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Postoperative adjuvant chemotherapy with mitomycin C and UFT for curatively resected rectal cancer. Results from the Cooperative Project No.7 Group of the Japanese Foundation for Multidisciplinary Treatment of Cancer

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Abstract
Background. This study was conducted to evaluate the significance of postoperative adjuvant chemotherapy using mitomycin C (MMC) and UFT (tegafur; uracil at 1:4 molar ratio) in combination for rectal cancer.
Methods. The Japanese Foundation for Multidisciplinary Treatment of Cancer conducted a prospective randomized controlled trial in 834 patients who had undergone curative resection for rectal cancer (T3 or T4 and/or N1, N2, or N3 according to TNM classification) from February 1986 to December 1988. The patients were randomly allocated to a treatment group (MMC/UFT, 416 patients) and a control group (surgery alone, 418 patients). For the patients in the treatment group, 20 mg of MMC was sprinkled on the operating field upon completion of surgery. MMC was injected intravenously (6 mg/m^2) on day 7, and then once a month for months 1–6 after surgery. UFT was administered at 400 mg/day, orally, for 1 year, beginning 3 weeks after surgery.
Results. There was no difference, in the 5-year survival rate between the two groups, but the 5-year disease-free survival rate in the MMC/UFT group (68.9%) was significantly higher than that (59.3%) in the control group ($P = 0.006$). The 5-year cumulative local recurrence rate was significantly lower in the MMC/UFT group (11.6%) than in the control group (19.0%) ($P = 0.007$).
Conclusion. We conclude that the adjuvant use of long-term oral UFT and intermittent MMC (i.v.) improves the disease-free survival rate of patients with curatively resected rectal cancer (T3 or T4 and/or N1, N2, or N3).

Key words Rectal cancer · Adjuvant chemotherapy · Disease-free survival · Mitomycin C · UFT

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Introduction

The number of patients with colorectal cancer has increased in Japan. In 1970, the mortality rates per 100000 persons were 8.5 for men and 8.0 for women, and by 1990 the rates had risen to 22.1 for men and 18.3 for women. According to the multi-institutional registry of large bowel cancer in Japan,[1] figures for 1986 showed that the 5-year survival rate for patients with colon cancer was 77.1% for those who had undergone curative resection, and there was a relatively good survival rate, of 65.8%, for Dukes' C patients. The 5-year survival rates for patients with rectal cancer were 72.7% for patients with curative resection and 57.1% for Dukes' C patients, worse than the figures for colon cancer patients.[1] A higher postoperative recurrence rate was observed for the rectal cancer patients. Nationwide studies of postoperative adjuvant chemotherapies have been conducted by several groups of investigators in Japan, as in other countries, with the aim of reducing this recurrence rate.[2–4] Although all these studies evaluated combination therapies of mitomycin C (MMC) and fluorinated pyrimidine derivatives, few studies have evaluated postoperative adjuvant chemotherapy in patients with rectal cancer.[4]

The Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMTC) was established in June 1980 for the purpose of establishing effective and appropriate multidisciplinary treatment plans for malignant tumors in Japan. To this end, it multicenter studies have been initiated.

This article is a report of postoperative adjuvant chemotherapy with a combination of MMC and UFT for rectal cancer, conducted as Cooperative Project no.7 of the JFMTC.

UFT is a combination drug consisting of tegafur, a masked compound of 5-fluorouracil (FU), and uracil at a molar ratio of 1:4. Uracil inhibits the degradation of 5-FU converted from tegafur, enabling high 5-FU concentrations to be retained in the tumor over long periods. A high response rate of colorectal cancer to UFT was shown in a clinical study.[5] In the combination therapy of MMC and UFT, drugs with theoretically different action mechanisms are expected to exert additive effects. The favorable effects of this combination therapy were observed in nude mice with transplanted human colorectal cancer.[6]

The MMC/UFT combination as adjuvant chemotherapy is expected to suppress postoperative recurrence. In this study, we investigated the value of this combination as adjuvant chemotherapy for patients with rectal cancer who had undergone curative resection in a multicenter cooperative study.

Patients and methods

Patient selection

Patients with rectal cancer who satisfied all the following criteria were enrolled from 117 participating hospitals from February 1986 to December 1988.

1. Patients with rectal cancer in whom the depth of invasion observed macroscopically during surgery was T3, T4 on TNM classification and/or those who had metastasis to regional lymph nodes (including lateral lymph nodes), but who did not have distant metastasis, and who had undergone macroscopically curative resection (patients who were macroscopically stage II-IV according to the *General rules for clinical and pathological studies on cancer of the colon, rectum and anus* (3rd edition of the Japanese Research Society for Cancer of Colon and Rectum);[7]
2. Patients who were younger than 70 years and who had no serious complications (such as active ischemic heart disease);
3. Patients who had not been given other surgical therapy, radiotherapy, chemotherapy, or immunotherapy, alone or in combination;
4. Patients who had no synchronous or metachronous multiple primary carcinomas (patients with multiple cancer due to the concurrent presence of early colorectal cancer were not excluded);
5. Patients who satisfied the following requirements on preoperative laboratory tests: Leukocyte count $\geq 4000/\mu$ l; platelet count, $\geq 15 \times 10^4/\mu$ l; total protein, ≥ 6.0 g/dl (albumin-globulin ratio ≥ 1.0); aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤ 50 U, negative for urine protein; and
6. Patients who consented to participate in this study before their operation (or whose family gave such consent).

Randomization

Patients who satisfied the above criteria were registered with the Secretariat of the study by telephone prior to closure of the surgical wound on the day of surgery and then randomly allocated to a treatment group (MMC/UFT) or a control group (surgery alone) (Central Registration Method).

Treatment method – dose regimen (Fig. 1)

For patients in the treatment group, 20 mg of MMC was dissolved in 200 ml of a physiological saline solution, and then sprinkled into the abdominal cavity in patients with rectal cancer above the peritoneal reflexion, or sprinkled into the operating field in the pelvis after rectectomy in patients with rectal cancer below the peritoneal reflexion at the time of closure of the abdomen. MMC was administered intravenously, at a dose of 6 mg/m^2, seven times in total, on day 7 and 1, 2, 3, 4, 5, and 6 months after surgery. UFT was administered at 400 mg/day orally (200 mg two times daily), beginning 3 weeks after surgery, for 1 year.

Patients in the control group underwent surgery alone and were given no anticancer drugs.

If serious adverse reactions (e.g., leukopenia, thrombocytopenia) or postoperative complications (e.g., sutureline dehiscence, intestinal obstruction) occurred, the chemotherapy was discontinued by decision of the physicians in charge. When it became possible to start administration again, the patient returned to the planned protocol. Administration of the anti-cancer drugs was completed 12 months after surgery. When recurrence was detected, the responsibility for subsequent treatment was left to the physician in charge.

Follow-up procedures

Physical examination, hematological tests (red blood cells [RBC], white blood cells [WBC], platelet count, and hemoglobin level), biochemical tests (total protein, AST, ALT, alkaline phosphatase [Al-P], blood urea nitrogen [BUN], and carcinoembryonic antigen [CEA]), and urinalysis were conducted in all the randomized patients in weeks 1 and 2 after surgery and 1, 3, 6, 9, and 12 months after surgery.

The physicians in charge were requested to conduct medical consultations once every 3 months, up to 5 years after surgery to check for postoperative recurrence. Imaging diagnostic methods such as roentgenography,

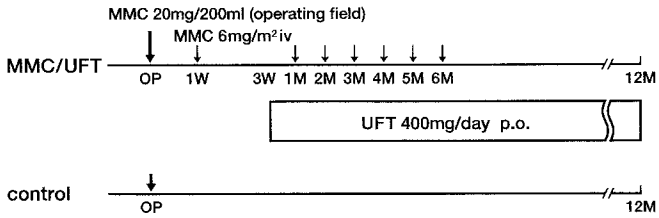

Fig. 1. Treatment schedules. *MMC*, mitomycin C; *UFT*, tegafur + uracil (molar ratio 1:4); *W*, week; *M*, month; *OP*, operation

ultrasonography, and computed tomography (CT) scans were performed to detect recurrence. The physicians in charge at the participating institutions described the results of these tests on case report forms (CRFs) every year and submitted them to the Secretariat of the study. Patients were requested to visit their physician to be examined for chemotherapy compliance every 2 weeks during the administration period.

Statistical methods

All analyses were conducted for all eligible patients, with ineligible patients excluded. The patient characteristics, symptoms and signs, and hematological findings were compared between the groups using the χ^2 test. The survival rate and disease-free survival rate were calculated by the Kaplan-Meier method, and the results for the two groups were compared by the stratified logrank test. The cumulative recurrence rate, according to the first site of failure, was calculated and analyzed in a manner similar to that used for the survival rate. All the statistical analyses were conducted by the Data Center of the JFMTC, using a statistical package (SAS system version. 6.04, SAS Institute Japan, Tokyo).

Results

A total of 834 patients (MMC/UFT group, 416; control group, 418 from 117 participating institutions were registered. Forty patients (4.8%; MMC/UFT group, 20; control group, 20) who did not satisfy the patient selection criteria were judged to be ineligible. These consisted of 16 patients who underwent macroscopically non-curative resection, 12 ineligible because of disease stage, 5 ineligible because of site of the disease, 3 ineligible because of laboratory test results, 3 with synchronous or metachronous multiple cancer, and 1 for other reasons (Table 1). Of the 794 eligible patients, 3 (2 in the MMC/UFT group and 1 in the control group) were lost to follow-up, and survival status or death could be confirmed for 791 patients (99.6%). One patient in the UFT/MMC group developed peritonitis, considered to be a surgical complication, on the 7th day after surgery and died of multiorgan failure on the 13th day after surgery.

Table 1. Summary of entered patients

No. of entered patients	MMC/UFT 416	Control 418
Ineligible	20(4.8%)	20(4.8%)
Macroscopically non-curative resection	6	10
Stage violation	7	5
Others	7	5
Eligible	396 (95.2%)	398 (95.2%)

Patient accrual:1986.2–1988.12.
MMC, mitomycin C; UFT, tegafur + uracil (molar ratio 1:4)

Patient characteristics

Table 2 shows the sex, age, site of disease, Dukes' classification, and histological curability for each group. There were no differences between the groups for any of these parameters. There were also no differences between the groups in terms of surgical technique (sphincter-preserving operation, abdomino-perineal resection), grade according to extent of lymph node dissection, or degree of differentiation of cancer tissue. Since macroscopic T and N classifications were applied to the eligibility criteria, patients classified as Dukes' A (15.6%) and Dukes' D (0.6%) according to the Dukes histological classification, were included among the eligible patients.

Chemotherapy compliance

In the MMC/UFT group, administration of MMC directly into the operating field was carried out in 98.0% of the patients (Table 3). MMC was intermittently injected intravenously seven times, the planned number of administrations, in 40% of the patients, and five times or more in 58.8% of the patients (Table 3). In regard to the planned total dose of UFT, of 137.6 g, 47.7% of patients received 80% or more of the planned total dose. However, 27.2% of the patients received only 40% or less of the originally planned total dose (Table 3). The most common reasons for discontinuation of administration included adverse effects of the drug in 14.4% of the patients (57/396), failure to visit the hospital to receive regular outpatient treatment for 8.1% (32/396), postoperative complications for 7.8% (31/396), and change of treatment due to recurrence for 6.8% in 27/396.

Complications and adverse effects

Signs and symptoms

The incidence rates of anorexia, nausea and vomiting, and skin pigmentation were 16.9%, 9.6%, and 3.3%, respectively, in the MMC/UFT group, and 9.6%, 5.8%, and 0%, respectively, in the control group, showing a significant difference between the groups. Diarrhea occurred in 12.1% of the patients in the MMC/UFT group and in 11.8% in the control group, with no significant difference between the groups (Table 4).

Table 2. Patient characteristics

No. of eligible patients		MMC/UFT 396	Control 398	*P* Value (χ^2 test)	
Sex	Male	250	247	0.755	NS
	Female	146	151		
Age (years)	<49	90	90	0.970	
	50–59	158	156		
	60–69	148	152		
Location of tumor	Rs (rectosigmoid)	82	81	0.943	
	Ra(upper rectum)	115	120		
	Rb(lower rectum)	199	197		
Dukes' classification	A	65	59	0.875	
	B	154	162		
	C	174	175		
	D[a]	3	2		
Histological curability	Curative resection	384	391	0.241	
	Non-curative resection	12	7		

NS, Not signifiant.
[a] Lymph node metastasis to group 4 lymph nodes[7]

Table 3. Drug Administration (MMC/UFT group)

MMC (operating field)

MMC	No. of patients
Administered	388 (98.0%)
Not administered	6 (1.5%)
Unknown	2 (0.5%)
Total	396

MMC (iv)

MMC (iv)	No. of patients
0	31 (7.8%)
1–4 Times	130 (32.8%)
5–8 Times	233 (58.8%)
Unknown	2 (0.5%)
Total	396

UFT

RP[a]	No. of patients
0	37 (9.3%)
≤0.4	71 (17.9%)
>0.4–0.8	96 (24.2%)
>0.8	189 (47.7%)
Unknown	3 (0.8%)
Total	396

[a] Relative Performance: Dose actually given planned dose (137.6 g)

Table 4. Incidence of complications and adverse effects
Signs and symptoms

No. of patients	MMC/UFT 396	Control 398	χ^2 test
Anorexia	16.9%	9.6%	$P = 0.002$
Nausea/Vomiting	9.6%	5.8%	$P = 0.038$
Stomatitis	1.5%	0.5%	$P = 0.148$
Diarrhea	12.1%	11.8%	$P = 0.840$
Skin pigmentation	3.3%	0%	$P < 0.001$

Hematologic and liver toxicities (≥grade 2) [8]

No. of patients	MMC/UFT 396	Control 398	χ^2 test
WBC	13.4%	2.8%	$P < 0.001$
Platelets	5.6%	0.3%	$P < 0.001$
Hemoglobin	8.8%	3.5%	$P = 0.002$
AST	7.1%	5.3%	$P = 0.277$
ALT	9.6%	8.3%	$P = 0.490$

Abnormal laboratory findings

Decreases in WBC count, platelet count, and hemoglobin level were more frequent in the MMC/UFT group. In the MMC/UFT group, leukopenia of grade 3 or greater severity (WBC count ≤ 1900/μl)[8] occurred in 0.5% of the patients and thrombopenia of grade 3 or greater severity (platelet count ≤ 49 × 10^3/μl) in 1.5%. There was no significant difference between the groups in elevations of AST and ALT (Table 4).

Survival

The 5-year survival rates were 70.1% in the MMC/UFT group and 66.3% in the control group, a result exhibiting no significant difference between the groups ($P = 0.338$; Fig. 2). No significant difference was observed in survival rates between the groups for patients with any of Dukes' A, Dukes' B, or Dukes' C/D cancers (Fig. 3).

Disease-free survival (DFS)

The 5-year DFS rates were 68.9% in the MMC/UFT group and 59.3% in the control group, and were thus significantly

superior in the MMC/UFT group ($P = 0.006$; Fig. 4). Analysis by Dukes' classification showed no significant difference between the treatment and control groups for Dukes' A or Dukes' B patients. For patients with Dukes' C/D cancer, the 5-year DFS rate was significantly superior in the MMC/UFT group compared with the control group ($P = 0.007$; Fig. 5).

Recurrence rate according to first site of failure

Five-year cumulative recurrence rates were calculated according to the first site of failure (local recurrence, liver recurrence, lung recurrence) and compared for the treatment and control groups (Table 5).

The overall 5-year cumulative local recurrence rate was 11.6% in the MMC/UFT group, significantly lower than the 19.0% in the control group ($P = 0.007$). However, no significant difference in the 5-year cumulative recurrence rates for liver or lung recurrence was observed between the groups. In the Dukes' C patients, although there was no difference in the liver recurrence rate, the local and lung recurrence rates were significantly lower in the MMC/UFT group that in the control group.

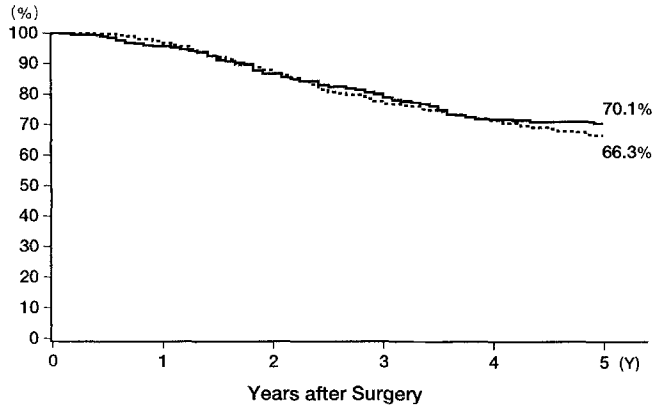

Fig. 2. Overall survival curves. (—MMC/UFT; $n = 396$; ····control; $n = 398$; $P = 0.338$, logrank test)

Discussion

Before 1986, when this study was started, there were no reports showing the usefulness of postoperative adjuvant chemotherapy for colorectal cancer in Japan. As full-scale nationwide randomized controlled studies, the Group of Research for Colorectal Cancer Treatment (Kajitani Group) supported by the Japanese Ministry of Health and Welfare, starting in 1974,[2] the Cooperative Study of Surgical Adjuvant Chemotherapy for Colorectal Cancer,[3] and the Colorectal Cancer Chemotherapy Study Group,[4] the latter two groups both starting in 1984, compared patients receiving adjuvant chemotherapy comprising MMC and oral fluorinated pyrimidine derivatives (5-FU, tegafur) and those receiving surgery alone. These studies were still

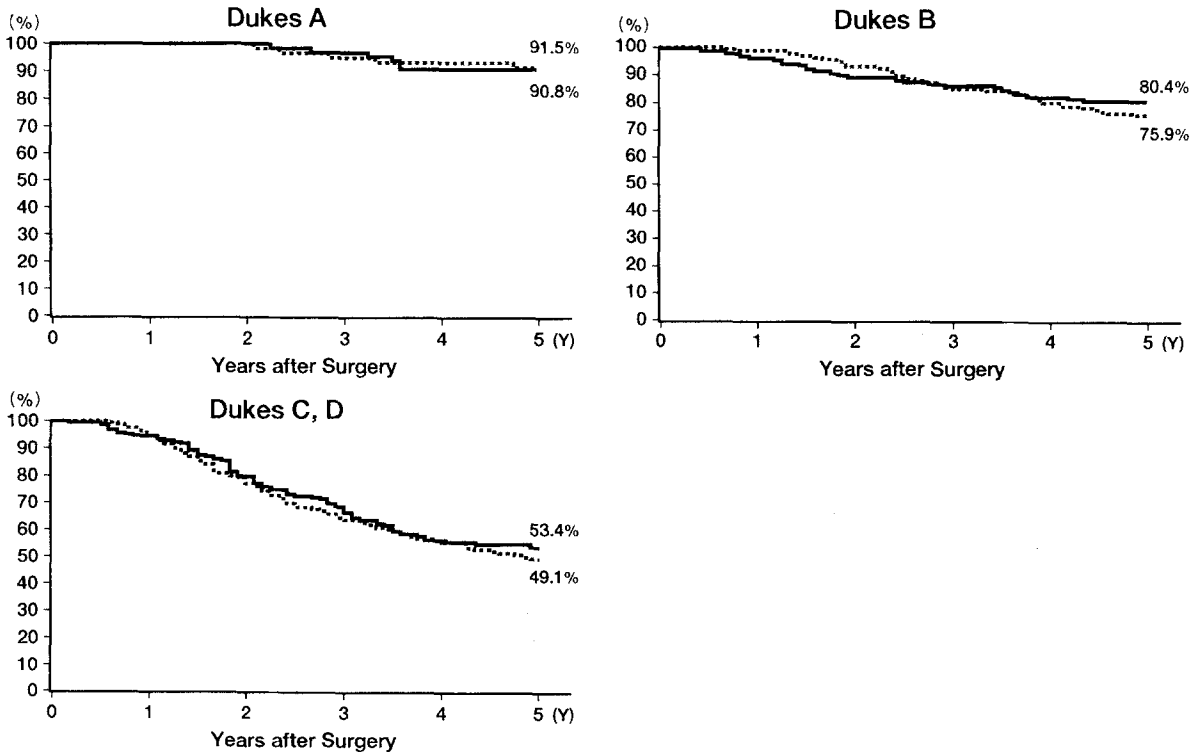

Fig. 3. Survival curves for patients with Dukes' A (—MMC/UFT; $n = 65$; ····control; $n = 59$; $P = 0.897$, logrank test) Dukes' B (—MMC/UFT; $n = 154$; ····control; $n = 162$; $P = 0.437$, logrank test) and Dukes' C, D cancer (—MMC/UFT; $n = 177$; ····control; $n = 177$; $P = 0.451$, logrank test)

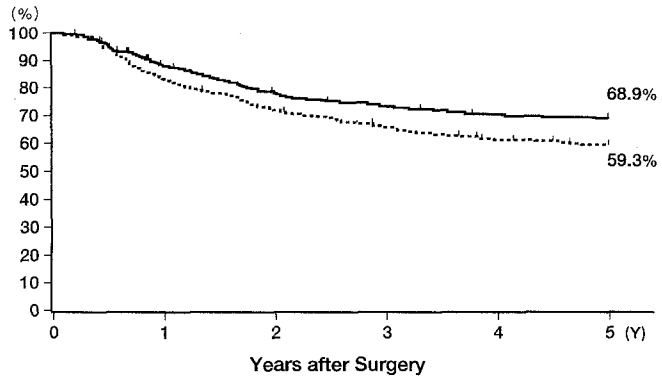

Fig. 4. Overall disease-free survival curves (—MMC/UFT; n = 396; ····control; n = 398; P = 0.006, logrank test)

ongoing and no results had been obtained at that time (1986).

Regarding the 5-year survival rate after curative surgery for colorectal cancer in Japan at that time (1986), although the 5-year survival rate for colon cancer was good, at about 80%, it was around 70% overall for rectal cancer and about 55% for Dukes stage C rectal cancer. The usefulness of adjuvant chemotherapy comprising MMC and an oral fluorinated pyrimidine, UFT, in patients with rectal cancer was therefore investigated in this study.

Although various adjuvant therapies have also been investigated in western countries, usefulness has been confirmed only for the combination therapy of 5-FU + semustine + vincristine by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and for the combina-

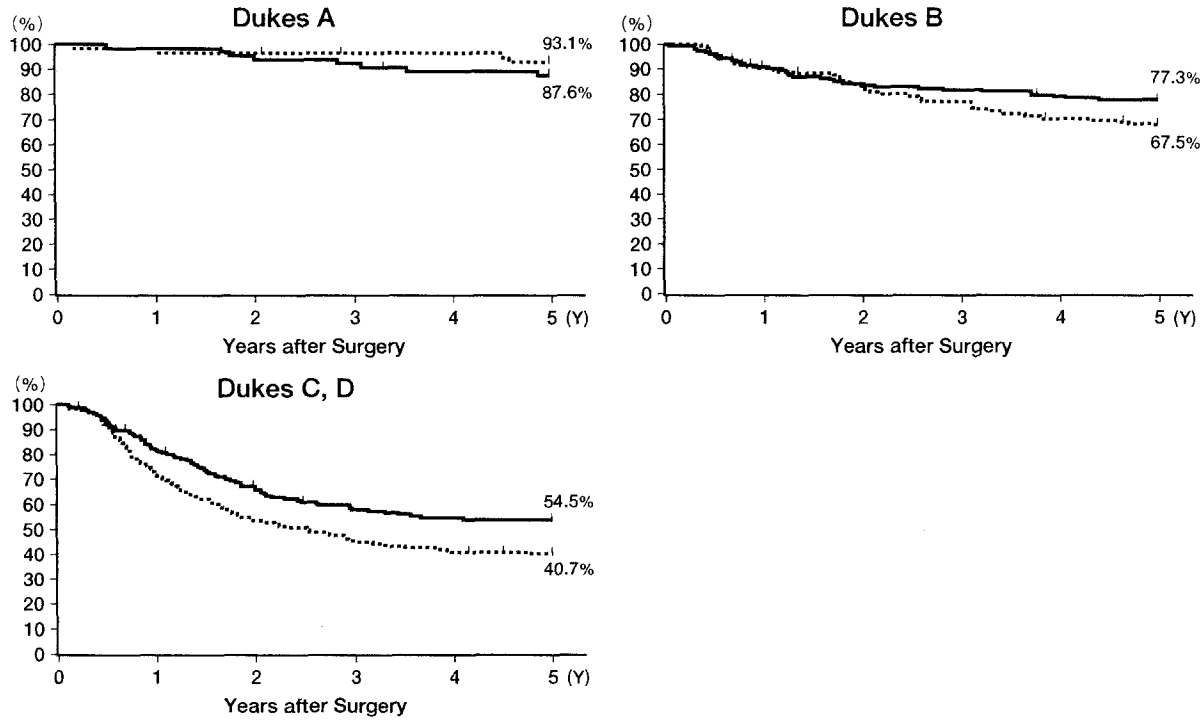

Fig. 5. Disease-free survival curves for patients with Dukes' A (—MMC/UFT; n = 65; ····control; n = 59; P = 0.312, logrank test) Dukes' B (—MMC/UFT; n = 154; ····control; n = 162; P = 0.080, logrank test) and Dukes' C, D cancer (—MMC/UFT; n = 177; ····control; n = 177; P = 0.007, logrank test)

Table 5. Cumulative 5-year recurrence rates according to first site of failure following resection

Site		MMC/UFT	Control	Logrank test
Local	Overall	11.6% (n = 396)	19.0% (n = 398)	P = 0.007
	Dukes' C	16.8% (n = 174)	33.5% (n = 175)	P = 0.001
Liver	Overall	12.5% (n = 396)	15.7% (n = 398)	P = 0.246
	Dukes' C	21.3% (n = 174)	22.4% (n = 175)	P = 0.710
Lung	Overall	9.3% (n = 396)	12.1% (n = 398)	P = 0.246
	Dukes' C	13.1% (n = 174)	23.5% (n = 175)	P = 0.036

tion therapy of radiation and 5-FU + semustine by the Gastrointestinal Tumor Study Group (GITSG) in reports published up to the time this study began.[9–11]

In the randomized controlled trial conducted by the Japanese Colorectal Cancer Chemotherapy Study Group mentioned above, survival and DFS in patients with rectal cancer were found to be significantly superior in the group receiving MMC + 5-FU (p.o.) compared with the group undergoing surgery alone, a result indicating the usefulness of adjuvant chemotherapy.[4] The Cooperative Study of Surgical Adjuvant Chemotherapy for Colorectal Cancer also evaluated the significance of MMC + tegafur in patients with rectal cancer. Although the overall survival rate was not improved in the treatment group compared with the group undergoing surgery alone, a significant recurrence-suppressing effect was obtained for patients with Dukes' C in the treatment group ($P = 0.048$).[3]

In this present study, patients with rectal cancer that was macroscopically Dukes' B and C and who had undergone curative resection, were randomly allocated to an MMC/UFT group and a control group (surgery alone) and no difference was observed in overall survival. However, DFS was significantly better in the MMC/UFT group and the recurrence-suppressing effect of this treatment was remarkable, especially in patients at advanced stages.

The patterns of rectal cancer recurrence were mainly local and liver and lung metastatic recurrence. Surgical treatment was performed in patients with recurrence for whom radical resection was indicated. The reported 5-year survival rates after surgery for recurrence have ranged from approximately 30% to 40%,[12–15] that is, favorable results. These findings suggest that the therapy after recurrence contributed to prolonging life, with no significant difference in the survival rate between control and treatment groups in present study. Considering the pain that patients suffer and the urogenital disorders caused by local recurrence, and the dysfunction associated with combined resection, the results of this study, i.e., the longer disease-free survival period for the treatment group, are considered significant from the viewpoint of quality of life.

The regimen used in this study included the sprinkling of MMC on the operating field during surgery to prevent implantation of cancer cells in the operating field. Although the local recurrence rate was suppressed in the treatment group, the effects of this local treatment itself, that is, the sprinkling of MMC into the operating field, have not been clarified.

Reductions in the WBC and platelet counts, and in the hemoglobin level, were observed as adverse effects of intermittent intravenous injections of MMC plus oral administration of UFT. In addition, anorexia, nausea, and vomiting were more frequent than in the control group. However, no severe adverse effects were observed. It is considered that this regimen is sufficiently tolerable for patients to receive ambulatory treatment.

Recently, the use of a higher daily dose of UFT has been investigated to enhance its antitumor effects. A daily dose of UFT, determined at 600 mg per body (400 mg/m^2) is administered for 5 consecutive days, followed by 2 drug-free days (weekly-5 method), to maintain administration compliance. In patients with advanced colorectal cancer and no previous treatment, UFT was administered according to the weekly-5 method, in combination with intermittent intravenous injection of MMC, at a dose of 6 mg/m^2 once every 2 weeks, and a response rate of 38.5% (5/13) was achieved; the incidence of digestive toxicity was 8%.[16] Thus, it will be necessary to investigate the use of this therapeutic method as postoperative adjuvant chemotherapy in the future.

At present, under the auspices of the Ministry of Health and Welfare of Japan, the National Surgical Adjuvant Study of Colorectal Cancer is conducting a randomized controlled study comparing a group receiving surgery alone and a treatment group receiving postoperative UFT alone (400 mg/m^2 per day, weekly-5 method, for 1 year) in patients with Dukes' C colon cancer and rectal cancer, in order to evaluate the significance of UFT therapy alone as adjuvant therapy.

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