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Long-Term Outcomes of Long-Course Chemoradiotherapy vs. Short-Course Radiotherapy Followed by Consolidation Chemotherapy in Rectal Cancer

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Purpose: Previous studies have demonstrated that short-course radiotherapy (SCRT), followed by consolidation chemotherapy (CCT), produces oncologic outcomes comparable to those of long-course chemoradiotherapy (LCRT). However, more recent long-term data have raised concerns regarding the durability of these benefits. This study aimed to assess the long-term surgical and oncologic outcomes of SCRT with CCT vs. LCRT, using data from the ESCORT trial.

Materials and Methods: This comparative study included 62 patients with locally advanced rectal cancer. Patients in the SCRT group (n=27) were prospectively enrolled in the ESCORT trial (NCT03676517), a single-arm phase II study conducted from 2018 to 2020. They received five daily fractions of 5 Gy, followed by two cycles of XELOX, and surgery after 4 weeks. A matched cohort of 35 patients who underwent LCRT during the same period was retrospectively identified from institutional records.

Results: With a median follow-up of 4.75 years for the SCRT group and 4.94 years for the LCRT group, the 5-year overall survival rates were similar between the groups (SCRT: 100% vs. LCRT: 97.1%, p=0.382). The 5-year disease-free survival (DFS) rates were 83.6% for SCRT and 70.3% for LCRT (p=0.237). In multivariable analysis, SCRT was not associated with inferior DFS (hazard ratio, 0.53; 95% confidence interval, 0.14–2.04). Delayed anastomosis-related complications occurred at similar rates (18.5% vs. 20.0%; p=0.884).

Conclusion: SCRT with CCT demonstrated long-term oncologic outcomes and surgical safety comparable to those of LCRT, supporting its role as a viable alternative, particularly in resource-constrained healthcare settings.

Key Words: Rectal neoplasm, neoadjuvant therapy, chemoradiotherapy, diseases free survival

INTRODUCTION

The management of locally advanced rectal cancer (LARC) has significantly evolved with advancements in preoperative treatment strategies.[1] Preoperative radiotherapy, delivered as either short-course radiotherapy (SCRT) or long-course chemoradiotherapy (LCRT), effectively reduces local recurrence and improves oncologic outcomes.[2,3] SCRT, followed by delayed surgery, has demonstrated similar rates of postoperative complications, local recurrence, and distant metastases when compared to LCRT. Furthermore, its shorter treatment duration allows for an earlier initiation of neoadjuvant chemotherapy during the waiting interval before surgery.[4]

Several randomized controlled trials (RCTs) have shown comparable outcomes between SCRT followed by consolidation chemotherapy (CCT) and LCRT in terms of survival and late toxicity.[5-7] However, in the RAPIDO trial, while the 3-year results showed a reduction in distant metastases with comparable locoregional failure rates, the 5-year results revealed an in-

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creased risk of local recurrence, raising concerns about the long-term safety of SCRT with the CCT approach.[8]

The ESCORT trial compared the short-term outcomes and cost-effectiveness of SCRT with CCT and LCRT in patients with LARC.[9] The pathologic complete response rate was higher in the SCRT with CCT group (18.5%) than in the LCRT group (5.7%), although the difference was not statistically significant. The 2-year recurrence-free survival rates were also comparable between the SCRT with CCT (91.9%) and LCRT (76.2%) groups. In terms of cost, SCRT with CCT was associated with significantly lower inpatient and outpatient treatment expenses. These findings suggest that SCRT with CCT may offer a more cost-effective alternative to LCRT while maintaining similar oncologic outcomes. However, long-term oncologic outcomes, including survival, late recurrence, and delayed complications, remain to be fully evaluated.

This study aims to evaluate the long-term oncologic outcomes and surgical safety of LCRT versus SCRT followed by CCT in patients with LARC, using data from the ESCORT trial.

MATERIALS AND METHODS

Patients and study design

This study presents a comparative analysis of the long-term outcomes between patients who received LCRT and those enrolled in the SCRT arm of the ESCORT trial (NCT03676517), a phase II single-arm study conducted at Severance Hospital between 2018 and 2020. Patients who provided informed consent for participation in the prospective ESCORT protocol received SCRT. The comparator cohort consisted of patients with LARC who underwent standard LCRT outside the trial during the same time frame. The LCRT cohort was composed of consecutively treated patients, as previously described in our short-term outcomes and cost-effectiveness analysis.[9] High-risk features for local failure or distant metastasis (DM) were identified based on the initial pelvic MRI. These features included cT3c–T4 tumors, cN2 nodal status, threatened or involved circumferential resection margin (CRM), extramural vascular invasion, and the presence of enlarged lateral pelvic lymph nodes.

In the SCRT group, patients were administered five daily fractions of 5 Gy over a 1-week period, followed by two cycles of CCT with XELOX. Each 3-week cycle consisted of capecitabine (1000 mg/m^2) administered orally twice daily from days 1–14 and oxaliplatin (130 mg/m^2) administered intravenously on day 1. Definitive surgery was scheduled approximately 4 weeks after the completion of preoperative chemotherapy.

Patients in the LCRT group received a total radiation dose of 50.4 Gy (45 Gy delivered in 25 fractions, plus a 5.4 Gy boost) over 5 weeks, concurrently with fluoropyrimidine-based chemotherapy. Surgical resection was performed 6–8 weeks after the completion of neoadjuvant therapy. Postoperative chemotherapy regimens were determined based on pathologic risk stratification. For the LCRT group with low-risk features, adjuvant therapy consisted of either 5-fluorouracil (400–425 mg/m^2) plus leucovorin (20 mg/m^2) administered intravenously once daily for 5 days (for 4 cycles), or capecitabine (1250 mg/m^2) administered orally twice daily for 14 days every 3 weeks (for 5 cycles). For the LCRT group with high-risk features, mFOLFOX-6 was administered for 8 cycles, which included oxaliplatin (85 mg/m^2) on day 1, leucovorin (200 mg/m^2) on day 1, 5-FU (400 mg/m^2 IV bolus on day 1), followed by 5-FU (1200 mg/m^2/day) as a continuous infusion over 46 hours.

The Severance Hospital Institutional Review Board approved this study (approval number:4-2025-0592) and waived the requirement for written informed consent due to the retrospective nature of the study. The study was performed in accordance with the Declaration of Helsinki and applicable local regulations.

Outcome measures

Delayed complications, occurring ≥30 days postoperatively, were assessed, including anastomotic complications (such as leaks, fistulas, stenosis), urinary complications, abdominal hernia, small bowel obstruction (without hernia), hematochezia, and fecal incontinence (defined as involuntary bowel movements persisting for ≥1 year after surgery).

This study evaluated disease-free survival (DFS), which was defined as the time from the initiation of preoperative treatment to the first occurrence of locoregional recurrence (LRR), DM, or death from any cause. Additionally, overall survival (OS) was assessed as the time from the initiation of preoperative treatment to death from any cause. Locoregional failure-free survival (LRFS) was defined as the time from the initiation of preoperative treatment to the reappearance of a tumor within the pelvis, while metastasis-free survival (MFS) was defined as the time from the initiation of preoperative treatment to the occurrence of DM outside the pelvis.

Follow-up

All patients underwent surgical resection with follow-up care conducted based on standard guidelines and at the physician's discretion. Follow-up evaluations were conducted every 3–6 months and included blood tests, as well as chest and abdominopelvic CT scans every 6–12 months. Colonoscopies were recommended at 1, 3, and 5 years postoperatively, with adjustments made based on clinical judgment.

Statistical analyses

All statistical analyses were performed using R version 4.1.0 (R-project, Institute for Statistics and Mathematics, Vienna, Austria). Categorical variables were compared using the chi-square test or Fisher's exact test, while continuous variables were analyzed using the Mann–Whitney U test. Survival outcomes, including DFS, OS, LRFS, and MFS, were estimated using the Kaplan–Meier method, with differences between groups assessed by the log-rank test.

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Univariable Cox proportional hazards regression analyses were performed to identify prognostic factors associated with survival outcomes. Variables with a *p*-value<0.2 in univariable analysis were considered for inclusion in the multivariable Cox regression model. Additionally, the treatment group variable, which was the primary variable of interest, was included in the multivariable model regardless of its statistical significance in the univariable analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. All statistical tests were two-sided, with a *p*-value<0.05 considered statistically significant.

Additionally, we performed a post-hoc sensitivity analysis using propensity score matching (PSM). Detailed results and further explanations are provided in the Supplementary Material (only online).

RESULTS

A total of 62 patients were included in the analysis: 27 patients received SCRT, and 35 patients received LCRT. The median follow-up period for all patients was 4.94 years (IQR: 4.72–5.11) in the LCRT group and 4.75 years (IQR: 3.99–5.02) in the SCRT group, with no significant difference between the groups (*p*=0.121). Patient characteristics, as well as pathologic and immediate postoperative outcomes previously published, are briefly summarized in Table 1 for reference.

Delayed complications

Delayed complications occurred in 23 patients (37.1%), including 8 patients in the SCRT group and 15 patients in the LCRT group, with no significant difference between the groups (29.6% vs. 42.9%; *p*=0.285) (Table 2). Anastomosis-related complications were identified in 12 patients (19.4%), including 5 patients in the SCRT group (18.5%) and 7 patients in the LCRT group (20.0%), with no significant difference (*p*=0.884). Specifically, anastomotic leaks (ALs) or pelvic fistulas occurred in 9 patients (14.5%), and anastomotic stenosis occurred in 3 patients (4.8%), with no significant intergroup differences. Other urinary and bowel-related complications also showed no significant differences between the groups.

Survivals

No significant differences were observed in the 5-year OS rates (LCRT: 97.1% vs. SCRT: 100%; *p*=0.382) or the 5-year DFS rates (LCRT: 70.3% vs. SCRT: 83.6%; *p*=0.237) between the treatment groups (Figs. 1 and 2). One patient in the LCRT group died 18 months after treatment due to anastomotic relapse. LRR occurred in three patients in the LCRT group, whereas no cases were observed in the SCRT group. DMs were identified in four patients in the SCRT group (all pulmonary metastases) and in eight patients in the LCRT group (lungs: 5, liver: 2, para-aortic lymph node: 1) however, no statistically significant differences were observed in 5-year LRFS (LCRT: 90.8% vs. SCRT: 100%; *p*=0.146) or MFS (LCRT: 76.3% vs. SCRT: 83.6%; *p*=0.443) (Figs. 3 and 4).

Multivariable Cox regression analysis indicated that SCRT was not a significant predictor of MFS (HR: 0.78; 95% CI: 0.19–3.08; *p*=0.725) or DFS (HR: 0.53; 95% CI: 0.14–2.04; *p*=0.360), after adjusting for age, sex, clinical tumor and node stage, clinical CRM involvement, tumor height, histologic grade and adjuvant chemotherapy (Tables 3 and 4). The median time to

Table 1. Baseline Characteristics and Pathologic Outcomes between SCRT and LCRT Groups

	SCRT (n=27)	LCRT (n=35)	*p*
Age (yr)	58.6±9.8	63.7±8.7	0.030
Male sex	16 (59.3)	22 (62.9)	0.798
Distance from AV (cm)	7.6±2.0	6.8±2.3	0.140
CEA >5 ng/mL	7 (25.9)	12 (34.3)	0.479
cT stage			0.201
T3	22 (85.2)	34 (97.1)	
T4	1 (3.7)	0 (0.0)	
cN stage			0.833
N 1, 2	26 (96.3)	31 (88.6)	
CRM (+)	13 (48.1)	25 (71.4)	0.054
EMVI (+)	12 (44.4)	19 (54.3)	0.304
Lateral LN (+)	7 (25.9)	10 (28.6)	>0.999
High-risk factors ≥3	6 (22.2)	14 (40.0)	0.524
Sphincter saving surgery	27 (100)	35 (100)	>0.999
Complete TME	26 (96.2)	33 (94.2)	>0.999
30-day complications	9 (33.3)	12 (34.3)	>0.999
ypT0–2	17 (63.0)	13 (37.1)	0.013
ypN0	19 (70.4)	22 (62.9)	0.905
pCRM ≤1 mm	1 (3.7)	0 (0.0)	0.435
pCR	5 (18.5)	2 (5.7)	0.223

SCRT, short-course radiotherapy; LCRT, long-course chemoradiotherapy; AV, anal verge; CEA, carcinoembryonic antigen; CRM, circumferential resection margin; EMVI; extramural vascular invasion; LN, lymph node; TME, total mesorectal excision; pCRM, pathologic circumferential resection margin; pCR, pathologic complete response.
Data are presented as mean±standard deviation or n (%).

Table 2. Comparison of Delayed Complications between SCRT and LCRT Groups

	SCRT (n=27)	LCRT (n=35)	*p*
All delayed complications	8 (29.6)	15 (42.9)	0.285
Anastomosis-related complications	5 (18.5)	7 (20.0)	0.884
Anastomotic leak or fistula	4 (14.8)	5 (14.3)	0.953
Anastomotic stenosis	1 (3.7)	2 (5.7)	0.715
Urinary complications	1 (3.7)	2 (5.7)	0.715
Fecal incontinence*	1 (3.7)	3 (8.6)	0.439
Hernia of abdominal cavity	2 (7.4)	3 (8.6)	0.867
Small bowel obstruction†	1 (3.7)	1 (2.9)	0.852
Hematochezia	0 (0.0)	1 (2.9)	0.376

SCRT, short-course radiotherapy; LCRT, long-course chemoradiotherapy.
Data are presented as n (%).
*Defined as involuntary bowel movements persisting ≥1 year after surgery; †Bowel obstruction due to parastomal hernia was not included.

DM was 16.9 months (IQR: 14.5–17.9) in the LCRT group and 21.9 months (IQR: 13.9–26.7) in the SCRT group, with no significant difference (p=0.682). Multivariate analyses of OS and LRFS were not conducted due to the low incidence of mortality and LRR events.

In the PSM analysis, 36 patients (18 per group) were matched (Supplementary Table 1, only online). The 5-year DFS was 88.9% in the SCRT group versus 66.7% in the LCRT group (HR: 0.184; 95% CI: 0.02–1.70; p=0.135), and the 5-year MFS was 88.9% vs. 72.2% (HR: 0.23; 95% CI: 0.03–2.15; p=0.198), respectively. OS and LRFS were not estimable due to the absence of events in one or both groups (Supplementary Table 2 and Supplementary Figs. 1–4, only online). These results are consistent with those of the primary analysis, although they were limited by the small sample size and number of events.

DISCUSSION

This study demonstrated that patients with LARC who received SCRT followed by two cycles of preoperative XELOX had favorable long-term oncologic outcomes, comparable to those of a matched cohort treated with LCRT. At the 5-year follow-up, DFS rates were 83.6% for the SCRT group and 70.3% for the LCRT group, reflecting a modest decline from the 2-year DFS rates previously reported (SCRT: 91.9% vs. LCRT: 76.2%).[9] These findings support the use of SCRT with CCT as a viable neoadjuvant strategy for selected patients with high-risk LARC. To date, two significant trials—the POLISH II and RAPIDO trials—have compared long-term outcomes for SCRT followed by CCT with conventional LCRT. In the POLISH II trial, patients were treated with three cycles of preoperative FOLFOX4, a regimen duration similar to the two cycles of XELOX used in our study. At 3-year and 8-year follow-ups, DFS in the SCRT arm was 53% and 43%, respectively, showing no significant difference from LCRT.[10] In contrast, the RAPIDO trial implemented a more intensive chemotherapy regimen—six cycles of XELOX or nine cycles of FOLFOX4 after SCRT—and reported a 5-year distant recurrence-free survival of 72.2%, which corresponds to a DFS of 72.2%.[8] Notably, the SCRT arm in RAPIDO

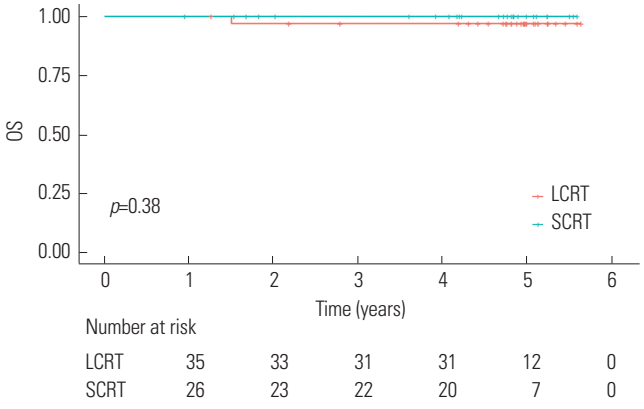

Fig. 1. Kaplan–Meier OS curves for SCRT and LCRT. The 5-year OS rates were 97.1% for LCRT and 100% for SCRT (p=0.382). SCRT, short-course radiotherapy; LCRT, long-course chemoradiotherapy; OS, overall survival.

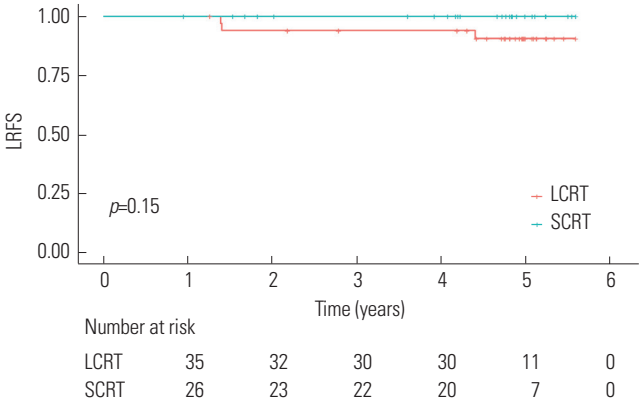

Fig. 3. Kaplan–Meier LRFS curves for SCRT and LCRT. The 5-year LRFS rates were 90.8% for LCRT and 100% for SCRT (p=0.146). SCRT, short-course radiotherapy; LCRT, long-course chemoradiotherapy; LRFS, locoregional failure-free survival.

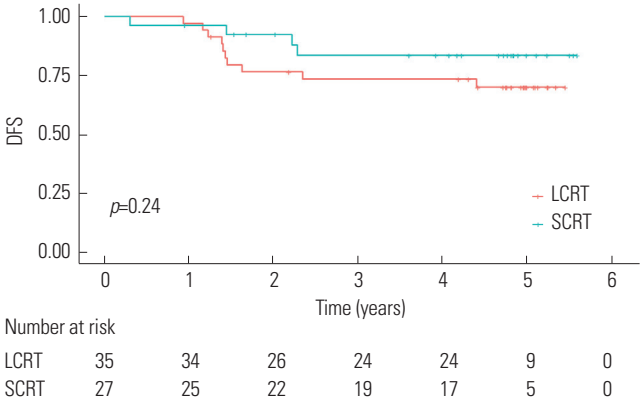

Fig. 2. Kaplan–Meier DFS curves for SCRT and LCRT. The 5-year DFS rates were 70.3% for LCRT and 83.6% for SCRT (p=0.237). SCRT, short-course radiotherapy; LCRT, long-course chemoradiotherapy; DFS, disease-free survival.

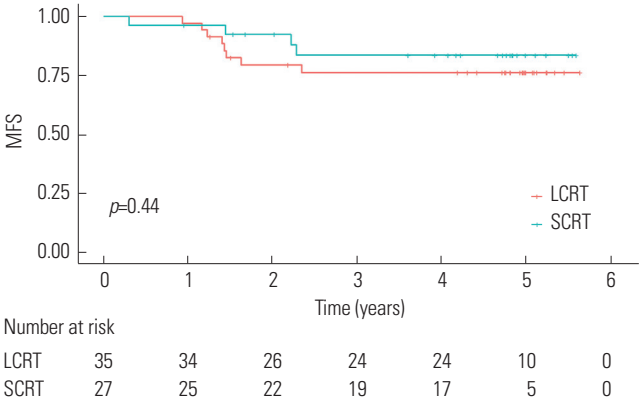

Fig. 4. Kaplan–Meier MFS curves for SCRT and LCRT. The 5-year MFS rates were 76.3% for LCRT and 83.6% for SCRT (p=0.443). SCRT, short-course radiotherapy; LCRT, long-course chemoradiotherapy; MFS, metastasis-free survival.

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Table 3. Multivariable Analysis for DFS

	Univariable		Multivariable	
	HR (95% CI)	*p*	HR (95% CI)	*p*
SCRT	0.50 (0.15–1.61)	0.246	0.53 (0.14–2.04)	0.360
Age >70 years	0.52 (0.11–2.36)	0.402		
Male sex	0.93 (0.31–2.80)	0.910		
CEA >5 ng/mL	1.90 (0.66–5.50)	0.233		
AV <5 cm	1.98 (0.61–6.31)	0.250		
cT4	4.80 (0.61–37.20)	0.133	45.4 (2.34–882)	0.011
cN1–2	$2.62x10^5$ (0.0–inf.)	0.998		
CRM (+)	5.33 (1.19–23.90)	0.028	7.60 (0.97–59.40)	0.053
PD or mucinous	3.26 (0.90–11.80)	0.070	3.56 (0.92–13.70)	0.064
ACT	0.16 (0.02–1.30)	0.086	0.24 (0.02–2.03)	0.191

DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; SCRT, short-course radiotherapy; CEA, carcinoembryonic antigen; AV, anal verge; c, clinical; CRM, circumferential resection margin; PD, poorly differentiated; ACT, adjuvant chemotherapy.

Table 4. Multivariable Analysis for MFS

	Univariable		Multivariable	
	HR (95% CI)	*p*	HR (95% CI)	*p*
SCRT	0.62 (0.18–2.08)	0.445	0.78 (0.19–3.08)	0.725
Age >70 years	0.28 (0.03–2.22)	0.231		
Male sex	1.21 (0.38–3.81)	0.747		
CEA >5 ng/mL	1.79 (0.56–5.64)	0.322		
AV <5 cm	1.62 (0.43–6.00)	0.468		
cT4	5.29 (0.67–41.40)	0.112	29.8 (1.70–521)	0.020
cN1–2	$2.62x10^5$ (0.0–inf.)	0.998		
CRM (+)	4.28 (0.93–19.60)	0.060	7.21 (0.89–58.50)	0.064
PD or mucinous	2.12 (0.46–9.70)	0.332		
ACT	0.14 (0.01–1.16)	0.068	0.23 (0.02–1.98)	0.182

MFS, metastasis-free survival; HR, hazard ratio; CI, confidence interval; SCRT, short-course radiotherapy; CEA, carcinoembryonic antigen; AV, anal verge; c, clinical; CRM, circumferential resection margin; PD, poorly differentiated; ACT, adjuvant chemotherapy.

demonstrated a lower risk of recurrence or death compared to LCRT (HR: 0.79; 95% CI: 0.63–1.00; *p*=0.048). Collectively, these findings suggest that the benefits of SCRT-based total neoadjuvant therapy (TNT) may be attributable to the early introduction of systemic chemotherapy, although the optimal number and intensity of consolidation cycles remain uncertain.

Although our study demonstrated favorable oncologic outcomes, caution must be exercised when interpreting these results, primarily due to substantial differences in tumor burden across studies. In the POLISH II and RAPIDO trials, 30% and 63% of patients, respectively, had cT4 disease, whereas only 1.6% of our cohort presented with tumors at that stage. This significant discrepancy in initial tumor depth likely contributed to the higher DFS observed in our SCRT group. Additionally, our study reported a higher rate of total mesorectal excision specimen completeness (95.1% vs. 80.6% in POLISH II),[5] which may have further influenced oncologic outcomes.

In our study, anastomosis-related complications occurred in 5 patients (18.5%) in the SCRT group and 7 patients (20.0%) in the LCRT group (*p*=0.884). AL or fistula was observed in 9 patients (14.5%), with no statistically significant differences between treatment arms. This comparable incidence suggests that shortening the radiotherapy course and incorporating CCT does not increase the risk of delayed anastomotic complications compared to conventional LCRT. Previous studies have reported delayed AL rates ranging from 1.3% to 6.7% in rectal cancer surgery, depending on the definition, patient risk factors, and timing of assessment.[11-13] However, direct comparisons of delayed AL rates between SCRT and LCRT remain limited. Previous RCTs, such as Stockholm III[14] and RAPIDO,[6] have evaluated the long-term toxicity of SCRT. However, these assessments primarily relied on patient-reported outcomes, focusing on subjective symptoms rather than objectively verified complications. In contrast, our study assessed delayed anastomotic complications using clinical and radiologic criteria, providing a more robust clinical evaluation. Delayed ALs are significant because they directly impact morbidity, often necessitating reintervention and adversely affecting patient recovery and quality of life.

Earlier studies,[15,16] particularly those from the Stockholm Rectal Cancer Study Group, raised concerns about increased surgical morbidity following SCRT. They suggested that inflammation and edema at the anastomotic site could complicate surgery. However, more recent data suggest that these complications were primarily attributable to excessively large radiation fields and the use of immediate surgery.[17] When SCRT is followed by an appropriate delay before surgery, as demonstrated in a previous report,[4] postoperative complication rates are comparable to those observed with LCRT, which is consistent with our findings.

While SCRT and LCRT demonstrated comparable oncologic outcomes in this study, the cost-effectiveness of SCRT, as confirmed in the initial phase of the ESCORT trial, remains a key advantage. Given the inefficiencies in Korea's healthcare delivery system, particularly the burden placed on rural patients who require repeated visits to tertiary hospitals, SCRT may offer a more practical and economically sustainable alternative.

Our study has several limitations. The small sample size reduces the statistical power to detect subtle intergroup differences, particularly in local recurrence rates. Additionally, while we employed a matched design to compare SCRT and LCRT groups, the absence of randomization introduces the potential for selection bias. Furthermore, our protocol included only two cycles of CCT, which may have been insufficient to fully eradicate micro-metastases and was less intensive than regimens used in other TNT studies.

In conclusion, the long-term follow-up of the ESCORT trial demonstrates that SCRT followed by two cycles of consolidation XELOX achieves oncologic outcomes comparable to those of LCRT in patients with high-risk LARC, without a correspond-

ing increase in delayed surgical morbidity. When considered alongside previously published cost-effectiveness data, these findings support the adoption of SCRT with CCT as a clinically and economically viable alternative to conventional LCRT—particularly in healthcare systems where the centralization of cancer care imposes financial burdens on patients. Further investigation is warranted to optimize the duration and intensity of CCT to enhance its therapeutic efficacy while maintaining tolerability.

AVAILABILITY OF DATA AND MATERIAL

The data supporting the findings of this study are available from the Severance Hospital Institutional Review Board. However, access to these data is restricted as they were used under a license for the current study and are not publicly available. These data may be requested from the authors upon reasonable request and with permission from the Severance Hospital Institutional Review Board.

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AUTHOR CONTRIBUTIONS

Conceptualization: Jong Min Lee, Nam Kyu Kim, and Min Soo Cho. Data curation: Jong Min Lee and Min Soo Cho. Formal analysis: Jong Min Lee. Investigation: Jong Min Lee and Min Soo Cho. Methodology: Jong Min Lee and Min Soo Cho. Project administration: Min Soo Cho. Supervision: Min Soo Cho. Validation: Jeehye Lee, Taehyung Kim, and Nam Kyu Kim. Visualization: Jong Min Lee. Writing—original draft: Jong Min Lee. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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