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Clinical outcomes of neoadjuvant chemoradiotherapy followed by total mesorectal excision in locally advanced rectal cancer with mesorectal fascia involvement

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Purpose: For the treatment of locally advanced rectal cancer (LARC), research on primary lesions with mesorectal fascia (MRF) involvement is lacking. This study analyzed the clinical outcomes and efficacy of dose-escalated neoadjuvant concurrent chemoradiotherapy (NCRT) to patients with LARC involving MRF.

Materials and Methods: We retrospectively reviewed 301 patients who were diagnosed with LARC involving MRF and underwent NCRT followed by total mesorectal excision (TME). Patients who received radiotherapy (RT) doses of ≤50.4 Gy were defined as the non-boost group, while ≥54.0 Gy as the boost group. Pathological tumor response and survival outcomes, including intrapelvic recurrence-free survival (IPRFS), distant metastases-free survival (DMFS) and overall survival (OS), were analyzed.

Results: A total of 269 patients (89.4%) achieved a negative pathological circumferential resection margin and 104 (34.6%) had good pathological tumor regression grades. With a median follow-up of 32.4 months, IPRFS, DMFS, and OS rates at 5-years were 88.6%, 78.0%, and 91.2%, respectively. In the subgroup analysis by RT dose, the boost group included more advanced clinical stages of patients. For the non-boost group and boost group, 5-year IPRFS rates were 90.3% and 87.0% ($p = 0.242$), 5-year DMFS rates were 82.0% and 71.3% ($p = 0.105$), and 5-year OS rates were 93.0% and 80.6% ($p = 0.439$), respectively. Treatment related toxicity was comparable between the two groups ($p = 0.211$).

Conclusion: Although this retrospective study failed to confirm the efficacy of dose-escalated NCRT, favorable IPRFS and pathological complete response was achieved with NCRT followed by TME. Further studies combining patient customized RT dose with systemic therapies are needed.

Keywords: Rectal cancer, Mesorectalfascia, Radiotherapy, Neoadjuvant treatment

Introduction

Colorectal cancer (CRC) is the third most common malignancy and fourth leading cause of death worldwide [1]. Through health screening programs using endoscopic intervention, early detection of CRC has increased [2]. Nevertheless, a substantial number of patients are

still not detected until they have reached advanced stages and 30%–40% of those patients are diagnosed with locally advanced rectal cancer (LARC) [3].

For the treatment of LARC, introduction of neoadjuvant chemoradiotherapy (NCRT) and total mesorectal excision (TME) has decreased the local failure rate to less than 5%–10% [4-7]. Despite these approaches, LARC with mesorectal fascia (MRF) involvement, also as known as "ugly rectal cancer," is a significant risk factor for treatment failure. For patients with MRF involvement, even after completion of NCRT, achieving R0 resection through TME is challenging. This is because surgical approaches to the tumor and en bloc resections are anatomically difficult [8,9]. Moreover, the possibility of the residual tumor tissue in the circumferential resection margin (CRM) may contribute to the low pathological complete response (pCR) rate and high distant metastasis rate, which demonstrates the necessity of alternative approaches [10]. Based on previous studies, NCRT, which combines intense chemotherapy regimens with dose-escalated radiotherapy (RT), improves tumor responses and may be a solution to this unmet clinical need [11-14]. However, relevant investigations of this treatment regimen have not been conducted. Thus, this study analyzed the clinical outcomes of patients with MRF involved LARC who underwent NCRT followed by TME, and furthermore, investigated the effectiveness of dose-escalated RT.

Materials and Methods

1. Patient eligibility and evaluation

We retrospectively reviewed the medical records of 337 patients who were diagnosed with LARC involving MRF and treated with NCRT followed by TME at the Samsung Medical Center from January 2015 to December 2020. We excluded patients with the following characteristics: (1) histologically proven as non-adenocarcinoma, (2) diagnosed with anal cancer, (3) lacking information for a pathological tumor regression grade (pTRG) or pretreatment carcinoembryonic antigen (CEA) level, (4) had distant metastasis at diagnosis, and (5) did not complete RT (Supplementary Fig. S1). Finally, a total of 301 patients were included in the analysis.

All patients underwent rectum magnetic resonance imaging (MRI) twice, within 4 weeks before NCRT (initial MRI) and within 6–8 weeks after completion of NCRT, before surgery. Clinical tumor staging and MRF involvement were evaluated by initial MRI and staging was based on the 7th edition of the American Joint Committee on Cancer guidelines [15]. MRF involvement was defined as the distance between tumor margin and MRF or levator ani muscle <1 mm or there was invasion [16]. Lateral pelvic lymph nodes (LPLN) involvement was defined as those with a diameter of ≥ 5 mm on initial MRI or computed tomography (CT) scans [17].

2. Treatments

The details in RT planning have been described in a previous study [18]. Gross tumor volume (GTV) was defined as all visible tumors based on pelvis CT and rectum MRI. The clinical target volumes (CTV) were defined as the volumes expanded from GTVs of 0.5–1.0 cm and regional lymphatic areas including presacral, internal iliac, obturator, and mesorectal areas. The planning target volume was delineated by expanding the CTV by 1.0 cm. Neoadjuvant chemotherapy consisted of capecitabine, 5-fluorouracil (5-FU) with intravenous bolus, and 5-fluorouracil plus leucovorin (FL) with intravenous infusion. All patients underwent surgical resection with TME 4–8 weeks after completion of NCRT. Adjuvant chemotherapy was administered to patients who were deemed necessary by the medical team based on their surgical pathology results.

3. Pathological tumor response evaluation and outcomes

pTRGs were evaluated according to the Dworak's TRG system [19]. Good and poor pTRGs were defined as pTRG 3 or 4, and pTRG 0, 1, or 2, respectively. The pCRMs were evaluated by pathologists, where the distance between the tumor and resection margin of <1 mm was defined as a positive pCRM and over 1 mm as a negative pCRM [20]. Intrapelvic recurrence (IPR) was defined as tumor recurrence involving at least one of the following sites: the anastomotic area, presacral area, regional lymphatics, and pelvic organ area. Distant metastasis (DM) was defined as any recurrence outside the pelvis, including liver, lung, peritoneum, bone, and/or non-regional lymph nodes.

Oncological outcomes were evaluated using intrapelvic recurrence-free survival (IPRFS), distant metastasis-free survival (DMFS), and overall survival (OS) as factors. IPRFS, DMFS, and OS were defined as the interval from the date of NCRT start to that of IPR, DM, and death or last day of visit, respectively.

4. Toxicity

NCRT followed by surgery may increase the risk of perioperative complications, including anastomotic leaks and postoperative anorectal dysfunction [21-23]. Therefore, we designated treatment-related complications within 6 months after surgery as grade ≥ 3 toxicities based on the Common Terminology Criteria for Adverse Events version 5.0.

5. Statistical analyses

The chi-square and t-tests were used to compare the distribution of patient characteristics in each treatment group. To identify the risk factors for pCRM and pTRG, logistic regression was performed in univariate and multivariate analysis. IPRFS, DMFS, and OS were cal-

culated using the Kaplan–Meier method and the log-rank test was used to compare differences between the groups. Cox regression analysis was chosen for univariate analysis to identify independent prognostic factors for survival outcomes. A p-value <0.05 was considered statistically significant, and the software SPSS version 23.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

Results

1. Patient's characteristics and treatments

Patient characteristics are summarized in Table 1. The median age was 58 years (range, 22 to 82 years), and 183 patients (60.8%) were male. Tumors were usually located below the anterior peritoneal reflection as defined as Rb (n = 260; 86.4%) and clinical staging at T3 (n = 220; 73.1%), and N1-2 (n = 288; 95.7%) were dominant. At the time of diagnosis, 149 patients (49.5%) had LPLN involvement, and the median pretreatment CEA level was 3.4 ng/mL (range, 0.4 to 274.0 ng/mL).

Table 1. Patient characteristics (n = 361)

Variable	Value
Age (yr)	
Median (range)	58 (22–82)
<65	212 (70.4)
≥65	89 (29.6)
Sex	
Male	183 (60.8)
Female	118 (39.2)
Tumor location	
Ra	41 (13.6)
Rb	260 (86.4)
Clinical T stage	
T3	220 (73.1)
T4	81 (26.9)
Clinical N stage	
N0	13 (4.3)
N1-2	288 (95.7)
LPLN	
No	152 (50.5)
Yes	149 (49.5)
Pretreatment CEA (ng/mL)	
Median (range)	3.4 (0.4–274.0)
<10	239 (79.4)
≥10	62 (20.6)
Median dose (Gy)	50.4 (45.0–60.0)
Neoadjuvant chemotherapy	
Capecitabine	284 (94.4)
FL	15 (5.0)
5-FU	2 (0.6)
Adjuvant chemotherapy	
No	30 (10.0)
Yes	271 (90.0)

Values are presented as number (%).
LPLN, lateral pelvic lymph node; CEA, carcinoembryonic antigen; FL, 5-fluorouracil and leucovorin; 5-FU, 5-fluorouracil.

All patients completed the prescribed neoadjuvant radiotherapy and chemotherapy. Median RT dose was 50.4 Gy, ranging from 45.0 Gy to 60.0 Gy. Neoadjuvant chemotherapy was concurrently administered with RT where 284 patients (94.4%) were treated with capecitabine while 15 (5.0%) received FL and 2 (0.7%) received 5-FU. After surgery, 271 patients (90.0%) received adjuvant chemotherapy.

2. Pathological tumor response and prognostic factors

Of all patients, 269 patients (89.4%) achieved negative pCRM and 104 (34.6%) showed good pTRG. The pCR defined as ypT0N0 was observed in 52 patients (17.3%). In univariate and multivariate analyses, pretreatment CEA level of ≥10 ng/mL was identified as an independent risk factor for positive pCRM (hazard ratio [HR] = 5.68; 95% confidence interval [CI], 2.52–12.80; p <0.001) and poor pTRG (HR = 2.57; 95% CI, 1.27–5.18; p = 0.008) (Table 2).

3. Survival outcomes analysis

The median follow-up was 32.4 months (range, 6.0 to 76.7 months). The IPRFS, DMFS, and OS rates at 3-year were 93.4%, 82.8%, and 97.6%, while 5-year rates were 88.6%, 78.0%, and 91.2%, respectively (Fig. 1). The univariate analysis for prognostic factors of IPRFS, DMFS, and OS are shown in Table 3, demonstrating that tumor location, clinical staging, LPLN status, pretreatment CEA level, pathological tumor response and boost were not statistically significant.

4. Treatment-related complications

In total, 183 patients (60.8%) underwent planned ileostomy. Grade ≥3 toxicities were observed in 13 patients (4.3%), while 5 (1.7%) for anastomotic leakage, 3 (1.0%) for unplanned ileostomy, and 2 (0.7%) for fistula. There were 3 patients (1.0%) who died due to surgical complications within 6 months after surgery.

5. Efficacy of dose-escalated RT

Our institution had a principle of applying dose-escalated RT based on the extent of primary tumor, and total dose had been decided by each physician's judgement. Through this approach, patients were divided into two groups by RT doses to primary rectal tumor with MRF involvement. Patients who received RT doses ≤50.4 Gy were defined as the non-boost group (n = 152; 50.3%), while those who received doses ≥54.0 Gy were the boost-group (n = 149; 49.3%) (Table 4). There were no patients who were treated with RT doses between 50.4 Gy and 54.0 Gy. For non-boost and boost group, the

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Table 2. Prognostic factors in univariable and multivariable analysis for pCRM and pTRG

Variable	Reference vs.	pCRM				pTRG			
		Univariable		Multivariable		Univariable		Multivariable	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)	< 65 vs. ≥ 65	1.01 (0.98–1.05)	0.401	1.01 (0.98–1.05)	0.382	1.02 (1.00–1.04)	0.055	1.02 (0.99–1.04)	0.160
Sex	Male vs. Female	0.79 (0.37–1.71)	0.555	0.72 (0.32–1.62)	0.428	0.54 (0.33–0.87)	0.012	0.51 (0.31–0.85)	0.009
Tumor location	Ra vs. Rb	1.12 (0.37–3.37)	0.845	1.24 (0.39–4.03)	0.715	0.57 (0.27–1.21)	0.145	0.58 (0.26–1.30)	0.189
Clinical T stage	T3 vs. T4	1.07 (0.47–2.42)	0.870	0.89 (0.37–2.14)	0.792	1.36 (0.78–2.35)	0.277	1.25 (0.70–2.23)	0.456
Clinical N stage	N0 vs. N1-2	-	-	-	-	0.84 (0.25–2.78)	0.770	0.70 (0.20–2.50)	0.584
LPLN	No vs. Yes	1.02 (0.49–2.13)	0.952	0.81 (0.37–1.78)	0.596	0.97 (0.60–1.56)	0.900	0.99 (0.59–1.66)	0.978
Pretreatment CEA (ng/mL)	< 10 vs. ≥ 10	4.85 (2.26–10.39)	< 0.001	5.68 (2.52–12.80)	< 0.001	2.32 (1.19–4.51)	0.013	2.57 (1.27–5.18)	0.008
Boost	Non-boost vs. Boost	1.02 (0.49–2.13)	0.952	0.80 (0.36–1.77)	0.581	1.23 (0.64–1.66)	0.907	0.85 (0.51–1.41)	0.530

pCRM, pathologic circumferential resection margin; pTRG, pathologic tumor regression grade; LPLN, lateral pelvic lymph node; CEA, carcinoembryonic antigen; HR, hazard ratio; CI, confidence interval.

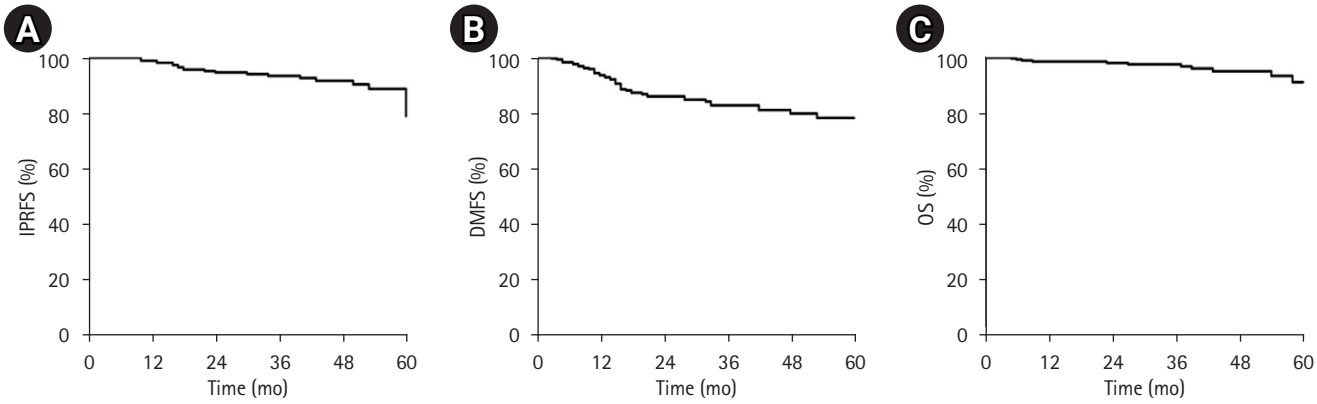

Fig. 1. Survival outcomes of locally advanced rectal cancer with mesorectal fascia involvement: (A) intrapelvic recurrence-free survival (IPRFS), (B) distant metastasis-free survival (DMFS), (C) overall survival (OS) rates.

Table 3. Prognostic factors in univariable analysis for survival outcomes

Variable	Reference vs.	IPRFS		DMFS		OS	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)	< 65 vs. ≥ 65	0.58 (0.19–1.75)	0.334	1.47 (0.81–2.67)	0.201	0.80 (0.21–3.03)	0.747
Sex	Male vs. Female	1.32 (0.54–3.22)	0.537	1.00 (0.55–1.83)	0.994	2.11 (0.64–6.94)	0.217
Tumor location	Ra vs. Rb	0.56 (0.19–1.68)	0.299	1.22 (0.48–3.09)	0.675	1.36 (0.17–10.61)	0.772
Clinical T stage	T3 vs. T4	0.94 (0.34–2.59)	0.903	0.67 (0.32–1.38)	0.276	2.45 (0.75–8.03)	0.140
Clinical N stage	N0 vs. N1-2	0.96 (0.13–7.23)	0.971	1.24 (0.30–5.12)	0.766	0.53 (0.07–4.19)	0.549
LPLN	No vs. Yes	1.22 (0.50–2.94)	0.665	1.29 (0.72–2.31)	0.389	0.85 (0.26–2.79)	0.791
Pretreatment CEA (ng/mL)	< 10 vs. ≥ 10	2.02 (0.77–5.31)	0.156	1.40 (0.71–2.76)	0.327	1.54 (0.41–5.79)	0.527
pCRM	Negative vs. Positive	2.24 (0.74–6.77)	0.154	1.25 (0.53–2.95)	0.608	1.60 (0.34–7.44)	0.551
pTRG	Good vs. Poor	1.15 (0.46–2.92)	0.763	1.72 (0.89–3.32)	0.107	2.37 (0.51–10.98)	0.270
Boost	Yes vs. No	0.58 (0.23–1.46)	0.247	0.62 (0.34–1.11)	0.108	0.61 (0.17–2.15)	0.442

IPRFS, intrapelvic recurrence-free survival; DMFS, distant metastasis-free survival; OS, overall survival; LPLN, lateral pelvic lymph node; CEA, carcinoembryonic antigen; pCRM, pathologic circumferential resection margin; pTRG, pathologic tumor response grade; HR, hazard ratio; CI, confidence interval.

Table 4. Patient characteristics by dose group (n = 301)

Variable	Non-boost (n = 152)	Boost (n = 149)	p-value
Age (yr)	56 (27–82)	58 (22–79)	0.457
< 65	110 (72.4)	102 (68.5)	
≥ 65	42 (27.6)	47 (31.5)	
Sex			
Male	94 (61.8)	89 (59.7)	0.708
Female	58 (38.2)	60 (40.3)	
Tumor location			
Ra	14 (9.2)	27 (18.1)	0.024
Rb	138 (90.8)	122 (81.9)	
Clinical T stage			
T3	120 (78.9)	100 (67.1)	0.021
T4	32 (21.1)	49 (32.9)	
Clinical N stage			
N0	8 (5.3)	5 (3.4)	0.416
N1-2	144 (94.7)	144 (96.6)	
LPLN			
No	82 (53.9)	70 (47.0)	0.227
Yes	70 (46.1)	79 (53.0)	
Pretreatment CEA (ng/mL)	2.5 (0.5–174.8)	4.5 (0.5–274.0)	0.008
< 10	130 (85.5)	109 (73.2)	
≥ 10	22 (14.5)	40 (26.8)	
Median dose (Gy)	50.4 (45.0–50.4)	54.0 (54.0–60.0)	< 0.001
Neoadjuvant chemotherapy			
Capecitabine	137 (90.1)	147 (98.7)	0.003
FL	14 (9.2)	1 (0.7)	
5-FU	1 (0.7)	1 (0.7)	
Adjuvant chemotherapy			
No	13 (8.6)	17 (11.4)	0.786
5-FU based chemotherapy[a]	99 (65.1)	77 (51.7)	
Others[b]	40 (26.3)	55 (36.9)	
Toxicities			0.211
Anastomosite leakage	2 (1.3)	3 (2.0)	
Un-planned ileostomy	0 (0.0)	3 (2.0)	
Fistula	0 (0.0)	2 (1.3)	
Death	1 (0.7)	2 (1.3)	

Values are presented as median (range) or number (%).
LPLN, lateral pelvic lymph node; CEA, carcinoembryonic antigen; FL, 5-fluorouracil and leucovorin; 5-FU, 5-fluorouracil.
[a]5-FU base chemotherapy including capecitabine and FL.
[b]Others including FOLFOX (oxaliplatin, folinic acid, 5-FU) and FOLFOX or FOLFIRI (5-FU, leucovorin, irinotecan) with bevacizumab or cetuximab.

median age was 56 years (rage, 27 to 82 years) and 58 years (range, 22 to 79 years), respectively. Boost group included more advanced stage of patients than non-boost group, in terms of clinical T stage (T3 vs. T4; non-boost group 78.9% vs. 21.1% and boost group 67.1% vs. 32.9%; p = 0.021), clinical N stage (N0 vs. N1-2; non-boost group 5.3% vs. 94.7% and boost group 3.4% vs. 96.6%; p = 0.416) and pretreatment CEA level of > 10 ng/mL (non-boost group 14.5%, boost group 26.8%; p = 0.008). Lateral pelvic lymph node involvement was also more frequent in boost RT group (non-boost group 46.1%, boost group 53.0%; p = 0.227).

Non-boost group received median RT dose of 50.4 Gy consisted of 50.4 Gy for 146 patients (96.1%), 45.0 Gy for 5 (3.3%), and 48.6 Gy for 1 (0.7%). In boost-group, median RT dose was 54.0 Gy with 54.0 Gy for 129 patients (86.6%), 55.0 Gy, 56.0 Gy, and 57.5 Gy for 1 patient each (0.7%) respectively, and 60.0 Gy for 17 (11.4%). The 137 patients (90.1%) in non-boost group and 147 (98.7%) in boost group were treated with capecitabine as a concurrent neoadjuvant chemotherapy, while others were 5-FU or FL (p = 0.003). The 139 patients (91.4%) in non-boost group and 132 (88.6%) in boost group received adjuvant chemotherapy and there was no significant difference in chemotherapy agent (p = 0.786).

The pathological tumor response was analyzed by pTRG, tumor downstaging, negative pCRM and pCR rates. Among the patients, 53 patients (34.9%) in non-boost group achieved good pTRG, while boost group had 51 patients (34.2%) (p = 0.907). Tumor downstaging, especially for T stage, occurred in 91 patients (59.5%) in non-boost group and 74 patients (49.7%) in boost group (p = 0.075) (Supplementary Table S1). In non-boost group, 136 patients (89.5%) achieved negative pCRM, while 133 (89.3%) in boost group (p = 0.952). In addition, 30 patients (19.7%) in non-boost group and 22 (14.8%) in boost group achieved pCR (p = 0.254).

For oncologic outcomes, IPRFS, DMFS, and OS were analyzed (Fig. 2). The 3-year and 5-year IPRFS were 94.2 and 90.3% for non-boost group and 93.0 and 87.0% for boost group (p = 0.242) whereas the 3-year and 5-year DMFS for non-boost group were 86.6 and 82.0% for boost group were 76.8 and 71.3% (p = 0.105). The 3-year and 5-year OS rates for non-boost group were 97.6 and 93.0% and for boost group were 97.9 and 80.6% (p = 0.439).

In addition, sphincter preservation was compared between two groups. In non-boost group, 17 patients (11.2%) needed permanent colostomy or ileostomy, while 13 (8.7%) in boost group (p = 0.476), implying that dose-escalated RT may improve sphincter preservation rate even for the LARC with MRF involvement.

The treatment related grade ≥ 3 toxicities were comparable between two groups (p = 0.211).

Discussion and Conclusion

We investigated the clinical outcomes of patients with LARC with MRF involvement who underwent NCRT followed by TME. In our study, pathological tumor response was evaluated by negative pCRM, good pTRG, and pCR with rates of 89.4%, 34.6%, and 17.3%, respectively. In terms of the oncological outcomes for all

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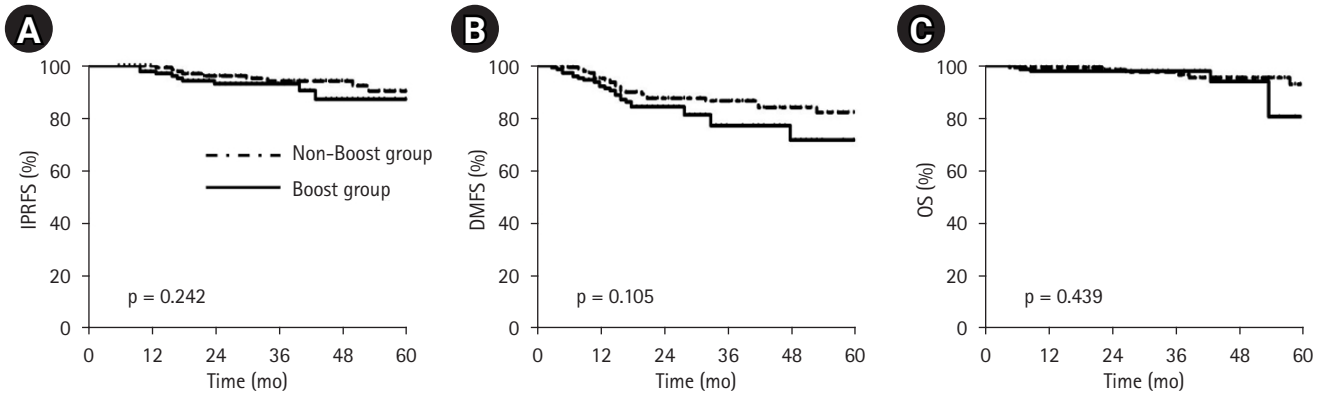

Fig. 2. Survival outcomes of locally advanced rectal cancer with mesorectal fascia involvement by dose group: (A) intrapelvic recurrence-free survival (IPRFS), (B) distant metastasis-free survival (DMFS), (C) overall survival (OS).

patients, the 3-year and 5-year IPRFS, DMFS, and OS rates were 93.4%, 82.8%, and 97.6% and 88.6%, 78.0%, and 91.2%, respectively. Furthermore, we compared dose-escalated RT to primary tumor with MRF involvement. In the boost group, receiving a median dose of 54.0 Gy, they included patients with more advanced stage than the non-boost group, receiving a median dose of 50.4 Gy. Pathological tumor response and survival outcomes were comparable without increased treatment related toxicities.

MRF involvement implies challenges in achieving adequate surgical resection in the TME era. It contributes to the presence of residual tumor with positive pCRM and subsequently increasing the incidence of local recurrence, DM, and cancer specific mortality [8,9,24-26]. Thus, controlling primary tumors with MRF involvement through NCRT before surgery is highly necessary for LARC treatment.

Previous studies have explored NCRT combined with dose-escalated RT to improve tumor control. In one study, patients with nonmetastatic cT2N0 rectal cancer underwent standard CRT (50.4 Gy) or extended CRT (54.0 Gy) [27]. Patients included in extended CRT group were more likely to achieve organ preservation and avoid surgical resection at 5 years, demonstrating that 54.0 Gy may be effective for primary rectal tumor control. There are several other studies for LARC. The KROG 04-01 trial delivered a total dose of 50.4 Gy consisting of 43.2 Gy in 24 fractions of whole pelvic RT with concomitant boost RT of 7.2 Gy in 12 fractions to the pelvis and tumor bed [28]. In this trial, a total of 94.2% of patients were clinical T3 and 5.8% were clinical T4. Of the patients, pCR rate was 11.6% and 5-year disease-free survival and OS rates were 66.0 and 75.3%. The rectal-boost trial also investigated the effectiveness of dose-escalated RT, where patients were treated either with standard dose of 50.0 Gy in 25 fractions as control group or with boost dose of 15.0 Gy in 5 fractions before a standard treatment of 50.0 Gy as intervention group [29]. Regarding patient characteristics, clinical T4 rates were 31.3% for control group and 17.2% for intervention group. For treatment outcomes, pathological or sustained clinical complete tumor response was 35.9% for the control group and 37.5% for the intervention group. Near-complete or complete tumor regression was 45.3% in the control group and 69.4% in the intervention group. The grade ≥3 toxicities were 9.4% in the intervention group. In our study, however, the good pTRG rate was 34.2% in the boost group, which is lower than those in previous studies. This considers that the patients included in our study had a higher tumor burden. Our patients had higher clinical T4 stage rates and all clinical T3 tumors were involved MRF. It also implies that the dose escalation between the non-boost group and the boost group was not as significant compared to other studies. The effect of the boost in our study did not demonstrate prominent improvements in clinical outcomes.

Another consideration for the RT dose is personalized prescription based on individual tumor genomics and using the radiosensitivity-index and genomic-adjusted radiation dose system [30-32]. While more research is needed for practical applications in clinical treatment, this can suggest a new approach for personalized RT and possibly improve survival outcomes effectively.

In survival outcomes, the DM rate was still high even with dose-escalated RT or adjuvant chemotherapy. This can be addressed through the RAPIDO trial, suggesting the effectiveness of total neoadjuvant treatment (TNT), which combines short-course radiotherapy (SCRT) with intensified chemotherapy, against LARC [33]. This study analyzed patients who were diagnosed with LARC, had high-risk features and 61.0% of the patients had MRF involvement. In this trial, the SCRT group showed improvement in pCR ($p < 0.001$) and disease-related treatment failure rates ($p = 0.019$), indicating that SCRT with intensified chemotherapy increased the possibility of tumor regression and is a potential opportunity for organ preservation. In addition, the SCRT group showed significantly reduced 3-year cumulative DM rates ($p = 0.005$), demonstrating that preoperative chemotherapy has high patient compliance compared to adjuvant chemotherapy. It also sug-

gested that the efficacy of postoperative chemotherapy might be lower than preoperative chemotherapy [34-36].

Improved outcomes in the RAPIDO trial may be due to the early initiation of systemic chemotherapy which potentially eradicated micro-metastases rather than by the specific RT scheme. The OPRA trial, which analyzed the TNT with long-course RT (LCRT), can provide the evidence for this question [37]. In this trial, patients with LARC were randomly assigned to two groups; induction chemotherapy followed by chemoradiotherapy or chemoradiotherapy followed by consolidation chemotherapy. All patients received a median 54.0 Gy of RT as LCRT. Both groups had above 80% DMFS rates. Also, patients achieving clinical complete response or organ preservation were significantly higher than those of other previous studies that analyzed NCRT followed by TME. This demonstrated that further randomized trials are needed to assess the superiority of various TNT schemes, including LCRT or SCRT, as well as different chemotherapy regimens.

There are several limitations in this study. This study is a retrospective study in a single institution, meaning that selection bias could have been present. Also, the patients who were in the non-boost and boost group showed significant differences in characteristics, therefore, adequate comparison was insufficient.

Our study does have strengths, as it represents a comprehensive analysis of patients with LARC involving MRF. Also, our study implies that dose-escalated RT could be one valid strategy in improving tumor control without increasing the risk of treatment related toxicities. In this respect, we suggested that a large-scaled prospective and randomized study of LARC treatment that combines higher doses of boost and intensified chemotherapy is needed.

In conclusion, favorable local control rate in the pelvis and pCR could be achieved through the application of NCRT followed by TME in patients with LARC with MRF involvement at the time of diagnosis, although this retrospective study failed to confirm the RT dose-escalation of NCRT. However, continuous research will be needed that validates the application of higher dose-escalation RT or molecular and/or patient customized dose prescription NCRT combined with more personalized systemic therapies.

Statement of Ethics

This study was conducted in accordance with the 1964 Declaration of Helsinki. This study was approved by the Institutional Review Board of Samsung Medical Center (approval number: 2022-10-113).

Conflict of Interest

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

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Author Contributions

Conceptualization, JIY, GSY; Investigation and methodology, JHL, JIY, GSY; Project administration, JHL, JIY, GSY; Resources, JHL, NK, JIY, GSY, HCP, WL, SHY, HCK, YBC, JWH, YAP, JKS, JOP, STK, YSP, JL, WKK; Supervision, JIY, GSY, HCP; Writing of the original draft, JHL; Writing of the review and editing, JHL, JIY, GSY; Software, JHL, JIY, GSY; Validation, JHL, JIY, GSY; Formal analysis, JHL, JIY, GSY; Data curation, JHL, NK, JIY, GSY, HCP, WL, SHY, HCK, YBC, JWH, YAP, JKS, JOP, STK, YSP, JL, WKK; Visualization, JHL, JIY, GSY.

Data Availability Statement

The data that supports the findings of this study are available upon request from the corresponding author.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2023.01032.

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