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Real impact of oxaliplatin in adjuvant chemotherapy for patients with stage III colon cancer based on the Multi-Institutional Registry of Large Bowel Cancer in Japan

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Abstract: Although fluoropyrimidine plus oxaliplatin is the standard of care for stage III colon cancer, fluoropyrimidine alone is also recommended for stage III patients in Japanese and other practice guidelines. We assessed efficacy of adjuvant fluoropyrimidine with or without oxaliplatin across a population of patients with stage III colon cancer in the Multi-Institutional Registry of Large Bowel Cancer in Japan. From the registry, we analyzed 6,834 stage III colorectal cancer patients. Approximately 70% of colorectal cancer patients received some form of chemotherapy. Of these, we analyzed those who received adjuvant chemotherapy between 2008 and 2011. Based on the TNM classification, the 5-year overall survival rates of colon and rectal cancer after the covariate adjustment by regimens of adjuvant chemotherapy were 95.7% with fluoropyrimidines and 90.6% with oxaliplatin-combined therapy at stage IIIA (Stratified log-rank $P < 0.001$), 86.5% and 80.8% at stage IIIB ($P < 0.001$), and 72.1% and 70.7% at stage IIIC ($P < 0.001$), respectively. Oxaliplatin did not enhance efficacy with regard to relapse-free survival as well as overall survival. Adjuvant fluoropyrimidine monotherapy and fluoropyrimidine plus oxaliplatin show comparable efficacy benefits for the treatment of stage III of Japanese colon cancer patients. This supports the use of fluoropyrimidine alone as a standard option for this patient group in Japan.

***Keywords*:** real-world data, colorectal cancer, oxaliplatin, guideline, postoperative chemotherapy

Introduction

Colorectal cancer is the second leading cause of cancer-related deaths worldwide (*1*). In Japan, there were 152,254 cases of newly diagnosed colorectal cancer in 2018, and 51,788 people died from colorectal cancer in 2020 in Japan (*2*). Postoperative adjuvant chemotherapy is given with the aim of killing any residual cancer cells to improve prognosis for cases in which R0 resection with curative intent was performed. Fluoropyrimidines and their biochemical modulation by leucovorin (LV) have been key drugs that are incorporated into treatment strategies for patients with advanced colorectal cancer at stage III and high-risk stage II (*3-5*). On the basis of results from the MOSAIC and XELOXA randomized trials, infused fluorouracil and LV with oxaliplatin (FOLFOX) and capecitabine with oxaliplatin (CapeOX) are widely used as standard postoperative adjuvant chemotherapies (*6-8*). Fluoropyrimidine plus oxaliplatin is the standard of care for stage III colon cancer but fluoropyrimidine alone is also recommended for stage III patients in Japanese and other practice guidelines (*6-9*). However, prolonged peripheral neuropathy, central venous access, and cost of care are significant problems when using oxaliplatin-based therapy (*8*).

In Japan, clinical trials of postoperative adjuvant chemotherapy have focused mainly on fluoropyrimidine-based regimens in both colon and rectal cancers because of convenient oral delivery and efficacy of the drug. Tegafur–uracil, UFT, is a combination drug comprising tegafur, a prodrug of 5-fluorouracil (5-FU) and uracil, an inhibitor of the 5-FU-degrading enzyme dihydropyrimidine dehydrogenase, in a molar ratio of 1:4. Although there were no significant differences in relapse-free survival (RFS) and overall survival (OS) in colon cancer, a benefit was observed in rectal cancer when the adjuvant UFT group and the surgery alone group were compared (*10*). A significant benefit was associated with adjuvant UFT in RFS and OS in patients with *RAS* mutation; on the other hand, there were no differences in RFS or OS between the adjuvant UFT group and surgery-alone group among patients without *RAS* mutation. The *RAS* mutation was considered predictive with respect to the efficacy of adjuvant UFT chemotherapy

in patients with resected stage III colorectal cancer (*11*). The non-inferiority of UFT/LV to 5-FU/LV as adjuvant hemotherapy for stage III colorectal cancer has been verified in both the JCOG0205 and the NSABP C-06 clinical trials (*12,13*). Therefore, UFT/LV has been widely adopted in Japan as standard adjuvant chemotherapy. S-1 is an oral anticancer drug that combines tegafur, a prodrug of 5-FU, with 2 modulators. The first is gimeracil, which reversibly inhibits DPD, the primary metabolizing enzyme of 5-FU, thereby extending the duration of 5-FU levels in the blood. The second is oteracil potassium, which reduces the activity and associated toxicity of 5-FU in gastrointestinal tissue (*14*). In the ACTS-CC trial (*15-17*), S-1 was not inferior to UFT/LV for stage III disease. Furthermore, S-1 plus oxaliplatin (SOX) was not superior to UFT/LV as adjuvant chemotherapy in the ACTS-CC02 trial (*18-20*). This latter trial focused on patients with high-risk stage III colon cancer, which is defined as N2 with any T or positive nodes around the origin of the feeding arteries. S-1 did not show non-inferiority with regard to disease-free survival (DFS) for stage III colon cancer in the JCOG0910 trial; 3-year DFS rates were 82.0% and 77.9% in the capecitabine and S-1 arms, respectively (*21*).

Here, we assessed the efficacy of adjuvant fluoropyrimidine with or without oxaliplatin across a population of stage III colon cancer patients that is present in the Japanese Multi-Institutional Registry of Large Bowel Cancer.

Methods

Patients who were diagnosed with colorectal cancer between January 1, 2008 and December 31, 2011 and were registered with the Multi-Institutional Registry of Large Bowel Cancer in Japan were enrolled in this study. Eligibility required that patients had undergone surgery for stage III colorectal cancer at a facility participating in this Registry according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus (7th edition) (*22*), and UICC TNM classification (7th edition) (*23*).

Pearson's chi-square test was used to determine whether there were differences between proportions. Survival functions for OS and RFS were estimated by the Kaplan-Meier method, and confidence intervals (CI) were calculated based on the Greenwood formula. The confidence intervals of median survival time were calculated using the Brookmeyer-Crowley method. Adjusted survival functions for OS and RFS were calculated based on the conditional method (*24*). Hazard ratio (HR) and adjusted HR for OS and RFS were obtained using Cox regression models. Competing risk analysis was performed to account for the impact of death due to other diseases. Death due to other diseases was treated as a competing risk event, and adjusted sub distribution HRs were calculated using the Fine–Gray model. Possible prognostic factors (*i.e.*, age, sex, histologic type, stage, pre-serum carcinoembryonic antigen (CEA), location, and postoperative chemotherapy) were adjusted in multivariable analyses as appropriate. The cut-off value of age was due to the definition of older age in Japan, and that of CEA was the normal upper limit value. This study was approved by the certified review boards.

A two-sided *P*-value < 0.05 was considered to be significant. R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) with gtsummary packge (*25*) was used for all statistical analyses.

Results

Data from 26,552 patients with colorectal cancer at 67 hospitals in Japan were collected; 6,843 patients at stage III were analyzed in this study (Figure 1). Median follow-up was 74.9 months in the oxaliplatin combined therapy group and 74.7 months in the fluoropyrimidine monotherapy group. Fluoropyrimidines consisted of 5-FU/*l*-leucovorin (*l*-LV), capecitabine, UFT/LV, and S-1. The oxaliplatin-combined regimen was oxaliplatin plus 5-FU/*l*-LV. Others included UFT, irinotecan plus 5-FU/*l*-LV, capecitabine plus oxaliplatin, and S-1 plus oxaliplatin. Infusional 5-FU/*l*-LV/oxaliplatin combination therapy (FOLFOX) was recommended as adjuvant chemotherapy in the JSCCR guidelines 2010 (*26*) for the treatment of colorectal cancer and – consistent with the 2009 version (*27*) – FOLFOX was not reimbursed by insurance.

The 5-, 7-, and 10-year OS rates were 75.9%, 68.3%, and 62.6%, and the 3-year, 5-, 7-, and 10-year RFS rates were 68.9%, 63.0%, 58.5%, and 54.0%, respectively (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=55*). The right colon consisted of cecum, C, and ascending, A, and transverse colon, T. The left colon consisted of descending colon, D, and sigmoid colon, S. The rectum was divided into rectosigmoid, RS, rectum above the peritoneal reflection, Ra, and rectum below the peritoneal reflection, Rb, as in the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus, the 7th edition by Japanese Society for Cancer of the Colon. The 5-year OS rates in right

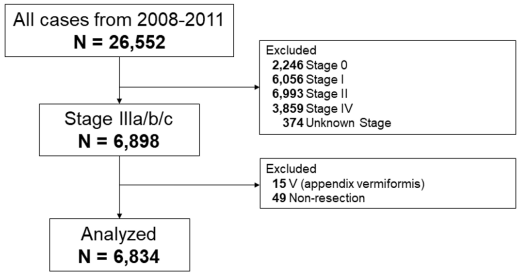


Figure 1. Flow diagram of the patient selection process.

colon (*N* = 1,892), left colon (*N* = 1,911), and rectum (*N* = 2,864) were 74.2%, 78.4%, and 76.3%, respectively (Figure 2).

Approximately 30% of colorectal cancer patients received some form of chemotherapy. The mean age of patients without adjuvant chemotherapy (73 years) was higher than that of those treated with Fluoropyrimidine monotherapy (64 years) and those treated with an oxaliplatin-combined regimen (61 years; Table 1). The proportions of death due to other disease were 30% in the no adjuvant chemotherapy group, 16% in the Fluoropyrimidine monotherapy group, and 10% in the oxaliplatin-combined regimen group (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=55*). The RFS rates in the right colon, left colon, and rectum were 66.1%, 65.8%, and 60.1%, respectively. Postoperative adjuvant chemotherapy was effective in all locations (Table 2).

The 5-year OS rates associated with colon and rectal cancer were 90.2% and 93.1% at stage IIIa, 78.2% and 78.2% at stage IIIb, 67.0% and 60.2% at stage IIIc, respectively (Figure 3). Factors associated with a significantly worse prognosis for OS were age 65 or more, male, rectal site, poorly differentiated adenocarcinoma (por)/mucinous adenocarcinoma (muc)/signet-ring cell carcinoma (sig)/others. For RFS, the factors were male, rectal site, and serum CEA level of 5 ng/mL or more at baseline in RFS (Table 3). Patients not treated with any adjuvant chemotherapy tended to be older and generally had colon cancer. T4 or N2 patients and stage IIIc patients were treated with oxaliplatin (Table 4). The 5-year OS rates associated with colon and rectal cancer after the

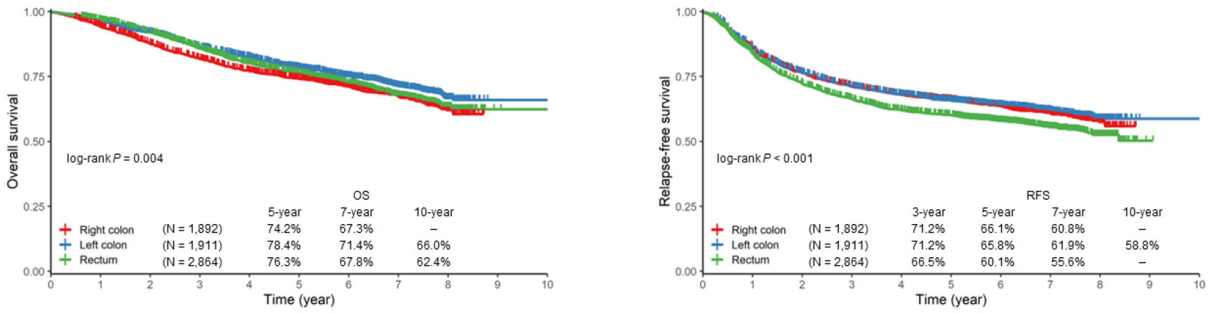


Figure 2. Overall survival (OS) and relapse-free survival (RFS) of colorectal cancer at stage III by primary lesion. Right colon; C, cecum, A, ascending, and T, transverse colon: left colon; D, descending and S, sigmoid colon: rectum; RS, rectosigmoid, Ra, rectum above the peritoneal reflection, and Rb, rectum below the peritoneal reflection.

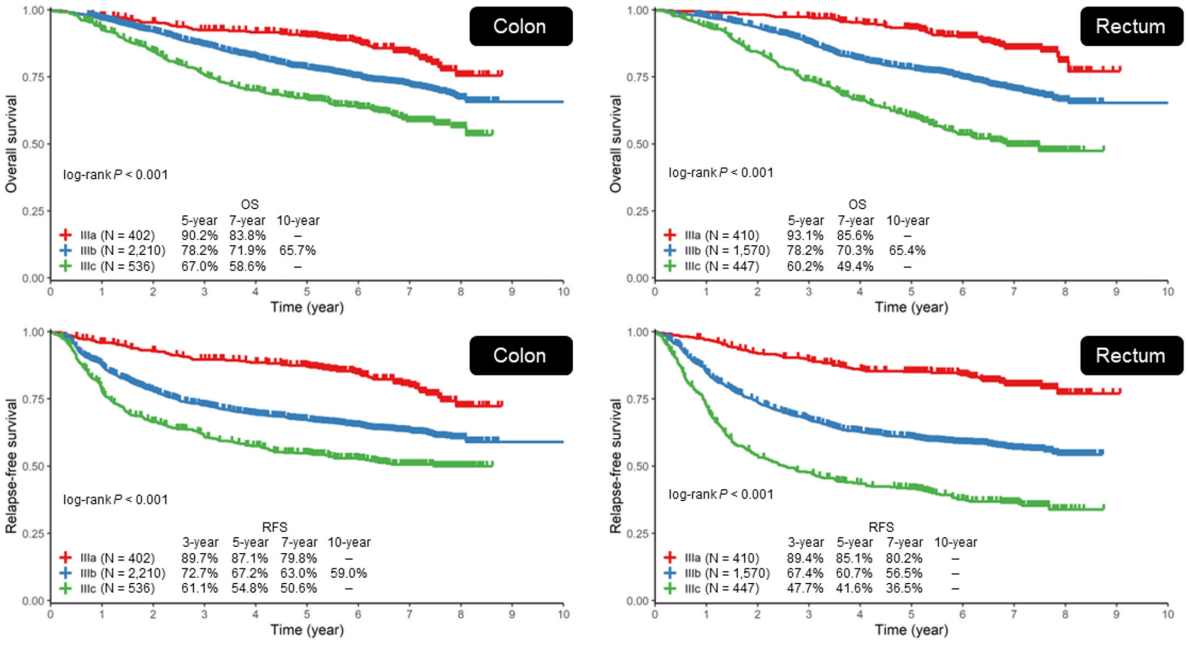


Figure 3. Overall survival (OS) and relapse-free survival (RFS) of colorectal cancer at stage III by Japanese classification. Colon; C, cecum, A, ascending, and T, transverse colon, D, descending and S, sigmoid colon: rectum; RS, rectosigmoid, Ra, rectum above the peritoneal reflection, and Rb, rectum below the peritoneal reflection.

Table 1. Patient characteristics

Variable	All, *N* = 6,834	Right colon, *N* = 1,892	Left colon, *N* = 1,911	Rectum, *N* = 2,864	Variable	All, *N* = 6,834
Sex					Right colon	
Male	3,846 (56%)	892 (47%)	1,072 (56%)	1,786 (62%)	C, cecum	468 (7.0%)
Female	2,988 (44%)	1,000 (53%)	839 (44%)	1,078 (38%)	A, ascending colon	889 (13%)
Age, mean (SD)	67 (12)	70 (11)	66 (12)	65 (12)	T, transverse colon	535 (8.0%)
Adjuvant chemotherapy					Left colon	
No adjuvant chemotherapy	1,935 (30%)	618 (35%)	556 (31%)	717 (27%)	D, descending colon	266 (4.0%)
Preoperative radiotherapy	121 (1.9%)	0 (0%)	2 (0.1%)	112 (4.2%)	S, sigmoid colon	1,645 (24%)
Postoperative radiotherapy	49 (0.8%)	5 (0.3%)	11 (0.6%)	29 (1.1%)	Rectum	
Preoperative chemotherapy	164 (2.6%)	12 (0.7%)	7 (0.4%)	135 (5.1%)	RS, rectosigmoid junction	908 (13%)
Postoperative chemotherapy	4,303 (68%)	1,139 (64%)	1,224 (68%)	1,853 (70%)	Ra, rectum above the peritoneal reflection	914 (14%)
Any adjuvant therapy	11 (0.2%)	6 (0.3%)	3 (0.2%)	1 (< 0.1%)	Rb, rectum below theperitoneal reflection	1,042 (15%)
Postoperative chemotherapy					P, proctos	60 (0.9%)
Fluoropyrimidine monotherapy	2,719 (76%)	752 (80%)	800 (79%)	1,124 (73%)	Colon/rectum	
Oxaliplatin combined therapy	514 (14%)	120 (13%)	132 (13%)	251 (16%)	Colon	3,803 (57%)
Others	329 (9.2%)	71 (7.5%)	85 (8.4%)	163 (11%)	Rectum	2,864 (43%)

N (%) or Mean (SD) are shown. Primary region was unknown in107 patients.

Table 2. The effect of adjuvant chemotherapy by location of primary colorectal cancer at stage III

Location/Treatment	*N*	OS						RFS					
		HR	95% CI	*P*-value	Adj. HR*	95% CI	*P*-value	HR	95% CI	*P*-value	Adj. HR*	95% CI	*P*-value
Colon													
No adjuvant chemotherapy	896	Reference			Reference			Reference			Reference		
Fluoropyrimidine monotherapy	1,320	0.35	0.30, 0.41	< 0.001	0.35	0.30, 0.42	< 0.001	0.49	0.42, 0.56	< 0.001	0.50	0.43, 0.58	< 0.001
Oxaliplatin combined therapy	202	0.55	0.43, 0.72	< 0.001	0.44	0.33, 0.60	< 0.001	0.78	0.63, 0.97	0.024	0.64	0.50, 0.83	< 0.001
Others	132	0.77	0.58, 1.02	0.067	0.78	0.58, 1.06	0.114	0.92	0.72, 1.19	0.533	0.98	0.75, 1.28	0.895
Right colon													
No adjuvant chemotherapy	465	Reference			Reference			Reference			Reference		
Fluoropyrimidine monotherapy	641	0.30	0.24, 0.38	< 0.001	0.30	0.24, 0.38	< 0.001	0.42	0.34, 0.52	< 0.001	0.42	0.34, 0.52	< 0.001
Oxaliplatin combined therapy	97	0.52	0.37, 0.74	< 0.001	0.41	0.27, 0.62	< 0.001	0.72	0.53, 0.98	0.034	0.63	0.44, 0.89	0.009
Others	59	0.59	0.38, 0.91	0.018	0.65	0.41, 1.04	0.071	0.71	0.48, 1.06	0.092	0.78	0.51, 1.18	0.243
Left colon													
No adjuvant chemotherapy	431	Reference			Reference			Reference			Reference		
Fluoropyrimidine monotherapy	679	0.41	0.33, 0.52	< 0.001	0.44	0.34, 0.56	< 0.001	0.57	0.47, 0.69	< 0.001	0.60	0.49, 0.74	< 0.001
Oxaliplatin combined therapy	105	0.60	0.41, 0.88	0.008	0.51	0.32, 0.81	0.004	0.85	0.63, 1.16	0.310	0.69	0.48, 1.00	0.049
Others	73	1.00	0.69, 1.45	0.995	0.95	0.63, 1.42	0.802	1.16	0.83, 1.62	0.381	1.20	0.84, 1.70	0.321
Rectum													
No adjuvant chemotherapy	635	Reference			Reference			Reference			Reference		
Fluoropyrimidine monotherapy	981	0.38	0.32, 0.45	< 0.001	0.38	0.32, 0.47	< 0.001	0.59	0.51, 0.68	< 0.001	0.58	0.49, 0.68	< 0.001
Oxaliplatin combined therapy	215	0.48	0.36, 0.63	< 0.001	0.38	0.28, 0.52	< 0.001	0.73	0.58, 0.91	0.006	0.58	0.45, 0.74	< 0.001
Others	130	0.60	0.43, 0.82	0.002	0.52	0.37, 0.74	< 0.001	0.76	0.58, 0.99	0.042	0.65	0.49, 0.87	0.004

*HRs were adjusted by age, sex, histologic type, stage, and Pre CEA. OS, overall survival; RFS, relapse-free survival.

Table 3. Multivariable analyses of patients with colorectal cancer at stage III (*N* = 2,718)

Variable	OS (univariable)			OS (Multivariable)			RFS (univariable)			RFS (Multivariable)		
	HR	95% CI	*P*-value	Adj. HR	95% CI	*P*-value	HR	95% CI	*P*-value	Adj. HR	95% CI	*P*-value
Postoperative chemotherapy												
Fluoropyrimidine monotherapy	Reference			Reference			Reference			Reference		
Oxaliplatin combined therapy	1.43	1.18, 1.73	< 0.001	1.11	0.88, 1.38	0.380	1.43	1.22, 1.67	< 0.001	1.14	0.96, 1.36	0.139
Age												
< 65	Reference			Reference			Reference			Reference		
≥ 65	1.25	1.07, 1.46	0.006	1.36	1.14, 1.62	< 0.001	0.96	0.85, 1.09	0.568	1.04	0.91, 1.18	0.611
Sex												
Male	Reference			Reference			Reference			Reference		
Female	0.86	0.74, 1.01	0.068	0.83	0.70, 0.99	0.040	0.81	0.71, 0.92	< 0.001	0.79	0.69, 0.90	< 0.001
Colon/Rectum												
Colon	Reference			Reference			Reference			Reference		
Rectum	1.09	0.93, 1.27	0.311	1.21	1.02, 1.44	0.032	1.33	1.17, 1.50	< 0.001	1.41	1.24, 1.62	< 0.001
Histologic Type												
well/mod	Reference			Reference			Reference			Reference		
por/muc/sig/others	2.00	1.63, 2.47	< 0.001	1.47	1.15, 1.88	0.002	1.51	1.26, 1.81	< 0.001	1.18	0.96, 1.45	0.110
Stage												
IIIa	Reference			Reference			Reference			Reference		
IIIb	2.30	1.65, 3.21	< 0.001	2.36	1.65, 3.38	< 0.001	2.67	2.05, 3.47	< 0.001	2.78	2.10, 3.68	< 0.001
IIIc	4.57	3.22, 6.49	< 0.001	4.45	3.03, 6.53	< 0.001	4.58	3.46, 6.06	< 0.001	4.38	3.23, 5.93	< 0.001
Pre CEA												
< 5 ng/mL	Reference			Reference			Reference			Reference		
≥ 5 ng/mL	1.43	1.13, 1.79	0.002	1.19	0.92, 1.52	0.183	1.63	1.36, 1.95	< 0.001	1.39	1.14, 1.68	< 0.001

OS, overall survival; RFS, relapse-free survival, well, well differentiated tubular adenocarcinoma; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous adenocarcinoma; sig, signet-ring cell carcinoma; pre CEA, pre-serum carcinoembryonic antigen.

covariate adjustment were 94.4% and 96.8% at stage IIIa, 86.5% and 85.7% at stage IIIb, 78.9% and 67.2% at stage IIIc by Japanese classification, respectively (Supplemental Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=55*).

The 5-year OS rates associated with colon and rectal cancer after the covariate adjustment by regimens of adjuvant chemotherapy were 95.7% with fluoropyrimidines and 96.8% with oxaliplatin-combined therapy at stage IIIA, 86.5% and 80.8% at stage IIIB, 72.1% and 70.7% at stage IIIC by the TNM classification, respectively (Figure 4). No additive effect of oxaliplatin was observed in stage III patients with any T, N1 or N2; this is consistent with results in the equivalent target population in the "MOSAIC" trial (Figure 5, Supplemental Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=55*). Fluoropyrimidine monotherapy was more effective than oxaliplatin-combined regimen in colon cancer patients with N1 (Supplemental Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=55*). Oral capecitabine imparted statistically significant benefit in OS and RFS compared with oral UFT/ LV (Figure 6).

Discussion

Adjuvant fluoropyrimidine monotherapy and fluoropyrimidine plus oxaliplatin show comparable efficacy benefits for the treatment of stage III of Japanese colon cancer patients, supporting fluoropyrimidine alone as a standard option for the adjuvant therapy of stage III cancer in Japan. Thirty percent of stage III colorectal cancer patients did not receive any adjuvant chemotherapy. We recommend that elderly patients with other concomitant diseases should not be given adjuvant chemotherapy.

In the ACTS-CC02 study, S-1 plus oxaliplatin therapy (SOX) was not superior to UFT/LV in terms of OS and disease-free survival (DFS) in patients with high-risk stage III colon cancer of any T, N2, or positive nodes around the origin of the feeding arteries (*18,20*). SOX was efficacious in patients with T4N2b disease. However, oxaliplatin-combined regimen was not superior to fluoropyrimidines in our real-world data even in the T4 population with or without N2b. The mean relative dose intensity (RDI) was 83.1% for UFT, 74.9% for S-1 and 73.6% for oxaliplatin in SOX in ACTS-CC02 (*20*). The RDI of S-1 in SOX therapy was similar to the 76.5% of RDI with S-1 monotherapy and 76.0% with UFT in ACTS-CC study, which showed the non-inferiority of S-1 to UFT/LV for stage III colon cancer (*16*). Therefore, oxaliplatin did not significantly reduce the RDI of S-1 in the SOX group. The additive effect of oxaliplatin was not shown in the unique randomized controlled trial of ACTS-CC02 in Japan.

ACHIEVE was a Japanese phase III trial that explored whether 3 months of adjuvant FOLFOX or CapeOX therapy was non-inferior to 6 months of treatment in patients with stage III colon cancer (*24-26*). The 5-year OS rates were 79.8% in the 3-months oxaliplatin-combined regimen group and 79.8% in the 6-month group in high-risk disease patients with T4 or N2 (*26*). Patients with CAPOX were significantly more likely to develop adverse events of grade 3 or more when they had a baseline creatinine clearance (CCr) less than 50 mL/

Table 4. Frequency of adjuvant chemotherapy

	Male *N* = 3,846	Female *N* = 2,988		*P*-value*	Age: ≤ 59 *N* = 1,674	Age: 60-69 *N* = 2,234	Age: 70-79 *N* = 1,973	Age: ≥ 80 *N* = 953	*P*-value*
Treatment				0.063					< 0.001
No adjuvant chemotherapy	1,155 (36.7%)	888 (36.1%)			261 (19.7%)	464 (25.5%)	646 (39.3%)	672 (82.2%)	
Fluoropyrimidine monotherapy	1,485 (47.2%)	1,234 (50.1%)			761 (57.5%)	1,063 (58.5%)	779 (47.4%)	116 (14.2%)	
Oxaliplatin combined therapy	309 (9.8%)	205 (8.3%)			210 (15.9%)	181 (10.0%)	117 (7.1%)	6 (0.7%)	
Others	195 (6.2%)	134 (5.4%)			92 (6.9%)	110 (6.1%)	103 (6.3%)	24 (2.9%)	
	Colon *N* = 3,803	Rectum *N* = 2,864		*P*-value*	T1-2 *N* = 1,076	T3 *N* = 3,786	T4 *N* = 1,842		*P*-value*
Treatment				< 0.001					< 0.001
No adjuvant chemotherapy	1,203 (38.0%)	789 (33.9%)			296 (34.4%)	1,162 (37.3%)	534 (35.0%)		
Fluoropyrimidine monotherapy	1,552 (49.1%)	1,124 (48.3%)			470 (54.6%)	1,501 (48.2%)	717 (47.0%)		
Oxaliplatin combined therapy	252 (8.0%)	251 (10.8%)			52 (6.0%)	284 (9.1%)	169 (11.1%)		
Others	156 (4.9%)	163 (7.0%)			43 (5.0%)	169 (5.4%)	107 (7.0%)		
	N1 *N* = 4,235	N2a *N* = 992	N2b *N* = 637	*P*-value*		IIIa *N* = 827	IIIb *N* = 3,842	IIIc *N* = 1,020	*P*-value*
Treatment				< 0.001					< 0.001
No adjuvant chemotherapy	1,339 (36.7%)	232 (27.8%)	146 (26.6%)			238 (33.7%)	1,185 (35.9%)	266 (30.5%)	
Fluoropyrimidine monotherapy	1,879 (51.4%)	428 (51.2%)	228 (41.5%)			400 (56.7%)	1,675 (50.7%)	382 (43.9%)	
Oxaliplatin combined therapy	226 (6.2%)	127 (15.2%)	135 (24.6%)			32 (4.5%)	250 (7.6%)	164 (18.8%)	
Others	209 (5.7%)	49 (5.9%)	40 (7.3%)			36 (5.1%)	192 (5.8%)	59 (6.8%)	

*Pearson's Chi-squared test.

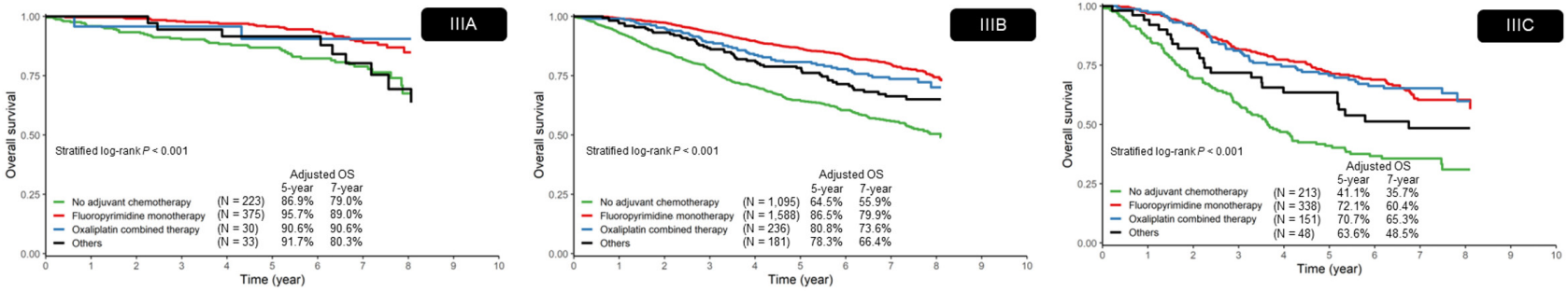
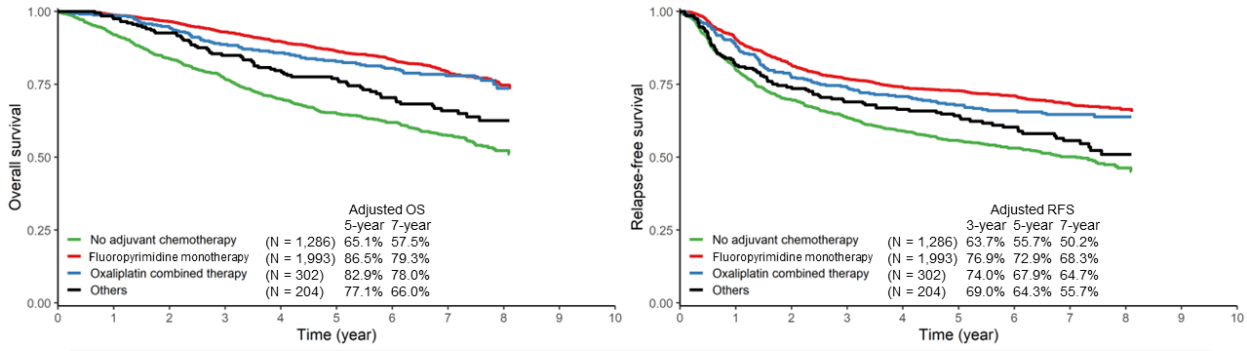


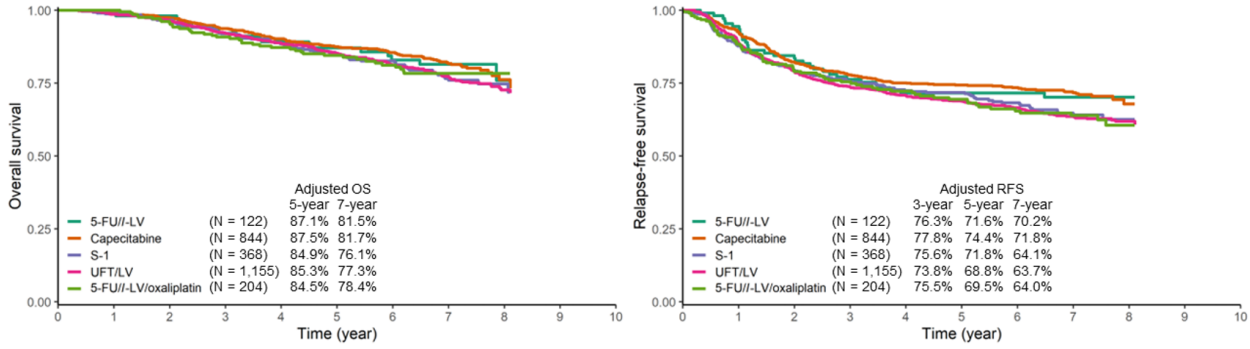
Figure 4. Overall survival (OS) of Stage IIIA/IIIB/IIIC colorectal cancer by the TNM classification after the covariate adjustment.



Treatment	N		OS HR	OS 95% CI	OS *P*-value	OS (competing risk analysis#) HR	OS (competing risk analysis#) 95% CI	OS (competing risk analysis#) *P*-value	RFS HR	RFS 95% CI	RFS *P*-value
No adjuvant chemotherapy	1,286	Crude	Reference			Reference			Reference		
Fluoropyrimidine monotherapy	1,993		0.34	0.30, 0.39	< 0.001	0.45	0.39, 0.52	< 0.001	0.51	0.45, 0.56	< 0.001
Oxaliplatin combined therapy	302		0.50	0.40, 0.62	< 0.001	0.70	0.55, 0.88	< 0.001	0.73	0.61, 0.88	< 0.001
Others	204		0.65	0.51, 0.83	< 0.001	0.84	0.64, 1.09	0.188	0.86	0.67, 1.02	0.074
No adjuvant chemotherapy	1,286	Adjusted*	Reference			Reference			Reference		
Fluoropyrimidine monotherapy	1,993		0.36	0.31, 0.42	< 0.001	0.46	0.39, 0.54	< 0.001	0.53	0.47, 0.59	< 0.001
Oxaliplatin combined therapy	302		0.41	0.31, 0.52	< 0.001	0.53	0.40, 0.70	< 0.001	0.61	0.50, 0.75	< 0.001
Others	204		0.66	0.50, 0.85	0.002	0.82	0.61, 1.09	0.170	0.83	0.66, 1.04	0.107

* HRs were adjusted by age, sex, location, histologic type, stage, and pre-serum carcinoembryonic antigen.
# Death due to other diseases was treated as a competing risk event, and the Fine-Gray model was used for analysis.

Figure 5. Overall survival (OS) and relapse-free survival (RFS) at stage III colon cancer with any T, N1 or N2 by the TNM classification.



Treatment	N		OS HR	OS 95% CI	OS *P*-value	RFS HR	RFS 95% CI	RFS *P*-value
Capecitabine	122	Crude	Reference			Reference		
5-FU//-LV	844		0.99	0.63, 1.57	0.980	1.20	0.85, 1.68	0.315
S-1	368		1.34	1.02, 1.76	0.034	1.34	1.07, 1.66	0.009
UFT/LV	1,155		1.28	1.04, 1.58	0.018	1.39	1.18, 1.64	<0.001
5-FU//-LV/oxaliplatin	204		1.51	1.09, 2.07	0.012	1.68	1.31, 2.15	<0.001
Capecitabine	122	Adjusted*	Reference			Reference		
5-FU//-LV	844		1.03	0.62, 1.69	0.917	1.05	0.72, 1.53	0.782
S-1	368		1.26	0.94, 1.69	0.129	1.27	1.01, 1.60	0.044
UFT/LV	1,155		1.26	1.01, 1.57	0.044	1.32	1.11, 1.57	0.002
5-FU//-LV/oxaliplatin	204		1.16	0.80, 1.66	0.440	1.33	1.01, 1.75	0.045

* HRs were adjusted by age, sex, location, histologic type, stage, and Pre CEA

Figure 6. Overall survival (OS) and relapse-free survival (RFS) of stage III colorectal cancer by regimen. 5-FU, 5-fluorouracil; *l*-LV, *l*-leucovorin; UFT, tegafur-uracil ; LV, leucovorin.

min (*24*). Based on this, we amended the protocol and added a CCr of more than 30 mL/min to the eligibility criteria; the CapeOX regimen was then initiated with a decreased dose of capecitabine of 1,500 mg/m^2 from 2,000 mg/m^2 per day in patients with a CCr of 30 to 50 mL/min and/or who were > 70 years old. The combination with oxaliplatin compromised the maximum tolerated dose of capecitabine due to toxicity. Therefore, caution should be exercised when interpreting the results of this clinical trial, particularly those related to the combination of oxaliplatin as adjuvant chemotherapy. We observed a significant efficacy of fluoropyrimidine monotherapy in this Japanese real-world study. Capecitabine was superior to S-1 for stage III patients in the previous JCOG0910 study (*21*). This drug also seemed to be more effective than UFT/LV, S-1, 5-FU/ *l*-LV/ oxaliplatin therapy in our current study, which used real world data (Figure 6).

Based on the results of previous adjuvant trials, oxaliplatin-combined regimens are considered standard adjuvant chemotherapy for patients with stage III colon cancer especially in Western countries. On the other hand, fluoropyrimidine monotherapies elicit favorable results when used as adjuvant chemotherapy in Japan, and are comparable to oxaliplatin-combined regimens that are used in Western countries. There are two factors that may contribute to a better outcome: D3 lymph node dissection

and thorough pathological examinations (*28-30*). Standard colon cancer surgery in the West employs resection of a long portion of the colon with limited central lymph node dissection (*31*). On the other hand, in Japan, resection of a shorter section of the colon is accompanied by extensive lymph node dissection in the central direction (D3 lymph node dissection) (*32*). Therefore, the physical location of the dissected lymph nodes is quite different in the two geographic locations, even if the number of dissected lymph nodes is similar (*33*). In the West, lymph nodes are removed from excised specimens, fixed with formalin and submitted for pathological examination. However, in Japan lymph nodes are removed from fresh excised specimens before formalin fixation and submitted for pathological examination after formalin fixation. Studies of large numbers of colon cancer patients from Japan and the United States revealed that 12 or more lymph nodes were examined in 68% and 37% of patients, respectively (*34,35*). Such differences in the frequency with which a given number of lymph nodes are examined may contribute to stage migration. Therefore, extrapolating the results from trials of adjuvant chemotherapy in Europe and the United States to the situation in Japan is not appropriate. Rather, clinical evidence based on Japanese surgery and pathological examination data should be used to guide treatment of patients in Japan.

In conclusion, adjuvant chemotherapy using fluoropyrimidines without oxaliplatin for stage III colorectal cancer elicited a significant effect on OS. Fluoropyrimidine monotherapy should be chosen for many Japanese colorectal cancer patients based on our analysis of real-world big data. Optimal chemotherapy in the adjuvant setting for colorectal cancer should therefore be chosen based on the medical environment in each country.

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