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Original Article

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The Impact of Surgical Timing on Pathologic Tumor Response after Short Course and Long Course Preoperative Chemoradiation for Locally Advanced Rectal Adenocarcinoma

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Purpose

A pooled analysis of multi-institutional trials was performed to analyze the effect of surgical timing on tumor response by comparing short course concurrent chemoradiotherapy (CCRT) with long course CCRT followed by delayed surgery in locally advanced rectal cancer.

Materials and Methods

Three hundred patients with cT3-4N0-2 rectal adenocarcinoma were included. Long course patients from KROG 14-12 (n=150) were matched 1:1 to 150 short course patients from KROG 10-01 (NCT01129700) and KROG 11-02 (NCT01431599) according to stage, age, and other risk factors. The primary endpoint was to determine the interval between surgery and the last day of neoadjuvant CCRT which yields the best tumor response after the short course and long course CCRT. Downstaging was defined as ypT0-2N0M0 and pathologic complete response (ypCR) was defined as ypT0N0M0, respectively.

Results

Both the long and short course groups achieved lowest downstaging rates at < 6 weeks (long 20% vs. short 8%) and highest downstaging rates at 6-7 weeks (long 44% vs. short 40%). The ypCR rates were lowest at < 6 weeks (both long and short 0%) and highest at 6-7 weeks (long 21% vs. short 11%) in both the short and long course arms. The downstaging and ypCR rates of long course group gradually declined after the peak at 6-7 weeks and those of the short course group trend to constantly increase afterwards.

Conclusion

It is optimal to perform surgery at least 6 weeks after both the short course and long course CCRT to obtain maximal tumor regression in locally advanced rectal adenocarcinoma.

Key words
Rectal neoplasms, Chemoradiotherapy, Surgery interval

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Introduction

Colorectal malignancy is one of the frequently diagnosed cancers worldwide and is second most commonly diagnosed in South Korean adults [1]. Current standard in the treatment of locally advanced rectal cancer (LARC) is a neoadjuvant radiotherapy (RT) followed by total mesorectal excision (TME). For neoadjuvant therapy, either short course RT alone or long course concurrent chemoradiotherapy (CCRT) is feasible since they are known to have comparable outcome [2]. To further enhance local control, the Korean Radiation Oncology Group (KROG) conducted multi-institutional prospective trials to evaluate the effect of preoperative short course CCRT [3,4]. The outcomes of short course CCRT trials were comparable to those of current therapies, but the field is still young and remains to be explored.

Meanwhile, the optimal time to perform surgery, another modifiable factor that may alter oncologic outcome has long been recognized since the advent of neoadjuvant RT. Traditionally, the patients underwent immediate surgery after short course RT, within 1 week after completion of RT. On the contrary, delayed surgery was given after long course CCRT in attempt to enhance tumor response. The effect of surgical timing after long course CCRT has been studied by several groups. The analyzed time intervals varied from less than 5 days to over 12 weeks [5-8]. Many studies report that longer interval yielded better outcome but there are some contradicting results as well [5-7,9,10]. The exact time point to perform surgery after long course CCRT is still uncertain. In case of short course RT, there are results that longer interval is better but the reported optimal time points are discordant [11-13]. In this investigation, the effect of surgical timing as a mode of intervention to enhance tumor response is explored by comparing short course CCRT with long course CCRT followed by delayed surgery.

Materials and Methods

1. Patient enrollment

The eligibility criteria were as follows: (1) histologically confirmed adenocarcinoma of the rectum; (2) classified as cT3-4N0-2 by magnetic resonance imaging (MRI) and/or endorectal unltrasonography (EUS); (3) no evidence of distant metastasis; (4) no history of other malignancy except for non-melanoma skin cancer; (5) Eastern Cooperative Oncology Group performance status of 0-2; and (6) adequate bone marrow, liver, and kidney functions. Three hundred patients who received preoperative CCRT were included. Half of the patients were enrolled in the short course CCRT group (n=150) and the other half were included in the long course CCRT group (n=150). The short course patients were enrolled in two prospective phase II trials (KROG 10-01 [NCT-01129700] and KROG 11-02 [NCT01431599]) conducted from February 2010 to July 2012 [3,4]. All of these patients were given full information prior to consent for participation in the trials. The long course patients were included in KROG 14-12, a retrospective multicenter investigation, performed between January 2003 and May 2014 [3,14]. The institutional review boards of all the participating institutions as well as the central review board of the KROG approved of the study protocols. Among the 1,804 enrolled long course patients, 150 patients were matched 1:1 to the 150 short course patients using the following criteria: (1) TNM stage, (2) age ±3 years, (3) tumor histology and grade, (4) distance of tumor from anal verge, (5) the level of pre-chemoradiotherapy carcinoembryonic antigen (CEA), (6) the type of surgery, and (7) the year in which surgery was performed (±2 years).

2. Treatment

The short course arm received either 25 Gy in five fractions concurrently with 5-fluorouracil, 400 mg/m^2/day (n=70, KROG 10-01) or 33 Gy in 10 fractions with capecitabine, 825 mg/m^2 twice everyday (n=80, KROG 11-02). The long course arm (n=150, KROG 14-12) underwent pelvic irradiation of 45 Gy in 25 fractions followed by a boost of 5.4 Gy to the rectal mass in three fractions. The long course patients were given one of the following three chemotherapeutic regimens concurrently with RT: (1) intravenous bolus 5-fluorouracil (5-FU; 400 mg/m^2/day) and leucovorin (20 mg/m^2/day) at the first and last weeks of RT, (2) oral capecitabine (825 mg/m^2) twice a day during RT, and (3) continuous 5-FU infusion (225 mg/m^2/day) during RT. The timing of surgery after CCRT was decided at physician's discretion. The time interval between the end of RT and surgery ranged from 4.9 to 14.7 weeks (median, 7.6 weeks). All patients underwent total TME after CCRT. The postoperative chemotherapy was considered according to the institutional policy.

3. Evaluation

Initial staging defined by the American Joint Committee on Cancer criteria, seventh edition, was performed with digital rectal examination, CEA, colonoscopy and biopsy, chest and abdomen computed tomography, pelvic MRI, and EUS if amenable. Certified colorectal pathologists examined the pathologic specimens to report the tumor histology and grade, lymph node metastasis, lymphovascular invasion, perineural invasion, and circumferential resection margin

Table 1. Patient and tumor characteristics of short course and long course groups

Characteristic	Short course (n=150)	Long course (n=150)	p-value
Age (yr)	61 (35-83)	63 (33-81)	
< 60	68 (45.3)	59 (39.3)	0.29
≥ 60	82 (54.7)	91 (60.7)	
Sex			
Male	102 (68.0)	96 (64.0)	0.47
Female	48 (32.0)	54 (36.0)	
Clinical T stage			
cT3	142 (94.7)	138 (92.0)	0.36
cT4	8 (5.3)	12 (8.0)	
Clinical N stage			
cN0	23 (15.3)	34 (22.7)	0.11
cN1-2	127 (84.7)	116 (77.3)	
Histological grade			
WD	19 (12.7)	28 (18.8)	0.11
MD	126 (84.0)	111 (74.5)	
PD	5 (3.3)	10 (6.7)	
Pre-CCRT CEA (ng/mL)	2.8 (0.4-68.1)	3.1 (0-61)	
< 5	112 (74.7)	102 (69.4)	0.31
≥ 5	38 (25.3)	45 (30.6)	
Distance of tumor from anal verge (cm)			
< 5	70 (46.7)	58 (38.7)	0.16
≥ 5	80 (53.3)	92 (61.3)	

Values are presented as median (range) or number (%). WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; CCRT, chemoradiotherapy; CEA, carcinoembryonic antigen.

(CRM). Involved CRM was defined as tumor cell within 1 mm or less from the resection margin. The final pathologic stage of the surgical specimen was compared with the initial clinical stage classified prior to neoadjuvant chemoradiation.

4. Endpoints and statistics

The primary endpoint of this study was to determine the interval between surgery and the last day of neoadjuvant CCRT which yields the best tumor response after the short course and long course CCRT. Secondary endpoint was tumor response after neoadjuvant CCRT evaluated with downstaging and pathologic complete response (ypCR) rates. Downstaging was defined as ypT0-2N0M0 and ypCR was defined as ypT0N0M0, respectively [3,4]. The factors associated with higher downstaging and ypCR rates were also analyzed. The difference between the short course and long course groups were evaluated using chi-squared test, Fisher exact test, Student's t test, and Mann-Whitney U test. The statistical significance was defined as an α-level of 0.05. The statistical analyses were performed using the Microsoft Excel and IBM SPSS standard ver. 24 network (IBM Corp., Armonk, NY).

5. Ethical statement

The study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (IRB No. KC13RIMI0425) and performed in accordance with the principles of the Declaration of Helsinki. Written informed consents were obtained.

Results

The patient and tumor characteristics are summarized in Table 1. The age, sex, initial clinical stage, and histological grades were evenly distributed between the short course and long course groups. There was no difference in pretreatment CEA levels and the distance of tumors from anal verge. The patients were well-balanced between the two groups.

Table 2. The downstaging, ypCR, and sphincter preservation rates

	Short course (n=150)	Long course (n=150)	p-value
Downstaging (ypT0-2N0)			
Yes	49 (32.7)	55 (36.7)	0.40
No	101 (67.3)	95 (63.3)	
ypCR (ypT0N0)			
Yes	12 (8.0)	20 (13.3)	0.10
No	138 (92.0)	130 (86.7)	
Sphincter preservation			
Yes	141 (94.0)	141 (94.0)	> 0.99
No	9 (6.0)	9 (6.0)	

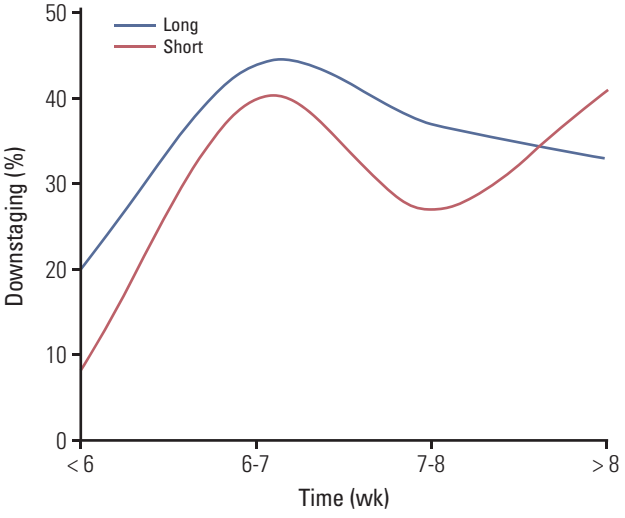
ypCR, pathologic complete response.

1. Tumor response and sphincter preservation

Downstaging was achieved in 32.7% (n=49) of the short course arm compared to 36.7% (n=55) of the long course group without statistically significant difference. There was no difference in the ypCR rates between the two groups (short course 8% vs. long course 13.3%, p=0.1). The sphincter preservation rates were identical between the two groups (94%, n=141 in both groups). The tumor response and sphincter preservation rates are summarized in Table 2.

2. Tumor response according to interval between chemoradiation and surgery

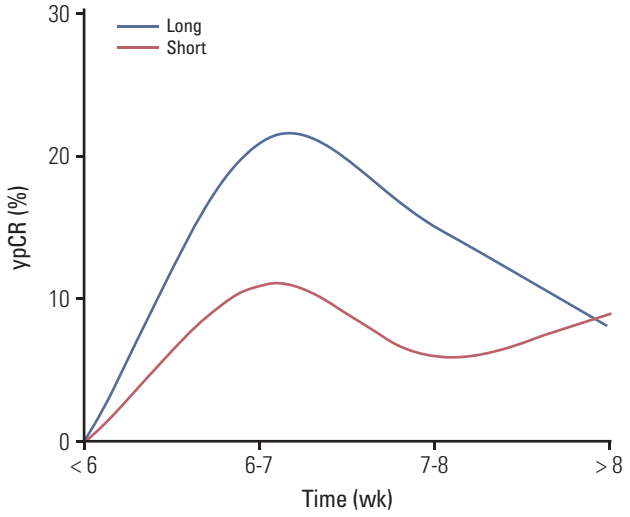
The downstaging rates and ypCR rates by weeks of the long course group were numerically higher than those of the short course group but the differences were statistically insignificant. The downstaging rates of the long course and short course arms by weeks are plotted in Fig. 1. Both the long and short course groups achieved lowest downstaging rates at < 6 weeks and highest downstaging rates at 6-7 weeks. In long course arm, the downstaging rate of 20% at < 6 weeks was much lower than the total rate of 37%. The peak downstaging rate at 6-7 weeks (44%) seemed to be higher than the total rate. Similarly, in the short course arm, the downstaging rate at < 6 weeks (8%) was markedly lower than the total rate of 33%. The rate at 6-7 weeks (40%) was higher than the total rate. However, after the peak at 6-7 weeks, long course and short course groups showed different pattern of downstaging rates. The rates of long course patients gradually declined after the peak at 6-7 weeks with a rate of 33% at > 8 weeks, which was lower than the total rate of 37%. On the other hand, the rate of the short course patients trends to constantly increase except for a temporary drop at 7-8 weeks.



	Weeks	< 6	6-7	7-8	> 8	Total
Long course	Downstaging	1	15	23	16	55
	Patients	5	34	62	49	150
	Downstaging rate (%)	20	44	37	33	57
Short course	Downstaging	1	21	14	13	49
	Patients	13	53	52	32	150
	Downstaging rate (%)	8	40	27	41	33

Fig. 1. Distribution of downstaging rates by weeks since completion of radiotherapy to surgery in short course and long course patients.

Likewise, in Fig. 2, the ypCR rates were lowest at < 6 weeks and highest at 6-7 weeks in both the short and long course arms. Both arms had ypCR rates of 0% at < 6 weeks. The highest ypCR rate of 21% at 6-7 weeks was numerically



	Weeks	< 6	6-7	7-8	> 8	Total
Long course	ypCR	0	7	9	4	20
	Patients	5	34	62	49	150
	ypCR rate (%)	0	21	15	8	13
Short course	ypCR	0	6	3	3	12
	Patients	13	54	51	32	150
	ypCR rate (%)	0	11	6	9	8

Fig. 2. Distribution of pathologic complete response (ypCR) rates by weeks since completion of radiotherapy to surgery in short course and long course patients.

higher than the total rate of 13% in the long course group. The ypCR rate of short course arm also peaked at 6-7 weeks achieving 11%, which was higher compared with the total rate of 8%. The patterns of ypCR rate by weeks in both groups were also similar to those of the downstaging rate. The rates of long course patients gradually declined after the peak at 6-7 weeks with a rate of 8% at > 8 weeks, which was definitely lower than the total rate of 13%. On the other hand, the rates of the short course patients trend to constantly rise except for a temporary drop at 7-8 weeks. Of note, there were higher rates of patients with adverse factors included in the 7-8 weeks compared with those of the rest of the weeks. The rates of adverse factors were as follows: (1) T4 primary, 7-8 weeks 9.1% vs. other weeks 4.3%; (2) node positivity, 7-8 weeks 87.9% vs. other weeks 83.8%; and (3) involved CRM, 7-8 weeks 12.1% vs. 7.7%.

3. Factors associated with tumor response

The factors associated with downstaging after short course and long course CCRT are summarized in Table 3. In univariate analysis, lower CEA, anal verge (AV) < 5 cm, and 6- to 7-week interval between RT and surgery were associated with higher odds for downstaging. In multivariate analysis, age < 60 years, CEA < 5 ng/mL, distance of tumor from AV < 5 cm, and 6- to 7-week interval between RT and surgery were statistically significant factors for downstaging. Table 3 also shows the factors associated with ypCR after short course and long course CCRT. Lower CEA was the only factor which was significantly associated with ypCR in both the univariate and multivariate analyses. Six- to 7-week interval between RT and surgery was marginally associated with ypCR in univariate analysis and the significance was not retained in the multivariate analysis.

Discussion

The treatment of LARC has evolved continuously over the past decades. For surgery, TME has become the current standard since first reported by Heald et al. in 1982 [15]. Likewise, the contemporary regimens of preoperative RT and CCRT have constantly developed since the 1980s [16-18]. Since the establishment of these treatments as the standard, the importance of when to operate after the completion of neoadjuvant therapy has been recognized. Both short course RT and long course CCRT are feasible based on the results of a phase III trial which compared the two options and reported comparable outcome [18]. The virtue of short course RT is in its rapidity. Therefore, most patients were operated immediately after short course RT. On the contrary, surgery was performed with longer interval after long course CCRT. Consequently, most studies reporting the impact of surgical timing is predominantly on the long course CCRT.

In prospective trials comparing immediate versus delayed surgery after long course CCRT, there was no statistically significant difference in tumor response between short and long intervals. The long course CCRT was given up to 45-54 Gy in conventional fractionation. Stein et al. [5] reported 7% higher ypCR rate in the long interval group (p=0.97). In a study by Fang et al. [19] and colleagues, ypCR rate was 6.6% higher in the short interval group (p=0.37). The recently published GRECCAR-6 trial reported that there was no difference in ypCR rate between the 7-week (15%) and 11-week (17.4%) groups (p=0.60) [9]. In retrospective analyses, there were some reports with significantly different tumor response between short and long intervals. The ypCR rates were superior in the long interval group in studies by Tulchinsky et al. (long 34.5% vs. short 16.7%, p=0.03) [6] and de Campos-Lobato et al. (long 31.1% vs. short 16.2%, p=0.03) [20]. On the contrary, ypCR rate was higher in the short

Table 3. Factors associated with downstaging and ypCR after chemoradiation

	Downstaging after chemoradiation					ypCR after chemoradiation				
	Downstaging, n (%)		Odds ratio (95% confidence interval)	p-value		ypCR, n (%)		Odds ratio (95% confidence interval)	p-value	
	No (n=196)	Yes (n=104)		Univariate	Multivariate	No (n=268)	Yes (n=32)		Univariate	Multivariate
Age (yr)										
< 60	85 (43.4)	42 (40.4)	1.0	0.21	0.01	111 (41.4)	16 (50.0)	1.0	0.07	< 0.01
≥ 60	111 (56.6)	62 (59.6)	0.6 (0.4-0.9)			157 (58.6)	16 (50.0)	0.3 (0.2-0.8)		
Sex										
Male	138 (70.4)	60 (57.7)	1.0	0.08	0.07	182 (67.9)	16 (50.0)	1.0	0.06	0.06
Female	58 (29.6)	44 (42.3)	1.5 (1.0-2.2)			86 (32.1)	16 (50.0)	2.0 (1.0-4.1)		
CEA (ng/mL)										
< 5	124 (63.9)	90 (87.4)	1.0	< 0.01	< 0.01	185 (69.5)	29 (93.5)	1.0	0.03	0.02
≥ 5	70 (36.1)	13 (12.6)	0.4 (0.2-0.7)			81 (30.5)	2 (6.5)	0.2 (0.0-0.8)		
Clinical T stage										
T3	180 (91.8)	100 (96.2)	1.0	0.11	0.49	248 (92.5)	32 (100)	1.0	0.29	0.88
T4	16 (8.2)	4 (3.8)	0.7 (0.2-1.9)			20 (7.5)	0	0.0		
Clinical N stage										
N0	29 (14.8)	28 (26.9)	1.0	0.12	0.73	49 (18.3)	8 (25.0)	1.0	0.60	0.80
N+	167 (85.2)	76 (73.1)	0.9 (0.6-1.5)			219 (81.7)	24 (75.0)	1.1 (0.5-2.5)		
Differentiation										
Well-Moderate	179 (91.8)	104 (100)	1.0	0.11	0.96	251 (94.0)	32 (100)	1.0	0.38	0.90
Poor	16 (8.2)	0	0.0			16 (6.0)	0	0.0		
Distance of tumor from anal verge (cm)										
< 5	71 (36.2)	57 (54.8)	1.0	0.04	0.049	110 (41.0)	18 (56.3)	1.0	0.20	0.20
≥ 5	125 (63.8)	47 (45.2)	0.7 (0.4-0.99)			158 (59.0)	14 (43.8)	0.6 (0.3-1.3)		
Interval to surgery after radiotherapy										
Others	145 (74.0)	68 (65.4)	1.0	< 0.01	< 0.01	194 (72.4)	19 (59.4)	1.0	0.09	0.88
6-7 wk	51 (26.0)	36 (34.6)	82.7 (19.5-350.3)			74 (27.6)	13 (40.6)	5.3×10^5 ($0.3\text{-}3.9\times10^6$)		

ypCR, pathologic complete response; CEA, carcinoembryonic antigen.

interval group according to an analysis by Habr-Gama et al. (short 11% vs. long 6%, p=0.009) [7]. Thus, there is still no consensus whether short or long interval yields better tumor response. Moreover, the criteria that divide short and long intervals are different among studies so it is difficult to propose a specific interval as the optimal time to perform surgery after long course CCRT.

The impact of surgical timing after short course RT alone has also been investigated. In the Lyon R90-01 trial, surgery was performed either within 2 weeks (short interval group) or 6-8 weeks (long interval group) after delivery of 39 Gy in 13 fractions [13]. Pathologic downstaging was observed more in the long interval group (p=0.007). A pooled analysis of the Dutch trial reported that pathologic stage was lower in patients who were operated after 8 days compared with patients who were immediately operated ($p < 0.001$) [11]. Even though there is consensus that delayed surgery yields greater pathologic response, the optimal timing of surgery after short course RT is also controversial.

In case of short course CCRT, no previous studies have reported the optimal timing of surgery. The outcomes of short course CCRT have been reported but the interval between surgery and CCRT were never a primary endpoint [3,14,21]. The ypCR rates after short course CCRT have been reported up to 21.1%, which is fairly comparable to those after long course CCRT or short course RT alone.

To find out the optimal time of surgery yielding maximal tumor response, we balanced the pretreatment demographics of short course and long course CCRT patients and then analyzed the pathologic response per weeks between neoadjuvant therapy and surgery. According to our data, the 6- to 7-week interval between RT and surgery was significantly associated with downstaging in multivariate analysis. Its association with ypCR was only marginal in univariate analysis due to the small number of events. In general, the response rate increased after 6 weeks but we also noticed a pattern that tumor response was different by weeks. This phenomenon may be explained by the pattern of response rather than a simple binary division of high or low response rate between a single time point. Previous studies were based on dichotomous analysis that tried to define a single time point. This may be one of the reasons why the interval criteria were different among previous studies and a single, clear-cut conclusion could not be drawn.

In addition, we noted that the patterns of pathologic response were different between short course and long course CCRT. Although as a hypothesis, this phenomenon directed our interest towards the radiobiology arising from the difference in delivered radiation between the two courses. Tumor response comes from the death of tumor cells. However, tumor cells go through accelerated repopulation which starts approximately 4 weeks after initiation of RT [22]. Accelerated repopulation is a response to radiation injury in the normal and tumor cells. Thus, it persists as long as the radiation injury continues. While accelerated repopulation is a phenomenon of the surviving clonogen, tumor regression is that of the sterilized cells. Tumor regression, which progresses regardless of radiation injury, may coexist with accelerated repopulation, which is induced by radiation injury.

Considering that accelerated repopulation starts 4 weeks after beginning RT, short course CCRT which has an overall treatment time of within 2 weeks is finished before accelerated repopulation begins. Tumor response rate increases with longer interval between RT and surgery. No specific interval for tumor regression has been reported in the *in vivo* and *in vitro* preclinical studies since they cannot be indefinitely observed. Surgery was performed median 13.1 weeks after initiation of RT and median 7.7 weeks after completion of RT in our data. In the literature, tumor regression was observed up to 20 weeks after initiation of RT in the British study and > 11 weeks after completion of RT in the Dutch study [23,24]. Thus, longer interval between short course CCRT and surgery will improve tumor response [25]. This phenomenon was also observed in our short course CCRT data which showed increment of tumor response rate after 6 weeks except for a transient drop at 7-8 weeks. Particularly high proportion of patients with poor prognostic factors was included at 7-8 weeks.

In case of long course RT, the epithelial tumor cells are known to go through accelerated repopulation by 4 to 6 weeks and require approximately 0.6 Gy/day to overcome the effect of repopulation [26]. The total treatment time in our long course CCRT group was 5.5 weeks, so given that accelerated repopulation starts at 4 weeks, the last 1.5 weeks (10 days) were under the effect of accelerated repopulation. As shown in Table 4, 6 Gy is required to overcome the treatment prolongation of 10 days in the long course arm. When the total doses for short course arm were converted to equivalent dose in 1.8 Gy fractions (EQD 1.8) and then compared with the total dose of long course arm, despite the 6 Gy loss caused by accelerated repopulation, long course arm still received 7.2-12.6 Gy more than the short course arm. Consequently, the difference in EQD 1.8 between the short and the long course arms led to the difference in the ypCR rate, which was numerically 5.3% higher in the long course arm.

The tumor response rate showed a peak at RT-surgery interval of 6-7 weeks and then declined afterwards. This appears to be because accelerated repopulation overcomes the increased tumor response by prolongation of interval at 6-7 weeks, or 11-12 weeks since the initiation of RT. There are several factors explaining the gap between the previously reported period of repopulation (4-6 weeks) and the point where tumor response declined (11-12 weeks) in our data.

Table 4. Dose and schedule difference leading to different patterns of pathologic complete response rate between the short course and the long course concurrent chemoradiotherapy groups

Course	Short		Long
Total dose (Gy)	25	33	50.4
Fractions	5	10	28
EQD 1.8 (Gy), a/b=10	31.8	37.2	50.4
BED (Gy), a/b=10	37.5	43.9	59.5
Median RT duration (day)	5	11	38
RT duration > 4 wk (when accelerated repopulation begins)	No	No	Yes
Possibility for accelerated repopulation, RT duration-wise	No	No	Yes
Pattern of ypCR by weeks after RT	↑ by weeks	↑ by weeks	↓ after 6-7 weeks
No. of days exceeding 4 wk (day)	-	-	10
Additional dose needed to overcome treatment prolongation (Gy)	-	-	6
Actual total dose considering the effect of treatment prolongation (Gy in EQD 1.8, a/b=10)	31.8	37.2	44.4
Additional dose needed for equivalent treatment effect as 44.4 Gy (Gy in EQD 1.8, a/b=10)	12.6	7.2	-
Total No. of patients	70	80	150
No. of patients with ypCR	3	9	20
Patient with ypCR (%)	4.3	11.3	13.3

EQD 1.8, equivalent dose in 1.8 Gy fractions; BED, biologically effective dose; RT, radiotherapy; ypCR, pathologic complete response.

Most reports of epithelial tumor cell repopulation are predominantly squamous cell carcinoma although the repopulation in adenocarcinoma has also been rarely documented [22,27]. Since accelerated repopulation is a response to radiation-induced injury, it may be observed not only in squamous cell carcinoma but also in adenocarcinoma. A Polish study reported that accelerated repopulation measured by tumor proliferation markers in rectal adenocarcinoma specimens obtained at diagnosis and surgery occurred approximately 4 weeks after completion of RT [28]. Previous reports are based on the data after RT alone but we delivered CCRT. Chemotherapeutic agents have been suggested to have a role in inhibition of tumor repopulation [29]. According to our data, preoperative CCRT delays tumor repopulation so that we can earn time to gain maximal pathologic tumor regression. Another reason may be due to the difference in outcome measures. The tumor response was determined by pathologic examination in our study while most of the previous data on accelerated repopulation evaluated clinical response [26]. Clinically complete response may still bear microscopic residual disease and longer time is required to obtain ypCR. Thus, we observed maximal tumor response > 6 weeks after long course CCRT and also after short course CCRT. The underlying concept of radiobiologic hypothesis

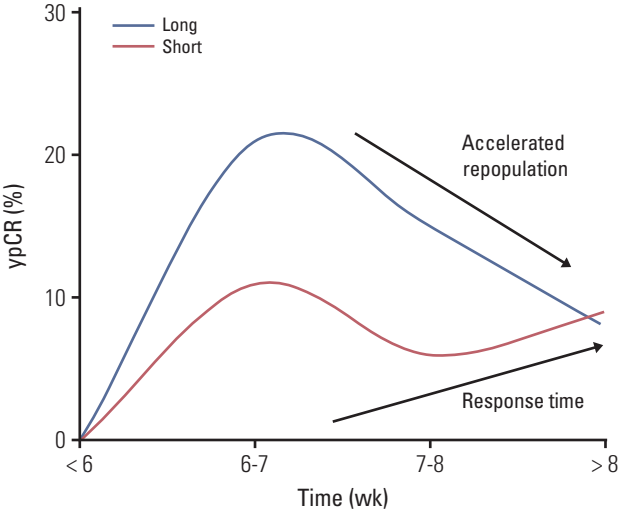


Fig. 3. A hypothesis of radiobiology behind the difference in distribution of pathologic complete response (ypCR) rates by weeks since completion of radiotherapy to surgery in short course and long course chemoradiation.

Table 5. The treatment characteristics, surgical timing, and tumor response between key prospective studies and current study

RT course	Group/Trial (year)	RT dose (Gy)	No.	Chemotherapy	Interval criteria	Endpoint	Response rate (%)	p-value
Long course CCRT	Stein et al. (2003) [5]	45-54	33	5-FU+irinotecan intravenous continuous infusion	4-8 wk vs. 10-14 wk	ypCR	14 vs. 21	0.97
	Fang et al. (2013) [19]	50.4	106	5-FU+leucovorin intravenous bolus 1st and 5th weeks	5-6 wk vs. > 6 wk	ypCR	18.8 vs. 12.2	0.37
	GRECCAR-6 (2016) [9]	45-50	265		7 wk vs. 11 wk	ypCR	15 vs. 17.4	0.60
Short course RT	Lyon R90-01 (1999) [13]	39	201	-	≤ 2 wk vs. 6-8 wk (median 13 days vs. 46 days)	Pathologic downstaging	10.3 vs. 26	< 0.01
	Van den Broek et al. (2013) [11]	25	642	-	< 8 days vs. ≥ 8 days	Pathologic stage	Lower in ≥ 8 days	< 0.01
Long course CCRT	This study (2016)	50.4	150	5-FU+Leucovorin intravenous bolus 1st and 5th weeks	≤ 6 wk vs. > 6 wk	ypCR	0 vs. 13	0.69
Short course CCRT		33	150	Oral capecitabine		ypCR	0 vs. 8	0.27
		25		5-FU+leucovorin intravenous bolus during RT days				

RT, radiotherapy; CCRT, concurrent chemoradiotherapy; 5-FU, 5-fluorouracil; ypCR, pathologic complete response.

is illustrated in Fig. 3.

We concentrated on radiobiolgically understanding the pattern of tumor response by weeks between RT and surgery. However, an interval criterion may also be derived from our data and is summarized with previous studies as shown in Table 5. Since the best response was observed in 6-7 weeks and all pathologic response appeared after 6 weeks, the minimum interval required to acquire desirable pathologic response is over 6 weeks. In that sense, our data is in accordance with previous studies on surgical timing, which generally suggest 6-8 weeks after long course CCRT or short course RT alone [13,30].

However, accelerated repopulation continues until the integrity of tissue is restored [31]. Considering the duration of acute toxicity is within 3 months, the duration of accelerated repopulation can be estimated to last approximately 12 weeks. To identify the duration of accelerated repopulation, we attempted to analyze the difference in ypCR rates between 8-12 weeks versus > 12 weeks. However, due to the reduction of resectability with longer surgical interval caused by fibrosis, there were too small number of patients operated after 12 weeks and was inadequate for analysis. Therefore, after 6-7 weeks, our data mainly comprises 8-12 weeks rather than > 12 weeks, which makes the ypCR rate curve look constantly declining.

The results of randomized trials conducted by the Royal Marsden Hospital (RMH) and the French group (GRECCAR-6) were recently reported. The trial designs were similar, comparing 6 weeks versus 12 weeks in the RMH trial and 7 weeks vs. 11 weeks in the GRECCAR-6 trial. However, the results were controversial and the RMH trial reported superior tumor response in the 12-week group while the GRECCAR-6 trial reported no difference in tumor response, sphincter preservation rate, and surgical complication between the 7-week and the 11-week groups [9,32].

Due to the novelty of short course CCRT, we did not have the luxury of a study population large enough to achieve statistically significant difference. To the best of our knowledge, we are the first to analyze the pathologic response by surgical timing in both short course and long course CCRT. We are also the first group to observe the pattern of tumor response by weeks and make a radiobiologically hypothetical approach. However, this is our major limitation. Although pertinent, our explanation for the difference in pattern between the short course and long course arms are based on the hypothesis of accelerated repopulation. Another limitation is that due to the small sample size, the difference between the two groups were numerical.

Although there is no high level evidence that ypCR directly correlates with survival as of yet, it is well-documented that patients who yielded ypCR at surgery have more favorable outcome at individual levels [33]. Thus, we analyzed the effect of surgical timing on pathologic tumor response. However, toxicity is another important endpoint in neoadjuvant therapy of LARC and we are still under the process of toxicity evaluation. Because toxicity deals with normal tissue and it has different alpha/beta ratio compared with tumor, we are planning to report it separately in the near future. Other endpoints commonly adopted in the neoadjuvant therapy of LARC are sphincter preservation rate and R0 resection rate. Since they are vulnerable to surgical factors, we did not take them under consideration. The ypCR rates in this study are a few percents lower than other data. This means our pathologic evaluation was more vigorously and thoroughly performed.

In conclusion, it is optimal to perform surgery at least 6 weeks after short course and long course CCRT in order to obtain maximal tumor regression in rectal adenocarcinoma. However, according to the results of recently reported randomized trials, it is still controversial whether surgery should be further delayed up to 11 to 12 weeks after completion of RT. Although the tumor response rates were comparable between short course and long course CCRT, the patterns of pathologic response were different by weeks of surgical timing between short course and long course CCRT.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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