Short-term outcomes and cost-effectiveness between long-term chemoradiation and short-term radiotherapy followed by consolidation chemotherapy for the treatment of locally advanced rectal cancer

Min Soo Cho

Department of Medicine

The Graduate School, Yonsei University

Short-term outcomes and cost-effectiveness between long-term chemoradiation and short-term radiotherapy followed by consolidation chemotherapy for the treatment of locally advanced rectal cancer

Min Soo Cho

Department of Medicine

The Graduate School, Yonsei University

Short-term outcomes and cost-effectiveness between long-term chemoradiation and short-term radiotherapy followed by consolidation chemotherapy for the treatment of locally advanced rectal cancer

Directed by Professor Nam Kyu Kim

Doctoral Dissertation
submitted to the Department of Medicine,
The Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Doctor of Philosophy in Medical Science

Min Soo Cho

December 2021

This certifies that the Doctoral Dissertation of Min Soo Cho is approved.

Thesis Supervisor: Nam Kyu Kim

Thesis Committee Member#1: Sang Joon Shin

Thesis Committee Member#2: Gyu Seog Choi

Thesis Committee Member#3: Tae Hyun Kim

Thesis Committee Member#4: Woong Sub Koom

The Graduate School
Yonsei University

December 2021

ACKNOWLEDGEMENTS

I give warm thanks to my thesis supervisor, Professor Nam Kyu Kim, for his supervision and encouragement to successfully complete this thesis. He taught me not only about surgery but also about treating patients.

In addition, I am deeply grateful to Professor Gyu Seog Choi and Sang Joon Shin for giving me the support needed to execute my ideas into actual research.
I sincerely thank Professor Tae Hyun Kim for providing guidance in writing the discussion section as well as the cost analysis so that my research could shine.
I appreciate Professor Woong Sub Koom for imparting an insight into the academic depth of radiotherapy for rectal cancer treatment.

Finally, I would like to express my gratitude to my parents and family members for their continuous care and love throughout my life.

Written by Min Soo Cho

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Short-term outcomes and cost-effectiveness between long-term chemoradiation and short-term radiotherapy followed by consolidation chemotherapy for the treatment of locally advanced rectal cancer

Min Soo Cho

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Nam Kyu Kim)

Introduction: Long-course chemoradiotherapy (LCRT) has been widely recommended in a majority of patients with locally advanced rectal cancer in Korea. Recently, encouraging data on short-course radiotherapy (SCRT) for rectal cancer has emerged. Moreover, there is continued controversy in terms of the optimal combinations of radiotherapy and chemotherapy in the preoperative treatment setting. Furthermore, there is still a paucity of studies evaluating total costs of care of SCRT vs. LCRT for the treatment of locally advanced rectal cancer in Korea. We aimed to compare these two methods in terms of short-term outcomes and cost analysis under Korean medical insurance system.

Materials and methods: In this study, magnetic resonance imaging-diagnosed high-risk rectal cancer patients either cT3b, cN1/2, involved circumferential resection margin (CRM), extramural vascular invasion, and enlarged lateral pelvic lymph node metastasis were enrolled in this study. Between 2018 and 2020, 62 patients underwent either SCRT or LCRT followed by total mesorectal excision (TME) and classified into two groups. Twenty-seven patients received 5 Gy × 5 with two cycles of XELOX (capecitabine 1,000 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 including tumor response, postoperative complications, TME completeness, and acute toxicities were

investigated. In addition, cost estimation including total cost of care and cost-effectiveness by the use of the cost-effectiveness plane was assessed between the two groups.

Result: The mean interval between TME and initiation of preoperative treatment was significantly shorter in the SCRT group than the LCRT group (12.7 ± 1.2 vs. 14.3 ± 1.1 weeks, $p < 0.001$). Pathological complete response was achieved in 18.5% and 5.7% of patients in the SCRT and LCRT groups, respectively ($p = 0.223$). T down staging (59.3% vs. 34.3%, $p = 0.072$) and N downstaging (55.6% vs. 57.1%, $p = 0.141$) were not significantly different between the SCRT and LCRT groups. Pathological CRM involvement was observed in 3.7% and 0.0% of patients in the SCRT group and LCRT group, respectively ($p = 0.435$). TME completeness was 96.2% and 94.2% in the SCRT and LCRT groups, respectively. Sphincter preserving surgery was performed in all patients of both groups. Within one month of surgery, no significant difference was seen in overall postoperative complications (SCRT group vs. LCRT group: 33.3 % vs. 34.3%, $p = 1.000$). The most common grade 2 adverse event during preoperative therapy was nausea (29.6%) in the SCRT group and proctitis (8.6%) in the LCRT group. There were no serious adverse events in both groups. The 2-year recurrence-free survival rate did not show significant difference between the groups (SCRT vs. LCRT: 91.9% vs. 76.2%, $p = 0.394$). In terms of direct medical costs, the average total cost per patient for SCRT was 18% lower for inpatient treatment (SCRT vs. LCRT: \$18,787 vs. \$22,203, $p < 0.001$) and 40% lower for outpatient treatment (SCRT vs. LCRT: \$11,955 vs. \$19,641, $p < 0.001$) compared to LCRT. Non-medical costs were estimated approximately 40% less in SCRT than LCRT (transportation costs: \$768 vs. \$1,280, $p < 0.001$, time costs; \$1280 vs. \$2,134, $p < 0.001$). In terms of cost-effectiveness, the cost-effectiveness plane demonstrated that SCRT has been shown to be the dominant treatment option with fewer recurrences and fewer complications at a lower cost.

Conclusion: SCRT combined with concurrent consolidation chemotherapy followed by delayed surgery was well-tolerated and achieved favorable

short-term outcomes. In addition, SCRT showed significant reduction of total cost of care and distinguished cost-effectiveness compared to LCRT.

Keywords: rectal cancer, consolidation chemotherapy, cost-effectiveness, short-course radiotherapy, total mesorectal excision

Short-term outcomes and cost-effectiveness between long-term chemoradiation and short-term radiotherapy followed by consolidation chemotherapy for the treatment of locally advanced rectal cancer

Min Soo Cho

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Nam Kyu Kim)

I. INTRODUCTION

Preoperative long-course chemoradiotherapy (LCRT) with optimized 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. According to the current National Comprehensive Cancer Network Clinical Guidelines in Oncology, preoperative radiotherapy is highly recommended for patients with T3-4 and/or node-positive rectal cancer in clinical staging. 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 looking at 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 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 that believe they can provide better care. This could pose some problems for South Korea's health care delivery system. Therefore, LCRT patients' daily visits to the hospital in rural areas for 5 weeks before surgery resulted in lowering the quality of life and increasing the total medical cost. Currently, there are 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, clinical application of SCRT with consolidation chemotherapy in Korea has been limited as this strategy is not covered under Korean health insurance system. 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. This 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 for adverse effect, postoperative outcomes, and cost estimation.

II. MATERIALS AND METHODS

1. Patient selection

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) (Figure 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 Figure 2. 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 $\leq$ 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 $\geq$ 5.0 mm). Additionally, other inclusion criteria required all patients to have an Eastern Cooperative Oncology Group performance score of 0-1 during the 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.

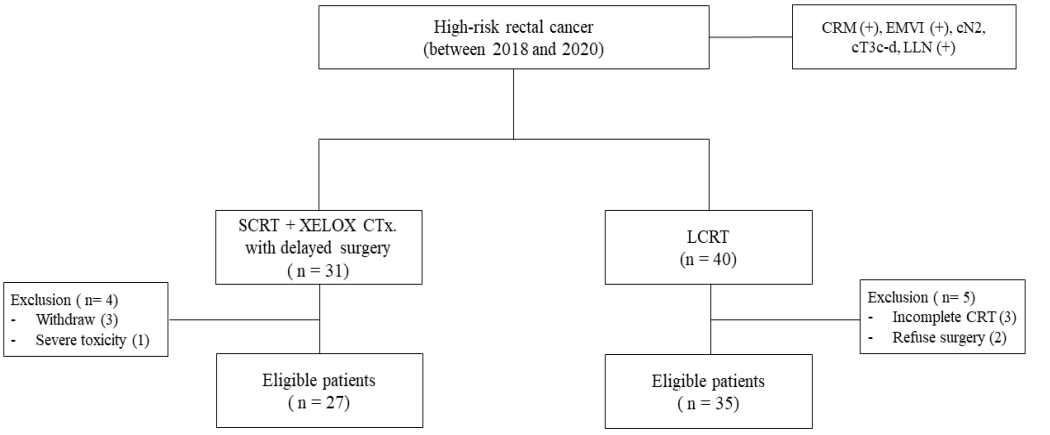

Figure 1. Patient flow. The included patients were categorized on the basis of whether they received SCRT with XELOX chemotherapy (27 patients of the SCRT group) or LCRT (35 patients of the LCRT group).

2. Risk stratification for high-risk rectal cancer

Before the preoperative treatment, all patients underwent 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]. Pelvic organ invasion was defined as an abutting tumor or direct tumor invasion to the internal and external anal sphincters, levator ani muscle, prostate, seminal vesicle, and vagina.

3. Preoperative treatments

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). All patients underwent three-dimensional conformal treatment planning using computed tomography simulation. Pelvic irradiation was administered with a 6-MV/10-MV dual photon linear accelerator. The pelvic radiation volume was as follows: the superior border at 1.5 cm above the sacral promontory (L5 level), the inferior border at the inferior margin of obturator foramen or 3 cm below the lower margin of tumor, the lateral border at 1.5 cm lateral to the bony pelvis, the anterior border at 3 cm anterior to the tumor, and the posterior border at 0.5 cm posterior to the sacral surface. The prescription dose was specified at the isocenter; the three-field treatment plan comprised a 6-MV photon posterior-anterior field and 6-MV/10-MV photon opposed lateral fields with wedges of 45°. In the boost treatment, five ports were used. Chemotherapy was administered concurrently with radiotherapy. The regimen included the following: intravenous chemotherapy with the administration of 425 mg/m^2 5-fluorouracil and 20 mg/m^2 leucovorin once per day during weeks 1 and 5 of radiotherapy. 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 1,000 mg/m^2 and oxaliplatin 130 mg/m^2) every 3 weeks (Figure 2).

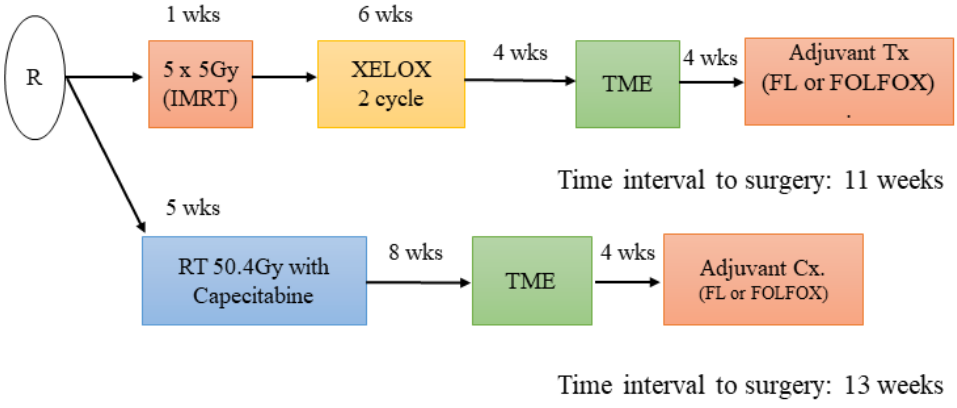

Figure 2. Study protocol. In the SCRT with consolidation chemotherapy group, preoperative radiation therapy consisted of short-course radiation (5 Gy × 5 in 1 week) with concurrent consolidation chemotherapy. Chemotherapy regimen was applied with two cycles of XELOX (capecitabine 1,000 mg/m^2 and oxaliplatin 130 mg/m^2) every 3 weeks. 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).

4. Surgery

In the LCRT group, surgery was scheduled 6 to 8 weeks after the completion of preoperative treatment. Surgery was performed by expert colorectal surgeons who adhered to the oncologic principals of TME with pelvic autonomic nerve preservation[16]. TME advocates for sharp pelvic dissection based on pelvic anatomy under direct vision along the plane of the proper rectal fascia, resulting in the en bloc removal of rectal cancer and surrounding mesorectum containing lymph nodes. In the SCRT with consolidation chemotherapy group, surgery was scheduled 4 weeks after the completion of preoperative treatment.

5. Adjuvant treatments

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 1,250 mg/m^2 capecitabine for 2 weeks (5 cycles). In the LCRT group with high-risk, mFOLFOX-6 (oxaliplatin 85 mg/m^2/day, LV 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 FL based regimen or mFOLFOX-6 according to risk stratification.

6. Assessment for adverse events related to preoperative treatment

Incidence of grade > 1 hematologic (neutropenia, anemia, and thrombocytopenia) and non-hematologic toxicity (nausea, vomiting, mucositis, diarrhea, hand-foot syndrome, anorexia, allergic reaction, dysuria, proctitis, and constipation) associated with treatment protocol was assessed by Common Terminology Criteria for Adverse Events v4.03 in the preoperative period.

7. Assessment of TME completeness

Although TME makes a considerable contribution toward reducing the local recurrence, a subset of rectal cancer patients experiences postoperative recurrence. Accordingly, TME completeness is an important predictor of local recurrence after surgery in rectal cancer patients. 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]. The current College of American Pathologists guideline for the macroscopic evaluation of excision completeness imprise the presence of mesorectal defects, coning, and the CRM status. TME completeness was

evaluated by macroscopic assessment of mesorectal excision as follows: complete, nearly complete, and incomplete[18].

8. Histopathologic assessment after surgery

Pathologic tumor staging of the resected specimen was performed in accordance with the guidelines of the American Joint Committee on Cancer TNM classification. CRM was defined as positive when a tumor cell or lymph node was within 1 mm of the margin. The evidence of ypCR was defined as the absence of residual tumor cell in the surgical specimen or the presence of lakes of mucus without tumor cells. The histology of all surgical specimens was reviewed and confirmed by an independent element and was classified on the basis of the Mandard tumor regression grade system[19]. Tumor downstage (T-downstage) was assessed by comparing the pretreatment clinical stage (cT and cN) with the posttreatment histopathologic stage (ypT and ypN). T-downstage was defined as ypT lower than cT, whereas N-downstage was defined as cN + converted to ypN -.

9. Postoperative outcomes

Postoperative complications were defined as any deviation from the general postoperative course. The modified classification system was used for analyzing surgical complications[20]. Grade I included minor complications not requiring active management with the exception of antipyretics, analgesics, diuretics, antiemetics, and physiotherapy. Wound care, such as wound opening, was also included in this grade. Grade II was defined as potentially life-threatening complications. Supplementary pharmacological treatment other than drugs used for grade I was required for grade II classification. Total parenteral nutrition and blood transfusion were also included in grade II. Grade III was defined as

complications causing disability or longer hospital stays. Grade III complications required surgical, endoscopic, or radiological intervention. These were further divided into two subgroups: grade IIIa, not requiring intervention under general anesthesia, and grade IIIb, requiring intervention under general anesthesia. Grade IV complications were defined as life-threatening, requiring intensive care unit management. Grade IV also consisted of two subgroups: grade IVa, including single organ dysfunction and grade IVb, including multi-organ dysfunction. Grade V was defined as patient death. In terms of tumor recurrence, the patients' medical records were reviewed to gather information regarding such recurrence. Local recurrence was defined as any clinical or histological evidence of tumor re-growth with or without distant metastasis near the primary site after the original surgery. Systemic recurrence was defined as any distant metastasis with or without local recurrence that was confirmed by imaging or histological biopsy.

10. Cost estimation

In this study, 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 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 health 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, recurrence-free survival [RFS]) 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[21-23]. 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.

11. Statistical analysis

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

III. RESULTS

1. Patient characteristics and perioperative outcomes

Patient characteristics are shown 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 = 0.03). 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.

Table 1. Patient characteristics and perioperative outcomes

	SCRT (n = 27)	**LCRT (n = 35)**	***P value***
Age	58.6 ± 9.8	63.7 ± 8.7	*0.03*
Sex			*0.798*
M	16 (59.3%)	22 (62.9%)	
F	11 (40.7%)	13 (37.1%)	
BMI	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, n (%)			*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, n (%)	13 (48.1%)	25 (71.4%)	*0.054*
EMVI, n (%)	12 (44.4%)	19 (54.3%)	*0.304*
Lateral LN, n (%)	7 (25.9%)	10 (28.6%)	*0.999*
Number of high-risk factors per patient, n (%)			*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, n (%)			*0.485*
LAR	22 (81.5%)	31 (88.6%)	
uLAR or CAA	5 (18.5%)	4 (11.4%)	
Type of surgery, n (%)			*0.127*
Robot	9 (33.3%)	19 (54.3%)	
Laparoscopy	18 (66.7%)	16 (45.7%)	
Ileostomy, n (%)	24 (88.9%)	30 (85.7%)	*0.426*
Sphincter saving, n (%)	27 (100%)	35 (100%)	*1.000*
TME completeness, n (%)			*1.000*
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*

Abbreviations: 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; TME, total mesorectal excision; SCRT, short-course radiotherapy

2. Postoperative complications

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 (Table 2).

Table 2. Postoperative complications

	SCRT (n = 27)	**LCRT (n = 35)**	***P value***
Overall complications, n (%)	9 (33.3%)	12 (34.3%)	*1.000*
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%)	

Abbreviations: LCRT, long-course radiotherapy; SCRT, short-course radiotherapy; SSI, surgical site infection; UTI, urinary tract infection

3. Pathologic outcomes

On pathologic examination, pathologic ypT stage was significantly different between the groups (p = 0.013). ypT0, ypT1, ypT2, ypT3, and ypT4 were observed in five (18.5%), four (14.8%), eight (29.6%), nine (33.3%), and one (3.7%) patients in the SCRT group and two (5.7%), 0 (0.0%), 11 (31.4%), 22 (62.9%), and zero (0.0%) patients in the LCRT group, respectively. However,

pathologic ypN stage did not show significant difference between the groups. Only one 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 3).

Table 3. Pathologic outcomes

	SCRT (n = 27)	**LCRT (n = 35)**	***P value***
Tumor size (cm), mean ± SD	1.5 ± 1.4	2.4 ± 1.5	*0.017*
Resection margin (cm), mean ± SD			
Proximal (cm)	14.5 ± 4.9	12.9 ± 4.2	*0.179*
Distal (cm)	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), mean ± SD	27 ± 8.3	30 ± 8.1	*0.878*

pCRM positivity, n (%)	1 (3.7%)	0 (0.0%)	*0.435*
pCR, n (%)	5 (18.5%)	2 (5.7%)	*0.223*
TRG (Mandard grade), n (%)			*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, mean ± SD	15.1 ± 7.4	12.8 ± 7.3	*0.225*
Histology, n (%)			*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, n (%)	16 (59.3%)	12 (34.3%)	*0.072*
N-downstage, n (%)	15 (55.6%)	20 (57.1%)	*0.141*

Abbreviations: pCRM, pathologic circumferential resection margin; SD, standard deviation; WD, well differentiated; MD, moderate differentiated; PD, poorly differentiated; TRG, tumor regression grade; LCRT, long-course radiotherapy; SCRT, short-course radiotherapy

4. Adverse events

An overview of adverse events during preoperative treatment is shown in Table 4. Grade 3 or higher adverse events during preoperative treatment occurred in zero of 27 patients (0.0%) in the SCRT group compared with one 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. There were no serious adverse events in both groups.

Table 4. Adverse events during preoperative treatment between the two groups

	SCRT (n = 27)				LCRT (n = 35)			
Grade	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

5. Tumor recurrence

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 three 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, seven patients (20.0%) had tumor 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 RFS rates were estimated as 91.9% and 76.2% for the SCRT and LCRT groups, respectively (p = 0.394) (Figure 3).

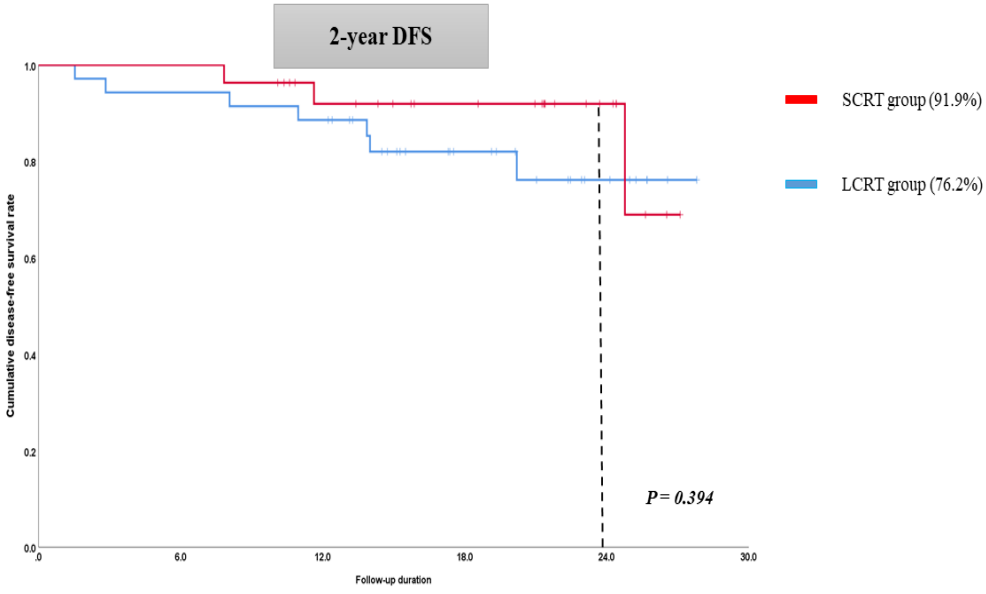

Figure 3. The 2-year recurrence-free survival rate between the SCRT group and LCRT group (SCRT vs. LCRT: 91.4% vs. 76.2%, p = 0.394)

6. Cost analysis

Table 5 exhibits direct medical and non-medical costs. Total direct costs for SCRT and LCRT were $39,709 and $56,789, respectively. Direct medical cost, including in-patient costs approximately 18% lower for SCRT (LCRT vs. SCRT: $22,203 vs. $18,787, $p < 0.001$) and out-patient costs approximately 40% lower for SCRT (LCRT vs. SCRT: $19,641 vs. $11,955, $p < 0.001$), was significantly different between the groups (Figure 4). 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: $1,280 vs. $768, $p < 0.001$) and time costs approximately 40% lower for SCRT (LCRT vs. SCRT: $2,134 vs. $1,280, $p < 0.001$) showed significant difference between the groups (Figure 5). ICER between the two groups is displayed in Table 6. Incremental cost was $17,080 less in the SCRT group. The RFS rate during the mean follow-up period of 24 months was 80.0% in LCRT and 88.9% in SCRT, respectively. In terms of RFS, incremental effectiveness was 8.9% higher in the SCRT group. ICER was calculated to be 1,979 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 17,080 less in the SCRT group. For RFS 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 (Figures 6 and 7).

Table 5. Direct cost between the two groups

	LCRT	SCRT	P value
Inpatient cost	$22,203	$18,787	< 0.001
Outpatient cost	$19,641	$11,955	< 0.001
Transportation cost	$1,280	$768	< 0.001
Time cost	$2,134	$1,280	< 0.001
Total cost	$56,789	$39,709	< 0.001

LCRT, long-course radiotherapy; SCRT, short-course radiotherapy

Table 6. Incremental cost-effectiveness ratios (ICER) between the two groups

Recurrence-free survival					
	Net cost	**Incremental cost**	**Survival rate without recurrence**	**Incremental effectiveness**	**ICER**
LCRT	$56,789		80.0%		
SCRT	$39,709	-$17,080	88.9%	8.9%	-1,979
Postoperative complications					
	Net cost	**Incremental cost**	**Survival rate without complications**	**Incremental effectiveness**	**ICER**
LCRT	$56,789		65.7%		
SCRT	$39,709	-$17,080	66.7%	1.0%	-17,080

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

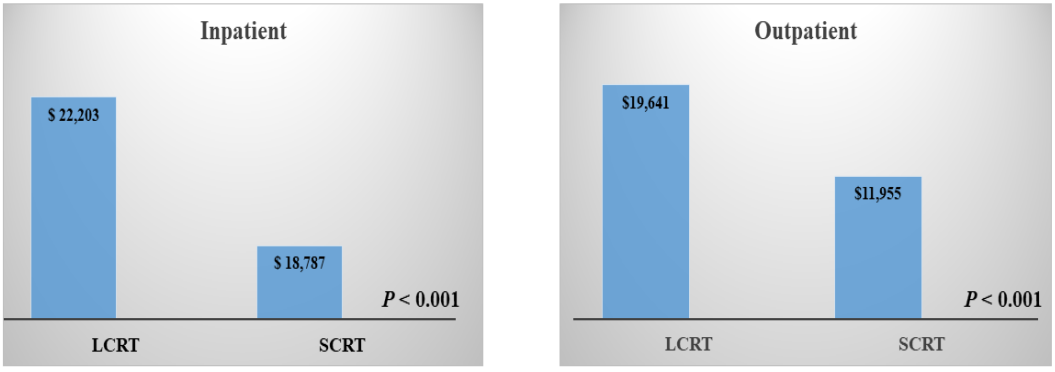

Figure 4. Direct medical cost between SCRT vs. LCRT. The average total cost per patient for SCRT was 18% lower for inpatient treatment ($p < 0.001$). The average total cost per patient for SCRT was 40% lower for outpatient treatment ($p < 0.001$).

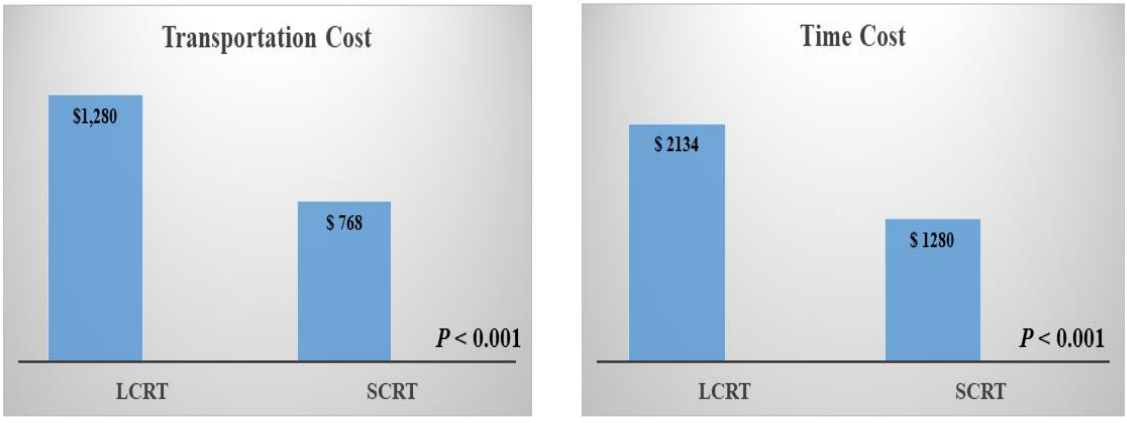

Figure 5. Direct non-medical cost between SCRT vs. LCRT. Both transportation cost and time cost were 40% lower in the SCRT group than those in the LCRT group ($p < 0.001$).

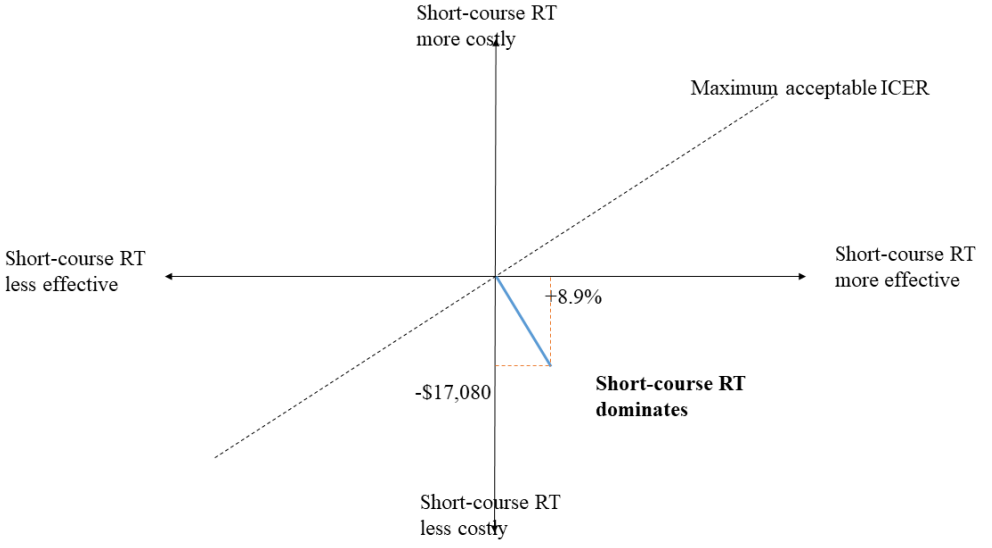

Figure 6. Cost-effectiveness plane according to tumor recurrence

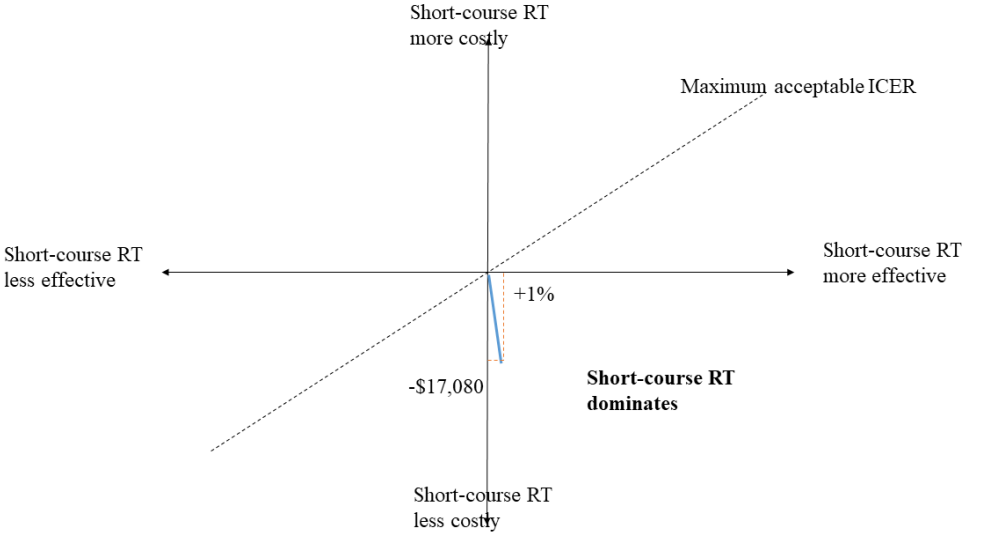

Figure 7. Cost-effectiveness plane according to postoperative complications

IV. 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[24]. 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, 25]. More recently, several randomized trials have been published on the promising outcomes of SCRT at par with those of LCRT[7, 8, 10, 26]. Moreover, there have been only two studies on SCRT in Korea[27, 28]. However, these studies did not show any discriminatory results of SCRT compared to LCRT because consolidation chemotherapy was not effectively provided to patients with SCRT, and the results were limited to clinical outcomes.

So far, studies regarding cost analysis focusing the total costs of care and cost-effectiveness comparison were rarely published. This is the first study to investigate clinical outcomes and cost-effectiveness between SCRT followed by consolidation chemotherapy and LCRT for high-risk rectal cancer treatment in Korea. This 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 RFS state and postoperative complications.

In this study, total direct costs including medical costs and non-medical costs were significantly lower in the SCRT group than in the LCRT group. In terms of radiotherapy, the cost is calculated according to the number of radiotherapy fractions by Korea's health insurance policies. In other words, patients undergoing LCRT 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 differs 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 (LCRT vs. SCRT: $1280 vs. $768, $p < 0.001$) and time costs (approximately 40% lower for SCRT (LCRT vs. SCRT: $2134 vs. $1280, $p < 0.001$).

During the follow-up period of 24 months, incremental effectiveness on RFS was 8.9% 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 can be seen from 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 the patients in the SCRT group improved their health with fewer recurrences and fewer complications at a lower cost. Although this study involved a relatively small number of patients, SCRT followed by consolidation chemotherapy showed significant reduction of total cost of care and cost-effectiveness, with similar clinical outcomes compared to LCRT.

This study significantly showed a shorter period between preoperative treatment and surgery in the SCRT group than in the LCRT group (LCRT vs. SCRT: 14.3 ± 1.1 weeks vs. 12.7 ± 1.2 weeks, $p < 0.001$). Previous 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[29, 30]. Moreover, there have been concerns about SCRT having lower efficacy in terms of tumor response and oncological safety in high-risk rectal cancer treatment than LCRT does. Nevertheless, although not statistically significant, SCRT had a trend toward higher rates of pCR than those of LCRT (SCRT vs. LCRT: 2 of 27 patients (18.5%) vs. 2 of 35 patients (5.7%), $p = 0.223$). In addition, 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 RFS rate between the two groups (SCRT vs. LCRT: 91.2% vs. 76.2%, $p = 0.394$). In early 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, addition of consolidation chemotherapy and delayed surgery 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 one 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 one of 27 patients (3.7%) in the SCRT group and anastomotic leakage in one 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 temporary 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 are major weaknesses of this study, whose results should therefore be interpreted with caution. Late toxicity outcomes were not investigated. Small number of patients were enrolled compared with previous randomized trials. This study was not a prospectively controlled randomized trial. In addition, 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 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.

V. CONCLUSION

SCRT followed by consolidation chemotherapy and delayed surgery was well-tolerated, and it achieved favorable short-term outcomes. In addition, significant reduction of 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.

REFERENCES

1 Kapiteijn E, Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001; 345 (9): 638-646.

2 Sebag-Montefiore D, Stephens RJ, Steele R et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009; 373 (9666): 811-820.

3 Sauer R, Becker H, Hohenberger W et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004; 351 (17): 1731-1740.

4 Martling A, Holm T, Johansson H et al. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. Cancer 2001; 92 (4): 896-902.

5 van Gijn W, Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011; 12 (6): 575-582.

6 Sauer R, Liersch T, Merkel S et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012; 30 (16): 1926-1933.

7 Erlandsson J, Holm T, Pettersson D et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol 2017; 18 (3): 336-346.

8 Bujko K, Wyrwicz L, Rutkowski A et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 x 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol 2016; 27 (5): 834-842.

9 Fernandez-Martos C, Brown G, Estevan R et al. Preoperative chemotherapy in patients with intermediate-risk rectal adenocarcinoma selected by high-resolution magnetic resonance imaging: the GEMCAD 0801 Phase II Multicenter Trial. Oncologist 2014; 19 (10): 1042-1043.

10 Bahadoer RR, Dijkstra EA, van Etten B et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol 2021; 22 (1): 29-42.

11 Bujko K, Nowacki MP, Nasierowska-Guttmejer A et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006; 93 (10): 1215-1223.

12 Raldow AC, Chen AB, Russell M et al. Cost-effectiveness of Short-Course Radiation Therapy vs Long-Course Chemoradiation for Locally Advanced Rectal Cancer. JAMA Netw Open 2019; 2 (4): e192249.

13 Wang S, Wen F, Zhang P et al. Cost-effectiveness analysis of long-course oxaliplatin and bolus of fluorouracil based preoperative chemoradiotherapy vs. 5x5Gy radiation plus FOLFOX4 for locally advanced resectable rectal cancer. Radiat Oncol 2019; 14 (1): 113.

14 Hanly P, Ceilleachair AO, Skally M et al. Direct costs of radiotherapy for rectal cancer: a microcosting study. BMC Health Serv Res 2015; 15: 184.

15 Smith NJ, Barbachano Y, Norman AR et al. Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. Br J Surg 2008; 95 (2): 229-236.

16 Kim NK, Kim YW, Cho MS. Total mesorectal excision for rectal cancer with emphasis on pelvic autonomic nerve preservation: Expert technical tips for robotic surgery. Surg Oncol 2015; 24 (3): 172-180.

17 Nagtegaal ID. Current concepts of colorectal cancer resection pathology. Histopathology 2015; 66 (1): 102-111.

18 Washington MK, Berlin J, Branton P et al. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. Arch Pathol Lab Med 2009; 133 (10): 1539-1551.

19 Mandard AM, Dalibard F, Mandard JC et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer 1994; 73 (11): 2680-2686.

20 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240 (2): 205-213.

21 Briggs AH, Goeree R, Blackhouse G et al. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. Med Decis Making 2002; 22 (4): 290-308.

22 O'Brien BJ, Drummond MF, Labelle RJ et al. In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care. Med Care 1994; 32 (2): 150-163.

23 Black WC. The CE plane: a graphic representation of cost-effectiveness. Med Decis Making 1990; 10 (3): 212-214.

24 Swedish Rectal Cancer T, Cedermark B, Dahlberg M et al. Improved

survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997; 336 (14): 980-987.

25 Ngan SY, Burmeister B, Fisher RJ et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012; 30 (31): 3827-3833.

26 Cisel B, Pietrzak L, Michalski W et al. Long-course preoperative chemoradiation versus 5 x 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: long-term results of the randomized Polish II study. Ann Oncol 2019; 30 (8): 1298-1303.

27 Chung MJ, Kim DW, Chung WK et al. Preoperative short- vs. long-course chemoradiotherapy with delayed surgery for locally advanced rectal cancer. Oncotarget 2017; 8 (36): 60479-60486.

28 Yeo SG, Oh JH, Kim DY et al. Preoperative short-course concurrent chemoradiation therapy followed by delayed surgery for locally advanced rectal cancer: a phase 2 multicenter study (KROG 10-01). Int J Radiat Oncol Biol Phys 2013; 86 (1): 34-39.

29 Francois Y, Nemoz CJ, Baulieux J et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol 1999; 17 (8): 2396.

30 Garcia-Aguilar J, Smith DD, Avila K et al. Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. Ann Surg 2011; 254 (1): 97-102.

ABSTRACT (IN KOREAN)

국소 진행성 직장암 치료에서 표준화학방사선요법과 단기방사선요법 후 공고요법 간의 단기 결과 및 비용 효율성

<지도교수 김 남 규>

연세대학교 대학원 의학과

조 민 수

배경: 표준화학방사선요법은 국내에서 국소 진행성 직장암 환자의 치료에 있어 널리 권장되어 왔다. 최근 직장암에 대한 단기 방사선 요법에 대한 고무적인 결과가 지속적으로 보고되고 있지만, 두 치료법 간의 치료효과에 대해서는 아직까지 논란의 여지가 있다. 더욱이 국내 의료전달시스템의 특성상 대부분의 직장암 환자들이 수도권지역의 대형병원으로 편중되는 현상으로 인해 삶의 질의 저하 및 불필요한 의료비용의 지출이 지속되고 있는 실정이다. 아직까지 국내에서 두 치료법 간의 치료결과와 비용효과분석에 대해 연구가 수행되지 않았고 이에 대한 연구가 절실히 필요한 상황이다. 따라서 본 연구는 두 치료법 간의 단기임상결과와 비용효과에 대해 분석해 보고자 하였다.

방법: 이 연구에서는 자기공명영상으로 진단된 cT3b, cN1/2, 원주 절제면(CRM), 벽외 혈관 침범(EMVI) 및 측면 골반 림프절 전이를 포함하는 고위험 직장암 환자가 이 연구에

등록되었다. 2018년에서 2020년 사이에 62명의 환자가 단기방사선요법 후 공고용법 또는 표준화학방사선치료를 받았다. 단기방사선치료군으로 분류된 27명의 환자들은 5일간의 방사선치료 후 XELOX (3주마다 카페시타빈 1,000mg/m2 및 옥살리플라틴 130mg/m2)의 2주기로 5Gy x 5를 받은 후 수술을 시행 받았다. 표준화학방사선치료군으로 분류된 35명의 환자는 카페시타빈 기반의 5주간의 장기방사선치료 후 수술을 시행 받았다. 종양 반응, 수술 후 합병증, 수술의 완전성 및 급성 독성을 포함한 단기 결과를 조사하였다. 또한 총 치료비용과 비용효과평면을 이용한 비용효과를 포함한 비용추정을 두 그룹 간에 평가하였다.

결과: 수술과 수술 전 치료 시작 사이의 평균 기간은 단기방사선치료군이 표준화학방사선치료군보다 유의하게 짧았다 (12.7 ± 1.2 vs. 14.3 ± 1.1주, p <0.001). 병리학적 완전 관해는 단기방사선치료군과 표준화학방사선치료군에서 각각 18.5% 및 5.7%의 결과를 나타났다(p = 0.223). 전직장간막절제의 완전성은 단기방사선치료군과 표준화학방사선치료군에서 각각 96.2%와 94.2%였으며 통계적으로 유의한 차이는 없었다. 수술 후 1개월 이내의 합병증 발생율은 두 치료군 간에 유의한 차이를 보이지 않았다. 수술 전 치료 중 가장흔한 2등급 이상반응은 단기방사선치료군에서 오심 (29.6%), 표준화학방사선치료군에서 직장염 (8.6%)으로 보고 되었으며, 4등급이상의 심각한 이상반응은 두 치료군 모두에서 관찰되지 않았다. 2년 무병

생존율은 두 치료군간에 유의한 차이를 보이지 않았다 (단기방사선치료군 vs. 표준화학방사선치료군: 91.9% vs. 76.2%, p = 0.394). 직접의료비분석에서 환자 1인당 평균 총비용은 단기방사선치료가 표준화학방사선치료에 비해 입원치료의 경우 18%, 외래치료의 경우 40% 낮았다. 비의료 비용은 단기방사선치료가 표준화학방사선치료보다 약 40% 적은 것으로 분석되었다 (교통비: 90만원 vs. 150만원, p <0.001, 시간 비용: 150만원 vs. 250만원, p <0.001). 비용 효율성면에서는 비용 효율성 평면 분석결과 단기방사선치료가 표준화학방사선치료에 비해 더 적은 비용으로 더 낮은 재발과 합병증으로 비용효율적인 치료 옵션인 것으로 나타났다.

결론: 단기방사선치료과 공고요법 후 지연수술법은 표준화학방사선치료과 비교하여 유의한 차이가 없는 임상결과를 보여 주었으며 총 진료비를 절감함과 동시에 비용효율성을 입증하였다.

핵심되는 말: 직장암, 단기방사선요법, 전직장간막절제술, 비용효율성, 공고요법