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Original Article

One-Week versus Two-Week Chemoradiotherapy Followed by Curative Surgery in Rectal Cancer: Long-Term Comparative Pooled Analysis of Two Prospective Multicenter Phase II Trials

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Purpose The optimal short-course chemotherapeutic regimen for rectal cancer has not been clearly defined until now. KROG 10-01 and KROG 11-02 prospective trials investigated the efficacy and safety of 1- and 2-week chemoradiotherapy (CRT), respectively.

Materials and Methods Patients eligible for KROG 10-01 and KROG 11-02 involved those with clinical T3-4N0-2M0 rectal cancers. They received preoperative CRT and total mesorectal excision. Patients in KROG 10-01 received radiation of 25 Gy in 5 fractions during 1 week with 5-fluorouracil/leucovorin. Patients in KROG 11-02 received radiation of 33 Gy in 10 fractions for 2 weeks with oral capecitabine.

Results A total of 150 patients consisting of 70 patients from KROG 10-01 and 80 patients from KROG 11-02 were collectively analyzed. With a median follow-up time of 89.2 months, the 5-year overall survival rate was 86.5% in 1-week CRT and 85.3% in 2-week CRT (p=0.841). The 5-year recurrence-free survival rate was 83.5% in 1-week CRT and 77.1% in 2-week CRT (p=0.448). One patient (1.4%) in 1-week CRT and 11 patients (13.8%) in 2-week CRT exhibited pathologic complete regression (ypT0N0M0) after radiotherapy (p=0.006). One-week CRT had significantly higher acute hematologic (12.8% vs. 3.8%, p=0.040) and nonhematologic (38.6% vs. 16.3%, p=0.002) toxicity than 2-week CRT.

Conclusion Both 1- and 2-week schedules of CRT showed favorable survival outcomes after 7 years of follow-up. But, 2-week course achieved more increased tumor response and decreased acute toxicity than 1-week course.

Key words Chemoradiation, Rectal neoplasms, Recurrence, Appointments and schedules, Survival

Introduction

Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is the current standard treatment for locally advanced rectal cancer [1-4]. Preoperative CRT reduces local recurrence and enables sphincter-saving surgery for lower-lying rectal cancer patients. The German rectal cancer study revealed that the 5-year cumulative incidence of local recurrence was 6% in preoperative CRT arm and 13% in postoperative CRT arm [1]. Current treatment guidelines recommend conventional long-course CRT as the preferred treatment for rectal cancer patients with cT3-4 tumors or node-positive disease [5-7].

Several European studies have reported favorable efficacies of short-course radiotherapy (RT) as preoperative treatment in rectal cancer [8-11]. Short-course RT involved 1-week schedule with a dose of 25 Gy in 5 fractions and exhibited advantages of short treatment time, good compliance, and low radiation toxicity profiles. Bujko et al. [8] suggested that overall survival (OS) and disease-free survival did not significantly differ between short-course and long-course arms. Therefore, short-course RT has been an option for the preoperative treatment of rectal cancer in European countries.

The addition of chemotherapy is strongly recommended in cases of preoperative long-course RT [2,12,13]. Unfortunately, no trial has prospectively investigated short-course RT with concurrent chemotherapy. To assess the efficacy and safety of preoperative short-course CRT, KROG 10-01 and KROG 11-02 prospective trials were conducted [14,15]. Patients were treated with short-course CRT of 25 Gy in 5

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fractions in KROG 10-01 and hypofractionated CRT of 33 Gy in 10 fractions in KROG 11-02. This study assessed the long-term oncologic outcomes of two trials by pooled analysis.

Materials and Methods

1. Study design and participants

Both KROG 10-01 (NCT01129700) and KROG 11-02 (NCT-01431599) were multi-institutional and prospective phase II trials. Common eligible criteria of both trials were as follows: (1) histologically confirmed adenocarcinoma, (2) staged T3-4N0-2M0 rectal cancer using magnetic resonance imaging and/or endorectal ultrasonography, (3) Eastern Cooperative Oncology Group performance status 0 to 2, (4) adequate hepatic, renal, and marrow function, and (5) no evidence of distant metastasis. For KROG 10-01, tumors accessible to digital rectal examinations were regarded as eligible. For KROG 11-02, tumors located within 8 cm from the anal verge were included. Institutional review boards at each participating center approved the study protocols before patient enrollment. Written informed consent was obtained from all patients.

2. Procedures

Physical examination, laboratory test including complete blood count, liver function test, renal function test and serum carcinoembryonic antigen (CEA), colonoscopy, computed tomography (CT) of the abdomen and pelvis, and pelvic magnetic resonance imaging were performed as the baseline work-up. Chest radiography or a CT scan was also obtained. Endorectal ultrasonography and ^{18}F-fluorodeoxyglucose positron emission tomography were performed if necessary. Lymph nodes sized > 5 mm were regarded as clinically positive nodes.

For KROG 10-01, radiation was delivered with a dose of 25 Gy per 5 fractions during 5 consecutive days. All patients were treated with the intensity-modulated radiotherapy (IMRT) technique using helical tomotherapy. For KROG 11-02, radiation was delivered with a dose of 33 Gy per 10 fractions over the course of 2 weeks. The majority of patients (98.8%) were treated using 3-dimensional RT with standard three- or four-field beam arrangements. Only one patient in KROG 11-02 received IMRT. CT simulation and the determination of target volume were conducted in a similar manner for both trials. All patients underwent simulation CTs in the prone position on the belly board [16,17]. Clinical target volume (CTV) included the gross tumor, mesorectum, and presacral, distal common iliac, and internal iliac lymphatic chains. Planning target volume was expanded from CTV with a margin ≥ 3 mm. The superior border of the treatment field was the lumbosacral junction, while the inferior border was > 3 cm distal to the tumor.

Preoperative concurrent chemotherapy was administered on the same day of RT in both trials. For KROG 10-01, 5-fluorouracil (5-FU) 400 mg/m^2/day and leucovorin 20 mg/m^2/day were administered by intravenous bolus injection during the 5 days of RT. For KROG 11-02, oral capecitabine 1,650 mg/m^2/day was administered 5 days per week (from Monday to Friday) for a total up to 10 days during 2 weeks of RT. TME was performed 4 to 8 weeks after CRT. After surgery, pathologic specimens were staged according to the American Joint Committee on Cancer Staging System, 7th edition. Tumor regression grades (TRG) were evaluated using the scale proposed by Dworak et al. [18]. Adjuvant chemotherapy was recommended 4 weeks after surgery regardless of the pathologic stage. Adjuvant chemotherapy regimens were as follows: (1) intravenous 5-FU (400 mg/m^2/day) and leucovorin (400 mg/m^2/day) for 5 consecutive days, every 4 weeks for a total of 6 months; (2) FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen consisting of an infusion of oxaliplatin (85 mg/m^2) and leucovorin (400 mg/m^2) followed by a bolus infusion of 5-FU (400 mg/m^2) on day 1 and continuous infusion of 5-FU (total 2,400 mg/m^2), every 4 weeks for a total of 6 months; (3) oral capecitabine 1,250 mg/m^2, twice a day for 2 weeks, every 3 weeks for a total of 6 months.

3. Outcomes

The primary endpoint of the current study was recurrence-free survival (RFS) according to the trial. The secondary endpoint included OS, locoregional recurrence, distant metastasis, and acute and chronic toxic effects. Tumor response was assessed by comparing clinical and pathological stages after CRT. Downstaging was defined as ypT0-2N0M0 (ypStage 0-I) and pathologic complete response (ypCR) was defined as ypT0N0M0. Treatment toxicity was evaluated regularly from the start of preoperative CRT. Toxicity was scaled according to the National Cancer Institute Common Terminology Criteria for Adverse Events, ver. 3.0.

4. Statistical analysis

We used individual patient data from two prospective trials. Categorical variables were compared using the chi-square test and continuous variables using t test. The survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. OS was calculated as the time interval between the date of the start of RT and the date of death or the last follow-up. RFS was calculated as the time interval between the date of the start of RT and the date of recurrence, death, or the last follow-up. Locoregional recurrence was defined as a recurrence within the pelvic cavity. Distant metastasis was defined as a recurrence or metas-

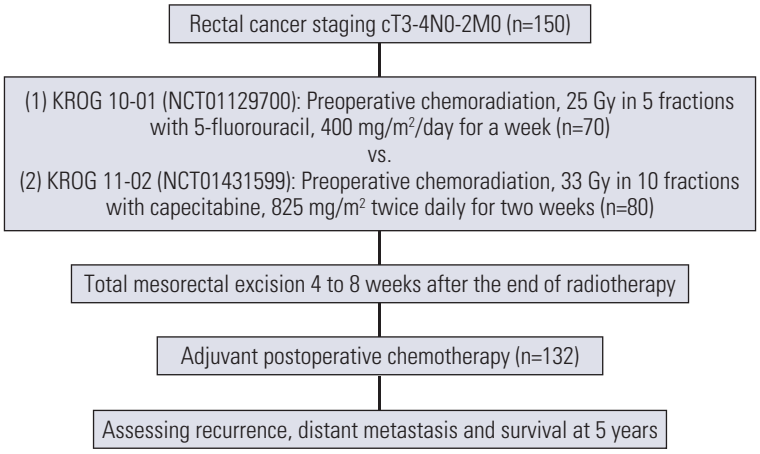

Fig. 1. Flow chart showing patient enrollment, treatment, and assessment.

tasis outside the pelvis. A Cox proportional hazard regression model was used to estimate the association using the hazard ratio (HR) and confidence interval (CI) between survival outcomes and variables. A value of $p < 0.05$ was regarded as statistically significant. All statistical analyses were conducted using R software ver. 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org).

Results

A total of 150 patients (70 patients in KROG 10-01 and 80 patients in KROG 11-02) were included in this pooled analysis (Fig. 1). Baseline patient characteristics did not exhibit any significant difference in age, sex, serum CEA, or clinical T and N categories (all $p < 0.05$). Details are provided in Table 1. In this pooled analysis, 132 patients received adjuvant chemotherapy 4 weeks after radical surgery. Of the 70 patients in KROG 10-01, 59 (84.2%) received adjuvant chemotherapy after surgery; leucovorin/5-fluorouricil (LF) regimen, 48 patients, FOLFOX, seven patients, and oral capecitabine, four patients. Of the 80 patients in KROG 11-02, 73 (91.2%) received adjuvant chemotherapy after surgery; LF regimen, 57 patients, FOLFOX, three patients, and oral capecitabine, 13 patients. Five patients in KROG 10-01 and four patients in KROG 11-02 did not complete their scheduled six cycles of LF regimen after surgery due to its toxicity.

The median follow-up time was 89.2 months (range, 8.4 to 132.3 months). OS and RFS rates at 5 years for the entire cohort were 85.8% and 80.2%, respectively. The 5-year OS rate was 86.5% in KROG 10-01 and 85.3% in KROG 11-02 (Fig. 2A), and the difference was not significant between the two trials (p=0.841). Median OS was not reached in both trials. The 5-year RFS rate was 83.5% in KROG 10-01 and 77.1% in KROG 11-02 (Fig. 2B). The 5-year RFS did not exhibit any significant difference (p=0.448). After adjusting for clinical and pathologic factors including age, sex, serum CEA, pathologic T category, pathologic N category, histologic grade, and surgical margin, no difference in RFS was observed between 1-week and 2-week schedules of CRT (HR, 1.269; 95% CI, 0.624 to 2.581; p=0.511) (Table 2). Pathologic N category (HR, 4.340; 95% CI, 1.780 to 10.585; p=0.001) was an independent prognostic factor for RFS on the multivariable analysis. Locoregional recurrence and distant metastasis rates were 8.0% and 17.5% for the entire cohort, respectively. The 5-year locoregional recurrence (4.9% vs. 10.6%, p=0.178) (Fig. 2C) and distant metastasis (13.3% vs. 21.3%, p=0.343) (Fig. 2D) rates did not differ significantly between the two trials.

Tumor response and surgical outcomes in detail are listed in Table 3. The median intervals between the end of RT and surgery was 7.2 weeks (range, 4.7 to 8.0) in KROG 10-01 and 7.5 weeks (range, 5.7 to 11.4) in KROG 11-02, respectively. Good tumor response including TRG 3-4 after CRT was significantly higher in KROG 11-02 compared with KROG 10-01 (18.8% vs 5.7%, p=0.032). The downstaging rate was 28.2% in KROG 10-01 and 33.8% in KROG 11-02 (p=0.495). Sphincter-preservation surgery was performed in 66 patients (94.3%) in KROG 10-01 and 75 patients (93.8%) in KROG 11-02 ($p > 0.99$). The involvement of the tumor on the surgical margin was not significantly different between the two trials (6.7% vs. 7.5%, p=0.913).

Acute severe toxic effects are shown in Table 4. One-week schedule of CRT had significantly higher grade 3-4 acute hematologic toxicity than 2-week schedule of CRT (12.8% vs. 3.8%, p=0.040). Grade 3 or 4 leukopenia occurred in nine patients (12.8%) for 1-week CRT and one patient (1.3%) for 2-week CRT, respectively. Severe acute nonhematologic and perioperative toxicity occurred in 27 patients (38.6%) for

Table 1. Characteristics of study participants

Characteristic	Total (n=150)	One-week CRT (n=70)	Two-week CRT (n=80)	p-value
Age (yr)				
≤ 60	73 (48.7)	37 (52.9)	36 (45.0)	0.431
> 60	77 (51.3)	33 (47.1)	44 (55.0)	
Sex				
Male	100 (66.7)	47 (67.1)	53 (66.2)	0.994
Female	50 (33.3)	23 (32.9)	27 (33.8)	
CEA (ng/mL)				
≤ 5	116 (77.3)	49 (70.0)	67 (83.8)	0.068
> 5	34 (22.7)	21 (30.0)	13 (16.2)	
Clinical T category				
cT3	142 (94.7)	67 (95.7)	75 (93.8)	0.865
cT4	8 (5.3)	3 (4.3)	5 (6.2)	
Clinical N category				
cN0	23 (15.3)	10 (14.3)	13 (16.2)	0.916
cN1-2	127 (84.7)	60 (85.7)	67 (83.8)	
Distance of tumor from anal verge (cm)				
≤ 5	70 (46.7)	30 (42.9)	40 (50.0)	0.484
> 5	80 (53.3)	40 (57.1)	40 (50.0)	
Histologic grade[a)]				
Low	146 (97.3)	68 (97.1)	78 (97.5)	0.997
High	4 (2.7)	2 (2.9)	2 (2.5)	

Values are presented as number (%). CEA, carcinoembryonic antigen; CRT, chemoradiotherapy. [a)]Low histological grade included well to-moderately differentiated adenocarcinoma. Poorly differentiated adenocarcinoma, mucinous carcinoma, and signet ring cell carcinoma were classified as high histological grade.

1-week CRT and 13 (16.3%) for 2-week CRT, and the difference was statistically significant (p=0.002). Long-term toxic effects occurred in seven patients (10.0%) for 1-week CRT and five patients (6.3%) for 2-week CRT, respectively (Table 5). The occurrence of the chronic toxicity had no significant difference between the 1-week and 2-week schedules (10.0% vs. 6.3%, p=0.398). Pelvic abscesses occurred in two patients for 1-weak CRT and one for 2-week CRT, and chronic diarrhea occurred only in one patient for 1-week CRT.

Discussion

The current study reported the long-term outcomes of pooled analysis of two trials that investigated preoperative short-course CRT and hypofractionated CRT in patients with locally advanced rectal cancer. With a median follow-up of 89 months, the 5-year OS rate and RFS rate were 85.8% and 80.2%, respectively. These results are comparable with previous historical outcomes, not only in terms of short-course RT but also long-course CRT [1,2,19]. Long-term toxic effects were acceptable at 7.3%.

Preoperative CRT is the current standard treatment associated with a reduction of local recurrence, an increase of sphincter-saving resection, and less treatment-related toxic effects [1,2]. However, patients receiving preoperative long-course CRT (50.4 Gy in 28 fractions) should tolerate the average treatment time of 5.5 weeks, the inconvenience, and medical costs. Several studies investigated the efficacy and safety of the short-course RT schedule (25 Gy in 5 fractions) to reduce treatment time [8-11,20]. Polish trial was the first randomized trial to compare preoperative long-course CRT and short-course RT [8]. The long-course CRT group received concurrent chemotherapy of LF regimen, while the short-course RT group was treated with RT alone. The 4-year OS and disease-free survival rates did not exhibit any significant difference between the long-course CRT group and the short-course RT group, but early radiation toxicity was higher in the long-course CRT group (18.2% vs. 3.2%, p < 0.01). The rates of pathologic complete regression were higher in the long-course CRT group compared with the short-course RT group (16.1% vs. 0.7%). A positive circumferential margin (12.9% vs. 4.4%, p=0.02) was also more common in the short-course RT group compared to the long-course CRT group.

In Stockholm trial, patients were randomly distributed into short-course RT with surgery within 1 week, short-

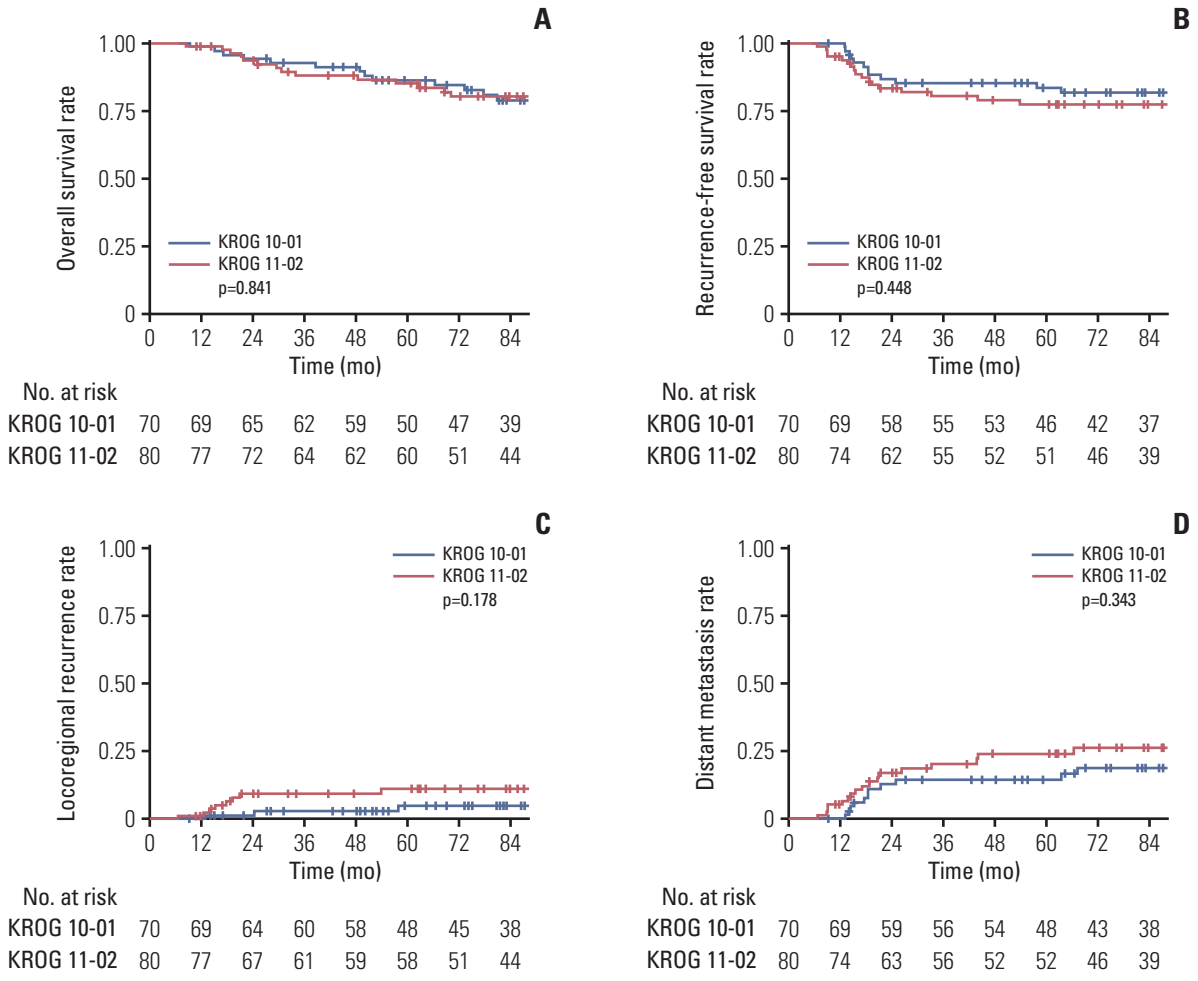

Fig. 2. Overall survival (A), recurrence-free survival (B), locoregional recurrence (C), and distant metastasis (D) by subgroup.

course RT with surgery after 4-8 weeks, and long-course RT with surgery after 4-8 weeks [9]. No concomitant chemotherapy was provided in the three arms. The 5-year OS was 73% versus 76% versus 78% (p=0.62). No significant difference between treatment arms was observed for the cumulative incidence of local recurrence, distant metastasis, and frequencies of hospitalization due to radiation toxicity and postoperative and surgical complications. TROG 01.04 trial compared short-course RT and long-course CRT in patients with T3 rectal cancer [11,21]. The 5-year local recurrence, distant metastasis, OS, and late toxicity did not exhibit any differences between the two treatment arms. Another randomized trial by Kairevice et al. [10] compared the long-course CRT and short-course RT groups. The 5-year RFS was 67% in the long-course CRT group and 45% in the short-course RT group, and the difference was statistically significant (p=0.01). The 5-year OS was 79% in the long-course CRT group and 62% in the short-course RT group (p=0.02). More patients in the long-course CRT group underwent pathologic complete regression and downstaging compared to the short-course RT group, but significant differences were not observed.

Based on these trials, current guidelines recommend both short-course RT and long-course CRT for preoperative treatment, but long-course CRT is advised in patients with T4 disease and those who are at risk of positive margins or R1/R2 resection [5-7]. This may be because short-course RT achieved comparable outcomes with long-course CRT in terms of OS and RFS, but not with regard to downstaging rate or pathologic complete regression [20,22,23]. With this background, KROG 10-01 and KROG 11-02 assessed the efficacy of short-course RT with concurrent chemotherapy. The addition of chemotherapy on preoperative long-course RT is known to enhance pathologic complete regression and decrease local recurrence. KROG 10-01 conducted short-course CRT with a dose of 25 Gy in 5 fractions with LF chemotherapy, which is the typical choice of chemotherapy regimen in long-course

Table 2. Prognostic factors associated with RFS

Variable	No. (%)	5-Year RFS	Univariate (p)	Multivariate (p-value) Hazard ratio (95% CI)
Age (yr)				p=0.745
≤ 60	73 (48.7)	0.806	0.758	1
> 60	77 (51.3)	0.799		0.886 (0.429-1.833)
Sex				p=0.193
Male	100 (66.7)	0.776	0.206	1
Female	50 (33.3)	0.856		0.592 (0.269-1.304)
CEA (ng/mL)				p=0.143
≤ 5	116 (77.3)	0.834	0.004	1
> 5	34 (22.7)	0.699		1.742 (0.828-3.664)
Clinical T category				p=0.443
cT3	142 (94.7)	0.800	0.547	1
cT4	8 (5.3)	0.875		0.411 (0.043-3.974)
Clinical N category				p=0.491
cN0	23 (15.3)	0.861	0.726	1
cN1-2	127 (84.7)	0.893		0.695 (0.247-1.958)
Surgery				p=0.617
LAR	141 (94.0)	0.798	0.658	1
APR	9 (6.0)	0.889		1.441 (0.344-6.030)
Pathologic T				p=0.126
ypT0-2	58 (38.7)	0.947	0.002	1
ypT3-4	92 (61.3)	0.712		4.928 (0.639-38.020)
Pathologic N				p=0.001
ypN0	93 (62.0)	0.932	< 0.001	1
ypN+	57 (38.0)	0.594		4.340 (1.780-10.585)
Downstaging				p=0.338
Yes	49 (32.67)	0.958	0.006	1
No	101 (67.33)	0.728		3.221 (0.295-35.174)
Histologic grade				p=0.718
Low	146 (97.3)	0.805	0.198	1
High	4 (2.7)	0.750		1.403 (0.223-8.825)
Surgical margin				p=0.514
Negative	140 (93.3)	0.812	0.055	1
Positive	10 (6.7)	0.675		1.439 (0.482-4.291)
CRT schedule				p=0.511
One week	70 (46.7)	0.835	0.403	1
Two weeks	80 (53.3)	0.774		1.269 (0.624-2.581)

APR, abdominoperineal resection; CEA, carcinoembryonic antigen; CI, confidence interval; CRT, chemoradiotherapy; LAR, low anterior resection; RFS, recurrence-free survival.

CRT. To avoid the risk of combining large fraction size of RT and cytotoxic chemotherapy, IMRT technique was applied to all patients [24].

However, the downstaging rate of KROG 10-01 was 28.2% and complete pathologic regression was observed in only one patient (1.4%). Grade 3 or higher acute toxicities occurred in more than one-third of patients (38%). KROG 11-02 adopted the 2-week course hypofractionated RT schedule of 33 Gy in 10 fractions instead of the common short-course RT schedule. The chemotherapy regimen was also modified with oral capecitabine [25-29]. Biologically effective doses of 25 Gy in 5 fractions and 33 Gy in 10 fractions are very similar (66.7 Gy3 vs. 69.3 Gy3) in terms of late effects when a/b is assumed to be 3. Two-week course CRT with oral capecitabine employed in the current trial showed lower toxicity than short-course CRT. As compared to IV bolus injection of 5-FU and leucovorin during the 5 days in KROG 10-01, just one cycle of capecitabine for 2 weeks with drug holidays dur-

Table 3. Tumor response and surgical outcome

Characteristic	Total (n=150)	One-week CRT (n=70)	Two-week CRT (n=80)	p-value
Tumor regression grade				
0-2	131 (87.3)	66 (94.3)	65 (81.2)	0.032
3-4	19 (12.7)	4 (5.7)	15 (18.8)	
Downstaging (ypT1-2N0M0)				
No	103 (68.7)	50 (71.4)	53 (66.2)	0.495
Yes	47 (31.3)	20 (28.2)	27 (33.8)	
Pathologic complete regression (ypT0N0)				
No	138 (92.0)	69 (98.6)	69 (86.2)	0.006
Yes	12 (8.0)	1 (1.4)	11 (13.8)	
Surgery				
Low anterior	141 (94.0)	66 (94.3)	75 (93.8)	0.987
Abdominoperineal	9 (6.0)	4 (5.7)	5 (6.2)	
Surgical margin				
Negative	140 (93.3)	66 (94.3)	74 (92.5)	0.913
Positive	10 (6.7)	4 (5.7)	6 (7.5)	

Values are presented as number (%). CRT, chemoradiotherapy.

Table 4. Grade 3 or higher acute and perioperative toxic effects

Type of toxicity	One-week CRT (n=70)			Two-week CRT (n=80)			p-value
	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	
Hematologic							
Leukopenia	5 (7.1)	4 (5.7)	9 (12.8)	1 (1.3)	0	1 (1.3)	
Anemia	1 (1.4)	0	1 (1.4)	2 (2.5)	0	2 (2.5)	
Thrombocytopenia	0	0	0	0	0	0	
Any hematologic effect	5 (7.1)	4 (5.7)	9 (12.8)	3 (3.8)	0	3 (3.8)	0.040
Nonhematologic							
Diarrhea	8 (11.4)	0	8 (11.4)	2 (2.5)	0	2 (2.5)	
Dysuria	2 (2.9)	0	2 (2.9)	0	0	0	
Anopelvic pain	13 (18.5)	0	13 (18.5)	2 (2.5)	0	2 (2.5)	
Anorexia	6 (8.5)	0	6 (8.5)	1 (1.3)	0	1 (1.3)	
Nausea and vomiting	2 (2.9)	0	2 (2.9)	0	0	0	
Postoperative ileus	1 (1.4)	0	1 (1.4)	1 (1.3)	0	1 (1.3)	
Wound dehiscence	5 (7.1)	0	5 (7.1)	1 (1.3)	0	1 (1.3)	
Anastomotic leakage	5 (7.1)	2 (2.9)	7 (10.0)	5 (6.2)	1 (1.3)	6 (7.5)	
Any nonhematologic effect	25 (37.7)	2 (2.9)	27 (38.6)	12 (15.0)	1 (1.3)	13 (16.3)	0.002

Values are presented as number (%). CRT, chemoradiotherapy.

Table 5. Long-term toxic effects

Type of toxicity	One-week CRT (n=70)	Two-week CRT (n=80)	p-value
Chronic diarrhea	1 (1.4)	0	
Pelvic abscess	2 (2.9)	1 (1.3)	
Anastomotic stricture	1 (1.4)	1 (1.3)	
Small bowel obstruction	2 (2.9)	1 (1.3)	
Ureteral stricture	1 (1.4)	2 (2.5)	
Any long-term toxic effects	7 (10.0)	5 (6.3)	0.398

Values are presented as number (%). CRT, chemoradiotherapy.

ing the weekend in KROG 11-02 could be effective and safe concurrent regimen with 2-week course RT [30].

The downstaging rate of KROG 11-02 was 33.8% that met the target range (30% to 40%). Pathologic complete regression rate was 13.8%, which was comparable to the previous results of long-course CRT trials [1,2,19]. Acute grade 3 toxic effects were observed in five patients (6.3%) and acute grade 4 toxic effects were not observed. Long-term toxic effects were also acceptable. KROG 11-02 achieved comparable downstaging rates and pathologic complete regression rates without excess toxicity and successfully shortened the treatment time from 5.5 weeks to 2 weeks. This was the first prospective trial investigating the hypofractionated schedule of preoperative CRT. Nevertheless, there are several limitations requiring these results to be interpreted with caution. Both KROG 10-01 and KROG 11-02 were designed as multicenter studies. But, both trials were single-arm studies with a relatively small numbers of patients. Randomized controlled trials with larger sample sizes are necessary to confirm the results of the present study.

In conclusion, preoperative 1-week or 2-week preoperative CRT in rectal cancer led to good survival outcomes and acceptable long-term toxic effects. However, 2-week schedule of CRT had significantly more favorable tumor response and acute toxicity after CRT than 1-week schedule of CRT.

Ethical Statement

Approval of an Institutional Review Board was achieved in each participating center and Korean Radiation Therapy Oncology Group (approval No. KROG 10-01 and KROG 11-02). Written informed consent was obtained from every patient.

Author Contributions

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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