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Impact of Fluoropyrimidine and Oxaliplatin-based Chemoradiotherapy in Patients With Locally Advanced Rectal Cancer

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Abstract. *Background/Aim: To evaluate the benefits of the addition of oxaliplatin (OX) to fluoropyrimidine (FP)-based neoadjuvant chemoradiotherapy (CRT) for patients with locally advanced rectal cancers (LARCs). Patients and Methods: We performed retrospective analyses comparing the pathological complete response (pCR) rate, overall survival (OS), recurrence-free survival (RFS), and local recurrence-free survival (LRFS) between FP-based and FP+OX-based CRT groups and for patients who had completed the CRT. Results: One hundred patients were included in the analyses: the pCR rate, OS, RFS, and LRFS were similar between these groups. The FP+OX group showed significantly more frequent incompleteness of the CRT compared to the FP group (p=0.049). Among the patients who had completed the CRT, the FP+OX group demonstrated significantly improved LRFS compared to the FP group (p=0.048). Conclusion: The addition of OX to an FP regimen in neoadjuvant CRT for LARC may reduce local recurrence in patients who have achieved good compliance to CRT.*

Neoadjuvant chemoradiotherapy (CRT) is a one of the standard treatments for locally advanced rectal cancer (LARC) worldwide (1-3). Fluoropyrimidine (FP)-based chemotherapy concomitant with radiotherapy (RT) is the most frequently used CRT regimen for LARC, and these agents are suggested to increase the radiosensitivity of the cancers (4-6).

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Oxaliplatin (OX) and irinotecan (IRI) are the other key chemotherapy agents which are used concomitantly with FP for colorectal cancers (CRCs), and in recent years, the effects of adding oxaliplatin or irinotecan to FP in neoadjuvant CRT settings has been evaluated in several studies including randomized controlled trials (RCTs) (7-14). The STAR-01 randomized phase III trial, which compared the overall survival (OS) between infused-fluorouracil (FU)-based CRT and infused-FU+OX-based CRT showed no significant difference between these treatments' outcomes (7). Similarly, the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-04 demonstrated that the addition of OX to 5-FU or capecitabine (Cape) did not improve the local control, disease-free survival (DFS), or OS rates (12). However, the phase 3 CAO/ARO/AIO-04 trial conducted in Germany, which compared the survival and CRT response between patients who received FU-based neoadjuvant CRT followed by FU-based adjuvant chemotherapy and patients who received FU+OX-based neoadjuvant CRT followed by FU+OX-based adjuvant chemotherapy, revealed improved DFS in patients administered the FU+OX regimen (9).

In Japan, the SHOGUN trial (a phase II study of CRT using S-1+OX) showed a high pathological complete response (pCR) rate of 27.3% and a good 3-year OS rate of 93%, with no severe toxicity, although the sample size was small (15-17). OX was induced on days 1, 8, 22, and 29 with a chemotherapy gap at day 22, which may be one of the factors contributing to the patients' good compliance. The authors speculated that the favorable toxicity profile led to the good result compared to previous studies.

The compliance to OX treatment in the STAR-01 and NSABP R-04 studies was actually fairly low, ranging from 62% to 75%. We thus hypothesized, that the addition of OX under a feasible chemotherapy regimen may have a certain benefit compared to FP alone. In this study, we retrospectively compared FP and FP+OX regimens among all patients and among those who had good compliance. As we hypothesized, our results showed that in the patients who

achieved good compliance to the FP+OX regimen, the local recurrence rate was lower compared to the patients who received the FP-alone regimen. This is, to our knowledge, the first study showing the ability of the addition of OX in neoadjuvant CRT settings for rectal cancer to improve local control.

Patients and Methods

Patients. We retrospectively analyzed the clinicopathological data of 126 patients with LARCs who underwent neoadjuvant CRT and subsequent surgery at Teikyo University Hospital (Tokyo) from 2007 to 2017. Patients with non-adenocarcinoma (n=8), anal fistula-related cancer (n=1), inflammatory bowel disease-associated cancer (n=1), or synchronous cancer in other organs (n=1) were excluded. Patients for whom FP was induced and who received an IRI-based chemotherapy regimen (n=4), patients in whom distant metastases were detected after neoadjuvant CRT (n=6), and patients who underwent non-curative surgery (n=5) were also excluded (Figure 1). Patients provided written informed consent for publication of their data. This study was approved by the Teikyo University ethics committee (no. 19-127). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and its later amendments.

Neoadjuvant chemoradiotherapy and surgery. Neoadjuvant CRT was performed as described (18). In summary, the total dose of radiotherapy was 50.5 Gy, which was given in 28 fractions on weekdays. The treatment planning was done with the aid of CT scans, and the target volume included the primary tumor, anus, and lymph nodes in the mesorectum and in the pelvis (lateral lymph nodes). As the chemotherapy regimen, tegafur-uracil and leucovorin (UFT/LV), Cape, or S-1 with oxaliplatin (SOX) were administered concomitantly with radiotherapy. UFT was induced at 300 mg/m^2/day, Cape was at 2500 mg/m^2/day, and S-1 was at 80 mg/m^2/day. SOX was induced as described in the SHOGUN study; S-1 was induced at 40-60 mg/m^2/day on days 1-5, 8-12, 22-26, and 29-33, and OX was induced at 60 mg/week on days 1, 8, 22, and 29 (16).

Total meso-rectal excision (TME) was performed at approx. 6-8 weeks after completion of the neoadjuvant CRT. Post-operative surveillance was conducted at 3-month intervals with the measurement of the patients' carcinoembryonic antigen (CEA) levels, at 6-month intervals with computed tomography (CT), and at 1-year intervals with a colonoscopy.

The CRT response grade was determined pathologically based on the Japanese Society for Cancer of the Colon and Rectum guidelines (ninth edition) as follows. Grade 0: No evidence of tumor response, Grade 1: <2/3 regression of the tumor cells, Grade 2: ≥2/3 regression of the tumor cells, Grade 3: complete regression. Grade 3 indicates a pCR, and Grades 2 and 3 were defined as good response (3).

Statistical analyses. The χ^2 test or Fisher's exact test was used for the comparisons of categorical data, and the Wilcoxon rank sum test was used for continuous variables. The 3-year OS was defined as the period between the date of surgery and the date of death from any cause within 3 years after surgery. The 3-year recurrence-free survival (RFS) was defined as the period between the date of surgery and the date of any tumor recurrence within 3 years after surgery. The 3-year local recurrence-free survival (LRFS) was defined as the period between the date of surgery and the date of tumor recurrence in the local region (the area in which the surgical procedures were performed) within 3 years after surgery.

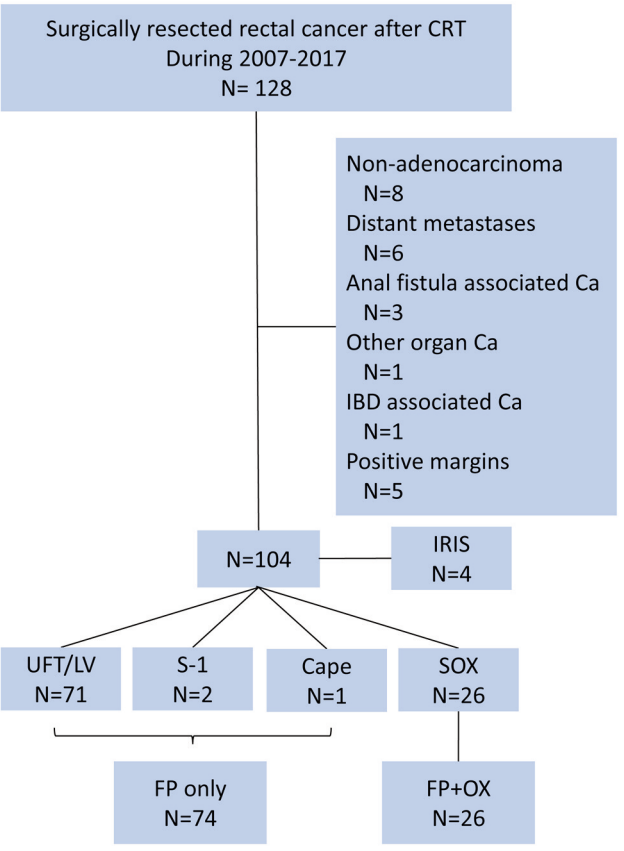

Figure 1. *Flow chart illustrating inclusion and exclusion criteria of the patients in the present study.*

We divided the patients into two groups: those who received FP alone-based CRT and those who received FP+OX-based CRT. We compared the groups' survival and clinicopathological factors. Survival was compared by determining the Kaplan–Meier curves, and the differences in survival were evaluated with the log-rank test. We defined 'incomplete CRT' as CRT with a total dose of <80% chemotherapy and/or a total dose of <45 Gy radiotherapy (19, 20). The pre-CRT clinicopathological factors were dichotomized into two groups using Youden indexes, which were calculated by depicting the receiver-operating characteristics (ROC) curves, and factors associated with incompleteness of the neoadjuvant CRT were evaluated by logistic regression model analyses. Differences with a *p*-value of <0.05 were considered significant in all analyses. All statistical calculations were performed using JMP Pro 15 statistical software (SAS Institute Japan, Tokyo, Japan).

Results

The FP+OX group showed a trend toward frequent incompletion of CRT compared to the FP group. The FP group comprised 74 patients, most of whom were treated with UFT/LV (n=70, %); two patients (3%) were treated with

Table I. *Comparison of clinicopathological factors between the FP-based CRT group and FP+OX-based CRT group.*

Characteristics (N, %)	FP-based CRT (N=74)	FP+OX-based CRT (N=26)	*p*-Value
Gender			
Male/Female	58 (78)/16 (22)	18 (69)/8 (31)	0.425
Age (Years)			
mean	63	64	0.792
Distance from AV (cm)			
≤5/>5	44 (60)/30 (40)	12 (46)/14 (54)	0.214
cStage			
2/3	28 (39)/45 (61)	9 (35)/17 (65)	0.815
ypStage			
0-1/2/3	31 (42)/24 (32)/19 (26)	9 (35)/11 (42)/6 (23)	0.650
Histology			
Well-Mod/Por-Muc	63 (86)/11 (14)	25 (96)/1 (4)	0.279
Adjuvant chemotherapy			
Absent/Present/Unavailable	54 (73)/20 (27)/1 (1)	7 (38)/16 (62)/0 (0)	**0.004**
Pre-CRT CEA (ng/ml)			
<5/≥5	44 (54)/30 (46)	15 (58)/11 (42)	0.739

AV: Anal verge; CEA: carcinoembryonic antigen. Bold values indicate statistical significance.

S-1, and one patient (1%) was treated with Cape. The FP+OX group comprised 26 patients, all of whom received the SOX regimen (Figure 1). The median post-surgery follow-up period was 1,937 days (range=45-4931 days). During the follow-up period, recurrence at distant sites occurred in 32 patients (32%), and recurrences in the local region were noted in 13 patients (13%).

Table I summarizes the clinicopathological factors of each CRT group. The FP+OX group received adjuvant chemotherapy (mostly UFT/LV) significantly more frequently compared to the FP group (62% *vs*. 27%, p=0.004). Compliance to the regimen was significantly better in the patients who received the FP regimen compared to those who received the FP+OX regimen (95% *vs*. 81%, p=0.049). The other clinicopathological factors were not significantly different between the two groups. The details of the cause of incompleteness of the CRT are provided in Table II.

The FP group and FP+OX group showed no significant difference in the pCR rate (9% *vs*. 15%, p=0.470) or the good response rate to CRT (55% *vs*. 46%, respectively; p=0.416). Although the 3-year OS (89% *vs*. 96%, p=0.153) and 3-year RFS (65% *vs*. 69%, p=0.651) were similar between the two groups, the FP+OX group showed a trend toward better LRFS compared to the FP group (84% *vs*. 9 %, p=0.060) (Figure 2A-C).

The FP+OX group demonstrated improved local recurrence-free survival compared to the FP group among patients who had good compliance to neoadjuvant CRT. We also compared the survival and CRT-response rate among the patients who completed the neoadjuvant CRT. The FP group and FP+OX group showed no significant difference in the pCR rate (10% *vs*. 19%, p=0.270) or the good response rate to CRT (54% *vs*. 48%, respectively; p=0.592). Regarding survival, the 3-year OS (90% *vs*. 100%, p=0.144) and 3-year RFS (64% *vs*. 71%, p=0.439) were similar between the FP and FP+OX groups, but the LRFS was significantly better in the FP+OX group compared to the FP group (83% *vs*. 100%, respectively; p=0.048) (Figure 2D-F).

Table II. *The reasons for incompleteness of the CRT in each group.*

Groups	Reason for incompleteness	N
FP-based CRT	Diarrhea	1
	Allergy (drug eruption)	1
	Thrombocytopenia	1
	Appendicitis	1
FP+OX-based CRT	Neutropenia	3
	Allergy (drug eruption)	1
	Recto-vaginal fistula	1

In the FP+OX group, incompleteness of neoadjuvant CRT was suggested to be associated with poor OS and LRFS. We then compared the survival between the groups with and without good compliance to the CRT in each chemotherapy regimen. In the FP group, the patients in the CRT-complete group and those in the CRT-incomplete group showed no significant difference in the 3-year OS (75% *vs*. 90%, p=0.316), 3-year RFS (67% *vs*. 64%, p=0.696), or 3-year LRFS (100% *vs*. 83%, respectively; p=0.413) (Figure 3A-C). In the FP+OX group, the 3-year RFS rates (60% *vs*. 71%, p=0.424) were similar between the two groups; however, the

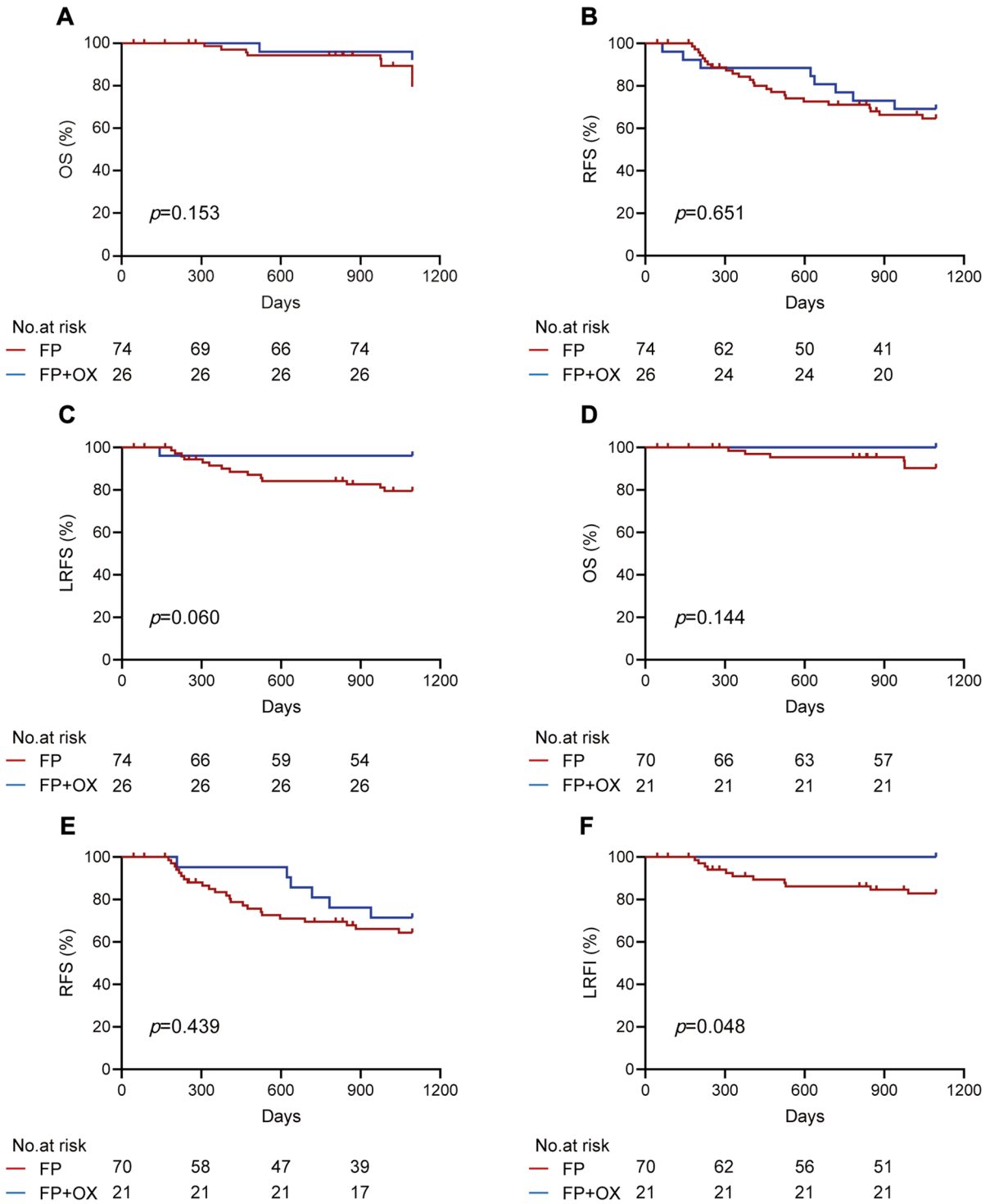

Figure 2. *Kaplan–Meier curves showing overall survival, recurrence-free survival, and local recurrence-free survival in fluoropyrimidine-based chemoradiotherapy group and fluoropyrimidine and oxaliplatin-based chemoradiotherapy group. A) The FP-based CRT group and the FP+OX-based CRT group showed similar 3-year OS (p=0.153). B) The FP-based CRT group and the FP+OX-based CRT group showed similar 3-year RFS (p=0.651). C) The FP+OX-based CRT group showed improved 3-year LRFS compared to the FP-based CRT group, although statistically not significant (p=0.060). D) The FP-based CRT group and the FP+OX-based CRT group showed similar 3-year OS among patients who had completed the CRT (p=0.144). E) The FP-based CRT group and the FP+OX-based CRT group showed similar 3-year RFS among the patients who had completed the CRT (p=0.439). F) The FP+OX-based CRT group showed significantly improved 3-year LRFS compared to the FP-based CRT group among the patients who had completed the CRT (p=0.048).*

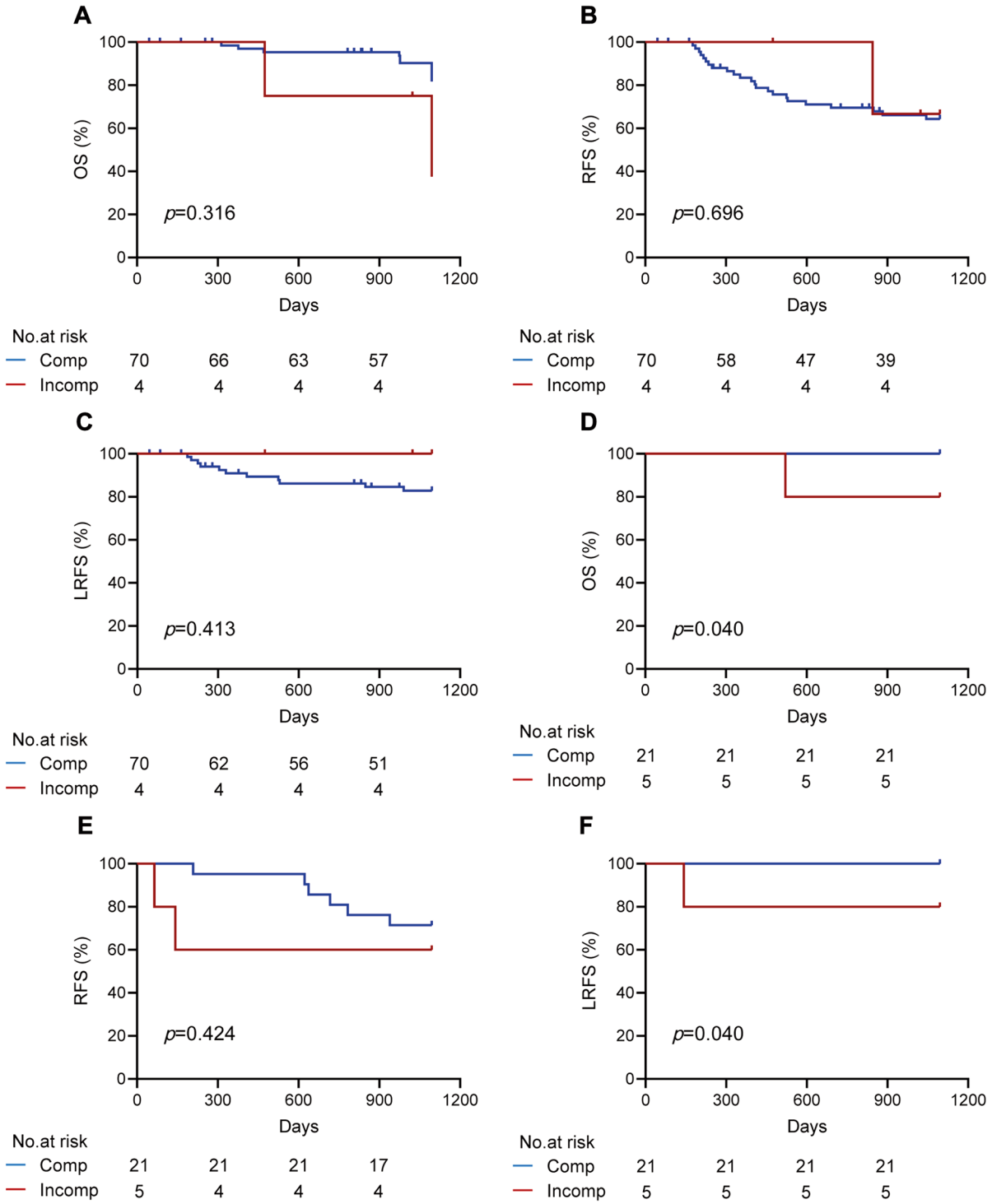

Figure 3. *Kaplan–Meier curves showing overall survival, recurrence-free survival, and local recurrence-free survival in fluoropyrimidine and oxaliplatin-based chemoradiotherapy-complete group and fluoropyrimidine and oxaliplatin-based chemoradiotherapy-incomplete group. A) The CRT-complete patients showed significantly improved 3-year OS compared to the CRT-incomplete patients (p=0.040) in FP-based CRT patients. B) The CRT-complete group and the CRT-incomplete group showed similar 3-year RFS (p=0.424) in FP-based CRT patients. C) The CRT-complete patients showed significantly improved 3-year LRFS compared to the CRT-incomplete patients (p=0.040) in FP-based CRT patients. D) The CRT-complete patients showed significantly improved 3-year OS compared to the CRT-incomplete patients (p=0.040) in FP+OX-based CRT patients. E) The CRT-complete group and the CRT-incomplete group showed similar 3-year RFS (p=0.424) in FP+OX-based CRT patients. F) The CRT-complete patients showed significantly improved 3-year LRFS compared to the CRT-incomplete patients (p=0.040) in FP+OX-based CRT patients.*

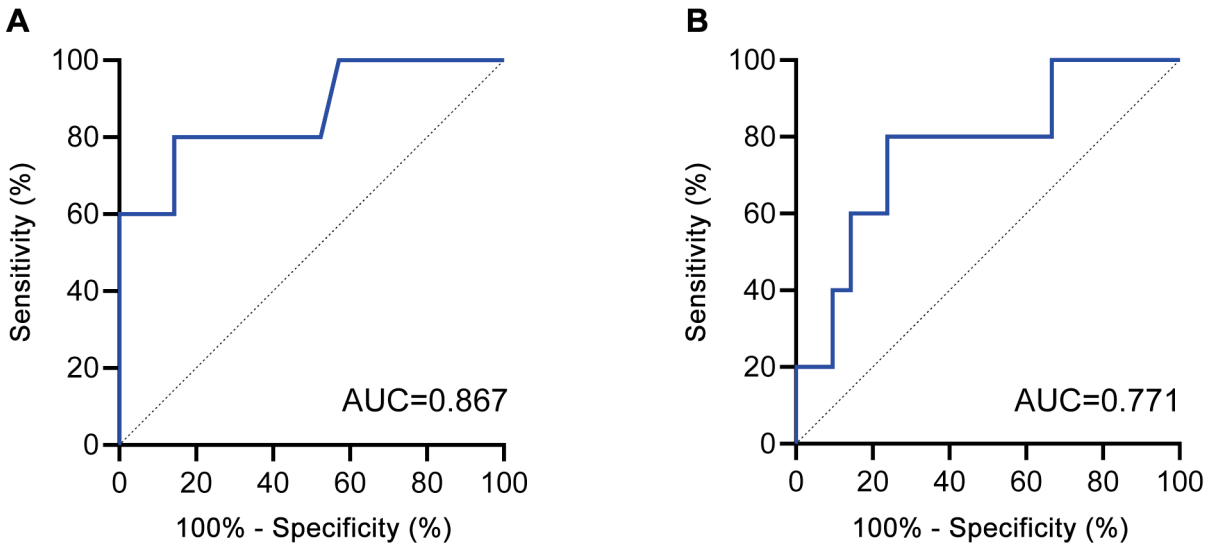

Figure 4. *Receiver operating characteristics curves of pre-chemoradiotherapy neutrophil count and lymphocyte count to predict the incompleteness of the chemoradiotherapy. A) Area under the curve was 0.867 with neutrophil count. B) Area under the curve was 0.771 with lymphocyte count.*

Table III. *Logistic regression analyses evaluating the factors associated with the treatment incompleteness in the fluoropyrimidine and oxaliplatin (FP+OX)-based chemoradiotherapy (CRT) group.*

Analyses			
Variables	OR	95%CI	*p*-Value
Gender			
Male/Female	0.60	0.08-4.54	0.621
Age (Years)			
≥65/<65	2.44	0.33-17.9	0.381
cStage			
III/II	0.27	0.03-2.02	0.201
CEA (ng/ml)			
≥5/<5	2.44	0.33-17.9	0.381
WBC (/μl)			
≥6300/<6300	-	-	0.996
Neutrophil (/μl)			
≥4914/<4914	24.0	1.95-295	**0.013**
Lymphocyte (/μl)			
≥1352/<1352	0.08	0.01-0.87	**0.038**
Monocyte (/μl)			
≥396/<396	8.00	0.75-85.7	0.086
Platelet (104/μl)			
≥25.4/<25.4	0.19	0.02-1.98	0.164
CRP (mg/dl)			
≥2.14/<2.14	-	-	0.993
Hemoglobin (g/dl)			
≥10.1/<10.1	0.25	0.03-2.18	0.210
Albumin (g/dL)			
≥3.8/<3.8	0.21	0.03-1.62	0.134
Cholesterol (mg/dl)			
≥210/<210	3.00	0.40-22.3	0.283

OR: Odds ratio; CI: confidence interval; CEA: carcinoembryonic antigen; CRP: C-reacted protein. Bold values indicate statistical significance.

CRT-complete patients showed significantly improved 3-year OS (80% *vs.* 100%, p=0.040) and 3-year LRFS (80% *vs.* 100%, p=0.040) compared to the CRT-incomplete patients (Figure 3D-F).

In the FP+OX group, the pre-CRT neutrophil count was a good marker to predict incompleteness of the neoadjuvant CRT. Because the completeness of the pre-CRT was suggested to be one of the key factors to achieve the effectiveness of FP+OX-based CRT, we investigated whether any of the pre-neoadjuvant CRT clinical factors could predict the incompleteness of the CRT in the patients who had received the FP+OX-based CRT. The results of the logistic regression analyses demonstrated that the pre-CRT neutrophil count (≥4,914) [odds ratio (OR)= 24.0, 95% confidence interval (CI)=1.95–295, p=0.013] and lymphocyte count (≥1,352) (OR=0.08, 95%CI=0.01–0.87, p=0.038) were significantly associated with incompleteness of the CRT (Table III). The ROC analysis revealed that in the FP+OX group, the pre-CRT neutrophil count had an area under the curve (AUC) of 0.867 and the pre-CRT lymphocyte count had an AUC of 0.771 to predict the incompleteness of the CRT (Figure 4A and B).

Discussion

We evaluated the benefit of adding OX to FP-based neoadjuvant CRT in LARC patients. The results of our retrospective analyses demonstrated that addition of OX improved the local recurrence-free survival in patients who achieved good compliance in their scheduled neoadjuvant CRT.

Several RCTs have compared FP-based CRT and FP+OX-based CRT in rectal cancer patients, and most of the RCTs failed to observe any benefit from the addition of OX (7, 8, 10, 12). One of the explanations for the discrepancy between these reported results and our present findings may be due to the low compliance to the FP+OX regimen. In the STAR-01 trial comparing FU-based CRT *vs*. FU+OX-based CRT, although the pCR rate and OS were similar between the two regimens, the percentage of patients who received a >80% dose of the FU+OX regimen was only 75% (7). Moreover, the authors did not mention the local recurrence rate. Similarly, in the NSABP R-04 trial comparing 5-FU/Cape-based CRT with 5-FU/Cape+OX-based CRT, the compliance for the OX regimen was only 62% with Cape and 69% with 5-FU (12).

The CAO/ARO/AIO-04 study was the only trial that demonstrated a benefit from the addition of OX; it compared FU-based CRT and FU+OX-based CRT (9). The patients who received the FU+OX-based CRT showed a higher pCR rate and better DFS compared to the patients who received the FU-based CRT. At 3 years, the cumulative incidence of local recurrence was 4.6% in the FU+OX-based CRT group and 2.9% in the FU-based CRT group, demonstrating the superiority of the FU+OX-based regimen. The compliance of the chemotherapy in that trial was fairly good, and 95.4% of the patients received >80% of the planned OX. It was thus suggested, that the compliance to a CRT regimen may be one of the key factors to achieve the benefit of the addition of OX.

Freischlag et al. demonstrated that achieving a complete radiation dose (45-50.4 Gy) was associated with lower risk of long-term mortality in patients with stage II and III rectal cancer who received neoadjuvant CRT (19). Moreover, a *post-hoc* analysis of the CAO/ARO/AIO-04 trial results evaluating the association between treatment adherence and oncologic outcomes showed that the patients with LARCs who had complete adherence to the neoadjuvant CRT, achieved significantly improved 3-year DFS compared to the patients with a reduced dose of neoadjuvant CRT (20). Consistent with the findings of that analysis, our present findings demonstrated that in the FP+OX group, the OS and LRFS were significantly superior in the patients who had completed their CRT compared to those who had not.

Moreover, because our results demonstrated that the adherence to CRT may be an important factor in the benefit of the addition of OX, we investigated factors associated with treatment failure in the patients who received the FP+OX-based CRT. Intriguingly, the pre-CRT neutrophil count and lymphocyte count were revealed to have a high potential to predict treatment failure in these populations. It has been reported that molecular factors including several single nucleotide polymorphisms (SNPs) can be used as markers to predict the toxicity of OX-based chemotherapy (21-23). However, these markers are costly and difficult to evaluate widely in institutional laboratories. It is easy and inexpensive to measure patients' neutrophil and lymphocyte counts in most institutions.

We acknowledge several study limitations. This was a retrospective cohort study, and a large prospective study is necessary. The FP group included heterogenous chemotherapy regimens, mostly UFT/LV. Comparisons of S-1 *versus* SOX as chemotherapy regimens in neoadjuvant CRT settings could determine the actual benefit of the addition of OX.

In conclusion, our study demonstrated that the addition of OX to an FP regimen in neoadjuvant CRT settings for rectal cancer may have the potential to reduce local recurrence in patients who achieved good compliance to the CRT. In addition, the pre-CRT neutrophil count can be used a marker to predict the completeness of CRT in patients who received an FP+OX regimen.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Y.O was involved in the analysis and interpretation of data and the drafting of the manuscript. T.O was involved in the study concept and design, the analysis and interpretation of data, and the drafting of the manuscript. K.O, M.T, Y.F, and R.S were involved in the acquisition of data. T.H, K.M, and K.N were involved in the critical revision of the manuscript for important intellectual content and material support. Y.H was involved in the study concept and study supervision.

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