JBUON 2019; 24(2): 470-478
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Differential effect of concurrent chemotherapy regimen on clinical outcomes of preoperative chemoradiotherapy for locally advanced rectal cancer

Eunji Kim[1], Kyubo Kim[2], Do Hoon Oh[3], Sae-Won Han[4], Tae-You Kim[4], Seung-Yong Jung[5], Kyu Joo Park[5], Gyeong Hoon Kang[6], Eui Kyu Chie[1,7]

Departments of [1]Radiation Oncology, [4]Internal Medicine, [5]Surgery, and [6]Pathology, Seoul National University College of Medicine, Seoul, Republic of Korea; [2]Department of Radiation Oncology, Ewha Womans University School of Medicine, Seoul, Republic of Korea; [3]Department of Radiation Oncology, Chung-Ang University Hospital, Seoul, Republic of Korea; [7]Institute of Radiation Medicine, Medical Research Center, Seoul National University, Seoul, Republic of Korea.

Summary

Purpose: *The purpose of this study was to evaluate the differential effect of chemotherapy regimen in preoperative chemoradiotherapy (CRT) for locally advanced rectal cancer.*

Methods: *The medical records of 279 patients who underwent preoperative CRT followed by surgery for cT3/4 rectal cancer from 2003 to 2010 were retrospectively reviewed. Thirty-four patients were treated with one cycle of i.v. bolus 5-fluorouracil (5-FU) during 1st week (group A), 214 patients with two cycles of i.v. bolus 5-FU during 1st and 5th week (group B), and 31 patients with oral capecitabine on the days with radiotherapy (group C). Propensity score matching was performed between three groups.*

Results: *Median follow-up was 60.1 months. Five-year locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS) and overall survival (OS) rates were 91.2, 83.3, 75.0, and 84.5%, respectively. Thirty-one patients per group were allocated to three groups via propensity score matching. On univariate analysis, concurrent chemotherapy regimen was not a significant prognostic factor for survival outcomes in the matched group analysis (OS, p=0.175; DFS, p=0.481; DMFS, p=0.515; LRFS, p=0.456). In addition, there was no significant difference in the sphincter preserving surgery rate, circumferential resection margin status, and pathologic response between three groups (p=0.441, 1.000, 0.818, respectively). As regards to treatment-related toxicity, 9 patients showed grade 3 neutropenia in group B, while there was no grade 3 or higher toxicity in groups A and C.*

Conclusion: *The concurrent chemotherapy regimen (5-FU #1 vs 5-FU #2 vs capecitabine) did not have a significant effect on treatment outcomes in locally advanced rectal cancer patients receiving neoadjuvant CRT.*

Key words: *chemoradiotherapy, chemotherapy regimen, neoadjuvant, rectal cancer*

Introduction

Several phase 3 studies showed that preoperative chemoradiotherapy (CRT) and total mesorectal excision is the standard of care for locally advanced rectal cancer [1-4]. More recent studies have intensified neoadjuvant CRT by adding oxaliplatin to standard regimen in locally advanced rectal cancer based on the results from an adjuvant treatment trial in stage III colon cancer [5]. Although the effect of oxaliplatin was mixed in advanced rectal cancer, the toxicity of treatment was increased with intensified chemotherapy [6-10]. In addition, the long-term outcome of the European Organisation

Correspondence to: Eui Kyu Chie, MD, PhD. Department of Radiation Oncology, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea.
Tel: +82 2 2072 3705, Fax: +82 2 765 3317, E-mail: ekchie93@snu.ac.kr
Received: 14/06/2018; Accepted: 12/07/2018

for Research and Treatment of Cancer 22921 trial failed to confirm the benefit of both preoperative and postoperative chemotherapy. Although this trial focused on the long-term effect of adjuvant chemotherapy, it also showed that preoperative chemotherapy does not affect 10-year DFS or OS [11].

Various concurrent chemotherapy regimens have been used to date in previous clinical trials [12-14]. It is still unclear which of these regimens is optimal. According to the NCCN guidelines, 5-fluorouracil (5-FU) and capecitabine are recommended as concurrent chemotherapy regimen [15]. In our institute, patients were treated with single or two cycles of 5-FU and capecitabine, based on previous studies [2-4,16]. Although the chemotherapy regimen has changed over time, the difference in treatment outcome was not analyzed. Therefore, we retrospectively analyzed locally advanced rectal cancer patients who were treated with neoadjuvant CRT followed by surgery to evaluate the impact of a single cycle of 5-FU compared to two cycles of 5-FU and capecitabine on clinical outcomes.

Methods

Patients

After institutional review board approval, we reviewed the medical records of patients who underwent preoperative CRT followed by surgery between July 2003 and December 2010. The inclusion criteria were as follows: (1) histologically confirmed rectal adenocarcinoma, (2) clinical T3-4, (3) no evidence of distant metastasis, and (4) total mesorectal excision following preoperative CRT. Patients with any other malignancies at diagnosis were excluded. All patients were examined with digital rectal examination, complete blood count, liver function tests, carcinoembryonic antigen level, colonoscopy, and computed tomography. Magnetic resonance imaging was also used in the majority of patients. Selected patients, treated more recently, also underwent positron emission tomography. Pathology of primary rectal lesion was confirmed by biopsy prior to treatment in all patients.

Treatment

After histologic and clinical diagnosis of primary rectal cancer, all 279 patients underwent preoperative concurrent CRT and total mesorectal excision. For radiotherapy, all patients were treated with 3-dimensitonal conformal radiotherapy in prone position. The gross tumor volume (GTV) consisted of tumor and suspicious lymph nodes at diagnostic work-up. The clinical target volume (CTV) covered GTV, mesorectal tissues and regional lymphatics such as the perirectal, presacral, and internal iliac nodes. The planning target volume (PTV) included the CTV plus a 1 cm margin. Dose prescription was 45 Gy in 25 fractions to PTV, followed by 5-9 Gy in 3-5 fractions to primary lesion and enlarged pelvic lymph nodes plus 1cm margin. The median total radiation dose was 50.4 Gy (range, 45-54).

Thirty-four patients received 5-FU (500 mg/m^2) intravenous (i.v.) bolus injection for 3 days during the first week of radiotherapy (Group A), 214 patients with two cycles of i.v. bolus 5-FU during 1st and 5th week of radiotherapy (Group B), and 31 patients with capecitabine (1650 mg/m^2) daily, on the days with radiotherapy (Group C). Our institute experienced a change in the concurrent chemotherapy regimen during neoadjuvant CRT from 2003 to 2010. When the concurrent chemotherapy was divided by time, all patients in group A were treated before 2008. More recently treated patients received two cycles of 5-FU or capecitabine.

Table 1. Patient and treatment characteristics (n=279)

Characteristics	*n (%)*
Age, years	
< 70	237 (84.9)
≥ 70	42 (15.1)
Gender	
Male	202 (72.4)
Female	77 (27.6)
ECOG performance status	
0, 1	276 (98.9)
2	3 (1.1)
Clinical T stage	
T3	258 (92.5)
T4	21 (7.5)
Clinical N stage	
N (-)	56 (20.1)
N (+)	223 (79.9)
Distance from anal verge, cm	
≤5	181 (64.9)
>5	98 (35.1)
Pretreatment CEA level, ng/mL	
≤5	197 (70.6)
>5	82 (29.4)
Pretreatment Hb level, g/dL	
<12 g/dL	157 (56.3)
≥12 g/dL	122 (43.7)
Concurrent chemotherapy	
5-FU #1	34 (12.2)
5-FU #2	214 (76.7)
Capecitabine	31 (11.1)
Sphincter preserving surgery	
Yes	260 (93.2)
No	19 (6.8)
Adjuvant chemotherapy	
Yes	248 (88.9)
No	31 (11.1)

CEA: carcinoembryonic antigen, Hb: hemoglobin

Surgery was performed at a median 57 days after preoperative CRT. The majority of patients (n=260, 93.2%) had sphincter preserving surgery. Abdominoperineal resection was performed in 18 patients. Adjuvant chemotherapy was administered to 248 patients (88.9%). Thirty one patients did not receive postoperative chemotherapy. The reasons of omission were as follows: pathologic complete regression in 8 patients, patient refusal in 15 patients, old age in 3 patients, medical comorbidity in 2 patients, and transfer to other hospital in 3 patients. The regimens of postoperative chemotherapy were fluorouracil-leucovorin (n=203), capecitabine (n=30), and FOLFOX (n=15).

Follow-up and statistical analysis

The date of endoscopic biopsy of primary tumor was used as the date of diagnosis. OS was defined as the interval from the date of diagnosis to the date of death from any cause. DFS was defined as the time from the date of diagnosis to any recurrent disease detection. DMFS was defined as the interval from the date of diagnosis to distant metastasis detection. LRFS was defined as the time from the date of diagnosis to the date of locoregional relapse detected in pelvic cavity.

Therapeutic response on surgical specimen was graded according to the Korean pathology standard report [17]. This report classified the pathologic effect from

Supplementary Table 1. Univariate analysis of factors affecting 5-yr clinical outcomes

Variables	*N*	*OS (%)*	*p value*	*DFS (%)*	*p value*	*DMFS (%)*	*p value*	*LRFS (%)*	*p value*
Age, years			0.133		0.245		0.5		0.663
≥ 65	188	78.9		71.2		86.5		95.1	
< 65	91	87.2		76.6		81.9		89.7	
Gender			0.037		0.064		0.089		0.690
Male	202	81.8		72.2		81.2		89.5	
Female	77	91.8		82.3		89.0		92.0	
Distance from AV, cm			0.001		0.021		0.019		0.073
≤ 5	181	79.8		70.6		79.1		89.6	
> 5	98	93.3		80.6		91.3		94.4	
Pathologic T stage			0.005		< 0.001		0.005		0.009
ypT0-1	54	96.3		96.2		98.1		100.0	
ypT2-4	225	81.5		69.8		79.6		88.7	
Pathologic N stage			< 0.001		< 0.001		< 0.001		< 0.001
ypN0	202	90.4		83.3		88.4		94.7	
ypN1-2	77	69.1		54.0		69.5		81.2	
Angiolymphatic invasion			< 0.001		0.001		0.002		0.092
Yes	34	66.8		54.2		65.6		81.2	
No	245	87.0		77.8		85.7		92.3	
Venous invasion			< 0.001		0.001		0.265		0.032
Yes	12	50.0		41.7		74.1		76.2	
No	267	86.1		76.5		83.7		91.9	
Perineural invasion			< 0.001		< 0.001		< 0.001		< 0.001
Yes	37	55.0		39.4		54.3		70.3	
No	242	88.9		80.5		87.7		93.8	
CRM status, cm			0.001		0.001		0.005		0.003
≤ 0.1	28	66.7		53.1		67.1		81.0	
> 0.1	251	86.6		77.7		85.1		92.2	
CRT response[†]			< 0.001		< 0.001		0.015		0.004
< Grade 4	191	79.7		68.1		79.5		88.3	
≥ Grade 4	88	94.2		89.3		91.5		97.0	
Concurrent chemotherapy			0.26		0.768		0.499		0.081
5-FU #1	34	79.4		70.4		88.2		81.7	
5-FU #2	214	84.8		76.6		83.6		93.2	
Capecitabine	31	87.1		70.5		76.6		89.6	

[†] By Korean pathology standard report; grade 4 refers to near total regression, OS: overall survival, DFS: disease-free survival, DMFS: distant metastasis-free survival, LRFS: locoregional recurrence-free survival, PS: performance status, AV: anal verge, CRM: circumferential resection margin, CRT: chemoradiotherapy

no regression to total regression as reported in previous studies [18,19]. The toxicities from radiotherapy were evaluated with the Common Terminology Criteria for Adverse Events (CTCAE) 4.0.

For the statistical analyses among treatment groups, the Pearson chi-square and the Fisher exact test were used. The Kaplan-Meier method was used to estimate survival rates. The log-rank test and the Cox proportional hazards regression model were used for the univariate and multivariate analyses, respectively. Factors with a p value less than 0.05 were regarded as statistically significant. Propensity score matching was performed

Table 2. Multivariate analysis of factors affecting clinical outcome

Variables	*OS, p value*	*DFS, p value*	*DMFS, p value*	*LRFS, p value*
Tumor location (AV > 5cm vs. ≤ 5cm)	0.003	0.012	0.032	-
Pathologic N-stage (ypN0 vs. ypN1,2)	0.005	0.001	0.026	0.021
Perineural invasion (No vs. Yes)	< 0.001	< 0.001	< 0.001	< 0.001
CRT response† (≥ Grade 4 vs. < Grade 4)	0.025	-	-	-

† By Korean pathology standard report; grade 4 refers to near total regression, OS: overall survival, DFS: disease-free survival, DMFS: distant metastasis-free survival, LRFS: locoregional recurrence-free survival, AV: anal verge, CRT: chemoradiotherapy

Supplementary Table 2. Patient and treatment characteristics according to concurrent chemotherapy

Variables	*No. of patients (%)*				*p value*
	Total (n=279)	*5-FU #1 (n=34)*	*5-FU #2 (n=214)*	*Capecitabine (n=31)*	
Age, years					0.160
< 70	237 (84.9)	31 (91.2)	177 (82.7)	29 (93.5)	
≥ 70	42 (15.1)	3 (8.8)	37 (17.3)	2 (6.5)	
Gender					0.139
Male	202 (72.4)	25 (73.5)	150 (70.1)	27 (87.1)	
Female	77 (27.6)	9 (26.5)	64 (29.9)	4 (12.9)	
ECOG performance status					0.004
0, 1	276 (98.9)	32 (94.1)	214 (100)	30 (96.8)	
2	3 (1.1)	2 (5.9)	0 (0.0)	1 (3.2)	
Clinical T stage					0.619
T3	258 (92.5)	31 (91.2)	197 (92.1)	30 (96.8)	
T4	21 (7.5)	3 (8.8)	17 (7.9)	1 (3.2)	
Clinical N stage					0.297
N (-)	56 (20.1)	10 (29.4)	39 (18.2)	7 (22.6)	
N (+)	223 (79.9)	24 (70.6)	175 (87.8)	24 (77.4)	
Distance from anal verge, cm					0.001
≤ 5	181 (64.9)	26 (76.5)	127 (59.3)	28 (90.3)	
> 5	98 (35.1)	8 (23.5)	87 (40.7)	3 (9.7)	
Pretreatment Hb level, g/dL					0.064
< 12	157 (56.3)	21 (61.8)	113 (52.8)	23 (74.2)	
≥ 12	122 (43.7)	13 (38.2)	101 (47.2)	8 (25.8)	
Sphincter preserving surgery					0.001
Yes	260 (93.2)	27 (79.4)	206 (96.3)	27 (87.1)	
No	19 (6.8)	7 (20.6)	8 (3.7)	4 (12.9)	
Adjuvant chemotherapy					0.620
Yes	248 (88.9)	30 (88.2)	192 (89.7)	26 (83.9)	
No	31 (11.1)	4 (11.8)	22 (10.3)	5 (6.1)	

Hb: hemoglobin

to minimise the bias between the groups. One-to-one matching was performed using the nearest-neighbour method. The analyses were performed using PASW Statistics for Windows, Version 23.0 (SPSS Inc., Chicago, IL, USA) and R version 3.4.0 (http://cran.rproject.org) with the MatchIt package for propensity score matching.

Results

Patients and treatment characteristics

A total of 279 patients who were diagnosed with locally advanced rectal cancer were treated with preoperative CRT and operation. Patient characteristics at baseline are shown in Table 1. The median age was 59 years (range, 31-82). All patients except three had an ECOG performance status of 0 or 1. The median CEA levels were 2.9 ng/ml (range, 0.9-330) at diagnosis and 1.3 ng/ml (range, 0.1-7.8) after surgery.

Treatment response

The median follow-up time was 60.1 months (range, 6-128). Complete tumor regression was found in 40 patients (14.3%) and 48 patients (17.2%) showed near total regression. The ypT stage was classified as ypT0-ypT1 and ypT2-ypT4 for statistical analysis. More than half of the patients had post-treatment pathologic stage of ypT3 (ypT0 14.0%; ypTis 0.7%; ypT1 5.4%; ypT2 24.7%; ypT3 54.8%; ypT4 0.4%). Regarding ypN stage, 202 patients (72.4%) showed ypN0 and 15 patients (5.4%) had ypN2 stage. Angiolymphatic, venous, and perineural invasion were found in 34 patients (12.1%), 12 patients (4.3%), and 37 patients (13.2%), respectively. Twenty-eight specimens (10%) showed close circumferential resection margin (CRM) defined as same or closer than 0.1cm.

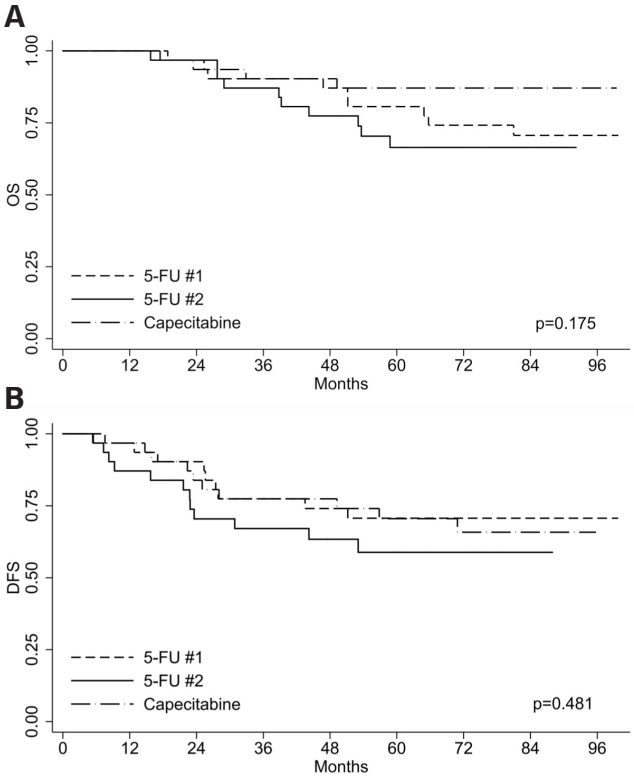

Figure 1. Survivals of matched patients according to concurrent chemotherapy. **A:** Overall survival (OS). **B:** Disease-free survival (DFS).

Prognostic factors for survival

Five-year OS, DFS, DMFS, and LRFS were 84.5%, 75.0%, 83.3%, and 91.2%, respectively. The univariate analysis of prognostic factors on the survival outcomes is shown in Supplementary Table 1. Concurrent chemotherapy regimen was not associated with survival end-points. In the multivariate analysis, perineural invasion and post-CRT nodal status (ypN- vs ypN+) were independent prognostic factors predictive of OS, DFS, DMFS, and LRFS (Table 2). Additionally, tumor location from anal verge was significant prognosticator for OS, DFS, and DMFS, and CRT response was the prognostic factor for OS.

Clinical outcome according to chemotherapy regimen

Patient and tumor characteristics according to concurrent chemotherapy regimen are shown in Supplementary Table 2. There were no significant differences among the three groups in age, gender, clinical stage, and prevalence of anemia. There were 3 patients with ECOG performance status 2, 2 treated with one cycle of 5-FU and one with capecitabine. The proportion of patients with tumor above 5cm from the anal verge was larger in group B (p=0.001).

Patient and tumor characteristics after propensity score matching is demonstrated in Table 3. In the matched analysis, 5-year OS in groups A, B, and C was 80.7, 66.5, and 87.1%, respectively (p=0.175, Figure 1A), and DFS was 70.7, 58.8, and 70.5% (p=0.481, Figure 1B). Five-year DMFS was 87.1, 76.7, and 76.6% (p=0.515), and LRFS was 76.7, 89.7, and 90.2% (p=0.456), respectively. Table 4 displays the treatment results of matched analysis. The rates of sphincter preservation surgery, CRM >0.1 cm, and CRT response ≥ grade 4 were not statistically different between the three groups, as well. Additionally, the events of locoregional recurrence and distant metastasis were also similar in the three groups.

Treatment-related toxicity

No patient experienced grade 3 or higher gastrointestinal toxicity and the distribution of grade

Table 3. Patient and tumor characteristics according to concurrent chemotherapy after propensity score matching

Characteristics	*No. of patients (%)*			*p value*
	5-FU #1 (n=31)	*5-FU #2 (n=31)*	*Capecitabine (n=31)*	
Age, years				
<70	28 (90.3)	23 (74.2)	29 (93.6)	0.111
≥70	3 (9.7)	8 (25.8)	2 (6.5)	
Gender				
Male	23 (74.2)	22 (71.0)	27 (87.1)	0.292
Female	8 (25.8)	9 (29.0)	4 (12.9)	
ECOG performance status				
0, 1	29 (93.6)	31 (100.0)	30 (96.8)	0.770
2	2 (6.5)	0 (0.0)	1 (3.2)	
Clinical T stage				
T3	28 (90.3)	30 (96.8)	30 (96.8)	0.613
T4	3 (9.7)	1 (3.2)	1 (3.2)	
Clinical N stage				
N (-)	10 (32.3)	12 (38.7)	7 (22.6)	0.427
N (+)	21 (67.7)	19 (61.3)	24 (77.4)	
Distance from anal verge, cm				
≤5	26 (83.9)	26 (83.9)	28 (90.3)	0.806
>5	5 (16.1)	5 (16.1)	3 (9.7)	

Table 4. Treatment outcomes according to concurrent chemotherapy after propensity score matching

Variables	*No. of patients (%)*			*p value*
	5-FU #1 (n=31)	*5-FU #2 (n=31)*	*Capecitabine (n=31)*	
Sphincter preserving surgery				
Yes	24 (77.4)	28 (90.3)	27 (87.1)	0.441
No	7 (22.6)	3 (9.7)	4 (12.9)	
CRM status, cm				
>0.1	28 (90.3)	29 (93.6)	29 (93.6)	1.000
≤0.1	3 (9.7)	2 (6.5)	2 (6.5)	
CRT response[†]				
<Grade 4	22 (71.0)	22 (71.0)	20 (64.5)	0.818
≥Grade 4	9 (29.0)	9 (29.0)	11 (35.5)	
Pathologic complete response				
No	25 (80.8)	27 (87.1)	27 (87.1)	0.816
Yes	6 (19.4)	4 (12.9)	4 (12.9)	
Locoregional recurrence				
No	24 (77.4)	28 (90.3)	27 (87.1)	0.335
Yes	7 (22.6)	3 (9.7)	4 (12.9)	
Distant metastasis				
No	27 (87.1)	24 (77.4)	24 (77.4)	0.538
Yes	4 (12.9)	7 (22.6)	7 (22.6)	

[†] By Korean pathology standard report; grade 4 refers to near total regression, CRM: circumferential resection margin, CRT: chemoradiotherapy

Table 5. Treatment-related toxicity

Toxicities[†]	*No. of patients*						*p value*
	5-FU #1 (n=34)		*5-FU #2 (n=214)*		*Capecitabine (n=31)*		
	Grade 1-2	*Grade 3*	*Grade 1-2*	*Grade 3*	*Grade 1-2*	*Grade 3*	
Gastrointestinal							
Nausea	11	0	42	0	4	0	0.126
Diarrhea	8	0	37	0	5	0	0.653
Enteritis	15	0	76	0	12	0	0.612
Hematologic							
Neutropenia	5	0	59	9	0	0	0.003
Anemia	1	0	44	0	2	0	0.053
Hand-foot syndrome	0	0	0	0	4	0	< 0.001

[†] By NCI CTCAE v4.0

1-2 toxicities across the groups were not statistically significant. However, the frequency of hematologic toxicity was different among the treated groups. Grade 3 treatment-related toxicity was observed only in group B patients, all of which were grade 3 neutropenia. Likewise, skin toxicity, which was grade 1-2 hand-foot syndrome, was only observed in 4 patients in group C (Table 5). During follow-up period, 5 patients underwent adhesiolysis. Four patients were in group B, and one in group C. Other treatment related late toxicity was not observed.

Discussion

In this study, we analyzed the clinical outcomes of neoadjuvant CRT for locally advanced rectal cancer according to preoperative chemotherapy regimens; one cycle of 5-FU vs two cycles of 5-FU vs capecitabine. In summary, 5-year OS, DFS, LRFS and DMFS were not statistically different among the groups, and different chemotherapy regimen did not result in statistically significant difference in tumor response, CRM status and sphincter preserving surgery rate when analyzed after propensity score matching as well in the entire cohort. With regard to treatment related toxicities, grade 3 neutropenia was observed in 9 patients (4.2%) who received two cycles of 5-FU, whereas only grade 1-2 toxicities in patients who received a single cycle of 5-FU.

Single cycle of 5-FU regimen employed in the current study originates from institutional phase II trial, which proved efficacy and safety as adjuvant treatment combined with radiotherapy for resectable rectal cancer [16]. Thus, patients in earlier time period were more likely treated with this regimen. In line with the intensification of concurrent chemotherapy regimen, an additional cycle was added following the recommendations of treatment guidelines. The mainstay of concurrent chemotherapy was later shifted to oral capecitabine, reflecting more focus on the patient comfort with proven efficacy compared to regimens employing intravenous delivery.

The optimal chemotherapy regimen in preoperative CRT is still under debate. Although preoperative CRT was regarded as a standard treatment strategy for locally advanced rectal cancer, chemotherapy regimens were not consistent between randomized trials [12-14]. The most recent NCCN guideline recommended various chemotherapy regimens such as continuous infusion of 5-FU, bolus 5-FU/leucovorin and capecitabine [15]. It is perceived that a recommended regimen has similar efficacy, whereas adverse event profile may be different. There have been many efforts to increase the outcomes by intensifying chemotherapy by combining an additional agent such as oxaliplatin, irinotecan and bevacizumab to standard preoperative CRT [6-10,20-23].

The result of this study shows that treatment outcomes of less than standard chemotherapy, as for instance one cycle of i.v. bolus 5-FU as in this study, would not be different from that of combination with standard chemotherapy, with less treatment-related events. Futhermore, long-term analysis of EORTC 22921 has failed to demonstrate the role of both neoadjuvant and adjuvant chemotherapy [11]. This would not mean there is no role of combined chemotherapy in locally advanced rectal cancer. In ADORE trial, intensified adjuvant chemotherapy with oxaliplatin to patients with stage III disease after neoadjuvant chemoradiotherapy showed improved results over standard fluoropyrimidine chemotherapy [24]. Furthermore,

more intensified chemotherapy in the neoadjuvant setting, often termed total neoadjuvant treatment (TNT) approach, has been introduced and is currently being explored in a prospective phase III trial [25]. Though findings seems contradictory, the results from two studies [1,24] stress the importance of patient selection. Inclusion criteria regarding treatment response or burden was non-existent for EORTC 22921, whereas only poor responders to standard preoperative chemoradiotherapy were included for ADORE trial. Likewise, poor responders to FOLFOX induction chemotherapy will be offered standard chemoradiotherapy in PROSPECT trial. However, outside clinical trials in a daily clinical setting, unselected patients would undergo standard of care treatment, which would be preoperative chemoradiotherapy. Numerous meta-analyses and reviews over the past decade have failed to nominate relevant factors for treatment response prediction [26-28]. In light of these findings, less than standard chemotherapy in combination with radiotherapy or radiotherapy alone may be a viable option for patients with poor performance, who may benefit from lower risk of treatment-related morbidity, where the likelihood of benefit from combined treatment is not quite substantial.

This study has several limitations. First, this is a single-institute retrospective study, thus not free from inherent study design. Second, compared treatments were not balanced in respect to patient number. Although we performed the propensity score matching, there might be limitations in the statistical analyses due to the small size of matched population. Inverse Probability Treatment Weight (IPTW) method could be an alternative to overcome limited sample size. However, there are issues with adaptation of IPTW. In this cohort, imbalance of patient distribution in performance status and tumor location were likely the cause of poor matching. Accordingly, limited effect of concurrent chemotherapy regimen needs to be validated through further investigations. However, with the lack of studies on concurrent chemotherapy regimen, a single cycle of 5-FU may bring insights into the treatment of locally advanced rectal cancer in daily practice.

In summary, the present study showed that treatment survival outcome was not significantly influenced by the regimen of concurrent preoperative chemotherapy in locally advanced rectal cancer. Although many groups have tried to show the superiority of intensified concurrent chemotherapy, our results indicate that one cycle of 5-FU, which may be considered suboptimal regimen, is associated with comparable clinical outcomes, as compared with standard chemotherapy regimen.

Conflict of interests

The authors declare no conflict of interests.

References

1. Sebag-Montefiore D, Stephens RJ, Steele R et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009;373:811-20.
2. Sauer R, Becker H, Hohenberger W et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-40.
3. Roh MS, Colangelo LH, O'Connell MJ et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 2009;27:5124-30.
4. Bosset JF, Calais G, Mineur L et al. Enhanced tumoricidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results-EORTC 22921. J Clin Oncol 2005;23:5620-7.
5. André T, Boni C, Mounedji-Boudiaf L et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-51.
6. Rödel C, Liersch T, Becker H et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 2012;13:679-87.
7. Allegra CJ, Yothers G, O'Connell MJ et al. Neoadjuvant therapy for rectal cancer: Mature results from NSABP protocol R-04. J Clin Oncol 2014;32 (Suppl): 390.
8. Schmoll HJ, Haustermans K, Price TJ et al. Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: Disease-free survival results at interim analysis. J Clin Oncol 2014;32 (Suppl): 3501.
9. Aschele C, Cionini L, Lonardi S et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 2011;29:2773-80.
10. Gérard JP, Azria D, Gourgou-Bourgade S et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 2012;30:4558-65.

11. Bosset JF, Calais G, Mineur L et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 2014;15:184-90.
12. Dewdney A, Cunningham D, Tabernero J et al. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol 2012;30:1620-7.
13. Gollins S, Myint AS, Haylock B et al. Preoperative chemoradiotherapy using concurrent capecitabine and irinotecan in magnetic resonance imaging–defined locally advanced rectal cancer: impact on long-term clinical outcomes. J Clin Oncol 2011;29:1042-9.
14. Hofheinz R-D, Wenz F, Post S et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 2012;13:579-88.
15. National Comprehensive Cancer Network NCCN guidelines version 1, 2018. Rectal cancer. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed 14 June 2018.
16. Im YH, Suh CI, Heo DS et al. The postoperative adjuvant radiation therapy and 5-fluorouracil maintenance chemotherapy for resectable rectal cancer. J Korean Cancer Assoc 1996;28:225-36.
17. Chang HJ, Park CK, Kim WH et al. A standardized pathology report for colorectal cancer. Korean J Pathol 2006;40:193-203.
18. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis 1997;12:19-23.
19. Mandard AM, Dalibard F, Mandard JC et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer 1994;73:2680-6.
20. Willeke F, Horisberger K, Kraus-Tiefenbacher U et al. A phase II study of capecitabine and irinotecan in combination with concurrent pelvic radiotherapy (CapIri-RT) as neoadjuvant treatment of locally advanced rectal cancer. Br J Cancer 2007;96:912-7.
21. Navarro M, Dotor E, Rivera F et al. A Phase II study of preoperative radiotherapy and concomitant weekly irinotecan in combination with protracted venous infusion 5-fluorouracil, for resectable locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2006;66:201-5.
22. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.
23. Crane CH, Eng C, Feig BW et al. Phase II trial of neoadjuvant bevacizumab, capecitabine, and radiotherapy for locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2010;76:824-30.
24. Hong YS, Nam BH, Kim KP et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. Lancet Oncol 2014;15:1245-53.
25. Alliance for Clinical Trials in Oncology. PROSPECT: chemotherapy alone or chemotherapy plus radiation therapy in treating patients with locally advanced rectal cancer undergoing surgery. ClinicalTrialsgov. Available at: https://clinicaltrials.gov/ct2/show/NCT01515787 (Accessed June 14, 2018).
26. Kuremsky JG, Tepper JE, McLeod HL. Biomarkers for response to neoadjuvant chemoradiation for rectal cancer. Int J Radiat Oncol Biol Phys 2009;74:673-88.
27. Spolverato G, Pucciarelli S, Bertorelle R et al. Predictive factors of the response of rectal cancer to neoadjuvant radiochemotherapy. Cancers (Basel) 2011;26:2176-wq94.
28. Dayde D, Tanaka I, Jain R et al. Predictive and prognostic molecular biomarkers for response to neoadjuvant chemoradiation in rectal cancer. Int J Mol Sci 2017;18. pii: E573.