ANTICANCER RESEARCH *26*: 1377-1384 (2006)

Potential Predictors of Long-term Survival after Surgery for Patients with Stage IV Colorectal Cancer

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Abstract. *Background: The prognosis of patients with colorectal cancer is considered to be affected by several factors. Recently, chemotherapy for this disease has been demonstrated to be effective for long-term survival. In this study, the potential predictors, including chemotherapy regimens for survival after surgery, in patients with stage IV colorectal cancer are presented. Patients and Methods: Univariate and multivariate analyses of potential predictors of survival after surgery were carried out for 56 patients with stage IV colorectal cancer who had undergone surgery, including 22 with rectal and 34 with colon cancer. Results: The survival in patients who had had a primary liver resection was longer than that in patients who had not (p=0.007). There was a significant difference among chemotherapy regimens (p=0.021). The survival in patients who were administered l-leucovorin/5-fluorouracil (l-LV/5FU) was longer than that in patients who received uracil-tegafur (UFT) and cisplatin (CDDP)/5FU (p=0.024, p=0.004, respectively). In multivariate analyses, there were 5 favorable factors that influenced overall survival after surgery: lymph node metastasis (p=0.029), no bone metastasis (p=0.012), no peritoneal invasion (p=0.018), no primary liver resection (p=0.004) and the chemotherapy regimen (p=0.008). Furthermore, the survival in patients with a continued l-LV/5FU plus modified IFL regimen (additional irinotecan) was longer than for those patients who received other regimens, in both univariate and multivariate analyses. Conclusion: Five factors, namely lymph node metastasis, bone metastasis, peritoneal invasion, primary liver resection and chemotherapy, are potential predictors of survival after surgery for patients with stage IV colorectal cancer.*

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Key Words: Colorectal cancer stage IV, *l*-LV/5FU, CPT-11.

Recently, technical advances have made it easier to perform colorectal surgery with a reduction in the operative mortality rate (1, 2). Patients with localized and early-stage disease have excellent prognoses after a curative resection, but the prognosis for patients with distant metastatic disease remains dismal (3). The prognosis of this disease is considered to be affected by numerous factors (4).

5-Fluorouracil (5FU) is an active drug available for this disease and its action is potentiated when it is combined with folinic acid, which acts as a precursor to the folate co-factor for thymidylate synthetase (5). One of these regimens is the weekly administration of leucovorin (LV; folinic acid, citrovorum factor) plus 5FU for 6 weeks, at 2-week intervals. This method is called the Roswell Park Memorial Institute (RPMI) regimen (6-8) and has been adopted in Japan. LV is available generally as a mixture of *l* and *d* diastereoisomers in equal proportions. Of these two isomers, only the *l*-form is thought to be biologically active (9, 10).

Irinotecan (CPT-11) is a topoisomerase I inhibitor that blocks the DNA replication step of the enzyme, leading to multiple single-strand DNA breaks, which eventually block cell division (11). Chemotherapy combined with CPT-11 has been demonstrated to be effective for patients with colorectal cancer. Though many authors have reported the clinical efficacy of LV/5FU or LV/5FU/CPT-11 chemotherapy in patients with colorectal cancer using racemic leucovorin (*d,l*-LV), that of *l*-LV/5FU or *l*-LV/5FU/CPT-11 chemotherapy has not been fully clarified and these regimens may be able to predict survival.

In this study, the potential predictors of survival after surgery for patients with stage IV colorectal cancer were identified.

Patients and Methods

Fifty-six patients with stage IV colorectal cancer, who had undergone surgery at Wakayama Medical University Hospital, Wakayama, Japan between 2001 and 2003, were enrolled. The patient data were collected and followed-up on from 2001 to 2004. Twenty-two patients had rectal cancer and 34 had colon cancer,

including 4 cecum, 10 ascending, 4 descending and 16 sigmoid colon cancer cases.

TNM clinical stage IV was described according to the UICC classification of malignant tumors (12).

A resection of the primary tumor in the rectum and colon was performed with a lymphadenectomy from along the rectal or large intestinal wall to around the main feeding artery. A primary liver resection was performed if no metastasis remained in the liver at the resection of the primary tumor.

One course of *l*-LV/5FU chemotherapy consisted of the weekly administration of *l*-LV and 5FU for 6 weeks, at 2-week intervals. During the chemotherapy, *l*-LV (Wyeth Co., Tokyo, Japan) 250 mg/m^2 was drip-infused intravenously for 2 hours and 5FU (Kyowa Hakko, Tokyo, Japan) 600 mg/m^2 was injected intravenously 1 hour after the start of *l*-LV administration. This regimen is termed a "modified RPMI regimen" because of the administration of *l*-LV alone, compared to the use of racemic leucovorin (*d,l*-LV) in the original RPMI regimen (6-8). If a liver resection had been performed or the liver function of patients with liver metastasis was stable, a total dose of 250 mg of 5FU was administered through the catheter of the intra-arterial infusion chemotherapy.

When *l*-LV/5FU chemotherapy was not effective and an additional agent had a tolerable level of side-effects, additional CPT-11 administration was performed; 100 mg of irinotecan (CPT-11) (Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan) was administered intravenously every 2 weeks during *l*-LV/5FU chemotherapy. This regimen of additional CPT-11 to *l*-LV/5FU after *l*-LV/5FU failure was defined as a "modified IFL regimen". On the other hand, when *l*-LV/5FU chemotherapy was effective or additional agents were intolerable due to side-effects, *l*-LV/5FU administration was continued (continued *l*-LV/5FU). For patients with heavy diarrhea before chemotherapy, a combination chemotherapy of cisplatin (CDDP) and 5FU was chosen, that is, 25 mg of CDDP (Bristol-Myers Co., Tokyo, Japan) and 750 mg of 5FU were administered intravenously and 250 mg of 5FU were administered through the catheter of the intra-arterial infusion chemotherapy every 1 or 2 weeks (CDDP/5FU).

Forty-nine patients agreed to these intravenous or intra-arterial infusion chemotherapies, including 30 patients with continued *l*-LV/5FU, 12 patients with the modified IFL regimen and 7 patients with CDDP/5FU, but 7 patients rejected it because of the high medical cost, or due to their own or their family's wishes. For the 7 patients without intravenous or intra-arterial infusion chemotherapy, uracil-tegafur (UFT) (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) (250 mg of tegafur per square meter of body-surface area per day) in the form of 100-mg capsules (100 mg of tegafur plus 224 mg of uracil) was taken orally after meals twice daily.

A comparative analysis was conducted among the cases in which each chemotherapy was performed.

The following factors were chosen as prognostic factors: age, gender, primary lesion, histopathological type, depth of invasion, lymph node metastasis, lymphatic invasion, venous invasion, liver metastasis, lung metastasis, bone metastasis, peritoneal invasion, direct tumor invasion of other organs, distant lymph node metastasis, primary liver resection, secondary liver resection, resection of near organs, resection of local recurrence, radiation therapy, intra-arterial infusion chemotherapy and chemotherapy. The ages of the patients ranged from 34 to 83 (median: 65 years) and they were divided into 2 groups: <65 and ≥65. The depths of invasion were defined according to the UICC criteria: T1, tumor invasion of submucosa; T2, muscularis propria; T3, subserosa or tumor penetration of serosa; and T4, tumor invasion of adjacent structures. Lymph node metastasis was also defined as follows: N0, no regional lymph node metastasis; N1, metastasis in 1 to 3 regional lymph nodes; and N2, metastasis in 4 or more regional lymph nodes. Lymphatic invasion of mild and strong means no or minimal lymphatic invasion and moderate or marked lymphatic invasion, respectively. Venous invasion of mild and strong means no or minimal venous invasion and moderate or severe venous invasion, respectively.

The side-effects of chemotherapy were recorded according to the criteria of NCI-CTC ver.2.

The range, mean and median follow-up periods of the patients in this study were 6 to 36 months, 19 months and 19 months, respectively.

Statistical analysis. Statistical analysis was performed with Stat View-J ver. 5.0 using a Windows XP operating system. The overall survival rate for prognostic factors was estimated by the Kaplan-Meier method and univariate analysis of the significance for each factor was evaluated by a log-rank test. Multivariate analysis of the overall survival time was performed with Cox's proportional hazards model. A p value of less than 0.05 was considered statistically significant.

Results

Univariate analysis of potential predictors of survival after surgery. The survival of patients who had undergone a primary liver resection was longer than those who had not (p=0.007) (Table I). There was a significant difference among chemotherapy regimens (p=0.021). The survival of patients who received continued *l*-LV/5FU was longer than for those who received UFT and CDDP/5FU (p=0.024 and p=0.004, respectively) (Figure 1) (Table I).

The relative overall survival (OS) was analyzed using Cox's proportional hazards model. There were 4 favorable factors that influenced overall survival after surgery. The OS in patients with lymph node metastasis of N0 and 1 was longer than that in patients with lymph node metastasis of more than N2 (p=0.029; RR, 12.3290; 95% CI, 1.2950-117.3812). The OS in patients without bone metastasis was longer than that in patients with it (p=0.012; RR, 0.0055; 95% CI, 0.0001-0.3200). The OS in patients without peritoneal invasion was longer than that in patients with it (p=0.018; RR, 0.0717; 95% CI, 0.0081-0.6358), and patients with a primary liver resection had a longer OS than those without (p=0.004; RR, 25.6173; 95% CI, 2.9025-226.1000). There was a significant difference among the chemotherapy regimens (p=0.008). The survival of patients with continued *l*-LV/5FU was longer than that of those who received UFT (p=0.036; RR, 0.0516; 95% CI, 0.0033-0.8190) and the survival of patients who received the modified IFL regimen was longer than for those who received UFT (p=0.042; RR, 0.0340; 95% CI, 0.0013-0.8825).

Table I. *Univariate analysis of potential predictors of survival after surgery.*

Variable	Overall survival (%)			MST (Months)	*p*
	1-year	2-year	3-year		
Age (yrs)					0.318
<65 (n=29)	84.5	39.7	19.9	22.0	
≥65 (n=27)	67.2	37.8		21.0	
Gender					0.792
Male (n=38)	85.9	36.2	10.1	22.0	
Female (n=18)	58.5	58.5		NC	
Primary lesion					0.862
Colon (n=34)	74.3	32.8	32.8	23.0	
Rectum (n=22)	81.1	46.0		22.0	
Histopathological type					0.860
Well-differentiated (n=31)	76.4	39.8	22.1	21.0	
Other type (n=25)	77.6	36.2		24.0	
Depth of invasion					0.703
T1, 2 (n=4)	75.0	25.0		20.0	
T3, 4 (n=52)	77.4	42.8	18.3	23.0	
Lymph node metastasis					0.652
N0, 1 (n=22)	74.7	47.4	23.7	23.0	
N2 ≤ (n=34)	79.0	36.6		20.0	
Lymphatic invasion					0.536
Mild (n=33)	80.1	28.5		21.0	
Strong (n=23)	72.4	62.0	31.0	25.0	
Venous invasion					0.543
Mild (n=29)	84.0	38.8		21.0	
Strong (n=27)	69.0	41.4	15.5	24.0	
Liver metastasis					0.395
– (n=17)	86.2	46.5		22.0	
+ (n=39)	72.6	36.4	19.4	21.0	
Lung metastasis					0.903
– (n=48)	77.9	41.0	22.8	22.0	
+ (n=8)	75.0	37.5		24.0	
Bone metastasis					0.064
– (n=54)	77.7	42.3	18.5	23.0	
+ (n=2)	50.0			3.0	
Peritoneal invasion					0.839
– (n=45)	79.6	40.1	17.6	21.0	
+ (n=11)	62.3	31.2		23.0	
Direct tumor invasion of other organs					0.757
– (n=46)	75.5	40.4	17.3	21.0	
+ (n=10)	80.0	40.0		24.0	
Distant lymph node metastasis					0.921
– (n=50)	75.6	40.8	17.8	22.0	
+ (n=6)	83.3			20.0	
Primary liver resection					0.007
– (n=43)	70.0	28.9		20.0	
+ (n=13)	100	80.0	53.3	NC	
Secondary liver resection					0.477
– (n=54)	78.4	40.6	17.7	22.0	
+ (n=2)	50.0			12.0	
Resection with near organs					0.551
– (n=45)	73.1	41.9	18.3	21.0	
+ (n=11)	90.0	24.0		22.0	
Resection of local recurrence					0.461
– (n=53)	75.2	39.3	16.8	21.0	
+ (n=3)	100	50.0		22.0	
Radiation therapy					0.986
– (n=52)	76.6	40.0	17.2	21.0	
+ (n=4)	75.0	37.5		22.0	
Intra-arterial infusion chemotherapy					0.735
– (n=27)	71.5	40.5		22.0	
+ (n=29)	84.1	49.5	26.4	21.0	
Chemotherapy					0.021
UFT (n=7)	42.9	21.4		12.0	
CDDP/5FU (n=7)	42.9	14.3	14.3	10.0	
Continued *l*-LV/5FU (n=30)	90.8	57.6		25.0	
Modified IFL (n=12)	88.9	35.6		23.0	

MST, median survival time; NC, not able to calculate; Well-differentiated, well-differentiated adenocarcinoma; T1, tumor invasion of submucosa; T2, muscularis propria; T3, subserosa or tumor penetration of serosa; T4, tumor invasion of adjacent structures; N0, no regional lymph node metastasis; N1, metastasis in 1 to 3 regional lymph nodes; N2, metastasis in 4 or more regional lymph nodes. Lymphatic invasion of mild and strong means no or minimal lymphatic invasion and moderate or marked lymphatic invasion, respectively. Venous invasion of mild and strong means no or minimal venous invasion and moderate or severe venous invasion, respectively.

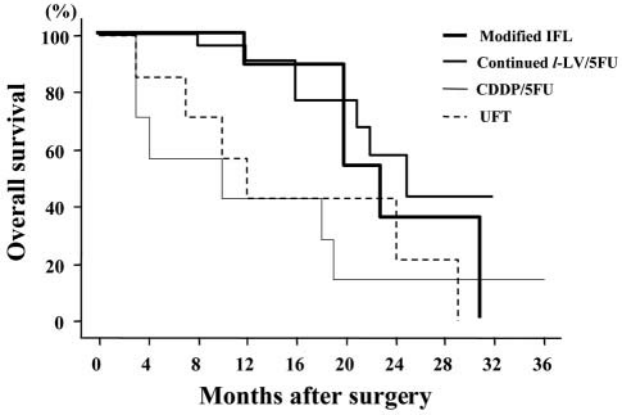

Figure 1. *Overall survival curves by the Kaplan-Meier method among patients with chemotherapy. The regimen of additional CPT-11 to l-LV/5FU after l-LV/5FU failure was designated as a "modified IFL regimen". When l-LV/5FU chemotherapy was continued, "continued l-LV/5FU regimen" was the designation. There was a significant difference among the chemotherapy regimens (p=0.021). The survival of patients who received the l-LV/5FU regimen was longer than in those who received UFT and CDDP/5FU (p=0.024, p=0.004, respectively).*

Effect on survival after surgery of the continued l-LV/5FU and modified IFL regimens. A continued *l*-LV/5FU regimen or a modified IFL regimen were used for patients with stage IV colorectal cancer and, therefore, the effects of these regimens were compared to other regimens.

In univariate and multivariate analyses, the OS in patients who received the continued *l*-LV/5FU regimen plus a

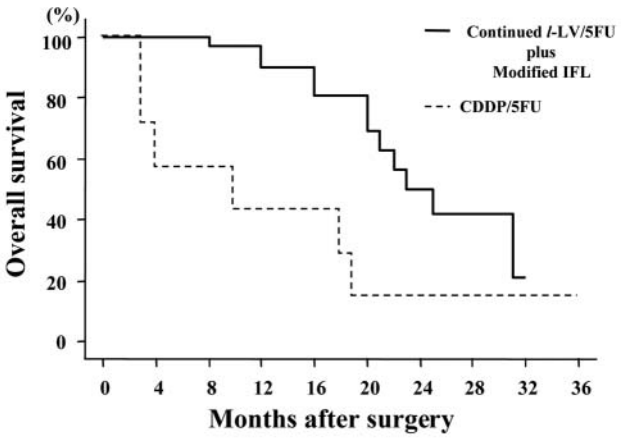

Figure 2. *Effect on survival after surgery of the continued l-LV/5FU regimen plus the modified IFL regimen compared with CDDP/5FU administration. In univariate and multivariate analyses, the survival of patients who received the continued l-LV/5FU regimen plus the modified IFL regimen was longer than that in patients who received CDDP/5FU (univariate analysis, p=0.006: multivariate analysis, p=0.011).*

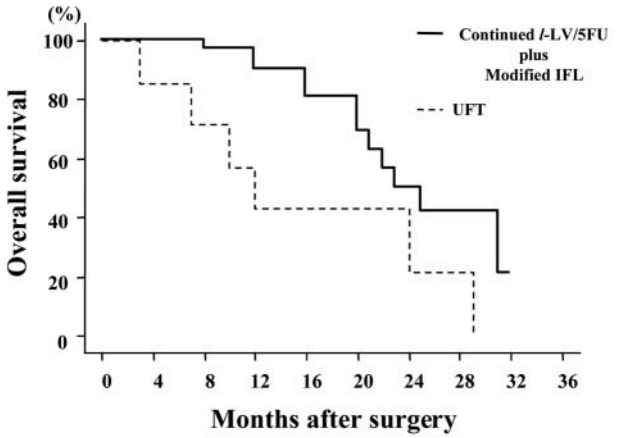

Figure 3. *Effect on survival after surgery of the continued l-LV/5FU regimen plus the modified IFL regimen compared with UFT administration. In univariate and multivariate analysis, the survival of patients who received the continued l-LV/5FU regimen plus the modified IFL regimen was longer than in patients who received UFT (univariate analysis, p=0.02: multivariate analysis, p=0.002).*

modified IFL regimen was longer than that for patients who received CDDP/5FU (univariate analysis, $p=0.006$: multivariate analysis, $p=0.011$) (Figure 2).

In univariate and multivariate analyses, the OS in patients who received the continued *l*-LV/5FU regimen plus a modified IFL regimen was also longer than in those who received UFT (univariate analysis, $p=0.02$: multivariate analysis, $p=0.002$) (Figure 3).

Occurrence of chemotherapy-induced toxic effects. The adverse reactions related to each regimen are shown in Table II. Patients receiving the modified IFL regimen displayed many chemotherapy-induced toxic effects. On the other hand, patients receiving UFT had no grade 3-4 toxicities.

Table II. *Occurrence of chemotherapy-induced toxic effects.*

	NCI-CTC grade 3-4 (%)			
	Continued *l*-LV/5FU	Modified IFL	CDDP/ 5FU	UFT
Anemia	0	8.3	0	0
Leucopenia	3.3	16.7	14.3	0
Neutropenia	3.3	16.7	14.3	0
Thrombocytopenia	0	8.3	0	0
Bilirubinemia	0	8.3	0	0
Increase of sGOT or sGPT	0	8.3	0	0
Nausea	0	8.3	14.3	0
Vomiting	0	8.3	14.3	0
Diarrhea	10.0	16.7	0	0
Stomatitis	0	8.3	0	0

NCI-CTC, National Cancer Institute-Common Toxicity Criteria (version 2.0).
SGOT, serum glutamic oxaloacetic transaminase.
SGPT, serum glutamic pyruvic transaminase.

Discussion

Colorectal cancer is one of the most common causes of malignancy-related death in the United States, Japan and most European countries (1, 2). The prognosis in patients with colorectal cancer is considered to be affected by numerous parameters (4). In this study, we tried to identify the potential predictors of survival after surgery for patients with stage IV colorectal cancer.

There have been several reports concerning the predictors of survival for patients with this disease. Colorectal cancer is a disease that occurs predominantly in older adults, but the age factor remains unclear in relation to prognosis (13, 14). Several analyses have shown a survival advantage for women as compared to men (15). Rectal cancer has a worse prognosis than colon cancer (16, 17). The degree of tumor differentiation has long been suspected to be a prognostic factor in colorectal cancer. Most patients with poorly-differentiated tumors have multiple poor prognostic factors (18). The involvement of adjacent organs has also been considered an important adverse prognostic factor. Furthermore, the surgical removal of an affected organ does not seem to alter the OS

for such patients (19). The lymph node status has long been recognized as one of the most important potential prognostic markers in patients with colorectal cancer. The TNM classification calls for at least 12 nodes to be examined, whereas recent reviews suggest that 14 nodes may be a better target (3, 20, 21). The prognostic value of the presence of venous invasion for OS remains controversial. Although some researchers have found it to be an independent prognostic factor, others have not been able to confirm this finding. In contrast, the presence of lymphatic invasion has been almost uniformly reported as a poor prognostic factor (18, 22). Patients with untreated metastatic disease, such as liver and lung metastases, have a median survival of less than 10 months and a 5-year survival of less than 5% (23). If no tumor remains, liver and lung resection for these metastases is reported to improve the survival rate (23, 24). Liver resection, in particular, has been recognized as the best treatment to offer long-term survival to patients with colorectal liver metastases (23, 24). Bone metastasis and peritoneal invasion are also recognized to be poor prognostic factors (18). Tumor markers were also predictive factors of survival, with CEA usually being regarded as an indicator of a poor prognosis and the recurrence of colorectal cancer (23, 24).

In previous randomized studies comparing surgery with or without pre-operative radiation therapy (RT), the OS in patients with pre-operative RT was reported to be better than that in patients without (25). The benefits seen with pre-operative RT were also significantly greater than those with post-operative RT (25). Some reports stated that hepatic arterial infusion chemotherapy after a liver resection in patients with advanced colorectal cancer offers survival benefits (26), while other reports have not found any survival benefit (27). Moreover, many authors reported that arterial infusion chemotherapy in patients with unresectable liver metastasis has no survival benefit (28).

In this study, 5 factors, namely lymph node metastasis, bone metastasis, peritoneal invasion, primary liver resection and chemotherapy, were considered important prognostic factors in univariate analysis.

The chemotherapies performed in this study consisted of 4 regimens: *l*-LV/5FU, *l*-LV/5FU/CPT-11, CDDP/5FU and UFT.

5FU is the most active drug currently available for colorectal cancer, its clinical efficacy being enhanced by biochemical modulation with LV (9). In a randomized phase III trial comparing 5FU/LV of the RPMI regimen in patients with advanced and metastatic colorectal cancer, the response rate was significantly higher than those of 5FU/MTX and 5FU (30.3-48.0%, 5.0%, 11.0-12.1%, respectively) without an improvement in median survival time (7, 8). In Japan, physicians usually advocate an RPMI regimen; we modified this regimen to *l*-LV/5FU (29, 30).

CPT-11 is a topoisomerase I inhibitor that blocks the DNA replication step of the enzyme, leading to multiple single-strand DNA breaks, which eventually block cell division (11). The response rate, median survival time and progression-free survival corresponding to a bolus 5FU and LV Mayo regimen plus CPT-11 infusion (IFL regimen or Saltz regimen) were superior to those of a bolus 5FU and the LV Mayo regimen (39.0% *vs.* 21.0%, 14.8 months *vs.* 12.6 months, 7.0 months *vs.* 4.3 months, respectively) (31). Response rate, median survival time, and time to progression of infusion 5FU and LV plus infusion CPT-11 were also superior to those of infusion 5FU and LV (49.0% *vs.* 31.0%, 17.4 months *vs.* 14.1 months, 6.7 months *vs.* 4.4 months, respectively) (32).

In a randomized study of continuous infusion of 5FU *vs.* 5FU plus CDDP in patients with metastatic colorectal cancer, there were no significant differences in either the duration of response (median, 6 and 4.7 months for the CDDP/5FU and 5FU groups, respectively) or survival (median 10 and 12 months, respectively). Patients who received CDDP/5FU experienced significantly greater toxicity compared to those who received 5FU alone (33).

UFT is composed of tegafur and uracil in a molar ratio of 1:4. Tegafur is converted to 5FU *in vivo*. The efficacy of oral UFT as adjuvant chemotherapy to curative resection of Dukes' B and C colorectal cancer was demonstrated in a multicenter prospective randomized trial (34). The 5-year disease-free survival rate in the UFT group (75.7%) was higher than that of the surgery alone group (60.1%).

We mainly used a regimen of *l*-LV/5FU for patients with colorectal cancer. In this study, when *l*-LV/5FU chemotherapy was not effective and an additional agent had a tolerable level of side-effects, additional CPT-11 administration was performed (modified IFL regimen). If *l*-LV/5FU chemotherapy was effective or an additional agent was intolerable due to side-effects, *l*-LV/5FU administration was continued (continued *l*-LV/5FU).

We have demonstrated that these regimens were effective and prolonged survival after surgery for patients with stage IV colorectal cancer.

Recently, oxaliplatin (trans-L-1,2-diminocyclohexane oxalatoplatinum, a platinum-based drug, which forms cross-linking adducts, thus blocking DNA replication and transcription) (35-38), cetuximab and bevacizumab (chimeric monoclonal antibodies that specifically bind to the epidermal growth factor receptor and vascular endothelial growth factor with high affinity, respectively) (39, 40) and capecitabine (an oral fluoropyrimidine carbamate designed to preferentially generate 5FU in tumor tissue through exploitation of the higher intratumoral concentrations of thymidine phosphorylase) (41-43), have been demonstrated to be effective for patients with colorectal cancer. Unfortunately, these agents are not approved in Japan. If

these agents could be used in Japan, they might potentially improve survival after surgery for patients with stage IV colorectal cancer.

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Received November 28, 2005
Revised February 2, 2006
Accepted February 9, 2006