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ORIGINAL ARTICLE

Final results of randomized trials by the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC)

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Abstract
Objective In the latter 1990s, adjuvant chemotherapy for completely resected Stage III colorectal cancer remained controversial in Japan. We conducted two independent randomized controlled trials in patients with Stage III colon and rectal cancer.

Methods Patients were randomly assigned to receive surgery alone or surgery followed by treatment with UFT (400 mg/m^2/day), given for five consecutive days per week for 1 year. The primary endpoint was relapse-free survival (RFS), and the secondary endpoint was overall survival (OS).

Results A total of 334 patients with colon cancer and 276 with rectal cancer were enrolled. The patients' characteristics were similar between the UFT group and the Surgery-alone group. There was no significant difference in RFS or OS in colon cancer. In rectal cancer, however, RFS and OS were significantly better in the UFT group than in the Surgery-alone group. The only grade 4 toxicity in the UFT group was diarrhea, occurring in one patient with colon cancer and one patient with rectal cancer.

Conclusions Postoperative adjuvant chemotherapy with UFT is successfully tolerated and improves RFS and OS in patients with Stage III rectal cancer. In colon cancer, the expected benefits were not obtained (hazard ratio = 0.89).

Keywords Stage III colon cancer · Stage III rectal cancer · UFT · Surgery alone · Randomized controlled trial

The Members of the National Surgical Adjuvant Study of Colorectal Cancer are listed in "Appendix".

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Introduction

In Japan, the westernization of lifestyles has become associated with an annual increase in the incidence of colorectal cancer. In 2006, a total of 41,097 persons died of colorectal cancer, accounting for 12.6% of all deaths from malignant tumors. In 2004, 100,137 patients were diagnosed with colorectal cancer (17.6% of all patients with cancer). Colorectal cancer is forecast to become the most prevalent type by 2015, surpassing gastric cancer and lung

cancer [1]. In Europe and North America, colorectal cancer is the second leading cause of death from cancer [2]. Globally, the prevention, early diagnosis, and development of improved treatments for colorectal cancer are thus very important tasks.

In Europe and North America, 40–50% of patients with colorectal cancer who undergo surgery alone die of metastasis or recurrence. In patients with Stage III colon cancer, postoperative adjuvant chemotherapy with fluorouracil (FU) and levamisole (LEV) can cut mortality by 33% [3]. The 1990 National Institutes of Health Consensus Conference thus recommended a combination of FU and LEV (FULEV) as standard adjuvant therapy for Stage III colon cancer. In addition, radiotherapy combined with chemotherapy was recommended as a standard adjuvant therapy for rectal cancer [4]. Subsequent studies reported that FU plus leucovorin (LV) is superior to FU plus LEV for the adjuvant therapy of colon cancer [5]. In the late 1990s, FU plus LV (FULV) was positioned as standard adjuvant therapy for Stage III colon cancer.

In Japan, clinical trials of postoperative adjuvant chemotherapy have focused mainly on oral fluoropyrimidine-based regimens in both colon and rectal cancer. Although meta-analyses suggest that oral FU derivatives were effective [6, 7], standard adjuvant regimens were not established for either colon or rectal cancer until the early 2000s. Preoperative or postoperative radiation was considered unnecessary, since lateral nodal dissection is the standard procedure in Japan. Furthermore, FULV, regarded as more effective than FU alone in Western countries, was not available in Japan until 1999; however, in one comparative study of FU alone and FULV in advanced cancer, there was a difference in overall response rate, but the difference in overall survival was not significant [8]. This prompted us to perform a randomized, controlled study, the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC), to examine whether postoperative adjuvant chemotherapy with uracil–tegafur (UFT) alone is useful for the treatment of Stage III colon and rectal cancer. Phase II studies found that UFT, which is widely used in Japan, is effective for the management of advanced cancers of the stomach, colon, rectum, breast, and other organs [9]. UFT monotherapy was used because LV was not available in Japan at the time of planning this study.

Methods

The present study was designed to examine the usefulness of postoperative adjuvant chemotherapy with UFT in patients with curatively resected Stage III colon or rectal cancer. The protocol was approved by the institutional review board at each participating center.

Patients and study design

The eligibility criteria in the study were as follows: (1) histologically confirmed adenocarcinoma; (2) curatively resected (R0 surgery) Stage III (any T, n1 or n2, M0) colon cancer and rectal cancer; (3) a performance status of 0–2 on the Eastern Cooperative Oncology Group scale; (4) an age of 20–75 years; (5) adequate function of main organs (white-cell count $\geq$ 4,000/mm^3, platelet count $\geq$ 100,000/mm^3, aspartate aminotransferase and alanine aminotransferase levels within twice the normal upper limit, serum total bilirubin level $\leq$ 1.2 mg/dL, blood urea nitrogen level $\leq$ 25 mg/dL, serum creatinine concentration $\leq$ 1.5 mg/dL, normal electrocardiogram), and (6) written informed consent obtained from the patient.

Patients who met the eligibility criteria were enrolled at the NSAS data center by telephone or fax within 6 weeks of after surgery and were randomly assigned to receive adjuvant chemotherapy with UFT (the UFT group) or surgery alone (Surgery-alone group) according to whether they had been diagnosed with colon cancer or rectal cancer. This was a non-blind study, and treatment was assigned by the minimization technique. Adjustment factors were T stage (T1/T2 vs. T3/T4) and N stage (n1 vs. n2/n3). In rectal cancer, the tumor site (upper vs. lower) was also used as an adjustment factor. Zelen's adjustment [10] was performed to balance the number of patients assigned to each treatment group according to center. Colon cancer, rectal cancer, and N stage were classified according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (5th edition, 1994) [11]. Cancers arising from the rectosigmoid were classified as rectal cancer (see the footnote to Table 1).

The primary endpoint was relapse-free survival (RFS), and the secondary endpoint was overall survival (OS). Both endpoints were evaluated separately for colon cancer and rectal cancer.

Treatment plan

In advanced recurrent colorectal cancer, UFT 400 mg/m^2/day in two divided doses is the recommended dosage according to Japanese Phase I/II study [12]. Therefore, we judged that UFT at 400 mg/m^2/day would be an optimum dosage for postoperative chemotherapy for colorectal cancer. UFT at 600 mg/day has been approved as the upper daily dosage limit in Japan, so we did not wish to use dosages at or above this limit. Although UFT has been given two or three times daily, we considered that the twice-daily dosage would be superior in terms of compliance. A 1-year treatment was chosen in reference to previous Japanese studies of oral FU [6, 7, 13]. In the UFT group, UFT (tegafur, 400 mg/m^2/day; 600 mg/day in patients with a body surface area of $\geq$1.25 m^2

Table 1 Patient characteristics

	Colon		Rectum	
	UFT ($n = 168$)	Surgery alone ($n = 164$)	UFT ($n = 139$)	Surgery alone ($n = 135$)
Sex				
Male	91	98	83	82
Female	77	66	56	53
Age				
Years, median (range)	62 (30–75)	61 (35–75)	59 (32–75)	58 (30–75)
Tumor location				
Right colon	73	72	–	–
Left colon	95	92	–	–
Upper rectum	–	–	82	82
(Rs)[a]			(43)	(39)
(Ra)[a]			(39)	(43)
Lower rectum	–	–	57	53
(Rb)[a]			(55)	(51)
(P)[a]			(2)	(2)
Depth of tumor invasion (T stage)				
T1	11	10	8	11
T2	13	14	21	16
T3	102	95	94	90
T4	42	45	16	18
Extent of positive lymph nodes (N stage: Japanese classification)[b]				
n1	138	133	110	105
n2	25	25	26	25
n3	5	6	3	5
No. of positive lymph nodes				
1–3	134	125	99	98
4-	34	39	40	37

n0 no lymph node metastasis, *n1* metastasis to group 1 lymph nodes, *n2* metastasis to group 2 lymph nodes, *n3* metastasis to group 3 lymph nodes, *n4* metastasis to group 4 lymph nodes

[a] The rectosigmoid surgically is classified as "Rs," which is defined as the bowel at the level between the promontorium and the lower margin of the second sacral vertebra. The border between "Ra" and "Rb" is defined as the bowel at the level of the peritoneal reflection, which corresponds approximately to the level of the middle Houston valve (Kohlrausch valve). The proctos ("P"), the anal canal, is defined as the portion between the upper edge of the puborectal muscle and anal verge

[b] Lymph nodes are grouped according to the independent lymphatic spread (groups 1–4). In the colon, two modes of lymphatic drainage are present: lymphatic drainage along to the intestine (paraintestinal drainage) and toward the mesenteric main lymph node (mesenteric drainage). In the rectum, three modes of lymphatic drainage are present: lymphatic drainage along to the intestine, toward the mesenteric main lymph node, and toward the pelvic wall (lateral drainage)

and 500 mg/day in those with a body surface area of <1.25 m^2) was given orally twice daily on weekdays (5 days per week) for 1 year, starting within 6 weeks after surgery.

Adverse events were graded according to the criteria of the Japan Clinical Oncology Group (JCOG) [14] as follows: grade 1, mild; grade 2, moderate; grade 3, severe; and grade 4, life-threatening. In the UFT group, the dose of UFT was decreased to 250 mg/m^2/day (400 mg/day in patients with a body surface area of ≥ 1.25 m^2 and to 300 mg/day in those with a body surface area of <1.25 m^2) if grade 2 or higher adverse events occurred during treatment. In Japan in the 1990s, surgeons were responsible for chemotherapy. Therefore, the dosage was reduced upon the occurrence of grade 2 toxicity, as safety was of the utmost importance.

Treatment was discontinued if the attending physician ruled out the continuation of treatment with UFT due to complications or adverse events, or if recurrence was confirmed.

In the Surgery-alone group, anticancer therapy was withheld until the confirmation of recurrence during follow-up.

Follow-up

All patients underwent blood cell count, serum chemical tests, urinalysis, CEA and CA 19-9 as tumor marker tests, chest radiography, and abdominal ultrasonography or computed tomography at 4-month intervals during the first 2 years and at 6-month intervals thereafter. Patients with rectal cancer additionally underwent computed tomography of the pelvis at 6-month intervals. In the UFT group, blood cell count, serum chemical tests, and urinalysis were performed every month during treatment.

Diagnosis of recurrence was based on the results of imaging studies. Cytologic or histologic examinations were performed if necessary. Elevated levels of CEA alone were not regarded as adequate evidence of recurrence. If the CEA was elevated, we checked for signs or symptoms suggestive of tumor recurrence and considered using further imaging studies (i.e., CT scan, MRI, and/or bone scintigram) as needed.

Case report forms for individual patients were submitted to the independent NSAS data center at 6-month intervals during the first 5 years and at yearly intervals thereafter. All events related to the study endpoints, such as recurrence, were evaluated by the Evaluation Committee; treatment assignments were masked at the time of evaluation.

Statistical analysis

There was a wide range in the results that were used as the basis for calculating the target number of subjects; therefore, it was difficult to identify the exact number of cases needed. We set the number in consideration of feasibility. We chose a sample size that would ensure at least 70% detection power even in the most disadvantageous case.

The method of Schoenfeld and Richer was used to estimate sample size. It was assumed that the RFS at 5 years in the Surgery-alone group would be 60–75% for colon cancer and 50–65% for rectal cancer, the enrollment period 2 years, and follow-up period after enrollment 5 years. We then estimated that samples of 390–624 patients with colon cancer and of 312–446 patients with rectal cancer would be required to show a significant difference in endpoints between the groups with an alpha level of 0.05 (one-sided), a statistical power of 80% ($\beta = 0.2$), and a hazard ratio of 0.67 (hazard decreased to 2/3 after treatment with UFT). In the present study, the target number of patients was, therefore, set at 500 for colon cancer and 400 for rectal cancer.

An interim analysis was planned 2 years after completion of enrollment. Early termination would be considered at the time of the interim analysis if the one-sided P value of log-rank test for primary endpoint fell below 0.005, according to the Lan and DeMets spending function method.

For RFS, either recurrence or death, whichever occurred earlier, was defined as an event. The survival time was defined as the period from the date of surgery until the date of an event. OS was defined as the period from the date of surgery to the date of death. All deaths, including deaths from other causes, were regarded as events. Data on patients showing event-free survival were censored at the time of the last follow-up visit. Survival was estimated using the Kaplan–Meier method. The log-rank test was used to compare differences in survival. Hazard ratios were calculated using Cox proportional hazards models. All P values were two sided.

Statistical analysis was performed by statistical analysts and the NSAS data center. All analyses were done using the Statistical Analysis System (SAS, version 8, SAS Institute Inc., Cary, NC, USA).

Results

Accrual and interim analysis

From October 1996 through April 2001, we enrolled 334 patients with colon cancer and 276 with rectal cancer. Although the numbers of enrolled patients fell short of the initially set goals, the enrollment period was not prolonged, since about 5 years has elapsed since the start of the study, and it was judged that the effectiveness of postoperative adjuvant chemotherapy could be evaluated by a meta-analysis with other studies.

An interim analysis was performed in 2003. Data and safety were assessed by an independent data monitoring committee (IDMC). The IDMC recommended publishing the results of the analysis, since the criteria for early termination had been met for rectal cancer and their effectiveness confirmed. On the basis of this recommendation, the results of the interim analysis for rectal cancer were published (median follow-up period, 3.0 years) [15].

The results of the present analysis are based on follow-up data received as of March 2006, 5 years after the completion of enrollment (median follow-up period, 6.2 years).

Patients' characteristics

Four registered patients were confirmed not to meet the eligibility criteria after enrollment (registration before

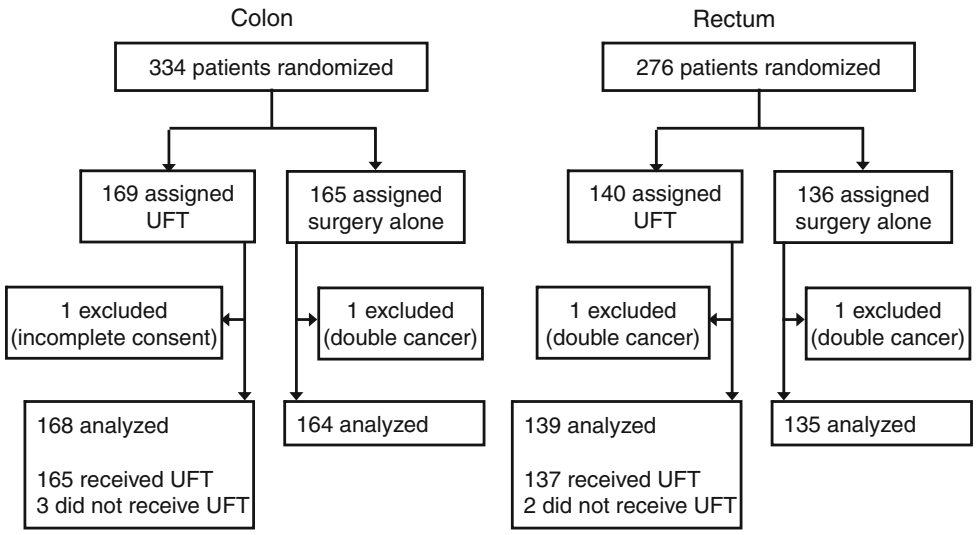

Fig. 1 CONSORT diagram

Table 2 Adverse events: grade 3/4

	Colon		Rectum	
Any events (grade 3/4)	UFT 19.4%/0.6%	Surgery alone 3.1%/0%	UFT 15.3%/0.7%	Surgery alone 2.2%/0.7%
Leukocytes	0%/0%	0%/0%	0%/0%	0%/0%
Neutrophils	2.6%/0%	0%/0%	0%/0%	0%/0%
Hemoglobin	0.6%/–	1.3%/–	0%/–	0%/–
Platelets	0%/0%	0%/0%	0%/0%	0%/0%
AST	2.5%/0%	0.6%/0%	2.2%/0%	0%/0%
ALT	3.1%/0%	0.6%/0%	2.2%/0%	0.8%/0%
Total bilirubin[a]	8.1%/0%	0%/0%	9.0%/0%	0.8%/0%
Anorexia	2.4%/–	0.6%/–	1.5%/–	0.7%/–
Nausea/vomiting	0.6%/–	0%/–	0.7%/–	0.7%/–
Diarrhea	0.6%/0.6%	0.6%/0%	0.7%/0.7%	0%/0.7%
Stomatitis	1.2%/0%	0%/0%	0%/0%	0%/0%
Rash	0.6%/0%	0%/0%	1.5%/0%	0%/0%
Fatigue	1.2%/0%	0%/0%	0.7%/0%	0%/0%

Japan clinical oncology group (JCOG) criteria

[a] Grade 3: $> 2 \times$ ULN (upper limit of normal)

obtaining informed consent, a history of breast cancer, synchronous esophageal cancer, and synchronous bladder cancer in one patient each). These patients were judged ineligible and excluded from the analysis. Data on 332 patients with colon cancer (UFT group, 168; Surgery-alone group, 164) and 274 with rectal cancer (UFT group, 139; Surgery-alone group, 135) were analyzed (Fig. 1).

The clinical characteristics of the patients, surgical procedures, and pathological findings were well balanced between the treatment groups (Table 1).

Adverse events and compliance

Adverse events were assessed according to the JCOG criteria [14]. In both the colon cancer and rectal cancer patients, the incidence of grade 3 or more severe adverse events was higher in the UFT group. However, grade 4 adverse events occurred in only one patient with colon cancer in the UFT group, one patient with rectal cancer in the UFT group, and one patient with rectal cancer in the Surgery-alone group (Table 2). There were no treatment-related or other deaths within 60 days of completion of treatment.

In the UFT group, the main reasons for treatment withdrawal were recurrence (16 patients), adverse events (17 patients), and refusal of the patient to continue treatment due to adverse events (16 patients) in patients with colon cancer; and recurrence (18 patients), adverse events (9 patients), and refusal of the patient to continue treatment because of adverse events (10 patients) in patients with rectal cancer. After excluding patients who discontinued treatment because of recurrence, the rate of treatment

completion was 72% in patients with colon cancer and 80% in those with rectal cancer. The median initial daily dose of UFT was 397 mg/m^2/day in patients with colon cancer and 395 mg/m^2/day in those with rectal cancer.

Relapse-free survival

At the time of the last follow-up, 49 patients with colon cancer in the UFT group, 51 with colon cancer in the Surgery-alone group, 46 with rectal cancer in the UFT group, and 59 with rectal cancer in the Surgery-alone group suffered recurrence or died. In patients with colon cancer, the 5-year RFS was 71.3% in the UFT group (95% confidence interval, 64.3–78.2%) and 69.6% in the Surgery-alone group (95% confidence interval, 62.4–76.7%). The hazard ratio for the UFT group, when compared with the Surgery-alone group, was 0.89 (95% confidence interval, 0.60–1.32), with no significant differences between the groups ($P = 0.56$). In patients with rectal cancer, the 5-year RFS was 68.9% in the UFT group (95% confidence interval, 61.1–76.8%) and 56.3% in the Surgery-alone group (95% confidence interval, 47.9–64.8%). The hazard ratio for the UFT group when compared with the Surgery-alone group was 0.66 (95% confidence interval, 0.45–0.97). The RFS was significantly better in the UFT group ($P = 0.033$; Fig. 2).

Overall survival

Overall, 36 patients with colon cancer in the UFT group, 42 with colon cancer in the Surgery-alone group, 29 with rectal cancer in the UFT group, and 43 with rectal cancer in the Surgery-alone group died. In patients with colon cancer, the 5-year overall survival (OS) was 81.3% in the UFT group (95% confidence interval, 75.4–87.3%) and 76.7% in the Surgery-alone group (95% confidence interval, 70.2–83.2%). The hazard ratio for the UFT group, when compared with the Surgery-alone group, was 0.82 (95% confidence interval, 0.53–1.29), with no significant difference between the groups ($P = 0.39$). In patients with rectal cancer, the 5-year OS was 85.3% in the UFT group (95% confidence interval, 79.4–91.3%) and 72.1% in the Surgery-alone group (95% confidence interval, 64.4–79.7%). The hazard ratio for the UFT group when compared with the Surgery-alone group was 0.60 (95% confidence interval, 0.38–0.97). OS was significantly better in the UFT group ($P = 0.034$; Fig. 3).

Patterns of relapse

As of the last follow-up, recurrence was diagnosed in 45 (26.8%) patients with colon cancer in the UFT group, 47 (28.7%) with colon cancer in the Surgery-alone group, 41 (29.5%) with rectal cancer in the UFT group, and 57 (42.2%) with rectal cancer in the Surgery-alone group. Analysis of patterns of relapse indicated that the rate of distant metastasis in patients with rectal cancer was lower in the UFT group (Table 3).

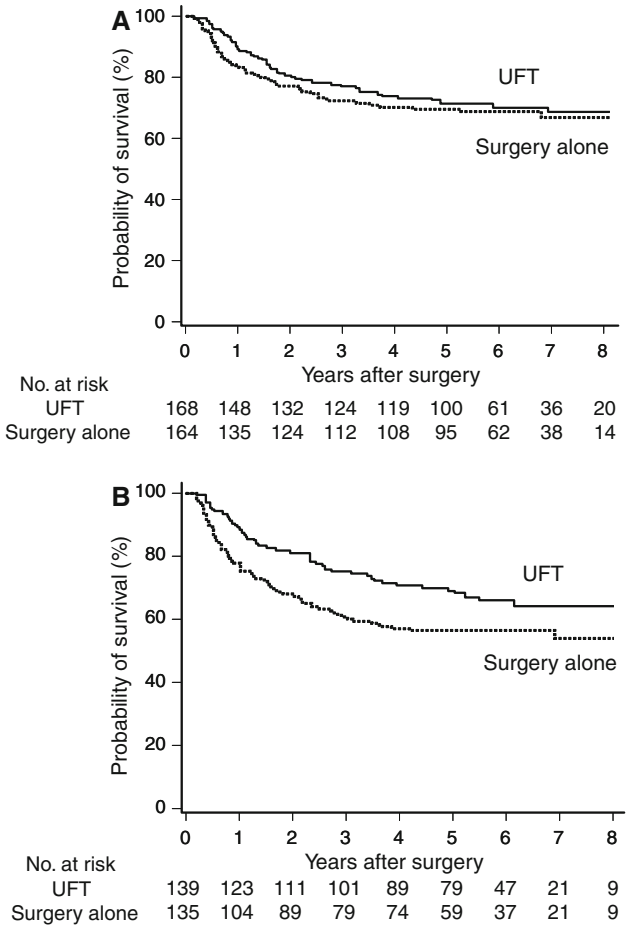

Fig. 2 Kaplan–Meier estimates of relapse-free survival by treatment, **a** colon cancer, **b** rectal cancer

Ancillary analysis

In the present study, we classified patients according to whether they had colon cancer or rectal cancer as defined by the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (5th edition, 1994) [11]. Cancers developing in the rectosigmoid were classified as rectal cancer. In Europe and North America, cancers arising from the rectosigmoid are usually included in clinical studies of postoperative adjuvant chemotherapy for colon cancer. Some studies have also included tumors with their lower margins located above the peritoneal reflection. To facilitate a comparison of our results with those of Western studies, we calculated RFS and OS for patients with colon cancer plus those with tumors arising

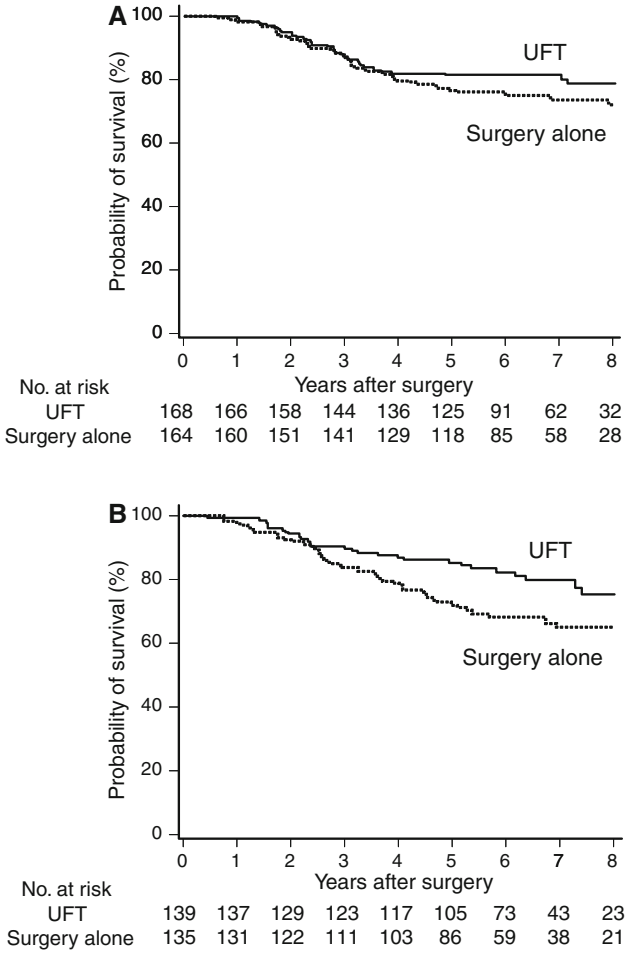

Fig. 3 Kaplan–Meier estimates of overall survival by treatment, **a** colon cancer, **b** rectal cancer

Table 3 Pattern of first relapse

	Colon		Rectum	
	UFT ($n = 168$)	Surgery alone ($n = 164$)	UFT ($n = 139$)	Surgery alone ($n = 135$)
Number of relapses	45	47	41	57
Local	1	1	9	11
Distant	44	44	30	42
Local and distant	0	2	2	4

from the rectosigmoid and for patients with colon cancer plus those with tumors located above the peritoneal reflection (upper rectal cancer). In patients with colon cancer plus those with rectosigmoid cancer, the 5-year RFS and OS were 74.2 and 85.1% in the UFT group and 67.4 and 76.2% in the Surgery-alone group, respectively. The hazard ratio was 0.73 (95% confidence interval, 0.51–1.04) in RFS and 0.69 (95% confidence interval, 0.46–1.05) in OS. In patients with colon cancer plus those with upper rectal cancer, the 5-year RFS and OS were 73.7 and 85.3% in the UFT group and 67.2 and 77.4% in the Surgery-alone group, respectively. The hazard ratio was 0.74 (95% confidence interval, 0.54–1.02) in RFS and 0.67 (95% confidence interval, 0.46–0.98) in OS. When cancers arising from the rectosigmoid or the upper rectum were included in the analysis, the difference in response between the treatment groups thus tended to increase.

Discussion

The regimen for UFT alone was either 2 years of treatment with continuous administration of 400 mg/m^2/day [16] or 1 year of treatment with 400 mg/m^2/day for 5 days followed by a 2-day washout (the present study and [13]). The latter has been more widely adopted in Japan because of superior compliance. The regimen for UFT + LV was five courses of 6 months of treatment consisting of UFT 300 mg/m^2/day for 28 days plus a 7-day washout. Improvement in efficacy was achieved with concurrent use of LV. When this study was carried out, LV tablets could not be used as they had not been approved in Japan; therefore, we used UFT alone.

In our study, RFS and OS did not differ significantly between the treatment groups in patients with colon cancer but were significantly better in the adjuvant chemotherapy group in patients with rectal cancer. These findings were consistent with the results obtained by the Tokai Adjuvant Chemotherapy Study Group for Colorectal Cancer [16], which also evaluated postoperative adjuvant chemotherapy with UFT. There were few grade 3 or higher adverse events, patient compliance was good, and chemotherapy with UFT was easily manageable.

An interim analysis showed that postoperative adjuvant chemotherapy with UFT was effective in patients with rectal cancer [15]. This finding was confirmed in the final analysis. In Japan, mesorectal excision with partial lateral lymph node dissection is performed as standard surgery; however, radiotherapy, considered a standard procedure in Europe and North America, has not been performed aggressively. Some studies have reported that preoperative radiotherapy (combined with chemotherapy) improves outcomes in patients with locally progressive disease [17]. Further studies of adjuvant chemoradiotherapy may thus be required to improve treatment outcomes in patients with locally advanced rectal cancer.

In patients with colon cancer, postoperative adjuvant chemotherapy with UFT was not confirmed to be effective, in contrast to the results obtained in patients with rectal cancer. This outcome may be due to the fact that only 334

of the initially scheduled 500 patients were enrolled and that the 5-year RFS in the Surgery-alone group was higher in patients with colon cancer (about 70%) than in those with rectal cancer. The study may, therefore, have been not sensitive enough to detect the effect of UFT in patients with colon cancer. Studies performed in Europe and North America in the 1980s have shown that adjuvant chemotherapy with methyl-CCNU, vincristine and FU (MOF), FULEV, or FULV was more effective than surgery alone in patients with colon cancer [3, 18–21]. Subsequent controlled studies comparing MOF with FULV [22] and FULEV with FULV [5] showed that DFS was significantly better with FULV. Combined chemotherapy with FULV was established as standard treatment for Stage III colon cancer in the latter half of the 1990s. More recently, controlled clinical trials comparing FULV with FULV with oxaliplatin (OX) (MOSAIC, NSABP C-07) in patients with Stage II/III colon cancer demonstrated that DFS was significantly better in the FULV plus OX group [23, 24]. At present, regimens combining FULV with OX with molecular targeted agents (bevacizumab, cetuximab) are being evaluated. FULV has also been compared with oral fluoropyrimidines (capecitabine, UFT and LV), and these treatments have been found to be equivalent in terms of efficacy [25, 26]. Oral fluoropyrimidines are now regarded as an alternative treatment to FULV. With respect to survival benefit, the adoption in Japan of FULV with OX regimens confirmed to be effective by clinical trials performed in Europe and North America, appears to be warranted.

Comparison of the results of Japanese clinical studies with those of studies performed in Europe and North America must take into account differences in surgical procedures and outcomes. Although direct comparisons are not feasible, the outcomes (RFS [DFS]) of patients with colon cancer in the Surgery-alone group of our study were superior to those of patients with Stage III colon cancer who received FULV and comparable to those in patients who received FULV with OX in the MOSAIC and NSABP C-07 studies [27]. We considered there seem to be two factors why the difference of the outcome between the western population and our results is [28]. The first is a difference in the standard nodal dissection procedures used in Japan and in the West. In Japan, D2 or D3 nodal dissection is conducted by dividing the dissection procedure into three parts (D1, D2, and D3) along the main surgical trunk artery root. In Western countries, dissection of the main trunk artery root is not performed, and only dissection below the D2 level is implemented. A retrospective multicenter study analysis by the Japanese Society for Cancer of the Colon and Rectum has revealed a 5–10% incidence of nodal metastasis in the region in which the dissection procedure differs between Japan and the West [29]. This difference in the dissection procedure may have caused the difference in surgical results.

The other factor was a substantial difference in the handling of surgical specimens. In Japan, the median number of lymph nodes examined was 17, and the number examined was less than 12 in 32% of surgical cases. According to the American SEER report, the median number of lymph nodes examined was nine, and the number examined was less than 12 in 63% of surgical cases [30]. Thus, a substantial difference in treatment results was likely to have been caused by "stage migration".

The Japanese Clinical Oncology Group (JCOG) is conducting a comparative study of the safety and efficacy of adjuvant oral fluoropyrimidines (UFT and LV) with FULV in patients with Stage III colon cancer (including tumors located in the upper rectum) [31]. Recruitment of 1,101 patients is complete. An interim analysis has demonstrated a 3-year DFS (FU+LV or UFT+LV) of about 75% [32]. Combination therapy of FULV with OX should also be critically evaluated, not only for survival benefit but also for adverse effects and economic factors.

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Conflict of interest statement None declared.

Appendix

Members of the National Surgical Adjuvant Study of Colorectal Cancer

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