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Safety and Efficacy of Modified FOLFOX6 plus High-Dose Bevacizumab in Second-Line or Later Treatment of Patients with Metastatic Colorectal Cancer

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Key Words

High-dose bevacizumab · Modified FOLFOX6 · Second-line treatment · Metastatic colorectal cancer

Abstract

Aim: The aim of this retrospective study was to show the efficacy and safety of modified FOLFOX6 plus high-dose bevacizumab (10 mg/kg/2 weeks) in the second-line or later treatment of metastatic colorectal cancer. ***Methods:*** A total of 24 consecutive patients treated between August 2007 and August 2009 were included in this retrospective study. None of the patients had received bevacizumab as part of prior treatment. ***Results:*** All 24 patients received modified FOLFOX6 plus high-dose bevacizumab and were followed for a median of 36.9 months. Overall response rate was 29%. Median progression-free survival was 7.5 months, and median overall survival was 17.3 months. Grade 3/4 adverse events were: neutropenia (54.2%), leukopenia (25.0%), neuropathy (12.5%), hypertension (12.5%), thrombocytopenia (8.3%), and decreased haemoglobin, gastrointestinal haemorrhage, wound complications, nausea, diarrhoea, mucositis and fatigue (each 4.2%). ***Conclusion:*** Modified FOLFOX6 plus high-dose bevacizumab may be useful in the second-line treatment of patients with metastatic colorectal cancer who have not received bevacizumab.

Introduction

With the more recent advent of the anticancer drugs irinotecan and oxaliplatin, first-line chemotherapy for unresectable advanced or metastatic colorectal cancer (mCRC) has remarkably progressed, incorporating the following agents: fluorouracil plus leucovorin plus oxaliplatin (FOLFOX; administered as either a 2- or 3-week schedule: FOLFOX4, modified FOLFOX6, mFOLFOX6) [1–3], capecitabine plus oxaliplatin (XELOX) [4], and fluorouracil plus leucovorin plus irinotecan (FOLFIRI) [3, 5]. At present, biological agents in combination with these chemotherapy regimens have been commonly used [6–9]. Since 1998 there has been improved outcome following hepatic resection and since 2004 the introduction of biological agents has contributed greatly to improved overall survival (OS) for mCRC [10].

The vascular endothelial growth factor antibody bevacizumab prolongs survival when used in combination with various chemotherapy regimens for first-line treatment of mCRC [6, 7, 11, 12] and has been recommended as standard treatment agent. Similarly, the epidermal growth factor receptor antibodies cetuximab and panitumumab prolong progression-free survival (PFS) when used in combination with the FOLFOX and FOLFIRI regimens in patients with the KRAS wild-type gene following subgroup analyses in various clinical studies [8, 9, 13].

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The introduction of second-line therapy occurs when patients do not respond to or are unable to tolerate first-line therapy, and this varies depending on the individual situations of the patients. FOLFIRI, irinotecan alone or, in patients with the KRAS wild-type gene, combined with cetuximab or panitumumab can be second-line treatment options if oxaliplatin-based chemotherapy was selected for first-line therapy [14–16]. The continuous use of bevacizumab from first-line therapy can be considered as a second-line treatment option combined with a chemotherapy regimen which was not used as part of the first-line treatment [17].

Clinical evidence for the use of high-dose bevacizumab (10 mg/kg/2 weeks) as part of a second-line chemotherapy regimen has been provided in a phase III clinical study by Giantonio et al. [18] where patients with mCRC previously treated with fluorouracil and irinotecan were assigned to one of three treatment groups: FOLFOX4 plus bevacizumab, FOLFOX4, or bevacizumab. The primary endpoint was OS and the dose of bevacizumab was 10 mg/kg every 2 weeks. The combination of bevacizumab with FOLFOX4 resulted in statistically significant improvements compared with FOLFOX4 alone for the primary endpoint OS (median 12.9 vs. 10.8 months, hazard ratio, HR: 0.75, $p = 0.0011$), and the secondary endpoints PFS (median 7.3 vs. 4.7 months, hazard ratio: 0.61, $p < 0.0001$) and overall response rate (RR; 22.7 vs. 8.6%, $p < 0.0001$). In the light of these findings, we conducted a retrospective study to evaluate the efficacy and safety of high-dose bevacizumab combined with mFOLFOX6 in the second-line or later treatment of patients with mCRC. We conducted this study because there are no reported data of high-dose bevacizumab in combination with mFOLFOX6, which is widely used in Japan for mCRC because it is a more simple delivery option than FOLFOX4 as no bolus injection of fluorouracil is given on day 2.

Patients in this retrospective study had not received bevacizumab as part of their prior treatment as this study was performed shortly after bevacizumab received regulatory approval in Japan.

Patients and Methods

Patients

A total of 24 consecutive patients treated at the Department of Surgery, Niigata Cancer Center Hospital, Niigata, Japan, between August 2007 and August 2009 were included in this retrospective study. All of them received high-dose bevacizumab (10 mg/kg/2 weeks) combined with mFOLFOX6 plus high-dose bevacizumab as second-line or later treatment. The 24 patients had been histologically diagnosed as having mCRC and had not received bevacizumab as part of their previous chemotherapy regimen. Information was available on evaluation of treatment response using imaging during treatment and on evaluation of safety; 21 of the 24 patients had measurable lesions and sufficient laboratory test values at the start of treatment.

Treatment

Patients received mFOLFOX6 (fluorouracil bolus 400 mg/m^2 + leucovorin 200 mg/m^2 + oxaliplatin 85 mg/m^2 followed by 46-hour intravenous infusion of fluorouracil 2,400 mg/m^2) plus high-dose bevacizumab (10 mg/kg) in 2-week cycles until disease progression or discontinuation because of adverse events. Bevacizumab was intravenously infused on the same day as mFOLFOX6 and prior to the mFOLFOX6 regimen.

The dose of a drug was reduced or the drug was discontinued, as appropriate, depending on the occurrence of grade 3 or 4 adverse events.

Assessments and Endpoints

Response to treatment was assessed every 4–6 cycles in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST version 1.0). Safety was assessed every treatment cycle in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

PFS was defined as the time from treatment initiation to disease progression or death from any cause, whichever was earlier. Time to treatment failure (TTF) was defined as the time from treatment initiation to disease progression, death from any cause or discontinuation of protocol treatment before it was completed, whichever was earlier. OS was defined as the time from treatment initiation to death from any cause.

Analyses

PFS, TTF and OS were estimated using the Kaplan-Meier method.

Results

Baseline Patient Characteristics

In total, 24 patients (8 male and 16 female) from Niigata Cancer Center Hospital, Niigata, Japan, were involved in this analysis. The baseline characteristics of the patients are described in table 1. In brief, their median age was 60.5 years (range 18–76); 14 had colon cancer and 10 had rectal cancer; the primary tumour was resected in 23 patients; 15 patients received mFOLFOX6 plus high-dose bevacizumab as second-line treatment and 9 received this regimen as third-line or later treatment (all 9 patients were treated with mFOLFOX6 alone as first-line treatment). The 24 patients were followed for a median of 36.9 months (range 21.8–45.8).

For 3 of the 15 patients who received second-line mFOLFOX6 plus high-dose bevacizumab, treatment was

Table 1. Baseline characteristics of patients (n = 24)

Characteristic	Value
Male/female, n	8/16
Median age (range), years	60.5 (18–76)
ECOG performance status (0/1), n	17/7
Colon/rectum, n	14/10
Primary tumour (no/yes), n	23/1
Metastatic sites, n	
Liver	11
Lung	12
Peritoneum	6
Lymph nodes	5
Bone	2
Number of metastatic sites, n	
1	12
2	10
3	2
Line number of bevacizumab, n	
2nd	15
3rd or later	9
Previous chemotherapy, n	
IRIS	18
FOLFIRI	7
mFOLFOX6	9[a]
RPMI	1
sLV5FU2	1
UFT/LV	3

[a] All 9 patients received mFOLFOX6 plus high-dose bevacizumab as 3rd or later line. In these patients, mFOLFOX6 alone was used as 1st line.

started as FOLFOX4 plus high-dose bevacizumab because of inpatient care but changed to mFOLFOX6 plus high-dose bevacizumab part way through due to changing to outpatient care.

Drug Treatment

The median duration of treatment for the 24 patients was 15.0 cycles (range 3–40) and median TTF was 6.8 months.

In 9 of the 24 patients, only bolus fluorouracil was stopped and the other treatments were continued. In 11 of the 24 patients, oxaliplatin was discontinued as a result of peripheral neuropathy and allergic reactions, and treatment was continued with a simplified leucovorin and fluorouracil regimen (sLV5FU2) plus high-dose bevacizumab. In 5 of the 24 patients, bevacizumab was stopped and treatment with mFOLFOX6 was continued.

The reasons for discontinuation of any treatment were: complete response (CR; 1/24 patients), disease progression (19/24 patients), adverse events (2/24 patients) and hepatic resection (2/24 patients).

Efficacy

The RR was 29% (CR in 1 patient and partial response, PR, in 6 patients) and the disease control rate was 87% (CR in 1, PR in 6 and stable disease in 14 patients). In 15 patients treated as second-line, RR was 33% (CR in 1 and PR in 4 patients) and disease control rate was 87% (CR in 1, PR in 4 and stable disease in 8 patients). In 9 patients treat as third-line or later, RR was 22% (PR in 2 patients) and disease control rate was 89% (PR in 2 and stable disease in 6 patients).

During the follow-up period, median PFS was 7.4 months (6.1–9.1), median TTF was 7.0 months (3.7–9.1) and median OS was 16.1 months (9.7–23.4; fig. 1).

The post-treatment regimen after mFOLFOX6 plus high-dose bevacizumab was FOLFIRI plus high-dose bevacizumab in 8 of the 24 patients, irinotecan plus cetuximab in 7 patients, IRIS in 1 patient, mFOLFOX6 in 1 patient and no treatment in 7 patients.

The median TTF of the 17 patients receiving treatment was 4.2 months. All patients discontinued treatment as a result of disease progression.

Tolerability

In 11 patients oxaliplatin was stopped because of neuropathy and allergic reaction, and treatment was continued with sLV5FU2 and high-dose bevacizumab.

Adverse events by severity grade are shown in table 2. Grade 3/4 adverse events were the following: neutropenia (13/24 patients; 54.2%); leukopenia (6/24 patients; 25.0%); neuropathy (3/24 patients; 12.5%); hypertension (3/24 patients; 12.5%); thrombocytopenia (2/24 patients; 8.3%), and decreased haemoglobin, gastrointestinal haemorrhage, wound complications, nausea, diarrhoea, mucositis and fatigue (each 1/24 patients; 4.2%; table 2). There were no reports of gastrointestinal perforation or venous thromboembolism.

Discussion

The results of this retrospective study show that the efficacy and safety profile of high-dose bevacizumab (10 mg/kg/2 weeks) combined with mFOLFOX6 in the second-line or later treatment of patients with mCRC were similar to previously reported treatment outcomes of sec-

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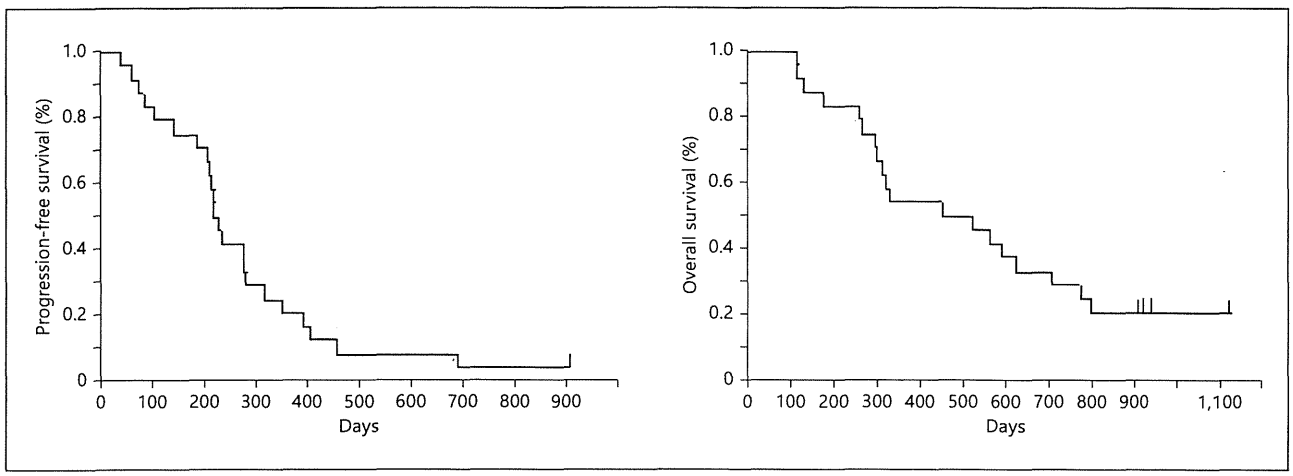

Fig. 1. PFS and OS in patients with unresectable colorectal cancer receiving second-line or later treatment of mFOLFOX6 plus high-dose bevacizumab (n = 24).

Table 2. Incidence of adverse events by severity grade (n = 24)

Adverse event	Number of patients				
grade	1	2	3	4	total
Neutropenia	7	4	9	4	24
Leukopenia	6	10	5	1	22
Haemoglobin decreased	14	5		1	20
Thrombocytopenia	17	1	2		20
Hypertension			3		3
Proteinuria	9	1			10
Gastrointestinal haemorrhage			1		1
Wound complications			1		1
Nausea	11		1		12
Diarrhoea	11	1	1		13
Mucositis	15	4	1		20
Hand and foot syndrome	10	3			13
Fatigue	17	4	1		22
Allergic reaction	3				3
Neuropathy	12	8	3		23

ond-line chemotherapy plus bevacizumab. RR, PFS and OS from this study together with those reported in the BEVACOLOR [19], the AVASIRI [20] and the E3200 [18] studies are shown in table 3. Adverse events specific to bevacizumab reported here and in the E3200 [18] study are illustrated in table 4.

The data on whether the optimal dose of bevacizumab is 2.5 or 5 mg/kg/week appear to differ depending on the type of cancer involved. In non-small-cell lung cancer, time to progression and OS trended towards greater improvement with 5 mg/kg/week rather than 2.5 mg/kg/week in the randomised phase II AVF0757g study (time to progression: 7.4 vs. 4.3 months, OS: 17.7 vs. 11.6 months) [21]. However, in the phase III AVAiL study, the primary endpoint of improvement in PFS was similar for cisplatin plus gemcitabine plus bevacizumab 5 or 2.5 mg/kg/week compared with cisplatin plus gemcitabine plus placebo (6.5 months, HR: 0.82, p = 0.03; 6.7 months, HR: 0.75, p = 0.003) [22]. In contrast, in metastatic breast cancer the addition of bevacizumab 5 mg/kg/week to docetaxel resulted in a better RR and longer PFS compared with docetaxel plus placebo (RR: 64.1%, p < 0.001; PFS: 10.1 months, HR: 0.77, p = 0.006), but this improvement was not seen with docetaxel plus bevacizumab 2.5 mg/kg/week (RR: 55.2%, p = 0.07; PFS: 9.0 months, HR: 0.86, p = 0.12) [23]. In a phase III study in metastatic renal cancer, the primary endpoint, time to progression, was prolonged with bevacizumab 10 mg/kg/2 weeks compared with placebo (4.8 months, HR: 2.55, p < 0.001) but not with bevacizumab 3 mg/kg/2 weeks (3.0 months, HR: 1.26, p = 0.053) [24]. At present there are no data confirming which dose is the most appropriate in colorectal cancer but, as shown in study E3200 [14] and also observed here, high-dose bevacizumab (5 mg/kg/week) is well tolerated in second-line or later treatment in patients who have not received first-line bevacizumab. In mCRC, the results of the randomised, controlled EAGLE trial [25] should help clarify the optimal dose for the continued use of bevacizumab from first-line treatment.

Table 3. Efficacy outcomes reported here and in 3 separate studies involving chemotherapy plus bevacizumab

Regimen	n	PFS months	OS months	RR %	Study
FOLFIRI	111	2.5	NR	4	v308 [26]
FOLFOX6	109	4.2	NR	15	v308 [26]
FOLFOX4	292	4.5	10.8	8.6	E3200 [18]
FOLFIRI + BV	14	7.8	21.7	36	BEVACOLOR [19]
FOLFOX + BV	30	5.3	13.9	29	BEVACOLOR [19]
FOLFIRI + HD-BV	25	11.6	21.4	32	AVASIRI [20]
FOLFOX4 + HD-BV	293	7.3	12.9	22.7	E3200 [18]
mFOLFOX6 + HD-BV	24	7.4	16.1	29	this study

BV = Bevacizumab; HD-BV = high-dose bevacizumab; NR = not reported.

Table 4. Incidence of grade 3/4 adverse events specific to bevacizumab reported here and in Study E3200

	E3200 [18] grade 3 or 4 (n = 287)	This study grade 3 or 4 (n = 24)	p value[a]
Hypertension	6.2%	12.5%	0.21
Proteinuria	6.7%	0%	0.38
Haemorrhage	3.4%	4.2%	0.59
Wound complications	–	4.2%	–
Nausea	10.1%	4.2%	0.49
Diarrhoea	–	4.2%	–
Mucositis	–	4.2%	–
Fatigue	–	4.2%	–
Neuropathy	16.3%	12.5%	0.78
Gastrointestinal perforation	1.0%	0%	1.0
Venous thromboembolism	3.4%	0%	1.0

[a] Fisher's exact test, two-tailed.

The results of the present study suggest that mFOLFOX6 plus high-dose bevacizumab (10 mg/kg/2 weeks) may be useful in the second-line treatment of patients who have not received first-line bevacizumab, although this was a retrospective study involving a relatively small number of patients (including 9 patients previously treated with mFOLFOX6 alone as first-line and treated with mFOLFOX6 plus high-dose bevacizumab as third-line or later). The results of the above ongoing, prospective, randomised, controlled trials should clarify this further.

Disclosure Statement

None.

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Factors predicting the response to oral fluoropyrimidine drugs: A phase II trial on the individualization of postoperative adjuvant chemotherapy using oral fluorinated pyrimidines in stage III colorectal cancer treated by curative resection (ACT-01 Study)

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Abstract. We evaluated the predictive relevance of several biomarkers on the survival of patients with stage III colorectal cancer treated with adjuvant chemotherapy of oral fluoropyrimidines. This was a multicenter phase II trial on adult patients with histologically confirmed resected stage III (Dukes' C) colorectal cancer. Patients received oral doxifluridine (800 mg/m^2/day) in 3 divided doses, or oral uracil/tegafur (UFT) (400 mg/m^2/day) in 2 divided doses for 5 days, every 7 days for 12 months with a 5-year follow-up. Outcome measures were disease-free survival and tissue markers [thymidine phosphorylase (TP), dihydropyrimidine dehydrogenase (DPD) protein levels and TP, DPD, thymidylate synthase (TS) and orotate phosphoribosyltransferase (OPRT) mRNA levels in tumor samples and TS tandem-repeat type in blood samples]. There was a significant association between the intratumoral TP/DPD enzyme ratio and disease-free survival when the model included the drug, the parameter and the interactions between them [hazard ratio (HR)=2.76; P=0.00469]. The 5-year disease-free survival rate was statistically significantly higher in patients with high TP/DPD ratios [median ≥2.63: 71.9%; 95% confidence interval (CI) 61.4-80.0] compared to patients with low TP/DPD ratios (<2.63: 57.0%; 95% CI 46.3-66.3) (log-rank P=0.0277) following adjuvant therapy with oral fluoropyrimidines. No significant association was observed between the intratumoral TP/DPD enzyme ratio (cut-off value 2.0) and the disease-free survival rate in the doxifluridine group; primary endpoint (log-rank P=0.6850). The magnitude of the intratumoral TP/DPD enzyme ratio may be a potential indicator for the individualization of postoperative adjuvant chemotherapy with oral fluoropyrimidines for stage III colorectal cancer.

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Key words: biomarkers, predictive markers, thymidine phosphorylase/dihydropyrimidine dehydrogenase ratio, disease-free survival

Introduction

The age-adjusted incidence of colon cancer in Japan in 2003 was second compared to stomach cancer in men (63.8/100,000 individuals) and breast cancer in women (35.9/100,000 individuals) (1). However, it is estimated that there will be 512,225 cases of colon cancer in Japan in 2020, surpassing the number of breast cancer cases from 2010 onwards as the most common type of cancer in women (1).

Adjuvant chemotherapy improves the overall survival in patients with resected stage III colon cancer (2). In the late 1990's, intravenous 5-fluorouracil/leucovorin (5-FU/LV) was established as the standard adjuvant treatment for patients with stage III colon cancer (3-5). Since then several oral fluoropyrimidines [i.e. capecitabine, uracil/tegafur (UFT) plus LV] have been demonstrated as an effective alternative to 5-FU/LV in the treatment of colon cancer (6,7).

Intratumoral expression of the metabolizing enzymes thymidine phosphorylase (TP), dihydropyrimidine dehydrogenase (DPD), thymidylate synthase (TS) and orotate phosphoribosyltransferase (OPRT) are important for the clinical activity of the drugs and may be predictive markers used to guide decision-making regarding the treatment for individual patients. For example, the TP/DPD ratio is significantly higher in cancer cell lines with high sensitivity to doxifluridine (an intermediate metabolite of capecitabine)

compared to those with lower sensitivity and the possibility of predicting the effectiveness of doxifluridine from the TP/DPD ratio has been demonstrated (8,9). The OPRT/DPD ratio may be a promising predictive marker for UFT (data reported in UFT plus LV) (10).

We conducted a multicenter phase II study on 204 stage III colorectal cancer patients to identify potential biomarkers predictive of outcome to adjuvant therapy with oral fluoropyrimidines. Patients were treated orally for 12 months (11) with doxifluridine or UFT, which were the standard drug treatments in Japan in 2001 when the study was initiated.

Patients and methods

Patients. Patients with histologically diagnosed stage III (i.e. Dukes' C) colorectal cancer who had undergone curative resection within the last 6 weeks prior to the start of the study were enrolled. Other inclusion criteria were: age 20 to 75 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, able to take oral medication, not treated with any prior therapy other than surgical resection and adequate organ function. Exclusion criteria were: cancer of the appendix or anal canal derived from the anal glands, synchronous or metachronous cancers or multiple invasive colon cancers (excluding intramucosal cancer).

Patients were recruited from 13 institutions belonging to the Japanese Society for Cancer of the Colon and Rectum which achieved a consensus on the appropriate surgical procedure and follow-up.

The study protocol was approved by the institutional review boards of each participating institution. The study was in accordance with the Ethical Guidelines for Clinical Studies of the Health, Labor and Welfare Ministry in Japan and was conducted in compliance with the Declaration of Helsinki. All patients provided written informed consent.

Study design. Patients were randomly assigned (1:1 ratio) to treatment groups. Tumor site (colon vs. rectosigmoid-upper rectum vs. lower rectum), depth of invasion [(sm/mp/ss, a1) vs. (se, a2/si, ai)], lymph node metastasis (n1 vs. n2/n3) and the study site were selected as stratification factors.

Treatment. Patients received oral doxifluridine (800 mg/m^2/day) in 3 divided doses or oral UFT (400 mg/m^2/day) in 2 divided doses for 5 days with 2 rest days and repeated weekly for 12 months. Patients were then followed up until confirmation of recurrence. On the occurrence of adverse events, dose reductions or temporary treatment interruptions were performed as per protocol.

Tissue samples and analysis. Sixty milligrams (5 mm^2) of tissue was obtained from each resected tumor, from the marginal portion of the primary lesion and not including necrotic tissue. The sample tissue was divided in half, frozen in liquid nitrogen and stored at -80°C or colder. For analysis of TS tandem repeat type, a 1 ml blood sample was collected within 3 months after surgery and stored at -80°C or colder.

Tissue specimens were sent to Nippon Roche Co., Ltd. (now Chugai Pharmaceutical Co., Ltd.) Research Center for analysis. TP and DPD protein levels were measured by ELISA (12,13) and TP, DPD, TS and OPRT mRNA levels were measured by RT-PCR using a LightCycler® (Roche Diagnostics KK, Tokyo, Japan). Identification of TS tandem repeat type was conducted by PCR-RFLP assay (14).

Evaluation. Physical examination, ultrasonography, chest X-rays and tumor marker measurements were performed before the beginning of the study treatment; every 4 months for the first year after surgery and every 6 months from the second year onwards. Suspected recurrence was confirmed via barium enema, CT or other appropriate diagnostic imaging modality.

Safety was evaluated from reports of adverse events, laboratory examination results and measurements of vital signs. Adverse events were classified according to the Common Toxicity Criteria of the National Cancer Institute (NCI-CTC, version 2). All patients were followed up for a maximum of 5 years until death, failure to follow up or completion of the study.

Study objectives. The primary objective was to examine the effect of the intratumoral TP/DPD enzyme ratio (cut-off value 2.0) on disease-free survival in the doxifluridine group. There were 3 secondary endpoints, which were examined on an exploratory basis: i) Effects of TP and DPD protein levels in tumor samples and the magnitude of the TP/DPD ratio on disease-free and overall survival with oral fluoropyrimidine adjuvant therapy. ii) Effects of TP, DPD, TS and OPRT mRNA levels in tumor samples and the magnitude of the TP/DPD ratio on disease-free and overall survival with oral fluoropyrimidine treatment. iii) Effects of the TS tandem repeat type from blood samples on disease-free and overall survival with oral fluoropyrimidine treatment.

Statistical analysis. Data were analyzed for the full analysis set, comprising all patients who started protocol treatment and in which TP and DPD protein levels were measured.

Time-to-event endpoints were analyzed using the Kaplan-Meier method and 5-year survival rates were estimated with 95% confidence intervals (CI). Differences between patient cohorts were examined with the log-rank test. Disease-free survival was defined as the period from the date of enrollment to the date of confirmation of either recurrence or death, whichever preceded. Recurrence was defined as the occurrence of metachronous colon cancer or secondary invasive cancer. Patients without recurrence or death at the time of analysis were censored at the final observation time. Overall survival was defined as the period from the date of enrollment to the date of confirmation of death from any cause. In the analysis of overall survival, patients who survived were censored at the final observation time.

Proportional hazard models were used for the analysis of disease-free and overall survival. We examined 3 different models: drug and the parameter (e.g., TP/DPD ratio), drug and the parameter and the interactions between them and stratification factors as covariates.

We estimated hazard ratios (HRs) and a two-sided Wald P-value for each model. A P-value of ≤ 0.05 was used to determine whether or not a factor had predictive value.

Further post-hoc exploratory analyses were performed. A Cox regression analysis was performed to identify a cut-off value for the intrartumoral TP/DPD enzyme ratio to distin-

Table I. Patient baseline characteristics.

	Doxifluridine (n=102)	Uracil/tegafur (n=102)
	n (%)	n (%)
Age, years		
Median (range)	63 (26-75)	62.5 (33-75)
Gender		
Male	55 (53.9)	60 (58.8)
Female	47 (46.1)	42 (41.2)
Tumor location		
Colon	59 (57.8)	57 (55.9)
Rectum	43 (42.2)	45 (44.1)
Histological type		
Well differentiated	35 (34.3)	32 (31.4)
Moderately differentiated	62 (60.8)	66 (64.7)
Poorly differentiated	4 (3.9)	3 (2.9)
Mucinous	1 (1.0)	1 (1.0)
Depth of invasion[a]		
sm, mp	13 (12.7)	12 (11.8)
ss, a1	53 (52.0)	57 (55.9)
se, a2	31 (30.4)	32 (31.4)
si, ai	5 (4.9)	1 (1.0)
Metastasis to lymph nodes[b]		
n1(+)	77 (75.5)	78 (76.5)
n2(+)	20 (19.6)	22 (21.6)
n3(+)	5 (4.9)	2 (2.0)
Histological stage		
IIIa	77 (75.5)	78 (76.5)
IIIb	25 (24.5)	24 (23.5)
Lymphatic invasion		
ly0	11 (10.8)	9 (8.8)
ly(+)	91 (89.2)	93 (91.2)
Venous invasion		
v0	18 (17.6)	20 (19.6)
v(+)	84 (82.4)	82 (80.4)
Histological curability		
R0	102 (100.0)	102 (100.0)

[a]For depth of invasion, cases with sm/mp/ss, a1 are categorized as T1-3. Cases with se, a2/si, ai are categorized as T4. [b]Metastasis to 1-3 lymph nodes is categorized as n1. Cases with more than 4 affected lymph nodes are categorized as n2. sm, submucosa; mp, muscularis propria; ss, subserosal; a1, sub-adventitia; se, serosa; a2, adventitia; si, adjacent structures.

guish between patients with good and poor outcomes. The effects of intratumoral TP/DPD enzyme ratio on disease-free survival by tumor site, T and N category were analyzed.

The sample size was estimated assuming an HR of 2.2 for the doxifluridine group based on Nishimura *et al* (9), who demonstrated that disease-free survival was significantly longer in the patient cohort with a TP/DPD ratio ≥2.0 with doxifluridine adjuvant therapy. An estimated 240 patients in total were required, with 120 patients in the doxifluridine group. Assuming a 5-year disease-free survival rate of 70% for patients with stage III (R0) colon cancer and 60% for rectal cancer, a colon:rectal cancer ratio of 55:45 and a 1-year enrollment period with a 5-year follow-up period, an α error of 0.05 (one-sided) and detection power (1-β) of 63% were ensured. Data were collected by EPS Co., Ltd. Statistical analyses were conducted under the supervision of T.T., at the Center for Medical Statistics.

Results

Two hundred and four patients were enrolled at 13 institutions from January 2002 to September 2003 and 102 patients were assigned to the doxifluridine group and 102 patients to the UFT group. One hundred and two patients in the doxifluridine group and 99 patients in the UFT group received treatment as allocated, respectively. The analysis set comprised 195 patients in which TP and DPD protein levels were measured (doxifluridine, n=98; UFT, n=97). There were no differences between the 2 groups in the distribution of patient baseline characteristics (Table I).

Compliance and safety. Seventy-seven patients completed treatment and 25 patients discontinued intervention in the doxifluridine group (death, n=1; relapsed/metastasis, n=7; adverse events related to study drugs, n=10; declined treatment, n=6; other, n=1). Sixty-seven patients completed treatment and 32 patients discontinued intervention in the UFT group (relapsed/metastasis, n=15; complications, n=1; adverse events related to study drugs, n=13; declined treatment, n=2; other, n=1).

Treatment compliance was similar in both groups (≥70% of treatment days completed for doxifluridine, 72.5%; UFT, 68.7%; ≥70% doses received for doxifluridine, 68.6%; UFT, 65.7%).

Adverse events were reported in 61 patients (59.8%) in the doxifluridine group and 71 patients (71.7%) in the UFT group and grade 3 events were reported in 7 patients in both groups (one patient had grade 4 anorexia and stomach pains caused by adhesive bowel obstruction) (Table II).

Adverse events assessed as grade ≥2 that resulted in treatment discontinuation or dose reduction were reported in 56 patients in the UFT group and 55 patients in the doxifluridine group (note: patients may have experienced ≥1 event).

Intratumoral markers. TP and DPD protein levels were measured in 195 patients and mRNA in 170 patients. Median TP and DPD protein levels and TP, DPD, TS and OPRT mRNA levels showed no significant differences between the 2 groups (Table III).

Assessment of marker predictiveness. For the effect of intratumoral TP/DPD enzyme ratio (cut-off value 2.0) on disease-free survival in the doxifluridine group, the primary study endpoint, there was no statistically significant difference between the 2 cohorts in the 5-year disease-free survival rate: TP/DPD ratio ≥2.0, 71.4% (95% CI 59.3-80.5) vs. TP/DPD ratio <2.0, 66.5% (95% CI 45.4-80.9) (log-rank P=0.6850) (Fig. 1).

Table II. Adverse events graded according to the Common Toxicity Criteria of the National Cancer Institute (version 2).

	Doxifluridine (n=102)					Uracil/tegafur (n=99)				
	G1	G2	G3	G4	Total	G1	G2	G3	G4	Total
Nausea	3	4			7	4	4	2		10
Vomiting							2	1		3
Anorexia	2	5	1		8	13	5	1	1[b]	20
Diarrhea	7	4	2		13	4	5	1		10
Stomatitis	5	1			6	2				2
Alopecia	1				1	2				2
Pigmentation change	3				3	4				4
Rash/desquamation	1	4			5	4	7			11
Fatigue[a]	5	2	1		8	8	4	1		13
Hematuria	3				3	2				2
Increased creatinine	3				3	2				2
Decreased WBC	7	3			10	4	7			11
Decreased platelet count	9				9	4				4
Decreased hemoglobin	7	6	1		14	13	7			20
Increased bilirubin	15	13			28	22	3			25
Increased GOT/GPT	11	3	1		15	22	5	2		29
Other	4	2	2		10[c]	6	1	1	1[b]	11[d]

[a]Lethargy, malaise and/or asthenia. [b]One patient had anorexia and stomach pains caused by adhesive bowel obstruction. [c]The severity of 2 of 10 patients not determined by grade. [d]The severity of 2 of 11 patients not determined by grade. GPT, glutamic-pyruvic transaminase; GOT, glutamic-oxaloacetic transaminase; WBC, white blood cell count.

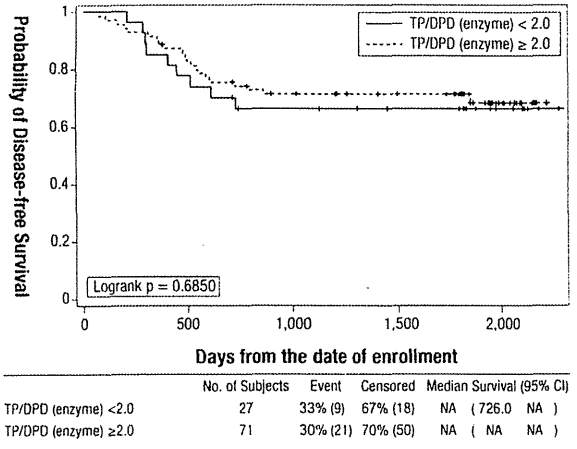


Figure 1. Disease-free survival by thymidine phosphorylase/dihydropyrimidine dehydrogenase (TP/DPD) ratio (cut-off value 2.0) in patients treated with doxifluridine (n=98).

Results for the secondary endpoints were as follows: i) The effect of the magnitude of intratumoral TP/DPD enzyme ratio on disease-free survival with oral fluoropyrimidine treatment was only significant (HR=2.76, P=0.00469) when analyzed in the model including the drug and the parameter and the interactions between them. Proportional hazards analysis showed that the effects of TP and DPD protein levels on disease-free survival and the effects of the parameters (i.e. TP, DPD protein levels and TP/DPD enzyme ratio) on overall survival were not significant in the models (data not shown).

The 5-year disease-free survival rate was statistically significantly higher in the cohort with a higher intratumoral TP/DPD enzyme ratio (median ≥2.63) compared to the cohort with a lower TP/DPD ratio (<2.63): 71.9% (95% CI 61.4-80.0) vs. 57.0% (95% CI 46.3-66.3) (log-rank P=0.0277) (Fig. 2A). The effects of the magnitude of the TP/DPD ratio on disease-free survival in each of the doxifluridine and UFT groups are shown in Fig. 2. In the UFT group, the 5-year disease-free survival rate was statistically significantly higher in the cohort with the higher TP/DPD ratio (median ≥2.63) than in the cohort with a lower TP/DPD ratio (median <2.63): 74.4% (95% CI 58.2-85.1) vs. 44.1% (95% CI 29.7-57.6) (log-rank P=0.0029) (Fig. 2C). In the doxifluridine group, the effect of the magnitude of the TP/DPD ratio on disease-free survival was not statistically significant (log-rank P=0.9541) (Fig. 2B).

ii) Proportional hazard analysis demonstrated that the effects of the parameters (i.e. intratumoral TP, DPD, TS and OPRT mRNA levels and TP/DPD mRNA ratio) on disease-free and overall survival were not significant in any of the models (data not shown).

iii) Proportional hazards analysis showed that the effects of the parameters (i.e. TS tandem repeat type 2R/2R, 2R/3R or 3R/3R) on disease-free and overall survival were not significant in the models (data not shown).

Exploratory analyses. An exploratory Cox regression analysis identified a cut-off value of 3.1 for the intratumoral TP/DPD

Table III. Intratumoral markers.

	Median (range)	
	Doxifluridine (n=98)	Uracil/tegafur (n=97)
Protein levels (U/mg protein)		
TP	81.3 (13.2-242.5)	80.3 (13.7-301.3)
DPD	34.4 (4.9-124.2)	32.8 (8.8-139.8)
TP/DPD	2.663 (0.54-6.94)	2.569 (0.75-9.57)
	Doxifluridine (n=85)	Uracil/tegafur (n=85)
mRNA levels (copy number)[a]		
TP	2.61 (0.21-21.49)	2.93 (0.24-141.16)
DPD	0.13 (0.02-1.92)	0.18 (0.006-1.57)
TP/DPD	19.47 (2.19-145.66)	22.06 (1.32-558.16)
TS	1.06 (0.23-14.86)	1.17 (0.04-20.40)
OPRT	0.82 (0.04-7.37)	0.88 (0.182-6.18)

[a]Values normalized by glucose-6-phosphate dehydrogenase. TP, thymidine phosphorylase; DPD, dihydropyrimidine dehydrogenase; TS, thymidylate synthase; OPRT, orotate phosphoribosyltransferase.

enzyme ratio to distinguish between patients with good and poor outcomes with oral fluoropyrimidine treatment. The 5-year disease-free survival rates in cohorts with TP/DPD ratios ≥3.1 and <3.1 were 77.7 and 56.1%, respectively (log-rank P=0.0059) (Fig. 3). Multiple regression analysis using Cox's method identified T4 (P=0.0068; HR=2.225; 95% CI 1.247-3.969) and intratumoral TP/DPD enzyme ratio ≥3.1 (P=0.0035; HR=0.394; 95% CI 0.211-0.735) as independent variables for prognosis. The P-values for other variables examined in the model (i.e. N category, tumor site, drug, TP/DPD mRNA ratio) were not statistically significant (data not shown).

Additionally, exploratory analyses to examine the effect of the intratumoral TP/DPD enzyme ratio on disease-free survival by tumor site, T stage and N stage in patients treated with oral fluoropyrimidines were conducted (Fig. 4). Analysis by tumor site displayed that the TP/DPD ratio was significantly associated with the disease-free survival (log-rank P=0.0033) in patients with colon cancer. Analysis by T category displayed an association between TP/DPD ratio and disease-free survival (log-rank P=0.0039) in patients with T4, but not T1-3. Analysis by N category displayed an association between TP/DPD ratio and disease-free survival (log-rank P=0.0224) in patients with N1, but without N2 disease.

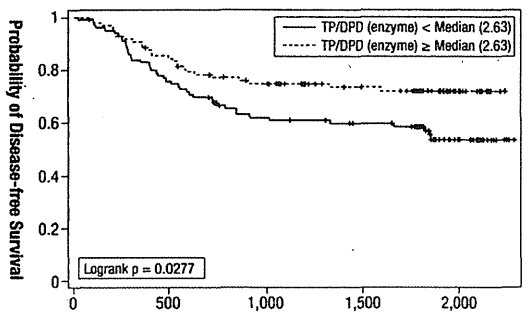
Discussion

In this study, we examined several biomarkers for their possible predictive value in relation to the outcome following adjuvant chemotherapy with oral fluoropyrimidines in patients with stage III colorectal cancer in order to identify subgroups of patients who may benefit from this intervention. Our findings on the predictive value of biomarkers in tumor cells and blood samples were unexpected.

The TP/DPD ratio is significantly higher in cancer cell lines with high sensitivity for doxifluridine and capecitabine compared to those with lower sensitivity (8). In addition, synergistic effects were observed when doxifluridine was used in combination with chemotherapeutic agents or radiotherapy *in vivo*, since tumor TP levels are increased by these treatments (15). This synergistic antitumor activity, which results from TP upregulation, is specific for doxifluridine, not for UFT or 5-FU (15). These data suggest that TP may be a potential factor for determining the outcome following doxifluridine treatment. There was a significant association between the magnitude of intratumoral TP/DPD enzyme ratio and disease-free survival (HR=2.76; P=0.00469) when the interaction between the drug and this parameter was analyzed. The 5-year disease-free survival rate in the group with a high TP/DPD ratio (median ≥2.63) was statistically significantly higher compared to the group with a low TP/DPD ratio (median <2.63; log-rank P=0.0277).

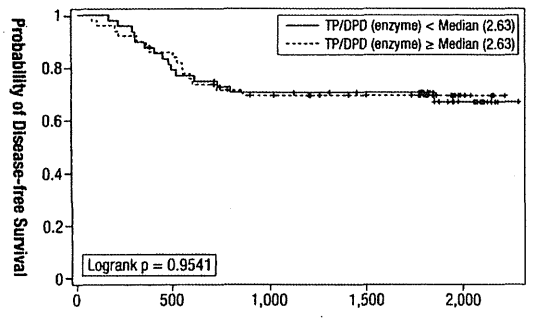
However, the effect of the intratumoral TP/DPD enzyme ratio (cut-off value both 2.0 and median of 2.63) on disease-free survival was not statistically significant in the doxifluridine group (log-rank P=0.6850, 0.9541, respectively). TP levels measured using tumor samples were found to be more important for doxifluridine (and capecitabine) compared to using normal or blood samples, since only fluoropyrimidine converted by TP in the tumor has a direct effect (16,17). For measurement, tissues which included both the tumor and stroma cells were used, since fluoropyrimidine converted in cells with high TP expression near the tumor may also have a tumor response (18). Unexpected results may be caused by TP levels not being stable before and after treatment initiation, since TP is induced by a number of cytokines (19,20). TP levels were measured from resected primary lesion tumors and outcomes were analyzed 5 years after treatment initiation,

A



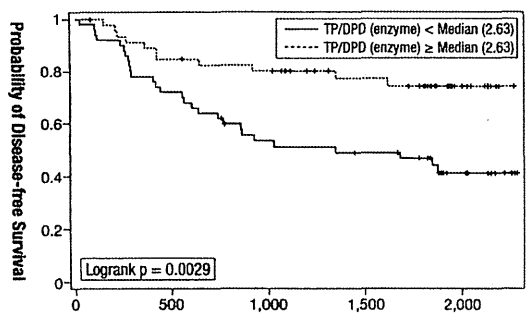
	No. of Subjects	Event	Censored	Median Survival (95% CI)
TP/DPD (enzyme) < Median (2.63)	98	44% (46)	56% (55)	NA (1,330 NA)
TP/DPD (enzyme) ≥ Median (2.63)	97	27% (26)	73% (71)	NA (NA NA)

B



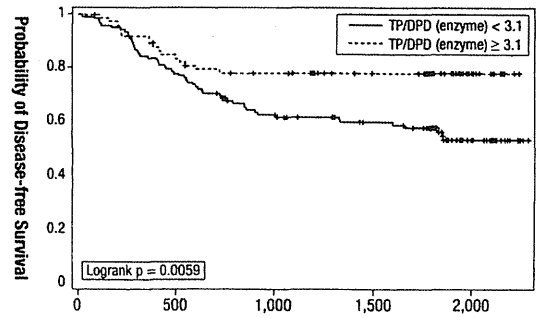
	No. of Subjects	Event	Censored	Median Survival (95% CI)
TP/DPD (enzyme) < Median (2.63)	48	31% (15)	69% (33)	NA (NA NA)
TP/DPD (enzyme) ≥ Median (2.63)	50	30% (15)	70% (35)	NA (NA NA)

C



	No. of Subjects	Event	Censored	Median Survival (95% CI)
TP/DPD (enzyme) < Median (2.63)	50	56% (28)	44% (22)	1,330 (729 NA)
TP/DPD (enzyme) ≥ Median (2.63)	47	23% (11)	77% (36)	NA (NA NA)

Figure 2. Disease-free survival according to thymidine phosphorylase/dihydropyrimidine dehydrogenase (TP/DPD) ratio (using median value as cut-off, i.e. 2.63) in patients treated with (A) oral fluoropyrimidines (n=195), (B) doxifluridine (n=98) and (C) UFT (n=97).



	No. of Subjects	Event	Censored	Median Survival (95% CI)
TP/DPD (enzyme) < 3.1	121	44% (53)	56% (68)	NA (1,597 NA)
TP/DPD (enzyme) ≥ 3.1	74	22% (16)	78% (58)	NA (NA NA)

Figure 3. Disease-free survival according to the thymidine phosphorylase/dihydropyrimidine dehydrogenase (TP/DPD) ratio (using cut-off value identified by Cox regression analysis, 3.1) in patients treated with oral fluoropyrimidines (n=195).

which may explain the different outcome from the *in vivo* study (8).

The effect of the intratumoral TP/DPD enzyme ratio (cut-off median of 2.63) on disease-free survival was statistically significant in the UFT group (log-rank P=0.0029). UFT confers its effect by maintaining high fluoropyrimidine levels in the blood and not in the tumor. However, since TP levels in the tumor catalyze the conversion between fluoropyrimidine and 2'-deoxy-5-fluorouridine (FUdR) [precursor of 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP) which has an antitumor effect] and high TP levels produce deoxy ribose-1-phosphate (dR1P) from thymidine (dR1P promotes the conversion between fluoropyrimidine and FUdR) (21), high TP expression may be meaningful for UFT.

The association between TS, OPRT and the sensitivity to fluoropyrimidine drugs has been observed in previous research (10,22-25). It has also been reported that combined analysis, such as analysis with TS and TP, DPD, with OPRT and DPD may predict efficacy or outcome of treatment with fluoropyrimidines more precisely (10,26-28). In the present study we did not demonstrate an association between any factors other than the TP/DPD enzyme ratio and the efficacy of fluoropyrimidine drugs.

For TS tandem repeat type, it was previously observed that the level of expression of the TS protein is higher and that fluoropyrimidine drugs are less efficacious in patients with the 3R/3R allele compared to those with 2R/2R or 2R/3R alleles (29). Previous research reported that TS tandem polymorphisms are potentially predictive biomarkers, not only of response, but also for the occurrence of adverse events. Conversely, other research has claimed that TS-tandem polymorphisms are not associated with the efficacy of fluoropyrimidine drugs (30). The results of our study were negative for the possibility that TS-tandem type is potentially predictive of an outcome following oral fluoropyrimidine adjuvant therapy.

Our study has several important design features. First, since this study targeted stage III cancer, the number of residual cancer cells persisting after standard curative resection may have had a major effect on postoperative survival. For this reason, the skill of the surgeon is a major factor. Since the institutions participating in our study belonged to the Japanese Society for Cancer of the Colon and Rectum, we hypothesize that surgeon-related factors were minimized. Other factors which may have influenced our findings were potential differences in the timing of the collection and handling of tissue specimens and the differences between individuals in medication compliance. Participating sites were rigorously drilled in the methodology for the collection of specimens. Institutions

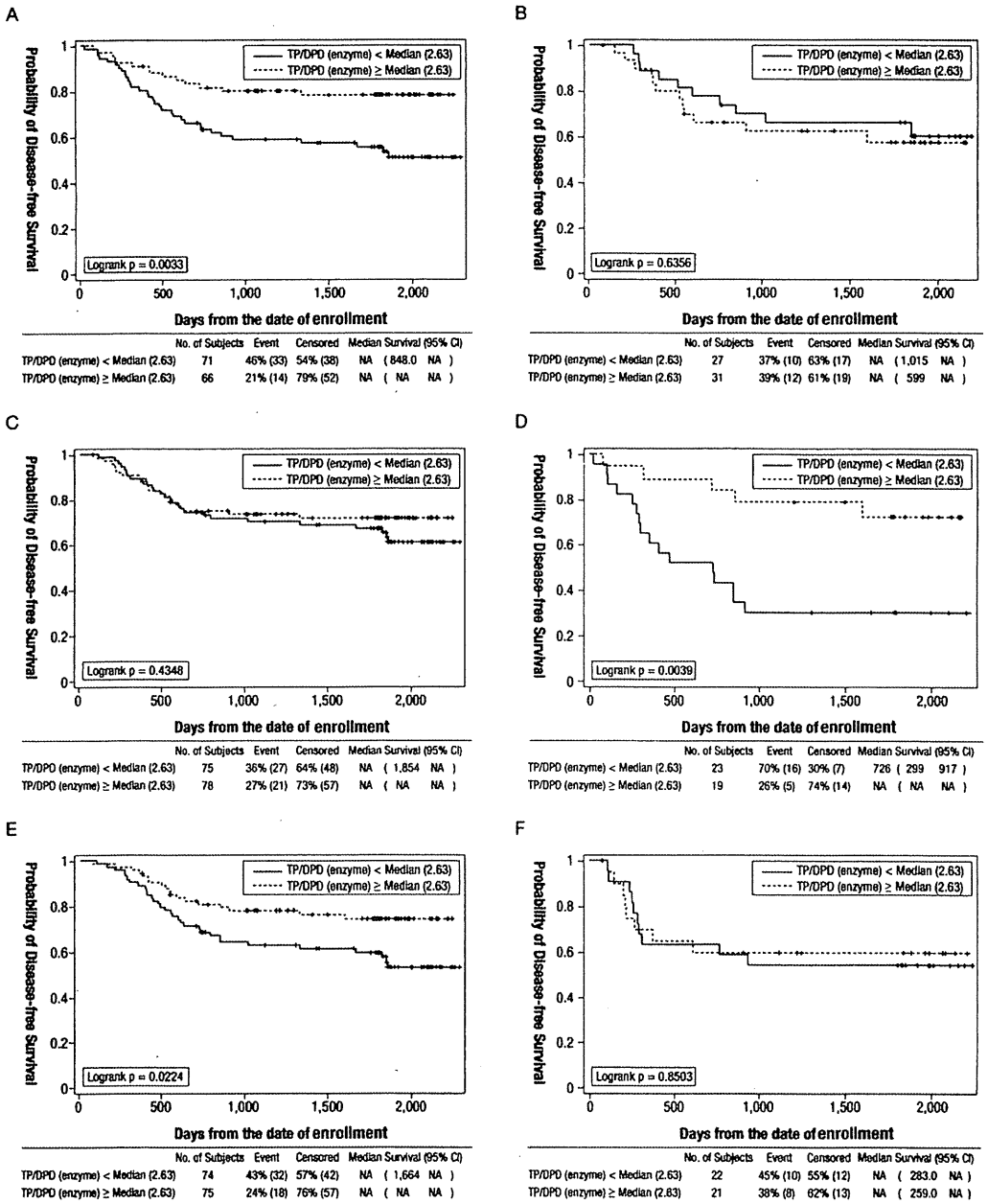


Figure 4. Disease-free survival according to the thymidine phosphorylase/dihydropyrimidine dehydrogenase (TP/DPD) ratio (using median value as cut-off, i.e. 2.63) by tumor type [(A) colon cancer; (B) rectal cancer], T stage [(C) T1-3; (D) T4] and N stage [(E) N1; (F) N2] in patients treated with oral fluoropyrimidines.

which returned specimens with considerable degradation during the study were provided with on-site guidance and the requirement for prompt processing was reinforced. Medication compliance was assessed every quarter by the investigator by directly interviewing each patient. Patients were asked for detailed reasons in the event of interruption or discontinuation of the medication. We hypothesize that biases in this study were minimal as a result of these measures.

Our study has some limitations. One of the most serious issues is that there was no control arm (i.e. surgery-alone group). TP is identical to platelet-derived endothelial cell growth factor (PD-ECGF) (31) and patients with high levels of tumoral TP expression have a poor prognosis (32,33). This may be important, since patients in the high-TP group may be especially responsive to doxifluridine (9), although there were no significant differences compared with UFT in our study. This may indicate that TP is a prognostic, as well as a predictive, marker. A surgery-alone group may have helped to clarify this issue and explain our unexpected results. In conclusion, the magnitude of the intratumoral TP/DPD enzyme ratio may predict outcomes in patients with stage III colorectal cancer who are treated with adjuvant chemotherapy with oral fluoropyrimidines. The intratumoral TP/DPD enzyme ratio may therefore allow the individualization of postoperative oral fluoropyrimidine adjuvant therapy in stage III colorectal cancer. Further exploration and verification of the magnitude

of the intratumoral TP/DPD enzyme ratio as a biomarker is required.

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手術手技

巨大会陰骨盤腫瘍に対する広範会陰腟後壁切除および大殿筋切除を伴う腹会陰式直腸切断術と薄筋皮弁による再建術

滝口 伸浩* 早田 浩明* 山本 宏*
永田 松夫* 鍋谷 圭宏* 池田 篤*

はじめに

直腸癌や会陰部中心の腫瘍で，広範囲会陰切除あるいは大殿筋切除を伴う腹会陰式直腸切断術や骨盤内臓全摘術では，多量の複合組織欠損が生じ，会陰部再建として薄筋皮弁などの移植が行われる[1)2)]。今回，われわれは右殿部から発生し骨盤内へ増殖した巨大な限局性線維性腫瘍(solitary fibrous tumor；以下SFT)[3)]に対して，広範会陰切除を伴う腹会陰式直腸切断術を施行し，薄筋皮弁による再建術により治療した1例を経験したので，手術手技を中心に報告する。

Ⅰ．症　例

症例は53歳女性で，右殿部腫瘤を主訴に近医受診。体表リンパ節の腫脹を認めず。右殿部に弾性軟の22 cm大の腫瘍を触知した。CTで右殿部腫瘤を認めたため，針生検が施行され，SFTの診断となった。

腹部—骨盤CTでは，右会陰部から骨盤部後腹膜にかけて長径170 mm大の球状腫瘤で子宮—腟，直腸壁を左前方に圧排している。腫瘍の背側は造影効果がみられ右大殿筋に浸潤している（図1）。

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key words
腹会陰式直腸切断術，広範会陰腟切除，薄筋皮弁再建

骨盤MRI：右会陰部から骨盤部後腹膜にかけて長径172 mmの腫瘤がみとめられ，腫瘍は外側で広く坐骨神経と接し，背側では右大殿筋内に浸潤している（図2）。

以上より，右殿部—骨盤内SFTの術前診断で手術を施行した。

手術所見：載石位の体位で正中切開で開腹。右殿部骨盤腫瘍は，腹腔内観察では子宮後面に位置し，被膜で覆われた腫瘍で右側は坐骨に近接し，直腸および腟には直接の浸潤はみられないものの接した状態である（図3）。術前診断でSFTであるものの，右大殿筋への浸潤もあり，直腸との剝離や腟との剝離は腫瘍の被膜損傷になると判断し，腟後壁とともに直腸肛門の合併切除とした。腹腔内操作とともに載石位による，広範囲会陰皮膚とともに右大殿筋を腫瘍からの距離を保ちなが

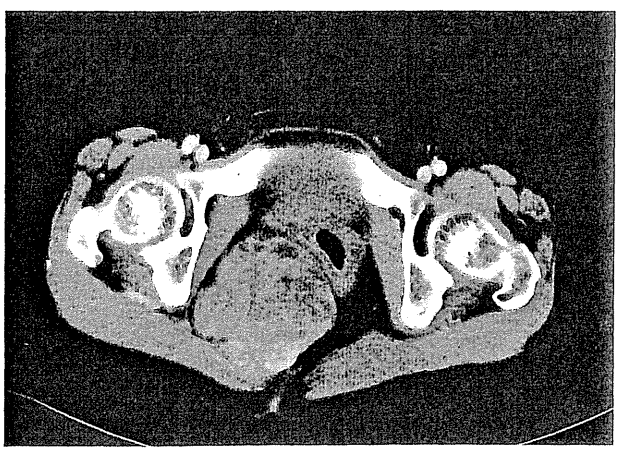

図1　骨盤CT
右会陰部から骨盤部後腹膜にかけての球状腫瘤で子宮-腟，直腸壁を左前方に圧排している。腫瘍の背側は造影効果がみられ右大殿筋に浸潤している。

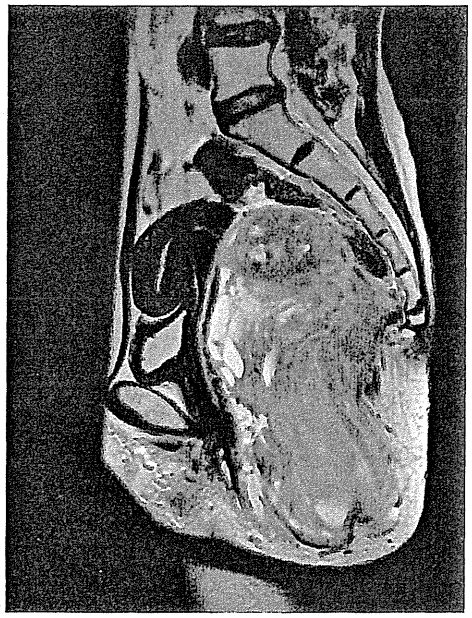

図2　骨盤 MRI
右会陰部から骨盤部後腹膜にかけて長径 172 mm の腫瘤。腫瘍は，背側では右大殿筋内に浸潤している。

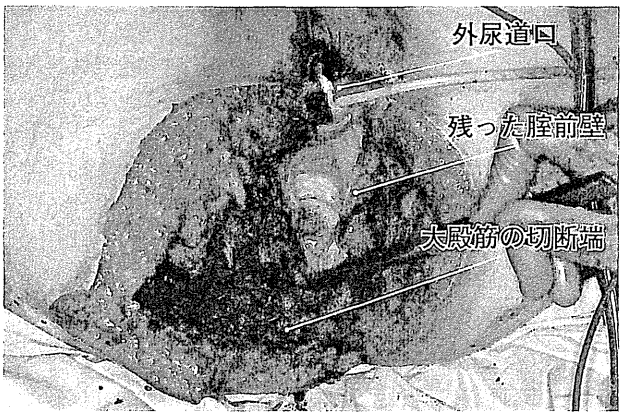

図4　標本摘出後の会陰部所見
広範会陰腟後壁切除および大殿筋切除を伴う腹会陰式直腸切断術を行った。腫瘍は被膜損傷なく，径会陰的に切除標本を摘出した。

ら坐骨に沿って腫瘍を切除し，腟後壁合併で腹会陰式直腸切断術で腫瘍を切除した。そのあと欠損部の再建を行った。腹腔操作で，骨盤底を作成し後腹膜経路で左側腹部にS状結腸人工肛門作成。ドレーン留置後閉腹。会陰再建は薄筋皮弁を右大腿内側より作成し，腟と皮弁の縫合により腟の再建，さらに皮弁と殿部皮膚と縫合することにより，欠損部の充塡および会陰形成を行った。

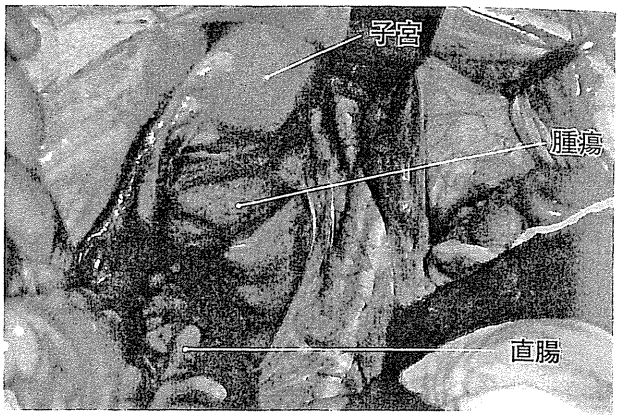

図3　開腹時の腫瘍所見
右殿部骨盤腫瘍は，腹腔内観察では子宮後面に位置し，被膜で覆われた腫瘍で右側は坐骨に近接し，直腸および腟には直接の浸潤はみられないものの接した状態である。

Ⅱ．手術手技のポイント

1．腫瘍切除

a）腹部操作

S状結腸を授動。上直腸動脈（SRA）をリガシュアで処理。RS直腸部分で自動縫合器により切離。後壁の剝離はTMEの層で剝離。左側骨盤底は直腸を腟の中央部まで剝離。右側は腫瘍が坐骨近くまで存在し，腹腔内からの操作は坐骨までの剝離とした。電気メスおよびリガシュアを適宜使用しながら，腫瘍被膜を損傷しないように剝離していくことが肝要である。

b）会陰操作

載石位の体位で，径会陰的に広範囲会陰皮膚切除を伴う右大殿筋切除を行うが，皮膚切離線の決定後深部へのアプローチは腫瘍の首座から遠い左側よりアプローチする。腹腔内に達し腟後壁を一部合併切除しながら前方左側から腫瘍を確認しながら，右大殿筋は大きく切除する。手術の進行とともに腫瘍の全貌が直視下に観察されるようになるので，右坐骨に沿って腫瘍を切除し被膜損傷無く標本を摘出した（図4）。

2．再建

a）腹部操作

腹部操作の再建を先行する。十分洗浄，止血確

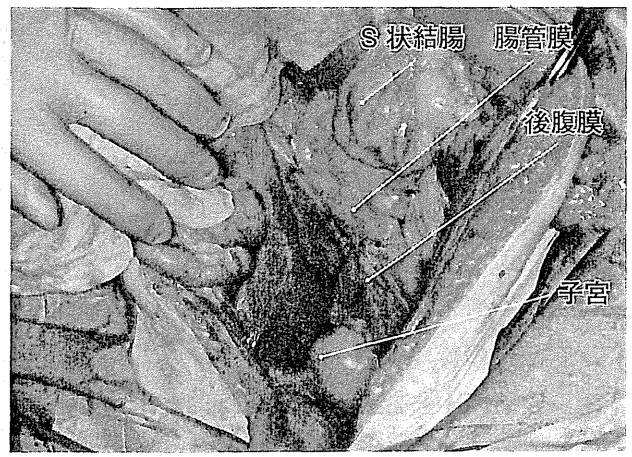

図5　骨盤底再建

後腹膜経路でS状結腸人工肛門を左側腹部に作成。子宮を後屈する形で腹膜と縫合することで骨盤底を作成した。

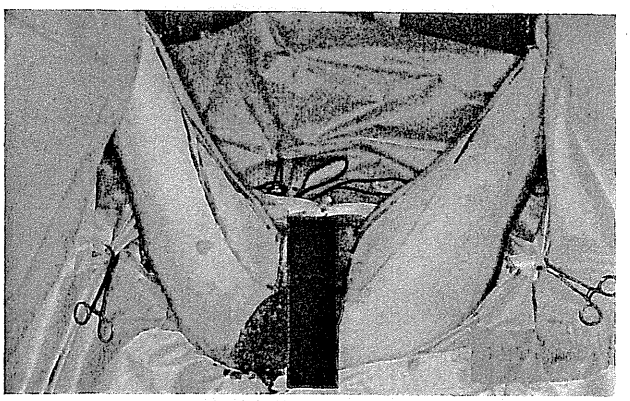

図6　薄筋皮弁の皮切デザイン

下肢を伸展させてピオクタニンで，両側の大腿薄筋皮弁のデザインをしておく。恥骨結節と顆骨結節を結ぶラインを前縁とするが，薄筋は大腿のもっとも内側で体表の直下にあり，大腿を少し外転すると，起始が皮膚の下ではっきりと盛り上がってくる。

認後，骨盤底の再建と人工肛門の造設を行う。後腹膜経路でS状結腸人工肛門を左側腹部に作成。また，本症例では子宮が残っているので，子宮を後屈する形で腹膜と縫合することで骨盤底を作成した（図5）。この手技は，骨盤死腔の縮小と腸閉塞リスクを軽減するためにも重要な処置である。腹壁はセプラフィルムを貼布して3層に縫合閉鎖する。

b）薄筋皮弁の作成

会陰再建では，下肢を伸展させてピオクタニンで，両側の大腿薄筋皮弁のデザインをしておく。恥骨結節と顆骨結節を結ぶラインを前縁とするが，薄筋は大腿のもっとも内側で体表の直下にあり，大腿を少し外転すると，起始が皮膚の下ではっきりと盛り上がってくる。筋のほぼ全長を描きその上に皮弁部分をひと回り大きく紡錘形に描く（図6）。デザインにそって皮切を行い薄筋皮弁を作成する。本症例では，右薄筋皮弁のみで再建可能であった。薄筋の栄養血管は大腿深動脈の分枝である内側大腿回旋動脈であり，神経支配は閉鎖神経（L2-L4）による，これらの血管，神経は，神経血管茎（neurovascular pedicle）となり，長内転筋の後面から薄筋の筋体に入る。筋皮弁の長さは約20 cm，幅は10 cmまで採取可能である。筋皮弁の前縁に切開を加え，長内転筋の筋体確認後，筋膜を切開し，長内転筋と大内転筋の間からくる薄筋のneurovascular pedicleを露出

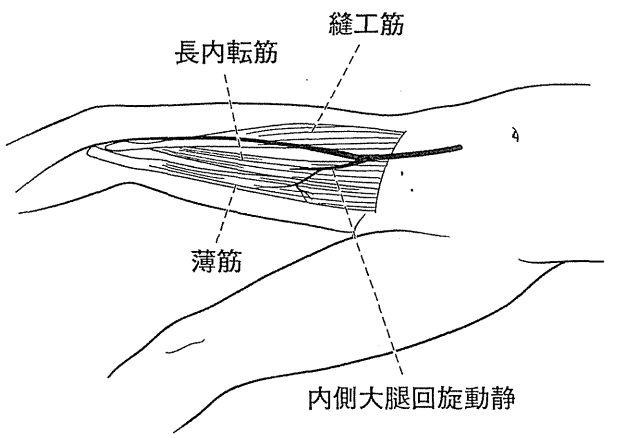

図7　薄筋および周囲の筋の血管神経

薄筋の栄養血管は大腿深動脈の分枝である内側大腿回旋動脈であり，神経支配は閉鎖神経（L2-L4）による，これらの血管，神経は，神経血管茎（neurovascular pedicle）となり，長内転筋の後面から薄筋の筋体に入る。

する。neurovascular pedicleは恥骨結合から6 cm～10 cmの部分で筋間の深部から筋に流入するのでていねいに剝離する（図7）。薄筋を全長にわたって同定し大腿末梢の薄筋が細くなっている部位で切離する。

c）骨盤欠損部の充塡と会陰腟作成

作成された薄筋皮弁を反時計回りに90度回転し，腟と皮弁の縫合により腟の再建，さらに皮弁と殿部皮膚と縫合することにより，欠損部の充塡および会陰形成術を行った（図8）。J-Vacドレーンを大腿皮下および骨盤死腔に留置。陰圧とする。腟縫合部にはペンローズドレーンを挿入留

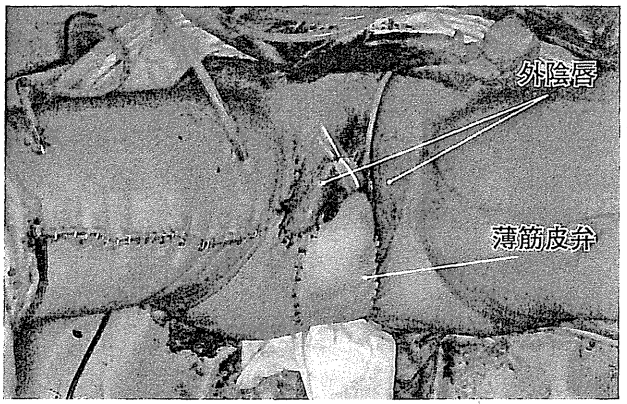

図8　骨盤欠損部の充塡と会陰腟作成

作成された薄筋皮弁を反時計回りに90度回転し，腟と皮弁の縫合により腟の再建，さらに皮弁と殿部皮膚と縫合することにより，欠損部の充塡および会陰形成術を行った。

置した。

d）術後経過

薄筋皮弁の血流や感染などの問題はなく，筋皮弁を移植したための特別な運動制限は行わなかった。術後経過はおおむね順調で術後30日で退院となった。術後2年経過したが，術後の腹部症状の出現などなく，再発所見もない。

Ⅲ．考　察

SFTは線維芽細胞様の紡錘形細胞が比較的厚い膠原線維束により隔てられて増殖し，限局的な腫瘤を形成する比較的まれな腫瘍である[3]。SFTの由来や生物学的特徴などについては不明な点が多く，疾患概念自体も完全に確立されたものではない。腫瘍の大きさが10 cmを越えるものは細胞学的悪性度との明らかな関係はないものの完全切除できないものも多く，局所再発を来しやすいとGoldら[4]は報告している。

完全切除を達成することが重要であり，手術操作の困難な会陰から骨盤にかけての腫瘍である今回の症例は，広範な会陰皮膚切除とともに大殿筋切除，腟後壁合併切除＋腹会陰式直腸切断術による術式でR0手術を遂行した。薄筋皮弁による組織欠損部分の充塡と，会陰および腟後壁再建が本術式の重要なポイントである。

今回の手術手技で，子宮を後屈させ腹膜と縫合する骨盤底の作成はイレウス予防および骨盤死腔の減少の観点から腹会陰式直腸切断術時の再建で有用である。薄筋皮弁は，①血行の安定性，②比較的大きな組織ボリュームが確保可能，③移植組織採取後の不利益が少ない，などの観点から会陰再建の第一選択となる。この筋皮弁を利用した最初の報告は1976年McCrawら[5]による腟再建である。このような，筋皮弁による再建は，通常形成外科医に委ねるが，切除から再建までの過程を考えると，消化器外科医が知識として持ち合わせている必要がある手技である。

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症　例

形態変化のみられたlymphoid stromaを伴う横行結腸癌の1例

千葉県がんセンター消化器外科[1]，同　臨床病理部[2]
池田　篤[1]　滝口伸浩[1]　早田浩明[1]
永田松夫[1]　山本　宏[1]　杉山孝弘[2]

61歳，男性．検診で横行結腸に2型の隆起性病変を認め当科紹介となる．当院での大腸内視鏡検査では病変は0－IIa＋IIc様に変化していた．生検結果はGroup1のため，再検査を施行したところ病変はさらに0－IIc様に変化していた．再検査時の生検結果もGroup1のため経過観察となった．約10カ月後の内視鏡検査にて，同部に1型腫瘍を認め，生検にてGroup5であったため手術を施行した．摘出標本の病理組織学的検査では，carcinoma with lymphoid stromaの所見を示す低分化腺癌，MPN2H0P0M0 stage IIIbと診断された．carcinoma with lymphoid stromaは胃癌で知られているが，大腸癌では自験例を含めて本邦報告例は8例のみだった．約1年の経過中に縮小，増大と形態変化をきたしたlymphoid stromaを伴う横行結腸癌の1例を報告する．

索引用語：大腸癌，carcinoma with lymphoid stroma，形態変化

はじめに

間質に著明なリンパ球浸潤を伴うcarcinoma with lymphoid stromaは胃癌で知られている[1)2)]が，大腸癌では報告も少なく稀な疾患である．

今回，われわれは10カ月間の経過観察中に内視鏡上，形態変化の認められたlymphoid stromaを伴う横行結腸癌の1例を経験したので報告する．

症　例

症例：61歳，男性．

主訴：便潜血陽性．

既往歴：てんかん．

現病歴：検診で便潜血陽性を指摘され，近医受診．大腸内視鏡検査にて横行結腸に2型病変（生検ではGroup1）を認めたため，精査・加療目的で当科紹介となる．

初診時現症：身長164.9cm，体重55.9kg，腹部は平坦，軟で腫瘤は触知しなかった．

初診時血液生化学検査所見：軽度の貧血と白血球減少を認める他は腫瘍マーカーを含めて異常は認められなかった．

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前医下部消化管造影検査（Fig. 1a）および大腸内視鏡検査（Fig. 1b）所見：横行結腸に中心陥凹した隆起性病変を認めた．大腸内視鏡検査では周堤が正常粘膜に覆われた粘膜下腫瘍様の形態を示していた．

当科大腸内視鏡検査所見：前医での内視鏡検査より約1カ月後の当科での検査では，前医での所見と比較して隆起が目立たなくなっており0－IIa＋IIc様に変化していた（Fig. 2a）．当科での生検結果もGroup1であったため，17日後に再検したところ，病変は襞の集中を伴う0－IIc様に変化していた（Fig. 2b）．再検での生検でもGroup1のため経過観察の方針となった．当院初回検査より約4カ月後の内視鏡検査では病変は瘢痕化しており（Fig. 2c），生検結果はGroup1だった．さらに6カ月後（初回検査より約10カ月後）の内視鏡検査では同部に隆起性病変を認め（Fig. 2d），生検にてGroup5（低分化腺癌）と診断されたため，手術目的で当科入院となった．

入院時血液生化学検査所見：初診時と同じく，軽度の貧血と白血球減少を認めるのみで腫瘍マーカーに異常は認めなかった．

術前大腸内視鏡検査：腫瘍部位のマーキングのため術前に内視鏡による点墨を施行した．その際の腫瘍の肉眼所見は前回と比較して縮小傾向が見られた（Fig. 3a）．