Initial experience of preoperative short-course radiotherapy followed by oxaliplatin-based consolidation chemotherapy for locally advanced rectal cancer

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Abstract

Purpose We analyzed the safety and feasibility of preoperative short-course radiotherapy (SCRT) followed by consolidation chemotherapy for patients with locally advanced rectal cancer (LARC).

Methods From April 2018 to May 2019, 19 patients with LARC were treated with SCRT followed by three cycles of consolidation chemotherapy with leucovorin, fluorouracil, and oxaliplatin (FOLFOX6) before surgery. Adjuvant chemotherapy relied on oxaliplatin. Tumor response, patient compliance, and toxicities were analyzed.

Results The median age was 60 years (range 44–71), and 16 of the patients were male. The median tumor height was 5 cm (range 0–9) from anal verge. All patients received a total dose of 25 Gy in five fractions. The number of cycles of FOLFOX6 before surgery was three in 17, four in one, five in one. Five patients required dose reductions in consolidation chemotherapy. The median interval between initiation of SCRT and surgery was 10.6 weeks (range 8.6–16.4). A pathologic complete response was seen in two patients (11%). Grade III toxicities to the preoperative treatment were seen in five patients (26%): diarrhea in two, a decreased white blood cell count in one, and anemia in two. Postoperative complications arising within 30 days developed in five patients (26%). During the median follow-up period of 20.4 months, there was no tumor recurrence.

Conclusion Preoperative SCRT followed by oxaliplatin-based consolidation chemotherapy showed acceptable toxicity and feasibility in patients with LARC. Prospective randomized trials are warranted to verify the efficacy and safety of this treatment strategy compared with conventional long-course concurrent chemoradiotherapy.

Keywords Rectal cancer · Short-course radiotherapy · Consolidation chemotherapy · Total mesorectal excision

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Introduction

Over several decades, innovative strategies have improved the oncologic outcomes of patients with rectal cancer [1], including standardization of total mesorectal excision (TME); preoperative chemoradiotherapy; diagnostic imaging, especially magnetic resonance imaging (MRI); and a multidisciplinary team (MDT) approach. These efforts have contributed to decrease local recurrence rates to around 5% of patients with locally advanced rectal cancer (LARC), as reported by some prospective studies [2, 3].

Widely used in most of the world, long-course concurrent chemoradiotherapy (LC-CCRT) has been accepted as a standard treatment modality for patients with LARC. This shows a downstaging effect on the tumors, high sphincter preservation, and low local recurrence rates. However, there are some concerns for patients' inconvenience, with high cost and frequent visits to hospital [4]. Moreover, there are also some concerns that about 25–30% of patients suffer from distant metastases, even after neoadjuvant chemoradiation and TME followed by adjuvant chemotherapy [3, 5–7]. In our clinical setting, we commonly encounter patients with complex rectal cancers showing threatening circumferential margins and suspicious but invisible distant metastases such as aggressive extramural vascular invasions and high circulating levels of carcinoembryonic antigen (CEA), for whom both chemoradiation and chemotherapy are necessary. We hypothesized that short-course chemoradiotherapy (SCRT) with consolidation chemotherapy might achieve as effective local control of tumors as LC-CCRT, and could provide potential benefits including early eradication of micrometastases by consolidation chemotherapy within a similar time interval as surgery. Moreover, this approach might provide better compliance that cannot be met currently by LC-CCRT.

Herein, we report our initial experience of preoperative SCRT and consolidation chemotherapy for LARC to evaluate its safety and feasibility for future clinical application.

Materials and methods

Patients

We reviewed our prospectively collected registry from April 2018 to May 2019 for patients with locally advanced rectal cancers who underwent SCRT followed by consolidation chemotherapy before surgery. The indications for SCRT and consolidation chemotherapy during the study period were as follows: (1) histologically confirmed rectal adenocarcinomas with the distal edge of the tumor located below the anterior peritoneal reflection (or ≤10 cm from the anal verge); and (2) clinical stage T3–4 tumors or node positivity. Patients with MRI-detected extramural vascular invasion (mrEMVI)

positivity or initial high CEA levels (> 7.0 ng/mL) were also considered for SCRT and consolidation chemotherapy before surgery. Patients diagnosed with distant metastases were excluded. Treatment protocols for all patients were determined through the our MDT meeting. This study has been approved by the research ethics committee of Kyungpook National University Chilgok Hospital (KNUCH 2020-04-024).
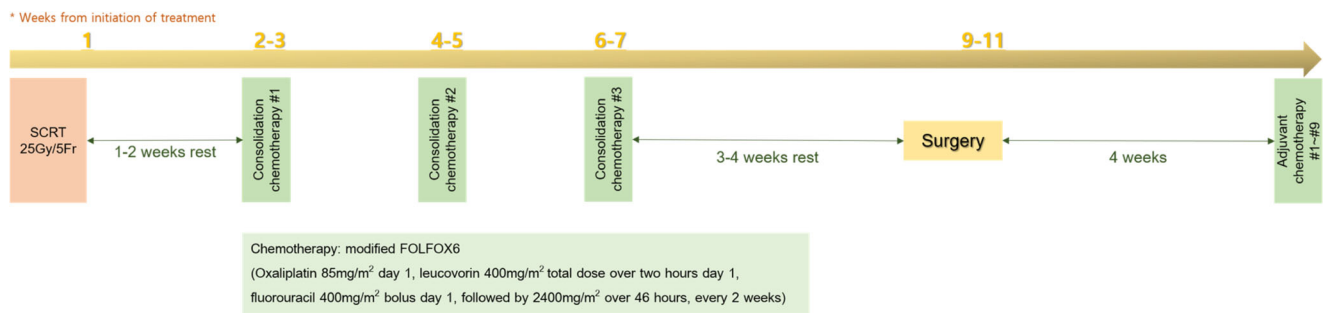
Treatment

Patients received a total dose of 25 Gy in five fractions on consecutive days. After a 1–2-week rest period, patients then received three cycles of consolidation chemotherapy. We used a modified FOLFOX6 regimen: oxaliplatin 85 mg/m^2 on day 1; leucovorin 400 mg total dose over 2 h on day 1; fluorouracil 400 mg/m^2 bolus on day 1; followed by 2400 mg/m^2 over 46 h (cycles repeated every 2 weeks). The interval between the last cycle of chemotherapy and surgery was 3–4 weeks (Fig. 1).

We performed a high ligation of the inferior mesenteric artery, medial-to-lateral mobilization of the left colon, complete splenic flexure mobilization, and sharp pelvic dissection. If the tumor had invaded the external anal sphincter, we performed abdominoperineal resection [8]. We performed selective lateral pelvic lymph node dissection for patients with suspected metastatic lateral pelvic lymph nodes on initial imaging regardless of their response to neoadjuvant treatment [9]. About 2 weeks after surgery, we decided on adjuvant treatment for patients through our MDT meetings. The most common regimen was a modified FOLFOX6. Twelve cycles of chemotherapy were planned before and after surgery. The interval from surgery to initiation of adjuvant chemotherapy was usually 4 weeks.

Evaluation

Before neoadjuvant treatment, staging workups were performed on all patients. These involved taking a medical history; physical examinations including a digital rectal examination; laboratory tests; assays for CEA; colonoscopy; chest radiography; computed tomography (CT) scanning of the chest, abdomen and pelvis; and MRI scans. Restaging was done 6–7 weeks after completing radiotherapy by abdominal/pelvis/chest CT scans and pelvic MRI. MRI and CT examinations were assessed by a specialized radiologist who has more than 10 years of experience in interpreting colorectal cancer imaging. An instance of mrEMVI was defined as a serpiginous extension of a tumor signal within a vessel, defined as a tubular structure containing a signal void on T2-weighted images and shown in continuity on adjacent slices (Fig. 2) [10, 11]. A five-point MRI tumor regression grade (mrTRG) was used to report tumor response to neoadjuvant therapy [12]. The pathological stage was classified according to the TNM staging system of the American Joint Committee

Abbreviations: SCRT, short-course radiotherapy

Fig. 1 Neoadjuvant treatment (short-course radiation followed by consolidation chemotherapy) protocol for patients with locally advanced rectal cancer in the study period. Abbreviations: SCRT, short-course radiotherapy

on Cancer, 7th edition [13]. Regression of the primary tumor following neoadjuvant chemoradiation was assessed based on the tumor regression grade (TRG) as described by Rödel et al. [14]. Patients with a complete pathology response (pCR) were characterized as having no residual tumor cells within the rectal wall in surgical biopsy specimens. The circumferential resection margin (CRM) was defined as the closest distance from the outermost region with viable tumor cells to the resected specimen.

Morbidity or toxicities

The common terminology criteria for adverse events (version 5) were used for evaluating acute toxicities during the period from the initiation of radiation to surgery [7]. Postoperative morbidities within 30 days were graded according to the Clavien–Dindo classification [15].

Statistical analysis

Continuous variables are described as the mean and standard deviation or as the median and range. Categorical variables are
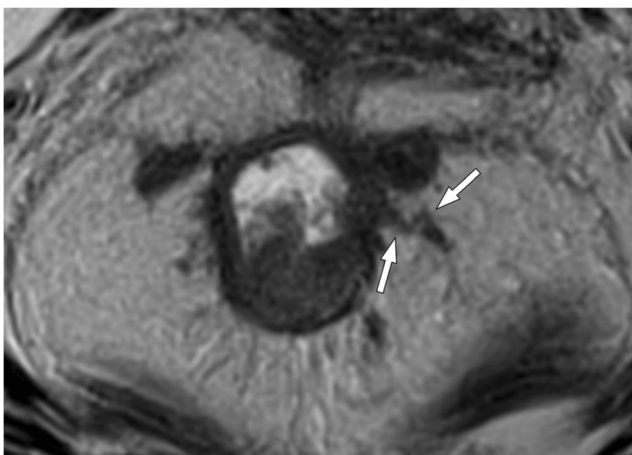
Fig. 2 Extramural venous invasion (arrow) in pretreatment magnetic resonance imaging in patients with locally advanced rectal cancer

described as frequencies and percentages. Times to events were measured from the initiation of radiotherapy and censored at the date of diagnosing any recurrence, or at the last outpatient clinic visit. All analyses were conducted using the R project for Statistical Computing, Version 4.0.1 (R Development Core Team, Vienna, Austria).

Results

Nineteen patients received sequential SCRT and FOLFOX6 therapy before surgery during the study period. Patient characteristics are summarized in Table 1. The median age of patients was 60 years (range 44–71), and 16 (84%) of the patients were male. The median tumor distance from the anal verge was 5 cm. Lower tumor distance ($\leq$ 5 cm), was seen in 11 patients (58%). An initial high CEA level (> 7 ng/mL) was seen in five patients. After SCRT and consolidation chemotherapy, such a high CEA level was seen in only one patient. A mrEMVI was seen in five and four patients in pre- and posttreatment MRI scans, respectively. In pretreatment MRI, mesorectal fascia involvement was seen in nine patients. After SCRT and consolidation chemotherapy, mesorectal fascial involvement was seen in three patients in posttreatment MRI. A good response (mrTRG 1–3) was seen in 13 of the remaining 16 patients (81%).

The median interval from completion of SCRT to initiation of chemotherapy was 10 days (range 4–24). The median interval from initiation of SCRT to surgery was 10.6 weeks (range 8.6–16.4). The median interval from completion of consolidation chemotherapy to surgery was 4.0 weeks (range 2.6–11.0).

All patients completed the planned schedule of SCRT without any interruption. Episodes of acute toxicity and the rate of adherence to the neoadjuvant treatment are listed in Table 2. Seventeen (90%) of the 19 patients received three cycles of FOLFOX6. Consolidation chemotherapy dose reduction was observed in five patients: four suffered neutropenia and one experienced a chemoport infection.

Table 1 Patient characteristics

	n = 19
Age, year	60 (44–71)
Sex	
Female	3 (15.8%)
Male	16 (84.2%)
ECOG PS	
0	2 (10.5%)
1	17 (89.5%)
Clinical T stage	
T3	13 (68.4%)
T4	6 (31.6%)
Clinical N stage	
N0	3 (15.8%)
N+	16 (84.2%)
Differentiation	
Well	4 (21.1%)
Moderate	15 (78.9%)
Tumor height, cm	5 (0–9)
≤ 5 cm	11 (57.9%)
> 5 cm	8 (42.1%)
CEA (pretreatment), ng/mL	3.1 (0.8–53.4)
Elevated (> 7.0 ng/mL)	5 (26.3%)
Normal (0~7.0 ng/mL)	14 (73.7%)
CEA (posttreatment)*, ng/mL	2.1 (0.7–7.6)
Elevated (> 7.0 ng/mL)	1 (5.6%)
Normal (0~7.0 ng/mL)	17 (94.4%)
mrEMVI (pretreatment)†	
Positive	5 (29.4%)
Negative	12 (70.6%)
mrEMVI (posttreatment)‡	
Positive	4 (25.0%)
Negative	12 (75.0%)
mrMRF (pretreatment) †	
Involved MRF (< 1 mm)	9 (52.9%)
Threatened MRF (1–2 mm)	-
Clear MRF (≥ 2 mm)	8 (47.1%)
mrMRF (posttreatment)‡	
Involved MRF (< 1 mm)	3 (18.8%)
Threatened MRF (1–2 mm)	1 (6.2%)
Clear MRF (≥ 2 mm)	12 (75.0%)
mrTRG‡	
2 (near complete regression)	6 (37.5%)
3 (moderate regression)	7 (43.7%)
4 (minimal regression)	3 (18.8%)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; mrEMVI, magnetic resonance imaging-detected extramural venous invasion; mrMRF, magnetic resonance mesorectal fascia status; mrTRG, magnetic resonance tumor regression grade

Proportions are presented for categorical data and median with range for all continuous data

*Exclude 1, no data

†One patient did not undertake an initial MRI, and one patient can not evaluate because of intussusception

‡Two patients did not undertake posttreatment MRI, and one patient undertake posttreatment MRI in another hospital

Operative and postoperative complications are summarized in Table 3. One of the 19 patients preferred to undergo transanal endoscopic microsurgery at another hospital. Laparoscopic surgery was performed in 16 patients (84%)

Table 2 Acute toxicity to the neoadjuvant treatment

	n=19
Radiotherapy dose reduction and/or delay	0
Number of cycles of consolidation chemotherapy	
3	17 (89.5%)
4	1 (5.3%)
5	1 (5.3%)
Consolidation chemotherapy dose reduction	5 (26.3%)
Toxicity grade 1–2	14 (73.7%)
Diarrhea	3
Anal pain	4
Abdominal pain	5
Anal hemorrhage	2
White blood cell decreased	13
Anemia	13
Platelet count decreased	4
Toxicity grade 3	5 (26.3%)
Diarrhea	2
White blood cell decreased	1
Anemia	2

Proportions are presented for categorical data

and conversion to open surgery was needed in one patient because of an ischemic change in the splenic flexure of the colon. The median operative time was 250 min. The protective stoma formation rate was 10/16 (63%). At the close-out date for analysis, no patients had stomata except for two who underwent abdominoperineal resection. Three patients (15.8%) exhibited lymph nodes larger than 5 mm in the short-axis diameter in the unilateral pelvic sidewall on the initial pelvic MRI. These patients underwent TME and lateral pelvic lymph node dissection. Two of those patients exhibited internal iliac lymph node metastasis, and one patient showed no lateral pelvic lymph node metastasis in the final pathologic reports. Postoperative complications occurred in five patients: one developed anastomotic leakage and was treated by rectal tube drainage without diversion of the stoma; one suffered atrial fibrillation at postoperative day 2, and ileus and urinary retention at postoperative day 7. This patient was diagnosed with anastomotic leakage with intra-abdominal fluid collection at postoperative day 9 and was then treated by percutaneous drainage without diversion of stoma. There was no mortality in the postoperative 30 days.

Pathology findings are summarized in Table 4. The pCR rate was 11% (Supplemental Figures S1 and S2). Good tumor response (TRG 3 and 4) was seen in 17 patients (90%). A pathological CRM-positive distance of ≤ 1 mm was shown in two patients. These patients had a positive CRM in both pre- and posttreatment MRI scans.

Fifteen of the 19 patients (79%) completed the planned 12 cycles of FOLFOX6 therapy. The other four patients

Table 3 Operative and postoperative outcomes within 30 days

	n=19
Type of operation	
LAR	12 (63.2%)
ISR	4 (21.1%)
APR	2 (10.5%)
TEM	1 (5.3%)
Operative approach	
Laparoscopic	16 (84.2%)
Robotic	2 (10.5%)
TEM	1 (5.3%)
LPND	3 (15.8%)
Open conversion	1 (5.3%)
Operative time, min*	250 (100–400)
Estimated blood loss, mL*	50 (10–300)
Protective stoma†	10/16 (62.5%)
Postoperative complication‡	5 (26.3%)
Anastomotic leakage	2
Ileus	2
Urinary retention	3
Atrial fibrillation	1
Grade of complications, n (%)	
I–II	6
III–IV	2
Mortality	0

Abbreviations: LAR, low anterior resection; ISR, intersphincteric resection; APR, abdominoperineal resection; TEM, transanal endoscopic microsurgery; LPND, lateral pelvic lymph node dissection

Proportions are presented for categorical data and median with range for all continuous data

*Exclude 1, no data

†Exclude 3, TEM, and APR

‡One patient has four complications (anastomotic leakage, ileus, urinary retention, and atrial fibrillation)

Table 4 Pathologic findings

	n=19
Pathologic T category *	
ypT0	2 (10.5%)
ypT2	7 (36.8%)
ypT3	8 (42.1%)
ypT4b	2 (10.5%)
Pathologic N category*	
ypN0	12 (63.2%)
ypN1†	5 (26.3%)
ypN2	1 (5.3%)
ypNx	1 (5.3%)
Pathologic stage*	
ypT0N0	1 (5.3%)
ypT2Nx	1 (5.3%)
I	5 (26.3%)
IIA	5 (26.3%)
IIC	1 (5.3%)
IIIA	2 (10.5%)
IIIB	3 (15.8%)
IIIC	1 (5.3%)
TRG	
TRG 2 (moderate)	2 (10.5%)
TRG 3 (good)	15 (78.9%)
TRG 4 (complete)	2 (10.5%)
CRM ‡	
CRM negative (> 1 mm)	15 (88.2%)
CRM positive (≤ 1 mm)	2 (11.8%)

Abbreviations: TRG, tumor regression grade; CRM, Circumferential resection margin

*The prescript "y" used to indicate that the tumor had been treated before surgical resection

†Two patients revealed internal iliac lymph node metastasis

‡Exclude 2, no data

discontinued for the following reasons. One patient received 10 cycles of FOLFOX6 because of a urinary tract infection. Two patients stopped postoperative chemotherapy after nine and six cycles because of poor performance status and diarrhea. One patient refused further treatment after receiving four cycles of FOLFOX6. The actual delivered dose intensity was about 80% for both fluorouracil and oxaliplatin.

The median follow-up duration was 20.4 months (range 7.7–26.6). There was no tumor recurrence during this period.

Discussion

The strategies for treating LARC usually involve a multidisciplinary approach. Radiation therapy might be one of the fundamental modalities in this. However, its role has been challenged in certain circumstances. Conventional LC-CCRT has led to low rates of local recurrence, but the incidence of distant metastases has not decreased as expected [3, 5–7]. Some have attempted to find ways to achieve better results in the treatment of LARC [16–21], especially paying attention to preoperative consolidation or induction chemotherapy with chemoradiation to treat micrometastases early and with increased treatment compliance. Nonetheless, when applied with LC-CCRT, this approach raises a few concerns regarding the exceptionally long period of neoadjuvant treatment with a doubtful response in some patients. Therefore, when considering preoperative chemoradiation and chemotherapy, SCRT seems to be a good alternative because it can be completed within 1 week if equivalent oncologic outcomes

are guaranteed compared with conventional LC-CCRT, as already reported by some groups [6, 7]. The waiting time from radiation to surgery could be a valuable period for consolidation chemotherapy to treat distant metastases. Accordingly, we conducted preoperative SCRT followed by three cycles of FOLFOX6 for patients with LARC, and our initial experience shows that it was safe and feasible.

Our indications for using SCRT followed by consolidation chemotherapy are different from those in other studies. The Polish II trial's eligibility criteria were cT4 or fixed cT3 lesion [7]. The CAO/ARO/AIO-12 trial included patients with cT3 or T4 rectal cancer [16]. During the study period in our study, the indications to adopt SCRT followed by consolidation chemotherapy focused on tumor characteristics suspicious of a high risk of systemic recurrence in preoperative evaluations, such as lymph node positivity or high CEA levels or adverse mrEMVI findings. Elevated CEA was associated with poor prognosis in colorectal cancer patients [22, 23]. Siddiqui et al. [10] and Chand et al. [24] reported that mrEMVI was a poor prognostic factor related to distant metastasis in patients with rectal cancer. One of the crucial roles for SCRT and consolidation chemotherapy is efficient control of distant metastases in patients with LARC. Although this study was an initial one with a relatively short follow-up period (median 20.4 months), there has been no recurrence. Long-term follow-ups of our results are needed to clarify the clinical benefit of our strategy.

Our study did not include a totally neoadjuvant treatment scheme. Instead, we adhered to the treatment strategies for locally advanced rectal cancer, which comprise neoadjuvant treatment followed by curative surgery and adjuvant chemotherapy. In the CAO/ARO/AIO-12 trial, adjuvant chemotherapy was not recommended [16]. The experimental arm in the RAPIDO trial comprised full-dose chemotherapy before surgery, after SCRT, and without the adjuvant setting [18]. These trials reported a high rate of pathological complete response (17–28%) and high compliance with systemic therapy in the group that received totally neoadjuvant treatment [16, 18]. Meanwhile, we chose three cycles of consolidation FOLFOX before surgery to make this similar to the conventional LC-CCRT. To provide personalized treatment, we planned the adjuvant chemotherapy after a MDT meeting that carefully reviewed the intraoperative findings and pathology reports for each patient. We attempt to reduce the need for unnecessary treatment, such as that given to patients who respond poorly to neoadjuvant treatment, and to avoid overadministration of chemotherapy in patients with low-risk disease.

We found a pCR rate of 2/19 (11%), slightly lower than in other trials with pCR rates of ~15% [6, 7, 25]. The reasons for this are unclear because this study was a small case series. However, there are two possible reasons. First, the interval from radiation to surgery might have been insufficient in our cohort, with a median time from initiating radiation to surgery

of 10.6 weeks (range 8.6–16.4). In a Polish II trial, the median interval between the initiation of irradiation and surgery in the SCRT group was 12.4 weeks, and the pCR rate was 17% [7]. Second, in this study, we applied three cycles of FOLFOX6 before surgery. In a phase II nonrandomized trial, increasing cycles of FOLFOX6 after chemoradiation and before surgery were associated with a higher rate of pCR with better compliance to chemotherapy and without significant increase in postoperative complications [26]. In the RAPIDO trial, SCRT followed by 18 weeks of chemotherapy and TME achieved a pCR rate of 27.7% [18]. Therefore, here, we prepared a prospective randomized trial comparing SCRT with LC-CCRT, considering the SCRT group to comprise four or more cycles of FOLFOX6 and increased the interval from radiation to surgery.

When adopting hypofractionated SCRT followed by consolidation chemotherapy before surgery for patients with LARC, treatment-related toxicities and postoperative complications are of concern compared with fully fractionated LC-CCRT. In terms of radiation- and chemotherapy-related toxicities, our results were similar to those of other studies. The incidence of grade 3 toxicity was 26% in our study. A German trial with LC-CCRT reported a 27% rate of grade 3–4 toxicities [5]. Another study reported that 27.1% of patients experienced grade 3–4 toxicities in the LC-CCRT treatment group [27]. In a recent two randomized trial, the rates of grade 3 or worse adverse events were 23–48 % in a SCRT group and 21–25% in an LC-CCRT group [7, 18]. The postoperative complication rate was also tolerable at 27%. Grade 3 complication was observed in one patient (5.3%). Other prospective studies with LC-CCRT reported postoperative morbidity rates of 25.0 to 36.0% [5, 25, 28]. In a Polish II trial, the respective postoperative complication and grade 3–4 complication rates were 19% and 8% in a SCRT group, and 21% and 6% in an LC-CCRT group [7].

MRI assessment of tumor downstaging might provide information on treatment response [11, 29, 30]. In our cohort, a good response (mrTRG 1–3) was seen in 13 of 16 patients (81%). A retrospective study reported that 72.8% of patients showed good responses (mrTRG 1–3) after SCRT alone [30]. Here, we conducted consolidation chemotherapy between radiation and surgery that might have influenced our results. However, the prognostic significance of the mrTRG system is controversial, and a prospective trial is ongoing to evaluate it [17, 31]. Further studies are warranted to evaluate the efficacy of mrTRG in the context of SCRT and in real clinical practice.

There were some limitations to our study. First, it was a retrospective study in a single center. Second, we analyzed a small number of patients with a relatively short follow-up period, so late toxicities and long-term oncologic outcomes could not be evaluated. Moreover, discrepancies in the administered consolidation chemotherapy might have influenced

our results. We have focused on the short-term outcomes of our strategy in this report. Based on these results, we expect that our proposed prospective multicenter randomized trial will clarify the safety and efficacy of SCRT followed by consolidation chemotherapy before surgery compared with LC-CCRT for patients with LARC.

In conclusion, our initial experience of a short course of radiotherapy followed by oxaliplatin-based consolidation chemotherapy for patients with LARC has shown acceptable toxicity profiles and feasibility. Further large-scale and long-term results of our scheme will help test these conclusions.

Declarations

Ethics approval All patients provided informed consent, and this study was approved by the institutional review board (KNUCH 2020-04-024).

Conflict of interest The authors declare no conflicts of interest.

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