Table 2 Recurrent sites, treatment and prognosis of recurrent cases

Case	Op. date	Intervals (months)	Recurrent Organ	Treatment	Prognosis
1	1995/3/28	4	Liver	Op+CT	16mo. DOD
2	1995/5/16	33	Peritonium	CT	6mo. DOD
3	1998/9/15	11	Liver	CT	13mo. DOD
4	1999/9/26	3	Liver	CT	3mo. DOD
5	1999/10/31	7	Liver	Op	63mo. AWD
6	1999/11/25	21	Liver	Op	48mo. AWD
7	2000/9/10	11	Local	Op+CT	13mo. DOD
8	2001/3/29	24	Lung	Op	29mo. AWD
9	2001/8/28	27	Lymphnode	Op	21mo. AWD
10	1998/7/28	66	Peritonium	CT	20mo. AWD
11	2001/6/7	36	Liver	Op	14mo. AWD
12	2002/6/25	24	Lung	Op	14mo. AWD

Op：operation, CT：chemotherapy, DOD：die of disease, AWD：alive without disease

mp癌であり，sm癌に根部（3群）リンパ節再発がみられた．一方，開腹症例では87例（13.6%）に再発を認めた．その初再発臓器は，肝43例(49.4%)，肺19例（21.8%），局所11例（12.6%），腹膜8例（9.2%），リンパ節4例(4.6%)，その他2例(2.3%)であった．開腹術ではstage II以上の症例が有意に多く，再発率が高かったが，再発様式においてはLACと開腹術とを比較しても差は認めなかった(χ^2検定，p=0.9193)．

手術から再発までの平均期間は22±18（3～66）カ月で,66カ月の1例を除いてすべてが3年以内であり，1年以内が5例，1～2年が3例，2～3年が3例であった．再発臓器別では，肝が3～36（3，4，7，11，21，36）カ月，肺が24カ月，腹膜が33カ月と66カ月，リンパ節節が27カ月，局所が11カ月であった．

5．再発後の治療および予後（Table 2）

肝転移：転移個数は単発が3例（症例5，6，11），2個が1例（症例3），3個が1例（症例1），4個以上が1例（症例4）であった．6例のうち4例（症例1，5，6，11）は手術を施行し，残りの2例（症例3，4）は化学療法を行った．手術を施行した4例のうち3例（症例5，6，11）は再発なく再手術後63，48，14カ月生存中であるが，1例（症例1）は残肝再発をきたし化学療法を行うも肺転移を伴い再発診断後16カ月に癌死した．化学療法を行った2例は3カ月と11カ月に癌死した．

肺転移：2例（症例8，12）とも単発で手術により遺残なく切除が可能であった．2例とも再発なく再手術後29カ月と14カ月生存中である．

腹膜再発：2例とも化学療法を行い，1例(症例2)は再発診断後6カ月に癌死し，もう1例（症例10）は20カ月生存中である．

リンパ節再発：他臓器への再発はなく，開腹下に根部リンパ節郭清を行い，再手術後21カ月経過し無病生存中である（症例9）．

局所再発：吻合部再発で発見され，開腹下に吻合部を含めて腸管切除を行った．しかし，3カ月後腹膜転移や肺転移が出現し，化学療法を施行するも再手術後13カ月に癌死した（症例7）．

考　察

LACは導入初期には早期大腸癌のみを適応としていたが，2002年4月より保険適応が大腸癌全体に拡大されたことにより，現在では進行癌にも施行している施設が多くなってきた[7]．しかし，進行大腸癌における遠隔成績がLACでも開腹手術と同じであるかは，いまだ判明していないため，現段階では進行癌に対してLACは標準治療とみなされてはいない．一方，海外でのRCT[1)~5)]の結果では，LACは開腹手術と治療成績で差がないことが証明されている．スペインのLacyらの報告では，対象症例は219例と少ないが，stage I，IIでは生存率に差がなく，stage IIIにおいては開腹手術よりLACで生存率が上回る傾向がみられた[4)]．また，アメリカのSurgical Therapy Study Groupは，開腹移行率が21%と高率ではあるが，872例を対象として3年生存率は開腹群の85%に対して腹腔鏡下群86%

であり，非劣性が証明されたと報告している[5]．

当院でLACを施行した根治度A症例の5年生存率は，prospectiveな比較ではないが，各stageで開腹術との間で統計学的に有意差を認めず，LACの予後が開腹術に劣っているとの証拠は認めなかった．そこで次に，port site recurrenceなどのLACに特異な再発様式があるのか，当院で施行したLAC症例の再発例について検討した．

再発12例の初再発臓器は，肝，肺，腹膜，リンパ節，局所であり，再発様式においてもLACは開腹術と統計学的に差を認めなかった．また，LAC症例のみに特異的な再発様式もみられなかった．しかし，術後早期の肝転移，mp癌の腹膜転移，sm癌の根部リンパ節転移などは一般的に稀な再発様式であり，それらについて検討した．

再発までの期間は，術後1年以内が5例で，中には3，4カ月目の肝再発例（症例1，4）も認めた．気腹が転移を早めるという報告はみられないが，気腹の影響も完全には否定できない[12),13)]．しかし，手術時すでに転移があり，腹腔鏡下では診断できなかったと考える方が妥当である．開腹で肝を触診していれば，肝転移は術中に診断できていたかもしれない．術前の画像検査では診断できず，術中所見で初めて判る場合もあり，LACでは触診ができない以上，触診を補う何らかの工夫が必要である．術中の腹腔鏡による詳細な腹腔内観察に加えて術中エコー検査は有用と思われる．さらに，術後の綿密な定期検査も重要である．

Port site recurrenceは1例もみられなかったが，腹膜再発を2例に認めた．2例ともmp癌のn0症例であり，通常は腹膜再発を起こすとは考えにくい．腹膜再発の2例や局所再発の1例はいずれもLAC導入初期の症例であり，気腹下で無意識に病巣や転移リンパ節に触れ腫瘍細胞が散布された可能性も考えられ，術中の未熟な操作に起因することも否定できないと反省している．再発例のほとんどが2001年までの症例であり，2002年以降の症例では当然観察期間も短いが再発例は1例のみであった．進行癌においてはLACの操作により再発が惹起されることも推定され，手技の未熟さが予後に与える影響は大きいと考えられる．手術操作の向上のためにはトレーニングシステムの確立も急務ではあるが，臨床においては最初から進行癌を適応とするのではなく，まず早期癌で鍛錬を積み，ある一定の技術や操作を習熟した後に，進行癌に移行するのが適切である．

リンパ節再発は，sm癌で初回手術時に2群リンパ節まで郭清を行い，組織学的にもリンパ節転移は認めなかった．根部リンパ節のみの再発であり，初回に3群まで確実に郭清を行っていれば再発は防げたと思われる．鏡視下では小腸が邪魔をして視野の展開が困難で血管根部まで十分に観察できないこともある．そのような場合には，ポートをもう一本追加してでも確実に血管根部まで観察し，開腹術と同様なリンパ節郭清を行うべきである．しかし，sm癌の根部リンパ節転移は稀であり，全国大腸癌登録においてsm癌で3群以上のリンパ節に転移を認めた症例は537例中2例（0.4%）にすぎなかった[14)]．本症例では組織学的にsm深層に多量の癌浸潤を認めており，やはり，進行癌に準じて3群リンパ節郭清を初回手術時に施行するか，少なくとも根部リンパ節まで詳細に観察すべきだったと悔やまれる．

進行癌では確実に3群までリンパ節郭清を行うことが必要で，開腹術に比べてLACでは操作が難しくなり，早期癌の場合よりも高度な技術を要する．横行結腸の場合は中結腸動脈根部の処理が，また，下部直腸では肛門側の腸管切離や側方郭清が技術的に困難であり，現状では横行結腸や下部直腸の進行癌はLACの適応にはなりにくい．それに対して，右側結腸やS状結腸，直腸S状部では，血管根部の剝離が比較的容易で手技に慣れれば3群リンパ節郭清も安定してできるため，鏡視下の手技に慣れた施設では進行癌症例までLACの適応を広げても問題はないと思われる[9)]．しかし，癌が漿膜面に露出している場合には，腹腔鏡下の操作にて癌細胞が散布され腹膜播種を生じる可能性も考えられ，より慎重な手術操作が必要である[15)16)]．

LACには長い手術時間や高い材料費，気腹の影響などの欠点も報告されているが，短期成績である整容性，入院期間の短縮，早期社会復帰が可能な点はLACの方が開腹術より優れている[17)~24)]．そして，進行癌においてLACと開腹手術との間で有害事象発生割合や長期生存率が同等であれば，進行癌症例にもLACの適応が拡がり，多くの大腸癌患者がその恩恵を受けることが可能となる．さらに，術後在院日数の短縮により医療経済の面からも社会に貢献できる．ただし，進行癌に対するLACの根治性を証明するためには，日本での長期予後や開腹術とのRCTの結果を待たなければならない．

結　語

LACに特異な再発様式はみられなかったが，術後早

期の再発や鏡視下操作に起因すると考えられた再発を認めた．進行大腸癌をLACの適応とするには，RCTにより開腹術と長期予後に差がないことを証明することも重要ではあるが，鏡視下での手技が原因と思われる再発を起こさないよう，術中の十分な腹腔内観察と慎重かつ高度な鏡視下テクニックの習得が必要と思われた．

文　献

1) Weeks JC, Nelson H, Gelber S, et al : Short term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer. JAMA 287 : 321—328, 2002
2) Tang CL, Eu KW, Tai BC, et al : Randomized clinical trial of the effect of open versus laparoscopically assisted colectomy on systemic immunity in patients with colorectal cancer. Br J Surg 88 : 801—807, 2001
3) Hazebroek EJ : A randomized clinical trial comparing laparoscopic and open resection for colon cancer. Surg Endosc 16 : 949—953, 2002
4) Lacy AM, Garcia-Valdecasas JC, Delgado S, et al : Laparoscopy - assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer : a randomized trial. Lancet 359 : 2224—2229, 2002
5) The Clinical Outcomes of Surgical Therapy Study Group : A comparison of laparoscopically assisted and open colectomy for colon cancer. N Eng J Med 350 : 2050—2059, 2004
6) 北野正剛，北島政樹，小西文雄 他：厚生労働省がん研究助成金「がんにおける体腔鏡手術の適応拡大に関する研究」第2回アンケート調査結果報告．国立がんセンター，東京，2002，p30—44
7) 日本内視鏡外科学会：内視鏡外科手術に関するアンケート調査—第7回集計結果報告—．日内視鏡外会誌　9：491—505，2004
8) Wexner SD, Cohen SM : Port site metastasis after laparoscopic colorectal surgery for cure of malignancy. Br J Surg 82 : 295—298, 1995
9) 小西文雄，河村　裕，岡田真樹：腹腔鏡下大腸切除術の欧米と本邦における現況．日内視鏡外会誌　7：6—12，2002
10) Itano O, Watanabe T, Jinno H, et al : Port site metastasis of sigmoid colon cancer after a laparoscopic sigmoidectomy : report of a case. Surg Today 33 : 379—382, 2003
11) 大腸癌研究会編：大腸癌取扱い規約．第6版，金原出版，東京，1998
12) Bessa X, Castells A, Lacy AM, et al : Laparoscopic-assisted vs. open colectomy for colorectal cancer : influence on neoplastic cell mobilization. J Gastrointest Surg 5 : 66—73, 2001
13) Dorrance HR, Oien K, O'Dwyer PJ : Effects of laparoscopy on intraperitoneal tumor growth and distant metastases in an animal model. Surgery 126 : 35—40, 1999
14) Japanese Society for Cancer of the Colon and Rectum : Multi-Institutional Registry of Large Bowel Cancer in Japan Vol. 24 Cases treated in 1998. 大腸癌研究会，宇都宮，2003
15) Steinert R, Lippert H, Reymond MA : Tumor cell dissemination during laparoscopy : prevention and therapeutic opportunities. Dig Surg 19 : 464—472, 2002
16) Chew DK, Borromeo JR, Kimmelstiel FM : Peritoneal mucinous carcinomatosis after laparoscopic-assisted anterior resection for early rectal cancer : report of a case. Dis Colon Rectum 42 : 424—426, 1999
17) Konishi F, Okada M, Nagai H, et al : Laparoscopic-assisted colectomy with lymph node dissection for invasive carcinoma of the colon. Surg Today 26 : 882—889, 1996
18) Falk PM, Beart RW, Wexner SD, et al : Laparoscopic colectomy : a critical appraisal. Dis Colon rectum 36 : 28—34, 1993
19) Fleshman JW, Nelson H, Peters WR, at al : Early results of laparoscopic surgery for colorectal cancer : a retrospective analysis of 372 patients treated by Clinical Outcomes of Surgery Therapy (COST) study group. Dis Colon Rectum 39 : 53—58, 1996
20) Franklin ME, Rosenthal D, Abrego-Medina D, et al : Prospective comparison of open vs laparoscopic surgery for carcinoma : five - year results. Dis Colon Rectum 39 : 35—46, 1996
21) Khallili TM, Fleshner PR, Hiatt JR, et al : Colorectal cancer : comparison of laparoscopic

with open approaches. Dis Colon Rectum 41 : 832—838, 1998
22) Curet MJ, Putrakul K, Pitcher DE, et al : Laparoscopically assisted colon resection for colon carcinoma. Surg Endosc 14 : 1062—1066, 2000
23) Dennis H, Jeanine T, Mehran A : Laparoscopic vs open resection for colorectal adenocarcinoma. Dis Colon Rectum 44 : 10—19, 2001
24) 久保義郎，栗田 啓，棚田 稔他：大腸癌に対する腹腔鏡補助下大腸切除術の治療成績—開腹術との比較—．日臨外会誌 62：879—884，2001

A STUDY OF RECURRENT CASES AFTER LAPAROSCOPY—ASSISTED COLECTOMY

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Laparoscopy-assisted colectomy (LAC) has been performed for a series of 254 cases of colorectal cancer in our institution until December, 2004. Of 246 cases performed curative resection, 12 cases of recurrent illness which were recorded until September 2005 were enrolled in this study. The male-to-female ratio was 6 : 6. The primary locations of those tumors were C in 2, A in 1, D in 2, S in 2, Rs in 3, and Ra in 2 cases, and the histological stages were I in 3, II in 3, IIIa in 5, and IIIb in 1 case. The initial recurrent organs were the liver in 6, lung in 2, peritoneum in 2, lymph node in 1, and a local area in 1. Tumor depth of invasion in two cases of peritoneal dissemination was T2 (mp) and that of lymph node metastasis was T1 (sm). No port site recurrence occurred. Recurrence within 1 year after the operation was noted in 5 cases. Of 8 patients operated on, 6 patients are alive without disease for 14～63 months. One patient is now under chemotherapy, and the remaining 5 patients died of cancer. There were some cases of early phase recurrence after the operation and another some cases of peritoneal recurrence probably caused by laparoscopic procedures.

Meticulous observation of the abdominal cavity, good acquaintance with special techniques, and careful operations are necessary for LAC in advanced cancers.

The expression of vascular endothelial growth factor determines the efficacy of post-operative adjuvant chemotherapy using oral fluoropyrimidines in stage II or III colorectal cancer

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Abstract. The aim of this study was to determine any correlation between the efficacy of post-operative adjuvant chemotherapy using oral fluoropyrimidines and the vascular endothelial growth factor (VEGF) expression in primary colorectal cancer tissues. The data were reviewed retrospectively on 342 patients with colorectal cancer at stage II or III, who underwent potentially curative resection between 1988 and 1998. Of these, 225 received post-operative administration of oral fluoropyrimidines such as UFT and 5'-DFUR, while the other 117 patients underwent surgery alone. Immunostaining for VEGF was performed using colorectal tumours. Overall, VEGF was positively expressed in primary tumour cells in 48% of patients. The disease-free survival rate and the overall survival rate in the chemotherapy group were higher than those in the surgery-alone group, although not significantly. However, the disease-free survival rate and the overall survival rate were similar between the two groups in patients with a tumour positive for VEGF. Multivariate analysis revealed that the VEGF expression was an independent factor for post-operative recurrence, and the VEGF expression and post-operative adjuvant chemotherapy were an independent factor for overall survival, in addition to the lymph node metastasis and the venous invasion. In conclusion, the efficacy of post-operative adjuvant chemotherapy using oral fluoropyrimidines may not be as great for patients with a tumour positive for VEGF having a greater risk of post-operative recurrence. The results support further investigation on efficacy of molecular targeting therapy for VEGF in combination with oral fluoropyrimidines as post-operative adjuvant therapy in colorectal cancer positive for VEGF.

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Key words: vascular endothelial growth factor expression, immunohistochemistry, post-operative adjuvant chemotherapy, oral fluoropyrimidine, colorectal carcinoma, molecular targeting therapy

Introduction

Colorectal cancer remains one of the leading causes of death in the world. The mainstay for treatment of colorectal cancer with curative intent is surgical resection. In node-positive or stage III patients, surgery-alone offers curability to ~50% of patients treated (1). Thus, addressing the high risk of recurrence involves the use of chemotherapy, immunotherapy, or molecular targeting therapy after surgical removal of the primary lesion.

Worldwide, infusion of 5-fluorouracil plus leucovorin (5-FU/LV) combination chemotherapy has been considered to be standard for stage III colon cancer for the past decade (2), whereas the current evidence does not support the use of adjuvant chemotherapy for all patients with stage II disease (3). Recently, FOLFOX (added oxaliplatin to bolus plus infusion 5-FU/LV) was reportedly more effective than 5-FU/LV in stage II or III colon cancer (4).

In Japan, since the 1980s, oral 5-FU derivatives (fluoropyrimidines) such as UFT (1:tegafur + 4:uracil) and 5'-deoxy-5-fluorouridine (5'-DFUR), an intermediate of capecitabine, have been used as post-operative adjuvant chemotherapy for colorectal cancer. A recent meta-analysis has reported that surgery combined with oral fluoropyrimidines was more effective in preventing recurrence in patients with colorectal cancer at stage II or III rather than surgery alone (5,6). Moreover, it has been shown that the post-operative adjuvant chemotherapy using capecitabine or UFT/oral LV is not inferior to bolus 5-FU/LV (Twelves C, *et al*, Proc ASCO, abs. 3521, 2005) (Wolmark N, *et al*, J Clin Oncol ASCO 22: 3508, 2004). In general, chemotherapy using oral fluoropyrimidines, when compared to that using intravenous 5-FU/LV, or its combination with irinotecan or oxaliplatin (7,8), has been characterized by a lower incidence of adverse effects, especially infrequent adverse effects of grade 3 or higher (9). This is the reason that chemotherapy using oral fluoropyrimidines can be continued on an out-patient basis without detriment to the patients' quality of life (QOL). For patients, these are critical benefits of the therapy using oral fluoropyrimidines. It is therefore important to know which patients do not respond to oral fluoropyrimidines, in order to employ more intensive chemotherapy or some effective molecular targeting therapy, for improving the clinical efficacy of treatment and for improving the patient's QOL.

Table I. Background of the patients and the tumours.

	Age[a] (mean ± SD)	Sex (M/F)	Stage (II/III)	Location (R/C)	N factor (N1/N2)	TIO (-/+)	Ly (-/+)	V (-/+)
Surgery-alone (n=117)	66.1±10.6	71/46	59/58	52/65	43/15	99/18	64/53	66/51
Chemotherapy (n=225)	61.7±10.2	139/86	97/128	98/127	83/45	204/21	122/103	138/87

[a]p<0.001; M, male; F, female; Stage, pathological stage according to the UICC criteria; R, rectum; C, colon; TIO, tumour invasion to adjacent organs; Ly, lymphatic invasion; V, venous invasion.

Vascular endothelial growth factor (VEGF), a diffusible glycoprotein produced by normal and neoplastic cells, has a crucial role in physiological and pathological angiogenesis (10), and has been implicated in tumour growth and metastasis (11). We have also previously reported VEGF expression in colorectal cancer as a factor of poor prognosis (12). VEGF blockade, alone or in combination with chemotherapeutic agents, is being tested in a number of clinical trials (13,14), including the first successful phase III trial (15). In the present study, we investigated the correlation between the efficacy of post-operative adjuvant chemotherapy using oral fluoropyrimidines and the VEGF immunoexpression in colorectal cancer tissues, and discuss the application of molecular targeting therapy for VEGF as post-operative adjuvant therapy.

Patients and methods

Patients and post-operative adjuvant chemotherapy. Among the 487 patients with a pathological stage II or III colorectal cancer according to the UICC classification of colorectal carcinomas who underwent potentially curative resection (R0) with lymphadenectomy including the mesenteric lymph nodes at Kurume University Hospital between 1988 and 1998, 342 patients were enrolled in this retrospective study. When the distal margin of clinical stage II or III rectal cancer is located below the peritoneal reflection, pre-operative adjuvant radiotherapy was indicated in our institute, and these patients were excluded from this study. The other exclusion criteria were age more than 80 years, pre-operative chemotherapy, any immunotherapy, any other radiotherapy and post-operative chemotherapy except oral fluoropyrimidines. Post-operative adjuvant chemotherapy using oral fluoropyrimidines such as UFT and 5'-DFUR was performed in 225 patients (chemotherapy group). The other 117 patients underwent surgery alone (surgery-alone group). UFT and 5'-DUUR was administered periodically for 1 year when recurrence did not occur. The chemotherapy started from 2 to 4 weeks after surgery. The oral dosages were 500 mg/m^2/day 5'-DFUR, and 250 mg /m^2/day UFT. The main reason for surgery alone was patient's choice after informed consent.

Follow-up. Follow-up investigations were performed through out-patient visits, by letter, and by telephone, and the most recent date of contact for each patient was regarded as the final date of confirmation. Adverse effects of chemotherapy were checked every month during the therapy. The most recent date was the last day of December 2004. The median follow-up period was 91 months. The presence or absence of any recurrence was determined according to our follow-up protocol consisting of a physical examination including digital examination every 2-3 months, measurement of serum tumour marker (carcinoembryonic antigen, CEA) level every 2-3 months, and/or by findings on barium enema or colonoscopy every 1-2 years, chest radiography every 6 months, and abdominal ultrasound (US), abdominal-computed tomography (CT) or abdominal magnetic resonance imaging (MRI) every 6 months up to 5 years, and according to a modified protocol case-by-case thereafter.

Immunohistochemistry. After an initial review of all available hematoxylin and eosin-stained (H&E) slides of the surgical specimens consisting of 342 primary tumours, 13 recurrent liver tumours and 6 recurrent lung tumours, we selected two paraffin blocks from each tumour, in which the invasive front edge and the viable tumour were clearly revealed. Serial 4-micron sections were recut from each block. One section from each block was stained by H&E again, a second was immunostained for VEGF. Immunostaining was performed using the avidin-biotin peroxidase complex method. Anti-human VEGF rabbit polyclonal IgG (R&D systems, Minneapolis, MN, USA) was used as the primary antibody. The primary antibody was detected using avidin-biotin peroxidase complex (Vector Laboratories, CA, USA) and 3, 3'-diaminobenzidine tetrahydrochloride as the chromogen. These sections were also counterstained with hematoxylin and mounted. For negative control, the sections were incubated with non-immune IgG in place of the primary antibody.

Statistical analysis. The background of the patients, the incidence and the mode of recurrence, and overall survival rate and disease-free survival rate analyzed by the Kaplan-Meier method, were compared between the chemotherapy group and the surgery-alone group. Multivariate analysis for the factors related to disease-free survival and overall survival was also carried out using Cox's proportional hazard model. All data were compiled and analyzed by statistical analysis software version 6.12 (SAS Institute, Cary, NC, USA). The differences in clinico-pathological characteristics between the two groups

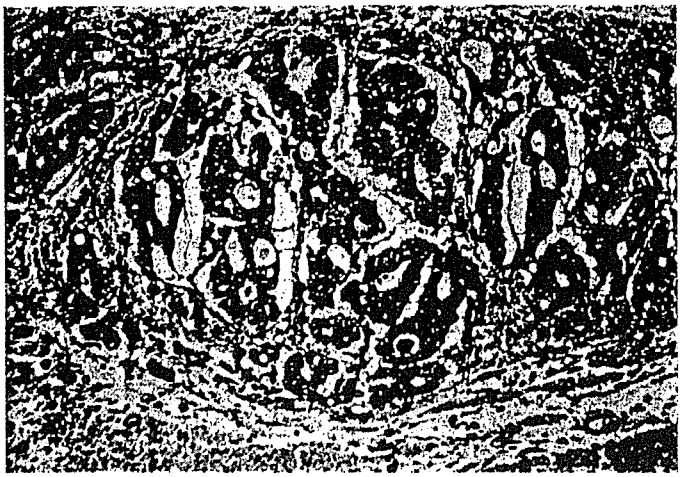

Figure 1. Immunostaining for VEGF in colorectal cancer tissue. VEGF observed in the cytoplasm of tumour cells as supranuclear staining. Original magnification of x100.

were assessed for statistical significance using the Chi-square test, Fisher's exact test, and Student's t-test. Differences between the groups in Kaplan-Meier plots were evaluated using the log-rank test.

Results

Background of patients. The background of patients and their tumours between the chemotherapy group and the surgery-alone group is summarized in Table I. The average age in the surgery-alone group was significantly higher than that in the chemotherapy group. However, there was no significant difference in sex, distribution of tumour stage, tumour location, N factor, incidence of tumour invasion to adjacent organs, lymphatic invasion, or venous invasion, between the two groups.

Immunoexpression of VEGF in primary colorectal cancer tissues. VEGF was expressed mainly in the cytoplasm of cancer cells (Fig. 1), and in the cytoplasm of a few neutrophilic leucocytes, monocytes-macrophages, and fibroblast cells. A sample with positive staining for VEGF in >10% of all tumour cells was defined as positive (positive cell ratio was >50% in most cases whose tumour cells were stained for VEGF) (12). Forty-eight percent of all primary colorectal tumours were positive for VEGF expression.

Correlation between the VEGF expression in primary tumour and recurrent tumour cells. Among 19 patients with recurrence to the liver or the lung which could be resected post-operatively, VEGF was positively expressed by the cancer cells in 12 primary and in 13 recurrent tumours. In 11 of 12 patients with primary tumours positive for VEGF, recurrent tumour cells also were positive for VEGF. There was a positive correlation (p=0.010) in VEGF expression between the primary and recurrent tumours (Table II).

Multivariate analysis for disease-free survival rate and overall survival rate. Various factors such as post-operative adjuvant chemotherapy, tumour location (colon vs. rectum), histological tumour grade (well-differentiated adenocarcinoma vs. others), tumour invasion to adjacent organs (- vs. +), pathological tumour stage (II vs. III), N factor (N0-1 vs. N2), lymphatic invasion (ly- vs. ly+) (16), venous invasion (v- vs. v+) (17), age, sex, and VEGF expression (- vs. +) were each evaluated for their independent contributions to the disease-free survival and the overall survival rate after operation using Cox's proportional hazards model. The positive VEGF expression was a significantly worse factor for recurrence, and the surgery-alone and the positive VEGF expression were a significantly worse factor for death, in addition to the stage III and the presence of venous invasion (Table III).

Relationship between the VEGF expression and the clinico-pathological factors. The relationships between the VEGF expression and the clinico-pathological factors are shown in Table IV. There was no significant correlation between the VEGF expression and the clinico-pathological factors including tumour location, lymph node metastasis and number of lymph node metastasis, tumour invasion to adjacent organs, lymphatic invasion, venous invasion, or histological grade of tumour.

Table II. Correlation of the VEGF expression between the primary and recurrent tumours.

		VEGF expression in the recurrent tumours		
		Negative	Positive	Total
VEGF expression in the primary tumours	Negative	5	2	7
	Positive	1	11	12
	Total	6	13	19

p=0.010 (Chi-square value was 8.146).

Table III. Multivariate analysis for the factors correlated to the disease-free survival and the overall survival rate.

Variable	p-value	95% CI	Hazard ratio
Disease-free survival rate			
Venous invasion (+)	p=0.0001	1.497-3.534	2.299
Stage III	p=0.0066	1.193-2.967	1.883
VEGF (+)	p=0.0199	1.085-2.564	1.667
Overall survival rate			
Stage III	p=0.0018	1.381-4.082	2.375
Venous invasion (+)	p=0.0034	1.274-3.378	2.075
Surgery-alone	p=0.0405	1.022-2.707	1.664
VEGF (+)	p=0.0453	1.010-2.695	1.650

Table IV. VEGF expression and clinico-pathological factors.

Factor	VEGF expression (%) (positive cases/ all cases)			p-value
Sex				0.999
Male	100	/210	(48)	
Female	65	/150	(48)	
Location				0.190
Colon	98	/192	(51)	
Rectum	65	/150	(43)	
N factor (stage)				0.128
N0 (stage II)	67	/156	(43)	
N1-2 (stage III)	96	/186	(52)	
Tumour invasion to adjacent organs				0.999
(-)	144	/303	(48)	
(+)	19	/39	(49)	
Lymphatic invasion				0.104
ly (-)	81	/186	(44)	
iy (+)	82	/156	(53)	
Venous invasion				0.912
v (-)	98	/204	(48)	
v (+)	65	/138	(47)	
Histology				0.507
Well	97	/210	(46)	
Others	66	/132	(50)	

Lymphatic and venous invasion were graded according to the Shirouzu's criteria. Well, well differentiated adenocarcinoma.

Disease-free survival and overall survival rate based on the VEGF expression. The disease-free survival rate in patients with a tumour positive for VEGF was significantly lower than that in patients negative for VEGF, and the overall survival rate in patients with a tumour positive for VEGF tended to be lower than that in patients negative for VEGF (Fig. 2).

Disease-free survival and overall survival rate based on adjuvant chemotherapy. In both groups, the major mode of recurrence was hematogenous metastasis, and no difference in the pattern of recurrence was found between the two groups (data not shown). The disease-free survival and the overall survival rate in the chemotherapy group were higher than those in the surgery-alone group, although not significantly (Fig. 3).

However, when the disease-free survival rates were stratified according to the prognostic factors demonstrated by the multivariate analysis such as the pathological stage (Fig. 4), the venous invasion, and the VEGF expression, then no significant difference in the disease-free survival rate was found between the chemotherapy group and the surgery-alone group in a tumour with venous invasion (p=0.523) (Fig. 5), or in a tumour positive for VEGF (p=0.235) (Fig. 6), contrary to the significant difference in patients with a tumour negative for venous invasion (p=0.002) (Fig. 5) or for VEGF (p=0.013) (Fig. 6).

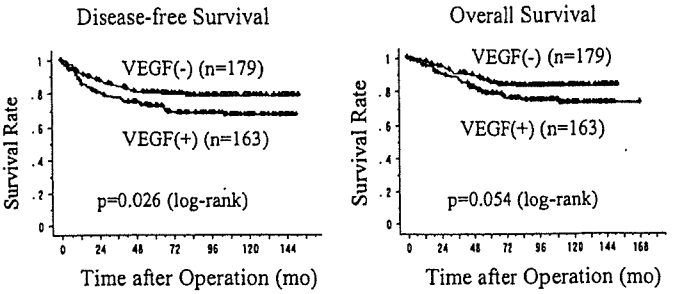

Figure 2. The disease-free survival curves according to VEGF expression. The disease-free survival rate (p=0.026) and the overall survival rate (p=0.054) in patients with a tumour positive for VEGF were lower than those negative for VEGF.

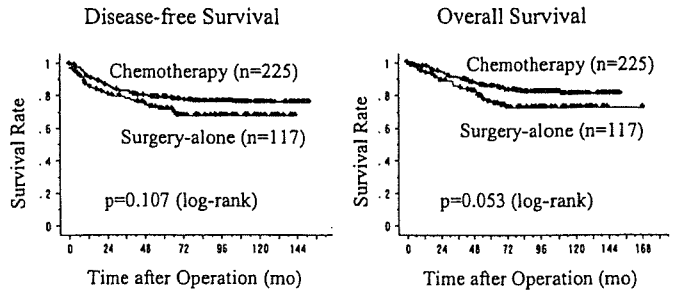

Figure 3. The disease-free survival and the overall survival curves according to post-operative adjuvant chemotherapy. The disease-free survival rate (p=0.107) and the overall survival rate (p=0.053) in the chemo-therapy group tended to be higher than those in the surgery-alone group.

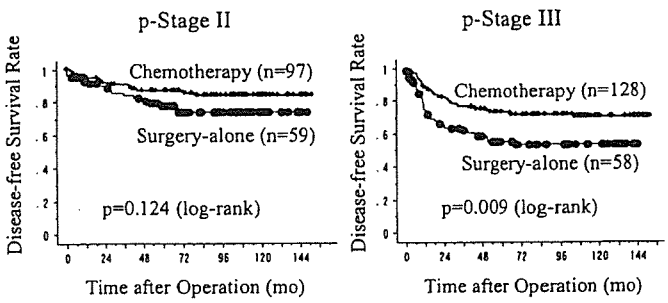

Figure 4. The disease-free survival curves according to post-operative adjuvant chemotherapy-stratified to the pathological stage. There was significant difference (p=0.009) in disease-free survival rate in stage III tumours between the chemotherapy group and the surgery-alone group, but not in stage II tumours (p=0.124).

Discussion

A recent meta-analysis has reported that post-operative oral fluoropyrimidines such as UFT and 5'-DFUR were more effective in patients with colorectal cancer at stage II or III than surgery alone (5,6). Moreover, it has been shown that the post-operative adjuvant chemotherapy using capecitabine

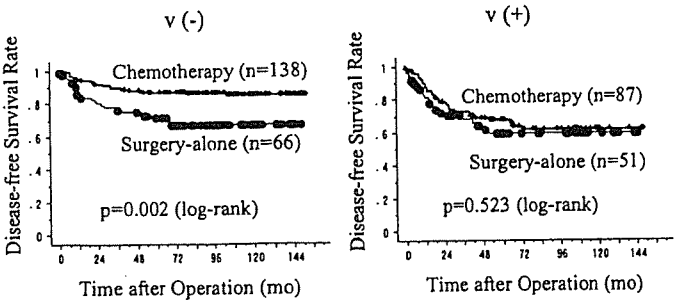

Figure 5. The disease-free survival curves according to post-operative adjuvant chemotherapy-stratified to the presence of venous invasion. There was significant difference (p=0.002) in disease-free survival rate in tumours without venous invasion between the chemotherapy group and the surgery-alone group, but not in tumours with venous invasion (p=0.523).

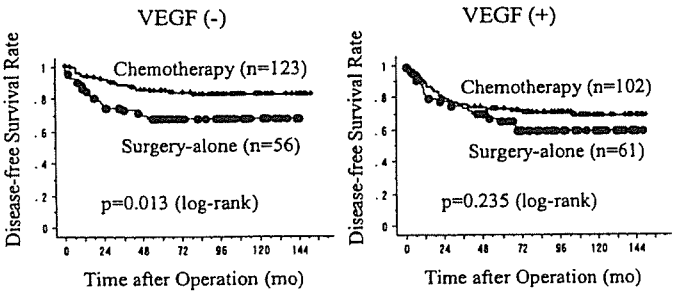

Figure 6. The disease-free survival curves according to post-operative adjuvant chemotherapy-stratified to the VEGF immunoexpression. There was significant difference (p=0.013) in disease-free survival rate in tumours negative for VEGF between the chemotherapy group and the surgery-alone group, but not in tumours positive for VEGF (p=0.235).

or UFT/oral LV is not inferior to bolus 5-FU/LV. In our retrospective study, the comparison of disease-free survival rate and overall survival rate, and the multivariate analyses supported the efficacy of post-operative adjuvant chemotherapy using oral fluoropyrimidines.

However, in biologically aggressive tumours with venous invasion, the adjuvant chemotherapy could not reduce the risk of recurrence. Our results also indicated that disease-free survival benefit of post-operative adjuvant chemotherapy using oral fluoropyrimidines did not reach significance in tumours positive for VEGF, contrary to the significant efficacy in tumours negative for VEGF. The retrospective and small sample number generally may have obscured the possible benefit. However, our results show that further investigation concerning molecular targeting therapy for VEGF is worthwhile. VEGF plays a key role in the development and progression of human malignancies including colorectal cancer. In particular, VEGF participates in the early stages of tumourigenesis and tumour growth including metastatic tumours. Thus, VEGF is attractive as a target for cancer treatment (18), and clinical application of the molecular targeting therapy alone or in combination with chemotherapeutic agents may be good adjuvant therapy after curative resection of the primary tumour in which VEGF activity is high and implicated in tumour progression and metastasis. Our multivariate analysis showed that VEGF expression was an independently significant factor for poor disease-free survival. The VEGF expression was suspected to be implicated in the development of post-operative recurrent tumours independently, indicating a target as post-operative adjuvant therapy. Moreover, the positive correlation of VEGF expression between the primary tumours and the recurrent liver or lung tumours indicated that VEGF was implicated in the development of post-operative recurrence even in a secondary organ. These results suggested that inhibition in the VEGF activity might prevent post-operative tumour growth and secondary spreading of micrometastases, in particular in tumours positive for VEGF.

With regard to the rationale for a combination of anti-angiogenic drugs with chemotherapeutic agents, anti-angiogenic agents may improve the delivery of chemotherapeutic agents by altering the tumour vasculature and through decreasing the elevated interstitial pressure in tumours (19,20). Moreover, conventional cytotoxic chemotherapeutics affect the endothelium of the growing tumour vasculature, and there is evidence that the anti-proliferative or pro-apoptotic actions of chemotherapeutic agents such as paclitaxel, cisplatinum, and adriamycin on human endothelial cells in culture are suppressed by the presence of VEGF (21,22). A high local concentration of VEGF in the tumour micro-environment might therefore induce or promote multidrug resistance, by inducing a highly specific chemoprotective effect towards the VEGF receptor 2-positive endothelial cells of the tumour (21-23). Chemotherapy itself might also induce or up-regulate the expression of VEGF and other endothelial-cell pro-survival growth factors in tumour cells (24). Therefore, the combination of a chemotherapeutic agent with a drug that blocks VEGF or its receptor might selectively amplify the pro-apoptotic effects of chemotherapeutic agents against activated endothelial cells (25). A randomized placebo-controlled phase III clinical study with bevacizumab (anti-VEGF antibody) in combination with intravenous 5-FU/LV and irinotecan for advanced colorectal cancer demonstrated a statistically significant prolongation of survival, compared with only the chemotherapy regimen (15). Micrometastasis would be also a good candidate for molecular targeting therapy to VEGF in combination with 5-FU-based chemotherapy as post-operative adjuvant therapy in colorectal cancer. One of the proposed benefits of targeting therapies is the reduction of toxicity and improved QOL. However, when these drugs are combined with maximum tolerable doses of chemotherapy these benefits may not be realized. Anti-angiogenic drugs might also improve the efficacy of a continuous low-dose chemotherapy regimen such as oral fluoropyrimidines, for which the side effects would be much more tolerable, and the two types of drug such as bevacizumab and oral fluoropyrimidines could be administered together over a long period in a post-operative adjuvant setting.

Although a targeting therapy for VEGF may theoretically be effective in a VEGF overexpressing tumour such as trastuzumab (Herceptin) for human epidermal growth factor receptor 2 (HER2/neu) in breast cancer (26), it is not yet proven whether VEGF inhibitors are more effective in tumours positive for VEGF immunoexpression or its grade. Accordingly, any correlation between the VEGF expression

and the efficacy of targeting therapy for VEGF should be investigated to clarify predictive factors for targeting therapy in terms of more effective therapy.

In conclusion, the efficacy of post-operative adjuvant chemotherapy using oral fluoropyrimidines such as UFT and 5'-DFUR may not be a good option for patients with a tumour positive for VEGF having a greater risk of post-operative recurrence. Further investigation is recommend on the efficacy of targeting therapy for VEGF such as bevacizumab in combination with oral fluoropyrimidines as post-operative adjuvant therapy for colorectal cancer, in particular in tumours positive for VEGF.

Acknowledgements

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References

1. Greenlee RT, Murray T, Bolden S and Wingo PA: Cancer Statistics, 2000. CA Cancer J Clin 50: 7-33, 2000.
2. International Multicentric Pooled Analysis of Colon Cancer Trials (IMPACT) investigators: Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. Lancet 345: 939-944, 1995.
3. International Multicentric Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) investigators: Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. J Clin Oncol 17: 1356-1363, 1999.
4. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I and De Gramont A: Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) investigators: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350: 2343-2351, 2004.
5. Sakamoto J, Hamada C, Kodaira S, Nakazato H and Ohashi Y: Adjuvant therapy with oral fluoropyrimidines as main chemotherapeutic agents after curative resection for colorectal cancer: individual patient data meta-analysis of randomized trials. Jpn J Clin Oncol 29: 78-86, 1999.
6. Meta-Analysis Group of the Japanese Society for Cancer of the Colon and Rectum and the Meta-Analysis Group in Cancer: Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5-year results from three randomized trials. J Clin Oncol 22: 484-492, 2004.
7. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL and Miller LL: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 343: 905-914, 2000.
8. De Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, De Braud F, Wilson C, Morvan F and Bonetti A: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18: 2938-2947, 2000.
9. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, Maroun J, Walde D, Weaver C, Harrison E, Burger HU, Osterwalder B, Wong AO and Wong R: Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 19: 2282-2292, 2001.
10. Ferrara N, Gerber HP and LeCouter J: The biology of VEGF and its receptors. Nat Med 9: 669-676, 2003.
11. Kondo Y, Arii S, Mori A, Furutani M, Chiba T and Imamura M: Enhancement of angiogenesis, tumour growth, and metastasis by transfection of vascular endothelial growth factor into LoVo human colon cancer cell line. Clin Cancer Res 6: 622-630, 2000.
12. Harada Y, Ogata Y and Shirouzu K: Expression of vascular endothelial growth factor and its receptor KDR (kinase domain-containing receptor)/Flk-1 (fetal liver kinase-1) as prognostic factors in human colorectal cancer. Int J Clin Oncol 6: 221-228, 2001.
13. Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, Griffing S and Bergsland E: Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 21: 60-65, 2003.
14. Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, Steinberg SM, Chen HX and Rosenberg SA: A randomized trial of bevacizumab, an anti-vascular endothelial cell growth factor antibody, for metastatic renal cancer. N Engl J Med 349: 427-434, 2003.
15. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R and Kabbinavar F: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metatatic colorectal cancer. N Engl J Med 350: 2335-2342, 2004.
16. Shirouzu K, Isomoto H, Morodomi T and Kakegawa T: Carcinomatous lymphatic invasion: prognostic significance in patients with rectal carcinoma - a long-term prospective study. Cancer 75: 4-10, 1995.
17. Shirouzu K, Isomoto H, Kakegawa T and Morimatsu M: A prospective clinicopathologic study of venous invasion in colorectal cancer. Am J Surg 162: 216-222, 1991.
18. Morgan B, Thomas AL, Drevs J, Hennig J, Buchert M, Jivan A, Horsfield MA, Mross K, Ball HA, Lee L, Mietlowski W, Fuxuis S, Unger C, O'Byrne K, Henry A, Cherryman GR, Laurent D, Dugan M, Marme D and Steward WP: Dynamic contrast-enhanced magnetic resonance imaging as a biomarker for the pharmacological response of PTK787/ZK 222584, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinases, in patients with advanced colorectal cancer and liver metastases: results from two phase I studies. J Clin Oncol 21: 3955-3964, 2003.
19. Jain RK: Normalizing tumour vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med 7: 987-989, 2001.
20. Willett CG, Boucher Y, Di Tomaso E, Duda DG, Munn LL, Tong RT, Chung DC, Sahani DV, Kalva SP, Kozin SV, Mino M, Cohen KS, Scadden DT, Hartford AC, Fischman AJ, Clark JW, Ryan DP, Zhu AX, Blaszkowsky LS, Chen HX, Shellito PC, Lauwers GY and Jain RK: Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nat Med 10: 145-147, 2004.
21. Sweeney CJ, Miller KD, Sissons SE, Nozaki S, Heilman DK, Shen J and Sledge GW Jr: The anti-angiogenic property of docetaxel is synergistic with a recombinant humanized monoclonal antibody against vascular endothelial growth factor or 2-methoxyestradiol but antagonized by endothelial growth factors. Cancer Res 61: 3369-3372, 2001.
22. Tran J, Master Z, Yu JL, Rak J, Dumont DJ and Kerbel RS: A role for survivin in chemoresistance of endothelial cells mediated by VEGF. Proc Natl Acad Sci USA 99: 4349-4354, 2002.
23. Castilla MA, Caramelo C, Gazapo RM, Gonzalez-Pacheco FR, Martin O, Tejedor A, Bragado R and Arroyo MV: Role of vascular endothelial growth factor (VEGF) in endothelial cell protection against cytotoxic agents. Life Sci 67: 1003-1013, 2000.
24. Gorski DH, Beckett MA, Jaskowiak NT, Calvin DP, Mauceri HJ, Salloum RM, Seetharam S, Koons A, Hari DM, Kufe DW and Weichselbaum RR: Blockage of the vascular endothelial growth factor stress response increases the anti-tumour effects of ionizing radiation. Cancer Res 59: 3374-3378, 1999.
25. Klement G, Baruchel S, Rak J, Man S, Clark K, Hicklin DJ, Bohlen P and Kerbel RS: Continuous low-dose therapy with vinblastine and VEGF receptor-2 antibody induces sustained tumour regression without overt toxicity. J Clin Invest 105: R15-R24, 2000.
26. Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, Slamon DJ, Murphy M, Novotny WF, Burchmore M, Shak S, Stewart SJ and Press M: Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 20: 719-726, 2002.

Original articles

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SURGICAL ENDOSCOPY
and Other Interventional Techniques

A multicenter study on laparoscopic surgery for colorectal cancer in Japan

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Abstract
Background: Laparoscopic colectomy for malignant disease technically is feasible but not widely accepted because there are no large-series studies or data on long-term outcomes. A retrospective, multicenter study investigating a large series of patients was conducted in Japan to evaluate preliminary long-term results of laparoscopic surgery for colorectal cancer.
Methods: The study group comprised 2,036 patients who underwent laparoscopic colorectal resection April 1993 to August 2002 in 12 participating surgical units (Japanese Laparoscopic Surgery Study Group).
Results: Of the 1,495 patients with colon cancer, 781 (59%) had International Union Against Cancer (UICC) stage I, 248 (19%) had stage II, and 284 (22%) had stage III disease. Cancer recurred for 61 (4.1%) of 1,367 curatively treated patients (median follow-up period, 32 months; range, 6–125 months). The 5-year survival rate was 96.7% for stage I, 94.8% for stage II, and 79.6% for stage III disease. Of the 541 patients with rectal cancer, 220 (56%) had stage I, 62 had (16%) stage II, and 108 (28%) had stage III disease. Cancer recurred for 30 (5.6%) of 476 curatively treated patients (median follow-up period, 25 months; range 6–102 months). The 5-year survival rate was 95.2% for stage I, 85.2% for stage II, and 80.8% for stage III disease.
Conclusions: The findings indicate that laparoscopic surgery for colorectal cancer yields an oncological outcome as good as that reported for conventional open surgery in the Japanese Registry for all disease stages.

Key words: Laparoscopic surgery — Colorectal cancer — Multicenter study — Outcome — Survival rate

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Rapid advances in instruments and techniques have promoted widespread use of laparoscopic surgery as a treatment for colorectal disease. Multiple clinical studies confirm the usefulness of laparoscopic colectomy [5, 14], and investigators report faster recovery, less pain, shorter hospital stay, and a quicker return to normal activities with laparoscopic than with conventinal open colectomy [3, 4, 9, 10]. Thus, it is generally accepted that laparoscopic colectomy is less invasive and more beneficial than open colectomy.

However, laparoscopic surgery for the treatment of malignancies remains controversial because of concerns about the adequacy of lymphadenectomy, the extent of resection, early findings of port-site metastases, and the lack of data on long-term results. Several randomized controlled trials comparing laparoscopic and conventional open surgery were conducted in Western countries in the late 1990s. In a recent study of patients with stage III tumors, Lacy et al. [12] reported superior long-term surgical results in terms of cancer-related survival with laparoscopic colectomy than with conventional open colectomy. However, the long-term oncologic results of laparoscopic surgery for colorectal cancer remain unclear [7, 13, 19].

In Japan, laparoscopic surgery for colorectal cancer was introduced in 1992. To date, individual institutions have reported decreased invasiveness, improved quality of life for patients, and satisfactory short-term oncologic results [1, 6, 11, 16, 20], but there have been no large-scale studies in Japan.

Thus we designed a retrospective study to analyze the data obtained from 12 surgical units participating in the Japanese Laparoscopic Surgery Study Group, supported in part by a Grant-in-Aid for Cancer Research from the Japanese Ministry of Health, Labour, and Welfare. We report the perioperative results and pre-

liminary long-term outcomes for large number of patients who underwent laparoscopic surgery for colorectal cancer in Japan.

Materials and methods

The study group consisted entirely of patients who underwent laparoscopic resection for colorectal cancer in the 12 participating institutions during the period April 1993 to August 2001. Each surgeon in the participating institutions had experienced at least 30 laparoscopic surgeries for colorectal cancer as an operator. All the participating surgeons were personally responsible for obtaining the written informed consent of their patients. Clinical data including patient age, sex, surgical procedures, body mass index (BMI), conversion to open surgery, previous laparotomy, postoperative complications, and postoperative oncologic outcome, and histopathologic data including histologic type, depth of tumor invasion, lymph node metastasis, and TNM stage International Union Against Cancer (UICC) were obtained for each patient.

All the patients underwent standard mechanical cathartic bowel preparation with polyethylene-glycol (+) electrolyte solution the day before surgery. Laparoscopic colonic resection consisted of the following procedures: mobilization of the colon under carbon dioxide pneumoperitoneum, division of the mesentery and ligation of the main vessels inside the peritoneal cavity or via a minilaparotomy resection of the tumor-bearing portion of the colon via a minilaparotomy approximately 5 cm long, anastomosis for a right or transverse colectomy extraabdominally via the minilaparotomy, or anastomosis for a sigmoid colectomy or low anterior resection inside the peritoneal cavity with a circular stapler introduced transanally, and observation and irrigation of the peritoneal cavity under a reestablished pneumoperitoneum. Conversion from laparoscopically assisted surgery to open surgery was allowed at the surgeon's discretion for the patient's safety and because of technical difficulties, the presence of associated conditions, or findings of advanced disease or inadequate oncologic margins.

All patients were monitored postoperatively by means of physical examinations; blood tests; serum carcinoembryonic antigen testing at least every 3 months for the first year, every 6 months for the next 2 years, and yearly for 5 years; liver ultrasonography; abdominal and pelvic computed tomography scanning, chest x-ray; and colonoscopy at least yearly.

Differences in categorical variables among postoperative complications, tumor recurrences, and other clinicopathologic data were analyzed by chi-square test, and differences in continuous variables were analyzed by the Student's *t*-test. Survival rates were calculated using the Kaplan–Meier method

Results

During the study period, 2,036 patients (1145 men, 891 women) underwent laparoscopic cancer. colorectal resection 1,495 for colon cancer and 541 for rectal cancer. The laparoscopic surgical procedures for colon and rectal cancer are shown in Table 1. Sigmoid colectomy was the most common laparoscopic procedure for colon cancer patients, and anterior resection was the most common for rectal cancer patients. The clinicopathologic characteristics of patients with colon and rectal cancer are shown in Table 2. The rate of conversion to open surgery was 4.8% of patients with colon cancer and 4.4% of patients with rectal cancer. The reasons and frequencies of conversion are given in Table 3.

Of the 1,495 patients with colon cancer, 188 (12.6%) had postoperative complications (Table 4). Complications occurred more frequently after transverse colectomy than after other surgical procedures ($p < 0.05$).

Table 1. Laparoscopic procedures for colorectal cancer

	Patients *n* (%)
Colon cancer	1495 (100)
Ileocecal resection	188 (13)
Right colectomy	409 (27)
Transverse colectomy	206 (14)
Left colectomy	132 (9)
Sigmoid colectomy	560 (37)
Rectal cancer	541 (100)
Anterior resection	500 (92)
Abdomino perineal resection	41 (8)

Table 2. Clinicopathologic characteristics of patients with colorectal cancer

	Patients *n* (%)	
	Colon cancer (n = 1495)	Rectal cancer (n = 541)
Previous laparotomy		
Absence	1061 (71)	400 (74)
Presence	434 (29)	141 (26)
BMI		
<26	1051 (77)	406 (75)
26 to 32	314 (21)	124 (23)
>32	30 (2)	11 (2)
Histologic type		
Well	1017 (68)	292 (54)
Moderate	403 (27)	211 (39)
Poor	15 (1)	6 (1)
Others	60 (4)	32 (6)
Depth of invasion		
T1	493 (33)	147 (27)
T2	239 (16)	124 (23)
T3	449 (30)	146 (27)
T4	314 (21)	124 (23)
Lymph node metastasis		
Absence	1151 (77)	384 (71)
Presence	344 (23)	157 (29)
Curability		
Curable	1405 (94)	487 (90)
Noncurable	90 (6)	54 (10)
Tumor staging[a]		
Stage I	837 (56)	287 (53)
Stage II	269 (18)	87 (16)
Stage III	299 (20)	149 (26)
Stage IV	90 (6)	27 (5)

BMI, body mass index
[a] International Union Against Cancer (UICC-TNM) staging

The presence of complications was not associated with any other factor, such as tumor stage or patient age, sex, history of laparotomy, or body mass index (BMI). Curative surgery was performed for 1,411 patients (94.4%), but not for 84 patients (5.6%) because of liver metastasis (n = 46), lung metastasis (n = 13), peritoneal dissemination (n = 20), or metastases (n = 5).

Cancer recurred in 61 (4.3%) of the 1411 curatively treated patients during a median follow-up period of 32 months (range, 6–125 months) (Table 5). Recurrence was not associated with any surgical procedure or conversion to open colectomy. The 5-year survival rate was 96.6% for the patients with stage I, 94.8% for those with stage II, and 79.6% for those with stage III disease (Fig. 1). The 5-year survival rates were not associated

Table 3. Reasons for conversion to open surgery[a]

	Patients *n* (%)	
	Colon cancer	Rectal cancer
Advanced disease	34 (47)	11 (46)
Intraoperative complications	22 (31)	7 (29)
Bleeding	15 (21)	4 (16)
Injury to other organs	7 (10)	3 (13)
Adhesion	4 (6)	3 (13)
No visualization of critical structures	4 (6)	2 (8)
Complicating disease	2 (3)	0
Others	6 (8)	1 (4)
Total	72 (100)	24 (100)

[a] There were 1,495 patients with colon cancer and 541 patients with rectal cancer

Table 4. Postoperative complications[a]

	Patients *n* (%)	
Postoperative complications	Colon cancer	Rectal cancer
Bowel obstruction	31 (19)	13 (20)
Anastomotic leakage	22 (14)	22 (33)
Postoperative bleeding	5 (3)	1 (1)
Wound infection	97 (60)	29 (43)
Pneumonia	4 (2)	0
Intraabdominal abscess	3 (2)	2 (3)
Total	162 (100)	67 (100)

[a] There were 1,495 patients with colon cancer and 541 patients with rectal cancer

Table 5. Tumor recurrence[a]

	Patients *n* (%)	
	Colon cancer	Rectal cancer
Tumor recurrence	61 (100)	30 (100)
Location of recurrence		
Liver	35 (65)	14 (48)
Lung	6 (11)	2 (7)
Peritoneum	7 (13)	6 (21)
Locoregional	2 (4)	4 (14)
Lymph node	4 (7)	3 (10)
Portsite	0	0

[a] There were 1,411 patients with colon cancer and 508 patients with rectal cancer

with any surgical procedure, presence of complications, or conversion to open colectomy.

Of the 541 patients with rectal cancer, 76 (14.1%) experienced had postoperative complications (Table 4). The complications were not associated with any of the factors studied, including surgical procedure, tumor stage, sex, age, history of laparotomy, or BMI.

Curative surgery was performed for 508 patients (93.9%), but not for 33 patients (6.1%) because of liver metastasis (n = 13), lung metastasis (n = 5), peritoneal dissemination or (n = 4), or and other metastases (n = 11). Cancer recurred in 30 (5.9%) of the 508 curatively treated patients during a median follow-up period of 25 months (range, 6–102 months) (Table 5).

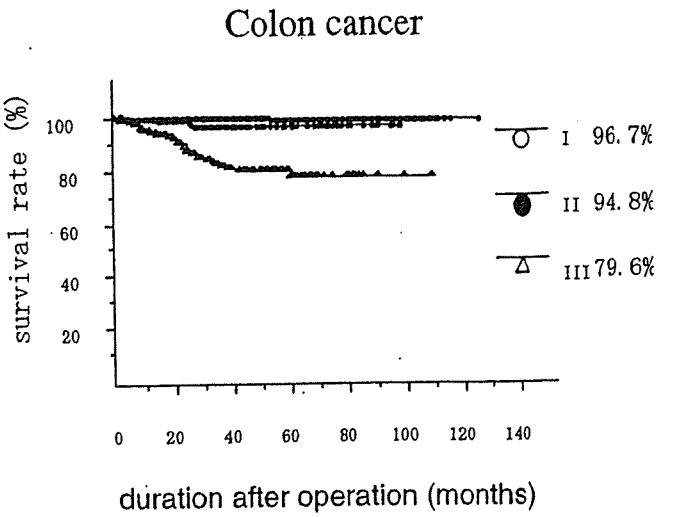

Fig. 1. The survival rate for 1,411 curatively treated patients with colon cancer is, shown. The 5-year survival rate was 96.7% for stage I, 94.8% for stage II, and 79.6% for stage III disease. International Union Against Cancer (UICC-TNM) staging was used.

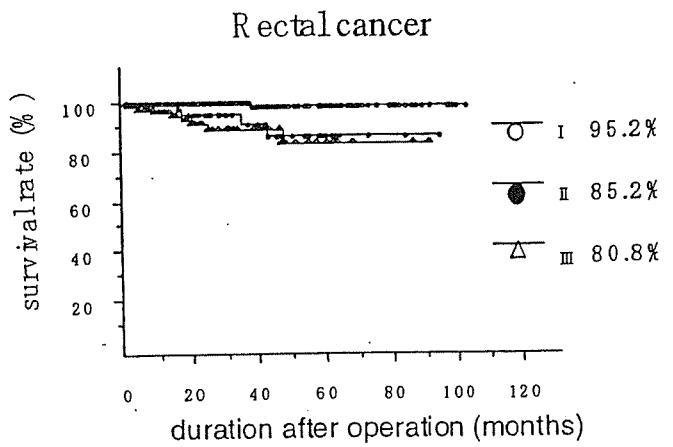

Fig. 2. The survival rate for 508 curatively treated patients with rectal cancer is shown. The 5-year survival rate was 95.2% for stage I, 85.2% for stage II, and 80.8% for stage III disease. International Union Against Cancer (UICC-TNM) staging was used.

Recurrence was not associated with any surgical procedure or conversion to open colectomy. The 5-year survival rate was 95.2% for the patients with stage I, 85.2% for those with stage II, and 80.8% for those with stage III disease (Fig. 2). The 5-year survival rates were not associated with any surgical procedure, presence of complications, or conversion to open colectomy. No port-site or abdominal wall recurrences were found in any of the 2,036 patients.

Discussion

This multicenter study reflects 10 years of experience with laparoscopic surgery for colorectal cancer in a large patient series in Japan. The short-and long-term outcomes for our patients suggest that laparoscopic surgery is a safe and effective treatment for colorectal cancer, in light of reported outcomes for conventional open surgery.

The records of the Multi-Institutional Registry of Large Bowel Cancer in Japan indicate that the 5-year survival rates for those undergoing curative open surgery were 93.4% (stage I), 84.5% (stage II), and 74.0% (stage III) for colon cancer, and 93.9% (stage I), 79.8% (stage II), and 64.7% (stage III) for rectal cancer (UICC stages) [15]. The 5-year survival rates of patients undergoing laparoscopic surgery in our study are as good as those for patients undergoing conventional open surgery for disease at each stage of the UICC stages. In fact, the 5-year survival rate for our stage II colon cancer patients undergoing laparoscopic surgery was superior to that reported for patients undergoing conventional open surgery (94.8% vs 84.5%). Furthermore, the 5-year survival rate for our stage III rectal cancer patients undergoing laparoscopic surgery was superior to that reported for patients undergoing conventional open surgery (80.8% vs 64.7%). Lacy et al. [12] reported recently that the cancer-related survival rate after laparoscopic surgery was significantly higher than that after conventional open surgery for patients with stage III tumors. The superiority of laparoscopic over open colectomy may involve the relation between immunologic status and surgical stress. Our study investigated a large series of patients undergoing laparoscopic surgery, but it was an uncontrolled study. To evaluate the oncologic outcome of laparoscopic surgery, long-term results of prospective randomized controlled trials are needed.

Among the curatively treated patients in our study, 4.1% of the patients with colon cancer and 5.6% of those with rectal cancer had recurrence. The rates and types of recurrence were similar to those reported for conventional open surgery. There were many reports of patients with port-site metastases and abdominal incisional recurrence [2]. In recently reported laparoscopic series, the frequency of port-site metastasis has been very low, ranging from 0% to 1.3% [17]. It was considered that port-site metastases were related to the unskillful laparoscopic technique in early periods. Experimental studies investigating murine models showed that carbon dioxide pneumoperitoneum, as comparsed with laparotomy, reduced lung metastases and peritoneal dissemination and enhanced liver metastases [8, 18]. Conclusions about the influence of carbon dioxide pneumoperitoneum on tumor development cannot be drawn from these studies because the data on ecological outcome are inadequate.

In this study, postoperative complications were observed in 12.6% of patients with colon cancer and 14.1% of patients with rectal cancer, and the frequency of complications was consistent with that in previous studies [3, 9, 12]. No specific laparoscopic complications were detected. An examination of the relation between the occurrence of complications and surgical procedures showed that postoperative complications occurred more frequently for patients undergoing transverse colectomy than in patients undergoing any other procedure. The technical difficulties in ligating the roots of middle colic vessels in laparoscopic surgery may account for this finding.

In our series, about three-fourths of all the patients underwent laparoscopic right colectomy, sigmoid colectomy, or anterior resection. Histopathologic examination showed that Tl, T2, T3, and T4 disease each accounted for one-fourth of the total patients, and that stage I disease was present in more than half of our patients. Curative surgery was performed for 94.4% of all patients with colon cancer and 93.9% of those with rectal cancer. These findings suggest that laparoscopic surgery for colorectal cancer has been accepted as a radical treatment for potentially curable patients in Japan.

We conclude from our findings that laparoscopic surgery is safe treatment for colorectal cancer, with an oncologic outcome as good as that of conventional open surgery. The results of our nonrandomized retrospective clinical analysis must be confirmed by large-scale prospective randomized trials.

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References

1. Adachi Y, Sato K, Kakisako K, Inomata M, Shiraishi N, Kitano S (2003) Quality of life after laparoscopic or open colonic resection for cancer. Hepatogastroenterology 50: 1348–1351
2. Alexander RJ, Jaques BC, Mitchell KG (1993) Laparoscopically assisted colectomy and wound recurrence (letter). Lancet 341: 249–250
3. Curet MJ, Putrakul K, Pitcher DE, Josloff RK, Zucker KA (2000) Laparoscopically assisted colon resection for colon carcinoma; perioperative results and long-term outcome. Surg Endosc 14: 1062–1066
4. Fleshman JW, Nelson H, Peters WR, Kim HC, Larach S, Boorse RR, Ambroze W, Leggett P, Bleday R, Stryker S, Christenson B, Wexner S, Senagore A, Rattner D, Sutton J, Fine AP (1996) Early results of laparoscopic surgery for colorectal cancer: a retrospective analysis of 372 patients treated by clinical outcomes of Surgery Therapy (COST) Study Group. Dis Colon Rectum 39: S53–S58
5. Goh YC, Eu KW, Seow-Choen F (1997) Early postoperative results of a prospective series of laparoscopic vs open anterior resections for rectosigmoid cancers. Dis Colon Rectum 40: 776–780
6. Hasegawa H, Kabeshima Y, Watanabe M, Yamamoto S, Kitajima M (2003) Randomized controlled trial of laparoscopic versus open colectomy for advanced colorectal cancer. Surg Endosc 17: 636–640
7. Hazebroek EJ, Color Study Group (2002) COLOR: a randomized clinical trial comparing laparoscopic and open resection for colon cancer. Surg Endosc 16: 949–953
8. Hirabayashi Y, Yamaguchi K, Shiraishi N, Adachi Y, Kitamura H, Kitano S (2002) Development of port-site metastasis after pneumoperitoneum: a scanning electron microscopy study. Surg Endosc 16: 864–868

9. Hong D, Tabet J, Anvari M (2001) Laparoscopic vs open resection for colorectal adenocarcinoma. Dis Colon Rectum 44: 10–19
10. Khallili TM, Fleshner PR, Hiatt JR, Sokol TP, Manookian C, Tsushima G, Phillips EH (1998) Colorectal cancer: comparison of laparoscopic with open approaches. Dis Colon Rectum 41: 832–838
11. Khonishi F, Okada M, Nagai H, Ozawa A, Kashiwagi H, Kanazawa K (1996) Laparoscopic-assisted colectomy with lymph node dissection for invasive carcinoma of the colon. Surg Today 26: 882–889
12. Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM, Visa J (2002) Laparoscopy-assisted colectomy versus open colectomy for treatment of nonmetastatic colon cancer: a randomised trial. Lancet 29: 2224–2229
13. Milsom JW, Böhm B, Harnmerhofer KA, Fazio V, Steiger E, Elson P (1998) A prospective, randomized trial comparing laparoscopic versus conventional techniques in colorectal cancer surgery: a preliminary report. J Am Coll Surg 187: 46–55
14. Monson JR, Hill AD, Darzi A (1995) Laparoscopic colonic surgery (review). Br J Surg 82: 150–157
15. Multi-Institutional Registry of Large Bowel Cancer in Japan, Vol. 23 (2002) Cases treated in 1994. Japanese Society for Cancer of the Colon and Rectum, Tokyo, Japan
16. Nishiguchi K, Okuda J, Toyoda M, Tanaka K, Tanigawa N (2001) Comparative evaluation of surgical stress of laparoscopic and open surgeries for colorectal carcinoma. Dis Colon Rectum 44: 223–230
17. O'Rourke N, Price PM, Kelly S, Sikora K (1993) Tumour inoculation during laparoscopy (letter). Lancet 342: 368
18. Shiromizu A, Suematsu T, Yamaguchi K, Shiraishi N, Adachi Y, Kitano S (2000) Effect of laparotomy and laparoscopy on the establishment of lung metastasis in a murine model. Surgery 128: 799–805
19. Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G, Clinical Outcomes of Surgical Therapy (COST) Study Group (2002) Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. JAMA 16: 321–328
20. Yamamoto S, Watanabe M, Hasegawa H, Kitajima M (2001) Oncologic outcome of laparocopic versus open surgery for advanced colorectal cancer. Hepatogastroenterology 48: 1248–1251

特集 変わってきた癌化学療法

大腸癌の化学療法

Systemic chemotherapy for metastatic colorectal cancer in 2006

高張 大亮 島田 安博
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切除不能転移性大腸癌に対する化学療法は，1990年代後半から10年足らずの間に大きな進歩が見られている．長年のKey Drugであった5FUに加え，新規薬剤としてCPT-11やoxaliplatinが臨床導入され，さらに経口抗癌剤の臨床評価により，簡便性，安全性が客観的に検証された．最近では分子標的治療薬の大腸癌における有用性が示されることになり，切除不能転移性大腸癌の生存期間は無治療の8ヵ月から今や2年を超える時代となった．臨床現場では適切な薬剤選択と治療継続の判断を行うことがますます重要となっている．国際的標準治療の変化を常にフォローしながら，最善の治療法を患者に提供することが求められている．

はじめに

国立がんセンターホームページに掲載されている「がんの統計'05」[1]によると，本邦における結腸・直腸癌の年齢調整死亡率(2003年)は男性で肺癌，胃癌，肝臓癌に次いで4番目，女性ではついに胃癌を抜き1番目となっている．大腸癌による年間死亡者数は2005年には年間3.9万人であったが，2015年には6万人にのぼると推定されている．大腸癌治療の中心はあくまで外科的切除であるが，一方で外科的切除によって治癒し得ない，いわゆる切除不能転移性大腸癌の治療法の確立と普及が本邦において急務となっている．

本稿では，切除不能転移性大腸癌に対する化学療法につき解説する．

I. 切除不能転移性大腸癌に対する化学療法の適応

切除不能転移性大腸癌の予後はBSC(best supportive care)群では8ヵ月とされ，化学療法により12ヵ月に延長することが可能であるというメタアナリシスの報告がある[2]．これを根拠として，全身状態のよい症例では，積極的に化学療法を行うことが勧められている．大腸癌では，切除不能転移病巣を有する症例においても自覚症状や臨床検査値異常を認めることは少なく，食欲不振，下痢，悪心・嘔吐，白血球減少などの化学療法に伴う有害事象による全身状態の一過性の低下との兼ね合いで治療を考慮する必要がある．なお，骨転

国立がんセンター中央病院消化器内科
Key words：大腸癌／化学療法／5FU／CPT-11／oxaliplatin／分子標的治療薬

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移や脳転移などを認める症例では，化学療法の選択よりも，局所症状のコントロールを目的として放射線照射や適応がある場合には手術療法が選択される．

II. 切除不能転移性大腸癌に対する化学療法の変遷

大腸癌の化学療法は，1950年代に開発された5FU に代表されるフッ化ピリミジン系抗癌剤をkey drug として進歩してきた．しかし，その後は約40年の長きにわたりフッ化ピリミジン系抗癌剤の至適投与法の検討や，Biochemical modulation の理論に基づいた抗腫瘍効果の増強に主眼が置かれていた．1980年代には5FU とロイコボリン(LV)の併用療法が注目され，5FU 単剤に比べ，奏効率は上昇したが，生存期間を有意に延長させることはできなかった．

1．5FU 投与法の検討－5FU+LV の至適投与法

5FU+LV の投与方法については5FU の急速静注による RPMI(Rosewell Park Memorial Institute)の weekly 法[3]，Mayo clinic の5日間法[4]，5FU の持続点滴による de Gramont 法[5]やAIO 法[6]がある(表1)．従来，特にアメリカではRPMI の weekly 法のような急速静注法が汎用されてきていたが，一方，ヨーロッパではフランス中心に持続点滴法が検討され，LV の2時間点滴直後に5FU の急速静注と22時間の持続点滴を2日間にわたり実施する de Gramont 法が有害事象の点で優れるとして汎用されている．Mayo Clinic 法と de Gramont 法との第 III 相試験の結果，後者が消化器症状や白血球減少などの有害事象で頻度や程度が低く，奏効率や無増悪期間・生存期間で優れると報告されている[5]．最近では，CPT-11 や oxaliplatin などとの併用療法の第 III 相試験成績により，5FU+LV の投与方法も急速静注から持続点滴へと移行している．

2．CPT-11の臨床評価と新しい併用療法

1990年代に入り，CPT-11が登場し，大腸癌化学療法は新たな局面を迎えることになった．CPT-11は，日本国内で開発されたI型DNA トポイソメラーゼ阻害剤であり，5FU 耐性大腸癌に対しても有効であることが報告されている[7]．1998年，イギリス中心に5FU 治療抵抗性症例を対象としたBSC 群との第 III 相試験により二次治療としての臨床的意義が検証された[8]．その後，2000年にはアメリカおよびヨーロッパにおいて一次治療としての意義が検討され，アメリカでは急速静注，ヨーロッパからは持続点滴，と投与スケジュールは異なるものの従来の5FU+LV との比較においてCPT-11併用群の生存期間の延長が検証された[9][10]．これにより，転移性大腸癌の標準治療は5FU+LV から5FU+LV+CPT-11併用療法へと書き換えられることとなった．アメリカでは急速静注法であるIFL 療法(表1)が標準とされ，転移性大腸癌や術後補助療法の第 III 相試験での対照群として設定された．その後，アメリカで行われた2つの第 III 相試験(N9741試験，C89803試験)において，IFL 療法での有害事象の頻度および60日以内の早期死亡例が問題となり，投与スケジュールの修正がなされている[11](表1)．

一方，ヨーロッパでは，de Gramont 法にCPT-11を併用するFOLFIRI 療法(表1)が検討され，高い奏効率と認容性が報告されている[12]．主たる副作用は下痢，悪心・嘔吐，白血球減少であるが，2週ごとの投与が可能である．また，後述する oxaliplatin と異なり，蓄積性の末梢神経障害がないことから，まだCPT-11の臨床的価値は十分認められると考えられる．

3．Oxaliplatin の臨床評価と新しい標準療法

Oxaliplatin はcisplatin とは抗腫瘍スペクトラムが異なる本邦で開発された第3世代白金系抗がん剤である[13]．本邦での臨床開発では十分な臨床効果を示すことができず，フランスを中心とした海外臨床試験の結果，その有効性が見出され，単独よりも5FU+LV との併用療法にて高い奏効率

表1 切除不能転移性大腸癌に対する化学療法レジメン(文献41より改変)

study	Common dosing regimens	Cycle Frequency
Rosewell Park (RPMI) (3)	5FU 500mg/m² day1～5 LV 500mg/m² day1～5	Weekly×6, Every 8weeks
Mayo clinic (4)	5FU 425mg/m² day1～5 LV 20mg/m² day1～5	Every 4～5weeks
de Gramont (5) (LV5FU2)	5FU 400mg/m² bolus 5FU 600mg/m² CI 22hrs LV 200mg/m² (days1,2)	Every 2weeks
AIO (6)	5FU 2000mg/m² CI 24hrs LV 500mg/m² (day1)	Weekly×6, Every 8weeks
IFL (10)	CPT-11 125mg/m² LV20mg/m² 5FU 500mg/m² (day1)	Weekly×4, Every 6weeks
reduced IFL (11)	CPT-11 100mg/m² LV20mg/m² 5FU 400mg/m² (day1)	Weekly×4, Every 6weeks
FOLFIRI (12)	CPT-11 180mg/m² day1 LV500mg/m² day1 5FU 400mg/m² bolus days1,2 5FU 2.4～3g/m² CI 46hrs day1～2	Every 2weeks
FOLFOX4 (15)	L-OHP 85mg/m² day1 LV200mg/m² day1,2 5FU 400mg/m² bolus days1,2 5FU 600mg/m² CI 22hrs days1,2	Every 2weeks
modified - FOLFOX6 (22)	L-OHP 85mg/m² day1 LV200mg/m² day1 5FU 400mg/m² bolus days1 5FU 2,400mg/m² CI 46hrs days1～2	Every 2weeks
mFOLFOX6 +BV (32)	BV 5mg/m² day1 L-OHP 85mg/m² day1 LV350mg/m² day1 5FU 400mg/m² bolus days1 5FU 2,400mg/m² CI 46hrs days1～2	Every 2weeks

LV：Leucovolin BV：bevacizumab

が報告された．悪心・嘔吐，食欲低下，下痢，白血球減少，血小板減少，肝機能低下などの有害事象が認められるが，腎機能低下は少ない．しかし，特異的な有害事象として咽頭・喉頭の違和感，末梢神経炎がある．とくに後者は蓄積性があり，850 mg/m² 以上でその頻度が高くなり，回復性が遷延するとされる[14]．もっとも有名な併用療法は，FOLFOX4 療法[15]，すなわち de Gramont 法に，oxaliplatin 85 mg/m² を併用し，2週ごとに繰り返す方法である(表1)．IFL 療法抵抗性症例を対象とした二次治療での FOLFOX 療法の評価は，de Gramont 法や oxaliplatin 単独と比較して，奏効率，無増悪生存期間などで優れる結果が報告されている[16]．これらの臨床試験成績から，oxaliplatin の大腸癌治療における意義は徐々に認知されるようになったが，最終的にはアメリカでの Intergroup 試験である N9741試験[17] の結果がもっとも大きなインパクトを与えた．N9741試験は，初回化学療法症例を対象として IFL 療法を対照群とし，FOLFOX4 療法と IROX (CPT-11+oxaliplatin)療法を試験群とした3アームの第 III 相試験である．2003年の ASCO において中間解析結果が報告され，FOLFOX4 療法が奏効率(45%)，無増悪期間(8.7ヵ月)，全生存期間

表2 N9741試験の成績(文献17より)

	FOLFOX4	IFL	IROX
症例数	267	264	264
奏効率%	45	31	35
TTP(月)	8.7	6.9	6.5
MST(月)	19.5	15.0	17.4

TTP：無増悪期間 MST：生存期間中央値

表3 GERCOR試験の成績(文献18より)

	FOLFOX6	FOLFIRI
症例数	111	109
奏効率%	54	56
PFS(月)	8.0	8.5
MST(月)	20.6	21.5

PFS：無増悪生存期間 MST：生存期間中央値

(19.5ヵ月)においてIFL療法，IROX療法を有意に上回るという結果であった(表2)．米国では，この結果oxaliplatinが大腸癌の一次療法として承認されている．続いて2004年にはTournigandらによりFOLFIRI/FOLFOXをクロスオーバーさせた第III相試験が行われ(GERCOR試験)[18]，それぞれの初回治療法の奏効率(56% vs 54%)，無増悪生存期間(8.5 vs 8.0ヵ月)，および全生存期間(21.5 vs 20.6ヵ月)は同等の結果が得られた(表3)．ここに，切除不能転移性大腸癌の化学療法は20ヵ月超の生存期間中央値が得られる時代に到達した．Groteyらは主な第III相試験の検討において5-FU/LV，CPT-11，oxaliplatinの3種類の薬剤が全治療期間内に使用された症例の割合と全生存期間が相関することを明らかにしており，この3剤を治療期間中に使い切ることで20ヵ月を超える生存が得られるとしている[19]．FOLFOX療法は現時点では比較試験で検討されているFOLFOX4療法やその5FU+LVの2日間の繰り返し投与を1日に簡便化したFOLFOX6療法[20]やFOLFOX7療法[21]が使用されている．しかしながら，どのレジメンが優れているかについては比較検討がされておらず十分なデータがない．本邦ではその簡便さよりFOLFOX6療法が好まれ，さらに，oxaliplatinの投与量を85 mg/m^{2}に減量したmodified FOLFOX6(mFOLFOX6)療法(表1)の有用性が報告され[22]，当院においても主にこのレジメンを使用している．また，oxaliplatinの神経毒性のためFOLFOXを継続できない場合が少なくないことが判明し，oxaliplatinのdose intensityを高める検討がなされた．2004年ASCOで発表されたOPTIMOX1(FOLFOX4 vs FOLFOX7×6+5FU/LV×12+FOLFOX7×6)の結果は両者とも奏効率：約58%，全生存期間：約20ヵ月で同等であったが，神経毒性は後者で有意に減少した[15]．現在もoxaliplatinの神経毒性を回避する目的でいくつかの臨床試験が行われている．

4．経口抗癌剤の臨床評価とその位置づけ

経口抗癌剤は主に本邦において開発され，汎用されてきた歴史がある．とくに術後補助療法ではその利便性から長期にわたり使用されてきたが十分な臨床的意義は確認されていなかった．1990年代に入り，転移性大腸癌を対象として，標準治療と考えられる5FU+LV療法を対照群として，経口抗癌剤を試験群として各薬剤複数の第III相比較試験が実施され，UFT/LVおよびcapecitabineなどが検討された[23)-27]．その結果，capecitabineのみで非劣性が検証され，アメリカにおいて大腸癌の一次治療薬として経口抗癌剤が承認されることになった．UFT/LVはUFTの配合比につき指摘され無増悪生存期間で非劣性は検証されたが，アメリカでは承認されなかった．しかし，欧州，日本では非劣性の検証がされたと判断され大腸癌に対して承認されている．

capecitabine は現在 5FU+LV を含む各種併用療法において，置換可能かどうかを検討する比較試験でその併用療法での意義が検討されている．たとえば，FOLFOX 療法の infusional 5FU+LV の部分を経口抗癌剤である capecitabine へ置換した XELOX (capecitabine+oxaliplatin) 療法[28] は第 II 相試験において奏効率：55%，無増悪生存期間：7.7ヵ月，生存期間中央値：19.5ヵ月と FOLFOX 療法と同程度の治療成績を認めた．

この結果よりさらに，XELOX±bevacizumab および FOLFOX±bevacizumab の比較試験が実施された (TREE1，2 試験：次項参照)．また国内でも S1 と oxaliplatin との併用療法の検討がなされているところである．これらの結果，経口抗癌剤が静注療法に置き換えることが可能となれば，利便性，医療経済性などの患者負担や臨床現場での負担が大幅に軽減することが可能となりその意義は大きい．

5．分子標的治療薬の出現

2003年の ASCO において，大腸癌領域においても分子標的治療薬の臨床応用がはじめて報告された．まず，bevacizumab (Avastin) の第 III 相試験成績[29] の報告である．本剤は，血管内皮細胞増殖因子 VEGF (Vascular endotherial growth factor) に対するヒト化単クローン抗体である．IFL 療法を対照群として IFL+bevacizumab 併用群を試験群として初回化学療法例を対象に比較検討がなされた．結果は，奏効率 (35 vs 45%)，無増悪生存期間 (6.2 vs 10.6ヵ月)，全生存期間 (15.6 vs 20.3ヵ月)，のいずれにおいても併用群が有意に優れるというものであった (表 4)．有害事象では出血，血小板減少，蛋白尿，高血圧などが認められ，併用群において消化管穿孔が低頻度であるが認められている．本剤は，血管新生阻害剤として初めて生存期間を延長するという事実を示し，2004年 2 月にはアメリカにおいて承認されている．続いて現在の標準治療の一つである FOLFOX 療法と bevacizumab の併用療法の有効性が二次治療症例を対象としたランダム化第

表 4　IFL+Bevacizumab vs IFL 第 III 相試験の成績 (文献29より)

	IFL+Bevacizumab	IFL
症例数	402	411
奏効率%	44.8	34.8
PFS (月)	10.6	6.2
MST (月)	20.3	15.6

PFS：無増悪生存期間　MST：生存期間中央値

III 相試験 (E3200試験)[30] で示された (生存期間中央値 bevacizumab 無 vs 有=10.8 vs 12.9ヵ月) (表 5)．この結果を受け，現在海外においては FOLFOX 療法＋bevacizumab 併用療法が初回治療に対する標準治療と認識されている．さらに本レジメンの初回治療の有用性を検討した比較試験の結果 (TREE1，2 試験)[31][32] は2006年の ASCO でその最終解析が公表され，oxaliplatin と 3 つの異なるフッ化ピリミジンの併用療法 (mFOLFOX6，bFOL＝bolusSFU+oxaliplazin，CapeOX＝XELOX) に bevacizumab を加えることにより，毒性は忍容可能な範囲にとどまりつつ，奏効率の改善と無増悪期間，全生存期間の延長が得られた．3 群併せての生存期間中央値は bevacizumab 無 vs 有=18.2 vs 24.4ヵ月と bevacizumab の併用でついに 2 年を超えた (表 6)．

また，EGFR (Epidermal growth factor receptor) に対するマウス－ヒトキメラ単クローン抗体である cetuximab (Erbitux) も同年の ASCO においてその CPT-11抵抗性大腸癌に対する比較試験成績 (BOND 試験)[33] が報告された (表 7)．EGFR 陽性で CPT-11治療抵抗性の症例に対して cetuximab 単独と cetuximab＋CPT-11併用群を比較する試験であり，奏効率 (11% vs 23%) や無増悪期間 (1.5 vs 4.1ヵ月) での優位性は検証されたが，全生存期間では有意でなかった．主な有害事象はキメラ抗体であるため infusion reaction が認められること，にきび様の皮疹，爪の変形，肺臓炎などが報告されている．本剤もヨーロッパに続き，2004年 1 月にアメリカにて承認された．現在，一時治療として，CRYSTAL 試験 (FOLFIRI±cetuximab) が，二次治療として FOLFOX 抵抗