ROJ Radiation Oncology Journal

Preoperative chemoradiation for locally advanced rectal cancer: comparison of three radiation dose and fractionation schedules

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Purpose: The standard radiation dose for patients with locally rectal cancer treated with preoperative chemoradiotherapy is 45–50 Gy in 25–28 fractions. We aimed to assess whether a difference exists within this dose fractionation range.

Materials and Methods: A retrospective analysis was performed to compare three dose fractionation schedules. Patients received 50 Gy in 25 fractions (group A), 50.4 Gy in 28 fractions (group B), or 45 Gy in 25 fractions (group C) to the whole pelvis, as well as concurrent 5-fluorouracil. Radical resection was scheduled for 8 weeks after concurrent chemoradiotherapy.

Results: Between September 2010 and August 2013, 175 patients were treated with preoperative chemoradiotherapy at our institution. Among those patients, 154 were eligible for analysis (55, 50, and 49 patients in groups A, B, and C, respectively). After the median follow-up period of 29 months (range, 5 to 48 months), no differences were found between the 3 groups regarding pathologic complete remission rate, tumor regression grade, treatment-related toxicity, 2-year locoregional recurrence-free survival, distant metastasis-free survival, disease-free survival, or overall survival. The circumferential resection margin width was a prognostic factor for 2-year locoregional recurrence-free survival, whereas ypN category was associated with distant metastasis-free survival, disease-free survival, and overall survival. High tumor regression grading score was correlated with 2-year distant metastasis-free survival and disease-free survival in univariate analysis.

Conclusion: Three different radiation dose fractionation schedules, within the dose range recommended by the National Comprehensive Cancer Network, had no impact on pathologic tumor regression and early clinical outcome for locally advanced rectal cancer.

Keywords: Rectal neoplasms, Neoadjuvant therapy, Chemoradiotherapy, Radiotherapy, Dose fractionation

Introduction

The mainstay of treatment for locally advanced rectal cancer (T3-4 and/or N+) has been surgery. With the introduction of the total mesorectal excision method, a substantial decrease in the risk of locoregional failure has been achieved [1,2]. However, even with the total mesorectal excision method, surgery alone was found to have an inferior outcome compared to surgery combined with chemoradiotherapy (CRT) for locally advanced rectal cancer. The results of prospective randomized trials demonstrated that local control and survival were improved with adjuvant CRT [3,4].

Although CRT administered both preoperatively and postoperatively could be beneficial, preoperative CRT became the standard treatment based on the German CAO/ARO/AIO 94 trial, in which preoperative CRT was associated with

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pathologic tumor response, improved tolerance, and increased likelihood of sphincter preservation in the distal rectum [5]. The Medical Research Council (MRC) CR07 trial, which re-evaluated the role of preoperative radiotherapy (RT), showed that hypofractionated preoperative RT resulted in superior local control and disease-free survival (DFS) compared to selective postoperative RT [6].

The current National Comprehensive Cancer Network (NCCN) guidelines for rectal cancer recommend a total radiation dose of 45–50 Gy in 25–28 fractions for preoperative CRT. In our institution, three radiation dose fractionation schedules within this dose fractionation range were used for preoperative CRT in patients with locally advanced rectal cancer. We hypothesized that there is no difference in pathologic response and clinical outcome among the different radiation dose and fractionation schedules. The aim of this study was to evaluate pathologic response and clinical outcome among patients treated with 3 dose fractionation schedules.

Materials and Methods

We performed a retrospective analysis of patients with pathologically proven, locally advanced (cT3-4 and/or cN+) rectal cancer treated with preoperative CRT followed by radical resection at the institution. Between September 2010 and July 2013, 175 rectal cancer patients were treated with the aim of preoperative CRT. Of those patients, 12 developed distant metastasis during or after CRT, before radical resection (liver, 7; lung, 2; and distant lymph node, 3); 5 refused radical resection; and 4 did not complete the planned treatment schedule. Excluding those 21 patients, we reviewed 154 cases. Patient medical records were analyzed after approval was granted by the Kyungpook National University Hospital Institutional Review Board (IRB) with a waiver of the need for consent (IRB No. KNUH 2015-01-017). Data collected included patient factors (age, sex, and comorbidities), tumor factors (histology, clinical stage, pathologic stage, and completeness of resection), treatment factors (type of chemotherapy, dose of radiation therapy, type of surgery performed, and type of anastomosis), and clinical outcome (complications, tumor recurrence, and survival).

Pelvic radiotherapy was delivered with a four-field technique (anteroposterior/posteroanterior/right/left) using 10 MV photon beams from a linear accelerator. Patients were placed in the prone position. The superior field edge was placed at the L5/S1 interspace. The inferior field edge was at the anal verge or 2 cm below the tumor. Anteroposterior/posteroanterior fields

had a 2-cm margin from the pelvic brim. Lateral treatment fields encompassed the entire sacrum posteriorly. The anterior border was 3 to 4 cm in front of the rectal wall. Three dose fractionation regimens were used: 56 patients were treated with 50 Gy in 2 Gy per fraction (group A), 50 were treated with 50.4 Gy in 1.8 Gy per fraction (group B), and 49 were treated with 45 Gy in 1.8 Gy per fraction (group C). Patients were not randomly allocated to these treatment groups, but dose fractionation regimens were selected based on their physician's preference and treatment policy at the time. Boost RT to primary tumor were not given. All fields were treated daily. Portal dosimetry was performed on the first day of treatment. Patients were examined weekly during the course of radiotherapy. In general, 2 cycles of 5-fluorouracil (425 mg/m^2 for 4 consecutive days) and leucovorin (20 mg/m^2 for 4 consecutive days) were administered intravenously during radiotherapy. A recovery period of 8 weeks after preoperative CRT was prescribed prior to surgery. During the recovery period, patients received one additional cycle of 5-fluorouracil/leucovorin.

All patients were staged preoperatively and postoperatively according to the American Joint Committee for Cancer (AJCC) Staging Manual 7th edition. Pretreatment clinical staging was performed using abdominopelvic computed tomography, pelvic magnetic resonance imaging, and whole-body (upper legs to skull) ^{18}F-fluorodeoxyglucose positron emission tomography scanning.

Patients with no residual, viable tumor cells in the surgical specimen (ypT0N0) were classified as having a pathologic complete response (pCR). To quantify tumor response to preoperative CRT, we used the standardized 5-point tumor regression grading (TRG) which was described by Dworak et al. [7]. The characteristics of each grade were as follows: grade 0, no regression; grade 1, minor regression (dominant tumor mass with obvious fibrosis in 25% or less of the tumor mass); grade 2, moderate regression (dominant tumor mass with obvious fibrosis in 26% to 50% of the tumor mass); grade 3, good regression (dominant fibrosis outgrowing the tumor mass; more than 50% tumor regression); and grade 4, total regression (no viable tumor cells, only fibrotic mass). Positive circumferential resection margin (CRM) was defined as the presence of tumor cell within 1 mm or less from the inked radial margin.

Follow-up consisted of examinations every 3 months for the first year and then every 6 months subsequently. Most patients underwent pelvic computed tomography scans. Other imaging tests, such as pelvic magnetic resonance imaging and positron

emission tomography scans, were performed, based on patient symptoms or signs. Follow-up data were obtained from patient medical records. Treatment-related toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) ver. 4.0 (NCI, Bethesda, MD, USA).

The primary endpoint of this study was pathologic tumor response after preoperative CRT; pCR rate and TRG. The secondary endpoint included treatment-related complication, locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), DFS and overall survival (OS). All events were measured from the date of the initiation of preoperative CRT. The time to the first defining event was assessed in terms of the following endpoints: LRFS, with recurrence at the primary site or regional lymph nodes as

the event; DMFS, with disease metastasis to distant sites as the event; DFS, with any type of disease recurrence or death due to any cause as the event; and OS, with death due to any cause as the event. The LRFS, DMFS, DFS, and OS were estimated using the Kaplan-Meier method, and the differences were compared using log-rank tests. The p-values of <0.05 were considered statistically significant. Multivariate analysis using the Cox proportional hazards model was performed to identify independent predictors among the various potential prognostic factors. Differences between patient characteristics were analyzed using chi-squared tests and one-way analysis of variance (ANOVA) when appropriate. Statistical analyses were performed using the R statistical language (R Project ver. 3.1.3) (http://www.R-project.org).

Table 1. Patient and treatment characteristics

Characteristic	Group A (50 Gy in 25 fx) (n = 55)	Group B (50.4 Gy in 28 fx) (n = 50)	Group C (45 Gy in 25 fx) (n = 49)	p-value
Age (yr)	63 (44–84)	62 (42–80)	64 (43–82)	0.842
Gender (male:female)	38:17	34:16	32:17	0.915
Location from anal verge (cm)				
Mean ± SD	4.2 ± 2.6	4.3 ± 2.4	5.1 ± 2.6	0.072
≤4	32 (58.2)	25 (50.0)	21 (42.9)	0.576
4-8	19 (34.5)	19 (38.0)	21 (42.9)	
≥8	4 (7.3)	6 (12.0)	7 (14.3)	
Pretreatment CEA (ng/mL)				0.930
≤5	39 (70.9)	37 (74.0)	36 (73.5)	
>5	16 (29.1)	13 (26.0)	13 (26.5)	
Clinical staging				
cT				0.746
2	2 (3.6)	3 (6.0)	2 (4.1)	
3	44 (80.0)	40 (80.0)	43 (87.8)	
4	9 (15.4)	7 (14.0)	4 (8.2)	
cN				0.943
0	16 (29.1)	11 (22.0)	10 (20.4)	
1	20 (36.4)	19 (38.0)	17 (34.7)	
2	19 (34.5)	20 (40.0)	22 (44.9)	
Surgery type				0.589
LAR	51 (92.7)	45 (90.0)	45 (91.8)	
APR	2 (3.6)	2 (4.0)	0 (0)	
ISR	2 (3.6)	3 (6.0)	4 (8.2)	
Administration of adjuvant chemotherapy				0.964
Total	46 (83.7)	43 (86.0)	42 (85.7)	
5-FU	34 (61.8)	32 (64.0)	30 (61.2)	
Capecitabine	9 (16.4)	10 (20.0)	9 (18.4)	
FOLFOX	3 (5.5)	1 (2.0)	3 (6.1)	

Values are presented as median (range) or number (%).
SD, standard deviation; CEA, carcinoembryonic antigen; LAR, low anterior resection; APR, abdominoperineal resection; ISR, intersphincteric resection; 5-FU, 5-fulorouracil; FOLFOX, folinic acid (leucovorin), fluorouracil, oxaliplatin.

Table 2. Pathologic results

	Group A (50 Gy in 25 fx) (n = 55)	Group B (50.4 Gy in 28 fx) (n = 50)	Group C (45 Gy in 25 fx) (n = 49)	p-value
Pathologic complete response	12 (21.8)	13 (26.0)	10 (20.4)	0.786
Tumor regression grade				0.377
0	0 (0)	3 (6.0)	2 (4.1)	
1	10 (18.2)	9 (18.0)	10 (20.4)	
2	16 (29.1)	9 (18.0)	6 (12.2)	
3	17 (30.9)	16 (32.0)	21 (42.9)	
4	12 (21.8)	13 (26.0)	10 (20.4)	
Pathologic staging				
ypT				0.950
0	12 (21.8)	13 (26.0)	10 (20.4)	
1	4 (7.3)	2 (4.0)	1 (2.0)	
2	11 (20.0)	10 (20.0)	11 (22.4)	
3	27 (49.1)	24 (48.0)	25 (51.0)	
4	1 (1.8)	1 (2.0)	2 (4.1)	
ypN				0.789
0	42 (76.4)	42 (84.0)	41 (83.7)	
1	10 (18.2)	6 (12.0)	7 (14.3)	
2	3 (5.5)	2 (4.0)	1 (2.0)	
Circumferential resection margin				0.868
Close (≤1 mm)	2 (3.6)	3 (6.0)	4 (8.2)	
Negative (>1 mm)	38 (69.1)	33 (66.0)	30 (61.2)	
Unknown	15 (27.3)	14 (28.0)	15 (30.6)	

Values are presented as number (%).

Results

1. Patient characteristics
Patient characteristics were well balanced among the three dose-fractionation groups (Table 1). There were 104 male and 50 female. The median age was 63 years (range, 42 to 84 years). Clinical T category was T2, T3, and T4 in 7 (4.5%), 127 (82.5%), and 20 (13.0%) patients, respectively. Clinical N category was N0, N1, and N2 in 37 (24.0%), 56 (36.4%), and 61 (39.6%) patients, respectively. Tumor distance from the anal verge was ≤4, >4 and <8 cm, or ≥8 cm in 78 (50.6%), 59 (38.0%), and 17 (11.0%) patients, respectively. The median follow-up period was 29 months (range, 5 to 48 months).

2. Acute toxicity of chemoradiotherapy
All of the regimens were well tolerated. One hundred-six patients (68.8%) experienced diarrhea. Grade 3 diarrhea developed in 10 patients, and no patients experienced grade 4 diarrhea. One patient experienced grade 2 radiation cystitis, which required conservative management. Grade 3 and 4 acute renal failure developed in 1 patient each after adjuvant

chemotherapy, but neither patient showed progression to chronic renal failure. In summary, grade ≥3 acute toxicity developed in 6 (10.9%), 2 (4.0%), and 3 (6.1%) patients in groups A, B, and C, respectively, with no significant difference among the three groups (p = 0.368).

3. Surgical procedures
The median time from the end of preoperative CRT to radical resection was 58 days (range, 33 to 97 days). The type of surgery depended on the location of the tumor and the surgeon's decision. The most common operation performed was a low anterior resection in 141 patients (91.6%). Other operations included abdominoperineal resection in 4 patients (2.6%) and intersphincteric resection in 9 patients (5.8%). The overall sphincter preservation rate was 97.4%. There was no significant difference in the sphincter preservation rate among the three groups. Four patients in whom preservation of the sphincter failed had tumor extension to the anal verge. In a subgroup analysis of low rectal cancer ≤4 cm from anal verge, the sphincter preservation rate were 93.8%, 92%, and 100% for group A, B, and C, respectively (p = 0.381).

Table 3. Postoperative complications

	Group A (50 Gy in 25 fx) (n = 55)	Group B (50.4 Gy in 28 fx) (n = 50)	Group C (45 Gy in 25 fx) (n = 49)	p-value
Acute				0.330
Wound infection	1 (1.8)	2 (4.0)	0 (0)	
Anastomotic leak	2 (3.6)	1 (2.0)	1 (2.0)	
Bowel obstruction	0 (0)	1 (2.0)	0 (0)	
Bowel perforation	1 (1.8)	0 (0)	0 (0)	
Fistula	1 (1.8)	2 (4.0)	0 (0)	
Incisional hernia	1 (1.8)	0 (0)	1 (2.0)	
Total	6 (10.9)	6 (12.0)	2 (4.1)	
Chronic				0.540
Fecal frequency	6 (10.9)	3 (6.0)	6 (12.2)	
Fecal incontinence	2 (3.6)	0 (0)	2 (4.1)	
Impotence	2 (3.6)	2 (4.0)	0 (0)	
Urinary incontinence	2 (3.6)	0 (0)	0 (0)	
Total	10 (18.2)	6 (12.0)	8 (16.3)	

Values are presented as number (%).

4. Pathologic results

Pathologic results are summarized in Table 2. On examination of the resected specimens, pCR (TRG 4) was achieved in 35 patients (22.7%). The pCR rates in groups A, B, and C were 21.8%, 26.0%, and 20.4%, respectively. Among 119 patients who failed to achieve pCR, TRG was grade 3 in 54 patients (35.1%), grade 2 in 31 patients (20.1%), grade 1 in 29 patients (18.8%), and grade 0 in 5 patients (3.2%). The good response rate (TRG 3+4) was 57.8%. No difference was found among the 3 dose-fractionation groups regarding the pCR rate, TRG, or good response rate. Of the 119 patients who failed to achieve pCR, CRM was measured in 110 patients. Nine patients (5.8%) had a positive CRM (CRM ≤1 mm). Among the three dose-fractionation groups, the incidence of positive CRM did not differ significantly. Pretreatment carcinoembryonic antibody level was not a predictor of pCR or TRG.

5. Postoperative complications

Table 3 shows the incidence of acute and chronic postoperative complications. The incidence of postoperative complications did not differ among the 3 dose-fractionation groups. Postoperative complications occurred in 37 patients (24.0%), with 13 patients (8.4%) experiencing acute complications and 24 patients (15.6%) experiencing chronic complications. Acute postoperative complication rates were 10.9%, 12.0%, and 4.1% in groups A, B, and C, respectively (p = 0.330). In the comparison between two groups (group A+B vs. group C), acute postoperative complication rates were

11.4% and 4.1% in group A+B and group C, respectively (p = 0.140). Anastomotic leakage was the most frequent acute postoperative complication and fecal frequency was the most frequent chronic complication. Three patients (1.9%) died postoperatively, 1 from perianal abscess (group A), 1 from bowel perforation (group A), and 1 from bowel obstruction (group B). Grade 2 fecal incontinence developed in 4 patients (2.6%). Grade 2 erectile dysfunction was recorded in 4 patients (2.6%). Grade 2 urinary incontinence occurred in 2 patients (1.3%).

6. Locoregional recurrence-free survival (LRFS)

Locoregional recurrence developed in 9 patients during the follow-up period. The 2-year LRFS for the entire patient population was 94.0%. The 2-year LRFS rates were 98.0%, 87.6%, and 95.9% in groups A, B, and C, respectively (p = 0.293) (Table 4, Fig.1). Achievement of pCR (TRG 4) or good responsiveness according to TRG (TRG 3+4) was not correlated with improvement in LRFS. A positive CRM was found to be correlated with worse LRFS in univariate (p = 0.034) but not in multivariate analyses (Table 4).

7. Distant metastasis-free survival (DMFS)

Distant metastasis occurred in 30 patients, and the 2-year DMFS rate for the entire patient population was 79.8%. The 2-year DMFS rates in groups A, B, and C were 80.8%, 84.5%, and 74.0%, respectively (p = 0.570) (Table 4, Fig.1). The most frequent sites of distant metastasis were the lung

and liver with 89.7% and 24.1%, respectively. In univariate analysis, good responsiveness according to TRG (p = 0.018), ypT category (p < 0.001), ypN category (p < 0.001), and carcinoembryonic antigen level (p = 0.015) were associated with DMFS. In multivariate analysis, ypN category (p < 0.001) showed a significant correlation with DMFS (hazard ratio [HR], 3.94; 95% confidence interval [CI], 1.79 to 8.65; p < 0.001).

Table 4. Prognostic factors influencing actuarial rates of LRFS, DMFS, DFS, and OS

Parameter	No. of patients	LRFS		DMFS		DFS		OS	
		2-yr (%)	p-value	2-yr (%)	p-value	2-yr (%)	p-value	2-yr (%)	p-value
Dose fractionation schedule of RT			0.293		0.570		0.885		0.117
A (50 Gy in 25 fx)	55	98.0		80.8		77.3		93.8	
B (50.4 Gy in 28 fx)	50	87.6		84.5		78.0		98.0	
C (45 Gy in 25 fx)	49	95.9		74.0		72.4		97.8	
Age (yr)			0.941		0.246		0.201		0.170
≤60	89	95.1		77.3		73.2		95.1	
>60	65	92.6		83.4		80.0		100	
Gender			0.474		0.419		0.145		0.325
Male	104	94.5		78.6		73.0		94.8	
Female	50	95.9		82.4		82.7		95.7	
Location from anal verge (cm)			0.659		0.302		0.383		0.794
<4	57	93.5		75.5		71.9		98.1	
≥4	97	94.2		82.1		78.3		95.5	
Pretreatment CEA (ng/mL)			0.621		0.015		0.045		0.882
≤5	112	94.5		84.8		80.3		96.2	
>5	42	92.9		66.9		65.2		96.8	
cT category			0.913		0.327		0.044		0.084
2–3	134	95.0		81.2		78.8		97.5	
4	20	94.7		70.3		59.1		89.4	
cN category			0.450		0.677		0.787		0.924
0	37	92.8		79.3		76.9		97.0	
1–2	117	94.3		79.9		75.8		96.3	
Surgery type			0.240		0.556		0.780		0.271
LAR	141	94.5		80.5		76.4		96.1	
APR	4	50.0		100		100		100	
ISR	9	100		51.9		51.9		100	
Pathologic complete response			0.919		0.054		0.021		0.961
Yes	35	97.0		93.9		93.9		95.4	
No	119	94.3		75.6		70.9		100	
Tumor regression grade			0.796		0.018		0.018		0.367
0–2	65	92.7		70.3		66.8		98.8	
3–4	89	94.9		86.4		82.8		93.0	
ypT category			0.716		<0.001		<0.001		0.502
1–2	74	95.4		94.0		89.6		98.6	
3–4	80	92.8		66.3		63.6		94.3	
ypN category			0.603		<0.001		<0.001		0.031
0	125	94.5		81.6		81.6		98.3	
1–2	29	92.3		53.2		53.2		87.8	
Circumferential resection margin (mm)			0.034		0.373		0.432		0.312
≤1	9	59.3		57.1		50.8		100	
>1	101	95.5		77.5		75.3		96.6	
Unknown	44	94.9		87.6		81.0		95.4	

LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival; DFS, disease-free survival; OS, overall survival; RT, radiotherapy; CEA, carcinoembryonic antigen; LAR, low anterior resection; APR, abdominoperineal resection; ISR, intersphincteric resection.
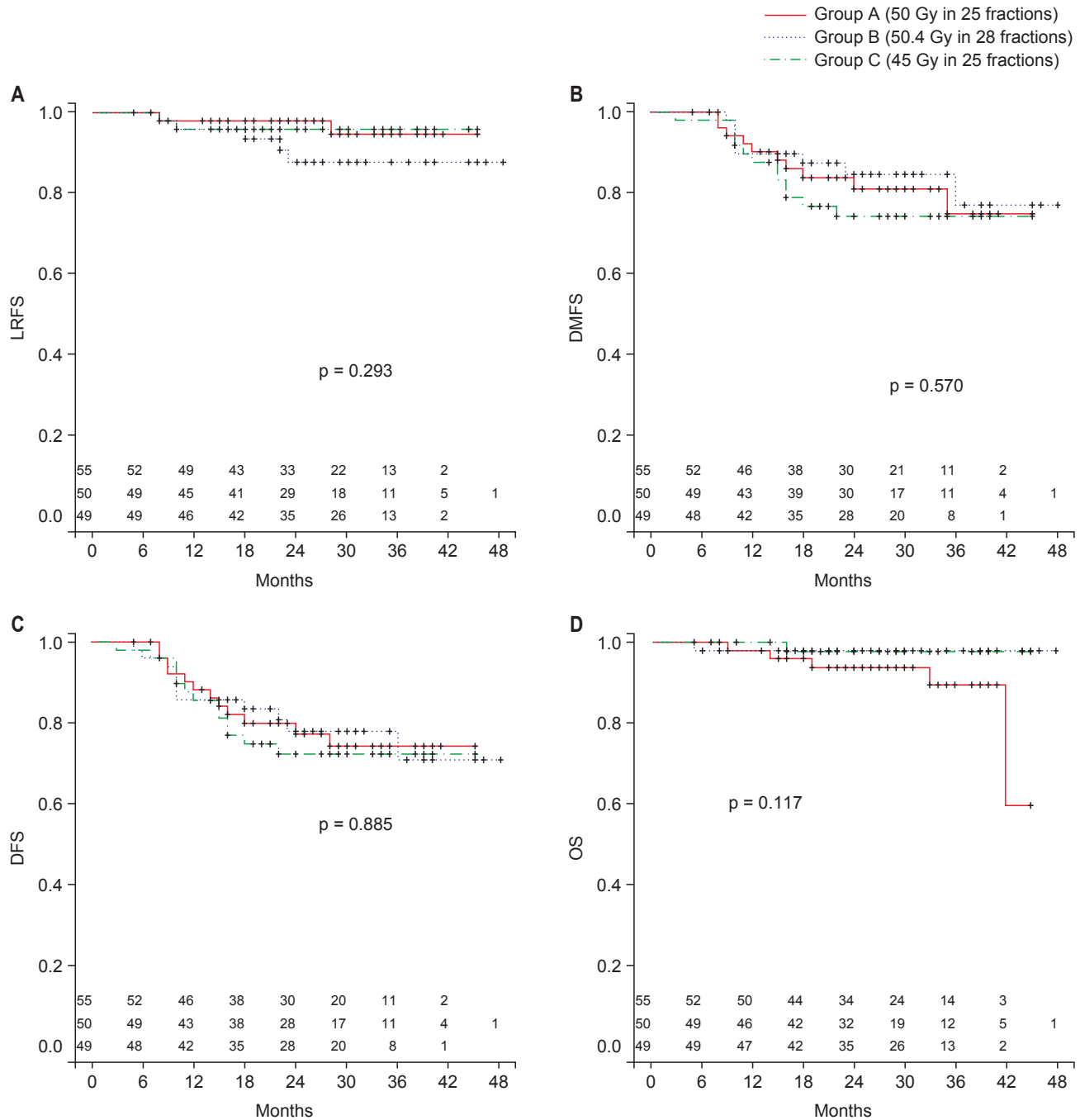
Fig 1. (A) Locoregional recurrence-free survival (LRFS), (B) distant metastasis free-survival (DMFS), (C) disease-free survival (DFS), and (D) overall survival (OS) according to three dose fractionation schedules.

8. Disease-free survival (DFS) and overall survival (OS)

The 2-year DFS and OS rates for the entire patient population were 76.1% and 96.5%, respectively. In groups A, B, and C, the 2-year DFS rates were 77.3%, 78.0%, and 72.4%, respectively (p = 0.885), and the 2-year OS rates were 93.8%, 98.0%, and 97.8%, respectively (p = 0.117) (Fig. 1). Achievement of pCR (p

= 0.021), good responsiveness of TRG (p = 0.018), ypT category (p < 0.001), ypN category (p < 0.001), and carcinoembryonic antigen level (p = 0.045) were significantly correlated with DFS. In multivariate analysis, ypN category was associated with inferior DFS (HR, 3.40; 95% CI, 1.63 to 7.09, p = 0.001). With respect to OS, ypN category was associated with OS in

univariate (p = 0.031) and multivariate analyses (HR, 6.27; 95% CI, 1.21 to 32.54; p = 0.029).

Discussion and Conclusion

Although preoperative CRT has become the standard of treatment in patients with cT3-4 and/or N+ disease, there is still controversy as to the optimal radiation dose fractionation schedule. A long course of radiation therapy at a dose of 45–50 Gy in 1.8–2 Gy per fraction over 5 to 5.5 weeks (as given in the German and National Surgical Adjuvant Breast and Bowel Project [NSABP] R-03 trials) has been thought to be "standard," whereas the short-course RT at a dose of 25 Gy in 5 Gy per fraction (as given in the MRC CR07 trial) is often used in parts of Europe. The Polish trial demonstrated that the short-course RT (25 Gy in 5 fractions) was as effective as the conventional fractionated long-course RT (50.4 Gy in 28 fractions) [8]. Though a higher pCR rate was seen with long-course RT (16% vs. 1%), along with fewer positive radial margins (4% vs. 13%) and considerable size reduction of the tumor, no differences in sphincter preservation rate, local control, or OS were observed. The Australian trial compared short-course (25 Gy in 5 fractions) and long-course CRT (50.4 Gy in 28 fractions) [9]. Despite the fact that pathologic tumor regression was significantly more common in patients randomly assigned to long-course RT, no difference in 3-year local control, 5-year OS, or late toxicity was found between the two arms of the trial. However, a meta-analysis of 21 randomized clinical trials showed that a biologically effective dose (BED) >30 Gy_{10} with long-course RT showed a benefit in terms of the sphincter preservation rate, suggesting that the increased change in pathologic downstaging might lead to clinical benefits such as sphincter preservation [10]. Based on these results, long-course RT has been recommended for sphincter preservation.

In a phase II dose escalation study by Chan et al. [11], 3 dose schedules (40 Gy/20 fractions, 40 Gy/20 fractions + postoperative 18 Gy/9 fractions, and 50 Gy/25 fractions) were compared, in which the schedule of 50 Gy was associated with improved 5-year local control (p = 0.0011). Wiltshire et al. [12] compared 3 dose fractionation schedules (40 Gy in 20 fractions, 46 Gy in 23 fractions, and 50 Gy in 25 fractions). They reported that radiation doses ≥46 Gy were associated with improvement in LRFS, DFS, and OS, but there was no difference between 46 Gy and 50 Gy. The authors also showed a trend toward an increased pCR rate with higher doses (15%, 23%, and 33%, respectively) (p = 0.07). Gerard et al. [13] compared 2 dose fractionation schedules (45 Gy

in 25 fractions and 50 Gy in 25 fractions) in a randomized fashion, although the chemotherapy regimens were different from each other (capecitabine and capecitabine + oxaliplatin, respectively). The pCR rate was marginally improved (p = 0.09) and major pathologic response was improved significantly (p = 0.02) with 50 Gy in 25 fractions. However, the interpretation of the results from the studies of Chen et al. [11] and Gerard et al. [13] needs to be cautious as they performed modifications to both radiation dose and chemotherapy regimens at the same time.

In contrast to previously mentioned studies [11-14], our study demonstrated no differences among the three dose fractionation schedules in terms of pathologic tumor response, locoregional recurrence, distant metastasis, and survival. Using the α/β ratio of 10 Gy for tumor cell kill, we calculated a BED10 of 60.0 Gy_{10} for group A (50 Gy in 25 fractions), of 59.5 Gy_{10} for group B (50.4 Gy in 28 fractions), and of 53.1 Gy_{10} for group C (45 Gy in 25 fractions). Thus, the radiation doses of groups A and B were similarly higher than those of group C. No statistically significant differences were found between group A+B and group C. Thus, our study suggests that there might be no clear dose-response relationship within the BED range from 53.1 Gy_{10} to 60.0 Gy_{10}. To examine the BED as a surrogate of normal tissue toxicity, BED3 was calculated using the α/β ratio of 3. The BED3 of groups A, B, and C were 83.3 Gy_3, 80.6 Gy_3, and 72.0 Gy_3, respectively. The acute postoperative complication rate was grossly higher in group A+B (≥80.6 Gy_3) than in group C (11.4% vs. 4.1%), although no statistical significance was found (p = 0.140). It is possible that the dose-response relationship exists in terms of normal tissue toxicity because normal tissue generally has a smaller α/β ratio than tumor cells within the BED range from 72.0 Gy_3 to 83.3 Gy_3.

In the present study, the achievement of pCR and good TRG score (3+4) were associated with improved 2-year DMFS and DFS. Multiple studies have demonstrated the pathologic tumor response following preoperative CRT has a prognostic value for patients with locally advanced rectal cancer [15-17]. According to the recent updated results from the CAO/ARO/AIO-94 trial by Fokas et al. [18], complete (TRG 4) and intermediate TRG (TRG 2+3) were associated with improved DMFS and DFS after a median follow-up period of 132 months. Additionally, our results showed that higher TRG was associated with incremental CRM width in multivariate analysis. This suggests that greater the number of tumor cells killed by preoperative CRT, more adequate surgical margin would be achieved. Though the degree of pathologic tumor response such as pCR

and TRG, have some prognostic value, radiation dose escalation for the achievement of them are need to be cautious.

Several phase III dose-escalation trials and a meta-analysis demonstrated a dose-response relationship with regard to pCR for locally advanced rectal cancer [13,19-21]. Nevertheless, questions have existed as to the validity of pathologic tumor response for an early endpoint as a surrogate of long-term clinical outcome. In the analysis by Glynne-Jones et al. [22], pCR did not predict late outcomes such as local control or survival. The authors noted that whether we are actually altering the natural history of the disease with preoperative CRT or merely revealing a biological subgroup that would have had a favorable outcome anyway remained uncertain. Fokas et al. [18] also pointed out that the inherent aggressiveness of a tumor related to its biologic phenotype might reflect resistance to CRT and, at the same time, a higher incidence of distant metastasis. Appelt et al. [20] presented the results of a randomized phase III trial evaluating the addition of a brachytherapy boost (10 Gy in 2 fractions) to long-course preoperative CRT (50.4 Gy in 28 fractions) for locally advanced rectal cancer. They reported that, despite the fact that the degree of tumor response was higher in the brachytherapy boost arm, no differences in 5-year OS, progression-free survival, or LRFS were found. The authors noted that, although pathologic tumor regression was a prognostic factor, this did not imply that it was a valid surrogate clinical endpoint. In our study, as in that of Fokas et al. [18], TRG was associated with DMFS and DFS, but was not associated with LRFS. An association between pathologic tumor response and DMFS might suggest the possibility that CRT-resistant tumors which inherently had more biologic potential for distant metastasis were selectively included in the poor pathologic regression group. In this respect, it appears unreasonable to intensify the radiation dose for preoperative CRT based on results from the trials using pathologic tumor response as an endpoint.

The prognostic significance of the CRM status for local control and survival has been well established [2,14,23,24]. An analysis using data from the MRC CR07 and National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) C016 trials found that the 3-year local recurrence rates of CRM-positive patients and CRM-negative patients were 17% and 6%, respectively (p = 0.0011) [2]. Birbeck et al. [14] reported the clinical outcomes of 586 patients, of whom 165 patients had positive CRMs. CRM-positive patients showed significantly higher local recurrence rates (38% vs. 10%) and lower survival rates (40% vs. 79%) than CRM-negative patients. Similarly, in our study, a close CRM (≤1 mm) was associated with inferior

2-year LRFS (59.3% vs. 95.5%).

Our study has some limitations. First, there may be concealed selection biases due to its retrospective design, although patient and tumor characteristics seemed to be similar in each of the groups. Second, a small sample size might be insufficient to detect a potential statistical difference. Third, a relatively short follow-up period for oncologic outcomes is another limitation, especially for OS. Nevertheless, we think these results are still valid. Patients included in our retrospective study were treated during the same time period at a single institute; thus, RT and surgical techniques, pathologic evaluation, and chemotherapy were homogeneous.

In conclusion, comparison of three radiation dose fractionation schedules for locally advanced rectal cancer showed no impact of radiation dose fractionation schedules on the pCR rate and 2-year cumulative incidence of toxicity, LRFS, DMFS, DFS, or OS. Large prospective randomized trials are needed to confirm these results in the future.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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