

# Clinicopathological Outcomes in Patients With Locally Advanced Rectal Cancer Undergoing Preoperative Short-Versus Long-course Chemoradiotherapy With Delayed Surgery

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**Abstract.** *Background/Aim:* We aimed to compare the clinicopathological outcomes in patients with locally advanced rectal cancer after short- or long-course concurrent chemoradiotherapy (CCRT) followed by delayed surgery. *Patients and Methods:* The records of 94 patients with cT3-4N0-2M0 rectal cancer who received CCRT between 2010 and 2017 were reviewed. Short-course radiotherapy (RT) was delivered with a median total dose of 25 Gy in five fractions (n=27), and long-course RT was delivered with a median total dose of 50.4 Gy in 28 fractions (n=67). The following concurrent chemotherapy regimens were administered: 5-fluorouracil plus leucovorin in 58 and capecitabine in 24; in 12 cases agents were unknown. The median interval between CCRT and surgery was 8 weeks. Adjuvant chemotherapy was administered after surgery in 80 patients (5-fluorouracil plus leucovorin, n=54; capecitabine, n=9; other, n=14; and unknown, n=3). Propensity-score

matching analysis was conducted. *Results:* The median follow-up duration was 4.3 years. There were no statistically significant differences between the short- and long-course RT groups in sphincter preservation (85.2% vs. 92.5%, p=0.478), pathological complete remission (18.5% vs. 14.9%, p=0.905), downstaging (44.4% vs. 26.9%, p=0.159), and negative circumferential resection margin (92.6% vs. 89.6%, p=0.947) rates. No differences were found in survival outcomes between the short- and long-course groups at 3 years (overall survival: 91.8% vs. 88.1%, p=0.790; disease-free survival, 75.2% vs. 72.5%, p=0.420; locoregional relapse-free survival, 90.5% vs. 98.4%, p=0.180; and distant metastasis-free survival, 79.6% vs. 73.5%, p=0.490). Similar results were observed after PSM. *Conclusion:* Clinically, short-course CCRT may be a feasible alternative to long-course CCRT in patients with locally advanced rectal cancer.

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Colorectal cancer was the fourth most common cancer and the third leading cause of cancer-related death in South Korea in 2019 (1). Although the incidence of colorectal cancer has been steadily decreasing since 2012, it remains one of the leading causes of death from cancer (1). Approximately 40% of patients with colorectal cancer are diagnosed with regional metastasis requiring multimodal treatment (1).

Numerous clinical trials have examined important issues in radiotherapy (RT) for rectal cancer, such as the timing of RT (preoperative vs. postoperative) and surgery (immediate vs. delayed), RT schedule (short vs. long), and concurrent chemotherapy regimen (2-7). For locally advanced rectal cancer,



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the National Comprehensive Cancer Network guidelines recommend long-course concurrent chemoradiotherapy (CCRT) or short-course RT before surgical resection (8). Long-course RT typically delivers a total dose of 45-50.4 Gy with 1.8-2 Gy per fraction, whereas short-course RT consists of 25 Gy in five fractions (9). At the Kyung Hee University Hospital at Gandong, both RT regimens are permitted, and chemotherapy is also concurrently administered to patients receiving short-course RT (*i.e.* short-course CCRT) to improve pathological response (10). This is unique as previous studies have not concurrently administered chemotherapy with short-course RT. To offer enough time for tumor regression, surgery is delayed, being performed 8 weeks after RT, and maintenance chemotherapy is administered during this interval (4, 11, 12). The decision to administer adjuvant chemotherapy is determined by pathological findings.

We previously compared short-course and long-course CCRT in patients with locally advanced rectal cancer. With a 2-year follow-up, sphincter preservation, pathological complete remission (CR), downstaging rates and toxicity profiles in the short-course group were not different from those in the long-course group (13). Additionally, the 2-year overall survival (OS) did not differ between the two groups (13). In this study, we evaluated treatment outcomes after short- and long-course CCRT followed by delayed surgery in patients with locally advanced rectal cancer with a more extended follow-up period. We also compared the clinicopathological aspects after propensity-score matching (PSM).

## Patients and Methods

**Study population.** This retrospective cohort study was approved by the Institutional Review Board of Kyung Hee University Hospital at Gangdong (no. KHNCM 2021-06-043). The requirement for informed consent was waived because of the retrospective design. This study was conducted in accordance with the principles of the Declaration of Helsinki.

The medical records were reviewed of patients with newly diagnosed cT3-4N0-2M0 rectal cancer, according to the eighth edition of the American Joint Committee on Cancer TNM staging system (14), who received preoperative CCRT between 2010 and 2017 at the Kyung Hee University Hospital at Gangdong. The exclusion criteria were as follows: (i) Double primary cancer or a history of other malignancies and inflammatory bowel disease; (ii) participation in a prospective clinical trial investigating survival outcomes of rectal cancer; (iii) did not complete RT; (iv) palliative or no surgery for rectal cancer; and (v) no follow-up imaging work-up after treatment completion.

Finally, 94 patients were analyzed and divided into two groups based on the RT regimen: There were 27 patients in the short-course CCRT group and 67 in the long-course CCRT group. The RT regimen was chosen based on factors such as the surgeon's preference and the distance between the patient's residence and the hospital, which was the most important factor for selecting a short-course schedule.

**Treatment.** All patients received short- or long-course RT with concurrent chemotherapy. Short-course RT consisted of 25 Gy in five fractions delivered to the pelvis using intensity-modulated RT (except for one patient who was treated with 22.5 Gy in five fractions). For patients who received long-course RT, three-dimensional conformal RT was used to administer a total dose of 50.4 Gy at 1.8 Gy per fraction: 45 Gy to the pelvis and an additional boost of 5.4 Gy to gross tumors. However, one patient received 46.8 Gy in 26 fractions.

Preoperative RT was delivered with concurrent chemotherapy intravenously [5-fluorouracil and leucovorin (FL), n=58] or orally (capecitabine, n=24). Twelve patients had no information on concurrent chemotherapy regimens because they received chemotherapy at other hospitals and no electronic medical records were available. Generally, the maintenance chemotherapy regimen employed was the same as the concurrent chemotherapy regimen. However, seven patients did not receive maintenance chemotherapy, and five patients who received capecitabine were treated with a different type of maintenance chemotherapy (FL, n=3 and FL with oxaliplatin, n=2).

Delayed surgery (low anterior resection or abdominal perineal resection) was performed at a median of 8 weeks (interquartile range=7-9 weeks) after CCRT. Adjuvant chemotherapy with FL, capecitabine, or other regimens was administered to 54, nine and 14 patients, respectively; 14 patients did not receive adjuvant chemotherapy. Adjuvant treatment in three patients was unknown.

**Toxicity.** The following toxicities were collected from the patient's medical records: Hematological, skin, wound complications, diarrhea, ileus, hematuria, and urinary frequency. Toxicities were graded according to version 5.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events (15) and severe toxicities were defined as those of grade 3 or more.

**Statistical analysis.** Baseline and toxicity data between the short-course and long-course groups were compared using the chi-squared test, Fisher's exact test, or independent *t*-test, as appropriate. PSM was conducted to address any imbalance in baseline characteristics between the two groups. The propensity-score model included clinical T/N stage, pretreatment carcinoembryonic antigen (CEA), CCRT regimen, and the number of dissected lymph nodes. The propensity score was estimated from a logistic regression model. Then, one-to-two matching between the two groups was performed using the nearest-neighbor method without caliper matching. Kaplan-Meier curves were generated for all time-to-event endpoints [OS, disease-free survival (DFS), locoregional relapse-free survival (LRRFS), and distant metastasis-free survival (DMFS)], with time zero defined as the day of surgery. The log-rank test was used to compare differences in the survival curves. All statistical analyses were performed using R version 4.1.2 (<https://www.r-project.org/>), with  $p < 0.05$  considered statistically significant for two-sided tests.

## Results

The median follow-up duration was 4.3 years (interquartile range=1.8-5.0 years). Baseline patient characteristics for the short- and long-course groups before and after PSM are summarized in Table I. There were no significant differences between the two groups in age at diagnosis, clinical T/N

Table I. Baseline characteristics before and after propensity-score matching (PSM).

Characteristic		Before PSM			After PSM		
		Short-course (n=27)	Long-course (n=67)	<i>p</i> -Value	Short-course (n=20)	Long-course (n=40)	<i>p</i> -Value
Age, years	Median (IQR)	60 (55-69.5)	61 (54-68.5)	0.963	59 (55-68.5)	63 (57-72)	0.284
Sex, n (%)	Male	17 (63.0)	48 (71.6)	0.564	14 (70.0)	28 (70.0)	>0.99
	Female	10 (37.0)	19 (28.4)		6 (30.0)	12 (30.0)	
cT stage, n (%)	cT3	20 (74.1)	59 (88.1)	0.173	15 (75.0)	35 (87.5)	0.391
	cT4	7 (25.9)	8 (11.9)		5 (25.0)	5 (12.5)	
cN stage, n (%)	cN0	7 (25.9)	13 (19.4)	0.674	6 (30.0)	12 (30.0)	>0.99
	cN+	20 (74.1)	54 (80.6)		14 (70.0)	28 (70.0)	
Distance from anal verge <sup>a</sup> , cm	Median (IQR)	5.0 (2.0-6.5)	5.0 (4.0-6.8)	0.494	5.0 (2.0-6.0)	5.0 (3.5-6.0)	0.821
Pretreatment CEA <sup>a</sup> , ng/ml	Median (IQR)	3.21 (1.24-30.48)	4.00 (2.31-8.52)	0.049	2.05 (1.16-4.13)	4.01 (2.84-7.78)	0.903
Concurrent chemotherapy regimen <sup>a</sup> , n (%)	FL	24 (92.3)	34 (60.7)	0.003	19 (100.0)	31 (100.0)	-
	Capecitabine	2 (7.7)	22 (39.3)		0 (0)	0 (0)	
Surgery, n (%)	Low anterior resection	23 (85.2)	62 (92.5)	0.478	17 (85.0)	36 (90.0)	0.887
	Abdominal perineal resection	4 (14.8)	5 (7.5)		3 (15.0)	4 (10.0)	
Dissected lymph nodes <sup>a</sup>	Median (IQR)	19 (15-24)	21 (16-29)	0.852	19 (15-25)	25 (20-31)	0.364
Adjuvant chemotherapy regimen <sup>a</sup> , n (%)	None	3 (11.5)	11 (16.9)	0.521	3 (15.8)	10 (25.6)	0.852
	FL	19 (73.1)	35 (53.8)		14 (73.7)	25 (64.1)	
	Capecitabine	1 (3.8)	8 (12.3)		1 (5.3)	1 (2.6)	
	Other	3 (11.5)	11 (16.9)		1 (5.3)	3 (7.7)	

CEA: Carcinoembryonic antigen; FL: 5-fluorouracil+leucovorin; IQR: interquartile range. <sup>a</sup>Available data only.

stage, or distance of the lesion from the anal verge. However, the pretreatment CEA level in the long-course CCRT group was significantly higher than that in the short-course group (median: 4.00 *vs.* 3.21 ng/ml, *p*=0.049). Regarding concurrent chemotherapeutic regimens, more patients in the short-course group than in the long-course group were treated with FL (92.3% *vs.* 60.7%, *p*=0.003). Other treatment modalities, including surgery and adjuvant chemotherapy, were not different between the two groups. After PSM, 20 patients in the short-course CCRT group were successfully matched with 40 patients in the long-course CCRT group (Table I).

In both groups, CEA levels decreased after RT and surgery (Table II). Although the CEA level before treatment was higher in the long-course group, there was no difference in CEA levels between the two groups after treatment. Pathological CR was observed in five (18.5%) patients in the short-course group and 10 (14.9%) patients in the long-course group, and there was no statistical difference. Twelve (44.4%) and 18 (26.9%) patients receiving short- and long-course CCRT, respectively, achieved downstaging (ypT0-2N0) (*p*=0.159). There were more patients with ypT0-2 disease in the short-course CCRT group than in the long-course CCRT group, albeit with marginal significance [14

(51.9%) *vs.* 20 (29.9%); *p*=0.076]. However, the number of patients with ypN0 disease was not different between the two groups [19 (70.4%) *vs.* 41 (61.2%); *p*=0.548]. In the initial work-up imaging, 11 (42.3%) patients in the short-course group and 20 (43.5%) in the long-course group had mesorectal fascia involvement, but the proportions of patients with positive circumferential resection margins in final surgical pathology were similar for the groups [2 (7.4%) in the short-course group *vs.* 7 (10.4%) in the long-course group; *p*=0.947]. The differences in treatment response after PSM were consistent with those before PSM (Table II).

The Kaplan-Meier survival curves are shown in Figure 1 (before PSM) and Figure 2 (after PSM). In the entire cohort (Figure 1), the OS rates at 3 years were 91.8% and 88.1% in the short-course and long-course groups, respectively (*p*=0.790). The 3-year DFS, LRRFS, and DMFS rates in the short-course group were 75.2%, 90.5%, and 79.6%, respectively, whereas those in the long-course group were 72.5%, 98.4%, and 73.5%, respectively (*p*=0.420, 0.180, and 0.490, respectively). In the matched cohort (Figure 2), the 3-year OS, DFS, LRRFS, and DMFS rates in the short-course group were 94.4%, 76.4%, 93.3%, and 76.4%, respectively, and those in the long-course group were 92.3%, 74.4%,

Table II. Treatment response before and after propensity-score matching (PSM).

Characteristic	Before PSM			After PSM		
	Short-course (n=27)	Long-course (n=67)	p-Value	Short-course (n=20)	Long-course (n=40)	p-Value
Median CEA <sup>a</sup> (IQR), ng/ml	2.22 (1.38-4.56)	2.19 (1.71-5.22)	0.167	1.77 (1.16-2.93)	4.58 (1.97-6.05)	0.581
After radiotherapy						
After surgery	1.40 (0.60-3.11)	1.70 (1.12-3.29)	0.404	0.85 (0.50-2.70)	2.70 (1.64-4.00)	0.656
Complete remission, n (%)	22 (81.5)	51 (85.1)	0.905	15 (75.0)	34 (85.0)	0.555
Downstaging <sup>b</sup> , n (%)	5 (18.5)	10 (14.9)	0.159	5 (25.0)	6 (15.0)	0.402
No	15 (55.6)	49 (73.1)		10 (50.0)	26 (65.0)	
Yes	12 (44.4)	18 (26.9)		10 (50.0)	14 (35.0)	
Mesorectal fascia involvement <sup>a,c</sup> , n (%)	15 (57.7)	26 (56.5)	>0.99	11 (57.9)	11 (55.0)	>0.99
No						
Yes	11 (42.3)	20 (43.5)		8 (42.1)	9 (45.0)	
Circumferential resection margin, n (%)	25 (92.6)	60 (89.6)	0.947	19 (95.0)	36 (90.0)	0.869
Negative						
Positive	2 (7.4)	7 (10.4)		1 (5.0)	4 (10.0)	

CEA: Carcinoembryonic antigen; FL: 5-fluorouracil+leucovorin; IQR: interquartile range. <sup>a</sup>Available data only. <sup>b</sup>Described as ypT0-2N0. <sup>c</sup>In work-up imaging.

100%, and 76.5%, respectively; there were no significant differences in survival between the groups.

In terms of toxicity profiles (grade ≥3), the most common problem was wound complications confined to surgical scars or anastomosis sites, experienced by six patients (22.2%) in the short-course group and eight patients (11.9%) in the long-course group (Table III). However, toxicity profiles did not differ according to the duration of CCRT. There were no grade 5 toxicities in our study population.

### Discussion

Our study compared the outcomes of short-course and long-course CCRT in patients with locally advanced rectal cancer. With regard to pathological treatment responses and survival outcomes, there were no statistically significant differences between the short-course and long-course groups considering the entire cohort or after PSM. The most common toxicity was wound toxicity, but there were no significant differences in toxicity profiles between the two groups.

In our study, the pathological CR rate of short-course CCRT was 18.5%, which was lower than that (28.4%) of short-course RT in the Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) trial (5). RAPIDO was a very recently published randomized phase III trial comparing short-course RT (25 Gy/5 fractions) followed by chemotherapy and surgery (experimental group) with long-course CCRT (50.4 Gy/28 fractions or 50 Gy/25 fractions) with oral capecitabine followed by surgery with/without adjuvant chemotherapy (standard of care group) (5). This regimen differs from our hospital's regimen in not administering concurrent

chemotherapy during short-course RT. However, we assumed that the higher pathological CR rate in the RAPIDO trial was due to a longer period between RT and surgical resection. While this interval at our hospital was 8 weeks, the RAPIDO trial had a period exceeding 20 weeks (5). Both studies performed surgery 8 weeks after long-course CCRT, and the similarity in pathological CR rates of 14% further supports this explanation. Conversely, the fact that the RAPIDO trial did not administer additional chemotherapy between long-course CCRT and surgery may emphasize that the interval between RT and surgery is more critical than the administration of additional chemotherapy for achieving pathological CR.

Notably, downstaging was more frequently observed in patients who underwent short-course CCRT than in those who underwent long-course CCRT, even though the difference was not statistically significant. In particular, the proportion of patients with ypT0-2 disease was higher in the short-course group (51.9%) than in the long-course group (29.9%). The short-course group in our study had similar proportions of patients with ypT0-2 disease as the short-course group in the RAPIDO trial, whereas our long-course group had a lower proportion of patients with ypT0-2 disease than in the RAPIDO trial (29.9% vs. 46.0%) (5). We observed a lower rate of pathological CR in our patients who received short-course CCRT but a higher rate of downstaging of T-stage, indicating that short-course CCRT is more effective in downstaging of primary lesions.

In South Korea, the proportion of patients with rectal cancer who receive RT is increasing (16). It is uncertain what proportion of patients receive preoperative RT, but there is no doubt that the number of patients with stage II/III rectal

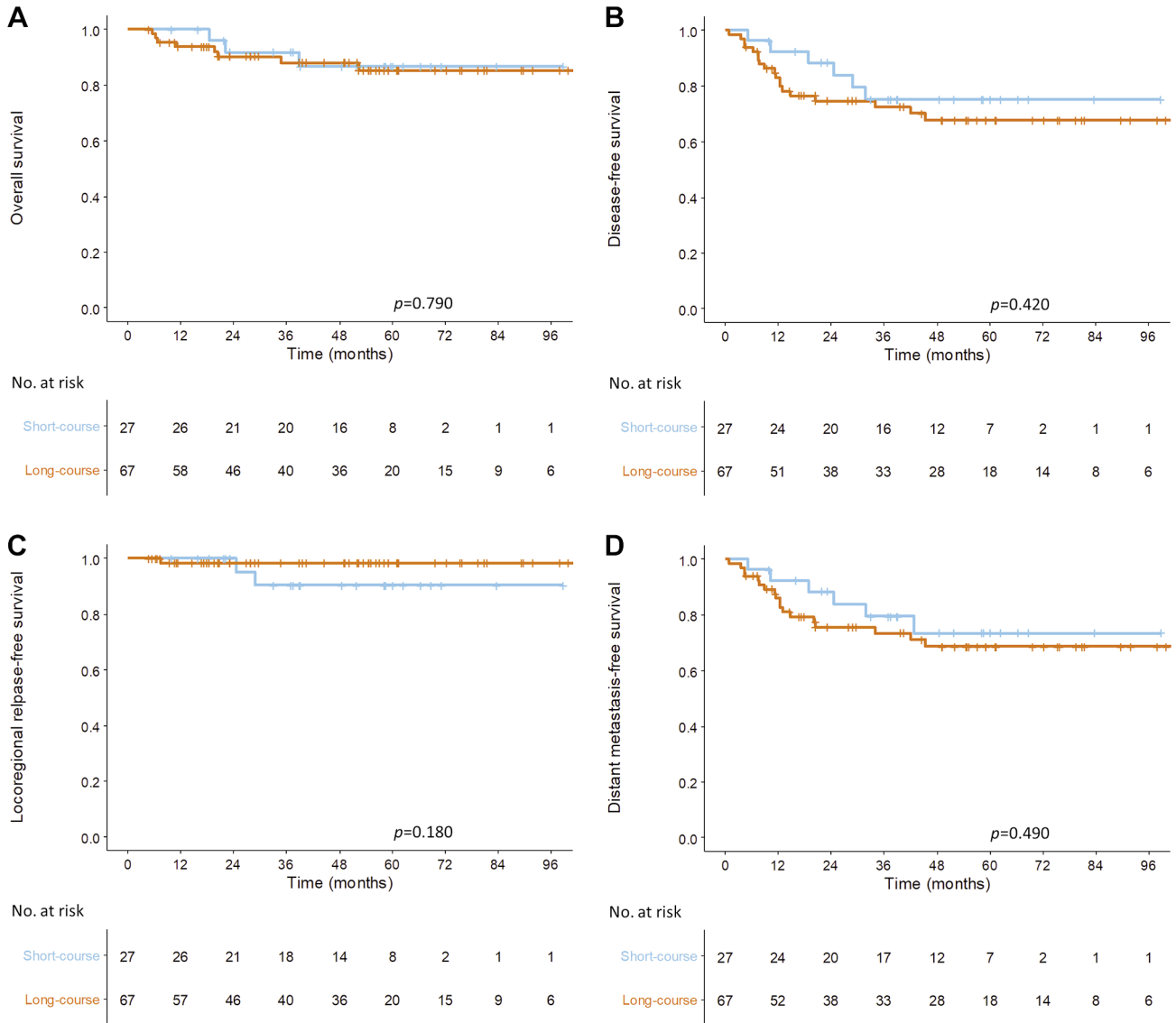


Figure 1. Kaplan-Meier curves of overall (A), disease-free (B), locoregional relapse-free (C) and distant metastasis-free (D) survival before propensity-score matching.

cancer who are eligible for preoperative RT is also increasing. In the unique situation of South Korea, where the vast majority of medical expenses for patients with cancer are covered by National Health Insurance, the increase in the number of patients is linked to an increase in socioeconomic burden (17). In this regard, implementing long-course RT in patients with rectal cancer might result in significant social medical expenses. Additionally, long-course RT is an important issue even in developing countries with limited resources and can result in long waiting times for patients due to the lengthy treatment period (18).

The Coronavirus Disease 2019 pandemic has greatly changed hospital utilization, especially of emergency

departments (19). Efforts to reduce unnecessary hospital stays have been made. However, for patients with cancer, delaying treatment can affect survival outcomes; therefore, visits to cancer care institutions during the pandemic were necessary (20). Rectal cancer is a type of cancer in which the risk of complications increases with chemotherapy and RT delays (20). Hence, short-course treatments were useful during the pandemic. A shorter treatment course can improve access to hospitals and reduce the hospital burden while still offering patients necessary treatment.

Although our findings provide valuable insights into the treatment of patients with locally advanced rectal cancer, some limitations should be considered. Firstly, this study was

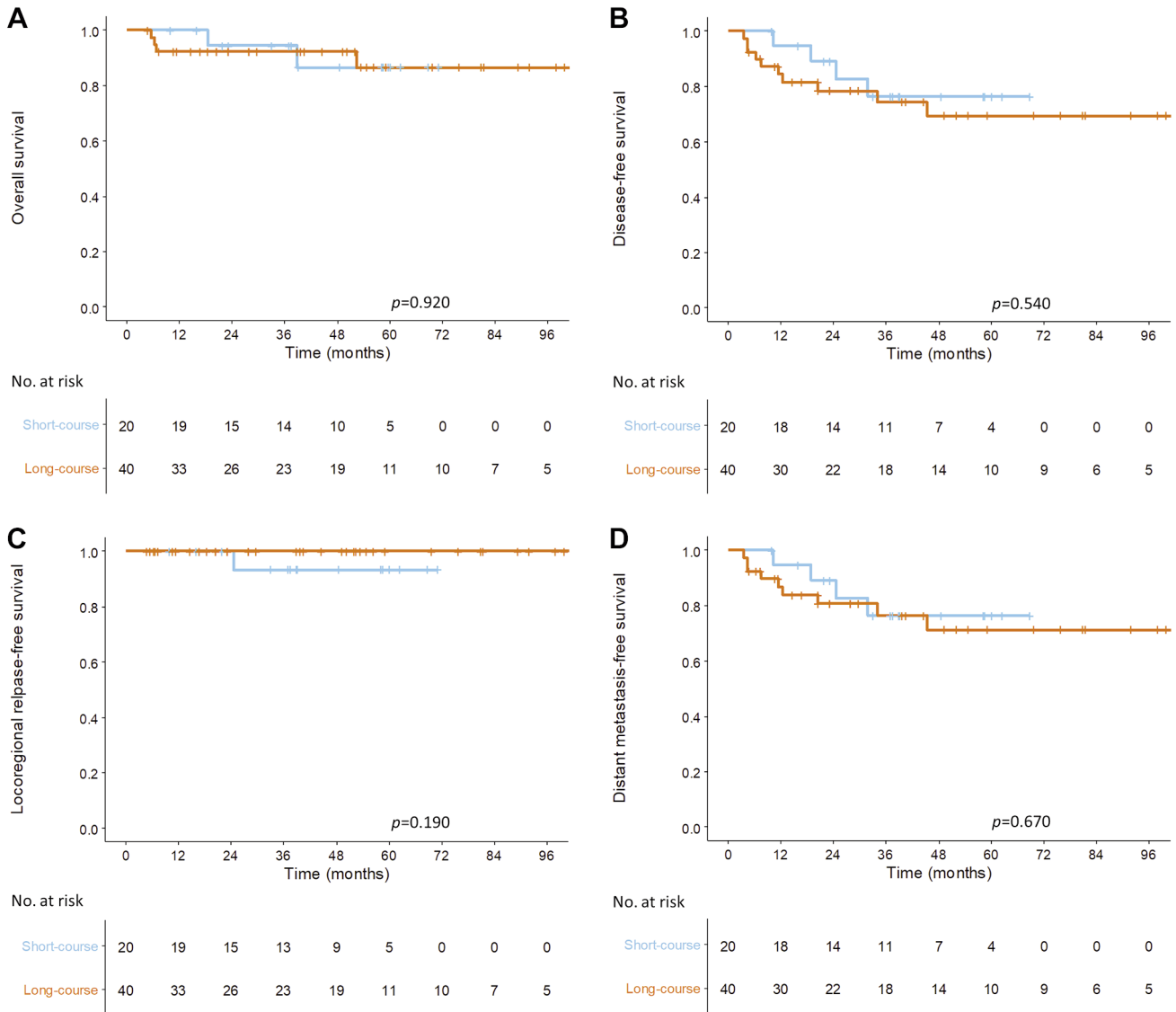


Figure 2. Kaplan-Meier curves of overall (A), disease-free (B), locoregional relapse-free (C) and distant metastasis-free (D) survival after propensity-score matching.

a retrospective cohort review, which has inherent flaws such as patient selection bias. Secondly, although we included more patients in the short-course group and extended the follow-up duration compared to our previous report (13), the number of patients was still small. Finally, various chemotherapy regimens were applied to the patients, and information on chemotherapy was not available for some of them. Although we attempted to adjust for this using PSM, it cannot be completely ruled out that this may have influenced the results.

Currently, a phase II randomized controlled trial, total neoadjuvant therapy with short-course radiotherapy *versus* long-course neoadjuvant chemoradiotherapy in locally

Table III. Toxicity profiles of the entire cohort.

Grade ≥3 toxicity	Frequency, n (%)		p-Value
	Short-course (n=27)	Long-course (n=67)	
Hematological	3 (11.1)	3 (4.5)	0.469
Skin	0 (0)	1 (1.5)	>0.99
Wound complications <sup>a</sup>	6 (22.2)	8 (11.9)	0.344
Diarrhea	1 (3.7)	3 (4.5)	>0.99
Ileus	2 (7.4)	3 (4.5)	0.948
Hematuria	0 (0)	0 (0)	–
Urinary frequency	0 (0)	0 (0)	–

<sup>a</sup>Problems confined to surgical scars or anastomosis sites.

advanced rectal cancer, Korean trial (TV-LARK) has been initiated. The trial aims to enroll 348 patients who will be randomly assigned into two treatment arms. Patients in the standard treatment arm will receive preoperative CCRT for 5 weeks (50.4 Gy in 28 fractions) with capecitabine, followed by delayed surgery and adjuvant chemotherapy. In the experimental arm, patients will be treated with short-course RT (25 Gy in five fractions) and four subsequent cycles of capecitabine plus oxaliplatin for 12 weeks. Surgical resection will be performed within 1-2 weeks after completion of chemotherapy, and adjuvant chemotherapy will be administered based on the postoperative stage. The primary endpoint of TV-LARK is the pathological CR rate, and the results of the study will give further guidance for the standard treatment of stage II/III rectal cancer in South Korea.

In conclusion, the results of the present study suggest that short-course CCRT combined with delayed surgery can be considered as an alternative treatment option for locally advanced rectal cancer, with comparable survival outcomes and toxicity profiles to those of long-course CCRT. Furthermore, cost-effectiveness studies on short-course CCRT should be considered.

### Conflict of Interest

The Authors declare that they have no conflicts of interest.

### Authors' Contributions

Conceptualization: WKC. Supervision: WKC. Data curation: JSK, MJC, DYL, SHL, S: KJ, BEY, CSC, and WKC. Methodology: JSK. Formal analysis and visualization: JSK. Writing: original draft: JSK. Writing: review and editing: JSK, MJC, DYL, SHL, S: KJ, BEY, CSC, and WKC. All Authors have read and agreed to the published version of the article.

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