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Short-Term Outcomes and Cost-Effectiveness between Long-Course Chemoradiation and Short-Course Radiotherapy for Locally Advanced Rectal Cancer

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Purpose: Long-course chemoradiotherapy (LCRT) has been widely recommended in a majority of rectal cancer patients. Recently, encouraging data on short-course radiotherapy (SCRT) for rectal cancer has emerged. In this study, we aimed to compare these two methods in terms of short-term outcomes and cost analysis under the Korean medical insurance system.

Materials and Methods: Sixty-two patients with high-risk rectal cancer, who underwent either SCRT or LCRT followed by total mesorectal excision (TME), were classified into two groups. Twenty-seven patients received 5 Gy×5 with two cycles of XELOX (capecitabine 1000 mg/m^2 and oxaliplatin 130 mg/m^2 every 3 weeks) followed by TME (SCRT group). Thirty-five patients received capecitabine-based LCRT followed by TME (LCRT group). Short-term outcomes and cost estimation were assessed between the two groups.

Results: Pathological complete response was achieved in 18.5% and 5.7% of patients in the SCRT and LCRT groups, respectively (p=0.223). The 2-year recurrence-free survival rate did not show significant difference between the two groups (SCRT vs. LCRT: 91.9% vs. 76.2%, p=0.394). The average total cost per patient for SCRT was 18% lower for inpatient treatment (SCRT vs. LCRT: \$18787 vs. \$22203, p<0.001) and 40% lower for outpatient treatment (SCRT vs. LCRT: \$11955 vs. \$19641, p<0.001) compared to LCRT. SCRT was shown to be the dominant treatment option with fewer recurrences and fewer complications at a lower cost.

Conclusion: SCRT was well-tolerated and achieved favorable short-term outcomes. In addition, SCRT showed significant reduction in the total cost of care and distinguished cost-effectiveness compared to LCRT.

Key Words: Rectal cancer, short course radiotherapy, long-course chemoradiation, cost effectiveness

INTRODUCTION

Long-course chemoradiotherapy (LCRT) with total mesorectal excision (TME) provides significant benefits in terms of reducing the risk of local recurrence, increasing sphincter preservation rates, and increasing the probability of curative resection for locally advanced rectal cancer.[1-5] Nowadays, this treatment strategy is widely recommended in the majority of patients with locally advanced rectal cancer in Korea. Although the local recurrence rate has been stable at 5%–6% in patients undergoing LCRT, systemic recurrence rates are still in excess of 20% and now represent the main cause of death in these patients.[6] Consequently, more recent trials have been examining the administration of systemic chemotherapy in the neoadjuvant setting for patients with high-risk disease, ranging from a few cycles of chemotherapy to total neoadjuvant therapy, to

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provide early treatment of disseminated micrometastases, thus improving control of systemic disease.[7-9] Recently, the RAPIDO trial showed a higher response rate and reduction in the probability of disease-related treatment failure in patients receiving short-course radiotherapy (SCRT) followed by systemic chemotherapy and TME compared with patients receiving LCRT and optional adjuvant chemotherapy.[10] Short-term radiation therapy and its results were reported in the European literature in the past, and SCRT following delayed surgery for rectal cancer has begun to receive more attention from colorectal surgeons and radiation oncologists in North America and Korea.[5,7,11] LCRT is the gold standard for the treatment of rectal cancer in Korea. However, patients have been centered on large hospitals around Seoul, as they believe these hospitals can provide better quality of care. This could pose some problems for the healthcare delivery system in Korea. As a result, LCRT patients' daily visits to hospitals in rural areas for 5 weeks before surgery resulted in lowering the quality of life and increasing the total medical cost. Currently, there have been a few studies related to the economic evaluation of SCRT vs. LCRT. These studies demonstrated that SCRT is a cost-effective strategy compared to LCRT for patients with locally advanced rectal cancer.[12-14] Currently, the clinical application of SCRT with consolidation chemotherapy in Korea has been limited, as this strategy is not covered under the national health insurance system of Korea. To date, SCRT data are still lacking in Korea in terms of clinical outcomes and cost estimates. In addition, there are no well-designed studies comparing SCRT with LCRT in the Korean population. Therefore, the present study aimed to investigate the outcomes of the two treatment strategies—SCRT with consolidation chemotherapy followed by delayed surgery and LCRT—for high-risk rectal cancer in terms of adverse effects, postoperative outcomes, and cost estimation.

MATERIALS AND METHODS

A total of 62 patients were consecutively enrolled in this study between 2018 and 2020. We compared SCRT followed by two cycles of XELOX with matched patients receiving LCRT during the study period. The included patients with same indications were categorized on the basis of whether they received SCRT with XELOX chemotherapy (27 patients of SCRT group) or LCRT (35 patients of LCRT group) (Fig. 1). In this study, patients in the SCRT group were prospectively enrolled from a phase 2 single-arm ESCORT trial (NCT03676517) conducted at our institution. The study protocol is described in Fig. 1. This study was approved by the Institutional Review Board of Severance Hospital (4-2018-0612). Patients were eligible for inclusion if they were aged between 19 and 80 years with histopathologically confirmed primary adenocarcinoma with distal extension less than 10 cm from the anal verge. The high-risk factors were defined on baseline magnetic resonance imaging (MRI), with at least one of the following criteria: clinical tumor (cT) stage cT3c or cT3d or any cT4, clinical nodal (cN) stage N2, involved circumferential resection margin (CRM) (tumor or lymph node ≤1.0 mm from mesorectal fascia), extramural vascular invasion (EMVI) (tumor cell deposits within the extramural vascular structure), or enlarged lateral pelvic lymph node (short-axis diameter ≥5.0 mm). Additionally, other inclusion criteria required all patients to have an Eastern Cooperative Oncology Group performance score of 0–1 during treatment, be available for follow-up, and provide written informed consent. The exclusion criteria were as follows: cT4 with infiltration of the anterior pelvic organ including the bladder and vagina, direct invasion of the internal or external anal sphincter, recurrent stage IV rectal cancer at initial diagnosis, synchronous cancer, previous chemotherapy or radiation therapy, a history of hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis, and incomplete preoperative treatment. Before the preoperative treatment, all patients un-

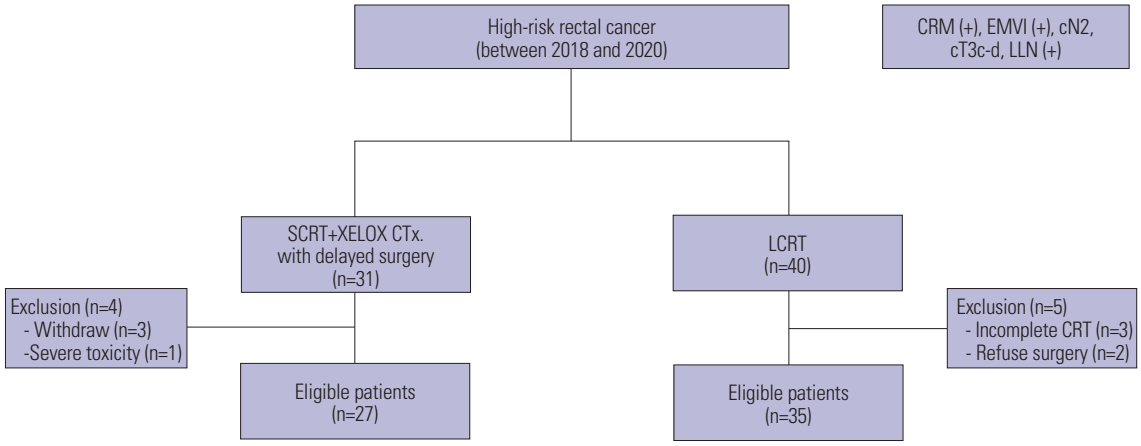

Fig. 1. Patient flow. The included patients were categorized on the basis of whether they received SCRT with XELOX chemotherapy (27 patients of SCRT group) or LCRT (35 patients of LCRT group). CRM, circumferential resection margin; EMVI, extramural vascular invasion; LLN, lateral lymph node; SCRT, short-course radiotherapy; LCRT, long-course chemoradiotherapy.

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derwent high-resolution MRI. Clinically involved CRM was defined as lymph nodes or tumor deposits within 2.0 mm of the mesorectal fascia. In our institution, a wide CRM (<2.0 mm) was used on the basis of 1.0 mm at pathology, with an additional 1.0-mm safety margin to supplement MR measurement errors. EMVI were identified on the basis of tumor cell deposits within the extramural vascular structures during the baseline MRI (that is, a tumor signal in the vessel's lumen, vessel expansion with a tumor signal, or irregular vessel contours with a tumor signal in large anatomical vessels).[15] In the LCRT group, preoperative radiation therapy consisted of a total dose of 45 Gy in 25 fractions that was delivered to the pelvis, followed by a 5.4 Gy boost to the primary tumor over a period of five weeks (1.8 Gy for 5 days). In the SCRT with consolidation chemotherapy group, preoperative radiation therapy consisted of short-course radiation (5 Gy×5 in 1 week) with concurrent consolidation chemotherapy. Chemotherapy regimen was given in two cycles of XELOX (capecitabine 1000 mg/m^2 and oxaliplatin 130 mg/m^2) every 3 weeks. Surgery was scheduled 6 to 8 weeks after the completion of preoperative treatment in the LCRT group. Surgery was performed by expert colorectal surgeons who adhered to the oncologic principals of TME with pelvic autonomic nerve preservation.[16] In the SCRT with consolidation chemotherapy group, surgery was scheduled 4 weeks after the completion of preoperative treatment. In the LCRT group with low-risk, adjuvant chemotherapy consisted of either 400–425 mg/m^2 5-fluorouracil plus 20 mg/m^2 leucovorin for 5 days (4 cycles) or 1250 mg/m^2 capecitabine for 2 weeks (5 cycles). In the LCRT group with high-risk, mFOLFOX-6 (oxaliplatin 85 mg/m^2/day, leucovorin 200 mg/m^2/day, 5-FU 400 mg/m^2/day, and 5-FU 1200 mg/m^2/day for 2 weeks) was administered to patients in eight cycles. In the SCRT with consolidation chemotherapy group, adjuvant chemotherapy consisted of either an 5-fluorouracil, leucovorin based regimen or mFOLFOX-6 according to risk stratification. Adverse event was assessed by Common Terminology Criteria for Adverse Events v4.03 in the preoperative period. A macroscopic evaluation of the surgical plane reflects the completeness of TME excision and is an important indicator of surgical quality and prognostic factor for rectal cancer outcomes.[17] TME completeness was evaluated by macroscopic assessment of mesorectal excision as follows: complete, nearly complete, and incomplete.[18] Pathologic tumor staging of the resected specimen was performed in accordance with the guidelines of the American Joint Committee on Cancer tumor, node, metastases (TNM) classification. CRM was defined as positive when a tumor cell or lymph node was within 1 mm of the margin. The histology of all surgical specimens was reviewed and confirmed by an independent element and was classified according to the Mandard tumor regression grade system.[19] For cost estimation, we estimated the direct cost between the two treatment strategies, which was defined as the sum of both medical and non-medical costs. Medical costs included health insurance payments covered by the National Health Insurance (NHI) and out-of-pocket expenses for insurance (co-payment) and services not covered by NHI. Non-medical costs included the cost of transportation to healthcare providers and the cost of time. Transportation cost per person (average cost per day: $20.15) was based on the Korea health panel survey report. Time cost per person (average cost for time value of non-business travel per day: $8.15) was based on the Korea Transport Institute. The medical costs of rectal cancer patients were obtained from the electronic medical records at Severance Hospital. These records contained details of all payments made, including costs covered by NHI and non-covered payments for hospitalization and physician services. A cost-effectiveness analysis was conducted to evaluate improvement in the effects [postoperative complications, disease-free survival (DFS)] associated with SCRT compared to LCRT. The result was summarized as an incremental cost-effectiveness ratio (ICER). The underlying calculation for the ICER comparing SCRT vs. LCRT in patients with high-risk rectal cancer was described as below:

$$\text{ICER} = \frac{\text{Net cost (SCRT)}-\text{Net cost (LCRT)}}{\text{Effect (SCRT)}-\text{Effect (LCRT)}}$$

The cost-effectiveness plane displays the variability between costs and effectiveness.[20-22] The plane comprises four quadrants according to the absolute value of the incremental cost and incremental effectiveness. Each quadrant has a different implication for the decision. The vertical axis divides the plane according to incremental effectiveness (positive to the right, negative to the left), and the horizontal axis divides the plane according to the incremental cost (positive above, negative below). If the ICER for SCRT compared to LCRT falls in the southeast quadrant, with negative costs and positive effects, SCRT is more effective (better survival or less complications) and less costly than LCRT. In this quadrant, SCRT is always considered cost-effective. If the ICER falls in the northwest quadrant, with positive costs and negative effects, SCRT is more costly and less effective than LCRT. In this quadrant, SCRT is never considered cost-effective.

Statistical analysis

Categorical variables were analyzed using the χ^2 test or Fisher's exact test, and continuous variables were analyzed using the Student's t test. The Kaplan–Meier method with log-rank test was used to calculate the cumulative 2-year DFS rate. All analyses were performed using IBM SPSS software (version 25.0; IBM Corp., Armonk, NY, USA): all tests were two-tailed, and differences were considered statistically significant at p-values <0.05.

RESULTS

Patient characteristics and postoperative outcomes are shown

Table 1. Patient Characteristics and Postoperative Outcomes

	SCRT (n=27)	LCRT (n=35)	*p* value
Age (yr)	58.6±9.8	63.7±8.7	0.030
Sex			0.798
Male	16 (59.3)	22 (62.9)	
Female	11 (40.7)	13 (37.1)	
BMI (kg/m^2)	24.2±3.4	23.7±3.0	0.521
Distance from AV (cm)	7.6±2.0	6.8±2.3	0.140
Time interval (wk)	12.7±1.2	14.3±1.1	<0.001
Baseline MRI findings			
cT stage			0.201
T2	3 (11.1)	1 (2.9)	
T3	23 (85.2)	34 (97.1)	
T4	1 (3.7)	0 (0.0)	
cN stage			0.833
N0	1 (3.7)	2 (5.7)	
N1	13 (48.1)	14 (40.0)	
N2	13 (48.1)	20 (54.3)	
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
Number of high-risk factors per patient			0.524
1	15 (55.6)	16 (45.7)	
2	6 (22.2)	5 (14.3)	
3	2 (7.4)	4 (11.4)	
4	4 (14.8)	7 (20.0)	
5	0 (0.0)	3 (8.6)	
CEA, mean	4.9±6.9	11.3±19.9	0.121
Operation name			0.485
LAR	22 (81.5)	31 (88.6)	
uLAR or CAA	5 (18.5)	4 (11.4)	
Type of surgery			0.127
Robot	9 (33.3)	19 (54.3)	
Laparoscopy	18 (66.7)	16 (45.7)	
Ileostomy	24 (88.9)	30 (85.7)	0.426
Sphincter saving	27 (100)	35 (100)	>0.999
TME completeness			>0.999
Complete	26 (96.2)	33 (94.2)	
Nearly complete	1 (3.8)	2 (5.8)	
Incomplete	0 (0.0)	0 (0.0)	
Hospital stay (day)	7.8±2.9	8.7±4.5	0.340
Overall complications	9 (33.3)	12 (34.3)	>0.999
Chyle	1 (3.7)	2 (5.7)	
Ileus	1 (3.7)	1 (2.9)	
Anastomotic leakage	0 (0.0)	1 (2.9)	
Metabolic acidosis	0 (0.0)	1 (2.9)	
Obstruction	0 (0.0)	1 (2.9)	
Deep SSI	1 (3.7)	0 (0.0)	
Superficial SSI	0 (0.0)	1 (2.9)	
Urinary retention	5 (18.5)	4 (11.4)	
UTI	1 (3.7)	1 (2.9)	

AV, anal verge; BMI, body mass index; CEA, carcinoembryonic antigen; CRM; circumferential resection margin; EMVI; extramural vascular invasion; CAA, coloanal anastomosis; LAR, low anterior resection; LCRT, long-course radiotherapy; LN, lymph node; SSI, surgical site infection; SCRT, short-course radiotherapy; TME, total mesorectal excision; UTI, urinary tract infection.
Data are presented as mean±standard deviation or n (%).

in Table 1. The mean age of the LCRT group was significantly higher than that of the SCRT group (63.7±8.7 vs. 58.6±9.8, p=0.030). The mean time interval from preoperative treatment to surgery was significantly longer in the LCRT group than that in the SCRT group (14.3±1.1 vs. 12.7±1.2, p<0.001). There were no relevant differences between the two groups in terms of sex, body mass index, clinical tumor T or N stage, tumor location, clinical CRM involvement, clinical EMVI, clinical lateral pelvic lymph node, number of high-risk factors per patient, mean preoperative carcinoembryonic antigen levels, operation name, type of surgery, rate of ileostomy, and mean hospital stay. All patients received sphincter preserving surgery in both groups. The overall complications showed no significant differences between the groups. Early postoperative complications (within 30 days) occurred in 9 of 27 patients (33.3%) in the SCRT group and in 12 of 35 patients (34.3%) in the LCRT group. Urinary retention was the most common complication in both groups, with the count being 5 of 27 patients (18.5%) in the SCRT group and 4 of 35 patients (11.4%) in the LCRT group. Anastomotic leakage occurred in 1 of 35 patients (2.9%) in the LCRT group. On pathologic examination, pathologic ypT stage was significantly different between the groups (p=0.013). ypT0, ypT1, ypT2, ypT3, and ypT4 were observed in 5 (18.5%), 4 (14.8%), 8 (29.6%), 9 (33.3%), and 1 (3.7%) patients in the SCRT group and 2 (5.7%), 0 (0.0%), 11 (31.4%), 22 (62.9%), and 0 (0.0%) patients in the LCRT group, respectively. However, pathologic ypN stage did not show significant difference between the groups. Only 1 of 27 patients (3.7%) with involvement of CRM was pathologically confirmed in the SCRT group, while no patient was reported with involvement of CRM in the LCRT group (p=0.435). There were no relevant differences between the two groups in terms of tumor regression grade (p=0.392), mean harvested lymph node number (p=0.225), and histology (p=0.658). T-downstage was observed in 16 of 27 patients (59.3%) in the SCRT group and 12 of 35 patients (34.3%) in the LCRT group, while N-downstage was observed in 15 of 27 patients (55.6%) in the SCRT group and 20 of 35 patients (57.1%) in the LCRT group. Neither T (p=0.072) nor N-downstage (p=0.141) showed significant differences between groups (Table 2). An overview of adverse events during preoperative treatment is shown in Table 3. Grade 3 or higher adverse events during preoperative treatment occurred in 0 of 27 patients (0.0%) in the SCRT group compared with 1 of 35 patients (2.8%) in the LCRT group. The most common grade 2 adverse event during preoperative treatment was nausea (29.6%) in the SCRT group and proctitis (8.6%) in the LCRT group and there were no serious adverse events in both groups (Table 3). The mean follow-up period was 25.1 months in the SCRT group and 23.9 months in the LCRT group. Tumor recurrence, including local and systemic recurrence, occurred in 3 patients (11.1%) in the SCRT group. All patients with tumor recurrence in the SCRT group had systemic recurrence. The site of systemic recurrence was the lung. In contrast, 7 patients (20.0%) had tu-

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Table 2. Pathologic Outcomes

	SCRT (n=27)	LCRT (n=35)	*p* value
Tumor size (cm)	1.5±1.4	2.4±1.5	0.017
Resection margin (cm)			
Proximal	14.5±4.9	12.9±4.2	0.179
Distal	1.8±1.2	1.7±1.2	0.745
Pathologic T stage			0.013
ypT0	5 (18.5)	2 (5.7)	
ypT1	4 (14.8)	0 (0.0)	
ypT2	8 (29.6)	11 (31.4)	
ypT3	9 (33.3)	22 (62.9)	
ypT4	1 (3.7)	0 (0.0)	
Pathologic N stage			0.905
ypN0	19 (70.4)	22 (62.9)	
ypN1	7 (25.9)	11 (31.4)	
ypN2	1 (3.7)	2 (5.7)	
pCRM (≤1.0 mm), (mm)	27±8.3	30±8.1	0.878
pCRM positivity	1 (3.7)	0 (0.0)	0.435
pCR	5 (18.5)	2 (5.7)	0.223
TRG (Mandard grade)			0.392
1	5 (18.5)	2 (5.7)	
2	7 (25.9)	8 (22.9)	
3	13 (48.1)	20 (57.1)	
4	2 (7.4)	5 (14.3)	
Harvested LN number	15.1±7.4	12.8±7.3	0.225
Histology			0.658
WD	5 (18.5)	4 (11.4)	
MD	19 (70.4)	28 (80.0)	
PD	2 (7.4)	3 (8.6)	
Mucinous	1 (3.7)	0 (0.0)	
T-downstage	16 (59.3)	12 (34.3)	0.072
N-downstage	15 (55.6)	20 (57.1)	0.141

pCR, pathologic complete response; pCRM, pathologic circumferential resection margin; LN, lymph node; WD, well differentiated; MD, moderate differentiated; PD, poorly differentiated; TRG, tumor regression grade; LCRT, long-course radiotherapy; SCRT, short-course radiotherapy.
Data are presented as mean±standard deviation or n (%).

mor recurrence in the LCRT group. The most common sites of systemic recurrence were the lung (n= 5, 14.2%), followed by liver (n=1, 2.8%). Local recurrence was only diagnosed in the anastomosis site (n=1, 2.8%). The overall 2-year DFS rates were estimated as 91.9% and 76.2% for the SCRT and LCRT groups, respectively (p=0.394) (Fig. 2). Total direct costs for SCRT and LCRT were $39709 and $56789, respectively. Direct medical cost, including in-patient costs approximately 18% lower for SCRT (LCRT vs. SCRT: $22203 vs. $18787, p<0.001) and out-patient costs approximately 40% lower for SCRT (LCRT vs. SCRT: $19641 vs. $11955, p<0.001), was significantly different between the groups. Average visits per patient was 64 days in the LCRT group and 38 days in the SCRT group. Average time value of non-business travel per day was approximately 4 hours per patient. Direct non-medical cost including transportation costs approximately 40% lower for SCRT (LCRT vs. SCRT: $1280 vs. $768, p<0.001) and time costs approximately 40% lower for SCRT (LCRT vs. SCRT: $2134 vs. $1280, p<0.001) showed significant difference between the groups. Incremental cost was $17080 less in the SCRT group. The DFS rate during the mean follow-up period of 24 months was 76.2% in LCRT and 91.9% in SCRT, respectively. In terms of DFS, incremental effectiveness was 15.7% higher in the SCRT group. ICER was calculated to be 1088 less in the SCRT group. In terms of postoperative complications, incremental effectiveness was 1.0% higher in the SCRT group, and ICER was calculated to be 17080 less in the SCRT group (Table 4). For DFS and postoperative complications, the ICER for SCRT compared with LCRT fell in the southeast quadrant. This value means that SCRT has a negative cost and a positive effect. The cost-effectiveness plane demonstrated that SCRT is the dominant treatment option with fewer recurrences and fewer complications at a lower cost than that in LCRT (Fig. 3).

DISCUSSION

Over the past two decades, SCRT has been the most preferred treatment for stages II and III rectal cancer in European countries. In a Swedish rectal cancer trial, the results demonstrated an increased survival rate and a decreased local recurrence rate with SCRT compared with surgery alone.[23] Similarly, a Dutch TME trial showed that preoperative SCRT reduced the 10-year local recurrence by more than 50% relative surgery alone and significantly improved the 10-year survival in patients with a negative CRM and stage III rectal cancer.[5] Subsequently, the Polish Rectal Cancer trial and Trans-Tasman Radiation Oncology Group trial 01.04 showed that SCRT was as effective as LCRT in the aspects of local control and survival.[11,24] More recently, several randomized trials have been published on the promising outcomes of SCRT at par with those of LCRT.[7,8,10,25] Moreover, there have been only two studies on SCRT in Korea.[26,27] However, these studies did not show any discriminatory results of SCRT compared to LCRT since consolidation chemotherapy was not effectively provided to patients with SCRT, and the results were limited to clinical outcomes. So far, studies focusing of the analysis of total costs of care and cost-effectiveness comparison have been rarely published. This is the first study to investigate the clinical outcomes and cost-effectiveness between SCRT followed by consolidation chemotherapy and LCRT for high-risk rectal cancer treatment in Korea. Our study showed that SCRT followed by two cycles of consolidation chemotherapy before surgery had favorable clinical outcomes compared with LCRT. In addition, the SCRT group showed significantly lower costs and more cost-effectiveness for patients with high-risk rectal cancer, especially in DFS state and postoperative complications. In this study, total direct costs including medical costs and non-medical costs were significantly

Table 3. Adverse Events During Preoperative Treatment between the Two Groups

	Toxicity grade							
	SCRT (n=27)				LCRT (n=35)			
	1	2	3	4	1	2	3	4
Non-hematological toxicity								
Nausea	14 (51.9)	8 (29.6)	-	-	2 (5.7)	1 (2.8)	1 (2.8)	-
Vomiting	3 (11.1)	1 (3.7)	-	-	1 (2.8)	-	-	-
Mucositis	2 (7.4)	-	-	-	-	-	-	-
Diarrhea	5 (18.5)	3 (11.1)	-	-				-
Hand-foot syndrome	11 (40.7)	6 (22.2)	-	-	-	1 (2.8)	-	-
Anorexia	1 (3.7)	2 (7.4)	-	-	1 (2.8)	-	-	-
Allergic reaction	-	-	-	-	1 (2.8)	-	-	-
Proctitis	3 (11.1)	1 (3.7)	-	-	9 (25.7)	3 (8.6)	-	-
Dysuria	2 (7.4)	-	-	-	3 (8.6)	1 (2.8)		-
Constipation	1 (3.7)	1 (3.7)	-	-	4 (11.4)	2 (5.7)		-
Hematological toxicity			-	-				-
Neutropenia	4 (14.8)	-	-	-	3 (8.6)	-	-	-
Anemia	4 (14.8)	-	-	-	11 (31.4)	2 (5.7)	-	-
Thrombocytopenia	-	-	-	-	3 (8.6)	-	-	-

LCRT, long-course radiotherapy; SCRT, short-course radiotherapy.
Data are presented as n (%).

Table 4. Direct Cost and ICER between the Two Groups

	LCRT	SCRT	*p* value
Inpatient cost	$22203	$18787	<0.001
Outpatient cost	$19641	$11955	<0.001
Transportation cost	$1280	$768	<0.001
Time cost	$2134	$1280	<0.001
Total cost	$56789	$39709	<0.001

Two-year disease-free survival	Net cost	Incremental cost	Disease-free survival rate	Incremental effectiveness	ICER
LCRT	$56789		76.2		
SCRT	$39709	-$17080	91.9	15.7	-1088
Postoperative complications	**Net cost**	**Incremental cost**	**Survival rate without complications**	**Incremental effectiveness**	**ICER**
LCRT	$56789		65.7		
SCRT	$39709	-$17080	66.7	1.0	-17080

LCRT, long-course radiotherapy; SCRT, short-course radiotherapy; ICER, incremental cost-effectiveness ratio.

lower in the SCRT group than in the LCRT group. In terms of radiotherapy, the cost was calculated according to the number of radiotherapy fractions according to Korea's health insurance policies. In other words, patients undergoing LCRT tend to visit the hospital more often than those undergoing SCRT, which result in significantly higher transportation and time costs in LCRT. In this study, since the number of out-patient treatment visits differed for each group, direct medical costs were calculated only for out-patient treatment. As a result, out-patient costs were approximately 40% lower for SCRT. In addition, it was investigated that the decrease in the number of hospital visits in the SCRT group sequentially reduced both transportation (approximately 40% lower for SCRT) and time costs (approximately 40% lower for SCRT). During the follow-up period of 24 months, incremental effectiveness on DFS was 15.7% higher in the SCRT group, while incremental effectiveness on postoperative complications was investigated to be 1.0% higher in the SCRT group than in the LCRT group. As shown in the cost-effectiveness plane in this study, the simulation results for SCRT fell in the southeast quadrant, indicating that SCRT achieved cost savings with positive treatment effectiveness. These results indicate that patients in the SCRT group improved their health with fewer recurrences and fewer complications at a lower cost compared to those in the LCRT group. Although this study included a relatively small number of patients, SCRT followed by consolidation chemotherapy showed significant reduction in the total cost of care and cost-effectiveness, with similar clinical outcomes compared to LCRT. This study showed a significantly shorter period between preoperative treatment and surgery in the SCRT group than in the LCRT group. Previous

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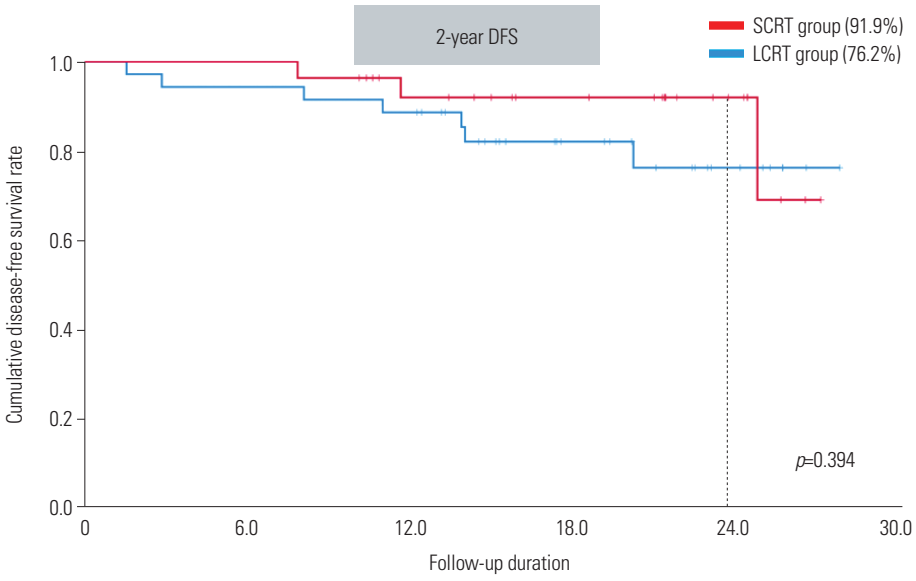

Fig. 2. The cumulative disease-free survival between SCRT and LCRT groups (p=0.394). LCRT, long-course radiotherapy; SCRT, short-course radiotherapy; DFS, disease-free survival.

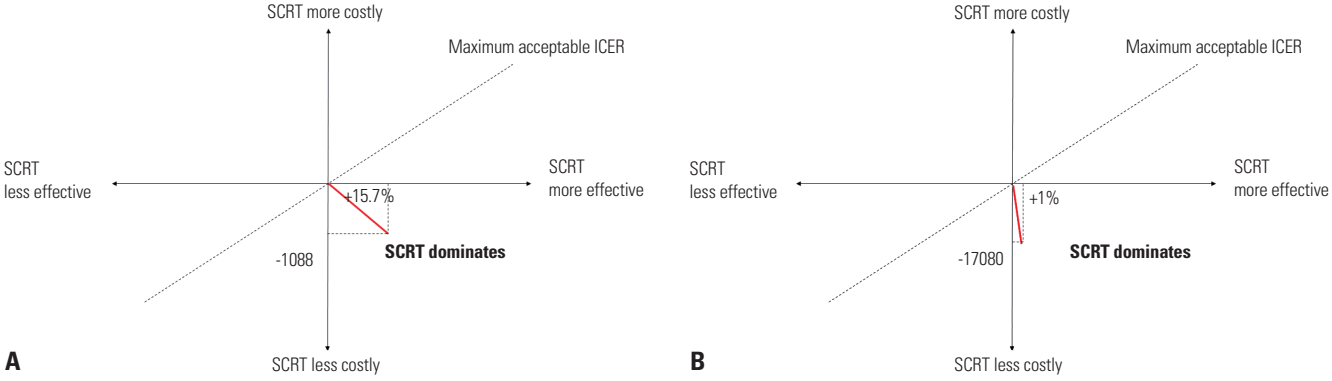

Fig. 3. Cost-effectiveness plane. (A) Cost-effectiveness plane according to tumor recurrence. (B) Cost-effectiveness plane according to postoperative complications. The ICER for SCRT versus LCRT, located in the southeast quadrant, indicates that SCRT is a more cost-effective option with fewer recurrences and complications than LCRT. SCRT, short-course radiotherapy; ICER, incremental cost-effectiveness ratio.

studies have shown that increasing the interval between preoperative treatment and surgery is associated with better pCR rates and higher sphincter preservation rates in rectal cancer treatment.[28,29] Moreover, there have been concerns about SCRT having lower efficacy in terms of tumor response and oncological safety in high-risk rectal cancer treatment compared to LCRT. Nevertheless, although not statistically significant, SCRT had a trend toward higher rates of pCR than those of LCRT. In addition, the overall tumor response, including T-downstage and N-downstage after completion of preoperative treatment, did not differ between groups. Moreover, there was no significant difference in the 2-year DFS rate between the two groups. The relatively lower pCR rate in the LCRT group compared to prior studies could be due to a small sample size and selection bias, and our study's larger proportion of high-risk cancer patients may also have played a role. In previous trials, SCRT with immediate surgery yielded fewer pCR results compared to LCRT for patients with rectal cancer. However, recent randomized trials have shown that SCRT with extended break and consolidation chemotherapy prior to surgery are significantly associated with higher pCR rate. Although the results of this study are limited, the addition of consolidation chemotherapy and delayed surgery may potentially have benefits in achieving pCR and increasing survival rate. However, details of the optimal combinations remain to be determined. This study showed that a regimen of SCRT and two cycles of XELOX chemotherapy was well-tolerated and led to lower rates of adverse events. Only 1 patient (2.8%) in the LCRT group was observed with grade 3 or higher adverse events during preoperative treatment. Late adverse events were not within the scope of this study. Postoperative complications were in line with those reported in previous studies. In the present study, deep surgical site infection in 1 of 27 patients (3.7%) in the SCRT group and anastomotic leakage in 1 of 35 patients (2.8%) were observed as grade III complications, which is a relatively low complication rate. However, in our study, more than 85% of patients had a tem-

porary ileostomy after primary surgery in both groups, which might have masked the actual number of anastomotic leakages. There was no mortality within 30 days after immediate surgery. There were several limitations to our study. Patients in the SCRT group were prospectively enrolled through the ESCORT study, whereas patients in the LCRT group were retrospectively enrolled at the same time and with the same indications as those in the SCRT group. These factors were major weaknesses of this study, whose results should therefore be interpreted with caution. Late toxicity outcomes were not investigated. Compared to previous randomized trials, a small number of patients were enrolled in the present study. Moreover, this study was not a prospectively controlled randomized trial, and cost data were retrospectively reviewed. There was insufficient follow-up to investigate long-term adverse events and oncologic outcomes, since this study only focused on short-term outcomes and cost analysis. In addition, this study did not include translational research using human tissue and serum markers. However, a prospective, randomized, and multicenter trial (SOLAR trial) is currently underway in relation to a translational study in Korea, and it is expected that more detailed results between the two treatment strategies will be obtained through this clinical trial in the future. Finally, the analysis of cost-effectiveness was limited due to the lack of quality-adjusted life year calculation. However, if long-term follow-up is carried out in the future, cost-effectiveness analysis through a Markov model is possible. In conclusion, SCRT followed by consolidation chemotherapy and delayed surgery was well-tolerated, and it achieved favorable short-term outcomes. In addition, significant reduction in the total cost of care and distinguished cost-effectiveness were manifested in the SCRT group compared to the LCRT group. Although the effect of SCRT has already been well-established in Western countries, if the same effect is proven in Korea, this approach will pave way for rectal cancer patients, especially those under the Korean medical delivery system.

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AUTHOR CONTRIBUTIONS

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