the theory that impairment of the antigen-presenting function of DCs or increasing regulatory DCs holds patients with colorectal liver metastasis in immunosuppressive state and thus leads to a poor outcome after hepatic resection. Several investigators have suggested reducing the number of impaired nonregulatory DCs[23] or inactivating the function of regulatory DCs by immunosuppressive drugs might be necessary to impair DC immunotherapy.[26,27] Functional analyses of the peripheral blood monocyte subset should be performed in the future.

In conclusion, the absolute number of preoperative peripheral blood monocytes is an independent factor that influences cancer-related survival after hepatic resection for patients with liver metastasis from colorectal cancer, and it may be related to tumor growth. The function of DCs in patients with an increased preoperative peripheral blood monocyte count may be impaired, and a new strategy to induce DC maturation may be necessary for DC-based immunotherapy to be effective in these patients.