Efficacy of hypofractionated preoperative chemoradiotherapy in rectal cancer

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Abstract. The efficacy and toxicity of hypofractionated preoperative chemoradiotherapy (HPCRT) combined with oral capecitabine was evaluated in patients with rectal cancer. HPCRT was delivered by intensity-modulated radiotherapy of either 33 Gy to the whole pelvis or 35 Gy in 10 fractions to the primary tumor and 33 Gy to the surrounding pelvis. Surgery was performed 4-8 weeks after HPCRT completion. Oral capecitabine was administered concurrently. A total of 76 patients were eligible for this study, and patient numbers in clinical stages I, II, III and IVA were 5, 29, 36 and 6, respectively. Tumor response, toxicity and survival were analyzed. A total of 9/76 patients (11.8%) achieved a pathological complete response. Sphincter preservation was achieved in 23/32 (71.9%) and 44/44 (100%) of patients with a distal extent from the anal verge of ≤5 and >5 cm, respectively. A total of 28/76 patients (36.8%) achieved tumor-downstaging and 25/76 (32.9%) achieved nodal (N)-downstaging. The 5-year disease-free survival (DFS) and overall survival rates were 76.5% and 90.6%, respectively. In the multivariate analysis for DFS, pathological N stage and lymphovascular space invasion were notable prognostic factors. A total of 6 patients in stage IVA underwent salvage treatments for lung or liver metastasis after HPCRT completion, and all 6 were alive at the last follow-up. Only 4 patients experienced grade 3 post-operative complications. No grade 4 toxicities were observed. HPCRT of 33 or 35 Gy in 10 fractions showed similar results to those of long-course fractionation. This fractionation scheme could be beneficial for patients with early stage disease, locally advanced rectal cancer, simultaneous distant metastasis requiring early intervention or for patients who wish to avoid multiple hospital visits.

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Abbreviations: AV, anal verge; BED10, biological equivalent dose assuming α/β=10 by linear-quadratic model; CRT, chemoradiotherapy; DFS, disease-free survival; HPCRT, hypofractionated preoperative CRT; IMRT, intensity-modulated radiotherapy; LRT, long-course radiotherapy; LRFS, locoregional failure-free survival; LVI, lymphovascular space invasion; N, nodal; OS, overall survival; pCR, pathological complete remission; PNI, perineural invasion; SRT, short-course radiotherapy; SIB, simultaneous integrated boost; T, tumor; TRG, tumor regression grade

Key words: preoperative chemoradiotherapy, rectal cancer, hypofractionation, IMRT

Introduction

Preoperative long-course radiotherapy (LRT) of typically 50.4 Gy in 28 fractions is the standard treatment for locally advanced rectal cancer; it gained popularity from the German CAO/ARO/AIO-94 trial, which reported several advantages of preoperative chemoradiotherapy (CRT), such as lower local recurrence, a higher rate of sphincter preservation and lower acute toxicity than postoperative CRT (1). Along with the ongoing practice of LRT, clinical trials assessing the change in radiotherapy schedule to short-course radiotherapy (SRT) consisting of 25 Gy in 5 fractions were carried out (2-4) which advocated a higher local control rate in SRT compared with that in surgery alone, as well as SRT being a simpler treatment than LRT in view of a much shorter schedule. It is challenging to compare the two schedules due to the difference in patient selection for each trial. Randomized trials were performed to compare the relative advantages of LRT and SRT, which reported no statistically significant difference in oncological outcomes (5,6) or health-related quality of life (7,8). However, advocates for SRT emphasize its lower acute toxicity, lower cost and greater convenience for patients with cancer compared with LRT (5,9,10). Meanwhile, advocates for LRT highlight higher rates of pathological complete remission (pCR), a higher sphincter preservation rate and lower local recurrence, especially in distant tumors, compared with SRT (11,12). In the clinical setting, some patients prefer shorter CRT followed by minimally invasive surgery, such as local excision for clinical T1-2N0 stages according to the American Joint Committee on Cancer staging system (AJCC), 8th edition (13). Without compromising the advantages of

LRT, a shorter radiotherapy schedule would be preferable for patients who want to avoid multiple hospital visits for LRT or for those with distant metastases or double primary cancers requiring early intervention. To optimize the advantages of LRT and SRT, a phase II multi-institutional clinical trial was carried out for locally advanced rectal cancer, involving a 2-week course of preoperative CRT of 33 Gy in 10 fractions, which included oral capecitabine followed by radical surgery performed 6-8 weeks after completion of CRT (14). The long-term outcomes of this 2-week course were recently updated and they were comparable to historical SRT or LRT in view of survival rates and acceptable toxicities (15). The radiotherapy of this study was delivered by a 3D three- or four-field box technique (16). However, in the present study, intensity-modulated radiotherapy (IMRT) was performed for hypofractionated preoperative CRT (HPCRT) of 33 Gy or 35 Gy in 10 fractions combined with oral capecitabin in patients in various stages of rectal cancer. The results of these fractionation schedules were analyzed to investigate toxicities, tumor responses and survival outcomes in patients with rectal cancer.

Materials and methods

Patients. Between June 2016 and May 2021, patients who were diagnosed with rectal adenocarcinoma and had adequate laboratory data, such as information regarding bone marrow, liver and kidney function, were eligible for inclusion in this study. Patients were required to have an Eastern Cooperative Oncology Group (17) performance status of 0-2 and be ≥18 years old. Pretreatment workups included an estimation of carcinoembryonic antigen (CEA) level, colonoscopy, chest radiography, computed tomography of the abdomen and pelvis, magnetic resonance imaging and 18 F-fluorodeoxyglucose positron emission tomography, if required. The study also included patients with clinical stage IVA or simultaneous presence of additional primary cancers who preferentially received HPCRT rather than the conventional LRT for early intervention. The study was approved by the Institutional Review Board of Chonnam National University Hwasun Hospital (Hwasun, South Korea; approval no. CNUHH-2010-009), and all patients submitted written informed consent upon enrollment.

Treatment. HPCRT was delivered either by a schedule that included the following: i) 33 Gy in 10 fractions to the whole pelvis with IMRT, the protocol of which was performed during the earlier study period; or ii) 35 Gy in 10 fractions to the primary bulky tumor via simultaneous integrated boost (SIB) and 33 Gy to the remaining pelvis with IMRT, the protocol of which was performed during later study period. In most patients, oral capecitabine was concurrently administered at a dose of 1,650 mg/m^2/day 5 days/week (from Monday to Friday) for up to 10 days during radiotherapy. Follow-up examinations were repeated before surgery. Radical surgery was performed 4-8 weeks after the completion of HPCRT. After surgery, the pathological stage was determined according to the AJCC staging system. Postoperative chemotherapy was recommended 4 weeks after surgery, according to the postoperative pathological stage and patient performance status (Fig. 1).

Evaluation of response and toxicity. After HPCRT, tumor response was evaluated based on the pathological finding of tumor and nodal status and tumor regression grade (TRG), as determined by pathologists. Primary tumor (T) and nodal (N) downstaging was defined as the lowering of the T and N stage from clinical staging to postoperative pathological staging, respectively. Overall downstaging was defined as overall pathological stage being lower than the initial clinical stage. TRG was defined as follows: grade 0, no regression; grade I, minor regression and fibrosis of ≤25%; grade II, moderate regression and fibrosis of 26-50%; grade III, good regression and fibrosis of 51-99%; or grade IV, total regression and fibrosis of 100% (18). Acute toxicities of the gastrointestinal and genitourinary system were assessed from the initiation of HPCRT and throughout the first 3 months after surgery. Late toxicities were defined as those that occurred thereafter. Toxicity was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (19).

Statistical analysis. Locoregional recurrence was defined as recurrence within the pelvic cavity and anastomosis site. Distant metastasis was defined as recurrence outside of the pelvis. Locoregional failure-free survival (LRFS) was defined as the interval between the start of HPCRT and the date of locoregional recurrence, censoring the last follow-up case without locoregional recurrence. The last follow-up was defined as the date of the last patient visit to hospital or date of death. Disease-free survival (DFS) was defined as the interval between the initiation of HPCRT and the date of any first recurrence, censoring the last follow-up case without any recurrence. Overall survival (OS) was calculated from the initiation of HPCRT to the date of death or last follow-up. Survival for all patients was calculated using the Kaplan-Meier method. Statistical significance between the groups was analyzed using a log-rank test. A Cox proportional hazard regression model was used for multivariate analysis. Statistical analyses were performed using SPSS (version 25.0; IBM Corp.). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient and treatment characteristics. A total of 116 patients received HPCRT. A total of 40/116 patients were excluded, as they underwent surgery at other hospital, they refused to receive surgery or they received systemic chemotherapy for newly developed distant metastases after HPCRT but before surgery. The remaining 76 patients were included in the study and patient characteristics are detailed in Table I. The number of patients with initial clinical stages I, II, III and IVA were 5, 29, 36 and 6, respectively. By MRI, the distal extent of the tumor ≤5 cm from the anal verge (AV) and the distal extent of the tumor >5 cm from the AV were observed in 32 and 44 patients, respectively. A total of 6 patients had initial distant metastasis, including metastases of the lung in 3 patients and of the liver 3 patients. In total, 3 patients initially had synchronous double primary cancers, and each had either lung, gall bladder or colon cancer. Radiotherapy was performed with a daily fraction size of 3.3 and 3.5 Gy in 37/76 (48.7%) and 39/76 (51.3%) patients, respectively, for

Table I. Patient and treatment characteristics.

Clinicopathological features	Value
Age, years[a]	70 (42-89)
Sex, n (%)	
Male	42 (55.3)
Female	34 (44.7)
Pre-CRT T-stage, n (%)	
T1	1 (1.3)
T2	7 (9.2)
T3	63 (82.9)
T4	5 (6.6)
Pre-CRT N-stage, n (%)	
N0	35 (46.1)
N1	28 (36.8)
N2	13 (17.1)
Pre-CRT M-stage, n (%)	
M0	70 (92.1)
M1a	6 (7.9)
Pre-CRT overall stage, n (%)	
I	5 (6.6)
II	29 (38.2)
III	36 (47.4)
IVa	6 (7.9)
Pathological T-stage, n (%)	
0	9 (11.8)
T1	4 (5.3)
T2	13 (17.1)
T3	45 (59.2)
T4a	5 (6.6)
Pathological N-stage, n (%)	
N0	54 (71.1)
N1	13 (17.1)
N2	9 (11.8)
Pathological overall stage, n (%)	
0	9 (11.8)
I	13 (17.1)
II	30 (39.5)
III	18 (23.7)
IVa	6 (7.9)
Pre-CRT distance from AV, cm[a]	5.5 (1.3-9.5)
Pre-CRT CEA level, ng/ml[a]	4.99 (0.90-53.70)
Post-CRT/pre-op CEA level, ng/ml[a]	3.17 (0.50-35.47)
Post-op CEA nadir level, ng/ml[a]	1.73 (0.49-10.87)
Radiotherapy duration, months[a]	14 (12-23)
CRT to surgery interval, days[a]	52 (16-86)
CRM, mm[a]	6.0 (0-18.0)
Surgery, n (%)	
LAR	32 (42.1)
LATA	20 (26.3)
uLAR	9 (11.8)
APR	8 (10.5)
TAE	6 (7.9)
ISR	1 (1.3)

[a]Data are presented as the median (range). CRT, chemoradiotherapy; T, tumor; N, node; M, metastasis; AV, anal verge; CEA, carcinoembryonic antigen; pre-op, pre-operative; CRM, circumferential resection margin; LAR, low anterior resection; LATA, laparoscopic abdominal transanal proctocolectomy with coloanal anastomosis; uLAR, ultra LAR; APR, abdominal perineal resection; TAE, transanal excision; ISR, intersphinteric resection.

a median of 14 days (range, 12-23 days). Concurrent chemotherapy with capecitabine was administered to most patients; however, a single patient received Taxol® and cisplatin for the treatment of double primary lung cancer, and another patient only received radiotherapy due to immune thrombocytopenia. The median interval between HPCRT and surgery was 52 days (range, 16-86 days). The surgeries performed included low anterior resection, laparoscopic abdominal transanal proctosigmoidectomy with coloanal anastomosis, ultra-low anterior resection and abdominoperineal resection in 32 (42.1%), 20 (26.3%), 9 (11.8%) and 8 (10.5%) patients, respectively. Postoperative adjuvant chemotherapy was administered to 52/76 (68.4%) patients according to pathological stage or performance status. The treatment information is detailed in Table I and Fig. 1.

Treatment outcomes. A total of 9/76 (11.8%) patients achieved a pCR, and the treatment characteristics of pCR are shown in Table II. The number of patients in pathological overall stage 0, I, II, III and IVA was 9 (11.8%), 13 (17.1%), 30 (39.5%), 18 (23.7%) and 6 (7.9%), respectively. The median post-CRT distal extent of the tumor from the AV by MRI was 5.75 cm (range, 1.8-10.8 cm), which increased from the pre-CRT extent of 5.5 cm (range, 1.3-9.5 cm). The median post-CRT tumor length by MRI was 2.0 cm (range, 0-4.0), which decreased from the pre-CRT length of 4.2 cm (range, 2.0-6.6). Sphincter preservation was achieved in 24/32 (75.0%) patients with an initial tumor distal extent ≤5 cm from the AV and in all 44 (100.0%) patients with an initial distal extent of >5 cm. Prior to HPCRT, 27 patients were candidates for abdominoperineal resection (≤4 cm from AV; clinical stage T3-4), and 20 of these patients (74.1%) underwent anal sphincter-saving surgery. The overall rate of sphincter preservation was 89.5% (68/76 patients). The median postoperative CEA nadir level was 1.73 ng/ml (range, 0.49-10.87 ng/ml), which decreased from the pre-CRT median level of 4.99 ng/ml (range, 0.9-53.7 ng/ml) and post-CRT/preoperative level of 3.17 ng/ml (range, 0.50-35.5 ng/ml). The other outcomes are presented in Table I. A total of 28/76 (36.8%) patients achieved T-downstaging and 25/76 (32.9%) patients achieved N-downstaging. Overall downstaging was achieved in 34/76 (44.7%) patients. A detailed breakdown of the downstaging is shown in Tables III-V. According to the 5-cm cut-off of tumor distal extent from the AV or the cut off of a median

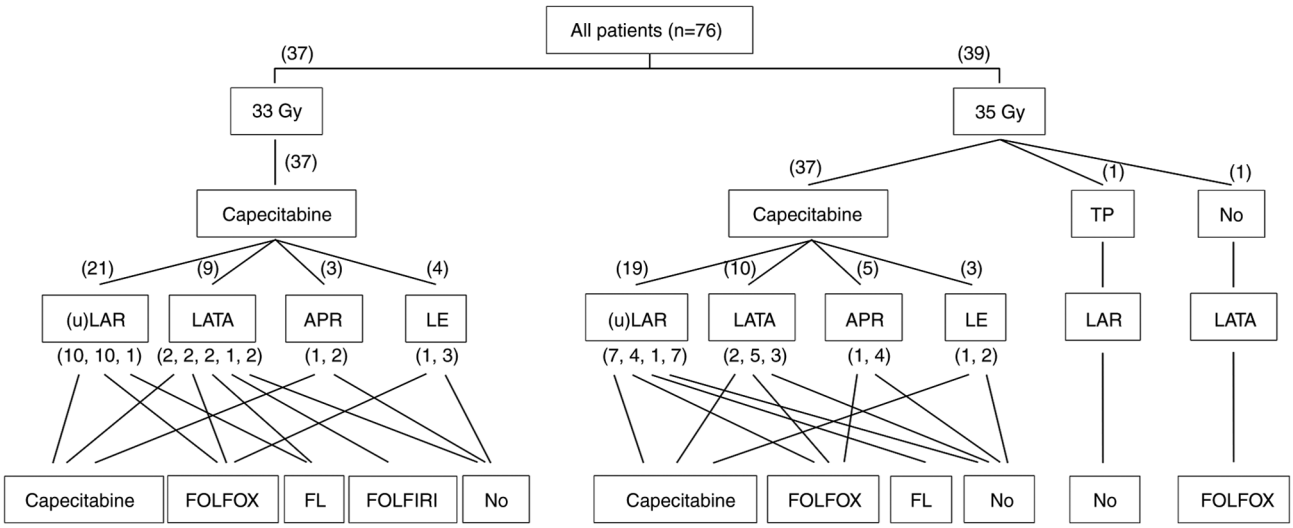

Figure 1. Detailed treatment characteristics of HCRT, surgery and postoperative chemotherapy in the patient cohort. A number in brackets represents the number of each subgroup of patients. Multiple numbers in one bracket means the corresponding numbers of patients who received each adjuvant chemotherapy regimen in order. TP, paclitaxel and cisplatin; (u)LAR, ultra low anterior resection or low anterior resection; LATA, laparoscopic abdominal transanal proctocolectomy with coloanal anastomosis; APR, abdominoperineal resection; LE, local excision (transanal excision, intersphincteric resection); FOLFOX, fluorouracil, leucovorin and oxaliplatin; FL, fluorouracil and leucovorin; FOLFIRI, fluorouracil, leucovorin and irinotecan.

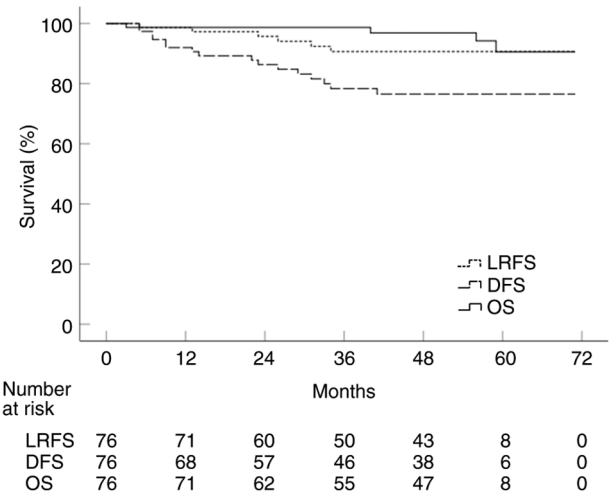

Figure 2. LRFS, DFS and OS in the patient cohort. LRFS, locoregional failure-free survival; DFS, disease-free survival; OS, overall survival.

52 days between radiotherapy and surgery, there were no marked differences in TRG or downstaging between the two groups.

Survival and prognostic factors. The follow-up period ranged from 3 to 71 months (median, 54). In all 76 patients, the 5-year LRFS, DFS and OS were 90.6, 76.5 and 90.6%, respectively (Fig. 2). The results of univariate analyses for LRFS, DFS and OS are shown in Table VI. The results of multivariate analyses are shown in Table VII. The pT stage was found to be the only significant prognostic factor for LRFS (P<0.001; Fig. 3A). However, there was no statistical significance between pT-stage subgroups, as the hazard ratios for pT3 or pT4 stage were extremely high compared to those for pT0-2 stage with no locoregional failure (Tables VI and VII). In the multivariate analysis for DFS, notable variables included pN stage (Fig. 3B) and lymphovascular space invasion (LVI; Fig. 3C). The 5-year DFS rate of patients with negativity for both LVI and PNI (LVI^- and PNI^-) versus patients with positivity for either LVI or PNI (LVI^+ or PNI^+) was also significantly higher (P=0.015; Fig. 3D). Upon multivariate analysis for OS, no significant variables were found. A total of 6/76 (7.9%) patients with initial stage IVA had one or more salvage treatments such as surgery, chemotherapy or stereotactic radiotherapy after completion of HPCRT, and all were alive at the last follow-up. A single patient with colon cancer and a single patient with gall bladder cancer out of a total of 3 with initial double primary tumors underwent surgical resection, and the other patient with lung cancer was treated with concurrent CRT. All 3 patients were followed up and demonstrated no evidence of disease or stable disease.

Patterns of failures and complications. A local failure occurred in 4/76 (5.3%) patients, a regional failure occurred in 4/76 patients (5.3%) and distant metastasis occurred in 13/76 patients (17.1%) as a component of failure. The pattern of failure is illustrated in Fig. 4. Sites of distant metastasis were identified in the lung, bone, distant lymph nodes and liver in 10 (13.2%), 2 (2.6%), 2 (2.6%) and 1 (1.3%) patients, respectively. Patients with two or more sites were separately counted. Only 1 patient (1.3%) developed an acute grade 3 complication of anastomosis leakage, while 3 patients (3.9%) experienced late grade 3 complications such as rectovaginal fistula at anastomosis, anal bleeding from anastomosis and anastomotic leakage. No grade 4 toxicity was observed. A detailed breakdown of the complications of all grades is shown in Table VIII.

Discussion

In the present study, the rates of T-downstaging, N-downstaging and overall downstaging were 36.8, 32.9 and

Table II. Patient and treatment characteristics of patients who achieved a pathological complete response.

Patient	Age, years	Sex	Pre-RT T-stage	Pre-RT N-stage	Pre-RT CEA, ng/ml	Pre-operative CEA, ng/ml	Post-operative CEA nadir, ng/ml	Total dose, Gy	CCTx regimen	Operation type	RT-operation interval, days	Last follow-up status	OS time, months
1	74	M	2	0	2.75	1.75	1.38	35	Capecitabine	TAE	59	Alive	55
2	68	F	3	2a	2.46	2.35	1.53	35	Capecitabine	LATA	52	Alive	57
3	75	F	3	0	7.8	3.44	2.08	35	Capecitabine	uLAR	45	Alive	59
4	72	F	2	0	4.42	3.74	2.68	33	Capecitabine	TAE	56	Alive	27
5	80	F	3	0	2.96	2.25	1.09	35	Capecitabine	LATA	58	Alive	14
6	83	M	3	0	26.54	7.08	4.33	35	Capecitabine	LAR	86	Alive	51
7	69	F	3	0	3.32	2.4	1.61	33	Capecitabine	LATA	55	Alive	59
8	48	F	3	1	6.05	0.5	0.49	33	Capecitabine	LAR	54	Alive	71
9	71	M	3	1	32.89	5.66	2.36	33	Capecitabine	LAR	47	Alive	58

M, male; F, female; RT, radiotherapy; CEA, carcinoembryonic antigen; CCTx, concurrent chemotherapy; TAE, transanal excision; LATA, laparoscopic abdominal transanal proctocolectomy with coloanal anastomosis; LAR, low anterior resection; uLAR, ultra LAR; OS, overall survival.

Figure 3. LRFS according to (A) pT-stage, DFS according to (B) pN-stage, (C) LVI and (D) status of both LVI and PNI in the patient cohort. LRFS and DFS were calculated using the Kaplan-Meier method and compared using the log-rank test. pT-stage, pathological tumor stage; pN-stage, pathological node stage; LVI, lymphovascular space invasion; PNI, perineural invasion; LRFS, locoregional failure-free survival; DFS, disease-free survival.

Table III. Changes to T stage pre- and post-chemoradiotherapy in the 76 patients.

	Pathological T stage				
Clinical T stage	pT0	pT1	pT2	pT3	pT4
T1, n	0	1	0	0	0
T2, n	2	3	0	1	1
T3, n	7	0	12	41	3
T4, n	0	0	1	3	1
Total T-downstaging, n (%)	28 (36.8)				

T, tumor.

Table IV. Changes to N stage pre- and post-chemoradiotherapy in the 76 patients.

	Pathological N stage		
Clinical N stage	pN0	pN1	pN2
N0, n	31	4	0
N1, n	17	7	4
N2, n	6	2	5
Total N-downstaging, n (%)	25 (32.9)		

N, node.

Table V. Changes to overall stage pre- and post-chemoradiotherapy in the 76 patients.

	Pathological overall stage, n				
Clinical overall stage	0	I	II	III	IVa
I, n	2	2	1	0	0
II, n	4	6	16	3	0
III, n	1	1	20	14	0
IVA, n	0	0	0	0	6
Total overall downstaging, n (%)[a]	34 (44.7)				

[a]6 patients with initial clinical stage IVA were excluded.

44.7%, respectively. In total, 1 out of 3 patients with synchronous double primary cancer achieved overall downstaging of primary rectal cancer. The pCR rate was 11.8%, and the overall rate of sphincter preservation was 89.5%. These results were comparable with those of historical LRT studies (1,6) and similar to the 2-week course KROG study (14). The comparable outcomes of the present study could be attributed to dose prescription of 33 Gy [biological equivalent dose assuming

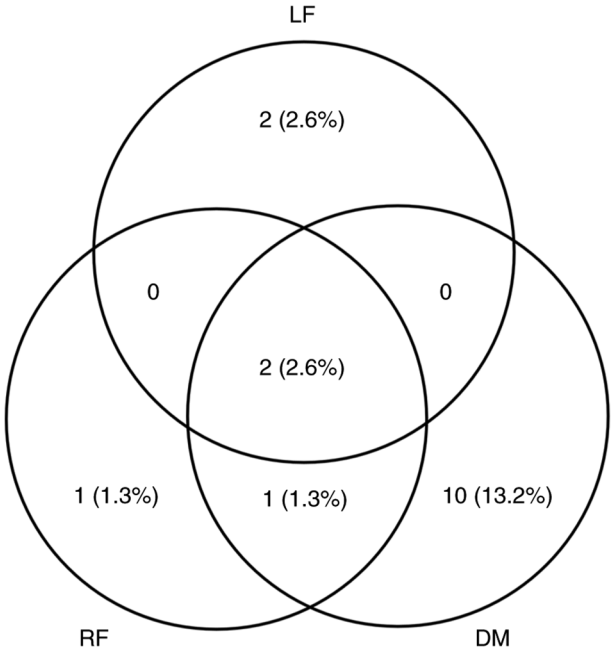

Figure 4. Venn diagram illustrating the patterns of failure in the patient cohort. LF, local failure; RF, regional failure; DM, distant metastasis.

α/β=10 by linear-quadratic model (BED_{10}), 43.9 Gy],or 35 Gy (BED_{10}, 47.3 Gy), which is between SRT of 25 Gy (BED_{10} 37.5 Gy) and LRT of 50.4 Gy (BED_{10}, 59.5 Gy). Oral capecitabine was prescribed as the concurrent chemotherapy agent, followed by delayed surgery with a median interval of 52 days to allow tumor regression before surgery. This study showed comparable toxicities to previous LRT results (1,6). Only 4/76 (5.3%) patients developed acute or late grade 3 toxicities and there were no grade 4 toxicities in any patients, including the SIB IMRT 35 Gy patient cohort. A single patient received 35 Gy and was treated with Taxol® and cisplatin concurrently due to synchronous lung cancer and acute grade 2 diarrhea. All patients had one or more weekend to rest without receiving HPCRT, but received IMRT to limit the radiation dose to normal organs. SIB IMRT of 35 Gy was performed to the gross tumor to improve the pathological regression. However, in the groups of patients with 35 Gy versus 33 Gy, the pCR rate was 12.8 and 10.8%, respectively (P=0.786), the sphincter preservation rate was 87.2 and 91.9%, respectively (P=0.503), and the 5-year DFS was 85.7 and 63.9% (P=0.067), respectively. None of these differences were statistically significant between the two groups. The 5-year LRFS, DFS and OS rates were 90.6, 76.5 and 90.6%, respectively. These survival rates were comparable to previous LRT results (1,6) or the recently updated 2-week CRT KROG study (15), despite the fact that the present study included patients with synchronous double primary or distant metastasis. A total of 5/76 patients with early clinical stages, such as T1-2N0, were included. Of these patients, 2 had synchronous double primary cancers, 2 preferred HPCRT followed by local excision rather than upfront radical surgery and 1 strongly demanded SRT due to having to travel long-distances to receive CRT. A total of 4/5 patients underwent sphincter preservation surgery. Thus, all the patients had a median radiotherapy duration of 2 weeks, which is 4 weeks shorter than the conventional 6-week LRT,

Table VI. Univariate analysis for 5-year survival outcomes.

		LRFS		DFS		OS	
Variables	No. of patients	Survival rate, %	P-value	Survival rate, %	P-value	Survival rate, %	P-value
Age, years							
≤70	39	86.2	0.185	72.1	0.575	96.2	0.091
>70	37	97.2		83.2		79	
Sex							
Female	34	83.5	0.215	71.1	0.268	95	0.483
Male	42	95.1		81.1		86.5	
Pre-CRT T-stage							
T1-2	8	100	0.481	100	0.358	100	0.768
T3	63	90.6		73.7		89.5	
T4	5	80		80		100	
Pre-CRT N-stage							
N0	35	100	0.005[a]	87.4	0.183	78.7	0.067
N1	28	91.1		72.7		100	
N2	13	69.2		59.3		100	
Pre-CRT M-stage							
M0	70	91.7	0.48	76.3	0.728	90	0.587
M1a	6	80		80		100	
Pre-CRT overall stage							
I	5	100	0.202	100	0.323	100	0.094
II	29	100		84.8		77.2	
III	36	84.7		67.6		100	
IVa	6	80		80		100	
Distance from AV, cm							
≤5	32	88.3	0.613	69.2	0.184	78.7	0.126
>5	44	92.2		81.8		96.8	
Pathological T-stage							
0	9	100	<0.001[a]	100	0.054	100	0.032[a]
T1-2	17	100		85.2		56.3	
T3	45	92		73.2		97.8	
T4	5	40		40		100	
Pathological N-stage							
N0	54	92.9	0.005[a]	84.7	0.031[a]	86.6	0.422
N1	13	100		60.6		100	
N2	9	61		53.3		100	
Pathological overall stage							
0	9	100	0.62	100	0.062	100	0.008[a]
I	13	100		80.2		42.9	
II	30	88		81.2		96.7	
III	18	88.1		54.3		100	
IVa	6	80		80		100	
Pre-CRT CEA, ng/ml							
≤5	38	96.3	0.116	80.7	0.139	80.8	0.187
>5	38	85.5		67		96.6	
Pre-CRT/Post-op CEA, ng/ml							
≤2.5	24	94.7	0.398	86	0.212	88.9	0.758
>2.5	52	88.8		72.3		91.6	

Table VI. Continued.

Variables	No. of patients	LRFS Survival rate, %	LRFS P-value	DFS Survival rate, %	DFS P-value	OS Survival rate, %	OS P-value
Post-op CEA nadir, ng/ml							
≤2.5	59	91.5	0.435	78.6	0.264	94.7	0.015[a]
>2.5	17	87.5		68.2		75.5	
Radiotherapy duration, days							
≤14	46	89.7	0.67	72.8	0.384	85.1	0.116
>14	30	92		82.4		100	
Fraction size, Gy							
3.3	37	88.5	0.515	69.4	0.164	90.7	0.647
3.5	39	93.3		85.7		93	
CRT to surgery internal, days							
≤52	44	86.9	0.232	75.4	0.758	89.6	0.429
>52	32	96.8		78.9		91.7	
CRM, mm							
>1	45	82.3	0.889	73.8	0.655	90.4	0.537
≤1	31	80.4		80		90	
LVI							
No	71	91.6	0.124	79.4	0.001[a]	94	0.674
Yes	5	80		30		100	
PNI							
No	57	95.2	0.014[a]	83.7	0.008[a]	87.3	0.232
Yes	19	77.3		56.4		100	
TRG							
1,2	28	92.1	0.817	73.3	0.634	86.1	0.719
3,4	48	89.5		78.7		93	
Adjuvant chemotherapy							
No	24	100	0.154	75.3	0.652	48.4	<0.01[a]
Yes	52	87.7		77.5		100	

[a]P<0.05. LRFS, locoregional failure-free survival; DFS, disease-free survival; OS, overall survival; Pre-CRT, pre-chemoradiotherapy; AV, anal verge; CEA, carcinoembryonic antigen; Pre-op, pre-operative; CRM, circumferential resection margin; LVI, lymphovascular space invasion; PNI, perineural invasion; TRG, tumor regression grade.

and due to the shorter CRT duration, patients could receive surgery 4 weeks earlier than those receiving traditional LRT.

In the multivariate analysis for LRFS in this study, only pT-stage was an independent prognostic factor. It is well known that patients with sterilized tumors after preoperative CRT have an excellent prognosis with respect to LRFS or DFS (18,20). A total of 9 patients who achieved pCR in the current study had experienced no recurrence at the last follow-up. In the multivariate analysis for DFS, pN stage and LVI were significant prognostic variables. The pN stage is a well-known prognostic factor for survival, and is integral to the AJCC staging system (21). The prognosis of patients with remnant lymph node metastasis after CRT is poor, even in cases of complete primary tumor response (22). Likewise, patients with more advanced pathological primary tumors (pT3-4) with pN0 stage showed slightly better recurrence-free survival or OS than those who were pT0-2, but pN^+ (23). It is well known that the LVI is an independent prognostic factor for survival. Song *et al* (24) reported that LVI was a significant prognostic factor affecting distant failure-free survival. Saadoun *et al* (25) developed a nomogram with eight variables, including pathological stage, LVI and PNI, which provided individual risk prediction for recurrence. In the current study, DFS of patients who were both LVI^- and PNI^- versus that of patients who were LVI^+ or PNI^+ significantly differed, although patients who were LVI^+ or PNI^+ received postoperative adjuvant chemotherapy (5-fluorouracil and oxaliplatin) more frequently than patients who were LVI^- and PNI^- (18/20 vs. 34/56; P=0.023). Therefore, more aggressive

Table VII. Multivariate analysis for 5-year survival outcomes.

	LRFS		DFS		OS	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Pre-CRT N-stage						
N0		0.260		0.608		0.441
N1		0.937		0.468		0.202
N2		0.928		0.325		0.950
Pathological T-stage						
0	-	0.044[a]		0.305		0.694
T1-2	1.000 (0.000-∞)	>0.999		0.505		0.323
T3	10416.259 (0.000-∞)	0.942		0.793		0.989
T4	106440.674 (0.000-∞)	0.927		0.132		0.981
Pathological N-stage						
N0		0.362	-	0.027[a]		0.799
N1		0.306	3.987 (1.187-13.388)	0.025[a]		0.531
N2		0.287	4.157 (1.185-14.580)	0.026[a]		0.832
Pathological overall stage						
0		0.992		0.598		0.421
I		0.987		0.376		0.323
II		0.914		0.600		0.165
III		0.767		0.463		0.504
IVa		0.838		0.308		0.559
Post-op CEA nadir, ng/ml						
≤2.5		0.045[b]		0.190		0.074
>2.5						
LVI						
No		0.187	-	0.002[a]		0.834
Yes			8.879 (2.201-35.809)			
PNI						
No		0.018[b]		0.059		0.530
Yes						
Adjuvant chemotherapy						
No		0.537		0.195		0.398
Yes						

[a]P-values of variables in the equation by forward conditional selection method in Cox regression analysis. [b]Although these P-values are <0.05, the variables are not included in the final equation. LRFS, locoregional failure-free survival; DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; pre-CRT, pre-chemoradiotherapy; pre-op, pre-operative; CEA, carcinoembryonic antigen; LVI, lymphovascular space invasion; PNI, perineural invasion.

adjuvant chemotherapy should be considered to improve DFS for these patients.

A limitation of this study was the small patient cohort and the slow accrual rate given the study duration. The CRT option to select patients with a preference for HPCRT or even with synchronous distant disease or double primary cancer was provided. However, the treatment protocol was the same, except the total dose of 33 or 35 Gy, throughout the entire study period, and treatment consistency was maintained. A randomized controlled study comparing HPCRT and long-course CRT in a larger patient cohort is required in the future. Another limitation refers to the heterogenous patient characteristics, ranging from early to advanced clinical stage (I to IVA) or to the synchronous double primary cancer. However, most patients experienced the advantages of HPCRT, which include convenience, low cost, shorter radiotherapy time and earlier surgical or other radical treatments for distant disease or double primary cancer.

Table VIII. Gastrointestinal and genitourinary toxicities.

A, Gastrointestinal toxicities

	Grade 3		Grade 2		Grade 1	
CTCAE	Symptom	n (%)	Symptom	n (%)	Symptom	n (%)
Acute	Anastomosis leakage	1 (1.3)	Anal pain	8 (10.6)	Anal pain	4 (5.3)
			Diarrhea	5 (6.7)	Diarrhea	3 (4)
					Rectal mucositis	3 (4)
Late	Anal hemorrhage	1 (1.3)	Diarrhea	24 (32)	Anal pain	5 (6.7)
	Anastomosis leakage	1 (1.3)	Anal pain	4 (5.3)	Constipation	2 (2.7)
	Rectovaginal fistula	1 (1.3)	Anal fissure	1 (1.3)	Diarrhea	2 (2.7)
			Constipation	1 (1.3)	Anal hemorrhage	1 (1.3)
					Fecal incontinence	1 (1.3)
					Rectal mucositis	1 (1.3)

B, Genitourinary toxicities

	Grade 3		Grade 2		Grade 1	
CTCAE	Symptom	n (%)	Symptom	n (%)	Symptom	n (%)
Acute					Dysuria	1 (1.3)
Late			Urinary retention	2 (2.7)	Dysuria	1 (1.3)
			Urinary frequency	1 (1.3)	Urinary incontinence	1 (1.3)

CTCAE, Common Terminology Criteria for Adverse Events version 5.0.

In conclusion, HPCRT of 33 or 35 Gy in 10 fractions showed comparable results to historical conventional LRT studies. This shorter fractionation scheme may be beneficial, without reducing oncological outcomes, for patients with early stage disease, locally advanced rectal cancer, simultaneous distant metastasis and other double primary cancer requiring early intervention, or for patients who cannot attend the hospital multiple times.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TKN conceived and designed the study. IJC, YHK, JYS, MSY, SJA and SHC acquired data. TKN, IJC and JUJ confirm the authenticity of all the raw data. IJC and JUJ performed the statistical analysis. IJC, JUJ and TKN interpreted the results, analyzed the data and drafted the manuscript. All authors read and approved the final version of the manuscript.

Ethical approval and consent to participate

The study was established, according to the ethical guidelines of the Helsinki Declaration and was approved by Institutional Review Board of Chonnam National University Hwasun Hospital (Hwasun, South Korea; approval no. CNUHH-2010-009). Informed consent was obtained from all patients and/or their legal guardian(s).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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